EDITORIAL (SEE BUNCK ET AL., P. 2041)

Incretin-Based Therapy and the Quest for Sustained Improvements in β-Cell Health

Incretin-based therapies, principally glucagon-like peptide-1 receptor (GLP-1R) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, have slowly gained traction in the therapy of type 2 diabetes. DPP-4 inhibitors, which exert their activities through potentiation of endogenous GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) action (1), are well tolerated and may be combined with multiple oral agents, making them well suited for use at multiple stages in the treatment of type 2 diabetes. GLP-1R agonists require injection, and are less well tolerated due principally to gastrointestinal adverse events (nausea, and less commonly diarrhea and vomiting). Hence, like insulin, they are frequently considered for use in patients who have failed to achieve adequate glycemic control on one or more oral agents alone. However, long-acting GLP-1R agonists are more potent glucose-lowering agents compared with DPP-4 inhibitors (2), and they may produce weight loss, two major points of differentiation with meaningful clinical impact.

As the field of incretin biology gained prominence after clinical observations describing the importance of gut-derived factors in the potentiation of glucose-dependent insulin secretion, it is not surprising that the β-cell continues to be viewed as the predominant target of incretin action. Indeed, both GLP-1 and GIP robustly potentiate glucose-dependent insulin secretion in nondiabetic human subjects, and GLP-1 restores or enhances β-cell glucose sensing and insulin secretion even in diabetic patients with considerable loss of β-cell responsivity to glucose or sulfonylureas. Both GLP-1 and GIP also exhibit robust proliferative and antiapoptotic actions on rodent β-cells in experimental models of type 2 diabetes (3), and GLP-1 exerts salutary effects on the molecular mechanisms underlying β-cell function and enhances β-cell survival in studies with human islets cultured ex vivo (4,5). Hence, there has been considerable anticipation that incretin-based therapies may exert "disease-modifying" effects in type 2 diabetes through a combination of mechanisms including enhancing β-cell proliferation and/or reduction in the rate of β-cell loss, ultimately leading to preservation of β-cell function.

Bunck et al. (6) now report a follow-up analysis of an original group of 69 patients with type 2 diabetes randomized to treatment for 52 weeks with either exenatide or insulin glargine. β-Cell function was reassessed in 36 diabetic subjects previously on a background therapy of metformin and treated with exenatide (16 subjects) or insulin glargine (20 subjects) who completed 3 years of treatment. Parameters of insulin sensitivity and β-cell function were assessed using euglycemic hyperinsulinemic and hyperglycemic clamps with arginine stimulation at week 172, 4 weeks after discontinuation of exenatide or glargine. Subjects treated with exenatide or glargine achieved similar levels of HbA_{1c} (6.6 vs. 6.9%, respectively) at the end of the study period. Exenatide-treated patients exhibited weight loss (5.7 kg), increased insulin sensitivity, and a greater disposition index (DI) (a reflection of β-cell function adjusted for insulin sensitivity) after 3 years of therapy. Subjects treated with insulin glargine (final mean dose of insulin glargine achieved was 33.7 units) experienced a greater reduction in fasting plasma glucose and weight gain (2.1 kg). The authors conclude that 3 years of exenatide therapy is associated with an improvement in β-cell health (6).

As there are very few reports describing the consequences of prolonged treatment with incretin-based therapy, the results described by Bunck et al. are intriguing. The authors are to be commended for following patients for 3 years, and for their careful assessments of β-cell function and insulin sensitivity using clamp technology. Furthermore, the study design used (glucose and arginine stimulation) to assess β-cell function in the current report, 4 weeks after cessation of therapy and without exogenous administration of exenatide, provides more useful information relative to that collected in the original series of studies where assessment of β-cell function in clamp studies was carried out with concurrent acute exenatide administration (7). Nevertheless, the current study does have several limitations, including a very small number of subjects, a nonblinded trial design, and a small but potentially important HbA_{1c} difference favoring exenatide (6). The lack of forced titration to compel further increases in the dose of insulin glargine may have precluded additional improvements in glycemic control and β-cell function in the insulin-treated group. Of the 36 patients randomized to exenatide therapy at the start of the study, only 16 completed the 3-year treatment period, whereas a greater proportion, 20/33 patients, completed the 3-year course of insulin glargine. It is possible that patients managing and/or electing to continue exenatide for the full 3 years of treatment represent a highly select group of responders with better results (tolerability, weight loss, and glucose control) relative to those subjects who discontinued therapy.

