

Ketogenic diets and tumour hypoxia – Kulturkampf and “The Insurgency”

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The two papers in this section are each, in their way, subversive, but for quite different reasons.

In the first review, Redfern and colleagues describe in detail the steps activated in solid tumours by hypoxia resulting from insufficient angiogenesis in the mass [1]. It is deliberately termed “hypoxic prison breakout” being unlike the response of any other tissue to periods of ischaemia and reperfusion [2;3]. Whereas these responses are generally conservative and involve a re-grouping of mitochondrial energy metabolism and a constructive avoidance of cell death [4], cancer cells do it differently. They will, metaphorically pack their bags and go somewhere more congenial. What the reader would describe as “normal” energy metabolism is stood on its head. Firstly, many tumour lines exhibit aerobic glycolysis (lactic fermentation) or the “Warburg Effect” whereby most ATP is generated through glycolysis not through oxidative phosphorylation in Krebs’ Cycle (tricarboxylic acid cycle, TCA Cycle). In itself this is a cause of mitochondrial dysmorphism because the failure to generate protons within the mitochondrial matrix will collapse the typical shape of the cristae and lead to a reversal of ATP synthesis. In a recent review, Chinopoulos and Seyfried argue the case for this and hypothesise that mitochondrial substrate-level phosphorylation meets the energy need [5]. Secondly, the tumour cells require a ready supply of 3-carbon and 4-carbon precursors for synthesis of ribose sugars and purines and pyrimidines, something complete glycolysis or fatty acid β -oxidation can never supply through acetate. In the early days of clinical nutrition research, Eric Newsholme provided an elegant and satisfying explanation for the phenomenon of muscle glutamine efflux and wastage as a means provide these substrates for the immune system (Figure 1). In essence, he visualised the TCA Cycle as being split into a first half in muscle, the second half completing in the rapidly dividing lymphocytes [6]. Something similar happens in tumour cells which become reliant on exogenous glutamine and glucose supply [5]. They describe the situation for glioblastoma multiforme, an uncontrollable and unmanageable primary brain tumour and hypothesise that anaplerotic inputs of glucose and glutamine via pyruvate/oxaloacetate and glutamine/2-oxoglutarate, respectively will provide fuel for substrate-level ADP phosphorylation in

which succinate-CoA ligase plays a key “*channeling*” role. In contrast, inputs from ketones cannot achieve this. One way, therefore to exploit this fundamental metabolic weakness in glioblastoma is to remove supply of either glutamine or glucose. The latter may be achieved by removing dietary glucose to render the patient ketotic.

In the second review, Danielle DeCampo and Eric Kossoff describe the clinical evidence which supports use of the low-carbohydrate ketogenic diet (KD), which deliberately induces a metabolic ketoacidosis as a means of reducing the frequency of seizures in patients with epilepsy [7].

There is no doubt that the diet works for many patients, and several mechanisms of action have been suggested (Table 1). One of us (GG) became interested in the topic whilst supervising a graduate student who was investigating the effect of a ketogenic diet in paediatric patients with refractory epilepsy at the National Hospital for Neurology and Neurosurgery in London. It was found that in the group who could comply with the diet (~50% with intensive dietetic help) the number of seizures and use of antiepileptic medication was significantly reduced. These findings have been replicated by many other researchers, and DeCampo and Kossoff carefully and exhaustively describe this in their review [7]. They are also the subject of two recent, important, position papers on how to provide a ketogenic dietetic service and apply best practice to treatment for children and adults [8].

In the United Kingdom, paediatric dietitians and doctors have reported on practical steps necessary to set up an effective ketogenic diet service within the British National Health Service [9-11]. This is because of a desire to generalise better clinical practice and clinical data in face of poor quality of evidence, a common complaint about much clinical nutrition practice [12]. It was found that adverse reactions to the diet and poor palatability were the commonest reasons for discontinuation [12]. What is now known is that KD leads to a reduction in emergency hospital admissions [13;14] but with little apparent overall effect on Quality of Life or overall costs compared to anti-epileptic drugs [13;15].

Clearly, more research is needed in order to improve compliance and nutritional quality of the diet which, classically, provides 87-90% of energy from fats [8].

