Perspectives in Diabetes

Postprandial Hyperglycemia and Diabetes Complications

Is It Time to Treat?

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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.
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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.

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 hyperglyemia (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

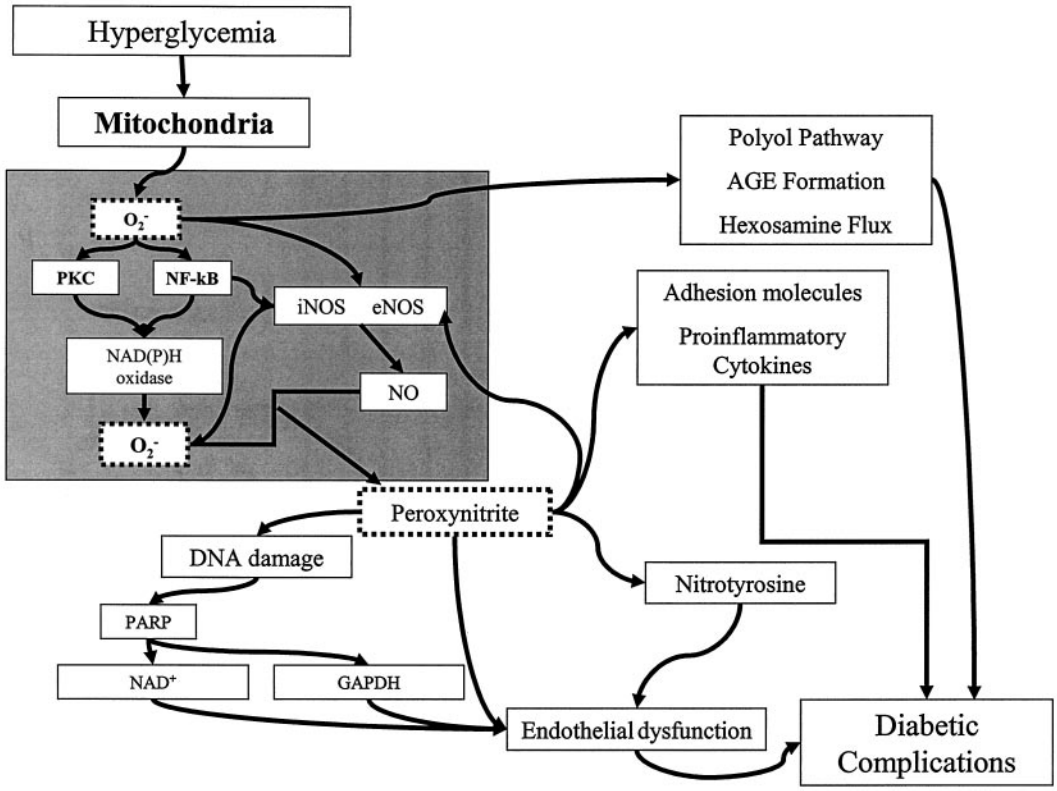

FIG. 1. In endothelial cells, glucose can pass freely, in an insulin-independent manner, through the cell membrane. Intracellular hyperglycemia induces overproduction of superoxide at the mitochondrial level. Overproduction of superoxide is the first and key event in the activation of all other pathways 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-κB (NF-kB), and increased hexosamine pathway flux. O_2^- reacting with NO produces peroxynitrite ($ONOO^-$). Superoxide overproduction reduces eNOS activity but, through nuclear factor-κB 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-κB 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 sulfydryl 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.

