Refeeding Low Weight Hospitalised Adolescents with Anorexia Nervosa

Graeme O’Connor

University College London

Dissertation submitted to University College London for the degree of Doctor of Philosophy (PhD)

March 2014

## Declaration

## 

I, Graeme O’Connor, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm this has been acknowledged in the thesis.

Signature………………………………………………………………………………………………………………………………..

Date……………………………………………………………………………………………………………………………………….

# Abstract

Refeeding adolescents with anorexia nervosa (AN) carries risks, the extent of which have been much debated but subject to little research. As such, the optimal nutritional management of such patients is unknown, and the lack of evidence from interventional studies has led to worldwide disparities in clinical management recommendations. In this first randomised controlled trial in this area, we tested the hypothesis that refeeding with a higher energy intake than that currently recommended in Europe, improves outcomes in low weight adolescents with AN.

The aim of this study was to investigate the association between total energy intake on QTc interval, heart rate and hypophosphataemia. The primary outcome was QTc interval (ms). Secondary outcomes were heart rate, electrolytes (phosphate, magnesium and potassium) and anthropometry (weight [kg] and %BMI).

Participants were 38 adolescents’ aged 10-16years with a DSM IV diagnosis of AN recruited from six acute paediatric services around the UK and were randomly allocated to commence refeeding at 1200kcal/ day (intervention) or at 500kcal/ day (control). Energy intake was incrementally increased by 200kcal day up to 80% of estimated energy requirements.

The results showed that compared to controls, adolescents randomised to the higher calorie group had a greater weight gain. However, randomised groups did not differ statistically in QTc interval or heart rate. Refeeding hypophosphataemia (serum phosphate <0.9mmol/l) developed in a proportion of patients. However, there was no statistical difference in the incidence or severity of refeeding hypophosphataemia between the two groups. Participants that were below 68%BMI and those with low WBC’s (WBC <3.8 x 109/l) had a greater reduction in post refeeding phosphate.

Together, these findings suggest that oral refeeding at 1200kcal/ day (38kcal/ kg/ day) which increases incrementally to 1900kcal/ day (58kcal/ kg/ day) is more beneficial for the majority of patients than commencing refeeding at 500kcal/ day in low weight adolescents with AN. The findings from this study challenge current European and UK recommendations.

Table of Contents

[Declaration 2](#_Toc384718809)

[Abstract 3](#_Toc384718810)

[Table of Tables 17](#_Toc384718811)

[Table of Figures 19](#_Toc384718812)

[Table of Appendices 20](#_Toc384718813)

[Abbreviations in text 21](#_Toc384718814)

[Chapter 1: Background to Anorexia nervosa 22](#_Toc384718815)

[“Nothing tastes as good as skinny feels” – Kate Moss 22](#_Toc384718816)

[1.1 Definition 22](#_Toc384718817)

[1.2 Mortality Rate 22](#_Toc384718818)

[1.3 Prevalence and Incidence 23](#_Toc384718819)

[1.4 Diagnostic Criteria 24](#_Toc384718820)

[1.7 Causes of Anorexia Nervosa 25](#_Toc384718821)

[1.7.1 Puberty 25](#_Toc384718822)

[1.7.2 Environmental 26](#_Toc384718823)

[1.7.3 Psychiatric 27](#_Toc384718824)

[1.7.4 Genetic 27](#_Toc384718825)

[1.7.5 Neurobiological - Appetite hormones 28](#_Toc384718826)

[1.7.6 Ghrelin 28](#_Toc384718827)

[1.7.7 Leptin 29](#_Toc384718828)

[1.7.8 Serotonin 30](#_Toc384718829)

[1.7.9 Dopamine 31](#_Toc384718830)

[1.8 Consequences of anorexia nervosa 32](#_Toc384718831)

[1.8.1 Bone Mineral Density 32](#_Toc384718832)

[1.8.2 Cardiovascular 33](#_Toc384718833)

[1.9 Treatment 33](#_Toc384718834)

[1.9.1 Family-Based Therapy (FBT) 34](#_Toc384718835)

[1.9.2 Neuropsychopharmacology 35](#_Toc384718836)

[1.9.2.1 Metabolic Syndrome 36](#_Toc384718837)

[1.9.3 Selective Serotonin Reuptake Inhibitors (SSRI) 37](#_Toc384718838)

[1.10 Summary 38](#_Toc384718839)

[Chapter 2: Pathophysiology of starvation 39](#_Toc384718840)

[2.1 Introduction 39](#_Toc384718841)

[2.2 Stages of Starvation 39](#_Toc384718842)

[2.2.1 Insulin and Glucagon homeostasis 39](#_Toc384718843)

[Diagram 2.1 – Fuel metabolism during the early stages of starvation 41](#_Toc384718844)

[2.2.2 Gluconeogenesis 42](#_Toc384718845)

[Diagram 2.2 – Gluconeogenesis from adipose and muscle tissue within the mitochondria 43](#_Toc384718846)

[2.2.3 Ketone bodies 44](#_Toc384718847)

[2.3 Malnutrition: Famine Vs Anorexia Nervosa 44](#_Toc384718848)

[2.4 Definition of Malnutrition 46](#_Toc384718849)

[2.5 Measurement of Ideal Body Weight 47](#_Toc384718850)

[2.6 History of Famines 47](#_Toc384718851)

[2.7 Food Availability 48](#_Toc384718852)

[2.8 Medical Conditions Associated with Malnutrition 50](#_Toc384718853)

[Table 2.1 – Medical conditions associated with macronutrient deficiencies 51](#_Toc384718854)

[2.9 Physiological implications of starvation 52](#_Toc384718855)

[2.9.1 Hormonal - Insulin 52](#_Toc384718856)

[2.9.2 Insulin Sensitivity and Resistance 53](#_Toc384718857)

[2.9.3 Insulin response to test meals in malnourished AN 54](#_Toc384718858)

[2.9.4 Cardiovascular 55](#_Toc384718859)

[2.9.5 Immunology 56](#_Toc384718860)

[2.9.6 Electrolytes 57](#_Toc384718861)

[2.9.7 Growth and bone density 58](#_Toc384718862)

[2.9.8 Behaviour and Cognition 61](#_Toc384718863)

[2.9.9 Body Composition and Energy Expenditure 62](#_Toc384718864)

[Table 2.2 – Comparison of Resting Energy Expenditure of malnourished patients with AN with healthy weight controls 65](#_Toc384718865)

[2.10 Summary 67](#_Toc384718866)

[Chapter 3: Refeeding the malnourished adolescent with AN 68](#_Toc384718867)

[3.1 Introduction 68](#_Toc384718868)

[3.2 History of the Refeeding Syndrome 68](#_Toc384718869)

[3.2.1 Prisoners of War 69](#_Toc384718870)

[3.2.2 Minnesota Starvation Experiment 69](#_Toc384718871)

[3.2.3 Parenteral Nutrition 70](#_Toc384718872)

[3.3 Clinical Manifestations of Refeeding 71](#_Toc384718873)

[3.3.1 – Rate of Refeeding 71](#_Toc384718874)

[3.3.2 Impact of carbohydrate 72](#_Toc384718875)

[3.3.3 Impact of Insulin 72](#_Toc384718876)

[3.3.4 Glucose Metabolism 73](#_Toc384718877)

[3.4 Refeeding Hypophosphatemia 73](#_Toc384718878)

[3.5 Refeeding Hypomagnesaemia 74](#_Toc384718879)

[3.6 Refeeding Hypokalaemia 75](#_Toc384718880)

[3.7 Delirium 76](#_Toc384718881)

[Diagram 3.1 Pathophysiology of refeeding 77](#_Toc384718882)

[3.8 Summary of Clinical Manifestation of Refeeding 78](#_Toc384718883)

[Chapter 4: Refeeding Hypophosphatemia in malnourished patients with anorexia nervosa: A Systematic Review 79](#_Toc384718884)

[4.1: Introduction 79](#_Toc384718885)

[4.2 Risk factors for Refeeding Hypophosphatemia 80](#_Toc384718886)

[4.4: Methods for literature review 81](#_Toc384718887)

[4.4.1 Search Strategy 81](#_Toc384718888)

[4.4.2 Inclusion criteria 81](#_Toc384718889)

[4.4.3: Exclusion criteria 82](#_Toc384718890)

[Table 4.1 Inclusion and exclusion criteria established for the systematic review 82](#_Toc384718891)

[4.5 Statistics for literature review 83](#_Toc384718892)

[4.6 Results for literature review 83](#_Toc384718893)

[Figure 4.1 Flow chart of included studies that explored the impact energy intake and malnutrition had on post refeeding nadir phosphate levels. 84](#_Toc384718894)

[4.6.1 Serum Phosphate levels 85](#_Toc384718899)

[4.6.2 Nutritional Intervention 85](#_Toc384718900)

[4.6.3 Ideal Body Weight Calculation 86](#_Toc384718901)

[4.6.3 Energy intake 86](#_Toc384718902)

[4.6.4 Association between %BMI and Hypophosphatemia 87](#_Toc384718903)

[Figure 4.2: Association between malnutrition (%BMI) and post refeeding serum phosphate (mmol/ l) (r = 0.62 p= 0.01) 88](#_Toc384718904)

[4.6.5 Association between energy intake (kcal/ day) and Hypophosphatemia 89](#_Toc384718905)

[Figure 4.3 Relationship between energy intake and post refeeding nadir phosphate 90](#_Toc384718906)

[90](#_Toc384718907)

[4.7 Discussion for literature review 91](#_Toc384718908)

[4.7.1 Energy Intake and Refeeding Hypophosphatemia 91](#_Toc384718909)

[4.7.2 Degree of Malnutrition and Incidence of Refeeding Hypophosphatemia 97](#_Toc384718910)

[4.8 Limitations 99](#_Toc384718911)

[4.9 Conclusion for literature review 100](#_Toc384718912)

[Table 4.2- Chart Reviews: Energy intake and incidence of Refeeding Hypophosphatemia in adolescents with Anorexia Nervosa. 101](#_Toc384718913)

[Table 4.3 Case Reports: Energy intake and post refeeding serum phosphate in adolescents with Anorexia Nervosa. 102](#_Toc384718914)

[(Continue) Table 4.3 Case Reports: Energy intake and post refeeding serum phosphate in adolescents with Anorexia Nervosa. 103](#_Toc384718915)

[Chapter 5 Refeeding and Cardiovascular Parameters in Anorexia Nervosa: Meta-Analysis and Systematic Review 104](#_Toc384718916)

[5.1 Introduction 104](#_Toc384718917)

[5.1.1 Correcting QT interval adjusting for heart rate 104](#_Toc384718918)

[5.1.2 Normal and prolonged QTc interval in adolescents 105](#_Toc384718919)

[5.2 Methods – Literature Search: Malnutrition and QTc interval 106](#_Toc384718920)

[5.2.1 Literature Search 106](#_Toc384718921)

[5.2.2 Selection Criteria 107](#_Toc384718922)

[5.2.3 Exclusion Criteria 107](#_Toc384718923)

[5.2.4 Main and Subgroup Analyses 108](#_Toc384718924)

[5.2.5 Statistical Analysis 109](#_Toc384718925)

[5.3 Results - literature search: Malnutrition and QTc interval 109](#_Toc384718926)

[Figure 5.1- Flow chart of the included studies that investigated the impact energy intake and malnutrition had on QT interval. 110](#_Toc384718927)

[Table 5.1 – QTc interval in malnourished patients with AN 113](#_Toc384718932)

[(Continued) Table 5.1 – QTc interval in malnourished patients with AN 114](#_Toc384718933)

[5.4 Results – Meta-analysis: Malnutrition and QTc interval 115](#_Toc384718934)

[Figure 5.2 – Difference between QTc interval in malnourished patients compared to healthy controls 116](#_Toc384718935)

[Figure 5.3 – Difference in the incidence of QTc interval prolongation between malnourished patients and healthy control 118](#_Toc384718936)

[5.4.1 Results – Literature search: Refeeding and QTc interval 119](#_Toc384718937)

[Table 5.2 – QT interval pre and post weight restoration 121](#_Toc384718938)

[5.4.2 Results - Meta-Analysis: Refeeding and QTc interval 122](#_Toc384718939)

[Figure 5.4 - QTc interval before and after refeeding malnourished patients with AN 123](#_Toc384718940)

[5.5 Discussion – Malnutrition and refeeding on QTc interval 124](#_Toc384718941)

[5.5.1 Summary of main findings 124](#_Toc384718942)

[5.5.2 QTc Interval and malnutrition 124](#_Toc384718943)

[5.5.3 The impact of Refeeding on QTc interval 127](#_Toc384718944)

[5.5.4 Psychotropic Medication and QTc interval 129](#_Toc384718945)

[5.6 Summary 131](#_Toc384718946)

[Chapter 6 Refeeding and Weight Gain 132](#_Toc384718947)

[6.1 Introduction 132](#_Toc384718948)

[6.1.1 Indirect Calorimetry and Predictive Energy Requirement Formulas 132](#_Toc384718949)

[6.1.3 Tissue Accretion during Refeeding 134](#_Toc384718950)

[6.2 Methods – Literature search: Refeeding and Weight Gain 135](#_Toc384718951)

[6.2.1 Search Strategy 135](#_Toc384718952)

[6.2.2 Inclusion 135](#_Toc384718953)

[6.2.3 Exclusion 135](#_Toc384718954)

[6.2.4 Quality Assessment of Trails 136](#_Toc384718955)

[6.2.5 Data Synthesis (Statistical Methods) 137](#_Toc384718956)

[6.3 Results – Literature search: Refeeding and Weight Gain 137](#_Toc384718957)

[Figure 6.1 Flow chart of included studies in the review on refeeding and weight gain 140](#_Toc384718958)

[6.4 Discussion – Refeeding and Weight Gain 141](#_Toc384718963)

[6.4.1 Diet Induced Thermogenesis 142](#_Toc384718964)

[6.4.2 Weight gain in Adolescents 143](#_Toc384718965)

[6.4.3 Activity Level 143](#_Toc384718966)

[6.5 Conclusion 144](#_Toc384718967)

[Table 6.1 – Energy intakes, resting energy expenditure and weight changes throughout refeeding 146](#_Toc384718968)

[(Continued) Table 6.1 – Energy intakes, resting energy expenditure and weight changes throughout refeeding 147](#_Toc384718969)

[Chapter 7: Refeeding Treatment Guidelines 148](#_Toc384718970)

[7.1 Introduction 148](#_Toc384718971)

[7.2 Adult/ Adolescent Treatment Guidelines 149](#_Toc384718972)

[7.2.1 Solomon and Kirby 149](#_Toc384718973)

[7.2.2 National Institute of Clinical Excellence Guidelines (NICE) – Nutrition Support 150](#_Toc384718974)

[7.2.3 MARSIPAN –Management of Really Sick Inpatients with AN 152](#_Toc384718975)

[7.2.4 Mehler’s Refeeding Guidelines 153](#_Toc384718976)

[7.2.5 Kraft’s Refeeding Guidelines 154](#_Toc384718977)

[7.2.6 Royal College of Psychiatrists Guidelines – nutritional management of AN 155](#_Toc384718978)

[7.3 Young People Refeeding Treatment Guidelines 157](#_Toc384718979)

[7.3.1 The World Health Organisations (WHO) – Management of Severe Malnutrition 158](#_Toc384718980)

[7.3.2 Cape Town Metropole Paediatric Group Guidelines 159](#_Toc384718981)

[7.3.3 The Junior MARSIPAN (Management Really Sick Inpatient with Anorexia Nervosa) 160](#_Toc384718982)

[7.4 Carbohydrate and Refeeding Guidelines 161](#_Toc384718983)

[7.5 Europe verse North American Refeeding Guidelines 162](#_Toc384718984)

[7.6 Summary of Refeeding Treatment Guidelines 163](#_Toc384718985)

[Table 7.1 Adult Refeeding Treatment Guidelines 164](#_Toc384718986)

[Table 7.2 Children Refeeding Treatment Guidelines 165](#_Toc384718987)

[**Chapter 8 – General Methods: Hypotheses and study aim and design** 166](#_Toc384718988)

[8.1 Aims of Study 166](#_Toc384718989)

[8.2 Hypotheses 167](#_Toc384718990)

[8.2.1 Primary Hypotheses and design 167](#_Toc384718991)

[8.2.2 Secondary Hypothesis 167](#_Toc384718992)

[8.3 Study Design 167](#_Toc384718993)

[8.4 Ethical Approval 167](#_Toc384718994)

[8.5 Informed Consent 168](#_Toc384718995)

[8.6 Data Protection 168](#_Toc384718996)

[8.7 Sample size 168](#_Toc384718997)

[8.7.1 Primary Outcome Measure 168](#_Toc384718998)

[8.8 Recruitment 172](#_Toc384718999)

[8.9 Inclusion and Exclusion Criteria 172](#_Toc384719000)

[8.9.1 Inclusion Criteria 172](#_Toc384719001)

[8.9.2 Exclusion Criteria 173](#_Toc384719002)

[8.10 Materials and Methods 173](#_Toc384719003)

[8.10.1 Randomisation 173](#_Toc384719004)

[8.10.2 Materials for Dietary Intervention 173](#_Toc384719005)

[8.10.3 Methodology for Dietary Intervention 173](#_Toc384719006)

[Table 8.2 – Expected Macronutrient intake within the two groups 175](#_Toc384719007)

[Table 8.3 Estimated Energy Requirements (EAR) (SACN 2011) 176](#_Toc384719008)

[8.11 Materials for anthropometric measures 177](#_Toc384719009)

[8.11.1 Methodology for anthropometric measures 177](#_Toc384719010)

[8.12 Materials for Cardiovascular parameters 178](#_Toc384719011)

[8.12.1 Methodology for cardiovascular parameters 178](#_Toc384719012)

[8.12.2 Electrode Placement: 178](#_Toc384719013)

[Diagram 8.1 – 12 lead positioning for ECG 179](#_Toc384719014)

[8.12.2 Recording: 180](#_Toc384719015)

[8.12.3 QT interval measurement 180](#_Toc384719016)

[8.12.3 Corrected QT interval (QTc) 180](#_Toc384719017)

[Diagram 8.2 – PQRST cardiac wave 181](#_Toc384719018)

[Table 8.3 – Formulas for correcting QT interval 182](#_Toc384719019)

[8.12.4 Heart Rate 182](#_Toc384719020)

[8.13 Materials for biochemical measures 183](#_Toc384719021)

[8.13.1 Methodology for biochemical measures 184](#_Toc384719022)

[8.13.2 Glucose 184](#_Toc384719023)

[8.13.3 Phosphate 185](#_Toc384719024)

[8.13.4 Potassium 186](#_Toc384719025)

[8.13.5 Magnesium 186](#_Toc384719026)

[8.13.6 Sodium 187](#_Toc384719027)

[8.13.7 Calcium 188](#_Toc384719028)

[8.13.8 Materials for Insulin measures 188](#_Toc384719029)

[8.13.9 Methodology for Insulin 188](#_Toc384719030)

[8.13.10 Homeostatic Model Assessment (HOMA) 189](#_Toc384719031)

[8.13.11 Materials for Haematology 190](#_Toc384719032)

[8.13.12 White Blood Cells 190](#_Toc384719033)

[8.14 Statistical Methods 191](#_Toc384719034)

[**Chapter 9: Implication of refeeding on cardiovascular and anthropometric parameters in malnourished adolescents with anorexia nervosa** 192](#_Toc384719035)

[9.1 Introduction 192](#_Toc384719036)

[9.2 Methods Overview 192](#_Toc384719037)

[9.2.1 Cardiovascular 193](#_Toc384719038)

[9.2.2 Anthropometric 193](#_Toc384719039)

[Figure 9.1 – CONSORT flow diagram for randomisation 194](#_Toc384719040)

[9.3 Baseline Characteristics 195](#_Toc384719049)

[9.4 Number of Participants 195](#_Toc384719050)

[9.5 Compliance 196](#_Toc384719051)

[Table 9.1 – Baseline Characteristics for randomisation 197](#_Toc384719052)

[9.6 Nutritional Composition 198](#_Toc384719053)

[Table 9.2 – Percentage of total intake of macronutrients throughout refeeding 199](#_Toc384719054)

[9.7 Statistical Analysis 200](#_Toc384719055)

[9.7.1 Primary Outcome - QTc interval 200](#_Toc384719056)

[9.7.2 QTc interval prolongation (>440ms) 201](#_Toc384719057)

[Table 9.3 – Control Group (low-calorie): Pre and post refeeding cardiac outcomes 202](#_Toc384719058)

[Table 9.4 – Treatment Group (high-calorie): Pre and post refeeding cardiac outcomes 203](#_Toc384719059)

[Table 9.5 – Cardiac parameters 4 days post refeeding comparison between groups 204](#_Toc384719060)

[9.8 Other Cardiovascular Outcomes 205](#_Toc384719061)

[9.8.1 Heart Rate 205](#_Toc384719062)

[9.8.2 QTc Dispersion 205](#_Toc384719063)

[Figure 9.2 – Heart rate (BPM) before and after 4 days of refeeding in the control (low-calorie) and intervention (high-calorie) groups 206](#_Toc384719064)

[9.9 Secondary Outcomes 207](#_Toc384719066)

[9.9.1 Nutritional 207](#_Toc384719067)

[Figure 9.3 - Energy intake (kcal/ day) at baseline and after 10 days of refeeding in the low and high calorie programmes 208](#_Toc384719068)

[Figure 9.4 - Energy intake (kcal/kg/day) at baseline and after 10 days of refeeding in the low and high calorie programmes 209](#_Toc384719069)

[9.10 Anthropometric Outcomes 210](#_Toc384719070)

[9.10.1 Weight (kg) 210](#_Toc384719071)

[9.10.2 %BMI 210](#_Toc384719072)

[Table 9.6 – Anthropometric changes within the control group (low calorie) 211](#_Toc384719073)

[Table 9.7 – Anthropometric changes within the treatment group (high calorie) 212](#_Toc384719074)

[Table 9.8 – Change in anthropometric measure between randomised refeeding programmes 213](#_Toc384719075)

[Figure 9.5 – weight change between randomised groups at 4 and 10 days of refeeding 214](#_Toc384719076)

[9.11 Non-Randomised Analysis 215](#_Toc384719077)

[9.11.1 Baseline QTc interval 215](#_Toc384719078)

[9.11.2 Change in QTc interval post refeeding 215](#_Toc384719079)

[9.11.3 Change in heart rate post refeeding 215](#_Toc384719080)

[Table 9.9 – Relationship between cardiovascular and anthropometric outcomes at baseline and four days post refeeding 216](#_Toc384719081)

[Table 9.10 Relationship between change in QTc interval with change in weight post refeeding - adjusting for covariates age, gender and height. 218](#_Toc384719083)

[9.12 Discussion 219](#_Toc384719084)

[9.12.1 Baseline Measurement 219](#_Toc384719085)

[9.12.2 Refeeding and QTc interval 220](#_Toc384719086)

[9.12.3 Refeeding and Heart Rate 221](#_Toc384719087)

[9.12.4 Refeeding and Weight gain 222](#_Toc384719088)

[9.12.5 Nasogastric Tube Feeding 224](#_Toc384719089)

[9.13 Summary of Discussion 226](#_Toc384719090)

[**Chapter 10: Determinates of Refeeding Hypophosphatemia in Adolescents with Anorexia Nervosa: Randomised Controlled Trial** 227](#_Toc384719091)

[10.1 Introduction 227](#_Toc384719092)

[10.2 Methods 228](#_Toc384719093)

[10.2.1 Statistical Analysis 228](#_Toc384719094)

[10.3 Results - Baseline characteristics 229](#_Toc384719095)

[Table 10.1 Baseline characteristics for electrolytes and biochemical markers 230](#_Toc384719096)

[10.4 Results - Biochemical and Electrolyte changes with refeeding 231](#_Toc384719097)

[10.4.1 within group: Low Calorie (Control Group) 231](#_Toc384719098)

[10.4.2 within Group: High Calorie (Intervention Group) 231](#_Toc384719099)

[10.4.3 Between Randomised Groups 231](#_Toc384719100)

[10.5 Refeeding Hypophosphatemia between Randomised Groups 232](#_Toc384719101)

[Table 10.2 Control (low-calorie) within group electrolyte changes between baseline and post refeeding nadir. Glucose, insulin, HOMA-IR and WBC change between baseline and end of 10 days refeeding. 233](#_Toc384719102)

[Table 10.3 Intervention (high-calorie) within group electrolyte changes between baseline and nadir post refeeding. Glucose, insulin, HOMA-IR and WBC change between baseline and end of 10 days refeeding. 234](#_Toc384719103)

[Table 10.4 Between randomised groups: Electrolyte change between baseline and nadir. Glucose, insulin, HOMA-IR and WBC change from baseline and end of 10 days refeeding. 235](#_Toc384719104)

[Table 10.5 – Chi square table comparing rates of refeeding hypophosphatemia between randomised groups 236](#_Toc384719105)

[10.6 Non- Randomised Analysis 237](#_Toc384719106)

[10.6.1 Total energy intake and carbohydrate intake 237](#_Toc384719107)

[10.6.2 Dietary Phosphate 237](#_Toc384719108)

[10.6.3 White Blood Cell Count 237](#_Toc384719109)

[10.6.4 Insulin and HOMA-IR 238](#_Toc384719110)

[10.6.5 Anthropometrics – weight and %BMI 238](#_Toc384719111)

[Table 10.6 Regression analysis showing the relationship between nutritional, biochemical and anthropometric determinates and post refeeding phosphate 239](#_Toc384719112)

[Table 10.7 – Relationship between post refeeding phosphate and baseline white blood cell count - adjusting for covariates %BMI and HOMA IR 240](#_Toc384719113)

[Figure 10.1 – Relationship between WBC X109/l and post refeeding nadir phosphate (mmol/l) 241](#_Toc384719114)

[241](#_Toc384719115)

[Figure 10.2 – Relationship between HOMA IR and post refeeding nadir phosphate 242](#_Toc384719116)

[Figure 10.3 – Relationship between baseline %BMI and post refeeding nadir phosphate (mmol/l) 243](#_Toc384719117)

[243](#_Toc384719118)

[10.7 Summary of Results 244](#_Toc384719119)

[10.8 Discussion 244](#_Toc384719120)

[10.8.1 Baseline 244](#_Toc384719121)

[10.8.2 Energy intake and Refeeding Hypophosphatemia 244](#_Toc384719122)

[10.8.3 Naso-gastric tube feeding 246](#_Toc384719123)

[10.8.4 WBC and Refeeding Hypophosphatemia 246](#_Toc384719124)

[10.8.5 %BMI and Refeeding Hypophosphatemia 247](#_Toc384719125)

[10.8.6 Insulin Sensitivity and Refeeding Hypophosphatemia 248](#_Toc384719126)

[10.9 Conclusion 248](#_Toc384719127)

[**Chapter 11: Overall Discussions and Conclusions** 249](#_Toc384719128)

[11.1 Key Findings 249](#_Toc384719129)

[11.2 Cardiovascular 249](#_Toc384719130)

[11.2.1 QTc Interval (ms) 249](#_Toc384719131)

[11.2.2 Heart Rate (bpm) 250](#_Toc384719132)

[11.3 Nutritional 250](#_Toc384719133)

[11.3.1 Total energy intake (kcal/ day and kcal/ kg/ day) 250](#_Toc384719134)

[11.3.2 Nasogastric Tube Feeding 250](#_Toc384719135)

[11.4 Anthropometric 250](#_Toc384719136)

[11.4.1 Weight (kg) 250](#_Toc384719137)

[11.4.2 %BMI 251](#_Toc384719138)

[11.5 Electrolytes and Biochemical markers 251](#_Toc384719139)

[11.5.1 Phosphate 251](#_Toc384719140)

[11.5.2 Magnesium 251](#_Toc384719141)

[11.5.3 Potassium 252](#_Toc384719142)

[11.5.4 White blood cell count 252](#_Toc384719143)

[11.5.5 Insulin Sensitivity 252](#_Toc384719144)

[11.6 Non Randomised Analysis 252](#_Toc384719145)

[11.6.1 Cardiovascular and anthropometric 252](#_Toc384719146)

[11.7 Determinants of refeeding hypophosphataemia 253](#_Toc384719147)

[11.7.1 Energy intake (kcal/ day and kcal/ kg/ day) and carbohydrate intake (g/kg/day) 253](#_Toc384719148)

[11.7.2 White Blood Cells (x109) 253](#_Toc384719149)

[11.7.3 %BMI 253](#_Toc384719150)

[11.7.4 Insulin Sensitivity 253](#_Toc384719151)

[11.8 Summary of Results 254](#_Toc384719152)

[11.9 Discussion of Results 255](#_Toc384719153)

[11.9.1 Refeeding programme and cardiovascular outcomes 255](#_Toc384719154)

[11.9.2 Refeeding programme and anthropometric outcomes 256](#_Toc384719155)

[11.9.3 Refeeding programme and hypophosphataemia 257](#_Toc384719156)

[11.9.4 Psychological Impact of Refeeding 258](#_Toc384719157)

[11.10 Determinates of refeeding hypophosphatemia 259](#_Toc384719158)

[11.10.1 White blood cells 259](#_Toc384719159)

[11.10.2 %BMI 260](#_Toc384719160)

[11.10.3 HOMA-insulin sensitivity 260](#_Toc384719161)

[11.10.4 Nasogastric Tube Feeding 261](#_Toc384719162)

[11.11 Mechanisms for Relationship of WBC and refeeding hypophosphatemia 262](#_Toc384719163)

[Diagram 11.1 interplay between reduced body fat with bone mineral density and formation of granulocytes (WBC’s) and hypophosphatemia 266](#_Toc384719164)

[11.12 Mechanisms for relationship of %BMI and post refeeding phosphate 267](#_Toc384719165)

[11.13 Mechanism for relationship between energy intake and post refeeding phosphate 268](#_Toc384719166)

[11.14 Implications for Clinical Practice 270](#_Toc384719167)

[11.15 Strengths and Limitations 272](#_Toc384719168)

[11.16 Recommendations for future research 274](#_Toc384719169)

[11.17 Conclusions 276](#_Toc384719170)

[Acknowledgements 277](#_Toc384719171)

[Information of work in this thesis 279](#_Toc384719172)

[Concept and design 279](#_Toc384719173)

[Author’s role 279](#_Toc384719174)

[Data collection 279](#_Toc384719175)

[Data analysis 279](#_Toc384719176)

[Thesis construction 280](#_Toc384719177)

[**Appendix 1-1** 281](#_Toc384719178)

[Appendix 1 – GP Research information letter 282](#_Toc384719179)

[Appendix 2 – Participant Information Sheet for Parents 283](#_Toc384719180)

[Appendix 3 Information sheet for child/ adolescent 286](#_Toc384719181)

[Appendix 4 – Consent form for parents 289](#_Toc384719182)

[Appendix 5 - Meal Plan 500 290](#_Toc384719183)

[Appendix 6 - Meal Plan 1200 291](#_Toc384719190)

[Appendix 7 - Meal Plan 1800 292](#_Toc384719197)

[Appendix 8 Food Portions 293](#_Toc384719204)

[Apprendix 9 –Research Protocol 296](#_Toc384719205)

[References 299](#_Toc384719206)

# Table of Tables

**Table 2.1** Medical conditions associated with macronutrient deficiencies………………………….51

**Table 2.2** Resting Energy Expenditure of malnourished patients with AN…………………..……...65

**Table 4.1** Inclusion and exclusion criteria established for the systematic review…………..……82

**Table 4.2** Chart Reviews: Energy intake and incidence of Refeeding Hypophosphatemia in adolescents with Anorexia Nervosa. 101

**Table 4.3** Case Reports: Energy intake and post refeeding serum phosphate in adolescents with Anorexia Nervosa. 102

**Table 5.1** QTc interval in malnourished patients with AN 113

**Table 5.2** QT interval pre and post weight restoration 121

**Table 6.1** Energy intakes, resting energy expenditure and weight changes throughout refeeding………………………………………………………………………………………………………………………….146

**Table 7.1** Adults/ Adolescents Refeeding Treatment Guidelines 164

**Table 7.2** Children Refeeding Treatment Guidelines 165

**Table 8.1** Sample size calculation…………………………………………………………………………………… 169

**Table 8.2** Expected Macronutrient intake within the two groups……………………………………..175

**Table 8.3** Estimated Energy Requirements (SACN 2011) 176

**Table 8.4** Formulas for correcting QT interval…………………………………………………………………..182

**Table 9.1** Baseline Characteristics 197

**Table 9.2** Percentage of total intake of Macronutrients of meal plans 199

**Table 9.3** Control Group (low-calorie): Pre and post refeeding cardiac outcomes 202

**Table 9.4** Treatment Group (high-calorie): Pre and post refeeding cardiac outcomes 203

**Table 9.5** Cardiac parameters 4 days post refeeding comparison between groups 204

**Table 9.6** Anthropometric changes within the control group (low calorie) 211

**Table 9.7** Anthropometric changes within the treatment group (high calorie) 212

**Table 9.8** Change in Anthropometric measurement between randomised refeeding groups 213

**Table 9.9** Correlation between cardiovascular and anthropometric outcomes at baseline and four days post refeeding 216

**Table 9.10** Relationship between change in QTc interval with change in weight post refeeding - adjusting for covariates age, gender and height. 218

**Table 10.1** Baseline characteristics for electrolytes and biochemical markers 230

**Table 10.2** Control (low-calorie) – within group electrolyte changes from baseline post refeeding 233

**Table 10.3** Intervention (high-calorie) within group electrolyte changes post refeeding 234

**Table 10.4** Electrolyte and biochemical changes from baseline to post refeeding between randomised refeeding programmes 235

**Table 10.5** Chi square table for comparison of refeeding hypophosphatemia between randomised groups 236

**Table 10.6** Regression analysis reporting a relationship between nutritional, biochemical and anthropometric determinates with post refeeding phosphate 239

**Table 10.7** Relationship between post refeeding phosphate and baseline white blood cell count - Adjusting for covariates %BMI and HOMA IR 240

# Table of Figures

[**Figure 4.1** Flow chart of the included studies that investigated the impact energy intake and malnutrition had on post refeeding serum phosphate level](#_Toc376168491)……………………………………………….84

**Figure 4.2** Association between malnutrition (%BMI) and post refeeding serum phosphate...............................................................................................................................88

**Figure 4.3** Relationship between energy intake and post refeeding serum phosphate……….90

**Figure 5.1** Flow chart of the included studies that investigated the impact energy intake and malnutrition had on QT interval……………………………………………………………………………………….110

**Figure 5.2** – Difference between QTc interval in malnourished patients compared to healthy controls………………………………………………………………………………………………………………………….…116

**Figure 5.3** – Difference in the incidence of QTc interval prolongation between malnourished patients and healthy control…………………………………………………………………………………………….118

**Figure 5.4** QTc interval before and after refeeding malnourished patients with AN………...123

**Figure 6.1** Flow chart of included studies for analysing the impact refeeding had on resting energy expenditure and weight………………………………………………………………………………………..140

**Figure 9.1** CONSORT flow diagram…………………………………………………………………………………..194

**Figure 9.2** Heart rate (BPM) before and after 4 days of refeeding in the control (low-calorie) and intervention (high-calorie) groups……………..………………………………………………………………206

**Figure 9.3** Energy intake (kcal/ day) at the start and end of 10 days of refeeding in the low and high calorie programmes……………………..……………………………………………………………………208

**Figure 9.4** Energy intake (kcal/kg/day) at the start and end of 10 days of refeeding in the low and high calorie programmes……………………………………………………………………………………..……….….209

**Figure 9.5** weight change between randomised groups at 4 and 10 days of refeeding……..214

**Figure 10.1** Relationship between WBC X109/l with post refeeding phosphate (mmol/l)...241

**Figure 10.2** Relationship between HOMA IR and post refeeding phosphate…………………….242

**Figure 10.3** Relationship between baseline %BMI and post refeeding phosphate (mmol/l)………………………………………………………………………………………………………………………..…242

# Table of Appendices

**Appendix 1** GP Research information letter 282

**Appendix 2** Participant Information Sheet for Parents 283

**Appendix 3** Information sheet for child/ adolescent 286

**Appendix 4** Consent form for parents…………………………………………………………………….289

**Appendix 5** Meal Plan 500 290

**Appendix 6** Meal Plan 1200 291

**Appendix 7** Meal Plan 1800 292

**Appendix 8** Food Portions 293

## Abbreviations in text

AN Anorexia Nervosa

ASD Autistic Spectrum Disorder

BMI Body Mass Index

BMD bone mineral density

CAT cognitive analytic therapy

CBT cognitive behavioural therapy

cAMP cyclic adenosine monophosphate

DNA Data Not Available

DXA dual energy X-ray absorptiometry

EBW expected body weight

FBT family-based therapy

FPP focal psychodynamic psychotherapy

IPT interpersonal psychotherapy

NGT Naso Gastric Tube

PN Parenteral Nutrition

SD Standard Deviation

SSCM specialist supportive clinical management

5-HT serotonin (5-hydroxytryptamine [5-HT])

%BMI Percentage median body mass index for 50th percentile for age, gender and height

# Chapter 1: Background to Anorexia nervosa

### “Nothing tastes as good as skinny feels” – Kate Moss

This chapter is a brief synopsis of a complex disease that is anorexia nervosa (AN) and will focus on aspects of AN that is pertinent and selective to the present study and this chapter is by no means meant to be an extensive discussion on AN.

## 1.1 Definition

AN is a prototypical eating disorder that has been consistently described since the 19th century ([Uher and Rutter 2012](#_ENREF_282)). According to the DSM-5 criteria, for a person to be diagnosed with AN, they must display:

•Persistent restriction of energy intake leading to significantly low body weight (in the context of what is minimally expected for age, sex, developmental trajectory, and physical health).

•Either an intense fear of gaining weight or of becoming fat, or persistent behaviour that interferes with weight gain (even though they are significantly underweight).

•Disturbance in the way one's body weight or shape is experienced, undue influence of body shape and weight on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight (American Psychiatric Association, 2013).

## 1.2 Mortality Rate

AN is a chronic, relapsing disease, which has a threefold greater risk of death than the general population ([Millar, Wardell et al. 2005](#_ENREF_169)) and the highest mortality rate of any psychiatric disorder ([Birmingham, Su et al. 2005](#_ENREF_21)). A recent meta-analysis of 35 published studies calculated the crude mortality rate for AN as 5.1 deaths per 1000 person years (95%CI 3.9 to 6.1), translating to 0.51% per year. One in five individuals with AN commit suicide ([Arcelus, Mitchell et al. 2011](#_ENREF_11)). If we compare this to the mortality rate of Type 1 diabetes which is 2.2 deaths per 1000 person years, this highlights the associated risk of increased death with AN ([Nielsen, Emborg et al. 2002](#_ENREF_193)).

## 1.3 Prevalence and Incidence

The lifetime prevalence estimates of AN from population-based studies of adults vary between 0.3% - 1% ([Preti, Girolamo et al. 2009](#_ENREF_218); [Swanson, Crow et al. 2011](#_ENREF_272)). The age of peak onset is 14-19 years ([Hoek 2006](#_ENREF_102)), with the majority of patients being female (95%) ([Smink, van Hoeken et al. 2012](#_ENREF_263))**.** Although epidemiological studies report that the overall incidence rate has remained stable over the past decade ([Hoek 2006](#_ENREF_102)), there has been an increase in the high-risk group of 15-19yrs females ([Halmi 2009](#_ENREF_89); [Smink, van Hoeken et al. 2012](#_ENREF_263)). Furthermore, individuals are presenting at an earlier age, reportedly as young as 8 years old ([Nicholls, Lynn et al. 2011](#_ENREF_192)). However, it is unclear whether this reflects earlier detection of AN cases or an earlier age at onset. ([Smink, van Hoeken et al. 2012](#_ENREF_263)) Of concern is the fact that young AN patients present at a lower percentage of ideal body weight and lose weight more rapidly than their elder counterparts ([Peebles, Wilson et al. 2006](#_ENREF_209)).

A study by Nicholls et al (2011) sought to estimate the incidence of early-onset (<13yrs) eating disorders in the UK by obtaining information from the Child and Adolescent Psychiatric Surveillance System, which obtains information on cases by questionnaires over a 14 month period. Notification of 208 cases provides an overall estimated incidence of 3 per 100 000 for early onset eating disorders (95%CI 2.6 to 3.5) ([Nicholls, Lynn et al. 2011](#_ENREF_192)). The importance of accounting for the needs of children and young adolescents in the treatment of eating disorders is critical and should ideally occur in a specialist centre by a team who are aware of the unique and individual needs of this vulnerable age group.

## 1.4 Diagnostic Criteria

One of the barrier to accurately calculating the incidence rate of AN is case ascertainment, which varies depending on the criteria used. Community studies that use dimensional measures in adolescents yielded a far greater prevalence of disordered eating (14-22%) ([Jones, Bennett et al. 2001](#_ENREF_113); [Holling and Schlack 2007](#_ENREF_103)), compared with those studies that applied the strict DSM IV diagnostic criteria ([Widiger T 1994](#_ENREF_304)). Furthermore, previous diagnostic disparities between ICD-10 and DSM-IV should be limited in the revised ICD-11 and DSM-V criteria. Changes to ICD-11 have yet to be agreed, but are likely to be strongly influenced by DSM-V, bringing the two classifications more closely in line ([Uher and Rutter 2012](#_ENREF_282)).

Hopefully, this will limit current variations in the recording of incidence rates between Europe and North America. Amendments around the diagnostic criteria of DSM-V (omitting amenorrhea and <85% ideal body weight) are likely to considerably increase the incidence of AN as many cases are currently diagnosed as ‘Eating Disorder Not Otherwise Specified’ (EDNOS) or atypical anorexia nervosa (ICD-10). It is hoped that these amendments will address the inordinate percentage of individuals who present for treatment or exist in the population who do not fulfil the current threshold criteria for AN ([Hebebrand and Bulik 2011](#_ENREF_97)).

## 1.7 Causes of Anorexia Nervosa

AN is a chronic, complex and serious mental disorder which is difficult to treat. AN is considered a multifactorial disorder with complex aetiology ([Zandian, Ioakimidis et al. 2007](#_ENREF_308)). This is further highlighted when assessing treatment outcomes, which have remained poor with high dropout and relapse rates. These have remained constant over the past 50 years ([Steinhausen 2002](#_ENREF_269)). Outlined below are some of the main ‘causes’ of AN. It is important to understand that no single factor is attributable to the development of AN but is often the result of a number of contributing factors.

### 1.7.1 Puberty

Puberty has been one of the most frequently discussed risk periods for the development of an eating disorder. This had originally been attributed to the physical changes associated with puberty, particularly an increase in adiposity seen in females ([Fornari and Dancyger 2003](#_ENREF_72)). Those who mature early are thought to be at particular risk given that they experience these physical changes earlier than their peers and may experience more body dissatisfaction and lack coping mechanisms to deal with these rapid changes accompanied with puberty ([Klump 2013](#_ENREF_132)).

A study by Herpertz-Dahlmann et al (2011) suggests that is it is highly probable that the rise in several mental disorders around puberty is a consequence of hormonal changes. Puberty-related maturation was particularly demonstrated in the brain regions of the hippocampus and amygdala, which are associated not only with the development of mood and anxiety disorders often present during the acute state but also with the long-term course of eating disorders. In addition, gonadal steroids have been shown to directly alter affective processing as well as neurotransmitters such as dopamine, serotonin, opioids, oxytocin and vasopressin. Several of these neurotransmitters appear to play a significant role in the pathophysiology of eating disorders ([Herpertz-Dahlmann, Seitz et al. 2011](#_ENREF_101)). Additionally, data from Twin studies suggest that puberty accounts for age differences observed previously and that there may be genetic links between processes occurring during puberty and eating disorder symptoms in girls ([Baker, Thornton et al. 2012](#_ENREF_13)).

### 1.7.2 Environmental

Environmental factors are known to increase the risk of AN. These include female gender, dieting, childhood sexual abuse, early childhood eating and digestive disorders ([Jacobi, Hayward et al. 2004](#_ENREF_110)). Societal influence in the form of the fashion industry and the media were believed to be influential on the incidence of AN, in that the portrayal of ‘perfect’ and often unrealistic body shape exacerbates underlying body image issues in the younger population. This may lead to disordered eating as adolescents try to emulate impossible images which have been airbrushed and digitally enhanced.

Epidemiological studies suggest this is not sufficient to be a causal mechanism, as AN transcends many cultures and has been described as early as the 1900s, before the influence of media and fashion ([Bemporad 1996](#_ENREF_15); [Keel and Klump 2003](#_ENREF_127)). However, numerous studies have found that exposure to media and magazine images increases body dissatisfaction in young women, through internalization of the thin-ideal ([Thompson-Brenner, Boisseau et al. 2011](#_ENREF_280)). Obviously, not all females feel the need to emulate images seen in the media and therefore other factors and predispositions must be involved. Some of these additional influences are outlined below.

### 1.7.3 Psychiatric

Other pyschopathologies usually pre-date the development of AN. It has been suggested that childhood anxiety represents one important genetically mediated pathway towards the development of AN and this is reflected in the onset of obsessive compulsive disorder before AN. Adolescent females that present with AN often have a history of exemplary school reports, centred around perfectionism. ([Kaye, Bulik et al. 2004](#_ENREF_123)). Interestingly, this attention to detail and fastidiousness seen in sufferers of AN can mimic those traits found in the autism spectrum disorders (ASD): rigidity, obsessiveness, and social withdrawal. Disentangling ASD traits with AN can be problematic and is currently the subject of much research ([Rastam 1992](#_ENREF_224)).

### 1.7.4 Genetic

Recently there has been a shift towards understanding biological rather than social perspectives ([Hasan and Hasan 2011](#_ENREF_94)). Recent research has focused on a possible genetic component along with a range of hormonal influences that predispose an individual to AN.

One area that is receiving much attention is epigenetics. Epigenetics refers to the study of changes in gene expression produced by chemical modification of the deoxyribonucleic acid (DNA) sequence. Many environmental factors influence epigenomic patterning, including stress and diet ([Bouchard, Rabasa-Lhoret et al. 2010](#_ENREF_25)). Epigenetic alterations can occur prenatally ([Heijmans, Tobi et al. 2008](#_ENREF_98)) as well as later in life. For example significant changes in diet and the resultant change in gene expression may increase the risk for an eating disorder ([Clarke, Weiss et al. 2012](#_ENREF_38)). Clarke et al (2010) expressed the need that further research is required to determine if these changes are merely a result of under nutrition or whether the extent of epigenetic change in response to diet, is a risk factor in itself.

### 1.7.5 Neurobiological - Appetite hormones

Hormonal regulators of appetite such as insulin, ghrelin and leptin have received much attention in relation to predisposition to and maintenance of AN. These key appetite hormones communicate with the brain regarding hunger and energy balance, and rapid weight loss can disrupt normal levels and functioning of these hormones ([Schwartz, Woods et al. 2000](#_ENREF_254)). Insulin’s impact on metabolism and biochemistry will be discussed further in chapter 2.2.1.

### 1.7.6 Ghrelin

Ghrelin is an important gastrointestinal orexigenic peptide hormone synthesised and secreted by the X/A-like cells in the oxyntic glands of the gastric fundic mucosa ([Sakata, Nakamura et al. 2002](#_ENREF_240)). Acylated ghrelin is a stimulator of growth hormone release, but its main physiological role is to control food intake and energy homeostasis ([Korbonits, Goldstone et al. 2004](#_ENREF_136)). Circulating levels of ghrelin decrease with feeding and increase before food intake, and are therefore involved in the long term regulation of body weight; concentrations of ghrelin depend on body stores of adipocytes ([Cummings 2006](#_ENREF_46)).

Elevated levels of ghrelin have been observed in patients with AN. A study by Tanaka et al (2003), compared fasting ghrelin levels in AN (n=39) with controls (n=11). Overnight fasted blood samples of ghrelin were analysed. The results found that ghrelin was negatively associated with body mass index (kg/m2) (r=0.47; P=<0.05). Furthermore, fasting ghrelin levels were significantly higher in cases of AN than controls (P<0.01). Tanaka et al (2003) concluded that there was significant correlation between ghrelin and BMI in AN patients ([Tanaka, Naruo et al. 2003](#_ENREF_277)). These findings were corroberated in a similar study by Nakai et al (2008) ([Nakai, Hosoda et al. 2003](#_ENREF_188); [Harada, Nakahara et al. 2008](#_ENREF_91)). Elevated levels of ghrelin have been shown to adversely affect bone turnover and reduce bone mineral density by its indirect regulation of growth hormone and cortisol ([Misra, Miller et al. 2005](#_ENREF_178)), which is a particular concern in this patient population, who are at high risk for osteoporosis.

Individuals with AN seem to be able to override signals from the hypothalamus to eat with the raising levels of ghrelin in response to altered adipose stores and weight. This neurobiological interplay coupled with the reward and gratification associated with feelings of hunger and emptiness is crucial in our understanding of the mechanisms involved in AN, in that individuals with AN are able to override these strong biological stimuli to eat.

### 1.7.7 Leptin

Leptin is secreted primarily from adipocytes, with receptors located throughout the body but predominately in adipocytes; its main role is to provide the central nervous system with a signal regarding the state of the body’s energy balance which in turn regulates appetite, food intake and body weight ([Kowalska, Karczewska-Kupczewska et al. 2011](#_ENREF_137)).

As leptin is secreted from adipose tissue, it is unsurprising that many studies have observed markedly reduced leptin levels in patients with AN. A study by Dostalova et al (2007) compared leptin levels in patients with AN and healthy controls, with BMI values of 15.4 kg/m2 (SD0.6) and 20.9 kg/m2 (SD0.7), respectively and percentage body fat of 4.1% (SD0.9) and 19.5% (SD2.6), respectively. Circulating leptin levels were significantly different between those with AN and the control group; 1.6ng/ml (SD0.2) and 10.8ng/ml (SD1.1) (P<0.001), respectively. Furthermore, a positive correlation was found between BMI and percentage body fat with leptin, (r=0.52, P=0.01).

Additionally, leptin has a role in regulating bone turnover. The expression of leptin and its receptors have been demonstrated in primary cultures of normal human osteoblasts and chrondrocytes. Reduced levels of leptin evident in low weight individuals with AN will reduce bone mineralisation and bone mineral density ([Reseland, Syversen et al. 2001](#_ENREF_229)).

Once again individuals with AN are overriding the body’s normal homeostatic role to maintain weight within a healthy range, which further highlights the multifactorial complexity of this illness.

### 1.7.8 Serotonin

Abnormalities in serotonergic neurotransmission have received much attention over the past decade. Several lines of reasoning have suggested that disturbances of serotonin (5-hydroxytryptamine [5-HT]) function are important in understanding the neuropathophysiological basis of eating disorders, including serotonin’s role in: feeding, dieting, mood, anxiety, obsessionality, perfectionism, behavioural inhibition, harm avoidance and social status ([Brewerton 2012](#_ENREF_27)).

A study by Bailer et al (2004) used a positron emission tomography to monitor 5-HT2A receptors in the central nervous system, which has been implicated in the modulation of feeding and mood ([Simansky 1996](#_ENREF_259)). Bailer et al (2004) monitored these receptors in 10 females who had been weight restored for more than one year and compared to 16 healthy controls. They found that altered 5-HT neural system activity persisted after recovery, supporting the possibility that this maybe a trait-related disturbance that contributes to the pathophysiology of AN. Furthermore, 5-HT2A was negatively associated with drive for thinness and novelty-seeking and positively correlated with harm avoidance (r=0.43, P=0.03) ([Bailer, Price et al. 2004](#_ENREF_12)). Whether abnormal levels of serotonin are the result of malnutrition or a predisposing anomaly is difficult to ascertain.

### 1.7.9 Dopamine

Dopamine is a monoamine neurotransmitter and has also been implicated to the neuropathophysiology of AN, given its demonstrated involvement in the regulation of feeding, mood, activity, sexual and social behaviour. Dopamine is particularly associated with the hedonic reward response to eating and the maintenance of eating, as well as other pleasurable activities ([Brewerton 2012](#_ENREF_27)). Individuals with AN often exercise compulsively, are anhedonic and ascetic, and find little in life that is rewarding aside from the pursuit of weight loss ([American Psychiatric Association](#_ENREF_8) 2006).

A study by Wagner et al (2007) sought to identify an association of altered striatal dopamine binding along with the response of the anterior ventral striatum to reward and loss in AN. Striatal responses to a monetary reward task were investigated using event related functional magnetic resonance imaging in 13 weight recovered females with AN, compared to 13 healthy controls. The results found that weight restored females with AN may have difficulties in differentiating positive and negative feedback which was directly linked to the reduced levels of cerebrospinal fluid dopamine metabolites found in AN patients in comparison to controls (P=<0.01) ([Wagner, Aizenstein et al. 2007](#_ENREF_291)).

## 1.8 Consequences of anorexia nervosa

The short and long term physiological and psychological consequences of AN are immense. Many of these complications can be attributed solely to the impact of malnutrition. Chronic malnutrition and very low body weight affect every physiological system in the human body. Long term complications include growth retardation if onset is in childhood/ adolescence ([Nicholls, Hudson et al. 2011](#_ENREF_191)); fertility issues as a result of amenorrhea ([Katz and Vollenhoven 2000](#_ENREF_119); [Mircea, Lujan et al. 2007](#_ENREF_172)); decreased bone mineral density and osteoporosis ([Brihaye Abadie, de Tournemire et al. 2003](#_ENREF_28)); metabolic alterations ([Obarzanek, Lesem et al. 1994](#_ENREF_199); [Platte, Pirke et al. 1994](#_ENREF_213)); impaired cognitive development as a result of structural brain changes ([Hay and Sachdev 2011](#_ENREF_95); [Oltra Cucarella, Espert Tortajada et al. 2011](#_ENREF_202)); and dampened immunological response secondary to an increase in bone marrow adipose tissue and decrease in granulocyte formation ([Hutter, Ganepola et al. 2009](#_ENREF_107)). These complications outlined above are discussed further in chapters 2.9 and 11.11.

### 1.8.1 Bone Mineral Density

Adolescence is a crucial time for linear bone growth and mineralisation, when bone formation should normally exceed bone resorption in order for peak bone mass to be acquired ([Theintz, Buchs et al. 1992](#_ENREF_279)). Altered hypothalamo-pituitary function, hypoestrogenism, and menstrual disturbances are well known features of low weight individuals with AN, with the duration of amenorrhoea being inversely correlated to both hip and lumbar bone mineral density ([Dominguez, Goodman et al. 2007](#_ENREF_56); [Mika, Holtkamp et al. 2007](#_ENREF_168)). Additionally, human growth hormone and insulin-like growth factor are important regulators of bone homeostasis, during periods of chronic low weight as seen in AN. The GH-IGF-1 axis is dramatically altered, reducing proliferation and differentiation of osteoblasts.

Given the impact these biological alterations have on bone mineral density evident in low weight individuals with AN, it is no surprise that a prospective observational study by Golden et al (2002) reported that in 50 adolescents with AN, 92% had bone mineral density readings within the osteopenic range and 26% within the osteoporotic range ([Golden, Lanzkowsky et al. 2002](#_ENREF_81)). Consequently, individuals with a history of AN have an increased long-term fracture risk compared to the general public ([Lucas, Melton et al. 1999](#_ENREF_153)).

### 1.8.2 Cardiovascular

Short term complications associated with low weight and malnutrition include: muscle atrophy which contributes to cardiovascular complications, namely, bradycardia, QT prolongation and left ventricular atrophy ([Swenne 2000](#_ENREF_273); [Ulger, Gurses et al. 2006](#_ENREF_283)); biochemical abnormalities include hypophosphatemia, hypomagnesaemia and hypokalaemia which can lead to ventricular tachycardia and death ([Crook, Hally et al. 2001](#_ENREF_44); [Boateng, Sriram et al. 2010](#_ENREF_23)). The cardiovascular implications of malnutrition are further discussed in detail in chapters 2.9.4 and 5.

## 1.9 Treatment

Chapter 7 discusses in detail the nutritional treatment programmes for refeeding of low weight individuals with AN. This section focuses on the psychological treatments available for children and adolescents with AN. Whilst most young people with AN are treated as outpatients, severe AN is typically treated in an inpatient setting using a multimodal treatment delivered by a multidisciplinary team and varies considerably depending on the age of the individual ([Watson and Bulik 2012](#_ENREF_297)). Additional challenges for treatment trials in AN include reluctance to participate, with a high dropout rate ([Berkman, Bulik et al. 2006](#_ENREF_16)), and low prevalence of the disorder, thus requiring a multicentre approach.

AN has the highest mortality rate of any psychiatric disorder ([Birmingham, Su et al. 2005](#_ENREF_21); [Arcelus, Mitchell et al. 2011](#_ENREF_11)), with the standardised mortality ratio elevated to 56.9 (95% CI 15.3, 145) ([Keel, Dorer et al. 2003](#_ENREF_126))(Keel, 2003). Onset typically occurs during adolescents and naturalistic follow-ups suggest that less than half of all patients fully recover, with the remainder chronically ill or only partially improved. Many treatment outcomes are based on weight or menstruation status rather than eating pathology ([Berkman, Lohr et al. 2007](#_ENREF_17)).

A recent systematic review and meta-analysis on the efficacy of family behavioural therapy (FBT) in adolescents with eating disorders was conducted by Couturier et al (2013). They compared FBT with individual therapy specific to adolescents. The main outcome measures were based on %BMI and abstinence of binging and purging. A total of 12 RCTs were identified and the results indicate that at 6-12 month follow-up FBT was superior to individual therapy (odds ratio 2.35; 95%CI 1.33, 4.14; P=0.003). ([Couturier, Kimber et al. 2013](#_ENREF_43)) Due to the complexity, individuality and varied aetiology of AN it is unlikely that there will be a treatment panacea for all cases and therefore clinicians’ experience and training is both vital and relevant.

### 1.9.1 Family-Based Therapy (FBT)

Emerging evidence supporting the effectiveness of FBT in the treatment and management of AN is promising. In FBT, the focus is on parental management of maintaining behaviours of AN (calorie restriction, excessive exercise and purging) that perpetuates and maintains extreme low weight ([Lock and Le Grange 2001](#_ENREF_152)). However, for effective FBT to occur, parent-therapist alliance is imperative to meet the full potential of therapeutic input.

A recent study by Forsberg et al (2013) monitored audiotape recordings of 41 adolescents with AN. Outcome was based on the working alliance inventory (Horworth and Greenberg, 1989), which consists of 12 items which assesses agreement on tasks and goals, and affective bond. Weight was also assessed throughout the 14 sessions over 6 months. Forsberg et al (2013) found that parent alliance was generally strong and that their scores are higher than the adolescent alliance. Importantly, both the mother and father scored equally high on alliance ([Forsberg, Lotempio et al. 2013](#_ENREF_73)).

