The Ketogenic Diet

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Contributor: Giuseppe Cerullo

The ketogenic diet (KD) is a therapeutic option for individuals with sarcopenic obesity due to its positive effect on VAT, adipose tissue, cytokines such as blood biochemistry, gut microbiota, and body composition. A KD's macronutrient profile is composed of 55 to 60% lipids, 30 to 35% protein, and 5 to 10% carbohydrates. This causes nutritional ketosis, in which fatty acids undergo partial beta-oxidation to produce ketone bodies, which are then used as a source of energy. Ketone bodies are used to replace glucose as a source of energy in most tissues throughout time. KD plays a role in treating nonalcoholic fatty liver disease (NAFLD) by lowering hunger and concurrently decreasing carbohydrate consumption, owing to two separate pathways, which include the general reduction of body weight and the modulation of insulin levels.

Keywords: ketogenic diet ; gut microbiota

1. The Effect of KD in Reduction of Inflammation

Cytokines are tiny proteins that cells produce and have a specific influence on cell interactions and communication. Cytokines can have an autocrine or paracrine effect on the cells that secrete them, as well as on neighboring cells and, in certain cases, distant cells (endocrine action). Pro-inflammatory and anti-inflammatory cytokines are both present [1]. Adipocytes and adipose tissue leukocytes release proinflammatory cytokines and leptin, which have a direct catabolic effect on muscle cells and also act indirectly via IR, reducing the anabolic effect of insulin on muscle cells [2].

Lim et al. [1] investigated the links between the chemokine monocyte chemoattractant protein-1 (MCP-1) and sarcopenia, obesity, and the SO characteristics in groups of older persons. Of the 143%, 25.2% were normal, 15.4% were sarcopenic, 48.3% were obese, and 11.2% were SO. MCP-1 levels were shown to be significantly higher in obese and SO patients, validating the idea of chronic inflammation caused by excess adiposity. As a result, inflammatory cytokines appear to have a key role in the pathogenesis of obesity.

Roubenoff et al. [3] found that aging is linked to increased production of catabolic cytokines, decreased circulating levels of insulin-like growth factor-1 (IGF-1), and sarcopenia acceleration (loss of muscle with age). The findings showed that higher levels of the catabolic cytokines TNF-alpha and interleukin-6 (IL-6), are linked to increased mortality in community-dwelling elderly adults, whereas insulin like growth factor-1 (IGF-1) levels have the opposite effect [4][5]. Chronic use of KD, on the other hand, causes the host to synthesize adenosine triphosphate (ATP) utilizing -hydroxybutyrate and reduces NOD-like receptor P3 (NLRP3) mediated inflammation. Similar studies indicated that the KD reduced fat mass in numerous fat depots, including visceral fat [6][7]. There-fore these findings are not applicable to all circumstances.

In diabetic and insulin-resistant conditions, elevated levels of TNF, IL-6, and IL-8 have all been recorded. Through autocrine and paracrine signaling, obesity-induced alterations in skeletal muscle, adipose tissue, and the liver cause localized inflammation and IR. IR in distant tissues is caused by endocrine-mediated interaction between insulin target tissues. The net result of these alterations is systemic inflammation and IR [8].

2. Effect of KD on Visceral Adipose Tissue in Sarcopenic Obesity

Visceral obesity is also linked to metabolic syndrome and insulin resistance indica-tors. VAT synthesizes and secretes various hormones to communicate with other central and peripheral organs as a metabolically active organ. Adipokines are hormones that are directly linked to metabolic balance, emphasizing the importance of adipose tissue in the regulation of energy homeostasis [9]. For different malignancies, visceral fat gain and muscle loss have been recognized as unfavorable prognostic variables [10].

Low muscle mass and quality, as well as visceral adiposity and sarcopenic visceral obesity, are all linked to death and recurrence after pancreatic cancer resection [11]. Ketone bodies are crucial alternative fuels that allow humans to survive

in periods of glucose deficiency caused by fasting or extended activity. Chronic use of KD, on the other hand, causes the host to generate ATP utilizing -hydroxybutyrate and reduces NLRP3-mediated inflammation [12][13].

Cunha et al. [14] found weight loss in the very low-calorie ketogenic (VLCK) diet group with VAT reduction in a trial of 46 patients. Another investigation on adiposity parameters and orexin-A serum profile by Valenzano et al. [15] found similar results, namely that the VLCK diet reduced VAT, improving adiposity and blood biochemistry, while Orexin-A levels considerably rose after dietary treatment.

