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Review Article

Potential Application of Ketogenic Diet to Metabolic Status and Exercise Performance: A Review

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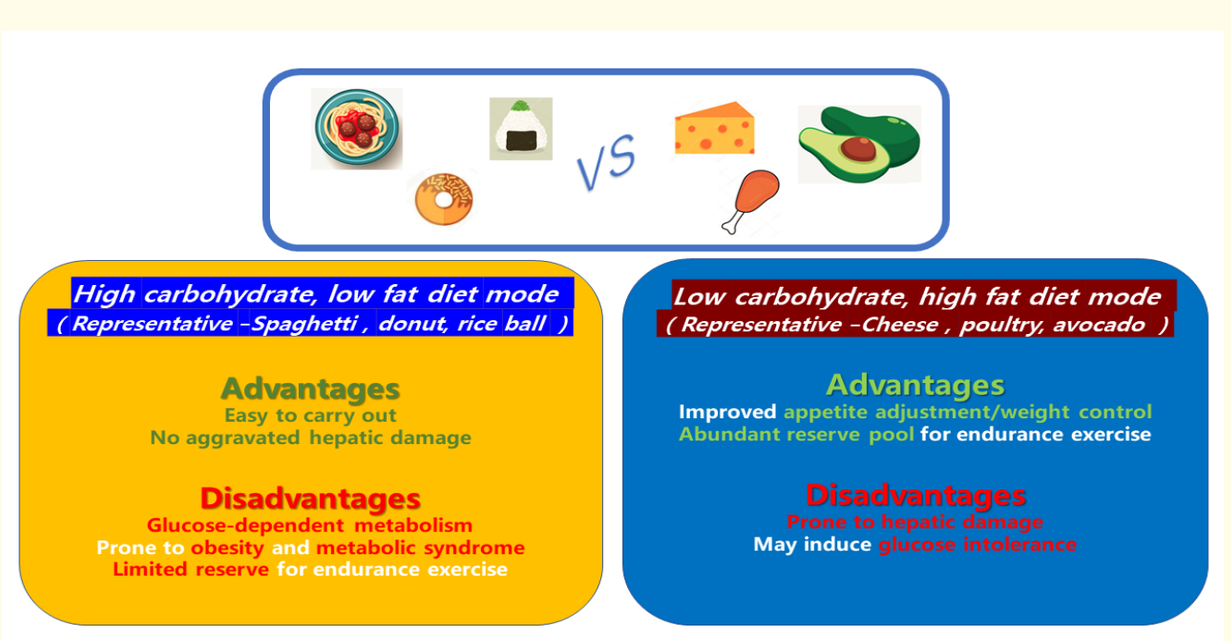
Abstract

Studies involving a ketogenic diet (KD) have shown that a KD may play various roles clinically, e.g. weight control, diabetes treatment, pain and inflammation treatment, cancer treatment, as well as being a nutrition approach for regular individuals or trained athletes. Here, we reviewed both exercise-based human trials and animal studies for the underlying mechanisms over the past 10 years (2007 - 2018), trying to get a glimpse of how a KD plays its role in the metabolic process. Though KD is not all-powerful, evidence shows that KD may induce hepatic damage or glucose intolerance. The mechanism of how KD plays its roles in various metabolic conditions requires investigation in further studies.

Keywords: *Ketogenic Diet; Metabolism; High-Fat Diet; Exercise*

An overview of ketogenic diet (KD)

Ketogenic diet (KD) is a nutritional approach consisting of high-fat, an adequate amount of protein, whereas carbohydrate is insufficient for metabolic demands. The initial employment of KD was the treatment for epilepsy, but studies have shown that KD may play various roles clinically, e.g. weight control, diabetes treatment, pain and inflammation treatment, cancer treatment, as well as a nutrition approach for common individuals or trained athletes. Glucose-induced metabolic activities in a classic KD diet should count for less than 5% of daily calorie intake [1,2]. Carbohydrates fail to maintain the circulation of oxaloacetate required for the Kreb's cycle, therefore pushing body to adopt fat-centered metabolism. Ketogenesis is the process when fat-adaptation happens, during which fatty acids are converted in mitochondria by β-oxidation into acetyl-CoA, then converted into ketone bodies (KB). KB consists of acetoacetate (AcAc), 3-hydroxybutyrate (3-HB), and a small amount of acetone, the main energy source during ketosis, and a term to define this metabolic stage. Adaption of KB utilization could liberate more available energy than glucose adaptation. Though the effect of KD on weight control is undeniably strong, the effect of KD on metabolic response is divided. Due to restriction, human trials often fail to investigate thoroughly the underlying mechanism, whereas animal study may dissatisfy the clinical demands. Here, we reviewed both exercise-based human trials and animal studies for the underlying mechanisms both over the past 10 years (2007 - 2018), trying to get a glimpse of how KD plays its role in the metabolic process.



