Glucose metabolism and hyperglycemia

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ABSTRACT
Islet dysfunction and peripheral insulin resistance are both present in type 2 diabetes and are both necessary for the development of hyperglycemia. In both type 1 and type 2 diabetes, large, prospective clinical studies have shown a strong relation between time-averaged mean values of glycemia, measured as glycated hemoglobin (HbA1c), and vascular diabetic complications. These studies are the basis for the American Diabetes Association’s current recommended treatment goal that HbA1c should be <7%. The measurement of the HbA1c concentration is considered the gold standard for assessing long-term glycemia; however, it does not reveal any information on the extent or frequency of blood glucose excursions, but provides an overall mean value only. Postprandial hyperglycemia occurs frequently in patients with diabetes receiving active treatment and can occur even when metabolic control is apparently good. Interventional studies indicate that reducing postmeal glucose excursions is as important as controlling fasting plasma glucose in persons with diabetes and impaired glucose tolerance. Evidence exists for a causal relation between postmeal glucose increases and microvascular and macrovascular outcomes; therefore, it is not surprising that treatment with different compounds that have specific effects on postprandial glucose regulation is accompanied by a significant improvement of many pathways supposed to be involved in diabetic complications, including oxidative stress, endothelial dysfunction, inflammation, and nuclear factor-κB activation. The goal of therapy should be to achieve glycemic status as near to normal as safely possible in all 3 components of glycemic control: HbA1c, fasting glucose, and postmeal glucose peak.

Am J Clin Nutr 2008; 87(suppl):217S–22S.

KEY WORDS Fasting hyperglycemia, postprandial hyperglycemia, glycated hemoglobin, type 2 diabetes, cardiovascular disease, risk, lifestyle

INTRODUCTION
Maintenance of a normal plasma glucose concentration requires precise matching of glucose utilization and endogenous glucose production or dietary glucose delivery. Glucose is derived from 3 sources: the intestinal absorption that follows the digestion of dietary carbohydrates, glycogenolysis, and gluconeogenesis. Glucose is transported into cells through multiple metabolic pathways: it may be stored as glycogen; it may undergo glycolysis to pyruvate; finally, it may be released into the circulation by the liver and kidneys, the sole organs containing glucose-6-phosphatase, the enzyme necessary for the release of glucose into the circulation.

In the fasting condition, plasma glucose concentrations are relatively stable, which indicates that rates of glucose production and utilization are equal. They average 2.2 mg·kg⁻¹·min⁻¹ (range: 1.8 to 2.6 mg·kg⁻¹·min⁻¹) in healthy adults after an overnight fast (1). After a meal, glucose absorption results in rates of exogenous glucose delivery into the circulation that can be more than twice the rate of postabsorptive endogenous glucose production, depending on the carbohydrate content of the meal and the rate and degree of glucose absorption. As glucose is adsorbed, endogenous glucose production is suppressed, and glucose utilization by liver, muscle, and fat accelerates (2). Thus, exogenous glucose is assimilated, and the plasma glucose concentration returns to approximately the fasting state.

Insulin is the dominant glucoregulatory hormone. In the fasting state, it regulates the plasma glucose concentration primarily by restraining hepatic glucose production; higher concentrations, such as those found after meals, are required to stimulate glucose utilization (3). Glucagon is a potent hyperglycemic hormone that acts almost exclusively on the liver to increase hepatic glucose production within minutes. Ingestion of carbohydrate elicits a prompt rise in insulin concentration and a decrease in glucagon concentration. The increase in insulin concentrations, which occurs before the rise in arterial glucose concentrations, is thought to be mediated largely via hormonal signals arising in the gastrointestinal tract (incretion effect) (4). The early insulin release allows increased glucose disposal during absorption and prevents hyperglycemia. If the rise in insulin concentration occurred only after glucose entered the circulation, much higher concentrations of the hormone would be required to correct the large change in glucose concentration that would result if absorption were unaccompanied by an early increase in utilization.

Islet dysfunction and peripheral insulin resistance are both present in type 2 diabetes and are both necessary for the development of hyperglycemia. Consequent to insulin deficiency (secretion or action), glucagon concentrations rise. A fall in the insulin-to-glucagon ratio causes increased production of glucose.
by the liver (basal hyperglycemia), whereas the absolute decrease in plasma insulin concentration or action reduces glucose utilization in peripheral tissues (postprandial hyperglycemia).