These considerations are both encouraging and discouraging because it is hard to predict which patients will both tolerate the diet and respond favourably. There is no doubt that parents of a child with epilepsy face a challenging experience. Although the diet may help reduce devastating symptoms, it also has the potential to divide families because the child is clearly segregated at mealtimes from their siblings. In addition, the burden of clinical care falls on the parents as a stressor, because of the strict attention to the child's diet in the home and outside. In a school setting it can also become an opportunity for bullying because the child is considered "different" [16]. This phenomenon was first noted in families who needed to provide a phenylalanine-free diet for a child with phenylketonuria [17]. It is a common finding in the case of children with Type 1 diabetes or Coeliac Disease [18] and becomes more marked in families where dietary deviation is more acutely life-threatening, as in the case of food allergy. To an extent, most families will attempt, purposefully to reconstruct a new internal normality in the face of the disruption of a chronic condition which demands strict dietary adherence [19].

This approach of inducing ketoacidosis, deliberately, is not for the fainthearted because in critical care medicine, metabolic acidosis is considered to be an emergency. Furthermore, most studies have shown that the chronic ketoacidosis engendered by the diet causes disordered bone mineralisation in susceptible individuals. For example, there have been several case-reports of children who developed hypercalcaemia, despite care being taken in buffering acidosis with bicarbonate and systematic review literature reviews have identified the excess bone disorder which arises long-term [20]. The confounding factor is, of course that some of the earlier anti-epileptic medications led to disorders of bone mineralisation so it is difficult to separate out the effects of drug and acid-base disturbance. The disturbances in bone metabolism caused by a ketogenic diet can be replicated in both mice [21] and rats [22]. It should be noted that the evidence in adults chronically consuming low-carbohydrate, ketogenic

diets is sparse with one study suggesting no change in bone biomarkers [23] and others showing disordered calcium metabolism and propensity to renal stone formation [24]. The advantages of dietary choices in treatment of type 2 diabetes, and these low-carbohydrate diets in particular have been discussed in detail, recently [25].

Most readers will recognise the process described above as being one of unfolding discovery of a promising new dietary treatment of an intractable condition, with vigorous clinical champions and extensive evidence-based discussion. The process of collecting data systematically (using rationalized, multi-centre treatments) can only but help to define the best indications for KD in treating epilepsy. This cycle of promising clinical findings, pilot studies, full clinical trials and systematic analysis is being repeated in relation to use of KD in cancer therapy [26]. The same has been true for several other innovations in clinical nutrition support. For example, high-fat enteral feeding in patients with Acute Respiratory Distress Syndrome (ARDS) initially showed great promise because of the twin beneficial effects of high n-3 fat intake on inflammation and of high fat oxidation on respiratory gas exchange. A recent systematic review concluded that the benefit was illusory (when compared to more modest fat intakes) and that high-fat diets could not be recommended [27]. This process of “relentless criticism” of new medical nutritional hypotheses was described first by Karl Popper in 1954 and is the normal way to do medical science which most readers will instantly recognise. It is also a rather slow process.

The same process is occurring in relation to use of the ketogenic diet to treat diabetes (Type 1 Diabetes [T1DM], Type 2 Diabetes [T2DM] and Gestational Diabetes [GDM]), migraine and other neurological diseases and cancer. In the case of T2DM, it is based on two metabolic considerations. Firstly, a low carbohydrate, high protein and fat diet leads to increased ketogenesis and is claimed to result in more controllable and predictable glycaemia and insulin dosing [28]. A recent single cohort study has shown that patients recruited via “TypeOneGrit”, an online Facebook community for people with T1DM, achieved excellent glycaemic control with this diet [29]. In T2DM, it is claimed that obesity is a result of

hyperglycaemia which “locks up” fat in adipose tissue from which it cannot be released by a hypocaloric low-fat diet (which will stimulate insulin secretion) but only by a hypocaloric low-carbohydrate diet [30]. This is the “*Insulin-Carbohydrate*” model of obesity and has been hotly contested on theoretical and experimental grounds [31]. Not least of these is that overfeeding or underfeeding with isocaloric low or high carbohydrate diets [32;33] has little detectable macronutrient-specific effect on weight change or energy expenditure. In other words, this data suggests that a “*calorie really is a calorie*” and that there is no metabolic magic in relation to ketogenic diets in this T2DM setting. Of course, further clinical trials will settle this matter according to sound Popperian principles.

However, not every KD proponent follows these rules as one of us discovered, after being contacted by a lawyer on social media about the MSc KD study. This person was informally collecting unpublished data from KD trials in support of Professor Tim Noakes who was undergoing disciplinary investigations in South Africa for advising a patient to treat their child with KD [34]. It should be stressed that the disciplinary complaint was not upheld because the panel did not consider that Professor Noakes was acting professionally in a doctor-patient relationship but was only giving advice. Further investigations revealed very active Facebooks groups dedicated to use of KD in sports and exercise, and the disorders described above. What was surprising was both the strength of passion amongst members of these groups allied, in some, with a profound ignorance of biochemistry, physiology and nutrition science. Others exhibited a distrust of established expert opinion. This seemed such a fascinating phenomenon, and so different from the evidence-based approach described above, that it begged informal qualitative research on several of the relevant Facebook pages. In essence, the terrain seemed dominated by medical doctors who publish popular books on low-carbohydrate diets for treatment of obesity and type 2 diabetes [35;36], citing sugar as the cause of obesity [37]. They were supported by journalists who published in the same vein [38;39] and a Professor of Biochemistry [40], amongst others.

