
Perspectives in Diabetes

Postprandial Hyperglycemia and Diabetes Complications

Is It Time to Treat?

Antonio Ceriello

Increasing evidence suggests that the postprandial state is a contributing factor to the development of atherosclerosis. In diabetes, the postprandial phase is characterized by a rapid and large increase in blood glucose levels, and the possibility that the postprandial “hyperglycemic spikes” may be relevant to the onset of cardiovascular complications has recently received much attention. Epidemiological studies and preliminary intervention studies have shown that postprandial hyperglycemia is a direct and independent risk factor for cardiovascular disease (CVD). Most of the cardiovascular risk factors are modified in the postprandial phase in diabetic subjects and directly affected by an acute increase of glycemia. The mechanisms through which acute hyperglycemia exerts its effects may be identified in the production of free radicals. This alarmingly suggestive body of evidence for a harmful effect of postprandial hyperglycemia on diabetes complications has been sufficient to influence guidelines from key professional scientific societies. Correcting the postprandial hyperglycemia may form part of the strategy for the prevention and management of CVDs in diabetes. *Diabetes* 54:1–7, 2005

D diabetes is characterized by a high incidence of cardiovascular disease (CVD) (1), and poor control of hyperglycemia appears to play a significant role in the development of CVD in diabetes (2). Recently, there has been increasing evidence that the postprandial state is an important contributing factor to the development of atherosclerosis (3). In diabetes, the postprandial phase is characterized by a rapid and large increase in blood glucose levels, and the possibility that these postprandial “hyperglycemic spikes” may be relevant to the pathophysiology of late diabetes complications is recently receiving much attention.

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CVD, cardiovascular disease; eNOS, endothelial nitric oxide synthase; ICAM, intracellular adhesion molecule; iNOS, inducible nitric oxide synthase; OGTT, oral glucose tolerance test; UKPDS, U.K. Prospective Diabetes Study.

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In this article, epidemiological data and preliminary results of intervention studies indicating that postprandial hyperglycemia represents an increased risk for CVD are surveyed and the proposed mechanisms involved in this effect are summarized.

Possible role of hyperglycemic spikes in CVDs

Fasting hyperglycemia and CVD. Over the last 10 years, many studies have shown an independent relationship between CVDs and glycemic control in patients with type 2 diabetes (2). These studies involved thousands of subjects, often newly diagnosed, who were followed up for periods ranging from 3.5 to 11 years and who were evaluated on the basis of various cardiovascular end points (2). It is necessary to underline that the majority of these studies used a single baseline fasting glycemic value or a single value of HbA_{1c} to predict cardiovascular events occurring many years later. For instance, the observational version of the U.K. Prospective Diabetes Study (UKPDS) showed that the mean HbA_{1c} value was a good predictor of ischemic heart disease (4). In particular, the multivariate analysis showed that per each 1% increment in HbA_{1c}, there was an ~10% increase in the risk of coronary heart disease (4). This evidence is not substantially different compared with the results of the interventional version of the UKPDS. In this trial, even the result was not significant ($P < 0.052$); intensive treatment leading to an ~1% reduction in HbA_{1c} levels led to a 16% reduction in the occurrence of myocardial infarction (5). Interestingly, in the UKPDS, there was a significant impact on cardiovascular events in the metformin-treated group (6). However, it is reasonable that metformin, improving insulin resistance, may have significantly improved the “cluster” of cardiovascular risk factors associated with insulin resistance.

The relationship existing between macroangiopathy and fasting plasma glucose or HbA_{1c} is weaker than that observed with microangiopathy (2). This was found in either cross-sectional or longitudinal studies. These data support the hypothesis that fasting plasma glucose or HbA_{1c} alone are unable to thoroughly describe the glycemic disorders occurring in diabetes and its impact on CVD. In addition to fasting glycemia and HbA_{1c}, emphasis has recently been given to the relationship between postprandial hyperglycemia and CVDs.

