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**Original Research Article**

# KETOGENIC DIET AND ITS ROLE IN ELIMINATING MEDICINAL TREATMENT IN VARIOUS DISEASES

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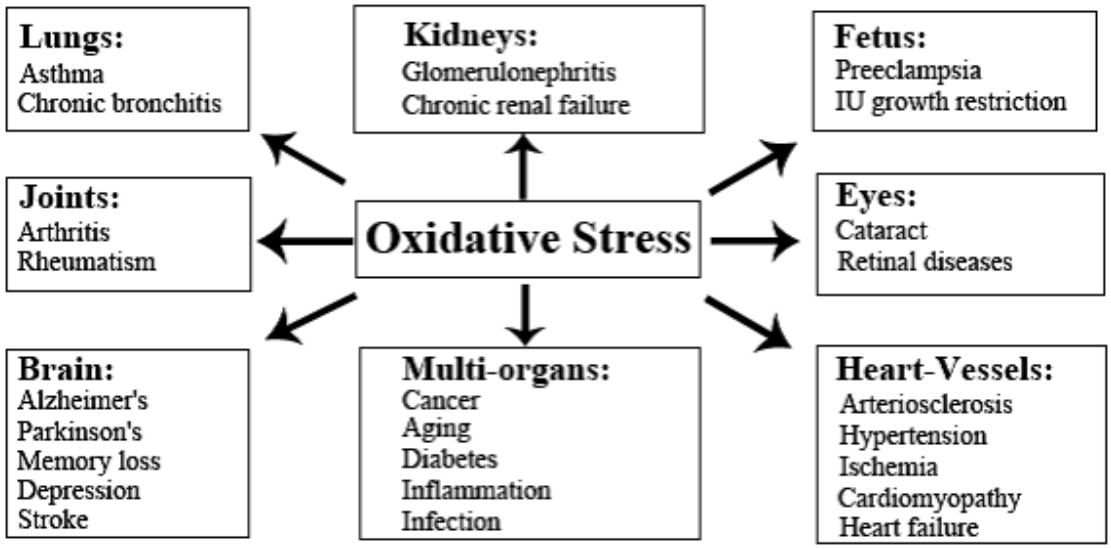
**Abstract**
Very-low-carbohydrate diets or ketogenic diets have been used 1920s to treat Epilepsy. Ultimately it finished medication. They have become widely known as one of the most common methods for obesity treatment. Now work over the last few years their therapeutic potential in many conditions, such as diabetes, polycystic ovary syndrome, acne, neurological diseases, cancer and the amelioration of respiratory and cardiovascular disease risk factors have been of help. The possibility that modifying food intake can be useful for reducing or eliminating medicinal treatment, which are often lifelong with significant side effects. It calls for serious investigation. Meaning of physiological ketosis in the light of this evidence is considered possible mechanisms for the therapeutic actions of the ketogenic diet on different diseases. There are still some well understood ideas about ketogenic diets, which may remove superfluous thinking. It could prove to be a boon later.

**Keywords: Ketogenic diet; cancer; diabetes; neurological diseases; obesity; cardiovascular diseases**

## Introduction

Very-low-carbohydrate ketogenic diets (VLCKD) could have a therapeutic role in numerous diseases. The use of VLCKD in treating epilepsy has been well lineated. Later they became popular for weight loss—especially as the 'Atkins Diet'.[1] Therapeutic use of ketogenic diets in many diseases has come out with positive results. It is an important direction for research as nutritional therapy can reduce reliance on medicinal treatments. It would bring significant benefits from an economic as well as a social point of view. Ketogenic diets are characterized by a reduction in carbohydrates (usually to less than 50 g/day) and a relative increase in the proportions of protein and fat.[3] They began to be successfully used in the treatment of epilepsy.[5] Alongside the huge amount of data

about the influence of correct nutrition on health status and disease prevention (encapsulated in various nutritional guidelines delivered by public health committees worldwide), there is also ample evidence to support the notion that a low-carbohydrate diet can lead to an improvement in some metabolic pathways and have beneficial health effects. To use 'food as medicine' is as attractive a concept as it helps in exploring the effects of VLCKD on human metabolism. In this study we will look at all the areas where ketogenic diets have been proposed as having potential clinical utility with a brief discussion of the evidence.




Storage energy derived from carbohydrates, and when there is an absence or scarcity of dietary carbohydrates the resulting reduced insulin level leads to a reduction in lipogenesis and fat accumulation. After a few days of fasting, or of drastically reduced carbohydrate consumption (below 50 g/day), glucose reserves become insufficient both for normal fat oxidation via the supply of oxaloacetate in the Krebs cycle (which gave origin to the phrase 'fat burns in the flame of carbohydrate') and for the supply of glucose to the central nervous system (CNS).[4] The CNS cannot use fatty acids as an energy source as they can't cross blood brain barrier; hence, it normally utilizes glucose. After 3–4 days without carbohydrate consumption the CNS is 'forced' to find alternative energy sources, and as demonstrated by the classic experiments of Cahill and colleagues[4] this alternative energy source is derived from the overproduction of acetyl coenzyme A (CoA). This condition seen in prolonged fasting, type 1 diabetes and high-fat/low-carbohydrate diets leads to the production of higher-than-normal levels of so-called ketone bodies (KBs), that is, acetoacetate, β-hydroxybutyric acid and acetone—a process called cytogenesis' and which occurs principally in the mitochondrial matrix in the liver.[6] The main KB produced in the liver is acetoacetate but the primary circulating ketone is β-hydroxybutyrate although the latter is not, strictly speaking, a KB because the ketone moiety has been reduced to a hydroxyl group. Under normal conditions of adequate dietary carbohydrate, the production of free acetoacetic acid is negligible and it is rapidly metabolized by various tissues, especially the skeletal and heart muscles. In conditions of overproduction of acetoacetic acid, it accumulates above normal levels and part of it is converted to the other two KBs leading to ketonemia and Ketonuria The characteristic 'sweet' breath odor of ketosis is caused by acetone, which is eliminated