Effects of KD on energy expenditure, body composition and weight control

In a study conducted in 2007, mice were fed by KD for 9 weeks. Despite calorie intake being the same in the KD and chow or high-fat diet (HFD) groups, oxygen uptake in the KD group was enhanced, indicating an up-regulated calorie expenditure. At the end of this study, KD mice attained an average weight of 23g. Absolute fat mass sustained whereas lean mass was decreased by KD [3]. In another study conducted by the same group, when switched to KD from HFD for 12 weeks, the average weight fell dramatically in nearly 2 weeks (From 38 ± 1.9g to 29.9 ± 0.58g). Oxygen uptake was higher in the KD group compared to HFD (increased 34% by KD diet compared to HFD). Juvenile Sprague-Dawley (SD) rats fed by KD for 2 weeks showed a slow-gain in weight; whereas rats fed by control diet gain approximately 100g weight in 2 weeks, rats fed by KD gained approximately 70g weight [4]. Another study, also conducted for 12 weeks showed that relative body fat had not been increased by KD, but the within group comparison revealed that the latter 6 weeks exhibited an increase of absolute fat free mass, from around 18g to 20g [5]. Absolute and relative omental adipose tissue mass as well as adipocyte size were lower in KD rats after 6-week feeding, whereas for brown adipocyte, only absolute mass decreased, with the size and relative mass remaining the same [6]. Interestingly, a study in 2014 conducted on C57BL/6 mice reported a regain of weight from the 5th week of KD administration, matching weight of the control group mice from the 10th week, untill the end of the 22nd week [7]. Although the mechanisms are not very clear at present, the effects of KD on extra energy expenditure and weight loss are undeniably strong.

Effects of KD on appetite-related factors

In mouse models, blood leptin concentrations remained the same for mice fed by HFD or KD for 5 weeks, each of which was previously fed by a 12-week HFD previously [3]. Appetite-related properties, melanin-concentrating hormone (MCH), neuropeptide Y (NPY), agouti gene-related protein (AGRP) and proopiomelanocortin (POMC) were not changed by continuous KD feeding [3]. However, when experiencing KD feeding switched from HFD to KD, MCH, NPY, and AGRP rose compared to chow-fed group, whereas POMC decreased. Serum leptin was found to be nearly 3-fold higher in KD group, whereas ghrelin remained the same [3]. In support of this study, another study conducted in Long Evans rats fed by KD for 6 weeks showed increased leptin concentrations in the blood; however, though NPY mRNA was not changed by KD, POMC mRNA was lower, indicating down-regulated appetite [8].

Blood biomarkers, inflammatory markers and other effects of KD

Non-esterified fatty acid (NEFA), alanine transaminase (ALT) and 3-HB rose in mice fed 9-week KD [3]. Glucose was lower in KD-fed mice. Cholesterol was not observed to be changed by 7-weeks or 9-weeks of KD feeding.

Insulin was reduced after 9-week KD feeding [3]. Hepatic inflammatory markers interleukin (IL)-1, tumor necrosis factor-α (TNF-α) and CC chemokine ligand (CCL) 2 in KD-feeding mice were higher compared to chow diet feeding. In adipose tissue, IL-6 was significantly lower, but plasminogen activator inhibitor-1 (PAI-1) was significantly higher [5]. Monocyte chemotactic protein-1 (MCP-1), IL-1β and IL-6 were found to be increased in blood after 22-week KD feeding [7].

