Pathophysiology of Hyperglycemia and the Role of the Incretin Pathways in Type 2 Diabetes Mellitus
FEATURED ARTICLES

4 Pathophysiology of Hyperglycemia and its Role in Macrovascular and Microvascular Disease in Type 2 Diabetes

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14 Differences in Mechanisms of Action, Efficacy, and Safety of Incretin Treatment Options

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LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

• Assess the pathophysiology of hyperglycemia, its role in macrovascular and microvascular diseases, and the role of incretin pathways in type 2 diabetes mellitus.

• Examine the differences in mechanism of action, efficacy, and safety of treatment options that target the incretin pathway.

• Incorporate evidence-based guidelines and recommendations into practice when considering the use of incretin-based therapies for type 2 diabetes.

• Examine approaches to managing the obese patient with type 2 diabetes.

• Utilize GLP-1 receptor agonists and DPP-4 inhibitors in combination with insulin and oral agents to achieve optimal glycemic control.

• Analyze the potential cardiovascular benefits of incretin therapies in addition to glycemic control.

INTRODUCTION

The complexity of the diabetes patient population and increasingly complex treatment strategies underscore the importance that all physicians have improved understanding of diabetes and incretin pathway pathophysiology, the role of incretin-based therapies and combination therapies in the treatment of type 2 diabetes mellitus (T2DM), and the potential role of incretin-based therapies in reducing cardiovascular risk. By acquiring knowledge and competence in managing diabetes effectively, clinicians will be better able to understand the utility of these agents in current and future treatment paradigms.

Vindico Medical Education has enlisted experts in the field of endocrinology to review and interpret the available research and clinical guidelines concerning the use of GLP-1 receptor agonists and DPP-4 inhibitors for the treatment of type 2 diabetes.

The articles included in this newsletter will address the pathophysiology of hyperglycemia and its role in macrovascular and microvascular diseases; the pathophysiology of the incretin pathways in T2DM; and the differences in MOA, efficacy, and safety of incretin treatment options. There is also an expert interview addressing the current research with DPP-4 inhibitors and GLP-1 receptor agonists.

I thank the contributors for sharing their valuable knowledge and perspectives on these exciting new developments and for participating in the preparation of this issue of Dialogues in Diabetes.

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Pathophysiology of Hyperglycemia and its Role in Macrovascular and Microvascular Disease in Type 2 Diabetes

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Every day in the United States more than 5,200 people are diagnosed with diabetes, 230 patients have a diabetes-related amputation, 133 people with diabetes progress to end stage renal disease (ESRD), and 55 people with diabetes become blind.1 Data from 2011 indicate that 8.3% of the U.S. population have diagnosed diabetes, and approximately 35% have prediabetes (Figure 1).2 By 2050, it is likely that 100 million people in the United States will have diabetes, 90% of which will be undiagnosed.3,4 There is a clear loss of life expectancy associated with diabetes.5 Awareness of the pathophysiology of hyperglycemia and its role in macrovascular and microvascular disease is required to fully appreciate the importance of treating diabetes early and aggressively, so that this rising epidemic can be circumvented.

Pathophysiology of Type 2 Diabetes

Insulin resistance develops early in the patient that will go on to develop type 2 diabetes mellitus (T2DM).6 Initially, this does not affect glucose levels, as β cells are able to compensate. Over time, however, the increased demand on glucose levels leads to dysfunction, resulting in mild elevations of fasting and/or postprandial glucose levels that encompass prediabetes. If prediabetes is not corrected, glucose levels will eventually increase to more than 126 mg/dL, and glycohemoglobin levels will approach 6.5%, leading to a diagnosis of diabetes. The β-cell function and mass will eventually decrease over time.7

Type 2 diabetes is believed to be a multifactorial disease, influenced by both genetic and environmental factors. Genes related to insulin resistance and abnormal β-cell secretion may be inherited. Environmental factors that contribute to insulin resistance include obesity, poor diet, and inactivity. These factors result in the insulin resistance phenotype, which includes atherosclerosis, obesity, hypertension, hyperinsulinemia, and endothelial dysfunction. Patients who additionally have genes that lead to abnormal β-cell function progress to prediabetes, which manifests as impaired glucose tolerance and impaired fasting glucose. There are at least 8 different mechanisms of hyperglycemia that are referred to as the “ominous octet,” and they include impaired insulin secretion, increased glucagon secretion, increased hepatic glucose production, increased glucose reabsorption in the kidney, decreased peripheral glucose uptake, impaired incretin effect, increased lipolysis, and neurotransmitter dysfunction.7 As patients progress, they become at risk for myocardial infarction, stroke, amputation, blindness, chronic renal failure, disability, and death.
Obesity and Type 2 Diabetes

Obesity is also increasing as an epidemic and is contributing to the diabetes epidemic. Poor diet, physical inactivity, and stress all potentiate the genetic susceptibility to obesity. Obesity is associated with insulin resistance, hyperinsulinemia, hypertension, abnormal lipid patterns (i.e., increased triglycerides, decreased high-density lipoprotein cholesterol (HDL-C), increased low-density lipoprotein (LDL) particles), endothelial dysfunction, a hypercoagulable state, and overt diabetes. The metabolic syndrome increases the risk of diabetes by 21-fold (Figure 2). These factors lead to the development of atherosclerosis.

Central to this issue is elevation of visceral fat, which is the metabolically active fat. Abdominal fat distribution is well-established to increase the risk of coronary artery disease in both men and women. Abdominal obesity specifically increases all cardiovascular events. For example, the Heart Outcomes Prevention Evaluation (HOPE) study demonstrated that risk of myocardial infarction, cardiovascular death, and all-cause death increased with increasing tertiles of abdominal obesity. Visceral fat is more highly associated with insulin resistance than peripheral fat as well as other aforementioned contributors to insulin resistance.