A recent study suggests that the mechanism by which KD causes visceral fat loss could be related to the satiety-increasing effect of higher dietary protein, and that this effect could be regulated by appetite-mediating hormones such as leptin, which is produced by adipose cells and is involved in the regulation of energy balance and fat storage by suppressing hunger [16].

Bertoli et al. [4] looked at how a 12-week KD altered adipose tissue activity indicators, VAT, and subcutaneous fat in children with glucose transporter 1 deficiency syndrome. Despite being a high-fat diet, the results showed lower fasting insulin levels, implying that KD had no effect on abdominal fat distribution over a short period of time.

3. Effect of KD on Nonalcoholic Fatty Liver Disease (NAFLD) in Sarcopenic Obesity

NAFLD is a condition in which fat accumulates in the liver and is one of the most common types of chronic liver disease in industrialized countries [17]. In Western countries, the prevalence of NAFLD is estimated to be 20–30% in the general population; in obese populations, this increases to 57.5–74% [17][18]. Insulin activity affects both the liver and the muscle. IR is thought to play a role in the pathogenesis of both NAFLD and sarcopenia. NAFLD is now recognized as both a cause and a result of IR. Hepatic steatosis is the initial stage of NAFLD, defined by intrahepatic triglyceride (IHTG) values greater than 55 mg/g liver (5.5%) or when more than 5% of hepatocytes show histological signs of triglyceride storage [18].

Petta et al. [19] reported the presence of fibrosis in sarcopenic patients to the extent that the prevalence of sarcopenia was linearly associated with the severity of fibrosis (OR 2.36, CI 1.16–4.77, p = 0.01). Furthermore, the presence of sarcopenia was seen in 48.3% of patients with severe fibrosis compared to 20.4% in the mild fibrosis group (i.e., a fibrosis grade less than or equal to two ($p < 0.01$)).

Obesity and IR, which are both common in NAFLD, play a critical role in the pathogenesis of liver damage and the advancement of cirrhosis and end-stage complications [20]. Other potential disease progression mechanisms (vitamin D insufficiency, hyperuricemia, industrial fructose intake, menopausal status, etc.) have been hypothesized, and they are typically shared by NAFLD, obesity, and IR, further complicating the complicated interplay between NAFLD and metabolic dysfunction [21]. Tendler et al. [22] found that a low-carbohydrate, KD reduced mean weight by −12.8 kg and improved histologic fatty liver disease after six months in research on the effect of low-carbohydrate, KD on NAFLD. Watanabe et al. [23][24] recently published a study that found that a low-carbohydrate diet (LCD) improves liver fat metabolism in obese NAFLD patients.

Browning et al. [25] used a carbohydrate-restricted (20 g/d) or calorie-restricted (1200–1500 kcal/d) diet on NAFLD individuals for two weeks vs. an isocaloric formula as a placebo in a clinical investigation. The weight reduction was observed to be similar in both groups (−4.0 1.5 kg in the calorie-restricted group and −4.6 1.5 kg in the carbohydrate-restricted group). Although liver triglycerides reduced with weight loss, they decreased much more in carbohydrate-restricted patients (−55 14%) than in calorie-restricted subjects (−28 23%).

Mice lose weight, develop ketosis, and produce hepatic gene expression patterns that suggest reduced de novo lipogenesis and increased fatty acid oxidation when fed a micronutrient supplemented KD that is high in fat (93.3% kcal), low in carbohydrate (1.8%), and low in protein (4.7%) [26][27].

4. Gut Microbiota in Sarcopenic Patients and Effect of Ketogenic Diet

There are up to 1014 bacteria, viruses, fungi, protozoa, and Archaea in the human gut microbiota. This gene pool has been predicted to be 150 times larger than the host's, weighing between 175 g and 1.5 kg [28]. Early childhood influences the composition of the gut microbiota, which is influenced by geographical factors, the method of delivery (vaginal or cesarean), breastfeeding, weaning age, antibiotic exposure, and dietary regimens [29][30]. Even though two phyla (Bacteroidetes and Firmicutes) account for up to 99% of species, the healthy adult gut microbiota contains bacteria from ten phyla. Bacteroidetes' average relative abundance is generally inversely proportional to Firmicutes', and vice versa [31].

According to studies, the gut microbiota's resilience declines around the age of 65, making its overall composition more sensitive to lifestyle changes, pharmacological therapy such as antibiotics, and disease [32]. Aging is linked to decreased microbiota richness, higher inter-individual variability, and pathobiont overrepresentation. Given that changes in the quality, quantity, and function of gut microbiota with age may contribute to chronic inflammation and anabolic resistance, its role in the development of aging sarcopenia should be explored. Furthermore, therapies that improve microbiome expression and function may help to reduce age-related decreased muscle performance and the associated negative clinical outcomes [33].

