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The therapeutic potential of the ketogenic diet in selected neurodegenerative diseases and psychiatric disorders

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Abstract

Background: Pharmacoresistance in central nervous system (CNS) pathologies remains a major clinical challenge. The ketogenic diet (KD) is emerging as a potential multimodal metabolic therapy. Ketone bodies appear to remodel neuronal bioenergetics and modulate neurotransmission, laying the groundwork for the developing field of metabolic psychiatry.

Aim & Methods: This narrative review (2010–2026) evaluates the neurobiochemical mechanisms of ketone bodies and the potential of the KD as an adjuvant intervention in selected neurodegenerative (Alzheimer's, Parkinson's) and psychiatric (bipolar disorder, schizophrenia, treatment-resistant depression) conditions.

Results: Evidence suggests that β -hydroxybutyrate (BHB) crosses the blood-brain barrier via monocarboxylate transporters to fuel the tricarboxylic acid cycle, potentially bypassing the neuronal insulin resistance—often termed type 3 diabetes—implicated in Alzheimer's disease. At the cellular level, BHB may exert neuroprotective effects by inhibiting the NLRP3 inflammasome, which appears to reduce the release of proinflammatory cytokines. Furthermore, ketosis is associated with amino acid pathway remodeling; it may stimulate glutamic acid decarboxylase (GAD) activity, potentially shifting the neurotransmitter balance toward inhibitory GABAergic transmission relevant to mood stabilization. Additionally, BHB acts as an endogenous histone deacetylase (HDAC) inhibitor, which might upregulate brain-derived neurotrophic factor (BDNF) expression and facilitate neurogenesis.

Conclusions: The KD is a promising neurometabolic intervention that may target underlying CNS pathomechanisms through mitochondrial optimization, anti-inflammatory effects, and epigenetic modifications. Despite encouraging initial reports, widespread implementation requires strict metabolic monitoring. Large-cohort randomized trials remain necessary before integrating ketogenic protocols into standard neuro-psychiatric treatment algorithms.

Keywords: ketogenic diet; β -hydroxybutyrate; metabolic psychiatry; Alzheimer's disease; bipolar disorder; neuroinflammation; neuroplasticity.

1. Introduction

Contemporary neurology and psychiatry, despite unprecedented advancements in psychopharmacology and molecular neurobiology, are facing a growing crisis related to treatment resistance in central nervous system (CNS) disorders. Pathologies such as bipolar disorder, schizophrenia, treatment-resistant depression (TRD), and progressive neurodegenerative diseases are characterized by a complex, multifactorial etiology where classic paradigms based solely on monoaminergic hypotheses or the amyloid cascade prove insufficient [1, 2]. This exhaustion of therapeutic options necessitates a redefinition of the clinical approach and a search for interventions targeting the fundamental bioenergetic processes of the brain. Within this context, the field of metabolic psychiatry is rapidly expanding, with the ketogenic diet (KD) taking center stage as an advanced, multimodal neurometabolic therapy [3, 4].

The historical use of dietary interventions in neurology dates back to antiquity, when fasting was employed to alleviate seizures. The modern era of ketogenic therapies began in 1921 when Rollin Turner Woodyatt discovered that the production of ketone bodies—analogueous to a state of fasting—could be achieved in individuals consuming an extremely low-carbohydrate and high-fat diet. Shortly thereafter, Russell Wilder of the Mayo Clinic coined the term "ketogenic diet" and successfully implemented this regimen in the treatment of pediatric epilepsy [5]. Despite its remarkable efficacy, the introduction of antiepileptic drugs (AEDs) in the mid-20th century marginalized the KD in medical practice. The method experienced a renaissance in the 1990s, ultimately consolidating the ketogenic diet's position in official guidelines as the treatment of choice for patients with pharmacoresistant epilepsy, as well as in specific metabolic defects such as glucose transporter type 1 deficiency syndrome (GLUT1 DS) and pyruvate dehydrogenase deficiency (PDHD) [6, 7, 8].

From a neurobiochemical perspective, a properly formulated ketogenic diet induces a state of physiological nutritional ketosis. This metabolic state is achieved through severe carbohydrate restriction (typically below 20–50 g per day), combined with a moderate protein intake carefully adjusted to lean body mass, and a high proportion of dietary fat [9]. Under conditions of critically low insulin and elevated glucagon levels, hepatocytes undergo enhanced beta-oxidation of fatty acids. The resulting surplus of acetyl-CoA is redirected into the ketogenesis pathway, producing three primary ketone bodies: acetoacetate (AcAc), β -hydroxybutyrate (BHB—the predominant and most stable metabolite), and volatile acetone [10]. A clear distinction must be drawn here between therapeutic nutritional ketosis and pathological diabetic ketoacidosis (DKA). In nutritional ketosis, blood ketone concentrations fluctuate within a safe range of 0.5–3.0 mmol/L (peaking at 5–7 mmol/L during prolonged fasting), and the body's buffering systems effectively maintain physiological blood pH. Conversely, during DKA—resulting from an absolute insulin deficiency (e.g., in uncontrolled type 1 diabetes)—ketone concentrations exceed 10–15 mmol/L, accompanied by glucotoxicity and a life-threatening drop in pH [9, 11].

Modern clinical practice utilizes several variations of the ketogenic diet, differing in their strictness and macronutrient ratios, which allows for the personalization of therapy based on patient tolerance [7]. The classic ketogenic diet (cKD) relies on a ketogenic ratio of 4:1 or 3:1 (the ratio of fat grams to the combined grams of protein and carbohydrates), necessitating the precise weighing of every meal and frequently requiring hospitalization during the induction phase in children. A significant breakthrough was the introduction of a diet based on medium-chain triglyceride (MCT) supplementation. Fatty acids such as caprylic acid (C8) are absorbed directly into the portal vein, bypassing the lymphatic system, and undergo rapid conversion to ketone bodies in the liver, independent of carnitine. This enables the generation of deep ketosis while simultaneously allowing for a more liberal allowance of carbohydrates and proteins in the diet [11]. In the treatment of adult neurological and psychiatric patients, the Modified Atkins Diet (MAD) and Low Glycemic Index Treatment (LGIT) are gaining increasing popularity. These variants demonstrate significantly improved adherence while maintaining a potent neuromodulatory potential [1, 7].

The transition from treating refractory epilepsy to applying the ketogenic diet in psychiatric disorders and neurodegenerative diseases stems from a deeper understanding of the pathophysiology of these conditions. Disorders such as Alzheimer's disease, Parkinson's disease, and schizophrenia share common, detrimental denominators: progressive glucose hypometabolism in specific brain regions, mitochondrial dysfunction, chronic neuroinflammation driven by microglial activation, and profound oxidative stress [2, 3, 12]. Ketone bodies, particularly β -hydroxybutyrate, are no longer viewed merely as an alternative rescue fuel for the nervous tissue. Contemporary scientific evidence indicates that BHB acts as an advanced signaling molecule capable of exerting epigenetic modifications, inhibiting inflammatory cascades, and directly regulating membrane receptors. This paper aims to critically analyze these unique, pleiotropic mechanisms in the context of their therapeutic potential for the most severe pathologies of the central nervous system.

2. Materials and methods

2.1. Study design

This paper was designed as a comprehensive narrative review, grounded in the rigorous principles of evidence-based medicine (EBM). Although the structure of the manuscript is narrative in nature, the process of literature collection, selection, and critical appraisal was conducted utilizing a systematic search strategy and rigorous methodological elements to ensure comprehensive and objective coverage of the topic. The primary objective of this study design was to minimize selection bias and ensure maximum objectivity in evaluating the therapeutic potential of the ketogenic diet in selected central nervous system disorders.

2.2. Literature search strategy

To identify current and reliable scientific evidence, an in-depth query of the largest and most reputable medical and interdisciplinary databases was conducted: PubMed/MEDLINE, Scopus, Web of Science

(Core Collection), and Google Scholar. The literature search encompassed publications released between January 1, 2010, and May 2026, allowing for the capture of the most recent literature from the period of the most dynamic development in metabolic psychiatry.

The search process was based on advanced algorithms utilizing Boolean logical operators (AND, OR, NOT) combined with the standardized Medical Subject Headings (MeSH) vocabulary. The following multilevel search strings were applied:

- Intervention domain: ("ketogenic diet" OR "ketosis" OR "beta-hydroxybutyrate" OR "BHB" OR "ketone bodies" OR "metabolic therapy" OR "very low-carbohydrate diet");
- Neurodegenerative disease domain: ("neurodegenerative diseases" OR "Alzheimer's disease" OR "AD" OR "Parkinson's disease" OR "PD" OR "neurodegeneration" OR "cognitive impairment");
- Psychiatric disorder domain: ("psychiatry" OR "bipolar disorder" OR "BD" OR "schizophrenia" OR "treatment-resistant depression" OR "TRD" OR "major depressive disorder" OR "mental illness").

Furthermore, to maximize search sensitivity, the snowballing method was employed. This involved manually screening the reference lists of key review articles, meta-analyses, and clinical guidelines to identify valuable publications that might have been omitted during the primary electronic search.

2.3. Inclusion and exclusion criteria

To guarantee the highest substantive quality of the included materials, rigorous inclusion and exclusion criteria were established for the final synthesis.

Inclusion criteria comprised:

1. Original randomized controlled trials (RCTs), cohort studies, case-control studies, and thoroughly documented case reports/case series involving patients diagnosed with psychiatric or neurodegenerative disorders who underwent a ketogenic diet protocol.
2. *In vivo* (animal model) and *in vitro* studies precisely elucidating the neurobiochemical pathways of ketone bodies (e.g., NLRP3 inflammasome inhibition, epigenetic modifications via HDAC inhibition, modulation of MCT transporters).
3. Meta-analyses and systematic literature reviews published in peer-reviewed scientific journals.
4. Papers published in English or Polish.
5. Studies assessing the state of ketosis using objective biomarkers (preferably capillary blood β -hydroxybutyrate concentration).

Exclusion criteria comprised:

1. Publications lacking peer-reviewed status, including articles from journals of questionable reputation (predatory journals), as well as preprints and conference abstracts without full-text availability.
2. Articles based solely on the authors' opinions, lacking grounding in EBM data.
3. Studies in which the dietary intervention was vague or poorly defined (e.g., patients reporting a "low-carbohydrate diet" with a concurrent lack of any serum, urine, or breath ketone measurements), thereby preventing the verification of physiological ketosis.
4. Studies in which the phenomenon of nutritional ketosis was erroneously equated with, or difficult to distinguish from, diabetic ketoacidosis.
- 5.

2.4. Data synthesis

Due to the significant heterogeneity of the included studies—encompassing variations in the applied diet models (e.g., classic ketogenic diet vs. modified Atkins diet), intervention duration, psychometric tools utilized (e.g., PANSS, PHQ-9, UPDRS scales), and studied populations—conducting a robust quantitative meta-analysis was not feasible. Therefore, a method of critical qualitative synthesis was employed.

The extracted data were subjected to thematic categorization and organized into logical, structured modules corresponding to the manuscript's architecture. In the first stage, data concerning the fundamental neurobiochemical pathways of ketone bodies were isolated and synthesized. Subsequently, the results of clinical studies were grouped and divided into specific nosological entities within neurodegenerative diseases (AD, PD) and psychiatric disorders (BD, schizophrenia, depression). During the synthesis of clinical results, particular attention was given to verifying the methodological rigor of the described studies. This included evaluating the degree of patient adherence to dietary recommendations, the methods of ketone body measurement, and the reported adverse effects, which enabled an objective assessment of the benefit-to-risk ratio of the discussed neurometabolic interventions.

3. Neurobiochemical basis of ketone body action in the CNS

3.1. The ketogenesis pathway and transport to the brain

The production of ketone bodies (ketogenesis) is a highly specialized metabolic process occurring almost exclusively within the mitochondrial matrix of hepatocytes. It is triggered in response to a profound reduction in blood glucose availability and a decrease in the insulin-to-glucagon ratio. This state, induced by a rigorous ketogenic diet (KD) or prolonged fasting, leads to a cascade of neuroendocrine changes, initiated by the activation of hormone-sensitive lipase (HSL) in adipose tissue. This enzyme catalyzes the hydrolysis of stored triglycerides into glycerol and non-esterified fatty acids (NEFA) [10].

Released into the bloodstream, long-chain fatty acids are transported in complexes with albumin to the liver, where they enter the hepatocyte cytosol and are activated to acyl-CoA. Because the inner mitochondrial membrane is impermeable to long-chain acyl-CoA derivatives, their transport into the mitochondrial matrix requires the carnitine shuttle. This process is controlled by the rate-limiting enzyme, carnitine palmitoyltransferase 1 (CPT-1), whose activity is markedly disinhibited under low-insulin conditions due to a decline in malonyl-CoA levels (the physiological inhibitor of CPT-1) [10]. On the inner side of the membrane, the CPT-2 enzyme regenerates acyl-CoA, which subsequently undergoes beta-oxidation, resulting in the massive generation of two-carbon acetyl-CoA molecules.