**POSTPRANDIAL HYPERGLYCEMIA**

The profile of postprandial hyperglycemia is determined by many factors, including the timing, quantity, and composition of the meal; the carbohydrate content of the meal; and the resulting secretion of insulin and inhibition of glucagon secretion. Because the absorption of food continues for 5 to 6 h after a meal in persons with and without diabetes, the optimal time to measure postprandial blood glucose concentrations remains an open question. Postchallenge hyperglycemia refers to the glucose peak after a predefined load of glucose, ie, during an oral glucose tolerance test (OGTT). The 75-g OGTT was standardized by the World Health Organization (5) and is now the reference test for categorizing glucose tolerance. The relation between values of postprandial and postchallenge hyperglycemia is poorly understood, and differences depend in part on the ability of mixed meals containing amino acids to provoke greater insulin secretion than glucose alone. In one study, glycemia at 2 h after an OGTT was closely related to 2-h glycemia after a standardized meal (6), which suggests that subjects with high concentrations of postchallenge glycemia are also likely to have exaggerated glucose peaks after a normal meal in daily life.

Diabetes is diagnosed when the fasting plasma glucose concentration is consistently ≥ 7 mmol/L (126 mg/dL) or when the 2-h plasma glucose concentration (after drinking a 75-g glucose load) is consistently ≥ 11.1 mmol/L (200 mg/dL). These thresholds are much higher than the “normal” fasting and 2-h mean glucose concentrations of 5.1 mmol/L (92 mg/dL) and 5.4 mmol/L (97 mg/dL), respectively. These concentrations were chosen because they effectively differentiated persons at high risk of eye disease from persons at low risk (7). It is now clear that fasting or 2-h glucose concentrations that are well below the diabetes cutoffs are cardiovascular disease risk factors (8, 9) and that a progressive relation between glucose and cardiovascular disease risk extends from normal glucose concentrations right into the diabetes range with no clear lower threshold (9, 10).

Diabetes affects an estimated 20.8 million persons in the United States, 7% of the current population, and the lifetime risk of developing diabetes for those born in 2000 is 35% (11, 12). Many of these persons will develop diabetes-specific microvascular pathology in the retina, renal glomerulus, and peripheral nerve and accelerated atherosclerotic macrovascular disease affecting the arteries that supply the heart, brain, and lower extremities. In both type 1 and type 2 diabetes, large, prospective clinical studies have shown a strong relation between time-averaged mean values of glycemia, measured as glycated hemoglobin A1c (HbA1c), and diabetic complications (13, 14). These studies are the basis for the American Diabetes Association’s current recommended treatment goal that HbA1c should be < 7% (15) However, only about one-third of patients diagnosed as having diabetes achieve that goal (16) and even fewer reach the target concentration for HbA1c of 6.5% advocated by the American College of Endocrinology (17).

**GLYCATED HEMOGLOBIN AS A CARDIOVASCULAR DISEASE RISK FACTOR**

HbA1c is an easily measured biochemical marker that strongly correlates with the level of ambient glycemia during a 2- to 3-mo period. Tests for HbA1c are also inexpensive and can be done at any time of day. The concentration of HbA1c strongly predicts the risk of incident eye, kidney, and nerve disease in persons with type 1 and type 2 diabetes mellitus. Epidemiologic evidence also indicates that HbA1c is a progressive risk factor for cardiovascular disease in both persons with diabetes and those without diabetes. Selvin et al (18) performed a meta-analysis of 10 cohort studies involving 7435 persons with type 2 diabetes and 3 cohort studies involving 1688 persons with type 1 diabetes. For type 2 diabetes, a 1–percentage point absolute increase in HbA1c was associated with a significant 18% increase in the risk of coronary heart disease or stroke and a 28% increase in the risk of peripheral vascular disease. Khaw et al (19) analyzed the relation of one HbA1c measurement to incident cardiovascular events in a 6-y cohort study of 10 232 diabetic and nondiabetic men and women aged 45-79 y. After adjustment for other risk factors, there was a significant 21% increase in cardiovascular events for every 1–percentage point increase in HbA1c concentration above 5%. Similar relations were observed for total mortality (22% for men and 28% for women). These results indicate that the HbA1c concentration is an independent progressive risk factor for incident cardiovascular events, regardless of diabetes status. These reports also show that the HbA1c concentration can now be added to the list of other clearly established indicators of cardiovascular disease risk, such as blood pressure and cholesterol concentration. As suggested by Gerstein (20), the presence or absence of diabetes is likely to become less important than the concentration of HbA1c in the assessment of cardiovascular disease risk (similar to the fact that a diagnosis of hyperlipidemia has become less important than the concentration of LDL cholesterol).

