The impact of eating behavior on psychological symptoms typical of reactive hypoglycemia: a pilot study comparing women with polycystic ovary syndrome to controls.

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ABSTRACT. The idea that diet can affect mood and behavior in women with polycystic ovary syndrome (PCOS) by altering blood glucose levels has become popular in recent years. This paper describes an online survey ($N=462$) of 24 women with PCOS, 299 healthy control women, 47 women who possibly had undiagnosed PCOS, and 92 men. The groups were compared for symptoms of mood and behavioral symptoms typical of reactive (postprandial) hypoglycemia. The outcome measures were two questionnaires that measure states associated with hypoglycemia: the Hypoglycemia Symptom Checklist -7 (HSC-7), which measures behavioral symptoms and the Mood Adjective Checklist (MACL), which measures emotional states. Controlling for age and body mass index (BMI) using between-groups analysis of covariance (ANCOVA), the women with PCOS scored significantly higher than the other three groups ($p < 0.001$) on the outcome measures. These differences remained statistically significant in a subset of twelve women with PCOS compared to twelve healthy control women closely matched for age, BMI, and eating behavior. The findings are suggestive of hypoglycemia-related mood and behavioral problems in PCOS. Future research should test whether blood glucose levels correlate with these symptoms in PCOS, and whether a low glycemic index ('low-GI') diet improves the symptoms.

Keywords: polycystic ovary syndrome, eating behavior, mood, hypoglycemia, low-GI diet.

Introduction

Polycystic ovary syndrome (PCOS) affects up to 10% of women (Ledger & Clark, 2003). As well as the classical symptoms of menstrual irregularity and testosterone excess, women with PCOS might report light headedness, trembling or faintness that they may attribute to low blood glucose levels (Marsh, Steinbeck, Atkinson, Petocz, & Brand-Miller, 2010). Women with PCOS are hyperinsulinemic compared to healthy women of a similar body mass index (BMI) (Diamanti-Kandarakis & Papavassiliou, 2006) and it is plausible that some of them experience symptoms caused by a sudden fall in blood glucose. In support of the hypoglycemia hypothesis, some PCOS patients say that their supposed hypoglycemia symptoms are associated with a craving of sweet food or drinks. Anecdotally, many treating physicians are skeptical that such symptoms are related to hypoglycaemia.

Reactive (or 'postprandial') hypoglycemia (RH) occurs when blood glucose levels drop two to five hours after a meal, especially a meal high in carbohydrates. Reactive hypoglycemia is under-researched, but there is evidence to suggest that this condition is more common in women with PCOS than in other women. For example, Sorensen & Johansen (2010) found a 12.4% rate of reactive hypoglycemia in women with no reported history of plasma glucose dysregulation, and by contrast a study of 64 lean women with PCOS found a 50% rate of reactive hypoglycemia (Altuntas, Bilir, Ucak, & Gundogdu, 2005). Kasim-Karakas, Cunningham, & Tsodikov (2007) assessed 28 obese women with PCOS using a 5-hour oral glucose tolerance test (OGTT) and found a reactive hypoglycemia rate of 66%.

Reactive hypoglycemia (typically mid-afternoon) may contribute to weight gain

in PCOS (Magnotti & Futterweit, 2007); this could occur because insulin induces the production of androgens such as testosterone, that in turn increase visceral fat (Stanley & Misra, 2008). Reactive hypoglycemia has been described as one of the "subtle symptoms" of PCOS (Brand-Miller, Farid & Marsh 2004, p.9) and a low glycemic index (GI) diet may be a way of controlling this problem. Marsh, Steinbeck, Atkinson, Petocz & Brand-Miller (2010) found that the low-GI diet significantly improved insulin resistance, menstruation (probably due to improved insulin sensitivity) and emotional quality of life in moderately overweight women with PCOS.Findings from two other recent studies (Galletly et al 2007; Herriot, Whitcroft, & Jeanes, 2008) appear to support the efficacy of the low-GI diet for women with PCOS in relation to mood and other symptoms related hypoglycemia.