Under physiological conditions, acetyl-CoA enters the tricarboxylic acid (TCA) cycle (Krebs cycle) via condensation with oxaloacetate. However, during severe carbohydrate deprivation and enhanced gluconeogenesis, the hepatic pool of oxaloacetate becomes profoundly depleted, as it is redirected toward glucose synthesis to meet the obligatory demands of strictly glucose-dependent structures, such as erythrocytes. In the absence of oxaloacetate, the surplus of acetyl-CoA cannot enter the Krebs cycle and is obligatorily shunted into the ketogenesis pathway [10, 11].

The process of ketogenesis involves a strictly defined sequence of enzymatic reactions. Initially, the enzyme thiolase (acetyl-CoA acetyltransferase) catalyzes the condensation of two acetyl-CoA molecules into acetoacetyl-CoA. This is followed by the crucial, rate-limiting step of the entire pathway: 3-hydroxy-3-methylglutaryl-CoA synthase (HMGCS2)—an enzyme upregulated by the stimulation of the FOXA2 transcription factor and a decline in insulin levels—incorporates a third acetyl-CoA molecule to form HMG-CoA. Subsequently, HMG-CoA lyase cleaves this compound, releasing acetyl-CoA alongside the first primary ketone body, acetoacetate (AcAc) [13].

Acetoacetate can undergo spontaneous, non-enzymatic decarboxylation into volatile acetone (which is largely excreted via the lungs and, to a lesser extent, the kidneys, serving no significant metabolic function). Alternatively, and critically from a neurobiological perspective, it is reduced to β -

hydroxybutyrate (BHB) by the mitochondrial enzyme D- β -hydroxybutyrate dehydrogenase (BDH1). This reaction is dependent on the intramitochondrial NADH/NAD⁺ ratio. Given the high intensity of hepatic beta-oxidation during ketosis, this ratio remains elevated, driving the conversion of AcAc to BHB and establishing β -hydroxybutyrate as the quantitatively dominant metabolite (often reaching a blood ratio of 4:1 or even 5:1 relative to acetoacetate) [10, 13].

To harness the neuroprotective and energetic potential of ketone bodies, they must safely and efficiently penetrate from the bloodstream into the central nervous system (CNS). Although these molecules are water-soluble, at a physiological blood pH (7.35–7.45), they exist as charged anions (the pK_a for BHB is 4.7). Consequently, their capacity for passive diffusion across the lipophilic blood-brain barrier (BBB) is highly restricted. Their cellular and transcellular transport is mediated by a family of specialized proton symporters known as monocarboxylate transporters (MCTs), encoded by genes of the *SLC16* family [14].

This transport relies on a precisely organized arrangement of isoforms [13, 14]:

1. MCT1 (encoded by the *SLC16A1* gene): Strongly expressed on the capillary endothelial cells comprising the BBB, as well as on the surface of astrocytes. It serves as the primary "entry gate" for BHB and AcAc into the CNS interstitial space.
2. MCT2 (encoded by the *SLC16A7* gene): Exhibits the highest affinity (the lowest K_m) for β -hydroxybutyrate among all isoforms. It is localized almost exclusively on neuronal cell membranes, enabling them to exceptionally efficiently and rapidly uptake BHB from the extracellular space, even at relatively low cerebrospinal fluid concentrations.
3. MCT4 (encoded by the *SLC16A3* gene): Found predominantly on astrocytes, it is characterized by a relatively low affinity for ketones but a high transport capacity for lactate. It may play a supportive role in the metabolic model known as the astrocyte-neuron lactate shuttle (ANLS).

A clinically significant phenomenon in the context of adaptation to the ketogenic diet is transporter plasticity. Initially, the brain, fully adapted to glycolysis, exhibits a relatively slow uptake of ketones. However, chronic exposure to elevated blood concentrations of BHB and AcAc during strict adherence to the KD leads to robust upregulation—an increase in gene expression and protein density of MCT1 on endothelial cells and MCT2 on neurons. This process multiplies the efficiency of ketone body uptake and utilization as a dominant energy substrate (capable of meeting up to 60–70% of the human brain's total energy requirements), thereby mitigating the energy deficits resulting from the neuronal insulin resistance typical of neurodegenerative processes [1, 14].

3.2. The ketone energy pathway and optimization of mitochondrial bioenergetics

Upon crossing the blood-brain barrier and the cell membranes of target neurons and astrocytes via MCT transporters, ketone bodies are rapidly internalized into the mitochondrial matrix, where they become a highly preferential respiratory substrate. The process of intracellular ketone body catabolism (ketolysis) is significantly more direct and thermodynamically efficient than multistep cytosolic glycolysis. Understanding the energetic superiority of ketosis requires a detailed analysis of the enzymatic pathway that profoundly modifies the efficiency of oxidative phosphorylation (OXPHOS) [10, 13].

The process of ketolysis in the central nervous system proceeds in three tightly coupled enzymatic stages:

1. **Oxidation of β -hydroxybutyrate:** The initial step is the conversion of β -hydroxybutyrate (BHB) back to acetoacetate (AcAc). This reaction is catalyzed by mitochondrial D- β -hydroxybutyrate dehydrogenase (BDH1). During this reaction, a molecule of NAD⁺ is reduced to NADH. The resulting reducing equivalent directly fuels complex I of the respiratory chain, generating a proton gradient at the very beginning of the pathway, which drives the synthesis of approximately 2.5 ATP molecules [10].
2. **Activation of acetoacetate:** Subsequently, AcAc must be activated to a form capable of entering the tricarboxylic acid (TCA) cycle. This is mediated by a specific enzyme: succinyl-

CoA:3-ketoacid coenzyme A transferase (SCOT, encoded by the *OXCT1* gene). This reaction involves the transfer of a coenzyme A (CoA) moiety from succinyl-CoA to acetoacetate, resulting in the formation of acetoacetyl-CoA and free succinate. This is a critical point in the pathway for two reasons. First, transferring the CoA moiety from a Krebs cycle intermediate allows for the thermodynamically "free" activation of the ketone, bypassing the need for intracellular ATP consumption (a mandatory step in fatty acid activation, for instance). Second, the *OXCT1* gene is not expressed in the liver. The absence of the SCOT enzyme in hepatocytes is an evolutionary safeguard preventing a "futile cycle"—the liver is the sole producer of ketone bodies, but lacking SCOT, it cannot consume them, obligating their export to peripheral tissues and the CNS [4, 13].

3. **Thiolytic cleavage:** In the final step, intramitochondrial acetoacetyl-CoA thiolase (ACAT1) catalyzes the reversible cleavage of acetoacetyl-CoA with the participation of an additional free coenzyme A molecule. This process yields two separate acetyl-CoA molecules, which immediately enter the Krebs cycle, condensing with oxaloacetate to form citrate [10].

This architecture of the ketolytic pathway confers unprecedented bioenergetic benefits, meticulously described by Richard Veech in his seminal works on the thermodynamics of ketone bodies. The oxidation of BHB in neurons increases the intracellular redox potential within mitochondria. The pool of reduced coenzyme Q (CoQH₂) expands, while simultaneously widening the NAD⁺/NADH ratio in both the cytosol and the mitochondrial matrix [4].

From a physiological standpoint, deriving energy from ketone bodies increases the free energy (Gibbs energy) of ATP hydrolysis by approximately 25-27% compared to glucose oxidation alone (an increase from roughly -47 kJ/mol to over -56 kJ/mol). A ketone-fueled brain thus possesses ATP with a substantially higher thermodynamic potential to drive crucial ion pumps—including the sodium-potassium pump (Na⁺/K⁺-ATPase), which is absolutely critical for neuronal survival, as well as calcium pumps. This directly stabilizes resting membrane potentials and prevents calcium influx-induced neurotoxicity [4, 15]. Furthermore, ketolysis is characterized by a higher P/O ratio (the ratio of ATP molecules produced per oxygen atom consumed). This implies that ketone-metabolizing mitochondria generate more usable energy while simultaneously reducing oxygen consumption and markedly curtailing the emission of reactive oxygen species (ROS), thereby mitigating electron "leakage" from complexes I and III of the respiratory chain [10, 16].

In the context of CNS pathology, the most unique feature of the ketone energy pathway is its capacity to completely bypass carbohydrate metabolism "bottlenecks". Complex neurodegenerative diseases and certain psychiatric disorders strongly correlate with diminished glucose transport across the blood-brain barrier (GLUT1 hypofunction) and the downregulation of GLUT3 on neurons. Moreover, these conditions frequently feature progressive failure of cytosolic pyruvate kinase and impairment of the multi-enzyme pyruvate dehydrogenase complex (PDHC), which bridges glycolysis with the Krebs cycle [16].

Because ketone bodies are directly converted to acetyl-CoA within the matrix, circumventing both the glycolytic steps and the PDHC complex, the state of ketosis effectively bypasses these blocked pathways. It delivers highly efficient ("high-octane") fuel directly to the TCA cycle, effectively extinguishing the neuronal energy deficit and rescuing cells from substrate starvation-induced apoptosis. This mechanism is termed "metabolic rescue" and constitutes the physiological foundation of the ketogenic diet's neuroprotective action [3, 16].

4. Pleiotropic neuroprotective and psychotropic mechanisms

4.1. Modulation of neurotransmitter systems

The disruption of homeostasis between excitatory and inhibitory neurotransmission constitutes a fundamental pathomechanism underlying the majority of central nervous system disorders. Excitotoxicity, resulting from the excessive activation of glutamate receptors (particularly NMDA and AMPA subtypes) and a massive influx of calcium ions into neurons, directly induces apoptotic pathways and serves as a key vector of degeneration in Alzheimer's disease, Parkinson's disease, and epilepsy.

Conversely, a deficit in inhibitory signaling (primarily within the gamma-aminobutyric acid [GABA] system) strongly correlates with the pathogenesis of schizophrenia, bipolar disorder, and anxiety states [2, 12, 17]. Ketone bodies, specifically β -hydroxybutyrate (BHB) and acetoacetate (AcAc), are no longer viewed merely as passive energy substrates; rather, they have gained recognition as active neuromodulators capable of the multilevel tuning of synaptic activity [15].

A pivotal mechanism through which the ketogenic diet (KD) modifies neuronal network balance is the direct rearrangement of amino acid metabolism, leading to a significant increase in the concentration of inhibitory GABA in the synaptic cleft, with a concomitant reduction in the pool of excitotoxic glutamate. This phenomenon stems directly from alterations within the mitochondrial tricarboxylic acid (TCA) cycle. The massive influx of acetyl-CoA derived from ketolysis mandates its condensation with oxaloacetate to form citrate. This results in a profound depletion of the intracellular pool of free oxaloacetate. Under physiological conditions, oxaloacetate is an essential cosubstrate for aspartate aminotransferase (AST), an enzyme that converts glutamate into aspartate (an excitatory amino acid). The reduced availability of oxaloacetate during ketosis inhibits this transamination reaction, thereby preventing the loss of glutamate to aspartate. Instead, the accumulated glutamate becomes a highly accessible substrate for glutamic acid decarboxylase (GAD). This facilitates an intensified conversion of glutamate to GABA, constituting the most potent endogenous mechanism for elevating the seizure threshold and stabilizing hyperactive neuronal networks within the limbic system [15, 18].

Independent of stimulating GABA synthesis, ketone bodies exhibit the capacity for presynaptic inhibition of glutamate release. Studies on synaptic vesicle architecture demonstrate that acetoacetate structurally and electrochemically mimics chloride ions (Cl^-). In synaptic vesicles, glutamate is stored via vesicular glutamate transporters (VGLUTs), the activity of which is strictly dependent on intracellular chloride concentrations. It has been shown that AcAc competitively binds to the allosteric chloride site on VGLUT transporters, markedly reducing their throughput. Consequently, when presynaptic vesicles fuse with the cell membrane, they release a substantially smaller quantal amount of glutamate into the synaptic cleft. This directly mitigates excitotoxicity without impairing the basal neurotransmission requisite for cognitive functions [15, 17].

Another critically important aspect is the impact of ketosis on glial interactions, specifically the glutamate-glutamine shuttle between astrocytes and neurons. Astrocytes play a critical role in clearing the synaptic cleft of excess released glutamate (via excitatory amino acid transporters, EAATs). Within astrocytes, glutamate is converted into neutral glutamine by the enzyme glutamine synthetase. The ketogenic diet significantly upregulates the expression of monocarboxylate transporters on astrocytes, amplifying their energy metabolism. The highly efficient, ketone-driven operation of astrocytic mitochondria facilitates the more robust utilization of extracellular glutamate and its accelerated recycling into glutamine, further lowering the concentration of this excitatory neurotransmitter in the cerebrospinal fluid of patients in deep ketosis [15, 18].

