

## Research Article

# Impact of Keto-Diet on Gut Flora- A Focus on Good Health and Wellbeing

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## ABSTRACT

The keto diet (KD) is characterized by high fat intake (70-80%), low carbohydrate content (5-10%), and moderate protein level (10-20%). It is widely followed for weight loss and management of epilepsy, making it one of the most popular diets globally. Despite being high in fat, KD offers several health benefits under specific conditions. It is particularly effective when the brain requires reduced glucose, prompting the body to use ketone bodies as an alternative energy source. By significantly limiting carbohydrate consumption, KD aids in weight loss and influences gut health by impacting gut microbiota. This review explores how KD affects the gut microbiota. Gut dysfunctions, such as those seen in irritable bowel syndrome (IBS), may stem from abnormal gut-brain interactions, and dietary interventions like KD can influence gut flora to various conditions. KD serves as an example of how a diet can alter the composition of gut microbiota. When KD has been effective in treating refractory epilepsy and other disorders, it has also demonstrated the potential to enhance athletic performance by modifying gut microbiota composition. Some studies report a positive impact on gut flora, while others note a reduction in bacterial diversity. However, KD generally shows an anti-inflammatory effect on certain diseases.

**Keywords:** Keto diet, gut health, irritable bowel syndrome, gut microbiota, Type 2 diabetes, diversity of bacteria.

## INTRODUCTION

The keto diet (KD), characterized by a high proportion of fat (70–80%), low carbohydrates (5–10%), and a moderate proportion of protein (10–20%), is often used to treat diseases and drug-resistant resistant diseases. Although evidence is emerging on KD's impact on intestinal microbiota, limited research has exposed its effects on the gut environment (Ferraris et al., 2021). Various neurological disorders have been linked to gut bacteria via the gut-brain axis and diet plays a crucial role in shaping the gut flora. KD follows a high-fat, low-carb, adequate protein diet regimen. While its effectiveness in reducing seizures is well-established, the underlying mechanisms remain unclear. Moreover, the diet has also shown potential in treating other conditions, such as depression, autism, Type 2 Diabetes mellitus (T2DM), Alzheimer's, and cancer. On KD, a notable reduction in the relative abundance of *Bifidobacteria sp.*, *E. rectaler sp.*, and *Dialisterspha* has been observed, while the relative abundance of *E. Coli sp.* tends to increase. A functional analysis alternations

in 29 SEED subsystems (SEED refers to collections of functionally related protein families), including the elimination of seven glucose metabolism-related pathways. *E. coli sp.* and *Bifidobacteria sp.* Diet plays a significant role in overall health and gut flora, and KD, in particular, leads to a reduction in bacteria that consume and thrive on fiber (Lindfeldt et al., 2019).

The relationship between altered gut microorganisms and various neurological diseases has recently garnered increased attention. Given the significant role of immunological mechanisms in the development of epilepsy, one of the most severe and common neurological disorders, a connection to the gut microbiota has been proposed (Fan et al., 2019). KD, which is low in carbohydrates and high in fat, may have an effect in treating several illnesses, including cancer (Nakamura et al., 2022).

**KD and Gut Health Interrelationship:** Research over the past several years has increasingly highlighted the crucial role gut microbiomes play in both disease and overall human health. The microbial cells that make up the gut microbiota are highly

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dynamic and influenced by external factors such as diet. Nutrients consumed are utilized by gut microorganisms for vital biological functions, producing metabolic outputs that are significant in human physiology. Understanding the impact of diet on gut microorganisms is essential, as the microbial community influences various processes, including the production of bioactive compounds, nutrient metabolism, pathogen defense, energy balance, nutrition metabolism, and immune system regulation. The KD, which has gained popularity, is a dietary approach used for weight loss and neurological disorders. It is characterized by high fat, moderate protein, and low carbohydrates. KD holds potential and promising future treatment strategies due to its ability to modify and influence gut flora. Given its impact on gut health, KD is a powerful tool that requires careful formulation and future research (Gregor et al., 2022).

A prospective study was conducted on ten pediatric patients with juvenile refractory epilepsy who recently joined the ketogenic diet program at UCLA Mattel Children's Hospital. Stool samples were collected from each patient one day before starting KD therapy (pre-KD) and again one month after adhering to a clinically guided KD regimen. When compared to comparable pre-KD controls, the 16S rRNA gene showed no significant difference in the diversity of bacteria present in the post-KD fecal microbiota. However, there were notable individual differences in the baseline microbiota composition. The study found that children with refractory epilepsy did not exhibit any consistent changes in gut microbiota composition following KD therapy. To assess seizure susceptibility at the cohort level, germ-free (GF) mice were vaccinated with a human donor stool sample. The study found that GF mice colonized with bacteria from the post-KD microbiome required higher current intensities to induce 6-Hz seizures compared to controls colonized with pre-KD microbiota. This suggested that the gut microbiota influences seizure susceptibility and the anti-seizure effects of KD in animal models of epilepsy. However, it remains unclear if these associations apply to human KD therapy. In animal studies, mice colonized with KD-associated microbiota exhibited increased resistance to seizure compared to pre-treatment controls. After human KD treatment, certain metagenomic and metabolomic features, such as those linked with amino acid metabolism, fatty acid  $\beta$ -oxidation, and anaplerosis, were observed and remained intact following microbiota transfer to mice. Additionally, mice inoculated with KD-associated gut bacteria displayed altered hippocampus transcriptomes, which are linked to susceptibility genes found in human epilepsy. These transcriptomic changes involved pathways related to ATP generation, glutathione metabolism, and oxidative phosphorylation. The findings suggest that KD-induced microbiome alternations may affect brain gene expression and play a role in seizure prevention in mice, highlighting the potential impact of microbial activities

modified by KD treatments for pediatric epilepsy (Lum et al., 2023).