Individuals with suspected postprandial hypoglycemia tend to have higher levels of psychological distress, including anxiety and depression, than other people (Berlin, Grimaldi, Landault, Cesselin, & Puech, 1994). The mood state typical of hypoglycemia has been described as 'tense-tiredness' (Thayer, 1989). Classic well-controlled studies of the effects of experimental induction of hypoglycemia in healthy participants found evidence of this 'tense-tired' mood state (Gold, MacLeod, Frier, & Deary, 1995; McCrimmon, Frier, & Deary, 1999). More recent research also suggests an effect of hypoglycemia on psychological functioning, for example, Bie-Olsen, Pedersen-Bjergaard, Kjaer, Lonsdale, Law, and Thorsteinsson (2010) induced hypoglycemia in twenty healthy men and found a statistically significant difference between scores before the induction and during induced hypoglycemia on the Edinburgh Hypoglycaemia Symptom Score Questionnaire (Hepburn, Deary, MacLeod, and Frier, 1994), a scale which includes psychological symptoms typical of hypoglycaemia, such

as anxiety and tiredness. Although there is subjective and objective evidence of reactive hypoglycemia in women with PCOS, and despite considerable evidence of anxiety and depression in PCOS (for example, Himelein & Thatcher, 2006) the possible link between reactive hypoglycemia and mood problems in PCOS has received surprisingly little scientific attention.

The present study was designed to test the hypothesis that women with PCOS have more symptoms of mood and behavioral disturbance typical of reactive hypoglycemia than women who do not have PCOS.

Method

Design

An online questionnaire survey was used to identify PCOS cases and controls. Comparisons were made between four groups: women with PCOS, healthy control women, women who possibly had undiagnosed PCOS, and men. From this sample, matches were found between women with PCOS and non-PCOS controls on age, self-reported BMI, and eating behavior. The main grouping variables were PCOS status and eating behavior. The outcome variables were questionnaires measuring symptoms typical of reactive hypoglycemia.

Questionnaires

Two measures of signs of reactive hypoglycemia were used:

The UWIST Mood Adjective Check List (MACL) (Matthews, Jones, & Chamberlain, 1990). This scale assesses happiness, tension, and energy levels using

three 8-item subscales, and changes in scoring on this measure has been found to reflect changes in arterialized venous blood glucose levels in studies of experimentally induced hypoglycaemia (Gold et al., 1995; McCrimmon et al., 1999). Similar mood changes are hypothesised to be seen in postprandial hypoglycemia because it is hypothesised that low blood glucose causes the mood changes regardless of whether hypoglycaemia is naturally occurring or experimentally induced. To increase sensitivity to degrees of mood, the present study expanded Matthews et al's checklist from a 'yes/no' format to a 4-point Likert scale prefixed with "I generally feel…" and response options of 'never, rarely, sometimes, often' e.g. 'I feel cheerful'. Higher scores indicate positive hedonic tone (happy mood), more tension, and more energy. On each subscale the maximum score is 32, and the minimum is eight.

The Hypoglycemia Symptom Checklist – 7 items (HSC-7). This short scale was designed for the present study to be a quick test for behavioral symptoms of hypoglycemia. The HSC-7 consists of four items related to symptoms of neuroglycopenia and three items related to autonomic symptoms of hypoglycemia. The neuroglycopenia symptoms are: clumsiness, confusion, sudden weakness, and difficulty in speaking. The autonomic symptoms are: unexplained palpitations, sweating, and shivering. The symptoms are rated for frequency of occurrence on a Likert scale from 1 (never) to 4 (often).

The symptoms listed in the HSC-7 have been variously identified in several sources (e.g. Ross, 1975; Deary, Hepburn, MacLeod, & Frier, 1993), which contributes to the face validity of the HSC-7. The HSC-7 also demonstrates good internal reliability; for the sample in the present study the Cronbach's alpha is 0.776. A principal components analysis of the HSC-7 using Varimax rotation with Kaiser

normalization indicated sound underlying components (Kaiser-Meyer-Olkin index = 0.830), with a good average factor loading (0.655). As mentioned above, the MACL has been validated against biological measures of hypoglycemia, and in the present study the HSC-7 subscales show moderate concurrent validity with the MACL (mean Pearson's $r = 0.44$).