Beyond the glutamate-GABA axis, the pleiotropic nature of ketogenic interventions manifests through robust modulation of the purinergic system. As previously established, ketolysis results in a surge of intracellular ATP production. A substantial fraction of this surplus ATP is co-released alongside neurotransmitters into the synaptic cleft. In the extracellular space, membrane ecto-nucleotidases rapidly hydrolyze ATP into adenosine. In the CNS, adenosine serves as a potent endogenous neuromodulator with neuroprotective and anticonvulsant properties. By binding to presynaptic A1 adenosine receptors, it induces cell membrane hyperpolarization, blocks the opening of voltage-dependent calcium channels (VDCCs), and secondarily inhibits the release of excitatory neurotransmitters. Moreover, the alteration of the intracellular ATP/ADP ratio induced by ketone bodies leads to the activation of specific ATP-sensitive potassium channels (KATP) located in the substantia nigra and hippocampus. This stabilizes the resting membrane potential and significantly impedes the generation of pathological spike discharges in patients with affective and neurodegenerative disorders [12, 17].

4.2. Mitigation of neuroinflammation as a disease-modifying mechanism

Chronic, sterile neuroinflammation, driven by the excessive and prolonged activation of resident central nervous system immune cells—particularly microglia and astrocytes—currently constitutes one of the

key pathogenetic vectors driving the progression of neurodegenerative diseases (AD, PD) and perpetuating cognitive deficits and negative symptoms in severe psychiatric disorders [2, 3]. This phenomenon is characterized by a sustained shift in microglial polarization from the neuroprotective M2 phenotype to the neurotoxic, proinflammatory M1 phenotype, resulting in the massive and uncontrolled release of cytokines, chemokines, and free radicals into the neuronal microenvironment. From a molecular perspective, β -hydroxybutyrate (BHB) transcends its classical role as a high-energy substrate, acting as a highly specific, endogenous signaling molecule (signaling metabolite) that robustly interferes with inflammatory signal transduction pathways [12, 19].

The most groundbreaking and well-documented anti-inflammatory mechanism of ketone bodies is the direct inhibition of the intracellular multiprotein complex—the NLRP3 (NOD-like receptor family, pyrin domain containing 3) inflammasome. This inflammasome is a pivotal component of innate immunity, and its chronic hyperactivation in the brain is indisputably linked to the formation of amyloid plaques, alpha-synuclein aggregation, and the kindling phenomenon in bipolar disorder [2]. Activation of NLRP3 is a two-step process: the first step (priming) requires the stimulation of Toll-like receptors (e.g., TLR4) and the nuclear transcription factor NF- κ B, which leads to the transcription of inactive cytokine precursors. The second step (activation proper) is triggered by cellular stressors, such as the efflux of potassium ions (K^+) from the cell, the production of reactive oxygen species (ROS) from damaged mitochondria, or the presence of phagocytosed amyloid-beta. Full activation induces the oligomerization of the adaptor protein ASC and the recruitment of pro-caspase-1, which undergoes autocatalytic cleavage into active caspase-1. Caspase-1, in turn, cleaves pro-IL-1 β and pro-IL-18 into their biologically active, highly proinflammatory forms, which are secreted into the extracellular space, initiating the inflammatory cascade and apoptosis (pyroptosis) [3, 19].

Studies conducted by Youm and colleagues have conclusively demonstrated that BHB, at concentrations achieved during physiological nutritional ketosis (1 to 3 mmol/L), directly and selectively inhibits the activation of the NLRP3 inflammasome [19]. β -hydroxybutyrate blocks the ASC protein oligomerization step and prevents the formation of ASC specks, entirely precluding caspase-1 activation. This phenomenon results in a marked, clinically corroborated decrease in the concentrations of interleukin-1 beta (IL-1 β) and interleukin-18 (IL-18) in the cerebrospinal fluid and serum. Of profound physiological significance is the fact that BHB exclusively inhibits the NLRP3 inflammasome without disrupting the function of other inflammasomes (such as NLRC4 or AIM2). This implies that the ketogenic diet precisely extinguishes sterile neuroinflammation without inducing systemic immunosuppression or impairing the body's capacity to combat actual pathogens [19].

Another parallel signaling pathway through which the state of ketosis modulates neuroinflammation is the activation of the G protein-coupled receptor HCA2 (hydroxycarboxylic acid receptor 2), also known as GPR109A. This receptor is highly expressed on microglial cells and peripheral macrophages infiltrating the nervous tissue under inflammatory conditions [18]. β -hydroxybutyrate is the principal physiological endogenous ligand for GPR109A. The binding of BHB to this receptor on the surface of glial cells induces an intracellular cascade leading to the profound inhibition of the NF- κ B transcription factor. The consequence of this phenomenon is the transcriptional arrest of a whole plethora of genes encoding inflammatory mediators, including inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and tumor necrosis factor-alpha (TNF- α) [12, 18].

Furthermore, this phenomenon possesses a robust immunometabolic component. To sustain its pathological functions, activated, proinflammatory microglia (M1) must drastically increase glucose uptake, shifting toward the metabolic pathway of enhanced aerobic glycolysis (the so-called Warburg effect) and turning away from efficient oxidative phosphorylation. The ketogenic diet, by cutting off the carbohydrate supply and compelling the derivation of energy from ketone bodies that directly fuel the mitochondria, "starves" this proinflammatory glycolytic pathway. The bioenergetic reprogramming from glycolysis to ketolysis within immune cells forcefully compels microglia to adopt the M2 phenotype, the function of which is strictly dependent on oxidative phosphorylation and intact mitochondria. Consequently, microglia regain their natural phagocytic functions, becoming capable of effectively clearing cellular debris and misfolded proteins, which is a *conditio sine qua non* for symptom remission in CNS degenerative processes [2, 3].

4.3. Reduction of oxidative stress and improvement of mitochondrial function

The central nervous system (CNS), due to its disproportionately high metabolic activity, consumes approximately 20% of the body's total oxygen pool while constituting a mere 2% of its mass. Oxidative phosphorylation (OXPHOS) in neurons, although highly efficient for ATP generation, carries the inevitable risk of the so-called "electron leak" phenomenon. Under physiological conditions, 1% to 2% of the oxygen reduced in mitochondria undergoes premature, one-electron reduction—primarily at complex I (NADH:ubiquinone oxidoreductase) and complex III (ubiquinol:cytochrome c oxidoreductase) of the respiratory chain. This process generates the highly reactive superoxide anion radical, which initiates the oxidative stress cascade. Given the high content of polyunsaturated fatty acids (PUFAs) in neuronal membranes, the relatively low activity of the brain's endogenous antioxidant systems compared to the liver, and the weak repair mechanisms of mitochondrial DNA (mtDNA), chronic oxidative stress constitutes a driving force behind the pathomechanisms of Alzheimer's disease, Parkinson's disease, and neurodegenerative processes secondary to severe affective episodes [2, 18].

The implementation of the ketogenic diet and the resultant elevation in β -hydroxybutyrate (BHB) concentration not only provide an alternative fuel but also physically and structurally optimize the function of mitochondrial machinery, profoundly reducing the production of reactive oxygen species (ROS) while simultaneously reinforcing intracellular antioxidant buffers [10, 12].

The first, strictly thermodynamic mechanism of oxidative stress reduction stems from the unique characteristics of ketolysis. As demonstrated by Veech's classical studies, the oxidation of BHB to acetoacetate within the mitochondrial matrix significantly broadens the NAD^+/NADH ratio and increases the intramitochondrial pool of reduced coenzyme Q (CoQH_2) [4]. This altered redox potential within the matrix optimizes electron flow through the proteins of the respiratory chain. The smoother and thermodynamically more favorable passage of electrons from complexes I and II to coenzyme Q prevents the excessive reduction of electron carriers. This phenomenon directly addresses the root cause of electron "leakage", drastically diminishing the formation of the superoxide anion radical at its very source, without concomitantly impairing the proton gradient required for ATP synthesis [4, 10].

A second, critically important neuroprotective pathway of ketosis is the induced upregulation of neuronal uncoupling proteins (UCPs), with particular emphasis on the UCP2, UCP4, and UCP5 isoforms, which are highly expressed in nervous tissue. In the presence of ketone body supply and free fatty acids, the expression of the genes encoding these proteins is stimulated [2, 18]. UCPs localize to the inner mitochondrial membrane and function as proton channels, enabling a controlled, gentle return of protons (H^+) from the intermembrane space to the matrix, bypassing ATP synthase. This process, termed mild uncoupling, leads to a marginal and bioenergetically entirely safe reduction of the mitochondrial membrane potential ($\Delta\Psi\text{m}$). According to the non-linear laws of mitochondrial bioenergetics, even a fractional drop in $\Delta\Psi\text{m}$ (by a mere 10–15%) exponentially decreases the half-life of reduced intermediates in the respiratory chain, resulting in a profound (up to 50–70%) inhibition of reactive oxygen species synthesis [3, 18].

The third pillar of the antioxidant response is genetic in nature and is predicated on the direct activation of the Nrf2 (Nuclear factor erythroid 2-related factor 2) transcription factor. Under homeostatic conditions, Nrf2 is sequestered in the cytosol by the inhibitor protein Keap1 and undergoes continuous ubiquitination and proteasomal degradation. It has been demonstrated that BHB (acting as a signaling molecule, *inter alia*, through its effect on histone deacetylases) facilitates the dissociation of the Nrf2-Keap1 complex. The liberated Nrf2 translocates to the cell nucleus, where it dimerizes with Maf proteins and binds to specific Antioxidant Response Elements (ARE) in the promoters of protective genes [12, 20].

The transcriptional activation of the Nrf2/ARE pathway by ketone bodies yields a robust overexpression of key endogenous detoxifying enzymes. These include:

- Superoxide dismutase 2 (SOD2 / MnSOD): the principal enzyme of the mitochondrial matrix, converting the superoxide anion radical into hydrogen peroxide.

- Catalase (CAT) and glutathione peroxidase (GPx): enzymes responsible for neutralizing hydrogen peroxide into a safe water molecule.
- Heme oxygenase-1 (HO-1): a highly cytoprotective enzyme that degrades pro-oxidant heme into biliverdin (a potent antioxidant) and carbon monoxide, which possesses vasodilatory and anti-inflammatory properties [18, 20].

Particular attention in the context of ketosis should be directed toward the metabolism of glutathione (GSH)—the most important low-molecular-weight antioxidant buffer in the brain. Through the Nrf2 axis, β -hydroxybutyrate directly increases the expression of glutamate-cysteine ligase (GCL)—the rate-limiting enzyme in *de novo* glutathione synthesis. Furthermore, by bypassing glycolysis and unburdening cytosolic carbohydrate metabolism, the ketogenic diet redirects any residual intracellular glucose into the pentose phosphate pathway. The heightened activity of this pathway generates an excess of reduced nicotinamide adenine dinucleotide phosphate (NADPH), which is an absolutely indispensable cofactor for glutathione reductase. This enzyme continuously regenerates active, reduced glutathione (GSH) from its oxidized, disulfide form (GSSG). The maintenance of a high GSH/GSSG ratio induced by ketogenic intervention constitutes one of the most formidable known barriers protecting nervous system cells from irreversible structural damage and the induction of cell death pathways [2, 4, 20].

4.4. Epigenetic changes and neuroplasticity

A paradigm shift in the perception of ketone bodies, with particular emphasis on β -hydroxybutyrate (BHB), from passive energy substrates to highly active endogenous epigenetic modifiers, represents one of the most crucial discoveries in contemporary neurobiology. Epigenetics in the central nervous system (CNS) refers to potentially reversible, heritable alterations in gene expression that occur without altering the underlying nucleotide sequence of DNA. The dysregulation of epigenetic mechanisms, leading to the pathological silencing of neuroprotective genes, lies at the very core of brain structure atrophy in Alzheimer's disease and is also responsible for structural alterations in hippocampal architecture in patients suffering from severe, treatment-resistant depression and schizophrenia [2].

The principal mechanism through which the state of nutritional ketosis accomplishes a profound transcriptional reprogramming of neurons is the direct inhibition of histone deacetylases (HDACs). Under conditions of physiological homeostasis, chromatin structure is dynamically regulated by two opposing enzymatic systems: histone acetyltransferases (HATs) and the aforementioned deacetylases (HDACs). DNA, bearing a strong negative charge (derived from phosphate groups), is tightly wrapped around octamers of histone proteins, the tails of which are rich in positively charged lysine residues. HDAC enzymes remove acetyl groups from these lysine residues, restoring their positive charge, which results in a strong electrostatic interaction between histones and DNA. This leads to the condensation of chromatin into a highly compacted, transcriptionally inactive form known as heterochromatin, thereby physically obstructing RNA polymerase's access to gene promoters [20].