TABLE 1
Epidemiological studies showing an association between postprandial hyperglycemia with risk of CVD and mortality

Hoorn Study	2-h glucose better predictor of mortality than HbA _{1c}	Ref. 9
Honolulu Heart Program	1-h glucose predicts coronary heart disease	Ref. 10
Chicago Heart Study	2-h postchallenge glucose predicts all-cause mortality	Ref. 11
DECODE	High 2-h postload blood glucose is associated with increased risk of death, independent of fasting glucose	Ref. 12
Coutinho et al.	2-h glucose associated with CHD	Ref. 13
Whitehall Study, Paris Prospective Study, and Helsinki Policemen Study	2-h postchallenge glucose predicts all-cause and CHD mortality	Ref. 14
Diabetes Intervention Study	Postmeal but not fasting glucose is associated with CHD	Ref. 15

CHD, coronary heart disease.

Postprandial hyperglycemia and CVD: epidemiological evidences. The oral glucose tolerance test (OGTT) has been mostly used in epidemiological studies that attempt to evaluate the risk of CVD. The main advantage of the OGTT is its simplicity: a single plasma glucose measurement 2 h after a glucose load determines whether glucose tolerance is normal, impaired, or indicative of overt diabetes. The caveats of the OGTT are numerous because 75 or 100 g glucose is almost never ingested during a meal and, more importantly, many events associated with ingesting a pure glucose solution do not incorporate the numerous metabolic events associated with eating a mixed meal. Moreover, the relationship between glycemia and the meal content is contingent upon the contents of the meal (7). However, it has recently demonstrated that the level of glycemia reached at 2 h after an OGTT is closely related to the level of glycemia after a standardized meal (mixed meal in the form of wafers containing oat-fractionation products, soy protein, and canola oil sweetened with honey: 345 kcal, 10.7 g fat, 12.1 g protein, 8.9 g simple sugars, 41.1 g starch, and 3.8 g dietary fibers), suggesting that the OGTT may represent a valid tool to reveal altered carbohydrate metabolism during the meal (8). Interestingly, the correlation is more consistent for the values of glycemia in the impaired glucose tolerance range (8).

From the epidemiological point of view, the Hoorn Study (9), the Honolulu Heart Study (10), the Chicago Heart Study (11), and, more recently, the DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) study (12) have clearly shown that the glucose serum level 2 h after an oral challenge with glucose is a powerful predictor of cardiovascular risk. This evidence is also confirmed by two important meta-analyses. The first, by Coutinho et al. (13), examined studies on 95,783 subjects. The second, which involved >20,000 subjects, pooled the data of the Whitehall Study, Paris Prospective Study, and Helsinki Policemen Study (14). The possible role of postprandial hyperglycemia as independent risk factor has also been supported by the Diabetes Intervention Study, which showed how postprandial hyperglycemia predicts infarction in type 2 diabetic subjects (15), and by another study, which associates postprandial hyperglycemia levels with mediointimal carotid thickening (16). Intriguing evidence comes from a study that demonstrates how mediointimal carotid thickening is correlated not only with postprandial glucose serum level but particularly with the glycemic spikes during the OGTT (17). In this study, postchallenge glucose spikes were defined as the difference between the maximal postchallenge glucose

level during OGTT, irrespective of the time after glucose challenge and the level of fasting plasma glucose (17). Epidemiological studies are summarized in the Table 1.

Indirect evidences of the unfavorable role of acute hyperglycemia on CVDs are also available. Hyperglycemia during a cardiovascular acute event is unfavorable from a prognostic point of view in the case of both myocardial infarction (18,19) and stroke (20,21). A worst prognosis has been demonstrated for both cases in diabetic and nondiabetic subjects (18–21). As far as infarction is concerned, it has been recently demonstrated by a meta-analysis that there is a continuous correlation between glucose serum levels and the seriousness of the prognosis even in nondiabetic subjects (22), while intensive insulin treatment during acute myocardial infarction reduces long-term mortality in diabetic patients (23). This is consistent with the evidence that in normal subjects, an acute increase of glycemia significantly prolongs the QT (24) and that during myocardial infarction, increased glucose level is capable of inducing such electrophysiological alterations as to favor the occurrence of arrhythmias whose outcome could even be fatal (25).