Visceral fat cells release free fatty acids, tumor necrosis factor-α (TNF-α), and leptin, all of which result in abnormalities in β-cell function. Visceral fat accumulation is inversely correlated with levels of adiponectin, a collagen-like protein with anti-diabetic, anti-hypertensive, and anti-atherogenic properties. The secretion of free fatty acids and TNF-α combined with reductions in adiponectin results in increased hepatic glucose output.

Other medical complications of obesity

There are multiple metabolic complications of obesity that must be addressed in these patients. Obesity can lead to asthma, abnormal pulmonary function, and obstructive sleep apnea, which leads to the hypoventilation syndrome. Nonalcoholic fatty liver disease, currently the most common cause of liver failure in the United States, is another potential consequence of obesity. Nonalcoholic fatty liver disease encompasses steatosis, steatohepatitis, and cirrhosis. Obesity is also associated with an increased risk of gall bladder disease as well as gynecological abnormalities, including abnormal menses, infertility, and polycystic ovarian disease. An increased risk of severe pancreatitis is associated with hypertriglyceridemia. Obesity carries with it severe debility due to osteoarthritis, as well as phlebitis with venous stasis, and associated skin changes. There is also an increased risk of gout associated with obesity. Both obesity and diabetes are correlated with an increased risk of cancer in the breasts, colon, esophageal, pancreatic, kidney, and prostate.

Complications: Hyperglycemia

The complications of diabetes are now understood to be consequences of the abnormal metabolic environment that ensues from hyperglycemia. These include abnormalities in glucose, its metabolites, and insulin hormones. However, complications do not develop in every person with these irregularities, suggesting that risk is engendered by individual susceptibility. Genetics and ethnic background may be epigenetic mechanisms of susceptibility. Furthermore, issues in the environment, such as smoking, diet, alcohol consumption, and pre-existing hypertension from other causes can also modify the risk of developing any specific complication in each individual patient. When these complications are discovered early, there is potential for reversibility. Eventually, however, a point is reached where the damage ensued is irreversible and end stages of each complication is reached. Moreover, unrecognized hyperglycemia in hospitalized patients markedly increases adverse outcomes more so than the hyperglycemia of patients admitted to the hospital who are known
to have diabetes. Therefore, early aggressive control of hyperglycemia is critical, and has been shown to reduce the risk of complications. In fact, for every 1% decrease in A1C, microvascular complications are reduced by 21%.

Complications of hyperglycemia begin to accrue with even minimal abnormalities in either fasting hyperglycemia or postprandial hyperglycemia associated with prediabetes. Postprandial glucose elevations increase variability, a predictor of increased mortality. Postprandial elevations also increase the risk of microvascular disease, adverse pregnancy outcomes, atherosclerotic vascular disease, and worsened cardiovascular complications. Specifically treating postprandial hyperglycemia can reduce these risks.

Hyperglycemia is a continuous risk factor, and no A1C threshold is apparent. Higher A1Cs are directly proportional to the duration of diabetes. Elevated blood sugars can occur as spikes and in a continuous manner, while both mechanisms cause diabetic complications (Figure 3). The spikes cause acute toxicity in tissues. Continuous hyperglycemia leads to chronic toxicity. Ultimately, elevated blood sugars lead to tissue lesions, which result in microvascular complications including retinopathy, nephropathy, and neuropathy. Elevated blood sugars also potentiate the macrovascular disease that the patients are already at risk for due to obesity and insulin resistance. These macrovascular complications include peripheral vascular disease (PVD), myocardial infarction (MI), and stroke.

**Diabetic retinopathy**

Diabetes is the leading cause of new cases of blindness in adults aged 20 to 74 years. Diabetic retinopathy is responsible for 12,000 to 24,000 new cases of blindness each year. Type 1 diabetes is associated with a 25% rate of retinopathy after 5 years of disease, 80% after 15 years of disease, and approximately 100% after 20 years of disease. However, retinopathy is observed in 21% of patients with type 2 diabetes upon diagnosis. More than 60% of patients with type 2 diabetes have some form of retinopathy after 20 years of disease. The costs of retinopathy are high, accounting for 500 million dollars per year in the United States.

Biochemical changes including endothelial dysfunction, increased leukocyte adhesion, basement membrane thickening, pericyte loss, and changes in retinal blood flow result in a progression of changes observed in the posterior eye. These changes include those associated with mild nonproliferative retinopathy, such as microaneurysms and retinal hemorrhages, as well as microvascular complications including diabetic macular edema, cotton wool spots due to leakage of fluid into the retinal area, and ultimately severe retinal hemorrhages. Retinopathy can also be moderate and more severe, manifesting as increased abnormalities observed in the posterior eye. Ultimately, there is ischemia in the retinal layers that results in formation of new blood vessels that reach into the vitreous. This state is referred to as proliferative retinopathy. Vision loss can result from macular edema or capillary nonperfusion, preretinal or vitreous hemorrhage, and distortion of the retina leading to tractional retinal detachment.

**Diabetic nephropathy**

Diabetes is the most common cause of kidney failure, accounting for more than 40% of new cases of ESRD. In 2001, 41,312 patients with diabetes began treatment for ESRD. The same year, it cost 22.8 billion dollars in public and private funds to treat patients with kidney failure. The number of new cases of ESRD in patients with diabetes has more than doubled since 1991, reaching nearly 50,000 cases per year in 2005. The majority of this increase is due to type 2 diabetes.

Studies have shown that reduced estimated glomerular filtration rate (eGFR) was associated with increased risk of death, CV events, and hospitalization independent of known factors.
Diabetic neuropathy

Diabetic neuropathy, the most common neuropathy in industrialized countries, is a heterogeneous group of conditions affecting somatic and autonomic nerves. Approximately 50% of patients with diabetes develop neuropathy after 25 years, and 10% develop symptomatic neuropathy. Major morbidities are pain, numbness, and foot ulceration. Diabetic neuropathy is responsible for approximately 75% of all nontraumatic foot amputations. Major signs of diabetic peripheral neuropathy are not evident at the onset of disease, although some patients do experience symptoms with mildly impaired glucose tolerance or impaired fasting glucose. Symptoms may occur at any time and intermittently. Periodic evaluation is essential for patients with type 2 diabetes because many are not aware of diabetic peripheral neuropathy.

