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Targeting postprandial hyperglycemia

Marc S. Rendell[a,b,*], Lois Jovanovic[c]

[a]Creighton Diabetes Center, Omaha, NE 68131, USA
[b]Rose Salter Medical Research Foundation, Omaha, NE 68114, USA
[c]Sansum Diabetes Research Institute, Santa Barbara, CA 93105, USA

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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].

* Corresponding reviewer. Creighton Diabetes Center, Omaha, NE 68131, USA.

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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,

intensive treatment of type 1 diabetic patients to lower HbA_{1c} resulted in a reduction of retinopathy and nephropathy [49,50]. There was also a beneficial effect on autonomic and peripheral neuropathy [51,52]. The effects of reducing HbA_{1c} appear to be exponential with greater benefits at higher HbA_{1c} levels [53] and are prolonged, continuing for several years after the cessation of intensive treatment [54,55]. Studies in type 2 diabetes mellitus support an association between worsening HbA_{1c} and microvascular disease similar to that in type 1 diabetes mellitus [56,57]. Data from the Steno Study and the United Kingdom Prospective Diabetes Study (UKPDS) showed that intensive therapy to control hyperglycemia reduced diabetes complications in patients with type 2 diabetes mellitus [58-61]. A prospective study of intensive insulin therapy in Japanese patients with type 2 diabetes mellitus showed significant reduction of progression of retinopathy, nephropathy, and neuropathy [62]. Several studies indicate that the risk of progression of microvascular disease is associated with both increased fasting and postprandial plasma glucose levels [63-65].

Despite the strength of the risk reduction of microvascular disease, the relationship between the lowering of HbA_{1c} and prevention of cardiovascular disease in diabetes is less clear cut. In 3 separate studies, the Diabetes Control and Complications Trial in type 1 diabetes mellitus, the UKPDS, and the Veterans Affairs Cooperative Study on Glycemic Control and Complication in type 2 diabetes mellitus, the reduction in myocardial infarctions and strokes with improved HbA_{1c} was far less impressive than the impact on microvascular outcomes [49,52,66]. The Veterans Affairs Cooperative Study of Diabetes Mellitus suggested a nonstatistically significant worsening of cardiovascular disease outcomes associated with more intensive therapy with insulin in patients who had failed sulfonylurea therapy. The UKPDS demonstrated a trend toward improved outcomes in the area of myocardial infarction, but worse outcomes with respect to stroke [61].

There is a relationship between elevated fasting plasma glucose and cardiovascular disease [67,68]. Very poorly controlled fasting plasma glucose is associated with a 4-fold increased risk of cardiovascular disease [69]. Intensive treatment of hyperglycemia in the Diabetes Control and Complications Trial did result in reduced thickness of the carotid intima [70]. However, meta-analyses of multiple studies show only a modest overall relationship between HbA_{1c} levels and the incidence of cardiovascular events [71-73].

In contrast, levels of PPG appear to be a much stronger predictor of cardiovascular disease than elevated fasting plasma glucose [5,74-82]. In the Chicago Heart Association Detection Project in Industry Study, 1-hour postprandial glucose values were significantly associated with mortality from coronary heart disease, stroke, cardiovascular diseases, and all-cause mortality in men and women [83,84]. In the Hoorn Study, after additional adjustment for known cardiovascular risk factors, a 5.8 mmol/L increase of postload glucose (corresponding to 2 SDs of the population distribution) was associated with a higher age- and sex-adjusted risk of all-cause (relative risk [RR], 2.20) and cardiovascular mortality (RR, 3.00) ($P < .05$) [85]. In the Islington Diabetes Survey, the risk of cardiovascular disease increased from 9% in people with 2-hour PPG of less than 120 mg/dL to 20% in those with a 2-hour PPG of more than 180 mg/dL [86]. This survey and the Honolulu Heart Study demonstrated that the risk of sudden cardiac death was increased both in IGT and diabetes [87]. In the Honolulu Heart Study, after adjustment for baseline body mass index, hypertension, cholesterol, triglycerides, smoking, alcohol consumption, and left ventricular hypertrophy or strain, the RRs for sudden death in individuals with high-normal (151-224 mg/dL), asymptomatic high glucose values (≥225 mg/dL), and diabetes compared with those with lower glucose values (<151 mg/dL) were 1.59, 2.22, and 2.76, respectively. In patients undergoing coronary stent placement, there was a strong correlation between 2-hour PPG during an oral glucose tolerance test and the degree of stenosis at follow-up [88]. Postprandial hyperglycemia is an independent risk factor for medio-intimal carotid thickening [89].

In 3 separate large studies, the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study, 2-hour PPG was a much stronger predictor of cardiovascular mortality than fasting plasma glucose [90]. Furthermore, many studies suggest that, even in the presence of normal FPG, elevated PPG levels cause increased cardiovascular risk. The Rancho Bernardo Study suggested that nondiabetic subjects with increased 2-hour postload glucose concentrations but with FPG levels of less than 126 mg/dL had increased cardiovascular risk [91]. In the Funigata Diabetes Study, IGT was associated with increased cardiovascular disease, but IFG was not a risk factor [92].