Differences in parent and adolescent alliance is not surprising given the denial and secretive features of AN, highlighting the importance of shared parental decision making and empowering parents in treatment even when their adolescent is unable to agree on tasks and goals and is ambivalent or refusing therapy.

### 1.9.2 Neuropsychopharmacology

The past two decades have seen a greater emphasis on the use of pharmacotherapy in children with mental and behavioural disorders ([Rasimas and Liebelt 2012](#_ENREF_223)). The high mortality rate associated with AN has led to an increased interest in the potential of pharmacological intervention. For many years antipsychotic agents were given to adolescents with schizophrenia. However, some of these agents are used off-label for other paediatric psychiatric disorders, including bipolar, obsessive-compulsive disorder, tics and anxiety ([Findling, Steiner et al. 2005](#_ENREF_67)).

The rationale behind the use of atypical antipsychotics in the AN population stems from the association between the irrational cognitions displayed in AN and those witnessed in delusional disorders. In both cases abnormal beliefs are ego syntonic. Furthermore, atypical antipsychotics are thought to have an impact on weight gain, anxiety and depression. This section will discuss the interaction of antipsychotics, which may affect co-morbidities often present in AN patients.

A systematic review by Brewerton et al (2012), identified nine RCT’s, four of which compared olanzapine with a placebo, the other studies compared a mixture of a placebo or olanzapine, risperidone, sulpiride or chlorpromazine. Outcome measures focused on weight gain, anxiety level, obsessive compulsive behaviours and depression ([Brewerton 2012](#_ENREF_27)). The four olanzapine and placebo RCT’s reported significant weight gain in two studies compared to the placebo (Bissada 2008 and Attia 2011). However, a meta-analysis was performed by Lebrow et al (2013) and they were unable to find a significant increase in weight compared to placebo (mean difference 0.18; 95%CI -0.36, 0.7kg; P=0.5, I2=26%) ([Lebow, Sim et al. 2013](#_ENREF_147)).

Furthermore, the meta-analysis performed by Lebrow et al (2013) reported that atypical antipsychotics had an adverse effect on anxiety, by increasing levels (mean difference 1.01; 95%CI 0.4 to 1.6). However, a significant improvement in depression was noted (mean difference -0.79; 95%CI -1.33 to -0.24).

### 1.9.2.1 Metabolic Syndrome

As previously mentioned, atypical antipsychotics have an impact on weight gain, which is a desirable outcome in low weight patients with AN. However, many studies have reported on the metabolic side effects of antipsychotics. The metabolic syndrome is the collective term given to a group of risk factors that raises risk for heart disease, Type2 diabetes mellitus and strokes ([Rasimas and Liebelt 2012](#_ENREF_223)).

A study on paediatric patients receiving olanzapine to treat schizophrenia for up to 32 weeks appeared very sensitive to the prolactin increasing effect of hyperprolactinemia. Patients also developed raised blood glucose, which was secondary to insulin resistance and developed borderline dyslipidaemias ([Kryzhanovskaya, Robertson-Plouch et al. 2009](#_ENREF_142)). A recent meta-analysis of atypical antipsychotic use in children demonstrated the mean weight gain compared with placebo was highest for olanzapine at 3.47kg (95% CI: 2.94, 3.99), which was also associated with the highest rate of metabolic laboratory abnormalities in cholesterol and triglycerides (95%CI: 0.58, 1.13) ([Pringsheim, Lam et al. 2011](#_ENREF_219)).

It is therefore essential that adolescents who are prescribed an atypical antipsychotic for an extended period of time have their lipids and glucoses levels closely monitored.

### 1.9.3 Selective Serotonin Reuptake Inhibitors (SSRI)

Although SSRIs have been of limited efficacy in the treatment of eating disorder psychopathology and comorbid symptoms of malnourished patients with AN, there is recent data suggesting that SSRIs may play a role in preventing relapse among weight-restored patients. A study by Kaye et al (2001) treated adolescents who had undergone inpatient weight restoration with fluoxetine and found that 29 of 31 patients maintained their weight at or above 85% of average bodyweight ([Kaye, Nagata et al. 2001](#_ENREF_124)).

However, SSRIs particularly fluoxetine have been shown to cause QTc interval prolongation by two mechanisms. First, by direct channel block, resulting in a delay in the potassium channel rectifier current ([Goodnick, Jerry et al. 2002](#_ENREF_82)) and secondly, indirectly by disrupting channel protein trafficking ([Rajamani, Eckhardt et al. 2006](#_ENREF_222)). Furthermore, when SSRIs are combined with atypical antipsychotics QTc interval prolongation can be further exacerbated ([Goodnick, Jerry et al. 2002](#_ENREF_82); [Sala, Vicentini et al. 2005](#_ENREF_242)). The impact of psychotropic and antipsychotic drugs is discussed further in relation to cardiac function in section 5.5.4.

These findings are sobering especially given that atypical antipsychotics are increasingly administered in adolescents with mental and behavioural disorders ([Rasimas and Liebelt 2012](#_ENREF_223)) . In light of the potentially adverse effects of atypical antipsychotics it is essential that a detailed and thorough assessment is performed on an individual basis with regular metabolic and cardiovascular monitoring.

## 1.10 Summary

AN is a debilitating complex multifactorial disease which places a huge burden and strain on families. Furthermore, AN has the highest mortality rate of any psychiatric disorder. It is essential that a definitive diagnosis is rapidly formulated, allowing for the prompt implementation of a family based multidisciplinary treatment programme for young people, as the physiological consequences of malnutrition and chronic low weight are immense and far-reaching. Low weight malnourished adolescents need to be refed effectively and safely to reverse the complications of malnutrition. The next chapter further discusses the implications of restrictive eating and low weight evident in AN.

# Chapter 2: Pathophysiology of starvation

## 2.1 Introduction

To further appreciate the complexities around the aetiology of AN it is essential to understand the interplay between physiological and behavioural adaptations which occur during the starvation process. This chapter will address the varying mechanisms involved in the starvation process with regards to aetiology, availability and quantity of macronutrients; and the impact this has on specific physiology of the human body.

Children and adolescents are at particularly high risk of developing malnutrition due to three factors: children have a higher energy need per unit of body mass compared to adults; they have limited energy reserves; and children, unlike adults, have a need for growth ([Joosten and Hulst 2008](#_ENREF_114)).

## 2.2 Stages of Starvation

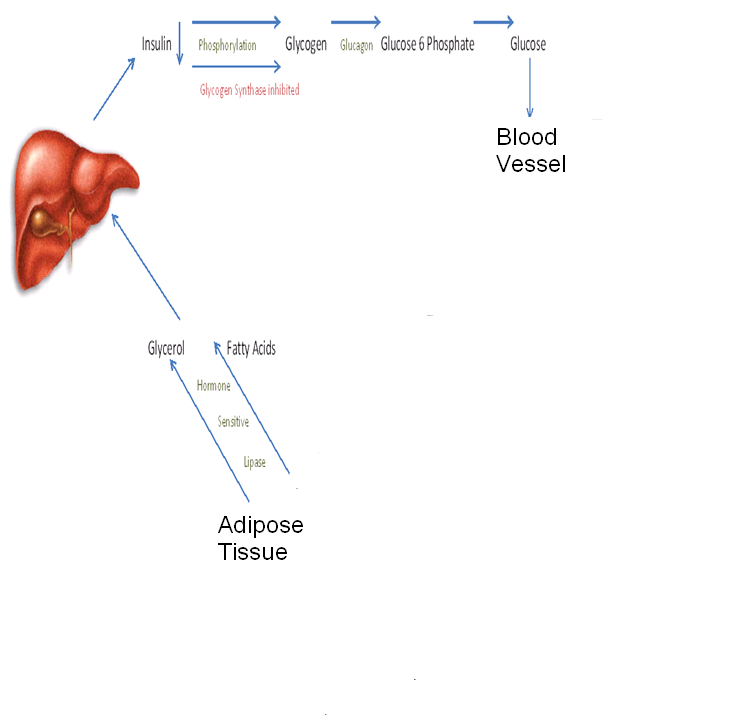
The early stages of starvation begin once the last consumed meal has been digested and the body has entered the post absorptive phase. During the post absorptive phase glucose and amino acids are transported from the intestines to the blood for cell metabolism and storage. Lipids absorbed from the intestines form chylomicrons and are transported via the lymphatic system.

### 2.2.1 Insulin and Glucagon homeostasis

During the early stage of starvation the liver regulates serum glucose levels by the homeostatic regulation of insulin and glucagon. Insulin concentrations begin to decrease which inhibits glycogen synthesis by triggering the cyclic adenosine monophosphate (cAMP) cascade leading to the phosphorylation and activation of phosphorylase and the inhibition of glycogen synthase. Glucagon levels rise in response to depleted serum glucose, breaking down stored glycogen, which forms glucose ([Crook, Hally et al. 2001](#_ENREF_44)).

The presence of glucagon and suppression of insulin also inhibits fatty acid synthesis by diminishing the production of pyruvate and by lowering the activity of acetyl Co-Enzyme A carboxylase by maintaining it in an unphosphorylated state (Diagram 2.1). This process maintains serum glucose levels until glycogen stores are near depletion (24-48hours); this is when the body enters phase two of starvation. The reduction in glycogen stores and low circulating serum insulin allows for the activation of hormone-sensitive lipase, which targets adipose tissue and breaks it down to form fatty acids and glycerol, which are utilized by the liver to produce other metabolites (acetyl Co-Enzyme A) for energy production through gluconeogenesis and production of ketones (Diagram 2.1).

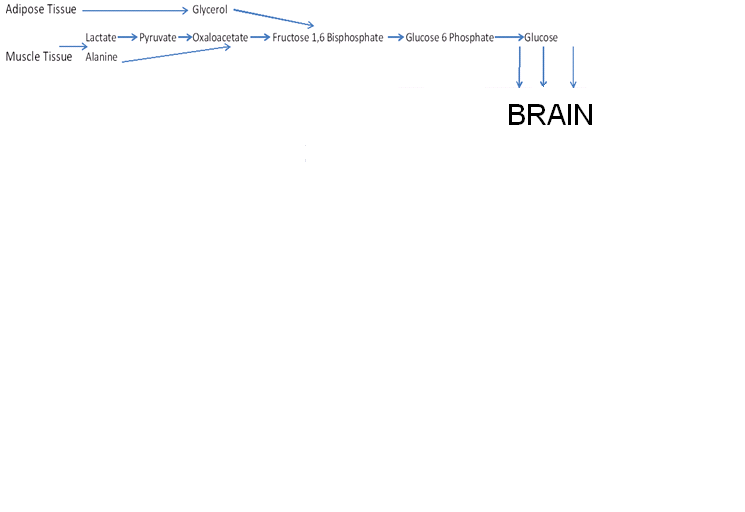
## Diagram 2.1 – Fuel metabolism during the early stages of starvation



### 2.2.2 Gluconeogenesis

The fatty acids derived from the degraded adipose tissue are transported to the liver, which is then used to generate energy for its own needs, switching off glycolysis in light of the low levels of serum glucose and increased concentration of acetyl Co-Enzyme A and citrate. Fatty acid oxidation now becomes the dominate fuel source for the liver and muscles. Hence, pyruvate, lactate, glycerol and alanine are exported to the liver for conversion to glucose via gluconeogenesis (Diagram 2.2). Gluconeogenesis is a backup mechanism when nutritional intake is restricted, ensuring a supply of glucose (40g/ day) is available for minimal functioning of the brain, central nervous system, renal medulla and retina ([Owen, Morgan et al. 1967](#_ENREF_205); [Prentice 2005](#_ENREF_217)).

## Diagram 2.2 – Gluconeogenesis from adipose and muscle tissue within the mitochondria



### 2.2.3 Ketone bodies

Proteolysis (muscle degradation) also provides amino acids and carbon for glucose production via gluconeogenesis; however muscle wasting is preserved with the formation of ketone bodies (acetoacetate and D-3-hydroxybutyrate), which again are activated with low circulating serum insulin. Their synthesis from acetyl Co-Enzyme A increases markedly because the citric acid cycle is unable to oxidize all the acetyl units generated by the degradation of fatty acid metabolism during oxidation. Ketone bodies represent the only effective alternative substrate for brain metabolism ([Robinson and Williamson 1980](#_ENREF_231)). Ketones along with a limited supply of glucose (via gluconeogenesis) now provide the energy for cell metabolism during acute starvation ([Brozek, Chapman et al. 1948](#_ENREF_31); [Schnitker, Mattman et al. 1951](#_ENREF_251)).

During the final stage of starvation, fat stores are depleted and the body relies more on proteolysis to provide the carbons for glucose and ketone formation resulting in extensive muscle loss from major organs including the heart, resulting in cardiac weakness and failure. The impact starvation has on the body’s physiological systems are discussed later in this chapter.

## 2.3 Malnutrition: Famine Vs Anorexia Nervosa

Malnutrition continues to be a major public health problem throughout the developing world (sub-Saharan Africa and India), affecting 13 million children under the age of 5 and accounting for approximately 1-2million preventable child deaths a year ([Martins, Toledo Florencio et al. 2011](#_ENREF_157)). This epidemic level of malnutrition is often the result of socioeconomic disparity, civil unrest and climate ([Kiros and Hogan 2001](#_ENREF_131)) .

Malnutrition is a condition that develops when individuals are unable to consume the correct amount of nutrients from their daily nutritional intake, which causes measurable adverse effects on body composition and function ([Joosten and Hulst 2008](#_ENREF_114)). Malnutrition can be observed in all weight categories including those who are overweight ([WorldHealthOrganisation2006](#_ENREF_270)). For the purpose of the present study, malnutrition will refer to those that are underweight and deficient in both macro and micronutrients.

Predominantely, AN affects individuals in the developed world and is responsible for a range of morbidities and mortality ([Birmingham, Su et al. 2005](#_ENREF_21)). Additionally, the aetiology and pathophysiology of malnutrition is markedly different between developed and developing societies. The commonalities and disparities of malnutrition between these two populations are discussed later.

However, a similarity that exists during malnutrition in developing and developed populations is the vast variability to which one copes with the associated complications of malnutrition. Individual adaptive ability in response to malnutrition is evident in times of famine or as seen in prisoners of war, where individuals will survive for months and years in suboptimal nutritional states whereas others will succumb to disease and death ([Schnitker, Mattman et al. 1951](#_ENREF_251); [Platte, Pirke et al. 1994](#_ENREF_213)). It is largely unknown what determines an individual’s susceptibility and fate to coping with malnutrition.

The ambiguity surrounding an individual’s adaptive ability to malnutrition has dictated refeeding treatment programmes. Invariably, nutrition is reintroduced conservatively in an attempt to avoid physiological overload which could trigger the refeeding syndrome. The refeeding syndrome is a phenomenon that can result in a catastrophic sequence of events causing neurologic, pulmonary, cardiac, neuromuscular, delirium and hematologic complications ultimately leading to death ([Crook, Hally et al. 2001](#_ENREF_44)). The mechanisms involved in the refeeding syndrome are detailed in chapter 3. However, what is deemed an effective and safe refeeding programme has been hindered due to the unpredictable manifestation of the refeeding syndrome accompanied with a lack of interventional studies, which have contributed to global disparities in refeeding practices.

## 2.4 Definition of Malnutrition

The World Health Organisation 2006 (WHO) has developed cut-off points for children to define malnutrition which focuses on weight for height as a marker for severity of malnutrition: -1 to -2 SD is deemed as underweight; -2 to -3 considered moderate malnutrition; and below -3 SD as severe malnutrition. Moderate malnutrition as define by WHO is comparable to the DSM IV criteria for AN, which states maintenance of body weight less than 85% ideal body weight (-2SD) for age-height-gender ([Widiger T 1994](#_ENREF_304)). However, this has now been replaced with a weight that is less than minimally normal of height- age (-1SD) ([Hebebrand and Bulik 2011](#_ENREF_97); [Call, Walsh et al. 2013](#_ENREF_33)).

## 2.5 Measurement of Ideal Body Weight

The nutritional status of children is focused on the deviation from expected body weight (EBW) and there are a number of ways in calculating ideal body weight which include: Body Mass Index Percentile median for age and gender (%BMI) ([Cole, Donnet et al. 1981](#_ENREF_39)); McLaren method ([McLaren and Read 1972](#_ENREF_161)) ; and Moore’s method ([Moore, Durie et al. 1985](#_ENREF_183)). Overall, there is moderate agreement between all three calculations of EBW, although there are specific limitations for each method. Moore’s method tends to estimate higher values of %EBW among older ages (>16yrs). Furthermore, the Moore’s method has larger discrepancies for %EBW at lower height percentiles (<20th percentile). The McLaren’s method provides larger estimates for %EBW than either the Moore or %BMI method for girls, but there is less bias for boys. In light of these discrepancies identified in the McLaren and Moore methods, it is recommended that %BMI is adopted using a computer software programme ([Le Grange, Doyle et al. 2012](#_ENREF_146)) such as that devised by Cole et al (1995). Of late, published literature in adolescents with AN have adopted %BMI due to ease of use and interpretation. The present study will also use %BMI as a measure of malnutrition.

## 2.6 History of Famines

Although a similar criterion is used to define malnutrition in famine and in patients with AN, the aetiology is different. Famines have been documented throughout the ages, from as early as 2000BC in Egypt to the great famine of Ireland in the 1890’s, to famines seen today in warfare and drought-stricken districts. A famine is a shortage of total food, so extreme and protracted that hunger and emaciation takes hold of entire populations; contributing to an increase in mortality from starvation and disease. Famines over the centuries have exerted a strong natural selection effect on human genome in respect to fertility and mortality ([Prentice 2005](#_ENREF_217)). This natural selection of survival over the centuries has resulted in extraordinary coping and adaptive mechanism by humans who are exposed to periods of food shortages or self-restriction as seen in famine or in AN sufferers. Physiological adaptions that occur to conserve energy expenditure include suppression of: the basal metabolic rate; body temperature; and growth ([Wang, Hung et al. 2006](#_ENREF_296)). The mechanisms behind these adaptations are largely unknown but are centered on the systematic reduction in energy expenditure in a bid to conserve energy. These physiological adaptations are described in detail later in this chapter.

During periods of starvation nutrition is occasionally consumed, albeit sporadically. Furthermore, the type of food available is dependent upon accessibility as seen in famine situations or individual self-restrictions as seen in AN. This variability in quantity and composition of nutritional intake during periods of starvation leads to different physiological pathways and therefore different physical conditions, which are outlined later in this chapter.

## 2.7 Food Availability

Famine foods need to meet two fundamental characteristics. First, they have to be edible without causing any adverse side effects and invariably require substantial processing prior to consumption; second, they must be available when all other crops and livestock have failed. Therefore, the vast majority of foods available during times of famine will be xerophytic plants, such as cacti and perennials, as well as leaves, stalks, inflorescences, and roots (tubers, corms and rhizomes) (World Health Organization 2006).

These robust plant based foods primarily consist of oligosaccharides and carbohydrates and are devoid of proteins and essential fats ([Ganzin 1985](#_ENREF_74); [Bryceson 1989](#_ENREF_32)). Furthermore, the inevitable protein deficiency that results from a sustained plant based diet is often coupled with micronutrient deficiencies especially fat and water soluble vitamins (vitamin A, B, C and E), iodine and iron ([WorldHealthOrganisation2006](#_ENREF_270)). Nutritional supplements available for refeeding in the developing world are discussed in chapter 7.3.1.

Compare this to the typical nutritional intakes of individuals with AN, whom often reduce total energy intake by restricting foods from all food groups ([Schebendach, Mayer et al. 2011](#_ENREF_249)). Foods that contain fat are often eliminated from the diet and to a lesser extent starchy foods which are substituted with protein foods ([Mayer, Schebendach et al. 2012](#_ENREF_160)). Similarly, as seen in famine, micronutrient deficiencies are also a major issue in sufferers of AN ([Setnick 2010](#_ENREF_255)).

A study by Misra et al (2006) monitored the nutritional intake of 39 outpatient adolescent females diagnosed with AN, and compared their nutritional intake with healthy controls. Participants were requested to complete a 4 day food diary; 3 schools days plus one weekend day. The results unsurprisingly reported that the AN group consumed less energy than the control group, 1649kcal/ day (110SD) and 1970kcal/ day (91SD) (P=0.03). Furthermore, the percentage of energy derived from fats was lower in the AN group 21% versus 30% (P <0.0001) ([Misra, Tsai et al. 2006](#_ENREF_180)).

Misra et al (2006) also identified that fat avoidance within the AN group substituted fat with carbohydrates and proteins as the AN groups consumed higher intakes than the control group (carbohydrates = 65% AN versus 60% control, p = 0.0009; protein = 20% AN versus 17% control, p <0.0001). The proportion of proteins derived from animal or vegetable sources were similar within both group. However, the AN group consumed higher proportions of carbohydrates derived from lactose (low-fat dairy products) and less from fructose compared to controls.

The study by Misra et al (2006) also reported that AN patients had significantly higher micronutrient intakes of vitamin A, B (riboflavin, B6), C and folate compared to healthy controls, which is contrary to the findings reported in developing countries. However, there was no significant difference in intake of calcium, iron, phosphate and zinc between the two groups. A reason for these findings may be attributed to the large quantity of fruit and vegetables consumed by AN patients, which are rich in micronutrients. Furthermore, this cohort was being managed in an outpatient setting, in adolescents who had a mean BMI of 16.5kg/m2, so participants were relatively stable and possibly consuming the lower reference nutrient intake for most micronutrients.

## 2.8 Medical Conditions Associated with Malnutrition

The absence or availability of protein foods consumed during periods of starvation lends itself to varying medical conditions. These have been outlined in Table 2.1 which illustrates how malnourished conditions are associated with famine and AN.

## Table 2.1 – Medical conditions associated with macronutrient deficiencies

|  |  |  |  |
| --- | --- | --- | --- |
| Malnourished Condition | Characteristics | Famine | Anorexia Nervosa |
| Kwashiorkor/ Protein- Energy Malnutrition (PEM) | Muscle wasting  Oedematous peripheral  Inability to adapt to reduced energy intake (dysadaptation)  Irritability  Anorexia  Skin and hair decolourisation  Free radical component | YES | RARELY |
| Marasmus | Muscle Wasting  Decrease physical activity  Normal appetite/ mental status  Adaptive qualities to poor energy intake | YES | NO |
| Severe Acute Malnutrition (SAM) | <70%BMI – wasted  Cardiovascular anomalies | YES | YES |
| Chronic Malnutrition | Stunted Growth  Reduced Bone Mineral Density  Micronutrient deficiencies Vit A/ Zinc/ Fe | YES | YES |

## 2.9 Physiological implications of starvation

### 2.9.1 Hormonal - Insulin

The significant role insulin plays throughout the starvation process was highlighted in chapter 2.1. However, there are a multitude of hormones involved in the regulation of weight and appetite; these hormones become deranged throughout starvation as adipose tissue is depleted. Hormones that are sensitive to alterations in adipose tissue are called adipocytokines and include leptin, adiponectin, insulin and resistin ([Dostalova, Smitka et al. 2007](#_ENREF_57)).

Adipocytokines are thought to influence insulin sensitivity which is increased in low weight patients with AN ([Delporte, Brichard et al. 2003](#_ENREF_50); [Misra, Miller et al. 2004](#_ENREF_176); [Kinzig, Coughlin et al. 2007](#_ENREF_130)). Conversely insulin resistance prevails in obesity and type 2 diabetes mellitus ([Weyer, Tataranni et al. 2001](#_ENREF_302)). It is thought that the cause of increased insulin sensitivity is related to hyperadiponectememia, induced by loss of fat mass ([Dostalova, Smitka et al. 2007](#_ENREF_57)). One possible factor that could contribute to increased insulin sensitivity in patients with AN is through the regulation of adipocytokine production in relation to the activity of the sympathoadrenal system ([Fasshauer, Klein et al. 2002](#_ENREF_64)).

It has been postulated that the lower fasting serum insulin levels seen in AN patients compared to controls is the direct result of reduced pancreatic secretion of insulin supported by a reduced C- peptide concentration also reported in AN patients. Additionally, the clearance rate of insulin is 50% higher than in controls which would also contribute to lower fasting serum insulin levels compared to controls ([Zuniga-Guajardo, Garfinkel et al. 1986](#_ENREF_309)).

Furthermore, along with increased insulin sensitivity numerous studies have reported a delayed plasma glucose and insulin peak in response to glucose ingestion/ intravenous infusion compared to healthy controls ([Unger, Eisentraut et al. 1963](#_ENREF_284); [Tanaka, Tatebe et al. 2003](#_ENREF_278); [Kinzig, Coughlin et al. 2007](#_ENREF_130)). Delayed gastric emptying and intestinal transit times seen in malnourished patients are thought to be the primary cause for this anomaly ([Holt, Ford et al. 1981](#_ENREF_104)). Another cause for delayed peak glucose and insulin levels has been attributed to slower eating habits reported in AN patients ([Kinzig, Coughlin et al. 2007](#_ENREF_130)).

### 2.9.2 Insulin Sensitivity and Resistance

In healthy weight adolescents, insulin resistance and increased leptin usually prevails, as a result of elevated levels of growth hormone and insulin-like growth factor 1 (IGF-1) ([Moran, Jacobs et al. 2002](#_ENREF_184)) and increased adiposity ([Moran, Jacobs et al. 1999](#_ENREF_185)). Pubertal insulin resistance is associated with decreased peripheral sensitivity and increased insulin secretion in response to increased IGF-1 ([Caprio 1999](#_ENREF_34)). However, in low weight adolescents with AN this normal physiological adaptation of insulin resistance is over-ridden, resulting in insulin and leptin sensitivity during this pivotal developmental growth phase. Puberty is driven by adipose stores, therefore low adipose stores delay puberty causing temporary or permanent growth stunting.

This anomaly around insulin sensitivity during adolescents is highlighted by a case control study (Misra et al. 2004). The authors investigated the impact of body composition on insulin sensitivity in 23 low weight (mean BMI 16kg/m2) AN adolescent females and 21 healthy weight females (mean BMI 21.7kg/m2). The fasting insulin levels in the AN group were lower than in the control group, 6.8Mu/ ml (0.6SD) and 14.5Mu/ ml (0.9SD), respectively (p<0.0001). However, circulating fasting glucose levels were similar in the two groups, 4.3mmol/l and 4.7mmol/l, respectively. The insulin resistance calculated using the HOMA-IR formula ([Radziuk 2000](#_ENREF_220)) was considerably different between the two groups. The AN group had an insulin resistance of 1.36 (0.14SD) and the control group measured an insulin resistance of 3.08 (0.2SD), (p<0.0001) ([Misra, Miller et al. 2004](#_ENREF_148)).

This study by Misra et al (2004) demonstrates that a low BMI during adolescents resulted in lower levels of fasting serum insulin, which is contrary to that expected in this age group, over-riding the normal insulin resistance expected in adolescents in response to an increase in growth hormone and IGF-1.

### 2.9.3 Insulin response to test meals in malnourished AN

Another case control study by Kinzig et al (2007) monitored serum glucose and insulin levels after a test meal of 650kcal in 13 low weight patients with AN (16.8kg/m2). Baseline fasting glucose levels were lower in the AN group compared to the controls, 75.6mg/ dl (1.6SD) and 85.1mg/ dl (2SD), respectively (p<0.01). However, baseline fasting insulin levels were similar in the AN and control group, 4.7 µU/ml (0.8SD) and 4.5 µU/ml (0.6SD). The mean difference from the baseline readings were then measured after the test meal at 30, 60, 90 and 120mins. The glucose response in the control group was much greater than the AN group, 36.1mg/ dl (3.2SD) and 16.9mg/ dl (4.8SD), respectively (p<0.01). However, no differences in peak insulin levels were reported between the groups. Therefore, although serum insulin levels were similar between the two groups the mean peak glucose level was much lower in the AN group ([Kinzig, Coughlin et al. 2007](#_ENREF_130)). These data suggest that insulin sensitivity results in efficient and rapid clearance of glucose in response to low circulating levels of insulin in the AN group.

Insulin plays a pivotal role in starvation and refeeding, but has received limited attention during the refeeding process and for this reason the present research will monitor fasting serum insulin and glucose levels during the refeeding process.

### 2.9.4 Cardiovascular

A detailed literature review and meta-analysis of cardiovascular adaptations to malnutrition are discussed in chapter 5. In brief, during this catabolic state of starvation body weight dramatically decreases accounting for a wide range of autonomic nervous system disturbances. These can be seen in up to 85% of AN sufferers ([Lesinskiene, Barkus et al. 2008](#_ENREF_151)) and account for a 5-10% mortality rate ([Isner, Roberts et al. 1985](#_ENREF_109)). Autonomic disturbances include: bradycardia (resting heart rate <50beats per minute); low arterial blood pressure (100/50mmHg); voltage decrease; T- wave inversion; atrophy of left ventricle; and QT interval prolongation ([Ulger, Gurses et al. 2006](#_ENREF_283)).

Most of the organic abnormalities described in AN patients are traditionally regarded as adaptive mechanisms of protection against chronic starvation. However, ventricular remodelling, which refers specifically to the reduction in muscle mass altering afterload, pump function, and myocardial mass ([St John Sutton, Plappert et al. 1985](#_ENREF_267)), appears to be extremely variable among patients with AN and apparently independent from the extent of weight loss and other markers of malnourishment. Indices of endocrine impairment seem to be the most relevant determinants of left ventricular hypotrophy in AN patients, independent of reduced haemodynamic load and BMI. In particular, IGF/GH ratio seems to particularly affect left ventricular mass in this population ([Carlomagno, Mercurio et al. 2011](#_ENREF_35)).

The QT interval is a measure of myocardial repolarisation and its length is associated with life threatening ventricular tachycardia ([Casiero and Frishman 2006](#_ENREF_36); [Schwartz, Mansbach et al. 2008](#_ENREF_253)). Repolarisation abnormalities are a common concern of clinicians treating patients with AN, due to the association between delayed repolarisation and sudden death. A QT interval corrected for heart rate (QTc), QTc interval > 460ms (girls) and >400ms (boys) is deemed to be high risk, and a QTc interval >600ms is a significant precursor for sudden cardiac death in AN ([Isner, Roberts et al. 1985](#_ENREF_109); [Durakovic, Korsic et al. 1989](#_ENREF_59)). Nevertheless, the QTc interval seems to be a poor predictive marker for the recognition of patients who are at particular risk of sudden death ([Jauregui-Garrido and Jauregui-Lobera 2012](#_ENREF_112)). Due to the high risks associated with QTc interval, this cardiac measure will be the primary outcome for the present study.

### 2.9.5 Immunology

Malnutrition has a variable effect on humoral immune function, as reflected in immunoglobulin levels ([Law, Dudrick et al. 1973](#_ENREF_145); [Neumann, Lawlor et al. 1975](#_ENREF_190)) and a profound impact on cellular immunity ([Bistrian, Blackburn et al. 1975](#_ENREF_22)). It has been shown that malnutrition-related immunodeficiency result in thymus alterations, particularly thymic atrophy ([Prentice 1999](#_ENREF_216)), causing depression and impairment in T-cell function. Consequently, this exposes the malnourished individual to viral, fungal and gram-negative bacterial infections ([Fock, Blatt et al. 2010](#_ENREF_70)). Thus, the impact of malnutrition plus infection is a relevant issue in health sciences including public health, since in many countries malnutrition and infections co-occur ([Savino and Dardenne 2010](#_ENREF_245)). Conversely, although malnourished AN patients do present with haematological and immunological changes outlined above, the majority of AN patients remain free from infectious complications ([Misra, Aggarwal et al. 2004](#_ENREF_173)).

Malnutrition results in a reduction in haematopoietic cell production as a result of hypoplastic bone marrow ([Xavier, Favero et al. 2007](#_ENREF_307)). As a result of this physiological adaptation to malnutrition AN sufferers are prone to leukopaenia with relative lymphocytosis ([Dunki Jacobs, Ruevekamp et al. 1989](#_ENREF_58)). Serous fat atrophy or gelatinous degradation of the bone marrow is described in AN patients and seems to be specifically related to carbohydrate intake ([Mehler and Howe 1995](#_ENREF_164); [Abella, Feliu et al. 2002](#_ENREF_4)). Furthermore, a relationship between leucocyte count with total body mass fat ([Lambert, Hubert et al. 1997](#_ENREF_143)) and duration of illness and severity ([Devuyst, Lambert et al. 1993](#_ENREF_52)) has been postulated. Fock et al (2010) suggests that the large number of lymphocytes produced each day by the marrow requires substantial amounts of nutrients. During a malnourished state, the body conserves energy for vital tissues (brain, heart, liver and kidneys), perhaps at the expense of lymphocyte production ([Fock, Blatt et al. 2010](#_ENREF_70)).

Approximately 22-34% of outpatients ([Miller, Grinspoon et al. 2005](#_ENREF_170)) and as many as 75% of hospitalized patients with AN are leukopaenic ([McLoughlin, Wassif et al. 2000](#_ENREF_162)). Leukopaenia and gelatinous bone degradation has been shown to resolve with nutritional restoration ([Hutter, Ganepola et al. 2009](#_ENREF_107)). The present study will monitor white blood cells, neutrophils and leukocytes as another marker of malnutrition, to investigate whether there is a relationship between white blood cell (WBC) counts and associated refeeding complications.

### 2.9.6 Electrolytes

The kidney is a major regulator of serum electrolyte homeostasis (phosphate, potassium and magnesium). During normal circumstances, the kidney can increase or decrease its reabsorptive capacity in the proximal tubule brush border membrane, mediated by sodium-dependent phosphate transport systems ([Takeda, Yamamoto et al. 2004](#_ENREF_275)). During periods of reduced energy intake and starvation, there is an increase in renal tubular reabsorption, decreasing electrolyte losses in the urine. This transcellular action disrupts phosphate homeostasis, a complex interplay between intestinal absorption, exchange with intracellular and bone storage pools and renal tubular reabsorption ([Berner and Shike 1988](#_ENREF_19)). In brief, during the latter stages of starvation, serum electrolytes are invariably unremarkable due to physiological adaptations which include: increased renal tubular reabsorption of phosphate, potassium and calcium; tissue breakdown and bone resorption; and dehydration, which can falsely mask abnormally low serum electrolyte levels ([Crook, Hally et al. 2001](#_ENREF_44); [Boateng, Sriram et al. 2010](#_ENREF_23)). Adverse biochemical anomalies do not usually manifest until the early stages of refeeding, and are discussed in chapter 3.3.

### 2.9.7 Growth and bone density

Linear bone growth and mineralisation is rapid during puberty and late adolescences, when bone formation should normally exceed bone reabsorption in order for peak bone mass to occur ([Theintz, Buchs et al. 1992](#_ENREF_279)). Impaired linear growth and possible permanent short stature are significant medical problems in adolescents with AN ([Eckhardt and Ahmed 2010](#_ENREF_61)). Invariably, short stature in AN is delayed growth, the result of delayed puberty from being low weight and having low adipose stores ([Prabhakaran, Misra et al. 2008](#_ENREF_215)). With a few exceptions, patients with AN ultimately reach their expected height ([Favaro, Tenconi et al. 2007](#_ENREF_65)).

Growth retardation is the result of disruption of the growth hormone (GH) - insulin growth factor-1 (IGF-1) axis associated with low weight ([Misra, Miller et al. 2003](#_ENREF_177)). Adolescents with AN have increased basal and pulsatile secretion of GH and low levels of IGF-1 ([Misra, Miller et al. 2003](#_ENREF_177)). Elevations in GH secretion coupled with low IGF-1 levels have led to the concept of a nutritionally mediated state of acquired GH resistance and therefore transient stunting. The mechanism of GH resistance is unclear. However, it has been postulated that elevated Fibroblast Growth Factor -21 may be responsible for GH resistance. ([Fazeli, Misra et al. 2010](#_ENREF_66))

Furthermore, low levels of IGF-1 have been linked with low bone mineral density (BMD). Other factors associated with the uncoupling of bone turnover in AN include low levels of oestrogen, testosterone, dehydroepiandrosterone, leptin, and high levels of cortisol ghrelin and peptide YY. These all contribute to low BMD and susceptibility to the development of osteopaenia and osteoporosis in later years (adulthood), increasing bone fracture risk ([Howgate, Graham et al. 2012](#_ENREF_105)).

A study by Jagielska et al (2002) investigated total body and lumbar spine BMD using a dual energy X-ray absorptiometry (DXA) scan in 61 adolescent girls (mean age 14.7 yrs SD 2.2) with AN, who were low weight (mean 70%BMI SD 9), with a mean chronicity of illness of 12.9 months (SD 15). Low total body bone mineral (>-2SD) was found in 24% of individuals and low lumber spine BMD in 36% of participants. A negative correlation was found between BMD and age, age of menarche, degree of malnutrition, chronicity and amenorrhea. A stepwise linear regression model showed that age of menarche was the most significant independent predictor for BMD ([Jagielska, Wolanczyk et al. 2002](#_ENREF_111)).

A study by Grinspoon et al (1999) reported similar findings, in that the duration of secondary amenorrhoea in patients with AN was inversely correlated with both lumbar and hip BMD density ([Grinspoon, Miller et al. 1999](#_ENREF_84)). Reductions in bone mass to the degree of osteopaenia and osteoporosis have been observed in over 90% of adolescents with AN who have been amenorrheic for more than 6 months ([Golden, Lanzkowsky et al. 2002](#_ENREF_81)). Therefore, adolescent girls that had delayed puberty and delayed menses secondary to low weight, results in a greater loss in bone mineral density, emphasising the importance of weight restoration during this critical growth phase.

Altered menstrual disturbances, hypothalamic-pituitary function and hypoestrogenism are well known features of active AN, and adversely affects BMD ([Soyka, Grinspoon et al. 1999](#_ENREF_266); [Dominguez, Goodman et al. 2007](#_ENREF_56)). Oestrogen metabolites have been shown to be potent agonists of cultured human osteoblast cells *in vitro* ([Delaveyne-Bitbol and Garabedian 1999](#_ENREF_49)).

Due to the potentially devastating and long-lasting effects of sub-optimal accrual of BMD in adolescents with AN, therapeutic strategies have been implemented to reduce the risks associated with low BMD. The most effective method to improve BMD is weight gain and recovery of menses ([Misra, Prabhakaran et al. 2008](#_ENREF_179)). However, this can be a lengthy process in the treatment of AN.

A randomised, double blind, placebo controlled study was carried out by Misra et al (2011), to examine the impact of physiologic oestrogen administration on BMD in girls with AN. 110 AN girls (mean 16.5 yrs SD 0.2, 84%BMI SD 0.6) were enrolled, 55 girls were randomised to receive either transdermal 17β-ostradiol patch twice weekly and medroxyprogesterone 2.5mg daily for 10 days each month if over 15 years or if under 15 years received escalating doses of ethinyl estradiol or placebo for 18 months. Additionally, 40 healthy weight controls were recruited (15.6 yrs SD 0.2, 106% SD 2.4). All controls and randomised participants received 1200mg of calcium carbonate and 400 IU of vitamin D daily. A DXA was used to assess spine and hip BMD. After 18months of intervention the supplemented randomised group had a significant increase in both the spine and hip BMD (p=0.044 and p=0.04, respectively). Additionally, bone mineral density changes were predicted inversely by baseline age and positively by weight change, demonstrating that physiologic oestrogen replacement increases spine and hip BMD ([Misra, Katzman et al. 2011](#_ENREF_174)). The mechanism behind transdermal oestrogen administration effectiveness is thought to be related to its impact on IGF-1, an important bone trophic hormone, which is often low in patients with AN. Oral administration provides relatively high oestrogen doses in oral contraceptives which suppress IGF-1 secretion, whereas, transdermal replacement doses of oestrogen does not suppress IGF-1 ([Weissberger, Ho et al. 1991](#_ENREF_299)). This novel concept of transdermal oestrogen administration as a means to optimise peak bone mass in amenorrheic adolescents with chronic eating disorders who have BMD <2.5 SD with closed epiphyses, is promising but further research is required.

### 2.9.8 Behaviour and Cognition

Pioneering research on behaviour and cognitive function in a starvation state was carried out in the early 1950’s. Much of the findings from this study are still referenced today. Keys et al (1950) subjected healthy male volunteers to 6-months of a semi-starvation programme. The study found that these previously healthy individuals developed unhealthy anorectic cognitions around food, including: food became the central topic of conversation, intruding constantly into the consciousness; impaired coherent and creative thinking (p 784); depression, anxiety and psychosis became the rule, and in some individuals discussion of suicide was noted (p785). This remarkable study is further discussed in chapter 3.2.2 with regards to refeeding ([Keys 1950](#_ENREF_129)).

Some of these symptoms identified by Keys et al (1950) have obvious benefits in a famine situation and may be a result of physiological evolution, for example preoccupation with food, maybe a helpful strategy to locate and obtain food ([Zandian, Ioakimidis et al. 2007](#_ENREF_308)). These stark behavioural changes identified in previously healthy males highlights the challenges associated with the perpetuating unhelpful cycle around food and cognition in low weight malnourished adolescents with AN. Reassuringly, many of these behaviours were immediately reversed during the refeeding process; as body weight increased, psychiatric symptoms decreased.

Nutrition plays a crucial role in the maturation and functional development of the central nervous system ([Alamy and Bengelloun 2012](#_ENREF_6)). Malnutrition has repeatedly shown to affect maturation of the brain and the development of cognitive functioning, resulting in behavioural abnormalities and disturbances in learning and memory ([Alamy and Bengelloun 2012](#_ENREF_6)). A case-control study by Chui et al (2008) investigated the brain structure and cognitive abilities of 66 females with AN. The magnetic resonance brain scan and cognitive testing reported abnormal cognitive functioning and brain structure compared with healthy individuals. Furthermore, they identified a relationship between menstrual function and cognitive function in this patient population ([Chui, Christensen et al. 2008](#_ENREF_37)). It is not known whether a neurobiological vulnerability predisposes to AN or if this is associated with maintenance of symptoms once the illness develops ([Hay and Sachdev 2011](#_ENREF_95)), This may link back to the epigenetics of AN which was discussed in chapter 1.7.4.

### 2.9.9 Body Composition and Energy Expenditure

As previously discussed starvation has a profound impact on the body’s energy stores, initially depleting glycogen stores and then depleting adipose and muscle tissue, which results in hormonal disturbances and altered body composition, ultimately affecting expected energy expenditure. Total energy expenditure consists of four factors: Basal Metabolic Rate; Resting Energy Expenditure; Diet Induced Thermogenesis; and Physical Activity Level ([Salisbury, Levine et al. 1995](#_ENREF_243)). Resting energy expenditure comprises the largest component of total energy expenditure ([Obarzanek, Lesem et al. 1994](#_ENREF_199)) and is largely determined by the amount of metabolically active fat free mass and fat mass. Oxidation of nutrients requires oxygen, by measuring oxygen consumption and carbon dioxide production also provides an estimation of energy production ([Ravussin, Lillioja et al. 1986](#_ENREF_225)).

Indirect calorimetry estimates individual resting energy expenditure by monitoring oxygen consumption and carbon dioxide production providing information on the amount and type of metabolically active tissue ([Ravussin, Lillioja et al. 1986](#_ENREF_225)). Along with alterations in body composition a reduction in resting energy expenditure is seen in malnourished patients with AN; additionally it is believed to be associated with a metabolic adaptation to starvation or metabolic efficiency. This metabolic adaptation is a protective mechanism that has evolved, allowing the body to function in a hypo-metabolic state; therefore conserving energy, whilst hunting and searching for food ([Soares, Kulkarni et al. 1992](#_ENREF_264); [Platte, Pirke et al. 1994](#_ENREF_213)). An accurate assessment of the nutritional requirements and composition of malnourished patients with AN is essential when formulating a refeeding programme which meets total energy expenditure whilst also eliciting weight gain.

A literature search was performed to explore the impact malnutrition (BMI <16kg/m2) has on resting energy expenditure in malnourished patients with AN, measured by indirect calorimetry (open circuit). The search was conducted using electronic medical publication databases including MEDLINE, EMBASE and CINAHL from 1975 up to June 2013, only English manuscripts were included. The key search terms were ‘resting energy expenditure’ AND ‘anorexia nervosa’. Table 2.2 displays the 8 studies that were selected for review.

A total of 96 AN patients and 120 controls were identified. The mean age was 21.4 years and 22 years, respectively. The mean BMI was 14.4kg/m2 and 21.7kg/m2, respectively. The mean resting energy expenditure in the AN patients was 945kcal/ day compared to 1186kcal/ day healthy controls (P <0.001).

The resting energy expenditure (kcal/ day) was significantly reduced in low weight patients with AN compared to healthy controls. This physiological adaptation must be taken in to account when devising a refeeding treatment programme. A study by Winter et al (2006) found that resting energy expenditure (kcal/ kg) was significantly higher in the malnourished AN group compared to the controls, 32kcal/kg/day and 25kcal/ kg/day (p <0.5), respectfully. However, the AN patients still had a lower overall total resting energy expenditure compared to the control group in relation to kcal/ day, 1058kcal/ day and 1828kcal/ day (p <0.0001), respectively. ([Winter 2006](#_ENREF_305)).

Conversely, other studies have found that low weight AN patients have a lower resting energy expenditure (kcal/ kg/day) and lower kcal/ day compared to healthy controls ([Keys 1950](#_ENREF_128); [Soares, Kulkarni et al. 1992](#_ENREF_264)); suggestive of possible metabolic adaptations with an increased efficiency in energy utilisation, in a bid to conserve energy. Although what these metabolic adaptation are have not been proven and seem to go beyond that expected from a reduction in tissue mass ([Winter 2006](#_ENREF_305)). Furthermore, the metabolic rate expressed per unit body weight may not reflect true variation in metabolic efficiency and is likely to be largely due to variations in body composition. Skeletal muscle although comprising 40-50% of body weight, contributes only 18-22% to the basal metabolic rate. In comparison, the brain and liver comprise 3-5% of total body weight requiring 40% of energy (Winter 2006).

In chapter 6 resting energy expenditure is explored further in relation to energy intake and weight gain during refeeding low weight patients with AN.

### Table 2.2 – Comparison of Resting Energy Expenditure of malnourished patients with AN with healthy weight controls

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author | Numbers | | Age | | | | BMI (kg/m2) | | | | REE (kcal/ day) | | | | P-value |
| AN | C | AN | SD | C | SD | AN | SD | C | SD | AN | SD | C | SD |  |
| Platte 1993  ([Platte, Pirke et al. 1994](#_ENREF_213)) | 6 | 12 | 27.5 | 7.8 | 25.2 | 2.4 | 15.2 | 1.3 | 20.9 | 1.9 | 1171 | 113 | 1379 | 146 | <0.001 |
| Scalfi 1993  ([Scalfi, Di Biase et al. 1993](#_ENREF_246)) | 19 | 24 | 22.4 | 4.4 | 22.2 | 2.9 | 14.6 | 1.8 | 21.1 | 1.5 | 833 | 155 | 1228 | 123 | <0.001 |
| Obarzanek 1994 ([Obarzanek, Lesem et al. 1994](#_ENREF_199)) | 10 | 8 | 23.3 | 1.9 | 27.5 | 1.3 | 14 | 1.4 | 22 | 3.1 | 742 | 38 | 1142 | 29 | <0.0001 |
| Pichard 1996 ([Pichard, Kyle et al. 1996](#_ENREF_211)) | 9 | 9 | 18 | NA | 18.5 | NA | 13.7 | 0.5 | 21.5 | 0.9 | 969 | 46 | 1391 | 53 | <0.05 |
| Polito 2000  ([Polito, Fabbri et al. 2000](#_ENREF_214)) | 16 | 22 | 25 | 5.0 | 26.0 | 6.0 | 15.5 | 1.2 | 21.0 | 1.5 | 925 | 102 | 1182 | 103 | <0.05 |
| Russell 2001 ([Russell, Baur et al. 2001](#_ENREF_236)) | 18 | 18 | 20.9 | 1.2 | 24.6 | 1.3 | 15.6 | 0.2 | 21.6 | 0.6 | 1038 | 19 | 1387 | 33 | <0.001 |
| Satoh 2002  ([Satoh, Shimizu et al. 2003](#_ENREF_244)) | 10 | 10 | 14 | 1.1 | 13.9 | 1.1 | NA | NA | NA | NA | 830 | 292 | 1335 | 286 | <0.01 |
| Winter 2005 ([Winter, O'Keefe et al. 2005](#_ENREF_306)) | 8 | 17 | NA | NA | NA | NA | 12.6 | 0.5 | 23.7 | 0.7 | 1058 | 134 | 1828 | 89 | <0.01 |

## 2.10 Summary

The pathway of starvation can manifest in a number of ways dependent upon the availability nutrients, if any. However, the physiological impact of starvation on the human body is immense and potentially long lasting. Centuries of sporadic famines has resulted in natural selection, allowing humans to withstand and to a certain degree adapt to long periods of starvation, whether the cause be famine (warfare/ drought) or from self-restriction (AN/ religion). However,these protective physiological adaptations to malnutrition do have consequences some of which are potentially life-threatening, and these can be further exacerbated during the refeeding process. The next chapter focuses on the physiological implications of refeeding the malnourished individual.

# Chapter 3: Refeeding the malnourished adolescent with AN

## 3.1 Introduction

Refeeding the severely malnourished patient (-3SD, <75%BMI) can provoke a constellation of metabolic disturbances that occur as a result of the reintroduction of nutrition. In brief, some patients that are refed develop fluid, glucose and electrolyte disturbances, along with neurologic, pulmonary, cardiac and haematologic complications ([Solomon and Kirby 1990](#_ENREF_265); [Kraft, Btaiche et al. 2005](#_ENREF_138)). The term refeeding syndrome was coined by Weinsier and Krundieck (1981) which encompasses all of these physiological anomalies associated with introduction of food to the malnourished patient ([Weinsier and Krumdieck 1981](#_ENREF_298)).

## 3.2 History of the Refeeding Syndrome

One of the earliest accounts of the refeeding syndrome can be traced back to the 1st Century during the first Great War between the Jews and the Romans. An influential historian of the time Josephus Titus Flavious, documented this conflict, reporting that the Romans captured and imprisoned a large number of Jewish people who were then starved over several months. Eventually, the Romans retreated and the Jewish people were released; on their release many people gorged on food. It was reported that many people died within days of their release which was attributed to the ordeal imposed whilst prisoners (http://www.ccel.org/j/josephus/works/war-7.htm). However, it is possible that the fate succumbed to many of these starved individuals were complications associated with the refeeding syndrome.

### 3.2.1 Prisoners of War

A study by Schnitker et al (1951) monitored Japanese prisoners who were imprisoned in the Philippines after being defeated. Prior to their capture many of the Japanese soldiers sought refuge in the surrounding rainforest and survived on minimal nutrition (800kcal/ day) for 6 months. Due to their severe malnourished state, many of the Japanese prisoners were admitted to the prison hospital. Once admitted, prisoners were commenced on small amounts of food which was rapidly increased to around 3600kcal/ day in the first week. Five patients died during the refeeding process, four of which were related to cardiovascular complications (17%) and was attributed to nutritional hypoproteinemia ([Schnitker, Mattman et al. 1951](#_ENREF_251)). Similar reported deaths after refeeding were seen across Europe in the post-siege era of World War II, especially from concentration camps ([Mollison 1946](#_ENREF_181); [Simonson, Henschel et al. 1948](#_ENREF_260)).

### 3.2.2 Minnesota Starvation Experiment

The deaths and cardiovascular anomalies witnessed whilst refeeding malnourished prisoners of war spurred on a group of researchers to investigate the physical and psychological mechanisms involved in starvation and refeeding. Keys et al (1950) run a gruelling starvation and refeeding study, which became the classic Minnesota experiment. They recruited 36 healthy male volunteers who were limited to 1600-1800kcal/ day for 6-months. Meals consisted of potatoes, turnips, bread and macaroni. Participants were also expected to carry out various housekeeping activities along with walking 35km/ week. This resulted in 1.1kg weight loss per week, ultimately losing 25% total body weight at the end of the 6 months ([Keys 1950](#_ENREF_129)).

Towards the end of the 6 month starvation experiment, electrocardiograms reported abnormal heart rate, amplitude of deflections and QTc interval prolongation in the majority of participants. In 3 participants, these abnormalities were so severe that cardiac failure was identified resulting in oedema. During the refeeding phase, participants were divided into one of four energy intake groups 2200, 2600, 3000 and 3400kcal/ day. However, because the weight gain was too slow in the 2200kcal/ day group the team increased energy intake to 2500kcal/ day.

This pioneering experiment not only monitored physical alterations but also monitored behaviour. Malnutrition was noted to have an impact on these previously mentally well participants, who subsequently developed symptoms of depression, apathy and anxiety; lost the ability to concentrate and began to socially withdraw; developed a preoccupation with food. These symptoms identified by the team are often present in AN patients, which are be perpetuated at low weights which can potentially sabotage therapeutic input. These mental symptoms which manifest at low weights emphasise the importance of establishing a refeeding programme that elicits sufficient weight gain allowing for channels to open for meaningful and effective therapeutic work.

### 3.2.3 Parenteral Nutrition

The development of parenteral nutrition reignited the associated risks with the refeeding syndrome. Parenteral nutrition is the direct intravenous supply of nutrition and was pioneered in the late 1970’s. Parenteral nutrition provided a life line for patients who were unable to absorb nutrients from the gastrointestinal tract. However, parenteral nutrition was in its infancy and resulted in many deaths from infection as well as refeeding syndrome. Many patients were emaciated by the time they received parental nutrition, and upon refeeding patients developed electrolyte abnormalities resulting in cardiac arrest, which was attributed to excessive energy intakes, with particularly high levels of glucose infusion at 26mg/kg/ min ([Weinsier and Krumdieck 1981](#_ENREF_298)). Parenteral nutrition is now significantly diluted and extensively hydrolysed with a maximum glucose infusion of 5mg/ kg/ min ([Singer, Berger et al. 2009](#_ENREF_261)).

The reasons why some people develop the refeeding syndrome and others do not is unclear; however, refeeding some people, whether it be oral, enteral or parenteral results in neurological, cardiovascular and respiratory disturbances which can lead to death. ([Silvis and Paragas 1972](#_ENREF_258); [Weinsier and Krumdieck 1981](#_ENREF_298); [Gustavsson and Eriksson 1989](#_ENREF_86); [Cooke, Chambers et al. 1994](#_ENREF_42)).

## 3.3 Clinical Manifestations of Refeeding

### 3.3.1 – Rate of Refeeding

The rate at which nutrition is reintroduced to low weight malnourished patients has long been implicated as a potential risk factor in the development of the refeeding syndrome. A detailed account of refeeding rate variability is given in chapter 7. The general premise has been to reduce initial refeeding rates, as the refeeding syndrome is believed to occur primarily from the reintroduction of carbohydrate, fluid, and sodium, in amounts greater than a weakened cardiopulmonary system can accommodate. The excess fluid and sodium intake results in volume expansion and fluid retention, which precipitate heart failure ([Brozek, Chapman et al. 1948](#_ENREF_31)). Furthermore, the rate at which refeeding is reintroduced has also been implicated with the most commonly reported symptom of the refeeding syndrome, refeeding hypophosphatemia ([Skipper 2012](#_ENREF_262)). Chapter 4 discusses in detail the implication of refeeding rates and refeeding hypophosphatemia.

### 3.3.2 Impact of carbohydrate

In chapter 2.2 the pathophysiology of starvation was outlined, stating that as glycogen and adipose tissue stores are depleted, energy production for physiological functioning is derived from ketones (glycerol and fatty acids) and glucose (gluconeogenesis – amino acids and glycerol). During refeeding there is an influx of carbohydrate which initiates the secretion of insulin required for the absorption of serum glucose. The rate at which glucose enters the cells is a function of both insulin concentration and the glucose gradient across the cell membrane ([Kaplan 1984](#_ENREF_117)). An increase in glucose utilisation can be seen when insulin levels rise above 10uU/ ml, causing an increase in insulin receptor affinity in both monocytes and erythrocytes ([Rizza, Mandarino et al. 1981](#_ENREF_230)). The rise in serum insulin inhibits the activation of hormone sensitive lipase and gluconeogenesis, reverting to the body’s preferred energy source – glucose.

### 3.3.3 Impact of Insulin

The release of insulin in response to carbohydrate ingestion drives the cellular uptake of glucose from the blood. In healthy subjects, insulin secretion is directly proportional to glucose consumption ([Metz and Best 1960](#_ENREF_166)). In AN the intracellular movement of glucose is heightened as a result of insulin sensitivity, ([Hermans and Lambert 2002](#_ENREF_100); [Delporte, Brichard et al. 2003](#_ENREF_50)) the antithesis to obese patients ([Scheen, Castillo et al. 1988](#_ENREF_250)). As glucose is rapidly drawn intracellular, active diffusion also facilitate the intracellular movement of fluid and electrolytes. ([Boateng, Sriram et al. 2010](#_ENREF_23)) Furthermore, phosphate is needed at a cellular level for the efficient utilisation of glucose into energy. Phosphate is a major anion and therefore particularly susceptible to this transcellular movement.

### 3.3.4 Glucose Metabolism

Glucose is absorbed into the cytosol and enters glycolysis and is phosphorylated and converted to pyruvate, the level of intracellular phosphate is an essential regulator in the glycolytic pathway ([Haglin 2001](#_ENREF_87); [Marinella 2005](#_ENREF_155)). Pyruvate undergoes decarboxylation in the presence of pyruvate dehydrogenase and thiamine. Acetyl Coenzyme A is produced and is now able to pass from the cytosol into the mitochondria. Efficient glucose metabolism for energy production requires a high demand for phosphate, supplying phosphorylated intermediates for glycolysis, Kreb’s Cycle and the electron transport chain to form adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (DPG).

Phosphate and thiamine are essential for effective glucose metabolism and are rapidly utilised during the refeeding process. Thiamine is an essential co-factor for the transfer of acetyl Co-Enzyme A from the cytosol into the mitochondria. If thiamine is not available pyruvate will not be decarboxylated and lactate will be formed resulting in lactic metabolic acidosis ([Travis, Sugerman et al. 1971](#_ENREF_281)). Thiamine supplementation is recommended during the refeeding process to facilitate glucose metabolism. ([NationalInstituteOfClinicalExcellence 2006](#_ENREF_189)) This interplay between glucose, thiamine and ATP can be seen in diagram 3.1.

## 3.4 Refeeding Hypophosphataemia

The demand for phosphate at a metabolic level during refeeding low weight patients with AN has implications on serum phosphate levels which can result in refeeding hypophosphataemia. Refeeding hypophosphataemia is the most consistently reported biochemical disturbance seen in the refeeding syndrome ([Skipper 2012](#_ENREF_262)). Refeeding the malnourished patient can have a profound influence on serum electrolytes, particularly phosphate. In the initial phase of refeeding a significant amount of phosphate is lost in gastric juices which contains 3mg/kg/day phosphate ([Berndt and Kumar 2009](#_ENREF_18)). Phosphate losses in gastric juices are replaced with serum phosphate resulting in an initial decrease in serum levels. Additionally, as highlighted earlier in this chapter phosphate has a wide-ranging physiological importance, especially in relation to the release of high energy phosphate by hydrolysis of adenosine triphosphate (ATP) providing the main energy source for various metabolic processes and for muscle contraction – resulting in further utilisation of serum phosphate.

