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Is the glucose ketone index a biomarker of metabolic flexibility?

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A Viewpoint on the Frontiers in Science Lead Article

The glucose ketone index: a proposed quantitative biomarker to support cancer and chronic disease prevention and management

Key points

- The glucose ketone index (GKI) integrates circulating glucose and β-hydroxybutyrate (βHB) concentrations and may provide a useful description of the circulating metabolic state across a range of glucose–ketone profiles, beyond just the presence or degree of nutritional ketosis.
- The GKI reflects the relative availability of glucose and ketones across nutritional, behavioral, and pharmacologic interventions and may offer a practical indicator of metabolic flexibility, even though it does not directly measure cellular substrate utilization, fat or ketone oxidation, insulin sensitivity, mitochondrial function, or energy expenditure.
- Future continuous monitoring of glucose and ketones could characterize their longitudinal dynamics and help determine whether the GKI adds more clinically meaningful information than either analyte alone.

Introduction

In their recent *Frontiers in Science* lead article, Lee et al. propose the glucose ketone index (GKI), the ratio of circulating glucose to β-hydroxybutyrate (βHB), as a quantitative biomarker for monitoring nutritional ketosis and supporting the prevention and management of cancer and chronic disease (1). Their central argument is that mitochondrial dysfunction underlies most chronic disease, and that the balance between these two fuels offers a practical, point-of-care readout of metabolic status. We suggest that the GKI may have value beyond dietary adherence by providing a simple, integrated description of the circulating glucose–ketone milieu across nutritional, behavioral, and pharmacologic

interventions. Importantly, however, the GKI reflects circulating substrate availability rather than direct cellular substrate utilization.

Evolution shaped two complementary fuel systems

Humans evolved to use both glucose- and fat-derived fuels according to nutrient availability. During feeding, glucose serves as an efficient energy source for tissues with obligate glucose requirements. During fasting, prolonged exercise, illness, or carbohydrate restriction, fatty acid oxidation increases and the liver produces ketone bodies that provide an alternative fuel for the brain, heart, skeletal muscle, and other tissues (2). These pathways function cooperatively, allowing continuous adaptation to changing nutrient availability.

In modern societies, however, frequent consumption of refined, carbohydrate-rich foods, a chronic positive energy balance, and reduced physical activity have diminished the need to transition between glucose and fat metabolism. In particular, it has been suggested that ingestion of refined sugar, high-fructose corn syrup, and high-glycemic carbohydrates may activate a "fat switch," a conserved survival response that stimulates food intake, insulin resistance, and fat accumulation (3). Chronic nutrient excess, particularly prolonged exposure to fructose, glucose, and insulin, promotes substrate overload, ectopic lipid accumulation, mitochondrial dysfunction, oxidative stress, and impaired insulin signaling. Metabolic flexibility declines as the ability to appropriately transition between carbohydrate and lipid metabolism is progressively lost, contributing to obesity, type 2 diabetes (T2D), metabolic dysfunction-associated steatotic liver disease (MASLD), chronic kidney disease (CKD), and cardiovascular disease (3–6). These observations support the concept that metabolic dysfunction is driven not by a single nutrient but by the chronic mismatch between nutrient availability and the body's capacity to appropriately regulate substrate utilization (3).

Why the glucose ketone index matters

Most clinical biomarkers quantify individual physiological processes rather than the dynamic relationship between glucose and fat metabolism. HbA1c integrates chronic glycemia, fasting insulin reflects basal insulin secretion, and continuous glucose monitoring (CGM) enables the continuous assessment of glycemia. The GKI combines circulating glucose and βHB concentrations into a single ratio and, therefore, provides a simple description of their relative availability. Because both metabolites respond to nutritional, behavioral, and pharmacologic interventions, longitudinal GKI measurements may provide information about changes in the circulating metabolic milieu that is not apparent from glucose measurements alone.

This distinction is clinically important because glucose concentrations may improve through mechanisms that do not necessarily restore metabolic health. Pharmacologic glucose lowering, for example, can normalize glycemia without substantially improving insulin resistance or metabolic flexibility. Conversely, elevated ketone concentrations may result from fasting, prolonged exercise, exogenous ketone supplementation, or sodium–glucose cotransporter-2 (SGLT2) inhibitor therapy, each reflecting different physiological contexts (7, 8). By integrating both measures, the GKI reflects the physiological response to nutritional and metabolic interventions rather than dietary adherence alone (1).

The two variables comprising the GKI are not merely markers of substrate availability; they exert opposing effects on the mitochondrion, the organelle at the center of the metabolic dysfunction described above. Sustained hyperinsulinemia promotes ceramide accrual and impairs mitochondrial respiration in insulin-sensitive tissues (9); in brown adipose tissue, it reduces mitochondrial uncoupling in a manner that lowers energy expenditure (9). βHB exerts the opposite effect, increasing mitochondrial respiration in adipose tissue while reducing the emission of reactive oxygen species and mitochondrial fission (10). Viewed this way, the GKI reflects not only which fuel predominates but the bioenergetic consequence of that predominance, offering a mechanistic rationale for the link between the index and the mitochondrial function proposed by Lee et al. However, the index alone cannot determine which substrates are being oxidized by individual tissues; establishing those relationships will require comparison with direct physiological measures of substrate utilization.