According to the Diabetes Intervention Study, postchallenge hyperglycemia and elevated PPG levels in type 2 diabetes mellitus directly correlated with the risk of cardiovascular disease, independent of FPG [93-95]. The Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study also indicated that elevated 2-hour postload plasma glucose is associated with an increased mortality risk independent of FPG, whereas the association of FPG to mortality was dependent on a high 2-hour postload glucose level [96]. These results were corroborated in different ethnic populations in the Funagata Diabetes study [92], the Cardiovascular Health Study [76], and the NHANES II Mortality Study [97,98]. In the NHANES II study, the multivariate adjusted RR of all-cause mortality was greatest for adults with diagnosed diabetes (RR, 2.11; 95% CI, 1.56-2.84), followed by those with undiagnosed diabetes (RR, 1.77; 95% CI, 1.13-2.75) and those with IGT (RR, 1.42; 95% CI, 1.08-1.87; $P < .001$) [98]. These associations were independent of

established cardiovascular disease risk factors. Increased mortality is not due to the progression of IGT to diabetes; in a 10-year study of more than 2500 individuals, subjects with IGT who did not progress to a diagnosis of diabetes had a multivariate adjusted hazard ratio of 1.49 (0.95-2.34) for CHD incidence, 2.34 (1.42-3.85) for cardiovascular disease mortality, and 1.65 (1.13-2.40) for all-cause mortality [99].

4. Potential impact of postprandial glucose control

Although there is a strong association between postprandial hyperglycemia and cardiovascular disease, the proof of causality is more tenuous. Many other cardiovascular risk factors are related to postprandial hyperglycemia and could play a major role [100]. Postprandial hyperglycemia and insulin resistance coexist. Insulin resistance is associated with increased cardiovascular disease [101].

However, there is evidence that targeting PPG levels in addition to FPG and HbA_{1c} results in improved cardiovascular outcomes. In the Kumamoto study, 110 insulin-requiring type 2 diabetic subjects were randomized into 2 groups. The first group was assigned to multiple insulin therapy and their goal was to maintain FPG of less than 140 mg/dL, 2-hour PPG of less than 200 mg/dL, HbA_{1c} of less than 7.0%, and mean amplitude of glycemic excursions of less than 100 mg/dL. The second group was assigned to conventional insulin therapy with the goal to maintain FPG of less than 140 mg/dL and avoid symptoms related to hyperglycemia or hypoglycemia. The multiple insulin therapy group significantly reduced their RRs of progression of retinopathy by 67% (95% CI, 49-79), photocoagulation by 77% (95% CI, 47-90), progression of nephropathy by 66% (95% CI, 42-80), clinical neuropathy by 64% (95% CI, 45-76), macrovascular complications by 54% (95% CI, 2-78), and diabetes-related death by 81% (95% CI, 28-95) [62,102,103].

In the Study to Prevent NIDDM (STOP-NIDDM) trial, acarbose, which reduces PPG by decreasing absorption of diasaccharides, was used to treat individuals with IGT. There was not only a 36% reduction in the risk of progression to diabetes, but also a 34% decrease in the development of new cases of hypertension and a 49% reduction in cardiovascular events [104,105]. Furthermore, in a subgroup of these patients in whom carotid intima media thickness was measured, the annual increase of intima media thickness (mean) was reduced by approximately 50% in the acarbose group vs placebo [106]. The incidence of silent myocardial infarctions was also reduced [107].

Despite methodological criticisms of the STOP-NIDDM trial [108], the benefit of reduction in PPG on carotid intima media thickness was confirmed in a study that compared the effect of repaglinide with that of glyburide [109]. After 12 months of treatment, the PPG peak was 148 ± 28 mg/dL in the repaglinide group and 180 ± 32 mg/dL in the glyburide group ($P < .01$). Hemoglobin A_{1c} showed a similar decrease in both groups (0.9%). Carotid intima media thickness regression, defined as a decrease of more than 0.020 mm, was observed in 52% of diabetic patients receiving repaglinide, but only in 18% of those receiving glyburide ($P < .01$).

5. Mechanisms of vascular damage by postprandial hyperglycemia

There are many potential mechanisms that may contribute to the strong association between postprandial hyperglycemia and cardiovascular disease. Abnormal vascular reactivity, aldose reductase activity, glycation, hypercoagulability, excess oxidative activity, and cytokine and intracellular adhesion molecular activity and protein kinase C overactivity may all be promoted by hyperglycemia.

