THE PATHOPHYSIOLOGIC BASIS FOR DIABETES TREATMENT: EVALUATING THE EFFECT OF INCRETIN-BASED THERAPIES

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ABSTRACT

Type 2 diabetes is a persistent public health challenge that requires innovative strategies to improve treatment options and long-term outcomes, especially in light of the cardiovascular risk posed by long-standing insulin resistance. Although therapeutic advances have traditionally targeted insulin resistance or insulin secretory abnormalities, it is now becoming clear that a complex hormonal mechanism is at work in type 2 diabetes and new treatment targets may be realized with a better understanding of these processes. The role that impaired islet β-cell function plays in diabetes, especially with respect to the incretins that are produced by these cells to regulate insulin and glucagon production in response to glucose, is now receiving attention, and several agents are now available that address the incretin hormonal response. This article will review current recommended diabetes treatment targets, the role of β cells and incretins in glucose response, and new agents that have been developed to address this pathophysiologic aspect of type 2 diabetes.

TYPE 2 DIABETES: THE MAGNITUDE OF THE PROBLEM

It is not surprising to those who routinely treat individuals with cardiometabolic disease that type 2 diabetes continues to have a considerable impact on public health. The magnitude of the problem increases annually, and it is estimated that 20.8 million Americans were affected by diabetes in 2007, resulting in total costs of $174 billion. Meanwhile, it was estimated that another 41 million had prediabetes in 2007. Diabetes is the sixth disease-specific cause of death in the United States, and is a leading cause of kidney failure, adult blindness, nontraumatic limb amputation, and cardiovascular disease. Diabetes is also a staggering problem worldwide, with experts projecting a 72% increase in the global burden of diabetes disease between 2003 and 2025, and prevalence rates are expected to correlate closely with the westernization of many countries.

Although insulin resistance, stemming from overweight and obesity, has been generally accepted as the dominant problem underlying type 2 diabetes, in reality it is a complicated disease that is affected by multiple disease mechanisms. Of note, researchers and clinicians are increasingly interested in the mechanisms underlying cardiovascular risk in patients with diabetes, and now look at the cardiometabolic syndrome as a host of problems linking insulin resistance, diabetes, and cardiovascular disease processes result in premature atherosclerosis and increased mortality.

MECHANISMS OF DISEASE IN DIABETES

Although insulin resistance is an important mechanism in the development of diabetes, many individuals exhibit insulin resistance without diabetes, showing there are other physiologic processes at work. It is well
known that β-cell function is critical to glucose control. Although there is a reasonable degree of compensation in β-cell function to the insulin resistance that occurs early in the diabetic disease course allowing the blood glucose level to remain near normal, long-standing type 2 diabetes is instead characterized by a progressive decline in β-cell function (Figure 1). Researchers interested in the etiology of type 2 diabetes now cite susceptible β cells as the core factor in the development of diabetes because these individuals do not have the normal enhanced β-cell mass and function (so-called compensation) to an environment that promotes insulin resistance. In fact, recent genetic analyses in type 2 diabetes have identified several susceptibility genes, most of which are linked to β cells. Thus, individuals without a genetic predisposition to type 2 diabetes can maintain normal glucose tolerance when exposed to an environment promoting insulin resistance, but those with susceptible β cells undergo a transition during which glucose tolerance becomes impaired. After this transition, a progressive worsening of β-cell function occurs, as well as an enhancement of programmed β-cell death that results in an approximate 40% reduction in β-cell mass in prediabetes and a 60% reduction of β-cell mass in established type 2 diabetes. Consequently, substantial attention has been focused on new diabetes therapies that improve β-cell function.

