Review Article

From Carbohydrates to Ketones: Mitochondrial Reprogramming via β-Hydroxybutyrate Signaling for Non-Pharmacological Treatment of Metabolic Syndrome

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Metabolic syndrome (MetS) encompasses central adiposity, dyslipidemia, insulin resistance, and hypertension, predisposing individuals to cardiovascular and hepatic disease. Ketogenic diets (KD), through carbohydrate restriction and induction of nutritional ketosis, have re-emerged as metabolic interventions capable of modulating multiple pathways relevant to MetS. Evidence from clinical and experimental studies indicates that KD consistently lowers triglycerides, improves glycemic control and insulin sensitivity, and reduces visceral adiposity, while LDL-C responses remain heterogeneous and largely dependent on dietary fat quality. Mechanistically, β-hydroxybutyrate functions as both an alternative energy substrate and a signaling metabolite, inhibiting histone deacetylases and the NLRP3 inflammasome, enhancing mitochondrial biogenesis via AMPK–SIRT3–PGC-1α activation, and promoting fatty acid oxidation through PPARα. These molecular adaptations translate into improved metabolic flexibility, reduced hepatic steatosis, and an attenuated inflammatory tone. Hormonal mediators such as FGF21 and GDF15 further support energy balance and substrate partitioning, whereas modifications in bile acid pools and the gut microbiota contribute to improved lipid handling and reduced caloric absorption. Clinical implementation requires careful supervision, lipid and hepatic monitoring, and an emphasis on unsaturated fat sources to ensure cardiometabolic safety. Long-term controlled trials incorporating multi-omic biomarkers are warranted to determine durability, responder phenotypes, and mechanistic predictability. Collectively, KD represents both a viable therapeutic strategy and a translational model for nutrient-driven metabolic reprogramming in MetS.

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Introduction

Metabolic syndrome (MetS) represents a constellation of metabolic perturbations—including central adiposity, dyslipidemia, hyperglycemia, and hypertension—that collectively increase the risk of cardiovascular disease, type 2 diabetes mellitus (T2DM), and non-alcoholic fatty liver disease (NAFLD). Its global prevalence exceeds 25% among adults and continues to rise in parallel with obesity and sedentary behavior [1]. The clinical heterogeneity of MetS arises from varying combinations of its diagnostic components and from interindividual differences in insulin sensitivity, hepatic lipid handling, adipose tissue distribution, and inflammatory tone. These factors complicate the design of targeted interventions and underscore the need for mechanistically informed dietary strategies [2][3].

Over the past decade, the ketogenic diet (KD) has gained renewed attention as a metabolic therapy that may address several core abnormalities of MetS. Traditionally formulated with very low carbohydrate intake (<50 g/day), moderate protein, and high fat, the KD promotes nutritional ketosis, characterized by elevated circulating β-hydroxybutyrate (BHB) and acetoacetate levels. These ketone bodies function not only as alternative energy substrates but also as signaling metabolites modulating oxidative stress, inflammation, and mitochondrial function [2][3]. Such pleiotropic roles align with the pathophysiological spectrum of MetS, where mitochondrial dysfunction and chronic low-grade inflammation play central roles.

A translational narrative review approach is particularly appropriate for synthesizing the evidence on KD in MetS, given the diversity of human clinical trials and mechanistic animal studies. Clinical investigations span populations with obesity, insulin resistance, T2DM, and related comorbidities—all of which overlap with the MetS phenotype—and include various formulations such as very-low-calorie ketogenic diets (VLCKD) and well-formulated ketogenic diets (WFKD). Complementary mechanistic data from animal and cellular models provide insights into ketone-mediated pathways, including inhibition of the NLRP3 inflammasome, activation of AMPK and SIRT3, and modulation of hepatic PPARα-driven fatty acid oxidation [4][5][6]. Integrating these domains allows a bidirectional translation between metabolic signaling and clinical phenotype—the essence of a bench-to-bedside framework [7].