mainly via respiration in the lungs. The pathway that results in the formation of 3-hydroxy-3-methylglutaryl–CoA from acetyl CoA also occurs in the cytosol of hepatic cells where it is used instead for the biosynthesis of cholesterol. Under normal conditions, the concentration of KBs is very low (<0.3 mmol/l) compared with glucose (~4 mmol), and as glucose and KBs have a similar Km for glucose transport to the brain the KBs begin to be utilized as an energy source by the CNS when they reach a concentration of about 4 mmol/l, which is close to the Km for the monocarboxylate transporter.[3,6] KBs are then used by tissues as a source of energy[3] through a pathway that leads to formation from β-hydroxybutyrate of two molecules of acetyl CoA, which are used finally in the Krebs cycle. It is interesting to note that the KBs are able to produce more energy compared with glucose because of the metabolic effects of ketosis—the high chemical potential of 3-β-hydroxybutyrate leads to an increase in the $\Delta G_0$ of ATP hydrolysis.[3] A further point to underline is, as shown in that glycemia, even though reduced, remains within physiological levels because of the fact that glucose is formed from two sources: from glycogenic amino acids and from glycerol liberated via lysis from triglycerides.[7]

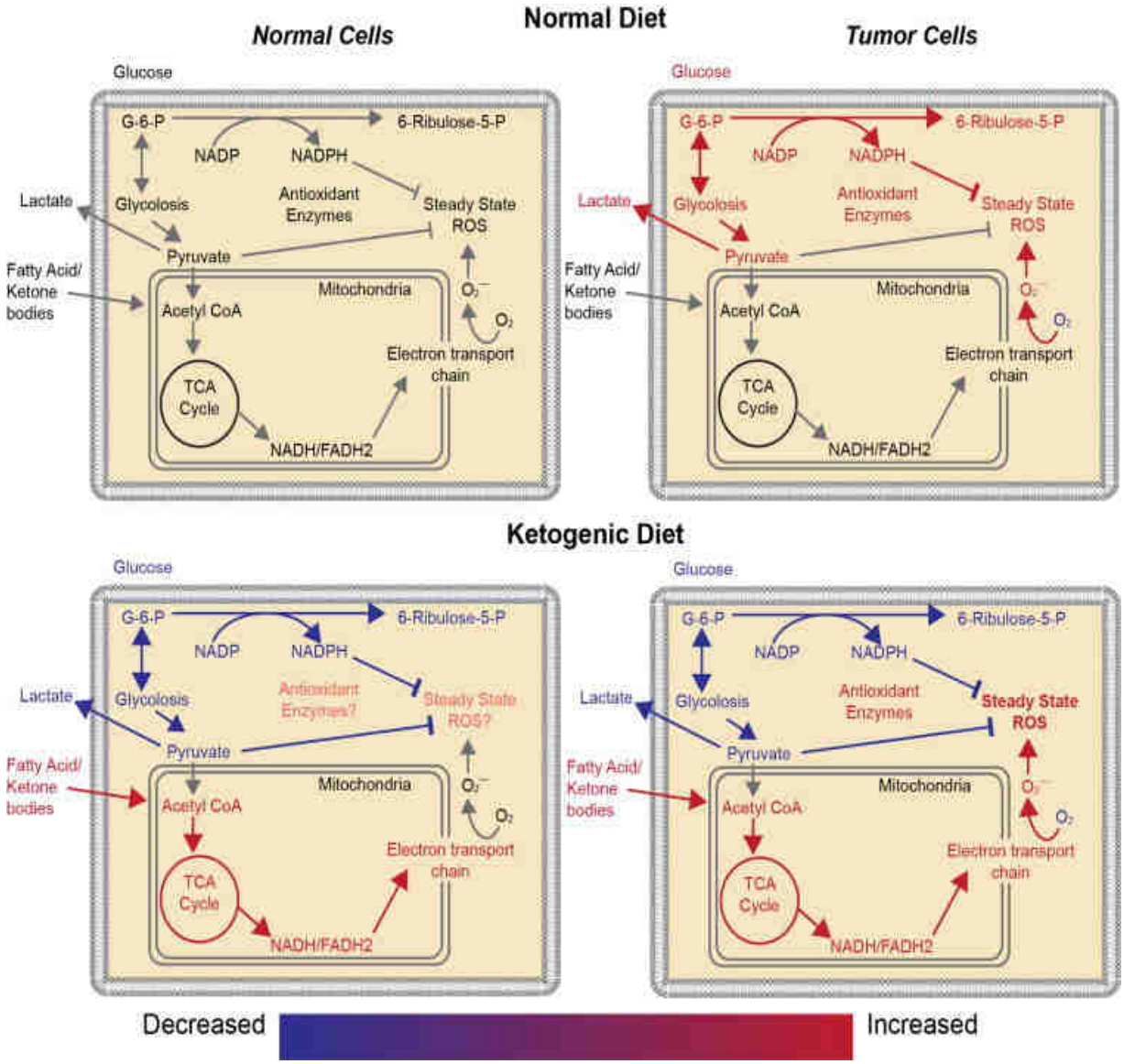
**Observation**

**Table 1.** Blood levels during a normal diet, ketogenic diet and diabetic ketoacidosis[11]

| **Blood levels** | **Normal diet** | **Ketogenic diet** | **Diabetic ketoacidosis** |
|---|---|---|---|
| Glucose (mg/dl) | 80–120 | 65–80 | >300 |
| Insulin (μg/l) | 6–23 | 6.6–9.4 | ≅ 0 |
| KB conc. (mM/l) | 0.1 | 7/8 | >25 |
| pH | 7.4 | 7.4 | <7.3 |

We would like to emphasize that ketosis is a completely physiological mechanism and it was the biochemist Hans Krebs who first referred to physiological ketosis to differentiate it from the pathological ketoacidosis seen in type 1 diabetes.