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Targeting postprandial hyperglycemia

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Abstract

In healthy individuals, blood glucose levels in the fasting state are maintained by the continuous basal-level insulin secretion. After a meal, the rise in postprandial glucose (PPG) is controlled by the rapid pancreatic release of insulin, stimulated by both glucose and the intestinal production of the incretins glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1. In diabetic individuals, postprandial insulin secretion is insufficient to suppress an excessive rise in PPG. There is increasing evidence that elevated PPG exerts a more deleterious effect on the vascular system than elevation of fasting plasma glucose. In particular, individuals with normal fasting plasma glucose but impaired glucose tolerance have significantly increased risk of cardiovascular events. With the recognition of the importance of PPG and the availability of new pharmacologic options, management of diabetes will shift to greater attention to PPG levels. The prototype for such an approach is in the treatment of gestational diabetes and diabetic pregnancies where PPG is the primary target of efforts at glycemic control. These efforts have been extremely successful in improving the outlook for diabetic pregnant women. There are many approaches to reduction of PPG; dietary management and promotion of exercise are very effective. Sulfonylureas, meglitinides, metformin, thiazolidinediones, and disaccharidase inhibitors all counteract PPG elevation. The development of glucagon-like peptide 1 agonists such as exendin and dipeptidyl peptidase IV inhibitors such as vildagliptin offers a new approach to suppression of PPG elevation. New semisynthetic insulin analogues permit a more aggressive response to postprandial glucose elevation, with lower risk of hypoglycemia, than with regular insulin. Inhaled insulin also has a rapid onset of action and offers benefits in PPG control. It is proposed that an aggressive treatment approach focusing on PPG, similar to the current standards for diabetic pregancies, be directed at individuals with diabetes and impaired glucose tolerance.

1. Introduction

Diabetes is characterized by abnormally high plasma glucose levels. A plasma glucose level of 126 mg/dL (7 mmol/L) or greater after a prolonged period of fasting is considered diagnostic of diabetes. However, it is after a meal that glucose levels are highest. In healthy individuals, blood glucose levels peak approximately 1 hour after the start of a meal. Postprandial glucose (PPG) levels at 1 hour normally range from 70 to 100 mg/dL (3.9 to 5.5 mmol/L), rarely exceeding 140 mg/dL (7.8 mmol/L), and usually return to preprandial levels after 2 to 3 hours [1,2].

There is a high correlation between fasting plasma glucose (FPG) levels and the magnitude of postmeal glucose excursions [3]. Postprandial glucose levels greater than 200 mg/dL (11 mmol/L) 2 hours after a meal, in the presence of characteristic symptoms, permit a diagnosis of diabetes, even in the absence of fasting glucose elevation. Measurement of the glucose levels after administration of a standard amount of glucose, typically 75 g as a glucose tolerance test, has been widely accepted as a surrogate for postmeal glucose response. Certainly, the response to pure glucose does not adequately reflect the effects of protein and fat ingestion during a typical meal. However, there has been no generally accepted standardization of a characteristic meal used to assess glucose response, so most studies on postprandial glucose rely on glucose tolerance testing. Impaired glucose tolerance (IGT) is characterized by normal FPG levels but a 2-hour value on the oral glucose tolerance test between 140 and 199 mg/dL. Individuals with IGT manifest abnormalities in both insulin action and early insulin secretion similar to those seen in patients with type 2 diabetes mellitus [4,5].

Impaired glucose tolerance tends to progress to diabetes [6] as a result of gradual loss of beta-cell function [7,8].

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Elevated glucose levels may be responsible, in part, for the decline in beta-cell function. The effects of hyperglycemia include reduced response to stimulus to secrete insulin and a gradual depletion of insulin stores. High postprandial glucose levels may lead to increased oxidative stress on the beta cell [9,10]. Inadequate insulin production during chronic hyperglycemia results from decreased insulin gene transcription due to hyperglycemia-induced changes in the activity of beta cell–specific transcription factors. Hyperglycemia may induce apoptosis of beta cells. These detrimental effects of excessive glucose concentrations are referred to as glucotoxicity [11-13].

Impaired fasting glucose (IFG) and IGT both are predictive of the later development of diabetes. In the Hoorn Study, the odds ratio for development of diabetes was 10.0 (95% confidence interval [CI], 6.1-16.5) for those having isolated IFG and 10.9 (95% CI, 6.0-19.9) for those with isolated IGT [14]. In long-term studies in Mauritius, IGT appeared to be a more sensitive predictor of progression than IFG levels [15].

