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UNVEILING GUT MICROBIOTA SIGNATURES LINKED TO THE KETOGENIC DIETARY THERAPY

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ABSTRACT – The aim of this paper was to explore the interplay between ketogenic dietary therapies (KDTs) and gut microbiota composition, focusing on their potential implications for rare neurological and inherited metabolic disorders (IMDs), and also autism spectrum disorder.

A literature search was conducted using PubMed (Medline) for articles published between 2016 and July 2025. A total of 251 articles were screened, and 22 were included based on relevance to KDTs, microbiota, and rare neurological or metabolic diseases in pediatric and adult populations.

KDTs have been reported to induce significant shifts in gut microbiota composition across rare neurological and metabolic disorders. Common findings included reduced levels of the genus *Bifidobacterium* and members of the Firmicutes-related genera, along with an increased abundance of *Bacteroides* and *Akkermansia*. In drug-resistant epilepsy, these changes correlated with seizure reduction; in autism spectrum disorder and mitochondrial disorders, KDTs modulated inflammatory and neuroactive microbial profiles. Microbiota was frequently modified in its composition and metabolite production, with a potential neuroprotective and metabolic effect.

While ketogenic diets represent a promising therapeutic strategy across rare neurological and metabolic disorders, their interplay with the gut microbiota is complex and unclarified yet. Mechanistic and translational studies will be essential to harness microbiota-driven effects, improve personalization of therapy, and ensure long-term safety in both pediatric and adult populations.

Keywords: Ketogenic dietary therapy, Gut microbiota, Inherited metabolic disorders, Rare neurological disorders.

Abbreviations: ASD = autism spectrum disorder; DRE = drug-resistant epilepsy; GABA = γ-aminobutyric acid; GLUT1 = glucose transporter type 1; GLUT1-DS = glucose transporter type 1 deficiency syndrome; GM = gut microbiota; GSD = glycogen storage disease; IMD = inherited metabolic disease; KD = ketogenic diet; KDT = ketogenic dietary therapy; SCFA = short-chain fatty acid.

INTRODUCTION

The gut microbiota (GM) is composed of trillions of microorganisms colonizing the gastrointestinal tract, contributing to maintaining homeostasis through multiple functions: modulation of the immune system, production of bioactive metabolites, digestion of indigestible substrates, and protection against pathogens.

Considering its central role in numerous aspects of human physiology, the interest of scientific research in the GM has recently increased[1].

Dysbiosis is defined as an alteration in the composition or function of the microbiota. This imbalance can affect the levels of neurotransmitters and short-chain fatty acids (SCFAs), increasing the level of harmful substances and disrupting the communication along the gut-brain axis (GBA) between the central nervous system (CNS) and the gut, with effects in both systems[2]. Dysbiosis has been associated with a wide spectrum of pathological conditions, including neurological and inherited metabolic diseases (IMDs)[3].

IMDs, which require strict dietary management, are linked to altered GM, reduced diversity, and lower levels of beneficial SCFAs. In phenylketonuria, key SCFAs-producing taxa like *Faecalibacterium* and *Roseburia* are depleted, while *Blautia* and *Clostridium* are enriched[4-6]. In glycogen storage diseases (GSDs), patients show increased *Enterobacteriaceae* and *Veillonellaceae*, with reduced *Faecalibacterium* and *Oscillospira*[7,8]. In GSD patients receiving uncooked cornstarch, *Faecalibacterium prausnitzii* decreases, while *Akkermansia muciniphila* increases[9].

The ketogenic diet (KD), characterized by high fat, low carbohydrates, and moderate protein, induces ketosis – a metabolic state where fat replaces glucose as the primary energy source. This shift leads to hepatic production of ketone bodies (β-hydroxybutyrate, acetoacetate, and acetone), which fuel peripheral tissues and the CNS[10]. While KD for obesity emphasizes caloric restriction and fat oxidation, ketogenic dietary therapies (KDTs) for drug-resistant epilepsy (DRE) and specific IMDs prioritize controlled macronutrient ratios to sustain nutritional ketosis[11]. IMDs benefiting from KDTs include GLUT1 deficiency syndrome, GSD types III and IV, phosphofructokinase (PFK) deficiency, and mitochondrial disorders such as pyruvate dehydrogenase complex deficiency[12,13]. KDTs may support brain function in congenital hyperinsulinism (CHI), particularly when conventional treatments fail[14]. In CHI, excessive insulin suppresses glucose, ketone, and lactate production, leading to hypoglycemia and potential brain injury. Like in GLUT1 deficiency, KDT can provide the brain with alternative fuel. Maiorana et al[15,16] reported CHI cases with drug-resistant hypoglycemia, intellectual disability, and epilepsy showing symptom improvement under KDT. Beyond metabolic support, KDTs may enhance mitochondrial respiration, promote neuronal long-term potentiation, and upregulate brain-derived neurotrophic factor, reducing oxidative stress and inflammation[17]. Preclinical and clinical evidence suggests KDTs also alter GM, impacting the GBA, systemic inflammation, and energy metabolism[18]. These effects may be mediated by microbiota-derived metabolites, including SCFAs and neurotransmitter precursors[1,18]. SCFAs, including acetic acid, propionic acid, and butyric acid, beyond providing energy for intestinal epithelial cells, regulate the immune system and inflammatory response, and serve as signaling molecules that contribute to overall gut health[17].