Therefore, during refeeding there is a high demand for phosphate e.g. gastric juices and glucose metabolism. The rapid utilisation of serum phosphate can result in a decrease in serum phosphate levels resulting in hypophosphataemia, which can have profound implications to the normal physiological functioning of the body. Refeeding hypophosphataemia dissipates the proton gradient in the mitochondria affecting oxidative phosphorylation and adenosine triphosphate (ATP) formation. Consequently, prolonged untreated disrupted phosphate homeostasis can have catastrophic outcomes, such as diaphragmatic weakness, arrhythmia, seizures, cardiac failure, respiratory failure, rhabdomyolysis, coma and sudden death (Diagram 3.1). In chapter 4 a in depth literature review explores the relationship between refeeding and refeeding hypophosphatemia.

## 3.5 Refeeding Hypomagnesaemia

Hypomagnesaemia has been reported during refeeding malnourished patients with AN ([Stanga, Brunner et al. 2008](#_ENREF_268); [O'Connor and Goldin 2011](#_ENREF_197); [Raj, Keane-Miller et al. 2012](#_ENREF_221)). Magnesium is the most abundant intracellular divalent cation, and is an essential cofactor to many enzymes. It is stored in bone, muscle and soft tissue ([Graber, Yee et al. 1981](#_ENREF_83)).

A recent retrospective chart review by Raj et al (2012) investigated the magnesium levels in 541 adolescents with AN who were admitted for refeeding; 86 (16%) adolescents developed hypomagnesaemia (<1.7mg/dl). Hypomagnesaemia developed on average on day 5 post refeeding and occurred in the older adolescents (>16yrs), and in those who had a longer duration of illness, and were more likely to be purging. The authors concluded that hypomagnesaemia develops later in the course of refeeding than hypophosphataemia, and should therefore be monitored throughout the refeeding process ([Raj, Keane-Miller et al. 2012](#_ENREF_221)).

The mechanism involved in refeeding hypomagnesaemia is not clear and is probably multifactorial, resulting from intracellular movement of magnesium ions as a result of glucose uptake ([Crook, Hally et al. 2001](#_ENREF_44)). Hypomagnesaemia can cause tremors, paraesthesia, tetany and ataxia, and if not corrected and continues to decrease can result in ventricular tachycardia leading to Torsade De Pointes (Diagram 3.1) ([Ebel and Gunther 1980](#_ENREF_60); [Wester and Dyckner 1982](#_ENREF_301)). Furthermore, hypomagnesaemia is an important mediator of both hypocalcaemia and hypokalaemia, therefore essential that magnesium levels are corrected rapidly ([Boateng, Sriram et al. 2010](#_ENREF_23)).

## 3.6 Refeeding Hypokalaemia

Potassium is a predominant monovalent intracellular cation essential for maintaining cell membrane action potential, and crucial for glycogen and protein synthesis; 98% of total body potassium resides in the intracellular space but is also concentrated in bone and cartilage ([Halperin and Kamel 1998](#_ENREF_90)).

Once again, refeeding hypokalaemia is the result of trans-cellular shifts as glucose is drawn intracellular by the action of insulin, which in turn draws water and electrolytes in to the cell. Insulin increases Na-K-ATPase pump activity which, indirectly and independent of its effect on glucose transport, causes influx of K+ in and efflux of Na+ out of the cells in a 2:3 ratio, leading to a K+ shift into muscle and liver cells. Namely, Na-K-ATPase extrudes three Na+ and pumps in two K+ when each molecule of ATP is hydrolysed ([West, Bendz et al. 1986](#_ENREF_300)).

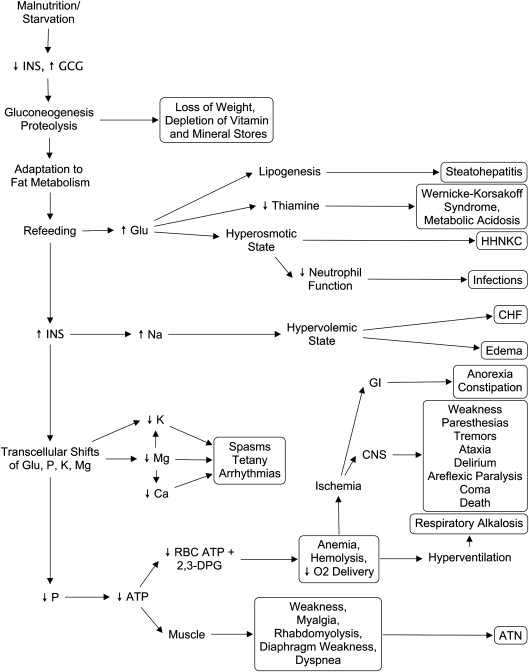
The features of hypokalaemia are numerous and consist of paralysis, paraesthesia, rhabdomyolysis, cardiac arrhythmias, hypotension and cardiac arrest ([Brown 1984](#_ENREF_30)). Severe hypokalaemia can be defined arbitrarily as a serum potassium level <3.0mmol/l ([Crook, Hally et al. 2001](#_ENREF_44)) (Diagram 3.1).

Refeeding hypokalaemia has been reported whilst refeeding malnourished patients with AN ([Fisher, Simpser et al. 2000](#_ENREF_68); [Stanga, Brunner et al. 2008](#_ENREF_268); [O'Connor and Goldin 2011](#_ENREF_197))**.** Case reports by Fisher et al (2000) and Stanga et al (2008) both reported that refeeding hypokalaemia was the result of episodes of binge eating prior to admission, in a bid to avoid ward admission. Neither case report outlined the quantity or type of food consumed prior to admission which resulted in mild hypokalaemia. However, a case report by O’Connor et al (2011) commenced conservative refeeding consistent with the NICE (2006) refeeding guidelines at 20kcal/ kg which still provoke a constellation of refeeding complications including hypokalaemia. The cases of refeeding hypokalaemia described by Fisher et al (2000), Stanga et al (2008) and O’Connor et al (2011) were all successfully corrected by oral potassium supplementation.

### 3.7 Delirium

Delirium has been associated with refeeding AN patients, albeit rare. The most commonly reported symptoms include memory problems, orientation, disorganised thought, paranoid ideas and agitation ([Norris, Pinhas et al. 2012](#_ENREF_194)). The cause of delirium is not fully understood, but has been linked to prolonged phosphate depletion affecting neurotransmitter functioning ([Kohn, Golden et al. 1998](#_ENREF_133)), which contribute to a reduction in central nervous system cholinergic activity and increased dopaminergic transmission ([Bourne, Tahir et al. 2008](#_ENREF_26)). Delirium is most commonly reported within the first 5-7 days of refeeding.

## Diagram 3.1 Pathophysiology of refeeding



## 3.8 Summary of Clinical Manifestation of Refeeding

The reintroduction of nutrition in malnourished patients can in some patients elicit a constellation of biochemical and cardiologic anomalies, all of which are initiated with the secretion and subsequent action of insulin. If insulin is indeed the driven force behind refeeding hypophosphataemia then limiting the carbohydrate intake may reduce the insulin secretion which in turn may reduce the trans-cellular movement of electrolytes and reduce the amount of phosphate required at a cellular level for glucose oxidation. Refeeding hypophosphataemia is the most commonly reported symptom of the refeeding syndrome, the next chapter further investigates the relationship between energy intake and refeeding hypophosphataemia.

# Chapter 4: Refeeding Hypophosphataemia in malnourished patients with anorexia nervosa: a Systematic Review

## 4.1: Introduction

Medically unstable adolescents with AN (bradycardic, hypotensive and low weight) are advised to be admitted to hospital for nutritional restoration to elicit weight gain whilst under close cardiovascular and biochemical monitoring. However, insufficient research in the field of refeeding the malnourished patient has resulted in a lack of consensus and ambivalence on an appropriate initial refeeding intake, consequently refeeding practices remain inconsistent ([Wagstaff 2011](#_ENREF_292)).

The ambivalence around refeeding stems from the physiological adaptations that occur during malnutrition which include: depletion of fat and fat free mass which subsequently reduces resting energy expenditure ([Van Wymelbeke, Brondel et al. 2004](#_ENREF_286); [Bossu, Galusca et al. 2007](#_ENREF_24)); cardiovascular alterations ([Lesinskiene, Barkus et al. 2008](#_ENREF_151); [DiVasta, Walls et al. 2010](#_ENREF_55)); and the metabolic adaptation to starvation - the ability to function in a hypo-metabolic state ([Platte, Pirke et al. 1994](#_ENREF_213); [Satoh, Shimizu et al. 2003](#_ENREF_244)). As a result of these physiological adaptations it is common practice to begin with low energy intake and increase slowly to avoid refeeding hypophosphataemia (chapter 7); however initiating very low energy intakes can have a deleterious effects on weight gain ([Garber, Michihata et al. 2012](#_ENREF_75)); which may exacerbate cardiac abnormalities, which are often corrected with weight gain ([Swenne 2000](#_ENREF_273); [Mont, Castro et al. 2003](#_ENREF_182)).

## 4.2 Risk factors for Refeeding Hypophosphataemia

Factors that are believed to influence or exacerbate refeeding complications include: rate of weight loss prior to refeeding ([Crook, Hally et al. 2001](#_ENREF_44); [Boateng, Sriram et al. 2010](#_ENREF_23); [Raj, Keane-Miller et al. 2012](#_ENREF_221)); the extent of malnutrition (baseline %BMI) ([Ornstein, Golden et al. 2003](#_ENREF_203); [Raj, Keane-Miller et al. 2012](#_ENREF_221); [O'Connor and Nicholls 2013](#_ENREF_198)); method of refeeding (enteral verse Parenteral)([Weinsier and Krumdieck 1981](#_ENREF_298); [Diamanti, Basso et al. 2008](#_ENREF_53)); carbohydrate load ([Kohn, Madden et al. 2011](#_ENREF_134); [O'Connor and Goldin 2011](#_ENREF_197)); and the rate at which nutrition is introduced ([Kohn, Golden et al. 1998](#_ENREF_133); [Whitelaw, Gilbertson et al. 2010](#_ENREF_303)). The rate at which nutrition is introduced has received much attention and tends to be the focal point of refeeding treatment guidelines ([Golden, Katzman et al. 2003](#_ENREF_79); [RoyalCollegeOfPsychiatrists 2005](#_ENREF_234); [NationalInstituteOfClinicalExcellence 2006](#_ENREF_189)).

However, the basis of recommended refeeding treatment guidelines are ascertained from clinical experience rather from scientific evidence ([Katzman 2012](#_ENREF_121)). It has been postulated that by reducing the total energy intake will in turn reduce the carbohydrate load which will subsequently lessen the insulin surge which drives phosphate disturbances due to phosphate utilisation in gastric juices and glucose metabolism (Chapter 3) ([Crook, Hally et al. 2001](#_ENREF_44); [O'Connor and Goldin 2011](#_ENREF_197)).

A systematic review was performed to address the perceived hypothesis that energy intake is associated with refeeding hypophosphataemia whilst refeeding low weight adolescents with AN.

## 4.4: Methods for literature review

## 4.4.1 Search Strategy

A literature search investigating the impact of refeeding on serum phosphate in malnourished adolescents with anorexia nervosa was conducted using electronic medical publication databases including MEDLINE, EMBASE and CINAHL from 1980 up to June 2013 including both English and non-English language studies.

The key search terms used: hypophosphataemia and anorexia nervosa; hypophosphataemia and refeeding and anorexia nervosa. The reference lists of all retrieved relevant studies were then searched to identify other potential studies.

## 4.4.2 Inclusion criteria

All relevant studies that reported specific energy intake during the initiation of refeeding malnourished adolescents with AN and monitored serum phosphate levels before and after refeeding were eligible for inclusion. Post feeding serum phosphate levels must have been reported. Participants were diagnosed with anorexia nervosa (restrictive and/ or binge-purge types) based on criteria outlined in DSM IV (chapter 1) ([Widiger T 1994](#_ENREF_304)).

The upper age limit for inclusion was 20 years old; no lower age limit was imposed. Refeeding hypophosphataemia was defined as post refeeding serum phosphate levels below 1.1mmol/l. Measure of malnutrition using ideal body weight must have accounted for height, gender and age.

## 4.4.3: Exclusion criteria

All studies that did not provide specific details on energy intake during the initial phase of refeeding were not included. Studies that administered oral or intravenous prophylactic phosphate at the start of refeeding were excluded. All studies that documented refeeding hypophosphataemia in malnourished adolescents on intensive care units, post-transplant (bone marrow, renal and liver) and oncology patients with or without AN as a comorbidity were excluded. All studies on adults were also excluded. Table 4.1 outlines the main inclusion and exclusion criteria.

## Table 4.1 Inclusion and exclusion criteria established for the systematic review

|  |
| --- |
| **Inclusion Criteria –**  All studies designed to investigate the effect refeeding and malnutrition had on serum phosphate (mmol/l).  Post refeeding serum phosphate obtained within 48hrs  Malnutrition measured as percentage ideal body weight – age and gender  Diagnosed with anorexia nervosa using DSM IV criteria  Male and female  <20yrs old  **Exclusion Criteria –**  Studies that had insufficient details about the energy intake during refeeding.  Studies that monitored refeeding hypophosphataemia in adolescents not diagnosed with anorexia nervosa or had AN with comorbidities (Diabetes Mellitus Type 1).  Adults over 20yrs old |

## 4.5 Statistics for literature review

The mean and range was calculated for energy intake (kcal/ day and kcal/ kg) and %BMI at the start of refeeding. A weighted mean was calculated to measure the incidence rate of refeeding hypophosphataemia. A Spearman’s correlation was performed to measure the associate between energy intake and serum phosphate nadir; and %BMI and serum nadir phosphate.

## 4.6 Results for literature review

The literature search identified 51 potentially eligible papers. After screening these for eligibility, 19 studies were included: 12 were case reports; 6 were retrospective chart reviews; and 1 was an observational study. The total number of participants was 1039 participants. Figure 4.1 outlines the selection process of eligible studies.

Many publications were excluded due to a lack of information around nutritional intake during the refeeding process. The upper age limit was 20 years and the lowest recorded was 10 years old. Table 4.2 represents the six chart reviews and one observational study and table 4.3 represents the 12 case reports.

## Figure 4.1 Flow chart of included studies that explored the impact energy intake and malnutrition had on post refeeding nadir phosphate levels.

Potential relevant studies identified and screened for retrieval (n=51)

Studies excluded after screening abstract (n= 6)

Studies retrieved for more detailed evaluation (n= 45)

Excluded due to (26):

Adult studies (n=9)

Prophylactic phosphate (n=1)

No energy intake details (n=4)

Review/ management (n=6)

Non AN patients:

Critical Care (n=2)

Renal (n=2)

Fistula gastro (n=2)

Abuse (n=1)

Studies used for final analysis and discussion (n=19)

## 4.6.1 Serum Phosphate levels

The majority of subjects’ baseline serum phosphate levels were within normal range prior to refeeding (1-1.8mmol/ l). Serum nadir phosphate levels were obtained within 48hrs of commencing refeeding. Nadir phosphate levels of those individuals that went into refeeding hypophosphataemia ranged from 0.2 – 1.1mmol/ l. The mean post refeeding nadir phosphate level in the studies and case reports were 0.65mmol/ l and 0.54mmol/ l, respectively.

The majority of the studies in this literature review deemed an episode of hypophosphataemia as serum levels below the lower reference range for adolescents (0.9mmol/l). If serum phosphate levels fell below 0.9mmol/ l then oral phosphate supplementation was given ([Ornstein, Golden et al. 2003](#_ENREF_203); [O'Connor and Goldin 2011](#_ENREF_197); [Garber, Michihata et al. 2012](#_ENREF_75)). Although Whitelaw et al (2010) gave prophylactic phosphate when serum levels dropped below 1.1mmol/l ([Whitelaw, Gilbertson et al. 2010](#_ENREF_303)). Of the 1039 adolescents identified in the studies, 131 developed refeeding hypophosphataemia. The incidence of refeeding hypophosphataemia in the studies ranged from 0 – 38%, with an average incidence of 14%.

## 4.6.2 Nutritional Intervention

Most patients (79%) were fed orally or enterally and 21% fed parenterally. The studies reported an average initial refeeding intake of 1500kcal/ day (38kcal/ kg), ranging from 1200-1900kcal/ day (30-48kcal/ kg). Most studies increased calorie intake by 200-300kcal/ day until estimated energy requirements for weight gain were met. Five of the seven retrospective/ observational studies were carried out in North America and reflected the recommended refeeding treatment guidelines of North America (30-40kcal/ kg) ([AmericanPsychiatricAssociation 2006](#_ENREF_10)). However, studies from Australia ([Whitelaw, Gilbertson et al. 2010](#_ENREF_303)) and Italy ([Diamanti, Basso et al. 2008](#_ENREF_53)) also commenced energy intakes reflective of the North American guidelines as opposed to the European treatment guidelines of 10-20kcal/ kg. ([Stanga, Brunner et al. 2008](#_ENREF_268))

## 4.6.3 Ideal Body Weight Calculation

Three of the seven studies ([Palla and Litt 1988](#_ENREF_206); [Alvin, Zogheib et al. 1993](#_ENREF_7); [Diamanti, Basso et al. 2008](#_ENREF_53)) used Moore’s method ([Moore, Durie et al. 1985](#_ENREF_183)) to calculate percent Ideal Body Weight (IBW), which accounts for age and gender. Three studies used weight for age, height and gender as %BMI (percentage median Body Mass Index for age -gender) ([Whitelaw, Gilbertson et al. 2010](#_ENREF_303); [Garber, Michihata et al. 2012](#_ENREF_75); [Raj, Keane-Miller et al. 2012](#_ENREF_221)) and one study used the National Childs Health Survey (NCHS) growth chart ([Ornstein, Golden et al. 2003](#_ENREF_203)). Disparities between these different methods are outlined in chapter 2.5. A height for weight below 85%BMI is used to define malnutrition which reflects the WHO definition of wasting - that is, weight for height below −2 SD. A healthy percentage ideal body weight usually falls between 95-105%BMI in the majority of the population ([Cole, Flegal et al. 2007](#_ENREF_40)). The percentage ideal body weights of the studies ranged from 70.5% to 81%BMI with a weighted mean of 77.9%BMI. The weight ranged from 36.3kg to 41kg, a mean of 39.25kg.

## 4.6.3 Energy intake

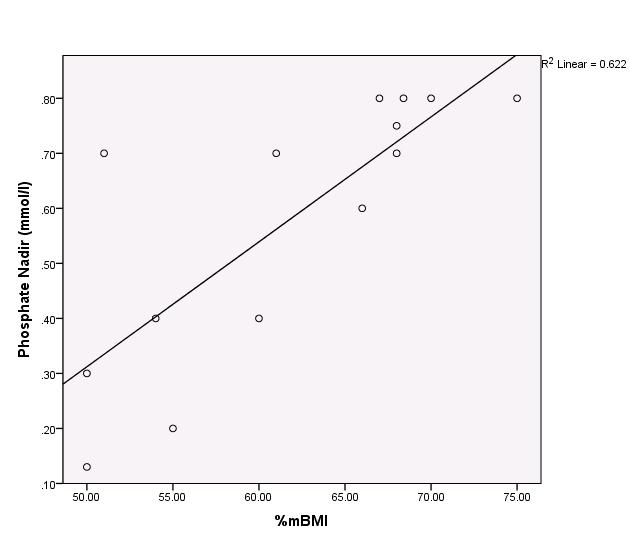
The case reports had an average initial refeeding intake of 972kcal/ day (31kcal/ kg) ranging from 125 – 1700kcal/ day (5 -65kcal/ kg). The admission %BMI was calculated for all the case reports and ranged from 50% to 70% (mean of 59%BMI). The average %BMI and initial refeeding intake on admission for both the studies and case reports were 68% and 1186kcal/ day, (33kcal/ kg) respectively. Table 4.3 outlines relevant information extrapolated from articles including refeeding rates, weights and nadir phosphate.

## 4.6.4 Association between %BMI and Hypophosphataemia

A correlation analysis was performed to test for a relationship between malnutrition as %BMI and post refeeding hypophosphataemia. The analysis included all the case reports (N=11), plus studies that included specific levels on refeeding nadir phosphate (N=3) ([Alvin, Zogheib et al. 1993](#_ENREF_7); [Ornstein, Golden et al. 2003](#_ENREF_203)).

A positive correlation (r= 0.6, p= 0.01) was found between malnutrition (%BMI) and post refeeding nadir phosphate (mmol/l). This Suggests that %BMI may be correlated to post refeeding serum phosphate levels. Figure 4.2 highlights that the lower the calculated %BMI in turn elicited the lowest post refeeding serum phosphate.

## Figure 4.2: Association between malnutrition (%BMI) and post refeeding serum phosphate (mmol/ l) (r = 0.62 p= 0.01)



## 4.6.5 Association between energy intake (kcal/ day) and Hypophosphatemia

A correlation analysis was also performed to test for a relationship between initial refeeding intake and corresponding post refeeding serum nadir phosphate. Only the chart and observational studies that provided specific information on initial refeeding intake and refeeding hypophosphataemia were included in the analysis (N=7). All case reports where included in the analysis (N=11). Figure 4.3 highlights that in this review a correlation could not be found between refeeding rate (kcal/ day) and refeeding hypophosphataemia (mmol/ l)( p= 0.7).

## Figure 4.3 Relationship between energy intake and post refeeding nadir phosphate

## 

## 4.7 Discussion for literature review

This review was unable to find a correlation between energy intake and post refeeding nadir phosphate, however an association was found between baseline %BMI and post refeeding nadir phosphate whilst refeeding malnourished adolescents with AN. The vast range in refeeding rates identified in this review (125-1900kcal/ day) may be fuelled by the unpredictable manifestation of refeeding hypophosphataemia coupled with insufficient interventional research in the area of refeeding malnourished patients, which has hindered the development of comprehensive global refeeding guidelines. However, the premise behind all of the refeeding rates are based on clinical experience rather from scientific evidence ([Katzman 2012](#_ENREF_121)); with the overriding principle being that limiting the total energy intake may reduce the insulin surge, which in turn will suppress the rapid intracellular movement of glucose, fluid and electrolytes particularly phosphate reducing the risk of refeeding hypophosphataemia. ([Crook, Hally et al. 2001](#_ENREF_44); [Boateng, Sriram et al. 2010](#_ENREF_23); [O'Connor and Goldin 2011](#_ENREF_197))

### 4.7.1 Energy Intake and Refeeding Hypophosphataemia

The data from this literature review reports that refeeding hypophosphataemia occurred in malnourished adolescents who commence a range of energy intakes (125kcal/ day – 1900kcal/ day); this lessens the possibility of a direct link between total energy intake and refeeding hypophosphataemia. Energy intakes as low as 125kcal/ day reduced serum phosphate to 0.4mmol/ l ([Kasai, Okajima et al. 2009](#_ENREF_118)), similarly energy intakes as high as 1900kcal/ day ([Whitelaw, Gilbertson et al. 2010](#_ENREF_303)) also reduced phosphate levels in malnourished adolescents with AN. Additionally, the correlation analysis also found no association between refeeding energy intake and nadir phosphate.

Of all the chart/ observational studies and case reports Whitelaw et al (2010) commenced the highest refeeding rates at 1900kcal/ day and reported the highest incidence of refeeding hypophosphataemia, affecting 38% of adolescents. Whitelaw et al (2010) performed a retrospective chart review on 29 adolescents (46 admissions) and set out to determine the incidence of refeeding hypophosphataemia by aggressively refeeding malnourished AN adolescents (72.9%BMI). On admission patients commenced 1900kcal/ day increasing to 2700kcal/ day by day 5. The mean weight gain within 2 weeks was 2.6kg (1.3 SD). They concluded that aggressive approaches to nutritional rehabilitation for hospitalised adolescents with AN is supported over the current refeeding treatment guidelines (1200 -1400kcal/ day).

However, there are a few conflicting issues with the study design: first, they used 1.1mmol/l as a definition of hypophosphataemia oppose to 0.9mmol/ l, which would generate a higher incidence of hypophosphataemia. Furthermore, they encouraged additional intake of dairy products to increase dietary phosphate intake, aiming for 1150mg/ day (900mg/ day is the Reference Nutrient Intake for adolescents [COMA1991]). Although exceeding current recommended phosphate requirements this practical approach allows for the supply of additional phosphate intake. Second, those identified at particular high risk of the refeeding syndrome (6 participants) were commenced on lower refeeding intakes of 1400kcal/ day and also commenced oral prophylactic phosphate. Factors that warranted a reduced refeeding intake for at risk individuals are not specified in the methods. However, selectively reducing the refeeding intakes and providing prophylactic phosphate supplementation for high risk patients contradicts the aim of the study. This altered intervention for at risk patients potentially masks the true incidence of refeeding hypophosphataemia in aggressively refed malnourished AN patients.

In contrast, Palla and Litt (1998) categorised hypophosphataemia as serum phosphate below 0.8mmol/l and did not record any incidences of refeeding hypophosphataemia. Nevertheless, they reported that initial phosphate levels were at the lower end of normal, which further decreased once refeeding was initiated at around 1500kcal/day ([Palla and Litt 1988](#_ENREF_206)). Therefore, it is possible that some patients may have developed mild hypophosphataemia and may have been accounted for if they had used similar definitions to the other studies. However, the serious complications associated with refeeding hypophosphataemia outlined in chapter 3.4 (diaphragmatic weakness, arrhythmia, seizures, coma and sudden death) often do not present until serum phosphate levels fall below 0.4mmol/l – this low level is directly cardio-toxic and can lead to myocardial ischemia ([Weinsier and Krumdieck 1981](#_ENREF_298); [Brooks and Melnik 1995](#_ENREF_29)).

Another retrospective chart review by Ornstein et al (2003) also set out to identify the incidence of refeeding hypophosphataemia. They commenced refeeding at 1200-1400kcal/ day in 69 malnourished AN adolescents (72.7%IBW), which were of a similar weight to those in the study by Whitelaw et al (2010). Of the 69 adolescents, 19 developed hypophosphataemia (27.5%), and required phosphate supplementation. The average weight gain after 4 weeks of refeeding was 4.9kg (no SD or p-values provided). They concluded that it was not possible to deduce safe refeeding guidelines from this study and simply state that refeeding hypophosphataemia occurs within the first week of refeeding.

Although Ornstein et al (2003) commenced refeeding at the recommended North American guidelines of 30-40kcal/ kg/ day (Chapter 7) this refeeding rate still elicited a relatively high incidence of hypophosphataemia. A possible cause for this may be attributed to the fact that all patients admitted were simultaneously commenced on intravenous 5% dextrose and a meal plan for 1200-1400kcal/ day. The potential deleterious effect of simultaneous enteral and parenteral glucose would have increased insulin requirements resulting in a greater need for phosphate at a cellular level for effective glucose metabolism (chapter 3.3), therefore exacerbating the risk and manifestation of hypophosphatemia. ([Ornstein, Golden et al. 2003](#_ENREF_203))

Other studies carried out by Garber et al (2012) and Raj et al (2012) also commenced refeeding at 1200kcal/ day and 1400kcal/ day respectively, in adolescents at 80%BMI. They observed incidence rates of refeeding hypophosphataemia of 20% and 14%, respectively; which again could be argued are relatively high rates. However, the observational study by Garber et al (2012) which reported a 20% incidence of hypophosphataemia may not reflect an accurate incidence rate. They investigated refeeding in 35 malnourished adolescents with AN. They were all refed orally with solid food or supplement drinks equivalent to <1400kcal/ day (mean intake 1205kcal/ day [289SD]) increasing to a mean of 1966kcal (349SD) on day 8. The mean weight gain over 16 days was 2.42kg (1.85SD). Of importance, individuals who had lower energy intake before admission were started on lower refeeding intakes. Unfortunately, the authors do not clarify what was deemed a low preadmission energy intake or what refeeding rate was commenced for these high risk participants.

Confusingly, Garber et al (2012) states that phosphate supplementation was only prescribed if serum phosphate dropped below 0.9mmol/l. The lowest recorded serum phosphate was 1.1mmol/l on day 5 of refeeding. However, 7 subjects still received phosphate supplementation with no justification. The ambiguity around phosphate supplementation in these 7 subjects raises questions around the utility of using 1200kcal/ day. One could speculate that phosphate supplementation were initiated because previously high baseline serum phosphate levels dropped rapidly whilst initial refeeding rate commenced at 1200kcal. Therefore, prophylactic phosphate was provided to avoid hypophosphataemia.

A multivariate linear regression by Garber et al (2012) reported that the higher refeeding rates predicted a faster weight gain (p=0.003) and shorter stay in hospital (p=0.03), after adjusting for %BMI and heart rate. In the U.K these findings will be of particular relevance to paediatric wards that focus discharge goals based on weight, often in a bid to free valuable bed spaces. Overall, the study by Garber et al (2012) is well designed and supports the efficacy of the North American refeeding guidelines (30-40kcal/ kg) (chapter 7). An energy intake of 1200kcal/ day elicited effective weight gain with no reported hypophosphataemia. However, the authors state that a weight gain of 1kg/ week is too conservative and represents a missed opportunity to maximise weight gain. The most effective weight gain in this patient group is unknown. Arguably, too rapid a weight gain may exacerbate symptoms of the metabolic syndrome (chapter 1.9.2.1), increase fat tissue accretion (chapter 6.1.3) and increase patient anxiety.

A follow-on quasi-experimental study by Garber et al (2013) commenced refeeding at a mean intake of 1764 (60 SD) kcal/ day and compared their findings to their previous study as discussed above ([Garber, Michihata et al. 2012](#_ENREF_75)). They reported that participants that commenced the higher refeeding programme gained weight more rapidly than the lower refeeding programme however after 14 days of refeeding there was no significant difference in weight gain between groups (P=0.6). Additionally, there was no significant difference between refeeding groups and hypophosphataemia (P=0.2). However, a problem with this quasi-experimental design is that all the participants in the higher refeeding programme commenced a multivitamin which contained phosphate whereas prophylactic multivitamin supplementation did not occur in the earlier lower calorie refeeding programme. Therefore, it is difficult to interpret the effectiveness and safety of refeeding at a higher refeeding programme as additional phosphate was provided.

In contrast to the aforementioned studies, case reports by Kasai et al (2009), Kohn et al (1998), Wada et al (1992) and O’Connor (2011) documented the lowest initial refeeding intakes commencing from 125 - 600 kcal/day (5-25kcal/kg/day) in individual adolescents with very low weights, between 51 -67%BMI. Regardless of these low refeeding rates which reflect the NICE (2006) and Solomon and Kirby (1990) refeeding guidelines (10-20kcal/kg/day), refeeding hypophosphataemia (0.4-0.8mmol/ l) and cardiovascular anomalies were still observed.

Conversely, case reports by Waldholtz et al (1988) and Kaysar et al (1991) reported refeeding hypophosphataemia (0.75mmol/ l and 0.13mmol/ l, respectively) whilst refeeding at much higher energy intakes of 1500kcal/ day and 1700kcal/ day, respectively; in very low weight adolescents 68%BMI and 50%BMI, respectively.

Refeeding hypophosphataemia occurred in malnourished adolescents who commence a range of initial refeeding treatment intakes (125kcal/ day – 1900kcal/ day). This observation lessens the possibility of a direct link between total energy intakes and refeeding hypophosphataemia. Energy intakes as low as 125kcal/ day reduced serum phosphate to 0.4mmol/ l ([Kasai, Okajima et al. 2009](#_ENREF_118)), similarly energy intakes as high as 1900kcal/ day ([Whitelaw, Gilbertson et al. 2010](#_ENREF_303)) also reduced phosphate levels in malnourished adolescents with AN.

The results challenge our physiological understanding of the refeeding syndrome previously outlined in chapter 3. The refeeding syndrome is supposedly driven by insulin ([Boateng, Sriram et al. 2010](#_ENREF_23)), insulin secretion is directly proportional to glucose consumption ([Metz and Best 1960](#_ENREF_166)). One may therefore expect the greater energy intake to cause the greater reduction in post refeeding serum phosphate. However, the insignificant result produced from the correlation analysis performed in this review warrant further investigation ideally in a well-designed randomised study. The present research will monitor the impact of nutritional load on serum insulin levels throughout the refeeding process. The paradoxical presentation of refeeding hypophosphataemia in malnourished adolescents who have commenced both high and low refeeding rates, further add to the complexity of this physiological phenomenon and suggests that refeeding hypophosphataemia may not be entirely correlated to energy intake. The inconsistent presentation of refeeding hypophosphataemia implies that other contributing factors are at play.

### 4.7.2 Degree of Malnutrition and Incidence of Refeeding Hypophosphataemia

Variable methods were used to measure ideal body weight as outlined in the results section of this review, however the variability of generated results is limited as all of the methods used in this review accounted for height, age and gender ([Le Grange, Doyle et al. 2012](#_ENREF_146)). Many of the studies identified in this review report a direct correlation between refeeding phosphate nadir and ideal body weight ([Kohn, Golden et al. 1998](#_ENREF_133); [Ornstein, Golden et al. 2003](#_ENREF_203); [Whitelaw, Gilbertson et al. 2010](#_ENREF_303)). Ornstein et al (2003) were the first to acknowledge this potential association between nadir phosphate and % ideal body weight (r=0.3 p=0.01).

Ornstein et al (2003) outlined that of the 4 subjects whose phosphate nadir dropped below 0.8mmol/l (specific phosphates nadir values are not provided) also had a mean ideal body weight of 63.5%. Compared to the 15 subjects whose nadir phosphate reduced to between 0.8-0.9mmol/l had a mean ideal body weight of 74%. However, of the 50 subjects whose phosphate did not fall below 0.9mmol/ l had a similar mean ideal body weight (73%IBW) to those 15 subjects whose phosphate levels did fall below normal levels. This observation further highlights the unpredictable nature of refeeding hypophosphataemia and emphasises the fact that not all low weight malnourished individuals develop refeeding complications.

The study by Whitelaw et al (2010) also sought to differentiate between those individuals who did and did not develop refeeding hypophosphataemia. As in Ornstein et al (2003) study specific nadir phosphate are not provided, but an episode of hypophosphataemia was defined by serum phosphate levels below 1.1mmol/l. The mean %BMI of the 17 subjects that developed hypophosphataemia was 68.4% (10.9SD) compared with 75.5%BMI (6.9SD) of those subjects who did not develop hypophosphataemia (P=0.007), additional analysis reported a positive correlation between %BMI and post refeeding nadir phosphate (P=0.007). They conclude that patients below 68%BMI are at greater risk of developing refeeding hypophosphataemia.

This relationship between percentage ideal body weight and nadir phosphate is further highlighted by Garber et al (2012) and Alvin et al (1993). Garber et al (2012) commenced refeeding at around 1200-1400kcal in patients who were 80%BMI. The lowest recorded serum phosphate was 1.1mmol/ l which is above the 0.9mmol/ l cut off for hypophosphataemia. However, as highlighted earlier 7 patients still received phosphate supplementation. ([Garber, Michihata et al. 2012](#_ENREF_75)) Similarly, Alvin et al also commenced refeeding at 1400kcal in adolescents who were much lower weights, mean 70%BMI. This elicited significant hypophosphataemia in 7 subjects, 2 of which dropped to 0.3mmol/ l. These data further support the potential relationship between %BMI and nadir phosphate nadir ([Alvin, Zogheib et al. 1993](#_ENREF_7)).

Furthermore, case reports by Fisher et al (2000), Huang et al (2001) and Gustavsson et al (1989) had the lowest recorded %BMI (49%, 55% and 56%, respectively) of all identified case studies which in turn reported the lowest post refeeding serum phosphate levels (0.3, 0.19, and 0.4mmol/ l, respectively). In each of these case reports refeeding rates commenced at around 1200kcal/day. ([Fisher, Simpser et al. 2000](#_ENREF_68)) ([Huang, Fang et al. 2001](#_ENREF_93)) ([Gustavsson and Eriksson 1989](#_ENREF_86))

Finally, Diamanti et al (2008) performed a retrospective chart review on 198 adolescent AN patients. Controversially, they routinely refed their patients via parenteral nutrition, the direct supply of nutrition intravenously, which has been shown to increase the rate of refeeding complications ([Weinsier and Krumdieck 1981](#_ENREF_298); [Marvin, Brown et al. 2008](#_ENREF_158); [Miller 2008](#_ENREF_171)). Diamanti et al (2008) compared the incidence of refeeding hypophosphatemia between parenteral (104 subjects) and enteral (94 subjects) refeeding methods. They reported refeeding hypophosphataemia in 6 subjects in the parenteral nutrition refeeding group and zero in the oral/ enteral refeeding group.

However, although parenteral nutrition is believed to increase the risk of hypophosphataemia, the parenteral refeeding group also had a significantly lower %BMI than the oral group, 75.3% versus 80.1% (p=0.001), respectively. This could account for the higher rate of refeeding hypophosphataemia. If %BMI is indeed associated with hypophosphataemia then it is essential to consider the disparity in %BMI between the parenteral and enteral refeeding groups. Interestingly, Diamanti et al (2008) acknowledges in their conclusion that parenteral nutrition was associated with a higher complication rate than oral treatment alone, but all complications resolved and recommends that parenteral nutrition be used as a method for refeeding malnourished AN patients ([Diamanti, Basso et al. 2008](#_ENREF_53)).

## 4.8 Limitations

This is a secondary data analysis. As such, the chart and observational data analysed in this review have been extrapolated from summative data and therefore only provide an overview of the true energy intakes, percentage ideal body weight and nadir phosphate.

Bias of over and under-reporting of hypophosphataemia should be limited assuming compiled data is consecutive as reported in the chart reviews. However, the fact that such a chart review was instigated may imply an increase of hypophosphataemia which prompted further investigations. This is especially pertinent as the retrospective chart reviews only included admission over the previous year, which could overestimate the incidence of refeeding hypophosphataemia in adolescents with anorexia nervosa.

A lack of information in articles regarding rate of weight loss prior to refeeding and nutritional composition of meal plans also limits the findings in this review as both are potential risk factors for refeeding hypophosphatemia. Finally, a lack of consensus from authors on what was deemed an episode of hypophosphataemia limited an accurate measure of incidence rates.

## 4.9 Conclusion for literature review

A correlation between energy intakes (kcal/ day) and refeeding hypophosphataemia could not be substantiated in this review, however, a correlation between baseline %BMI and refeeding hypophosphatemia seems more plausible - both factors need further investigation through a well-designed randomised controlled trial.

The next chapter is another literature review which focuses on the impact refeeding has on cardiovascular parameters.

## Table 4.2- Chart Reviews: Energy intake and incidence of Refeeding Hypophosphatemia in adolescents with Anorexia Nervosa.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *Author* | *Study design* | *Total Number* | *Number developed RH* | *Age*  *Mean* | *SD* | *Weight*  *mean*  *(Kg)* | *SD* | *Mean %*  *Body Weight* | *SD* | *Mean % body Weight with*  *RH* | *Initial Refeeding Intake*  *Kcal/day*  *(Kcal/ kg/day)* | *Feeding*  *route* |
| ([Palla and Litt 1988](#_ENREF_206)) | Retrospective  Chart Review | 47 | 0 | 15.5 | DNA | DNA | DNA | 74%IBW | DNA | DNA | 1500-1600 | Oral |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| ([Alvin, Zogheib et al. 1993](#_ENREF_7)) | Retrospective  Chart review | 92 | 7(9%) | 16.6 | DNA | DNA | DNA | 70.5%IBW | DNA | DNA | 1400 | 20 NGT  2- PN  56 Oral |
| ([Ornstein, Golden et al. 2003](#_ENREF_203)) | Retrospective  Chart review | 69 | 19(27.5%) | 15.5 | 2.4 | 39.2 | 7 | 72.7%IBW | 7.1 | 68 | 1200-1400  (30-34) | Oral and NGT |
| ([Diamanti, Basso et al. 2008](#_ENREF_53)) | Retrospective  Chart review | 104  94 | 7(7%)TPN  0 Oral | 14.9  15.2 | 1.4  1.0 | 36.3  41 | 0.5  0.6 | 75.3%IBW  80.1%BMI | 1.2  1.5 | 75 | 1400-1500  (38-41)  (34-36) | 104PN  94Oral |
| ([Whitelaw, Gilbertson et al. 2010](#_ENREF_303)) | Retrospective  Chart review | 45 | 17 (38%) | 15.7 | 1.4 | 41 | 6.8 | 72.9%BMI | 9.1 | 68 | 1400-1900kcal  (34-46) | Oral and NGT |
| ([Garber, Michihata et al. 2012](#_ENREF_75)) | Observational  Study | 35 | 7 (20%) | 16.2 | 1.9 | DNA | DNA | 80.1%BMI | 11.5 | DNA | 1200 | Oral |
| ([Raj, Keane-Miller et al. 2012](#_ENREF_221)) | Retrospective  Chart review | 541 | 74 (14%) | 16.8 | 2 | DNA | DNA | 81%BMI | 13 | DNA | 1400 | Oral and  NGT |

RH = Refeeding Hypophosphataemia; %BMI = percentage median Body Mass Index for 50th percentile BMI-age-and-gender; BMI = Body Mass Index; %IBW =percentage ideal body weight – Moore’s calculation; NGT = Naso Gastric Tube; PN = Parenteral Nutrition; SD = Standard Deviation; DNA = Data Not Available

### 

### **Table 4.3** Case Reports: Energy intake and post refeeding serum phosphate in adolescents with Anorexia Nervosa.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *Author* | *Study design* | *Total Number* | *Age* | *Weight*  *(kg)* | *%BMI* | *Refeeding Energy*  *Intake* | *Feeding*  *route* | *Phosphate*  *Nadir*  *(mmol/l)* |
| ([Fisher, Simpser et al. 2000](#_ENREF_68)) | Case Report | 1 | 16 | 25 | 50% | 1000kcal/day  40kcal/ kg/d | oral | 0.3 |
| ([Gustavsson and Eriksson 1989](#_ENREF_86)) | Case Report | 1 | 19 | 30.6 | 60% | 1400kcal/ day  45kcal/ kg/d | PN | 0.4  (Patient Died) |
| ([Hall, Kahan et al. 1994](#_ENREF_88)) | Case Report | 1 | 17 | 63 | 66% | 1200kcal/ day  20kcal/ kg/d | PN | 0.6 |
| ([Huang, Fang et al. 2001](#_ENREF_106)) | Case Report | 1 | 14 | 25.5 | 55% | 1000kcal/ day  39kcal/ kg/d | NGT  PN | 0.19 |
| ([Kaysar, Kronenberg et al. 1991](#_ENREF_125)) | Case Report | 1 | 16 | 26 | 50% | 1700kcal/day  65kcal/ kg/d | oral | 0.13 |
| ([Kasai, Okajima et al. 2009](#_ENREF_118)) | Case Report | 1 | 16 | 26.8 | 54% | 125kcal/ day  5kcal/ kg/d | Oral | 0.4 |
| ([Kohn, Golden et al. 1998](#_ENREF_133)) | Case series | 3 | 12  13  19 | 31  33  37 | 61%  70%  62% | 500kcal/day  16kcal/ kg/d  1200kcal/day  36kcal/ kg/d  1000kcal/day  27kcal/ kg/d | Oral  Oral  Oral | 0.7  0.8  supplemented |
| (Continue) Table 4.3 Case Reports: Energy intake and post refeeding serum phosphate in adolescents with Anorexia Nervosa. | | | | | | | | |
| *Author* | ***Study design*** | ***Total Number*** | ***Age*** | ***Weight***  ***(kg)*** | ***%BMI*** | ***Refeeding Energy***  ***Intake*** | ***Feeding***  ***route*** | ***Phosphate***  ***Nadir***  ***(mmol/l)*** |
| ([O'Connor and Goldin 2011](#_ENREF_197)) | Case Report | 1 | 10 | 23.75 | 67% | 600kcal/day  25kcal/ kg/d | NGT | 0.8 |
| ([Wada, Nagase et al. 1992](#_ENREF_289)) | Case  Report | 1 | 16 | 26 | 51% | 450kcal/ day  17kcal/ kg/d | PN | 0.7 |
| ([waldholtz BD 1988](#_ENREF_293)) | Case Report | 1 | 16 | 40.5 | 68% | 1500kcal/day  37kcal/kg/d | Oral | 0.75 |

%BMI = percentage median Body Mass Index for 50th percentile BMI-age-and-gender; NGT =Naso Gastric Tube; PN = Parenteral Nutrition

# Chapter 5 Refeeding and Cardiovascular Parameters in Anorexia Nervosa: Meta-Analysis and Systematic Review

## 5.1 Introduction

In a catabolic state such as starvation, as seen in AN, body weight dramatically decreases resulting in a range of autonomic nervous system disturbances. These disturbances can be seen in up to 85% of AN sufferers ([Lesinskiene, Barkus et al. 2008](#_ENREF_151)) and account for a 5-10% mortality rate ([Isner, Roberts et al. 1985](#_ENREF_109)). Food restriction, excessive exercise and subsequent weight loss can lead to an increase in vagal tone resulting in: bradycardia (resting heart rate <50beats per minute); low arterial blood pressure (100/50mmHg); voltage decrease; T- wave inversion; atrophy of left ventricle; and QTc (corrected for heart rate) interval prolongation ([Nudel, Gootman et al. 1984](#_ENREF_195); [Ulger, Gurses et al. 2006](#_ENREF_283)).

The QT interval is a measure of myocardial repolarisation and its prolonged length is a common concern of clinicians caring for patients with AN, due to the associated link between delayed repolarisation, torsade de pointes and sudden death ([Palla and Litt 1988](#_ENREF_206); [Cooke, Chambers et al. 1994](#_ENREF_42); [Casiero and Frishman 2006](#_ENREF_36); [Schwartz, Mansbach et al. 2008](#_ENREF_253)). It is reported that QT interval prolongation is a direct response to poor nutritional intake and low weight resulting in hypotrophic myocardial muscle.

### 5.1.1 Correcting QT interval adjusting for heart rate

A corrected QT interval (QTc) measurement is often adopted over a QT interval alone, adjusting for heart rate (R-R length). Bazett’s formula is the most commonly used method for adjusting corrected QT interval based on heart rate and is calculated by dividing the QT interval by the square root of the heart rate ([Bazett 1920](#_ENREF_14)). However, a major limitation to this formula proposed by Bazett is that it was based on only 39 young healthy men. This limitation is further highlighted when Bazett’s formula is used to calculate corrected QT in bradycardic and tachycardic patients. At slower heart rates the formula under corrects, potentially masking life threatening QT prolongation ([Kawataki, Kashima et al. 1984](#_ENREF_122); [Sagie, Larson et al. 1992](#_ENREF_239)). In light of the high proportion of AN patients that have bradycardia as a result of increased vagal tone, Bazett’s formula may not represent the true corrected QT interval.

A linear regression model has been developed to account for the shortfalls identified with Bazett’s formula. The Framingham Heart study, Sagie et al (1992) examined the initial baseline electrocardiogram on 5,209 subjects (28-62yrs old) over a 40 year period. Sagie et al (1992) state that the linear equation is more accurate than Bazett’s formula, in that Framingham’s linear regression corrects at different cycle lengths (bradycardia and tachycardia) and is therefore applicable to clinical practice ([Sagie, Larson et al. 1992](#_ENREF_239)).

### 5.1.2 Normal and prolonged QTc interval in adolescents

Normal QTc intervals for children and adolescents is around 410ms, with an upper limit of normal of 450ms ([Dickinson 2005](#_ENREF_54)). There is also a gender variation in QTc from the age of 14, with females having significantly longer QTc as a result of shortening of QTc in males, as opposed to prolongation in females ([Pearl 1996](#_ENREF_208)). A QTc interval > 460ms (girls) and >400ms (boys) is deemed to be high risk, ([Nicholls, Hudson et al. 2011](#_ENREF_191)). However, some studies indicate an increase in arrhythmias at >440ms ([Swenne 2000](#_ENREF_273); [Olivares, Vazquez et al. 2005](#_ENREF_201)) and QTc interval prolongation >600ms is a significant precursor for sudden cardiac death in AN ([Isner, Roberts et al. 1985](#_ENREF_109); [Durakovic, Korsic et al. 1989](#_ENREF_59)).

Nevertheless, the QTc interval seems to be a poor predictive marker for the recognition of patients who are at particular risk of sudden death ([Jauregui-Garrido and Jauregui-Lobera 2012](#_ENREF_112)). QT dispersion which is defined by inter-lead variation in QT segment length on a routine surface electrocardiogram ([Krantz, Donahoo et al. 2005](#_ENREF_140)) has been proposed as a more accurate marker for increased arrhythmic risk ([Swenne 2000](#_ENREF_273); [Mont, Castro et al. 2003](#_ENREF_182)). An increase in QT dispersion has been shown to positively correlate with heart rate variability, the result of increased sympathetic tone and/ or decreased vagal tone ([Ishida, Nakagawa et al. 1997](#_ENREF_108)).

However, ventricular remodelling appears to be extremely variable among patients, apparently independent of the extent of weight loss and other traditional markers of malnourishment. Indices of endocrine impairment seem to be the most relevant determinants of left ventricular hypotrophy in patients with AN, apparently independent of reduced haemodynamic load and BMI. In particular, Insulin Growth Factor/ Growth Hormone ratio and Free Thyroxin 3 seem to particularly affect left ventricular mass in this population ([Carlomagno, Mercurio et al. 2011](#_ENREF_35)).

It is reported that weight restoration rectifies many of the cardiac anomalies associated with malnutrition, especially heart rate and QT interval ([Nussinovitch, Gur et al. 2012](#_ENREF_196)). However, refeeding the malnourished patient can cause electrolyte disturbances, particularly hypomagnesaemia, hypophosphatemia and hypokalaemia which can exacerbate already compromised cardiac function leading to Torsade du Pointe and sudden death ([Mehanna, Moledina et al. 2008](#_ENREF_163)).

This review aimed to explore the literature regarding the frequency of QTc interval prolongation in malnourished patients with AN, and the impact refeeding and weight restoration has on QTc interval in patients with AN.

## 5.2 Methods – Literature Search: Malnutrition and QTc interval

### 5.2.1 Literature Search

A literature search investigating the impact malnutrition and refeeding had on QTc interval in malnourished adolescents with anorexia nervosa was conducted using electronic medical publication databases including MEDLINE, EMBASE and CINAHL from 1980 up to present, including both English and non-English language studies.

The key search terms used were ‘cardiac’ OR ‘QT’ OR ‘heart’ AND ‘anorexia nervosa’. The reference lists of all retrieved relevant studies were then searched to identify other potential studies. The second part of the search used key mesh terms ‘refeeding’ OR ‘weight restoration’ AND ‘QT interval’. This did not yield any additional studies to what had been retrieved from the previous search.

### 5.2.2 Selection Criteria

All relevant case-control studies and prospective observational studies that reported QT interval in malnourished patients with anorexia nervosa were eligible for inclusion. Additionally, all studies that reported QT interval before and after refeeding were eligible for inclusion.

The degree of malnutrition was measured by calculating body mass index (kg/m2). The mean BMI had to be below 17kg/m2 to be included in the analysis. The maximum mean period to refeed was 18 months. All refeeding methods (enteral, parenteral and oral) were included in the analysis.

The QTc interval measurements must have been manually extracted from a standard 12 lead ECG at a paper speed of 25mm/ s. Correction of QT interval in relation to heart rate were calculated using Bazett’s formula. Participants must have been diagnosed with AN using the DSM IV (Diagnostic and Statistical Manual for Mental Disorders). All age groups were included for analysis.

### 5.2.3 Exclusion Criteria

Studies which had measured QT variability/ dispersion but did not report QT interval measurements were excluded. Studies were excluded if QT interval measurements were not manually extracted and only reported ECG machine generated measurements. Studies that used regression models or other corrective QT interval methods were excluded.

|  |
| --- |
| **Inclusion Criteria –**  All studies designed to investigate the effect malnutrition had on QT interval in patients with AN.  All studies that investigated QT interval before and after refeeding in malnourished patients with AN  QT interval manually extracted from ECG report    Corrected QT interval was calculated using Bazett’s formula  State of malnutrition measured as BMI (kg/m2) and were below 17kg/ m2  Diagnosed with AN using DSM IV criteria  Both male and female  All age groups  **Exclusion Criteria –**  Studies that investigated other cardiac parameters (QT variability/ dispersion/ heart rate) but did not included QT interval measurements in malnourished patients with AN.  Used regression models to calculate corrected QT interval |

### 5.2.4 Main and Subgroup Analyses

The review explored the association between malnutrition and QTc interval (ms) in patients with AN compared to healthy controls. Subgroup analysis also monitored the incidence of QTc interval prolongation >440ms in malnourished AN patients and healthy controls. A further subgroup analysis monitored the impact refeeding and weight restoration had on QTc interval (ms) in patients with AN.

### 5.2.5 Statistical Analysis

This review calculated the odds ratio and mean difference with 95% confidence intervals by using crude 2x2 tables. For the test of heterogeneity, Higgins I2 was used, which measures the percentage of total variation across trials. I2 was calculated as follows:

I2 = 100% X (Q-df)/ Q

Where Q is Cochran’s heterogeneity statistic and df indicates degree of freedom. To calculate pooled odds ratio and mean difference both fixed and random effect models were used. An I2 value >50% was deemed as substantial heterogeneity and warranted a random model. An I2 <50% was deemed as no substantial heterogeneity and warranted a fixed model.

## 5.3 Results - literature search: Malnutrition and QTc interval

From a total of 271 existing studies designed to analyse cardiac function in malnourished patients with AN, 17 studies met the inclusion criteria. The included studies described twelve case-control studies (401 AN and 351 controls) and five observational studies (140 AN patients). No randomised controlled studies were found. Figure 5.1 describes the process of study selection and table 5.1 outlines identified studies that reported QT interval measurements in malnourished patients with AN. Table 5.2 outlines studies that reported QTc interval before and after refeeding.

## Figure 5.1- Flow chart of the included studies that investigated the impact energy intake and malnutrition had on QT interval.

Potential relevant studies identified and screened for retrieval (n=271)

Studies excluded after screening abstract (n=209)

Studies retrieved for more detailed evaluation (n=62 )

Excluded due to:

Review/ management (n=16)

Non AN patients (n=11)

Foreign (n=8)

Other cardiac measurements (n=9)

Potassium supplementation (n=1)

Studies used for final analysis and discussion (n=17)

12 case-control and 5 observational studies

Of which 8 studies investigated the impact of refeeding on QT interval

The mean age of AN subjects was 18.5yrs old and 19.2yrs old for controls, ranging from 15yrs to 26yrs old. The mean body mass index (BMI) for the AN subjects was 13.7kg/m2 and 20kg/m2 for controls. The mean QTc interval for AN subjects was 411ms and 404ms for controls. Of the twelve case control studies that investigated QT interval in malnourished patients with AN, seven reported a significantly higher QTc interval compared to controls. Three studies reported significantly higher QTc intervals in the control group and two studies were unable to identify any significant difference between case and control subjects (Table 5.1). All studies used sample t-tests to compare QTc interval between AN patients and controls.

Studies carried out by Ulger et al (2006) and Vazquez et al (2003) monitored cardiac abnormalities in young women with AN compared to controls and found the greatest mean QT interval difference between AN patients and controls, 48ms and 45ms, respectively. Both studies involved low weight adolescents, 13.7kg/ m2 (1.5SD), 15yrs (1SD) and 15kg/ m2 (2SD), 15yrs (2SD), respectively (Table 5.1). Vazquez et al (2003) performed a correlation analysis to assess the relationship between BMI and QT dispersion. The authors reported a negative correlation (r=0.4, p=0.001), highlighting that individuals with low BMI had larger QT dispersions ([Vazquez, Olivares et al. 2003](#_ENREF_287); [Ulger, Gurses et al. 2006](#_ENREF_283)).

Conversely, Roche et al (2005) reported that young adults (mean 19yrs 3SD) who were marginally malnourished 15.2kg/m2 (2.1SD) (normal BMI range for adults 19 – 25kg/m2) had a QTc interval that was higher in the control group compared to AN group. However, Roche et al (2005) did note that the AN group had a significantly larger QT dispersion compared to controls (p<0.001) which highlights the relative protective effect of increased vagal tone observed at a slightly slower heart rate; the body’s attempt to conserve energy in response to starvation. ([Roche, Barthelemy et al. 2005](#_ENREF_232))

Finally, Facchini et al (2006) was unable to find a difference in QTc interval between AN and controls. However, they did identify three patients with significantly prolonged QTc interval (mean 558ms). This anomaly was directly associated with abnormal ventricular repolarisations secondary to severe hypokalaemia. Furthermore, these three individuals who developed prolonged QTc interval were also very low weight (<14kg/m2), which may exacerbate QTc interval prolongation ([Facchini, Sala et al. 2006](#_ENREF_62)).

Eleven of the twelve case control studies also reported heart rate. Eight studies reported a significantly lower heart rate in the AN patients compared to controls. The other three studies were unable to identify any significant difference between the two groups.