**Effects of KD on Irritable Bowel Syndrome (IBS):** IBS is a long-term functional gastrointestinal disorder characterized by recurrent abdominal pain triggered by bowel movement or a dietary change. The pathophysiology of IBS appears to be influenced by variations in its composition. There is a mutualistic relationship between the host and the gut microbiota, which extract more calories and nutrients from food while also protecting the host from illnesses. The gut microbiota acts as a functional organ with well-defined activities. Diet can significantly alter the profile of the intestinal microbiota, yet the effectiveness of different dietary approaches in managing IBS is not fully understood. Low-FODMAP (fermentable oligosaccharides, monosaccharides, disaccharides, and polyols) diets may influence both gastrointestinal symptoms and the composition of gut flora. Various dietary approaches such as traditional nutritional guidance, a low-FODMAP diet, and a gluten-free diet, have been studied for their effects on IBS symptoms and as well as differences in gut flora between healthy individuals and IBS patients. While there is currently no perfect diet for IBS-D patients, it's essential to consider how different nutritional approaches may affect the intestinal microbiota composition. Defects in the mitochondrial network and bioenergetics have been linked to functional changes in irritable bowel syndrome. A KD, which is rich in fat, moderate in protein, and low in CHO, has been shown to affect mitochondrial function, oxidative stress, inflammation, and biogenesis. In a study aimed at inducing IBS in adult Wistar rats, newborn rats were subjected to maternal deprivation. The colons of the exposed rats, who were either given the KD or standard diet (IBS-Std) along with unexposed control rats, were analyzed for intestinal inflammation, cellular redox state, mitochondrial biogenesis, and autophagy. IBS-Std rats showed inflammation, increased oxidative stress, defective mitochondrial biogenesis, and elevated levels of cellular redox status (oxidatively modified purines) such as superoxide dismutases (SOD 1, SOD 2), and mitochondrial peroxiredoxin III (PrxIII) intestine inflammation cyclooxygenase-2 (COX-2) and Toll-like receptor-4 (TLR-4). Moreover, the decreased levels of Beclin-1 (multi-domain protein) and LC3 II (a first-generation mammalian protein that has been directly associated with autophagosome membranes) indicated reduced autophagy effectiveness. When mice affected by KD were fed, compensatory mechanisms were activated that may help restore mitochondrial function, reduce inflammation, and oxidative stress, and maintain baseline autophagy. These effects are potentially mediated through the up-regulating of the peroxisome proliferator-activated receptors/receptor-gamma co-activator-1 (PPAR- $\gamma$ /PGC-1 axis). PPAR is part of the nuclear receptor superfamily and plays a key role in regulating the expression of genes involved in immune and



inflammatory response, cell division, proliferation, and lipid metabolism. PGC-1 in particular, regulates the range of metabolic processes, including oxidative metabolism and energy balance, are regulated by PGC-1 (Chimienti et al., 2021).

IBS is a complex, multifactorial condition that involves intestinal permeability, mucosal neuro-immune interactions in gut mucosamicrobiota imbalance, and alternations in the gut-brain axis. Change in gut flora can increase the synthesis of compounds like sodium butyrate, a known inhibitor of histone deacetylases. IBS patients often exhibit an altered profile of methylation genes and micro-RNAs (miRNAs), along with elevated levels of butyrate-producing bacteria. Significantly, distinct miRNA profiles and gene acetylation patterns are linked to various causes of IBS. These molecule signatures may be identifying visceromotor dysfunctions and increased gut permeability which are common features of IBS (Dothel et al., 2023).

**KD and Athletic Performance:** An athlete's health and performance are significantly influenced by their gut bacteria. Diet plays a crucial role in shaping the composition of the gut microbiota, which in turn can affect athletic performance. One effective approach for athletes to achieve and maintain healthy body composition is the KD diet. A specific variation, the Ketogenic Mediterranean diet with phytoextracts (KEMEPHY) has intervention with the KEMEPHY diet, this dietary routine may provide a safe and effective way to preserve or regulate the gut flora composition in athletes who engage in regular physical activity (Mancin et al., 2022).

KD is a dietary approach typically aimed at promoting weight loss by limiting daily carbohydrate intake to less than 30g. While limited data exist for team sports, KD has shown inconsistent effects on sports performance. In a study of semi-professional football players, the goal was to find out how a KD affected various performance parameters. For thirty days, participants were randomized to either a Western diet (WD) or an iso-protein (1.8 g/Kg body weight/day) KD. Key performance measures included body weight and composition were cross-sectional areas (CSA), respiratory exchange ratio (RER), resting energy expenditure (REE), quadriceps isometric muscular strength, countermovement jump (CMJ), and yoyo intermittent recovery test duration. The results showed that compromising their muscle strength, power, or mass. Therefore, KD was a rapid weight loss goal for athletes decreased. Additionally, the KD was found to alter the gut microbiota of the athletes, suggesting it may have broader impacts on health and performance (Antonio Paoli et al., 2021).

**KD and Makeup of Gut Microbiota:** The KD modulates the composition of gut flora elaborated in Figure 1, and can enhance the metabolic profile. A study was conducted to evaluate whether popular restrictive diets such as the KD, fasting-mimicking diet (FMD), and intermittent fasting (IF), have similar effects to caloric restriction (CR). The goal was

to determine which restricted dietary strategy was the most effective and to explore whether the molecular mechanisms underlying the effects of the diets overlapped. For the study, eight mice were randomly assigned to the experimental groups: CR mice were given ad libitum chow for 4 weeks while the FMD group underwent three cycles of four days of fasting (50 percent of ad libitum intake on day one and 10 percent on days 2-4) followed by seven days of refeeding). The CR mice received continuous restriction, consuming 80% of the typical and ad libitum chow intake. In the IF group, mice fasted for 24 hours every other day for a total of 28 days (100% restriction), followed by a 24-hour chow ad libitum refeeding session. After the study, the mice were euthanized via anesthetic overdose, and their heart was pricked to collect their blood. Tissues were rapidly frozen in liquid nitrogen after collection and stored at 80°C for analysis. The study found that the effects of various diets are quite similar, especially for CR, IF, and FMD. However, the KD exhibited distinct differences from another diet, specifically in the composition of gut microbiota, the presence of a 50 kDa shorter version of the protein occludin, and a change in bile acids (Bas). According to the results, the restricted diets have comparable impacts on gut health, the specific changes induced by KD make it unique (Gregor et al., 2022).

The KD has traditionally been beneficial for patients with medically resistant seizures, and its effectiveness is believed to be linked to changes in microbiota composition. Research suggests microbiome compared to both healthy control and individuals with non-refractory epilepsy. A consistent finding in the literature is the higher prevalence of *Firmicutes spp.* in patients with refractory epilepsy compared to *Bacteroides spp.* which is less common. Whether drug-resistant epilepsy microbiome communities exhibit altered  $\alpha$ -diversity (Chatzikonstantinou et al., 2021).