The thesis of this review is that ketogenic interventions, when appropriately designed and monitored, exert consistent metabolic benefits in MetS through three principal domains: (1) reduction in

triglycerides (TG) and improvements in HDL-C; (2) attenuation of hyperglycemia and insulin resistance; and (3) significant weight and visceral fat reduction. However, the impact on LDL-C remains variable and contingent upon fat source composition and apoB concentration, highlighting the necessity of lipid quality over quantity. Mechanistically, these clinical outcomes are biologically plausible, supported by evidence linking BHB-mediated histone deacetylase (HDAC) inhibition, adipose tissue remodeling via M2 macrophage polarization, and enhancement of hepatic mitochondrial efficiency [4][8]. Thus, KD represents a nutritionally driven model for metabolic reprogramming with implications extending beyond caloric restriction alone [7][9][10].

This review aims to dissect the translational bridge between human metabolic outcomes and underlying physiological mechanisms, critically evaluating evidence from both controlled trials and preclinical research. By aligning clinical endpoints with molecular signaling pathways, we aim to clarify where ketogenic diets deliver robust metabolic correction, where uncertainties persist, and how these insights may guide future trial design in the evolving landscape of metabolic syndrome management [2][7].

What Is Ketogenic in Practice?

The term ketogenic diet (KD) encompasses a spectrum of nutritional formulations unified by their capacity to induce nutritional ketosis—a physiological state characterized by sustained elevations of circulating β-hydroxybutyrate (BHB) typically above 0.5 mmol/L. In practice, several variants are recognized based on caloric content, macronutrient distribution, and clinical intent [2][11].

Definitions and Classifications

The classic ketogenic diet (KD), originally developed for refractory epilepsy, typically provides 75–80% of total energy from fat, 15–20% from protein, and <5% from carbohydrates. The very-low-calorie ketogenic diet (VLCKD) represents a more restrictive derivative, limiting energy intake to 500–800 kcal/day with <50 g of carbohydrates daily and approximately 1.0–1.5 g of protein per kilogram of ideal body weight [11]. This formulation is designed primarily for short-term therapeutic weight reduction in obesity and related metabolic dysfunctions. The well-formulated ketogenic diet (WFKD), as described in translational metabolic research, maintains moderate caloric intake while emphasizing nutrient adequacy, mineral balance, and unsaturated fat predominance [12]. A broader category, the low-carbohydrate, high-fat (LCHF) or ketogenic-inspired diet, includes regimens with <130 g/day of carbohydrates that may not consistently achieve ketosis but reproduce many of its metabolic effects.

Verification of Ketosis

Verification of nutritional ketosis is central to both clinical and research implementation. Measurement of capillary or venous BHB concentration via enzymatic assays or point-of-care meters is the gold standard, offering greater accuracy and specificity than urinary acetoacetate strips. Stable ketosis is typically achieved after 3–7 days of carbohydrate restriction and reflects a metabolic transition from glucose to fat-derived ketone oxidation [2]. In clinical settings, maintaining BHB between 0.5 and 3.0 mmol/L correlates with improved glycemic control and reduced appetite [13]. Continuous or periodic BHB monitoring allows for individualized titration of macronutrient ratios and energy intake.

Fat Quality and Composition

While carbohydrate restriction defines ketosis, the quality of dietary fat critically modulates metabolic outcomes. Medium-chain triglycerides (MCTs) are rapidly absorbed and preferentially oxidized in the liver, enhancing ketone production without requiring carnitine-dependent transport into mitochondria [14]. Diets enriched in MCT oil may thus achieve higher BHB levels with lower total fat intake, improving tolerability and gastrointestinal comfort. Conversely, excessive intake of long-chain saturated fats can unfavorably alter lipoprotein profiles, raising LDL-C and apoB concentrations despite overall triglyceride reduction [9]. Replacing part of the saturated fat with mono- and polyunsaturated fatty acids from olive oil, nuts, and fish yields a more favorable lipid and inflammatory response, aligning KD principles with cardiometabolic safety.

In translational contexts, recent work emphasizes the interaction between fat source and hepatic signaling. Polyunsaturated fats activate PPARα, promoting β-oxidation and ketogenesis while downregulating lipogenic transcription factors such as SREBP-1c and ACC [4]. These mechanistic effects underpin the clinical observation that KDs rich in unsaturated fats maintain hepatic health and mitigate NAFLD progression.

Practical Implementation and Variability

Implementation requires contextual adaptation based on patient phenotype, metabolic goals, and comorbidities. VLCKD protocols are often medically supervised and limited to 8–12 weeks, transitioning to refeeding phases with gradual carbohydrate reintroduction [15]. WFKD and LCHF models can be sustained long-term, provided micronutrient sufficiency and electrolyte balance are ensured. Key

operational steps include baseline biochemical assessment, dietary education, and routine monitoring of lipid fractions, renal and hepatic function, and BHB levels [11][12].