REFERENCES

1. Kannel WB, McGee DL: Diabetes and cardiovascular diseases: the Framingham Study. *JAMA* 241:2035–2038, 1979
2. Laakso M: Hyperglycemia and cardiovascular disease in type 2 diabetes. *Diabetes* 48:937–942, 1999
3. Bonora E, Muggeo M: Postprandial blood glucose as a risk factor for cardiovascular disease in type II diabetes: the epidemiological evidence. *Diabetologia* 44:2107–2114, 2001
4. Stratton IM, Adler AI, Neil HAW, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR, the UK Prospective Diabetes Study Group: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–412, 2000
5. UK Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
6. UK Prospective Diabetes Study Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998
7. Vinik AI, Jenkins DJ: :Dietary fiber in management of diabetes. *Diabetes Care* 11:160–1173, 1988
8. Wolever TMS, Chiasson JL, Csima A, Hunt JA, Palmason C, Ross SA, Ryan EA: Variation of postprandial plasma glucose, palatability, and symptoms associated with a standardized mixed test meal versus 75 g oral glucose. *Diabetes Care* 21:336–340, 1998
9. de Vegt F, Dekker JM, Ruhè HG, Stehouwer CDA, Nijpels GBLM, Heine RJ: Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. *Diabetologia* 42:926–931, 1999
10. Donahue RP, Abbott RD, Reed DM, Yano K: Postchallenge glucose concentration and coronary heart disease in men of Japanese ancestry: Honolulu Heart Program. *Diabetes* 36:689–692, 1987
11. Lowe LP, Liu K, Greenland P, Metzger BE, Dyer AR, Stamler J: Diabetes, asymptomatic hyperglycemia, and 22-year mortality in black and white men: the Chicago Heart Association Detection Project in Industry study. *Diabetes Care* 20:163–169, 1997
12. The DECODE Study Group, the European Diabetes Epidemiology Group: Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet* 354:617–621, 1999
13. Coutinho M, Gerstein HC, Wang Y, Yusuf S: The relationship between glucose and incident cardiovascular events: a metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care* 22:233–240, 1999
14. Balkau B, Shipley M, Jarrett RJ, Pyörälä K, Pyörälä M, Forhan A, Eschwège E: High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men: 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. *Diabetes Care* 21:360–367, 1998
15. Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, Schmechel H, Ziegelasch HJ, Lindner J, the DIS Group: Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia* 39:1577–1583, 1996
16. Hanefeld M, Koehler C, Schaper F, Fuecker K, Henkel E, Temelkova-Kurktschiev T: Postprandial plasma glucose is an independent risk factor for increased carotid intima-media thickness in non-diabetic individuals. *Atherosclerosis* 144:229–235, 1999
17. Temelkova-Kurktschiev TS, Koehler C, Schaper F, Leonhardt W, Henkel H, Hanefeld M: Postchallenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose and HbA_{1c} level. *Diabetes Care* 23:1830–1834, 2000
18. Bellodi G, Manicardi V, Malavasi V, Veneri L, Bernini G, Bossini P, Distefano S, Magnanini G, Muratori L, Rossi G: Hyperglycemia and prognosis of acute myocardial infarction in patients without diabetes mellitus. *Am J Cardiol* 64:885–888, 1989
19. O' Sullivan JJ, Conroy RM, Robinson K, Hickey N, Mulcahy R: In hospital

prognosis of patients with fasting hyperglycemia after first myocardial infarction. *Diabetes Care* 14:758–760, 1991
20. Gray CS, Taylor R, French JM, Alberti KG, Venables GS, James OF, Shaw DA, Cartlidge NE, Bates D: The prognostic value of stress hyperglycaemia and previosly unrecognized diabetes in acute stroke. *Diabet Med* 4:237–240, 1987