[8] In physiological ketosis (which occurs during very-low-calorie ketogenic diets), ketonemia reaches maximum levels of 7/8 mmol/l (it does not go higher precisely because the CNS efficiently uses these molecules for energy in place of glucose) and with no change in pH, whereas in uncontrolled diabetic ketoacidosis it can exceed 20 mmol/l with a concomitant lowering of blood pH[9, 10.]There is no authentic evidence that the use of ketogenic diets in weight-loss therapy is effective; however, there are contrasting theories regarding the mechanisms through which they work. Some researchers suggest that there are not in fact any metabolic advantages in low-carbohydrate diets and that weight loss results from cutting down caloric intake, this may be due to increased satiety effect of protein.[12] Others instead promote the hypothesis that there is indeed a distinct metabolic advantage, which has recently been explored in more detail, raising interest in the role of VLCKD in weight loss and effects on metabolism in general.[13] Department of Agriculture has revealed that diets, calories cut will lead to loss of weight even when other essential micronutrients are low.[14] Persons on low-carbohydrate diet lose more weight during the first 3–6

months compared with those who follow balanced diets.[15,16,17]




One hypothesis is that the use of energy from proteins in VLCKD is an 'expensive' process for the body and so can lead to a 'waste of calories', and therefore increased weight loss compared with other 'less-expensive' diets.[13,18,19] The average human body requires 60–65 g of glucose per day, and during the first phase of a diet very low in carbohydrates this is partially (16%) obtained from glycerol, with the major part derived via gluconeogenesis from proteins of either dietary or tissue origin.[12] The energy cost of gluconeogenesis has been confirmed in several studies[7] and it has been calculated at ~400–600 Kcal/day (due to both endogenous and food source proteins.[18] But there is no direct evidence to support this intriguing hypothesis; on the contrary, a recent study reported that there were no changes in resting energy expenditure after a VLCKD[20] A simpler; perhaps more likely, explanation for improved weight loss is a possible appetite-suppressant action of ketosis.

