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PERSPECTIVE

The mystery of the ketogenic diet: benevolent pseudo-diabetes

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ABSTRACT
Designed a century ago to treat epilepsy, the ketogenic diet (KD) is also effective against obesity and diabetes. Paradoxically, some studies in rodents have found that the KD seemingly causes diabetes, contradicting solid clinical data in humans. This paradox can be resolved by applying the concept of starvation pseudo-diabetes, which was discovered in starved animals almost two centuries ago, and has also been observed in some rapamycin-treated rodents. Intriguingly, use of the KD and rapamycin is indicated for a similar spectrum of diseases, including Alzheimer's disease and cancer. Even more intriguingly, benevolent (starvation) pseudo-diabetes may counteract type 2 diabetes or its complications.

Introduction

A number of publications have alarmingly warned that the ketogenic diet (KD), or low carbohydrate-high fat (LC-HF) diet, may have detrimental metabolic effects that lead to the development of diabetes. For example, one study stated that "Long-term high-fat, low-carbohydrate KD leads to features that are also associated with the metabolic syndrome and an increased risk for type 2 diabetes in humans" [1]. Two other studies reported that "Use of LC-HF diets … should be balanced against potentially harmful metabolic side effects" [2] and that "Our results do not support the recommendation of an LCHFD for use in prediabetes [3]. Moreover, based on that last study, the news media reported to the public that "Following a low-carbohydrate, high-fat diet for just eight weeks can lead to rapid weight gain and health complications, a new mouse study has demonstrated. The study has prompted researchers to issue a warning about putting faith in so-called fad diets." Furthermore, the news title was alarming: "Paleo diet is dangerous, increases weight gain, diabetes expert warns." <www.sciencedaily.com/releases/2016/02/160218114753.htm> . It is noteworthy that these conclusions were based on mouse studies, which, as has been discussed, are irrelevant to humans [4,5]. But how can we explain the discrepancy between the clinical results from humans and the experimental results from mice? And are these metabolic alterations actually detrimental to the health of the mice?

The KD in brief

KDs are typically LC-HF diets, which cause ketosis (elevated blood levels of ketones namely acetoacetic acid and beta-hydroxybutyric acid) [6–13]. In the absence of glucose, the brain metabolizes ketones [6,13,14], which are produced in the liver from fatty acids and serve as substitutes for glucose as an energy source. The numerous variants of the KD are not well defined. For example, the distinction between a "ketogenic" diet and the Atkins diet is meaningless because Atkins diet is *also* a KD. The definition of a KD is a diet that causes ketosis, such as one that is low in carbohydrate (e.g. < 20 grams) and usually low in calories. Ketosis can be induced without fat consumption. As a striking example, complete fasting reliably induces ketosis after 1–3 days. In practice, KDs entail consumption of less than 20 grams of carbohydrates, regardless of fat and caloric intake [6,15]. There are numerous abbreviations that are used for KDs, including LC-HF, VLCKD (very low-calorie-ketogenic), and LCKD (low-carbohydrate ketogenic diet). Whenever possible, we will abbreviate them as KDs.

1. Kds are used to treat obesity and diabetes in humans

KDs are successfully being used in the treatment of obesity, non-alcoholic fatty liver disease, neurological diseases and cancer [6,7,9–11,16]. They are also being used in the treatment of type 2 diabetes [8,9,11–13,17–23]. When consuming the same numbers of calories, KDs are more effective than standard calorie restrictive diets for body weight reduction and improvement of glycemic control in diabetic patients [24–28], and enable discontinuation or reduction of medications in some diabetic patients [18,27,29]. In one study, for example, fat-free KDs (100 g/day protein and no fat/carbohydrates) enabled insulin discontinuation after one week in most patients [30].

2. Self-contradictory results in rodents

KDs extend the lifespan of adult mice [31,32]. Even a cyclic (alternated weekly) KD improves survival, health and memory in aged mice [33]. These results argue against KDs having detrimental effects. Typically, the KD induces a unique metabolic state associated with improved glucose tolerance and weight loss [34].

In ob/ob mice, a KD even improves glucose tolerance independently of weight loss [35]. Remarkably, the KD reverses diabetic nephropathy in two mouse models of diabetes [36]. The results of these studies are consistent with the clinical data.

On the other hand, a number of studies report that KDs have diabetogenic effects. It was found that, despite preventing weight gain in mice, the KD induces insulin resistance [37]. In addition, it was later shown that the KD causes glucose intolerance without weight loss in mice [1], and even increases weight gain and glucose intolerance in New Zealand Obese mice [3]. Other studies also reported insulin resistance and glucose intolerance in rodents fed a KD [1,2,38–42].

3. Starvation-induced pseudo-diabetes

Claude Bernard (in 1846) and W. L. Lehmann (in 1874) independently described "starvation diabetes" in rabbits and dogs during prolonged fasting [43,44]. When fasted animals are fed "a good meal with an abundance of carbohydrate, glucose will appear in the urine" [43]. This condition was named starvation pseudo-diabetes [43,44]. Starvation or prolonged fasting decreases insulin levels and causes insulin resistance as a compensatory response aimed at saving glucose for the brain. (Note: Low insulin secretion and insulin resistance are manifested as glucose intolerance – i.e., hyperglycemia and even glycosuria – after re-introducing carbohydrates). In addition, glucose is produced from certain amino acids in the liver (gluconeogenesis), which also produces ketone bodies from fatty acids (ketogenesis). Eventually, the ketones substitute for glucose as the main fuel for the brain. Ketosis is a prominent feature of prolonged fasting or starvation.

