Cardiovascular effects of acute hyperglycaemia: pathophysiological underpinnings

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Abstract

High admission blood glucose levels after acute myocardial infarction are common and are associated with an increased risk of death in subjects with and without diabetes. In this review, the possible toxic effects of acute hyperglycaemia are discussed as a possible explanation for the worse prognosis in subjects with myocardial infarction and concomitant hyperglycaemia. In particular, evidence supporting the hypothesis that acute hyperglycaemia may favour the appearance of cardiovascular disease through the generation of oxidative stress is presented.

doi:10.3132/dvdr.2008.038

Key words: endothelial dysfunction, oxidative stress, postprandial hyperglycaemia.

Introduction

Most cardiovascular disease (CVD) risk factors make similar contributions to risk among patients with and without diabetes, and the relationship between fasting plasma glucose or HbA1C levels and macrovascular complications among diabetic patients is not strong. For example, the United Kingdom Prospective Diabetes Study Group (UKPDS) study found that “intensive” control of fasting blood glucose (FBG) among diabetic patients reduced the relative risk for myocardial infarction (MI) by only 16%, as compared to conventional, diet-based therapy (p=0.052). What, then, accounts for the greatly increased cardiovascular (CV) risk among patients with diabetes? Postprandial hyperglycaemia (PPH), which captures “spikes” in blood glucose levels that may not be fully reflected in FBG or glycosylated haemoglobin (HbA1C) levels, has historically been overlooked as a CV risk factor among diabetic patients, those with isolated impaired glucose tolerance (IGT) and those in the general population.

Several studies have noted that acute hyperglycaemia, which is analogous to PPH, is an independent predictor of poorer outcomes. Some trials have suggested that control of acute hyperglycaemia improves survival among patients with acute coronary syndromes and MI, whether or not they have previous diabetic histories. Among patients with MI, acute hyperglycaemia has been independently associated with left ventricular dysfunction, larger infarct size, increased thrombophilia and acute increases in inflammatory immune markers. A pooled analysis of 15 cohort studies and clinical trials involving 1,556 non-diabetic patients hospitalised after MI found that those with blood glucose levels > 6.1–8.0 mmol/L (depending on the definition of stress hyperglycaemia used) had a 3.9-fold (95% confidence intervals [CI] 2.9–5.4) higher risk of death than those with lower levels; those with glucose levels > 8.0–10.0 mmol/L were also at increased risk for congestive heart failure and cardiogenic shock. Among patients with acute strokes, persistent hyperglycaemia has been shown to be an independent determinant of infarct expansion and later poorer functional outcomes; one study showed that hyperglycaemia could actually negate the benefits of thrombolytic therapy and arterial recanalisation.

Epidemiological evidence

There is ample evidence from epidemiological studies to show that PPH is an independent risk factor for CVD, not only among diabetic patients, but also among subjects in the general population with mildly elevated postprandial or post-challenge levels. In the Framingham Offspring Study, involving 3,370 subjects with no history of diabetes or cardiovascular disease, 2-hour post-challenge (PC) glucose level at baseline significantly predicted CV events after four years (relative risk [RR] 1.10; 95% CI 1.02–1.13), even after adjustment for FBG levels and non-glycaemic risk factors, but the converse did not hold. In the Diabetes Intervention Study, a prospective 11-year population-based study of 1,139 newly diagnosed diabetic patients who were deemed to be well controlled with diet alone, baseline postprandial glucose (PPG) levels predicted all-cause mortality, but FBG did not. In a more recent five-year study of 529 patients attending a diabetes clinic in Turin, Italy, baseline post-lunch glucose levels, but not FBG or HbA1C, significantly predicted CV events, particularly in women (third tertile versus first and second tertiles: hazard ratio [HR] 5.54, 95% CI 1.46–21.20, p<0.01 in women and HR 2.12, 95% CI 1.04–4.32, p<0.01 in men).