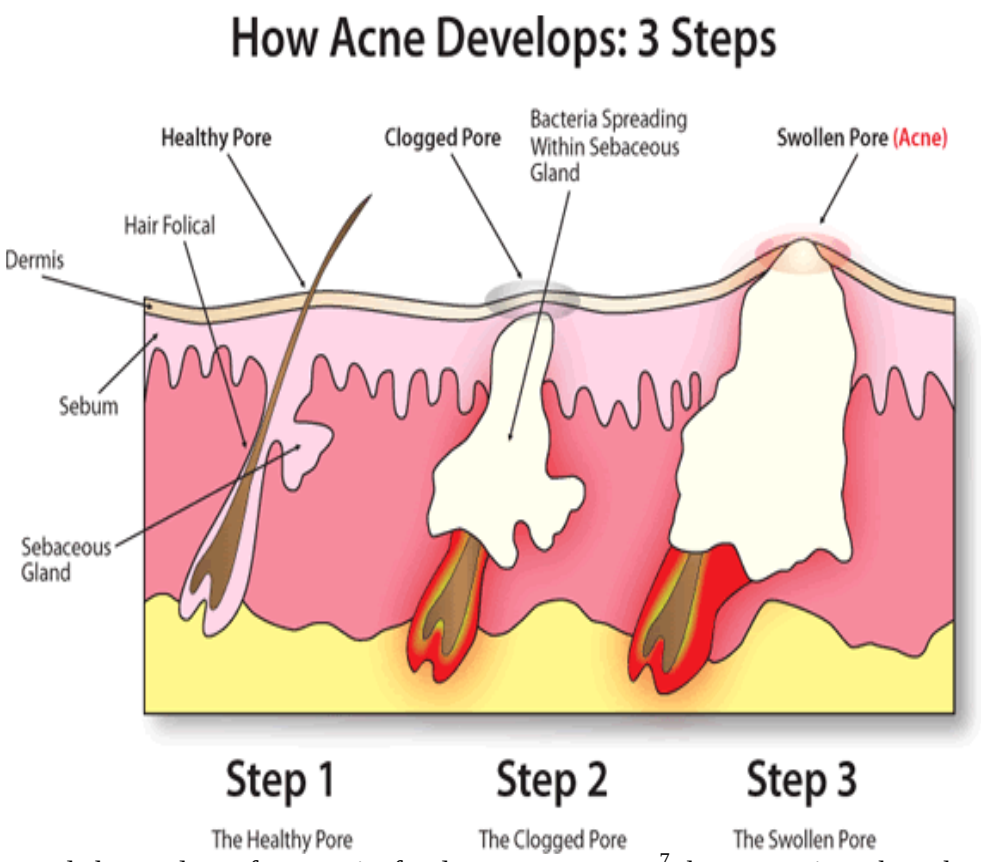
**Discussion**

The mechanism for this is not established but evidence supports direct action of KBs together with modifications in levels of hormones, which influence appetite, such as ghrelin and leptin.[21] Here we can summarize (listed in order of importance and available evidence) that the weight-loss effect of VLCKD seems to be caused by several factors:

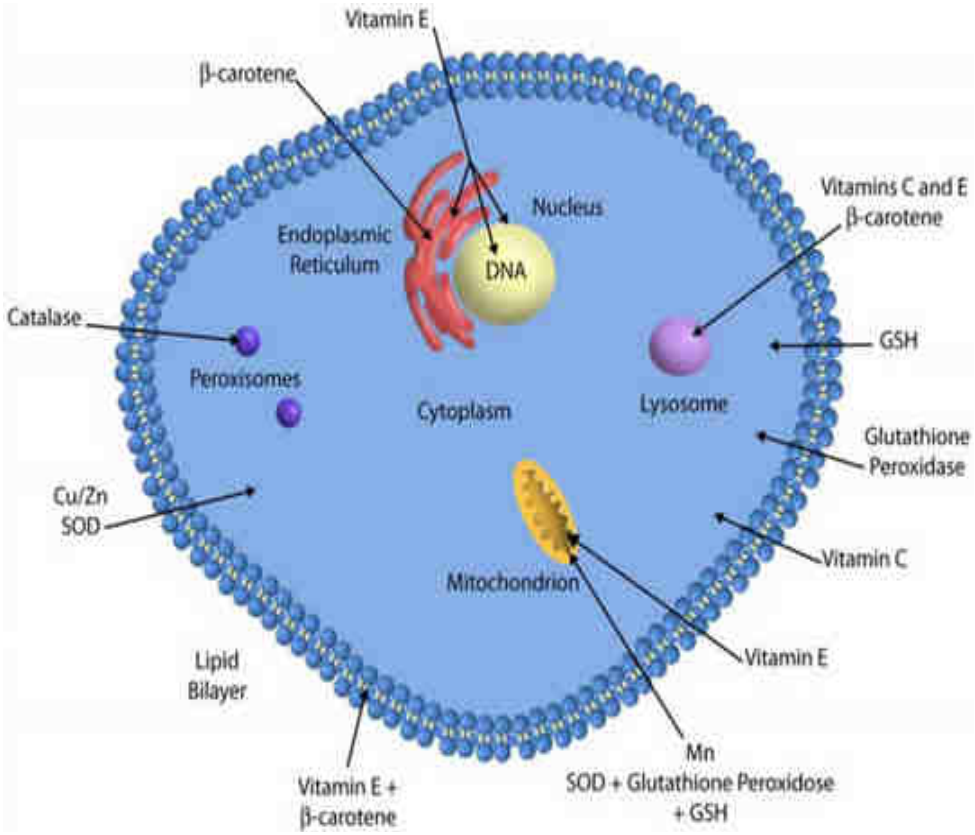
1. Reduction in appetite due to higher satiety effect of proteins,[12,22] effects on appetite control hormones[21]
2. Reduction in lipogenesis and increased lipolysis.[7,10]
3. Reduction in the resting respiratory quotient and, therefore, greater metabolic efficiency in consuming fats.[20, 24] Increased metabolic costs of gluconeogenesis and the thermic effect of proteins.[13,18]