## Table 5.1 – QTc interval in malnourished patients with AN

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Author | numbers | AGE | BMI kg/m2 | | QTc  (ms) | HR |
| ([Cooke, Chambers et al. 1994](#_ENREF_42)) | 23 AN  28 Control | 26  26 | (36kg) no BMI  (55kg) no BMI | 427  422 | | 76  70 |
| ([DiVasta, Walls et al. 2010](#_ENREF_55)) | 38  observational | 16.5 | 15.9 | 320 (30) | | 47 (12) |
| ([Durakovic, Korsic et al. 1989](#_ENREF_59)) | 30 AN  30 control | DNA | DNA | 421 (33)    390 (19)  **(P<0.001)** | | DNA |
| ([Facchini, Sala et al. 2006](#_ENREF_62)) | 29 AN  14 Control | 22 (5)  23 (2) | 14 (1.5)  20 (1) | 392 (25)  407 (17)  **(P=0.08)** | | 53  66  **(P<0.001)** |
| ([Krantz, Donahoo et al. 2005](#_ENREF_140)) | 6 AN  10 Control | 29 (3)  26 (2) | 16 (0.4)  20 (0.4) | 415 (12)  409 (6)  **(P=0.6)** | | 61 (3)  57 (3)  **(P=0.41)** |
| ([Krantz, Sabel et al. 2012](#_ENREF_141)) | 19 AN  observational | 25 (5) | 12 (2) | 415 | | 53 |
| ([Mont, Castro et al. 2003](#_ENREF_182)) | 31  observational | 16 (1.4) | 15(2.0) | 391 (18) | | 53 (17) |
| ([Nahshoni, Weizman et al. 2007](#_ENREF_187)) | 30  observational | 15 (9) | 15 (2) | 464 (37) | | DNA |
| ([Olivares, Vazquez et al. 2005](#_ENREF_201)) | 40 AN  40 Control | 15  15 | 15 (2)  20 (1.5) | 433 (33)  401 (17)  **(P<0.001)** | | 57 (12)  75 (11)  **(P<0.001)** |
| ([Panagiotopoulos, McCrindle et al. 2000](#_ENREF_207)) | 62 AN  62 Control | 15 (1.4) | 16 (2) | 392 (26)  406 (20)  **(P=0.02)** | | 58 (16)  78 (14)  **(p<0.001** |
| ([Roche, Estour et al. 2004](#_ENREF_233)) | 25 AN  25 Control | 19 (3)  19 (2) | 15 (2)  19 (2) | 399 (17)  416 (11)  **(P<0.01)** | | 65 (10)  75 (7)  **(<0.01)** |
| ([Roche, Barthelemy et al. 2005](#_ENREF_232)) | 10 AN  10 Control | 19 (3)  20 (3) | 14 (2)  23 (2) | 388 (20)  412 (14)  **(P<0.05)** | | 46 (9)  55 (4)  DNA |
| (Continued) Table 5.1 – QTc interval in malnourished patients with AN | | | | | | |
| ([Silvetti, Magnani et al. 1998](#_ENREF_257)) | 23 AN  observational | 14.7 (2) | 14 (1.3) | 400 (30) | | DNA |
| ([Swenne and Larsson 1999](#_ENREF_274)) | 92 AN  38 Control | 15 (1.7)    15 (1.6) | 15 (2)  20 (2) | 437 (19)  411 (16)  **(P<0.001)** | | 54 (12)  74 (11)  **(p<0.001)** |
| ([Takimoto, Yoshiuchi et al. 2004](#_ENREF_276)) | 43 AN  52 Control | 19 (4)  18 (0.5) | 14.5 (2)  20.3 (2) | 437 (38)  407 (20)  **(P<0.001)** | | 50 (10)  68 (10)  **(P<0.001)** |
| ([Ulger, Gurses et al. 2006](#_ENREF_283))Ulger  2006 | 11 AN  12 Control | 15 (1)  15 (2) | 13.7(1.5)  20 (.8) | 423 (29)  375 (25) | | 60 (8)  81 (7) |
| ([Vazquez, Olivares et al. 2003](#_ENREF_287))Vazquez  2011 | 30 AN  30 Control | 15 (2)  15 (2) | 15 (2)  20 (1) | 436 (35)  391 (24)  **(P<0.001)** | | 57 (12)  82 (12)  **(P<0.001)** |
|  |  |  |  |  | |  |

DNA – Data Not available

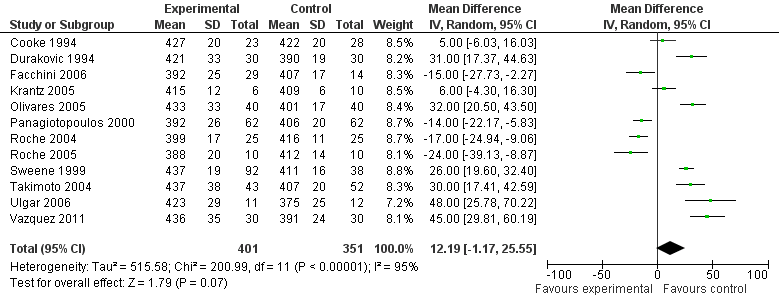
## 5.4 Results – Meta-analysis: Malnutrition and QTc interval

A meta-analysis was performed to investigate the mean difference QTc interval (ms) in malnourished patients with AN compared to healthy weight controls on the 12 case control studies identified in this review. Pooling the results of the 12 eligible studies for the meta-analysis, heterogeneity across studies was examined using I2 statistics (I2= 95%). Due to the high heterogeneity found between these studies, a random effect model was calculated to account for potential population variation.

The summarised random effect indicates a significant shorter QTc interval in healthy weight individuals compared to malnourished patients with AN, (12.2 95% CI 1.17, 25.55) (Figure 5.2).

## Figure 5.2 – Difference between QTc interval in malnourished patients compared to healthy controls

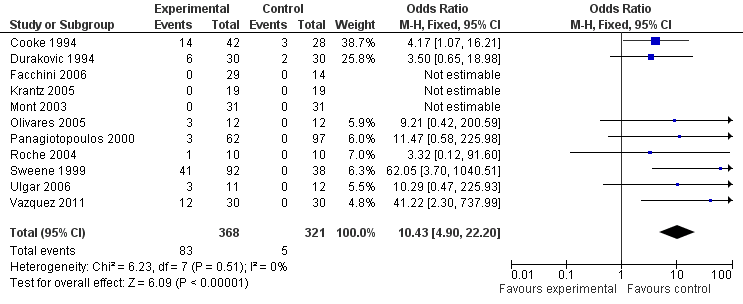
### 



Additionally, a meta-analysis on the case control studies was performed to investigate the odds ratio of QTc interval prolongation (>440ms) in patient with AN compared to healthy weight controls. A meta-analysis pooled the results of the 11 eligible studies which reported specific QTc intervals over 440ms, heterogeneity across studies was examined using I2 statistics (I2= 0%), therefore a fixed effect model was calculated to account for potential population variation.

The summarised random effect indicates a significant lower incidence of QTc interval prolongation in healthy weight individuals compared to malnourished patients with AN (10.43 95% CI 4.90, 22.20) (Figure 5.3).

### Figure 5.3 – Difference in the incidence of QTc interval prolongation between malnourished patients and healthy control



### 5.4.1 Results – Literature search: Refeeding and QTc interval

From a total of 17 studies that analysed QTc interval in malnourished patients with AN, 8 studies reported QTc interval measurements before and after refeeding. These studies encompassed a total of 220 patients which had a mean age of 17yrs old. The mean pre refeeding BMI was 14.7kg/m2 and the mean post refeeding BMI was 18.2kg/m2. All of the studies reported a highly significant increase in BMI post refeeding (p<0.001). The refeeding period ranged from 7 days to 14 months, with a mean refeeding period of 188 days (6 months).

The mean QTc interval pre refeeding was 411ms and the mean QTc interval post refeeding was 401ms. Five of the eight studies reported a significant reduction in QTc interval post refeeding, one study reported a significant increase in QTc interval post refeeding and two studies did not report any significant change before or after refeeding (Table 5.2)

A study by DiVasta et al (2010), monitored cardiovascular parameters before and after refeeding in 38 adolescents (mean BMI 16kg/m2). Heart rate increased by 1.3bpm with each day of refeeding adjusted for weight. The authors reported that the QTc interval was longer in participants with longer duration of amenorrhoea (p=0.05). The average time for a repeat of cardiovascular investigation after weight restoration was 3 months (87-411 days). Refeeding consisted of 1250-1750kcal/ day and increased by 250kcal/ day until energy requirements were met. A regression analysis for expected weight gain whilst refeeding, adjusting for age, ideal body weight and exercise, found that an increase of 0.3kg/ day could be achieved (2.1kg/ week) which resulted in a clinically significant weight gain on discharge (P<0.01). Similarly, another regression analysis highlighted the relationship between weight gain and increased heart rate (P<0.01) ([DiVasta, Walls et al. 2010](#_ENREF_55)).

All of the studies that monitored heart rate changes before and after refeeding reported an increase in heart rate after weight restoration and all those studies that reported QT dispersion reduced after weight restoration (Table 5.2). All studies used a two tailed paired t-test to compare QT interval (ms), QTc interval (ms), heart rate (bpm) and weight (kg) before and after feeding.

## 

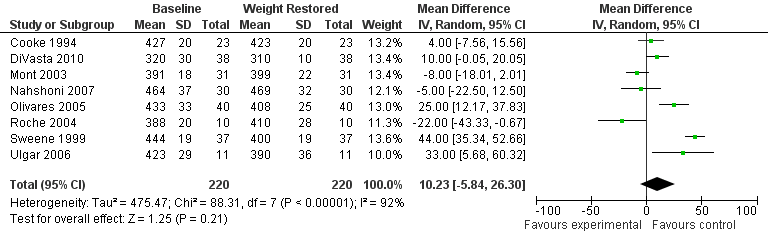
## Table 5.2 – QT interval pre and post weight restoration

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author | N | Age  Mean | Pre refeeding  BMI kg/m2 | Post refeeding  BMI kg/m2 | Pre heart  Rate  (SD) | Post heart  Rate  (SD) | Pre QTc  mean (SD) | Post QTc  mean (SD) | Pre QT  Dispersion | Post QT dispersion | Refeeding Time period |
| ([Cooke, Chambers et al. 1994](#_ENREF_42)) | 23 | 26 | 36kg | 51 | 76 | 83 | 427 | 423 |  |  | 88  (22-188) |
| ([DiVasta, Walls et al. 2010](#_ENREF_55)) | 38 | 16.5 | 15.9 | 18 (1.7)  **P<0.001** | 47 (12) | 60 (13)  **P<0.001** | 320 (30) | 310 (10)  **P=0.5** |  |  | 121 days |
| ([Mont, Castro et al. 2003](#_ENREF_182)) | 31 | 16 (1.4) | 15 (2) | 19 (1)  **P<0.001** | 53 (17) | 62 (18)  **P<0.05** | 391 (18) | 399 (22)  **P=0.8** | 42 (13) | 31 (10)  **P<0.001** | 240 |
| ([Nahshoni, Weizman et al. 2007](#_ENREF_187)) | 30 | 15 (9) | 15 (2) | 19 (1)  **P<0.001** |  |  | 464 (37) | 469 (32)  **P=0.5** | 70 (16) | 47 (16)  **P<0.001** | 120 |
| ([Olivares, Vazquez et al. 2005](#_ENREF_201)) | 40 | 15 | 15 (2) | 18 (2)  **P<0.000** | 57 (12) | 76 (18)  **P<0.000** | 433 (33) | 408 (25)  **P<0.000** | 53 (23) | 45.5 (23)  **P=0.037** | 9-18 months |
| ([Roche, Barthelemy et al. 2005](#_ENREF_232)) | 10 | 19 (3) | 15 (2) | 17.6 (4)  **P=0.05** | 46 (9) | 61 (16)  **p<0.05** | 388 (20) | 410 (28)  **p<0.05** |  |  | 150 |
| ([Swenne 2000](#_ENREF_273)) | 37 | 15.7(1.6) | 13.8 (2.4) | 15 | 51 |  | 444 (19) | 400 | 56 (8) | 33 (12) | 7days |
| ([Ulger, Gurses et al. 2006](#_ENREF_283)) | 11 | 15 (1) | 13.7 (1.5) | 21 (3)  **P<0.000** | 60 (8) | 76 (10)  **P<0.000** | 423 (29) | 390 (36)  **P<0.001** | 70.9 (30) | 38 (17)  **P<0.00** | 1yr |
|  |  |  |  |  |  |  |  |  |  |  |  |

### 5.4.2 Results - Meta-Analysis: Refeeding and QTc interval

A meta-analysis was performed on studies which monitored QTc interval (ms) before and after weight restoration. In pooling the results of the 8 eligible studies for the meta-analysis, heterogeneity across studies was examined using I2 statistics (I2= 92%). The summarised random effect model was unable to identify any change in QTc interval after refeeding and weight restoration (10.23 95% CI; -5.8, 26.3) (Figure 5.4).

## Figure 5.4 - QTc interval before and after refeeding malnourished patients with AN



## 5.5 Discussion – Malnutrition and refeeding on QTc interval

### 5.5.1 Summary of main findings

This meta-analysis of case control and observational studies found that malnutrition directly resulted in a longer QTc interval in AN patients compared to healthy weight controls and that the incidence of QTc interval prolongation (>440ms) is higher in patients with AN compared with healthy weight controls. However, refeeding and weight restoration did not significantly improve QTc interval in malnourished patients with AN.

### 5.5.2 QTc Interval and malnutrition

Of the 12 case-control studies identified in this review, seven reported that AN patients had prolonged QTc interval compared to controls. However, a study by Krantz et al (2012) whose aim was to ascertain whether cardiac abnormalities persist later in the disease, was unable to find a significant difference in QTc interval between patients with AN and controls (P=0.6); this study had a very small number of participants (6 AN and 10 controls) and encompassed the oldest cohort compared to the other studies (29yrs 3SD). The chronicity of AN was an influential aspect of the study by Krantz et al (2012), however the duration of illness in these older participants ranged from as low as 2 months to a more acceptable definition of chronicity of 72 months (mean 19 months 11 SD). The study only monitored 6 participants, which consisted of individuals being diagnosed with AN for only 2 months, this may have skewed the results in regards to the occurrence of cardiac adaptation and therefore reducing the validity of their insignificant finding.

However, even with this limited cohort Krantz et al (2012) did find a significant difference in QT dispersion between AN and controls (P=0.01). This implies that QT dispersion may precede QT interval prolongation or that QT dispersion is more common than QT interval prolongation. This latter implication is reinforced further in that heart rate was also not found to be different between case and controls (P=0.4), suggesting cardiac adaptation has either not occurred or has resolved with chronicity. ([Krantz, Sabel et al. 2012](#_ENREF_141)). Finally, Krantz et al (2012) concluded that causes of QT interval prolongation as previously seen in AN patients may be the result of congenital or electrolyte disturbances rather than an intrinsic feature of AN and that QT dispersion is increased in older more chronic AN. However, as highlighted earlier, their limited cohort (6 participants) and poor definition of chronic AN (2months) diminishes the validity of their conclusion.

One of the seven studies that did report a significant difference in QTc interval between AN and healthy controls was that conducted by Swenne and Larsson (1999) who monitored cardiovascular parameters in 58 adolescents with AN, mean BMI 15.5kg/m2. Although, they found a significant difference between QTc interval in AN and controls (p <0.001), no AN patients had a QTc interval >460ms. However, 26 adolescents had a QTc >440ms and 16 adolescents had a QTc >450ms along with bradycardia (mean 54bpm). QT dispersion was also noted to be significantly increased compared to controls (p<0.001).

Swenne and Larsson (1999) reported a high percentage of participants with QTc interval >440ms (72%). Furthermore, the adolescents involved in the study were not at a severely low body weight (15kg/m2 2SD) and were reported to be in the early stages of their disease (<1 yr). However, 21 of the 58 (36%) participants in the study had biochemical abnormalities – 11 related to potassium and 10 related to magnesium, both of which can directly affect cardiac function. However, the data do not allow for comparison between those participants that had biochemical anomalies and those with prolonged QTc interval. Therefore, it is not possible to conclude that biochemical disturbances are the cause of such high levels of QTc interval prolongation. It is also not clear as to why so many had biochemical disturbances ([Swenne and Larsson 1999](#_ENREF_274)).

In contrast to the aforementioned studies, Panagiotopoulos et al (2000) found that the control group had a significantly longer QTc interval than AN (P= 0.02). They monitored the QT interval and dispersion in 62 adolescents (15yrs 1.5SD) with a mean BMI 16kg/m2. However, the control participants were recruited from a cardiology clinic who had been referred for investigations into murmurs and functional chest pains. Although congenital QT interval prolongation had been ruled out by cardiologists, the fact that control participants had been referred to a specialist paediatric hospital (Sick Kids, Toronto) to investigate cardiac function does raise questions regarding the utility of this control group. An additional explanation for the control group having longer QTc intervals than AN patients is the degree of malnutrition. Participants were outpatients, suggesting medical compromise was not severe, which is further borne out by the mean BMI of 16kg/m2 in adolescents (15yrs) falls on the 5th percentile. This level of malnutrition may be insufficient to elicit structural cardiovascular adaptations.

However, the team concluded that although QTc interval may be normal, clinicians should not necessarily be reassured that the patient is not severely ill. Relative bradycardia and decreased amplitude of the R-wave in V6 are more useful markers of disease severity in patients with AN, because they were found to correlate significantly with lower BMI. ([Panagiotopoulos, McCrindle et al. 2000](#_ENREF_207))

A study by Swenne (2000) monitored QTc interval, heart rate and biochemical changes whilst refeeding 37 malnourished (mean BMI 13.8kg/m2) adolescents with AN over 7 days. Specific nutritional intakes are not provided but they aimed for a weight gain of 0.5-1kg/ week. Additionally, the author performed a detail of the history to explore the relationship with rate of weight loss, a perceived risk factor for the development of refeeding syndrome (chapter 4.2). This was the only study to differentiate between total overall weight loss and rate of weight loss prior to admission. It is this final rate of weight loss which is thought to relate to an increased risk of biochemical and cardiovascular anomalies on refeeding, the result of altered energy metabolism (chapter 2.9). Swenne (2000) reported an average weight loss over the year prior to admission of 14.2kg (3.1SD). However, the rate of weight loss prior to admission was >50g/ day (0.35kg/ week) in 29 participants and >100g/ day (0.7kg/ week) in 19 of the patients ([Swenne 2000](#_ENREF_273)). Unfortunately the authors do not differentiate between those participants that lost 50g/ day and 100g/ day with QTc interval which could have provided useful information on the impact rate of weight loss has on QTc interval. Current guidelines suggest that patients are at increased risk of refeeding syndrome if weight loss exceeds 1kg/ week ([JuniorMARSIPAN 2012](#_ENREF_116)).

### 5.5.3 The impact of Refeeding on QTc interval

Eight studies provided specific information on cardiovascular parameters and BMI (kg/m2) before and after weight restoration. In light of the associated risk QTc interval prolongation has on cardiac function this parameter is the primary focus for the review; however QT dispersion and heart rate will also be discussed in relation to refeeding and weight restoration (Table 5.2).

A study by Swenne (2000) reported a significant reduction in QTc interval during the early stages of refeeding and was the only study to monitor the immediate effect of cardiac changes within 7 days of refeeding. ECG’s were measured 3-7 times in the first week. Many of their patients were admitted via the emergency room and were not previously known to any mental health services; therefore eliciting accurate duration of illness was difficult. Prior to refeeding Swenne (2000) noted that 18 participants had a QTc interval > 440ms of which 13 patients had a QTc interval >450ms. Similarly, QT dispersion was noted to be prolonged (>50ms) in 23 patients. All electrolytes were within normal reference ranges. Over the first two weeks of refeeding patients gained an average weight of 133g/ day. No biochemical disturbances were noted, although serum phosphate was not monitored.

Swenne (2000) noted that QTc interval and dispersion decreased rapidly within the first three days of refeeding (p<0.001), concluding that QT interval pathology normalised promptly once refeeding had started even before significant weight had been gained. This prompt improvement in cardiac parameters before significant weight restoration during refeeding has also been reported with heart rate ([Rechlin, Weis et al. 1998](#_ENREF_226); [Shamim, Golden et al. 2003](#_ENREF_256)). The mechanism responsible for this rapid alteration remains unknown but highlights the importance of nutrition on the immediate rectification of cardiac anomalies seen in malnourished AN patients.

The Study by Roche et al (2004) found an improvement in heart rate and QTc dispersion after weight restoration at 5months (2SD) (Table 6.2), albeit on very low number of participants (10), which reduces the validity of their findings. Interestingly and of importance Roche et al (2004) reported no QTc interval prolongation prior to refeeding (388ms SD20), but after refeeding 1 participant did develop QTc interval prolongation; specific measurements and details are not provided, furthermore electrolytes abnormalities were not reported - as hypomagnesaemia can cause QTc prolongation. This may have been an ECG error or a manifestation of refeeding syndrome.

Conversely, DiVasta et al (2010) did not observe any significant change to QTc interval with refeeding. This is may be because QTc interval was well within normal range (310ms) prior to refeeding and levels of malnutrition were not severe - mean 16kg/m2 (just below the 5th percentile for adolescent females). However, even at this level of malnutrition the team did note reductions in left ventricular mass and function before weight gain, which improved marginally after weight gain. This suggests early sparing of cardiac muscle even with moderate degrees of malnutrition.

### 5.5.4 Psychotropic Medication and QTc interval

A prospective study carried out by Nahshoni et al (2007) monitored cardiovascular parameters in 30 adolescent in-patients with AN (mean BMI 15.2kg/m2). The mean QTc interval before refeeding was 464ms and after an average of 4.1 (4.5SD) months the mean QTc interval was 469ms. However, the uncorrected QT interval reduced from 471ms (52SD) to 424ms (31SD) (P<0.001) and the QT dispersion also decreased (Table 5.2). The authors suggest that this discrepancy between QTc and QT interval may be the result of an overestimation of QTc interval prolongation using Bazett’s formula ([Bazett 1920](#_ENREF_14)). Unfortunately, Nahshoni et al (2007) do not document heart rate values so it is not possible to verify this hypothesis. If participants had low heart rates (<60bpm) then this may contribute to the insignificant change in QTc interval seen in this study. ([Nahshoni, Weizman et al. 2007](#_ENREF_187))

However, Nahshoni et al (2007) do not consider the use of psychotropic drugs as a possible cause for such high incidence of QTc interval. They report that participants were medication free at the start of refeeding. However, by the time participants were discharged 22 of the 30 participants had commenced psychotropic medication (olanzapine and risperidone). It has been shown that psychotropic medication can have a direct impact on QTc interval, especially in terms of prolongation ([Vieweg 2003](#_ENREF_288)). Furthermore, QTc interval prolongation is exacerbated if psychotropic drugs are combined with an antidepressant ([Goodnick, Jerry et al. 2002](#_ENREF_82); [Sala, Vicentini et al. 2005](#_ENREF_242)). The precursor for QTc interval prolongation and subsequent delayed repolarisation caused by psychotropic medication is the result of a delay in the potassium channel rectifier current ([Goodnick, Jerry et al. 2002](#_ENREF_82)).

Nahshoni et al (2007) state that 20 of the 30 patients were also diagnosed with depression using criteria outlined in DSM IV, however they do not clarify if patients were medicated. This high level of medication with psychotropic drugs may have masked the potential benefit weight restoration has on QTc interval. Nahshoni et al (2007) make no reference in their conclusion to the possible effect medication may have had on their findings. They attributed the anomaly of prolonged QTc interval on discharge solely to the inadequacies of Bazett’s formula.

Similarly, Mont et al (2003) was unable to report a reduction in QTc interval after weight restoration. However, they too had increased the amount of participants on psychotropic and anti-depressant medication on follow up of cardiovascular monitoring (from 5 to 14 in a total of 29 participants). This may have skewed the results ([Mont, Castro et al. 2003](#_ENREF_182)).

This meta-analysis exploring QTc interval before and after weight restoration did not find an overall improvement in QTc interval. However, as outlined, the use of psychotropic and anti-depressant drugs in this population is common and a potential confounder and should be taken into consideration when monitoring the potential beneficial effect that weight restoration has on cardiac function.

## 5.6 Summary

This meta-analysis highlights the variable presentation of QT interval in malnourished patients with AN and suggests that they have longer QTc intervals than healthy weight controls and have a higher risk of QTc interval prolongation (> 440ms). Furthermore, the meta-analysis highlights the difficulty in assessing the effectiveness of refeeding and weight restoration on QTc interval, possibly due to the high percentage of patients that commence psychotropic and anti-depressant medication which prolong QTc interval.

Bradycardia and QT dispersion seem to manifest prior to QTc interval prolongation in malnourished individuals with AN. The present research will focus on the immediate interaction nutrition has on cardiac function by monitoring QTc interval and heart rate during the initial phase of refeeding, controlling for psychotropic and anti-depressant medication.

Most of the organic cardiovascular abnormalities described in patients with AN are regarded as adaptive mechanisms in a bid to conserve energy and tissue whilst in a malnourished state. Another way the body conserves energy is by suppressing the energy expenditure; the next chapter will discuss the impact of refeeding on body composition and resting energy expenditure.

# Chapter 6 Refeeding and Weight Gain

## 6.1 Introduction

Despite dramatic variations in day to day energy intake and energy expenditure, weight remains relatively stable in most animals and humans ([Bessesen 2011](#_ENREF_20)). However, in AN this homeostatic balance is disrupted by a marked restriction in energy intake, with or without compensatory behaviours such as excessive exercise and/ or purging, which results in a low body weight. Low weight malnourished patients with AN are often admitted to medical wards to establish a refeeding programme which elicits weight gain whilst cardiovascular and biochemical markers are monitored. Weight gain is imperative for the correction of cardiovascular anomalies (bradycardia, QT interval prolongation and ventricular weakness) which may have developed as a result of malnutrition ([Swenne 2000](#_ENREF_273); [Olivares, Vazquez et al. 2005](#_ENREF_201); [Ulger, Gurses et al. 2006](#_ENREF_283)).

It has been proposed that a 1-1.5kg/ week weight gain is a sufficient and achievable target whilst refeeding malnourished in-patients with anorexia nervosa ([RoyalCollegeOfPsychiatrists 2005](#_ENREF_234); [AmericanDieteticAssociation 2006](#_ENREF_9); [Reiter and Graves 2010](#_ENREF_228)). To meet this target weight gain of 1-1.5kg/ week, refeeding programmes are devised based on estimated energy expenditure calculated from either indirect calorimetry or predictive estimated energy requirement formulas.

### 6.1.1 Indirect Calorimetry and Predictive Energy Requirement Formulas

Formulating a refeeding treatment programme based on resting energy expenditure measured from indirect calorimetry has been postulated to be an effective and safe method to refeed malnourished patients with AN ([Cuerda, Ruiz et al. 2007](#_ENREF_45); [Gentile 2012](#_ENREF_76)). The resting energy expenditure comprises the largest component of the total energy expenditure ([Obarzanek, Lesem et al. 1994](#_ENREF_199)) and is determined by the amount of metabolically active fat and fat free mass. Indirect calorimetry estimates individual resting energy expenditure by monitoring oxygen consumption and carbon dioxide production providing information on the amount and type of metabolically active tissue ([Ravussin, Lillioja et al. 1986](#_ENREF_225)).

Indirect calorimetry is not always available in a clinical setting, therefore, resting energy expenditure is often estimated using predictive energy equations such as the Harris Benedict equation ([Harris and Benedict 1918](#_ENREF_92)) Henry equation ([Henry 2005](#_ENREF_99))and Schofield equation ([Schofield 1985](#_ENREF_252)). However, these predictive energy equations have limited utility in malnourished patients with AN as these patients exist in a hypo-metabolic state. The primary cause of this hypo-metabolic adaptive ability seen in malnourished patients with AN is largely unknown but is thought to extend beyond the decrease in fat and fat free mass ([Schebendach, Golden et al. 1995](#_ENREF_248); [Pichard, Kyle et al. 1996](#_ENREF_211); [de Zwaan, Aslam et al. 2002](#_ENREF_48)).

Predictive estimated energy equations have been shown to over-estimate resting energy expenditure in malnourished patients with AN ([Krahn, Rock et al. 1993](#_ENREF_139); [Schebendach, Golden et al. 1995](#_ENREF_248); [Russell, Baur et al. 2001](#_ENREF_236); [Gentile, Pastorelli et al. 2010](#_ENREF_78)); over calculating energy requirements may increase the risk of refeeding syndrome which has been attributed to the rate and quantity of nutrition ([Kohn, Golden et al. 1998](#_ENREF_133); [2004](#_ENREF_3); [NationalInstituteOfClinicalExcellence 2006](#_ENREF_189); [Whitelaw, Gilbertson et al. 2010](#_ENREF_303)). Therefore, in order to reduce the complications associated with refeeding it is essential to gauge a relatively accurate estimated energy requirement in these patients.

It has been proposed that for a malnourished patient with AN to gain 1kg of weight requires an additional energy intake of 5300kcal to 9700kcal above calculated resting energy expenditure ([Salisbury, Levine et al. 1995](#_ENREF_243)). A study by Walker et al (1979) observed that a mean excess of 5026kcal (335kcal/ day) was required to promote 1kg weight gain during the first 15 days of refeeding, but this figure increased to 7428kcal (390kcal/ day) during the subsequent 19 days. They surmised that energy requirements increased in that later part of refeeding due to an increase in metabolic tissue mass. Furthermore, they found that initial fat mass predicted the need for more calories to gain weight while initial lean mass did not ([Walker, Roberts et al. 1979](#_ENREF_247)). Additionally, pre-morbid weight also affects rate of weight gain, with individuals that were obese before becoming low weight, gaining weight more rapidly than those that were previously a healthy weight ([Walker, Roberts et al. 1979](#_ENREF_294); [Leibel, Rosenbaum et al. 1995](#_ENREF_150)).

This phenomena of increasing energy requirements throughout refeeding low weight patients is further highlighted in a study by Depsey et al (1984), they used indirect calorimetry to measure resting energy expenditure and calculated pre refeeding resting energy expenditure to be around 70% of that estimated from predicted requirements; however this value increased to 103% of estimated requirements after 63 (18SD) days of nutritional restoration ([Dempsey, Crosby et al. 1984](#_ENREF_51)).

### 6.1.3 Tissue Accretion during Refeeding

The energy cost of gaining 1g of fat mass is about 6 times greater than gaining 1g of fat free mass, 12kcal and 1.8kcal, respectively ([Forbes 1990](#_ENREF_71)). Regardless of this higher energy cost, fat mass is the predominant tissue that is accrued during the initial phase of refeeding AN patients ([Keys 1950](#_ENREF_129); [Mika, Herpertz-Dahlmann et al. 2004](#_ENREF_167)). A review by Cuerda et al (2007) demonstrated that by accurately calculating energy requirements by using indirect calorimetry as opposed to predictive energy formulas promoted an equal change in body mass composition; yielding a 38% recovery of weight from fat ([Cuerda, Ruiz et al. 2007](#_ENREF_45)). Whereas studies which fed more aggressively using predictive energy formulas yielded a 48 – 78% recovery of weight from fat ([Orphanidou, McCargar et al. 1997](#_ENREF_204); [Grinspoon, Thomas et al. 2001](#_ENREF_85)).

This review aimed to gauge an understanding of the amount of energy intake required to meet the recommended weight gain target of 1-1.5kg/ week whilst refeeding malnourished patients with AN.

## 6.2 Methods – Literature search: Refeeding and Weight Gain

### 6.2.1 Search Strategy

All trials included in this review were from peer reviewed publications. A literature search investigating the impact refeeding had on resting energy expenditure and weight gain in malnourished patients with anorexia nervosa was conducted using electronic medical publication databases including MEDLINE, EMBASE and CINAHL from 1975 up to present, only English language studies were included. The key search terms were ‘resting energy expenditure’ AND ‘resting metabolic rate’ AND ‘anorexia nervosa’. The reference lists of all retrieved relevant studies were then searched to identify other potential studies.

### 6.2.2 Inclusion

All studies that reported energy intake, resting energy expenditure and weight before and after refeeding in-patients with AN were included. Only studies that used open circuit indirect calorimetry to measure resting energy expenditure and reported original data were used in the analysis. Finally, all studies must have diagnosed AN using the DSM IV criteria; no age limit was imposed.

### 6.2.3 Exclusion

Studies were excluded: if they did not provide resting energy expenditure values before or after refeeding; if resting energy expenditure was only measured before and after a specific meal load or glucose meal was provided; if they used methods other than indirect calorimetry to analyse resting energy expenditure – such as food nomograms or dietary intake. Studies were excluded if participants had not been diagnosed with AN but were deemed as constitutionally thin individuals.

|  |
| --- |
| **Inclusion Criteria –**  All trials designed to study the effect refeeding had on:  Resting energy expenditure (kcal/ kg)  Energy intake (kcal/ kg)  Weight (kg)  Open circuit indirect calorimetry  Diagnosed with anorexia nervosa (DSM IV)  Male and female – no age restrictions  **Exclusion Criteria –**  Trials performed on low weight/ constitutional thin patients – no formal diagnosis of anorexia nervosa  Trials that used specific glucose loads to measure changes in energy expenditure  Trials that used energy intake of food nomograms to calculate resting energy expenditure |

### **6.2.4 Quality Assessment of Trails**

All identified studies were observational studies; no randomisation control trials have been performed in this area, therefore any findings elucidated in this review could not directly be linked produce definitive evidence of efficacy. However, to reduce study bias all participants were recruited consecutively to the studies. The established percentage of participants excluded or lost to follow up must not have been below 90%.

### 6.2.5 Data Synthesis (Statistical Methods)

The mean difference in resting energy expenditure (kcal/ kg), energy intake (kcal/ kg) and weight (kg) were included in the analysis.

## 6.3 Results – Literature search: Refeeding and Weight Gain

The literature search identified 27 potential papers. After screening, 8 studies met the inclusion criteria, all of which were observational studies and included a total of 182 participants. Figure 6.1 outlines the selection process for eligible studies. Six of the eight studies specifically focused on energy expenditure during refeeding and therefore also included information on body composition changes throughout refeeding. The other two studies focused on resting energy expenditure along with bone mineral density or protein turnover changes whilst refeeding.

The average age of participants was 22.5 years ranging from 14.5 to 31 years. The mean refeeding period was 8.3 weeks, ranging from 6-10 weeks. The mean weight gain over the total refeeding period was 7.5kg, which equated to a mean weekly weight gain of 0.88kg. The average starting refeeding energy intake was 1715kcal/ day (41.25kcal/ kg) and the average end refeeding energy intake was 2844kcal/ day (56.75kcal/ kg). The average resting energy expenditure at the start of refeeding was 1042kcal/ day (27kcal/ kg) compared to the average resting energy expenditure at the end of refeeding was 1316kcal/ day (29.5kcal/ kg). Five of the eight studies ([Obarzanek, Lesem et al. 1994](#_ENREF_200); [Pichard, Kyle et al. 1996](#_ENREF_211); [Satoh, Shimizu et al. 2003](#_ENREF_244); [Winter, O'Keefe et al. 2005](#_ENREF_306); [Sum 2011](#_ENREF_271)) provided information on resting energy expenditure in healthy controls, the mean resting energy expenditure was 1429kcal/ day (SD251). Table 6.1 displays data extracted from studies included for full analysis in this review.

The highest rate of weight gain identified by this review was 1.37kg/ week. This was reported in a study by Sum (2011) which monitored weight gain whilst refeeding 37 adults with AN. Participants’ mean BMI increased from 15.8kg/m2 to 20.4kg/m2, whilst fed a standard hospital diet of solid food consuming 1800kcal/ day (43kcal/ kg), which was around 700kcal above mean resting energy expenditure (1087kcal/ day). Daily energy intake increased between weeks 4-6 of the refeeding programme to 2600kcal/ day (48kcal/ kg), which was around 1200kcal above resting energy expenditure, which was 1378kcal/ day. Furthermore, Sum (2011) highlights the positive effect weight gain and increased energy expenditure had on bone mineral density within 9 weeks of refeeding. A positive correlation was found between spine bone mineral density (%) and resting energy expenditure (kcal/kg/day), which produced an r- value of 0.48 (p<0.02) ([Sum 2011](#_ENREF_271)).

Similar weight gains of 1.1kg/ week were achieved by Krahn et al (1993), in which participants were of a similar age and weight to those in Sum (2011) (Table 6.1). Krahn et al (1993) commenced refeeding at a lower rate to Sum (2011) at around 1200kcal/ day (31kcal/ kg/ day), which they continued for 1 week. The initial refeeding rate of 1200kcal/ day in the first week mimicked those requirements measured for the resting energy expenditure, of mean 1166kcal/ day (30kcal/ kg/ day). Energy intakes were increase after one week of refeeding, by 300kcal/ day for 1 week until energy intakes reached around 3000kcal/ day. By the end of the second week, weight had already increased by 3.3kg (1.7kg/ week). From 3 weeks onwards the refeeding rate increases to 3600kcal/ day until healthy target weights were achieved. ([Krahn, Rock et al. 1993](#_ENREF_139))

In contrast, studies by Pichard et al (1996) and Cuerda et al (2007) reported the lowest weight gains identified in this review, 0.5kg/ week and 0.6kg/ week, respectively. Both studies were carried out in adolescents who were markedly malnourished at the start of refeeding, 14kg/m2 and 15kg/m2, which increased to 16kg/m2 and 17kg/ m2 post refeeding, respectively ([Pichard, Kyle et al. 1996](#_ENREF_211); [Cuerda, Ruiz et al. 2007](#_ENREF_45)). Interestingly, Pichard et al (1996) was the only study in this review that clearly stated that they were aiming for a weight gain of 0.5kg/ week, as opposed to the recommended 1-1.5kg/ week. No justification for this reduced target weight gain was provided. Pichard et al (1996) commenced refeeding at mean intake of 1267kcal/ day (32kcal/ kg); the resting energy expenditure was 969kcal/ day (25kcal/ kg). During the second week of refeeding energy intake was increased by 300kcal with a mean energy intake of 1511kcal/ day; the resting energy expenditure was 1113kcal/ day. The weight gain after 2 weeks of refeeding at just 300-400kcal above resting energy expenditure was 0.7kg. Once again the measured resting energy expenditure per kg body weight remained the same at the start and end of refeeding at 30kcal/ kg.

Unfortunately, Cuerda et al (2007) do not provide accurate energy intakes during refeeding, reporting that initial refeeding commenced between 1000-1600kcal/ day, with a resting energy expenditure of 1135kcal/ day. By week 2 energy intakes are increased gradually to 2000-2500kcal, and by discharge 8 weeks later the resting energy expenditure is 1241kcal/ day.

Studies by Konrad et al (2007), Obarzanek et al (1994) and Van Wymelbeke et al (2004) commenced the highest refeeding rates, 2186kcal/ day, 2105kcal/ day and 2047kcal/ day, respectively. By the end of the refeeding programme energy intakes had increased to 3216kcal/ day, 3216kcal/ day and 2595kcal/ day. However, regardless of these high refeeding rates the average weekly weight gain did not quite meet the recommended target of 1kg week, 0.9kg, 0.9kg and 0.8kg/ week, respectively. ([Obarzanek, Lesem et al. 1994](#_ENREF_199); [Van Wymelbeke, Brondel et al. 2004](#_ENREF_285); [Konrad, Carels et al. 2007](#_ENREF_135))

## Figure 6.1 Flow chart of included studies in the review on refeeding and weight gain

Potential relevant studies identified and screened for retrieval (n=76)

Studies excluded after screening abstract (n= 60)

Studies retrieved for more detailed evaluation (n= 16)

Glucose meal provided before and after measurements (n=3)

Lack of post refeeding information (n=3)

Did not use indirect calorimetry (n=2)

Studies used for final analysis and discussion (n=8)

## 

## 6.4 Discussion – Refeeding and Weight Gain

This review aimed to identify the amount of energy intake required to elicit sufficient continuous weight gain whilst refeeding malnourished patients with AN. The data extracted from this review suggests that sufficient weight gain 0.7-1.3kg/ week may be achieved by commencing refeeding at 1500kcal/ day. The dichotomy faced with formulating an effective refeeding treatment guideline includes one that elicits sufficient weight gain (1kg/ week) without exacerbating symptoms of the refeeding syndrome.

The study by Sum (2011) highlights that the elusive 1kg/ week weight gain target is achievable by imposing relatively acceptable energy intakes starting at around 1800kcal/ day and gradually increasing to 2600kcal/ day over 4 weeks. Although resting energy expenditure per kg body weight remained the same before and after refeeding, in relative terms energy requirements increased as a result of increased weight and subsequent increase in metabolic tissue. Without data on the rate of weight gain at the start and end of refeeding it is not possible to concur with the current notion that different energy requirements per kg of body weight are required at early and late refeeding.

It is essential to gradually increase energy intake during refeeding to account for the accretion of new tissue which subsequently increases the metabolic rate. Daily increments of 200-300kcal have been adopted ([Krahn, Rock et al. 1993](#_ENREF_139); [O'Connor and Goldin 2011](#_ENREF_197); [Garber, Michihata et al. 2012](#_ENREF_75)). However, while the evidence behind these quantities is unclear, on the whole it seems to be sufficient in eliciting on going weight gain.

### 6.4.1 Diet-Induced Thermogenesis

### 

Although Krahn et al (1993) also achieved sufficient weight gains of 1.1kg/ week refeeding at an initial rate of 1200kcal/ day they rapidly increased energy intake to 3600kcal/ day. After two weeks of refeeding resting energy expenditure had increased from 1166kcal/ day (30 kcal/kg/day) to a mean of 1769kcal/ day (39kcal/ kg/ day). This is nearly 400kcal/ day higher than that seen in Sum (2011) which had participants of similar characteristics. It is likely that this higher measured resting energy expenditure reported in participants by Krahn et al (1993) is the result of an increase in diet induced thermogenesis, the direct metabolism of high calorie intake. This excessive calorie intake equated to an additional 12,800kcal/ week above the measured resting energy expenditure, which still elicited a similar weight gain to Sum (2011).

Studies by Sum (2011) and Krahn et al (1993) both yielded sufficient weight gain with very different energy intakes (2600 versus 3600kcal/ day) in similar subjects. However, the higher energy intake did not achieve a higher weight gain. Therefore, excessive energy intakes may be contraindicated in eliciting the recommended weight gains for two reasons. First, by increasing the energy intake over and above that required for tissue accretion will simply result in an increase in resting energy expenditure directly as a result of an increase in diet-induced thermogenesis; subsequently the individual will not gain additional weight because of the increased energy needs imposed by diet induced thermogenesis. Second, such high energy intakes may increase already heightened anxiety levels, reducing the likelihood of the patient to consume food orally and may therefore increase the use of nutritional supplementations and nasogastric tube feeding ([Hart, Abraham et al. 2010](#_ENREF_93)). However, it is important to mention that Krahn et al (1993) did not report any participants requiring supplementary tube feeding.

### 6.4.2 Weight gain in Adolescents

### 

An interesting anomaly arising from Pichard et al (1996), Cuerda et al (2007) and Sum (2011) studies is that they all feed at approximately 7000kcal/ week above the resting energy expenditure, however Sum (2011) reported much higher weight gains of 1.1kg/ week as opposed to 0.5kg; 0.6kg/ week. This anomaly may be due to the adolescent cohort in the studies by Pichard et al (1996) and Cuerda et al (2007). Adolescents require higher energy intakes than adults due to the additional requirements for growth, hence a possible reason why lower weight gains were reported in these studies. This highlights the importance of considering the developmental needs of adolescents when devising refeeding programmes. This issue is discussed further in chapter 7.

### 6.4.3 Activity Level

The study by Konrad et al (2007) did not manage to achieve the elusive 1kg/ week weight gain although they commenced refeeding with the highest energy intakes of all studies identified in this review. During the first 3 weeks the mean energy intake was 2185kcal/ day with a resting energy expenditure of 1015kcal/ day, an additional 1000kcal over the resting energy expenditure. By the end of the 6th week energy intake had increased to 3063kcal/ day with a mean resting energy expenditure of 1126kcal/ day. And by week 9 energy intakes were 3216kcal/ day with a resting energy expenditure of 1137kcal/ day, an additional 2000kcal/ day above resting energy expenditure. During this period the weight had increased by only 7kg. This is a clinically acceptable weight gain when dealing with complex and demanding patients with AN, however considering the high energy intakes imposed on patients a higher weight gain may have been expected. However, a possible cause for the limited weight gain seen in Konrad et al (2007) study is that participants were not bed bound and once medically stable were free to leave the ward between meals. Therefore, activity levels would have been higher. Furthermore, it would not be possible to monitor compensatory behaviours such as exercise and purging.

Reasons for lower than expected weight gains on high energy intakes cannot be deduced for the studies by Obarzanek et al (1994) and Van Wymelbeke et al (2004), which commenced similar refeeding rates and reported similar weight gains (table 6.1). All patients’ activities were strictly monitored throughout their stay, which included supervision to the bathroom. It may be that the recommended weight gain of 1-1.5kg/ week is not practical with regards to the amount of energy that is required to be consumed orally. Exceeding 3000kcal/ day is demanding in normal circumstances and would be particularly challenging for patients with AN.

Finally, an observation worth noting from the aforementioned studies is the lack of reference to biochemical and cardiovascular monitoring during feeding. Some studies alluded to cautious refeeding prior to commencing higher energy intakes but specific details were not provided.

## 6.5 Conclusion

This review highlights that although measured resting energy expenditure per kg body weight remains relatively stable before and after refeeding there is a significant change in overall resting energy expenditure measured per day rather than per kg body, suggesting that the body maintains a tight homeostatic rate of metabolism in relation to body weight and body composition throughout the refeeding process of malnourished patients with AN. The increase in measured resting energy expenditure experienced throughout the refeeding process highlights the importance of regularly recalculating estimated energy requirements and gradually increasing energy intakes to meet increased metabolic needs allowing for continuous weight gain.

An additional energy intake of 300-700kcal/ day above measured resting energy expenditure (total energy intake of 1300-1700kcal/ day) during the initial phases of refeeding elicited substantial weight gain. However, excessive energy intakes of >1000kcal/ day above measured resting energy expenditure seemed to adversely raise the resting energy expenditure which in turn may increase fat tissue accretion and did not increase overall rate of weight gain. Individual variability such as adolescent growth rate, individual body composition, pre-morbid weight and activity level, complicate the utility of a standard energy intake which elicits sufficient weight gain whilst refeeding malnourished patients with AN.

The individual variability associated with resting energy expenditure, development of cardiovascular anomalies and the unpredictable manifestation of refeeding hypophosphataemia coupled with a lack of evidence based research in refeeding all contribute to the ambivalence and disparity of refeeding low weight patients with AN. These global disparities in refeeding practices are discussed in the next chapter.

## Table 6.1 – Energy intakes, resting energy expenditure and weight changes throughout refeeding

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | Refeeding 0 – 2 weeks | | | | | | Refeeding 3 – 5 weeks | | | | | Refeeding 6 - 10 weeks | | | | | | Total Refeeding  Time  (weeks) | | Total weight gain kg  (kg gain/ week) | |
| Author | **Number**  **Participants** | **Age**  **(SD)** | **Energy**  **Intake**  **Kcal/day**  **(kcal/kg/day)** | **REE**  **(kcal/d)** | **WT**  **(SD)** | **BMI**  **(SD)** | **FM (%)** | **FM**  **(kg)** | **Energy**  **Intake**  **kcal/day**  **(kcal/kg/day)** | **REE**  **kcal/d**  **(kcal/kg/day)** | **WT** | **BMI** | **FM (%)** | **Energy**  **Intake**  **Kcal/ day**  **(kcal/kg/day)** | **REE**  **kcal/d**  **(kcal/kg/day)** | **WT** | **BMI** | **FM** | **FM**  **(kg** |
| ([Cuerda, Ruiz et al. 2007](#_ENREF_45)) | 11 | 14.7  (1.2) | 1400  (35) | 1106  (32) | 40.4  (3.3) | 15.1  (1.5) | 13.9 | 5.7 | DNA | DNA | DNA | DNA | DNA | 2265  (50) | 1241  (33) | 45.3  (2.0) | 17.1  (0.7) | 16.7 | 7.5 | 8 | | 4.9  (0.6) | |
| ([Krahn, Rock et al. 1993](#_ENREF_139)) | 10 | 19-38 | 1200  (31) | 1166  (30) | 39.1  (4.1) | 15 | 12 | 4.7 | 3300  (78) | 1409  (33) | 42.4 | 16.4 |  | 3600  (79) | 1769  (39) | 45.6  (3.5) | 17.5 | 19 | 8.7 | 6 | | 6.5  (1.1) | |
| ([Konrad, Carels et al. 2007](#_ENREF_135)) | 10 | 31 (12) | 2186  (53) | 1015  (25) | 41  (4.6) |  | 8 | 3.3 | 3063  (68) | 1126  (25) | 45 |  | 12 | 3216  (67) | 1137  (24) | 48  (3.9) |  | 15 | 7.2 | 8 | | 7  (0.9) | |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | |  | |
| ([Obarzanek, Lesem et al. 1994](#_ENREF_199)) | 10 | 23.3(1.9) | 2105  (54) | 897  (23) | 39.2  (0.9) | 15.1 | 11.9 | 4.7 | DNA | DNA | DNA | DNA | DNA | 3216  (68) | 1208  (25) | 47.4  (0.7) | 18 | 19.4 | 9.0 | 9 | | 8.2  (0.9) | |
| ([Pichard, Kyle et al. 1996](#_ENREF_212)) | 9 | 17(0.7) | 1267  (32) | 969  (46SD)  (25) | 38.8  (1.0) | 14  (0.5) | 7.9 | 3.0 | 1944  (49) | 1203  (30) | 39.5 | 14.3 | 8.9 | 2422  (55) | 1360  (31) | 44.1  (1.2) | 15.9  (0.3) | 13.7 | 6.0 | 10 | | 5.3  (0.5) | |
| (Continued) Table 6.1 – Energy intakes, resting energy expenditure and weight changes throughout refeeding | | | | | | | | | | | | | | | | | | | | | | | |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | |  | |
| Author | **Number**  **Participants** | **Age**  **(SD)** | **Energy**  **Intake**  **Kcal/day**  **(kcal/kg/day)** | **REE**  **(kcal/d)** | **WT**  **(SD)** | **BMI**  **(SD)** | **FM (%)** | **FM**  **(kg)** | **Energy**  **Intake**  **kcal/day**  **(kcal/kg/day)** | **REE**  **kcal/d**  **(kcal/kg/day)** | **WT** | **BMI** | **FM (%)** | **Energy**  **Intake**  **Kcal/ day**  **(kcal/kg/day)** | **REE**  **kcal/d**  **(kcal/kg/day)** | **WT** | **BMI** | **FM** | **FM**  **(kg** | **Total Refeeding**  **Time**  **(weeks)** | **Total weight gain kg**  **(kg gain/ week)** | |
| ([Sum 2011](#_ENREF_271)) | 37 | 23.4(4.8) | 1800  (43) | 1087  (128SD)  (26) | 41.5  (5.4) | 15.8  (1.6) |  |  | 2600 | DNA | DNA | DNA |  | 2600  (48) | 1378  (191SD)  (26) | 53.8  (4.7) | 20.4  (1.0) |  |  |  | |  | |
| ([Winter, O'Keefe et al. 2005](#_ENREF_306)) | 8 | NA | (30) | 1058  (134SD) | NA | 12.5  (0.5) |  |  | DNA | DNA | DNA | DNA |  | (30) | 1133  (94SD) | NA | 15.3  (0.6) |  |  | 6.8 | | DNA | |
| ([Van Wymelbeke, Brondel et al. 2004](#_ENREF_286)) | 87 | 23.4(7.9) | 2047  (55) | 1038  (28) | 37  (5.2) | 13.7  (0.9) | 11.3 | 4.0 | 2523  (63) | 1143  (28) | 40.2 | 14.9 | 13.2 | 2595  (57) | 1305  (29) | 45.4  (4.1) | 16.9  (1.1) | 16.9 | 7.7 | 10 | | 8.4  (0.8) | |
| mean | (Total 182) | 22.5 | 1715  (41) | 1042  (27) | 39.02 |  |  | 3.94 | 2482.5  (59) | 1220.3  (29) | 41.775 |  |  | 2844  (56.75) | 1316  (29.5) | 46.1 |  |  | 7.72 |  | | 7.5  (0.88) | |

# Chapter 7: Refeeding Treatment Guidelines

## 7.1 Introduction

The previous chapters have highlighted risks associated with refeeding malnourished patients with AN and outlined factors believed to influence or exacerbate the refeeding syndrome which include: rate of weight loss prior to refeeding ([Crook, Hally et al. 2001](#_ENREF_44); [Boateng, Sriram et al. 2010](#_ENREF_23); [Raj, Keane-Miller et al. 2012](#_ENREF_221)); the extent of malnutrition ([Ornstein, Golden et al. 2003](#_ENREF_203); [Raj, Keane-Miller et al. 2012](#_ENREF_221)); method of refeeding (enteral verse Parenteral) ([Weinsier and Krumdieck 1981](#_ENREF_298); [Diamanti, Basso et al. 2008](#_ENREF_53)); carbohydrate load ([Kohn, Madden et al. 2011](#_ENREF_134); [O'Connor and Goldin 2011](#_ENREF_197)); and the rate at which nutrition is introduced ([Kohn, Golden et al. 1998](#_ENREF_133); [Whitelaw, Gilbertson et al. 2010](#_ENREF_303)).

The rate at which nutrition is reintroduced has received much attention and tends to be the focal point of refeeding treatment guidelines ([RoyalCollegeOfPsychiatrists 2005](#_ENREF_234); [AmericanPsychiatricAssociation 2006](#_ENREF_10); [NationalInstituteOfClinicalExcellence 2006](#_ENREF_189)). In chapter 3, the pathophysiology of refeeding was discussed and was postulated that reducing the total energy intake will reduce the carbohydrate intake which subsequently lessens the insulin surge which drives the electrolyte disturbances, especially phosphate ([Crook, Hally et al. 2001](#_ENREF_44); [O'Connor and Goldin 2011](#_ENREF_197)). Subsequently, the premise of refeeding treatment guidelines is to start energy intakes low and increase energy intakes slowly. However, the origins of refeeding recommendations have been ascertained from clinical experience rather from scientific evidence ([Katzman 2012](#_ENREF_121)).

The complex physiological interaction that occurs whilst refeeding some malnourished patients has resulted in ambiguity and disparity in refeeding treatment guidelines around the world. However, the main aim of all proposed refeeding treatment guidelines is to avert or manage symptoms of the refeeding syndrome whilst encouraging sufficient weight gain. This chapter is a review of published refeeding treatment guidelines for the management of malnourished patients.

## 7.2 Adult/ Adolescent Treatment Guidelines

### 7.2.1 Solomon and Kirby

Guidance on a refeeding treatment programme for low weight individuals was first proposed by Solomon and Kirby (1990), who eloquently discussed the pathophysiology of refeeding the malnourished patient as discussed in chapter 3. They also highlighted the importance of avoiding high glucose intake from both enteral and parenteral routes during the initial phase of refeeding, although what is deemed a high glucose intake is not specified. However, they clearly state that the optimal way of avoiding the refeeding syndrome is uncertain.

Solomon and Kirby (1990) went on to recommend that nutritional repletion should begin with less than full restoration requirements and suggested refeeding at least the previous admission intake which for many patients translated to 20kcal/ kg or 1000kcal/ day (Table 7.1). They go on to recommend the gradual increase of calories and fluid over the next week allowing for the body’s metabolism to move from a catabolic to an anabolic state.

Solomon and Kirby (1990) clearly articulate the risks of refeeding (cardiovascular, biochemical and fluid shifts), and re-affirm that these risk factors are the reason for commencing refeeding at 20kcal/ kg, albeit based on clinical experience and not evidence based research. However, they point out the limitation of their guidelines and highlight the necessity for more research in the area of refeeding treatment. ([Solomon and Kirby 1990](#_ENREF_265))

### 7.2.2 National Institute of Clinical Excellence Guidelines (NICE) – Nutrition Support

These basic guidelines outlined by Solomon and Kirby (1990) were superseded with the publication of the National Institute of Clinical Excellence (NICE), Nutrition Support in Adults (2006). The NICE (2006) guidelines are currently the most widely adopted refeeding treatment guidelines used in the UK ([Wagstaff 2011](#_ENREF_292)).

However, once again the NICE (2006) refeeding recommendations are based on the experience of the guideline development group and are classed as “good practice point, a recommendation for good clinical practice”. At the outset of the document the authors highlight the lack of evidence in this section. All of the refeeding guidelines have been extrapolated from a previous publication by the main author ([Stroud, Duncan et al. 2003](#_ENREF_270)) of the NICE guidelines (2006) which again are based on clinical experience rather than evidence

The NICE guidelines (2006) deem those at high risk of refeeding syndrome as <BMI 16kg/ m2, 10-15% of body weight loss, poor absorptive capacity and minimal nutritional intake for >5days. They suggest that commencing refeeding at 20kcal/ kg/ day as proposed by Solomon and Kirby (1990) maybe too high ([Stroud, Duncan et al. 2003](#_ENREF_270)) and therefore recommend an initial refeeding rate of 5 – 10kcal/ kg (30kg adult = 150-300kcal/ day). However, the rationale for starting lower (5-10kcal/ kg) is not reported either from a clinical or scientific perspective. The guidelines go on to recommend increasing calorie intake so that calculated energy requirements are met within 4-7 days, which would equate to 250-300kcal increments a day.

Of importance, the NICE guideline (2006) is not specific to eating disorders, and actually excludes patients with eating disorders (p38). It was primarily devised to treat malnourished patients on intensive care, gastroenterological and surgical wards that required enteral tube feeding. Despite this, the NICE guidelines are considered to be relevant to patients with severe anorexia nervosa, and have been adopted as the primary treatment guideline for anorexia nervosa ([RoyalCollegeOfPsychiatrists 2010](#_ENREF_235); [Wagstaff 2011](#_ENREF_292)).

I should like to propose three reasons why the NICE refeeding guidelines (2006) may not be suitable for AN patients. First, the proposed refeeding treatment guidelines of 5-10kcal/ kg/ day are specific to severely unwell post-surgical and gastroenterological malnourished patients on intensive care units who are at higher risk of developing hyperglycaemia, hyponatraemia and oedema as a result of increased risk of metabolic problems from enteral tube feeding ([Stroud, Duncan et al. 2003](#_ENREF_270)), therefore warranting cautious refeeding. This is not representative of the vast majority of AN patients requiring refeeding an.

Second, the NICE guidelines (2006) are specific to naso-gastric enteral tube refeeding. Adherence to the NICE guidelines implies that naso-gastric tube feeding is the preferred method of refeeding AN patients. I would argue that a secondary aim of refeeding AN patients after weight restoration is to re-establish some level of a normal regular eating pattern. Of course, if severely malnourished patients are unable to meet initial refeeding requirements orally then naso-gastric tube feeding must be inserted, but this method of refeeding should not be considered the normal. Third, the NICE guidelines (2006) are specific to adults. Adolescents have entirely different energy requirements to adults, as discussed in chapter 6.4.2, this should be accounted for when devising refeeding programmes specific to the growth requirements of adolescents.

The NICE guidelines (2006) further restricted initial refeeding intakes (5-10kcal/ kg/ day) with regards to that suggested by Solomon and Kirby (1990) (20kcal/ kg/ day) in the belief that it may be protective against the refeeding syndrome and other metabolic problems. Such conservative refeeding rates imply that even the smallest amount of nutrition has the potential to trigger the refeeding syndrome. However, it is important to stress that these refeeding rates are based on clinical experience rather than evidence based research.

### 7.2.3 MARSIPAN –Management of Really Sick In-patients with AN

The Royal College of Psychiatrists, MARSIPAN (Management of Really Sick In-patients with AN) guidelines (2010) are the most recently published guidelines in the UK for the treatment of malnourished adults with AN. The authors refer to the lengthy debates that took place whilst trying to establish recommended refeeding guidelines in these malnourished individuals. These debates were the result of a split in clinicians’ treatment methods. The discussion focused on clinicians’ personal experiences which varied from refeeding at 5-20kcal/ kg to starting higher but monitoring closely, replacing electrolytes as required. However, the over-riding concerns of all clinicians was to prevent further weight loss whilst an in-patient and avoid the refeeding syndrome ([RoyalCollegeOfPsychiatrists 2010](#_ENREF_235)). The fact that such a discussion took place further highlights the ever present ambiguity and uncertainty in this area of refeeding. The root cause of this indistinctness around refeeding is an absence of evidence based research in this area.