21. Gray CS, French JM, Bates D, Cartlidge NE, Venables GS, James OF: Increasing age, diabetes mellitus and recovery from stroke. *Postgrad Med J* 65:720–742, 1989
22. Capes SE, Hunt D, Malmberg K, Gerstein HC: Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 355:773–778, 2000
23. Malmberg K, Norhammar A, Wedel H, Ryden L: Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the diabetes and insulin-glucose infusion in acute myocardial infarction (DIGAMI) study. *Circulation* 99:2626–2632, 1999
24. Marfella R, Nappo F, De Angelis L, Siniscalchi M, Rossi F, Giugliano D: The effect of acute hyperglycaemia on QTc duration in healthy man. *Diabetologia* 43:571–575, 2000
25. Gokhroo R, Mittal SR: Electrocardiographic correlates of hyperglycemia in acute myocardial infarction. *Int J Cardiol* 22:267–269, 1989
26. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, the STOP-NIDDM Trail Research Group: Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 359:2072–2077, 2002
27. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, the STOP-NIDDM Trial Research Group: Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 290:486–494, 2003
28. Hanefeld M, Chiasson JL, Koehler C, Henkel E, Schaper F, Temelkova-Kurktschiev T: Acarbose slows progression of intima-media thickness of the carotid arteries in subjects with impaired glucose tolerance. *Stroke* 35:1073–1078, 2004
29. Hanefeld M, Cagatay M, Petrowitsch T, Neuser D, Petzinna D, Rupp M: Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies. *Eur Heart J* 25:10–16, 2004
30. Esposito K, Giugliano D, Nappo F, Marfella R: Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. *Circulation* 29:2978–2984, 2004
31. Tsai EC, Hirsch IB, Brunzell JD, Chait A: Reduced plasma peroxyl radical trapping capacity and increased susceptibility of LDL to oxidation in poorly controlled IDDM. *Diabetes* 43:1010–1014, 1994
32. Jenkins AJ, Klein RL, Chassereau CN, Hermayer KL, Lopes-Virella MF: LDL from patients with well-controlled IDDM is not more susceptible to in vitro oxidation. *Diabetes* 45:762–767, 1996
33. Diwadkar VA, Anderson JW, Bridges SR, Gowri MS, Oelgten PR: Postprandial low density lipoproteins in type 2 diabetes are oxidized more extensively than fasting diabetes and control samples. *Proc Soc Exp Biol Med* 222:178–184, 1999
34. Ceriello A, Bortolotti N, Motz E, Pieri C, Marra M, Tonutti L, Lizzio S, Feletto F, Catone B, Taboga C: Meal-induced oxidative stress and low-density lipoprotein oxidation in diabetes: the possible role of hyperglycemia. *Metabolism* 48:1503–1508, 1999
35. Jorgensen RG, Russo L, Mattioli L, Moore WV: Early detection of vascular dysfunction in type I diabetes. *Diabetes* 37:292–296, 1988
36. Marfella R, Verrazzo G, Acampora R, La Marca C, Giunta R, Lucarelli C, Paolisso G, Ceriello A, Giugliano D: Glutathione reverses systemic hemodynamic changes by acute hyperglycemia in healthy subjects. *Am J Physiol* 268:E1167–E1173, 1995
37. Kawano H, Motoyama T, Hirashima O, Hirai N, Miyao Y, Sakamoto T, Kugiyama K, Ogawa H, Yasue H: Hyperglycemia rapidly suppresses flow-mediated endothelium-dependent vasodilation of brachial artery. *J Am Coll Cardiol* 34:146–154, 1999
38. Giugliano D, Marfella R, Coppola L, Verrazzo G, Acampora R, Giunta R, Nappo F, Lucarelli C, D'Onofrio F: Vascular effects of acute hyperglycemia in humans are reversed by L-arginine: evidence for reduced availability of nitric oxide during hyperglycemia. *Circulation* 95:1783–1790, 1997
39. Shige H, Ishikawa T, Suzukawa M, Ito T, Nakajima K, Higashi K, Ayaori M, Tabata S, Ohsuzu F, Nakamura H: Endothelium-dependent flow-mediated vasodilation in the postprandial state in type 2 diabetes mellitus. *Am J Cardiol* 84:1272–1274, 1999