Several lines of evidence point to beneficial effects of VLCKD on cardiovascular risk factors. In the past, there have been doubts expressed about their long-term safety and increased effectiveness compared with 'balanced' diets,[25] and clearly negative opinions regarding possible deleterious effects on triglycerides and cholesterol levels in the blood.[26] However, the majority of recent studies seem instead to amply demonstrate that the reduction of carbohydrates to levels that induce physiological ketosis (see above 'What is ketosis?' section) can actually lead to significant benefits in blood lipid profiles.[15,17,19] The VLCKD effect seems to be particularly marked on the level of blood triglycerides,[23,24] but there are also significant positive effects on total cholesterol reduction and increases in high-density lipoprotein.[14,18,19] Furthermore, VLCKD have been reported to increase the size and volume of low-density lipoprotein–cholesterol particles,[29] which is considered to reduce cardiovascular disease risk, as smaller low-density lipoprotein particles have a higher atherogenicity. There are also direct diet-related effects on overall endogenous cholesterol synthesis. A key enzyme in cholesterol biosynthesis is 3-hydroxy-3-methylglutaryl–CoA reductase (the target for statins), which is activated by insulin, which means that an increase in blood glucose and consequently of insulin levels will lead to increased endogenous cholesterol synthesis. Resistance is the primary feature underlying type 2 diabetes (T2D) but it also exists across a continuum in the general population, and to varying extents it disrupts insulin action in cells, which can cause a wide spectrum of signs and symptoms. A primary feature of insulin resistance is an impaired ability of muscle cells to take up circulating glucose. A person with insulin resistance will divert a greater proportion of dietary carbohydrate to the liver where much of it is converted to fat (that is, de novo lipogenesis), as opposed to being oxidized for energy in skeletal muscle.[23] Although Hellerstein[21]has recently reported that de novo lipogenesis contributes only ~20% of new triglycerides, this greater conversion of dietary carbohydrate into fat, much of it entering the circulation as saturated fat, is a metabolic abnormality that significantly increases risk for diabetes and heart disease. Thus, insulin resistance functionally manifests itself as 'carbohydrate intolerance'. When dietary carbohydrate is restricted to a level below which it is not significantly converted to fat (a threshold that varies from person to person), signs and symptoms of insulin resistance improve or often disappear completely. In studies that have evaluated well-formulated very-low-carbohydrate diets and documented high rates of compliance in individuals with T2D, results have been nothing short of remarkable. Bistrian et al.[23] reported withdrawal of insulin and major weight loss in a matter of weeks in T2D individuals who were fed a very-low-calorie and -carbohydrate diet. Gumbiner *et al.*[23] fed obese T2D individuals two types of hypocaloric (650 kcal) diets for 3 weeks,

they were matched for protein but one was much lower in carbohydrate content (24 vs. 94 g/day). Boden et al.[34] performed an in-patient study in obese T2D individuals who were fed a low-carbohydrate (<20 g/day) diet for 2 weeks. Plasma glucose fell from 7.5 to 6.3 mmol/l, hemoglobin A1C decreased from 7.3 to 6.8% and there were dramatic improvements (75%) in insulin sensitivity. In a longer study[25] obese T2D individuals were prescribed a well-formulated ketogenic diet for 56 weeks, and significant improvements in both weight loss and metabolic parameters were seen at 12 weeks and continued throughout the 56 weeks as evidenced by improvements in fasting circulating levels of glucose (−51%), total cholesterol (−29%), high-density lipoprotein–cholesterol (63%), low-density lipoprotein–cholesterol (−33%) and triglycerides (−41%). It is of interest to note that in a recent study in overweight non/diabetic subjects, it was reported that during ketosis fasting glucose was not affected, but there was an elevation in post-prandial blood glucose concentration. This data suggests a different effect of ketosis on glucose homeostasis in diabetic and non-diabetic individuals.[21] though significant reductions in fat mass often results when individuals restrict carbohydrate, the improvements in glycemic control, hemoglobin A1c and lipid markers, as well as reduced use or withdrawal of insulin and other medications in many cases, occurs before significant weight loss occurs. In summary, individuals with metabolic syndrome, insulin resistance and T2D (all diseases of carbohydrate intolerance) are likely to see symptomatic as well as objective improvements in biomarkers of disease risk if they follow a well-formulated very-low-carbohydrate diet. Glucose control improves not only because there is less glucose coming in, but also because systemic insulin sensitivity improves as well. Ketogenic diet has been recognized as an effective tool in the treatment of severe childhood epilepsy, but following the introduction of anticonvulsant drugs, the interest in ketogenic diet treatment waned until the 1990s, with subsequent research and clinical trials demonstrating its practical usefulness. Various studies have been carried out to understand its mechanism of action in epilepsy, but until now it remains largely uncertain.[5]Several hypotheses have been put forward trying to explain the mechanism of action of ketogenic diets: (1) a direct anticonvulsant effect of KBs; (2) a reduced neuronal excitability induced by KBs; [19] (3) an effect on the mammalian target of rapamycin pathway.[20] Most researchers suggest that the metabolic mechanism(s) activated by ketogenic diets (see above) may influence neurotransmitter activity in neurons and this is currently a field of active research. Although the mechanisms of action are not clear, the ketogenic diet is now considered an established part of an integrative approach, along with drug therapy, in the major epilepsy centers worldwide, [22] an important benefit being the reduction of drug use and concomitant reductions in severe side effects often associated with antiepileptic agents. In conclusion, the role of ketogenic diets in epilepsy treatment is well established and we are confident that this is also the case for weight loss, cardiovascular disease and T2D. The recent research reviewed here demonstrate improvements in many risk factors, such as weight, saturated fats, inflammation and other biomarkers, as a consequence of consuming well-formulated low-carbohydrate diets, and this work should encourage continued close examination of their therapeutic value.