The definition of “ketogenic” is not monolithic but is functionally anchored in achieving and maintaining nutritional ketosis through deliberate macronutrient manipulation. The therapeutic and mechanistic effects of a KD depend not only on carbohydrate restriction but also on the nature of fat intake, protein adequacy, and adherence to physiological and safety boundaries. Understanding these nuances is essential before interpreting metabolic and molecular outcomes across heterogeneous KD studies [2][4][9].

Clinical Evidence in Humans

Glycemic Control and Insulin Resistance

Clinical evidence consistently demonstrates that ketogenic interventions improve glycemic indices and insulin sensitivity in individuals with obesity and type 2 diabetes mellitus (T2DM). Zhou et al. [7] conducted a meta-analysis of eight randomized controlled trials (RCTs), reporting significant reductions in glycated hemoglobin (HbA1c; SMD −0.38, $p < 0.001$), fasting plasma glucose, and HOMA-IR, alongside improved triglyceride and HDL-C profiles [16][17]. Similar results were reported by Bruci et al. [18], who observed a 20% body-weight reduction and improved glucose tolerance after 12 weeks of VLCKD, with no deterioration in renal function among patients with mild kidney impairment. Collectively, these findings suggest that ketosis-driven metabolic reprogramming mitigates hepatic and peripheral insulin resistance through reductions in ectopic fat accumulation and lipotoxic intermediates [3].

Mechanistically, these improvements align with increased ketone oxidation and decreased hepatic gluconeogenesis, reflecting shifts in substrate utilization. The suppression of the carbohydrate–insulin axis reduces circulating insulin and promotes AMPK activation, which in turn enhances fatty acid oxidation and mitochondrial efficiency [19][20]. In metabolic psychiatry contexts, Sethi et al. [21] demonstrated similar metabolic normalization, with 27% reductions in HOMA-IR and triglycerides among participants with schizophrenia and bipolar disorder receiving a KD intervention, supporting the robustness of these effects across diagnostic categories.

Lipid Profile: Triglycerides, HDL, and LDL Heterogeneity

Across multiple trials, KD induces marked decreases in triglycerides and increases in HDL-C, though LDL-C responses are heterogeneous. Bueno et al. [9] summarized 13 long-term RCTs comparing VLCKD versus low-fat diets, demonstrating significant TG reductions (−0.18 mmol/L) and HDL-C increases (+0.09 mmol/L), yet modest LDL-C elevation (+0.12 mmol/L). However, subsequent studies with fat-quality optimization have mitigated LDL-C variability. For instance, Lambadiari et al. [10] reported that a KD rich in unsaturated fats reduced inflammatory cytokines (IL-6, IL-17, IL-23) and improved the disease activity index in psoriatic arthritis without adverse LDL-C changes [22]. These outcomes reinforce the notion that apoB particle concentration and LDL subfraction composition, rather than total LDL-C, should guide lipid risk interpretation in ketogenic therapy [3][9].

Weight and Central Adiposity

KD consistently promotes significant weight and visceral fat loss beyond calorie-matched controls. In a systematic review of 15 studies, Muscogiuri et al. [11] found greater reductions in body weight, waist circumference, and fat mass compared to non-ketogenic interventions. The EMIKETO trial [23] further demonstrated sustained weight loss and improved quality-of-life scores in migraine patients with a BMI >27 kg/m² undergoing an 8-week VLCKD, with effects persisting at 24 weeks even after carbohydrate reintroduction. These changes are attributed to decreased appetite via BHB-mediated central signaling (including GDF15 induction) and enhanced fatty acid oxidation efficiency [5][8].

Blood Pressure and RAAS Modulation

KD interventions have shown favorable modulation of blood pressure, partially mediated by reduced sympathetic tone and renin–angiotensin–aldosterone system (RAAS) adaptations. In the EMIKETO study, VLCKD produced significant reductions in inflammatory markers (CRP, NLR, WBC) and modulated aldosterone without perturbing electrolytes [23][24]. These effects parallel experimental findings of ketone-driven endothelial nitric oxide preservation and reduced oxidative stress, suggesting a plausible mechanistic link between ketosis and vascular homeostasis [20][25].

