Letter to Editor
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Beyond HbA1c: Artificial Intelligence and Gut Microbiome Metabolites for Predicting Diabetic Complications

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Dear Editor,

I am writing to draw attention to the remarkable advances in integrating artificial intelligence (AI) and gut microbiome metabolomics for predicting diabetic complications. Despite achieving recommended HbA1c targets, many patients continue to develop diabetic microvascular complications (1). HbA1c reflects mean glycaemia over approximately 90 days, captures neither glycemic variability nor mechanistic heterogeneity (2) and is confounded by hemoglobin variants, anemia, and ethnicity (3). An increasingly evidence-based avenue for more comprehensive risk stratification is the integration of artificial intelligence (AI) with gut microbiome metabolomics tools that are beginning to reveal metabolite signatures predicting nephropathy, retinopathy, and peripheral neuropathy with performance exceeding HbA1c-anchored models alone.

The mechanistic basis is substantive. Dysbiosis in type 2 diabetes is characterized by depletion of short-chain fatty acid-producing bacteria and increased uremic toxin-generating species, promoting glomerular inflammation and renal fibrosis (4). In diabetic retinopathy, distinct gut microbiota composition has been documented compared with diabetes controls, implicating the gut-retina axis as an independent injury pathway (5). For diabetic peripheral neuropathy, metabolomics identified serum formate-a microbial influenced metabolite-as a novel biomarker, with lower concentrations significantly associated with neuropathy severity (6).

Most associations remain predictive rather than definitively causal; whether restoring

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specific metabolites attenuates complication progression requires interventional trials. Nonetheless, AI is well placed to extract clinically relevant signal from high-dimensional metabolomic data. A machine-learning study integrating metabolomic data from 2,772 adults in the Singapore Epidemiology of Eye Diseases cohort showed metabolite-informed models outperformed traditional logistic regression in detecting diabetic kidney disease and retinopathy, with external validation in the UK Biobank (7). A 2025 review in Briefings in Bioinformatics synthesized 58 studies, concluding that cross-scale data fusion integrating metabolomics, proteomics, microbiome features and clinical variables warrants prospective validation as an emerging predictive paradigm (8). A prospective study in Nature Medicine demonstrated that multimodal profiles incorporating gut microbiome features alongside continuous glucose monitoring improved complication risk profiling relative to HbA1c alone (9).

Real barriers remain: metabolomic profiling is costly and methodologically unstandardized, and existing models are predominantly cross-sectional and retrospectively derived. Two priorities follow. First, prospective longitudinal studies should integrate gut microbiome metabolomics alongside HbA1c and continuous glucose monitoring, powered to detect complication-specific signatures with adequate ethnic diversity. Second, AI model development should adopt standardized reporting frameworks such as TRIPOD+AI to enable cross-study comparison and meta-analysis.

HbA1c will remain indispensable. The convergence of gut microbiome metabolomics and AI-driven prediction, however, could complement existing risk stratification and identify patients at risk of complications not captured by HbA1c alone provided the field commits to rigorous prospective validation.

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