

From multidimensional regulation of insulin secretion to islet function-guided precision nutrition

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The regulation of insulin secretion by pancreatic β -cells is essential for maintaining glucose homeostasis and overall metabolic health. In a recent review entitled "Nutrient and non-nutrient regulators of insulin secretion," published in *Nature Reviews Endocrinology*, Kolic and colleagues comprehensively summarized the patterns of basal and stimulated insulin secretion in humans. This review highlights that, in addition to glucose, amino acids, fatty acids, other metabolic fuels, pharmaceuticals, food additives, and environmental exposures can modulate β -cell function through shared or distinct pathways.¹ However, the review primarily synthesizes mechanisms and evidence gaps. It does not develop an operational framework for applying them to dietary decision-making. Our commentary therefore deliberately focuses on nutrition. Nutrient exposure is modifiable and can be standardized as a challenge, whereas non-nutrient regulators are treated mainly as contextual modifiers. We hypothesize that incorporating dynamic islet functional characteristics into nutritional guidance could improve the prediction of dietary responses and the selection of dietary strategies compared with approaches based on postprandial glucose alone (Figure 1).

FROM MULTIDIMENSIONAL REGULATION TO A TRANSLATIONAL GAP

Rather than functioning solely as an insulin-secreting structure, the pancreatic islet represents a dynamic endocrine unit composed of β -cells, α -cells, and other endocrine cell types. Through the coordinated secretion of insulin, glucagon, and other islet hormones, this multicellular network maintains glucose and energy homeostasis under fasting, postprandial, and stress conditions.

Pancreatic β -cell dysfunction is particularly heterogeneous and evolves dynamically over time, initially manifesting as alterations in the pattern of insulin secretion. Impairment of first-phase insulin secretion and disruption of pulsatile insulin release may precede overt hyperglycaemia. During the progression from normal glucose tolerance to prediabetes and type 2 diabetes, β -cells may initially exhibit compensatory hypersecretion, followed by inadequate postprandial insulin release, defective proinsulin processing, endoplasmic reticulum stress, and progressive loss of the mature β -cell phenotype. Accordingly, β -cell dysfunction should be conceptualized as a continuum characterized by progressive disturbances in the magnitude, timing, pulsatility, and substrate specificity of insulin secretion.