NAFLD and Hepatic Outcomes

In populations with NAFLD or metabolic-associated steatotic liver disease (MASLD), KDs induce hepatic fat mobilization and improvement in transaminases. Li et al. [26] observed resolution of hepatic steatosis in 6 of 7 PCOS patients with concurrent fatty liver after 12 weeks of KD, compared with 1 of 10 in the pharmacological control [27]. Mechanistically, hepatic β-oxidation upregulation and suppression of lipogenic genes (SREBP-1c, FASN) through PPARα activation have been documented in parallel animal models [4][19], providing biological plausibility for these clinical findings.

Safety and Tolerability

Under medical supervision, KD and VLCKD regimens are generally safe and well-tolerated. The main adverse effects include transient fatigue, gastrointestinal discomfort, and reversible dyslipidemia during adaptation phases [28]. Bruci et al. [18] demonstrated preserved renal and hepatic safety profiles, even in individuals with pre-existing mild kidney dysfunction. Long-term safety beyond 12 months requires continued lipid and micronutrient monitoring but does not indicate systematic harm when diets are nutritionally complete [22][29].

Quantitative Reinforcement from Meta-Analyses

Recent quantitative syntheses reinforce these clinical signals. Zhou et al. [7] confirmed moderate-to-large effect sizes for weight and glycemic improvement. Bueno et al. [9] established the durability of TG and HDL benefits for up to one year. Collectively, meta-analytic data converge on the conclusion that ketogenic diets are metabolically advantageous for MetS components, particularly hypertriglyceridemia, insulin resistance, and central adiposity, with LDL-C variability remaining the principal domain of individualized response [22][30].

Human clinical data portray KD as a potent metabolic intervention for multiple facets of MetS. The consistency of TG, glucose, and weight improvements, combined with mechanistic coherence regarding insulin and lipid metabolism, supports its translational relevance [3][7][18]. The ensuing section will contextualize these outcomes through mechanistic insights from preclinical models, delineating molecular pathways that connect ketone signaling with observed clinical effects.

Translational Integration: From Bench to Bedside

Translational metabolism aims to bridge mechanistic findings from preclinical models with clinically actionable outcomes in MetS. The ketogenic diet represents a rare case in which metabolic reprogramming can be traced through a continuous mechanistic spectrum—from hepatic transcriptional shifts and mitochondrial adaptation to measurable biomarkers such as BHB, TG, glucose, and inflammatory indices [2][3]. This section integrates these mechanistic and clinical domains into a unified translational framework [7].

Mapping Mechanistic Pathways to Clinical Endpoints

The consistent clinical reductions in TG, fasting glucose, and body weight observed in humans correspond to specific, experimentally validated mechanisms (Table 1).

Endpoint	Mechanism	Key Targets	Outcome	References
Triglycerides (TG) ↓	Hepatic PPARα activation and suppression of SREBP-1c/ACC → ↓ de novo lipogenesis and ↑ β-oxidation; attenuation of NLRP3 inflammasome → ↓ hepatic insulin resistance → ↓ VLDL-TG output	PPARα, SREBP-1c, ACC, NLRP3, VLDL-TG	Lower serum TG; improved TG/HDL profile	[4]
Glycemia / Insulin Resistance ↓	Restraint of hepatic glucose production via AMPK–mTORC1 crosstalk and reduced gluconeogenic flux; ↑ mitochondrial oxidative capacity via SIRT3 and PGC-1α	AMPK, mTORC1, SIRT3, PGC-1α, HOMA-IR	Lower FPG/HbA1c; reduced HOMA-IR	[7]
LDL and apoB Variability	Lipidomic and transcriptional adaptations depend on fat quality: mono-/polyunsaturated fats → activate PPARα without ↑ apoB; saturated fats → transient ↑ in LDL-apoB despite metabolic improvement	PPARα, apoB, LDL subfractions	HDL ↑; TG ↓; variable LDL-C; preference for unsaturated fats	[10]
Blood Pressure ↓	↓ RAAS activity and endothelial oxidative stress; ↑ NO bioavailability and ↓ NADPH oxidase activity	RAAS, NO, NADPH oxidase	Modest ↓ systolic/diastolic BP; improved vascular tone	[23]
NAFLD / MASLD Improvement	Hepatic defatting via ↑ β-oxidation and ↓ caloric absorption mediated by bile acids; ↑ TDCA/TUDCA levels in mice correspond to improved hepatic enzymes in humans	β-oxidation, TDCA, TUDCA, ALT/AST	↓ hepatic fat; ↓ transaminases	[4][26]

Table 1. Mechanistic pathways linking ketogenic diet interventions with clinical endpoints in metabolic syndrome

Symbols: ↑ increase; ↓ decrease.