Diabetic neuropathies are classified as symmetric polyneuropathies and focal/multifocal neuropathies. Symmetric polyneuropathies include distal symmetric sensory motor neuropathy, autonomic neuropathy, and acute painful neuropathy. Systemic polyneuropathy is the most common form of diabetic neuropathy. This condition affects distal lower extremities. The longer axons of the legs are more susceptible, yet as the length of the axon damage rises, the hands, which are a function of shorter axons, will begin to develop discomfort. This is referred to as “stocking-glove” sensory loss and symptoms. Symptoms include paresthesias and dysesthesias of the feet and hands (predominant at night), paroxysmal lancinating pain, deep aching and muscle cramping, and autonomic dysfunction. Complications of symmetric polyneuropathies include ulcers, Charcot arthropathy, dislocation, stress fractures, and ultimately amputation.

With autonomic neuropathies, which are rare, the damage to the nerves affect autonomic nerves controlling internal organs. Manifestations may include pupillary abnormalities, changes in heart rate, further changes in sympathetic and parasympathetic tone, gastroparesis, gall bladder disease, large intestine symptoms, bladder dysfunction, and erectile dysfunction. Gastrointestinal autonomic neuropathy is characterized typically by symptoms of gastroparesis including anorexia, nausea, vomiting, undigested food many hours after eating, early satiety, and diabetic enteropathy including diarrhea and constipation. Cardiovascular autonomic neuropathy includes exercise intolerance and postural hypotension. Patients with diabetes can also experience polyradiculopathy, including lumbar polyradiculopathy, which is often referred to as diabetic amyotrophy, which can manifest as thigh pain followed by muscle weakness and asymmetric atrophy.

Mononeuropathy is another potential complication of diabetes. This can manifest as either single nerve damage, such as the nerve of the eye, carpal tunnel syndrome, elbow symptoms, and unilateral foot drop. Sometimes these mononeuropathies occur simultaneously, in a condition referred to as mononeuropathy multiplex. Mononeuropathies often resolve spontaneously after approximately 6 months.

Cardiac complications

As previously mentioned, type 2 diabetes and cardiovascular disease are closely associated. This occurs from the concordance of risk factors that accrue with obesity, the insulin resistance syndrome, and hyperglycemia. Heart disease is increased from 2-fold to 4-fold in patients with type 2 diabetes and accounts for 80% of all diabetic mortality (75% from coronary atherosclerosis, 25% from cerebral of peripheral vascular disease). Cardiovascular disease causes
more than 75% of all hospitalizations for diabetic complications, and more than 50% of patients with newly diagnosed type 2 diabetes already have pre-existing cardiovascular disease.\textsuperscript{32,33}

Among adults aged 60 years and older with diabetes, 30% have coronary heart disease, 14% have congestive heart failure, 14% have had a stroke, and 21% have peripheral arterial disease.\textsuperscript{34} A1C levels predict coronary heart disease, with higher levels increasing the risk of cardiovascular events and coronary heart disease mortality (Figure 4).\textsuperscript{35} Furthermore, postprandial glucose levels independently increase and determine cardiovascular disease. This is true even for postprandial glucose levels that are in the normal range; as they rise, elevations in fatal heart disease and total heart disease are observed.\textsuperscript{36}

**Biochemical Mechanisms Behind the Macrovascular and Microvascular Complications of Diabetes**

The biochemical pathophysiology of the microvascular and macrovascular complications of diabetes has been established to a substantial degree. High glucose levels result in an increased flux through the glycolytic pathways in many tissues. This leads to multiple changes in biochemical pathways that cause damage to tissues. For example, as the metabolism of glucose through the typical oxidative phosphorylation pathway is increased, reactive oxygen species are increased, which can cause multiple alterations in tissue throughout the body, such as changes in gene expression, altered nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) function, and oxidative stress. Resulting cellular dysfunctions and damage include abnormal angiogenesis, aberrant cell growth and survival, hyperpermeability, basement membrane matrix thickening, abnormal blood flow, increased glucocyte adhesion contractility, cardiomyopathy, and thrombosis.\textsuperscript{37}

Moreover, the reactive oxygen species damage DNA, which causes an elevation of poly [ADP-ribose] polymerase-1 (PARP-1) levels in the nucleus. This enzyme leaks out of the nucleus and causes ADP ribosylation of glyceraldehyde 3-phosphate dehydrogenase (GAPDH), reducing its activity. The reduced activity of GAPDH results in increased flux of glucose through 4 well-defined pathways: the polyol pathway, the hexosamine pathway, the protein kinase C (PKC) pathway, and the advanced glycation product endpoint (AGE) pathway.

Increased activity of the hexosamine pathway causes altered gene expression and increased inflammation. Increased activity of the polyol pathway causes a shift in water and ion content, which can lead to cataracts. Polyol accumulation, osmotic shifts, efflux of myo-inositol, reduced ATP, decreased synthesis of reduced glutathione, reduced NADPH, and decreased Na/K ATPase activity are other consequences of increasing the activity of this pathway. Biochemical consequences of the AGE formation include crosslinks of extracellular matrix proteins, which will occur in many tissues. Advanced glycation products can also be ingested in food, especially if charred, causing similar damage to multiple tissues. Low density lipoprotein and hemoglobin can become glycosylated, altering their functions throughout the body. Lastly, increased flux through diacyl glycerol (DAG) and PKC activity has multiple effects, including increased oxidative pathways, increased transforming growth factor-β activity (which increases collagen and fibronectin), increased plasminogen activator inhibitor-1 (which can affect fibrinolysis), and increased vascular endothelial growth factor (which can increase vascular permeability and angiogenesis). Others effects include increased nuclear factor k-light-chain-enhancer of activated β cells (NF-kB), which results in abnormal pro-inflammatory gene expression.

Therefore, through the basic mechanism of increased blood sugar with flux through its pathway of metabolism, increased oxidative pathways, and increased flux through other alternate pathways, damage to multiple tissues occurs, ultimately leading to the microvascular and macrovascular complications of diabetes.