But achieving the beneficial effects of pseudo-diabetes does not require complete fasting; any severe carbohydrate/calorie restrictions can yield the same effects. For example, healthy volunteers practicing severe calorie restriction develop "diabetic-like" glucose intolerance; nonetheless, calorie restriction improves health in humans and prevents type 2 diabetes [45,46]. As summarized in 1945, "the phenomenon of starvation diabetes has been repeatedly reported in one connection or another" [44]. As a more recent example, Koffler *et al.* rediscovered starvation diabetes during a strenuous weight reduction and warned about its detrimental effects [47]. Glucose intolerance caused by low-carbohydrate diet was suggested to be a physiological state [48].

4. Kd-induced pseudo-diabetes in rodents

Ketosis is a prominent feature of KDs and diabetes. In several rodent studies, the KD caused insulin resistance, glucose intolerance [1,2,38–40], and even dyslipidemia and pro-inflammatory effects [1,49]. This combination of insulin-resistance, glucose intolerance, lipolysis, gluconeogenesis, ketosis and ketonuria matches the description of starvation pseudo-diabetes. In rodents fed a KD, pseudo-diabetes is reversed upon cessation of the KD [38]. In a human study ketosis caused glucose intolerance in overweight non-diabetic subjects [50].

5. Rapamycin-induced pseudo-diabetes

As recently as 2019, it was warned that "the side effects associated with long-term rapamycin treatment … seemed to preclude the routine use of rapamycin as

a therapy for age-related diseases" [51]. I disagree. It is not the side effects in rodents, per se, but such warnings that have halted the use of rapamycin for life extension. Still, rapamycin and its analog, everolimus, have already been studied for the prevention and treatment of age-related diseases [52], potentially giving humans a chance to live longer and healthier lives in our lifetime. [See the forthcoming article "The fear of immortality: but it is more dangerous not to use anti-aging drugs than to use them"].

Rapamycin, an inhibitor of the nutrient-sensing mTOR pathway, is a calorie-restriction mimetic [53–55]. It is therefore predictable that rapamycin may cause conditions resembling starvation pseudo-diabetes in some rodent models [56–58]. This condition was misinterpreted as a deleterious side effect, despite the increased longevity of rapamycin-fed mice [59]. A "side effect" that is associated with life extension is not so detrimental after all.

Like KDs, rapamycin may increase or decrease insulin resistance, depending on the treatment duration and the specific model being studied [See the forthcoming article "Fasting and rapamycin: diabetes versus benevolent hyperglycemia"]. Rapamycin prevents insulin resistance caused by nutrient infusion in humans [60] and decreases insulin resistance in diabetic rodents [61–64]. In both rats and mice, rapamycin (sirolimus) prevents diabetic nephropathy [65–77]. In numerous independent studies, rapamycin was found to prolong life in a variety of mouse strains (see for references [78–81]). Rapamycin also improved metabolic functioning in non-human primates [82], and no symptoms of pseudo-diabetes were observed in relatively healthy elderly and healthy volunteers [83–87].

6. Benevolent pseudo-diabetes prevents type 2 diabetes

Rapamycin-induced metabolic alterations are reversible and even benevolent [63,79,88–92]. For example, despite hyperglycemia, rapamycin ameliorates nephropathy in a mouse model of type 2 diabetes [75]. Fasting, which causes starvation pseudo-diabetes, has been successfully used for the prevention and treatment of type 2 diabetes. A very low calorie diet prevents and reverses diabetes, especially at its early stages [46,93–99]. As

mentioned above, Fontana et al found that severe calorie restriction may cause insulin resistance in some human subjects, and they insightfully suggested that this kind of "insulin resistance" slows aging in mice [45]. Although animals fed a KD may exhibit glucose intolerance, they differ from diabetes patients in part because they are healthy [40].

KDs, which cause benevolent pseudo-diabetes, are effective for the prevention and treatment of type 2 diabetes in humans. In a remarkable study of healthy people, ketonuria after spontaneous (overnight) fasting was associated with a reduced risk of diabetes. Indeed, Kim et al suggested that spontaneous ketosis may prevent the development of diabetes [100]. Ketogenesis is suppressed in aged mice and rapamycin increases ketone production [101]. Also, metformin increases blood levels of beta-hydroxybutyrate and alpha-ketoglutarate in cancer patients [102]. Remarkably, alpha-ketoglutarate inhibits MTOR and extends lifespan in Drosophila [103].

7. Conclusion

KDs have been safely used for many years by millions of humans to treat obesity and diabetes. Like fasting, KDs may cause the symptoms of starvation pseudo-diabetes especially in some rodent models, but starvation pseudo-diabetes is beneficial and is not type 2 diabetes. In fact, it may counteract type 2 diabetes. Starvation pseudo-diabetes is associated with deactivation of mTOR, whereas type 2 diabetes is associated with hyperactivation of mTOR [57]. Thus, the warning that KD may cause type 2 diabetes in humans is not justified and contradicts what is observed in clinical practice. Nearly identical warnings have halted development of rapamycin and everolimus as antiaging drugs. Of course, caution is necessary, as rodent research indicates, but it should be recognized that excessive caution may preclude medical options that are already being safely used in humans.

Disclosure statement

No potential conflict of interest was reported by the author.

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