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Peer Review

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

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I. Summary and Overall Impression

This manuscript provides a timely and comprehensive translational review on the role of Ketogenic Diets (KD) in the non-pharmacological management of Metabolic Syndrome (MetS). The authors effectively summarize the consistent clinical benefits of KD—including improvements in triglycerides, glycemic control, and central adiposity—and align these outcomes with underlying molecular mechanisms, particularly the signaling roles of beta-hydroxybutyrate (BHB) (e.g., inhibition of HDACs and the NLRP3 inflammasome, and activation of AMPK-SIRT3-PGC-1alpha pathways).[1]

The paper's greatest strength lies in its critical examination of current clinical trial limitations. This analysis, which highlights the urgent need for standardized protocols, **should be widely recognized by researchers and clinicians** to prevent the misinterpretation or underestimation of KD efficacy stemming from flawed or poorly monitored study designs.

II. Major Comments

The core findings and recommendations of this review are robust, but two key areas require expansion to maximize the manuscript's translational impact, particularly concerning the necessary separation of BHB-driven effects from macronutrient effects.

1. Strengthening the Critique on Methodological Flaws and Need for Standardization (BHB and Biomarker Absence):

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The manuscript rightly stresses that many current trials rely solely on macronutrient composition (nutritional KD) rather than verifiable metabolic status (nutritional ketosis). This crucial point must be amplified: Failure to standardize and verify stable blood BHB levels (e.g., 0.5-3.0 mmol/L) risks misclassification bias and fundamentally limits the interpretability of KD outcomes. The effect seen in nutritional KD could be attributed either to high fat intake, low carbohydrate intake, or the presence of BHB.

The authors correctly propose that future trials mandate BHB concentration measurement and include a multi-omic biomarker panel (e.g., ApoB, FGF21, GDF15).1 I recommend moving the call for these standardized, mechanistically relevant biomarkers to a more prominent position, perhaps integrating Table 2 material directly into the main text of the "Knowledge Gaps" section, to underscore its importance as a mandatory criterion for future studies.

2. Expanding the Discussion on Exogenous Ketone Use to Isolate Mechanisms:

The paper mentions that Medium-Chain Triglycerides (MCTs) can enhance ketone production. However, to definitively address the critical mechanistic gap identified—namely, differentiating effects stemming from the ketogenic macronutrient profile (low-carb/high-fat) versus those directly mediated by BHB signaling—the authors must discuss the importance of clinical trials utilizing Exogenous Ketones (Ketone Salts or Esters).

Exogenous ketone supplementation provides a unique experimental tool to raise circulating BHB levels (the mechanistic effector) without imposing the stringent macronutrient restrictions of a nutritional KD. Inclusion of this discussion is vital for addressing the inherent causality dilemma in nutritional KD studies: is the benefit due to low glucose, high fat, or high BHB. Trials utilizing direct BHB intake are paramount for the precision nutrition model that the authors advocate.

III. Minor Comments

1. **Terminology Precision:** In the definitions section, please ensure maximum clarity when discussing "Low-Carbohydrate, High-Fat (LCHF) or ketogenic-inspired diets" which *may not* consistently achieve ketosis. Reiterate that these diets, while reproducing *some* metabolic effects, fall outside the strict definition of KD, which is "functionally anchored in achieving and maintaining nutritional ketosis". This prevents conceptual blurring for non-expert readers.
2. **Abbreviations:** Although a full abbreviation list is provided, consider defining abbreviations (e.g., FGF21, GDF15) when they are first introduced in the main body text (especially in the "Biomarker

Alignment" section) to improve reading flow.

Recommendation: Major Revision (Due to the critical need to incorporate the discussion on exogenous ketones as a necessary future research direction for mechanistic validation).

Declarations

Potential competing interests: No potential competing interests to declare.