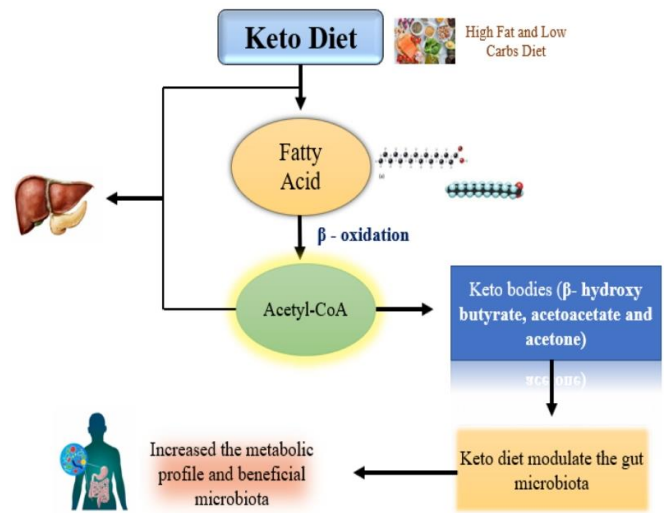


Figure 1. KD that alternates the gut microbiota in the human body.



In a study, examining changes in endocannabinoid receptor expression in intestinal tissue, we explored the molecular mechanisms through which a low-carbohydrate diet, like the KD, may improve gastrointestinal symptoms and function in an animal model of IBS. We discovered that rats administered KD exhibited significant cell repair near the base of their intestinal crypts, a histological sign of IBS, as well as activation of CB1 and CB2 receptors (cannabinoid receptors). Additionally, the diet also affected intestinal membrane permeability and glucose metabolism in treated rats, leading to the overexpressing of tight junction proteins and the glucose transporter GLUT1 (A uni-porter protein, it is often referred to as facilitated glucose transporter member). One of the molecular mechanisms by which the KD operates involves the CB receptor, supporting the hypothesis that dietary therapy of IBS rats may result in cannabinoid-mediated protection at the intestinal level (Gigante et al., 2021).

Another study examined the safety and temporal changes in  $\beta$ -hydroxybutyrate (BHB), blood ketone bodies including acetoacetic acid (AcAc when ketogenic formulas (KF) were frequently administered within the guidelines of aKD in 20 healthy adults. By the fourth day of KF administration, levels of total ketone bodies, AcAc, and BHB significantly increased after both lunch and dinner. In terms of anthropometric, metabolic, nutritional, urological, and gastrointestinal parameters, KF did not raise any notable safety concerns. Additionally, changes in the gut microbiome were observed due to the KD. *Firmicutes* associated with KF intake (Nakamura et al., 2022).

Similarly, another research compared the composition of gut bacteria before and after KD treatment in children with drug-resistant epilepsy (DRE) and exposed its connection to fecal Short-chain fatty acids (SCFAs). This cross-sectional study examined alterations in the fecal microbiomes and SCFAs of 12 children with DRE and 12 healthy controls. This disease cohort was analyzed both before and after the first six months of KD therapy. Before the treatment, children with DRE exhibited higher microbial alpha diversity and a significant increase in Actinobacteria at the phylum level, along with an increase in general *Blautia sp.*, *Bifidobacterium sp.*, *Enterococcus*, *Bacteroides sp.*, and *Anaerostipes sp.*. At six months of KD therapy, the abundance of these eight epileptic-associated taxa was reversed, with increases in *Subdoligranulum sp.*, *Dialister sp.*, and *Bifidobacterium sp.*, and decreases in *Actinomyces sp.*, *Enterococcaceae sp.*, *Akkermansia sp.*, and *Actinomyces sp.* Notably, the study found that contained were more prevalent in patients with a KD compared to those with a favorable response set. Additionally, the study revealed a statistically significant correlation between the changes in microbial genera and SCFA concentration after six months of KD therapy, suggesting a strong relationship between gut microbes and SCFA. These findings indicate that KD may significantly

improve the pathophysiology of DRE in children, potentially through microbiota dysbiosis. The antiseizure efficacy of KD may be influenced by gut microbiota and microbial metabolism (Gong et al., 2021).

In this study, specific inflammatory markers were shown to decrease during KD therapy, and certain forms of epilepsy were linked to inflammation. The gut microbiota plays a significant role in regulating immune function and the level of inflammation. This observational study treated 28 drug-resistant epileptic children with KD and collected fecal and serum samples at baseline and three months after the dietary intervention. During the therapy, both microbial and inflammatory changes were observed in the gut, demonstrating that KD exerts an inflammatory effect. Using advanced bioinformatics and machine learning techniques, the study identified that tumor necrosis factor (TNF) level and specific *Bifidobacteria spp.* Profiles were associated with responders before the initiation of KD. Interestingly, during KD treatment, the taxonomic and inflammatory profiles of responders and non-responders became more similar than at baseline. Children with drug-resistant epilepsy were more likely to benefit from KD therapy when they had higher *Bifidobacteria spp.* and TNF at the starting treatment. The study introduces a novel marker for predicting anti-epileptic response to KD treatment, reflecting the interaction between the immune system and gut microbiota. This characteristic could potentially be used to identify patients likely to respond favorably to KD at the outset (Dahlin et al., 2022).

In another study, feces samples from these animals were analyzed in a large-scale microbiome investigation using 16S rRNA gene sequencing. Wild-type and Dravet mice were administered either the CD or the KD. Both the Dravet phenotype and experience of the KD were associated with alterations in the microbial. Detailed microbiological research revealed significant changes in the gut microbiota of wild-type and Dravet mice. The Chao index showed that Dravet mice exhibited a decreased species richness compared to wild-type controls. In Dravet mice, the ratio of *Firmicutes spp.* to *Bacteroidetes spp.* phyla increased, indicating microbial dysbiosis. After switching to the CD or KD, several bacterial phyla and genera were controlled in Dravet mice. Unexpectedly, the severity of the phenotype was significantly associated with the absence of the *Romboutsiaspecies spp.* and the presence of the *Clostridium spp.* genus. In KD-treated Dravet mice, the *Firmicutes spp.* and *Bacteroidetes phyla spp.* were more abundant. This comprehensive microbiome analysis revealed significant alternation in the gut microbiota and dysbiosis due to *Scn1a* genetic mutation. KD exposure future influenced the gut flora in Dravet mice. Interestingly, the seizure phenotype in Dravet mice was linked to the abundance of certain microbial species (Miljanovic & Potschka, 2021).