Similarly to the NICE guidelines (2000) the MARSIPAN refeeding guidelines (2010) are based on clinician’s individual practice. These were ascertained by an electronic mailing questionnaire which sought to identify clinicians experiences and practices of refeeding malnourished individual with AN. The authors draw attention to the wide variation in the application of NICE guideline (2006), some physicians and dietitians applying it strictly and others regarding it not applicable to this patient group. In any case, it is highly probable that many of the refeeding practices identified from the questionnaire would have been influenced by the NICE guidelines (2006), which in turn would have influenced the MARSIPAN (2010) recommended refeeding guidelines. This is evident in that the MARSIPAN guidelines (2010) echo the NICE guidelines (2006) by recommending an initial refeeding rate of 5-10kcal/ kg/ day in a medical setting.

However, the MARSIPAN guidelines (2010) acknowledge that an initial refeeding rate of 5-10kcal/kg/day may be prudent and therefore must increase to 20kcal/kg/day within two days. Furthermore, the MARSIPAN guidelines state that if the patient is in a psychiatric setting then an initial refeeding rate of 20kcal/kg/day appears safe, assuming appropriate electrolyte and cardiovascular monitoring are adhered to.

The fact that no advances have been made since Solomon and Kirby’s refeeding guidelines (1990) highlights the gap and lack of research in the field of refeeding treatment. This has halted the development and progression of effective and safe refeeding guidelines further limiting our knowledge in the treatment of both the under-feeding and refeeding syndrome.

### 7.2.4 Mehler’s Refeeding Guidelines

In North America a practical guideline for refeeding in AN was published by Mehler et al (2010) which coincided with the publication of MARSIPAN (2010). Mehler et al (2010) also adopted elements of the NICE guidelines (2006), specifically the identification criteria for patients at risk of refeeding syndrome (Table 7.1). However, they did not opt to use the same initial refeeding rates as the NICE guidelines (2006). Instead, Mehler et al (2010) based their initial refeeding rates on estimated energy requirements using the Harris- Benedict equation. On a positive note, the origins and to some extent the rationale for their recommended intake of 600-1000kcal/ day (30kg adult = 20-33kcal/ kg), can be accounted for, focusing on meeting individuals resting energy expenditure.

However, there are a number of inaccuracies surrounding their rationale for using estimated energy requirement calculations in the treatment of refeeding AN patients. First, they report that estimated energy requirement calculations such as the Harris Benedict formula, is an accurate method of calculating energy requirements in AN patients. However, two review articles that monitored energy requirements in AN patients reported that predictive estimated energy requirement formulas over estimate energy requirements in this cohort, therefore potentially over-feeding these patients that are hypo-metabolic (Chapter 6.1). If nutritional load is indeed a potential risk factor for the development of refeeding syndrome then this could have deleterious implications. (De Zwaan et al ([de Zwaan, Aslam et al. 2002](#_ENREF_48)) ([Cuerda, Ruiz et al. 2007](#_ENREF_45)))

Second, Mehler et al (2010) states that the refeeding syndrome is preventable by starting low and increasing slow. However, numerous case reports have reported this not to be the case ([Wada, Nagase et al. 1992](#_ENREF_289); [Kohn, Golden et al. 1998](#_ENREF_133); [Kasai, Okajima et al. 2009](#_ENREF_118); [O'Connor and Goldin 2011](#_ENREF_197)). Once again the assumption that the nutritional load is a precursor for the refeeding syndrome is put forward, but with no evidence. ([Mehler, Winkelman et al. 2010](#_ENREF_165))

### 7.2.5 Kraft’s Refeeding Guidelines

Continuing with the theme of estimated energy intakes as a means for calculating refeeding treatment guidelines of malnourished individuals with AN, Kraft et al (2005) recommended initial refeeding rates at 25% of estimate energy requirements. This would equate to 500kcal (15kcal/ kg) in a 30kg patient. The energy intake is increased over 3-5 days to meet estimated energy requirements. ([Kraft, Btaiche et al. 2005](#_ENREF_138)) Interestingly, Kraft et al (2005) review predates the NICE guidelines, although the treatment refeeding guidelines mirrors that of the NICE guidelines commencing initial refeeding rate at 15kcal/ kg. This focus on reduced energy intake in the treatment of refeeding malnourished AN patients further implicates the nutritional load as the offender for the refeeding syndrome.

Kraft et al (2005) went on to recommend that those patients that do develop refeeding syndrome should halt nutritional intervention immediately and commence on IV dextrose (10%) while electrolytes are corrected. However, this intervention contradicts our current understanding and may exacerbate the refeeding syndrome and contradicts the rationale for commencing refeeding at lower rates - to reduce the carbohydrate load and subsequent insulin surge. This seems counterproductive to deliver intravenous glucose in patients that do develop the refeeding syndrome. If the refeeding syndrome is indeed exacerbated by glucose then an intervention of IV dextrose could have a deleterious impact.

### 7.2.6 Royal College of Psychiatrists Guidelines – nutritional management of AN

A distinction between the method of refeeding and subsequent refeeding treatment is proposed by the Royal College of Psychiatrists (RCPsych 2005) – Guidelines for the nutritional management of AN. The RCPsych (2005) state that the nutritional refeeding route should dictate which refeeding treatment guideline is applied. Those individuals that are able to consume oral food are suggested to start an initial refeeding intake of 1400kcal/ day. Whereas, individuals that refuse oral intake and require nasogastric continuous tube feeding are suggested to commence an initial refeeding rate of 5-10kcal/ kg/ day) referencing the study by Stroud et al (2003), which was intended for post-surgical intensive care patients ([Stroud, Duncan et al. 2003](#_ENREF_270)).

The RCPsych (2005) are the only guidelines that have drawn a distinction between a different refeeding guideline based on nutritional intervention. However, there is no rationale as to why those patients with AN on continuous enteral tube refeeding should commence a lower refeeding rate than those refeeding orally. However, studies have reported that parenteral nutrition, the direct supply of nutrition intravenously can increase symptoms of the refeeding syndrome including death ([Weinsier and Krumdieck 1981](#_ENREF_298); [Diamanti, Basso et al. 2008](#_ENREF_53)) and therefore malnourished AN patients on parenteral nutrition warrant additional monitoring. However, the rationale for an increased risk between enteral tube verse oral feeding in AN patients has not be substantiated.

The NICE guidelines (2006) and Stroud et al (2003) make specific reference to the risk of refeeding malnourished patient using enteral tube feeding to surgical intensive care patients, with particular emphasis on the development of hyponatremia and hyperglycaemia. The RCPsych (2005) have adopted this perceived increased risk of refeeding complications to enteral feed patients with AN, who are not representative of post-surgical patients on intensive care units.

The RCPsych (2005) suggest commencing different refeeding rates dependent on feeding route. This anomaly can be further highlighted by illustrating the actual consumed energy intake in the oral verses enteral tube refeeding method in a 30kg patient. An individual with AN who is commenced on continuous tube feeding as advised by the RCPsych (2005) would receive 15ml/ hour (15kcal) over 20 hours (15kcal x 20 = 300kcal/ day) = 10kcal/ kg/ day. Compare this to an individual managing an oral intake who would commence 45kcal/ kg/ day – 1400kcal/ day. This equates to 1100kcal/ day difference between the two refeeding interventions. Physiologically gastric emptying would be more rapid following a liquid feed oppose to a solid meal, which could impact the rate of insulin release and subsequent electrolyte utilisation. The notion that enteral nutrition poses a greater risk for the refeeding syndrome needs further attention along with associated risk of bolus versus continuous feeding.

The present study will address this unknown regarding perceived risk of refeeding complications and route of refeeding by stratifying participants fed by enteral tube and oral refeeding during the randomisation process which will allow for appropriate analysis to further investigate this ambiguity regarding refeeding method and risk of refeeding syndrome.

## 7.3 Young People Refeeding Treatment Guidelines

The aforementioned treatment guidelines are specifically catered to the adult population and in some cases adolescents. Admission of children and adolescents with AN to paediatric wards is a much more common event than admission of adults to medical wards. This is likely to be because of epidemiology, developmental differences in risk (including the fact that children and adolescents are less experienced at calculating risk), service factors (in that paediatric admission is often a stop gap between out-patient and in-patient service) and because young people are usually brought for treatment regardless of whether they like it or not.

Young people present with a set of unique nutritional obstacles in that they require energy not only for normal homeostatic metabolism but also for growth and development and often have limited energy reserves. These additional constraints may have implications on the most appropriate refeeding treatment programme whilst refeeding malnourished adolescents with AN. Refeeding treatment guidelines will need to encompass sufficient energy to sustain normal metabolism, growth and development, and catch up weight gain; which is suggestive that refeeding treatment guidelines in adolescents may differ from those of adults. The following is a review of published refeeding treatment guidelines specific for the management of malnourished children and adolescents.

### 7.3.1 The World Health Organisations (WHO) – Management of Severe Malnutrition

The World Health Organisations (WHO) – Management of Severe Malnutrition (2006) largely focuses on malnutrition seen in the developing world (famine and disaster situations) providing practical guidance for physicians. Initial focus is on providing hydration and treatment of infection, the WHO (2006) reports that nearly all severely malnourished children present with an underlying infection. This is contrary to the presentation of children with AN, who on the whole do not have any underlying infection ([Misra, Aggarwal et al. 2004](#_ENREF_173)).

The WHO guidelines (2006) acknowledge that severely malnourished children present with biochemical abnormalities and often malabsorb protein, fat and sodium, as a result of chronic diarrhoea. In light of fat and protein malabsorption they recommend increasing carbohydrate intake which seems to be better tolerated, receiving 70% of total energy intake from carbohydrate, (normal recommendation 45-60%), which is achieved by consuming F-75 formula (75kcal/ 100ml). Once children regain an appetite they are transferred from the F-75 to the F-100 formula (100kcal/ 100ml and 55% total energy intake from carbohydrates), usually within 7 days. It is only now that the WHO guidelines (2006) allude to complications of the refeeding syndrome, stating that the transfer from F-75 to F-100 should be gradual to avoid the risk of heart failure (Table 7.2).

Furthermore, although the WHO guidelines (2006) appreciate that a degree of malabsorption, biochemical disturbances and heart failure are risks of refeeding malnourished children they do not restrict the total energy intake and recommend normal estimated energy requirements:

7 – 10yrs 75kcal/ kg

11 – 14yrs 60kcal/ kg

15 -18yrs 50kcal/ kg

Adults 35-40kcal/ kg

It is worth mentioning that the WHO (2006) report that the highest mortality rate occurs in the first two days of treatment. They state that the main cause of death during the early phase of treatment is attributed to diarrhoea and acute respiratory infection; which are not indicative of complications associated with refeeding syndrome. Therefore, these guidelines highlight the possibility of commencing normal energy requirements during the initial phase of refeeding, eliciting rapid weight gain.

Although the WHO guidelines (2006) are not intended for AN patients and the physiological presentations differ to that of AN patients (e.g. sepsis) the refeeding treatment guidelines are profoundly different to the previously mentioned adult guidelines. Interestingly, although refeeding complications are acknowledged during the refeeding process (>7 days) the WHO guidelines (2006) places no association between refeeding complications and initial refeeding intake or carbohydrate load. Hence, the WHO (2006) recommends full energy requirements and provides additional carbohydrates to counteract malabsorption from other macronutrients.

### 7.3.2 Cape Town Metropole Paediatric Group Guidelines

The Cape Town Metropole Paediatric Group (2009) developed refeeding guidelines for malnourished children. Unlike the WHO guidelines (2006) the Cape Town guidelines (2009) detail the pathophysiology involved in refeeding the malnourished patient as outlined in chapter 3. In response to this physiological process of refeeding they have suggested commencing initial refeeding guidelines at 75% of estimated energy requirements which equates to 45 -55kcal/ kg/ day (Table 7.2). Once again, why 75% was deemed appropriate is not discussed except stating, cautious use of calories is advised to avoid complications associated with the refeeding syndrome ([Marino 2009 March](#_ENREF_156)).

### 7.3.3 The Junior MARSIPAN (Management Really Sick In-patient with Anorexia Nervosa)

The Royal College of Psychiatrists, Junior MARSIPAN (Management Really Sick In-patient with Anorexia Nervosa) guidelines (2011) takes a somewhat pragmatic view to refeeding, suggesting that refeeding should not be less than previously consumed before admission or initially aim for 1000kcal/ day (30kg patient = 33kcal/ kg). However, a potential issue arising from reported nutritional intake prior to admission places much emphasis on the reliability and honesty of the historian. For example if a diet history is obtained from the patient they may over or under estimate what they have eaten. Unfortunately, the deceptive nature of AN means that the parents/ cares and sufferers may have a distorted view of the true nutritional intake.

The Junior MARSIPAN guidelines (2011) also add a caveat that very high risk patients (baseline electrolyte and cardiovascular abnormalities, hypothermic and <75%BMI) should commence refeeding treatment at 5-10kcal/ kg/ day (Table 7.2). The premise for these conservative recommendations in paediatric patients is once again based on the pathophysiology of refeeding. However, the guidelines are explicit regarding daily 200-300kcal increments until estimated requirements are met, ensuring that any electrolyte anomalies are corrected rather than halting or reducing nutritional intake. Another caveat to Junior MARSIPAN (2011) is limiting total energy intake from carbohydrate to 50%. The rationale for this is attributed to our current understanding of refeeding the malnourished patient as discussed in chapter 3.

## 7.4 Carbohydrate and Refeeding Guidelines

Specifically limiting carbohydrate intake in the initial refeeding phase in a bid to avert or reduce the symptoms of refeeding syndrome is briefly addressed in MARSIPAN (2010), Junior MARSIPAN (2011), Stanga et al (2008) and Reiter and Graves (2010) guidelines. The aforementioned guidelines highlight the potential benefit of not exceeding the recommended carbohydrate intake of 50% total energy intake. Additionally, Reiter and Graves (2010) recommend that patients’ access to simple sugars should be limited. This concept of limiting carbohydrate intake further acknowledges our current physiological understanding of refeeding the malnourished patient, with respect to altered energy metabolism and insulin sensitivity both of which are thought to exacerbate the refeeding syndrome as explained in chapter 3.

Therefore, assuming that nutrition and more specifically carbohydrates may contribute to the development of the refeeding syndrome based on our physiological understanding, and ensuring excessive amounts of carbohydrates are not consumed may reduce the symptoms of the refeeding syndrome. This novel concept that carbohydrate rather than total energy intake may exacerbate symptoms of the refeeding syndrome will be addressed in the present study.

Furthermore, as it is currently not possible to predict who will develop the refeeding syndrome all at risk patients are imposed with a reduced energy intake refeeding programme. Therefore, it is essential to identify if indeed energy intake and specifically carbohydrates do affect the progression of the refeeding syndrome and more importantly identify those patients that are at particular risk of developing the refeeding syndrome.

## 7.5 Europe verse North American Refeeding Guidelines

A disparity that can be extrapolated from the published treatment programmes for refeeding malnourished patients with AN is the stark difference in initial refeeding rates between North America and Europe. As already mentioned Mehler et al (2010) adopted aspects of the NICE guidelines (2006) but chose not to comply with the NICE guidelines (2006) refeeding rates of 5-10kcal/ kg/ day and adopted a higher refeeding rate of 20-30kcal/ kg/ day, based on resting energy expenditure calculations.

The American Psychiatric Association eating disorders clinical practice guidelines (2012) recommends with moderate clinical confidence that patients at high risk of refeeding syndrome should commence an energy intake of 30-40kcal/ kg/ day. Energy intake should then be gradually increased to 70-100kcal/ kg, which would equate to 2100 -3000kcal/ day for a 30kg patient. Similarly, Reiter and Graves guidelines (2010) also recommend commencing initial refeeding rates of 30-40kcal/ kg/ day. All the aforementioned guidelines state that over feeding a malnourished patient can result in the refeeding syndrome and therefore limiting energy intake is general practice. However, there is no mention or rationale as to the origin of these figures of 30-40kcal/ kg, except that it is general practice.

Conversely, the European guidelines recommend starting refeeding at 5-10kcal/ kg/ day, significantly lower than the North American guidelines. This is further highlighted by Stanga et al (2008) which are not specific to AN but do encompass patients with AN, along with other high risk groups: elderly; cancer; and chronic alcoholism. Again, the focus is limiting initial refeeding rates to 10kcal/ kg/ day and maintaining total energy intake from carbohydrate at 50-60%, which is the normal recommended intake as a percentage of total energy intake (SACN, 2011). Stanga et al (2008) state that the rationale for such low energy intake it to control the glucose absorption in an attempt to avoid hyperglycaemia, osmotic diuresis and non ketotic coma, all symptoms of the refeeding syndrome. ([Stanga, Brunner et al. 2008](#_ENREF_268))

It is not possible to interpret from the literature as to why Europe and North America have adopted such varied refeeding guidelines. Although the scientific rationale remains constant throughout the guidelines, the North American guidelines are specific to eating disorder patients whereas the European guidelines are not. However, what is not clear is the rationale for adopting specific refeeding rates of 5-10kcal/ kg/ day in Europe and 30-40kcal/ kg/ day in North America. Once again the recommended refeeding guidelines seem to be based on clinical experience rather from scientific evidence ([Katzman 2012](#_ENREF_121)).

## 7.6 Summary of Refeeding Treatment Guidelines

The vast majority of guidelines discussed have recommended a reduction in initial refeeding rates, the exception being the WHO guidelines which recommend normal estimated energy requirements. On the whole the rationale attributed to these recommendations is based on the risks associated with the pathophysiology of refeeding the malnourished patient, outlined in chapter 3.

However, what is deemed an appropriate reduction in initial refeeding rates remains unknown and has led to variable interpretations, which are based on clinical experiences rather than interventional studies. The ultimate goal of a successful refeeding guideline is one that elicits sufficient weight gain without compromising physiological functioning. The proposed research will directly explore the significance of high and low refeeding treatment programmes in malnourished young people with AN.

## Table 7.1 Adult Refeeding Treatment Guidelines

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | RISK FACTORS | | | | TREATMENT | | | | | |
| Author/ Prof Body | **BMI** | **Weight loss**  **3-6months** | **No/ limited nutritional intake** | **Cardiac markers** | **Refeeding rate** | **HypoPO supp** | **HypoMg supp** | **hypoK** | **Vitamin Supp** | **Other** |
| American Psychiatric Association 2006 | <70% |  |  |  | 30-40kcal/ kg/d  1000-1600kcal/day | Supplement | Supplement | Supplement  Rehydration | NS |
| Kraft 2005 | NS  Marasmus | NS | NS |  | 25% of EAR | IV 0.16-0.64mmol/kg | IV 1-1.5mEq | IV 20-80mEq | Thiamine 100mg |
|  |  |  |  |  |  |  |  |  |  |  |
| MARSIPAN 2010 | EDU  <10 |  | 2-3weeks | ECG anomalies | 20kcal/ kg/d  5-10kcal/ kg |  |  |  | Thiamine200-300mg/d and multivitamin | Restrict Carbohydrate.  Additional PO4 - milk |
| Mehler  2010 | <14 | 10-15% | 5-10days | Arrhythmias | 600 -1000kcal/ day  20-25kcal/kg/d |  |  |  | Thiamine200-300mg/d and multivitamin |  |
| NICE 2006 | <14 | 10-15% | 15days | Arrhythmias | 5-10kcal/kg/day | 0.3-0.6mmol/kg | 0.4mmol/kg | 2-4mmol/kg | Thiamine200-300mg/d and multivitamin |  |
| Reiter and Graves – ASPEN | <14 |  |  |  | 30-40kcal/ kg/d |  |  |  |  |  |
| Royal College of Psychiatrists 2005 | <14 | NS |  |  | Oral 1400kcal  Enteral 5-10kcal/kg/day |  |  |  | Vitamin B and C |  |
| Soloman and Kirby 1990 |  |  |  |  | 20kcal/kg/day  1000kcal/ day |  |  |  |  |
| Stanga  2008 | Malnutrition |  |  |  | 10kcal/ kg/ day | 0.5-0.8mmol/kg | 0.3-0.4 mmol/kg | 1-3mmol/kg | Thiamine | Sodium and carbohydrate restriction |

EDU –Eating Disorder Unit

NS – Not Specified

EAR – Estimated Average Requirements

## 

## Table 7.2 Children Refeeding Treatment Guidelines

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | RISK FACTORS | | | | TREATMENT | | | | |
| Author/ Prof Body | **BMI** | **Rate of wt loss** | **No/ limited nutritional intake** | **Cardiac markers** | **Refeeding rate** | **HypoPO supp** | **HypoMg supp** | **hypoK** | **Vitamin Supp** |
| Cape Town Metropole Paediatric Group  (2009) | <70% |  | 7-10days |  | 45 -55kcal/ kg/d |  |  |  | Thiamine  1-2mg/ kg Intramuscular |
| Junior MARSIPAN (2011) | <70% | 15% body wt over 3months | >3days | Bradycardia  Tachycardia | 20kcal/ kg  1000kcal/ day |  |  |  | Thiamine 200mg oral |
| World Health Organisation (2006) | <70%  -3 SD |  |  |  | 60-75kcal/ kg/d |  |  |  | Multivitamin |

**Chapter 8 – General Methods: hypotheses and study aim and design**

**8.1 Aims of Study**

There is a lack of consensus on what constitutes best practice with regards to an effective refeeding programme whilst treating medically unstable low weight individuals with AN. The manifestation of the refeeding syndrome is unpredictable and does not affect all malnourished low weight individuals with AN. There are many perceived risk factors which have been attributed to the exacerbation of symptoms especially refeeding hypophosphatemia. It has been postulated that by reducing the total energy intake during refeeding will in turn reduce the carbohydrate intake which will subsequently lessen phosphate losses in gastric juices and reduce the phosphate utilisation in glucose metabolism.

This study aims to ascertain whether total energy intake has a direct impact on the physiological recovery of low weight hospitalised adolescents with AN. The outcome measures will monitor cardiovascular, biochemical and anthropometric factors. Therefore, based on this information I propose two main hypotheses that were tested in this study.

**8.2 Hypotheses**

**8.2.1 Primary Hypotheses**

* *A Higher-calorie refeeding programme will improve QTc interval and heart rate in low weight adolescents with AN.*
* *A higher-calorie refeeding programme will elicit a greater weight gain in low weight adolescents with AN.*

**8.2.2 Secondary Hypothesis**

* *A higher-calorie refeeding programme will result in a greater reduction in serum electrolytes in low weight adolescents with AN.*

**8.3 Study Design**

This was a randomised controlled trial of hospitalised adolescents between 10-16 years old with AN who were randomised to receive 500kcal/ day (control group) or 1200kcal/ day (intervention group) over the first 10 days of refeeding.

**8.4 Ethical Approval**

Ethical approval for this study was granted by The National Research Ethics Service – Central London Division on the 28th February 2011.

**8.5 Informed Consent**

On admission to the paediatric ward written informed consent was obtained from parents. Written assent was not gained in this cohort due to the mental and physical state of participants and their potential unwillingness to be refed may have resulted in a high number of participants not partaking in the study. Furthermore, guidance on this matter was sought from service users and carers meeting, families and sufferers (young ambassadors) were supplied by BEAT (Beating Eating Disorders Charity).

**8.6 Data Protection**

Each participant was provided with a study number on recruitment at all of the research centres. No personal details of the patient were received by the principal investigator. Information collected as part of the study, e.g. weight, nutritional intake, bloods and ECG were all coded with the participant’s unique patient study identifier number. Collected data was delivered by recorded delivery to the principle investigator where information was stored in a locked cabinet until entered into a password secured database.

**8.7 Sample size**

**8.7.1 Primary Outcome Measure**

The main outcome of this study is to determine if energy intake impacts on the cardiovascular recovery rate of malnourished adolescents with AN. The sample size was developed from the studies in table 8.1, which measured change in QTc interval in low weight and weight restored patients with AN, providing guidance on expected standard deviation in QTc interval before and after weight gain.

**Table 8.1** - Studies which contributed to the sample size by estimation of standard deviation of mean difference QTc interval before and after refeeding

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Author | Number | QTc low weight  (ms) | QTc post weight gain (ms) | Mean difference  (ms) |
| Cooke 1994 | 41 | 380 | 360 | 20 |
| DiVasta 2010 | 38 | 450 (50 SD) | 400 (30 SD) | 50 |
| Mont 2003 | 31 | 411 (41 SD) | 388 (36 SD) | 23 |
| Nahshoni 2007 | 30 | 471 (50 SD) | 424 (31 SD) | 47 |
| Olivares 2005 | 40 | 433 (34 SD) | 408 (25 SD) | 25 |
| Roche 2005 | 10 | 374 (29 SD) | 345 (55 SD) | 29 |
| Ulgar 2006 | 11 | 414 (40 SD) | 378 (18 SD) | 36 |
| Mean |  | 419 (35) | 386 (27) | 33 (12) |

***8.7.2 Power Statement***

In order to have an 80% chance of detecting a difference of 15ms in mean QT interval within 4 days of refeeding between the two refeeding programmes, at the 5% level of significance, it was calculated that 16 participants would be required in each group, assuming that the standard deviation of the mean difference QT interval before and after refeeding in each group is 12ms.

A mean difference in QTc interval before and after weight restoration is 33ms (12SD) observed over a number of months (Table 8.1). Therefore, a mean difference between groups after 4 days of treatment of 15ms was deemed a clinically important difference ([Sakpal 2010](#_ENREF_241)).

Type 1 Error Significance level = 0.05

Type II Error = 80%

Standard deviation of mean differences = 12ms

Clinical importance = mean difference in QTc interval of 15ms between refeeding groups within the first 4 days of refeeding.

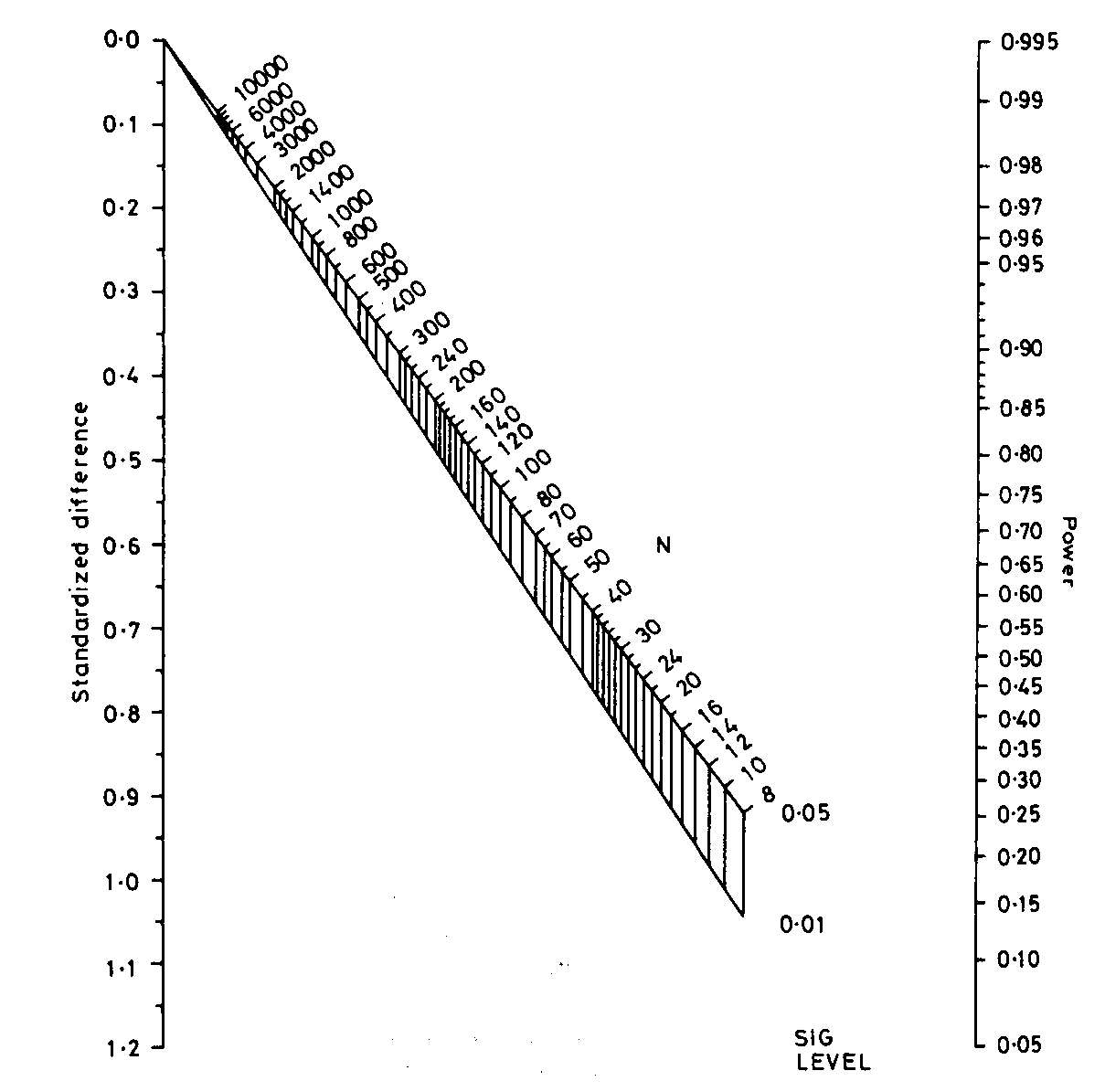
Standardised difference = 15ms/ 12SD = 1.2

[2 X 7.9(80% power)/ (1.2 x 1.2)] + 1 = 16 per group

Altman’s Normogram – sample size predictor for this study

Standardised difference = 15ms/ 12SD = 1.2

Sample size = 26 (13 in each arm) – Altman’s Normogram



**8.8 Recruitment**

Centres which have been recruited and trained to carry out the refeeding protocol include:

1. London, Great Ormond Street Hospital Foundation Trust,
2. Manchester Children’s Hospital
3. Middlesborough, James Cook NHS University Hospital
4. Luton and Dunstable NHS Foundation Trust
5. Royal Devon and Exeter NHS Foundation Trust
6. Poole NHS Foundation Trust

A total of 36 malnourished adolescents with AN Restrictive Type were recruited to the present study.

**8.9 Inclusion and Exclusion Criteria**

The following inclusion and exclusion criteria were devised in order to keep the confounding factors of this study to a minimum.

**8.9.1 Inclusion Criteria**

Adolescents (male or female) who are admitted to one of the recruited specialist centres and have been diagnosed with an eating disorder (DSM IV, 2005), aged 10 -16yrs old and have a %BMI < 78% and had an acute weight loss >0.2kg in the past week and required nutritional rehabilitation via enteral or oral route.

**8.9.2 Exclusion Criteria**

Those patients that have any medical condition that may influence biochemical or cardiovascular parameters above expected in AN i.e. diabetes Type 1; or malabsorption disorders that may alter the absorption of energy intake e.g. coeliac disease or inflammatory bowel disease. Patients were also excluded if they were on or started on any psychotropic medication (SSRI’s) or any atypical antipsychotic medication (Chapters 1.9.2 and 5.5.4).

## 8.10 Materials and Methods

### 8.10.1 Randomisation

Stratified randomisation was generated using the SIMIM minimisation computer program ([Wade, Pan et al. 2006](#_ENREF_290)) which allocated newly admitted participants from any of the recruiting centers to either the control group of 500kcal/ day or the treatment group 1200kcal/ day. Stratification will occur for %BMI dividing participants into <69.9%BMI and between 70 – 78%BMI; and finally stratification for those participants that commenced on enteral or oral feeding.

**8.10.2 Materials for Dietary Intervention**

* Food Portion list for macronutrient intake (Appendix 8)
* Meal plan templates 500kcal – 2200kcal/ day (Appendix 5-7)

**8.10.3 Methodology for Dietary Intervention**

Structured meal plans have been devised to ensure that all participants consume similar macronutrients based on the recommended intake (SACN 2011) (Table 8.1). To ensure participants received similar macronutrient intakes, portion sizes of common foods were calculated into 200kcal portions which could then be transferred in to a template forming a meal plan between 500 – 1800kcal/day (Appendix 5-7).

Due to the potential effect fluid intake could have on weight, weight was closely monitored and controlled throughout the 10 days of refeeding by ensuring that 1500ml/ day of fluid was consumed for all patients in both groups.

Calorie intake will be increased by 200kcal/day until estimated calorie requirements are met. Estimated calorie requirements will be calculated to 80% of average estimated requirements based on the Scientific Advisory Committee on Nutrition recommendations ([SACN 2011](#_ENREF_237)) (Table 8.2).

## Table 8.2 – Expected Macronutrient intake within the two groups

|  |  |  |
| --- | --- | --- |
| Nutrient | 500kcal/day - Control | 1200kcal/day - Treatment |
| Carbohydrate % | 50-60 | 50-60 |
| Carbohydrate (grams/ day) | 60 - 75 | 150 - 180 |
| Fat % | 30-35 | 30-35 |
| Fat (grams/day) | 15 - 20 | 40 - 50 |
| Protein % | 10-15 | 10-15 |
| Protein (grams/ day) | 12 -18 | 30 - 45 |

## Table 8.3 Estimated Energy Requirements (EAR) (SACN 2011)

|  |  |  |  |
| --- | --- | --- | --- |
| Age | Boys  Energy (kcal/ day) | Girls  Energy (kcal/ day) | 80% EAR Meal Plan Target |
| 10 | 2032 | 1936 | 1600 |
| 12 | 2247 | 2103 | 1700 |
| 14 | 2629 | 2342 | 1800 |
| 16 | 2964 | 2414 | 1900 |

## 8.11 Materials for anthropometric measures

* Digital scale
* Wall mounted stadiometer
* % median body mass indicator excel programme

**8.11.1 Methodology for anthropometric measures**

Anthropometric measurements of participants’ weight and height were made. To obtain the participants weight a digital scale was used and recorded on day 1 (admission), 4, 8 and 10. Participants were weighted in the morning before breakfast in their underwear. Participants were requested to step onto the scale and stand with their hands by their sides and remained still until requested to step of the scale. Their weight was recorded to the nearest 0.1kg.

To measure the participant’s height a wall mounted stadiometer was used and they were asked to stand with their back to the wall, with their feet together flat on the floor and their heels touching the metal heel plate on the wall. Their buttocks, backs, shoulders and head were against the backboard of the stadiometer, with their head in the horizontal Frankfurt plane position – ear holes are level with eye sockets. The head plate was gently lowered and placed onto their head while participants breathed normally. Measurements were recorded to the nearest 0.01cm.

Imputing the height, weight and date of birth into the weight for height excel programme then calculated the body mass index, % median body mass index and percentiles for height and weight ([Cole, Freeman et al. 1995](#_ENREF_41)) .

## 8.12 Materials for Cardiovascular parameters

* 12 lead Electrocardiogram (ECG) – 0.05Hz-100Hz Auto mode bandwidths and 0.5Hz-40Hz Front Panel Auto mode
* Heart Rate digital monitor
* Skin Preparation equipment - alcohol wipes and abrasive tape
* 1mm/5mm graph paper

### 8.12.1 Methodology for cardiovascular parameters

Participants ECGs were recorded on day 1 (admission) and day 4 of trial. The reason for repeating an ECG on day 4 was based on findings from a study by Swenne (2000) and our pilot data. Both found that after 7 days of refeeding the heart rate had normalised in participants who were previously bradycardic. Therefore, to capture these cardiovascular changes before normalisation occurred it was decided to re-measure at day 4. Ideally, an ECG would have been carried out daily, but limitations on costs and staff resources hindered this level of monitoring.

The participant’s preparation area was clean and tidy with minimal distraction. Participants were requested to remove any clothing around the thoracic area and had free access to arms and legs. Electrode placement areas were cleaned with alcohol wipes.

### 8.12.2 Electrode Placement:

Limb Leads – to ensure consistency between recordings electrodes were attached to both arms and legs, slightly proximal to the wrist and ankle. (Right Arm RA, Left Arm LA, Left Leg LL, Right Leg RL)

Precordial (chest) leads – Diagram 8.1 outlines chest electrode positions.

V1 – Forth intercostal space at the right sternal edge

V2- Forth intercostal space at the left sternal edge

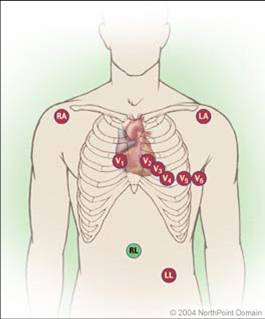
V3 – Midway between V2 and V4

V4 – Firth intercostal space in the mid-clavicular line

V5- Left anterior axillary line at same horizontal level as V4

V6 – Left mid-axillary line at same horizontal level as V4 and V5

**Diagram 8.1 – 12 lead positioning for ECG**



### 

### 8.12.2 Recording:

It was ensured the subject were as relaxed as possible by allowing them to cover themselves with a gown once electrodes are positioned and secure. The 12-lead ECG and rhythm strip was recorded at 25mm/s with a gain setting of 10mm/mV.

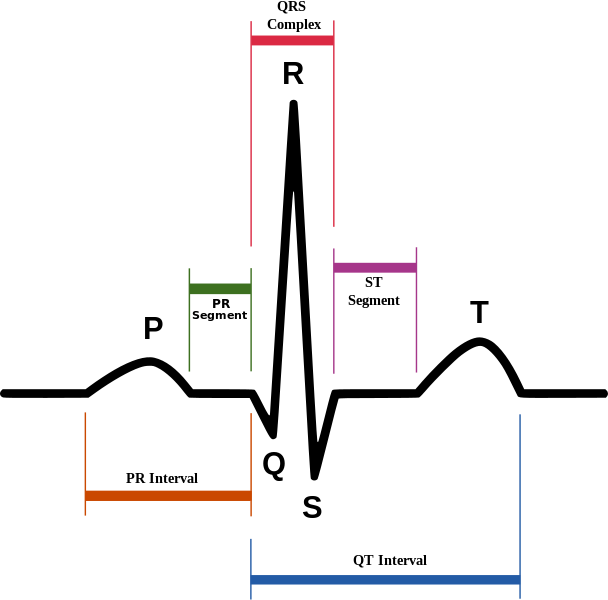
### 8.12.3 QT interval measurement

On a 12-lead ECG, the QT interval is measured from the beginning of the QRS complex to the end of the T wave (Diagram 8.2). Blinded to randomisation manual measurements of the QT interval were taken from leads II or V5 and averaged over three to five successive beats, with the maximum measured interval taken as the final result. Measurements made from these leads have the greatest positive and negative predictive value in detecting abnormal QT intervals. Dr Lee Hudson, consultant paediatrician measured and recorded ECG calculations.

### 8.12.4 Corrected QT interval (QTc)

Both Bazett’s and Framingham QT interval correction formulas were used (Table 8.3). This is due to the inadequacies of Bazett’s formula when calculating QTc interval in bradycardic and tachycardic patients – a detailed discussion of this disparity can be found in chapter 5.1.1 ([Bazett 1920](#_ENREF_14); [Sagie, Larson et al. 1992](#_ENREF_239)).

**Diagram 8.2 – PQRST cardiac wave**

[](http://upload.wikimedia.org/wikipedia/commons/9/9e/SinusRhythmLabels.svg)

## 

## Table 8.4 – Formulas for correcting QT interval

|  |  |  |
| --- | --- | --- |
| **Correction** | **Formula** | **Comment** |
| Bazett | QTc=QT/√RR | Widely used for its simplicity; overcorrects at heart rates > 100 bpm and undercorrects at heart rates < 60 bpm |
| Framingham | QTc=QT+0.154(1-RR) | Relatively consistent correction from bradycardic to tachycardic heart rates |

***8.12.5 QT dispersion***

The measurement of QT dispersion was calculated by measuring the QT interval in all 6 chest leads and then calculating the maximum QT interval minus minimum QT interval ([Malik and Batchvarov 2000](#_ENREF_154)). A corrected QT dispersion was not calculated as it has been repeatedly reported that there is no justification as there is no difference between corrected and uncorrected intervals ([Malik and Batchvarov 2000](#_ENREF_154))

**8.12.6 Heart Rate**

Heart rate was measured manually 4hrly during the first week of admission and then reduced to daily during the second week if the participant had medically stabilised. Medical stabilisation was based on temperature, blood pressure, heart rate and biochemistry (RCPsych 2012, Junior MARSIPAN). Heart/pulse rates was monitored as outlined by the Royal College of Nursing, Standards for measuring, assessing and monitoring vital signs in infants, children and young people (2011). Heart rate was measured using the radial artery and counted for one minute. <http://www.rcn.org.uk/__data/assets/pdf_file/0004/114484/003196.pdf>

## 8.13 Materials for biochemical measures

VITROS chemistry Products – glucose, potassium, magnesium, phosphate, calcium and sodium

VITROS Chemistry Products Calibrator Kit 1

• Quality control materials, such as VITROS Chemistry Products Performance Verifier I and II for serum and plasma

• Isotonic saline or reagent-grade water

• 6N HCl

• VITROS Chemistry Products FS Diluent Pack 2 (BSA/Saline) or VITROS Chemistry Products FS Diluent Pack 3 (Specialty

Diluent/Water) (for on-analyzer dilution)

Figure 9.3 – VITROS multi-layer Slide analysis

1. Upper slide mount

2. Spreading layer (TiO2)

3. Reagent layer

4. Support Layer

5. Lower slide mount

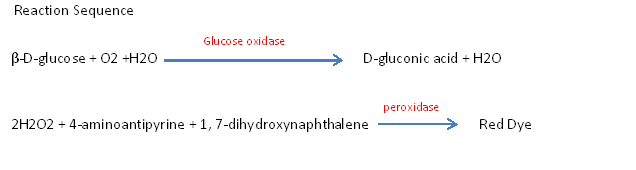
**8.13.1 Methodology for biochemical measures**

Biochemical analyses were performed at each multicentre using the same techniques described below. On admission (baseline) a venopuncture will be taken to monitor biochemistry (phosphate, magnesium, potassium, sodium and calcium,) plus glucose and insulin. Further biochemistry (phosphate, magnesium, potassium, sodium and calcium,) plus glucose and insulin will be collected pre-breakfast on day 2, 4, 6, 10.

There were two main reasons for alternating the days of biochemical (Day 1, 2, 4, 6 and 10) and weight (Day 1, 4, 8 and 10) measurements (Appendix 9 – Research Protocol). At the preliminary stages of this study we sought the input from service users (BEAT), who reported that it might be overwhelming to be weighed and have bloods taken on the same day and if these could be separated then it would be less stressful. Secondly, participants were admitted to busy paediatric wards and therefore by spreading out the clinical workload would be beneficial to ward staff. However, on day 4 participants were required to have an ECG, bloods and be weighed.

**8.13.2 Glucose**

Plasma glucose was determined using an enzymatic colorimetric test. Blood is deposited on the slide and evenly distributed by the spreading layer to the under layers. The oxidation of sample glucose is catalysed by glucose oxidase to form hydrogen peroxidase and gluconate. This reaction is followed by an oxidative coupling catalysed by peroxidase in the presence of dye precursors to produce a dye. The intensity of the dye is measured by reflected light ([Curme, Columbus et al. 1978](#_ENREF_47)).



Reaction Sequence

Glucose oxidase

β-D-glucose + O2 +H2O D-gluconic acid + H2O

peroxidase

2H2O2 + 4-aminoantipyrine + 1, 7-dihydroxynaphthalene Red Dye

**8.13.3 Phosphate**

The analysis of plasma phosphate is based on the reaction of inorganic phosphate with ammonium molybdate to form phosphomolybdate complex at acid pH, as described by Fiske and Subbarow ([Fiske and Subbarow 1929](#_ENREF_69)). P-Methylaminophenol sulphate, an organic reductant reduces the complex to form a stable heteropolymolydbenum blue chromophore. Blood is deposited on the slide and evenly distributed by the spreading layer to the under layers and the concentration of phosphorous is determined by reflectance spectrophotometry.

**8.13.4 Potassium**

The VITROS K+ Slide is a multilayered, analytical element coated on a polyester support that uses direct potentiometry for measurement of ionic potassium. The slide consists of two ion-selective electrodes, each containing valinomycin (an ionophore for potassium), a reference layer,r and a silver chloride layer coated on a polyester support. A drop of subjects plasma and a drop of VITROS Reference Fluid on separate halves of the slide results in migration of both fluids toward the center of the paper bridge. A stable liquid junction is formed connecting the reference electrode to the sample indicator electrode.

Each electrode produces an electrical potential in response to the activity of potassium applied to it. The potential difference poised between the two electrodes is proportional to the potassium concentration in the sample.

**8.13.5 Magnesium**

The VITROS Mg Slide is a multilayered, analytical element coated on a polyester support.

A drop of patient sample is deposited on the slide and is evenly distributed by the spreading layer to the underlying layers. Magnesium (both free and protein-bound) from the sample then reacts with the formazan dye derivative in the reagent layer; the high magnesium affinity of the dye dissociates magnesium from binding proteins. The resulting magnesium-dye complex causes a shift in the dye absorption maximum. The amount of dye complex formed is proportional to the magnesium concentration present in the sample and is measured by reflection density.

**Reaction Sequence**

chelator

Mg2 + Ca+2 Mg+2 + formazan dye derivative

pH 9.75

Mg+2 + Ca+2-chelator complex Mg+2-dye complex

**8.13.6 Sodium**

The VITROS Na+ Slide is a multilayered, analytical element coated on a polyester support that uses direct potentiometry 2 for measurement of sodium ions. The slide consists of two ion-selective electrodes, each containing methyl monensin (an ionophore for sodium), a reference layer, and a silver layer and a silver chloride layer coated on a polyester support. A drop of patient sample and a drop of VITROS Reference Fluid on separate halves of the slide results in migration of both fluids toward the centre of the paper bridge. A stable liquid junction is formed that connects the reference electrode to the sample electrode.

Each electrode produces an electrochemical potential in response to the activity of sodium. The potential difference between the two electrodes is proportional to the sodium concentration in the sample.

**8.13.7 Calcium**

The VITROS Ca Slide is a multilayered, analytical element coated on a polyester support.

A drop of patient sample is deposited on the slide and is evenly distributed by the spreading layer to the underlying layers. The bound calcium is dissociated from binding proteins, allowing the calcium to penetrate through the spreading layer into the underlying reagent layer. There, the calcium forms a complex with Arsenazo III dye, causing a shift in the absorption maximum. After incubation, the reflection density of the coloured complex is measured spectrophotometrically. The amount of coloured complex formed is proportional to the calcium concentration in the sample.

Reaction Sequence

pH 5.6

Ca+2 + Arsenazo III coloured complex

**8.13.8 Materials for Insulin measures**

IMMULITE 2000 Insulin - Insulin Bead Pack

Insulin Reagent Wedge

Insulin adjustors and controls

### 8.13.9 Methodology for Insulin

IMMULITE 2000 Insulin is a solid phase enzyme-labelled chemiluminescent immunometric assay. The solid phase (bead) is coated with monoclonal murine anti-insulin antibody. The liquid phase consists of alkaline phosphatase (bovine calf intestine) conjugated to monoclonal murine anti-insulin antibody.

The patients sample and reagent are incubated together with the coated bead for 60minutes. During this time, insulin in the sample forms the antibody sandwich complex with the monoclonal murine anti-insulin antibody on the bead, enzyme conjugated polyclonal sheep anti-insulin antibody and enzyme conjugated monoclonal murine anti-insulin antibody in the reagent. Unbound patient sample and enzyme conjugate are then removed by centrifugal washes.

Finally, chemiluminescent substrate is added to the reaction tube containing the bead and the signal is generated in proportion to the bound enzyme.

Incubation cycle: 1 x 60minutes

Time to first result: 65minutes

**8.13.10 Homeostatic Model Assessment (HOMA)**

HOMA model is a structural glucose/ insulin feedback system which can non-invasively assess both beta cell function and insulin sensitivity from fasting arterialised plasma glucose and insulin values. The model assumes that the control of plasma glucose and insulin in the fasting state is governed by a self-contained feedback loop between the pancreas, liver and insulin-sensitive and insulin-insensitive glucose metabolising tissues, and that the principle difference between individuals can be expressed in terms of difference in relative beta cell responsiveness to glucose, and in peripheral and hepatic sensitivity to insulin and glucose. ([Hermans and Lambert 2002](#_ENREF_100)).

Insulin sensitivity was calculated using HOMA – fasting plasma insulin (µU/ ml) x fasting plasma glucose (mmol/ l)/ 22.5 ([Matthews, Hosker et al. 1985](#_ENREF_159)).

### 8.13.11 Materials for Haematology

Automated Haematology System XE-5000

http://www.sysmex.com.br/pdf/manuais/XE\_Series\_-\_Pre\_Training\_Manual\_-\_ENGLISH\_-\_02-05.pdf

### 8.13.12 White Blood Cells

White blood cells (leukocytes) can be broadly classified as lymphocytes, monocytes, or granulocytes (4DIFF). Granulocytes can be further classified as neutrophils, basophils, or eosinophils, depending on the dye-affinity of the granules. The applicable analysis procedure is explained here.

4DIFF Analysis Procedure:

A 4DIFF analysis is used to identify and analyze the following white cell groups: lymphocytes, monocytes, eosinophils, neutrophils, including immature granulocytes, and basophils.

1. Blood is aspirated from the manual aspiration pipette to the sample rotor valve.

2. 18 μL of blood, measured by the sample rotor value, is diluted with 0.882 mL of STROMATOLYSER-4DL, and then sent to the reaction chamber as the diluted sample. At the same time, 18 μL of STROMATOLYSER-4DS, is added to dilute the sample to a ratio of 1:51. After reacting for about 22 seconds in this condition, the red blood cells are hemolyzed and the white blood cells are stained.

3. The sheath injector piston sends 40 μL of diluted sample to the optical detector block.

4. In the optical detector block, the sample is analyzed via flow cytometry method utilizing a semiconductor laser.

The detection method detects the size of blood cells by changes in direct-current resistance and the density of the blood cell interior by changes in radio-frequency resistance.

## 8.14 Statistical Methods

Initial analysis were conducted on an intention-to-treat basis. Student’s independent t-test was used to detect differences in continuous normally distributed data between the high and low refeeding groups.

Additionally, non-randomised analysis was performed by multiple linear regression to assess the relationship between:

1. Changes in QTc interval and heart rate with change in weight post refeeding. Adjusting for age, gender and height.
2. Changes in post refeeding phosphate with baseline white blood cells. Adjusting for %BMI, chronicity and HOMA-IR.

All analyses were conducted in SPSS for Windows (version 19; SPSS Inc. Chicago) with statistical significance level at P <0.05. Dr Angie Wade (biostatistician – Institute of Child Health) and Dr Lee Hudson (Paediatrician – Great Ormond Street Hospital) reviewed the statistical methods and sample size calculations.

**Chapter 9: Implication of refeeding on cardiovascular and anthropometric parameters in malnourished adolescents with anorexia nervosa**

**9.1 Introduction**

Low weight patient’s with anorexia nervosa (AN) present with a range of autonomic nervous system disturbances. These disturbances can be seen in up to 85% of AN sufferers ([Lesinskiene, Barkus et al. 2008](#_ENREF_151)) and account for a 5-10% mortality rate ([Isner, Roberts et al. 1985](#_ENREF_109)). Food restriction, excessive exercise and subsequent weight loss can lead to an increase in vagal tone resulting in: bradycardia (resting heart rate <50beats per minute); low arterial blood pressure (100/50mmHg); voltage decrease; T- wave inversion; atrophy of left ventricle; and QTc interval prolongation ([Nudel, Gootman et al. 1984](#_ENREF_195); [Ulger, Gurses et al. 2006](#_ENREF_283)).

It has been postulated that refeeding low weight patients may have a beneficial impact on cardiovascular functioning before any meaningful weight gain has occurred (Chapter 5). This chapter reports associations of refeeding on QTc interval and heart rate measurements in low weight hospitalised adolescents with AN.

**9.2 Methods Overview**

The hypothesis that refeeding influences QTc interval and heart rate was investigated in low weight adolescents with AN. Participants were randomly assigned to one of two refeeding programmes (low-calorie 500kcal/ day or high-calorie 1200kcal/ day), energy intake was then increased gradually by 200kcal/ day to around 1800-1900kcal/ day, which equates to around 80% estimated average requirements (SACN 2011).

Although the initial total energy intake will differ between refeeding programmes the percentage of total energy intake from macronutrients (carbohydrate, fat and protein) was controlled by incorporating meal plan templates (Appendix 5-8).

### 9.2.1 Cardiovascular

All participants had at least two ECG’s, one at baseline (day of admission) and one on day four. If QTc interval prolongation (>440ms) or arrhythmias were noted then additional ECG’s were carried out, however for purposes of analysis only data reported on day 1 and 4 were included in final analysis. Data from ECG readings were used to determine QT interval, QTc interval, QTc dispersion and resting heart rate for each individual. The QTc interval was calculated using both Bazett’s and Framingham formula due to the inadequacies of using Bazett’s formula in bradycardic participants (Chapter 5.1).

**9.2.2 Anthropometric**

All participants had their weight and height measured at baseline with a digital weighing scale (to the nearest 0.01kg) and a stadiometer (to the nearest 0.01cm), respectively. Weights were then repeated on days 3, 5, 8 and 10 every morning before breakfast; height was not re-measured due to the short study period. Body mass index (BMI) and percentage median BMI for age, height and gender (%BMI) were calculated using the Weight4Height programme version 4.23 UK ([Cole, Freeman et al. 1995](#_ENREF_41)). Methods are reported in detailed in chapter 8.

## Figure 9.1 – CONSORT flow diagram for randomisation

Assessed for Eligibility at screening

N=41

Declined

4 = >78%BMI

1 = unclear diagnosis

(n=5)

Randomisation

1200kcal/ day

Treatment

500kcal/ day

Control

18 Reviewed

18 Reviewed

## 9.3 Baseline Characteristics

Table 9.1 describes the characteristics of recruited adolescents including cardiovascular, nutritional and anthropometric data between the control and treatment group. There were no significant differences between control and treatment group demonstrating successful randomisation. Although there is a predominately higher number of females to males (34:2) this is representative of the reported prevalence of 1- 5% of diagnosed cases being male ([Hoek 2006](#_ENREF_102)).

A normality plot indicated that all parameters of baseline characteristics were normally distributed and therefore mean (SD) are provided to describe spread and central distribution. The average age of recruited participants was 13.8yrs old (1.8yrs) (range 11-16yrs) with a mean %BMI of 69.8% (5.8). The mean QTc interval (ms) was within normal range in both treatment programmes calculated with Bazett’s and Framingham formulas. The mean heart rate (bpm) was below normal for this age group.

## 9.4 Number of Participants

The primary analysis was intention-to-treat and involved all subjects who were recruited and completed the 10days of refeeding. All participants that met the inclusion criteria participated in the study; furthermore all of the 36 participants recruited completed 10 days of refeeding. Reasons for no dropouts may be attributed to:

1. Short follow up period (10 days)
2. Adequate training to research collaborators with regards to explanation and importance of study

## 9.5 Compliance

Compliance with the refeeding programme was assessed by the participants’ willingness to meet the increasing meal plan orally. However, if this was not achieved then supplementary drinks would be introduced or naso-gastric tube feeding was commenced - 89% of participants managed their full meal plan orally. However, eight participants (22%) required supplementary top up drinks; over the 10 days of refeeding, the mean daily intake in the form of supplements was 245ml (66SD) [equivalent of 588kcal (243SD)]. All participants were supplemented with Fortisip Compact (Nutricia) (2.4kcal/ml); the macronutrient composition was comparable to that outlined in the meal templates (Table 8.2). Fortisip Compact contains 50% total energy intake (TEI) from carbohydrates (29g/100ml), 35% TEI from fats (9.3g/100ml) and 15% TEI from protein (9.6g/100ml).

11% (four participants) were unable to meet their nutritional requirements orally and had to start naso-gastric tube feeding (two in the low calorie and two in the high calorie programme). All four participants commenced naso-gastic tube feeding within 36hrs of admission.

Participants that were consuming less than 80% (lower reference range) of their expected energy intake for more than two days were classified as non-adherent. However, because a naso-gastric tube was inserted in any participant that was not achieving 80% of expected intake no participants were classified as non-compliers

**Table 9.1 – Baseline Characteristics for randomisation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | All  N=36 | Low-calorie  (500kcal)  N=18 | High-calorie (1200kcal)  N=18 | P-value |
| Demographics | | | | |
| Age (yrs) | 13.8 (1.8) | 14.1 (1.8) | 13.7 (1.8) | 0.6 |
| Height(m) | 1.57 (0.1) | 1.61 (0.1) | 1.52 (0.2) | 0.1 |
| Weight (kg) | 33.7 (6.3) | 34.6 (5) | 32.9 (7) | 0.4 |
| BMI (kg/m2) | 13.4 (1.1) | 13.3 (1.1) | 13.5 (1.3) | 0.6 |
| %BMI | 69.8(5.8) | 68.2 (4.6) | 71.4 (6.6) | 0.2 |
| Weight loss week (kg) prior to admission | 0.5 (0.2) | 0.5 (0.3) | 0.6 (0.3) | 0.2 |
| Chronicity (months) | 10.0 (5.7) | 9.5 (5.4) | 10.4 (6.2) | 0.2 |
| Nutrition - % total energy intake | | | | |
| Carbohydrates | 50.4 (10) | 50.6 (11) | 50.2 (9) | 0.9 |
| Fat | 32.2 (8.4) | 32.1 (10.1) | 32.3 (6.9) | 0.95 |
| Protein | 17.3 (5.2) | 16.9 (5) | 17.6 (5.6) | 0.7 |
| Cardiovascular Parameters | | | | |
| QT interval  (ms) | 419 (49) | 431 (33) | 408 (60) | 0.2 |
| QTc Bazette  (ms) | 404 (30) | 403 (26) | 404 (34) | 0.9 |
| QTc  Framingham  (ms) | 399 (29) | 405 (27) | 392 (31) | 0.2 |
| Heart Rate  (beats/ min) | 57 (9) | 52 (7) | 63 (11) | 0.06 |

## 9.6 Nutritional Composition

Analyses were performed to test whether the macronutrient intake (carbohydrate, fat and protein) as a percentage of total energy intakes were similar in each group throughout the refeeding process. The macronutrient intake as a percentage of total energy intake were not significantly different at day 1, 4 or 10 (Table 9.2), highlighting that macronutrients were controlled using the meal plan templates.