Eating behavior was assessed by asking participants (a) whether they followed a specific kind of diet (e.g. low-GI, calorie controlled, the Atkins diet etc), and (b) to say a few words about their eating behavior (e.g. whether they eat healthily, binge eat etc). Responses to these two questions underwent content analysis, and consequently participants were classified into one of four categories: healthy eating, unhealthy eating (e.g. "I eat a lot of junk food"), binge &/or comfort eating, or 'other'. Note that the resulting categories are a broad assessment of eating habits, not diagnoses of eating disorders. Those who reported binging or comfort eating were combined into one group because both eating behaviors were often reported by the same participant, possibly supporting the suggestion by Grucza, Przybeck, & Cloninger (2007) that binging and comfort eating share a common underlying mood dysregulation. Eating was categorised as 'other' if a participant's response did not fall into any of the three aforementioned categories e.g. "I eat whatever is in the fridge". This measure relies on conventional content analysis, a well established approach to categorization based on qualitative methods (Graneheim & Lundman, 2004). As a qualitative measure it is not amenable to psychometric validation using quantitative methods such as Cronbach's alpha or principal components analysis.

Demographics, lifestyle (e.g. alcohol consumption), presence of medical conditions and medication use were also assessed.

Participants

Women with PCOS were recruited from the *Verity* PCOS support group website.

Controls were recruited from *Psychological Research on the Net,* a website dedicated to

online research in a range of topics in psychology. Responses were anonymous.

Because the control group website is accessed by the general public, up to 10% of the

respondents from this source may have had PCOS. However all potential cases of

PCOS – including undiagnosed cases - were identifiable because the survey included

questions based on the diagnostic criteria for PCOS.

Inclusion to the PCOS group was based upon self-report of (a) having PCOS,

and (b) having two of the three necessary conditions for PCOS, as defined by the

Rotterdam criteria (1/ multiple ovarian cysts; 2/ elevated testosterone, or hirsutism or

acne; 3/ irregular periods). Twenty-four women fulfilled these criteria. A further 47

women reported either (a) having two of the three diagnostic criteria but did not identify

as having PCOS or (b) identified as having PCOS but only reported having one of the

three diagnostic criteria; these cases were categorised as 'Possible PCOS'. The female

control group consisted of 299 women who reported one or no symptoms associated

with PCOS, and did not identify as having PCOS.

In total, 536 people accessed the questionnaire between March and June 2009.

Of these, 32 did not go on to fill in the form, leaving an uptake rate of 94%. A further

42 were excluded because they did not give key information e.g. their sex. This left 462

people (24 women with PCOS, 299 controls, and 47 'Possible PCOS', and 92 men), a

completion rate of 86%. One woman with PCOS was excluded from matching as she

did not report her weight, but she was included in any total-sample (*N=462*) analyses

that did not require this information.

Ethics

This study was approved by the Department of Psychology Ethics Committee, City University, London. To indicate their consent, participants read an information sheet and consent form and ticked a checkbox.

Data analysis

All variables passed the Kolomogorov-Smirnov test of normality and all ANCOVA models passed Levene's tests of homogeneity of variance, thus comparisons of continuous data were performed using parametric tests. For categorical outcomes, Fisher's exact test was used because expected frequencies were less than five in all cases. Less than 5% of data was missing, and missing data was replaced with the median for each participant's score on the relevant scale or subscale.

Results

The results are presented in two sections. The first section describes comparisons across the four groups, and the second section compares 12 women with PCOS to 12 healthy control women matched for age, self-reported BMI, and eating behavior.

Comparisons across the four groups

The mean ($\pm$ *SD*) ages of the participants were PCOS (31.3 ± 7.7), Possible PCOS (26.6 ± 9.0), healthy control women (24.5 ± 9.1), healthy control men (29.1 ± 8.0). The mean

BMIs were PCOS (29.5 ± 6.3), Possible PCOS (19.2 ± 3.3), healthy control women (21.1 ± 3.6), healthy control men (25.7 ± 5.2).

Twenty-two of the women with PCOS and 283 of the healthy control women gave information regarding their eating behavior. The different categories of eating behavior were represented at significantly different rates in the PCOS group compared to healthy control women (Fisher's Exact = 10.294, $p < 0.025$, 2-sided). Of the 22 women with PCOS who indicated their eating behavior, 21% reported healthy eating compared to 28% of the control women; nobody in the PCOS group reported unhealthy eating compared to 17% of the control women, and 58% of the PCOS group reported binge &/or comfort eating compared to 32% of control women. Five of the 22 women with PCOS (23%) and two of the 283 healthy control women (0.7%) were on a low-GI diet. Three of the five women with PCOS on a low-GI diet also binged &/or comfort ate.