**Diabetes Standards of Care and Treatment Targets**

National outcomes-based standards of diabetes care have been developed that focus on important features of the disease. Guidelines from the American Diabetes Association (ADA) emphasize tight control of glycemia, blood pressure, and lipids, because these have all been shown to impact macrovascular or microvascular disease. The ADA guidelines suggest that individuals with diabetes should achieve a target glycated hemoglobin (A1C) of less than 7%, fasting plasma glucose (FPG) of 70 to 130 mg/dL, and postprandial glucose of less than 180 mg/dL. Meanwhile, the American Association of Clinical Endocrinologists suggests tighter glucose control with an A1C of less than 6.5%, FPG of 110 mg/dL, and postprandial glucose of less than 140 mg/dL.

The ADA also recommends a blood pressure target of less than 130/80 mm Hg, a low-density lipoprotein cholesterol (LDL-C) target of less than 100 mg/dL, and a triglyceride target of less than 150 mg/dL in patients with diabetes. The National Cholesterol Education Program has proposed a more aggressive LDL-C target of 70 mg/dL or lower for high-risk patients with diabetes and preexisting vascular disease. The ADA guidelines also recommend routine practices that address the other sequelae common in diabetes, including annual dilated eye examinations, urinary protein analyses, foot examinations, and influenza immunizations, in addition to regular aspirin usage and pneumococcal vaccination.

For the most part, type 2 diabetes management has been based on a traditional understanding of disease pathogenesis that includes a triad of insulin resistance secondary to decreased insulin-mediated muscular glucose uptake, increased hepatic glucose production, and impaired pancreatic insulin secretion, with a variety of agents that target one of these pathogenic features. For instance, sulfonylureas, repaglinide, nateglinide, and incretin therapies target the impaired insulin secretion. Acarbose and miglitol target the gut and reduce its ability to absorb dietary carbohydrates. Metformin reduces hepatic glucose production, and agents such as rosiglitazone and pioglitazone reduce insulin resistance in muscle tissue.

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**Figure 1. Natural History of Type 2 Diabetes**

![Graph showing the natural history of type 2 diabetes]

IGT = impaired glucose tolerance.

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Despite the availability of multiple agents, many patients with diabetes are failing to reach treatment goals. The most recent report from the National Health and Nutrition Examination Survey, which described data collected from 1999 to 2002, found that only 50% of patients with diabetes achieved a target A1c of less than 7%, 36% achieved LDL-C levels of less than 100 mg/dL, and 40% achieved a blood pressure of less than 130/80 mm Hg.11

GLYCEMIC CONTROL AND β-CELL FUNCTION AS A THERAPEUTIC TARGET

The introduction of newer agents has brought the potential to impact a more complex range of hormonal issues contributing to the pathogenesis of type 2 diabetes. For example, individuals with type 2 diabetes exhibit not only impairment in postprandial insulin response, but also an impairment in the normal fall in glucagon levels during a meal, therefore type 2 diabetes is also characterized by persistently high mealtime glucagon levels (Figure 2).12 Until recently, therapeutic intervention in type 2 diabetes had no oral agents that impacted glucagon, but the introduction of the new incretin agents now allows clinicians to also impact impaired postprandial glucagon.

The importance of glucagon and its role in hyperglycemia is now being established. In a study of patients with type 2 diabetes who either had glucagon levels remain constant (glucagon infusion after glucose ingestion) or suppressed (2-hour delay in glucagon infusion after glucose ingestion), the decreased glucagon levels after the glucose challenge correlated with significantly lower postprandial glucose levels \( (P < 0.001) \).13 These findings suggest that the postprandial hyperglycemia in type 2 diabetes is a factor of not only the failure to secrete insulin, but is also due to the failure to downregulate glucagon production. Consequently, postprandial glucagon regulation, like postprandial insulin regulation, has emerged as an important target for therapeutic intervention.

INCRETINS AND THEIR ROLE IN INSULIN RESPONSE

Incretins, including glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP), are gut-derived hormones that are secreted in response to nutrient ingestion, resulting in insulin secretion from islet β cells and a suppression of glucagon production from α cells. Incretins stimulate insulin secretion in a glucose-dependent manner, and only exert this effect when glucose levels are above basal levels. This was demonstrated in a study of insulin response in healthy individuals receiving either intravenous or oral glucose. Insulin response was significantly greater when receiving oral glucose versus the intravenous glucose due to the gut-based incretins.14 At the same time, the incretin GLP-1 also causes glucagon levels to fall. In type 2 diabetes, these incretin effects are impaired and have therefore been investigated as a target for therapy.