Groundbreaking research by Shimazu and colleagues [20] unequivocally demonstrated that BHB at physiological concentrations (in the range of 1–2 mmol/L, characteristic of the ketogenic diet) acts as a potent, endogenous, and competitive inhibitor of class I and class IIa histone deacetylases (with a particular affinity for HDAC2 and HDAC3). The blockade of HDAC enzymes by β -hydroxybutyrate shifts the balance robustly in favor of acetyltransferases (HATs). A massive hyperacetylation of lysine residues ensues (e.g., at positions H3K9 and H3K14), neutralizing their positive charge. The consequence is the relaxation of the chromatin structure and its transition into the transcriptionally active euchromatin form. This phenomenon is termed epigenetic derepression [2, 20]. Furthermore, recent studies indicate that BHB can directly participate in a novel, recently identified post-translational histone modification: lysine β -hydroxybutyrylation (Kbhb). This process occurs independently of acetylation and further amplifies the activation of promoters for genes involved in cellular adaptation to severe metabolic stress [21].

Clinically and neurobiologically, the most significant beneficiary of this epigenetic derepression is the gene encoding brain-derived neurotrophic factor (BDNF). In the course of chronic stress, chronic

inflammation, or neurodegenerative pathologies, the *Bdnf* gene promoter undergoes profound silencing via histone deacetylation. It has been shown that HDAC inhibition via ketogenic intervention precisely opens the chromatin in the region of the *Bdnf* promoter IV. This results in an exponential surge in the synthesis of this pivotal neurotrophic protein in the cerebral cortex and, critically for psychiatry, in the hippocampus [22].

The neurotrophic cascade initiated by BDNF forms the foundation of neuroplasticity. The synthesized BDNF is secreted into the extracellular space and binds to its specific receptor endowed with tyrosine kinase activity—TrkB (Tropomyosin receptor kinase B). The activation of TrkB triggers two fundamental intracellular signaling pathways:

1. The PI3K/Akt pathway (Phosphatidylinositol 3-kinase / Protein kinase B): This is the principal anti-apoptotic pathway that promotes neuronal survival by inhibiting cell death cascades induced by oxidative stress and excitotoxicity [2].
2. The MAPK/ERK pathway (Mitogen-activated protein kinases): This directly stimulates the local translation of synaptic proteins stored as mRNA within dendrites. This process promotes the structural growth (arborization) of the dendritic tree, as well as the formation and maturation of new dendritic spines, providing the physical substrate for the formation of new memory traces [23].

The significance of this cascade is paramount. In light of the neurogenic hypothesis of depression, the primary cause of persistent affective symptoms is the loss of the hippocampus's capacity to generate new neurons. Ketogenic stimulation of the BHB/HDAC/BDNF axis robustly upregulates the process of adult neurogenesis within the subgranular zone (SGZ) of the hippocampal dentate gyrus [2, 22]. The newly generated, highly plastic neurons integrate into existing networks, conditioning the improvement of cognitive functions and the flexibility of emotional responses. Furthermore, the diet-induced elevation in BDNF directly lowers the threshold for generating long-term potentiation (LTP)—the electrophysiological substrate of learning and memory consolidation processes. This establishes the KD as an intervention with proven potential in halting the progression of mild cognitive impairment (MCI) toward full-blown dementia [2, 20, 22].

5. Application of the ketogenic diet in neurodegenerative diseases

5.1. Alzheimer's disease (AD) as "type 3 diabetes"—overcoming neuronal insulin resistance

For decades, the amyloid cascade hypothesis remained the dominant paradigm in the pathophysiology of Alzheimer's disease (AD), positing that the extracellular aggregation of pathological amyloid-beta (A β) peptides and intracellular tangles of hyperphosphorylated Tau protein constituted the primary cause of neuronal death. However, consecutive clinical trial failures involving monoclonal antibodies directed against amyloid deposits have compelled a reevaluation of this framework. Contemporary neurobiology increasingly emphasizes that protein aberrations are secondary to a progressive, long-standing bioenergetic crisis within the brain. This observation has culminated in the formulation of a hypothesis designating Alzheimer's disease as "type 3 diabetes" [16, 24].

The foundation of this concept rests on a documented, brain-specific insulin resistance. In AD patients, the insulin receptor signaling cascade is severely impaired, manifesting as the pathological hyperphosphorylation of insulin receptor substrate 1 (IRS-1) at serine residues rather than tyrosine residues. This signaling blockade precludes the proper translocation of glucose transporters (particularly insulin-dependent GLUT4 in the hippocampus) to the cell membrane. Furthermore, a global downregulation of the endothelial GLUT1 and neuronal GLUT3 transporters is observed. Consequently, the nervous tissue's capacity to uptake and metabolize glucose experiences a precipitous decline. Advanced neuroimaging studies utilizing fluorodeoxyglucose positron emission tomography (FDG-PET) unequivocally demonstrate that regional glucose hypometabolism—initially encompassing the parietotemporal cortex and the posterior cingulate gyrus—precedes the onset of the first clinical symptoms of dementia by 10 to even 20 years [16].

In the face of such a profound energetic deficit, an intervention utilizing the ketogenic diet (KD) represents an exceptionally elegant "metabolic rescue" strategy. The protective potential of the KD stems from the unique pharmacokinetics of ketone bodies. β -hydroxybutyrate (BHB) and acetoacetate (AcAc) do not rely on the GLUT transporters that are dysfunctional in AD; instead, they readily cross the blood-brain barrier via monocarboxylate transporters (MCTs). Crucially for the disease pathomechanism, both the intracellular uptake of ketones by neurons and their subsequent mitochondrial ketolysis proceed in a completely insulin-independent manner [24]. Studies utilizing carbon isotopic tracers (^{11}C -acetoacetate PET) have demonstrated that in patients with early-stage AD, whose capacity for glucose utilization had dropped by several dozen percent, the uptake and metabolism of ketone bodies remained entirely intact and comparable to those of age-matched healthy volunteers [16].

Beyond restoring bioenergetic homeostasis, ketogenesis directly interferes with the cascades leading to the aggregation of pathological proteins. Oxidative stress and ATP deficiency are potent stimulators of glycogen synthase kinase 3β (GSK- 3β)—the enzyme responsible for the pathological hyperphosphorylation of Tau protein, which leads to the destruction of neuronal microtubules. Ketosis, by optimizing respiratory chain efficiency and generating a larger ATP pool at a reduced oxygen cost, physiologically inhibits GSK- 3β overactivity, thereby stabilizing the cytoskeleton [3]. Furthermore, BHB, through the previously discussed blockade of the NLRP3 inflammasome in microglia, prevents the release of proinflammatory cytokines that physiologically promote the amyloidogenic cleavage of amyloid precursor protein (APP) by β - and γ -secretases. The enhanced energetic profile of microglia also favors their repolarization toward the M2 phenotype, which amplifies the phagocytosis of pre-existing amyloid plaques [3].

The translation of these molecular mechanisms into clinical efficacy is reflected in an increasing number of randomized controlled trials (RCTs) involving human subjects. In a study by Krikorian and colleagues conducted on individuals with mild cognitive impairment (MCI)—a clinical precursor to AD—a mere 6-week intervention based on carbohydrate restriction yielded a measurable improvement in verbal memory recall. The authors demonstrated a strong, positive correlation between blood ketone concentrations and the improvement of cognitive functions [25]. Furthermore, a study by Taylor et al. provided robust evidence that even a rigorous ketogenic diet protocol is highly feasible in patients diagnosed with mild to moderate Alzheimer's disease. The achievement of sustained nutritional ketosis in this cohort resulted in a clinically significant improvement on the ADAS-cog (Alzheimer's Disease Assessment Scale-Cognitive Subscale), confirming that the metabolic resynchronization of the CNS constitutes a potent and safe tool capable of modifying the trajectory of this hitherto incurable disease [26].

5.2. Parkinson's disease (PD) – compensation of mitochondrial deficits and neuromodulation of the nigrostriatal system

Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by a progressive and irreversible course. Its classical pathomorphological substrate is the selective degeneration and loss of dopaminergic neurons within the *substantia nigra pars compacta* (SNpc) and the presence of eosinophilic, intracellular aggregates of pathologically misfolded alpha-synuclein, known as Lewy bodies. Although dopamine substitution therapy (levodopa) alleviates motor symptoms in the early stages of the disease, it fails to halt progressive neurodegeneration and over time leads to debilitating motor complications, such as dyskinesias [2]. In the search for disease-modifying therapies, contemporary neurobiology has focused on the primary causes of dopaminergic neuron death, wherein ketogenic interventions find robust mechanistic justification [12].

A fundamental element of PD pathogenesis, which underpins the metabolic treatment paradigm, is profound mitochondrial bioenergetic dysfunction. In both sporadic and genetically determined forms of the disease (e.g., mutations in the *PARK2*, *PINK1*, and *LRRK2* genes), a pathological, diminished activity of respiratory chain complex I (NADH:ubiquinone oxidoreductase) is observed. The blockade at the level of complex I causes a massive electron "leak" and the generation of extreme quantities of reactive oxygen species (ROS), which damage vulnerable lipid membranes, proteins, and mitochondrial DNA (mtDNA). This phenomenon drastically reduces ATP production. In the case of the highly energy-demanding substantia nigra neurons, which possess extensive axonal arborization, this leads to the

inevitable failure of ion pumps, cell membrane depolarization, and the induction of the intrinsic apoptotic pathway [2, 3].

The ketogenic diet intervenes in this destructive cascade through a phenomenon termed "metabolic bypass." The catabolism of β -hydroxybutyrate (BHB) within the mitochondrial matrix supplies acetyl-CoA directly to the tricarboxylic acid cycle, circumventing glycolysis and potential pyruvate dehydrogenase (PDH) complex deficits. Most crucially for PD pathophysiology, however, although the oxidation of ketone bodies still utilizes complex I (via NADH generation), the concomitant rewiring of cellular metabolism stimulates an increased electron flux through complex II (succinate dehydrogenase). This results directly from the enhanced production of succinate during the activation of acetoacetate by the SCOT enzyme. The increased activity of complex II allows for a partial bypass of the blocked complex I and sustains electron transfer to coenzyme Q. This mechanism restores efficient ATP production, protects against the collapse of the mitochondrial membrane potential, and halts the pathological release of proapoptotic cytochrome c from the intermembrane space into the cytosol [2, 12].

Concurrently, ketosis exerts a profound impact on intracellular protein homeostasis (proteostasis), which is critical in the context of alpha-synuclein aggregation. The radical restriction of carbohydrate intake leads to a decline in insulin and insulin-like growth factor 1 (IGF-1) concentrations, resulting in reduced activity of the mTOR (mechanistic target of rapamycin) kinase pathway. The inhibition of mTOR, coupled with the activation of AMP-activated protein kinase (AMPK)—resulting from the transient fluctuation in the ATP/AMP ratio during adaptation to ketosis—constitutes the most potent known signal inducing macroautophagy. In dopaminergic neurons, this process amplifies the vacuolar degradation of misfolded alpha-synuclein, preventing its oligomerization and deposition as toxic Lewy bodies. Simultaneously, a specific type of autophagy—mitophagy (often impaired in PD patients)—is upregulated. This enables the selective removal of damaged, pro-oxidant mitochondria and their replacement with new units (a phenomenon of mitochondriogenesis stimulated by PGC-1 α) [3].

The previously described anti-inflammatory potential remains equally significant. The course of PD involves the chronic activation of resident microglia within the striatum and SNpc, frequently initiated by phagocytosed extracellular alpha-synuclein deposits. By inhibiting the assembly of the NLRP3 inflammasome complex, β -hydroxybutyrate directly abrogates the release of interleukin-1 β (IL-1 β), thereby extinguishing chronic neuroinflammation and shielding the surviving neurons from secondary damage [2].

The efficacy of the aforementioned biomolecular cascades finds robust confirmation in randomized controlled trials (RCTs). A landmark study conducted by Phillips and colleagues (2018) analyzed Parkinson's disease patients assigned to a low-fat diet group and a strict ketogenic diet group. After an 8-week intervention, both groups exhibited some improvement in motor symptoms; however, a fundamental difference emerged regarding non-motor symptoms (NMS). The group subjected to ketosis demonstrated a highly statistically and clinically significant reduction in the MDS-UPDRS (Part I) score, encompassing improvements in mood disorders (depression, anxiety), cognitive functions, and sleep quality, alongside a reduction in symptoms of dysautonomia (e.g., thermoregulatory or bowel motility disturbances) [27]. These findings demonstrate that the ketogenic diet acts systemically in PD, repairing the bioenergetic architecture not only within the nigrostriatal pathway but across extensive neuronal networks of the brainstem, cortex, and limbic system.

