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Defective Glucagon-Like Peptide 1 Secretion in Prediabetes and Type 2 Diabetes Is Influenced by Weight and Sex. Chicken, Egg, or None of the Above?



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Glucagon-like peptide 1 (GLP-1) is considered to be the primary incretin hormone, released in response to food ingestion and contributing to meal assimilation. GLP-1 is a powerful insulin secretagogue, stimulating insulin secretion and suppressing glucagon secretion in a glucose-dependent manner (1), and indeed, numerous pharmacologic agents use the GLP-1 pathway to produce effective glucose-lowering therapy (2). Given the antidiabetogenic actions of GLP-1, it is a reasonable question to wonder whether defects in GLP-1 secretion contribute to the pathogenesis of type 2 diabetes. Over the years, multiple studies have examined this question. However, the evidence to suggest decreased GLP-1 secretion in prediabetes and diabetes has been mixed at best, with decreased (3–5), normal (6,7), or increased (8) GLP-1 concentrations reported in subjects with prediabetes or type 2 diabetes.

Subsequently, Nauck et al. (9) undertook a meta-analysis of studies comparing active and total GLP-1 in people with diabetes and weight-matched control subjects and concluded that after an oral glucose challenge or after a mixed meal, the integrated, incremental concentrations of GLP-1 did not differ between patients with type 2 diabetes and control subjects. GLP-1 concentrations were unaffected by weight or age. In addition, we examined active and total GLP-1 concentrations in 165 subjects with varying degrees of glucose tolerance and demonstrated that integrated GLP-1 concentrations were not significantly associated with glucose tolerance or with indices of insulin secretion and action. We concluded that defects in postprandial GLP-1 secretion do not play a significant role in the pathogenesis of prediabetes (10).

This state of affairs has been challenged by the work of Færch et al. (11) who report in this issue of *Diabetes* that the GLP-1 response to an oral glucose challenge is reduced in a large cohort of subjects who have prediabetes, diabetes,

and obesity. The subjects underwent a 75-g oral glucose tolerance test, during which glucose, insulin, and GLP-1 concentrations were measured at three time points. As expected, glucose intolerance and overt type 2 diabetes were associated with decreased insulin and higher glucose concentrations. At 120 min in men, GLP-1 concentrations were decreased in subjects with prediabetes and type 2 diabetes; however, this did not result in differences in integrated GLP-1 concentrations. The other notable findings were an increase in postchallenge concentrations of GLP-1 in women despite adjustment for weight and decreased fasting GLP-1 concentrations in overweight and obese subjects. Other correlations included an inverse relationship between 30-min glucose and GLP-1 concentrations. Contrary to prior reports, GLP-1 was positively associated with insulinogenic, insulin sensitivity, and disposition indices.

There are several caveats associated with these findings (Fig. 1). The temporal course of hormonal concentrations as well as the absolute concentrations at a given time point is the result of two net processes—secretion and clearance. This is especially important with hormones that undergo clearance prior to appearing in the systemic circulation. In the latter category, insulin-based measures of insulin secretion are confounded by first-pass hepatic insulin extraction, which, in part, is affected by glucose tolerance status, thereby introducing a systematic error in the measurement of β -cell function (12). Indeed, although defects in insulin secretion are present in prediabetes and diabetes, it would be a mistake to conclude on the basis of a cross-sectional study that decreased GLP-1 secretion is the cause of decreased insulin secretion.

The other caveat relates to the time course of GLP-1 concentrations in the circulation, which reflect nutrient appearance in the proximal small intestine. Typically,

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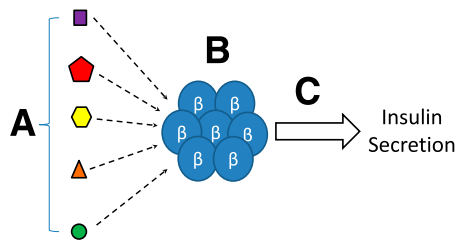


Figure 1—Defective response to insulin secretagogues may arise from A) decreased concentrations of a given secretagogue, B) loss of β -cell responsiveness to that secretagogue (defective sensing), or C) a partial inability of β -cells to secrete insulin in response to stimulation.

a liquid challenge empties quite rapidly, with the most significant changes in GLP-1 concentrations occurring over the first 45 min after ingestion (13). The sparse sampling schedule used by Færch et al. assumes that GLP-1 concentrations at 30 min are equivalent to GLP-1 secretion. This is clearly subject to the vagaries of gastric emptying and fasting gastric volumes that determine liquid gastric emptying. A more frequent sampling schedule may have provided a better characterization of postchallenge GLP-1 and insulin concentrations.

Undoubtedly, enteroendocrine hormone concentrations can be affected by factors other than intraluminal nutrient. For example, raising active concentrations of GLP-1 and gastric inhibitory polypeptide by inhibiting dipeptidyl peptidase-4 actually decreases the secretion of these hormones by L and K cells, respectively (14). Conversely, blockade of the GLP-1 receptor increases postprandial GLP-1 concentrations (15). Association of fasting GLP-1 concentrations with glucagon concentrations is another observation whose significance remains uncertain (7,10). Similarly, the association of GLP-1 concentrations with obesity and insulin resistance also observed in this cohort but not in others (10) requires further study.

Finally, when examining the role of GLP-1 in the pathogenesis of diabetes, it is important to consider the nature of the β -cell defect present (Fig. 1). Diabetes and prediabetes are characterized by a defective β -cell response to glucose and likely other secretagogues, such as arginine, glucagon, and incretin hormones. Although a mechanistic model to describe the contribution of intravenous GLP-1 infusion to β -cell secretion has been described, it has yet to be applied to an oral challenge where the β -cell is responding to multiple stimuli (16). It remains to be ascertained whether a defective response to one secretagogue is emblematic of a failure of the β -cell or a selective inability to respond to one but not to other secretagogues. Longitudinal prospective studies will be required to determine the contributions of decreased incretin secretion and specific defects in the incretin response (if any) to the pathogenesis of diabetes.

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