**Table 9.2 – Percentage of total intake of macronutrients throughout refeeding**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | All  N=36 | Control  N=18 | Treatment  N=18 | Mean Diff  (95% CI) | P-value |
| Day 1  % Carbohydrate | 50.4 (10) | 50.6 (11) | 50.2(9) | 0.4(-7.4,8.2) | 0.9 |
| Day 4  % Carbohydrate | 51.6 (9.7) | 53.3(10.3) | 49.9 (9.2) | 3.3(-4.1,10.8) | 0.3 |
| Day 10  % Carbohydrate | 50.8 (9.3) | 50.6 (10.2) | 51 (8.8) | -0.3(-7.6,6.8) | 0.9 |
| Day 1  % Fat | 32.2 (8.4) | 32.1 (10.1) | 32.3 (6.9) | -0.2(-6.8, 6.4) | 0.95 |
| Day 4  % Fat | 31.3 (8.5) | 29.6 (9.7) | 33 (7.2) | -3.4(-9.9, 3.1) | 0.3 |
| Day 10  % Fat | 33.4 (9.3) | 33.3 (9.3) | 33.5 (9.7) | -0.1(-7.4, 7.1) | 0.95 |
| Day 1  % Protein | 17.3 (5.2) | 16.9 (5.0) | 17.6 (5.6) | -0.6(-4.7, 3.4) | 0.7 |
| Day 4  % Protein | 17.2 (5.3) | 17.3 (4.2) | 17.1 (6.3) | 0.1(-4.0, 4.3) | 0.9 |
| Day 10  % Protein | 15.9 (3.5) | 15.9 (3.3) | 15.8 (3.9) | 0.1(-2.6, 2.9) | 0.9 |

## 9.7 Statistical Analysis

## 9.7.1 Primary Outcome - QTc interval

Analyses were first performed to test whether refeeding within each group had a significant impact on QT, QTc interval (Bazett’s and Framingham heart rate correction formulas), QTc dispersion and heart rate; Second, whether there was a difference between the two groups after four days of refeeding in QT, QTc interval (Bazett’s and Framingham heart rate correction formulas), QTc dispersion and heart rate.

## QT interval (before correction for heart rate)

After four days of refeeding, subjects on both the low-calorie and high-calorie refeeding programme were found to have a reduction in QT interval. For the high-calorie programme, the reduction in QT interval was from 408ms to 375ms (mean difference: 33ms; 95% CI 11, 54ms; P=0.05), and for the low-calorie programme the reduction in QT interval was from 431ms to 410ms (mean difference: 21ms; 95% CI -0.1, 43ms; P=0.06). The mean difference in QT interval between the two randomised groups after 4 days of refeeding was 35ms; 95% CI 8, 61ms; P=0.01.

## QTc interval (corrected for heart rate)

After the QT interval was corrected for heart rate, neither refeeding programme reported a significant reduction in QTc interval using either Bazett’s or Framingham formulas. The low-calorie programme QTc interval (Bazett’s formula) reduced from 403ms to 399ms (mean difference: 4m; 95% CI: -10, 18ms; P=0.6) and the QTc interval (Framingham) reduced from 405ms to 394ms (mean difference: 11ms; 95% CI -6, 28; p=0.2) (Table 9.3).

Similarly, the high-calorie programme also reported no significant change in QTc interval after 4 days of refeeding using either Bazett’s or Framingham correction formulas: 404ms to 395 (mean difference: 9ms; 95% CI -5, 23ms; P=0.2) and 392 to 388 (mean difference: 4ms; 95% CI -6, 15ms; P=0.4), respectively (Table 9.4).

There was no significant difference in the post refeeding QTc interval between refeeding programmes using Bazett’s or Framingham formulas: mean difference 4ms; 95% CI -15, 23.7ms; P=0.6 and mean difference 7ms; 95% CI -13, 24ms; P=0.5, respectively (Table 9.5).

## 9.7.2 QTc interval prolongation (>440ms)

Prior to refeeding five participants had QTc prolongation (three in the low-calorie and two in the high-calorie programmes), after 4 days of refeeding the incidence of QTc interval prolongation reduced to three participants (two in the low-calorie and one in the high-calorie programme).

**Table 9.3 – Control Group (low-calorie): Pre and post refeeding cardiac outcomes**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Control | Baseline  N=18 | 4 days  refeeding  N=18 | Mean Diff  (95% CI) | P-value |
| QT (ms) | 431 (32) | 410(33) | 21(-0.9,43) | 0.06 |
| QTc Bazzet (ms) | 403 (26) | 399 (30) | 4(-11, 18) | 0.6 |
| QTc Framingham (ms) | 405 (27) | 394 (32) | 10(-6, 28) | 0.2 |
| Heart Rate  (beats/ min) | 51 (7) | 58 (10) | -6(-10, -3) | 0.001 |

**Table 9.4 – Treatment Group (high-calorie): Pre and post refeeding cardiac outcomes**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Treatment | Baseline  N=18 | 4 days  refeeding  N=18 | Mean Diff  (95% CI) | P-value |
| QT (ms) | 408 (60) | 375 (44) | 33(11,54) | 0.005 |
| QTc Bazzet (ms) | 404 (34) | 395 (27) | 9(-5,23) | 0.2 |
| QTc Framingham (ms) | 392 (31) | 388 (23) | 4(-7,15) | 0.4 |
| Heart Rate  (beats/ min) | 63 (23) | 67 (19) | -3(-7,1) | 0.1 |

**Table 9.5 – Cardiac parameters 4 days post refeeding comparison between groups**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | All  N=36 | Control  N=18 | Treatment  N=18 | Mean Diff  (95%CI) | P-value |
| QT (ms) | 399 (42) | 410 (33) | 375 (44) | 35(8,61) | 0.01 |
| QTc Bazzet  (ms) | 397 (28) | 399 (30) | 395 (27) | 4(-15, 24) | 0.6 |
| QTc Fram  (ms) | 391 (28) | 394 (32) | 388 (23) | 6(-13,24) | 0.5 |
| Mean change in QTc Fram | -7 (28) | -6 (35) | -8 (20) | 2(-17,21) | 0.8 |
| Heart Rate  (beats/ min) | 62 (16) | 58 (10) | 67 (19) | -8(-19,2) | 0.1 |
| Mean change in HR | 7 (6) | 7 (7) | 8 (5) | -1(-5,3) | 0.5 |

**9.8 Other Cardiovascular Outcomes**

### 9.8.1 Heart Rate

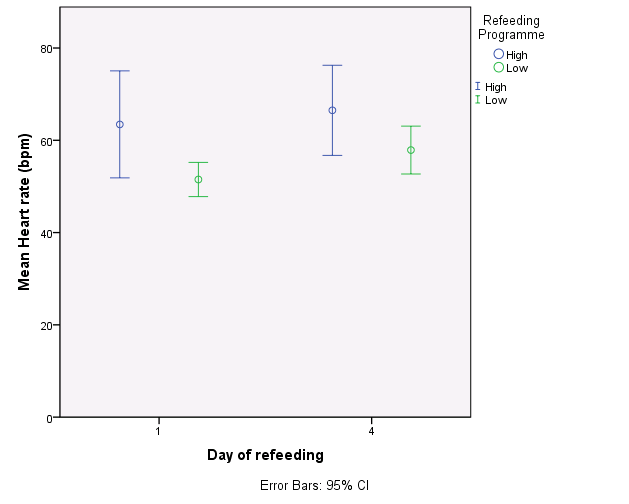
After 4 days of refeeding heart rate significantly increased in the low-calorie refeeding programme from 51beats/ min to 58beats/ min (mean difference: 7beats/ min; 95% CI -10, -3 beats/ min; P=0.01) (Table 9.3). The high-calorie programmes heart rate also increased but not significantly: 63 to 67 (mean difference: 4beats/ min; 95% CI 1, -1; P=0.2) (Table 9.4).

There was no significant mean difference in heart rate between the refeeding programmes after 4 days of refeeding: 58beats/ min and 66beats/ min, respectively (mean difference: 8beats/ min; 95% CI -19, 2 beats/ min; P= 0.1) (Table 9.5, Figure 9.2).

### 9.8.2 QTc Dispersion

Although QTc dispersion reduced in both refeeding programmes after 4 days of refeeding neither refeeding programme reported a significant reduction in QTc dispersion: 27ms to 23ms (mean difference: 4ms; 95% CI -8, 14ms; P=0.5) and 23ms to 20ms (mean difference: 3ms; 95% CI -6, 12ms; P=0.5), respectively.

**Figure 9.2 – Heart rate (BPM) before and after 4 days of refeeding in the control (low-calorie) and intervention (high-calorie) groups**

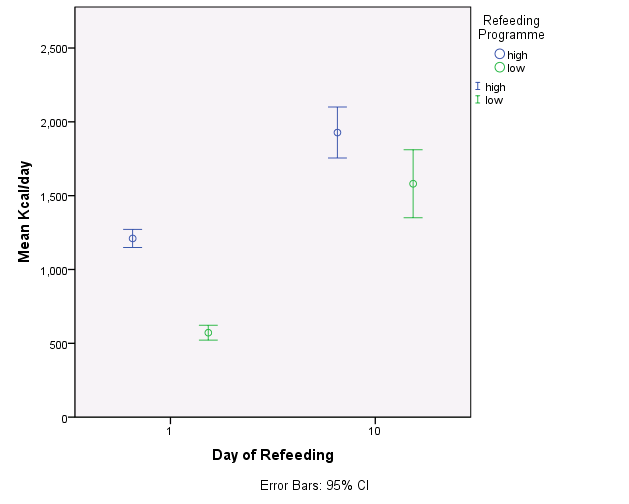
****

## 9.9 Secondary Outcomes

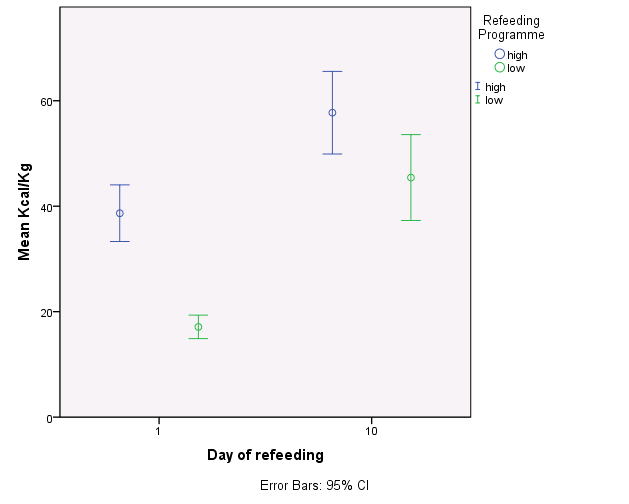
### 9.9.1 Nutritional

The mean energy intake on day one of refeeding in the low-calorie and high-calorie group was 550kcal/ day (SD 117), [16kcal/ kg (SD 5)] and 1205kcal/ day (SD 131), [38kcal/ kg (SD 10)], respectively. After ten days of refeeding the energy intake remained significantly different between the two groups. The mean intake after ten days of refeeding in the low-calorie programme was 1581kcal/ day, SD399 (45kcal/ kg, SD14) compared to 1927kcal/ day SD311, (58kcal/ kg, SD14) in the high-calorie programme: mean difference -346kcal/ day; 95% CI -618, -74kcal; P=0.01 (Figure 9.3). This remained significant when calculated for kcal/ kg (mean difference -12kcal/ kg; 95% CI -23, -1.5kcal; P =0.02 (Figure 9.4).

**Figure 9.3 - Energy intake (kcal/ day) at baseline and after 10 days of refeeding in the low and high calorie programmes**



**Figure 9.4 - Energy intake (kcal/kg/day) at baseline and after 10 days of refeeding in the low and high calorie programmes**



**9.10 Anthropometric Outcomes**

### 9.10.1 Weight (kg)

Analyses were performed to test: 1) whether refeeding had a significant impact on weight change (kg) after 4 and 10 days of refeeding within each refeeding programme (paired T-test). 2) Whether there was a difference in weight change (kg) between the two randomised refeeding programmes after 10 days of refeeding (Independent T-test).

After 4 days of refeeding the low-calorie group saw an overall reduction in mean weight change of -0.1kg (SD 0.6) and the high-calorie group saw an increase in the mean weight change of 0.2kg (SD 0.7). However, this was not a significant difference in mean weight change between randomised groups after 4 days of refeeding (0.3kg; 95% CI -0.7kg, 0.2kg; P=0.1).

After 10 days of refeeding both refeeding programmes reported a significant within group increase in weight; the low refeeding group had a mean increase of 0.66kg (P=0.003) (Table 9.6) and the high refeeding group had a mean increase of 1.0kg (P=0.001) (Table 9.7). However, after 10 days of refeeding the difference in weight gain between randomised groups was not significant (P=0.2) (Table 9.8). The weight change throughout the 10days of refeeding between randomised groups is illustrated in Figure 9.5.

**9.10.2 %BMI**

After 10 days of refeeding both refeeding programmes reported a significant increase within randomised groups for %BMI. The low-calorie programme increased from 68.2 to 70.4% (mean difference: 1.6%; 95% CI -2.2,-1%; P<0.000). The high-calorie programme increased from 71.4 to 73.2% (mean difference: -2.6% 95%CI -3.7, -1.5%; <0.000). However, after 10 days of refeeding there was no significant change in %BMI between randomised refeeding groups (-1.0 95% CI -2.1, 0.1; P=0.09).

**Table 9.6 – Anthropometric changes within the control group (low calorie)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Control | Baseline  (n=18) | 10 days  refeeding  (n=18) | Mean difference  95% CI | P-value |
| Weight (kg) | 34.6 (5.1) | 35.2 (5.2) | -0.6(-0.9,-0.4) | <0.000 |
| Change in weight (kg) | 0 | 0.65(0.51) | -0.6(-0.9,-0.4 | 0.003 |
| %BMI | 68.6 (4.4) | 70.3 (4.6) | -1.6(-2.2,-1.0) | <0.000 |
| Change in %BMI | 0 | 1.6 (1.2) | -1.6(-2.2,-1.0) | <0.000 |

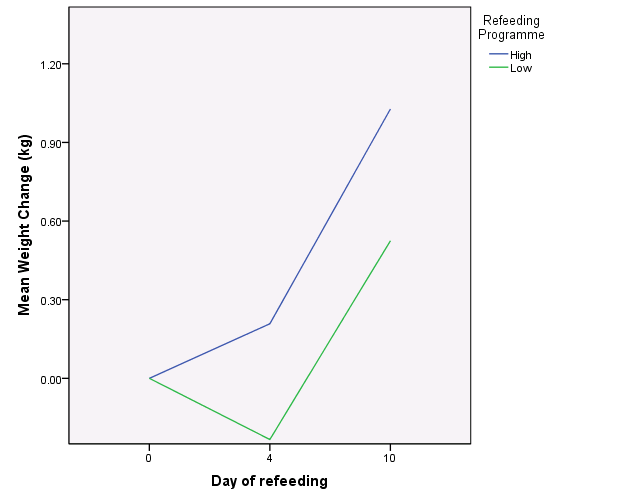
**Table 9.7 – Anthropometric changes within the treatment group (high calorie)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Treatment | Baseline  N=18 | 10 days  refeeding  n=18 | Mean Diff 95% CI | P-value |
| Weight (kg) | 32.9 (7.3) | 33.9 (7.5) | -1.0(-1.5,-0.5) | <0.000 |
| Change in weight (kg) | 0 | 1.03 (1.08) | -1.0(-1.6, -0.5) | 0.001 |
| %BMI | 71.9 (5) | 73.2 (6) | -2.6(-3.7,-1.5) | <0.000 |
| Change in %BMI | 0 | 2.6(2.1) | -2.6(-3.7,-1.5) | <0.000 |

**Table 9.8 – Change in anthropometric measure between randomised refeeding programmes**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | All  N=36 | Control  N=18 | | Treatment  N=18 | | | | Mean Diff  95%CI | P-value |
| 4days refeeding | | | | | | | | | |
| Weight (kg) | 33.9 (6.2) | 34.6 (5.0) | | 33.1 (7.3) | | | 1.5(-2.7,5.7) | | 0.5 |
| Change in weight (kg) | 0.06 (0.67) | -0.09 (0.56) | | 0.21 (0.73) | | | -0.3(-0.7,0.2) | | 0.1 |
| % BMI | 69.8 (5.8) | 68.2 (4.6) | | 71.4 (6.6) | | | -3.2(-7.5, 1.0) | | 0.1 |
| Change in %BMI | 0.5 (1.6) | 0.05 (1.4) | | 1.0 (1.7) | | | -0.9(-2.2,0.2) | | 0.1 |
| 10days Refeeding | | | | | | | | | |
| Weight (kg) | 34.6 (6.4) | | 35.2 (5.2) | | 33.9 (7.5) | 1.3(-3.1, 5.6) | | | 0.5 |
| Change in weight (kg) | 0.84 (0.85) | | 0.66 (0.51) | | 1.02 (1.09) | -0.3(-0.9,0.2) | | | 0.2 |
| %BMI | 71.9 (5.9) | | 70.3 (4.6) | | 73.5 (6.6) | -3.2(-7.1,0.7) | | | 0.1 |
| Change in %BMI | 2.0 (1.9) | 1.6 (1.2) | | 2.6 (2.1) | | -1.0(-2.1, 0.1) | | | 0.09 |

**Figure 9.5 – weight change between randomised groups at 4 and 10 days of refeeding**



**9.11 Non-Randomised Analysis**

Previous studies have reported a relationship between weight (kg) with QTc interval and heart rate in that the lower the weight the higher the QTc interval (chapter 5.4). Furthermore, some studies reported that whilst refeeding QTc interval improved before any meaningful weight gain had occurred. Therefore, it was important to further investigate this relationship by performing non-randomised analysis.

**9.11.1 Baseline QTc interval**

No relationship was found between baseline QTc interval (Framingham and Bazett’s formula) and baseline %BMI or baseline heart rate (Table 9.9).

**9.11.2 Change in QTc interval post refeeding**

No relationship could be found between change in QTc interval (Framingham and Bazett’s formula) and change in weight (kg) or %BMI or heart rate (bpm) (Table 9.9). This was tested further by adjusting for covariates for age, gender and height (Table 9.10).

**9.11.3 Change in heart rate post refeeding**

No relationship could be found between change in heart rate (bpm) and change in weight (kg) or change in %BMI (Table 9.9).

**Table 9.9 – Relationship between cardiovascular and anthropometric outcomes at baseline and four days post refeeding**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Correlation coefficient**  **R2** | **Mean Difference**  **(95% CI)** | **p-value** |
| **Baseline QTc interval (Framingham)** | | | |
| **Baseline %BMI** | 0.00 | 0.01(-2.0, 2.3) | 0.9 |
| **Baseline Heart rate** | 0.01 | -0.2(-0.7,0.4) | 0.5 |
| **Baseline QTc interval (Bazett’s)** | | | |
| **Baseline %BMI** | 0.005 | 0.4(-1.6,2.4) | 0.7 |
| **Baseline Heart rate** | 0.08 | 0.5(-0.1,1.3) | 0.09 |
| **Change in QTc interval (Framingham) post feeding** | | | |
| **Change in weight (kg)** | 0.05 | -3(-18,12) | 0.6 |
| **Change in %BMI** | 0.000 | -0.06(-7.3,7.2) | 0.9 |
| **Change in Heart rate** | 0.01 | 0.5(-1.1,2) | 0.5 |
| **(Continued) Table 9.9 Relationship between cardiovascular and anthropometric outcomes at baseline and four days post refeeding** | | | |
| **Change in QTc interval (Bazett’s) post refeeding** | | | |
| **Change in weight (kg)** | 0.04 | -8(-23,6) | 0.2 |
| **Change in %BMI** | 0.003 | -0.9(-8.3,6.3) | 0.7 |
| **Change in heart rate** | 0.004 | -0.3(-1.9,1.4) | 0.7 |
| **Change in HR** | | | |
| **Change in weight (kg)** | 0.08 | -0.8(-2.3,0.8) | 0.6 |
| **Change in %BMI** | 0.04 | -0.8(-2.3,0.8) | 0.3 |

**Table 9.10 Relationship between change in QTc interval with change in weight post refeeding - adjusting for covariates age, gender and height.**

|  |  |  |
| --- | --- | --- |
| **Adjusted** | | |
| **Correlation Coefficient**  **R2** | **Mean Difference**  **(95%CI)** | **P-value** |
| 0.02 | -4.7(-23.9, 14.5) | 0.6 |

## 9.12 Discussion

**9.12.1 Baseline Measurement**

The mean %BMI reported in the present study is the lowest recorded in all studies that have previously observed refeeding in adolescents with AN ([O'Connor and Nicholls 2013](#_ENREF_198)). The mean %BMI and mean BMI was 69%BMI and 13.4kg/m2, respectively. The lowest reported %BMI was 57.9% and the highest was 78%.

Invariably, studies which have implemented a refeeding programme do not explicitly report on the actual percentage of total energy intake of macronutrients but state that a dietitian devised a meal plan to meet healthy eating recommendations ([Gentile, Pastorelli et al. 2010](#_ENREF_77)). However, two studies did report on specific macronutrient intake and are discussed later. In the present study, after 10 days of refeeding when participants were receiving 80% of estimate energy intake the actual percentage of total energy intake consumed from carbohydrates was at the lower end of the healthy range and protein intake was at the higher end (Department of Health - healthy eating guidelines –carbohydrates 50-65%, Fats 30-35% and Protein 10-15%).

A study by Garber et al (2012) found similar outcomes to the present study in that a higher percentage of protein was consumed which replaced fat and therefore reduced the total energy intake from fat ([Garber, Michihata et al. 2012](#_ENREF_75)). In contrast, a study by Whitelaw et al (2010) devised meal plans that were high in fat (up to 40%) and protein, which replaced carbohydrate intake ([Whitelaw, Gilbertson et al. 2010](#_ENREF_303)).

A possible reason for the carbohydrate intake being at the lower end of the reference range in the present study may be due to the perceived associated link between carbohydrates and risk of refeeding hypophosphatemia. Therefore, there may have been some ambivalence from dietitians about incorporating larger amounts of carbohydrates. This observation could also have been due to chance or unintentional bias. Meal plan templates were devised to reduce the risk of large variability in macronutrients intakes between participants, and macronutrient intake as a percentage of total energy intake was not significantly different throughout refeeding, highlighting that macronutrients were controlled using the meal plan templates. However, the templates still allowed for some range of intake, albeit still within healthy range.

**9.12.2 Refeeding and QTc interval**

The findings of the present study were consistent with those reported by Divasta et al. (2010) who observed a normal mean baseline QTc interval and found that after 5 days of refeeding mean QTc interval did not significantly change in low weight (mean 78%BMI SD 9) adolescents with AN. However, the present study found that refeeding did resolve or improve QTc interval prolongation (QTc interval >440ms) in 80% of participants. QTc interval prolongation did worsen in one participant in the low-calorie refeeding programme, who lost weight (0.4kg) in the first four days of refeeding. Similarly, a study by Roche et al (2005) reported no QTc interval prolongation prior to refeeding (388ms SD20), but one participant did develop QTc interval prolongation post refeeding; specific measurements and details were not provided.

Although refeeding reduced the incidence of QTc interval prolongation in the present study for the majority of participants, we were unable to associate change in weight with change in QTc interval. The mechanism responsible for reversing QTc interval prolongation in malnourished patients being refed is unclear but has been attributed to weight restoration ([Vazquez, Olivares et al. 2003](#_ENREF_287); [Olivares, Vazquez et al. 2005](#_ENREF_201)). Additionally, it has been reported that beneficial cardiac alterations have been observed in low weight patients with AN prior to any meaningful weight gain. A study by Swenne (2000) reported that 56% of participants had a QTc interval >440ms, and a significant reduction in QTc interval was observed after 7 days of refeeding (P<0.001) suggesting that refeeding alone resulted in an improved QTc interval because these improvements were observed before any meaningful weight gain had occurred ([Swenne 2000](#_ENREF_273)).

However, although Swenne. (2000) reported a significant increase in BMI from 13.8 to 15kg/ m2 (P <0.05) within 7 days, they did not provide specific data on energy intake throughout the refeeding proces. Therefore, it is not possible to deduce that QTc interval improves solely from refeeding, as arguably a 1.2kg/m2 weight increase in 7 days is clinically meaningful and making it difficult to support the hypothesis that refeeding alone improves QTc interval.

**9.12.3 Refeeding and Heart Rate**

In the present study, participants’ heart rate improved equally in both randomised refeeding programmes. Bradycardia is the most frequently reported arrhythmia found in AN patients, and results from vagal hyperactivity ([Nudel, Gootman et al. 1984](#_ENREF_195)). Refeeding and weight restoration have previously been found to reduce vagal tone and normalise heart rate ([Cooke, Chambers et al. 1994](#_ENREF_42); [Swenne 2000](#_ENREF_273); [Mont, Castro et al. 2003](#_ENREF_182); [Olivares, Vazquez et al. 2005](#_ENREF_201); [Roche, Barthelemy et al. 2005](#_ENREF_232); [Ulger, Gurses et al. 2006](#_ENREF_283); [DiVasta, Walls et al. 2010](#_ENREF_55)).

In contrast to the present study, Divasta et al, (2010) observed a relationship between weight gain and change in heart rate. They reported that supine pulse rate increased with each subsequent day of feeding (P<0.01). Interestingly, heart rate has been reported to increase even in the early phase of refeeding, when weight restoration was deemed insufficient ([Rechlin, Weis et al. 1998](#_ENREF_226); [Shamim, Golden et al. 2003](#_ENREF_256)), Suggesting that the cardiovascular improvements reported with refeeding are the result of other subtle physiological adaptations causing changes in heart rate.

Heart rate appears to be more susceptible to changes in weight and refeeding than QTc interval. Although vagal hyperactivity has beneficial effects regarding energy conservation ([Roche, Barthelemy et al. 2005](#_ENREF_232)), essential during times of famine, it can be detrimental to cardiac function, for example left ventricular weakness. The mechanism responsible for this almost immediate cardiac alteration during refeeding remains unknown but highlights the importance of nutritional rehabilitation in low weight patients with AN.

**9.12.4 Refeeding and Weight gain**

The rate of weight gain reported in the intervention group (1200kcal/ day) in the present study was 100g/ day which was comparable to that in a recent study by Garber et al (2012). They monitored the effect of refeeding low weight (mean 80.1%BMI) adolescents with AN, starting at 1200kcal/ day (289SD) and refed over a mean period of 17days (6.4SD). At the end of refeeding, mean intake was 2668kcal/ day (387SD). Garber et al (2012) reported a mean daily weight gain of 123g, a total mean weight gain of 2.1kg (1.98SD). However, Garber et al (2012) reported an initial weight loss in the first few days of refeeding despite intakes of 1200kcal ([Garber, Michihata et al. 2012](#_ENREF_75)).

The present study along with that of Golden et al (2013) reported no initial weight loss when commencing refeeding at 1200kcal/ day. Golden et al (2013) retrospectively reviewed the medical charts of 310 adolescents (mean 78%BMI), of which 88 commenced refeeding at a mean intake of 1163kcal/ day (SD107) compared to 222 adolescents who commenced a mean intake of 1557kcal/ day (SD265). After 16 days of refeeding the lower calorie group (1163kcal/ day) gained 200g/ day, a total weight gain of 3.6kg. Interestingly, the high calorie group (1557kcal/ day) gained less total weight, 2.9kg.

The rate of weight gain reported in the present study is considerably lower than that observed by Whitelaw et al (2010), who monitored refeeding over 14 days in low weight (mean 73%BMI) adolescents with AN. They reported a mean daily weight gain of 185g/ day, a mean total weight gain of 2.6kg. The majority of their participants commenced refeeding at 1900kcal/ day and increased up to 2700kcal/ day. ([Whitelaw, Gilbertson et al. 2010](#_ENREF_303))

Although Whitelaw et al (2010), commenced a higher mean refeeding programme (1900kcal/ day) than Golden et al (2013) (1163kcal/ day), they were unable to elicit higher rates of weight gain, which could be the result of an increase in diet induced thermogenesis as discussed in chapter 6. Reassuringly, the present study and that by Golden et al (2013) and Garber et al (2011) illustrate that recommended weight gains of 1kg/ week ([Reiter and Graves 2010](#_ENREF_228)) can be achieved when refeeding at a modest 1200kcal/ day and increasing to 2500kcal/ day.

In the present study, after 10 days of refeeding participants receiving the high-calorie refeeding programme (1200kcal/ day) consumed a significantly higher energy intake than the low-calorie group. This was not simply due to the low-calorie programme starting on fewer calories as there was ample time to achieve the 80% EAR target. This discrepancy between energy intakes can be attributed to the additional 80% compliance allowance (if participants did not meet 80% of expected energy intake for longer than 24hrs a naso-gastric tube was sited), indicating that the low calorie refeeding programme were towards the lower end of compliance compared to the high calorie refeeding programme which was near 100% compliance with energy intake targets. Furthermore, the low-calorie programme lost weight in the first 4 days of refeeding and gained half as much weight as the high-calorie programme after 10 days of refeeding.

The present study and that of Whitelaw et al (2010) demonstrate that most adolescents with AN can manage high calorie intakes orally and although refeeding at higher energy intakes may heighten patient anxiety levels, it may also help to achieve higher energy intakes than commencing at lower refeeding rates. It is important to highlight that the studies by Garber et al (2012), Whitelaw et al (2010) and Golden et al 2013 were all carried out at specialist eating disorders units and therefore staff would be trained to contain and manage issues that arise from refeeding.

In contrast, the present study was carried out in both generic psychiatric units and general paediatric wards, and sufficient weight gain was still achieved. This may be the result of having clear expectations laid out from the outset in the form of the study protocol, and enforcing boundaries around meal plans, including strategies to deal with eating difficulties (supplement drink top ups and naso-gastric tube feeding), subsequently reducing battles around mealtimes and increasing compliance.

**9.12.5 Nasogastric Tube Feeding**

In the present study, the high-calorie refeeding programme did not result in more nasogastric tube feeding than that reported in the study by Whitelaw et al (2010), even though they commenced refeeding at much higher rates. In the present study four participants (11%) required a significant amount of their nutritional requirements from nasogastric tube feeding, compared to 7 participants (15%) in the study by Whitelaw et al (2010).

However, a study by Gentile et al (2010) reported a considerably higher rate of nasogastric tube feeding of 90% in low weight (11.3BMI, SD0.7), young adults (23yrs, SD7.6) ([Gentile, Pastorelli et al. 2010](#_ENREF_78)). A reason for this higher incidence rate of nasogastric tube feeding may be due to the older age group of AN participants, compared to the present study. Children and adolescents are more inclined to adhere to advice from health professionals. Furthermore, chronicity of AN may also play a part in resisting an oral meal plan, possibly due to entrenched eating disorder psychopathology, participants in the study by Gentile et al (2010) had been diagnosed with AN for a mean period of 5yrs. The mean time of diagnosis for the present study was 10months.

Interestingly, a retrospective chart review by Agostino et al (2013) evaluated a refeeding programme that commenced all admitted AN patients on naso-gastric feeding. The study compared the results of 31 adolescents (mean age 14.9yrs, SD 2.1) who were exclusively nasogastric fed with 134 adolescents (14.9yrs SD 1.7) who commenced an oral meal plan. In two weeks of refeeding, the nasogastric fed group gained significantly more weight than the oral meal plan group, 1.22kg, (SD0.9) and 0.69kg (SD0.6) (P=0.004), respectively; and the nasogastric fed group had a significantly reduced hospital admission, 33.8days (SD11) and 50.9days (SD24), (P=0.0002), respectively. ([Agostino, Erdstein et al. 2013](#_ENREF_5))

However, the nasogastric fed group commenced a significantly higher initial refeeding programme than the oral meal plan group; 1617kcal (SD276) and 1069kcal (SD212) (P=0.001) respectively. Therefore, their conclusion, that “exclusive nasogastric feeding is more beneficial than an oral meal plan with regards to improved weight gain” may not be valid; since this could be attributed to the higher energy intake in the nasogastrically fed group.

The low incidences reported of naso-gastric tube feeding in the present study is reassuring in that if the increased anxiety of higher energy intake can be suitably managed and contained then nasogastric tube placement can be avoided. Furthermore, the present study highlights that refeeding at the high-calorie programme does not result in higher level of tube feeding, suggesting that this level of refeeding is manageable. Reasons for why it is desirable to avoid nasogastric tube feeding in this patient group is one it has been reported to increase the length of hospital stay and two it is intrusive and traumatic ([Morris, Bramham et al. 2014](#_ENREF_186)). Once again it is important to highlight that the present study was conducted on generic paediatric wards where specialist support and skill for refeeding may not be readily available.

Participating centres of the present study reported a beneficial impact with the structured meal plan, giving staff confidence, by providing staff and patients with clear expectations of what was required at each meal and snack time, with timely calorie increments. Previously many of the partaking centres did not use structured meal plans or have clear refeeding protocols.

**9.13 Summary of Discussion**

Refeeding at 1200kcal/ day reduced the incidence QTc interval prolongation and improved heart rate within four days. Furthermore, the 1200kcal/ day refeeding programme elicited continual weight gain throughout the 10 days of refeeding and did not result in a higher incidence a naso-gastric tube feeding. Although the 500kcal/ day programme also resulted in a reduction in the incidence of QTc interval prolongation and improvement in heart rate participants lost weight in the first four days of refeeding, this is an undesirable outcome in these low weight medically unstable patients. There appears to be no advantage to refeeding at the lower rate.

**Chapter 10: Determinants of Refeeding Hypophosphataemia in Adolescents with Anorexia Nervosa: Randomised Controlled Trial**

**10.1 Introduction**

Refeeding some low weight patients with AN results in refeeding hypophosphataemia. However, the precursors and predictive markers for refeeding hypophosphataemia are unclear. As discussed in chapter 7 much emphasis has been attributed to energy intake and the subsequent utilisation of phosphate in carbohydrate metabolism. However, an increasing amount of literature is disputing this relationship between energy intake and hypophosphatemia ([Ornstein, Golden et al. 2003](#_ENREF_203); [Golden, Keane-Miller et al. 2013](#_ENREF_80); [O'Connor and Nicholls 2013](#_ENREF_198)).

Therefore, to investigate other potential determinants of hypophosphataemia this study monitored %BMI, which has previously been linked with refeeding hypophosphataemia ([Ornstein, Golden et al. 2003](#_ENREF_203); [Whitelaw, Gilbertson et al. 2010](#_ENREF_303)). Furthermore, an additional marker of malnutrition will be monitored, white blood cell count (WBC‘s), which like %BMI is often low in patients with AN (chapter 2). Finally, serum glucose, insulin and insulin sensitivity (Homeostatic Model Assessment – Insulin Resistance [HOMA-IR]), will be monitored in relation to hypophosphataemia.

**10.2 Methods**

As described in chapter 9

On admission (day 1) a venepuncture was taken to monitor serum phosphate, magnesium, potassium, sodium and calcium. Additionally glucose (mmol/ l), insulin (µU/ ml), and a full blood count were also taken. Subsequent overnight fasting venopunctures were carried out on day 2, 4, 6 and 10 of refeeding. Insulin sensitivity was calculated using HOMA-IR – fasting plasma insulin (µU/ ml) x fasting plasma glucose (mmol/ l)/ 22.5 ([Matthews, Hosker et al. 1985](#_ENREF_159)). An episode of refeeding hypophosphataemia was defined as serum phosphate levels reducing to or below 0.9mmol/ l (([Ornstein, Golden et al. 2003](#_ENREF_203)).

### 10.2.1 Statistical Analysis

The present study aimed to assess determinants of post refeeding phosphate. To detect a change in serum phosphate of 0.25mmol/ l with a standard deviation of 0.2mmol/ l (0.6mg/dl) ([Ornstein, Golden et al. 2003](#_ENREF_203); [Garber, Michihata et al. 2012](#_ENREF_75)), assuming a two tailed alpha error probability of 5% and a power of 80%, a sample size of 15 participants would be required in each group, a total of 30 participants.

The primary outcome was change in post refeeding phosphate (mmol/ l). Secondary outcomes included change in weight (kg), %BMI and biochemical measures (phosphate, magnesium, calcium and potassium), glucose, insulin and white blood cells (x109/ l). An independent sample t-test was used to compare continuous data between interventions for the primary and secondary outcomes. A paired t-test was used to test for within intervention change for continuous data.

In secondary non-randomised analysis, linear regression models were fitted. All hypothesis testing was 2 sided and all effect sizes and their 95% confidence interval (95% CI) were evaluated using the general linear model. All analyses were conducted using SPSS for Windows (version 18.0; SPSS Inc, Chicago) and statistical significance was taken as p<0.05.

**10.3 Results - Baseline characteristics**

Characteristics of participants as chapter 9

Mean baseline levels of serum phosphate, potassium and magnesium were normal. There was no significant difference in baseline electrolytes between the two randomised refeeding programmes. Baseline glucose levels of the participants were below that expected compared to healthy individuals, with a mean fasting glucose level of 4mmol/ l (normal range 4.5-5.5mmol/l); with the lowest baseline recorded at 3.0mmol/ l. Similarly, baseline insulin levels were lower than that expected compared to healthy adolescents; with the lowest recorded at 1.7µmol/l (normal range 2.5-4.0µmol/l. This in turn resulted in an increase in the insulin sensitivity. There were no significant differences in baseline serum glucose, insulin and HOMA-IR between the two randomised refeeding programmes.

The WBC was low in participants in the present study with a mean of 4.5 x 109/l (normal range 5.5-10 x 109/l), with the lowest recorded of 2.0 x 109/l (Table 10.1). There was no significant difference in baseline WBC between randomised groups.

**Table 10.1 Baseline characteristics for electrolytes and biochemical markers**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | All  (N=36) | Low Calorie  (N=18) | High Calorie (N=18) | P-Value |
|  |  |  |  |  |
| Age (yrs) | 13.8 (1.8) | 14.1 (1.8) | 13.7 (1.8) | 0.6 |
| Height (m) | 1.57 (0.1) | 1.61 (0.1) | 1.52 (0.2) | 0.1 |
| Weight (kg) | 33.7 (6.3) | 34.6 (5) | 32.9 (7) | 0.4 |
| BMI (kg/m2) | 13.4 (1.1) | 13.3 (1.1) | 13.5 (1.3) | 0.6 |
| %BMI | 69.(8 5) | 69 (4) | 71 (5) | 0.2 |
| Weight loss week (kg) | 0.5 (0.2) | 0.5 (0.3) | 0.6 (0.3) | 0.2 |
| **Nutrition - % Total Energy Intake**  Carbohydrates (%)  Fat (%)  Protein (%)  **Electrolytes**  Phosphate (mmol/l)  Magnesium (mmol/l)  Potassium (mmol/l)  **Biochemical Parameters**  Glucose (mmol/l)  Insulin (µmol/l)  HOMA-IR  White Blood Cell Count  x109/ l | 50.4 (10)  32.2 (8.4)  17.3 (5.2)  1.27 (0.15)  0.90 (0.08)  4.0 (0.35)  4.0 (0.5)  2.5 (0.9)  0.4 (0.2)  4.5 (1.2) | 50.6 (11)  32.1 (10.1)  16.9 (5)  1.26 (0.1)  0.89 (0.07)  4.04 (0.3)  4.1 (0.4)  2.6 (1.1)  0.4 7 (0.24)  4.2 (1.1) | 50.2 (9)  32.3 (6.9)  17.6 (5.6)  1.29 (0.2)  0.9 (0.09)  4.02 (0.4)  3.9(0.7)  3.6 (3.1)  0.61 (0.2)  4.7 (1.2) | 0.9  0.95  0.7  0.4  0.6  0.8  0.2  0.4  0.3  0.1 |
|  |  |  |  |  |

**10.4 Results - Biochemical and Electrolyte changes with refeeding**

### 10.4.1 within group: Low Calorie (Control Group)

In the control group there was no significant difference in the mean nadir (lowest recording from baseline reading) for serum phosphate, magnesium or potassium after refeeding (Table 10.2).

In the control group there was no significant mean change in insulin, glucose, HOMA IR or WBC between baseline and at the end of 10 days refeeding.

**10.4.2 within Group: High Calorie (Intervention Group)**

In the intervention group there was no significant difference in mean nadir (lowest recording from baseline reading) for potassium or phosphate. However, the mean nadir in serum magnesium significantly reduced (p=0.05) post refeeding (Table 10.3).

In the intervention group there was no significant difference in mean change in insulin, glucose, HOMA IR or white blood cell count from baseline and at the end of 10 days refeeding.

**10.4.3 Between Randomised Groups**

There was no significant difference in the mean change from baseline and post refeeding nadir phosphate, magnesium and potassium between randomised refeeding programmes (Table 10.4). After 10 days of refeeding there was no difference in WBC x 109/ l between randomised refeeding programmes (95%CI -0.2 to 0.04 109/l; P=0.6). There was no significant difference in insulin, glucose and HOMA IR between randomised refeeding programmes after refeeding (Table 10.4).

**10.5 Refeeding Hypophosphataemia between Randomised Groups**

The incidence of refeeding hypophosphataemia between randomised groups was as follows: the low calorie group reported 2 participants and the high calorie group reported 5 participants with refeeding hypophosphataemia, of which one was NGT fed.

Refeeding hypophosphataemia was defined as serum phosphate levels below 0.9mmol/l. Of the seven participants that developed refeeding hypophosphataemia serum levels dropped within 48hours of refeeding, two of which reduced to below 0.6mmol/ l and required oral phosphate supplementation. The other five participants normalised their phosphate without any other intervention apart from refeeding.

A Chi square analysis found no significant difference between the incidence of refeeding hypophosphatemia between randomised groups (P=0.4)

**Table 10.2 Control (low-calorie) within group electrolyte changes between baseline and post refeeding nadir. Glucose, insulin, HOMA-IR and WBC change between baseline and end of 10 days refeeding.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Electrolyte | Baseline | Post feeding | Mean Difference  (95%CI) | p-value |
| Phosphate mmol/l (range 1.0-1.7 mmol/ l) | 1.25 (0.13) | 1.28 (0.21) | 0.06(-0.15, 0.1) | 0.7 |
| Magnesium mmol/l (range 0.7-1.0mmol/l) | 0.89 (0.07) | 0.87 (0.06) | 0.01(-0.01,0.05) | 0.16 |
| Potassium mmol/l (range 3.5-5.0) | 4.0 (0.3) | 4.2 (0.3) | 0.1(-0.5, 0.05) | 0.9 |
| Glucose (mmol/l) | 4.1 (0.4) | 4.1 (0.4) | -0.05(-0.4,0.3) | 0.7 |
| Insulin (µmol/l) | 2.6 (1.1) | 3.1 (1.2) | -0.05(-1, 0.7) | 0.4 |
| HOMA IR | 0.47 (0.24) | 0.57(0.26) | -0.1(-0.3,0.1) | 0.4 |
| White Blood Cells (x109/l) | 4.2 (1.1) | 4.3 (1.0) | -0.5(-1.5,0.13) | 0.3 |

**Table 10.3 Intervention (high-calorie) within group electrolyte changes between baseline and nadir post refeeding. Glucose, insulin, HOMA-IR and WBC change between baseline and end of 10 days refeeding.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Electrolyte | Baseline | Post feeding | Mean Diff  (95%CI) | p-value |
| Phosphate mmol/l (range 1.0-1.7 mmol/l) | 1.29 (0.16) | 1.32 (0.29) | 0.05(-0.14,0.09) | 0.7 |
| Magnesium mmol/l (range 0.7-1.0 mmol/l) | 0.9 (0.09) | 0.86 (0.07) | 0.02(0, 0.08) | 0.05 |
| Potassium mmol/l (range 3.5-5.0 mmol/l) | 4.0 (0.4) | 4.2 (0.3) | 0.1(-0.4, 0.1) | 0.6 |
| Glucose (mmol/l) | 3.9 (0.7) | 4.3 (0.3) | -0.4(-0.8,0.1) | 0.1 |
| Insulin (µmol/l) | 3.6 (3.1) | 3.8 (1.7) | -0.2(-2, 2) | 0.8 |
| HOMA IR | 0.61(0.57) | 0.72(0.33) | -0.1(-0.4,0.2) | 0.4 |
| White Blood Cells (x109/l) | 4.7 (1.2) | 4.8 (1.3) | -0.4(-1.4,0.3) | 0.2 |
|  |  |  |  |  |

**Table 10.4 Between randomised groups: Electrolyte change between baseline and nadir. Glucose, insulin, HOMA-IR and WBC change from baseline and end of 10 days refeeding.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Electrolyte | Control  (low-energy) | Intervention  High-energy) | Mean Diff  (95%CI) | p-value |
| Phosphate  (mmol/l) | 0.07 (0.33) | 0.03 (0.24) | 0.05(-0.2, 0.2) | 0.6 |
| Magnesium  (mmol/l) | -0.02 (0.07) | -0.04 (0.08) | 0.03(-0.02,0.08) | 0.3 |
| Serum  Potassium  (mmol/l) | 0.2 (0.5) | 0.2 (0.5) | 0.02(-0.3,0.4) | 0.9 |
| Glucose (mmol/l) | 0.1 (0.4) | 0.5 (0.8) | -0.5(-1.1, 0.05) | 0.8 |
| Insulin (µmol/l) | 0.4 (1.8) | 0.2 (2.0) | -0.2(-1.7, 2.2) | 0.8 |
| HOMA IR | 0.2 (0.26) | 0.3(0.33) | -0.07(-0.21, 0.07) | 0.3 |
| White Blood Cells (x109/l) | 0.2 (0.8) | 0.15(1.3) | -0.5(-1.3,0.2) | 0.4 |
|  |  |  |  |  |

**Table 10.5 – Chi square table comparing rates of refeeding hypophosphatemia between randomised groups**

|  |  |  |  |
| --- | --- | --- | --- |
| **Group** | **Refeeding Hypophosphatemia** | | **Total** |
| **Yes NO** | |
| **Treatment**  **High calorie** | 5 | 13 | 18 |
| **Control**  **Low calorie** | 2 | 16 | 18 |
| **Total** | 7 | 29 | 36 |
| **Chi Square** | 1.5 | | |
| **P-Value** | 0.4 | | |

**10.6 Non- Randomised Analysis**

Previous studies have reported a relationship between malnutrition (%BMI), total energy intake and carbohydrate intake with hypophosphatemia. Therefore, the purpose of non-randomised analysis was to investigate the relationship between malnutrition (%BMI and WBC’s) with post refeeding nadir phosphate using regression analysis.

**10.6.1 Total energy intake and carbohydrate intake**

There was no association between total energy intake kcal/ kg/day or kcal/ day and post refeeding nadir phosphate (P= 0.6 and 0.9, respectively) (Table 10.6, Figure 10.1). Additionally, there was no association between carbohydrate intake (g/kg/day) with post refeeding nadir phosphate (P= 0.7) (Table 10.6).

**10.6.2 Dietary Phosphate**

There was no association between dietary intake of phosphate with post refeeding nadir phosphate (p=0.2) (Table 10.6).

**10.6.3 White Blood Cell Count**

There was a significant association between baseline WBC (x109/l) and nutritional status assessed by %BMI (R2 0.1; 95% CI 0.0 to 0.2; P=0.05).

There was also an association between WBC x (109/ l) and post refeeding nadir phosphate (mmol/ l) (R2 0.2; 95%CI 0.03 to 0.2mmo/ l; P=0.01) (Table 10.6, Figure 10.2). Results were adjusted for covariates %BMI and HOMA-IR to test whether the association remained, and the relationship between post refeeding phosphate nadir and baseline remained significant (P=0.03) (Table 10.7)

**10.6.4 Insulin and HOMA-IR**

There was no association between baseline %BMI or energy intake (kcal/ kg/ day) and HOMA IR (R2 0.005; 95% CI -0.8, 1.2%BMI; P=0.6 and R2 0; 95%CI -23, 22kcal; P=0.9, respectively). Additionally, no association was found between HOMA IR and post refeeding nadir phosphate (R2 0.08; 95%CI -0.8 to 0.07 mmol/l; P=0.1) (Table 10.6, Figure 10.3).

### 10.6.5 Anthropometrics – weight and %BMI

An association was found between baseline %BMI and post refeeding nadir phosphate. Participants with the lowest %BMI had the largest reduction in post refeeding phosphate (R2 0.1; 95%CI 0.001 to 0.03mmol/l; P=0.03) (Table 10.6, Figure 10.33). However, no association was found between rate of weight change (kg) or %BMI change, with post refeeding nadir phosphate (R2 0.04; 95% CI -0.1 to 0.2kg; P=0.3 and R2 0.07; 95%CI -0.01 to 0.09%; P=0.1, respectively).

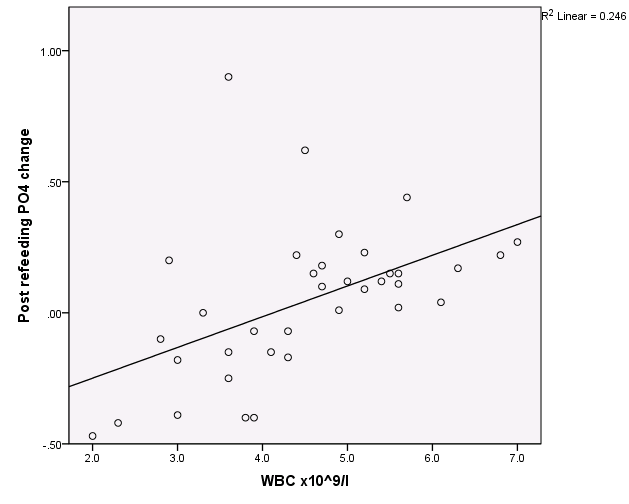
**Table 10.6 Regression analysis showing the relationship between nutritional, biochemical and anthropometric determinates and post refeeding phosphate**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Correlation coefficient  R2 | Mean Difference  95% CI | p-value |
| Nutritional | | | |
| Kcal/ day | 0.06 | 0.1(-0.2, 0.4) | 0.6 |
| Kcal/kg/day | 0.01 | 0.03(-0.2, 0.2) | 0.8 |
| Carbohydrate/  Day (grams) | 0.005 | 0.1(-0.2, 0.4) | 0.7 |
| Carbohydrate (g)/ kg/ day | 0.001 | 0.03(-0.2, 0.3) | 0.8 |
| Oral Phosphate  (mg/ day) | 0.05 | 0.2(-0.05,0.5) | 0.2 |
| Biochemical | | | |
| White Blood (cells x 109) | 0.2 | 0.1 (0.03 to 0.2) | 0.01 |
| Insulin (µmol/l) | 0.09 | 0.1 (0.03 to 0.2) | 0.09 |
| HOMA IR | 0.08 | -0.3 (-0.8 to 0.07) | 0.1 |
| Anthropometric | | | |
| %BMI | 0.1 | 0.02 (0.01 to 0.04) | 0.03 |

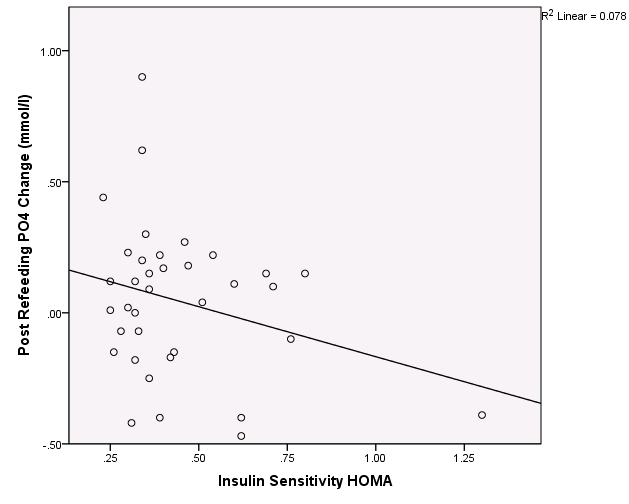
**Table 10.7 – Relationship between post refeeding phosphate and baseline white blood cell count - adjusting for covariates %BMI and HOMA IR**

|  |  |  |
| --- | --- | --- |
| **Adjusted** | | |
| **Correlation Coefficient**  **R2** | **95%CI** | **P-value** |
| 0.34 | 0.09(0.01,0.16) | 0.03 |

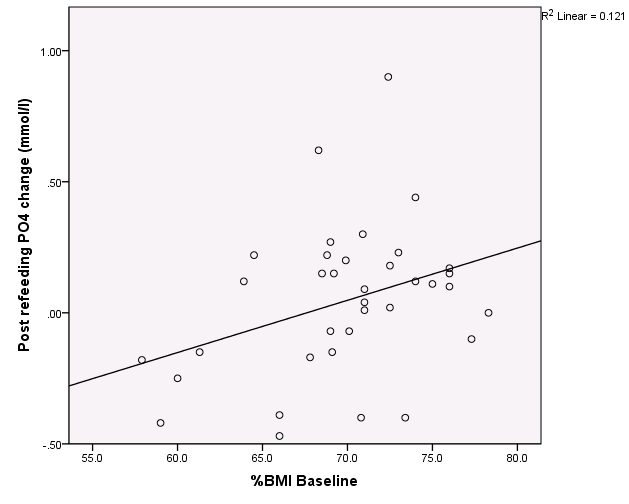
## Figure 10.1 – Relationship between WBC X109/l and post refeeding nadir phosphate (mmol/l)



## Figure 10.2 – Relationship between HOMA IR and post refeeding nadir phosphate



## Figure 10.3 – Relationship between baseline %BMI and post refeeding nadir phosphate (mmol/l)



**10.7 Summary of Results**

This study sought to identify determinants of refeeding hypophosphatemia in low weight adolescents with AN. Results showed a significant relationship between post refeeding phosphate and baseline WBC’s. Furthermore, baseline %BMI was also independently associated with post refeeding nadir phosphate. However, insulin and insulin sensitivity were not associated with post refeeding nadir phosphate. Additionally, total energy intake and carbohydrate intake were not associated with post refeeding phosphate.

**10.8 Discussion**

**10.8.1 Baseline**

The baseline serum phosphate levels reported in the present study were slightly higher than those by Ornstein et al (2003), who reported admission levels of 1.16mmol/ l, albeit still within normal range (0.9 – 1.8mmol/ l). Similarly, Gentile et al (2010) reported lower baseline serum phosphate levels; although these authors do not give specific values they do state that 35% of participants had a low serum phosphate level compared to normal, which was significantly higher than the percentage of participants that presented with low magnesium and potassium, 3% and 6% respectively.

**10.8.2 Energy intake and Refeeding Hypophosphataemia**

Higher energy intakes have been purported to increase the risk of refeeding hypophosphatemia due to the demand for and utilisation of phosphate during the formation of adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (DPG) during glucose oxidative phosphorylation ([Crook, Hally et al. 2001](#_ENREF_44); [Haglin 2001](#_ENREF_87); [Marinella 2005](#_ENREF_155); [O'Connor and Goldin 2011](#_ENREF_197)).

In the present study, at baseline no participants had hypophosphatemia (serum phosphate below 0.9mmol/l). However, once refeeding commenced hypophosphatemia developed in two participants on the low-calorie and five participants on the high calorie refeeding programme.

This incidence of refeeding hypophosphatemia in the high-calorie refeeding programme represents 27% (5 out of 18 participants) of participants, compared to 11% in the low-calorie group. In contrast, a retrospective chart review by Golden et al (2013) reported similar incidence rates of hypophosphatemia in both the high (1557kcal/ day, 265SD) and low (1163kcal/ day 107SD) refeeding programme of 15% and 18%, respectively. Interestingly, a retrospective chart review by Whitelaw et al (2010) commenced participants on higher refeeding rates (1900kcal/ day) and reported higher rates of refeeding hypophosphatemia (43%). However, they defined hypophosphatemia as <1.1mmol/ l, as opposed to 0.9mmol/ l, which would have increased the incidence. Furthermore, participants that were very low weight (cut-off not specified) were perceived as high risk of refeeding complications and were commenced on a lower refeeding programme of 1400kcal/ day. The design of the study makes interpretation of a possible association between energy intake and hypophosphatemia difficult due to variation in treatments.

In the present study, refeeding did cause an average of 19% across groups (7 out of 36 participants) to develop hypophosphatemia. Although a marginally higher proportion of participants developed refeeding hypophosphatemia in the high-calorie refeeding programme (Chi square P=0.4) there was no overall association between energy intake or carbohydrate intake and post refeeding nadir phosphate. Therefore, reducing the likelihood that refeeding hypophosphatemia is solely dependent upon energy intake.

These original findings from the first RCT to investigate the relationship between energy intake and post refeeding phosphate concur with the results of a systematic review ([O'Connor and Nicholls 2013](#_ENREF_198)) which reported on findings from observational and chart reviews, in which no association was found between post refeeding phosphate and total energy intake (R20.04, P=0.7).

**10.8.3 Naso-gastric tube feeding**

In the present study, of the four participants that required NGT feeding, one developed refeeding hypophosphataemia (25%) compared to six fed orally (19%). In light of the small numbers it is not possible to comment on the impact NGT feeding has on the development of refeeding hypophosphataemia but warrants further investigation. Unfortunately, the aforementioned studies in this section have not differentiated between feeding route (oral or enteral) and hypophosphataemia and therefore comparisons cannot be drawn.

**10.8.4 WBC and Refeeding Hypophosphataemia**

The present study is the first to identify an association between post refeeding phosphate and baseline WBC in low weight adolescents with AN. In the seven participants who developed refeeding hypophosphataemia, the mean WBC was 3.9 x 109/l compared to the overall mean of 4.5 x 109/ l (P=0.07) (reference range 5.5-10 x 109/ l). Furthermore, the present study found a relationship between WBC and %BMI.

Studies by Lambert et al (1997) and Devuyst et al (1993) also reported mean WBC below normal reference range of 4.5 x109/L (SD 0.4) and 4.9 x109/L (SD 1.9), respectively. The mean BMI was 14kg/ m2 (0.5SD) in both studies. However, Nagata et al (1999) reported even lower WBC of 3.5 (X109/L) in participants who had lower mean BMI of 11.6kg/m2. Conversely, Misra et al (2004) reported normal WBC levels in participants who had a mean BMI of 16kg/ m2 (SD 1.4).

The potential mechanisms for relationship between WBC’s, %BMI and post refeeding phosphate are discussed in chapter 11.

**10.8.5 %BMI and Refeeding Hypophosphataemia**

The present study was able to relate baseline %BMI with post refeeding nadir phosphate, which had previously been described ([Ornstein, Golden et al. 2003](#_ENREF_203); [Whitelaw, Gilbertson et al. 2010](#_ENREF_303); [Golden, Keane-Miller et al. 2013](#_ENREF_80); [O'Connor and Nicholls 2013](#_ENREF_198)). The present study reported the lowest mean %BMI of all other published studies, with a mean %BMI of 69%BMI ([O'Connor and Nicholls 2013](#_ENREF_198)). In this low weight sample, we found an incidence of refeeding hypophosphatemia of 19%.

This is considerably lower than that reported by Whitelaw et al (2010), who reported an incident rate of refeeding hypophosphatemia of 38% in participants who report a similar mean %BMI of 73%. However, a more lenient definition of hypophosphataemia was adopted (<1.1mmo/ l), which would have increased the incidence of hypophosphataemia, making it difficult to compare results. If the present study had also defined hypophosphatemia as <1.1mmol/l as opposed to 0.9mmol/ l the incidence would have been similar at 33% (12 participants).