Summary

The etiology of diabetes and the biochemical mechanisms involved as a result of hyperglycemia underscore the importance of controlling blood sugar in the midst of the obesity and diabetes epidemics. Early aggressive control is critical, and treating postprandial hyperglycemia is just as important as treating fasting hyperglycemia. In addition to treating blood sugar, it is also important that blood pressure, LDL, HDL, triglycerides, and non-HDL are treated to recommended goals. Treatment of these metabolic factors can reduce the risk of complications in patients with diabetes.

References


Full references are available at www.healio.com/endocrinology/education-lab.
The contributions of β-cell dysfunction and insulin resistance to the pathogenesis of type 2 diabetes are well-established. The pivotal study examining this issue demonstrated that insulin resistance increased and insulin secretion declined by nearly 80% among patients who progressed to type 2 diabetes. Among a control population, on the other hand, insulin resistance increased, but β-cell compensation for the insulin resistance was complete and subjects were able to maintain normal glucose tolerance.1 These data indicate that insulin secretory dysfunction plays a key role in the pathogenesis of type 2 diabetes.

After the onset of type 2 diabetes, it is apparent that β-cell function declines. When patients with newly diagnosed type 2 diabetes were followed for up to 6 years, they were found to experience a progressive decline in β-cell function, as measured by homeostasis model assessment (HOMA)-B score during that time period. In contrast, insulin sensitivity, which was also impaired, remained low during the same time period.2

The defects in β-cell function are not only related to the ability of β cells to secrete insulin, but may also be potentially related to a decrease in β-cell mass. Patients with type 2 diabetes have been shown to experience a 40% to 60% decrease in β-cell mass relative to control subjects without diabetes.3 Interestingly, patients with impaired fasting glucose also had a significant decrease in β-cell mass relative to those without diabetes, indicating that impairments in β-cell mass may contribute to the early pathogenesis of type 2 diabetes (Figure 1).

In addition to the defects in insulin secretion and insulin sensitivity, there are other abnormalities that contribute to the pathogenesis of hyperglycemia in type 2 diabetes. For example, glucagon secretion is high in patients with type 2 diabetes and is not suppressed in response to a meal as it should be.4 The impairment in insulin secretion coupled with the hyperglucagonemia lead to increases in endogenous glucose production by the liver.

The defects in insulin resistance and islet cell dysfunction in type 2 diabetes can be summarized as follows:

- Insulin resistance is apparent in skeletal muscle, fat, and liver.
- Insulin secretion by β cells is deficient.
- Responsiveness to glucose is reduced.
- Both fasting and postprandial glucagon secretion rates are increased, and as a result, endogenous glucose production is elevated in both fasting and postprandial periods.
- β-cell mass is reduced, and there is also evidence that α-cell mass may be increased.5

In addition to these well-known defects in type 2 diabetes, it is also apparent that there are other metabolic abnormalities, including neurotransmitter dysfunction, increased glucose absorption by the kidneys, increased lipolysis in adipocytes, and a decreased incretin effect (Figure 2).6

**Glucoregulatory Properties of Incretin Hormones**

A glucose challenge administered orally results in insulin levels that are approximately 2-fold higher than those that follow an intravenous glucose challenge.7 This effect is due to incretin hormones, principally glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). GLP-1 is released from L cells in the ileum and colon, whereas GIP is released from K cells in the duodenum. Both are released as active hormones into the circulation and stimulate insulin secretion in a glucose-dependent manner. Both GLP-1 and GIP bind to specific transmembrane receptors that are present on target tissues, including β cells. This
interaction leads to the activation of adenyl cyclase. This enzyme converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), which has downstream effects through protein kinase A (PKA) and exchange protein activated by cAMP (EPAC). These downstream effects lead to increased insulin gene transcription, biosynthesis, and secretion, as well as a variety of other physiological effects. Importantly, when glucose levels are in the normal range, neither GLP-1 nor GIP stimulates insulin production.

In addition to their direct effects on insulin secretion, GLP-1 and GIP have been shown to inhibit β-cell apoptosis in human islets. Moreover, GLP-1 and GIP are broadly expressed and therefore are associated with a number of other physiological effects in addition to their pancreatic effects. In the brain, GLP-1 may have neuroprotective effects, and is known to decrease appetite. In the heart, GLP-1 increases cardiac output and may have cardioprotective effects. In the stomach, GLP-1 is also known to decrease glucagon secretion in the pancreas. GIP has effects in the β-cell that overlap with those of GLP-1, as well as effects on adipocytes to increase lipogenesis and effects on bone. There are some differences in the effects of GLP-1 and GIP (Table, page 12). GIP does not inhibit gastric emptying or glucagon secretion as GLP-1 does. Also, GLP-1, not GIP, has been shown to reduce food intake and body weight.

The actions of GLP-1 and GIP are regulated by dipeptidyl peptidase-4 (DPP-4), a ubiquitous serine protease. This enzyme circulates in the blood, but is also present in other tissues throughout the body, including the kidney, lung, adrenal gland, liver, intestine, spleen, testes, pancreas, central nervous system, lymphocytes, and macrophages. DPP-4 cleaves 2 amino acids at the N-terminal of GLP-1 and GIP, rendering the hormones inactive. This inactivation occurs rapidly, resulting in relatively short half-lives for GLP-1 (2 min) and GIP (7 min).

Incretin Defects in Type 2 Diabetes

The incretin effect is markedly diminished in type 2 diabetes. In glucose-tolerant individuals, the insulin secretion in response to an isoglycemic glucose challenge administered orally is more than 2-fold higher than the insulin secretion following an intravenous glucose challenge. In patients with type 2 diabetes, this enhancement of insulin secretion is only approximately 25% of that observed in glucose-tolerant individuals. Analyses of studies that have examined GLP-1 and GIP secretion have concluded that the impairment in GLP-1 secretion in patients with type 2 diabetes is minimal to none, whereas GIP secretion is normal or increased in patients with type 2 diabetes relative to those with normal glucose tolerance.