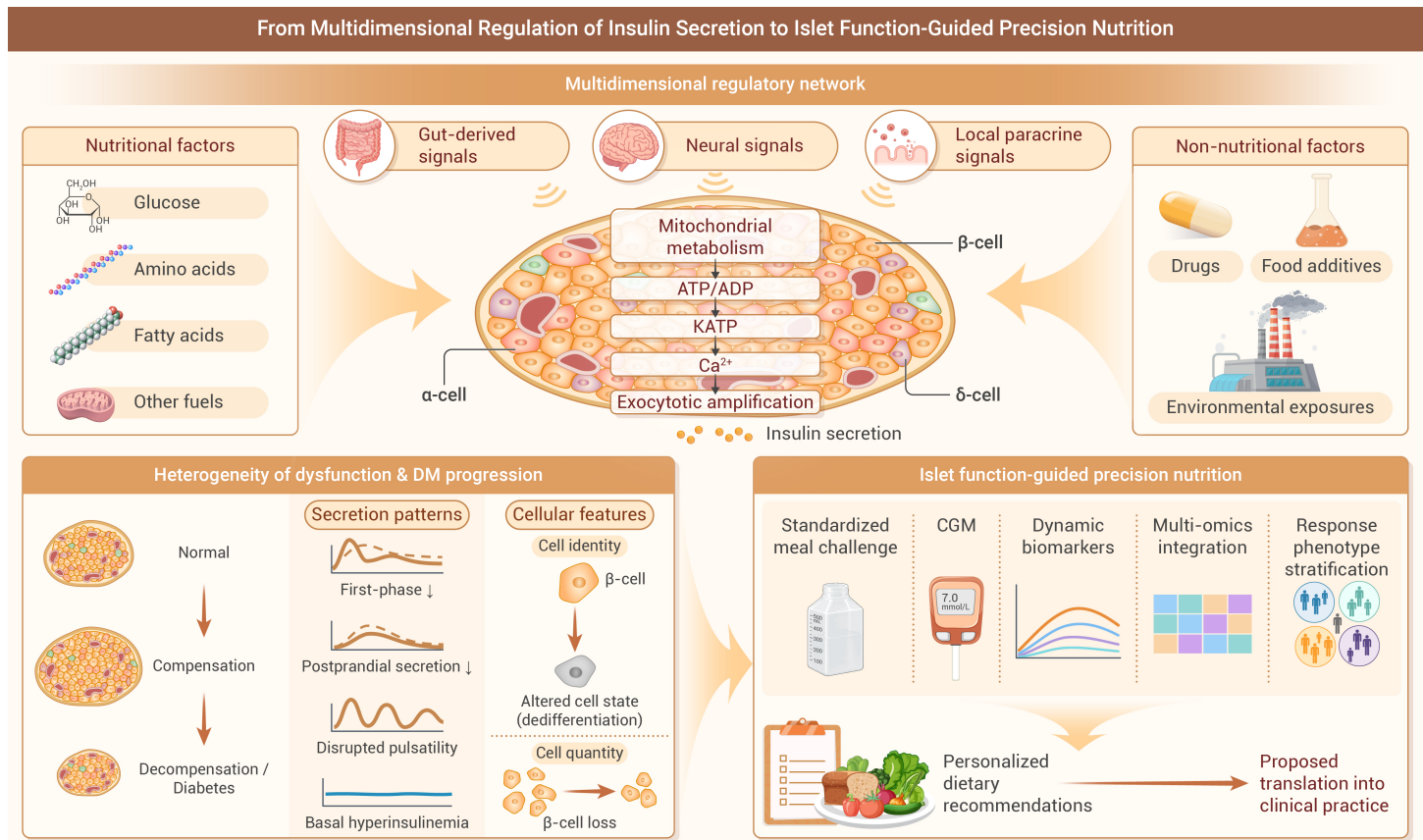


Figure 1. From multidimensional regulation of insulin secretion to islet function-guided precision nutrition Genetic and environmental factors regulate insulin secretion and islet function through nutritional, gut-derived, neural, paracrine, and non-nutritional signals, contributing to the heterogeneous progression of islet dysfunction. Building on this concept, the proposed islet function-guided precision nutrition framework integrates standardized meal challenges, continuous glucose monitoring, dynamic biomarkers, and multi-omics data to identify nutrient-response phenotypes and generate mechanism-informed, personalized dietary recommendations. The proposed precision nutrition framework remains conceptual and should be tested in prospective studies. Abbreviations: ATP, adenosine triphosphate; ADP, adenosine diphosphate; KATP, ATP-sensitive potassium channel; Ca^{2+} , calcium ion; CGM, continuous glucose monitoring; DM, diabetes mellitus.

The review's major strength is its integration of nutrient sensing with basal secretion, reactive oxygen species, β -cell workload, life stage, circadian organization, and non-nutrient exposures.¹ Yet findings from isolated islets, animal models, and high-dose exposure studies cannot carry the same translational weight as repeated human responses to habitual foods. Acute fatty acid or reactive oxygen species signalling can support secretion, whereas chronic exposure can increase β -cell stress; dose, duration, disease stage, and metabolic context therefore determine whether a response is adaptive or maladaptive. Importantly, the relationship between hyperinsulinaemia and insulin resistance is not strictly unidirectional. Insulin resistance increases the secretory burden imposed on β -cells, whereas persistent basal hyperinsulinaemia may, in turn, promote insulin receptor desensitization and further aggravate insulin resistance. The direction and magnitude of this relationship are context dependent and may vary according to genetic background, disease stage, and the type and duration of relevant exposures. Peripheral insulin concentrations also reflect both secretion and clearance. This commentary therefore addresses the translational gap between a mechanistic map and nutrition guidance.

WHY A DYNAMIC ENDOCRINE-METABOLIC PHENOTYPE IS NEEDED

Pancreatic islet function varies throughout the day, with intrinsic circadian clocks regulating islet gene expression and insulin secretory capacity. These rhythms are integrated with cycles of feeding and fasting, while changes in meal timing, dietary composition, and sleep can alter circadian alignment and metabolic conditions.² An individual's response to a nutrient challenge may therefore reflect not only the nutrient stimulus but also the timing of assessment and preceding exposures. Repeated measurements across the day and as these conditions change may provide a more complete characterization of daily variation and changes in islet responsiveness than a single static measurement.