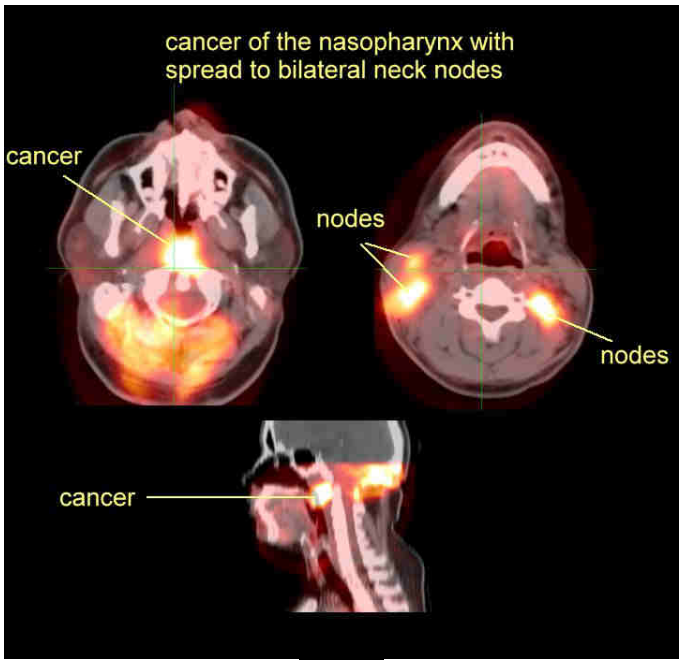



It is suggested that at least for certain food types there is a nutritional influence on the development of acne. These foods include those with a high glycemic load and milk.[11, 23, 24] Other acne varies significantly between different populations and is substantially lower in non-Westernized populations that follow traditional diets,[25] a common factor among these traditional diets being a low glycemic load.[16] Various studies have provided evidence that high-glycemic-load diets are implicated in the etiology of acne through their capacity to stimulate insulin, androgen bioavailability and insulin-like growth factor-1 (IGF-1) activity, whereas the beneficial effects of low-glycemic-load diets, apart from weight and blood glucose levels, also include improved skin quality.[24] The clinical and experimental evidence does in fact suggest ways in which insulin can increase androgen production and affect via induction of steroidogenic enzymes,[7] the secretion by the pituitary gland of gonadotropin-releasing hormone and the production of sex hormone-binding globulin.[6] Insulin is also able to reduce serum levels of IGF-binding protein-1 increasing the effect of IGF-1.[19] These insulin-mediated actions can therefore influence diverse factors that underlie the development of acne. In summary, there is persuasive, although not yet conclusive, clinical and physiological evidence that the ketogenic diet could be effective in reducing the severity and progression of acne and randomized clinical trials will be required to resolve the issue.[11] Carcinogenesis is a complex process involving multiple sequential mutations, which occur randomly in the DNA of normal cells over many years, even decades, until finally specific genes are mutated and cell growth becomes out of control resulting in the full neoplastic phenotype and often metastasis.

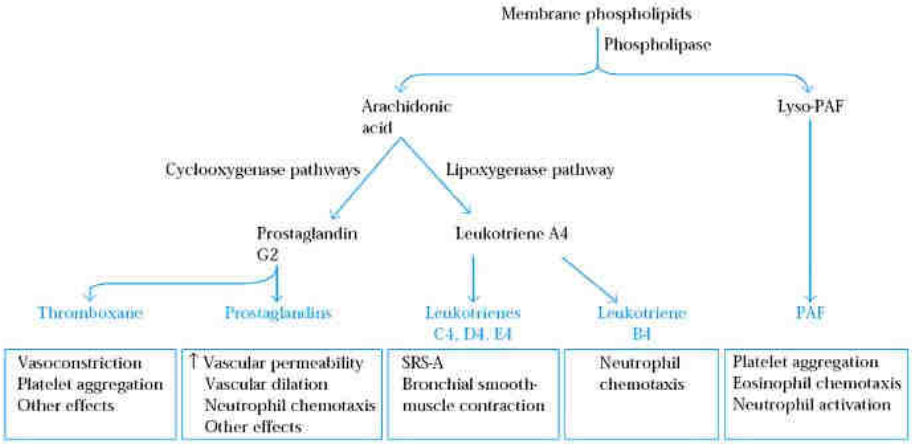



There is evidence that hyperinsulinaemia, hyperglycemia and chronic inflammation may affect the neoplastic process through various pathways, including the insulin/IGF-1 pathway, and most cancer cells express insulin and IGF-1 receptors. Insulin has been shown to stimulate mitogenesis (even in cells lacking IGF-1 receptors)[50] and it may also contribute by stimulating multiple cancer mechanisms, including proliferation, protection from apoptotic stimuli, invasion and metastasis.[21] The IFG1/insulin pathway may also enhance the promotion and progression of many types of cancer cells and facilitate cancer diffusion through angiogenesis.[52] Insulin may act directly, but also indirectly through IGF-1, as it reduces hepatic IGF-binding protein-1 and -2 productions, [23] thereby increasing the levels of circulating, free active IGF-1, which may have a role in cancerogenesis due to its mitogenic and antiapoptotic activity. Dysfunctional mitochondria may unregulated some oncogenes of the phosphatidylinositol 3-kinase/Akt mammalian target of rapamycin signaling pathway.[18] Akt, a downstream of insulin signalling,[59] is involved in changes in tumor cell metabolism and increases resistance to apoptosis; it also decreases β-oxidation and increases lipid synthesis in the cytosol.[20] Hence, it seems a reasonable possibility that a very-low-carbohydrate diet could help to reduce the progression of some types of cancer, although at present the evidence is preliminary.[21] A very recent paper by Fine et al.[21] suggest that the insulin inhibition caused by a ketogenic diet could be a feasible adjunctive treatment for patients with cancer. In summary, perhaps through glucose 'starvation' of tumor cells and by reducing the effect of direct insulin-related actions on cell growth, ketogenic diets show promise as an aid in at least some kind of cancer therapy and is deserving of further and deeper investigation—certainly the evidence justifies setting up clinical trials. Polycystic ovary syndrome (PCOS) is a common endocrine disorder in females, with a high prevalence (6–10%); [22]symptoms