A number of studies have suggested that there is a diminished response to GLP-1 and GIP in patients with type 2 diabetes. During a GLP-1 infusion, responses to glucose as well as insulin responses were approximately 2-fold higher in individuals with normal glucose tolerance. The GLP-1 infusion also enhanced insulin secretion in response to hyperglycemic clamps in individuals with normal glucose tolerance. However, these insulin levels were only increased to approximately those achieved with glucose alone in healthy individuals. In another study, a GLP-1 infusion that enhanced GLP-1 levels to physiologic ranges markedly increased insulin secretion in response to hyperglycemic clamps in individuals with normal glucose tolerance, but had no effect in patients...
with type 2 diabetes. In contrast, pharmacologic GLP-1 levels that resulted in plasma GLP-1 levels approximately 3-fold higher than the aforementioned study were able to enhance insulin secretion in patients with type 2 diabetes. A study by Dr. Nauck and colleagues demonstrated that, compared to a saline infusion, a 4-hour GLP-1 infusion normalized glucose levels in patients with poorly controlled diabetes whose fasting glucose levels were approximately 240 mg/dL. This was associated with increases in insulin secretory capacity and suppression of glucagon. In this study, insulin secretion and the suppression of glucagon decreased by the fourth hour as glucose levels returned to the normal range, exemplifying the glucose-dependent properties of GLP-1 on both β cells and α cells.

Due to a short half-life of GLP-1, continuous administration is necessary in order to improve glucose excursions. In a single-center, randomized, parallel, double-blind, placebo-controlled trial, 40 hospitalized patients were randomized to receive infusions of either placebo or GLP-1 4 or 8 ng/kg/min for either 16 or 24 hours per day for 7 days. Twenty-four hour profiles of glucose, glucagon, and insulin were measured at predetermined intervals. The GLP-1 8 ng/kg/min dose administered for 24 hours was more efficacious than any of the other doses (P ≤ 0.05). The 16-hour infusion decreased plasma glucose levels, but at the termination of the infusion, plasma glucose levels rapidly returned to baseline. In contrast, the 24-hour infusion of GLP-1 suppressed glucose levels throughout the entire period. The results of this study suggest that GLP-1 should be administered continuously in order to obtain optimal glycemic control.

In contrast to the effects of GLP-1, the incretin response to GIP infusions in patients with type 2 diabetes is markedly blunted. Whereas a small first-phase response was noted in a study of 8 patients with type 2 diabetes, the second-phase response was strikingly decreased in comparison to the large increase in insulin secretion observed with GLP-1 at pharmacologic doses in the same patients. The etiology of the lack of response to GLP-1 and GIP remains unclear in humans, but there is evidence that hyperglycemia downregulates incretin receptor expression. This effect is observed most prominently for the GIP receptor, for which diabetes causes a marked diminution in pancreatic β cells. This effect is also observed, albeit to a lesser extent, with the GLP-1 receptor.

In addition to its association with multiple metabolic abnormalities, type 2 diabetes is a progressive disease. Abnormalities in insulin resistance and insulin secretion are observed during the prediabetes phase,
Incretin Therapies

These data suggest that incretin therapies may be useful in the treatment of type 2 diabetes. Incretin-based therapies could address multiple defects in type 2 diabetes, including impairments in insulin secretion, hypersecretion of glucagon, and rapid gastric emptying. Other benefits of incretin therapies which are a consequence of their glucose-dependent actions are that they do not cause hypoglycemia and have favorable effects on body weight.

Incretin therapies can be divided into 2 categories (Figure 3). The first is GLP-1 analogues, which are peptide hormones that mimic the action of GLP-1 and are resistant to DPP-4 inactivation. They are injectable therapies which can be divided into 2 large classes: the exendin-4 based class which includes exenatide, exenatide long-acting release (LAR), and lixisenatide, and the human GLP-1 class, which includes liрагlutide and others under development (eg, albiglutide, dulagliptide). The other approach to enhancing the beneficial effect of incretin therapies in type 2 diabetes is to block DPP-4. A number of DPP-4 inhibitors are commercially available, including sitagliptin, saxagliptin, linagliptin, vildagliptin, and alogliptin.\textsuperscript{32,33}

In summary, the incretin system plays a key role in the regulation of blood sugar, and its effects are diminished in patients with type 2 diabetes. Therapies that target the incretin system have proven to be beneficial in the treatment of this progressive disease. Healthcare professionals must be aware of the importance of the incretin system in the pathophysiology of type 2 diabetes.

References


Full references are available at www.healio.com/endocrinology/education-lab
Type 2 diabetes mellitus (T2DM) is a common metabolic disorder that affects 26 million Americans and is characterized by multiple pathophysiologic defects. Although progressive β-cell failure, insulin resistance in muscle, and insulin resistance in liver constitute the core metabolic/endocrine disturbances in T2DM, at least five other abnormalities have been documented: (i) insulin resistance in the fat cell leading to accelerated lipolysis, elevated plasma free fatty acid (FFA) levels, and lipotoxic effects on the β-cell, muscle, and liver; (ii) β-cell resistance to the stimulatory effect of GLP-1 and GIP on insulin secretion; (iii) increased glucagon secretion by the alpha cell and enhanced hepatic sensitivity to glucagon; (iv) enhanced glucose reabsorption by the kidney; and (v) brain resistance to the appetite suppressant effects of insulin and leptin, resulting in weight gain, insulin resistance, and β-cell dysfunction. Collectively, these eight pathophysiologic disturbances have been referred to as the Ominous Octet. Following ingestion of a meal or glucose load, the amount of insulin secreted by the pancreatic β-cell is from 2-fold to 3-fold greater than if the same plasma glucose profile is reproduced by intravenous glucose and this has been referred to as the incretin effect. Two gastrointestinal hormones, glucose-dependent insulinotrophic polypeptide (GIP, secreted by the K cells in the early small intestine) and glucagon-like peptide-1 (GLP-1 secreted by the L cells in the large bowel) are responsible for 90% of this incretin effect and account for approximately half of the insulin that is secreted by normal glucose tolerant individuals following a typical mixed meal. Both GIP and GLP-1 are secreted within minutes after meal ingestion and this response is mediated via neural connections from the stomach/upper GI tract to the hypothalamus/brain stem and back to the K and L cells via vagus nerve. Importantly, neither GIP nor GLP-1 cause the release of insulin unless the plasma glucose concentration is increased. GIP and GLP-1 are rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4) and have a half-life from 3 to 4 minutes. Thus, when food is completely absorbed from the stomach and the plasma glucose concentration begins to fall, GIP and GLP-1 levels rapidly decline, thereby removing the stimulus for insulin secretion. This glucose-dependent effect of both GIP and GLP-1 on insulin secretion prevents the development of postprandial hypoglycemia. GLP-1 also inhibits glucagon secretion by the pancreatic alpha cells and GLP-1, but not GIP, promotes satiety and inhibits the appetite centers in the hypothalamus leading to weight loss. GLP-1 also exerts a number of beneficial effects on cardiovascular risk factors.