A recent systematic review[19] analysing the effects of KDTs on the GM reported consistent shifts in microbial composition and metabolites (i.e., SCFAs, branched-chain fatty acids, trimethylamine N-oxide, beta-hydroxybutyrate and N-acetylserotonin) alongside the overall improvement in neurological disorders, such as reduced seizure frequency, cognitive and behavioural enhancements, and better quality of life. Ketogenic dietary patterns were further confirmed to induce specific microbial signatures, such as a reduction in *Bifidobacterium* spp. and *Firmicutes*, and an increase in Bacteroidetes, *Akkermansia muciniphila*, and certain *Lactobacillus* spp. and *Roseburia* spp., with downstream effects on host inflammation and intestinal immune tone[20].

These microbiota-mediated changes linked to elevated ketone bodies may contribute to the observed neurological benefits[20].

However, the mechanisms linking KDTs and GM remain incompletely understood. Larger, longitudinal studies are needed to clarify causal relationships and assess long-term safety, particularly in the context of rare metabolic disorders, where evidence is still limited. This study aims to identify and characterize the GM signatures associated with the KD, with a focus on their functional implications in conditions such as rare neurological disorders and IMDs, and also autism spectrum disorder (ASD).

METHODS

For this narrative review, a PubMed (MEDLINE) search was conducted between 2016 and July 2025, using the following keywords and combinations: ("ketogenic diet"[Title/Abstract] OR "ketogenic diets"[Title/Abstract]) AND ("microbiota"[Title/Abstract] OR "microbiome"[Title/Abstract] OR "gut microbiota"[Title/Abstract] OR "gut microbiome"[Title/Abstract] OR "intestinal microbiota"[Title/Abstract]) NOT ("very low calorie ketogenic diet"[Title/Abstract] OR "very low energy ketogenic therapy"[Title/Abstract] OR "obesity"[Title/Abstract] OR "diabetes"[Title/Abstract]).

A total of 251 documents were initially collected. Studies whose titles and abstracts were not relevant to the research question were excluded. The most relevant publications, including original research articles, meta-analyses, clinical trials, and observational studies, were selected for inclusion. Studies whose titles and abstracts were not relevant to the research question were excluded. Articles involving either paediatric or adult populations were considered, while studies focusing on the KD and GM without reference to a specific rare metabolic or neurological disease were excluded. Letters to the editor were excluded. A total of 23 articles were selected. The flow selection of papers is illustrated in Figure 1.