A related consideration is that both terms of the ratio are governed by a common upstream regulator. Insulin restrains lipolysis and hepatic ketogenesis at concentrations well below those required to lower circulating glucose (4), so ketone production is suppressed long before glycemia rises. The GKI, therefore, functions in part as an accessible surrogate for the ambient insulin state, which is rarely measured in routine practice despite hyperinsulinemia preceding hyperglycemia by years in the natural history of insulin resistance. This interpretation clarifies why glycemic improvement that is achieved pharmacologically may leave the GKI largely unchanged and why interventions that lower insulin—whether nutritional, behavioral, or pharmacologic—move both terms of the ratio in the same favorable direction.

This distinction becomes increasingly important as precision nutrition moves beyond dietary prescriptions toward individualized metabolic responses (6). Individuals consuming identical diets often exhibit different metabolic responses owing to differences in genetics, medications, lifestyle, and underlying metabolic health. Consequently, biological adaptation may be more informative than dietary adherence alone.

The GKI across modern metabolic therapies

The expanding landscape of metabolic therapies provides an opportunity to reconsider how metabolic adaptation should be assessed. Although the GKI has primarily been discussed in the context of ketogenic or carbohydrate-restricted nutrition, its broader value may lie in evaluating the integrated physiological effects of

diverse interventions that influence glucose and fat metabolism. As obesity, T2D, MASLD, and CKD are increasingly managed using combination approaches, a common biomarker reflecting underlying metabolic adaptation may become particularly valuable.

Lifestyle interventions including carbohydrate restriction, calorie restriction, intermittent fasting, and exercise promote metabolic flexibility through overlapping mechanisms. Carbohydrate restriction most directly lowers the GKI by reducing circulating glucose while promoting endogenous ketone production (1). Calorie restriction and intermittent fasting similarly shift substrate utilization toward greater fatty acid oxidation and ketogenesis by inducing the metabolic switch from glucose utilization to lipid-derived fuels (7), while exercise enhances glucose disposal, mitochondrial function, and metabolic flexibility (5). Despite these shared physiological effects, considerable interindividual variability exists, highlighting the need for objective biomarkers that assess metabolic response rather than adherence to a specific intervention.

Modern pharmacologic therapies also influence the metabolic pathways reflected by the GKI. GLP-1 receptor agonists and dual- or triple-incretin agonists improve glycemic control while suppressing appetite, slowing gastric emptying, and reducing energy intake, frequently resulting in spontaneous calorie restriction (8). These effects promote weight loss, improve insulin sensitivity, reduce hepatic steatosis, and may partially recapitulate metabolic adaptations to caloric restriction, including greater fat oxidation (8). In contrast, SGLT2 inhibitors lower glucose availability through urinary glucose excretion, reduce circulating insulin concentrations, increase glucagon secretion, and promote endogenous ketone production (8). Although these therapies act through mechanisms different from those of nutritional interventions, they converge on improving metabolic homeostasis. A lower GKI during pharmacologic treatment may arise through mechanisms that differ substantially from those operating during carbohydrate restriction, fasting, or exercise. These examples underscore that the GKI is best interpreted as a context-dependent measure of circulating glucose and ketone availability rather than as a mechanism-specific measure of metabolic adaptation.

The future of the GKI: continuous metabolic monitoring and precision medicine

The evolution of CGM transformed diabetes care by shifting disease management from isolated glucose measurements to the continuous assessment of glycemia. A similar transformation may occur for ketone monitoring. Emerging continuous ketone sensors and future dual glucose–ketone biosensors have the potential to convert the GKI from a static calculation into a continuously monitored biomarker of metabolic adaptation. Such technologies could enable the assessment of longitudinal GKI trajectories, variability, and disease-specific therapeutic ranges rather than relying on isolated measurements.

The integration of wearable biosensors, digital therapeutics, artificial intelligence, and remote care platforms further expands the potential applications of the GKI. Continuous glucose and ketone monitoring could provide a fuller picture of metabolic flexibility, allowing clinicians to personalize nutritional and pharmacologic interventions while generating real-world evidence linking GKI trajectories with clinical outcomes. However, before routine clinical implementation, prospective studies are needed to determine whether the GKI provides incremental predictive or therapeutic value beyond its component measurements, establish the effects of nutritional and pharmacologic context on interpretation, test whether longitudinal GKI measurements correlate with validated measures of metabolic flexibility or predict clinically meaningful outcomes, and establish disease-specific GKI targets.

Conclusions

Lee et al. propose that the GKI could be used as a quantitative biomarker for monitoring nutritional ketosis. We suggest its value may extend further, reflecting the balance between two evolutionarily conserved fuel systems. Rather than serving solely as a marker of carbohydrate restriction, the GKI has the potential to quantify metabolic flexibility and therapeutic response across nutritional, behavioral, and pharmacologic interventions. We therefore propose the GKI as a candidate, context-dependent biomarker of the circulating metabolic state rather than an established measure of metabolic flexibility. Future research should determine whether static or longitudinal GKI measurements provide more information than glucose or ketone concentrations alone, whether they correlate with direct measures of substrate utilization and metabolic flexibility, and whether GKI-guided care improves clinical outcomes.

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Author contributions

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