In type 2 diabetic patients the meal-induced release of GLP-1 and GIP variably have been reported to be normal, decreased, or increased. On mean, no major impairment in incretin hormone secretion has been demonstrated. In contrast, severe resistance to the stimulatory effect of both GLP-1 and GIP on glucose-stimulated insulin secretion is well documented. However, the stimulatory effect of GLP-1 on insulin secretion can be overcome by infusing a pharmacologic dose of GLP-1 or by the subcutaneous injection of a GLP-1 receptor agonist that raises the plasma GLP-1 level into the pharmacologic range. In contrast, DPP-4 inhibitors, which cause only a modest, more physiologic increase in plasma GLP-1 (and GIP) levels, have a weak stimulatory effect of insulin secretion. This difference in plasma GLP-1 levels explains why the GLP-1 receptor agonists always
produce a greater improvement in glycemic control than the DPP-4 inhibitors.\textsuperscript{15-17} This pharmacokinetic difference also explains the greater inhibition of glucagon secretion by the GLP-1 receptor agonists and their weight-reducing effect compared to the DPP-4 inhibitors that are weight neutral. A major attribute of the GLP-1 analogues is their durable effect (documented for up to 3 years) to improve \(\beta\)-cell function\textsuperscript{18} and maintain the reduction in AIC.\textsuperscript{19}

Exenatide twice-daily was the first GLP-1 receptor agonist approved by the FDA and has its major mechanism of action to reduce the postprandial plasma glucose excursion.\textsuperscript{20} Half of the reduction in postprandial glucose is explained by delayed gastric emptying and the other half is explained by the inhibition of the basal rate of hepatic glucose production (HGP).\textsuperscript{21} Of the reduction in HGP, half is explained by the increase in plasma insulin response and half by the inhibition of glucagon secretion.\textsuperscript{21} In patients with T2DM with a starting AIC of 8.0\% to 8.2\%, one can expect a decrement in AIC of ~1.0\% to 1.2\% and a weight loss of 4 to 8 lbs over the first 6 to 12 months.\textsuperscript{15,22-24} Since exenatide is given twice daily with the two largest meals and has a short biological half life, the third meal of the day will not be covered and the elevated rate of hepatic glucose production (HGP) (the primary determinant of the fasting plasma glucose concentration) that occurs throughout the sleeping hours will not be affected. Therefore, the reduction in AIC would be expected to be significantly less than observed with longer acting GLP-1 receptor agonists, such as once-weekly exenatide and once-daily liraglutide that provide 24-hour glycemic control and have major effects on both the fasting and postprandial plasma glucose levels. GLP-1 receptor agonists are approved for use in combination with all oral antidiabetic agents and work well even in patients with long-standing T2DM.

In a head-to-head 24-week study comparing twice-daily exenatide vs. exenatide once-weekly,\textsuperscript{24} exenatide once-weekly, as expected, produced a significantly greater decline in AIC than exenatide twice-daily (-1.6\% vs. -0.9\%, \(P<.01\)) and significantly greater weight loss (5.1 lbs vs. 3.1 lbs, \(P<.01\)). Similarly, a direct comparison of liraglutide vs. twice-daily exenatide demonstrated a 0.33\% greater decrease in the AIC with liraglutide,\textsuperscript{23} while a one-year study demonstrated a greater decrease in AIC by 0.2\% with liraglutide vs. once-weekly exenatide,\textsuperscript{23} although the clinical significance of this small difference is unclear. Weight loss was not significantly different between liraglutide and once-weekly exenatide in this study.\textsuperscript{25} Rates of nausea with once-weekly exenatide, liraglutide, and twice-daily exenatide were 14\%, 25\%, and 35\%, respectively,\textsuperscript{23,24} and discontinuation due to gastrointestinal adverse effects (nausea or vomiting) was less than 1\% with all three GLP-1 analogues. The lower incidence of GI adverse effects with once-weekly exenatide is explained by the gradual increase in plasma exenatide concentration that takes 7 to 8 weeks to reach steady state levels. Because the stimulatory effect of all GLP-1 analogues on insulin secretion is glucose dependent, hypoglycemia is uncommon unless they are used in combination with a sulfonylurea or basal insulin (once-weekly exenatide is not approved for use with basal insulin and no GLP-1 analogue is approved for use with rapid acting insulin).