Postprandial hyperglycemia and CVD: intervention studies. One of the major concerns about the role of postprandial hyperglycemia in CVD has been, until now, the absence of intervention studies. Evidences are now coming.

The STOP-NIDDM trial has presented data indicating that treatment of subjects with impaired glucose tolerance with the α -glucosidase inhibitor acarbose, a compound that specifically reduces postprandial hyperglycemia, is associated not only with a 36% reduction in the risk of progression to diabetes (26) but also with a 34% risk reduction in the development of new cases of hypertension and a 49% risk reduction in cardiovascular events (27). In addition, in a subgroup of patients, carotid intima media thickness was measured before randomization and at the end of the study (28). Acarbose treatment was associated with a significant decrease in the progression of intima-media thickness, an accepted surrogate for atherosclerosis (28). Furthermore, in a recent meta-analysis of type 2 diabetic patients, acarbose treatment was associated with a significant reduction in cardiovascular events, even after adjusting for other risk factors (29). Finally, very recently, the effects of two insulin secretagogues, repaglinide and glyburide, known to have different efficacy on postprandial hyperglycemia, on carotid intima-media thickness and markers of systemic vascular inflammation in type 2 diabetic patients have been evaluated (30). After 12 months, postprandial glucose peak was 148 ± 28 mg/dl

in the repaglinide group and 180 ± 32 mg/dl in the glyburide group ($P < 0.01$). HbA_{1c} 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 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 (30). Therefore, evidence is emerging and suggests that treating postprandial hyperglycemia may positively affect the development of CVD.

Mechanisms involved. Acceptance of the hypothesis that postprandial hyperglycemia has a direct, harmful effect on the cardiovascular system requires, at the very least, a link between acute hyperglycemia and one or more risk factors for CVD. Most cardiovascular risk factors are affected directly by an acute increase of glycemia in individuals with diabetes and are modified in the postprandial phase. LDL oxidation in diabetes is related to metabolic control (31,32), and it has been shown in type 2 diabetic patients that after meals, LDL oxidation increases (33) and that this phenomenon is in strict relationship with the degree of hyperglycemia (34).

Endothelial function is altered early in diabetes. It has been demonstrated that in diabetic subjects, the vasodilating response to stimuli is diminished and that this anomaly is related to glycemic control (35). In vivo studies have demonstrated that hyperglycemic spikes induce, in both diabetic and normal subjects, an endothelial dysfunction (36–38). This effect of hyperglycemia is probably linked with a reduced production/bioavailability of nitric oxide (NO), since hyperglycemia-induced endothelial dysfunction is counterbalanced by arginine (38). Furthermore, it is very interesting that a rapid decrease of flow-mediated vasodilation has been shown in the postprandial phase in type 2 diabetic patients and that the decrease correlated inversely with the magnitude of postprandial hyperglycemia (39).

The possible role of hyperglycemia in the activation of blood coagulation has previously been reviewed (40). It emerges that acute glycemic variations are matched with a series of alterations of coagulation that are likely to cause a thrombosis. This tendency is documented by studies demonstrating that when hyperglycemia is induced, a shortening of the fibrinogen half-life (41) and an increase in fibrinopeptide A (42,43), in fragments of prothrombin (44), in factor VII (45), and in platelet aggregation (46) can be found in both normal and diabetic subjects. These data indicate that during experimental hyperglycemia, the coagulation is activated.

It is interesting that it already has been documented that in diabetic subjects, postprandial hyperglycemia causes an overproduction of thrombin (47). The phenomenon is strictly dependent on the glycemic levels reached (47).

Adhesion molecules regulate the interaction between endothelium and leukocytes (48). They participate in the process of atherogenesis because their greater expression would imply an increase in the adhesion of leukocytes (monocytes in particular) to the endothelium (49). It is well known that this is considered one of the early stages

of the process leading to atheromatous lesion. Among the various proadhesive molecules, intracellular adhesion molecule (ICAM)-1 has received particular interest. Increase in the circulating form of this molecule has been demonstrated in subjects with vascular disease (50) and with diabetes, with or without vascular disease (51,52). These increases have been considered the indication of the activation of the atherogenic process.