In another study, the effects of the KD were evaluated in a rat model of IBS to determine its impact on 5-HT levels, the 5-



HT transporter (SERT), the neurotrophin brain-derived neurotrophic factors (BDNF), and its receptor TrkB. Wistar rats were subjected to maternal deprivation for ten weeks as infants and then fed either an IBS-Std or a KD (IBS-KD) diet. Control rats (Ctrl-Std and Ctrl-KD) were not exposed to maternal deprivation. IBS-Std rats showed disrupted serotoninsignaling in the gut, with increased mucosal 5-HT content and decreased levels of SERT, 5-HT<sub>3B</sub>, and 5-HT<sub>4</sub>. In the brain, the stress-induced drop in neurotrophin level led to an overexpression of the BDNF receptor, TrkB. The KD has a dual effect in restoring BDNF and repairing the damage. 5-HT systems. Although KD did not affect the levels of transporters or receptors, it did suppress the elevated mucosal 5-HT. Additionally, KD increased BDNF levels in the brain, which triggered a negative feedback loop, resulting in the TrkB downregulation of TrkB to maintain physiological balance (Orlando et al., 2022).

Another study examined the safety of ketogenic formulae (KF) in 20 healthy individuals, focusing on sequential changes in blood ketone bodies, specifically BHB and AcAc when KF was provided within the parameters of KD. By the fourth day of KF administration, the levels of total keto bodies, ketone bodies, AcAc, and BHB significantly increased after both lunch and supper. In terms of anthropometric, urological, metabolic, gastrointestinal characteristics, and nutritional, KF did not present any substantial safety concerns. Additionally, the study noted changes in the gut microbiome due to the KDs, particularly a decreased *Firmicutes spp.* Decreased with KF consumption. This study provides baseline information about the value of KF in a KD, demonstrating its biochemical safety and metabolic compatibility at various dosages. Moreover, KF had minimal to no impact on the gut flora, indicating a neutral and safe effect on the microbiome (Nakamura et al., 2022).

**KD and Gut Health in Epilepsy Patients:** Figure 2 illustrates the impact of the KD on the gut health of epileptic patients. The epilepsy group showed a higher prevalence of Actinobacteria compared to the healthy group but had lower levels of Bacteroidetes. Additionally, the richness of the gut microbiota in epilepsy patients was 1.6-1.7 times lower than that of healthy controls, indicating significant differences in species compositions. The ATP-binding cassette transporter was identified as the strongest functional biomarker. In terms of species biomarkers for uncontrolled epilepsy, the *Bifidobacterium longum* group, *Enterococcus faecium* spp. group, and *Enterococcus lentus* spp. were species biomarkers prominent. These findings suggested a clear association between gut bacterial dysbiosis and intractable epilepsy, even after controlling for factors that might influence the gut microbiota (Lee et al., 2021).

In another study, 32 age-matched individuals and 8 children with intractable epilepsy, aged 1 to 7 years old, were examined. Stool samples were collected and questionnaires about diet and bowel habits were completed at the two

different analyzing the compositions of gut microbiota. Compared to the healthy group, the epilepsy group had higher abundance of *Actinobacteria spp.* and fewer *Bacteroidetes spp.* The ATP-binding cassette was identified as the most significant functional biomarker. Additionally, *Enterococcus faecium* spp. Group, *Bifidobacterium longum* spp. Group, and *E. lentus* spp. Species biomarkers associated with uncontrolled epilepsy. Their study established a link between gut bacterial dysbiosis and intractable epilepsy, even after controlling for factors that could influence the gut microbiota (Lee et al., 2021).

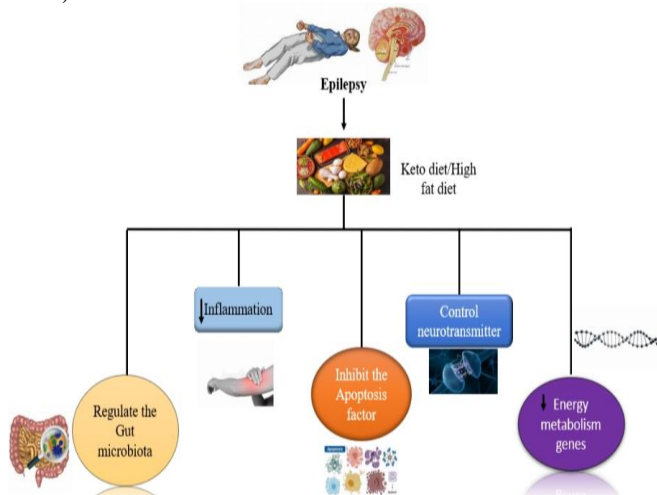
In a pilot study, we conducted 16S rRNA sequencing on the gut microbial communities of eight children at the onset of their seizures and again one year after starting anti-seizure medication. We compared these results with the gut microbial of seven healthy children of the same age and gender. Our finding revealed that drug-naïve individuals had microbiome profiles similar to those with refractory epilepsy, characterized by an increase in *Akkermansia spp.* and Proteobacteria and a decrease in relative abundance of *Faecalibacterium spp.* Abundance. As seen in drug-resistant epilepsy, a bacterial-mediated pro-inflammatory environment may play a role in seizures development of seizures in children with newly diagnosed epilepsy and may also shift in response to treatment in those with drug-responsive epilepsy (Ceccarani et al., 2021).

Drug-resistant epilepsy (DRE) affects one-third of epileptic patients and is often worsened by polydrug toxicity, as well as mental and cognitive commodities. A deeper understanding of the gut-brain axis and the microbiome is likely to offer insight into the pathophysiology of epilepsy, resistance to anti-seizure medications (ASM), and potential treatment strategies. Gut modifications in linked neuromodulators, disturbance of the blood-brain barrier, and inflammation are all linked to gut dysbiosis. The gut microbiota composition of DRE patients differs from that of drug-sensitive patients and healthy controls. For some DRE patients, the modified Atkins and ketogenic diets have been shown to reduce seizures. These low-carb dietary intervention alters the function and taxonomic composition of the gut microbiome, and the microbiota composition varies between diet responders and non-responders. Dietary changes can influence the microbiome, promote specific microbial relationships, and modulate brain neurotransmitter levels, all of which can impact seizure activity. Additionally, probiotics can modify composition, potentially contributing to improved outcomes in epilepsy management (Holmes et al., 2020).