Of the 462 participants, 52.8% reported that they were not taking any medication, 13.2% were taking contraception, 5.0% were taking psychiatric medication, 2.2% were taking metformin, 10% were taking other medications (mostly vitamins or allergy medications), 1.5% were taking more than one type of medication, 10.2% said they were taking medication but did not indicate what type, and 5.2% did not state whether they were taking medication or not. Regarding medical conditions, of the 462 participants 13.2.0% reported a psychological or behavioural issue (mostly depression or anxiety), 4.3% reported hypoglycemia, 2.8% reported hypothyroid, 2.8% reported endometriosis, and 1.9% reported insulin resistance. The PCOS group's scores showed more evidence of mood and behavioral effects of hypoglycemia than the other three groups (Table 1). Using ANCOVA to control for any effect of age and BMI, the four

groups were compared on the psychometric measures. Significant group differences were found for the Mood Adjective Checklist subscales: energy (F (3, 458) = 14.965, p < 0.001), tension (F (3, 458) = 9.385, p < 0.001), hedonic tone (F (3, 458) = 14.127, p < 0.001). Significant group differences were also found for the Hypoglycemia Symptom Checklist -7 (F (3, 458) = 10.067, p < 0.001). The PCOS group had more symptoms typical of reactive hypoglycemia than the other groups for each outcome measure. Least Significant Difference (LSD) comparisons of the main effects found that the PCOS and Possible PCOS groups both had significantly more symptoms typical of reactive hypoglycemia than the healthy female controls on all measures (minimum p < 0.003) and than the healthy men on all measures (minimum p < 0.009). Compared to the Possible PCOS group, the PCOS group had significantly lower energy (p < 0.007), more negative hedonic tone (p < 0.003), nonsignificantly more tension (p < 0.059) and nonsignificantly more symptoms on the HSC-7 (p < 0.352). Healthy control women didn't score significantly differently to the healthy control men on any of the measures (maximum p < 0.143).

Matching 12 healthy control women to 12 women with PCOS

Twelve healthy control women were matched to 12 women with PCOS on age, BMI and eating behavior. Four of the matched pairs reported healthy eating behavior, six pairs binged &/or comfort ate, and the eating behavior of two pairs was classified as 'other'. Mean ($\pm SD$) age and BMI were closely matched (PCOS age 31.5 $\pm$ 8.9; matched controls 30.1 $\pm$ 9.2 years old; PCOS BMI 28.8 $\pm$ 6.1; matched controls 29.4 $\pm$ 5.9). One woman with PCOS and one healthy control woman who reported experiencing hypoglycemia were paired; all other medical conditions were excluded.

Irritable bowel syndrome (IBS) was not excluded because IBS may, at least in part, have a psychological aetiology (Choung, Locke, Zinsmeister, Schleck, & Talley, 2009). Fewer than half of the matched participants consumed alcohol, and those who did were light drinkers (PCOS = 5.0 ± 2.7 units per week, and controls = 3.2 ± 4.1) compared the average of 9.0 units per week for women in England & Wales (Office of National Statistics, 2008).

The PCOS group reported significantly more symptoms typical of reactive hypoglycemia than matched controls on all measures (Table 2).

Discussion

Women with PCOS reported significantly more mood and behavioral symptoms associated with reactive hypoglycemia than healthy women. This is the first time that such differences have been demonstrated. The differences remained statistically significant after controlling for age, BMI and eating behavior. Before and after matching, the PCOS group reported significantly less energy, more tension, less happiness, with more behavioural symptoms that may be associated with hypoglycemia. Women with PCOS also demonstrated the pattern of 'tense-tiredness' combined with lower mood that has been observed in studies of experimentally induced hypoglycaemia (Gold et al., 1995; McCrimmon et al., 1999).

Based on recent evidence regarding the high rates of hypoglycemia in PCOS and the benefits of a low-GI diet, it might be speculated that the type of food eaten may have an impact on the symptoms typical of hypoglycemia reported by the women with PCOS in this study. A limitation of the present study is that the number of women in the

present sample following a low-GI diet was not sufficient to assess its affect on the outcome measures. Also the five women with PCOS who were on a low-GI diet also binged &/or comfort ate, which might obscure any observable benefit of eating low-GI foods. A future study should assess blood glucose levels and psychological outcomes in women with PCOS on a low-GI diet compared to women with PCOS on other diets, controlling for eating behavior.