5.1. Abnormal vasodilation

There are abnormalities in vascular reactivity observed in diabetes. Endothelial function is altered early in diabetes. Elevated glucose concentrations are also associated with an increase in the secretion of endothelin 1 [110]. In diabetes mellitus and obesity, both endothelium-dependent and endothelium-independent vasodilation are diminished [111,112]. Acetylcholine-induced endothelium-mediated vasodilation is also diminished in diabetes mellitus [113,114]. Similarly, insulin-induced vasodilation is reduced in both type 2 diabetes mellitus and obesity [115-117]. There is a reduction in nitric oxide synthesis in diabetes [118,119]. Insulin stimulates nitric oxide release [120] and also increases the expression of nitric oxide synthetase [121]. Postprandial hyperglycemia suppresses endothelium-dependent vasodilation [122,123]. Reduction of postprandial hyperglycemia with insulin aspart improved flow-mediated vasodilation [124]. Hyperglycemia inhibits nitric oxide synthetase expression [125]. The effect of hyperglycemia on endothelial dysfunction is counteracted by arginine, acetylcholine, or nitroprusside administration [126-129].

5.2. Aldose reductase abnormalities

Aldose reductase uses NADPH to reduce glucose to sorbitol. The accumulation of sorbitol leads to a decrease in nicotinamide adenine dinucleotide (NADPH), *myo*-inositol, and Na^+,K^+–dependent adenosine triphosphatase and glutathione. These biochemical changes cause endothelial injury [130-132].

5.3. Glycation

Hyperglycemia gives rise to a direct chemical reaction of glucose with amino groups, which proceeds to an irreversible conversion to advanced glycation endproducts. These molecules accumulate in poorly controlled diabetic individuals. One of the key sites of deposition is in the vascular basement membrane. A potential relationship exists between advanced glycation endproduct concentrations and vascular damage [133-135].

5.4. Hypercoagulability

Diabetes is a hypercoagulable state [136]. Hypercoagulability accelerates the development of atherosclerosis. Hyperglycemia contributes to the acceleration of the clotting process in diabetes [137,138]. Platelet aggregability is markedly increased by hyperglycemia [139]. Hyperglycemia appears to stimulate the cascade of clotting factors [140]. Hyperglycemia has been shown to shorten fibrinogen half-life and stimulate thrombin formation [141-146].

5.5. Endothelial inflammatory activity

Atherosclerosis involves an inflammatory response of the endothelium [147,148]. There are a number of adhesion molecules that activate the interaction between leukocytes and the endothelium [149]. In addition to the stimulation of the clotting process, postprandial hyperglycemia appears to stimulate the adhesion molecules. The concentration of the intracellular adhesion molecules intracellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin increase in response to an oral glucose tolerance test [150-155]. Acute hyperglycemia increases the production of factors that accelerate inflammation such as interleukin 6, interleukin 18, and tumor necrosis factor [156,157]. Repaglinide treatment, which reduced PPG levels more than glyburide treatment, led to a greater decrease in interleukin 6 ($P = .04$) and C-reactive protein ($P = .02$) levels in the same study that showed greater carotid intima medial regression with repaglinide [158].

5.6. Excess oxidative activity

Diabetes is a state of increased oxidative activity. The reduced antioxidant activity in diabetes is directly related to postprandial hyperglycemia [159-162]. The oxidation of low-density lipoprotein is a key step in lipid-induced atherosclerosis. Low-density lipoprotein oxidation is increased by hyperglycemia, presumably accelerating damage to the vascular wall [163-166].

5.7. Hyperglycemia and protein kinase C activation

It has been suggested that the common pathway for endothelial abnormalities in diabetes is activation of protein kinase C [167,168]. Activation of protein kinase C may lead to induction of several growth factors including transforming growth factor β and vascular endothelial growth factor as well as nuclear transcription factor. Although these changes are thought to impact most on microangiopathy, the effects on the endothelial cell may result in damage to large blood vessels.

5.8. Time course of postprandial hyperglycemia effects

Evidence suggests that there are rapid effects of glucose on the cardiovascular system. In the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction study, tight glycemic control in patients in the period immediately after an acute myocardial infarction provided a favorable impact on cardiovascular outcomes [169]. In the 3 1/2 years after this very brief period of intervention, there were 102 (33%) deaths in the treatment group compared with 138 (44%) deaths in the control group (RR, 0.72; 95% CI, 0.55-0.92; $P = .011$). The effect was most apparent in patients who had not previously received insulin treatment and who were at a low cardiovascular risk.

It is likely that hyperglycemia promotes cardiovascular disease by accumulation of multiple effects, some of short duration and others slowly progressive. It is unlikely that one single mechanism is preponderant in the glucose-induced genesis of cardiovascular disease.

6. Treatment approaches to postprandial glucose

6.1. Diet and physical activity

It is possible to slow the progression of IGT to overt diabetes by promotion of dietary control and exercise activity [170]. In a Finnish study, 522 middle-aged subjects (mean age, 55 years) with IGT were randomized to receive either brief diet and exercise counseling (control group) or intensive individualized instruction on weight reduction, food intake, and guidance on increasing physical activity (intervention group) [171]. After an average follow-up of 3.2 years, there was a 58% relative reduction in the incidence of diabetes in the intervention group compared with the control subjects.