**GLYCATED HEMOGLOBIN AND GlUCOSE EXCURSIONS**

The measurement of HbA1c concentrations is considered the gold standard for assessing long-term glycemic control at present and is regarded as a key therapeutic target for the prevention of diabetes-related complications. The HbA1c concentration, although a useful measure of metabolic control and the efficacy of diabetes therapeutic interventions, is an integrated summary of circadian blood glucose concentrations during the preceding 6–8 wk (21). It therefore does not reveal any information on the extent or frequency of blood glucose excursions but provides an overall mean value only. This being the case, one can argue that the HbA1c concentration is not necessarily the best or most clinically useful glycemic indicator of the risk of complications, particularly at the lower end of elevated HbA1c concentrations. For instance, in patients in whom glucose concentrations fluctuate markedly, the HbA1c concentration may indicate adequate metabolic control; however, such patients are exposed to the risks of hypoglycemia and the possibly harmful effects of excessive postprandial hyperglycemic excursions.

The contribution of the postprandial glucose concentration to overall glycemic control in persons with diabetes remains largely undefined. The best determinant of HbA1c concentrations in
patients with type 1 and 2 diabetes is mean daily glycemia (22, 23). However, studies indicate that postprandial hyperglycemia contributes up to 70% of total daytime hyperglycemia (24, 25). Therefore, it is not surprising that in the large cohort of patients with type 1 diabetes in the Diabetes Control and Complications Trial, postprandial hyperglycemia was predictive of HbA1c concentrations in a manner similar to that of mean daily glycemia (22). In type 2 diabetes, a positive correlation with HbA1c concentration was reported for postprandial and preprandial glucose concentrations (23). An explanation for apparent discrepancies in the data was recently provided by a study showing that the contribution of postprandial glucose excursions changes with the degree of control: the contribution of postprandial glucose in HbA1c concentration predominates in patients with fairly good control, whereas the contribution of fasting hyperglycemia increases as glycemic control worsens (26).

**POSTPRANDIAL HYPERGLYCEMIA AND CARDIOVASCULAR DISEASE RISK**

Many epidemiologic data show that the 2-h glucose concentration measured during an OGTT is an independent cardiovascular disease risk factor, whereas fasting glucose is not (8, 27–31). Clearly, the OGTT is nonphysiologic and cannot be equated to the consumption of a meal. However, 2 studies have confirmed that postprandial hyperglycemia is an independent risk factor for cardiovascular diseases in type 2 diabetes in the clinical setting. The Diabetes Intervention Study showed that in type 2 diabetes the 1-h postprandial glucose concentration can be used to predict the risk of myocardial infarction (32). More recently, a prospective study with a mean follow-up of 5 y showed that PPG is an independent risk factor for coronary heart disease in patients with type 2 diabetes, particularly in women (33).

Interventional trials also suggest a link between postprandial hyperglycemia and cardiovascular disease risk. The STOP-NIDDM trial showed that treatment of subjects with impaired glucose tolerance with the α-glycosidase inhibitor acarbose, a compound that specifically reduces postprandial hyperglycemia, is associated with a 36% reduction in the risk of progression to diabetes (34), a 34% risk reduction in the development of new cases of hypertension, and a 49% reduction in the risk of cardiovascular events (35), particularly silent myocardial infarction (36). Furthermore, in a recent meta-analysis of type 2 diabetic patients, acarbose treatment was associated with a significant reduction in cardiovascular events compared with placebo treatment, also after adjustment for other risk factors (37). Very recently, the effects of 2 insulin secretagogues, repaglinide and glyburide, which are known to have different efficacy on postprandial hyperglycemia, on carotid intima-media thickness, and on markers of systemic vascular inflammation in type 2 diabetic patients have been evaluated (38). After 12 mo, the postprandial glucose peak was 148 ± 28 mg/dL in the repaglinide group and 180 ± 32 mg/dL in the glyburide group (P < 0.01). HbA1c showed a similar decrease in both groups (0.9%). Carotid intima-media thickness regression, defined as a decrease of >0.020 mm, was observed in 52% of the diabetic subjects receiving repaglinide and in 18% of those receiving glyburide (P < 0.01). Interleukin-6 (P = 0.04) and C-reactive protein (P = 0.02) decreased more in the repaglinide group than in the glyburide group. The reduction in carotid intima-media thickness was associated with changes in postprandial but not fasting hyperglycemia. Therefore, evidence is emerging and suggests that treating postprandial hyperglycemia may positively affect the development of cardiovascular disease.