Moreover, in this study, eleven healthy parents who were not starting KD and twelve patients who were beginning KD were enrolled. Fecal samples were collected before and three months before commencing KD. The ketogenic ratio was 4:1 in seven children, 3.5:1 in two, and 3:1 in three at the second time point. Before starting the diet, the mean hydroxybutyric acid ketone levels were  $0.3 \pm 0.2$ , (range of 0.1-0.8), which



increased to 4.1-1.2mmol/L, with (range) 1.4-5.6) after 3 months. Regarding seizure frequency, five of the twelve children were responders, experiencing a reduction of over 50% in seizures. Although three patients were non-responders in terms of seizure frequency, three patients reported shorter seizure durations and less postictal fatigue. Ten children who did not show progression in these areas were also non-responders in terms of seizure frequency and diet tapering during the three-month follow-up (Lindfeldt et al., 2019).



**Figure 2. Impacts of KD on gut health in epileptic patients.**

Furthermore, this study investigated the effects of adding prebiotic fiber added to KD on spasms, fecal gut microbiota, hippocampus mitochondrial metabolism, developmental milestones, and metabolites in an animal model of infantile Spasm Syndrome. Animals were randomly assigned to either the KD or KD + PRE diets following infantile Spasm Syndrome induction. Although the addition of PRE reduced circulating ketones and increased glucose levels, it did not affect the occurrence of spasms. PRE also altered carnitine levels, it did not affect the occurrence of spam. Although the addition of PRE reduced circulating ketones and increased glucose levels, it did not affect the occurrence of spam. A third reference group, breastfed by dams and free of infantile Spasm Syndrome was for comparison. The KD + PRE improved microbial diversity and increased the relative abundance of beneficial bacteria, including *Lactobacillus johnsonii* spp., *Pseudopodium* spp., and *Bifidobacterium* spp. Developmental milestones such as negative geotaxis, and surface righting, and between KD and KD + PRE, expect more frequent ultrasonic vocalizations in the KD + PRE group. In conclusion, while PRE supplementation enhanced metabolic markers and gut microbial diversity, it did not influence spasms or lead to significant developmental outcomes (Mu et al., 2022).

In a prospective study involving 20 individuals undergoing KD treatment, including men and 6 women clinical efficiency, electroencephalogram (EEG) changes, and laboratory tests were assessed. Feces samples were collected before the start of treatment and six months of therapy. The composition of the gut microbiota was analyzed using 16S rDNA sequencing to identify any flora potentially associated with the efficacy of the KD. After six months of treatment, two patients were seizures-free, and three experienced a 90% reduction of 50% EEG improvements were observed in all 10 patients. Fecal microbial profiles after KD treatment reduced alpha diversity compared to baseline, significantly higher levels of *Bacteroidetes* spp. and lower levels of *Firmicutes* spp. Additionally, the non-responsive group showed higher levels of *Clostridiales* spp., *Rikenellaceae* spp., *Ruminococcaceae* spp., *Lachnospiraceae* spp., and *Alistipes* spp. The KD appears to decrease gut flora diversity and species richness. Targeting specific gut flora may offer a potential treatment strategy and serve as an indicator of alternations in gut microbiota that may be associated with different KD efficacy outcomes (Gong et al., 2021).

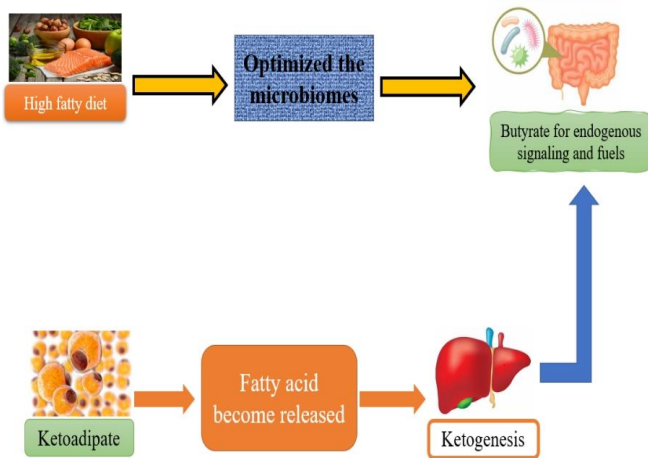
**Influence of KD on gut microbiota in various disorders:** In young healthy mice (12–14 weeks old), KD intervention altered gut flora, improved neurovascular function, and reduced the risk for dementia. In the present study, we showed that at 16 weeks on the KD, mice experienced a significant increase in CBF and P-glycoprotein transport across the blood-brain barrier (BBB), which facilitated the removal of amyloid-beta, a characteristic of Alzheimer's disease. The neurovascular improvements were linked to the induction of mTOR and increased endothelial nitric oxide synthase protein expression. The KD also led to a rise in their native abundance of beneficial gut microbiota, including *Akkermansiamuciniphila* spp. and *Lactobacillus* spp., *Desulfovibrio* spp., and *Turicibacter* spp., Additionally, the KD reduced blood ketone and glucose levels, as well as body weight, which may be related to changes in the gut microbiota (Ma et al., 2018).

In a non-blind intervention study, adults over 65 years old, referred for a colonoscopy due to severe diarrhea were selected. Participants completed a four-day diary, the Hospital Anxiety and Depression scale, and a standardized assessment of gastrointestinal symptoms before and after the intervention, guided by a dietitian. Twenty individuals were included, with a mean age of 76. Adhered to the reduced FODMAP diet was satisfactory, with no clinically significant changes, in macro- or micronutrient intake during the intervention, despite a decrease in average daily FODMAP consumption from 20.82 g to 3.75 g. All gastrointestinal symptoms, including diarrhea (9.8/88; SD = 9.58), showed clinical improvement following the diet. This suggests that the low-FODMAP diet can offer clinical benefits for older adults (O'Brien et al., 2020).