In the Diabetes Prevention Program, about 45% of the participants were from minority groups (eg, African American, Hispanic) [172,173]. Subjects were randomized to 1 of 3 intervention groups, which included the intensive nutrition and exercise counseling ("lifestyle") group or either of 2 masked medication treatment groups: the biguanide metformin group or the placebo group. The latter interventions were combined with standard diet and exercise recommendations. After an average follow-up of 2.8 years, a 58% relative reduction in the progression to diabetes was observed in the lifestyle group (absolute incidence, 4.8%) compared with placebo-treated subjects (absolute incidence, 11.0%) [174].

In the Da Qing IGT and Diabetes Study conducted in mainland China, 577 individuals with IGT were randomized to treatment with dietary control, exercise, or the combination and compared with an untreated subgroup [175]. After adjustment for differences in baseline body mass index and fasting glucose, the diet, exercise, and diet plus exercise interventions were associated with 31% ($P < .03$), 46% ($P < .0005$), and 42% ($P < .005$) reductions in risk of developing diabetes, respectively [175].

Dietary management is more than mere reduction of energy expenditure. Reducing carbohydrate intake is key [176-178]. However, normal carbohydrate levels can be maintained if the carbohydrates chosen have a low tendency to raise glucose. The glycemic index compares the plasma glucose levels attained after eating a certain food to the

levels after ingesting pure glucose. Thus, this index is a direct measure of PPG. Consumption of foods with a low glycemic index results in lower PPG levels [179-181]. Low glycemic index meals are associated with much lower PPG levels than high glycemic index meals [182,183]. In a study comparing a reduced carbohydrate diet with a normal but low glycemic index carbohydrate diet and a high glycemic index normal carbohydrate diet, the low glycemic index diet was as effective in reducing postprandial glucose as the reduced carbohydrate diet [184,185]. A diet high in fat reduces postprandial glucose levels as compared with a diet high in carbohydrate [186]. Slowly digestible carbohydrate meals result in lower postprandial glucose and lipid levels than diets with readily available carbohydrate [187-189]. There is a definite advantage in eating carbohydrates with a high fiber content [190-192].

The addition of supplementary fiber to meals is also beneficial in reducing postprandial glucose levels [193-195]. β-Glucan supplementation has proven quite beneficial [196,197]. There are ethnic differences in the glycemic response to carbohydrates. In one study, Asians appeared to have higher postprandial glucose response to a variety of ingested carbohydrates than whites [198].

The appreciation that PPG values are primarily dependent on carbohydrate intake has led to the technique of carbohydrate counting; patients taking premeal insulin flexibly adjust their dose of insulin in accordance with the number of grams of carbohydrate or the number of carbohydrate exchanges consumed [199-202]. This technique has been very successful, particularly in patients treated with intensive insulin management, including insulin pumps [203,204].

6.2. Pharmacologic interventions

Several diabetes prevention trials in patients with IGT used pharmacologic therapy, and all have reported a significant lowering of the incidence of diabetes. The biguanide metformin reduced the risk of IGT progression to diabetes by 31% in the Diabetes Prevention Program [174]. The α-glucosidase inhibitor acarbose reduced the risk by 32% in the STOP NIDDM trial [104,105]. In the Troglitazone in Prevention of Diabetes study, 235 Hispanic women with previous gestational diabetes were randomized to receive either placebo or troglitazone, a thiazolidinedione drug now withdrawn from clinical use. After a median follow-up of 30 months, the annual incidence of type 2 diabetes mellitus in the 2 groups was 12.3% and 5.4%, respectively [205,206].

All oral hypoglycemics have a favorable effect on postprandial hyperglycemia [207]. Sulfonylureas reduce postprandial glucose through stimulation of insulin secretion and perhaps additional extrapancreatic effects [208]. Metformin reduces hepatic gluconeogenesis after a meal [209-211].

The thiazolidinediones improve postprandial peripheral glucose utilization [210,212-215]. There has been recent enthusiasm for the use of meglitinides, repaglinide, and nateglinide rather than sulfonylureas in generating an acute insulin response to a meal, thereby reducing postprandial hyperglycemia [216]. These agents produce an earlier insulin response than glyburide resulting in reduced postprandial hyperglycemia [217-224]. However, there do not appear to be differences in postprandial glucose with meglitinides as compared with glipizide [225]. In a short-term study, repaglinide therapy was more successful in lowering postprandial glucose levels than glimepiride [226]. However, this advantage was not sustained in a 1-year comparison [227]. The insulin peak resulting from meglitinides is of shorter duration than that of the sulfonylureas, resulting in a reduced incidence of hypoglycemia [217,220,223].