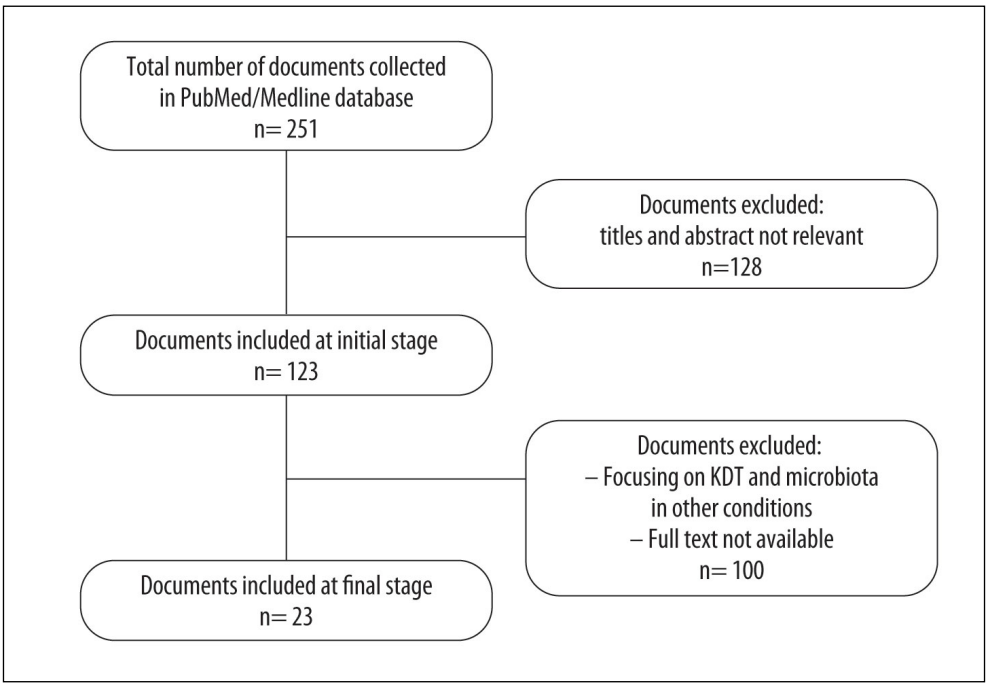

Figure 1. Flowchart of the paper selection.

DRUG-RESISTANT EPILEPSY

The GM community ecology in patients with DRE was found to be significantly altered compared with healthy subjects. Furthermore, in several human studies[21-23] of DRE, KDTs were associated with marked shifts in GM composition.

In a Korean study[24], eight children with intractable epilepsy not on KDTs were compared with 32 healthy controls. They showed a general reduction in Bacteroidetes and enrichment in Actinobacteria, with a higher (but not statistically significant) proportion of Verrucomicrobia and a lower (but not statistically significant) proportion of Proteobacteria, including higher relative abundances of Actinomycetaceae, Bifidobacteriaceae, Coriobacteriaceae, Corynebacteriaceae, and Enterococcaceae, while *Faecalibacterium prausnitzii* and *Bacteroides vulgatus* characterized healthy children. Another study[25] from China on 14 pediatric patients (aged 1.95 $\pm$ 3.1 years) with refractory epilepsy showed a significant increase of *Bacteroides* and *Prevotella* spp. after one week of KDTs, while *Cronobacter* spp. and Proteobacteria, which were elevated compared with healthy peers before KDTs, decreased.

A total of 64% of the study subjects showed a reduction in the frequency of seizures by 50%. After KDT's initiation, two Chinese studies[26,27] reported lower alpha diversity, compared to controls, decreased abundance of Firmicutes and increased levels of Bacteroidetes. In a pediatric cohort[25] of 12 patients with DRE following KDTs for 6 months, before KDTs, alpha diversity was higher than in matched healthy controls, and Actinobacteria and, at a genus level, *Enterococcus, Anaerostipes, Bifidobacterium*, *Bacteroides*, and *Blautia* showed a significant increase. After 6 months of KDTs, the GM of patients was characterized by the decreases in *Bifidobacterium* spp., *Akkermansia* spp., Enterococcaceae and Actinomyces and increases in *Subdoligranulum* spp., *Dialister* spp. and *Alloprevotella* spp. ($p<0.05$)[22].

Lindefeldt et al[28] analyzed the GM of 12 European children with DRE and observed that, following 3 months of KDT, the overall alpha-diversity remained largely unchanged; however, there was a marked decrease in *Bifidobacterium* spp. levels and a notable rise in *Escherichia coli* abundance. Moreover, the SCFAs content increased after KDTs[22], underlying that KDTs might ameliorate SCFAs concentrations.

Another study, based in Sweden, on 28 children with DRE[29] identified KDTs as an anti-inflammatory treatment and especially underlined that children with DRE may respond more favourably to KDTs when inflammation was slightly higher, particularly when *Bifidobacteria* spp. (*B. longum* and *B. breve*) and tumor necrosis factor are elevated, with >50% seizure reduction[29].

In most of these studies, the relationship between KDT and improvements in epilepsy seems to be influenced by GM composition and its functional activity, through interaction with the immune system[29].

Importantly, these microbial shifts may also modulate the GBA, a complex bidirectional communication network linking intestinal physiology with neural activity, thereby providing a plausible mechanistic pathway through which KDTs induced GM changes may influence seizure control[18].