One of the strengths of the present study is the novelty of the research focus, the use of the internet to maximise the numbers recruited, and the use of a bespoke assessment measure of eating habits. However these strengths also have corresponding limitations. For example, although the internet can increase the statistical power of analyses because of greater numbers, self-report is relied on more heavily than studies recruiting in hospital clinics where objective assessments can be made. Thus although some studies have found that self-report of height and weight can be reasonably accurate (Goodman et al, 2000; Dahl et al., 2010), research ideally should assess these variables objectively where possible. Another limitation is that although the categorisation of eating habits using qualitative methods may have the advantage of increasing sensitivity to unique properties of the sample in question, future researchers might consider using a validated questionnaire to assess eating habits because this will make their findings more easily comparable to studies using similar measures. Similarly, the HSC-7 has not yet been validated against a physiological measure of hypoglycaemia. In the present study the HSC-7 has proved to have good psychometric properties and sensitivity to symptoms seen in hypoglycaemia, but a future study might seek to validate the HSC-7 against an objective measure of blood glucose.

The findings of this study suggest that effectively controlling diet and weight in PCOS is not only an important health issue, but also has implications for improving the troubling symptoms that may be caused by reactive hypoglycemia. When women with PCOS report hypoglycemia symptoms to their clinicians, these symptoms warrant investigation in the form of an extended oral glucose tolerance test. Readings should be taken every 30 minutes over 4 hours; reactive hypoglycemia is diagnosed if there is a sharp peak in capillary glucose after an hour followed by a sharp trough, or a trough that goes below 54 mg/dl (Marks, 1987). This test may on occasions be inconclusive because outside the laboratory hypoglycemia symptoms appear at higher blood glucose levels (Brun, Fedou, & Mercier, 2000). However where the diagnosis of reactive hypoglycemia is confirmed, a low-GI diet is a logical management option.

In conclusion, this is the first study to demonstrate that women with PCOS have significantly more mood and behavioural symptoms that may be associated with reactive hypoglycemia than healthy women, and this finding is potentially of clinical importance to women with PCOS and the health professionals who help them.

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Table 1

Mean ($\pm$ Standard Deviation) scores on the three Mood Adjective Checklist subscales (MACL) and Hypoglycemia Symptom Checklist – 7 (HSC-7) in the four groups constituting the total sample (N=462).

Outcome measure	PCOS (n=24)	Possible PCOS (n=47)	Control Women (n=299)	Men (n=92)
Energy [a]	16.8 $\pm$ 3.0	19.2 $\pm$ 3.3	21.1 $\pm$ 3.6	21.4 $\pm$ 3.7
Tension [a]	20.9 $\pm$ 5.2	19.2 $\pm$ 3.3	17.3 $\pm$ 3.8	17.2 $\pm$ 3.7
Hedonic Tone [a]	18.9 $\pm$ 5.0	22.1 $\pm$ 4.7	24.3 $\pm$ 4.3	24.2 $\pm$ 4.1
HSC-7 [b]	2.6 $\pm$ 0.6	2.5 $\pm$ 0.5	2.1 $\pm$ 0.6	2.0 $\pm$ 0.7

[a] Mood Adjective Checklist (MACL) subscale

[b] Hypoglycemia Symptom Checklist – 7

Table 2

Comparison of the 12 PCOS and 12 healthy matched control women on symptoms typical of hypoglycemia.

Outcome measure	Group	*M*	*SD*	*t*	*p**
Energy [a]	PCOS	16.8	3.4	-3.883	0.002
	Control	21.4	2.5		
Tension [a]	PCOS	19.7	5.8	2.078	0.031
	Control	16.3	2.6		
Hedonic Tone [a]	PCOS	19.2	5.1	-5.472	0.001
	Control	26.2	2.6		
HSC-7 [b]	PCOS	2.6	0.6	2.214	0.025
	Control	2.0	0.7		

* Probability value is one-tailed

[a] Mood Adjective Checklist (MACL) subscale

[b] Hypoglycemia Symptom Checklist – 7