The disaccharidase inhibitors have a direct effect on postprandial hyperglycemia by blocking breakdown of disaccharides to monosaccharides by the enzymes in the brush border of the small intestine, which is essential for absorption of carbohydrates. So these agents (acarbose and miglitol) effectively compensate for defective early-phase insulin by delaying and decreasing absorption of monosaccharides [228]. Thus, there is a lower glycemic peak, permitting diminished early-phase insulin secretion to cope more effectively with glucose disposal. The overall glucose-lowering effect of these agents is somewhat inferior to that of the sulfonylureas [229-231], but the effect on postprandial hyperglycemia is much greater than on fasting glucose levels [230-234].

The incretin effects, which are triggered by orally ingested glucose, suggest a potentially useful role in combating postprandial hyperglycemia. Glucagon-like peptide 1 infusions have shown more promising results than those of gastric inhibitory polypeptide [235]. Short-term administration of GLP-1 is effective at stimulating insulin secretion, suppressing glucagon release, and normalizing glucose levels after an overnight fast. Subcutaneous administration of GLP-1 has also been effective at reducing prandial glucose excursions in type 2 diabetes mellitus, acting through increased insulin levels, but also decreased glucagon levels, increased satiety, and delayed gastric emptying [236]. Several studies have now shown that GLP-1 can lower glucose levels even in patients with severe beta-cell impairment [237]. Subcutaneous infusion of GLP-1 resulted in lower overall glycemic levels than pioglitazone treatment, and the effect was additive [238]. Treatment with the long-acting GLP-1 derivative liraglutide significantly reduced overall 24-hour glucose levels as well as those of glucagon [239]. Continuous subcutaneous infusion of GLP-1 for 3 months lowered capillary blood glucose levels in elderly type 2 diabetic subjects [240]. The glycemic effects of GLP-1 are associated with improvement in endothelial function [241].

The use of native GLP-1 to treat diabetic patients is limited because the peptide cannot be taken orally and because it is rapidly metabolized in the circulation. Glucagon-like peptide 1 is inactivated by the enzyme

dipeptidyl peptidase IV and has a very short half-life in the circulation (~1.5 minutes). Exendin is a reptilian peptide with affinity for the mammalian GLP-1 receptor and relative resistance to degradation [242]. Treatment with exendin 4 has reduced postprandial hyperglycemia in type 1 diabetes mellitus, confirming that the mechanism of action does not rely solely on insulin secretion [243]. In 377 sulfonylurea-treated subjects with initial HbA_{1c} of 8.6% ± 1.2% given exenatide 10 μg twice daily, HbA_{1c} dropped −0.9% ± 0.1% and weight was reduced −1.6 ± 0.3 kg from baseline ($P < .05$ vs placebo) [244]. In 272 metformin-treated patients with initial HbA_{1c} of 8.2% ± 1.1%, after 30 weeks of treatment with 10 μg exenatide, HbA_{1c} levels dropped by 0.8% ± 0.1% and weight decreased by 2.8 ± 0.5 kg [245]. Exenatide has been approved by the US Food and Drug Administration and is in clinical use.

An alternative to supplementation of GLP-1 is to inhibit the rapid degradation of this hormone by dipeptidyl peptidase IV [246,247]. Vildagliptin is a competitive inhibitor of this enzyme. In a 4-week study in diet-treated type 2 diabetic patients, vildagliptin markedly reduced postprandial glucose without raising insulin levels [248]. Similar results were obtained in a study with vildagliptin added to stable ongoing metformin treatment [249,250]. Postprandial glucagon levels were reduced by vildagliptin treatment. Other drugs in this class include sitagliptin [251,252] and saxagliptin [253].

6.3. Pramlintide

Pramlintide is a synthetic analogue of the beta-cell hormone amylin. Like GLP-1, it inhibits glucagon secretion, delays gastric emptying, and acts as a satiety agent [254]. Co-administration of pramlintide with lispro or regular human insulin reduced PPG excursions by 81% compared with lispro insulin alone [255,256]. The lowering of PPG by pramlintide is associated with a decrease in markers of oxidative stress [257]. Adjunctive therapy with pramlintide lowers HbA_{1c} without weight gain and with less hypoglycemia in type 1 diabetes mellitus [258]. Pramlintide has been approved by the US Food and Drug Administration and is in clinical use.