Furthermore, a high-fat diet impacts human gut flora, (described in Figure 3). In this study, the synthesis of SCFA and fecal water toxicity was examined to understand how 1 month of KD affects gut flora in epileptic patients. A total of seven patients were enrolled. Fecal samples were collected before and after a month of KD (4:1 ketogenic ratio),. SCFA was analyzed using GC-FID, and fecal water toxicity was assessed with the comet test on Caco-2 cell culture. Post-KD, there was a significant level, a 64% decrease in acetate levels, a 33% decrease in propionate levels, and a 20% decrease in butyrate. Although genotoxicity slightly declined, the diet did not impact the cytotoxicity of fecal water collected from stool samples (Ceccarani et al., 2021).

In another study, rats developed HSV-1 neurotropic infection and HSE more slowly when following a KD, a low-carb high-fat diet. The KD reduced viral infection, neuro-inflammation, weight loss, and neurodegenerative signs, which enhanced survival rates in HSE mice. The protective effects of the KD's against HSV-1-related neuroinflammation and the progression of HSE were decreased by an antibiotic-induced that reduced gut flora. This indicated the HSE through its impact on gut microbiota. Antibiotics-induced disruption of gut flora weekend KD protective effects against neuroinflammation and HSE development, suggesting the gut microbiota's crucial role in KD therapeutic benefits (Shan et al., 2023).



**Figure 3. High-fat diet influences the gut flora.**

Similarly, alternation in gut microbiota has been linked to metabolic changes associated with T2DM and overweight/obesity. While it is well-known that diet has a significant influence on GM, limited research has examined the effects of a very low-calorie ketogenic diet (VLCKD) on gut microorganisms, especially in T2DM. In this study, we compared anthropometrics, lifestyle, life quality, and biochemical variables. Eleven patients were randomly divided into two groups 6 and 5 followed a hypocaloric MD (MEDI), and five followed the VLCKD (KETO), Evaluated were randomly divided into three different time points:

baseline (T0), two months later (T2), and three months later (T3). The results indicated that while biochemical improvements between the two diets were not significantly different, the VLCKD had more pronounced positive impacts on anthropometric measures than the MEDI. In the KD group, there was a significant increase in the *Verrucomicrobiota spp.* phylum, *Verrucomicrobiae spp.*, *Akkermansia spp.*, and the *Christensenellaceae spp.* family, *Verrucomicrobiales spp.*, *Eubacterium spp.*, and *Akkermansiaceae spp.*, along with a decrease in microbial taxa previously associated with obesity. For the MEDI group, the phylum expanded considerably at T2 and T3, and the *Firmicutes spp.* Phylum increased significantly at T3. Additionally, only the KETO group showed a metagenomic change linked to certain metabolic pathways. Both dietary approaches improved health, but the VLCKD showed superior outcomes in terms of body composition and gut microbiota profile (Deledda et al., 2022).

**KD and Gut Flora of Athletes:** In another study, it was observed that diet and physical activity significantly influence future bacteria, even among sedentary individuals. Although diet's impact on athletic performance is well-recognized, few studies have directly compared elite athletes. In this research, athletes were randomly assigned to one of three diets: high carbohydrate, periodized carbohydrate, or ketogenic low carbohydrate high-fat diet. Stool samples were collected before and after a three-week intensive training program, and microbiota profiles were analyzed using 16S rRNA gene amplicon sequencing. The baseline microbiota profiles' showed distinct "enterotypes" dominated by either *Prevotella* or *Bacteroides spp.* Dominating by enterotypes. *Bacteroides spp.* and *Dorea had spp.* Higher relative abundances due to the low carb, high fat diet, but *Faecalibacterium* had lower relative abundances, even though enterotypes were generally stable and persisted following treatment. Notably, the low carbohydrate high-fat intervention revealed significant negative associations between fat oxidation and *Bacteroides spp.* as well as between the economy test and the *Dorea* (Murtaza et al., 2019).

In this study, sixteen male soccer players were randomly assigned to follow either the KEMEPHY diet or the Western diet. Research compared the composition of the gut microbiota, body composition, and performance evaluations were compared before and after the 30-day intervention using 16S rRNA amplicon sequencing. Alpha-diversity measures and PERMANOVA explored the association between macronutrient intake and microbial composition. Additionally, A linear discriminant analysis of the post-intervention data was also conducted at various taxonomic levels. The analysis identified distinct differences between the two groups in the western diet, there was a higher prevalence of Actinobacteria-related *Bifidobacterium spp.*, *Butyricoccus spp.*, and *Acidaminococcus spp.* In contrast, those on the KEMEPHY diet showed higher *Clostridia* UCG-014 (order, family, and genus), *Butyricimonas spp.*,



*Odoribacterter* spp. genera, *Marinifilaceae* spp. family, and *Ruminococc* spp. Genera. Despite these specific differences, the overall composition of the gut microbiota did not significantly change in athletes following the 30-day KEMPEHY intervention. This suggests that the KEMPEHY diet could be a safe option for athletes who regularly exercise, potentially helping to maintain or manage gut microbiota without causing drastic changes. Different dietary patterns and macronutrient distribution, such as those in a KD, may have varied effects on the human gut microbiota (Mancin et al., 2022).

Moreover, participants in the study were divided into 2 groups. The research group consisted of amateurs aged 18-60 who followed a typical diet with at least 50%. A stool sample of 10 grams was collected from each participant, and SCFAs in these samples were analyzed using gas chromatography. Additionally, participants completed a 72-hour food diary and a Food Frequency Questionnaire (FFQ). This analysis revealed notable differences in the SCFA level between the

two groups. Specifically, the levels of butyric, iso-butyric, valeric, isovaleric acids, and acetic varied. In the research group, SCFA levels in the stool were strongly correlated with the intake of certain foods (fish, nuts, vegetables, seeds, poultry, sugar, fruits, red meat, sugar substitutes, and lipids), according to Spearman's rank correlation analysis. The findings suggested that on a KD, consuming a diet rich in berries, leafy vegetables, cruciferous and nuts may improve the profile of SCFA profile produced by the gut microbiota. By increasing the intake of plant-based foods, the negative effects of microbiome alterations typically seen with high fat and protein in KD could be avoided and reduced, respectively, by altering the diet to include more plant items. This approach may reduce the risk of proteolytic fermentation, which can have harmful effects (Zhang et al., 2018). Table 1, lists various studies exploring the impact of KD on gut microbiota in different populations, including epileptic patients, athletes, and those with various disorders.