A study of human islets obtained from 140 donors showed that glucose elicited the strongest insulin secretory response in most samples. Nevertheless, 9% and 8% of the samples exhibited stronger responses to amino acids and fatty acids, respectively.³ These findings indicate that population-level averages may obscure subgroups with distinct nutrient specific response phenotypes. However, responses observed under ex vivo stimulation conditions cannot be directly extrapolated to physiological responses to habitual dietary intake in vivo. Dynamic multi-omics profiling in humans also showed that mixed meals and distinct macronutrient challenges elicited heterogeneous trajectories of insulin, glucagon, GLP-1, and GIP.⁴ Nevertheless, these investigations primarily characterized acute nutrient challenges, and their within-person reproducibility and long-term implications remain to be established.

Given the central role of pancreatic islets in maintaining whole-body energy homeostasis and the heterogeneity of nutrient responses, future personalized dietary strategies should account for both an individual's islet functional state and their response phenotype to specific nutrient challenges. The phenotype should distinguish secretion from clearance while interpreting β -cell output in the context of insulin sensitivity, glucagon and incretin responses, timing, medication, and exposure context.

GENETIC AND ENVIRONMENTAL CONTEXT OF DYNAMIC ISLET PHENOTYPES

Accumulating evidence supports a substantial genetic contribution to interindividual variation in insulin secretion. A genome-wide association study of eight indices of β -cell function in approximately 26,000 participants identified 55 independent genetic signals across 44 loci and, through integration with human islet multi-omic datasets, prioritized 92 candidate effector genes relevant to β -cell secretory function and islet biology.⁵ However, the phenotypic expression of genetic effects is not fixed and may be modified by nutrient load, meal timing, pharmacological exposure, and environmental chemicals. The marked variation in islet responses among individuals exposed to comparable nutritional or non-nutritional stimuli further suggests that islet function emerges from interactions between inherited susceptibility and environmental context.

Assessment of islet function should therefore consider both inherited susceptibility and the environmental and metabolic context in which it is

expressed. Genetic or static omic profiles alone are unlikely to capture an individual's current functional state, as secretory responses may vary with diet, physical activity, sleep, medication use and disease stage.

ISLET FUNCTION-GUIDED PRECISION NUTRITION STRATEGIES

Precision nutrition should extend beyond dietary prescriptions based on isolated genetic variants, single glucose measurements or static omic profiles. Using postprandial glucose as the principal prediction target and intervention endpoint may obscure important physiological differences. Similar postprandial glucose profiles may arise from different combinations of impaired insulin secretion, compensatory hypersecretion, reduced insulin clearance, peripheral insulin resistance and altered glucagon or incretin responses. Moreover, normoglycaemia may be maintained through compensatory insulin hypersecretion. These considerations support assessing islet function alongside glycaemia when developing personalized dietary strategies. An islet-guided approach would characterize how different nutrients affect islet function in the context of genetic predisposition and environmental exposures, interpret these responses alongside changes in glycaemia, and translate reproducible findings into a limited set of testable dietary strategies.

The proposed dynamic precision nutrition framework would treat islet responses as outcomes of nutrient challenges as well as features for predicting individual meal responses. Repeated standardized mixed-meal tests would compare meals with controlled differences in nutrient source, amount or macronutrient composition. Serial glucose, insulin and C-peptide measurements would characterize response magnitude, timing and recovery. Physiological modelling could provide estimates of β -cell responsiveness and insulin sensitivity, with insulin clearance assessed where the sampling protocol and model assumptions permit. Machine-learning models could combine these physiological features with meal composition and clinical, dietary and behavioural data to predict individual glycaemic and secretory responses. Where available, genetic data could inform analyses of inherited variation in nutrient responsiveness, while multi-omic measurements before and after meal challenges could characterize associated molecular changes. The incremental predictive value of adding these data would be assessed against models based on the core measures alone. Model evaluation would require participant-level cross-validation and validation in independent cohorts. A dietitian and the individual could then use these predictions to select one or two feasible changes in carbohydrate source, portion size, macronutrient composition or meal timing. Selection should reflect a prespecified physiological objective while accounting for nutritional adequacy, food preferences and affordability. Insulin secretion would be interpreted in relation to the glucose stimulus and insulin sensitivity; lower glucose or insulin concentrations alone would not establish improved islet function. Selected dietary changes would be tested in repeated, randomized within-person comparisons, with islet and glycaemic outcomes informing subsequent dietary advice. Longer-term trials should assess adherence and determine whether islet-guided strategies improve metabolic outcomes compared with glucose-guided approaches.

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DECLARATION OF INTERESTS

The authors declare no competing interests.