Prediabetes: Evaluation of β-Cell Function

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β-Cell function should be expressed as insulin secretion in relation to the prevailing and changing glucose concentration and interpreted in light of prevailing insulin resistance. Characterizing alterations in β-cell function in individuals with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) (collectively termed "prediabetes") has been a hotly pursued topic among clinical investigators over the past several years. Because IFG and IGT are both associated with elevated risk of progression to overt type 2 diabetes and cardiovascular events (1–3), it is important to understand the specific defects in β-cell function that occur in these settings. Such knowledge could translate into targeted therapeutic interventions that could potentially delay or halt the progression of IFG/IGT to frank diabetes.

In this issue of *Diabetes*, Abdul-Ghani and colleagues (4) attempt to characterize changes in β-cell function in a group of middle-aged, obese, predominantly female Mexican Americans with and without prediabetes using the frequently sampled oral glucose tolerance test (OGTT) and in subgroups using the hyperglycemic clamp technique. Applying published models and methods (5), the authors identified distinct defects in β-cell function in response to oral/intravenous glucose load in individuals with IFG and IGT and attempted to define specific abnormalities in glucose and time-dependent β-cell responsiveness in these subjects. They concluded that while first-phase insulin secretion was decreased in subjects with IFG, both first and second phases of insulin secretion were abnormal in those with IGT.

It is important to consider these results in the context of a growing body of literature on this topic that applies various methodologies in different ethnic groups. A prior report (6) in a sizable population that used relatively simple and less precise methods suggested a progressive increase and then a decline in insulin response following OGTT from NGT to IGT to IFG. In contrast, applying the hyperglycemic clamp technique, Meyer et al. (7) concluded, in concordance with the present report, that first-phase insulin response was decreased in both IFG and IGT, whereas second-phase insulin response was reduced only in IGT. Abdul-Ghani et al. (8) have also reported a progressive decline in insulin secretion from IFG to IGT to combined IFG/IGT in Mexican American subjects using the insulinogenic index following an OGTT.

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In a cohort of whites responding to a mixed meal, Bock et al. (9) described lower disposition indices (DI; composite of insulin secretion appropriate to the prevailing level of insulin action) in those with IGT compared with those with IFG. Furthermore, DI dynamic (analogous to first-phase insulin secretion), which assesses the appropriateness of insulin secretion in response to a change in glucose, and DI static (analogous to second-phase insulin secretion), which assesses the appropriateness of insulin secretion to a given glucose level, were both impaired in subjects with IGT with the severity of the dynamic defect increasing as glucose tolerance worsened. In contrast, Ferrannini et al. (5) used an OGTT model and reported that while the static response of insulin secretion was decreased in IGT, the dynamic response to a change in glucose was intact. These contrasting findings could be related to differences in glucose challenges (mixed meal vs. OGTT), models used, and/or to the descriptors applied (DI vs. insulin secretion index).

It is also important to consider the robustness, assumptions, and limitations of the models used to estimate β-cell function in various reports. Investigations (10–12) suggest that first (dynamic) phase of insulin secretion likely relates to exocytosis of insulin from secretory vesicles docked to the membrane, whereas the second (static) phase of insulin secretion reflects insulin granule translocation and maturation. In order to permit granule mobilization and second-phase release, remodeling of the cortical actin web is believed to be necessary. In β-cells, key molecules involved in cytoskeletal reorganization activate 5–15 min after a rise in the glucose concentration (13), suggesting an inherent delay in glucose-stimulated insulin secretion. As has been extensively discussed in a prior review (14), the model used by Abdul-Ghani and colleagues (15) in the current study does not account for the delay between the glucose signal and release of new insulin into the circulation. Use of the potentiation factor has been proposed to mathematically compensate for this deficiency, at least in part, but the potentiation factor has no obvious mechanistic counterpart on the cellular level. Additionally, complex modeling assumptions that are beyond the scope of this commentary introduce difficulties in appropriate physiological interpretation of the parameters of the model.

Nevertheless, most, if not all, recent reports demonstrate identifiable, distinctive, and often progressive abnormalities in β-cell function in response to a glucose challenge in individuals with IFG, IGT, and combined IFG/IGT. Interestingly, nonglucose nutrient-induced insulin secretion was not found to be abnormal in IFG/IGT or combined IFG/IGT (16). Taken together, the results imply a specific defect/s in β-cell function as it relates to a glucose (but not nonglucose nutrient) challenge in individuals with prediabetes.

What is the take-home message regarding therapeutic strategies to restore insulin secretion in prediabetes based on current knowledge? While studies in prediabetic rodents (17,18) have suggested a beneficial role of glucagon-like peptide 1–based therapy on restoring insulin secretion, a recent report (19) in humans with prediabetes exposed to

short-term treatment with a dipeptidyl peptidase-4 inhibitor did not confirm those observations. Clearly, longer-term clinical trials assessing different pharmacological approaches are needed to evaluate the effect of these agents on restoring β-cell function in individuals with prediabetes and thus prevent the progression to frank diabetes with its attending portfolio of microvascular and macrovascular complications.

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