6. The ketogenic diet in the treatment of psychiatric disorders

6.1. Bipolar disorder (BD) – normothymic mechanisms and limbic system stabilization

Bipolar disorder (BD) is among the most severe, chronic psychiatric conditions, characterized by cyclic aberrations in mood, psychomotor drive, and cognitive functions, oscillating between episodes of mania (or hypomania) and profound depression. Contemporary biological psychiatry views BD as a neuroprogressive disease, in which each subsequent affective episode exerts a neurotoxic effect, increasing the brain's allostatic load, exacerbating cognitive deficits, and shortening periods of euthymia. Treatment resistance in BD, particularly in rapid cycling phenotypes, poses a formidable clinical

challenge. The application of the ketogenic diet (KD) in this indication is predicated on the fascinating convergence of BD pathophysiology with seizure mechanisms, as well as the biochemical structural homology between ketone bodies and classical normothymic agents (mood stabilizers) [2, 28].

The conceptual foundation for metabolic intervention in BD is the kindling phenomenon within the limbic system, specifically in the amygdala and hippocampus. This hypothesis, drawn directly from epileptology, posits that repeated, subthreshold stress stimuli (psychological or biochemical) permanently lower the excitability threshold for pathological neuronal discharges. Over time, these discharges become spontaneous and generate full-blown affective episodes without the involvement of an external trigger. The fact that antiepileptic drugs (AEDs), such as valproic acid, carbamazepine, and lamotrigine, constitute the first line of pharmacological treatment for BD provides the strongest evidence for shared pathological pathways between epilepsy and bipolarity [29]. Given the potent anticonvulsant potential of ketosis, documented by a century of clinical practice, the implementation of this dietary regimen in patients with BD is fully neurobiologically justified [2].

The most compelling argument for the direct normothymic action of ketosis is the structural and functional homology between the primary ketone body, β -hydroxybutyrate (BHB), and valproic acid (VPA). Both of these compounds are short-chain/medium-chain fatty acids. Their mechanisms of action at the molecular level exhibit a remarkable overlap [29]. First, both VPA and BHB are confirmed endogenous inhibitors of histone deacetylases (HDACs). This mediates the aforementioned epigenetic derepression of the *Bdnf* gene, leading to the reversal of hippocampal atrophy and exerting an antidepressant effect. Second, both compounds modulate amino acid neurotransmission by robustly stimulating glutamic acid decarboxylase (GAD) activity, which results in a surge of inhibitory GABA. Finally, the efficacy of normothymic drugs in suppressing mania is believed to stem, *inter alia*, from the depletion of the intracellular inositol pool (the so-called inositol depletion hypothesis), which attenuates excessive signaling via G protein-coupled receptors (GPCRs). Preclinical studies suggest that carbohydrate restriction and ketolytic pathways mimic this effect, dampening the hyperactivity of the phosphatidylinositol cascade [29, 30].

Mood stabilization in BD via ketogenic intervention is also predicated on silencing pathological bioenergetic oscillations. Magnetic resonance spectroscopy (MRS) studies of BD patients reveal a state of permanent oxidative stress, a decline in intracellular pH (cerebral lactic acidosis resulting from glycolytic aberrations), and mitochondrial respiratory chain dysfunction. The ketogenic diet, by supplying thermodynamically clean acetyl-CoA while bypassing glycolysis, stabilizes the ATP/ADP ratio. This phenomenon is of critical importance for the functioning of ATP-sensitive potassium channels (KATP). The opening of these channels, driven by BHB-induced alterations in the adenylate nucleotide pool, hyperpolarizes the neuronal membrane. This acts as a potent, physiological "brake" against escalating hyperexcitability, protecting the patient from transitioning into a manic phase [28, 30].

Additionally, chronic neuroinflammation is considered a factor driving the relapse rate in BD. Levels of proinflammatory cytokines, such as IL-1 β and TNF- α , increase markedly during manic and depressive episodes and correlate directly with the severity of cognitive symptoms. The robust blockade of the NLRP3 inflammasome complex by BHB [19] profoundly diminishes the level of neuroinflammation. In the context of bipolarity, this translates to the attenuation of neuroprogression and the prolongation of remission periods [30].

Evidence from clinical trials, although still in a phase of intensive development, yields exceptionally promising results. A breakthrough was the publication by Phelps and colleagues of a case series analyzing female patients diagnosed with bipolar II disorder, in whom the implementation of a ketogenic diet led to unprecedented mood stabilization. The patients themselves rated this normothymic effect as paramount over other somatic benefits (such as weight loss) [31]. In 2022, Danan et al. conducted a widely discussed, retrospective analysis of 31 patients hospitalized in a French psychiatric facility due to severe, treatment-resistant mental illnesses (primarily BD and schizophrenia) [32]. The results were striking: the implementation of a strictly monitored ketogenic diet resulted in a distinct symptomatic improvement on psychometric scales in 100% of the BD patients. Furthermore, a substantial proportion (over 40%) achieved full clinical remission, allowing for the safe, gradual tapering of

psychopharmacological polypharmacy. These studies, supported by more recent analyses confirming the KD's capacity to maintain patients in a state of sustained euthymia [30], position the ketogenic diet as one of the most innovative and pathophysiologically rational add-on therapies in the management of refractory bipolar disorder.

6.2. Schizophrenia – restoration of glutamatergic homeostasis and reversal of early bioenergetic deficits

Schizophrenia is a chronic, debilitating neurodevelopmental disorder characterized by a profound disintegration of cognitive functions, perception, and affect. For decades, the dominant paradigm explaining its pathogenesis was the dopaminergic hypothesis, positing overactivity of transmission within the mesolimbic pathway (responsible for positive symptoms, i.e., hallucinations and delusions) and hypoactivity within the mesocortical pathway (generating negative symptoms and cognitive deficits). Although classical antipsychotic drugs (D2 receptor antagonists) effectively suppress psychotic floridity, they remain largely ineffective against negative and cognitive symptoms, additionally inducing a severe iatrogenic metabolic syndrome. Contemporary biological psychiatry is redefining schizophrenia, viewing it as a systemic metabolic disorder of the brain, wherein dopaminergic dysfunction is merely a secondary phenomenon trailing primary bioenergetic deficits, oxidative stress, and aberrations in glutamatergic neurotransmission [33, 34]. The implementation of the ketogenic diet (KD) represents an attempt to target these fundamental, "root" pathological mechanisms.

The primary neuroimaging substrate in schizophrenia is the phenomenon of hypofrontality—a drastic reduction in blood flow and glucose metabolism within the dorsolateral prefrontal cortex (DLPFC). Positron emission tomography (PET) studies demonstrate that in the brains of patients with schizophrenia (even those in their first episode and naïve to pharmacotherapy), pathological insulin resistance and impairment of the glycolytic pathway occur. The depletion of intracellular ATP within highly energy-demanding cortical networks precludes the proper maintenance of resting potentials and the generation of gamma oscillations (30–80 Hz), which are critical for higher cognitive functions. β -hydroxybutyrate (BHB), crossing the blood-brain barrier via monocarboxylate transporters (MCTs), completely circumvents the blocked glycolytic pathway. The state of ketosis delivers a robust influx of acetyl-CoA directly into the mitochondrial matrix, instantaneously rectifying the energetic deficit within the prefrontal cortex. This mechanism of "metabolic rescue" is considered the central axis of improvement concerning pharmacotherapy-resistant cognitive and negative symptoms (such as anhedonia, alogia, or avolition) [33].

From the standpoint of neuropharmacology, the most coherent theory of schizophrenia pathogenesis currently is the NMDA receptor hypofunction hypothesis. It posits a primary deficit in neurotransmission at NMDA-type glutamate receptors located on cortical parvalbumin-positive (PV+) inhibitory interneurons. When these critical GABAergic interneurons lose their excitatory drive (due to the dysfunctional NMDA receptor), they cease to inhibit their target pyramidal cells. Consequently, a paradoxical, uncontrolled, and massive surge of glutamate occurs, literally "flooding" the nervous system. This leads to acute excitotoxicity and secondary dopaminergic hyperactivity within the striatum [35]. The ketogenic diet precisely counters this pathological cascade. As Kraeuter et al. [35] demonstrated in a precise animal model of schizophrenia induced by the administration of MK-801 (a potent NMDA antagonist), the state of ketosis completely reversed the behavioral abnormalities resulting from this hypofunction. The rewiring of the tricarboxylic acid cycle by BHB enhances GABA production (via GAD enzyme stimulation) and reduces the pool of released glutamate. This directly compensates for the inhibitory deficit resulting from the impaired PV+ interneurons and stabilizes hyperactive synaptic networks [33, 35].

Another key aspect is the impact of ketosis on the reduction of the profound oxidative stress that represents a hallmark of schizophrenia pathophysiology. A critical decline in the concentration of reduced glutathione (GSH)—the principal endogenous antioxidant of the CNS—is observed in the cerebrospinal fluid of these patients. The accumulation of reactive oxygen species (ROS) secondary to GSH deficiency damages the lipid structures of myelin, leading to disruptions in white matter integrity (dysconnectivity), which correlates with the development of formal thought disorders. As described in previous sections, β -hydroxybutyrate robustly stimulates *de novo* glutathione synthesis enzymes via the

activation of the Nrf2 transcriptional pathway. The highly efficient, ketone-driven oxidative phosphorylation curtails the formation of the superoxide anion radical within the respiratory chain, thereby safeguarding myelin sheaths from lipid peroxidation and enabling astrocytes to undertake white matter repair processes [33].

The translation of these solid neurobiological foundations into efficacy within clinical psychiatry has yielded groundbreaking observations in recent years. Historically, early reports, such as the case study by Kraft and Westman (2009) [36], signaled the possibility of complete resolution of auditory hallucinations in a patient with schizophrenia and comorbid obesity following the implementation of a rigorous low-carbohydrate diet. However, a genuine renaissance of this approach was initiated by the publications of Dr. Christopher Palmer (2019) [34], a prominent specialist in metabolic psychiatry. In a series of meticulously documented case reports involving patients with severe, long-standing, and treatment-resistant schizoaffective disorder and schizophrenia, Dr. Palmer demonstrated that the implementation of a ketogenic diet resulted not only in drastic weight reduction but, primarily, in striking clinical remission of productive psychotic symptoms (hallucinations and paranoid delusions). This remission was so stable and profound that it permitted the gradual, safe tapering of burdensome psychopharmacological polypharmacy [34].

These findings were subsequently bolstered by broader analyses, notably the study by Danan et al. (2022) [32], which included hospitalized patients with refractory psychiatric disorders. The results within the subpopulation of patients with schizophrenia confirmed a statistically and clinically significant decline in Positive and Negative Syndrome Scale (PANSS) scores. The implementation of restrictive ketosis led to multidimensional improvement: nourishing the energy-starved brain, suppressing neuroinflammation, and completely reversing metabolic syndrome parameters, which are often induced by the prior use of atypical antipsychotics (olanzapine, clozapine). Consequently, the application of the ketogenic diet ceases to be regarded as a mere curiosity; it emerges as a rigorously reasoned form of disease-modifying treatment in schizophrenia.

6.3. Major depressive disorder and treatment-resistant depression – modulation of the gut-brain axis and neurogenesis

Major depressive disorder (MDD), particularly in its treatment-resistant form (TRD), constitutes one of the leading causes of disability worldwide. The phenomenon of treatment resistance, typically defined as the lack of adequate clinical response to at least two adequate trials of antidepressants from different pharmacological classes at appropriate dosages and duration, affects up to 30% of MDD patients. The classical monoaminergic hypothesis (positing an absolute deficit of serotonin, noradrenaline, or dopamine) proves vastly insufficient to elucidate TRD pathogenesis. The contemporary Evidence-Based Medicine (EBM) paradigm shifts the focus toward neuroplasticity disturbances, systemic low-grade inflammation, and profound intestinal dysbiosis [2, 30]. The implementation of restrictive metabolic interventions, such as the ketogenic diet (KD), represents an innovative strike against these multilevel pathological cascades, offering mechanisms extending far beyond the simple blockade of neurotransmitter reuptake.