How are we to interpret these findings in the context of the known actions of GLP-1? The relative improvements in β-cell function described by Bunck et al. (6) were quite modest; glucose- and arginine-stimulated C-peptide levels were similar in exenatide- versus glargine-treated subjects, and first- and second-phase glucose-stimulated C-peptide levels were lower in subjects receiving exenatide. However, improvements in β-cell function in subjects treated with exenatide were revealed in part through calculation of the DI, as β-cell function was relatively enhanced even when corrected for the degree of improved insulin sensitivity. Although it is tempting to attribute these results to salutary effects of sustained exenatide administration on the diabetic β-cell, the importance of weight loss as a confounding variable cannot be easily dismissed. As noted by the authors, modest amounts of weight loss produce significant improvements in β-cell function in subjects with obesity and/or diabetes. Weight loss often improves β-cell function in association with

concurrent reductions in insulin resistance (8,9), hence precise elucidation of mechanisms responsible for improved β-cell function after weight loss, perhaps encompassing reduction of systemic and local islet inflammation and glucolipotoxicity, can be challenging. Even a short period of calorie restriction for 7 days yields significant improvements in both insulin secretion and insulin sensitivity (10), and 3 months of lifestyle modification, principally diet and exercise, results in significantly improved β-cell function even after correcting for corresponding changes in insulin sensitivity in obese subjects with type 2 diabetes (11). Accordingly, mechanistic interpretation of the findings of modestly improved β-cell health in the exenatide-treated patients studied by Bunck et al. is challenging.

The early enthusiasm for incretin-mediated preservation or enhancement of β-cell mass and function was based on extensive preclinical studies predominantly in rodents and complemented by studies using cell lines and islets (3,4). More recent experimentation has demonstrated that although younger rodents exhibit considerable capacity for β-cell regeneration, older animals do not, and the aging rodent β-cell fails to exhibit a significant proliferative response to exogenous GLP-1R activation (12,13). Even less is known about the potential for older diabetic human β-cells to exhibit a proliferative or cytoprotective response to GLP-1R agonists in vivo. Hence initial enthusiasm for the potential for incretin-based therapies to modify the natural history of type 2 diabetes has been tempered by recent preclinical science and the results of clinical trials, demonstrating reasonable efficacy but little evidence for durability in studies using DPP-4 inhibitors (14,15). Whether a long-acting GLP-1R agonist such as liraglutide or exenatide once weekly will prove more effective at sustaining or improving β-cell function remains unclear. Although 2 years of liraglutide treatment produced better glucose control compared with diabetic patients receiving glimeprimide, less than 45% of the randomized patients completed the 2-year study, and no formal assessment of β-cell function after drug washout was reported (16).

How should clinicians view the current results reported by Bunck et al. in the context of their clinical practice? Although it is reassuring to learn that a subset of patients treated with exenatide twice daily and metformin will maintain a good clinical response and improved β-cell function for 3 years, the treat-to-target design of this study resulted in 14/36 exenatide-treated subjects receiving more than the clinically recommended maximum dose of 10 μg exenatide twice daily. Hence the real world applicability of the current data set, even in this small selected group of responders, is uncertain. Optimistic clinicians will suggest that the second generation more potent long-acting GLP-1R agonists (liraglutide and exenatide once weekly), if used earlier in the course of the disease, may be more likely to achieve a durable glycemic response and long-lasting improvements in β-cell function. A more cautious observer will point out that exenatide therapy has not yet produced consistent or sustained improvement in β-cell function in patients with type 1 diabetes and islet transplantation, nor in C-peptide–positive patients early in the course of type 1 diabetes (17).

It seems clear that incretin therapies offer considerable advantages for many patients in regard to reduction of hypoglycemia, less frequent need for self-monitoring of blood glucose, and control of body weight (18). Furthermore, the long-acting GLP-1R agonists (liraglutide and exenatide once weekly) are more potent than exenatide twice daily, and appear to be as effective—and in some instances more effective—than commonly used antidiabetic agents (16,19). Although considerable evidence suggests that these agents exert multiple complementary actions that should directly and indirectly enhance β-cell health, it seems premature to definitively conclude that therapy with GLP-1R agonists is likely to be associated with sustained preservation or enhancement of β-cell function in subjects with type 2 diabetes.

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