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Metabolic modulation of glioblastoma by dietary intervention: a systematic review

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Abstract

Objective: To systematically evaluate and critically synthesize preclinical and clinical evidence on the efficacy, safety, mechanistic rationale, and interpretive limitations of ketogenic diet (KD) and methionine restriction (MR) in glioma treatment.

Methods: We systematically searched PubMed and Embase from inception through August 19, 2026, for in vivo preclinical and clinical studies evaluating KD or MR in glioma. Clinical studies were eligible with or without a non-diet comparator because most available studies were early-phase, single-arm feasibility investigations. We extracted intervention, comparator, concurrent oncologic treatment, metabolic, safety, feasibility, and outcome data; assessed risk of bias using design-appropriate tools; and conducted narrative and structured direction-of-effect syntheses.

Results: A total of 43 eligible reports were included: 14 preclinical and 18 clinical KD reports and 9 preclinical and 2 clinical studies of MR. Preclinical effects were heterogeneous: several diet-only experiments reduced growth or prolonged survival, whereas others showed limited activity; selected combinations with radiation, antiangiogenic therapy, glutamine targeting, or immune modulation produced greater effects. Clinical evidence primarily supported feasibility and metabolic activity, not independent efficacy, because most studies were small, uncontrolled, and confounded by concurrent or prior treatment. MR showed preclinical activity, but clinical evidence remained limited to two small chemotherapy-combination trials.

Conclusion: KD and MR have biologic rationale and can alter systemic or intratumoral metabolism, but current clinical data do not establish an independent survival benefit. Their effects cannot be separated reliably from surgery, radiotherapy, chemotherapy, bevacizumab, corticosteroids, and other co-interventions in most studies. Randomized trials with intention-to-treat analysis, standardized glucose-ketone index reporting, treatment and corticosteroid documentation, and longitudinal nutritional assessment are required before these diets can be recommended as effective glioma therapy.

Keywords: Dietary intervention; Glioblastoma; Glioma metabolism; Ketogenic diet; Metabolic therapy; Methionine restriction.

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