The first fundamental pathway through which ketosis reverses depressive symptoms is the dampening of the aforementioned neuroinflammation. In the psychiatric literature, the "macrophage theory of depression" currently holds a well-established position, grounded in the observation of the so-called sickness behavior phenomenon. Elevated concentrations of proinflammatory cytokines, notably interleukin-1 β (IL-1 β) and tumor necrosis factor (TNF- α), penetrate the blood-brain barrier and induce a state of chronic activation in microglia. These cytokines directly activate the enzyme indoleamine-2,3-dioxygenase (IDO), which "steals" tryptophan (the precursor of serotonin), converting it into neurotoxic quinolinic acid. This directly exacerbates anhedonia and psychomotor retardation. As demonstrated in pivotal molecular studies, β -hydroxybutyrate (BHB) is a potent endogenous inhibitor of the NLRP3 inflammasome complex [19]. This blockade halts the maturation and release of IL-1 β , interrupting the pathological action of the IDO enzyme. This results in the suppression of quinolinic acid production and the redirection of the tryptophan pool back into the serotonin synthesis pathway, physiologically reversing anhedonia symptoms in MDD patients [2, 19].

A second, equally crucial mechanism is the reversal of brain structure atrophy. Severe, recurrent depressive episodes indisputably correlate with a progressive volume loss in the hippocampus and prefrontal cortex. This stems from the inhibition of neurogenesis and a decline in brain-derived neurotrophic factor (BDNF) concentrations. The ketogenic diet intervenes in this process at an epigenetic level. BHB, acting as a physiological inhibitor of histone deacetylases (HDACs), induces chromatin relaxation [20]. This epigenetic derepression leads to enhanced transcription at promoter IV of the *Bdnf* gene. The subsequent surge of BDNF and the activation of its target TrkB receptor trigger intracellular cascades (e.g., the PI3K/Akt pathway) that stimulate the process of adult neurogenesis within the subgranular zone of the hippocampal dentate gyrus [22]. The regeneration of neuronal networks within this emotionally critical region constitutes an absolute prerequisite for achieving sustained clinical remission, rendering BHB a molecule with a profile akin to the most advanced neurotrophic agents [30].

The third therapeutic pillar of ketosis in treatment-resistant depression is the robust modulation of the gut-brain axis. Recent microbiomic research indicates that TRD patients exhibit profound dysbiosis, characterized, *inter alia*, by a decline in the populations of bacteria producing short-chain fatty acids (SCFAs), such as butyrate. A restrictive ketogenic diet (particularly in variants based on high-quality plant fats, MCTs, and adequate non-digestible fiber intake) induces an immediate and profound rearrangement of the gut microbiota composition. As demonstrated by the groundbreaking research of Olson's team (published in *Cell*), ketosis promotes a dramatic expansion of selective bacterial strains, including *Akkermansia muciniphila* and *Parabacteroides* [37]. This alteration is not merely an epiphenomenon; the ketogenically altered microbiome systemically modulates amino acid metabolism within the intestinal lumen, which translates into an elevated GABA-to-glutamate ratio in the portal circulation and hippocampus. This implies that the desired antidepressant neurochemical changes in the brain are largely dictated by gut bacteria adapting to the state of ketosis [37].

The translation of these three-pronged mechanisms (immunological, epigenetic, and microbiomic) into the realm of clinical psychiatry is becoming a reality supported by EBM research. A review by Włodarczyk et al. [30] unequivocally emphasizes the potential of the ketogenic diet not only in the treatment of acute depressive episodes but, above all, in maintaining long-term euthymia and preventing relapses. Even stronger evidence was provided by a recent randomized controlled trial (RCT) published in 2025 [38], evaluating the efficacy of KD in patients with a clinically confirmed diagnosis of defined treatment-resistant depression. Patients adhering to a rigorous ketogenic protocol, in whom the presence of capillary blood ketone bodies was verified, achieved a highly statistically and clinically significant reduction in Patient Health Questionnaire-9 (PHQ-9) depression scores compared to the control group. These results, characterized by a large effect size, ultimately validate the ketogenic diet as a highly effective, pleiotropic metabolic intervention in a patient population for whom classical psychopharmacology has exhausted its capabilities.

7. Safety, clinical challenges, and adverse effects

Despite the potent neuroprotective and neuromodulatory potential whose mechanisms have been thoroughly analyzed in this paper, the ketogenic diet (KD) remains an intervention of an extreme metabolic nature. The radical reprogramming of the entire body's bioenergetic pathways—transitioning from glycolysis toward dominant fatty acid beta-oxidation and hepatic ketogenesis—carries specific iatrogenic risks. The implementation of this dietary regimen in neurological and psychiatric populations necessitates a rigorous risk-benefit analysis, strict supervision by an interdisciplinary team (physician, clinical dietitian), and familiarity with management algorithms for adverse effects [39].

The most substantial pragmatic barrier limiting the widespread implementation of the KD is the issue of patient adherence (compliance). Strict adherence to the mandated macronutrient ratios—requiring a drastic reduction in carbohydrate intake to 20–50 g per day—poses a formidable behavioral and psychosocial challenge. As studies analyzing ketogenic interventions demonstrate, drop-out rates in the initial weeks can be high [39, 40]. This situation is particularly problematic for psychiatric patients (e.g., during the acute phase of schizophrenia or profound depression), who exhibit significant deficits in executive functions, avolition, and anhedonia, which preclude complex meal preparation and weighing. Consequently, in adult clinical practice, there is a growing shift away from the classic ketogenic diet

(with 3:1 or 4:1 ratios) toward the Modified Atkins Diet (MAD) or diets based on medium-chain triglyceride (MCT) supplementation. These variants generate therapeutic blood concentrations of β -hydroxybutyrate (BHB) while maintaining significantly higher long-term tolerability [39, 41].

The early stage of diet implementation, typically lasting from the first to the fourth week, is referred to as the keto-adaptation phase. It is associated with transient, acute adverse effects collectively termed the "keto-flu" in colloquial literature. The pathophysiology of this syndrome is rooted in profound water and electrolyte disturbances. The depletion of glycogen reserves in the liver and skeletal muscles entails the immediate release of structural water (approximately 3 grams of water per gram of depleted glycogen). Concurrently, the precipitous drop in insulin levels releases the kidneys from its antinatriuretic effect. This induces enhanced osmotic diuresis, resulting in a massive loss of sodium, and secondarily potassium and magnesium, via the urine [40, 41]. Patients frequently exhibit dizziness, severe fatigue, orthostatic hypotension, painful muscle cramps, and a transient cognitive decline (so-called "brain fog"). This cognitive blunting stems from the fact that the brain has not yet developed a sufficient density of monocarboxylate transporters (MCTs) to efficiently utilize ketones, whereas the glucose supply has already been radically restricted. Prophylactic intervention involves the aggressive, preemptive administration of fluids and mineral salts (e.g., bone broths) or the short-term use of exogenous ketones (BHB salts or esters), which facilitates a smooth, asymptomatic transition through the adaptation phase [41].

The long-term maintenance of nutritional ketosis necessitates the strict monitoring of internal organ function. One of the most frequently documented metabolic complications is the development of kidney stones (nephrolithiasis), affecting 3% to even 7% of patients on chronic KD. The pathomechanism of this phenomenon is twofold: first, a diet rich in protein and fat lowers urine pH (tubular acidosis); second, ketone bodies competitively inhibit uric acid excretion in the proximal tubules. This culminates in the formation of urate and calcium stones. This necessitates the routine monitoring of urine pH and, in many protocols, the prophylactic administration of potassium citrate as a urine-alkalizing and calcium-binding agent [39].

Particular controversy within the medical community, including cardiology, surrounds the impact of a restrictive high-fat diet on the lipid profile. As meta-analyses demonstrate [42], a subset of patients exhibits a significant increase in low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B (ApoB) concentrations during the initial months of the ketogenic diet. Nevertheless, EBM dictates caution in interpreting these results without a lipoprotein subfraction analysis. Ketosis induces a drastic, highly beneficial decline in triglyceride (TG) concentrations (a consequence of the complete inhibition of hepatic *de novo* lipogenesis) and a significant increase in the HDL fraction. Moreover, the elevated LDL during ketosis has been shown to undergo a transformation from a highly atherogenic phenotype (small dense LDL, sdLDL) to a phenotype of large, buoyant particles (lbLDL), which exhibit a negligible potential for penetrating the vascular endothelium and forming atherosclerotic plaques [42]. Despite this mechanistic concession, monitoring the atherogenic profile in certain patients (so-called hyper-responders) is obligatory. In cases of extreme hyperlipidemia, dietary intervention involves substituting saturated fatty acids (SFAs) with monounsaturated fatty acids (MUFAs, e.g., from olive oil).

The final, yet absolutely paramount safety consideration concerns absolute contraindications. Implementing the KD constitutes a categorical medical error, threatening the patient's life, in the presence of genetically determined defects in lipid metabolism and ketogenesis pathways. Absolute contraindications include: porphyrias (hepatic enzyme induction may trigger an acute attack), primary carnitine deficiency (essential for transporting long-chain fatty acids into mitochondria), carnitine palmitoyltransferase deficiencies (CPT-I and CPT-II), and enzymatic beta-oxidation defects (such as medium-chain acyl-CoA dehydrogenase [MCAD] deficiency). Administering the KD to these patients leads to profound, sudden hypoglycemia, hepatomegaly, massive liver enzyme release, and coma, as their bodies are incapable of generating ketones to compensate for the lack of glucose [39]. The early exclusion of these pathologies (often routinely screened via neonatal testing) is a prerequisite and mandatory condition for qualifying patients for neurometabolic treatment.

Considering the aforementioned limitations—particularly cardiological concerns related to a high intake of saturated fatty acids (SFAs) and the proinflammatory issues induced by highly processed diet variants—contemporary clinical dietetics and metabolic psychiatry have developed highly optimized therapeutic models. To minimize iatrogenic risks while preserving the full neuroprotective potential of ketone bodies, treatment algorithms increasingly incorporate "Clean Keto" and Mediterranean Ketogenic Diet (Med-Keto) protocols [43].

In the classical, often lay approach (referred to in Anglo-Saxon literature as "dirty keto"), the state of ketosis is sometimes achieved through the consumption of highly processed meat products (rich in nitrites and advanced glycation end-products, AGEs), refined seed oils abundant in proinflammatory omega-6 fatty acids (linoleic acid), and artificial sweeteners. While biochemically capable of generating β -hydroxybutyrate (BHB), this model simultaneously induces systemic oxidative stress, damages the vascular endothelial glycocalyx, and leads to profound intestinal dysbiosis, which stands in stark contradiction to therapeutic goals in psychiatry [44, 45].

The answer to this problem is the Clean Keto paradigm. This model rigorously emphasizes nutrient density and the anti-inflammatory nature of the food matrix. It is predicated on the absolute elimination of ultra-processed foods in favor of organic, wholesome protein and fat sources (e.g., free-range animal meat, eggs, wild-caught fish) and a substantial intake of complex carbohydrates derived exclusively from non-starchy, leafy green vegetables (e.g., spinach, kale, broccoli). Such an intervention delivers an essential pool of prebiotic fiber, which, synergistically with ketosis, promotes the proliferation of short-chain fatty acids (SCFAs) in the intestinal lumen, critical for blood-brain barrier (BBB) integrity and the optimization of the gut-brain axis [45].

An even more advanced modification, currently considered the "gold standard" of cardiological safety in chronic metabolic therapies, is the Spanish Ketogenic Mediterranean Diet (SKMD / Med-Keto). It represents a fusion of two of the most potent, evidence-based medicine (EBM) nutritional interventions: profound carbohydrate restriction inducing BHB production, and the fatty acid and antioxidant profile characteristic of the traditional Mediterranean diet [43, 44].

The neurobiological and cardiological superiority of the Med-Keto protocol rests on the radical restructuring of the supplied lipid panel. Saturated fatty acids (SFAs), which may exacerbate the atherogenic LDL fraction in some patients (hyper-responders), are deliberately restricted in this model in favor of monounsaturated fatty acids (MUFAs)—with particular emphasis on oleic acid, the primary sources of which are extra virgin olive oil (EVOO) and avocados. Cold-pressed olive oil additionally provides a potent array of polyphenols (including oleuropein, hydroxytyrosol, and oleocanthal). Oleocanthal exhibits unique structural and functional pharmacological activity analogous to ibuprofen (a non-steroidal anti-inflammatory drug, NSAID), acting as a direct inhibitor of cyclooxygenase enzymes (COX-1 and COX-2). This amplifies the anti-inflammatory properties of BHB itself at the microglial level [43].

Furthermore, Med-Keto mandates the intake of omega-3 polyunsaturated fatty acids (PUFAs) (EPA and DHA), sourced from fatty marine fish. Docosahexaenoic acid (DHA) is an absolutely critical structural component of neuronal membranes and synapses. A high omega-3 index in cell membranes increases their fluidity, which optimizes the kinetics of neurotransmitter receptors (including the sensitivity of dopaminergic and serotonergic receptors), while simultaneously providing substrates for the synthesis of resolvins and protectins—specialized pro-resolving mediators (SPMs) that extinguish neuroinflammation [43, 44].