The soluble form of ICAM-1 is stored in the cells and can be quickly expressed outside them as a consequence of various stimuli. It has been demonstrated that acute hyperglycemia in both normal and diabetic subjects is a sufficient stimulus for the circulating level of ICAM-1 to increase, thus activating one of the first stages of the atherogenic process (53,54).

The concept of atherosclerosis as an inflammatory disease even in diabetes is now well established (55). Studies support the evidence that an acute hyperglycemia during a hyperglycemic clamp (56) or in the postprandial state (57) can increase the production of plasma interleukin-6, tumor necrosis factor- α , and interleukin-18.

Postprandial hyperglycemia and oxidative/nitrosative stress. Recent studies demonstrate that hyperglycemia induces an overproduction of superoxide by the mitochondrial electron-transport chain (58). Superoxide overproduction is accompanied by increased NO generation, due to endothelial NO synthase (eNOS) and inducible NO synthase (iNOS) uncoupled state, a phenomenon favoring the formation of the strong oxidant peroxynitrite, which in turn damages DNA (59). DNA damage is an obligatory stimulus for the activation of the nuclear enzyme poly(ADP-ribose) polymerase. Poly(ADP-ribose) polymerase activation in turn depletes the intracellular concentration of its substrate NAD⁺, slowing the rate of glycolysis, electron transport, and ATP formation and produces an ADP ribosylation of the GAPDH (glyceraldehyde-3-phosphate dehydrogenase) (59). These processes result in acute endothelial dysfunction in diabetic blood vessels that, convincingly, contributes to the development of CVD (59). These pathways are summarized in Fig. 1.

Several indirect and direct evidences support the concept that acute hyperglycemia works through the production of an oxidative and nitrosative stress.

Indirect evidence is obtained through the use of antioxidants. The fact that antioxidants can hinder some of the effects acutely induced by hyperglycemia, such as endothelial dysfunction (36,60,61), activation of coagulation (44), and plasmatic increase of ICAM-1 (53) and interleukins (57), suggests that the action of acute hyperglycemia is mediated by the production of free radicals.

Direct evidence is linked to the estimate of the effects of acute hyperglycemia on oxidative stress markers. It has been reported that during oral glucose challenge, a reduction of the antioxidant defenses is observed (62–64). This effect can be observed even in more physiologic situations that are present during meal consumption (65). The role of hyperglycemia is highlighted by the fact that giving two different meals, which will result into two different levels of postprandial hyperglycemia, the greater drop in the antioxidant activity is linked with the higher levels of hyperglycemia (34). The evidence that in diabetic subjects, LDLs are more prone to oxidation in the postprandial