It should be stressed that the diet is designed to allow better control of blood glucose and insulin dosing and in neither T1DM or T2DM does the diet cure the condition but it may provide better symptom relief than conventional diet and glycaemic medication therapy.

This “low carbohydrate, high fat” approach has proved controversial. For example when it was promulgated in a report by the National Obesity Forum (NOF) in the UK [41], it led to the resignation of several board members of NOF on the grounds that they had not been consulted before publication. The report has also been widely criticised on evidential grounds [42].

An informal qualitative research approach was used in order to understand this “low-carb” phenomenon. The Capability-Opportunity-Motivation-Behaviour (COM-B) model attempts to discover drivers of behaviours and relies on analysis of structured interviews to reveal themes which can be codified and analysed. It differs from quantitative research in that when no new themes emerge with successive interviews, then saturation has occurred and further interviews are unnecessary. In quantitative research, in contrast, the sample size is calculated beforehand in order to avoid Type 1 and Type 2 statistical errors. This qualitative methodology was the basis of our own research on food insecurity in British urban populations to discover why people attend Foodbanks and how good their diet was [43]. The present social media qualitative research was however, informal because the effort required to analyse extensive Facebook threads would have been excessive. It was based on persistent questioning of many protagonists on their understanding of underlying principles – for example:-

- Is truncal obesity a major risk factor for T2D in your opinion?
- Do over- and under-feeding studies with different macronutrient composition suggest that “*a calorie really is a calorie*”?
- Is there an underlying problem when people claim to lose weight on an estimated ketogenic diet intake of 4,500kcal/day and estimated energy expenditure of 2,500kcal/day?

- Have you considered enrolling in a nutrition science course?
- Is glucose truly a non-essential nutrient and why does the body make so much of it during a KD?

The following themes emerged from this informal study (Table 2) and some particularly robust responses were received from some highly educated contributors.

*“get the **** off my page. You don't know what the **** you are talking about.”* Case 1 – PhD, runs courses on treatment of diabetes with KD.

“George represents the academia I left as you can see for good reason. I have no intention to return and become dumified (i.e. made stupid)”. Case 2 – PhD who “treats” people online with KD and declines to publish the data

“And again, your success with starvation diets is only the soft bigotry of low expectations.” Case 4 – PhD who thought I was a technocrat and threatened to sue.

In contrast, other highly-educated individuals were discovered who recognised the scientific basis of nutrition and were prepared to engage in vigorous academic and polemic argument against some of the excessive claims of the KD “movement” [44]. Some salient features of their arguments were that in its present form, popular KD failed often to meet current dietary guidelines because of its excessive cholesterol, saturated fat and salt content and because it could be nutritionally deficient. Furthermore, it was argued that KD worked no better than other weight-reducing diets. This situation therefore represents a low-carbohydrate diet insurgency against established nutritional science [41] and an informal counter-insurgency against the low-carbohydrate diet movement itself [44].

What does this mean for medical nutrition? In relation to artificial nutrition support in hospital it is irrelevant, because patients will generally do as directed and are reliant on hospital provision. In the

community, however, it is noteworthy that patients and their carers will attempt to comply with dietary recommendations for metabolic (i.e. PKU) or neurological (i.e. epilepsy) disease from dietitians and doctors. However, the nexus of obesity and metabolic disease seems to occupy a different domain and is a cause of “heart-sink” for many dietitians and primary care physicians because of the modest results from current programmes. This has provided an excellent marketing opportunity for advocates of all “alternative” diets. If, of course, simple weight loss could reverse T2DM then the manner in which that was done would be less relevant and there would be no specific metabolic unique selling point. The only matters of concern would be that diet patients were consuming during weight loss was nutritionally adequate (apart from energy content) and how best it could be nuanced into a diet fit for lifetime weight control, which itself fit best with current dietary recommendations.