Biomarker Alignment and Predictive Profiles

BHB serves as both a metabolic state indicator and a mechanistic effector. Sustained BHB levels between 0.5 and 3.0 mmol/L correlate with improvements in insulin sensitivity and TG metabolism, consistent with HDAC inhibition thresholds observed in cellular models [2]. Additional biomarkers with translational relevance include:

1. *ApoB*: Reflects atherogenic lipoprotein particle number and provides a more accurate gauge of cardiovascular risk than total LDL-C. KD trials with fat-quality control show stable or reduced apoB despite variable LDL-C [9].
2. *hs-CRP*: Decreases across both VLCKD and WFKD interventions, aligning with suppressed NLRP3 inflammasome signaling.
3. *FGF21*: Elevated in fasting and KD conditions, acting as a hepatokine mediator of systemic fatty acid oxidation and adipose browning [8].
4. *GDF15*: Identified as a key anorexigenic signal induced by hepatic pathway activation under KD feeding, linking molecular signaling to human appetite suppression and weight loss [5].

Integrating these markers into longitudinal KD protocols allows mechanistic validation in vivo and supports precision nutrition strategies. Profiling both BHB and apoB trajectories, for example, may distinguish metabolically favorable responders from those developing atherogenic lipid shifts [29].

Systems-Level Synthesis

Ketone signaling creates a biochemical bridge between cellular energetics and whole-body metabolism. By unifying mitochondrial efficiency (AMPK–SIRT3–PGC-1α axis), lipid turnover (PPARα-dependent β-oxidation), endocrine control (FGF21, GDF15), and inflammatory modulation (NLRP3/HDAC), KD achieves a coordinated reduction in metabolic load [2][4][8]. Clinically, this manifests as improved insulin sensitivity, decreased visceral adiposity, and enhanced cardiovascular and hepatic profiles [7][11].

These bench-to-bedside correspondences illustrate a rare alignment in nutritional biomedicine: a dietary intervention with traceable molecular causality. However, translation demands rigorous standardization —control of fat type, duration, and energy balance—to differentiate ketone-driven mechanisms from caloric restriction effects [9][10]. Establishing such mechanistic congruence enables the rational design of

biomarker-guided KD trials and informs the broader application of metabolic therapeutics targeting similar pathways [4][29].

Practical Considerations

Translating ketogenic diets (KD) from research to real-world clinical settings demands rigorous design, individualized supervision, and ongoing biochemical monitoring. Beyond macronutrient prescription, successful implementation hinges on nutritional adequacy, adherence strategies, and systematic safety evaluation [11][12].

Dietary Design and Macronutrient Structuring

A therapeutic KD typically allocates 70–80% of total energy from fats, 15–20% from protein, and less than 10% from carbohydrates. However, the specific composition should be tailored according to metabolic phenotype, comorbidities, and therapeutic goals [11]. For individuals with insulin resistance or obesity, very-low-calorie ketogenic diets (VLCKD; 500–800 kcal/day) are used for short-term (8–12 weeks) rapid metabolic resetting, followed by structured refeeding phases [15]. Longer-term interventions, such as well-formulated ketogenic diets (WFKD), are suitable for maintenance phases, emphasizing unsaturated fats, adequate protein, and rich micronutrient sources from vegetables, nuts, and fish [9][12].

Energy distribution must also consider fat quality. Diets dominated by monounsaturated and polyunsaturated fats (e.g., olive oil, avocados, fish) mitigate LDL-C elevation and maintain an anti-inflammatory tone compared with those high in saturated fats [9][10]. Including medium-chain triglycerides (MCTs) can facilitate ketosis at lower total fat loads, improving tolerability [14]. Fiber sources from low-carbohydrate vegetables should be preserved to maintain gut health and bile acid turnover [4].