**Table 1. Effect of KD on gut flora composition.**

Subject	Objective	Methodology	Result	References
<b>KD affects the composition of gut microbiota</b>				
Maternal or neonatal rats (48 rats)	This study investigated the impact of a KD expression of CB receptors in intestinal tissue.	<ul style="list-style-type: none"> <li>Two groups of mice were involved, one group was fed a KD for 10 weeks, while the other received a regular diet.</li> <li>After treatment, animals were slaughtered, and then performed PCR and western blotting.</li> </ul>	<ul style="list-style-type: none"> <li>It improved intestinal permeability and CB receptors.</li> <li>An extended period of ketosis KD would help treat IBS.</li> </ul>	(Gigante et al., 2021)
Wistar rats	Find the effects of KD on 5-HT, and IBS.	<ul style="list-style-type: none"> <li>After being fed either an IBS-KD or an IBS-Std for ten weeks.</li> <li>Wistar rat samples that had been deprived of their mothers as babies were investigated.</li> </ul>	<ul style="list-style-type: none"> <li>KD boosted BDNF levels</li> <li>Produced negative feedback.</li> <li>Also minimizing the negative effects of an IBS animal model.</li> </ul>	(Orlando et al., 2022)
Male mice (8 mice in each of the 5 groups)	Effects of different restrictive diets on mice's gastrointestinal tract.	<ul style="list-style-type: none"> <li>Rat was randomly given diets like IF, KD, CR, FMD, and control diets, from all groups provided energy-restricted diet.</li> </ul>	<ul style="list-style-type: none"> <li>A restricted diet may improve gut health</li> </ul>	(Gregor et al., 2022)
20 males (aged 20-40 years)	Temporal variations in blood ketone bodies AcAc, and BHB were examined.	<ul style="list-style-type: none"> <li>This study compared parallel groups in a double-blind, randomized fashion.</li> <li>Individuals regularly consumed KF while on KD.</li> <li>KD was administered, and fecal samples were obtained for examination.</li> </ul>	<ul style="list-style-type: none"> <li>Gut flora changes because of KDs.</li> <li>KF demonstrated a decline in the phylum <i>Firmicutes</i>.</li> <li>BHB and AcAc levels were also increased after lunch and dinner.</li> </ul>	(Nakamura et al., 2022)
12 children	Find the makeup of intestinal microbiota before and after KD in children.	<ul style="list-style-type: none"> <li>This is a study cross-section study that was carried out in 12 children of the healthy control group compared with the DRE group.</li> <li>Evaluate the alterations in SCFAs and fecal microbiomes.</li> <li>Analysis of the disease cohort was done both before and after the first six months of KD therapy.</li> </ul>	<ul style="list-style-type: none"> <li>The anti-seizure effects of KD might be influenced by gut microbiota and microbial metabolism.</li> <li>After therapy, the fecal SCFA concentration rose.</li> </ul>	(Gong et al., 2021)



## Keto Diet and Gut Microbiota

Subject	Objective	Methodology	Result	References
28 children	Identify Bifidobacteria and tumor necrosis that alter during KD in epileptic patients.	<ul style="list-style-type: none"> <li>• KD was used to treat epilepsy.</li> <li>• After 3 months of diet delivery.</li> <li>• Fecal and serum were collected for analysis.</li> </ul>	<ul style="list-style-type: none"> <li>• KD has shown an anti-inflammatory impact on epileptic children.</li> <li>• Identify inflammatory and gut microbial therapy.</li> </ul>	(Dahlin et al., 2022)
Dravet and wildtype Mice	The effects of <i>Scn1a</i> deficiency and KD on the gut microbiota	<ul style="list-style-type: none"> <li>• The CD or the KD was fed to Dravet mice.</li> <li>• Fecal samples carried from animals were used for extensive microbiome study using 16S rRNA gene sequencing.</li> </ul>	<ul style="list-style-type: none"> <li>• KD changed the gut profile of mice.</li> <li>• Signs of dysbiosis in the gut because of the <i>Scn1a</i> genetic defect.</li> </ul>	(Miljanovic & Potschka, 2021)
<b>KD on gut health in epilepsy patients</b>				
Fecal samples from 12 children	The effects of diet on the gut flora and overall health were examined.	<ul style="list-style-type: none"> <li>• Providing high fat (1:4) and low CHO and an adequate protein diet (1:2) to children.</li> <li>• Then fecal samples were collected for analysis.</li> </ul>	<ul style="list-style-type: none"> <li>• Fiber-consuming bacteria become less prevalent during KD.</li> </ul>	(Ceccarani et al., 2021)
A stool sample was collected from children.	They compared the gut microbiome of kids with intractable epilepsy to healthy controls using a cohort study to lessen the influence of potentially confounding factors.	<ul style="list-style-type: none"> <li>• A stool sample was collected from 8 epilepsy children at the age of 1 to 7 years and 32 healthy controls.</li> <li>• Questionnaires about their food and bowel habits at two different times and examined the components of the gut microbiota.</li> </ul>	<ul style="list-style-type: none"> <li>• The gut bacterial dysbiosis related to intractable epilepsy in a cohort</li> <li>• That could affect the gut microbiota.</li> </ul>	(Lee et al., 2021)
Sprague-Dawley rats	Does the addition of prediabetics in the KD diet improve the metabolic profile?	<ul style="list-style-type: none"> <li>• Random diets were provided to animals including KD or KD + PRE.</li> </ul>	<ul style="list-style-type: none"> <li>• Spasms developmental outcomes were unaffected by PRE.</li> <li>• Although both metabolic indices and gut microbiota diversity were significantly improved.</li> </ul>	(Mu et al., 2022)
Children (6 females or 3 males) Age between 13-16 years old	This is a pilot study, to investigate the gut microbiome critical element in epilepsy onset.	<ul style="list-style-type: none"> <li>• In this study, 16S rRNA sequencing was done.</li> <li>• Eight children had their gut microbial populations analyzed both before and after receiving an anti-seizure drug.</li> <li>• The fecal sample was investigated after 4 and 12 months</li> </ul>	<ul style="list-style-type: none"> <li>• Children with the pelvic disease had higher concentrations of the microorganisms <i>Akkermansia spp.</i> and <i>Proteobacteria.</i></li> <li>• But <i>Faecalibacterium spp.</i> had a lower relative abundance.</li> </ul>	(Ceccarani et al., 2021)
20 participants	Assess the gut microbiome of epilepsy patients receiving KD treatment has changed in composition	<ul style="list-style-type: none"> <li>• 14 males and 6 females (20 patients) were given KD after that blood and laboratory samples were taken.</li> <li>• By 16S rDNA sequencing, the makeup of the gut microbiota was examined.</li> </ul>	<ul style="list-style-type: none"> <li>• The type and amount of organisms in the gut microbiota may decline as a result of KD.</li> </ul>	(Zhang et al., 2018)
<b>KD on gut microbiota in different diseases</b>				
A stool sample was collected from patients (Ages between 2 and 46 years)	Find out if a month of KD changes the ecology in the gut. Analyzed the short-chain fatty acid production.	<ul style="list-style-type: none"> <li>• KD was provided to 7 patients (3 males or 4 females) then collected their stool samples.</li> <li>• Examined to produce SCFA.</li> </ul>	<ul style="list-style-type: none"> <li>• The 1 month of KD significantly reduces SCFA production.</li> <li>• Because SCFA generated by the gut microbiota has several benefits for human metabolism</li> </ul>	(Ceccarani et al., 2021)