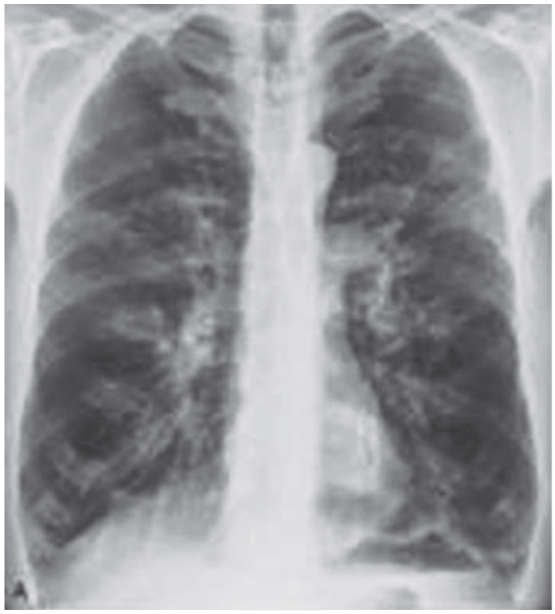
include hyperandrogenism, ovulatory dysfunction, obesity, insulin resistance and subfertility. Insulin resistance and related hyperinsulinaemia is actually a very common feature affecting about 65–70% of women with PCOS; [13] it is seen most frequently in obese patients, affecting 70–80%, compared with only 20–25% of lean PCOS sufferers.[22] Despite this observation, insulin resistance and hyperinsulinaemia appear to be linked to PCOS independently of obesity, and modifications in the normal cellular mechanisms of insulin signaling have been demonstrated in both lean and obese patients. Furthermore, high blood levels of insulin can act by increasing androgenous hormonal stimulation of the ovarian theca cells as well as potentiating gonadotropin-stimulated ovarian androgen steroidogenesis—although recent data has suggested that the insulin-induced increase in ovarian hormone secretion is not accompanied by increased steroid metabolism[24]Hyperinsulinaemia may also affect the central actions of androgen by impairing progesterone inhibition of the gonadotropin-releasing hormone pulse generator.[15] Insulin has also been shown to increase expression of adrenal steroidogenic enzyme mRNA[17]as well as adrenal responsiveness to adrenocorticotropic hormone.[16] Women with PCOS frequently demonstrate many of the signs related to metabolic syndrome, such as insulin resistance, obesity, glucose intolerance, T2D, dyslipidemia and also high levels of inflammation. Finally, although we only have preliminary evidence of the positive effects of VLCKD in PCOS, [17] there are clear mechanisms that are consistent with the physiological plausibility of such dietary therapy. Emerging data suggest a possible therapeutic utilization of ketogenic diets in multiple neurological disorders apart from epilepsy,[18] including head ache, neurotrauma, Alzheimer's and Parkinson's disease, sleep disorders, brain cancer, autism and multiple sclerosis.[19] Although these various diseases are clearly different from each other, a common basis potentially explaining ketogenic diet efficacy could be a neuroprotective effect in any disease in which the pathogenesis includes abnormalities in cellular energy utilization, which is a common characteristic in many neurological disorders.[16] The exact mechanism(s) by which a ketogenic diet may act is still poorly understood; however, some published reports can provide useful suggestions. For example, KBs were recently reported to act as neuroprotective agents by raising ATP levels and reducing the production of reactive oxygen species in neurological tissues, [20] together with increased mitochondrial biogenesis, which may help to enhance the regulation of synaptic function.[30] Moreover, the increased synthesis of polyunsaturated fatty acids stimulated by a KD may have a role in the regulation of neuronal membrane excitability: it has been demonstrated, for example, that polyunsaturated fatty acids modulate the excitability of neurons by blocking voltage-gated sodium channels.[21] Another possibility is that by reducing glucose metabolism, ketogenic diets may activate anticonvulsant mechanisms, as has been reported in a rat model.[22] In addition, caloric restriction per se has been suggested to exert neuroprotective effects, including improved mitochondrial function, decreased oxidative stress and apoptosis, and inhibition of proinflammatory mediators, such as the cytokines tumor necrosis factor-α and interleukins.[23] Clinical benefits of ketogenic diets in most neurological diseases remain largely speculative and uncertain, with the significant exception of its use in the treatment of convulsion diseases.




