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Commentary

Ketogenic dietary intervention as therapy for thrombocytopenia

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Chemotherapy-induced thrombocytopenia (CIT) is a common complication that increases bleeding risks and necessitates chemotherapy dose reduction or discontinuation, which decreases therapeutic benefits and worsens the chances of survival.[1] Current therapeutic options, such as platelet transfusion, administration of recombinant interleukin (IL)-11, and treatment with thrombopoietin receptor agonists, have potential drawbacks, including transfusion-related allergic reactions, fluid retention-induced heart disease, and the emergence of anti-thrombopoietin antibodies. In their recent study, Xie et al.[2] investigated the therapeutic potential of the ketogenic diet in CIT. Their results demonstrated that ketogenic diets increased platelet counts in mice by inducing megakaryopoiesis and thrombocytopoiesis via the metabolism of β-hydroxybutyrate (β-OHB) mediated by 3-β-hydroxybutyrate dehydrogenase and monocarboxylate transporter 1 (MCT1). Mechanistic studies in megakaryocytes have shown that β-OHB promotes the expression of *GATA1* and *NFE2*, two key regulators of megakaryocyte maturation and platelet production,[3,4] in a promoter-related histone H3 acetylation manner. More importantly, a retrospective clinical study indicated that the ketogenic lifestyle inversely correlates with the incidence of CIT in patients with cancer receiving conventional chemotherapy either alone or in combination with hormones or monoclonal antibodies. Strikingly, ketogenic diets or dietary β-OHB supplementation protected healthy cells from damage by chemotherapy or radiation and increased the sensitivity of cancer cells to chemotherapy.[5–7]

The study by Xie et al.[2] is impressive as it convincingly showed that ketogenic diets or dietary β-OHB supplementation ameliorated CIT in mouse models by inducing β-OHB-dependent expression of *GATA1* and *NFE2* in megakaryocytes. The use of megakaryocyte-specific MCT1 knockout mice and an MCT1-specific inhibitor helped to establish that MCT1 in megakaryocytes was critical for ketogenic diet-induced thrombocytopoiesis. The use of clinical samples from cancer patients receiving chemotherapy also provided compelling clinical correlates with mechanistic rodent findings, which collectively indicated that ketogenic diets might be used for the treatment of CIT. However, randomized controlled trials in larger patient cohorts will be critically needed in the future to confirm the therapeutic potential of ketogenic diets or dietary β-OHB supplementation in the treatment of CIT. It also remains unclear whether the concentration of chemotherapeutic agents could be elevated or whether patient survival would improve with a ketogenic diet. In addition, factors such as the dosing regimen, dosage form, and pharmacokinetics of β-OHB merit further investigation.

Although there is no direct evidence in support of the stimulating effect of the ketogenic diet on platelet counts in conditions other than CIT, this possibility is worth investigating. For instance, thrombocytopenia is commonly observed in approximately 5–10% of all pregnancies.[8] Whether the ketogenic diet, as a nontoxic and low-cost dietary intervention, can provide a complementary therapeutic strategy to patients that receive conventional medical treatment for thrombocytopenia also requires further investigation. In addition, it is possible that ketogenic dietary intervention is a promising therapeutic option for the treatment of immune-related thrombocytopenia caused by immune disorders, systemic infections, drugs (e.g., heparin and trimethoprim), or vaccinations (e.g., vaccines against influenza and COVID-19). Immune thrombocytopenia (ITP) is an autoimmune disease that causes a wide range of conditions, from mild mucocutaneous bleeding to life-threatening hemorrhage.[9] Although the pathophysiology of ITP remains obscure,

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glucocorticoids are used as the first-line treatment for ITP.[9] The concomitant use of a ketogenic diet with glucocorticoids could provide a better therapeutic outcome.

Overall, a nontoxic and low-cost ketogenic dietary intervention or dietary β-OHB supplementation may be a promising therapeutic option for treating thrombocytopenia induced by various causes.

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Author contributions

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Data availability statement

None.

Conflicts of interest

None.

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