Despite the superior efficacy of the GLP-1 receptor agonists in reducing AIC and promoting weight loss,\textsuperscript{15-17} the DPP-4 inhibitors hold ~80\% of the incretin market in the United States. Oral administration and paucity of adverse effects account for their dominant market share. DPP-4 inhibitors have a modest effect in enhancing insulin secretion, while their major mechanism of action is mediated via inhibition of glucagon secretion. As monotherapy, the DPP-4 inhibitors cause a modest reduction in AIC (0.6 to 0.7\%) with a starting AIC of 8.0\% to 8.2\% and their durability begins to wane after the first year of therapy.\textsuperscript{26,27} However, when combined with metformin, much more robust decreases in AIC are observed.\textsuperscript{28,29} Considerable data demonstrate that metformin augments GLP-1 secretion by the L-cells\textsuperscript{29-31} and the elevated GLP-1 levels can be maintained by the concomitant administration of a DPP-4 inhibitor.\textsuperscript{30} DPP-4 inhibitors can be combined with all other classes of oral antidiabetic agents (pioglitazone, sulfonylureas, SGLT2 inhibitors) and insulin, although the reduction in AIC when combined with insulin is very modest. The only adverse effect occurring in more than 5\% of individuals treated with a DPP-4 inhibitor is upper respiratory tract illness. Post-marketing reports of pancreatitis have been reported with both the DPP-4 inhibitors and GLP-1 receptor agonists, but a causal association has not been established. Patients should be monitored carefully for signs and symptoms of pancreatitis. In addition, GLP-1 agonist therapy causes an increased
incidence of thyroid-C cell tumors in rats. Human relevance has not been determined by clinical or nonclinical studies. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

Summary

The incretinomimetics – both the GLP-1 receptor agonists and DPP-4 inhibitors – represent a significant advance in the treatment of patients with T2DM. DPP-4 inhibitors have the advantage of ease of administration and lack of adverse effects, but the reduction in AIC is modest and begins to wane after the first year of therapy. GLP-1 receptor agonist cause a more robust and durable reduction in AIC, enhance and preserve β-cell function for up to three years, and promote weight loss but must be given by injection and are associated with gastrointestinal adverse effects. GLP-1 receptor agonists correct six of the defects that comprise the Ominous Octet: (i) replace deficient GLP-1 levels; (ii) overcome the severe GLP-1 resistance at the level of the β-cell, thereby augmenting insulin secretion; (iii) inhibit the elevated rates of glucagon secretion by the alpha cell and reduce plasma glucagon concentrations; (iv) increase in insulin and inhibition of glucagon secretion decrease hepatic glucose production; (v) offset the brain’s resistance to the appetite-suppressant effects of insulin and leptin and promote weight loss; (vi) weight loss indirectly improves insulin sensitivity in muscle.

References

**Expert Interview with Michael A. Nauck, MD, PhD**

**Compare and contrast the available GLP-1 receptor agonists and their effects on AIC, postprandial glucose, and weight loss capabilities.**

*Michael A. Nauck, MD, PhD:* The long-acting GLP-1 receptor agonists, liraglutide once-daily and exenatide once-weekly, achieve a steady plasma drug concentration, in contrast, the short-acting agonist exenatide, achieves a peak drug concentration shortly after injection followed by a fall close to zero, necessitating repeat injections. Also, long-acting GLP-1 receptor agonists appear to have a better effect on fasting, and are more efficacious in lowering AIC compared to short-acting formulation. Weight loss, liraglutide, and exenatide once-weekly have similar effects. However, in a head-to-head comparison, liraglutide appeared to be more effective than exenatide once-weekly. This may simply be a consequence of the differences in dose selection.

The FDA has approved insulin for use with liraglutide and glargine insulin for use with exenatide. Since exenatide appears to work faster and slightly better on postprandial glucose, would exenatide be a better combination with insulin?  
**Dr. Nauck:** In the absence of robust head-to-head studies, any attempt at a comparison is theoretical. If you combine any of these two agents with basal insulin, titrated so that the fasting glucose is in the target range, the only way to further improve AIC is by minimizing the increase in postprandial glycemia. It is my biased opinion that the short-acting agents like exenatide provide a more profound control of postprandial glycemia compared to the long-acting GLP-1 receptor agonists liraglutide or exenatide once-weekly.

**Compare and contrast the available DPP-4 inhibitors in regard to their efficacy, excretion, and drug interactions.**  
**Dr. Nauck:** The DPP-4 inhibitors, sitagliptin, vildagliptin, alogliptin, saxagliptin, and linagliptin have similar efficacy, and on average achieve a reduction in AIC between 0.6% and 0.9%. Renal functional impairment may require dose reduction. For example, sitagliptin, used at 100 mg/day in patients with healthy kidneys is recommended at 50 mg/day in patients with moderate renal insufficiency and at 25 mg/day in those with severe renal insufficiency. The exception is linagliptin, excreted via the biliary system, which can be dosed at 5 mg/day in all patients. Regarding drug interactions, saxagliptin reacts with cytochrome P450 system. Therefore, dose reduction may be necessary if administering other drugs that also interact with this system.

**How do the DPP-4 inhibitors and the GLP-1 receptor agonists compare in terms of their adverse effects on hypoglycemia, AIC, postprandial glucose, and weight loss? Also, can you comment on the perceived role of incretin-based therapies in preserving β-cell function?**  
**Dr. Nauck:** The adverse effects of DPP-4 inhibitors are comparable to placebo. In contrast, vomiting, nausea, and diarrhea are the most common adverse effects with GLP-1 receptor agonists. There is good evidence that neither DPP-4 inhibitors nor GLP-1 receptor agonists can cause severe hypoglycemia, except when used in combination with other causative drugs, such as insulin, sulfonylureas, and nateglinide. With respect to AIC, head-to-head comparisons show more effective reduction with a GLP-1 receptor agonist than a DPP-4 inhibitor. Generally, short-acting GLP-1 receptor agonists appear to have better control of postprandial glucose than DPP-4 inhibitors. For weight loss, DPP-4 inhibitors are weight-neutral where as significant reduction in weight has been reported with GLP-1 receptor agonists. Studies have failed to demonstrate a lasting beta cell effect with incretin-based therapies. Initial studies involving the islets of young rodents fueled this speculation, because exposure to GLP-1 receptor agonists elicits growth in their beta cell mass, which is not observed in older animals. The type 2 diabetic population is more similar to the older animal group.