Hemoglobin A_{1c} (HbA_{1c}) has become the standard measure for assessing and monitoring long-term glycemic control, reflecting both basal and postprandial glucose levels. There is a high correlation between postprandial glucose levels and HbA_{1c} [16]. In fact, postprandial glucose values may contribute more to elevation of HbA_{1c} than fasting glucose values. In National Health and Nutrition Examination Survey (NHANES) III, there was a high prevalence of postchallenge (postprandial) hyperglycemia (based on 2-hour glucose tolerance test) among individuals with diabetes, rising from 39% in those with optimal control (HbA_{1c}, <7.0%) to more than 99% in those who had fair (HbA_{1c}, 7.0%-7.9%) and poor control (HbA_{1c}, >8.0%) [17]. In a study of 404 individuals with normal HbA_{1c} levels (<6.0%) undergoing a glucose tolerance test, 60% had normal glucose tolerance, 6% had type 2 diabetes mellitus, 33% had IGT, but only 1% had isolated IFG, and, of the 161 individuals with abnormal glucose tolerance, 80% had normal FPG [18]. In individuals with relatively well-controlled diabetes, postprandial glucose levels contribute more to the elevation of the HbA_{1c} value than fasting glucose. In a study of 66 type 2 diabetic patients, postlunch plasma glucose correlated significantly and independently with HbA_{1c}, but prebreakfast plasma glucose and prelunch plasma glucose did not [19]. In a subsequent study of 290 patients with type 2 diabetes mellitus, it was demonstrated that the relative contribution of postprandial glucose (PPG) to HbA_{1c} levels increased progressively from 30% in patients at the highest level of HbA_{1c} to about 70% in those at the lowest level of HbA_{1c} [20].

2. Mechanisms of postprandial hyperglycemia

In nondiabetic individuals, basal glucose levels are maintained within a narrow range by continuous low-level insulin secretion into the portal circulation, which regulates the rate of hepatic glucose production during the periods between meals. Glucose is rapidly absorbed after oral glucose ingestion. In the postprandial state, the degree of the rise in blood glucose is determined by the difference between the amount of glucose entering and the amount leaving the circulation [21]. As soon as the blood glucose concentration starts to rise, there is an increase in rapid pulsatile insulin secretion. The rise in insulin secretion increases uptake of glucose by the liver, muscle, kidney, adipose tissue, and other insulin-dependent tisssues. Hepatic and renal gluconeogenesis are also suppressed by insulin release [22]. Glucose excursions are therefore kept within a narrow range as a result of the effect of insulin on its target organs. The physiologic response of the beta cell to an increase in plasma glucose concentration is biphasic, with a first-phase insulin release (0-10 minutes) followed by a steady and longer-lasting second phase. Rapid early-phase insulin secretion is the chief determinant of PPG levels. The loss of early-phase insulin response characterizes type 2 diabetes mellitus and IGT. Even patients with good dietary control of diabetes have diminished release of insulin in the first half hour after a meal [23-25].

As a result of decreased early-phase insulin release, glucose disposal by the liver and by extrahepatic tissues is reduced in diabetes [26-29]. In type 2 diabetic patients, there may be abundant insulin release at later times. However, the decreased early-phase insulin levels result in a substantial elevation of the peak glucose [30]. Early-phase insulin secretion is stimulated by the rise in glucose absorbed from the gut after a meal, but glucose is not the only stimulant for postprandial insulin release. When glucose is absorbed from the gastrointestinal tract, insulin secretion is stimulated much more than it is when glucose is infused intravenously to reach equivalent serum concentration [31,32]. This effect is called the incretin effect and is estimated to be responsible for 50% to 70% of the insulin response to glucose. It is caused mainly by the 2 intestinal insulin stimulating hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [33-35]. These peptides not only stimulate pancreatic insulin secretion, but also inhibit glucagon secretion and reduce gastric emptying [36]. GLP-1 and GIP secretion are stimulated primarily by glucose ingestion [37]. Fatty acid ingestion also stimulates incretin production [38,39]. The GLP-1 response to a meal is decreased in type 2 diabetes mellitus [40-45]. GIP and GLP-1 levels appear to be normal in type 1 diabetes mellitus [46]. However, the stimulating effects of both incretins on insulin secretion are diminished in type 2 diabetes mellitus [47,48].

3. Postprandial hyperglycemia and cardiovascular disease

There is a well-established relationship between high HbA_{1c} levels and micro- and macrovascular disease in diabetes. In the Diabetes Control and Complications Trial,