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Peer Review

Review of: "Metabolic Diets and Fasting in Oncology: Integrating Guideline-Based Nutrition, Nutrition Assessments and Biomarker-Driven Clinical Pathology"

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This manuscript addresses a timely and clinically relevant topic by integrating guideline-based oncology nutrition with metabolic dietary interventions, malnutrition, sarcopenia, cachexia, and biomarker-informed assessment.

A major strength of the review is its overall cautious interpretation. The author clearly distinguishes evidence-based oncology nutrition from experimental metabolic interventions and appropriately states that fasting regimens, fasting-mimicking diets, time-restricted eating, and ketogenic diets should not be considered established anticancer treatments. The integration of nutritional vulnerability, body composition, cachexia, and translational biomarkers is also potentially valuable.

However, several aspects should be revised or expanded to strengthen the manuscript.

1. Methodological transparency

The main limitation concerns the methodology of the narrative review. The manuscript reports searches of PubMed/MEDLINE, Web of Science, and Scopus, supplemented by hand-searching, but the search strategy, eligibility criteria, study-selection process, and criteria used to prioritize individual studies are not described in sufficient detail.

Although this is explicitly a narrative rather than a systematic review, greater methodological transparency would improve reproducibility and reduce the risk of selective citation.

I would suggest that the author specify at least:

the exact date of the last literature search;

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the time interval considered, avoiding approximate formulations;

a complete example search strategy for at least one major database, including free-text terms, indexed terms where applicable, and Boolean operators;

explicit inclusion and exclusion criteria;

the study designs prioritized for each research question;

the criteria used to select mechanistic and translational studies;

whether and how the methodological quality and relevance of the included sources were critically assessed.

A pragmatic approach could be to add a short methodological table including: **database, search period, main search terms, eligibility criteria, and prioritized type of evidence**.

Because this is a narrative review, the author may also consider using the **SANRA (Scale for the Assessment of Narrative Review Articles)** as a reference to improve reporting quality. I would not recommend requiring PRISMA unless the author intends to redesign the manuscript as a systematic review.

2. Hierarchy of evidence

The manuscript combines clinical guidelines, randomized trials, prospective and observational studies, systematic reviews, and mechanistic or preclinical evidence. This broad approach is appropriate for a translational review, but the different levels of evidence should be more clearly distinguished throughout the manuscript.

In particular, feasibility, safety, biomarker modulation, pathological or surrogate endpoints, clinical efficacy, and survival outcomes should not be presented as equivalent levels of evidence.

I would suggest organizing the evidence into distinct domains:

Clinical efficacy: clinically relevant oncological outcomes such as PFS, OS, recurrence, or validated tumor response.

Safety and feasibility: adherence, adverse events, tolerability, treatment discontinuation, and nutritional risk.

Surrogate or pathological endpoints: pathological response, imaging endpoints, and other surrogate measures.

Metabolic and biological modulation: IGF-1, insulin, glucose, ketones, inflammatory markers, and body composition.

Mechanistic/preclinical evidence: autophagy, tumor metabolism, immune microenvironment, and experimental models.

This distinction would help prevent biomarker changes from being implicitly interpreted at the same evidentiary level as demonstrated clinical benefit.

A summary table could use a structure such as:

Intervention | Tumor/setting | Study design | N | Main endpoint | Main result | Level of evidence | Main limitations

For example, the DIRECT trial could be presented as randomized evidence of metabolic modulation and signals in radiological and pathological endpoints, while clearly stating that the study was not powered to demonstrate a survival benefit.

3. Clinical heterogeneity

The manuscript discusses highly heterogeneous tumor types, treatment settings, and nutritional interventions. Findings from breast cancer, glioblastoma, gastrointestinal malignancies, advanced disease, survivorship, and different treatment contexts cannot necessarily be generalized across settings.

This heterogeneity should be acknowledged more explicitly not only in the Methods section but also in the interpretation of the evidence.

A summary table stratified by type of intervention, tumor type, treatment setting, study design, sample size, main endpoint, and main findings would substantially improve clarity and would allow readers to better assess the strength and applicability of the available evidence.

4. Biomarker-informed assessment

The proposed integration of IGF-1, insulin, glucose, ketones, inflammatory markers, body composition, and tissue biomarkers is scientifically plausible and represents one of the most interesting aspects of the manuscript.

However, these biomarkers should be clearly presented as candidate or exploratory biomarkers. At present, the manuscript does not establish that they are validated predictive biomarkers for selecting patients for fasting or ketogenic interventions in routine oncology practice.

A clearer distinction between:

target-engagement biomarkers;

safety biomarkers;

prognostic biomarkers;

predictive biomarkers;

would significantly strengthen this section and reduce the risk of attributing a level of clinical maturity that is not supported by the current evidence.

5. Translational and mechanistic interpretation

The sections addressing autophagy, tumor metabolism, immune modulation, spatial transcriptomics, and metastatic morphogenesis are interesting, but some of these concepts remain primarily hypothesis-generating.

The manuscript would benefit from a clearer separation between:

mechanisms supported by human clinical data;

findings derived mainly from experimental models;

translational hypotheses that remain speculative.

In particular, links between systemic metabolic interventions and complex tumor morphogenetic programs should be explicitly framed as hypotheses for future research rather than presented at the same evidentiary level as clinical findings.

6. Nutritional safety and patient selection

The sections addressing malnutrition, sarcopenia, and cachexia are among the strongest parts of the manuscript and, in my view, should play an even more central role in the clinical interpretation.

Restrictive dietary interventions may be inappropriate or potentially harmful in patients with ongoing weight loss, reduced muscle mass, inadequate nutritional intake, or established cachexia.

This point should be emphasized as a fundamental prerequisite when interpreting and designing studies of metabolic interventions in oncology.

From a clinical perspective, before asking whether a metabolic intervention may be effective, it is essential to establish in which patients it can be studied without increasing nutritional risk.

Minor comments

The manuscript would benefit from a dedicated limitations section.

Terminology should be standardized, particularly when distinguishing fasting, intermittent fasting, fasting-mimicking diets, and time-restricted eating.

Some sections are repetitive, particularly those addressing the lack of demonstrated survival benefit and the importance of nutritional screening, and could be condensed.

The term “biological activity” should be used cautiously. Phrases such as “metabolic and biological modulation” or “measurable metabolic and biological effects” would better reflect the current level of evidence and reduce the risk of confusion with demonstrated antitumor activity.

Overall assessment

This is a relevant and potentially useful narrative review with an overall clinically appropriate message and an interesting translational perspective.

Its main strengths are the integration of nutritional risk, sarcopenia, cachexia, and biomarkers, together with the clear distinction between evidence-based supportive nutrition and experimental metabolic interventions.

However, substantial revision is required to improve methodological transparency, clarify the hierarchy of evidence, address clinical heterogeneity, and more clearly distinguish established clinical findings from exploratory biomarkers and mechanistic hypotheses.

I therefore consider the manuscript publishable after major revision.

Declarations

Potential competing interests: No potential competing interests to declare.