These findings apply not only to patients already...
diagnosed with diabetes, but also to subjects in the general population. The cross-sectional Islington Diabetes Survey (conducted among 223 subjects aged over 40 years without diabetic histories) showed that while the prevalence of coronary heart disease increased linearly with increasing 2-hour glucose levels and HbA1C, the former was a more accurate predictor. Several longitudinal studies have confirmed related results. The eight-year Hoorn Study, following 2,363 non-diabetic subjects aged 50–75 years, found that while FPG predicted CV and all-cause mortality in the diabetic range only, 2-hour PC glucose levels were predictive even in the non-diabetic range. After adjustment for sex, age and known cardiovascular risk factors, subjects with values more than two standard deviations above the population mean had a relative risk of 2.20 for all-cause mortality and 3.00 for cardiovascular mortality (p<0.05). In the Honolulu Heart Program, following 6,394 men aged 45–70 years of Japanese ancestry for a mean of 12 years, PC glucose levels were linearly related to the risk of fatal coronary heart disease (CHD); adjusted relative risk in the lowest quintile of 1-hour glucose levels was one half of that in the fourth quintile and one third of that in the highest quintile (p<0.05); the correlation with the combined end point of fatal CHD or non-fatal MI was also significant (p<0.001). In the prospective seven-year Rancho Bernardo Study of 1,858 subjects aged 50–89 years with no diabetes or MI history, isolated 2-hour PC glucose levels ≥ 11.1 mmol/L (in the presence of FPG < 7.0 mmol/L) at baseline predicted subsequent fatal CVD in women but not men, independently of other cardiovascular risk factors (HR 2.6; 95% CI 1.4–4.7). Finally, the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study analysed data from 13 prospective European studies involving 25,364 individuals who were followed for a mean of 7.3 years. For each strutum of FBG, the mortality risk increased with increasing 2-hour PC glucose level, but the converse did not hold true. Thus, 2-hour PC glucose levels were stronger and more reliable predictors of mortality than FPG. It is important to note that among subjects with FBG < 6.1 mmol/L, 8.9% of the men and 11.9% of the women had 2-hour PC glucose levels ≥ 7.8 mmol/L, and the hazard ratios for mortality in this group was 1.55 (95% CI 1.38–1.82) for 2-hour PC glucose levels ≥ 7.8–11.1 mmol/L and 2.00 (1.46–2.75) among those with 2-hour PC glucose levels ≥ 11.1 mmol/L. If clinicians relied exclusively on FBG, many at-risk patients in these studies would not have been identified.

Meta-analyses of very large study populations have also borne out the predictive importance of PPG. One of these examined the relationship between 2-hour oral glucose tolerance test (OGTT) glucose levels and mortality over 20 years among 17,285 non-diabetic males aged 44–55 years who had been enrolled in the Whitehall, Paris Prospective and Helsinki Policemen Studies. Coronary heart disease was the most frequent cause of death in all three of the included studies. Even after adjustment for other risk factors, all-cause mortality risk increased progressively with 2-hour PC glucose levels to a hazard ratio of 1.4 (95% CI 1.1–1.6) in the group with the highest 20% over those with the lower 80% of values. Mortality also increased with FPG, but the increase did not reach statistical significance until the highest 2.5 percentile. Thus, even among subjects without diabetes, elevated 2-hour PC glucose levels carried increased cardiovascular risk. Finally, a very large meta-regression analysis of data from 95,783 subjects (nearly all men) over 12 years from 20 published prospective studies showed clearly that cardiovascular risk begins to increase well below the accepted thresholds for the diagnosis of diabetes. The hazard ratio was 1.33 (95% CI 1.06–1.67) for a FBG level of 6.1 mmol/L, but 1.58 (95% CI 1.19–2.10) for even a modestly elevated 2-hour PC glucose level of 7.8 mmol/L. These results are not surprising, given that the current diagnostic cut-off values were chosen on the basis of increased risk for microvascular complications such as retinopathy and nephropathy, rather than for macrovascular disease.