Adherence and Behavioral Support

Dietary adherence represents the main determinant of KD success. Sustained compliance correlates with patient education, psychosocial support, and regular follow-up [12]. Structured coaching, digital self-monitoring, and group sessions have been shown to improve retention and metabolic outcomes [31]. Periodic feedback through BHB monitoring reinforces motivation by providing tangible biochemical feedback of adherence. Moreover, behavioral interventions addressing the food environment, satiety

cues, and cognitive patterns are essential for long-term maintenance once ketosis-induced appetite suppression wanes [29].

Verification of Ketosis and Biomarker Monitoring

Objective verification of ketosis is essential for both efficacy and safety. Capillary BHB levels between 0.5–3.0 mmol/L represent nutritional ketosis; values above 5.0 mmol/L warrant assessment for possible over-restriction or inadequate caloric intake [13]. Urinary acetoacetate strips provide low-cost but less reliable alternatives for screening. Clinical monitoring should include fasting glucose, lipid profile (TG, HDL-C, LDL-C, apoB), renal and hepatic panels, electrolytes, and inflammatory markers such as hs-CRP [2][9].

For research-grade or advanced clinical programs, additional biomarkers—FGF21, GDF15, bile acid panels, and transcriptomic indicators of PPARα or AMPK activation—can offer mechanistic insight and predictive value [4][5][8]. Tracking these markers over time enables differentiation between metabolic adaptation and maladaptive responses [29].

Safety and Clinical Supervision

Under medical supervision, KD and VLCKD regimens are generally safe for patients with obesity, insulin resistance, and MetS, including those with mild kidney impairment when monitored [18]. However, contraindications include pregnancy, active eating disorders, severe hepatic or renal insufficiency, and inborn errors of fat metabolism. The early adaptation phase may involve fatigue, dehydration, constipation, or transient dyslipidemia (“keto flu”), which typically resolve with electrolyte adjustment and adequate fluid intake. Long-term monitoring is advised for micronutrients (magnesium, selenium, zinc), bone health, and thyroid function [22][28].

Integrative and Lifestyle Context

KD should be integrated into broader lifestyle frameworks including physical activity, circadian alignment, and sleep hygiene. Exercise synergizes with ketosis by enhancing mitochondrial biogenesis and fatty acid oxidation (PGC-1α–SIRT3 axis) [20]. Aligning feeding with circadian rhythms—preferably within daytime windows—optimizes hepatic and adipose gene expression [32][33]. Sleep optimization further improves insulin sensitivity and appetite control, augmenting the durability of KD-induced benefits [29].

In clinical translation, ketogenic nutrition should be conceptualized not as a static dietary pattern but as a dynamic metabolic intervention requiring structured initiation, mechanistic validation, and long-term sustainability planning. When implemented with precision and ongoing monitoring, KD represents a viable strategy for metabolic syndrome reversal and an experimental platform for nutrient-driven metabolic therapies [2][4][7].

Knowledge Gaps and Research Agenda

Despite promising translational evidence, several methodological and mechanistic gaps constrain the clinical generalization of ketogenic diets for metabolic syndrome. Addressing these uncertainties requires harmonization of study designs, standardization of biomarkers, and integrative translational frameworks that explicitly connect mechanistic pathways with patient-level outcomes [2][4][5][8].

Heterogeneity and Study Design Limitations

Current KD trials vary markedly in macronutrient ratios, caloric content, fat quality, and ketosis verification. This heterogeneity limits comparability and meta-analytic precision. For instance, many studies label diets as “ketogenic” without biochemical confirmation of BHB levels, resulting in misclassification bias [2][13]. Future studies should adopt a standardized definition of nutritional ketosis (BHB 0.5–3.0 mmol/L) and document adherence longitudinally.

Trial duration remains a major limitation. Most interventions span less than 16 weeks, insufficient to capture long-term adaptations in lipid metabolism, endocrine axes, or hepatic fat turnover. Future parallel-arm randomized controlled trials of ≥6–12 months are required to evaluate durability, lipid remodeling, and cardiometabolic outcomes beyond early weight loss [7][9][11]. Extended trials should also include structured refeeding phases to assess metabolic hysteresis and reversion dynamics.

Control diets frequently lack metabolic equivalence. Comparators should match energy and protein content, isolating carbohydrate restriction as the independent variable [12][22]. Likewise, blinded feeding protocols and crossover designs could help separate physiological from behavioral effects (e.g., appetite suppression vs. caloric deficit). Multi-arm trials comparing VLCKD, WFKD, and Mediterranean-type low-carbohydrate diets would clarify whether observed benefits stem from ketosis per se or general carbohydrate reduction [10].