Clinical trials demonstrate that patients managed on the Mediterranean Ketogenic Diet protocol achieve deep, therapeutic ketosis, with a concurrent, statistically significant reduction in blood pressure, a decrease in inflammatory biomarkers (such as hs-CRP), and a radical improvement in their lipid profile (a decline in LDL and triglycerides alongside an increase in protective HDL) [43]. The application of Clean Keto and Med-Keto variants thus resolves the clinician's primary dilemma: it permits the long-term utilization of the neurotropic properties of β -hydroxybutyrate in psychiatry without compromising the patient's cardiovascular system, constituting a highly sustainable and evolutionarily coherent form of disease-modifying neurotherapy.

8. Discussion

The turn of the decade in neurobiology and clinical psychiatry is characterized by a gradual yet systematic departure from isolated, single-neurotransmitter theories of central nervous system (CNS) disease pathogenesis. The scientific evidence accumulated and systematized in this paper, grounded in the Evidence-Based Medicine (EBM) paradigm, sheds new light on the ketogenic diet (KD). Historically marginalized as the exclusive domain of pediatric epileptology, this intervention is currently emerging as a fundamental tool of a novel medical discipline: metabolic psychiatry.

The focal point of this discussion is the redefinition of the role of ketone bodies. β -hydroxybutyrate (BHB) can no longer be viewed merely as an alternative fuel bypassing neuronal insulin resistance, although in neurodegenerative diseases (such as Alzheimer's and Parkinson's) this mechanism of "metabolic rescue" conditions the deceleration of brain structure atrophy. The greatest added value of ketogenic interventions is their action as potent endogenous signaling metabolites. The direct blockade of the NLRP3 inflammasome complex, the epigenetic derepression of BDNF via histone deacetylase (HDAC) inhibition, and the restoration of balance within the glutamate-GABA axis constitute cascades that precisely target the pathophysiological "bottlenecks" of schizophrenia, treatment-resistant depression (TRD), and bipolar disorder (BD) [2, 19, 20, 30].

In the context of the current state of knowledge, psychiatric pharmacotherapy—based on SSRIs, SNRIs, or atypical antipsychotics—is largely symptomatic and frequently associated with the emergence of a severe metabolic syndrome, which paradoxically fuels the neuroprogression of the underlying disease [32]. The ketogenic diet offers a profile unique in medicine: it is a systemic intervention (a network-level reset) that simultaneously reverses iatrogenic metabolic disturbances and restructures brain bioenergetics at the mitochondrial level. The score reductions on the PANSS, PHQ-9, and MDS-UPDRS scales documented in randomized controlled trials (RCTs) indicate a profound clinical efficacy of ketosis, often surpassing standard treatment algorithms in patients designated as treatment-resistant [27, 32, 38].

It is also worth emphasizing the evolution of the approach to macronutrients itself. The transition from classic, micronutrient-poor, and saturated fat-based "dirty" keto toward the Clean Ketogenic Diet (Clean Keto) and the Mediterranean Ketogenic Diet (Med-Keto) alleviates historical objections from the cardiological community. Supplementation with omega-3 fatty acids (DHA/EPA), olive oil polyphenols, and prebiotic fiber potentiates the neuroprotective nature of the intervention, simultaneously extinguishing intestinal dysbiosis and reducing systemic oxidative stress [43, 45].

9. Limitations

Despite highly promising prospects, the interpretation of the data accumulated in the literature encounters substantial methodological barriers that require critical appraisal. These limitations can be divided into two primary categories: those related to the rigor of the scientific studies themselves, and those stemming from clinical pragmatics.

9.1. Study heterogeneity and lack of protocol standardization

The primary challenge in synthesizing the literature on KD in psychiatry and neurology is the extreme heterogeneity of research protocols. The included studies differ drastically in terms of the diet variant utilized (classic 4:1 KD vs. Modified Atkins Diet vs. ketosis stimulated by MCT oil or exogenous ketone supplementation). Furthermore, many studies, particularly older ones, lack strict, objective monitoring of ketone bodies (relying solely on imprecise urine strips rather than capillary blood BHB measurements). This impedes the establishment of an optimal therapeutic "ketosis window" for specific nosological entities [2, 28]. There is an urgent need to standardize clinical protocols that clearly define the target serum BHB values requisite for achieving an antipsychotic or normothymic effect.

9.2. Structural limitations of randomized controlled trials (RCTs)

Double-blind, placebo-controlled randomized trials represent the gold standard of EBM. However, in the case of dietary interventions, full blinding of investigators and patients is inherently impossible. A patient undergoing restrictive carbohydrate reduction and entering the keto-adaptation phase is almost

invariably aware of their assignment to the interventional arm, which inevitably introduces expectation bias and the placebo effect. Additionally, the majority of currently available clinical trials in metabolic psychiatry are studies with a relatively short observation period (typically 6 to 12 weeks) and small sample sizes, which limits the statistical power of conclusions regarding long-term prophylactic efficacy in preventing relapses [28, 30].

9.3. Adherence and drop-out rates

A limitation inextricably linked to the ketogenic intervention is poor long-term tolerability. Rigorous requirements for meal preparation and a radical shift in social habits lead to a high drop-out rate, particularly in patient cohorts with executive function deficits typical of schizophrenia or dementia [39, 40]. This phenomenon distorts statistical analysis within the Intention-to-Treat (ITT) model, frequently resulting in an underestimation of the diet's potential. Moreover, initial adverse effects (the "keto-flu" syndrome) may be misconstrued by psychiatric patients as an exacerbation of their mental state, resulting in premature treatment discontinuation.

9.4. Knowledge gaps regarding long-term safety

Despite the implementation of Med-Keto models, the long-term consequences of maintaining continuous ketosis for years (extending beyond observations in pediatric epilepsy patients) in adults with cardiometabolic comorbidities remain incompletely investigated. The long-term impact of extreme carbohydrate restriction on the thyroid axis (the possibility of euthyroid sick syndrome, manifesting as a decline in T4 to T3 conversion) and on bone mineral density in adult patients also remains unclear, necessitating close monitoring in future multicenter cohorts [39].

9.5. Lack of precision medicine

Current literature lacks sufficient data regarding the genetic and phenotypic predictors of response to the ketogenic diet. For instance, there are indications that Alzheimer's disease patients who are carriers of the ApoE4 (Apolipoprotein E4) allele exhibit a significantly poorer cognitive response to high-fat interventions compared to non-carriers, due to altered lipid metabolism in astrocytes [16]. The absence of routine genotyping prior to diet initiation constitutes a substantial limitation to the development of personalized metabolic psychiatry.

Resolving the aforementioned dilemmas through the design of multicenter, long-term cross-over trials incorporating the cross-supplementation of exogenous ketone bodies appears to be an absolute priority for the scientific community over the coming decade.

10. Conclusions

Based on a rigorous analysis of the accumulated scientific literature, encompassing both advanced preclinical models and the latest randomized clinical trials (RCTs), an unprecedented picture of the ketogenic diet (KD) emerges as a multidirectional, potent neurometabolic intervention. It is justified to definitively discard the historical, reductionist paradigm that reserved the application of nutritional ketosis exclusively for cases of refractory pediatric epilepsy. Contemporary Evidence-Based Medicine (EBM) provides irrefutable proof that the optimization of bioenergetic pathways via the induction of ketone body synthesis constitutes the foundation of a novel, dynamically expanding field: metabolic psychiatry.

From the perspective of molecular neurobiology, the pivotal conclusion drawn from this review concerns the complete redefinition of the role of β -hydroxybutyrate (BHB). This molecule transcends far beyond its function as an alternative energy substrate bypassing neuronal insulin resistance. BHB has proven its properties as a highly specific, endogenous signaling metabolite. Through its documented capacity to directly inhibit the NLRP3 inflammasome complex, BHB precisely extinguishes sterile neuroinflammation at its very source. Simultaneously, acting as a physiological inhibitor of histone deacetylases (HDACs), it induces the epigenetic derepression of BDNF transcription, which is a *conditio sine qua non* for restoring neuroplasticity, reversing hippocampal atrophy, and stimulating adult neurogenesis. These phenomena, coupled with the stabilization of the glutamate-GABA axis and the

activation of the antioxidant Nrf2 pathway, prove that the ketogenic intervention strikes at the "root" pathophysiological mechanisms of CNS damage, rather than merely their superficial symptoms.

Regarding clinical practice, the compiled data permit the conclusion of a high, often striking efficacy of the ketogenic diet in disorders hitherto deemed treatment-resistant. In neurodegenerative diseases, such as Alzheimer's and Parkinson's, the induction of ketosis acts as a specific "metabolic bypass" for dysfunctional respiratory chain complexes, which measurably improves cognitive functions and alleviates non-motor symptoms. Conversely, in the realm of severe psychiatric disorders—schizophrenia, bipolar disorder (BD), and treatment-resistant depression (TRD)—the KD exhibits a documented normothymic and antipsychotic potential. The capacity of ketolysis for a network-level reset and the compensation of GABAergic deficits means that this intervention frequently facilitates the achievement of sustained remission and the safe, gradual tapering of burdensome psychopharmacological polypharmacy.

Concurrently, a critical analysis of the safety profile dictates the necessity for the evolution of dietary protocols themselves. For metabolic interventions to be safely implemented as a chronic adjuvant therapy, a departure from classic, "dirty" diet variants is imperative, moving toward models optimized for nutrient density and anti-inflammatory properties, such as the Clean Ketogenic Diet (Clean Keto) and the Mediterranean Ketogenic Diet (Med-Keto). Utilizing high-quality monounsaturated and polyunsaturated fatty acids (EVOO, omega-3) while simultaneously nurturing the gut microbiome allows for the maximization of neurotropic benefits while abrogating cardiovascular and metabolic risks.

In conclusion, the ketogenic diet represents a highly promising, pathophysiologically rational, and biochemically grounded form of disease-modifying therapy. However, its incorporation into the official algorithms and guidelines of psychiatric and neurological societies necessitates the conduction of further multicenter randomized clinical trials on large patient cohorts. An equally pressing need is the development of personalized medicine, incorporating genetic profiling (e.g., ApoE4 status) to qualify patients for the optimal treatment model. The realization that disrupted brain bioenergetics lies at the core of psychiatric and neurodegenerative diseases opens an entirely new chapter in medicine—a chapter in which appropriately reprogrammed metabolism becomes the most potent medication available.

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References

- [1] Mikołajec, P., Jolanta Mędyk, Michał Rogulski, Yauheniya Patarocha, Aleksandra Ślusarska, Paulina Błasiak, ... Barbara Bilecka. (2025). The Effects of the Ketogenic Diet on Disorders of Central Nervous System. *Journal of Education, Health and Sport*, 78, 57586. <https://doi.org/10.12775/JEHS.2025.78.57586>
- [2] Mentzelou, M., Dakanalis, A., Vasios, G. K., Gialeli, M., Papadopoulou, S. K., & Giaginis, C. (2023). The Relationship of Ketogenic Diet with Neurodegenerative and Psychiatric Diseases: A Scoping Review from Basic Research to Clinical Practice. *Nutrients*, 15(10), 2270. <https://doi.org/10.3390/nu15102270>
- [3] Pawłowska, M., Kruszka, J., Porzych, M., Garbarek, J., & Nuskiewicz, J. (2025). Ketogenic Metabolism in Neurodegenerative Diseases: Mechanisms of Action and Therapeutic Potential. *Metabolites*, 15(8), 508. <https://doi.org/10.3390/metabo15080508>
- [4] Veech R. L. (2004). The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism. *Prostaglandins, leukotrienes, and essential fatty acids*, 70(3), 309–319. <https://doi.org/10.1016/j.plefa.2003.09.007>
- [5] Sampaio L. P. (2016). Ketogenic diet for epilepsy treatment. *Arquivos de neuro-psiquiatria*, 74(10), 842–848. <https://doi.org/10.1590/0004-282X20160116>
- [6] Domańska, N., Bojarska, M., Bogucka, J., Brzyska, A., Kosowska, M., & Pieciewicz-Szczęsna, H. (2025). Beyond the seizures: Ketogenic Diets in the battle against drug-resistant epilepsy. *Journal of Education, Health and Sport*, 77, 56870. <https://doi.org/10.12775/JEHS.2025.77.56870>
- [7] Kossoff, E. H., Zupec-Kania, B. A., Auvin, S., Ballaban-Gil, K. R., Christina Bergqvist, A. G., Blackford, R., Buchhalter, J. R., Caraballo, R. H., Cross, J. H., Dahlin, M. G., Donner, E. J., Guzel, O., Jehle, R. S., Klepper, J., Kang, H. C., Lambrechts, D. A., Liu, Y. M. C., Nathan, J. K., Nordli, D. R., Jr, Pfeifer, H. H., ... Practice Committee of the Child Neurology Society (2018). Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. *Epilepsia open*, 3(2), 175–192. <https://doi.org/10.1002/epi4.12225>
- [8] D'Andrea Meira, I., Romão, T. T., Pires do Prado, H. J., Krüger, L. T., Pires, M. E. P., & da Conceição, P. O. (2019). Ketogenic Diet and Epilepsy: What We Know So Far. *Frontiers in neuroscience*, 13, 5. <https://doi.org/10.3389/fnins.2019.00005>
- [9] Cuber, I., Aghadi, A., Białowas, E., Dybała, E., Mazurek, M., & Górna, M. (2023). Ketogenic diet - a literature review. *Journal of Education, Health and Sport*, 13(4), 132–141. <https://doi.org/10.12775/JEHS.2023.13.04.014>
- [10] Puchalska, P., & Crawford, P. A. (2017). Multi-dimensional Roles of Ketone Bodies in Fuel Metabolism, Signaling, and Therapeutics. *Cell metabolism*, 25(2), 262–284. <https://doi.org/10.1016/j.cmet.2016.12.022>