INCRETINS AS THERAPEUTIC TARGET

After GLP-1 and GIP are released from the gut in response to glucose, they are quickly metabolized to inactive peptides by dipeptidyl peptidase-4 (DPP-4). Consequently, native GLP-1 and GLP-1 agonists, in addition to agents that suppress DPP-4, have been investigated as diabetes therapeutic agents. In one study of female subjects with type 2 diabetes who had fasted overnight, an infusion of synthetic GLP-1 during breakfast resulted in a dose-dependent increase in plasma insulin response and postprandial decrease in glucagon.15 In animal studies, GLP-1 infusion has demonstrated the ability to raise the β-cell mass through both enhanced β-cell proliferation and low-

Figure 2. Defective Post-Meal Insulin and Glucagon in Type 2 Diabetes

NGT = normal glucose tolerance.
ered β-cell apoptosis. Demonstrating this was a study in Zucker diabetic rats involving the administration of a 2-day infusion of GLP-1, resulting in an observed increased insulin secretion due to a significant decrease in islet β-cell apoptosis (P < .001), a significant increase in β-cell proliferation (P < .05), and a significant increase in β-cell mass (P < .01). Although an increase in β-cell mass has yet to be demonstrated in humans, therapeutic GLP-1 augmentation may offer a new strategy to address the impaired incretin response seen in type 2 diabetes.

Interest in incretins as therapeutic agents in type 2 diabetes has resulted in the development of several GLP-1 analogs (incretin mimetics), in addition to DPP-4 inhibitors to prevent the rapid inactivation of GLP-1 and GIP. Exenatide, a synthetic GLP-1 analog, is currently approved in the United States for the management of individuals with type 2 diabetes who have been unable to adequately achieve glycemic control with conventional oral antidiabetic agents (OADs). Exenatide is delivered by twice-daily subcutaneous injection, and most adverse effects reported with exenatide have been gastrointestinal in nature. Another GLP-1 analog, liraglutide, is currently in development and is specifically formulated to bind to albumin, allowing for once-daily dosing. Exenatide long-acting release, an extended-release formulation designed for once-weekly dosing, is also under development. Clinicians should note that exenatide has been associated with pancreatitis, which required a change in labeling, and patients at risk for pancreatitis should not receive exenatide.

A series of DPP-4 inhibitors are also under development to address incretin dysfunction in type 2 diabetes. Sitagliptin is the only DPP-4 inhibitor currently approved for type 2 diabetes in the United States, and is an oral agent that is approved for use alone or in conjunction with standard OADs to improve glycemic control. Sitagliptin does not appear to have the gastrointestinal side effects or weight loss that is seen with exenatide. Instead, so far, it has shown few side effects, with weight neutrality, and very little hypoglycemia. Other DPP-4 inhibitors currently under development include vildagliptin (which is approved in Europe), alogliptin, and saxagliptin.

**CONCLUSIONS**

Type 2 diabetes continues to represent a critical target for intervention due to the potential consequences of uncontrolled disease, including cardiovascular complications, in addition to limb amputation, blindness, and impaired immunity. Although a range of OADs have been available to achieve glycemic control in patients with diabetes who do not require insulin, many individuals still fail to achieve recommended therapeutic targets. Research has increasingly moved from insulin resistance as a therapeutic target for new therapies to the role that β-cell function plays in contributing to the failed insulin response to glucose in individuals with established type 2 diabetes. Incretins, including GLP-1 and GIP, are produced by β cells and initiate insulin secretion in response to food intake, and also reduce glucagon levels, both of which are blunted in type 2 diabetes. New agents, including GLP-1 analogs and DPP-4 inhibitors, address incretin pathophysiology and may become attractive alternatives to traditional agents in type 2 diabetes management.