In fact, most studies have reported a reduction in seizure frequency following the initiation of KDTs. However, accumulating evidence highlights that alterations in specific gut bacterial populations may act as biomarkers of the therapeutic response to KDT in epilepsy. Despite the growing number of studies on the impact of the KD on the GM in DRE, the results should be interpreted with caution due to the limited number of patients involved, the heterogeneous etiology of epilepsy, and the specific composition of the diet.

GLUCOSE TRANSPORTER TYPE 1 DEFICIENCY SYNDROME

Regarding GLUT1 deficiency, only one study[30] was identified that evaluated the effects of the KDTs on GM composition. Fecal samples from six patients affected by GLUT1-DS were analysed before starting the dietary treatment and after 3 months of KDTs. At the phylum level, no significant changes were observed in Firmicutes and Bacteroidetes, while a significant increase in the *Desulfovibrio* spp., a sulphate-reducing bacterium reported in inflammatory bowel disease and other inflammatory conditions[31], was detected[30].

AUTISM SPECTRUM DISORDER

A common microbial signature and specific metabolic product have been identified in patients with ASD[32], who often exhibit gastrointestinal issues. A meta-analysis[33] of 18 studies including 493 ASD children showed higher abundances of *Bacteroides*, *Parabacteroides*, *Clostridium*, *Faecalibacterium*, and *Phascolarctobacterium*, and lower levels of *Coprococcus* and *Bifidobacterium* compared with controls. These findings suggest gut dysbiosis in ASD, which may contribute to symptom severity.

In animal models of ASD, KDTs increased the levels of *Akkermansia* spp., *Parabacteroides* spp., *Bacteroides* spp., and *Desulfovibrio* spp.[34]. In the study of Olivito et al[35] in a mouse model of ASD (BTBR), KDTs increased relative abundances of putatively beneficial microbiota (i.e., *Akkermansia* spp. and *Blautia* spp.), while reversing the increase of *Lactobacillus* spp. in mice feces. In a case of a 17-year-old girl affected by ASD, KDTs provided a reduction in Firmicutes with an increase of Bacteroidetes and Proteobacteria[36].

Bolte[37] and later others[38,39] suggested the involvement of exotoxins produced by clostridia, such as p-cresol, in the onset of the ASD regressive form (the *Clostridium* hypothesis)[37-39]. P-cresol has been suggested as a possible urinary biomarker in ASD, and its concentration correlates with slow fecal transit (constipation)[40]. Moreover, an interesting correlation of p-cresol with ASD disease, and specifically with the absence of antibiotic treatment, was highlighted[41].

Clinically, children with ASD, in addition to the neuropsychiatric symptoms, often experience gastrointestinal issues, like functional constipation, which is the most common problem, followed by diarrhea/chronic diarrhea, abdominal pain or discomfort, bloating, gas or flatulence, soiling, incontinence or bedwetting, reflux or heartburn, nausea or vomiting, and pain or difficulties in bowel movement[41,42].

Recently, propionic acid has also been linked to ASD[42]. Shultz et al[43] showed that intracerebroventricular injection of propionic acid in rodents induces social impairment, as well as behavioral, neuropathological, and biochemical changes associated with ASD[44].

However, considering that fecal SCFAs differ in ASD children, reported to be either lower or higher, it is needed to elucidate the contribution of microbial metabolites to ASD.

MITOCHONDRIAL DISORDERS

In the study by Wang et al[27], patients with mitochondrial epilepsy on KDTs were compared with a control group of patients with mitochondrial epilepsy not on KDTs. Microbial diversity was significantly higher in the control group, according to the Chao1 diversity. Regarding composition, Firmicutes abundance was relatively lower in the KDTs group, while the Bacteroidetes phylum was increased in the KDTs group, with a significant rise of *Bacteroides fragilis,* which led to the increase in *Bacteroides* spp. abundance. It was also observed an increase in the taxon *Blautia sp.* N6H1.15 at the genus level and *Anaerotignum lactatifermentans* at the species level in the KD group[27]. *Actinobacteria* increased significantly in the control group[27]. Figure 2 shows the changes in the composition of the GM in diseases that benefit from KDT.