An observational study by Garber et al (2012), reported a similar incidence of refeeding hypophosphatemia to the present study, of 21%. The sample in their study had a significantly higher mean %BMI of 80% compared to the present study (69%BMI), but used the same definition of hypophosphatemia (<0.9mmol/ l). This finding is conflicting in that a higher mean %BMI should have lowered incidence of refeeding hypophosphatemia if there is a relationship between %BMI and post refeeding phosphate.

**10.8.6 Insulin Sensitivity and Refeeding Hypophosphatemia**

The present study found participants to be insulin sensitive, which is consistent with previous observations of insulin hypersensitivity in AN. Studies by Delporte et al, (2003) and Hermans et al, (2002), monitored insulin sensitivity (HOMA) in low weight (mean BMI 14kg/ m2) participants with AN. They reported a mean HOMA sensitivity of 116% and 143% (normal 100%), respectively. Additionally, when Hermans et al, (2002) stratified results according to median insulin sensitivity, those with high insulin sensitivity were found to have similar BMIs and body compositions. Delporta et al, (2003) reported insulin sensitivity to be 40% higher in low weight AN participants compared to healthy controls and that insulin sensitivity was positively correlated to adiponectin (a fat derived hormone) (R2 = 0.25, p=<0.05). ([Hermans and Lambert 2002](#_ENREF_100); [Delporte, Brichard et al. 2003](#_ENREF_50)).

The present study found no association between %BMI and insulin sensitivity. Furthermore, insulin hypersensitivity did not significantly alter between refeeding interventions at the end of 10 days refeeding. Additionally, the insulin sensitivity reported in this study did not rectify after 10 days of refeeding, which suggests that insulin sensitivity may not improve until a significant increase in adipose tissue and percentage body fat is accrued.

## 10.9 Conclusion

Refeeding low weight adolescents with AN had a limited bearing on electrolytes and biochemistry between interventions throughout refeeding for most participants. However, in some participants refeeding did elicit refeeding hypophosphataemia. Potential determinants for increased risk of developing refeeding hypophosphataemia may be attributed to baseline WBC’s and baseline %BMI but not HOMA IR. Furthermore, refeeding hypophosphatemia was not associated with energy intake or carbohydrate intake when starting refeeding.

**Chapter 11: Overall Discussions and Conclusions**

**11.1 Key Findings**

To my knowledge this is the first randomised controlled trial to investigate the effect of total energy intake on cardiovascular, biochemical and anthropometric outcomes in low weight hospitalised adolescents with AN.

The main hypotheses for this randomised controlled trial are outlined in Chapter 8.2. The aim of the RCT was to test whether a higher refeeding intake had any detrimental effect on QTc interval, heart rate, serum biochemistry and weight when refeeding low weight hospitalised adolescents with AN. Additionally, this study sought to identify potential determinants of the most commonly reported symptom of the refeeding syndrome, characterised by refeeding hypophosphatemia.

**11.2 Cardiovascular**

### 11.2.1 QTc Interval (ms)

In chapter 9, participants randomised to both the low-calorie and high-calorie refeeding programmes had a significant decrease in QT interval from baseline and four days of refeeding. Furthermore, there was a significant difference between the high and low refeeding programmes, with the high-calorie refeeding programme resulting in a significantly lower QT interval than the low-calorie programme. However, when QT interval was corrected for heart rate (Framingham and Bazett’s formula) neither refeeding programme resulted in a significant reduction in QTc interval post refeeding, furthermore there was no significant difference in post refeeding QTc interval between the two refeeding programmes.

Additionally, with the exception of one participant in the low calorie refeeding programme refeeding improved the QTc interval in participants who had QTc interval prolongation at baseline (>440ms).

**11.2.2 Heart Rate (bpm)**

Both the low and high-calorie refeeding programme resulted in an increase in heart rate (bpm) after four days of refeeding; the differences reaching significance only in the low-calorie refeeding programme. However after four days of refeeding there was no significant difference in heart rate (bpm) between the two refeeding programmes.

## 11.3 Nutritional

**11.3.1 Total energy intake (kcal/ day and kcal/ kg/ day)**

After 10 days of refeeding participants receiving the high-calorie refeeding programme consumed a significantly higher amount of calories compared to the low calorie group. This was despite both refeeding programmes having the same target energy intake.

**11.3.2 Nasogastric Tube Feeding**

In chapter 9.12.5, it was reported that the incidence of nasogastric tube feeding was the same for both the low and high-calorie refeeding programme.

## 11.4 Anthropometric

**11.4.1 Weight (kg)**

In chapter 9the RCT investigated the impact of a refeeding programme on weight (kg) change and found that the low-calorie refeeding programme resulted in weight loss in the first 4 days of refeeding. However, after 10 days of refeeding a significant increase in weight was found.

The high-calorie refeeding programme resulted in a consistent significant weight gain throughout the 10days of refeeding. After 10days of refeeding the high-calorie refeeding programme, participants had gained considerably more weight than those on the low-calorie refeeding programme. The weight change after 4 days refeeding was significantly different between the two groups. However, despite this variation in weight change at 4 and 10 days there was no significant difference in weight change between randomised refeeding programmes.

**11.4.2 %BMI**

The %BMI significantly increased in participants in both the low and high-calorie refeeding programme; there was no significant difference between the two refeeding programmes after 4 and 10 days of refeeding.

**11.5 Electrolytes and Biochemical markers**

**11.5.1 Phosphate**

In chapter 10an RCT investigated the impact of refeeding on post refeeding nadir phosphate found that serum phosphate significantly increased in the high-calorie refeeding programme but no change was observed in the low-calorie group. However, there was no significant difference between refeeding programmes post refeeding.

Seven participants (19%) developed refeeding hypophosphataemia (<0.9mmol/l). There were five incidences among participants receiving the high-calorie refeeding programme and two in the low-calorie programme.

**11.5.2 Magnesium**

In both refeeding programmes the serum magnesium significantly decreased post refeeding albeit remaining within normal range. No participants developed hypomagnesaemia post refeeding. Furthermore, there was no significant difference in serum magnesium between refeeding programmes post refeeding.

**11.5.3 Potassium**

There was no significant difference in post refeeding serum potassium within groups or between refeeding programmes.

**11.5.4 White blood cell count**

Participants presented with a low mean baseline white blood cells in both refeeding programmes. There was no significant difference in white blood cell count within groups and between refeeding programmes post refeeding.

**11.5.5 Insulin Sensitivity**

Participants presented with insulin sensitivity at baseline and remained insulin sensitive after 10 days of refeeding. There was no difference in insulin sensitivity between the two refeeding programmes after 10 days of refeeding.

**11.6 Non Randomised Analysis**

### 11.6.1 Cardiovascular and anthropometric

In chapter 9, it was highlighted that both the low and high-calorie refeeding programme reduced the incidence of QTc interval prolongation (>440ms). However, non-randomised analysis found no association between change in QTc interval and change in weight (kg and %BMI) or with change in heart rate (bpm) after four days of refeeding.

Similarly, heart rate significantly improved in both refeeding programmes after four days of refeeding. However, non-randomised analysis found no association between change in heart rate (bpm) and change in weight (kg and %BMI).

**11.7 Determinates of refeeding hypophosphataemia**

In the present study refeeding low weight adolescents with AN resulted in seven participants (19%) developing refeeding hypophosphatemia (<0.9mmol/l). In chapter 10 a number of potential determinants were monitored to explore associations with refeeding hypophosphatemia.

**11.7.1 Energy intake (kcal/ day and kcal/ kg/ day) and carbohydrate intake (g/kg/day)**

No association was found between total energy intake (kcal/day and kcal/ kg/ day) and post refeeding hypophosphataemia. Similarly, no association was found between carbohydrate intake (g/kg/day) and post refeeding hypophosphatemia.

**11.7.2 White Blood Cells (x109)**

A significant association was identified between baseline total white blood cell count (x109) and post refeeding phosphate. Participants that had white blood cells below the normal reference range reported the greatest reduction in post refeeding phosphate.

**11.7.3 %BMI**

A significant association was found between %BMI and post refeeding phosphate. Participants that were at a lower %BMI had the greatest reduction in post refeeding phosphate from baseline measurement.

**11.7.4 Insulin Sensitivity**

No association was identified between fasting insulin levels and HOMA- insulin sensitivity with post refeeding phosphate. However, as previously reported in other studies (chapter 2) this study also found that low weight participants with AN had considerably lower fasting insulin levels than that expected in a healthy weight population.

Non-randomised analysis found no association between insulin sensitivity and baseline %BMI, or post refeeding nadir phosphate.

**11.8 Summary of Results**

In summary, this RCT found that both the low and high-calorie refeeding programme equally improved QTc interval (ms) and heart rate (bpm). After 10 days of refeeding the high-calorie refeeding programme resulted in a significantly higher consumption of total energy intake but this did not result in a significantly higher weight gain (kg and %BMI).

Non-randomised analysis found no association between total energy intake or carbohydrate intake or HOMA-IR with post refeeding nadir phosphate. However, baseline white blood cell (x109) and%BMI were associated with post refeeding nadir phosphate.

**11.9 Discussion of Results**

**11.9.1 Refeeding programme and cardiovascular outcomes**

The finding that both refeeding programmes equally resulted in a limited improvement on QTc interval was not unexpected. In chapter 5 a literature review and meta-analysis found that the impact of refeeding on QTc interval was negligible. However, the present study importantly highlights that neither the low or high-calorie refeeding programme exacerbated QTc interval - on the contrary, for the majority of participants both refeeding programmes reduced the incidence of QTc interval prolongation (>440ms). Similarly, in the present study we observed an improvement in heart rate in both refeeding programmes, as expected. In chapter 5**,** a literature review found a significant improvement in all studies that monitored heart rate pre and post refeeding.

In the only published study to have monitored the immediate effect of refeeding on QTc interval, Swenne et al (2000) reported a considerable reduction in QTc interval after 7 days of refeeding, as well as a reduction in the incidence of QTc interval prolongation.

Therefore, the significance of these findings support the hypothesis that refeeding with a higher-calorie programme (1200kcal/ day) compared to the low-calorie programme is safe and effective with regards to QTc interval and heart rate. Refeeding at 1200kcal/ day reduced the incidence of QTc interval prolongation and improved heart rate and showed no deleterious effect on QTc interval or heart rate.

Furthermore, non-randomised analysis found no association between improvements in QTc interval and heart rate and anthropometric changes (weight gain in kg or increase %BMI) which may suggest that nutritional rehabilitation in itself or other subtle anthropometric changes are contributing to the improvements seen in cardiovascular parameters. Other potential markers that maybe contributing to the improvement in QTc interval prolongation and heart rate are discussed further below in the section on future research.

**11.9.2 Refeeding programme and anthropometric outcomes**

The finding that both the low and high-calorie refeeding programme significantly increased weight (kg) and %BMI was not unexpected. Additionally, it was also expected that the high-calorie refeeding programme would elicit a greater increase in weight (kg) and %BMI, albeit not significant. However, although statistically not significant, the control (low-calorie group) lost weight after four days of refeeding whilst on a medical unit. This is clearly an undesirable outcome. Again, although statistically not significant, the low refeeding group gained nearly half as much as the high refeeding group, which is arguably clinically significant and would be a more desirable outcome in this group of patients.

The findings from the present study supports previous studies which have shown the benefits of commencing higher refeeding programmes (Garber et al [2012] 1200kcal/ day and Whitelaw et al [2010] 1900kcal/ day) on rate of weight gain while refeeding low weight hospitalised adolescents with AN.

However, as highlighted in chapter 6.4, excessively high energy intakes (>3000kcal/ day) may increase diet induced thermogenesis ([Schebendach 2003](#_ENREF_247)) and therefore limit the rate of weight gain due to a direct significant increase in resting energy expenditure. Furthermore, gradually increasing weight in relation to resting energy expenditure reduces adipose tissue accretion and promotes lean mass formation ([Cuerda, Ruiz et al. 2007](#_ENREF_45)).

In the present study the high-calorie refeeding programme produced a mean of 1kg weight gain within 10 days of refeeding, which emphasises that adequate weight gain (0.5-1kg/ week) can be achieved whilst following a meal plan that slightly exceeds the hypo-metabolic resting energy expenditure found in low weight AN adolescents of around 1000kcal/ day ([Cuerda, Ruiz et al. 2007](#_ENREF_45)). Therefore, excessively high refeeding programmes (>2500kcal/ day) may be unnecessary in these low weight hospitalised adolescents as it is likely to enhance anxiety as opposed to enhancing rate of weight gain.

**11.9.3 Refeeding programme and hypophosphataemia**

The finding that refeeding in low weight adolescents caused hypophosphataemia was not unexpected. However, this is the first RCT to investigate the association between energy intake and hypophosphataemia. In chapter 3, the pathophysiological understanding of refeeding hypophosphataemia indicates that there may be an association between energy intake and hypophosphataemia due to phosphate losses in gastric juices during digestion and phosphate utilisation in carbohydrate metabolism.

In the present study we did not find an association between energy intake and post refeeding nadir phosphate. In chapter 4, Figure 4.3, a Pearson’s correlation of published data on refeeding hypophosphataemia also did not support a direct association between energy intake and refeeding hypophosphataemia. ([O'Connor and Nicholls 2013](#_ENREF_198)).

This observation rejects the hypothesis that total energy intake (kcal/ day and kcal/ kg/ day) and carbohydrate intake (g/ kg/ day) is associated with post refeeding phosphate when commencing refeeding up to 1200kcal/ day in low weight adolescents with AN. This is the first RCT that has substantiated that refeeding up to 1200kcal/ day did not adversely affect post refeeding phosphate. Mechanisms as to why refeeding was tolerated following this refeeding programme are discussed later in this chapter.

The present study did find an association between refeeding hypophosphataemia and baseline WBC and %BMI. An area for discussion would be the use of prophylactic phosphate supplementation in these high risk patients. Prophylactic phosphate supplementation is already practiced routinely in some centres in the UK and internationally. The obvious benefit is avoidance of serious medical complications associated with hypophosphataemia. However, the disadvantages are cost implications, side effects (diarrhoea) and palatability.

### 11.9.4 Psychological Impact of Refeeding

Energy intake during refeeding must achieve a compromise between the need to restore normal nutrition as quickly as possible and the patient’s limited physical and psychological ability to tolerate eating (RCPsyh 2005). The present study did not directly measure the psychological impact of refeeding at different rates. It may be plausible to assume that the high-calorie group would have experienced a higher anxiety level and therefore higher incidences of NGT feeding. In fact, the high-calorie group consumed a higher amount of energy compared to the low-calorie group after 10 days of refeeding (chapter 9.12.4) and there was not a higher incidence of NGT feeding.

A study by Konrad et al (2007) refed 10 hospitalised women with AN and monitored their psychological status along with weight and resting energy expenditure. They reported a significant improvement in scores on Eating Attitudes Test-26, Eating Disorders Inventory-2, Brief Symptom Inventory – depression subscale, and Mizes Anorectic Cognitions Scale (p<0.05). However, body dissatisfaction did not improve. The study by Konrad et al (2005) aligns with the findings from the Minnesota starvation study which also found that anorexic cognitions diminished with weight gain (chapter 2).

However, it is important to acknowledge that refeeding a patient with AN is going to elicit stress and anxiety and if weight gain can be achieved with the minimal amount of calories whilst containing anxiety then this should be encouraged. In chronic starvation energy requirements are depressed because body cell mass is depleted and there is a conservative metabolic response to starvation. It is therefore possible to promote weight gain with a relatively low energy intake at first which increases gradually in accordance with the accretion of body fat which in turn drives the resting energy expenditure. This also allows the patient time to psychologically adapt to an increase in energy intake (Strober et al, 1997).

**11.10 Determinates of refeeding hypophosphataemia**

**11.10.1 White blood cells**

The present study identified a potential association between baseline WBC and post refeeding phosphate. An association between WBC and post refeeding nadir phosphate was not expected, as neutropenia is a common presentation in low weight patients with AN, due to the association between %BMI and WBC’s (chapter 2.9).

As previously reported, the present study observed an overall reduction in WBC count, and those participants who developed hypophosphataemia (<0.9mmol/ l) had considerably lower WBC than the overall mean.

Further research is required to substantiate this link; a hypothesis is put forward and is discussed further below. However, a potential limitation of WBC as a marker for post refeeding phosphate is that it is an inflammatory marker and therefore participants that have an infection which will raise the WBC, distorting true circulating level of WBC. However, most low weight patients with AN have a suppressed inflammatory response due to a reduction in granulocyte and lymphocyte production as a result of alterations in bone marrow constitution. The mechanism explaining the association between WBC and post refeeding phosphate are discussed later in this chapter.

**11.10.2 %BMI**

The finding that %BMI was associated with post refeeding phosphate was not unexpected, as previous retrospective studies ([Ornstein, Golden et al. 2003](#_ENREF_203); [Whitelaw, Gilbertson et al. 2010](#_ENREF_303)) and a systematic review (Chapter4) ([O'Connor and Nicholls 2013](#_ENREF_198)) reported that participants with the lowest weight and percentage body fat had the lowest post refeeding phosphate.

In light of this increased risk of refeeding hypophosphataemia in very low weight patients with AN, Leclerc et al (2013), devised a refeeding programme which was specific to participants who were over 70%BMI. It was carried out in 28 adolescents (mean age 14.7yr, SD1.5); refeeding commenced at 1500kcal/ day. Participants that were below 70%BMI (n=11) were excluded from the study and presumably commenced on a lower energy intake, although this is not reported. One participant developed hypophosphataemia which required phosphate supplementation, although no clinical signs were noted. Information on refeeding and incidence of hypophosphataemia in the 11 excluded participants (<70%BMI) would have provided useful information in this area of limited data ([Leclerc, Turrini et al. 2013](#_ENREF_148)).

**11.10.3 HOMA-Insulin Resistance**

The finding of no association between HOMA-IR and refeeding hypophosphataemia was unexpected. In chapter 3 the pathophysiology of refeeding hypophosphatemia is linked with insulin as the driving force. Therefore, it was expected that participants who developed hypophosphataemia or had a greater reduction in post refeeding phosphate would have had a higher level of circulating fasting insulin levels and subsequently reduced insulin sensitivity, this was not case.

Additionally, since the amount of insulin being secreted is directly proportional to glucose intake it was expected that the high-calorie refeeding programme would have elicited a greater insulin response and therefore have a higher circulating faster insulin levels. This was not the case, similar fasting insulin and glucose levels were observed in both refeeding programmes.

Therefore, it is not possible to support the hypothesis that circulating fasting insulin levels are associated with refeeding hypophosphataemia. Low weight adolescents with AN are hypersensitive to insulin and therefore have low circulating levels, which are tightly controlled by homeostasis regardless of the quantity of carbohydrate consumed.

**11.10.4 Nasogastric Tube Feeding**

This study differentiated between the incidence of refeeding hypophosphataemia in participants nasogastric fed and those fed by an oral meal plan. Only one of the four participants that required nasogastric tube feeding developed hypophosphataemia.

A retrospective chart review by Agostino et al (2013) whose primary outcome measure was length of hospital stay in patients fed exclusively nasogastrically compared with an oral meal plan. The study also monitored the incidence of hypophosphataemia and found that one participant in the nasogastric fed group and eight participants in the oral meal plan group developed hypophosphataemia (P=0.009) ([Agostino, Erdstein et al. 2013](#_ENREF_5)). However, prophylactic phosphate supplementation was provided in the nasogastric fed group whereas supplementation was only given if needed in the oral meal plan group. Due to the disparity in prophylactic phosphate supplementation between the NGT and oral group it is not possible to substantiate whether one feeding method is beneficial over another.

**11.11 Mechanisms for Relationship of WBC and refeeding hypophosphatemia**

In the present study post refeeding nadir phosphate was associated with baseline WBC’s. This was surprising in that neutropenia is often present in low weight patients with AN. However, it has not previously been associated to post refeeding nadir phosphate. This section aims to examine possible mechanisms for this finding.

Healthy bone marrow consists of haematopoietic cells, osteoblasts, mesenchymal stem cells, fibroblasts and adipocytes. The bone marrow is structured as sinuses, a continuous layer of endothelial cells, forming a barrier which releases specific blood cells as required in to the blood. All blood cells originate from the haematopoietic stem cell located in the bone marrow. The formation of all blood cells is called haematopoiesis; the type of blood cell that is produced is dependent on specific lineage progenitors. The myeloid progenitor cell forms granulocytes also known as white blood cells (neutrophils, eosinophils and basophils). Granulocytes have a lifespan of a few days.

Adolescence is a crucial time for the optimisation of bone mass, of which up to 40% is attributed to nutritional intake ([Heaney, Abrams et al. 2000](#_ENREF_96)). A study by Fock et al. (2010) explains that a large number of lymphocytes are produced each day by the marrow which requires a large amount of nutrients. Fock et al. (2010) suggests that during periods of malnutrition the body conserves energy for vital tissue (brain, heart, liver and kidneys), perhaps at the expense of lymphocyte production. ([Fock, Blatt et al. 2010](#_ENREF_70))

Moreover, periods of reduced energy intake causes dysregulation of the GH-IGF-1 axis and suppresses leptin levels as a direct result of a decrease in body fat (Chapter 2) resulting in bone marrow aplasia due to a disruption in bone marrow mesenchymal stem cell function, shifting away from osteoblast and haematopoietic (granulocytes) formation and paradoxically sending more cells down the bone marrow adipocyte lineage ([Abella, Feliu et al. 2002](#_ENREF_4)). Additionally, a reduction in osteoblast lineage is exacerbated as a result of a decreased intake of phosphorous and protein, exhausting extracellular phosphorous and amino acid pools, which are crucial for the mineralisation of bone extracellular matrix ([Penido and Alon 2012](#_ENREF_210)).

Furthermore, amenorrhoea found in AN is accompanied with oestrogen deficiency and increased cortisol production (Chapter 2) which contributes to bone mineral losses ([Legroux-Gerot, Vignau et al. 2005](#_ENREF_149); [Misra and Klibanski 2010](#_ENREF_175)). Additionally, reduced energy intake increases the mobilization of the bodies stored adipocyte increasing serum level of free fatty acids, which activate PPAR-Y2 and stimulates adipocyte differentiation in the bone marrow ([Sadie-Van Gijsen, Hough et al. 2013](#_ENREF_238)).

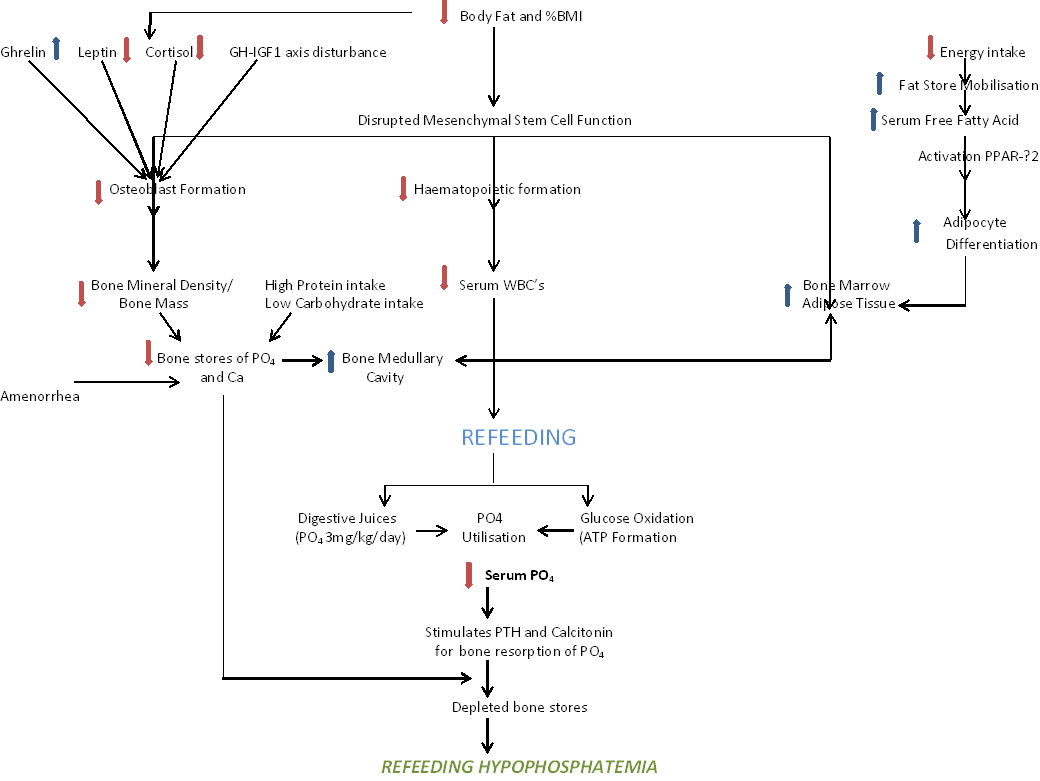
These physiological adaptations decrease mineralisation of bone extracellular matrix and bone mass causing an increase in the bone medullary cavity. Paradoxically, as body fat is depleted the additional space created in the bone medullary cavity as a result of decreased bone mineral density is replaced with bone marrow adipose tissue as opposed to osteoblasts and haematopoietic cells. A study by Di Lorgi et al. (2010), investigated the relationship between bone mineral content and bone marrow adipose tissue in 39 healthy young women. An inverse association between the amount of bone marrow adipose tissue with bone mineral content was reported in this longitudinal study over 2 yrs (R2 = 0.4, P=0.01). Additionally, an association can be found with bone mass and total body fat ([Devuyst, Lambert et al. 1993](#_ENREF_52); [Lambert, Hubert et al. 1997](#_ENREF_143); [Misra, Aggarwal et al. 2004](#_ENREF_173)).

It has been proposed that a reason for a shift to bone marrow adipose tissue formation replacing haematopoietic cells is as a potential source of energy, which is mobilised during the final stages of starvation. Once this bone marrow adipose tissue is released from the bone during the final stages of starvation it is replaced with a fluid that is rich in hyaluronic acid ([Hutter, Ganepola et al. 2009](#_ENREF_107)).

Another contributing factor to a decrease in bone mineral density is the typical nutritional intake adopted by individuals with AN which is low in fat and carbohydrate and high in protein ([Mayer, Schebendach et al. 2012](#_ENREF_160)). This nutritional constitution has also been linked to an increase in acid load and an increase in urinary calcium losses which further exacerbates bone loss, increasing space within the bone medullary cavity ([Wang, Amato et al. 2001](#_ENREF_295); [Reddy, Wang et al. 2002](#_ENREF_227); [Hutter, Ganepola et al. 2009](#_ENREF_107)). Interestingly, no evidence has linked duration of illness to bone marrow health, bone mineral deterioration seems to occur at any stage in the chronicity of AN and is dependent on weight and percentage body fat ([Lambert, Hubert et al. 1997](#_ENREF_143)). In the present study all participants had been diagnosed with AN for less than 1 year, which further illustrates the relatively short period necessary for the manifestation of altered bone marrow and bone mineral status.

Hence, when neutropenic, low weight individuals with AN are refed, they are unable to readily replace the phosphate which has been expended for digestive juices (3mg/ kg/ day) ([Berndt and Kumar 2009](#_ENREF_18)) and for glucose metabolism (ATP formation) ([Lardy and Ferguson 1969](#_ENREF_144)), due to depleted bone phosphate stores. So, once serum phosphate levels reduce, phosphate homeostasis is activated stimulating the parathyroid hormone and calcitonin to increase bone resorption of phosphate ([Berndt and Kumar 2009](#_ENREF_18)). However, due to depleted bone phosphate stores, resorption of phosphate is limited and unable to readily replace low serum levels resulting in a continual reduction in serum phosphate which, if not replaced, can lead to refeeding hypophosphataemia.

Therefore, if bone phosphate stores are depleted to the extent that the additional medullary cavity has been filled with adipocytes, which has resulted in a decreased production of granulocytes and subsequent reduction in serum WBC, then it has no relevance to the quantity of nutrition that is given, since serum phosphate that has been utilised for digestion and glucose oxidation cannot be readily replaced. In the present study participants that had WBC below 3.8 x 109/ l with no underlying infection had the greatest reduction in post refeeding phosphate. This complex interplay of reduced body fat with bone mineral density and formation of granulocytes (WBC’s) is depicted in graph 11.1.



**Diagram 11.1 interplay between reduced body fat with bone mineral density and formation of WBC and hypophosphataemia.**

**11.12 Mechanisms for relationship of %BMI and post refeeding phosphate**

The present study found an association between %BMI and post refeeding nadir phosphate. Although this association has been described in previous studies no explanation for this relationship has been hypothesised.

A possible mechanism for the association between baseline %BMI and post refeeding phosphate may be linked to body composition and WBC production. Lambert et al, (1997) investigated the link between body fat and weight with WBC in 10 young people with AN compared to 19 healthy controls. They found a significant reduction in lymphocytes and neutrophils in the AN group compared to controls (p<0.005), concluding that haematological changes in AN are correlated with body fat depletion and that a reduction in body adipose tissue adversely affects haematopoiesis in the bone marrow ([Lambert, Hubert et al. 1997](#_ENREF_143)). Therefore, as body fat stores are gradually reduced, so too is the %BMI and weight. Therefore individuals with AN that present with low %BMI implying depleted/ reduced total body fat, which as described by Lambert et al (1997) affects bone marrow haematopoiesis of lymphocytes. The present study also linked %BMI with immune function (WBCx109/l), (chapter 10) highlighting that participants with the lower %BMI also had lower WBC x 109/ l.

Therefore, as described in the previous section a decrease in total body fat paradoxically results in an increase in bone marrow adipose tissue to fill the medullary cavity. During refeeding, phosphate homeostasis is disrupted when serum phosphate is utilised for digestion and glucose metabolism and is not readily replaced due to depleted phosphate stores resulting in refeeding hypophosphatemia. Diagram 11.1.

The relationship suggests that the lower an individual’s %BMI the greater the reduction in post refeeding phosphate. In the present study participants that were below 68%BMI had the greatest reduction in post refeeding phosphate. Similarly, studies by Whitelaw et al, (2010) and Leclerc et al (2013) reported that individuals were deemed at higher risk of refeeding hypophosphatemia if below 65%BMI and 70%BMI respectively.

**11.13 Mechanism for relationship between energy intake and post refeeding phosphate**

The present study found no association between energy intake (kcal/ kg/ day, kcal/ day and carbohydrate g/ kg/ day) and post refeeding phosphate whilst commencing refeeding at 1200kcal/ day (38kcal/ kg) and increasing to 1900kcal/ day.

A possible reason for refeeding being tolerated at this rate may relate to the body’s capacity to utilise and metabolise nutrients at a reduced percentage body fat and %BMI. In chapter 7, a detailed review highlighted that low weight adolescents had a reduced resting energy expenditure compared to healthy controls, 1042kcal/ day (SD175) and 1429kcal/ day (SD251) (P<0.001), respectively.

Therefore, by refeeding just above the nutritional requirements for resting energy expenditure infers that the body does not have to cope with excessive or surplus energy intake and can therefore utilise nutrients at a maximum level without overloading an already compromised and strained body. Furthermore, in light of sufficient weight gain achieved throughout the 10 days of refeeding also infers that nutrients were adequately and sufficient utilised.

However, as highlighted in chapter 7, as the percentage body fat increases, so to will the resting energy expenditure. The systematic review performed in chapter 7 found that after 2 weeks of refeeding the resting energy expenditure increased from 1042kcal/ day to 1220kcal/ day. It is therefore essential to continue to increase the energy intake gradually to account for the newly accrued metabolically active tissue, ensuring continual weight gain.

Previous studies have only commenced high risk patients on around 1200-1400kcal/ day ([Whitelaw, Gilbertson et al. 2010](#_ENREF_303); [Garber, Michihata et al. 2012](#_ENREF_75)), which is marginally above the resting energy expenditure and therefore may account for the relatively high tolerance level of refeeding. However, if higher refeeding programmes were imposed then the occurrence of refeeding complications may be more prevalent as a result of a greater demand for phosphate during digestion and metabolism. However, starting at higher refeeding rates may be unnecessary as adequate weight gain is achieved at 1200kcal/ day.

**11.14 Implications for Clinical Practice**

Our findings support the hypothesis that refeeding low weight adolescents with AN at 1200kcal/ day had no adverse effects on cardiovascular parameters and generated significant weight gain, which has considerable implications for clinical practice. Nutritional rehabilitation is an essential component of inpatient treatment of medically unstable low weight adolescents with AN ([Golden, Katzman et al. 2003](#_ENREF_79)). However, in some patients the reintroduction of nutrition can cause the refeeding syndrome, a potentially life-threatening shift in fluids and electrolytes from extracellular to intracellular spaces ([Katzman 2005](#_ENREF_120)). Because of this link between reintroduction of nutrition and refeeding syndrome, some refeeding guidelines have erred on the side of caution due to the perceived association between quantity and risk. However, paucity in interventional research has fuelled ambivalence amongst clinicians treating these complex patients which can result in further weight loss in an inpatient setting – the underfeeding syndrome. Recently there has been a shift towards more aggressive refeeding using high calorie refeeding programme (>1200kcal/ day).

The present study refed very low weight (mean 69%BMI) adolescents with AN at 1200kcal/ day, which had no adverse effect on QTc interval (ms) and reduced the incidence of QTc interval prolongation, improved heart rate (bpm), and elicited a mean weight gain of 1kg in 10 days. However, refeeding did result in cases of hypophosphataemia in both the high and low calorie refeeding programmes, suggesting that refeeding hypophosphataemia may not be linked to quantity of nutrition reintroduced.

Along with identifying that refeeding was beneficial with regards to cardiovascular parameters, the present study also identified potential clinical markers that may increase participants risk of refeeding hypophosphataemia, providing clinicians with additional information on potential high risk patients. Participants that were very malnourished (<69%BMI) and participants that had low baseline white blood cell counts (<3.5x109/l) were at a higher risk of a greater reduction in post refeeding phosphate. However, commencing a refeeding programme at a lower energy intake does not reduce the risk. Therefore these high risk participants should commence on 1200kcal/ day due to the benefits to QTc interval, heart rate and weight gain.

**11.15 Strengths and Limitations**

The present study was a randomised controlled trial which provides the best form of evidence for the effectiveness of an intervention; the study appropriately randomised participants following the intention-to-treat model and was sufficiently powered. The design of an RCT ensures, similar characteristics of participants across groups at baseline, it controls for variables, it determines causality and minimises the risk and bias of imbalances of unknown contributing factors.

However, random allocation, does not protect controlled trials against all types of bias which may occur throughout the trial, for example poor compliance and drop-outs. The present study had a 100% follow up of participants which is probably due to the very short follow up period of 10 days. Furthermore, compliance was maintained in those participants that were unable to meet 80% of expected intake by introducing supplementary energy drinks or insertion of a naso-gastric tube. An additional strength of this study was that the primary outcome measurement (QTc interval) was performed blinded to treatment allocation enhancing internal validity ([Juni, Altman et al. 2001](#_ENREF_115)).

This study has some limitations. First, although we did exceed the sample size the overall number of participants is relatively small. However, the participants recruited represent a representative sample of medically unstable AN adolescents within the UK by virtue of its multicentre design.

Second, although food charts were completed to a high standard, variable nutritional composition of foods may have resulted in some inconsistencies with nutritional analysis which may have altered actual consumption of nutrients. However, due to no association found between energy intake and post refeeding phosphate it is unlikely that any discrepancies in nutritional analysis would have significantly altered our findings.

Thirdly, insufficient detail on admission hydration status may have influenced the initial rate of weight gain in the first 48hours, which may have influenced the overall weight gain. It is hoped that this discrepancy would be balanced out by the randomisation process and therefore reduce the potential overall effect.

Finally, it was difficult to monitor participants for longer than 10 days as many were transferred to specialist psychiatric units once medically stable. However, all pertinent physiological anomalies (hypophosphatemia and QTc interval prolongation) were captured within the first week of refeeding.

**11.16 Recommendations for future research**

1 - In light of the beneficial effect refeeding had on the incidence of QTc interval prolongation and improved heart rate, an association with weight gain could not be substantiated. This may be a result of the small sample size which was originally calculated to detect a difference in QTc interval (ms) between refeeding programmes. Similarly, a meta-analysis performed in this thesis was unable to support an association between weight change with QTc interval change during refeeding. A larger sample size may ascertain whether improvements in cardiovascular parameters are a result of weight gain or whether it is attributable to refeeding alone as proposed by Swenne et al (2005).

Additional anthropometric monitoring may be warranted to capture reasons for improvements in cardiovascular parameters before weight gain is affected, including monitoring of percentage body fat and circulating leptin levels.

2- In view of the potential association between post refeeding phosphate and baseline WBC, it would be worthwhile continuing exploring this potential association. Furthermore, it is important to substantiate the proposed mechanism behind this potential link with regards to depleted bone mineral density and increased bone marrow adipose tissue. A Dual Energy X-Ray Absorptiometry (DXA) scan could be used to monitor baseline bone density with post refeeding phosphate.

3- A final recommendation for research is a contentious one and is regarding how high refeeding should be commenced. Arguably, eliciting 1kg weight gain in 10 days following a 1200kcal/ day refeeding programme is sufficient, with regards to eating disorder recommendation. However, studies by Whitelaw et al (2010) and Leclerc et al (2013) have commenced refeeding at higher rates (1900kcal/ day and 1500kcal/ day, respectively), but either excluded high risk participants or commenced refeeding at a lower rate. Therefore, it would be worth investigating refeeding at 1500kcal/ day but to include high risk participants, especially in that this study has challenged an association between post refeeding phosphate with energy intake.

A consideration for incorporating the above recommendations would be to collaborate with other international eating disorder units particularly in North America, Canada and Australia; this would ensure a more rapid recruitment to meet a substantial sample size in a timely period.

**11.17 Conclusions**

In conclusion, this first randomised controlled trial to investigate the effect of refeeding programmes in low weight adolescents with AN found that an initial refeeding rate of 1200kcal/ day (38kcal/ kg), incrementally (200kcal/ day) increased to 1900kcal/ day (58kcal/ kg) significantly increased weight and %BMI, improved heart rate and had no adverse effect on QTc interval. Additionally, there was no significant increase in the incidence or severity of refeeding hypophosphatemia.

Furthermore, after 10 days of refeeding participants consumed a significantly higher energy intake than at baseline or than those in the lower calorie group. Together, these findings suggest that oral refeeding at 1200kcal/ day (38kcal/ kg/ day) and increasing incrementally to 1900kcal/ day (58kcal/ kg/ day) is more beneficial on average than commencing refeeding at 500kcal/ day for low weight adolescents with AN.

Refeeding syndrome, as measured by refeeding hypophosphatemia, is a risk for a proportion of patients. This study found that participants with low WBC’s (WBC <3.8 x 109/l) had a greater reduction in post refeeding phosphate. Similarly, participants that were below 68%BMI had a greater reduction in post refeeding phosphate.

**Acknowledgements**

I would sincerely like to acknowledge the help and advice I received from the following people:

Atul Singhal

Dasha Nicholls

Vanessa Shaw

Julie Lanigan

Lee Hudson

I would also like to thank the dietitians and consultant paediatricians at each of the collaborating centres:

**Great Ormond Street Foundation Hospital**

Jonathon Goldin

**Manchester Children’s Foundation Hospital**

Jane Whittaker

Sarah LeGrice

Sarah Cawtherley

**Luton and Dunstable District General Hospital**

Sarah Fuller

Michael Eisenhut

**Poole Foundation Trust**

Mark Tighe

Sarah Currel

**Devon and Exeter Foundation Trust**

Karen Street

Susannah Costelloe

**James Cook University Hospital (Middlesbrough)**

Ginny Birrel

Ruth Weatherall

Additionally, I would like to thank the British Dietetic Association and Great Ormond Street Children’s Charity for providing charitable funds towards this research.

**Information of work in this thesis**

**Concept and design**

The original idea for the RCT was conceived by me, initiated after observing numerous adolescents inpatients with aAN developing refeeding syndrome whilst following non-evidenced based refeeding guidelines. From this I published a case report ([O'Connor and Goldin 2011](#_ENREF_197)), which then rapidly grew into a larger research project. Thankfully I had the support around me to develop this research idea into a PhD.

**Author’s role**

My roles in this research was to gain ethical approval, find funding, recruit and train centres on protocol as the principle investigator. I was involved in the monitoring and compliance of protocols at all participating centres.

**Data collection**

I undertook and/ or supervised the following aspects of data collection:

Obtained informed consent for study participants for ECG’s and venopunctures.

Collected anthropometric and physiological data

Data input

**Data analysis**

Design of meal plan templates for nutritional analysis

Assembled master database

Analysed all data

**Thesis construction**

The final thesis was constructed and designed by me. Help in proof reading/ editing was provided by CriticalEditing.com, Dasha Nicholls and Atul Singhal

**Appendix 1-1**

1. Letter to GP
2. Participant information sheet – Carer
3. Participant information sheet – patient
4. Consent Form
5. Meal template

## Appendix 1 – GP Research information letter

Graeme O’Connor

Nutrition and Dietetics Department

6th Floor Cardiac Wing

Great Ormond Street Hospital

WC1N 3JH

0208 4059200 ext 5351

**GP Research Information Letter**

Dear Dr.

**RE: Name**

**DOB**

The above named patient has consented to take part in a national multi-centred research study headed by Great Ormond Street Children’s Hospital. They were recruited due to being admitted to a paediatric ward with a diagnosis of anorexia nervosa requiring nutritional rehabilitation.

The study is looking to investigate the effect of total energy intake during the early stages of refeeding in acute starvation in children with anorexia nervosa. Participants will be randomly assigned to one of two refeeding programs where physiological recovery rate will be monitored by observing biochemical and cardiovascular markers.

It is hoped that the results of this study will develop national evidence based refeeding guidelines for children with anorexia nervosa.

If you would like further information on this research project please contact the lead researcher based at Great Ormond Street Hospital contact information above.

Kind Regards

Graeme O’Connor RD PgDip FCP BSc (Hons)

Research Student

Specialist Paediatric Dietitian

## Appendix 2 – Participant Information Sheet for Parents

**Participant Information Sheet For the Parents**

**Study on the body’s recovery rate following a period of low food intake and the introduction of food**

We are asking you to consider allowing your child to take part in a research project. Before you decide it is important for you to understand why the research is being done and what it will involve for your child. Please take the time to read this information sheet and discuss it with your family, friends, doctor or dietitian if you want to. Ask us if there is anything that is not clear or if you would like to know more. Your child will also receive information about the study which they may receive once the study is completed or when they are less ill.

**PART 1**

**What is the purpose of the study?**

When the body does not have adequate or the right types of nutrition it changes its normal way of working to account for the reduction in food intake. This change means that the body begins to breakdown its own stores to help feed the body.

When adequate food is re- introduced the body switches back to its preferred and most efficient way of working, which can cause problems with the heart and blood and is collectively known as the refeeding syndrome.

Our aim is to find out if one way of introducing nutrition is better than another so that we can reduce as many complications associated with refeeding.

**Why has your child been chosen?**

Your child has been invited to take part in the study because they have endured a period of minimal food intake for a period of time and as a result have been admitted to a children’s ward for close monitoring.

**Do I have to take part?**

No. If you decide not to take part you do not have to give a reason. Your treatment will not be affected. If you decide to take part we will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving reason and will not affect the standard of care given to your child.

**What will happen to my child if they take part?**

Your child would be involved in the study for two weeks while they are on a children’s unit and will be visited by a member of the research team every day.

Randomised Trial – sometimes we don’t know which way of treating the patient is best. To find out we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better than the other. Your child would be started on one of two possible food introduction programs both of which are currently practiced around the United Kingdom and are therefore deemed as safe. One feeding program starts at 500kcal/day and the other feeding program starts at 1200kcal/day, both are increased by 200kcal/day until target nutritional requirements are met.

Due to your child’s medical state they will need to undergo close observation this would occur whether or not your child was apart of the study. The observations that will occur are blood tests and heart monitoring to make sure that the body is coping with the food given.

**What are the potential benefits/ disadvantages of taking part?**

There are no immediate potential benefits or disadvantages, as your child would receive this treatment regardless of the study, however the results from the observations may indicate that one of the two feeding programs enhance the body’s recovery rate better than the other.

**What if there is a problem?**

Any complaints in the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in part 2.

**Will my child’s details from this study be kept confidential?**

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in part 2

**If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.**

**Part 2**

**What if relevant new information becomes available?**

Sometimes we get new information about the treatment being studied. If this happens, a member of the research team will tell you and discuss whether you should continue in the study. If you decide now to carry on, a member of the research team will make arrangements for your care to continue.

**What will happen if I don’t want my child to continue with the study?**

If you withdraw from the study, we will destroy all your identifiable samples, but we will need to use the data collected up to your withdrawal.

Or

You can withdraw from treatment but keep in contact with us to let us know your progress. Information collected may still be used. Any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish.

**What if there is a problem?**

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (0207 4059200 ext 5351 – Graeme O’Connor – Lead Investigator). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

In the unlikely event that something does go wrong and your child is harmed during the research and this is due to someone’s negligence then you may have grounds for a legal action for compensation against Great Ormond Street Children’s Hospital, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

**Will my child’s details be kept confidential?**

If your child joins the study, some parts of their medical records and the data collected for the study will be looked at by authorised persons from the company sponsoring and/or the company organising the research. They may also be looked at by people from the company, by representatives of regulatory authorities and by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

All information which is collected about your child during the course of the research will be kept strictly confidential, and any information about your child which leaves the hospital will have your name and address removed so that your child cannot be recognised.

Data collected during the study may be sent to associated researchers to countries where the laws don’t protect your privacy to the same extent as the Data Protection Act in the UK but the company will take all reasonable steps to protect your privacy*.*

**Involvement of the General Practitioner**

Your child’s GP will be notified that they are taking part in this research study

**What will happen to any samples given?**

Your child will not be expected to provide any additional blood samples that would normally be required for suitable monitoring. No blood samples will be kept after study has been completed.

**Who is funding the research?**

The National Institute of Health Research

**What will happen to the results of the study?**

The results will be reported in a medical publication and it is hoped that national guidelines will be developed to help other children in similar situations around the United Kingdom.

**Who has reviewed the study?**

The study has been checked by paediatricians, children’s psychiatrists, dietitians and national research ethics services.

If you are willing for your child to participate in this study please request a consent form from the research team.

If you have any queries regarding the study please contact Graeme O’Connor on 02074059200 ext 2354 or email graeme.oconnor@nhs.net

## Appendix 3 Information sheet for child/ adolescent

**Children’s Information Sheet about a research project**

**The research project is looking to see how your body behaves with food being eaten after such a long time without enough food**

When you were taken to the hospital your mum and/or dad were asked if they would allow you to take part in a project that was going to see how your body behaved with food being given after such a long time without any food eaten.

Before your mum and/or dad made up their minds it was important that they understood why the research was being done and what it involved for you. You may have received information about the study once it had finished because you were too ill when you were admitted to the ward.

**PART 1**

**What is the purpose of the study?**

When the body does not have adequate or the right types of nutrition it changes its normal way of working to account for the reduction in food intake. This change means that the body begins to breakdown its own stores to help feed the body.

When adequate food is re- introduced the body switches back to its preferred and most efficient way of working, which can cause problems with the heart and blood and is collectively known as the refeeding syndrome.

Our aim is to find out if one way of introducing nutrition is better than another so that we can reduce as many complications associated with feeding.

**Why were you chosen?**

You were invited to take part in the study because you had small amounts of food eaten over a long time, which meant you had to go to hospital for close monitoring. It is during this close monitoring time when food was given to you to eat, that we wanted to see what your body does, especially your blood and heart

**What happened to you as part of this project?**

You were involved in the study for two weeks while on the children’s unit and were visited by a member of the research team every day.

Sometimes we don’t know which way of treating the patient is best. To find out we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better than the other. Your child would be started on one of two possible food introduction programs both of which are currently practiced around the United Kingdom and are therefore deemed as safe.

Due to your bodies medical state you needed to undergo close observation this would have occur whether or not you were apart of the study. The observations that occurred are blood tests and heart monitoring to make sure that the body is coping with the food given.

**What are the potential benefits/ disadvantages of taking part?**

There are no immediate potential benefits or disadvantages, as you would have receive this treatment regardless of the study, however the results from the observations may indicate that one of the two feeding programs enhance the body’s recovery rate better than the other.

**What if there is a problem?**

Any complaints in the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in part 2.

**Will my details from this study be kept secret?**

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in part 2

**Part 2**

**What if relevant new information becomes available?**

Sometimes we get new information about the treatment being studied. If this happens, a member of the research team will tell you and discuss whether you should continue in the study. If you decide now to carry on, a member of the research team will make arrangements for your care to continue.

**What will happen if I don’t want to continue with the study?**

If you withdraw from the study, we will destroy all your identifiable samples, but we will need to use the data collected up to your withdrawal.

Or

You can withdraw from treatment but keep in contact with us to let us know your progress. Information collected may still be used. Any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish.

**What if there is a problem?**

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (0207 4059200 ext 5351 – Graeme O’Connor – Lead Investigator). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

In the unlikely event that something does go wrong and you are harmed during the research and this is due to someone’s negligence then you may have grounds for a legal action for compensation against Great Ormond Street Children’s Hospital, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

**Will my details be kept secret?**

If you join the study, some parts of their medical records and the data collected for the study will be looked at by authorised persons from the company sponsoring and/or the company organising the research. They may also be looked at by people from the company, by representatives of regulatory authorities and by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital will have your name and address removed.

Data collected during the study may be sent to associated researchers to countries where the laws don’t protect your privacy to the same extent as the Data Protection Act in the UK but the company will take all reasonable steps to protect your privacy*.*

**Involvement of the General Practitioner**

Your GP will be notified that they are taking part in this research study

**What will happen to any samples given?**

You will not be expected to provide any additional blood samples that would normally be required for suitable monitoring. No blood samples will be kept after study has been completed.

**Who is funding the research?**

British Dietetic Association and Great Ormond Street Hospital Charity

**What will happen to the results of the study?**

The results will be reported in a medical publication and it is hoped that national guidelines will be developed to help other children in similar situations around the United Kingdom.

**Who has reviewed the study?**

The study has been checked by paediatricians, children’s psychiatrists, dietitians and national research ethics services.

If you are willing for your child to participate in this study please request a consent form from the research team.

If you have any queries regarding the study please contact Graeme O’Connor on 02074059200 ext 5352 or Bleep 0306 or email [graeme.oconnor@nhs.net](mailto:graeme.oconnor@nhs.net)

Local Investigator Details: Name

Contact Number

# Appendix 4 – Consent form for parents

**Parent/Guardian CONSENT FORM**

**Title of the Research project: Investigate the effect on total energy intake on the physiological recovery rate of children with anorexia nervosa**

**Sponsor Protocol No**: 09NT11

**Investigator:** Graeme O’Connor

**Contact details:** : 02074059200/ 07958543828

🖳: Graeme.oconnor@gosh.nhs.uk

**Subject Identification No for this trial:**

Please **initial box** to indicate agreement:

|  |  |  |
| --- | --- | --- |
| 1 | I confirm that I have read and understand the information sheet dated 28/03/2010 (version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. |  |
| 2 | I understand that my child’s participation is voluntary and that he/she is free to withdraw at  any time, without giving any reason, without his/her medical care or legal rights being affected. |  |
| 3 | I agree to my child’s GP being informed of his/her participation in the study. |  |
| 4 | I agree to my child taking part in the above study. |  |

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Name of Child

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_

Name of Parent/Guardian Date Signature

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_

Name of Person taking consent Date Signature

(if different from Investigator)

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_

Investigator Date Signature

## Appendix 5 - Meal Plan 500

|  |  |
| --- | --- |
| **Breakfast** |  |
| Carbohydrate | ½ portion |
| Spread | - |
| Jam | - |
| Milk | ½ portion |
| Fruit juice | - |
|  |  |
| **Mid-morning** |  |
| Fruit/biscuits |  |
| Milk/fruit juice |  |
|  |  |
| **Lunch** |  |
| Sandwich of: |  |
| Protein | ½ portion |
| Carbohydrate | ½ portion |
| Fat |  |
| Salad garnish | When avail |
| Pudding/fruit/milk | - |
|  |  |
| **Mid-afternoon** |  |
| Biscuits/fruit |  |
| Spread | - |
| Milk/fruit juice |  |
|  |  |
| **Evening meal** |  |
| Protein | ½ portion |
| Carbohydrate | ½ portion |
| Vegetables | - |
| Pudding/fruit/milk |  |
|  |  |
| **Bedtime** |  |
| Carbohydrate/Fruit |  |
| Milk | ½ portion |

## Appendix 6 - Meal Plan 1200

|  |  |
| --- | --- |
| **Breakfast** |  |
| Carbohydrate | ½ portion |
| Spread | - |
| Jam | - |
| Milk | 1 portion |
| Fruit juice | - |
|  |  |
| **Mid-morning** |  |
| Fruit/biscuits | ½ portion |
| Milk/fruit juice |  |
|  |  |
| **Lunch** |  |
| Sandwich of: |  |
| Protein | ½ portion |
| Carbohydrate | ½ portion |
| Fat | ½ portion |
| Salad garnish | When avail |
| Pudding/fruit/milk | ½ portion |
|  |  |
| **Mid-afternoon** |  |
| Biscuits/fruit | ½ portion |
| Spread | - |
| Milk/fruit juice | - |
|  |  |
| **Evening meal** |  |
| Protein | ½ portion |
| Carbohydrate | ½ portion |
| Vegetables | - |
| Pudding/fruit/milk | 1 portion |
|  |  |
| **Bedtime** |  |
| Carbohydrate/Fruit | ½ portion |
| Milk | 1 portion |

## Appendix 7 - Meal Plan 1800

|  |  |
| --- | --- |
| **Breakfast** |  |
| Carbohydrate | 1 portion |
| Spread | - |
| Jam | - |
| Milk | 1 portion |
| Fruit juice | - |
|  |  |
| **Mid-morning** |  |
| Fruit/biscuits | 1 portion |
| Milk/fruit juice |  |
|  |  |
| **Lunch** |  |
| Sandwich of: |  |
| Protein | 1 portion |
| Carbohydrate | 1 portion |
| Fat | ½ portion |
| Salad garnish | When avail |
| Pudding/fruit/milk | 1 portion |
|  |  |
| **Mid-afternoon** |  |
| Biscuits/fruit | 1 portion |
| Spread | - |
| Milk/fruit juice | ½ portion |
|  |  |
| **Evening meal** |  |
| Protein | 1 portion |
| Carbohydrate | ½ portion |
| Vegetables | - |
| Pudding/fruit/milk | 1 portion |
|  |  |
| **Bedtime** |  |
| Carbohydrate/Fruit | ½ portion |
| Milk | 1 portion |

## Appendix 8 Food Portions

All equal to **1 portion** unless otherwise stated

**Carbohydrate:**

**Bread:**

2 slices bread

1 med. bread roll

**Rice/Pasta:**

½ cup cooked rice (brown/white)

1 small can spaghetti

1 cup cooked pasta

**Biscuits:**

2 Custard Creams

2 Marie (1/2 portion)

3 Nice (1/2 portion)

3 Shortcake

3 Digestive

1 Fox’s Caramel Rocky biscuit

3 Jaffa cakes

**Other snacks:**

1 Twix bar

1 Jaffa Cake bar

1 Flake

1 pkt Milky Way Magic Stars (30g)

1 pkt Hula Hoops (34g)

1 pkt Walkers Crisps (34g)

**Potato:**

1 jacket potato (med)

1 boiled potato (med)

10-12 chips

1 roast potato (small-med)

2 scoops mashed potato (with butter)

**Breakfast cereal:**

Weetabix x 2

Rice Crispies (30g) – 1/3 mug (standard ward mug)

Cornflakes (30g) – 1/3 mug (standard ward mug)

**Fruit**

2 apples

2 oranges

1 large banana

small bunch grapes

200mls juice (1/2 portion)

250mls Ribena

250mls Lucozade

**Protein**

**Meat**

2 slices meat (medium)

1 small chicken leg, breaded

2 sausages

3 fishfingers

½ serve lasagne (1 serve = approx 300kcals)

1 serve cottage pie (approx 150g)

4 chicken nuggets

1 beef burger, fried

**Vegetarian options**

2 eggs, or 1 egg in 1dsp mayonnaise/salad cream

½ large tin (200g) baked beans

1 tbsp peanut butter

30g nuts (shelled)

25g (1 individual portion) cheddar-type cheese

2 individual portions processed cheese ie. Dairylea

**Milk**

200ml whole milk

300ml semi-skimmed milk

1 mug hot chocolate/Ovaltine or similar milky drink

1 carton yoghurt (fruit or natural)

3 tsp Nesquik in 200mls semi-skimmed milk

**Fat**

2 rounded tsp butter/4 small teaspoons butter

1 tbsp mayonnaise/salad cream

Peanut paste – see ‘protein’ section

**Miscellaneous**

½ tin Cream of chicken soup

½ tin Cream of tomato soup

### Apprendix 9 –Research Protocol

|  |  |
| --- | --- |
| **Research Protocol** |  |
| **Day 1** | **Checked** |
| Contact Graeme O’Connor PI (research dietitian) 02074059200 ext 2354 - 07958543828 |  |
| Patient and parent information sheets provided |  |
| Consent gained |  |
| SpR/ consultant to request an emergency 12 lead ECG (baseline) |  |
| 6 hourly vital sign monitoring HR, BP, Temperature – ensure patient has been resting for 10mins prior to measurements |  |
| Weight and height |  |
| Request biochemistry – PO4, K, Na, Mg, Ca (baseline)   * INSULIN and Glucose   Urine Dipstick – Check for ketones (if positive check every day until negative) |  |
| Start Thiamine 100mg bd – orally. To continue for 10 days |  |
| Meal Plan 500 or 1200kcal – discus with patient food choices based on portion chart |  |
| Ensure nurses have completed food/ feed record chart |  |
| **Day 2** |  |
| ECG if not done on day 1 |  |
| Morning resting vital sign monitoring HR, BP, Temperature – ensure patient has been resting for 10mins prior to measurements |  |
| Request biochemistry – PO4, K, Na, Mg, Ca   * INSULIN and Glucose   **Take bloods in the morning before breakfast - overnight fast** |  |
| Ensure required amount of nutrition has been administered and increase meal plan/ feed by 200kcal (700 or 1400kcal/day) – depending on biochemistry |  |
| Ensure nurses have completed food/ feed record chart |  |
| **Day 3** |  |
| Morning resting vital sign monitoring HR, BP, Temperature – ensure patient has been resting for 10mins prior to measurements |  |
| Ensure required amount of nutrition has been administered and increase meal plan/ feed by 200kcal (until BMR and 1.2AF reached) |  |
| Ensure nurses have completed food/ feed record chart  Organise ECG 12 lead for to tomorrow |  |
| **Day 4** |  |
| Morning resting vital sign monitoring HR, BP, Temperature – ensure patient has been resting for 10mins prior to measurements |  |
| Request biochemistry – PO4, K, Na, Mg, Ca   * INSULIN and Glucose   **Take bloods in the morning before breakfast - overnight fast**  **ECG 12 Lead** |  |
| Ensure required amount of nutrition has been administered and increase meal plan/ feed by 200kcal ((until BMR and 1.2AF reached) |  |
| Ensure nurses have completed food/ feed record chart  **WEIGH** |  |
| **Day 5** |  |
| Morning resting vital sign monitoring HR, BP, Temperature – ensure patient has been resting for 10mins prior to measurements |  |
| Ensure required amount of nutrition has been administered and increase meal plan/ feed by 200kcal (until BMR and 1.2AF reached) |  |
| Ensure nurses have completed food/ feed record chart |  |
| **Day 6** |  |
| Request biochemistry – PO4, K, Na, Mg, Ca   * INSULIN and Glucose   **Take blood in the morning before breakfast - overnight fast** |  |
| Morning resting vital sign monitoring HR, BP, Temperature – ensure patient has been resting for 10mins prior to measurements |  |
| Ensure required amount of nutrition has been administered and increase meal plan/ feed by 200kcal (until BMR and 1.2AF reached) |  |
| Ensure nurses have completed food/ feed record chart |  |
| **If ECG on day 4 reported Q-Tc prolongation >0.44s (440ms) repeat ECG** |  |
| **Day 7 - 9** |  |
| Morning resting vital sign monitoring HR, BP, Temperature – ensure patient has been resting for 10mins prior to measurements |  |
| Ensure required amount of nutrition has been administered and increase meal plan/ feed by 200kcal (until BMR and 1.2AF reached) |  |
| Ensure nurses have completed food/ feed record chart  **Day 8 - WEIGH** |  |
| **Day 10** |  |
| Request biochemistry – PO4, K, Na, Mg, Ca   * INSULIN and Glucose   **Take blood in the morning before breakfast - overnight fast** |  |
| Stop Thiamine 200mg bd |  |
| Morning resting vital sign monitoring HR, BP, Temperature – ensure patient has been resting for 10mins prior to measurements |  |
| Ensure required amount of nutrition has been administered and increase meal plan/ feed by 200kcal (until BMR and 1.2AF reached) |  |
| Ensure nurses have completed food/ feed record chart  **WEIGH** |  |

# References

**American Dietetic Association** (2006). American Dietetic Association Position Statement 2006: Nutritional intervention in the treatment of anorexia nervosa., Journal American Dietetic Association.