Pathophysiological mechanisms

Recent preclinical and clinical studies suggest that acute hyperglycaemia is associated with increased cardiovascular risk via a wide variety of mechanisms, both at the cellular and tissue level and at the biochemical level.

Cellular and tissue pathophysiology

Acute increases in plasma glucose levels have significant haemodynamic effects, even in normal subjects. In one study, maintenance of plasma glucose levels at 15.0 mmol/L for two hours in healthy subjects significantly increased mean heart rate (+9 beats per minute [b.p.m]; p<0.01), systolic (+20 mmHg; p<0.01) and diastolic blood pressure (+14 mmHg, p<0.001) and plasma catecholamine levels; these haemodynamic effects were abolished by infusion of glutathione, suggesting that these changes are mediated by an oxidative pathway. If this is so, one would expect glucose levels to affect endothelial function as well; and indeed, a study of flow-mediated endothelium-dependent vasodilation (FMD) of the brachial artery among 52 subjects during an OGTT found significant decreases at one and two hours among those with impaired glucose tolerance or diabetes, but not in control subjects. In fact, plasma glucose levels were negatively correlated with FMD. Endothelial function also normalised after two hours in the controls but remained impaired in the group with IGT, and especially in the group with diabetes (figure 1). This evidence is consistent with the finding that modulating PPH with a variety of approaches avoids its deleterious effects on endothelial function.

PPH has also been associated with myocardial perfusion defects. In a recent prospective study, 20 patients with well controlled diabetes and 20 healthy controls were given a standard mixed meal, and myocardial contrast echography was used to assess myocardial perfusion. Before the meal, the two groups had similar myocardial flow velocity, blood volume and blood flow. In the PC state, all these parameters increased significantly in the normal controls. In those with diabetes, however, flow velocity increased only slightly and blood volume and flow actually decreased significantly (figure 2). There was a significant correlation between changes in blood volume and the degree of PPH in the diabetic patients. These data suggest that PPH-related myocardial perfusion defects are related to impaired coronary
microvascular circulation and represent an early marker of diabetic CV damage.23 A follow-up study showed that treatment with analog insulin (but not regular insulin) significantly decreased PPH and partly reversed the postprandial myocardial perfusion defects seen among diabetic patients. Since PPG levels < 6.7 mmol/L were achieved by 60% of the diabetic patients receiving insulin analog but only 30% of those receiving regular insulin, the differing effects of the two regimens on myocardial perfusion appeared to be directly related to their differing effects on acute postprandial hyperglycaemia.24

Hyperglycaemia also adversely affects left ventricular function and electrophysiological correlates of cardiac function. One study found that among 529 patients with a first anterior wall MI who received a coronary angioplasty or thrombolytic therapy within 12 hours after chest pain began, acute plasma glucose levels were inversely correlated with pre-discharge left ventricular ejection fraction (LVEF) in both diabetic and non-diabetic patients, even after adjusting for acute LVEF. In addition, among patients with acute hyperglycaemia (> 10.0 mmol/L), each 1.0 mmol/L increase in plasma glucose independently predicted an increase in the relative risk of 30-day mortality (odds ratio [OR] 1.12; 95% CI 1.03–1.22; p=0.009). These findings suggest that acute hyperglycaemia may not be merely a marker of severe myocardial damage, but a potential direct cause of abnormal left ventricular function. Similarly, it may not be serving simply as an indicator of the diabetic state, since it remained predictive of poorer outcomes even after adjustment for HbA1C level.25 An observational study conducted during the pre-perfusion era in 10 patients with acute MI and acute hyperglycaemia (but HbA1C < 8%) and 15 matched MI cases without acute hyperglycaemia found that the degree of hyperglycaemia was correlated with the extent of the infarct, the magnitude of ST-segment elevation and infarct site (hyperglycaemic patients tended to have more extensive anterior MIs and fewer anteroseptal or inferior MIs).26 It is also possible that hyperglycaemia precipitates arrhythmias: in one study among 20 healthy subjects whose plasma glucose levels were raised to 15.0 mmol/L for two hours, QTc, QTc dispersion and PR intervals all increased significantly by the 2-hour mark; these increases were unaffected by infusion of octreotide, a somatostatin analog that inhibits the release of insulin.27