Hindpaw inflammatory swelling and thermal nociception are reported to be attenuated by KD in juvenile and adult rats [9]. Similarly, Wistar rats fed by KD for 2 weeks before lipopolysaccharide (LPS) administration, display alleviate fever and lower concentrations of pro-inflammatory cytokine IL-1β, TNF-α but not prostaglandin (PG) E_2 circulating in the blood. These reports indicate anti-inflammatory properties of KD [10]. In a recent report, C57BL/6 mice assigned to KD for one year increased median life span and survival compared to controls, as well as improved physiological function [11]. Glucose tolerance in ob/ob mice is reported to be improved [12]. In another recent study, when combined with aerobic training, hepatic steatosis could be prevented and insulin sensitivity was improved concurrently, with 6-week KD feeding [13].

KD and exercise

KD enhanced exercise capacity in untrained human subjects in an article published in 2007 [14]. KD increased maximal oxygen uptake and improved lactate threshold in off-road cyclists, and cycling time was improved by nutritional ketosis [15,16]. Six second sprint and critical power test performance in well-trained athletes was enhanced by KD [17]. However, KD may also result in a reduction of performance. In a pilot case study of endurance athletes, KD failed to enhance endurance capacity or body composition and well-being [18]. An increase in perceptions of fatigue, and a direct relationship between blood ketone body (KB) and fatigue induced by KD were also reported in well-trained athletes [19]. In an animal study, KD did not impair the acute or chronic hypertrophic responses to resistance exercise [20]. In another recent animal model, KD-fed mice showed enhanced endurance exercise capacity without aggravated muscle injury [21]. The potential mechanism can be attributed to the ketogenic-adaptation. The KD also showed a potential preventive effect on organ injuries induced by acute exhaustive exercise, and is promising for endurance exercise [21].

Key genes and enzymes during ketosis

Hepatic metabolism and energy expenditure are altered remarkably by KD. Fibroblast growth factor 21 (FGF21), regulated by peroxisome proliferator-activated receptor α (PPARα), is shown to be a key regulator during ketosis, since mice lacking FGF21 present ineffective ketogenic-adaptation. Skeletal muscle is another major organ involved with ketosis [21]. In a study conducted in male mice, both fatty acid oxidation and exercise performance were reduced in muscle peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α) deficient mice, suggesting that PGC-1α is also a key factor in physiological ketosis, and KD-adapted exercise [22]. Uncoupling protein (UCP)-1 protein and UCP2 mRNA expression were both enhanced by long-term KD in the liver and adipose tissue [3], indicating increased thermogenesis by KD. However, another study showed that brown adipose tissue UCP-1 did not change [20]. Interestingly, β-adrenergic receptor deficient mice failed to lose weight, whereas circulating FGF21 was nearly 3-fold compared to the wild type mice [21]. In another study conducted in SD rats, 6-week KD and voluntarily resistance-loaded wheel running were assigned but mitochondrial complex 2 substrates played a critical role when separated from gastrocnemius and this complex presented higher respiratory control ratio [23].

Adverse effects of KD

KD was reported to cause hepatic insulin resistance in several studies, which could be attributed to increased hepatic diacylglycerol content that may lead to impaired insulin signaling. Hepatic steatosis and inflammation, as well as increased endoplasmic reticulum (ER) stress is found in mice fed by 12-week KD: increased accumulation and size of F4/80+ macrophages were found in 12-week KD-fed mice, indicating local inflammation; apoptosis-related gene X-box binding protein 1 (Xbp1) was found to increase in liver, indicating ER stress and hepatocyte apoptosis; histological study showed that KD induced obvious fat vacuoles [5]. As the primary site for lipid metabolism, patients with impaired hepatic function such as nonalcoholic fatty liver should be cautious. Pancreas α-cell and β-cell masses were both reduced following a 22-week KD administration, thus leading to glucose intolerance [7]. Restricted intake of carbohydrate-enriched fruits or cereals may induce headache, according to several ketogenic diet studies [25, 26]. Multi-task test that requires higher mental processing may be adversely affected by ketogenic diet according to a study [27].

Conclusion

KD has been used for nearly a century as a treatment for epilepsy; however in the recent decades other virtues of KD were discovered. Amongst these virtues, obesity treatment is the most thoroughly discussed. In this review, the potential applications of KD to metabolic states such as energy homeostasis and weight control, appetite adjustment, anti-inflammatory potential and exercise performance were summarized. It must be mentioned that deleterious consequences can occur from KD, as it may cause glucose intolerance, and adverse effects of KD on the liver should be considered. Some refined and restricted applications should be done. Further investigations should be considered and wide-spread application of KD is preferred in the future.

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