Patients affected with Alzheimer's disease show a higher incidence of seizures compared with unaffected people, [19] and it has recently been reported that neuronal excitability is enhanced, [15, 16] and neuronal circuits and mitochondrial homeostasis are altered. [17]On the basis of the reports described above, these results indicate a possible role of the ketogenic diet in the treatment of Alzheimer's disease in the clinic. Supporting evidence is provided by a study, which reported that at least in selected conditions a significant clinical improvement was observed in Alzheimer's patients fed a ketogenic diet.[18] It was suggested that this was, at least in part, related to improved mitochondrial function secondary to the reported protective effects of KBs against the toxic consequences of the exposure of cultured neurons to β-amyloid.[9] These promising results should encourage further research that is necessary to improve our understanding about the potential benefits of ketogenic diets in this debilitating and, thus far, irreversible disease. The possible beneficial effects of ketogenic diets on mitochondrial activity described above has also been proposed to explain the improved scores on a standard gravity scale of Parkinson' disease exhibited by some patients.[21]In addition, the typical mitochondrial respiratory chain damage that occurs in animal models of Parkinson's disease was reduced by a ketogenic diet; [19] however, the real utility of this diet remains largely speculative and uncertain.



Traumatic brain injury may lead over time to epilepsy. Because of the effective use of the ketogenic diet in reducing seizures (see above), it has been suggested that it may also improve the clinical status in brain injury, especially by reducing the incidence of long-term consequences, such as epilepsy.[19] Positive effects of a ketogenic diet have also been reported in reducing the cortical contusion volume in an age-dependent manner in an animal model of cortical injury, which is related to the maturation-dependent variability in brain ketone metabolism.[19] These findings were also supported by the demonstration that a ketogenic diet reduced post-traumatic cognitive and motor function impairment, at least in a rat model.[23] The antiepileptogenic activity of the ketogenic diet after traumatic brain damage is controversial though, [24] and further studies are needed to increase related knowledge. Dysfunction in energy production, that is, mitochondrial function impairment, is likely to have a role in the pathogenesis of many neurodegenerative diseases, perhaps including amyotrophic lateral sclerosis. On this basis, a ketogenic diet has been proposed as a collateral therapeutic approach in this disease.[25] Nevertheless, direct experimentation and clinical trials in humans are still lacking at the present time, and to avoid the possibility of generating false hopes the preliminary data from animal models obviously have to be considered very cautiously. The metabolic effects of a ketogenic diet imply a higher-than-usual oxidation of fats, which leads in turn to reduce respiratory exchange ratio values.[20, 17] metabolic carbon dioxide output may be calculated as the product of alveolar ventilation multiplied by the fractional alveolar carbon dioxide concentration. Pulmonary ventilation differs from alveolar ventilation only by the amount of physiological dead space, and there is no reason to suspect a change in physiological dead space when a dietary manipulation is applied. Hence, following a ketogenic diet-induced decrement of the respiratory exchange ratio and of metabolic carbon dioxide output, a decrease in arterial carbon dioxide partial pressure or of pulmonary ventilation, or of both, is expected. If verified, these effects might be useful in the treatment of patients with respiratory failure; however.



If we equate de facto ketogenic diets with high-protein diets (which are not always correct) then the risks proposed by critics of this type of dietary approach are essentially those of possible kidney damage due to high levels of nitrogen excretion during protein

metabolism, which can cause an increase in glomerular pressure and hyperfiltration.[12] There is not wide agreement between studies; however, some infer the possibility of renal damage from animal studies, [9, 20] whereas others, looking at both animal models, meta-analyses and human studies, propose that even high levels of protein in the diet do not damage renal function.[11,12] In subjects with intact renal function, higher dietary protein levels caused some functional and morphological adaptations without negative effects.[23] There may actually be renal-related effects, but on blood pressure rather than morphological damage. The amino acids involved in gluconeogenesis and/or production of urea in general have blood-pressure-lowering effects, whereas acidifying amino acids tend to cause a rise in blood pressure. Subjects with renal insufficiency, even subclinical, kidney transplant patients and people with metabolic syndrome or other obesity-related conditions, will be more susceptible to the hypertensive effect of amino acids, especially of the sulphated variety.[24] The well-documented correlation between obesity and reduced nephron quantity on raised blood pressure puts subjects with T2D or metabolic syndrome at risk, even if in diabetics with kidney damage the effects are not always consistent with the hypothesis.[12,15,16] In fact, although some authors have reported a positive influence of a reduction in protein intake from 1.2 to 0.9 g/kg, over the short term, on albuminuria in T2D,[17] the same authors have subsequently stated instead that dietary protein restriction is neither necessary nor useful over the long term.[8] Moreover, it should be noted that ketogenic diets are only relatively high in protein[18,16] and that some recent studies have demonstrated that VLCKD can even cause a regression of diabetic nephropathy in mice.[9] With regard to possible acidosis during VLCKD, as the concentration of KBs never rises above 8 mmol/l[10] this risk is virtually inexistent in subjects with normal insulin function.

**Conclusion**

Ketogenic diets are commonly considered to be a useful tool for weight control and many studies suggest that they could be more efficient than low-fat diets, although there is not concordance in the literature about their absolute effectiveness and even some doubts rose about safety. But there is a 'hidden face' of the ketogenic diet: its broader therapeutic action. There are new and exciting scenarios about the use of ketogenic diets, as discussed in this review, in cancer, T2D, PCOS, cardiovascular and neurological diseases. Further studies are warranted to investigate more in detail the potential therapeutic mechanisms, its effectiveness and safety, and we would invite all researchers to face this challenge without prejudice.

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