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Incretin-based therapies for type 2 diabetes mellitus: New therapeutic mechanisms

Almost a decade into the 21st century, the global epidemic of diabetes—which accelerated in the 1970s—shows no sign of slowing. At the same time, our insights into both type 1 and type 2 diabetes mellitus (T2DM) have increased at a similarly rapid rate.

At the beginning of the 1970s, it was far from clear whether improved glycemic control made much difference in the long-term well-being of people with diabetes other than to relieve their symptoms of hyperglycemia and decrease the likelihood of diabetic ketoacidosis or hyperglycemic hyperosmolar nonketotic coma. Concerns were expressed about the risk/benefit ratio of antihyperglycemic drugs—so there is nothing new under the sun! The drugs available in the United States were limited to insulin and sulfonylureas. The rest of the world also had access to metformin, but, in truth, its potential was underestimated until much later.

■ RECOGNIZING THE VALUE OF GLYCEMIC CONTROL

Out of this milieu of scientific uncertainty grew the two clinical trials that effectively ended the debate about the value of glycemic control: the Diabetes Control and Complications Trial (DCCT)¹ for type 1 diabetes, and the United Kingdom Prospective Diabetes Study (UKPDS)^{2,3} for T2DM. The conduct of these trials was facilitated by the timely demonstration of the utility of glycosylated hemoglobin (HbA1c) as an objective measure of glycemic control, and of microalbuminuria as a marker of early nephropathy.

Both the DCCT and the UKPDS, in their initial “end of study” analyses in the 1990s, established the role of glycemic control in reducing the risk of retinopathy, neuropathy, and nephropathy—the microvascular complications of diabetes. Additionally, the UKPDS demonstrated that in T2DM, hypertension management was at least as important as glycemic control in reducing the risk of microvascular complications.

Neither the DCCT nor the UKPDS was powered to determine initially whether glycemic control was a risk factor for cardiovascular disease; however, careful

longer-term surveillance of the patient cohorts in the studies has recently borne fruit in this regard. Reports from both studies have shown that efforts to control glycemia early in the course of diabetes are rewarded many years later by a decreased risk of cardiovascular events and death.^{4,5} This is true even when excellent glycemic control achieved early on is not sustained indefinitely. It has also become widely recognized that the management of diabetes, with prevention of microvascular and cardiovascular disease as major aims, involves much more than a simple preoccupation with glycemic control—important as that is.

■ NEW TREATMENT OPTIONS

Concurrent with the DCCT and the UKPDS being conducted with, in effect, the therapeutic tools of the 1970s, considerable strides were being made in the development of new classes of antihyperglycemic agents for use in T2DM. These include the thiazolidinediones (TZDs), alpha-glucosidase inhibitors, nonsulfonylurea insulin secretagogues (also known as glinides), and, more recently, the incretin-based drugs that are the focus of this supplement to the *Cleveland Clinic Journal of Medicine*.

Understandable enthusiasm for tapping into the hitherto unexploited pathways and mechanisms targeted by a new drug class is inevitably tempered by known, or sometimes unforeseen, adverse effects. Some of the adverse effects typically associated with antihyperglycemic drugs used before the incretin-based therapies became available include hypoglycemia, weight gain, and fluid retention; all of these are perceived as possibly increasing the risk of the very thing we are striving to avoid in diabetes—cardiovascular morbidity and mortality. Such is the concern about this risk—epitomized, rightly or wrongly, in the controversial meta-analysis of clinical trials involving rosiglitazone⁶—that the US Food and Drug Administration now requires new antihyperglycemic drugs not only to meet efficacy standards for improving glycemia but also to show no sign of increased cardiovascular risk. The requirement must be met in preapproval trials, to be followed by postmarketing studies to prove the lack of cardiovascular risk.

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As the contributions in this supplement point out, incretin-based therapies generally are either weight neutral or promote weight loss; by their modes of action, they are unlikely to cause hypoglycemia; and, as shown thus far, they are unassociated with fluid retention or increased likelihood of heart failure. Continued vigilance regarding cardiovascular risk will be important for the new incretin-based therapies, however.

■ BETA-CELL FUNCTION STILL A CHALLENGE

Another aspect of T2DM highlighted by the UKPDS is the degree of pancreatic beta-cell function loss—typically about 50% or more—at the time of clinical diagnosis, and the steady decline in function thereafter.⁷ This, as much as the understandable fatigue with lifestyle modification that normal humans experience, accounts for the frequent failure of oral antihyperglycemic monotherapy or dual therapy to maintain satisfactory glycemic control over the years. Relieving hyperglycemia at the time of diagnosis by *any* means usually leads to a temporary improvement in beta-cell function, but the possibility of slowing or even reversing the long-term decline has been an elusive therapeutic goal.

Although direct quantitative assessment of beta-cell function in humans is difficult in routine practice or outside of strict research protocols, a randomized study comparing different monotherapies for T2DM showed that over several years, the rise in HbA1c was more gradual with rosiglitazone than with glyburide or metformin; this suggests that, at least compared with metformin and sulfonylureas, the TZDs may have some longer-term benefit with respect to beta-cell function.⁸

That incretin-based treatments may help preserve or improve beta-cell function has been suggested by animal data.⁹ Proving that that is the case in humans will be much more challenging. A recent randomized study in patients with T2DM already taking metformin showed that addition of exenatide for 1 year resulted in improved beta-cell function, assessed by C-peptide responses to glucose and to arginine during a combined euglycemic-hyperinsulinemic and hyperglycemic clamp procedure. The improvement was evident compared with baseline function and with patients randomized to receive insulin glargine in addition to metformin for a year.¹⁰ However, 4 weeks after exenatide and glargine were discontinued, the beta-cell function had reverted to the pretreatment level and was not significantly different in the two groups of patients. Moreover, 3 months after treatment discontinuation, the HbA1c levels, which had decreased during the year to a similar extent in both groups, had returned to pretreatment levels. The investigators

acknowledged that it was impossible in their study to “discriminate between acute and long-term effects of exenatide on beta-cell function.”¹⁰ So, in my opinion, the challenge remains to show that meaningful long-term effects on beta-cell function can be achieved with incretin-based therapy.

That said, there is no doubt that the incretin-based therapies bring a new dimension to our ability to treat diabetes. The articles in this supplement will provide both the specialist and nonspecialist with a better understanding of these relatively new therapies.

■ DISCLOSURES

Dr. Kennedy reported that he has received honoraria from Merck and Co., Inc. He reported that he received an honorarium for serving as editor of this supplement, peer-reviewing the articles, and writing the introduction. The honorarium was paid by the *Cleveland Clinic Journal of Medicine* from an educational grant provided by Amylin Pharmaceuticals, Inc., and Eli Lilly and Company, which funded the development and production of the supplement.

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