Biochemical pathophysiology

The biochemical effects of PPH are myriad and complex. Numerous studies have noted its effect on immune markers of inflammation, intracellular adhesion molecules, and production of advanced glycation end products (AGEs). A study in which insulin secretion was blocked and subjects were maintained at plasma glucose levels of 15.0 mmol/L for five hours found that levels of interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) and the pro-inflammatory cytokine IL-18 rose significantly and returned to baseline within three hours in the control group (n=20). However, patients with IGT (n=15) had significantly higher TNF-α and IL-6 levels at baseline, and cytokine levels reached significantly higher peaks and stayed elevated for a significantly longer period of time than in the control subjects. All changes in plasma cytokine levels were abolished by infusion of the antioxidant glutathione, consistent with the hypothesis that hyperglycaemia, especially in the form of spikes, is linked to immune activation via an oxidative mechanism.28

Another study matching diabetic patients (n=9) and healthy controls (n=7) found increases in circulating intercellular adhesion molecule (ICAM)-1 in both groups during OGTT; these increases were also abolished by glutathione. Glutathione administered without a glucose load decreased circulating ICAM-1 levels in the diabetic group but not the control group, again suggesting that hyperglycaemia...
increases ICAM-1 levels via an oxidative mechanism. In another study investigating the effects of insulin on soluble ICAM-1, normal subjects (n=10) whose plasma glucose levels were raised to 15.0 mmol/L experienced an upsurge in ICAM-1, which normalised within two hours as long as insulin was available. Diabetic subjects (n=10) had significantly higher baseline ICAM-1 levels, which were further increased by blockade of insulin secretion and did not return to baseline. On the other hand, keeping glucose levels at 5.5 mmol/L in diabetic patients (with an artificial pancreas or L-arginine infusion) decreased circulating ICAM-1 to the levels seen among control patients.

In the presence of hyperglycaemia, proteins and lipids are irreversibly glycated by non-enzymatic mechanisms, and these advanced glycated end products (AGEs) accumulate in the cells and extracellular space of blood vessels, enhancing atherogenic processes. A cell surface receptor for AGEs (a "RAGE") has been isolated; binding of AGEs and other pro-inflammatory ligands to this signal-transducing receptor has a multitude of effects, including increased smooth muscle cell proliferation, migration and activation of mononuclear phagocytes, induction of cytokines such as TNF-α, and in endothelial cells, increased vascular permeability, oxidative stress, vasoconstriction and expression of adhesion molecules. In theory, molecules that target AGE-related processes – traps for reactive intermediates in AGE formation, AGE-cleaving agents or RAGE inhibitors – might be beneficial in treating or preventing atherosclerosis in patients with diabetes.

The central role of oxidative stress
It has been suggested that four key biochemical changes induced by hyperglycaemia – (a) increased flux through the polyol pathway (in which glucose is reduced to sorbitol, reducing levels of both NADPH and reduced glutathione), (b) increased formation of AGEs, (c) activation of protein kinase C (with effects ranging from vascular occlusion to expression of pro-inflammatory genes), and (d) increased shunting of excess glucose through the hexosamine pathway (mediating increased transcription of genes for inflammatory cytokines and plasminogen activator inhibitor-1 [PAI-1]) – are all activated by a common mechanism: overproduction of superoxide radicals. Excess plasma glucose drives excess production of electron donors (mainly NADH/H+) from the tricarboxylic acid cycle; in turn, this surfeit results in the transfer of single electrons (instead of the usual electron pairs) to oxygen, producing superoxide radicals and other reactive oxygen species (instead of the usual end product, H2O). The superoxide anion itself inhibits the key glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and in consequence, glucose and glycolytic intermediates spill into the polyol and hexosamine pathways, as well as additional pathways that culminate in protein kinase C activation and intracellular AGE formation (figure 3).