40. Ceriello A: Coagulation activation in diabetes mellitus: the role of hyperglycaemia and therapeutic prospects. *Diabetologia* 36:1119–1125, 1993
41. Jones RL, Peterson CM: Reduced fibrinogen survival in diabetes mellitus a reversible phenomenon. *J Clin Invest* 63:485–493, 1979
42. Jones RL: Fibrinopeptide A in diabetes mellitus: relation to levels of blood glucose, fibrinogen disappearance, and hemodynamic changes. *Diabetes* 34:836–841, 1985
43. Ceriello A, Giugliano D, Quatraro A, Dello Russo P, Marchi E, Torella R: Hyperglycemia may determine fibrinopeptide A plasma level increase in humans. *Metabolism* 38:1162–1163, 1989
44. Ceriello A, Giacomello R, Stel G, Motz E, Taboga C, Tonutti L, Pirisi M, Falleti E, Bartoli E: Hyperglycemia-induced thrombin formation in diabetes: the possible role of the oxidative stress. *Diabetes* 44:924–928, 1995
45. Ceriello A, Giugliano D, Quatraro A, Dello Russo P, Torella R: Blood glucose may condition factor VII levels in diabetic and normal subjects. *Diabetologia* 31:889–891, 1988
46. Sakamoto T, Ogawa H, Kawano H, Hirai N, Miyamoto S, Takazoe K, Soejima H, Kugiyama K, Yoshimura M, Yasue H: Rapid change of platelet aggregability in acute hyperglycemia: detection by a novel laser-light scattering method. *Thromb Haemost* 83:475–479, 2000
47. Ceriello A, Taboga C, Tonutti L, Giacomello R, Stel G, Motz E, Pirisi M: Post-meal coagulation activation in diabetes mellitus: the effect of acarbose. *Diabetologia* 39:469–473, 1996
48. Ruosladti E: Integrins. *J Clin Invest* 187:1–5, 1991
49. Lopes-Virella MF, Virella G: Immune mechanism of atherosclerosis in diabetes mellitus (Review). *Diabetes* 41 (Suppl. 2):86–91, 1992
50. Blann AD, McCollum CN: Circulating endothelial cell/leukocyte adhesion molecules in atherosclerosis. *Thromb Haemostas* 72:151–154, 1994
51. Cominacini L, Fratta Pasini A, Garbin U, Davoli A, De Santis A, Campagnola M, Rigoni A, Zenti MG, Moghetti P, Lo Cascio V: Elevated levels of soluble E-selectin in patients with IDDM and NIDDM: relation to metabolic control. *Diabetologia* 38:1122–1124, 1995
52. Ceriello A, Falleti E, Bortolotti N, Motz E, Cavarape A, Russo A, Gonano F, Bartoli E: Increased circulating ICAM-1 levels in type-2 diabetic patients: the possible role of metabolic control and oxidative stress. *Metabolism* 45:498–501, 1996
53. Ceriello A, Falleti E, Motz E, Taboga C, Tonutti L, Ezsol Z, Gonano F, Bartoli E: Hyperglycemia-induced circulating ICAM-1 increase in diabetes mellitus: the possible role of oxidative stress. *Horm Metab Res* 30:146–149, 1998
54. Marfella R, Esposito K, Giunta R, Coppola G, De Angelis L, Farzati B, Prolisso G, Giugliano D: Circulating adhesion molecules in humans: role of hyperglycemia and hyperinsulinemia. *Circulation* 101:2247–2251, 2000
55. Plutzky J: Inflammation in atherosclerosis and diabetes mellitus. *Rev Endocr Metab Disord* 5:255–259, 2004
56. Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, Quagliaro L, Ceriello A, Giugliano D: Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. *Circulation* 106:2067–2072, 2002
57. Nappo F, Esposito K, Cioffi M, Giugliano G, Molinari AM, Paolisso G, Marfella R, Giugliano D: Postprandial endothelial activation in healthy subjects and in type 2 diabetic patients: role of fat and carbohydrate meals. *J Am Coll Cardiol* 39:1145–1150, 2002
58. Brownlee M: Biochemistry and molecular cell biology of diabetic complications. *Nature* 414:813–820, 2001
59. Ceriello A: New insights on oxidative stress and diabetic complications may lead to a "causal" antioxidant therapy. *Diabetes Care* 26:1589–1596, 2003