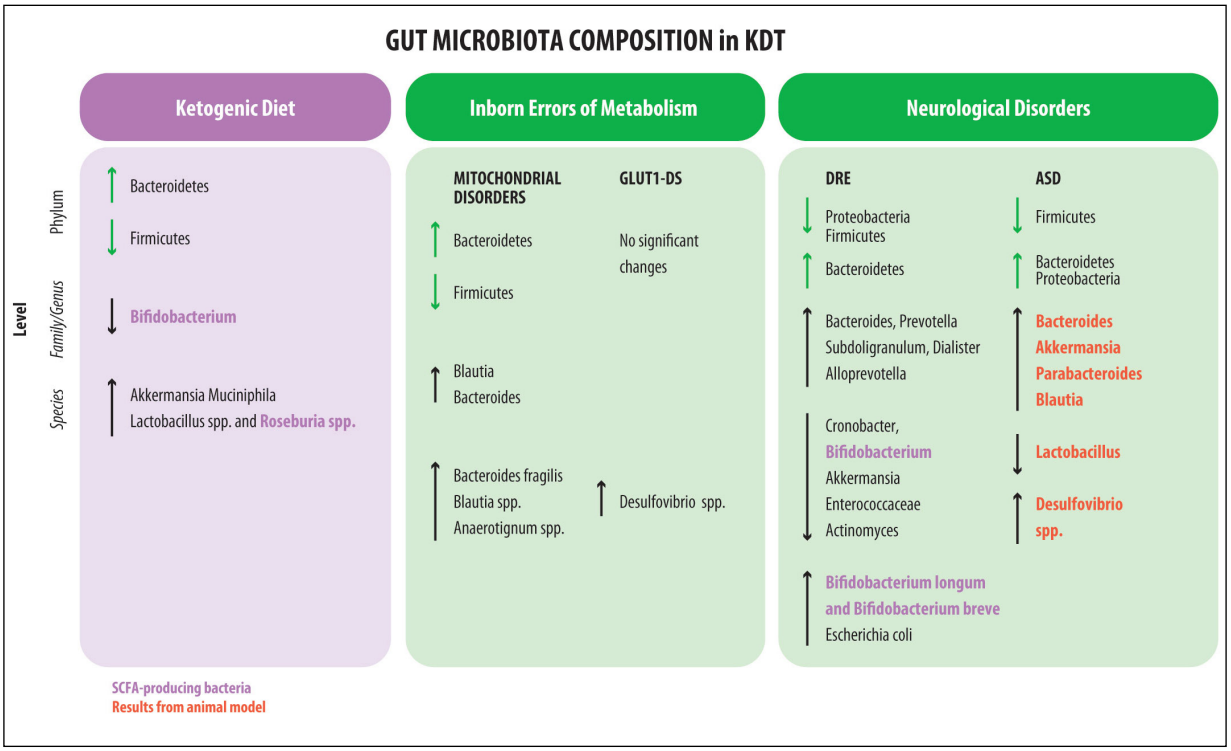

Figure 2. Gut microbiota composition in the ketogenic diet and in different neurological and inborn errors of metabolism after ketogenic diet therapy.
The results in the animal model are shown in orange. GLUT1-DS = glucose transporter type 1 deficiency syndrome; DRE = drug-resistant epilepsy; ASD = autism spectrum disorder; KDT = ketogenic dietary therapy; SCFA = short-chain fatty acid.

DISCUSSION

According to the clinical evidence reported in this narrative review, KDTs elicit extensive metabolic reprogramming in the brain, progressively replacing glucose with ketone bodies as the predominant energy source[45], which can provide up to 60-70% of cerebral energy requirements[46]. This metabolic shift is associated with an elevation in the cerebral Nicotinamide adenine dinucleotide $(NAD)^+$/NADH ratio, with potential downstream effects on inflammatory signaling, DNA repair, and circadian rhythm regulation. KDT also modulates amino acid turnover, enhancing flux through the glutamate–glutamine cycle and increasing the availability of glutamate for γ-aminobutyric acid (GABA) synthesis, resulting in a higher GABA/glutamine ratio and potentially dampened excitatory neurotransmission[47]. A decrease in GABA levels and its signalling pathways has been implicated in various clinical features associated with neurological disorders, such as stereotypies, hypersensitivity, and seizures. Some bacteria, such as Bifidobacteria and Lactobacilli, are capable of secreting neurotransmitters, particularly GABA. Moreover, these same taxa have been shown to promote intestinal mucosal integrity by reducing both local and systemic inflammation. The CNS is highly susceptible to inflammatory processes; notably, neuroinflammation has been demonstrated to trigger seizures in patients with epilepsy. A direct role of the GM in inducing inflammation and, subsequently, the onset of seizures has been proposed and investigated in animal models[42].