There is ample evidence from in vitro and animal studies that marked fluctuations in glucose levels, as seen in diabetic patients, have consequences that are even more deleterious than those of continuous high glucose levels.
For example, in cultures of human umbilical vein endothelial cells (HUVEC), levels of nitrotyrosine (a marker of oxidative stress), ICAM-1, vascular cellular adhesion molecule-1 (VCAM-1), E-selectin, IL-6 and 8-hydroxydeoxyguanosine (a marker of oxidative damage of DNA) were all increased after incubation in a medium containing 20 mM glucose compared with a 5 mM glucose medium, but alternating the two media caused even greater increases.\(^{33-35}\) In addition, intermittent hyperglycaemic conditions increased rates of cellular apoptosis and stimulated the expression of caspase-3 (a pro-apoptotic protein) but decreased bcl-2 (an anti-apoptotic protein); these effects were abolished by adding superoxide dismutase (a free radical scavenger) or inhibitors of the mitochondrial electron transport chain, suggesting that overproduction of free radicals in the mitochondria mediates the apoptotic effects of increased glucose concentrations.\(^{36}\)

Fluctuating glucose levels have also been shown to mediate other changes in human cells. In renal cortical fibroblast cultures, for example, intermittent hyperglycaemia increased the synthesis of extracellular matrix, collagen IV, tissue inhibitor of metalloproteinase (TIMP-1) and fibronectin – all components of renal interstitial fibrosis. Interestingly, TGF-β1 levels remained elevated in the presence of fluctuating high glucose levels, but normalised after 48 hours of exposure to constant high glucose levels. Similarly, constant high glucose levels did not induce increases in collagen synthesis or TIMP-1 expression, but did increase the MMP-2 and MMP-9 isoforms of matrix metalloproteinase, thus mitigating against the accumulation of extracellular matrix that is seen in interstitial fibrosis.\(^{37}\) Such findings are consistent with the possibility that under conditions of continuous hyperglycaemia, cells develop compensatory mechanisms that may not be available if the hyperglycaemia is intermittent.

The Goto-Kakizaki (GK) rat is a widely used animal model of diabetes without obesity. One study found that a single bolus injection of glucose (causing an acute spike in glucose concentrations) was sufficient to cause a reversible increase in the number of monocytes adhering to endothelial cells in the thoracic aorta; monocyte adhesion is considered an early event in the pathogenesis of atherosclerosis. The effect was not inhibited by octreotide and was therefore independent of increases in insulin levels, but was not seen in rats with streptozotocin-induced diabetes and chronic hyperglycaemia.\(^{38}\) Similarly, GK rats fed twice daily to induce spikes of PPH had greater degrees of monocyte adhesion than did diabetic rats fed ad libitum, despite significantly higher mean HbA1C levels in the latter group; the effect was often accompanied by intimal thickening of the aorta.\(^{39}\) Insulin and nateglinide, at doses that reduced PPH without significantly affecting HbA1C levels, reduced both monocyte adhesion and aortic intimal thickness,\(^{40}\) as did a 12-week course of acarbose.\(^{41}\)