60. Title LM, Cummings PM, Giddens K, Nassar BA: Oral glucose loading acutely attenuates endothelium-dependent vasodilation in healthy adults without diabetes: a effect prevented by vitamin C and E. *J Am Coll Cardiol* 36:2185–2191, 2000
61. Beckman JA, Goldfine AB, Gordon MB, Creager MA: Ascorbate restores endothelium-dependent vasodilation impaired by acute hyperglycemia in humans. *Circulation* 103:1618–1623, 2001
62. Ceriello A, Bortolotti N, Crescentini A, Motz E, Lizzio S, Russo A, Ézsol Z, Tonutti L, Taboga C: Antioxidant defenses are reduced during oral glucose tolerance test in normal and non-insulin dependent diabetic subjects. *Eur J Clin Invest* 28:329–333, 1998
63. Tessier D, Khalil A, Fulop T: Effects of an oral glucose challenge on free radicals/antioxidants balance in an older population with type II diabetes. *J Gerontol* 54:541–545, 1999
64. Konukoglu D, Hatemi H, Ozer EM, Gonen S, Akcay T: The erythrocyte glutathione levels during oral glucose tolerance test. *J Endocrinol Invest* 20:471–475, 1997
65. Ceriello A, Bortolotti N, Motz E, Crescentini A, Lizzio S, Russo A, Tonutti L, Taboga C: Meal-generated oxidative stress in type 2 diabetic patients. *Diabetes Care* 21:1529–1533, 1998

66. Ceriello A, Cavarape A, Martinelli L, Da Ros R, Marra G, Quagliaro L, Piconi L, Assaloni R, Motz E: The post-prandial state in type 2 diabetes and endothelial dysfunction: effects of insulin aspart. *Diabet Med* 21:171–175, 2004
67. Ceriello A, Quagliaro L, Catone B, Pascon R, Piazzola M, Bais B, Marra G, Tonutti L, Taboga C, Motz E: Role of hyperglycemia in nitrotyrosine postprandial generation. *Diabetes Care* 25:1439–1443, 2002
68. Beckman JS, Koppenol WH: Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly. *Am J Physiol* 271:C1424–C1437, 1996
69. Shishehbor MH, Aviles RJ, Brennan ML, Fu X, Goormastic M, Pearce GL, Gokce N, Keaney JF Jr, Penn MS, Sprecher DL, Vita JA, Hazen SL: Association of nitrotyrosine levels with cardiovascular disease and modulation by statin therapy. *JAMA* 289:1675–1680, 2003
70. Pennathur S, Wagner JD, Leeuwenburgh C, Litwak KN, Heinecke JW: A hydroxyl radical-like species oxidizes cynomolgus monkey artery wall proteins in early diabetic vascular disease. *J Clin Invest* 107:853–860, 2001
71. Marfella R, Quagliaro L, Nappo F, Ceriello A, Giugliano D: Acute hyperglycemia induces an oxidative stress in healthy subjects (Letter). *J Clin Invest* 108: 635–636, 2001
72. Ceriello A, Taboga C, Tonutti L, Quagliaro L, Piconi L, Bais B, Da Ros R, Motz E: Evidence for an independent and cumulative effect of postprandial hypertriglyceridemia and hyperglycemia on endothelial dysfunction and oxidative stress generation: effects of short- and long-term simvastatin treatment. *Circulation* 106:1211–1218, 2002
73. Ceriello A, Quagliaro L, Piconi L, Assaloni R, Da Ros R, Maier A, Esposito K, Giugliano D: Effect of postprandial hypertriglyceridemia and hyperglycemia on circulating adhesion molecules and oxidative stress generation and the possible role of simvastatin treatment. *Diabetes* 53:701–710, 2004
74. Ceriello A, Quagliaro L, D'Amico M, Di Filippo C, Marfella R, Nappo F, Berrino L, Rossi F, Giugliano D: Acute hyperglycemia induces nitrotyrosine formation and apoptosis in perfused heart from rat. *Diabetes* 51:1076–1082, 2002
75. Mihm MJ, Jing L, Bauer JA: Nitrotyrosine causes selective vascular endothelial dysfunction and DNA damage. *J Cardiovasc Pharmacol* 36: 182–187, 2000
76. Taskinen MR, Lahdenpera S, Syvanne M: New insights into lipid metabolism in non-insulin-dependent diabetes mellitus. *Ann Med* 28:335–340, 1996