6.4. Insulin

Long-term studies such as the UKPDS suggest that oral therapy with a single agent is not adequate to achieve an acceptable HbA_{1c}. The number of patients achieving glycemic control while receiving single-agent therapy declined steadily in the UKPDS, from 47% to 50% at 3 years, 34% to 37% at 6 years, to 24% to 28% at 9 years [59,60]. However, even combinations of multiple oral hypoglycemic agents may eventually fail to achieve glycemic control [259]. In the UKPDS, there was a progressive degradation of glycemic control despite the addition of multiple agents [260]. The addition of basal insulin supplementation is very effective in reducing HbA_{1c} when combinations of oral hypoglycemic agents no longer adequately maintain levels [261-263]. The use of insulin glargine as a basal insulin supplement has been more successful than NPH insulin in both type 1 and type 2 diabetes mellitus in reducing the incidence of nocturnal hypoglycemia [264-271]. Insulin detemir (Levemir; Novo Nordisk, Copenhagen, Denmark) is a further long-acting analogue (14- to 24-hour activity profile, dependent on dose) that can provide basal insulin coverage with 1 or 2 injections per day [272-277]. Basal insulin treatment has very little effect on postprandial glucose levels, and, therefore, the use of short-acting insulins at mealtime is indicated to directly target postprandial hyperglycemia in both type 1 and type 2 diabetes mellitus. Several semisynthetic insulin analogues now exist with more rapid absorption and disappearance kinetics than regular human insulin [278-281]. These include lispro insulin, aspart insulin, and glulisine insulin. These insulins have a similar affinity for the insulin receptor and a metabolic potency identical to that of regular human insulin [282-287]. However, amino acid substitutions in the native insulin molecule give these insulins less tendency to form dimers and hexamers in solution. As a result, there is more rapid absorption of the synthetic insulins than regular human insulin after subcutaneous injection, with onset of action within 10 to 15 minutes [283-286,288]. The peak effect is more rapid than regular insulin, occurring within 15 to 60 minutes, and there is a faster disappearance, resulting in lower risk of later hypoglycemia [283-286,288]. As a result, these rapid-acting insulin analogues can be used aggressively at the time of a meal to promote disposal of postprandial glucose [283,284,286]. In patients with type 1 and type 2 diabetes mellitus, these insulins reduce postprandial hyperglycemia faster and more effectively than regular human insulin [281,284-286]. All of the new semisynthetic rapid-acting insulins have a lower incidence of nocturnal hypoglycemia than regular human insulin with improved glycemic control in type 1 and type 2 diabetic patients [289-297]. The duration of action of insulin aspart is longer (6 hours) than that of insulin lispro (4 hours) or of glulisine, but, even so, there is a lower incidence of hypoglycemic reactions than with regular human insulin, which has a much longer duration of action [295,296,298,299]. When used in external pumps, insulin lispro provides better glycemic control than buffered regular human insulin [300-302].

Timing of rapid-acting insulin injections in relation to meals can be crucial in the success of PPG-lowering therapy. With its slow onset of action, regular insulin must be injected 30 to 45 minutes before a meal to ensure that peak concentrations coincide with increased PPG. In reality, however, most patients on regular insulin do not take the injection 30 to 45 minutes before a meal; instead, they sometimes administer regular insulin as they sit down to eat or even after a meal [303]. The onset of action of rapid-acting insulin occurs within 1 hour of dosing and the duration of action is generally less than 4 hours, mimicking

temporal patterns of native insulin bioavailability. For this reason, rapid-acting insulins may be injected 0 to 15 minutes before the start of a meal, making the regimen much easier to follow. Some patients take their short-acting insulin analogue injections after a meal. Although postprandial insulin administration is not ideal, it permits a closer match to the amount of food actually consumed at the meal [304-306].

6.5. Inhaled insulin

Inhaled insulin is rapidly absorbed from the alveoli. Estimates of the bioavailability achievable with the current inhalation systems are typically in the neighborhood of 10% of that experienced with subcutaneously administered insulin [307]. Most of the losses are in the device, mouth, and throat, with approximately 30% to 50% of the insulin deposited in the lungs being absorbed. Despite the rapid absorption of inhaled insulin, the duration of action is longer than that of the rapid-acting subcutaneous insulin analogues. Inhaled insulin treatment provides better postprandial glucose control than injection of regular human insulin [308]. The inhalation of insulin premeals improves postprandial glycemia in both type 1 and type 2 diabetic patients inadequately controlled with oral hypoglycemics [309,310].

7. Pregnancy as the prototype for targeting PPG

In recognition of the importance of postprandial glucose reduction, both the American Diabetes Association and the American Association of Clinical Endocrinologists have established target goals for PPG levels as well as for HbA_{1c} and FPG [1,2] (Table 1).

The American Diabetes Association recommends a PPG level of less than 180 mg/dL, whereas the American College of Endocrinology in association with the American Association of Clinical Endocrinologists suggests an even more stringent 140 mg/dL. Despite these recommendations, there is less emphasis on postprandial glucose than on reduction of fasting and premeal levels in present-day diabetes management. The one major area of emphasis on postprandial glucose has been in diabetic pregnancies. Because the risk of complications in the fetus is increased as the maternal glucose rises, normalization of plasma glucose is vital to a successful pregnancy in diabetes [311-314]. Maternal hyperglycemia as assessed by glycosylated hemoglobin is related to increased risk of congenital malformations, spontaneous abortions, and macrosomia. However, in day-to-day management, maintaining the peak postprandial glucose concentration in the reference range is paramount to avert the complications associated with diabetes and pregnancy. The first observation that postprandial glucose concentrations related to risk of complications of pregnancy was in 1991, when it was shown that the peak postprandial glucose concentration (1 hour after the first bite of food) was the strongest predictor of subsequent neonatal macrosomia [314]. In this analysis of 317 type 1 diabetic women performing 8 to 10 self-monitored glucose concentrations per day, the mean and fasting blood glucose only weakly correlated with risk of macrosomia. The 1-hour postprandial glucose emerged as predicting increased risk when it was greater than 120 mg/dL.