**MECHANISMS OF HYPERGLYCEMIA-INDUCED VASCULAR DAMAGE**

At least 4 major pathways are involved in hyperglycemia-induced vascular damage: enhanced polyol activity, causing sorbitol and fructose accumulation; increased formation of advanced glycation end products; activation of protein kinase C and nuclear factor κB; and increased hexosamine pathway flux. There are many reasons to think that hyperglycemic states trigger all of these deleterious metabolic events through a single process: overproduction of superoxide by the mitochondrial electron-transport chain. This elegant and unifying theory developed by Brownlee (39) seems to indicate that activation of oxidative stress by hyperglycemia plays a major role in the pathogenesis of diabetic complications. Because all these metabolic alterations occur more particularly in endothelial cells, it has been postulated that they can result in endothelial dysfunction and contribute to vascular damage (40).

Activation of oxidative stress plays a pivotal role in the effects of the above-mentioned mechanisms and risk factors associated with, or induced by, sustained hyperglycemia. However, evidence is increasing that other glycemic disorders such as rapid glucose swings might play an important role. Emphasis has been given to the relation between postprandial hyperglycemia and, more generally, hyperglycemic spikes and diabetic complications. For instance, it has been established that postprandial hyperglycemia induces an overproduction of superoxide that, after reacting with nitric oxide, produces a subsequent nitrosative stress with generation of such metabolic derivatives as peroxynitrite and nitrotyrosine. The toxicity of these substances can lead to endothelial damage and, furthermore, to microvascular and macrovascular complications. By reducing postprandial excursions, oxidative and nitrosative stress can be diminished (41).

Nitrotyrosine is thought to be a relatively specific marker of oxidative damage mediated by peroxynitrite (42) and was recently shown to be an independent predictor of cardiovascular disease (43). Nitrotyrosine formation is detected during acute hyperglycemia in the artery wall of monkeys (44), in working hearts from rats during hyperglycemia (45), and in the plasma of healthy and diabetic subjects (46, 47). Thus, oxidative stress, irrespective of atherosclerotic disease stages, seems to represent a key phenomenon in acute vascular disease progression.

Glucose variations over time are not limited to postprandial hyperglycemic excursions, because blood glucose concentrations in patients with diabetes are always fluctuating from hyperglycemic peaks to glucose nadirs. Such fluctuations are particularly marked in type 1 diabetes and, to a lesser degree, in patients with type 2 diabetes treated with insulin. However, patients with type 2 diabetes can also experience such peak and trough patterns with acute glucose variations. Peaks usually correspond to maximum values after meals, particularly at midmorning (48), whereas troughs are observed over interprandial periods (49), especially in patients who are treated with insulin secretagogues and who are at risk of hypoglycemic episodes (50).
In one study involving patients with type 2 diabetes, Monnier et al. (51) measured 24-h excretion of 8-iso-prostaglandin F₂α, an indicator of free radical production, while patients used a continuous blood glucose monitoring system; fasting glucose concentrations and HbA₁c also were determined. There was a linear correlation between increased free radical production and the magnitude of glucose fluctuations, but not with the 24-h mean glucose concentration, fasting plasma glucose concentrations, or even the HbA₁c concentration. 8-iso-Prostaglandin F₂α concentrations were 4 times higher in patients with the greatest glycemic variability than in patients having the lowest glycemic variability. We reported that exposure of lean nondiabetic subjects to the same magnitude of glycemic excursion reported by Monnier et al. (51) doubled circulating nitrotyrosine concentrations (46). Moreover, oscillatory hyperglycemia causes more acute increments in plasma concentrations of some proinflammatory cytokines, such as interleukin-6, interleukin-18, and tumor necrosis factor-α, than does chronic hyperglycemia in both healthy and glucose-intolerant subjects (52). All this seems strictly related to the ability of hyperglycemic spikes to reduce the availability of nitric oxide (53).