77. Karpe F, de Faire U, Mercuri M, Bond MG, Hellenius ML, Hamsten A: Magnitude of alimentary lipemia is related to intima-media thickness of the common carotid artery in middle-aged men. *Atherosclerosis* 141:307–314, 1998
78. Cavallero E, Dachet C, Neufcou D, Wirquin E, Mathe D, Jacotot B: Postprandial amplification of lipoprotein abnormalities in controlled type II diabetic subjects: relationship to postprandial lipemia and C-peptide/glucagon levels. *Metabolism* 43:270–278, 1994
79. Heine RJ, Dekker JM: Beyond postprandial hyperglycemia: metabolic factors associated with cardiovascular disease. *Diabetologia* 45:461–475, 2002
80. Ceriello A, Motz E: Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. *Arterioscler Thromb Vasc Biol* 24:816–823, 2004
81. De Caterina R: Endothelial dysfunctions: common denominators in vascular disease. *Curr Opin Lipidol* 11:9–23, 2000
82. The Diabetes Control and Complications Trial Research Group: The relationship of glycemic exposure (HbA_{1c}) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes* 44:968–983, 1995
83. Avignon A, Radauceanu A, Monnier L: Nonfasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes. *Diabetes Care* 20:1822–1826, 1997
84. Soonthornpun S, Rattarasarn C, Leelawattana R, Setasuban W: Postprandial plasma glucose: a good index of glycemic control in type 2 diabetic patients having near-normal fasting glucose levels. *Diabetes Res Clin Pract* 46:23–27, 1999
85. Monnier L, Lapinski H, Colette C: Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA_{1c}. *Diabetes Care* 26:881–885, 2003
86. Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE: Defining the relationship between plasma glucose and HbA_{1c}: analysis of glucose profiles and HbA_{1c} in the Diabetes Control and Complications Trial. *Diabetes Care* 25:275–278, 2002
87. Bastyr EJ 3rd, Stuart CA, Brodows RG, Schwartz S, Graf CJ, Zagar A, Robertson KE: Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA_{1c}: IOEZ Study Group. *Diabetes Care* 23:1236–1241, 2000
88. Home PD, Lindholm A, Hylleberg B, Round P: Improved glycemic control with insulin aspart: a multicenter randomized double-blind crossover trial in type 1 diabetic patients: U.K. Insulin Aspart Study Group. *Diabetes Care* 21:1904–1909, 1998
89. Shichiri M, Kishikawa H, Ohkubo Y, Wake N: Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care* 23 (Suppl. 2):B21–B29, 2000
90. Singleton JR, Smith AG, Russell JW, Feldman EL: Microvascular complications of impaired glucose tolerance. *Diabetes* 52:2867–2873, 2003
91. World Health Organization: *Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva, World Health Org., 1999
92. American Diabetes Association: Standards of medical care in diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1):S15–S35, 2004
93. American College of Endocrinology: American College of Endocrinology consensus statement on guidelines for glycemic control. *Endocr Pract* 8:5–11, 2002
94. Alberti KGMM, Gries FA: Management of non-insulin-dependent diabetes mellitus in Europe: a consensus view. *Diabet Med* 5:275–281, 1988
95. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee: Canadian Diabetes Association 2003 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes* 27 (Suppl. 2):1–163, 2003
96. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, Ebrahim S, Faergeman O, Graham I, Mancia G, Manger Cats V, Orth-Gomer K, Perk J, Pyorala K, Rodicio JL, Sans S, Sansoy V, Sechtem U, Silber S, Thomsen T, Wood D, the Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice: European guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 24:1601–1610, 2003
97. American Diabetes Association: Postprandial blood glucose (Review). *Diabetes Care* 24:775–778, 2001