Superoxide anion increases the expression of inducible nitric oxide synthase (iNOS),\(^ {42}\) resulting in more nitric oxide (NO). However, the same superoxide anion also scavenges NO, combining with it to form the peroxynitrite ion (ONOO\(^ {−}\)),\(^ {43}\) a strong oxidant which in turn can oxidise tyrosine residues in proteins to form nitrotyrosine. One study involved the perfusion of isolated rat hearts for two hours with solutions of glucose 11.1 mmol/L, 33.3 mmol/L or 33.1 mmol/L plus glutathione. In the hearts perfused with high glucose concentrations, coronary perfusion pressure was significantly increased; there was a 40% increase in NO levels and an upregulation of iNOS, but a 300% increase in the production of superoxide species; nitrotyrosine and cardiac cell apoptosis were also significantly increased. All these effects were substantially prevented by glutathione, which effectively removes reactive oxygen species including peroxynitrite.\(^ {44}\) Interestingly, peroxynitrite has been shown to produce nitrated tyrosine residues in the insulin receptor substrate-1 protein, impairing its protein kinase-catalysed phosphorylation, an essential step in the insulin signal transduction pathway; in addition, peroxynitrite markedly decreased the activity of the protein kinase (phosphatidylinositol-3-kinase) itself.\(^ {45}\)

Finally, in a study of the relationship between oxidative stress and ischaemia/reperfusion injury, mice were fed with placebo, sucrose or sucrose plus acarbose, and then underwent 30 minutes of coronary artery ligation followed by 24 hours of reperfusion in vivo. Ischaemia/reperfusion injury was significantly increased in the sucrose-only group, but the presence of acarbose reversed the effect. The extent of myocardial inflammation was similar with all three treatments, but oxidative stress (as measured by MDA, a lipid peroxidation product) was increased only in the sucrose group, and not in the sucrose plus acarbose group. Thus, intermittent hyperglycaemia exacerbated the cardiac damage of acute ischaemia/reperfusion injury.\(^ {46}\)

Several of the studies discussed above furnish indirect evidence for the role of oxidative mechanisms by showing that treatment with a potent antioxidant such as glutathione attenuated some of the deleterious effects of PC hyperglycaemia. More direct evidence for the central role of oxidative stress is derived from clinical studies that measured markers of oxidative stress. For example, among 20 diabetic patients, either a low-carbohydrate or a high-carbohydrate meal increased levels of plasma glucose, insulin, triglycerides and malondialdehyde (a marker for lipid peroxidation), and decreased non-esterified fatty acids and total radical-trapping antioxidant parameter (TRAP; a global measure of antioxidant capacity in the plasma). However, the high-carbohydrate meal (designed to produce higher PPG levels) increased glucose and malondialdehyde, decreased TRAP significantly more, and rendered low-density lipoprotein (LDL) more susceptible to oxidation than did the low-carbohydrate meal.\(^ {47}\) The decrease in TRAP highlights the fact that oxidative stress may also ensue from the failure of normal antioxidant defences: the same group found that during the OGTT, TRAP was reduced from baseline in both well controlled non-smoking diabetic and healthy age-matched subjects (20 in all), as were levels of protein-bound thiol (-SH) groups, vitamins C and E and uric acid.\(^ {48}\) Another group demonstrated that among subjects with normal or impaired glucose tolerance, glutathione levels in erythrocytes were similar after a 12-hour fast, but two hours after a glucose load, these levels decreased approximately twice as much.
among those with IGT. Finally, a case-control study examined the ratio of glutathione levels after oral glucose challenge among male diabetic patients aged over 65 and normal controls. Those with diabetes had significantly higher serum levels of oxidised glutathione at baseline, as well as higher levels of total and oxidised glutathione and a decreased intracellular total:oxidised glutathione ratio and ascorbic acid. In response to oral glucose challenge, both groups (not only the diabetic group) had increased intracellular levels of total and oxidised glutathione and decreased ascorbic acid and total:oxidised glutathione ratio.