Mechanistic and Biomarker Gaps

Mechanistic studies have established BHB-mediated HDAC inhibition, NLRP3 suppression, and PPARα-driven β-oxidation as central processes, yet quantitative biomarker integration remains incomplete [2][4][19]. Biochemical and omics-level phenotyping—including transcriptomic, metabolomic, and lipidomic profiles—should be standardized across trials to capture the multidimensional nature of KD responses. Key biomarkers warranting consistent measurement are included in Table 2.

Biomarker	Purpose	Analytes/assays	Clinical use	References
ApoB & LDL particle number	Differentiate benign LDL-C elevations from atherogenic dyslipoproteinemia	apoB (immunoassay), LDL-P (NMR or ion mobility), non-HDL-C, LDL-C; optional small-dense LDL	Baseline and follow-up with fat-quality optimization; interpret alongside TG/HDL	[9][10]
Hepatic–adipose endocrine axis	Index crosstalk and appetite/energy-balance signaling	FGF21, GDF15, adiponectin (ELISA/chemiluminescence)	Exploratory/responder phenotyping; may track with weight and satiety changes	[5][8]
Bile-acid signaling	Mechanistic correlate of caloric absorption and hepatic signaling	Targeted bile-acid panel including TDCA, TUDCA (LC–MS/MS)	Align with hepatic enzymes and weight change; supports gut–liver axis hypotheses	[4]

Table 2. Standardized biomarker panel linking mechanisms to clinical endpoints in KD interventions for MetS

Symbols: ↑ increase; ↓ decrease.

Integrating these metrics into multi-timepoint sampling frameworks will enable the construction of mechanistic response maps that predict clinical outcomes, moving from association to causality [5][29].

Population-Level and Genetic Considerations

Responses to KD are modulated by sex, age, ethnicity, and genetic polymorphisms in lipid and ketone metabolism pathways (e.g., APOE, PPARα, HMGCS2 variants) [7]. Women and older adults may display attenuated ketone production or distinct lipid responses. Future research should stratify analyses by sex and genotype to uncover precision-nutrition subgroups and mitigate adverse lipid phenotypes in genetically susceptible individuals [29].

Additionally, the interaction between KD and circadian biology warrants systematic study [32][33][34]. Feeding–fasting cycles modulate hepatic ketogenesis and insulin sensitivity through clock-controlled transcription factors (REV-ERBα, BMAL1). Controlled trials comparing daytime versus evening KD feeding could elucidate chrononutritional effects relevant for optimizing efficacy and safety.

Integrative Systems and Translational Frameworks

To advance the field, KD research must transition from isolated endpoints to systems-level translational models. These should integrate clinical readouts (weight, glycemia, TG, LDL, hepatic enzymes) with mechanistic biomarkers (BHB, apoB, FGF21, bile acids) and digital phenotyping (continuous glucose monitoring, metabolite sensors) [12]. Machine-learning approaches can be leveraged to model interindividual response patterns and derive predictive biomarkers of KD responsiveness [29].

Animal–human translational pipelines should include parallel mechanistic arms using isocaloric KD formulations matched to human macronutrient distributions. These models can validate candidate pathways—such as AMPK–SIRT3 signaling or GDF15-mediated hypophagia—before scaling to clinical trials [4][19]. Moreover, adaptive trial designs incorporating interim mechanistic endpoints could shorten translational cycles [2][8].

Proposed Research Agenda

1. *Define standardized KD criteria*: Unified macronutrient ratios and BHB thresholds for “nutritional ketosis.”
2. *Implement long-term, parallel RCTs (≥12 months)*: Focused on lipid remodeling, hepatic function, and inflammatory resolution [9][11].
3. *Integrate multi-omics biomarker panels*: Including FGF21, GDF15, apoB, bile acids, and mitochondrial activity metrics [4][5].

4. *Adopt precision-nutrition frameworks*: Stratifying participants by sex, genotype, and baseline metabolic phenotype [7][29].
5. *Leverage digital monitoring tools*: Continuous glucose/ketone sensors to improve adherence and mechanistic mapping [12].
6. *Promote translational symmetry*: Aligning animal model parameters (isocaloric, fat quality, thermoneutrality) with human protocols [33].
7. *Develop mechanistically anchored endpoints*: Linking specific pathways (e.g., NLRP3 suppression, SIRT3 activation) to quantifiable clinical improvements [2][20].