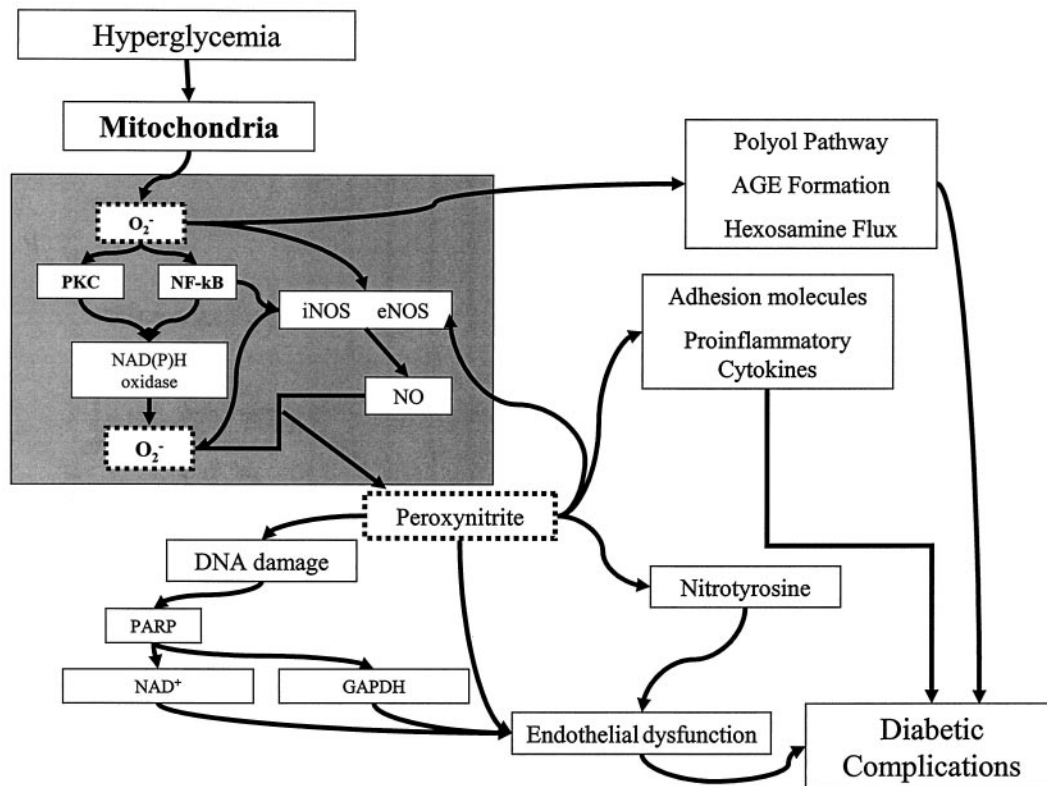


FIG. 1. In endothelial cells, glucose can pass freely, in an insulin-independent manner, through the cell membrane. Intracellular hyperglycemia induces overproduction of superoxide at the mitochondrial level. Overproduction of superoxide is the first and key event in the activation of all other pathways involved in the pathogenesis of diabetes complications, such as polyol pathway flux, increased advanced glycation end product (AGE) formation, activation of protein kinase C (PKC) and nuclear factor- κ B (NF- κ B), and increased hexosamine pathway flux. O_2^- reacting with NO produces peroxynitrite ($ONOO^-$). Superoxide overproduction reduces eNOS activity but, through nuclear factor- κ B and protein kinase C, activates NAD(P)H and increases iNOS expression; the final effect is an increased NO generation. This condition favors the formation of the strong oxidant peroxynitrite, which in turn produces, in iNOS and eNOS, an uncoupled state, resulting in the production of superoxide rather than NO, and damages DNA. DNA damage is an obligatory stimulus for the activation of the nuclear enzyme poly(ADP-ribose) polymerase. Poly(ADP-ribose) polymerase activation in turn depletes the intracellular concentration of its substrate NAD^+ , slowing the rate of glycolysis, electron transport, and ATP formation and produces an ADP ribosylation of the GAPDH. This process results in acute endothelial dysfunction in diabetic blood vessels that contributes to the development of diabetes complications. Nuclear factor- κ B activation also induces a proinflammatory condition and adhesion molecules overexpression. All of these alterations produce the final picture of diabetes complications.

phase matches these data (33). Even in this situation, higher levels of hyperglycemia are matched with a greater oxidation of LDLs (34). Finally, the evidence that managing postprandial hyperglycemia can reduce postprandial generation of the endothelial dysfunction (66) and oxidative and nitrosative stress (67) strongly supports this hypothesis.

Interesting and new data are available on the possible generation of nitrosative stress during postprandial hyperglycemia. The simultaneous overgeneration of NO and superoxide favors the production of a toxic reaction product, the peroxynitrite anion (68). The peroxynitrite anion is cytotoxic because it oxidizes sulfhydryl groups in proteins, initiates lipid peroxidation, and nitrates amino acids such as tyrosine, which affects many signal transduction pathways (68). The production of peroxynitrite can be indirectly inferred by the presence of nitrotyrosine (68), and it has recently been reported that nitrotyrosine is an independent predictor of CVD (69).

Several pieces of evidence support a direct role of hyperglycemia in favoring a nitrotyrosine overgeneration. Nitrotyrosine formation is not only detected in the artery wall of monkeys during hyperglycemia (70) but also in the plasma of healthy subjects during hyperglycemic clamp (71) or OGTT (72,73). Hyperglycemia is also accompanied

by nitrotyrosine deposition in a perfused working heart from rats, and it is reasonably related to unbalanced production of NO and superoxide, through iNOS overexpression (74). Nitrotyrosine formation is followed by the development of an endothelial dysfunction in both healthy subjects (71,72) and in coronaries of perfused hearts (74), and this effect is not surprising because it has been shown that nitrotyrosine can also be directly harmful to endothelial cells (75).