Table 1
Targets for glycemic control

	HbA_{1c} (%)	Fasting glucose (mg/dL)	Postprandial glucose (mg/dL)	Bedtime glucose (mg/dL)
AACE	<6.5	<110	<140	100-140
ADA	<7	80-120	100-180	100-140

AACE indicates American Association of Clinical Endocrinologists; ADA, American Diabetes Association.

The prevalence of type 2 diabetes mellitus in women with previous gestational diabetes mellitus is 10% per year, starting the first postpartum year. Thus, by the fifth year after gestational diabetes mellitus, up to 50% of the women have type 2 diabetes mellitus [315,316]. Adjustment of insulin therapy in women with gestational diabetes according to the results of postprandial, rather than preprandial, blood glucose values improves glycemic control and decreases the risk of neonatal hypoglycemia, macrosomia, and cesarean delivery [313].

The peak postprandial response in normal, healthy, pregnant women is at the 1-hour postprandial time point. The highest blood glucose levels in nondiabetic pregnant women are less than 105 mg/dL [317,318]. The American Diabetes Association treatment guidelines for pregnant diabetic women suggest that glucose levels can be as high as 140 mg/dL at the 1-hour and 120 mg/dL at the 2-hour postprandial time point. These recommendations are higher than the values advocated in the Diabetes in Early Pregnancy Trial [314]. Macrosomia is clearly related to postprandial glucose control [319,320].

There is a theory to explain how a transient elevation of postprandial glucose may cause overgrowth of the fetus. The renal threshold for glucose in the fetus is probably less than 110 mg/dL. We know this fact from the studies of the renal threshold for glucose in premature neonates (<30 weeks of gestation). When the maternal glucose level is greater than 110 mg/dL the intravenous glucose load for the fetus causes fetal glycosuria. Therefore, maternal diabetes out of control is associated with polyhydramios from fetal polyuria. After 20 weeks of gestation, the fetus begins to swallow the amniotic fluid. Minor, transient elevations of blood glucose on the maternal side not only result in elevations of blood glucose on the fetal side, but also result in glucose-enriched amniotic fluid ingested by the fetus for hours. This gut stimulus for insulin production in the fetus may be more potent than transient intravenous hyperglycemia. Thus, hyperglycemia for less than an hour once a day in the mother may produce a prolonged fetal insulin stimulus. Elevations of maternal glucose levels more frequently (eg, after every meal) may produce a more prolonged oral glucose load for the fetus, resulting in high

fetal insulin levels, which act as a growth factor for the developing fetus.

It is beneficial to treat pregnant women with IGT even if the criteria for gestational diabetes are not met [321]. The management of diabetic pregnancies focuses on 1-hour postprandial glucose values. Continuous glucose monitoring data confirm that 1 hour is the most reliable time point to measure peak glucose response to a meal [322]. In a study of women with gestational diabetes, 66 women were assigned to 1 hr monitoring group and 46 women to 2 hr monitoring group. Although HbA_{1c} levels were similar in the 2 groups, rates of macrosomia (7.5% vs 10.6%), large for gestational age (7.4% vs 15.2%), and birth by cesarean delivery (24% vs 30%) were increased in group 2 (2-hour PPG) [323]. A target 1-hour postprandial glucose value of 7.3 mmol/L (130 mg/dL) may be the level that optimally reduces the incidence of macrosomia without increasing the incidence of small-for-gestational-age infants [319,324].

When a pregnant woman has successful diabetes control with diet treatment alone, she only needs to monitor her blood glucose 4 times a day: fasting and 1 hour after each meal. Carbohydrate reduction is the cornerstone of dietary management of gestational diabetes [325]. Cutting carbohydrate intake to 40% of overall energy expenditure is successful in lowering postprandial glucose levels [326]. Further reduction of carbohydrate-derived energy expenditure to 25% has been advocated and appears to be safe [327]. In pregnancy, women are typically encouraged to consume energy and carbohydrate liberally with a typical weight gain target of 12.5 kg (about 22-25 lb). However, the more overweight the woman at conception, the less weight gain is desirable. For women who are greater than 150% of ideal body weight, less than 15 lb is recommended [328,329]. When a woman is greater than 200% above ideal body weight, then she need not gain any weight during pregnancy [330,331].

There is yet no proven role for the use of oral hypoglycemic agents in the treatment of gestational diabetes or in the treatment of type 2 diabetes mellitus in pregnancy [332,333]. Glyburide has been proposed for treatment of gestational diabetes, but sulfonylureas have known teratogenic effects in animals, and data on safety in type 2 diabetes mellitus are limited [334,335]. In a small study of 404 gestational diabetic pregnancies, there was no difference in outcome between insulin- and glyburide-treated patients [336].