Subject	Objective	Methodology	Result	References
11 patients (divided into 2 groups)	Find the dynamics of GM and clinic variables after introducing MD and VLCKDS on T2DM and obesity patient.	<ul style="list-style-type: none"> <li>Patients were divided into 2 groups (groups of 5 patients and 6 patients), and 2 diets were provided with MD or VLCKDS.</li> <li>Parameters were evaluated at baseline (T0), two months later (T2), and three months later (T3).</li> </ul>	<ul style="list-style-type: none"> <li>The VLCKD's positive effects on the GM phenotype, GM profile, and body composition</li> <li>The biomarkers of intestinal homeostasis significantly increased.</li> </ul>	(Deledda et al., 2022)
5 weeks old mice	KD may reduce the HSC infection in mice while using gut microbes.	<ul style="list-style-type: none"> <li>KD was introduced to 8<sup>th</sup>-week mice which helped to lower the HSV infection.</li> </ul>	<ul style="list-style-type: none"> <li>KD is a possible treatment approach that uses gut microbiota to treat HSE.</li> <li>KD reduced the               <ul style="list-style-type: none"> <li>✓ Weight of mice</li> <li>✓ Neuro-generative symptoms</li> <li>✓ Neuro-inflammation</li> </ul> </li> <li>KD enhances the survival rate of HSE mice</li> </ul>	(Shan et al., 2023)
20 participants (76 years old) also have chronic diarrhea	A low FODMAP diet is effective in chronic diarrhea.	<ul style="list-style-type: none"> <li>The Hospital Anxiety and Depression scale, a comprehensive examination of gastrointestinal symptoms, and a four-day dietary diary were all completed by the participants.</li> <li>A 6-week low-FODMAPS diet under the guidance of a nutritionist.</li> </ul>	<ul style="list-style-type: none"> <li>The LFD appears to be nutritionally safe, eases gastrointestinal issues</li> <li>It is a realistic intervention for an older population</li> </ul>	(O'Brien et al., 2020)
<b>KD affects the gut flora of athletes</b>				
A stool sample was collected from 21 male athletes.	Ketogenic Low Carbohydrate High Fat giving on training session.	<ul style="list-style-type: none"> <li>Athletes were allocated to a high carbohydrate or ketogenic low carbohydrate high-fat diet throughout a three-week intense training program.</li> <li>Collect from the beginning and end of the training.</li> </ul>	<ul style="list-style-type: none"> <li>Top endurance athletes, healthy mainstream athletes, and other elite endurance athletes all had enterotypes dominated by <i>Bacteroides</i> and <i>Prevotella</i> in their stool microbiota profiles.</li> </ul>	(Murtaza et al., 2019)
16 male soccer players	The impact of the KEMEPHY diet on the makeup of gut bacteria in athletes.	<ul style="list-style-type: none"> <li>Players eat a Western or KEMEPHY diet.</li> <li>Using 16S rRNA amplicon sequencing, body composition, performance evaluations, and gut microbiota composition were assessed before and after a 30-day intervention.</li> </ul>	<ul style="list-style-type: none"> <li>There were no discernible effects of time on the diversity of the microbial community.</li> <li>Regulate the composition of gut microbiota.</li> </ul>	(Mancin et al., 2022)
20 male and female	Evaluate the presence of SCFAs in the stools of healthy, active KD users	<ul style="list-style-type: none"> <li>Two groups of participants were formed (a control group and a study group). While athletes in the control group stick to a regular diet, those in the research group consume KD.</li> <li>To determine the presence of SCFAs in stool samples.</li> <li>An FFQ and a 72-hour food diary were completed by the participants.</li> </ul>	<ul style="list-style-type: none"> <li>KD may help the profile of short-chain fatty acids produced by the gut flora.</li> </ul>	(Gudan et al., 2022)



**Conclusion:** The KD is a popular eating plan that is characterized by low-CHO, high-fat, and adequate protein intake. Historically, KD was primarily used to treat, but it is now widely adopted for weight loss. In this review, our primary focus is evaluating the impact of KD on gut health. KD has been shown to improve participants' gut health and increase ketone levels in the blood, which can alter the gut health and increase ketone levels in the blood, which can alter the gut microbiota. Animal studies have also indicated that KD has positive effects on IBS in mice. Recently, KD has gained attention from athletes as a potential strategy for enhancing performance and altering body composition. It is well established that diet significantly influences the diversity and composition of gut bacteria. However, the effects of KD on gut microbiota have been shown to produce mixed results, while others have reported negative effects. Future research should investigate the influence of various diets on both immune system function and gut health.

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**Policy referred:** Public Health and Nutrition Policy; WHO Global Action Plan for the Prevention and Control of Non-Communicable Diseases (NCDs) –; National Dietary and Clinical Guidelines; Precision Medicine and Personalized Nutrition Policies.

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#### Abbreviation

TNF	Tumor Necrosis Factor
DRE	Drug refractory epilepsy
KEMEPHY	Ketogenic Mediterranean diet with phytoextracts
WD	Western diet
GM	Gut microbial
VLCKD	Low-calorie ketogenic diet
MD	Mediterranean diet
PERMANOVA	Permutational multivariate analysis of variance
CD	The control diet
HSE	Herpes simplex encephalitis
SCFAs	Short-chain fatty acids
FFQ	Food Frequency Questionnaire
KF	Ketogenic formulas
AcAc	Acetoacetic acid
BHB	β-hydroxybutyrate

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