However, dyslipidemia also is a recognized risk factor for CVD in diabetes (76), and postprandial hyperlipidemia contributes to this risk (77). In nonobese type 2 diabetic patients with moderate fasting hypertriglyceridemia, the atherogenic lipoprotein profile is amplified in the postprandial state (78). Such observations have raised the question of whether postprandial hyperlipidemia, which rises concomitantly with postprandial hyperglycemia, is the true risk factor (79). However, evidence suggests that postprandial hypertriglyceridemia and hyperglycemia independently induce endothelial dysfunction through oxidative stress (80). It is now well recognized that endothelial dysfunction is one of the first stages, and one of the earliest markers, in the development of CVD (81). Recent studies demonstrate both an independent and cumulative effect of postprandial hypertriglyceridemia and

hyperglycemia on endothelial function, with oxidative stress as the common mediator (72,73). This lends credence to the idea of a direct atherogenic role for postprandial hyperglycemia that is independent from that of lipids. **Conclusions.** The evidences described up to now prove that hyperglycemia can acutely induce alterations of the normal human homeostasis. It should be noticed that acute increases of glucose serum level not only cause alterations in healthy, normoglycemic subjects but also in diabetic subjects, who also have a basic hyperglycemia. On the basis of these evidences, it can be hypothesized that the acute effects of glucose serum level can add to those produced by chronic hyperglycemia, thus contributing to the final picture of complicated diabetes. The precise relevance of this phenomenon is not exactly comprehensible and quantifiable at the moment, but, due to the tendency to rapid variations of hyperglycemia constant in the life of diabetic patients (above all in the postprandial phase), it is proper to think that it may exert an influence on the onset of complications. Epidemiological studies (3) and preliminary intervention studies (27–30) seem to support this hypothesis.

Both the DCCT, in relation to type 1 diabetes (82), and the UKPDS, in relation to type 2 diabetes (5), have attested the importance of long-term glycemic control through HbA_{1c} for the prevention of complications. However, the DCCT investigators pointed out that HbA_{1c} alone is not a sufficient parameter to explain the onset of such complications and suggested that postprandial hyperglycemic excursions could reasonably favor the onset of diabetes complications (82). Evidence shows that postprandial glucose serum level is the major determinant of HbA_{1c} level after mean daily blood glucose (83–86) and that reducing postprandial hyperglycemia significantly reduces HbA_{1c} level in type 2 diabetic patients (87,88). On the basis of this evidence, it seems obvious that if postprandial hyperglycemia is important to determine the level of HbA_{1c}, which is fundamental in determining the degree of risk for diabetes complications, it can be supposed that postprandial glucose serum level will favor them to a similar degree.

Evidence accumulates suggesting that postprandial excursions of blood glucose may be involved in the development of diabetes complications, particularly (but not only) cardiovascular complications (89,90). However, many questions remain unanswered regarding the definition of postprandial glucose and, perhaps most importantly, whether postprandial hyperglycemia has a unique role in the pathogenesis of diabetic vascular complications and should be a specific target of therapy.

However, this alarmingly suggestive body of evidence for a harmful effect of postprandial hyperglycemia on diabetes complications has been sufficient to influence guidelines from key professional bodies, including the World Health Organization (91), the American Diabetes Association (92), the American College of Endocrinology (93), the International Diabetes Federation (94), the Canadian Diabetes Association (95), and, more recently, a large task force of European scientific societies focused on CVD (96).

Therefore, the real question seems to be, as recently underlined also by the American Diabetes Association

(97), “because CVD is the major cause of morbidity and mortality in patients with diabetes, and in type 2 diabetes in particular, understanding the impact on CVD events of treatment directed at specifically lowering postprandial glucose is crucial.” To address this fundamental question, future studies must be specifically designed to evaluate this new issue, which may significantly change the therapeutic approach to diabetes.

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