- [11] Kayode, T. O., Rotimi, E. D., Afolayan, A. O., & Kayode, A. A. A. (2020). Ketogenic diet: A nutritional remedy for some metabolic disorders. *Journal of Education, Health and Sport*, 10(8), 180–188. <https://doi.org/10.12775/JEHS.2020.10.08.021>
- [12] Rubio, C., López-Landa, A., Romo-Parra, H., & Rubio-Osornio, M. (2025). Impact of the Ketogenic Diet on Neurological Diseases: A Review. *Life (Basel, Switzerland)*, 15(1), 71. <https://doi.org/10.3390/life15010071>
- [13] Morris A. A. (2005). Cerebral ketone body metabolism. *Journal of inherited metabolic disease*, 28(2), 109–121. <https://doi.org/10.1007/s10545-005-5518-0>
- [14] Halestrap A. P. (2013). The SLC16 gene family - structure, role and regulation in health and disease. *Molecular aspects of medicine*, 34(2-3), 337–349. <https://doi.org/10.1016/j.mam.2012.05.003>
- [15] Bough, K. J., & Rho, J. M. (2007). Anticonvulsant mechanisms of the ketogenic diet. *Epilepsia*, 48(1), 43–58. <https://doi.org/10.1111/j.1528-1167.2007.00915.x>
- [16] Cunnane, S. C., Courchesne-Loyer, A., Vandenberghe, C., St-Pierre, V., Fortier, M., Hennebelle, M., Croteau, E., Bock, C., Fulop, T., & Castellano, C. A. (2016). Can Ketones Help Rescue Brain Fuel Supply in Later Life? Implications for Cognitive Health during Aging and the Treatment of Alzheimer's Disease. *Frontiers in molecular neuroscience*, 9, 53. <https://doi.org/10.3389/fnmol.2016.00053>
- [17] Gasior, M., Rogawski, M. A., & Hartman, A. L. (2006). Neuroprotective and disease-modifying effects of the ketogenic diet. *Behavioural pharmacology*, 17(5-6), 431–439. <https://doi.org/10.1097/00008877-200609000-00009>
- [18] Maalouf, M., Rho, J. M., & Mattson, M. P. (2009). The neuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies. *Brain research reviews*, 59(2), 293–315. <https://doi.org/10.1016/j.brainresrev.2008.09.002>
- [19] Youm, Y. H., Nguyen, K. Y., Grant, R. W., Goldberg, E. L., Bodogai, M., Kim, D., D'Agostino, D., Planavsky, N., Lupfer, C., Kanneganti, T. D., Kang, S., Horvath, T. L., Fahmy, T. M., Crawford, P. A., Biragyn, A., Alnemri, E., & Dixit, V. D. (2015). The ketone metabolite β -hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. *Nature medicine*, 21(3), 263–269. <https://doi.org/10.1038/nm.3804>
- [20] Shimazu, T., Hirschey, M. D., Newman, J., He, W., Shirakawa, K., Le Moan, N., Grueter, C. A., Lim, H., Saunders, L. R., Stevens, R. D., Newgard, C. B., Farese, R. V., Jr, de Cabo, R., Ulrich, S., Akassoglou, K., & Verdin, E. (2013). Suppression of oxidative stress by β -hydroxybutyrate, an endogenous histone deacetylase inhibitor. *Science (New York, N.Y.)*, 339(6116), 211–214. <https://doi.org/10.1126/science.1227166>
- [21] Xie, Z., Zhang, D., Chung, D., Tang, Z., Huang, H., Dai, L., Qi, S., Li, J., Colak, G., Chen, Y., Xia, C., Peng, C., Ruan, H., Kirkey, M., Wang, D., Jensen, L. M., Kwon, O. K., Lee, S., Pletcher, S. D., Tan, M., ... Zhao, Y. (2016). Metabolic Regulation of Gene Expression by Histone Lysine β -Hydroxybutyrylation. *Molecular cell*, 62(2), 194–206. <https://doi.org/10.1016/j.molcel.2016.03.036>
- [22] Sleiman, S. F., Henry, J., Al-Haddad, R., El Hayek, L., Abou Haidar, E., Stringer, T., Ulja, D., Karuppagounder, S. S., Holson, E. B., Ratan, R. R., Ninan, I., & Chao, M. V. (2016). Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body β -hydroxybutyrate. *eLife*, 5, e15092. <https://doi.org/10.7554/eLife.15092>

- [23] Yoshii, A., & Constantine-Paton, M. (2010). Postsynaptic BDNF-TrkB signaling in synapse maturation, plasticity, and disease. *Developmental neurobiology*, 70(5), 304–322. <https://doi.org/10.1002/dneu.20765>
- [24] Henderson S. T. (2008). Ketone bodies as a therapeutic for Alzheimer's disease. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics*, 5(3), 470–480. <https://doi.org/10.1016/j.nurt.2008.05.004>
- [25] Krikorian, R., Shidler, M. D., Dangelo, K., Couch, S. C., Benoit, S. C., & Clegg, D. J. (2012). Dietary ketosis enhances memory in mild cognitive impairment. *Neurobiology of aging*, 33(2), 425.e19–425.e4.25E27. <https://doi.org/10.1016/j.neurobiolaging.2010.10.006>
- [26] Taylor, M. K., Sullivan, D. K., Mahnken, J. D., Burns, J. M., & Swerdlow, R. H. (2017). Feasibility and efficacy data from a ketogenic diet intervention in Alzheimer's disease. *Alzheimer's & dementia (New York, N. Y.)*, 4, 28–36. <https://doi.org/10.1016/j.trci.2017.11.002>
- [27] Phillips, M. C. L., Murtagh, D. K. J., Gilbertson, L. J., Asztely, F. J. S., & Lynch, C. D. P. (2018). Low-fat versus ketogenic diet in Parkinson's disease: A pilot randomized controlled trial. *Movement disorders : official journal of the Movement Disorder Society*, 33(8), 1306–1314. <https://doi.org/10.1002/mds.27390>
- [28] Rog, J., Wingralek, Z., Nowak, K., Grudzień, M., Grunwald, A., Banaszek, A., & Karakula-Juchnowicz, H. (2024). The Potential Role of the Ketogenic Diet in Serious Mental Illness: Current Evidence, Safety, and Practical Advice. *Journal of clinical medicine*, 13(10), 2819. <https://doi.org/10.3390/jcm13102819>
- [29] Campbell, I. H., & Campbell, H. (2019). Ketosis and bipolar disorder: controlled analytic study of online reports. *BJPsych open*, 5(4), e58. <https://doi.org/10.1192/bjo.2019.49>
- [30] Włodarczyk, A., Cubala, W. J., & Stawicki, M. (2021). Ketogenic diet for depression: A potential dietary regimen to maintain euthymia?. *Progress in neuro-psychopharmacology & biological psychiatry*, 109, 110257. <https://doi.org/10.1016/j.pnpbp.2021.110257>
- [31] Phelps, J. R., Siemers, S. V., & El-Mallakh, R. S. (2013). The ketogenic diet for type II bipolar disorder. *Neurocase*, 19(5), 423–426. <https://doi.org/10.1080/13554794.2012.690421>
- [32] Danan, A., Westman, E. C., Saslow, L. R., & Ede, G. (2022). The Ketogenic Diet for Refractory Mental Illness: A Retrospective Analysis of 31 Inpatients. *Frontiers in psychiatry*, 13, 951376. <https://doi.org/10.3389/fpsy.2022.951376>
- [33] Sarnyai, Z., Krauter, A. K., & Palmer, C. M. (2019). Ketogenic diet for schizophrenia: clinical implication. *Current opinion in psychiatry*, 32(5), 394–401. <https://doi.org/10.1097/YCO.0000000000000535>
- [34] Palmer, C. M., Gilbert-Jaramillo, J., Westman, E. C. (2019). The ketogenic diet and remission of psychotic symptoms in schizophrenia: Two case reports. *Schizophrenia Research*, 208, 439–440. <https://doi.org/10.1016/j.schres.2019.03.019>
- [35] Krauter, A. K., Loxton, H., Lima, B. C., Rudd, D., & Sarnyai, Z. (2015). Ketogenic diet reverses behavioral abnormalities in an acute NMDA receptor hypofunction model of schizophrenia. *Schizophrenia research*, 169(1-3), 491–493. <https://doi.org/10.1016/j.schres.2015.10.041>

- [36] Kraft, B. D., Westman, E. C. (2009). Schizophrenia, gluten, and low-carbohydrate, ketogenic diets: a case report and review of the literature. *Nutrition & Metabolism*, 6, 10. <https://doi.org/10.1186/1743-7075-6-10>
- [37] Olson, C. A., Vuong, H. E., Yano, J. M., Liang, Q. Y., Nusbaum, D. J., & Hsiao, E. Y. (2018). The Gut Microbiota Mediates the Anti-Seizure Effects of the Ketogenic Diet. *Cell*, 173(7), 1728–1741.e13. <https://doi.org/10.1016/j.cell.2018.04.027>
- [38] Gao, M., Kirk, M., Knight, H., Lash, E., Michalopoulou, M., Guess, N., Stevens, R., Browning, M., Weich, S., Burnet, P. W. J., Jebb, S. A., & Aveyard, P. (2026). A Ketogenic Diet for Treatment-Resistant Depression: A Randomized Clinical Trial. *JAMA psychiatry*, 83(4), 331–340. <https://doi.org/10.1001/jamapsychiatry.2025.4431>
- [39] Kuźniar, J., Kozubek, P., Czaja, M., Sitka, H., & Wegenko, C. (2024). Ketogenic diet and intermittent fasting - impact on body weight and various diseases. *Journal of Education, Health and Sport*, 70, 55560. <https://doi.org/10.12775/JEHS.2024.70.55560>
- [40] Bartosik, K., Furtek, D., Ostrowicz, K., & Kurenda, K. (2025). The Impact of the Ketogenic Diet on Athletic Performance: A Systematic Literature Review. *Quality in Sport*, 43, 62344. <https://doi.org/10.12775/QS.2025.43.62344>
- [41] Harvey, C. J. D. C., Schofield, G. M., & Williden, M. (2018). The use of nutritional supplements to induce ketosis and reduce symptoms associated with keto-induction: a narrative review. *PeerJ*, 6, e4488. <https://doi.org/10.7717/peerj.4488>
- [42] Gjuladin-Hellon, T., Davies, I. G., Penson, P., & Amiri Baghbadorani, R. (2019). Effects of carbohydrate-restricted diets on low-density lipoprotein cholesterol levels in overweight and obese adults: a systematic review and meta-analysis. *Nutrition reviews*, 77(3), 161–180. <https://doi.org/10.1093/nutrit/nuy049>
- [43] Pérez-Guisado, J., Muñoz-Serrano, A., & Alonso-Moraga, A. (2008). Spanish Ketogenic Mediterranean Diet: a healthy cardiovascular diet for weight loss. *Nutrition journal*, 7, 30. <https://doi.org/10.1186/1475-2891-7-30>
- [44] Paoli, A., Rubini, A., Volek, J. S., & Grimaldi, K. A. (2013). Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. *European journal of clinical nutrition*, 67(8), 789–796. <https://doi.org/10.1038/ejcn.2013.116>
- [45] Muscogiuri, G., Barrea, L., Laudisio, D., Pugliese, G., Salzano, C., Savastano, S., & Colao, A. (2019). The management of very low-calorie ketogenic diet in obesity outpatient clinic: a practical guide. *Journal of translational medicine*, 17(1), 356. <https://doi.org/10.1186/s12967-019-2104-z>