**American Psychiatric Association**, N. G., Clearinghouse. "Practice guideline for the treatment of patients with eating disorders." Retrieved 11/2/2012, from <http://guidelines.gov/content.aspx?id=9318>.

**American Psychiatric Association** (2006). "Treatment of patients with eating disorders,third edition. American Psychiatric Association." Am J Psychiatry **163**(7 Suppl): 4-54.

**Royal College Of Psychiatrists** (2005). Royal College of Psychiatrist. 2005. Guidelines for the nutritional management of anorexia nervosa. CR130. London.

**Royal College Of Psychiatrists** (2010). Management of Really Sick Patients with Anorexia Nervosa: MARSIPAN. CR162. London.

**Royal College Of Psychiatrists** JuniorMARSIPAN (2012). Management of Really Sick Inpatients with Anorexia Nervosa <18yrs. Royal College of Psychiatrists CR168, .

**National Institute of Clinical Excellence**, 2005. National Collaborating Centre for Mental Health. Core interventions in the treatment and management of anorexia nervosa, bulimia nervosa and related eating disorders, The British Psychological Society and Gaskell.

**National Institute Of Clinical Excellence** (2006). Nutritonal Support in Adults: Oral, enteral and parenteral nutrition CG32. London: NICE.Royal College of Psychiatrists, 2011. Junior MARSIPAN: Management of really sick patients with anorexia nervosa - under 18yrs. CR168. London.

World Health Organisation: Management of severe malnutrition: a manual for physicians and other senior health workers. 2006. Geneva: W.H.O.

(2004). National Institute of Clinical Excellence. National Collaborating Centre for Mental Health. Core interventions in the treatment and management of anorexia nervosa, bulimia nervosa and related eating disorders, The British Psychological Society and Gaskell.

Abella, E., E. Feliu, et al. (2002). "Bone marrow changes in anorexia nervosa are correlated with the amount of weight loss and not with other clinical findings." Am J Clin Pathol **118**(4): 582-588.

Agostino, H., J. Erdstein, et al. (2013). "Shifting Paradigms: Continuous Nasogastric Feeding With High Caloric Intakes in Anorexia Nervosa." J Adolesc Health.

Alamy, M. and W. A. Bengelloun (2012). "Malnutrition and brain development: an analysis of the effects of inadequate diet during different stages of life in rat." Neurosci Biobehav Rev **36**(6): 1463-1480.

Alvin, P., J. Zogheib, et al. (1993). "[Severe complications and mortality in mental eating disorders in adolescence. On 99 hospitalized patients]." Arch Fr Pediatr **50**(9): 755-762.

American Psychiatric Association, N. G., Clearinghouse. "Practice guideline for the treatment of patients with eating disorders." Retrieved 11/2/2012, from <http://guidelines.gov/content.aspx?id=9318>.

AmericanDieteticAssociation (2006). American Dietetic Association Position Statement 2006: Nutritional intervention in the treatment of anorexia nervosa., Journal American Dietetic Association.

AmericanPsychiatricAssociation (2006). "Treatment of patients with eating disorders,third edition. American Psychiatric Association." Am J Psychiatry **163**(7 Suppl): 4-54.

Arcelus, J., A. J. Mitchell, et al. (2011). "Mortality rates in patients with anorexia nervosa and other eating disorders. A meta-analysis of 36 studies." Arch Gen Psychiatry **68**(7): 724-731.

Bailer, U. F., J. C. Price, et al. (2004). "Altered 5-HT(2A) receptor binding after recovery from bulimia-type anorexia nervosa: relationships to harm avoidance and drive for thinness." Neuropsychopharmacology **29**(6): 1143-1155.

Baker, J. H., L. M. Thornton, et al. (2012). "Pubertal development predicts eating behaviors in adolescence." Int J Eat Disord **45**(7): 819-826.

Bazett, H. (1920). "An analysis of the time-relations of electrocardiograms." Heart **7**: 353–370.

Bemporad, J. R. (1996). "Self-starvation through the ages: reflections on the pre-history of anorexia nervosa." Int J Eat Disord **19**(3): 217-237.

Berkman, N. D., C. M. Bulik, et al. (2006). "Management of eating disorders." Evid Rep Technol Assess (Full Rep)(135): 1-166.

Berkman, N. D., K. N. Lohr, et al. (2007). "Outcomes of eating disorders: a systematic review of the literature." Int J Eat Disord **40**(4): 293-309.

Berndt, T. and R. Kumar (2009). "Novel mechanisms in the regulation of phosphorus homeostasis." Physiology (Bethesda) **24**: 17-25.

Berner, Y. N. and M. Shike (1988). "Consequences of phosphate imbalance." Annu Rev Nutr **8**: 121-148.

Bessesen, D. H. (2011). "Regulation of body weight: what is the regulated parameter?" Physiol Behav **104**(4): 599-607.

Birmingham, C. L., J. Su, et al. (2005). "The mortality rate from anorexia nervosa." Int J Eat Disord **38**(2): 143-146.

Bistrian, B. R., G. L. Blackburn, et al. (1975). "Cellular immunity in semistarved states in hospitalized adults." Am J Clin Nutr **28**(10): 1148-1155.

Boateng, A. A., K. Sriram, et al. (2010). "Refeeding syndrome: treatment considerations based on collective analysis of literature case reports." Nutrition **26**(2): 156-167.

Bossu, C., B. Galusca, et al. (2007). "Energy expenditure adjusted for body composition differentiates constitutional thinness from both normal subjects and anorexia nervosa." American Journal of Physiology - Endocrinology And Metabolism **292**(1): E132-E137.

Bouchard, L., R. Rabasa-Lhoret, et al. (2010). "Differential epigenomic and transcriptomic responses in subcutaneous adipose tissue between low and high responders to caloric restriction." Am J Clin Nutr **91**(2): 309-320.

Bourne, R. S., T. A. Tahir, et al. (2008). "Drug treatment of delirium: past, present and future." J Psychosom Res **65**(3): 273-282.

Brewerton, T. D. (2012). "Antipsychotic agents in the treatment of anorexia nervosa: neuropsychopharmacologic rationale and evidence from controlled trials." Curr Psychiatry Rep **14**(4): 398-405.

Brihaye Abadie, I., R. de Tournemire, et al. (2003). "Anorexie mentale : conséquences sur la croissance et la minéralisation osseuse." Archives de Pédiatrie **10**(9): 836-840.

Brooks, M. J. and G. Melnik (1995). "The refeeding syndrome: an approach to understanding its complications and preventing its occurrence." Pharmacotherapy **15**(6): 713-726.

Brown, R. S. (1984). "Potassium homeostasis and clinical implications." Am J Med **77**(5A): 3-10.

Brozek, J., C. B. Chapman, et al. (1948). "Drastic food restriction; effect on cardiovascular dynamics in normotensive and hypertensive conditions." J Am Med Assoc **137**(18): 1569-1574.

Bryceson, D. F. (1989). "Nutrition and the commoditization of food in sub-Saharan Africa." Soc Sci Med **28**(5): 425-440.

Call, C., B. T. Walsh, et al. (2013). "From DSM-IV to DSM-5: changes to eating disorder diagnoses." Curr Opin Psychiatry **26**(6): 532-536.

Caprio, S. (1999). "Insulin: the other anabolic hormone of puberty." Acta Paediatr Suppl **88**(433): 84-87.

Carlomagno, G., V. Mercurio, et al. (2011). "Endocrine alterations are the main determinants of cardiac remodelling in restrictive anorexia nervosa." ISRN Endocrinol **2011**: 171460.

Casiero, D. and W. H. Frishman (2006). "Cardiovascular complications of eating disorders." Cardiol Rev **14**(5): 227-231.

Chui, H. T., B. K. Christensen, et al. (2008). "Cognitive function and brain structure in females with a history of adolescent-onset anorexia nervosa." Pediatrics **122**(2): e426-437.

Clarke, T. K., A. R. Weiss, et al. (2012). "The genetics of anorexia nervosa." Clin Pharmacol Ther **91**(2): 181-188.

Cole, T. J., M. L. Donnet, et al. (1981). "Weight-for-height indices to assess nutritional status--a new index on a slide-rule." Am J Clin Nutr **34**(9): 1935-1943.

Cole, T. J., K. M. Flegal, et al. (2007). "Body mass index cut offs to define thinness in children and adolescents: international survey." BMJ **335**(7612): 194.

Cole, T. J., J. V. Freeman, et al. (1995). "Body mass index reference curves for the UK, 1990." Arch Dis Child **73**(1): 25-29.

Cooke, R. A., J. B. Chambers, et al. (1994). "QT interval in anorexia nervosa." Br Heart J **72**(1): 69-73.

Couturier, J., M. Kimber, et al. (2013). "Efficacy of family-based treatment for adolescents with eating disorders: a systematic review and meta-analysis." Int J Eat Disord **46**(1): 3-11.

Crook, M. A., V. Hally, et al. (2001). "The importance of the refeeding syndrome." Nutrition **17**(7-8): 632-637.

Cuerda, C., A. Ruiz, et al. (2007). "How accurate are predictive formulas calculating energy expenditure in adolescent patients with anorexia nervosa?" Clin Nutr **26**(1): 100-106.

Cummings, D. E. (2006). "Ghrelin and the short- and long-term regulation of appetite and body weight." Physiol Behav **89**(1): 71-84.

Curme, H. G., R. L. Columbus, et al. (1978). "Multilayer film elements for clinical analysis: general concepts." Clin Chem **24**(8): 1335-1342.

de Zwaan, M., Z. Aslam, et al. (2002). "Research on energy expenditure in individuals with eating disorders: a review." Int J Eat Disord **32**(2): 127-134.

Delaveyne-Bitbol, R. and M. Garabedian (1999). "In vitro responses to 17beta-estradiol throughout pubertal maturation in female human bone cells." J Bone Miner Res **14**(3): 376-385.

Delporte, M. L., S. M. Brichard, et al. (2003). "Hyperadiponectinaemia in anorexia nervosa." Clin Endocrinol (Oxf) **58**(1): 22-29.

Dempsey, D., L. Crosby, et al. (1984). "Weight gain and nutritional efficacy in anorexia nervosa." Am J Clin Nutr **39**(2): 236-242.

Devuyst, O., M. Lambert, et al. (1993). "Haematological changes and infectious complications in anorexia nervosa: a case-control study." Q J Med **86**(12): 791-799.

Diamanti, A., M. S. Basso, et al. (2008). "Clinical efficacy and safety of parenteral nutrition in adolescent girls with anorexia nervosa." J Adolesc Health **42**(2): 111-118.

Dickinson, D. F. (2005). "The normal ECG in childhood and adolescence." Heart **91**(12): 1626-1630.

DiVasta, A. D., C. E. Walls, et al. (2010). "Malnutrition and hemodynamic status in adolescents hospitalized for anorexia nervosa." Arch Pediatr Adolesc Med **164**(8): 706-713.

Dominguez, J., L. Goodman, et al. (2007). "Treatment of anorexia nervosa is associated with increases in bone mineral density, and recovery is a biphasic process involving both nutrition and return of menses." Am J Clin Nutr **86**(1): 92-99.

Dostalova, I., K. Smitka, et al. (2007). "Increased insulin sensitivity in patients with anorexia nervosa: the role of adipocytokines." Physiol Res **56**(5): 587-594.

Dunki Jacobs, P. B., M. Ruevekamp, et al. (1989). "Dietary influences on cell proliferation in bone marrow." Eur J Cancer Clin Oncol **25**(6): 953-957.

Durakovic, Z., M. Korsic, et al. (1989). "[Corrected Q-T interval in the electrocardiogram in patients with anorexia nervosa]." Lijec Vjesn **111**(11): 374-376.

Ebel, H. and T. Gunther (1980). "Magnesium metabolism: a review." J Clin Chem Clin Biochem **18**(5): 257-270.

Eckhardt, S. M. and S. F. Ahmed (2010). "Linear growth in anorexia nervosa." J Pediatr Gastroenterol Nutr **51 Suppl 3**: S127-128.

Facchini, M., L. Sala, et al. (2006). "Low-K+ dependent QT prolongation and risk for ventricular arrhythmia in anorexia nervosa." Int J Cardiol **106**(2): 170-176.

Fairburn, C. G. (2005). "Evidence-based treatment of anorexia nervosa." Int J Eat Disord **37 Suppl**: S26-30; discussion S41-22.

Fasshauer, M., J. Klein, et al. (2002). "Hormonal regulation of adiponectin gene expression in 3T3-L1 adipocytes." Biochem Biophys Res Commun **290**(3): 1084-1089.

Favaro, A., E. Tenconi, et al. (2007). "Association between low height and eating disorders: cause or effect?" Int J Eat Disord **40**(6): 549-553.

Fazeli, P. K., M. Misra, et al. (2010). "Fibroblast growth factor-21 may mediate growth hormone resistance in anorexia nervosa." J Clin Endocrinol Metab **95**(1): 369-374.

Findling, R. L., H. Steiner, et al. (2005). "Use of antipsychotics in children and adolescents." J Clin Psychiatry **66 Suppl 7**: 29-40.

Fisher, M., E. Simpser, et al. (2000). "Hypophosphatemia secondary to oral refeeding in anorexia nervosa." Int J Eat Disord **28**(2): 181-187.

Fiske, C. H. and Y. Subbarow (1929). "Phosphorus Compounds of Muscle and Liver." Science **70**(1816): 381-382.

Fock, R. A., S. L. Blatt, et al. (2010). "Study of lymphocyte subpopulations in bone marrow in a model of protein-energy malnutrition." Nutrition **26**(10): 1021-1028.

Forbes, G. B. (1990). "Do obese individuals gain weight more easily than nonobese individuals?" Am J Clin Nutr **52**(2): 224-227.

Fornari, V. and I. F. Dancyger (2003). "Psychosexual development and eating disorders." Adolesc Med **14**(1): 61-75.

Forsberg, S., E. Lotempio, et al. (2013). "Parent-Therapist Alliance in Family-Based Treatment for Adolescents with Anorexia Nervosa." Eur Eat Disord Rev.

Ganzin, M. (1985). "[Nutrition in Africa]." Med Trop (Mars) **45**(2): 117-122.

Garber, A. K., N. Michihata, et al. (2012). "A prospective examination of weight gain in hospitalized adolescents with anorexia nervosa on a recommended refeeding protocol." J Adolesc Health **50**(1): 24-29.

Gentile, M. G. (2012). "Enteral nutrition for feeding severely underfed patients with anorexia nervosa." Nutrients **4**(9): 1293-1303.

Gentile, M. G., P. Pastorelli, et al. (2010). "Specialized refeeding treatment for anorexia nervosa patients suffering from extreme undernutrition." Clin Nutr **29**(5): 627-632.

Gentile, M. G., P. Pastorelli, et al. (2010). "Specialized refeeding treatment for anorexia nervosa patients suffering from extreme undernutrition." Clinical Nutrition **29**(5): 627-632.

Golden, N. H., D. K. Katzman, et al. (2003). "Eating disorders in adolescents: position paper of the Society for Adolescent Medicine." J Adolesc Health **33**(6): 496-503.

Golden, N. H., C. Keane-Miller, et al. (2013). "Higher Caloric Intake in Hospitalized Adolescents With Anorexia Nervosa Is Associated With Reduced Length of Stay and No Increased Rate of Refeeding Syndrome." J Adolesc Health.

Golden, N. H., L. Lanzkowsky, et al. (2002). "The effect of estrogen-progestin treatment on bone mineral density in anorexia nervosa." J Pediatr Adolesc Gynecol **15**(3): 135-143.

Goodnick, P. J., J. Jerry, et al. (2002). "Psychotropic drugs and the ECG: focus on the QTc interval." Expert Opin Pharmacother **3**(5): 479-498.

Graber, T. W., A. S. Yee, et al. (1981). "Magnesium: physiology, clinical disorders, and therapy." Ann Emerg Med **10**(1): 49-57.

Grinspoon, S., K. Miller, et al. (1999). "Severity of osteopenia in estrogen-deficient women with anorexia nervosa and hypothalamic amenorrhea." J Clin Endocrinol Metab **84**(6): 2049-2055.

Grinspoon, S., L. Thomas, et al. (2001). "Changes in regional fat redistribution and the effects of estrogen during spontaneous weight gain in women with anorexia nervosa." Am J Clin Nutr **73**(5): 865-869.

Gustavsson, C. G. and L. Eriksson (1989). "Acute respiratory failure in anorexia nervosa with hypophosphataemia." J Intern Med **225**(1): 63-64.

Haglin, L. (2001). "Hypophosphataemia in anorexia nervosa." Postgrad Med J **77**(907): 305-311.

Hall, D. E., B. Kahan, et al. (1994). "Delirium associated with hypophosphatemia in a patient with anorexia nervosa." J Adolesc Health **15**(2): 176-178.

Halmi, K. A. (2009). "Anorexia nervosa: an increasing problem in children and adolescents." Dialogues Clin Neurosci **11**(1): 100-103.

Halperin, M. L. and K. S. Kamel (1998). "Potassium." Lancet **352**(9122): 135-140.

Harada, T., T. Nakahara, et al. (2008). "Obestatin, acyl ghrelin, and des-acyl ghrelin responses to an oral glucose tolerance test in the restricting type of anorexia nervosa." Biol Psychiatry **63**(2): 245-247.

Harris, J. A. and F. G. Benedict (1918). "A Biometric Study of Human Basal Metabolism." Proceedings of the National Academy of Sciences **4**(12): 370-373.

Hart, S., S. Abraham, et al. (2010). "Weight changes during inpatient refeeding of underweight eating disorder patients." Eur Eat Disord Rev.

Hasan, T. F. and H. Hasan (2011). "Anorexia nervosa: a unified neurological perspective." Int J Med Sci **8**(8): 679-703.

Hay, P. J. and P. Sachdev (2011). "Brain dysfunction in anorexia nervosa: cause or consequence of under-nutrition?" Curr Opin Psychiatry **24**(3): 251-256 210.1097/YCO.1090b1013e3283453775.

Heaney, R. P., S. Abrams, et al. (2000). "Peak bone mass." Osteoporos Int **11**(12): 985-1009.

Hebebrand, J. and C. M. Bulik (2011). "Critical appraisal of the provisional DSM-5 criteria for anorexia nervosa and an alternative proposal." Int J Eat Disord **44**(8): 665-678.

Heijmans, B. T., E. W. Tobi, et al. (2008). "Persistent epigenetic differences associated with prenatal exposure to famine in humans." Proc Natl Acad Sci U S A **105**(44): 17046-17049.

Henry, C. (2005). "Basal metabolic rate studies in humans: measurement and development of new equations." Public Health Nutr **8**(7a): 1133-1152.

Hermans, M. P. and M. J. Lambert (2002). "HOMA-modelling of insulin sensitivity and β-cell function in anorexia nervosa." European Eating Disorders Review **10**(1): 41-50.

Herpertz-Dahlmann, B., J. Seitz, et al. (2011). "Aetiology of anorexia nervosa: from a "psychosomatic family model" to a neuropsychiatric disorder?" Eur Arch Psychiatry Clin Neurosci **261 Suppl 2**: S177-181.

Hoek, H. W. (2006). "Incidence, prevalence and mortality of anorexia nervosa and other eating disorders." Curr Opin Psychiatry **19**(4): 389-394.

Holling, H. and R. Schlack (2007). "[Eating disorders in children and adolescents. First results of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS)]." Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz **50**(5-6): 794-799.

Holt, S., M. J. Ford, et al. (1981). "Abnormal gastric emptying in primary anorexia nervosa." Br J Psychiatry **139**: 550-552.

Howgate, D. J., S. M. Graham, et al. (2012). "Bone metabolism in anorexia nervosa: molecular pathways and current treatment modalities." Osteoporos Int.

Huang, Y. L., C. T. Fang, et al. (2001). "Life-threatening refeeding syndrome in a severely malnourished anorexia nervosa patient." J Formos Med Assoc **100**(5): 343-346.

Hutter, G., S. Ganepola, et al. (2009). "The hematology of anorexia nervosa." Int J Eat Disord **42**(4): 293-300.

Ishida, S., M. Nakagawa, et al. (1997). "Circadian variation of QT interval dispersion: correlation with heart rate variability." J Electrocardiol **30**(3): 205-210.

Isner, J. M., W. C. Roberts, et al. (1985). "Anorexia nervosa and sudden death." Ann Intern Med **102**(1): 49-52.

Jacobi, C., C. Hayward, et al. (2004). "Coming to terms with risk factors for eating disorders: application of risk terminology and suggestions for a general taxonomy." Psychol Bull **130**(1): 19-65.

Jagielska, G., T. Wolanczyk, et al. (2002). "Bone mineral density in adolescent girls with anorexia nervosa--a cross-sectional study." Eur Child Adolesc Psychiatry **11**(2): 57-62.

Jauregui-Garrido, B. and I. Jauregui-Lobera (2012). "Sudden death in eating disorders." Vasc Health Risk Manag **8**: 91-98.

Jones, J. M., S. Bennett, et al. (2001). "Disordered eating attitudes and behaviours in teenaged girls: a school-based study." CMAJ **165**(5): 547-552.

Joosten, K. F. and J. M. Hulst (2008). "Prevalence of malnutrition in pediatric hospital patients." Curr Opin Pediatr **20**(5): 590-596.

Juni, P., D. G. Altman, et al. (2001). "Systematic reviews in health care: Assessing the quality of controlled clinical trials." BMJ **323**(7303): 42-46.

JuniorMARSIPAN (2012). Management of Really Sick Inpatients with Anorexia Nervosa <18yrs. Royal College of Psychiatrists CR168, .

Kaplan, S. A. (1984). "The insulin receptor." J Pediatr **104**(3): 327-336.

Kasai, M., Y. Okajima, et al. (2009). "[Anorexia nervosa with refeeding syndrome: prevention and treatment of RS]." Seishin Shinkeigaku Zasshi **111**(4): 388-397.

Katz, M. G. and B. Vollenhoven (2000). "The reproductive endocrine consequences of anorexia nervosa." BJOG: An International Journal of Obstetrics & Gynaecology **107**(6): 707-713.

Katzman, D. K. (2005). "Medical complications in adolescents with anorexia nervosa: a review of the literature." Int J Eat Disord **37 Suppl**: S52-59; discussion S87-59.

Katzman, D. K. (2012). "Refeeding hospitalized adolescents with anorexia nervosa: is "start low, advance slow" urban legend or evidence based?" J Adolesc Health **50**(1): 1-2.

Kawataki, M., T. Kashima, et al. (1984). "Relation between QT interval and heart rate. applications and limitations of Bazett's formula." J Electrocardiol **17**(4): 371-375.

Kaye, W. H., C. M. Bulik, et al. (2004). "Comorbidity of anxiety disorders with anorexia and bulimia nervosa." Am J Psychiatry **161**(12): 2215-2221.

Kaye, W. H., T. Nagata, et al. (2001). "Double-blind placebo-controlled administration of fluoxetine in restricting- and restricting-purging-type anorexia nervosa." Biol Psychiatry **49**(7): 644-652.

Kaysar, N., J. Kronenberg, et al. (1991). "Severe hypophosphataemia during binge eating in anorexia nervosa." Arch Dis Child **66**(1): 138-139.

Keel, P. K., D. J. Dorer, et al. (2003). "Predictors of mortality in eating disorders." Arch Gen Psychiatry **60**(2): 179-183.

Keel, P. K. and K. L. Klump (2003). "Are eating disorders culture-bound syndromes? Implications for conceptualizing their etiology." Psychol Bull **129**(5): 747-769.

Keys, A. (1950). "Energy requirements of adults." J Am Med Assoc **142**(5): 333-338.

Keys, A., Brozek, J, Henschel, A, Mickelson, O, Taylor, HD. (1950). "The Biology of Human Starvation." University of Minnesota Press **1, 2. Minneapolis**(2909).

Kinzig, K. P., J. W. Coughlin, et al. (2007). "Insulin, glucose, and pancreatic polypeptide responses to a test meal in restricting type anorexia nervosa before and after weight restoration." Am J Physiol Endocrinol Metab **292**(5): E1441-1446.

Kiros, G. E. and D. P. Hogan (2001). "War, famine and excess child mortality in Africa: the role of parental education." Int J Epidemiol **30**(3): 447-455; discussion 456.

Klump, K. L. (2013). "Puberty as a critical risk period for eating disorders: A review of human and animal studies." Horm Behav **64**(2): 399-410.

Kohn, M. R., N. H. Golden, et al. (1998). "Cardiac arrest and delirium: presentations of the refeeding syndrome in severely malnourished adolescents with anorexia nervosa." J Adolesc Health **22**(3): 239-243.

Kohn, M. R., S. Madden, et al. (2011). "Refeeding in anorexia nervosa: increased safety and efficiency through understanding the pathophysiology of protein calorie malnutrition." Curr Opin Pediatr **23**(4): 390-394.

Konrad, K. K., R. A. Carels, et al. (2007). "Metabolic and psychological changes during refeeding in anorexia nervosa." Eat Weight Disord **12**(1): 20-26.

Korbonits, M., A. P. Goldstone, et al. (2004). "Ghrelin--a hormone with multiple functions." Front Neuroendocrinol **25**(1): 27-68.

Kowalska, I., M. Karczewska-Kupczewska, et al. (2011). "Adipocytokines, gut hormones and growth factors in anorexia nervosa." Clin Chim Acta **412**(19-20): 1702-1711.

Kraft, M. D., I. F. Btaiche, et al. (2005). "Review of the refeeding syndrome." Nutr Clin Pract **20**(6): 625-633.

Krahn, D. D., C. Rock, et al. (1993). "Changes in resting energy expenditure and body composition in anorexia nervosa patients during refeeding." J Am Diet Assoc **93**(4): 434-438.

Krantz, M. J., W. T. Donahoo, et al. (2005). "QT interval dispersion and resting metabolic rate in chronic anorexia nervosa." Int J Eat Disord **37**(2): 166-170.

Krantz, M. J., A. L. Sabel, et al. (2012). "Factors influencing QT prolongation in patients hospitalized with severe anorexia nervosa." General Hospital Psychiatry **34**(2): 173-177.

Kryzhanovskaya, L. A., C. K. Robertson-Plouch, et al. (2009). "The safety of olanzapine in adolescents with schizophrenia or bipolar I disorder: a pooled analysis of 4 clinical trials." J Clin Psychiatry **70**(2): 247-258.

Lambert, M., C. Hubert, et al. (1997). "Hematological changes in anorexia nervosa are correlated with total body fat mass depletion." Int J Eat Disord **21**(4): 329-334.

Lardy, H. A. and S. M. Ferguson (1969). "Oxidative phosphorylation in mitochondria." Annu Rev Biochem **38**: 991-1034.

Law, D. K., S. J. Dudrick, et al. (1973). "Immunocompetence of patients with protein-calorie malnutrition. The effects of nutritional repletion." Ann Intern Med **79**(4): 545-550.

Le Grange, D., P. M. Doyle, et al. (2012). "Calculation of expected body weight in adolescents with eating disorders." Pediatrics **129**(2): e438-446.

Lebow, J., L. A. Sim, et al. (2013). "The effect of atypical antipsychotic medications in individuals with anorexia nervosa: a systematic review and meta-analysis." Int J Eat Disord **46**(4): 332-339.

Leclerc, A., T. Turrini, et al. (2013). "Evaluation of a Nutrition Rehabilitation Protocol in Hospitalized Adolescents With Restrictive Eating Disorders." J Adolesc Health.

Legroux-Gerot, I., J. Vignau, et al. (2005). "Bone loss associated with anorexia nervosa." Joint Bone Spine **72**(6): 489-495.

Leibel, R. L., M. Rosenbaum, et al. (1995). "Changes in energy expenditure resulting from altered body weight." N Engl J Med **332**(10): 621-628.

Lesinskiene, S., A. Barkus, et al. (2008). "A meta-analysis of heart rate and QT interval alteration in anorexia nervosa." World J Biol Psychiatry **9**(2): 86-91.

Lock, J. and D. Le Grange (2001). "Can family-based treatment of anorexia nervosa be manualized?" J Psychother Pract Res **10**(4): 253-261.

Lucas, A. R., L. J. Melton, 3rd, et al. (1999). "Long-term fracture risk among women with anorexia nervosa: a population-based cohort study." Mayo Clin Proc **74**(10): 972-977.

Malik, M. and V. N. Batchvarov (2000). "Measurement, interpretation and clinical potential of QT dispersion." J Am Coll Cardiol **36**(6): 1749-1766.

Marinella, M. A. (2005). "Refeeding syndrome and hypophosphatemia." J Intensive Care Med **20**(3): 155-159.

Marino, L. (2009 March). Refeeding Syndrome: Guidelines - Cape Town Metropole Paediatric Interest Group.

Martins, V. J., T. M. Toledo Florencio, et al. (2011). "Long-lasting effects of undernutrition." Int J Environ Res Public Health **8**(6): 1817-1846.

Marvin, V. A., D. Brown, et al. (2008). "Factors contributing to the development of hypophosphataemia when refeeding using parenteral nutrition." Pharm World Sci **30**(4): 329-335.

Matthews, D. R., J. P. Hosker, et al. (1985). "Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man." Diabetologia **28**(7): 412-419.

Mayer, L. E., J. Schebendach, et al. (2012). "Eating behavior in anorexia nervosa: before and after treatment." Int J Eat Disord **45**(2): 290-293.

McLaren, D. S. and W. W. Read (1972). "Classification of nutritional status in early childhood." Lancet **2**(7769): 146-148.

McLoughlin, D. M., W. S. Wassif, et al. (2000). "Metabolic abnormalities associated with skeletal myopathy in severe anorexia nervosa." Nutrition **16**(3): 192-196.

Mehanna, H. M., J. Moledina, et al. (2008). "Refeeding syndrome: what it is, and how to prevent and treat it." BMJ **336**(7659): 1495-1498.

Mehler, P. S. and S. E. Howe (1995). "Serous fat atrophy with leukopenia in severe anorexia nervosa." Am J Hematol **49**(2): 171-172.

Mehler, P. S., A. B. Winkelman, et al. (2010). "Nutritional rehabilitation: practical guidelines for refeeding the anorectic patient." J Nutr Metab **2010**.

Metz, R. and C. H. Best (1960). "Insulin and glucagon: a review." Practitioner **185**: 593-601.

Mika, C., B. Herpertz-Dahlmann, et al. (2004). "Improvement of nutritional status as assessed by multifrequency BIA during 15 weeks of refeeding in adolescent girls with anorexia nervosa." J Nutr **134**(11): 3026-3030.

Mika, C., K. Holtkamp, et al. (2007). "A 2-year prospective study of bone metabolism and bone mineral density in adolescents with anorexia nervosa." J Neural Transm **114**(12): 1611-1618.

Millar, H. R., F. Wardell, et al. (2005). "Anorexia nervosa mortality in Northeast Scotland, 1965-1999." Am J Psychiatry **162**(4): 753-757.

Miller, K. K., S. K. Grinspoon, et al. (2005). "Medical findings in outpatients with anorexia nervosa." Arch Intern Med **165**(5): 561-566.

Miller, S. J. (2008). "Death resulting from overzealous total parenteral nutrition: the refeeding syndrome revisited." Nutr Clin Pract **23**(2): 166-171.

Mircea, C. N., M. E. Lujan, et al. (2007). "Metabolic fuel and clinical implications for female reproduction." J Obstet Gynaecol Can **29**(11): 887-902.

Misra, M., A. Aggarwal, et al. (2004). "Effects of anorexia nervosa on clinical, hematologic, biochemical, and bone density parameters in community-dwelling adolescent girls." Pediatrics **114**(6): 1574-1583.

Misra, M., D. Katzman, et al. (2011). "Physiologic estrogen replacement increases bone density in adolescent girls with anorexia nervosa." J Bone Miner Res **26**(10): 2430-2438.

Misra, M. and A. Klibanski (2010). "Neuroendocrine consequences of anorexia nervosa in adolescents." Endocr Dev **17**: 197-214.

Misra, M., K. K. Miller, et al. (2004). "Hormonal and body composition predictors of soluble leptin receptor, leptin, and free leptin index in adolescent girls with anorexia nervosa and controls and relation to insulin sensitivity." J Clin Endocrinol Metab **89**(7): 3486-3495.

Misra, M., K. K. Miller, et al. (2003). "Alterations in growth hormone secretory dynamics in adolescent girls with anorexia nervosa and effects on bone metabolism." J Clin Endocrinol Metab **88**(12): 5615-5623.

Misra, M., K. K. Miller, et al. (2005). "Secretory dynamics of ghrelin in adolescent girls with anorexia nervosa and healthy adolescents." Am J Physiol Endocrinol Metab **289**(2): E347-356.

Misra, M., R. Prabhakaran, et al. (2008). "Weight gain and restoration of menses as predictors of bone mineral density change in adolescent girls with anorexia nervosa-1." J Clin Endocrinol Metab **93**(4): 1231-1237.

Misra, M., P. Tsai, et al. (2006). "Nutrient intake in community-dwelling adolescent girls with anorexia nervosa and in healthy adolescents." Am J Clin Nutr **84**(4): 698-706.

Mollison, P. L. (1946). "Observations on Cases of Starvation at Belsen." Br Med J **1**(4435): 4-8.

Mont, L., J. Castro, et al. (2003). "Reversibility of cardiac abnormalities in adolescents with anorexia nervosa after weight recovery." J Am Acad Child Adolesc Psychiatry **42**(7): 808-813.

Moore, D. J., P. R. Durie, et al. (1985). "The assessment of nutritional status in children." Nutrition Research **5**(8): 797-799.

Moran, A., D. R. Jacobs, Jr., et al. (2002). "Association between the insulin resistance of puberty and the insulin-like growth factor-I/growth hormone axis." J Clin Endocrinol Metab **87**(10): 4817-4820.

Moran, A., D. R. Jacobs, Jr., et al. (1999). "Insulin resistance during puberty: results from clamp studies in 357 children." Diabetes **48**(10): 2039-2044.

Morris, R., J. Bramham, et al. (2014). "Empathy and social functioning in anorexia nervosa before and after recovery." Cogn Neuropsychiatry **19**(1): 47-57.

Nahshoni, E., A. Weizman, et al. (2007). "Alterations in QT dispersion in the surface electrocardiogram of female adolescents diagnosed with restricting-type anorexia nervosa." J Psychosom Res **62**(4): 469-472.

Nakai, Y., H. Hosoda, et al. (2003). "Plasma levels of active form of ghrelin during oral glucose tolerance test in patients with anorexia nervosa." Eur J Endocrinol **149**(1): R1-3.

NationalInstituteOfClinicalExcellence (2006). Nutritonal Support in Adults: Oral, enteral and parenteral nutrition CG32. London: NICE.

Neumann, C. G., G. J. Lawlor, Jr., et al. (1975). "Immunologic responses in malnourished children." Am J Clin Nutr **28**(2): 89-104.

Nicholls, D., L. Hudson, et al. (2011). "Managing anorexia nervosa." Arch Dis Child **96**(10): 977-982.

Nicholls, D. E., R. Lynn, et al. (2011). "Childhood eating disorders: British national surveillance study." Br J Psychiatry **198**(4): 295-301.

Nielsen, S., C. Emborg, et al. (2002). "Mortality in concurrent type 1 diabetes and anorexia nervosa." Diabetes Care **25**(2): 309-312.

Norris, M. L., L. Pinhas, et al. (2012). "Delirium and refeeding syndrome in anorexia nervosa." Int J Eat Disord **45**(3): 439-442.

Nudel, D. B., N. Gootman, et al. (1984). "Altered exercise performance and abnormal sympathetic responses to exercise in patients with anorexia nervosa." J Pediatr **105**(1): 34-37.

Nussinovitch, M., E. Gur, et al. (2012). "QT variability among weight-restored patients with anorexia nervosa." Gen Hosp Psychiatry **34**(1): 62-65.

O'Connor, G. and J. Goldin (2011). "The refeeding syndrome and glucose load." Int J Eat Disord **44**(2): 182-185.

O'Connor, G. and D. Nicholls (2013). "Refeeding Hypophosphatemia in Adolescents With Anorexia Nervosa: A Systematic Review." Nutr Clin Pract.

Obarzanek, E., M. Lesem, et al. (1994). "Resting metabolic rate of anorexia nervosa patients during weight gain." Am J Clin Nutr **60**(5): 666-675.

Obarzanek, E., M. D. Lesem, et al. (1994). "Resting metabolic rate of anorexia nervosa patients during weight gain." Am J Clin Nutr **60**(5): 666-675.

Olivares, J. L., M. Vazquez, et al. (2005). "Cardiac findings in adolescents with anorexia nervosa at diagnosis and after weight restoration." Eur J Pediatr **164**(6): 383-386.

Oltra Cucarella, J., R. Espert Tortajada, et al. (2011). "Neuropsychology and anorexia nervosa. Cognitive and radiological findings." Neurologia.

Ornstein, R. M., N. H. Golden, et al. (2003). "Hypophosphatemia during nutritional rehabilitation in anorexia nervosa: implications for refeeding and monitoring." J Adolesc Health **32**(1): 83-88.

Orphanidou, C. I., L. J. McCargar, et al. (1997). "Changes in body composition and fat distribution after short-term weight gain in patients with anorexia nervosa." Am J Clin Nutr **65**(4): 1034-1041.

Owen, O. E., A. P. Morgan, et al. (1967). "Brain metabolism during fasting." J Clin Invest **46**(10): 1589-1595.

Palla, B. and I. F. Litt (1988). "Medical complications of eating disorders in adolescents." Pediatrics **81**(5): 613-623.

Panagiotopoulos, C., B. W. McCrindle, et al. (2000). "Electrocardiographic findings in adolescents with eating disorders." Pediatrics **105**(5): 1100-1105.

Pearl, W. (1996). "Effects of gender, age, and heart rate on QT intervals in children." Pediatr Cardiol **17**(3): 135-136.

Peebles, R., J. L. Wilson, et al. (2006). "How do children with eating disorders differ from adolescents with eating disorders at initial evaluation?" J Adolesc Health **39**(6): 800-805.

Penido, M. G. and U. S. Alon (2012). "Phosphate homeostasis and its role in bone health." Pediatr Nephrol **27**(11): 2039-2048.

Pichard, C., U. G. Kyle, et al. (1996). "Energy expenditure in anorexia nervosa: can fat-free mass as measured by bioelectrical impedance predict energy expenditure in hospitalized patients?" Clin Nutr **15**(3): 109-114.

Pichard, C., U. G. Kyle, et al. (1996). "Energy expenditure in anorexia nervosa: can fat-free massas measured by bioelectrical impedance predict energy expenditure in hospitalized patients?" Clinical Nutrition **15**(3): 109-114.

Platte, P., K. M. Pirke, et al. (1994). "Resting metabolic rate and total energy expenditure in acute and weight recovered patients with anorexia nervosa and in healthy young women." International Journal of eating disorders **16**(1): 45-52.

Polito, A., A. Fabbri, et al. (2000). "Basal metabolic rate in anorexia nervosa: relation to body composition and leptin concentrations." Am J Clin Nutr **71**(6): 1495-1502.

Prabhakaran, R., M. Misra, et al. (2008). "Determinants of height in adolescent girls with anorexia nervosa." Pediatrics **121**(6): e1517-1523.

Prentice, A. M. (1999). "The thymus: a barometer of malnutrition." Br J Nutr **81**(5): 345-347.

Prentice, A. M. (2005). "Starvation in humans: evolutionary background and contemporary implications." Mech Ageing Dev **126**(9): 976-981.

Preti, A., G. Girolamo, et al. (2009). "The epidemiology of eating disorders in six European countries: results of the ESEMeD-WMH project." J Psychiatr Res **43**(14): 1125-1132.

Pringsheim, T., D. Lam, et al. (2011). "Metabolic and neurological complications of second-generation antipsychotic use in children: a systematic review and meta-analysis of randomized controlled trials." Drug Saf **34**(8): 651-668.

Radziuk, J. (2000). "Insulin sensitivity and its measurement: structural commonalities among the methods." J Clin Endocrinol Metab **85**(12): 4426-4433.

Raj, K. S., C. Keane-Miller, et al. (2012). "Hypomagnesemia in Adolescents With Eating Disorders Hospitalized for Medical Instability." Nutr Clin Pract.

Rajamani, S., L. L. Eckhardt, et al. (2006). "Drug-induced long QT syndrome: hERG K+ channel block and disruption of protein trafficking by fluoxetine and norfluoxetine." Br J Pharmacol **149**(5): 481-489.

Rasimas, J. J. and E. L. Liebelt (2012). "Adverse Effects and Toxicity of the Atypical Antipsychotics: What is Important for the Pediatric Emergency Medicine Practitioner." Clin Pediatr Emerg Med **13**(4): 300-310.

Rastam, M. (1992). "Anorexia nervosa in 51 Swedish adolescents: premorbid problems and comorbidity." J Am Acad Child Adolesc Psychiatry **31**(5): 819-829.

Ravussin, E., S. Lillioja, et al. (1986). "Determinants of 24-hour energy expenditure in man. Methods and results using a respiratory chamber." J Clin Invest **78**(6): 1568-1578.

Rechlin, T., M. Weis, et al. (1998). "Alterations of autonomic cardiac control in anorexia nervosa." Biol Psychiatry **43**(5): 358-363.

Reddy, S. T., C. Y. Wang, et al. (2002). "Effect of low-carbohydrate high-protein diets on acid-base balance, stone-forming propensity, and calcium metabolism." Am J Kidney Dis **40**(2): 265-274.

Reiter, C. S. and L. Graves (2010). "Nutrition therapy for eating disorders." Nutr Clin Pract **25**(2): 122-136.

Reseland, J. E., U. Syversen, et al. (2001). "Leptin is expressed in and secreted from primary cultures of human osteoblasts and promotes bone mineralization." J Bone Miner Res **16**(8): 1426-1433.

Rizza, R. A., L. J. Mandarino, et al. (1981). "Dose-response characteristics for effects of insulin on production and utilization of glucose in man." Am J Physiol **240**(6): E630-639.

Robinson, A. M. and D. H. Williamson (1980). "Physiological roles of ketone bodies as substrates and signals in mammalian tissues." Physiol Rev **60**(1): 143-187.

Roche, F., J. C. Barthelemy, et al. (2005). "Refeeding normalizes the QT rate dependence of female anorexic patients." Am J Cardiol **95**(2): 277-280.

Roche, F., B. Estour, et al. (2004). "Alteration of the QT rate dependence in anorexia nervosa." Pacing Clin Electrophysiol **27**(8): 1099-1104.

RoyalCollegeOfPsychiatrists (2005). Royal College of Psychiatrist. 2005. Guidelines for the nutritional management of anorexia nervosa. CR130. London.

RoyalCollegeOfPsychiatrists (2010). Management of Really Sick Patients with Anorexia Nervosa: MARSIPAN. CR162. London.

Russell, J., L. A. Baur, et al. (2001). "Altered energy metabolism in anorexia nervosa." Psychoneuroendocrinology **26**(1): 51-63.

SACN (2011). "Scientific Advisory Committee on Nutrition (SACN). Dietary Reference Values for Energy. London TSO."

Sadie-Van Gijsen, H., F. S. Hough, et al. (2013). "Determinants of bone marrow adiposity: The modulation of peroxisome proliferator-activated receptor-gamma2 activity as a central mechanism." Bone **56**(2): 255-265.

Sagie, A., M. G. Larson, et al. (1992). "An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study)." Am J Cardiol **70**(7): 797-801.

Sakata, I., K. Nakamura, et al. (2002). "Ghrelin-producing cells exist as two types of cells, closed- and opened-type cells, in the rat gastrointestinal tract." Peptides **23**(3): 531-536.

Sakpal, T. V. (2010). "Sample size estimation in clinical trial." Perspect Clin Res **1**(2): 67-69.

Sala, M., A. Vicentini, et al. (2005). "QT interval prolongation related to psychoactive drug treatment: a comparison of monotherapy versus polytherapy." Ann Gen Psychiatry **4**(1): 1.

Salisbury, J. J., A. S. Levine, et al. (1995). "Refeeding, metabolic rate, and weight gain in anorexia nervosa: a review." Int J Eat Disord **17**(4): 337-345.

Satoh, Y., T. Shimizu, et al. (2003). "Resting energy expenditure and plasma leptin levels in adolescent girls with anorexia nervosa." International Journal of eating disorders **34**(1): 156-161.

Savino, W. and M. Dardenne (2010). "Nutritional imbalances and infections affect the thymus: consequences on T-cell-mediated immune responses." Proc Nutr Soc **69**(4): 636-643.

Scalfi, L., G. Di Biase, et al. (1993). "Bioimpedance analysis and resting energy expenditure in undernourished and refed anorectic patients." Eur J Clin Nutr **47**(1): 61-67.

Schebendach, J. (2003). "The use of indirect calorimetry in the clinical management of adolescents with nutritional disorders." Adolesc Med **14**(1): 77-85.

Schebendach, J., N. H. Golden, et al. (1995). "Indirect calorimetry in the nutritional management of eating disorders." Int J Eat Disord **17**(1): 59-66.

Schebendach, J. E., L. E. Mayer, et al. (2011). "Food choice and diet variety in weight-restored patients with anorexia nervosa." J Am Diet Assoc **111**(5): 732-736.

Scheen, A. J., M. Castillo, et al. (1988). "Insulin sensitivity in anorexia nervosa: a mirror image of obesity?" Diabetes Metab Rev **4**(7): 681-690.

Schnitker, M. A., P. E. Mattman, et al. (1951). "A clinical study of malnutrition in Japanese prisoners of war." Ann Intern Med **35**(1): 69-96.

Schofield, W. N. (1985). "Predicting basal metabolic rate, new standards and review of previous work." Hum Nutr Clin Nutr **39 Suppl 1**: 5-41.

Schwartz, B. I., J. M. Mansbach, et al. (2008). "Variations in admission practices for adolescents with anorexia nervosa: a North American sample." J Adolesc Health **43**(5): 425-431.

Schwartz, M. W., S. C. Woods, et al. (2000). "Central nervous system control of food intake." Nature **404**(6778): 661-671.

Setnick, J. (2010). "Micronutrient deficiencies and supplementation in anorexia and bulimia nervosa: a review of literature." Nutr Clin Pract **25**(2): 137-142.

Shamim, T., N. H. Golden, et al. (2003). "Resolution of vital sign instability: an objective measure of medical stability in anorexia nervosa." J Adolesc Health **32**(1): 73-77.

Silvetti, M. S., M. Magnani, et al. (1998). "[The heart of anorexic adolescents]." G Ital Cardiol **28**(2): 131-139.

Silvis, S. E. and P. D. Paragas, Jr. (1972). "Paresthesias, weakness, seizures, and hypophosphatemia in patients receiving hyperalimentation." Gastroenterology **62**(4): 513-520.

Simansky, K. J. (1996). "Serotonergic control of the organization of feeding and satiety." Behav Brain Res **73**(1-2): 37-42.

Simonson, E., A. Henschel, et al. (1948). "The electrocardiogram of man in semistarvation and subsequent rehabilitation." Am Heart J **35**(4): 584-602.

Singer, P., M. M. Berger, et al. (2009). "ESPEN Guidelines on Parenteral Nutrition: intensive care." Clin Nutr **28**(4): 387-400.

Skipper, A. (2012). "Refeeding syndrome or refeeding hypophosphatemia: a systematic review of cases." Nutr Clin Pract **27**(1): 34-40.

Smink, F. R., D. van Hoeken, et al. (2012). "Epidemiology of eating disorders: incidence, prevalence and mortality rates." Curr Psychiatry Rep **14**(4): 406-414.

Soares, M. J., R. N. Kulkarni, et al. (1992). "Energy supplementation reverses changes in the basal metabolic rates of chronically undernourished individuals." Br J Nutr **68**(3): 593-602.

Solomon, S. and D. Kirby (1990). "The refeeding syndrome: a review." Journal of Parenteral and Enteral Nutrition **14**(1): 90-97.

Soyka, L. A., S. Grinspoon, et al. (1999). "The effects of anorexia nervosa on bone metabolism in female adolescents." J Clin Endocrinol Metab **84**(12): 4489-4496.

St John Sutton, M. G., T. Plappert, et al. (1985). "Effects of reduced left ventricular mass on chamber architecture, load, and function: a study of anorexia nervosa." Circulation **72**(5): 991-1000.

Stanga, Z., A. Brunner, et al. (2008). "Nutrition in clinical practice-the refeeding syndrome: illustrative cases and guidelines for prevention and treatment." Eur J Clin Nutr **62**(6): 687-694.

Steinhausen, H. C. (2002). "The outcome of anorexia nervosa in the 20th century." Am J Psychiatry **159**(8): 1284-1293.

Stroud, M., H. Duncan, et al. (2003). "Guidelines for enteral feeding in adult hospital patients." Gut **52 Suppl 7**: vii1-vii12.

Sum, M. (2011). "Bone Mineral Density Accrual Determines Energy Expenditure with Refeeding in Anorexia Nervosa and Supersedes Return of Menses." Journal of Osteoporosis **2011**.

Swanson, S. A., S. J. Crow, et al. (2011). "Prevalence and correlates of eating disorders in adolescents. Results from the national comorbidity survey replication adolescent supplement." Arch Gen Psychiatry **68**(7): 714-723.

Swenne, I. (2000). "Heart risk associated with weight loss in anorexia nervosa and eating disorders: electrocardiographic changes during the early phase of refeeding." Acta Paediatr **89**(4): 447-452.

Swenne, I. and P. T. Larsson (1999). "Heart risk associated with weight loss in anorexia nervosa and eating disorders: risk factors for QTc interval prolongation and dispersion." Acta Paediatr **88**(3): 304-309.

Takeda, E., H. Yamamoto, et al. (2004). "Inorganic phosphate homeostasis and the role of dietary phosphorus." J Cell Mol Med **8**(2): 191-200.

Takimoto, Y., K. Yoshiuchi, et al. (2004). "QT interval and QT dispersion in eating disorders." Psychother Psychosom **73**(5): 324-328.

Tanaka, M., T. Naruo, et al. (2003). "Fasting plasma ghrelin levels in subtypes of anorexia nervosa." Psychoneuroendocrinology **28**(7): 829-835.

Tanaka, M., Y. Tatebe, et al. (2003). "Eating pattern and the effect of oral glucose on ghrelin and insulin secretion in patients with anorexia nervosa." Clin Endocrinol (Oxf) **59**(5): 574-579.

Theintz, G., B. Buchs, et al. (1992). "Longitudinal monitoring of bone mass accumulation in healthy adolescents: evidence for a marked reduction after 16 years of age at the levels of lumbar spine and femoral neck in female subjects." J Clin Endocrinol Metab **75**(4): 1060-1065.

Thompson-Brenner, H., C. L. Boisseau, et al. (2011). "Representation of ideal figure size in Ebony magazine: a content analysis." Body Image **8**(4): 373-378.

Travis, S. F., H. J. Sugerman, et al. (1971). "Alterations of red-cell glycolytic intermediates and oxygen transport as a consequence of hypophosphatemia in patients receiving intravenous hyperalimentation." N Engl J Med **285**(14): 763-768.

Uher, R. and M. Rutter (2012). "Classification of feeding and eating disorders: review of evidence and proposals for ICD-11." World Psychiatry **11**(2): 80-92.

Ulger, Z., D. Gurses, et al. (2006). "Follow-up of cardiac abnormalities in female adolescents with anorexia nervosa after refeeding." Acta Cardiol **61**(1): 43-49.

Unger, R. H., A. M. Eisentraut, et al. (1963). "The effects of total starvation upon the levels of circulating glucagon and insulin in man." J Clin Invest **42**: 1031-1039.

Van Wymelbeke, V., L. Brondel, et al. (2004). "Factors associated with the increase in resting energy expenditure during refeeding in malnourished anorexia nervosa patients." Am J Clin Nutr **80**(6): 1469-1477.

Van Wymelbeke, V., L. Brondel, et al. (2004). "Factors associated with the increase in resting energy expenditure during refeeding in malnourished anorexia nervosa patients." Am J Clin Nutr **80**(6): 1469-1477.

Vazquez, M., J. L. Olivares, et al. (2003). "[Cardiac disorders in young women with anorexia nervosa]." Rev Esp Cardiol **56**(7): 669-673.

Vieweg, W. V. (2003). "New Generation Antipsychotic Drugs and QTc Interval Prolongation." Prim Care Companion J Clin Psychiatry **5**(5): 205-215.

Wada, S., T. Nagase, et al. (1992). "A case of anorexia nervosa with acute renal failure induced by rhabdomyolysis; possible involvement of hypophosphatemia or phosphate depletion." Intern Med **31**(4): 478-482.

Wade, A., H. Pan, et al. (2006). "An investigation of minimisation criteria." BMC Med Res Methodol **6**: 11.

Wagner, A., H. Aizenstein, et al. (2007). "Altered reward processing in women recovered from anorexia nervosa." Am J Psychiatry **164**(12): 1842-1849.

Wagstaff, G. (2011). "Dietetic practice in refeeding syndrome." J Hum Nutr Diet **24**(5): 505-515.

waldholtz BD, A. A. (1988). "Hypophosphatemia during starvation in anorexia nervosa." International Journal of eating disorders **7**(4): 551-555.

Walker, J., S. Roberts, et al. (1979). "Caloric requirements for weight gain in anorexia nervosa." Am J Clin Nutr **32**(7): 1396-1400.

Wang, C., D. Amato, et al. (2001). "Gelatinous transformation of bone marrow from a starch-free diet." Am J Hematol **68**(1): 58-59.

Wang, T., C. C. Hung, et al. (2006). "The comparative physiology of food deprivation: from feast to famine." Annu Rev Physiol **68**: 223-251.

Watson, H. J. and C. M. Bulik (2012). "Update on the treatment of anorexia nervosa: review of clinical trials, practice guidelines and emerging interventions." Psychol Med: 1-24.

Weinsier, R. L. and C. L. Krumdieck (1981). "Death resulting from overzealous total parenteral nutrition: the refeeding syndrome revisited." Am J Clin Nutr **34**(3): 393-399.

Weissberger, A. J., K. K. Ho, et al. (1991). "Contrasting effects of oral and transdermal routes of estrogen replacement therapy on 24-hour growth hormone (GH) secretion, insulin-like growth factor I, and GH-binding protein in postmenopausal women." J Clin Endocrinol Metab **72**(2): 374-381.

West, M. L., O. Bendz, et al. (1986). "Development of a test to evaluate the transtubular potassium concentration gradient in the cortical collecting duct in vivo." Miner Electrolyte Metab **12**(4): 226-233.

Wester, P. O. and T. Dyckner (1982). "The importance of the magnesium ion. Magnesium deficiency-symptomatology and occurrence." Acta Med Scand Suppl **661**: 3-4.

Weyer, C., P. A. Tataranni, et al. (2001). "Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of type 2 diabetes development." Diabetes Care **24**(1): 89-94.

Whitelaw, M., H. Gilbertson, et al. (2010). "Does aggressive refeeding in hospitalized adolescents with anorexia nervosa result in increased hypophosphatemia?" J Adolesc Health **46**(6): 577-582.

Widiger T, F. A., Pincus H (1994). Diagnostic and Statistical manual of mental disorders (DSM) 4th Edition. Washington DC, American Psychiatric Association.

Winter, T. A. (2006). "The effects of undernutrition and refeeding on metabolism and digestive function." Current Opinion in Clinical Nutrition & Metabolic Care **9**(5): 596-602 510.1097/1001.mco.0000241670.0000224923.0000241675b.

Winter, T. A., S. J. O'Keefe, et al. (2005). "The Effect of Severe Undernutrition and Subsequent Refeeding on Whole-Body Metabolism and Protein Synthesis in Human Subjects." Journal of Parenteral and Enteral Nutrition **29**(4): 221-228.

Xavier, J. G., M. E. Favero, et al. (2007). "Protein-energy malnutrition alters histological and ultrastructural characteristics of the bone marrow and decreases haematopoiesis in adult mice." Histol Histopathol **22**(6): 651-660.

Zandian, M., I. Ioakimidis, et al. (2007). "Cause and treatment of anorexia nervosa." Physiol Behav **92**(1-2): 283-290.

Zuniga-Guajardo, S., P. E. Garfinkel, et al. (1986). "Changes in insulin sensitivity and clearance in anorexia nervosa." Metabolism **35**(12): 1096-1100.