**Concerns have been raised about risks of pancreatitis and pancreatic cancer and thyroid cancer with the GLP-1 receptor agonists. Can you comment on these concerns?**  
**Dr. Nauck:** The available data from human and animal studies does not support a causal relationship nor an elevated risk of cancer from GLP-1 receptor agonists, however, some studies have reported up to a two-fold increase in risk of acute pancreatitis. Few studies have reported early signs of neoplastic changes in pancreatic tissue when examined with immunohistochemistry. Whether these findings translate to increased cancer incidence is currently highly questionable. My personal view is that it would be difficult to design robust studies that can truly answer this question. In regard to thyroid cancer, unlike rodent thyroid C-cells that express a large quantity of GLP-1 receptors, and proliferate to form adenomas or even carcinomas when exposed to long-acting GLP-1 receptor agonists, human C-cells do not respond to GLP-1 or its receptor agonists, and in theory will not show a proliferative response.
CME Posttest

CME Instructions

1. Which of the following is NOT a characteristic of the insulin resistance phenotype?
   A. Hypertension
   B. Atherosclerosis
   C. Hyperinsulinemia
   D. Weight loss

2. Which of the following is one of the Ominous Octet of hyperglycemia?
   A. Decreased glucagon secretion
   B. Decreased hepatic glucose production
   C. Increased glucose reabsorption in the kidney
   D. Decreased lipolysis

3. Which of the following is associated with obesity?
   A. Insulin resistance
   B. Increased HDL-C
   C. Decreased LDL particles
   D. Increased insulin sensitivity

4. GLP-1:
   A. Is released from K cells in the duodenum
   B. Inhibits glucagon secretion
   C. Inhibits insulin secretion
   D. Promotes increased gastric emptying

5. GIP:
   A. Inhibits glucagon secretion
   B. Suppresses appetite
   C. Increases gastric emptying
   D. Stimulates insulin release in a glucose dependent fashion

6. Which of the following incretin-based therapies has the highest rate of nausea?
   A. Twice-daily exenatide
   B. Liraglutide
   C. Sitagliptin
   D. Linagliptin

7. Therapy with GLP-1 receptor agonists:
   A. Do not overcome GLP-1 resistance in the beta cell
   B. Have no significant effect on postprandial glucose
   C. Inhibit glucagon secretion
   D. Increase hepatic glucose production

8. Which of the following best describes the incretin defect in T2DM?
   A. Increased but delayed secretion of GLP-1 and GIP
   B. Insulinotropic responses to GIP are increased
   C. Upregulation of the β-cell GIP receptor
   D. Decreased insulinotropic responses to GLP-1

9. Which of the following DPP-4 inhibitors has NO significant renal excretion?
   A. Linagliptin
   B. Saxagliptin
   C. Alogliptin
   D. Sitagliptin

10. A 50-year-old overweight male continues to gain weight despite being on metformin 100-mg twice daily and glimepiride 4-mg once daily. His A1C is currently 7.9%. Which therapeutic strategy will help him lose weight and achieve better glycemic control?
    A. Increase glimepiride to 8 mg daily
    B. Add once-daily insulin glargine
    C. Add twice-daily exenatide
    D. Add a DPP-4 inhibitor
**POSTTEST**

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*Time spent on this activity: Hours  Minutes*  
(reading articles and completing the learning assessment and evaluation)  
This information MUST be completed in order for the quiz to be scored.

Release date: September 13, 2013  
Expiration date: September 13, 2014

**PRINT OR TYPE**

**Last Name**  
**First Name**  
**Degree**

Mailing Address

**City**  
**State**  
**Zip Code**

Date of Birth (used for tracking credits ONLY)

Phone Number  
FAX Number  
E-mail

**Degree:**  
Please select one  
**Specialty:**  
Please select one

- MD  
- PA  
- Primary Care  
- Cardiology  
- PhD  
- NP  
- Endocrinology  
- Research  
- DO  
- Other

**EVALUATION**  
(must be completed for your CME Quiz to be scored)

Please circle answers neatly and write legibly.

1. The content covered was useful and relevant to my practice.  
   Yes  
   No

2. The activity was presented objectively and was free of commercial bias.  
   Yes  
   No

   [Please use the additional comments field below to provide further information.]

   Additional comments regarding bias:

3. Based on the information I learned during this activity, I feel more confident in treating patients within my practice.  
   Yes  
   No

4. Knowledge acquired from this activity will be utilized to improve outcomes in my patients.  
   Yes  
   No

5. Future activities concerning this subject matter are necessary.  
   Yes  
   No

6. I plan to make the following changes to my practice:

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<tr>
<td>Utilize GLP-1 receptor agonists and DPP-4 inhibitors in combination with insulin and oral agents to achieve optimal glycemic control.</td>
<td>Y</td>
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<td>Assess the pathophysiology of incretin pathways in type 2 diabetes mellitus.</td>
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<td>Incorporate evidence-based guidelines and recommendations into practice when considering the use of incretin-based therapies for type 2 diabetes.</td>
<td>Y</td>
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<td>Analyze the potential cardiovascular benefits of incretin therapies in addition to glycemic control.</td>
<td>Y</td>
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<td>Other - Please explain:</td>
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7. These are the barriers I face in my current practice setting that may impact patient outcomes:

   | Lack of evidence-based guidelines | Yes | No |
   | Lack of applicable guidelines for my current practice/patients | Yes | No |
   | Lack of time | Yes | No |
   | Organizational/Institutional | Yes | No |
   | Insurance/Financial | Yes | No |
   | Patient adherence/compliance | Yes | No |
   | Treatment-related adverse events | Yes | No |
   | Other - Please explain: |

8. This activity supported achievement of each of the learning objectives.  
   Yes  
   No

   Please explain:

9. I see the following number of patients per week with type 2 diabetes mellitus:

   | A. | <10 |
   | B. | 10 to 25 |
   | C. | 26 to 50 |
   | D. | >50 |

10. Please list CE/CME topics that would be of value to you.

   Please explain:

**CME ACTIVITY REQUEST**

- Yes, I would like the opportunity to earn CME credits through activities sponsored by Vindico Medical Education.

**Required Field**