Metformin crosses the placenta and thus would not seem to be the treatment of choice during pregnancy [337]. However, metformin has been used since 1986 in pregnancies complicated by diabetes. In an early study, the outcome in these pregnancies had a higher complication rate than in pregnancies treated with insulin therapy [338]. However, in the polycystic ovarian syndrome, the use of metformin to improve the ovarian dysfunction has resulted in a decrease in the high spontaneous abortion rate [339,340]. Pregnancy outcomes in women with polycystic ovarian syndrome treated with metformin throughout pregnancy appear to be favorable without identifiable problems in the children in later years [341-345].

When a gestational diabetic woman needs to take insulin, her monitoring frequency must be increased. Both the insulin-requiring gestational diabetic woman and the type 1 diabetic pregnant woman must monitor their blood glucose 7 to 8 times a day: pre- and postprandial, bedtime, and 3 AM. Short-acting insulin can be used to aggressively control postprandial glucose. Lispro insulin can be used in diabetic pregnancies [346,347]. There is no increase in congenital anomaly rates in pregnancies where lispro insulin is used [348]. Continuous glucose monitoring provides improved data on postprandial glucose values in pregnancy [349,350].

8. Postprandial glucose as a priority

Despite the increasing recognition that elevation of PPG is detrimental, current-day practice patterns do not focus on reduction of postmeal values. The goal of treatment is to lower HbA_{1c} to nondiabetic levels. Self–blood glucose monitoring is used as a tool to guide therapy to lower HbA_{1c} and has proven to be beneficial, even in patients who are not insulin treated [351,352]. Typically, patients are advised to measure their fasting glucose values and then test before lunch, supper, and bedtime [353]. They are asked to chart these measurements, either on paper or using computer programs to download values stored on glucose oxidase meters. These numerical data are used to choose the treatment approach, essentially ignoring control of postprandial glucose.

Yet, several studies show that a focus on PPG leads to improvement in HbA_{1c} values. The use of PPG values to adjust repaglinide dosage led to improved HbA_{1c} levels in metformin-treated patients [354]. In a study of type 1 diabetic patients, an algorithm based upon postprandial glucose values demonstrated improved glycemic control over that achievable by use of preprandial glucose values [355]. In type 2 diabetes mellitus, an insulin treatment regimen directed at lowering postprandial hyperglycemia had a greater effect on reduction of HbA_{1c} than an approach focused on fasting glucose values [356,357].

The importance of measuring postprandial glucose is recognized [358,359]. The optimal time point to measure PPG is somewhat controversial because food absorption starts within minutes and continues for 5 to 6 hours after a meal. A measurement of plasma glucose 2 hours after the start of a meal, believed to approximate peak values in patients with diabetes, has become the standard for PPG testing, although in pregnant women, 1-hour PPG values are followed. The advent of continuous glucose monitoring will be extremely useful for assessing therapeutic response and adjusting dose schedules [360-363]. Continuous monitoring can accurately detect high PPG levels and nocturnal hypoglycemic events that may be unrecognized by intermittent blood glucose monitoring [364,365].

9. Conclusions

It is recognized that elevation of plasma glucose is detrimental. Numerous studies have demonstrated that lowering HbA_{1c} reduces the incidence of microvascular disease and diabetic neuropathy. However, HbA_{1c} reflects the mean plasma glucose over a prolonged period. It has now been recognized that the transient rise in blood glucose, which occurs after a meal, may have very specific deleterious effects on blood vessels. There is a marked increase in cardiovascular risk in individuals with postprandial hyperglycemia. Reduction of PPG levels has shown benefit in reducing cardiovascular events. For this reason, it is imperative to focus on suppression of PPG elevation in treatment not only of diabetic patients, but also individuals with IGT. The aggressive management of PPG in diabetic pregnancies furnishes an excellent model to be applied generally to diabetic patients. Promotion of changes in dietary and exercise activity has proven to be the most effective means of preventing the progression of IGT to diabetes. Pharmacologic agents including sulfonylureas, metformin, disccharidase inhibitors, and thiazolidinediones are all effective in reducing PPG elevation. Glucagon-like peptide 1 has a number of potential mechanisms affecting postprandial glucose elevation. Although GLP-1 is very short-lived in the circulation, agents that inhibit its degradation are now becoming available. Exogenous insulin is the required management for patients with type 1 diabetes mellitus and for individuals with advanced type 2 diabetes mellitus. New synthetic insulin analogues, which have rapid absorption and disappearance times, permit more aggressive management of mealtime hyperglycemia. Inhaled insulin that also manifests rapid absorption and disappearance also promises to improve the insulin management of postprandial hyperglycemia. Continuous glucose monitoring will increase the emphasis on PPG as our primary treatment target. The widespread adoption of PPG as our target will lead to improvement in HbA_{1c} levels and reduction in the deleterious clinical effects of hyperglycemia.

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