As mentioned above, superoxide anion combines with NO to produce peroxynitrite ion; this species is capable of peroxidating lipoproteins and damaging DNA; DNA damage then activates the nuclear enzyme poly (ADP-ribose) polymerase, depleting intracellular NAD+ and (among other effects) causing acute endothelial dysfunction. In one study involving 12 healthy subjects, infusion of L-arginine (to supply NO) reversed hyperglycaemia-induced increases in systolic and diastolic blood pressure, heart rate, plasma catecholamine levels, ADP-induced platelet aggregation and blood viscosity. However, infusing NG-monomethyl-L-arginine, which inhibits the synthesis of endogenous NO, produced effects that were very similar to those produced by hyperglycaemia. Thus, decreased NO availability may be one mechanism by which hyperglycaemia induces haemodynamic and rheological changes in blood. Furthermore, it has been shown that unlike normal controls, patients with diabetes have significantly elevated fasting nitrotyrosine levels as well as postprandial increases after intake of a standard mixed meal; the effect was significantly normalised by the rapid-acting insulin aspart but not by regular insulin (figure 4). Similar results have been obtained using different treatments including pramlintide and mitiglinide, drugs which target PPG.

Are the risks of PPH and hypertriglyceridaemia independent of each other?
Oxidative stress may also link insulin resistance with endothelial dysfunction, diabetes and CV disease. It has been noted that, like excess glucose, free fatty acids also induce the production of superoxide anion in the mitochondrion; in addition, oxidised free fatty acids reduce the translocation of the glucose transporter (GLUT)-4 receptor to the cell membrane of myocytes and adipocytes, resulting in insulin resistance. Calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers and statins have all been associated with decreases in the incidence of diabetes without affecting blood glucose levels, and all, like the thiazolidinediones, are intracellular antioxidants (figure 5). Moreover, not only glucose levels but also triglyceride levels increase after meals in diabetic patients. Therefore, it is reasonable to ask whether the effects seen with PPH are independent of those seen with hyperlipidaemia.

To address this question, nitrotyrosine levels and endothelial function (FMD) were measured in 50 subjects (30 diabetic, 20 controls) after three types of meals.
containing high fat, glucose or both. All three meals, especially the combined meal, increased nitrotyrosine levels and decreased FMD in non-diabetic and especially in diabetic subjects. However, both the high-fat and the glucose meals produced independent and cumulative degrees of endothelial dysfunction and inflammation. In addition, simvastatin treatment for 3–6 days reduced these effects without changing lipid parameters; after 12 weeks of treatment, the effects were further reduced while lipid parameters were improved. The same group extended these results by examining the effects of atorvastatin 40 mg daily, ibuseparide 300 mg daily or both on PPH endothelial dysfunction, oxidative stress and inflammation among 20 diabetic patients who received three different test meals. Before treatment, all three meals, but especially the combined meal, decreased FMD and increased levels of nitrotyrosine, C-reactive protein, ICAM-1 and IL-6 – all known predictors of cardiovascular disease. Either drug – and especially combined treatment – reduced these abnormalities after only one week, too short a time to effect significant changes in lipid parameters or blood pressure. These data confirmed the independent and cumulative effects of hyperglycaemia and hypertriglyceridaemia, as well as the key role played by oxidative stress in the mechanism of damage caused by these two conditions. Several of the most important mechanisms leading from hyperglycaemia (both acute and postprandial) to diabetic vascular complications are summarised in figure 6.

Finally, there is evidence that postprandial activation of the transcription factor nuclear factor-κB (NF-κB) can be avoided by modulating PPH, supporting the concept that PPH activates the various pathways shown in figure 6.