**POSTPRANDIAL HYPERGLYCEMIA: A TARGET OF THERAPY**

The precise relevance of postprandial hyperglycemia in the daily life of persons with diabetes was recently quantified (54). Self-assessed daily blood glucose curves were obtained over a 1-wk period, including 18 glucose readings before and 2 h after meals, from 3284 unselected outpatients with non-insulin-dependent type 2 diabetes mellitus who attended 500 different diabetes clinics operating throughout Italy. A postprandial blood glucose value >8.89 mmol/L (160 mg/dL) was recorded at least once in 84% of patients, which indicated that postprandial hyperglycemia is a frequent phenomenon in patients with type 2 diabetes mellitus receiving active treatment and can occur even when metabolic control is apparently good. In another study, 401 patients with type 2 diabetes were requested to monitor home blood glucose on 3 nonconsecutive days during a period of 1 mo (38). In particular, they assessed blood glucose just before and every 30 min after the main meal of the day for 2 h. The mean value of the postmeal incremental glucose peak was 70 ± 42 mg/dL. Most importantly, all patients had the glucose peak between 30 and 60 min after meal (Figure 1). Obviously, this contrasts with the current belief that the glucose peak occurs later after a meal and the recommendation of the American Diabetes Association to measure blood glucose 2 h after a meal (55).

Therefore, it is not surprising that treatment with various different compounds that have specific effects on postprandial glucose regulation, such as fast-acting insulin analogues, secretagogues acting on first-phase insulin secretion, amylin analogues, and acarbose, is accompanied by significant improvements, not only in oxidative stress (56–58) but also in endothelial dysfunction (59–61), myocardial blood flow (62), inflammation (37), and nuclear factor-κB activation (63).

Evidence also suggests that both postprandial hypertriglyceridemia and hyperglycemia induce endothelial dysfunction, through induction of oxidative stress (47, 64). Studies show independent but cumulative effects of postprandial hypertriglyceridemia and hyperglycemia on endothelial function, which suggests oxidative stress as the common mediator (65). This supports a specific and direct role of postprandial hyperglycemia, independent of lipidemia, in cardiovascular disease. Interestingly, it was shown recently that hyperlipidemia acts to generate oxidative stress in the mitochondria through the same pathways as hyperglycemia (66). The evidence described up to now proves that hyperglycemia can induce acute alterations in normal human homeostasis. Diabetic subjects also have basal hyperglycemia, and it can be hypothesized that the acute effects of mealtime hyperglycemia can exacerbate those produced by chronic hyperglycemia, thus contributing to the overall complexity of diabetes.

Therefore, at present, given the tendency for rapid variations in hyperglycemia throughout the life of patients with diabetes (above all in the postprandial phase), it is appropriate to think that this may exert an important influence on the onset of diabetes-associated complications. Thus, correcting postprandial hyperglycemia should form part of the strategy for the prevention and management of cardiovascular disease in diabetes.

**LIFESTYLE CHANGES**

Unhealthy diets and a lack of physical activity have contributed to a worldwide increase in the prevalence of obesity, type 2 diabetes, and the metabolic syndrome (67). But this epidemic is not inevitable. We know that lifestyle intervention can dramatically reduce the incidence of diabetes and slow the HbA₁c increase in both nondiabetic and diabetic persons (68–70). Moreover, some recent studies deal specifically with the effect of lifestyle changes on the resolution of the metabolic syndrome, a forerunner of type 2 diabetes and cardiovascular diseases (71). The first study was published in 2004 on 180 overweight subjects with the metabolic syndrome (72). After a 2-y lifestyle program focusing mainly on a Mediterranean-style diet, the net reduction in prevalence of the syndrome was 48%. In the participants in the Diabetes Prevention Program (73) who had impaired glucose tolerance at baseline, 18% of the placebo group and 38% of the lifestyle group no longer had the syndrome at 3 y. The Dietary Approaches to Stop Hypertension (DASH) diet used in the Iranian study (74) is similar to a Mediterranean-style diet. The weighted mean resolution of the syndrome was 24.4% for lifestyle changes (Figure 2). In 2 studies, resolution of the syndrome was dependent on reduction in waist circumference and weight.

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**FIGURE 1**. Meal-related home blood glucose monitoring obtained on 3 nonconsecutive days in 401 subjects with type 2 diabetes. The profile of the blood glucose curves did not differ significantly, and the glucose peaks occurred between 30 and 60 min after the meal. From reference 38.
loss (73, 74); in others, it was independent of weight changes (71).

Although there is no proof that these lifestyle changes are ultimately proven to reduce cardiovascular disease in our society, public health approaches to facilitate them urgently need to be implemented. The search for more and more effective drugs for the control of hyperglycemia will continue. In the meantime, lifestyle modifications may be a good companion to drugs for reducing the metabolic and cardiovascular burden of type 2 diabetes and associated hyperglycemias.

The contributions of the authors were as follows—DG: collection of data, analysis of data, writing of the manuscript; AC: significant advice and consultation; and KE: analysis of data and writing of the manuscript. None of the authors had any financial or personal conflicts of interest.

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