Rondanelli et al. [34] consolidate the present knowledge regarding the human microbiota in the elderly and the effects of probiotics in the elderly population in a systematic review. The results show that, when compared to the adult population, elderly people have a lower diversity of microbiota, with lower numbers of Firmicutes, Bifidobacteria, Clostridium cluster XIV, Faecalibacterium Prausnitzii, Blautia coccoides-Eubacterium rectal, and a higher presence of Enterobacteriaceae and Bacteroidetes, and a higher presence of Enterobacteriacea It was concluded that differences in the intestinal microbiota of the elderly may not be caused solely by aging, but may be linked to a decline in general health, malnutrition, and an increased need for medication, such as antibiotics and nonsteroidal anti-inflammatory drugs, all of which are common in the elderly [35].

The age-related changes in gut microbiota composition have been found to promote intestinal mucosa permeability in experimental models of aging. This phenomenon causes increased systemic absorption of bacterial products, such as lipopolysaccharide, which activates the inflammatory response and leads to higher levels of pro-inflammatory cytokines including IL-6 and TNF-alpha in the bloodstream [36].

Newell et al. [37] found that feeding a KD to juvenile male C57BL/6 (B6) and BTBR mice for 10–14 days exhibited an antimicrobial-like effect by considerably lowering overall host bacterial abundance in cecal and fecal waste. KD was also shown to reverse high *Akkermansia muciniphila* concentration in BTBR animals' cecal and fecal matter. In two seizure mouse models, KD affects the gut microbiome. Seizure protection is conferred through changes in the microbiota, which are both essential and sufficient. KD decreased gut bacterial alpha diversity in mice while increasing *A. muciniphila* and Parabacteroides relative abundance [38].

KD also raised the relative abundance of putatively beneficial gut microbiota (*Akkermansia muciniphila* and *Lactobacillus*) while decreasing the relative abundance of pu-tatively pro-inflammatory taxa (*Akkermansia muciniphila* and *Lactobacillus*) (*Desulfovibrio* and *Turicibacter*). KD also decreased blood glucose levels and body weight while increasing blood ketone levels, which could be linked to changes in the gut microbiome [39]. The LCD causes fast changes in the gut microbiota, which raises circulating folate levels and upregulates gene expression in the liver involved in folate-dependent one-carbon metabolism. Increases in folate-dependent one-carbon metabolism gene expression in the liver appear to be the added value of LCD. Since folate mediates the conversion of sarcosine to glycine, circulating sarcosine may increase in the presence of a folate shortage. In mouse fibroblasts, sarcosine stimulates autophagy in a dose-dependent manner, and changes in myocyte quality control mechanisms (including autophagy) may contribute to sarcopenia [30].

5. The Effect of KD on Physical Performance in Sarcopenic Obesity

Individuals who resistance train recreationally have been interested in dietary approaches that aid body fat loss while maintaining or leading to an increase in muscle mass. As a result, there is substantial evidence that increased protein diets can improve muscle mass increases while having little effect on body fat [30]. Recent research in rats [40], as well as prior findings in humans [30], suggests that following a low-carbohydrate, moderate-protein, high-fat KD can help sustain muscle mass growth while also reducing adiposity. As a result, the KD is advocated as an obesity-fighting therapy.

After a 12-week KD, obese adults lost weight, improved physical performance, cognitive function, eating behavior, and metabolic profile, according to a study conducted by Mohorko et al. [41]. The study found a significant reduction in appetite and body weight (men 18 9 kg vs. women −11 3 kg; $p = 0.001$), as well as enhanced physical performance ($p = 0.001$). Similarly, after a dietary carbohydrate restriction intervention experiment, Anguah et al. [42] investigated changes in food cravings and eating behavior. The researchers expected that even after a brief (four-week) period of low-carbohydrate restriction, decreases in food cravings and improved eating habits would be noticeable. In adult participants, dietary constraint was shown to be 102% higher, whereas disinhibition and hunger scores were lowered (17% and 22%, respectively).

Gregory et al. [43] looked at how a 6-week low-carbohydrate KD and CrossFit program affected body composition and performance. In comparison to the control group, the low-carbohydrate KD group lost weight, had a lower BMI, and had a

lower % body fat. The findings suggest that combining an low-carbohydrate KD with six weeks of CrossFit exercise can result in significant reductions in percent body fat, fat mass, weight, and BMI while preserving lean body mass and performance.

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