**Intervention studies**

Is the control of PPH useful in primary prevention of cardiovascular events? Acarbose decreases PPG spikes by inhibiting the hydrolysis of carbohydrates in the gut. The STOP-NIDDM trial, a randomised placebo-controlled trial enrolling 1,429 overweight or obese patients with IGT, compared the effects of either acarbose (100 mg t.i.d) or placebo over a mean follow-up period of 3.3 years. Acarbose treatment was associated with lower rates of incident diabetes (42% vs. 52%; HR 0.75; 95% CI 0.63–0.90; p=0.0015), regardless of age, sex and baseline body mass index; moreover, reduction of PPH with acarbose nearly halved the risk of major cardiovascular events (coronary heart disease, cardiovascular mortality, congestive heart failure and peripheral vascular disease) (HR 0.51; 95% CI 0.28–0.95; p=0.03), with an especially dramatic reduction in the risk of myocardial infarction (MI) (HR 0.09; 95% CI 0.01–0.72; p=0.02). An electrocardiographic sub-study including 1,181 of the subjects found ECG changes in fewer subjects receiving acarbose than placebo (33 vs. 39, respectively), and myocardial infarctions (Minnesota code 1-1 or 1-2) in 0.2% (n=1) of acarbose subjects, compared with 1.2% (n=7) of placebo subjects (p=0.07). Further analysis of a subgroup of 132 patients from the STOP-NIDDM trial also found that mean intimal-medial carotid thickness had increased by 0.05 mm in the placebo group but only 0.02 mm in the acarbose group (p=0.027).

Finally, a meta-analysis of seven randomised controlled trials carried out among patients with diabetes demonstrated that acarbose significantly reduced the risk of MI (HR 0.36; 95% CI 0.16–0.80; p=0.012) as well as cardiovascular events in general (HR 0.65; 95% CI 0.48–0.88; p=0.0061).

Repaglinide is a rapid-acting insulin secretagogue that also targets PPG. A recent randomised, single-blind 12-month intervention trial compared the effects of repaglinide (1.5–12 mg daily) and glyburide (5–20 mg daily), another insulin secretagogue, on PPG, carotid intima-media thickness (IMT) and inflammatory markers among 175 drug-naive diabetic patients aged 35 to 70 years. Although the two drugs had similar effects on HbA1c levels, repaglinide was associated with a significantly lower PPG peak than was glyburide (8.2 vs. 10.0 mmol/L; p<0.01). Moreover, regression of IMT by > 0.020 mm was seen in 52% of those receiving repaglinide but only 18% of those receiving glyburide (p<0.01), and repaglinide also reduced IL-6 and C-reactive protein levels to a significantly greater degree. Although long-term data are not yet available, these results would be consistent with a beneficial effect of PPG-targeting drugs on hard cardiovascular end points such as death or non-fatal MI.

**Conclusion**

Many clinicians caring for diabetic patients have a “fasting glucocentric” outlook: they focus on FBG and HbA1c levels as the main measures of glycaemic status when evaluating a diabetic patient’s cardiovascular risk. However, there is ample epidemiological evidence that just as acute hyperglycaemia portends a poorer clinical outcome among critically
ill patients, PPH predicts CV disease and mortality not only among patients already identified as diabetic, but also among subjects in the general population. Mounting mechanistic evidence suggests that acute hyperglycaemia has myriad adverse effects that are mediated through oxidative stress (e.g. production of superoxide anion). Moreover, some available interventional studies suggest that strategies directed toward decreasing PPH in outpatients and acute hyperglycaemia during hospitalisations for cardiovascular events may improve clinical outcomes.

In light of this accumulating evidence, several societies, including the American Diabetes Association,18 the Canadian Diabetes Association,19 the Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice20 and the World Health Organization,21 specifically address PPH in their guidelines. For example, the American Diabetes Association guidelines recommend a target 1–2-hour PPG level < 10.0 mmol/L and suggest that PPG be monitored in patients who are achieving their FBG get 1–2-hour PPG level < 10.0 mmol/L and suggest that PPH predicts CV disease and mortality not only among patients already identified as diabetic, but also among ill patients, PPH predicts CV disease and mortality not only among patients already identified as diabetic, but also among subjects in the general population. Mounting mechanistic evidence suggests that acute hyperglycaemia has myriad adverse effects that are mediated through oxidative stress (e.g. production of superoxide anion). Moreover, some available interventional studies suggest that strategies directed toward decreasing PPH in outpatients and acute hyperglycaemia during hospitalisations for cardiovascular events may improve clinical outcomes.

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