The Diabetes Remission Clinical Trial (DiRECT study) in primary care settings demonstrated that loss of a large amount of excess weight alone, resolves most T2DM [45;46]. It was achieved with a smart combination of initial rapid weight-loss with a nutritionally complete very-low calorie diet and subsequent intensive follow-up with sustainable reduced-energy diets. The authors have done well to operationalise this in a community setting. This comes more than 30 years after this “protein-sparing modified fast” was pioneered George Blackburn and Bruce Bistrian and colleagues [47]. Lean and colleagues conclude that *“Our findings suggest that type 2 diabetes is a clinical consequence of accumulation of excess weight, in ectopic sites by susceptible individuals, even in people with fairly low BMI.”* [46]. It seems really simple, then, the evidence is clear. Perhaps the war is over and it is time to stop majoring in the minors of macronutrient composition and focus on weight-loss *per se*. Of course, like implementation of KD in epilepsy and cancer, the devil will be in the evidence-based detail of mass implementation of weight-loss programmes to tackle the obesity/T2DM which is killing us.

Figure 1 Cell types which feed off other organs in the body

In this diagram (adapted from [6]), the cells of the immune system or tumour which exhibit a Warburg Effect receive substrates for cell growth and division (i.e. nucleic acid synthesis) from skeletal muscle (glutamine) and the diet (glucose). Excess anaplerotic substrates which can fill the TCA Cycle are generated elsewhere and supplied to the target organ. It is no different in concept to the Cori or Glucose-Alanine Cycles and presents a therapeutic opportunity to sensitise tumour cells to chemo- or radiotherapy by inhibiting glucose or glutamine supply. Muscle exports glutamine which is converted to glutamate and then 2-oxoglutarate by the lymphocyte or tumor cell.