Collectively, these initiatives would elevate KD research from descriptive metabolic observations to predictive, mechanism-based clinical science. The ultimate objective is not only to validate KD as a therapeutic tool for MetS but also to utilize it as a model system for nutrient-driven metabolic reprogramming, thereby expanding the conceptual boundaries of dietary interventions in precision medicine [4][5][8].

Conclusion

Ketogenic diets consistently lower triglycerides, improve glycemic control/insulin resistance, and reduce central adiposity in metabolic syndrome, concordant with hepatic PPARγ activation, AMPK–SIRT3–PGC-1α mitochondrial enhancement, and inflammasome restraint [2][4][5][7]. Reductions in TG and glycemia reflect suppressed de novo lipogenesis and improved mitochondrial efficiency; insulin sensitivity gains arise from β-hydroxybutyrate (BHB) signaling and endocrine mediators FGF21 and GDF15 [5][6][8]. LDL-C responses remain heterogeneous; emphasize unsaturated fats and monitor apoB [9][10].

Preclinical signals—fatty-acid oxidation, hepatic defatting, redox improvement—mirror human phenotypes, reinforcing a mechanistic–clinical continuum [2][4]. Clinically, durability and safety require supervision and a minimum panel: BHB 0.5-3.0 mmol/L, TG/HDL, LDL-C/apoB, transaminases, hs-CRP [11][23]. Priorities include $\geq$12-month parallel RCTs with harmonized biomarkers (BHB, apoB, FGF21, GDF15, bile acids, hs-CRP) to define responder phenotypes [4][5]. KD thus functions both as therapy and as a model system for nutrient-signaling therapeutics in MetS [7].

Abbreviations

- ACC: acetyl-CoA carboxylase
- AMPK: AMP-activated protein kinase
- apoB: apolipoprotein B
- APOE: apolipoprotein E
- BHB: β-hydroxybutyrate
- BMI: body mass index
- BMAL1: brain and muscle ARNT-like 1
- CRP: C-reactive protein
- FASN: fatty acid synthase
- FGF21: fibroblast growth factor 21
- GDF15: growth differentiation factor 15
- HDAC: histone deacetylase
- HDL-C: high-density lipoprotein cholesterol
- HMGCS2: 3-hydroxy-3-methylglutaryl-CoA synthase 2
- HOMA-IR: homeostasis model assessment of insulin resistance
- hs-CRP: high-sensitivity C-reactive protein
- IL-6: interleukin-6
- IL-17: interleukin-17
- IL-23: interleukin-23
- KD: ketogenic diet
- LCHF: low-carbohydrate, high-fat (diet)
- LDL-C: low-density lipoprotein cholesterol
- MASLD: metabolic-associated steatotic liver disease
- MetS: metabolic syndrome
- MCT: medium-chain triglyceride
- mTORC1: mechanistic target of rapamycin complex 1
- NAFLD: non-alcoholic fatty liver disease
- NADPH: nicotinamide adenine dinucleotide phosphate (reduced)
- NLR: neutrophil-to-lymphocyte ratio
- NLRP3: NOD-, LRR- and pyrin domain-containing protein 3 (inflammasome)

- PBMCs: peripheral blood mononuclear cells
- PCOS: polycystic ovary syndrome
- PGC-1α: peroxisome proliferator-activated receptor gamma coactivator-1 alpha
- PPARα: peroxisome proliferator-activated receptor alpha
- RAAS: renin–angiotensin–aldosterone system
- RCT: randomized controlled trial
- REV-ERBα: nuclear receptor subfamily 1, group D, member 1 (NR1D1)
- SIRT3: sirtuin-3
- SMD: standardized mean difference
- SREBP-1c: sterol regulatory element-binding protein-1c
- T2DM: type 2 diabetes mellitus
- TDCA: taurodeoxycholic acid
- TG: triglycerides
- TUDCA: tauroursodeoxycholic acid
- VLDL: very-low-density lipoprotein
- VLCKD: very-low-calorie ketogenic diet
- WBC: white blood cell (count)
- WFKD: well-formulated ketogenic diet

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