From a metabolic perspective, the KD enhances central insulin sensitivity, lowering glucose and insulin levels. Also, it attenuates oxidative stress and neuroinflammation, increases brain-derived neurotrophic factor expression, modulates ATP-sensitive potassium (KATP) channel activity, and reduces β-amyloid and tau accumulation, collectively supporting neuroprotection. These benefits stem from integrated metabolic, antioxidant, anti-inflammatory, and neurotrophic actions, although the long-term safety and efficacy of KDTs require further evaluation[45].

In other conditions, such as obesity, the KD promotes weight loss by shifting metabolism toward fat oxidation and ketone body production, with effects comparable to caloric restriction in animal models[48]. In humans, meta-analyses[49] indicate greater long-term efficacy compared to low-fat diets, though mechanisms remain debated and may involve altered GM composition.

Mitochondrial epilepsy is challenging to treat with a single antiepileptic medication due to the wide range of seizure types and clinical presentations; however, it is crucial to consider the drug's potential mitochondrial toxicity, and particular caution should be taken with agents that may disrupt the respiratory chain. KDTs may be an effective alternative, whose mechanism of action remains not entirely understood. Studies[27] have shown that the KD can reduce seizures by modulating the GM, as seen in both animal models and a clinical case of epilepsy remission after fecal microbiota transplantation. In addition, previous research[27] found that 40.9% of patients had a significant reduction in seizures after three months on the KDT, with especially positive results in those with MELAS or mtDNA mutations.

The above-reported studies suggest that an increase in *Bacteroides* appears to be a signature of KD[20], especially in epileptic patients following KDTs[25-27], since individuals with DRE have reduced levels of *B. fragilis* compared to healthy controls[21,24]. In previous studies[27], *Bacteroides fragilis* showed a significant impact in the adjuvant treatment of DRE. Supplementation with *Bacteroides fragilis* led to a seizure reduction of over 53% in around 61% of patients, supporting its therapeutic potential and protective effect on seizures[50]. On the other side, *Actinobacteriota* seems to be a biomarker for epilepsy patients at the phylum level, since it was significantly enriched in the control group of epileptic patients not on KDT[22,24,27].

Moreover, animal studies[51] have shown that administering *Bacteroides fragilis* can restore gut barrier function, alter GM composition, and improve behavioral abnormalities linked to ASD.

Individuals with ASD share an increased relative abundance of *Clostridium spp*. This taxon is well known for its proteolytic activity, which leads to the production of potentially toxic compounds that may affect intestinal homeostasis and permeability, and can also influence the survival of other beneficial microorganisms, such as lactic acid bacteria[42].

The KD boosts ATP and adenosine levels through altered energy metabolism, and adenosine, known for its strong anti-seizure and neuroprotective properties, may be a key factor in the diet's therapeutic effects[52,53]. For example, KDTs were found to reduce seizures in mice by increasing the activation of adenosine A1 receptors (A1Rs)[53].

The previously mentioned study by Wang et al[27] may indirectly suggest this potential effect; however, further research is required to clarify how microbiota alterations by KDTs impact metabolite profiles, especially because a longer period of KD intervention might lead to more significant changes in the GM. A clearer understanding of the connection between GM and the nervous system is needed to offer a theoretical foundation for managing mitochondrial epilepsy.

In the current literature, no other studies have been identified that investigate the composition of the GM in patients with IMDs, such as pyruvate dehydrogenase complex deficiency for glycogen storage diseases, undergoing KDT.

CONCLUSIONS

The available literature remains heterogeneous and largely correlative, with small sample sizes and limited longitudinal follow-up. It is still unclear whether microbiota changes are a direct consequence of dietary intervention or reflect secondary effects of the underlying disease, treatment response, or metabolic adaptations. Moreover, the functional significance of specific bacterial shifts – particularly whether they translate into meaningful metabolic or neurochemical changes – remains to be elucidated. Future research should therefore prioritize well-controlled, multi-omic studies that integrate microbiome, metabolome, and clinical endpoints. This approach may help clarify causal pathways and identify microbial signatures predictive of therapeutic response. In parallel, the potential of targeted microbiota interventions – such as probiotics, prebiotics, or adjuvant dietary strategies – warrants investigation to optimize efficacy and mitigate possible drawbacks of KDT, such as reduced abundance of beneficial taxa or diminished butyrate production.

In conclusion, while KDs represent a promising therapeutic strategy across rare neurological and metabolic disorders, their interplay with the GM is complex and only partially understood. Advancing from descriptive to mechanistic and translational studies will be essential to harness microbiota-driven effects, improve personalization of therapy, and ensure long-term safety in both pediatric and adult populations.

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