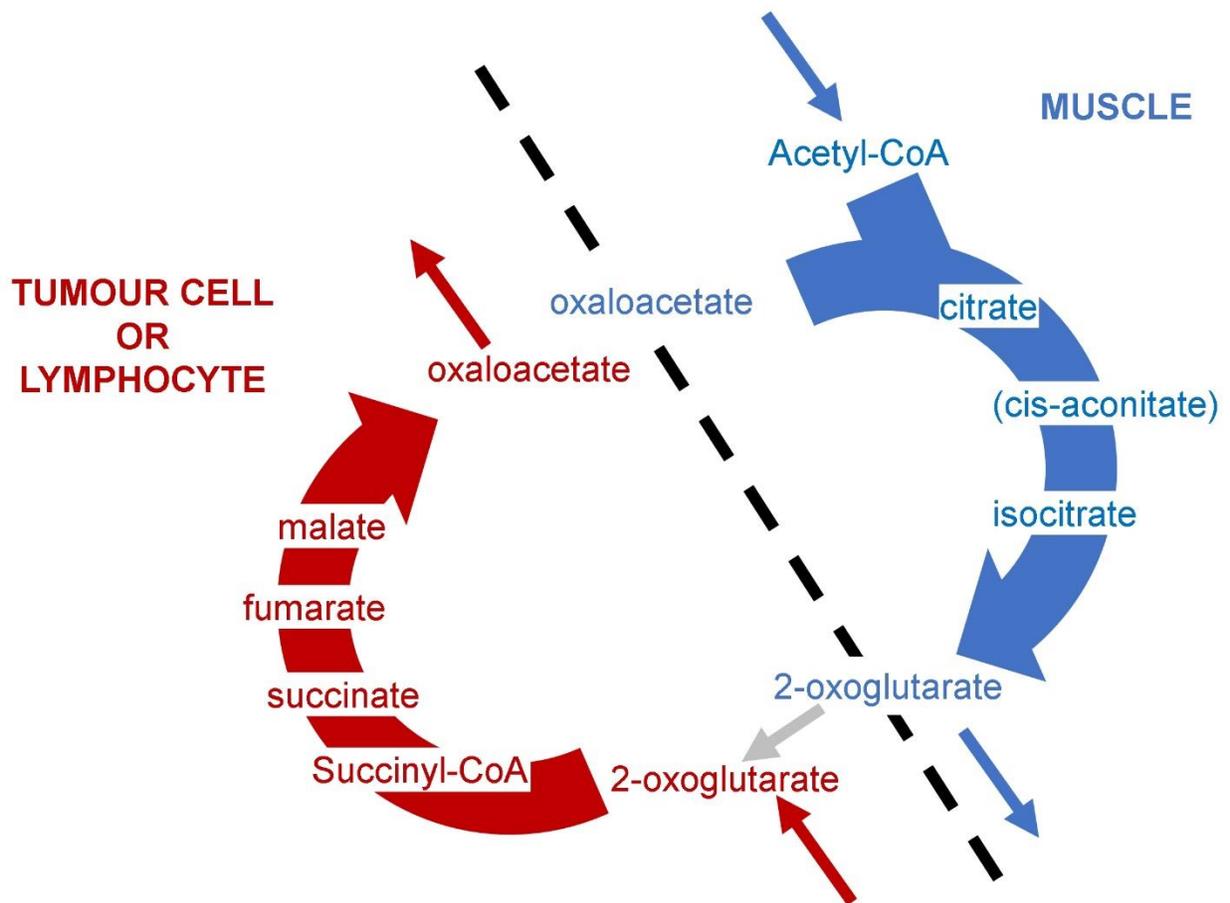


Table 1 Possible modes of action of the Ketogenic Diet in treatment of epilepsy

Hypothetic mode of action	Comments
1. Ketones act directly as anti-seizure agents	Demonstrated in animals and humans but no plausible mediating mechanism
2. Increased flux of acetylCoA with reduced glycolysis leads to less conversion of glutamate to aspartate, with beneficial effects on synthesis of gamma amino butyric acid (GABA) and neurotransmission.	Based mainly on changes in concentration of intracellular metabolites.
3. Improved cellular bioenergetics and mitochondrial function	May be mediated through NF E2-related factor 2 (Nrf2), a protective transcription factor that is activated by cellular stress.
4. Restriction in glycolysis flux and diversion of metabolites into the pentose phosphate shunt substrate (fructose-1,6-bisphosphate)	Reduction in NADH:NAD ⁺ ratio modulates histone acetylation
5. Fatty acids act directly as anti-seizure agents	Pleiotypic increase in plasma concentrations of all accessory molecules for fat metabolism (incl. Polyunsaturated fatty acids [PUFA]). Some evidence that PUFA supplementation reduces seizures.
6. Reduced oxidative stress	See 3. above
7. Increased efficiency of the tricarboxylic acid cycle (TCA) function through supplementation with “anaplerotic” substrates.	Experimentally, the KD increases neuronal ATP concentration. It is postulated that the increased presentation of acetyl-coA from ketones increases TCA cycle flux through “anaplerosis” (Greek: “filling up”) but this is a fundamental misunderstanding. Aspartate and glutamate feed this process as the metabolites oxaloacetate and α-ketoglutarate. Ketones feed in acetyl-coA which will be oxidised and cannot therefore fill up the TCA Cycle.
The reader is directed to recent detailed reviews on this [48;49]	

Table 2 Themes emerging from informal qualitative research on a social media site

Theme	Comments
Laws of Thermodynamics are irrelevant as is the concept of “ <i>calories in and calories out</i> ” (CICO). Not all calories are equal.	“Calories in” represents “matter in” and the more matter that goes in than goes out as CO ₂ , the more matter will remain in the body.
“ <i>Eat less, move more</i> ” is stupid because it hasn’t worked and obesity is epidemic	This recommendation was seen as far too simple and not informative about useful diets.
Dietary recommendations are stupid because they haven’t worked and that’s why obesity is epidemic	This is a category error because dietary guidelines are for populations, diets are for individuals. Most people do not follow guidelines but follow “diets”.
Ketones have magical properties and lead to “ <i>fat burning</i> ”	This was often cited in the context of eating <50g carbohydrate each day, the balance being fat. Since more fat is being consumed, more fat will be oxidised.
Glucose is not an “ <i>essential nutrient</i> ” so can be almost completely replace in the diet by fat	Glucose is not an essential nutrient. In fact the body will make equally large amounts as before on a KD. The extra fat is often saturated and from animals, because “industrial food oils” (i.e. n-3, n-6 and n-9) are too bioactive at these high doses. See below.
Saturated fat is not harmful in excess, cholesterol is not the cause of CVD, salt is not harmful	This topic was often associated with a disdain for nutritional epidemiology in general and Ancel Keys in particular.
The macronutrient composition of the diet is more important than simple weight-loss for T2DM remission	This view was often expressed by the most persistent KD advocates.
Reluctance to enrol on a mainstream nutrition course	This seemed partly because of suspicion that the teachers on the course would be prejudiced against low-carbohydrate diets.
It is possible to eat as much of a KD as you like and still lose weight and not feel hungry	Fear of “ <i>hunger feelings</i> ” and failure to achieve weight loss were common.
Fear of poor health and high cost of medicines and healthcare	This was more relevant to countries with commercialised healthcare systems and less important for countries like the UK or the Netherlands.
There is a conspiracy	The main conspirators were considered to be the Food and Pharmaceutical industries, doctors, dietitians and especially nutrition scientists. The professions were often considered to be both corrupt and obstructive to adopting KD.

Disclaimer

Tables 1 and 2 are original and have not been published before.

Figure 1 is an adaptation of a figure in [6]

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