Postprandial hyperglycaemia: to treat or not to treat?

MC Brindisi, R Rabasa-Lhoret, JL Chiasson

SUMMARY
Accumulating evidence suggests that the postprandial or the post-75 g glucose load rise in plasma glucose are a contributing factor to the development of atherosclerosis. Many epidemiological studies have shown that post-load hyperglycaemia is a strong and independent risk factor for cardiovascular disease. The few interventional studies available also support a role for postprandial or post-load hyperglycaemia on cardiovascular disease or mortality or on validated surrogates of atherosclerosis. The mechanism through which acute hyperglycaemia could exert its deleterious effects on the vessel wall is very likely multifactorial, but the overproduction of free radicals is probably involved. There is growing evidence that treating postprandial hyperglycaemia should probably be part of the strategies for the prevention and management of cardiovascular diseases in pre-diabetes as well as in diabetes.

Key-words: Postprandial hyperglycaemia · Post-load hyperglycaemia · Cardiovascular disease · Oxidative stress.

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Glucose intolerance is associated with an increased risk of mortality. Most studies have shown an association between 2-hour glycaemia following a 75 g glucose load and an increased risk for all cause, cardiovascular and cancer mortality [1,2]. More recently much attention has been given to the causal relationship between the postprandial hyperglycaemic state and atherogenesis [3]. A number of observational epidemiological studies have clearly shown that plasma glucose concentration after a glucose load is a strong predictor of CV risk in diabetic and non-diabetic populations of various ethnicities [1,4-11]. These observations have also been confirmed by 3 meta-analyses [2,12,13]. Even if the post-75 g glucose load is not a physiological test, with poor reproducibility, it is the reference test for the diagnosis of glucose intolerance. Furthermore, Wolever et al. have shown that the plasma glucose concentrations, measured 2 hours after 75 g of glucose or 2 hours after the solid mixed meal, are well correlated in subjects with normal glucose tolerance, impaired glucose tolerance (IGT) or diabetes [14].

Two independent studies have shown an association of postprandial or post-load hyperglycaemia and more specifically of glycaemic spikes with carotid intima-media thickness (CIMT), a validated surrogate of atherosclerosis [15,16]. Finally, postprandial and post-load but not fasting hyperglycaemia emerge as an independent risk factor for cardiovascular disease (CVD) and cardiovascular mortality [13,15-18]. If this was shown to be a cause-and-effect relationship, it would have a major impact on the strategies for screening and treating both pre-diabetes as well as diabetes mellitus.

Though the proof of a cause-and-effect relationship awaits confirmation, there is growing evidence that postprandial plasma glucose (PPG) per se could be a causal factor for CVD probably through the generation of oxidative stress [19-21]. Thus, in addition to aggressive treatment of classical risk factors such as smoking, hyperlipidemia and hypertension, a strategy specifically targeting PPG could well offer extra benefit by reducing CVD, in subjects with IGT and type 2 diabetes. The objective of this paper is to review, first, the epidemiological observations relating postprandial and/or post-load hyperglycaemia to CVD, secondly, the intervention studies supporting a cause-and-effect relationship, and finally, the available data on the potential pathogenetic mechanisms by which this hyperglycaemia could induce atherosclerosis.

**Epidemiological observations**

There is an abundance of prospective epidemiological observations showing a significant association between postprandial or post-load hyperglycaemia and CVD [1,4-11] (table I). These observations are supported by meta-analyses (table II). The meta-regression analysis of Coutinho et al. [12], reports a continuous relationship between 2-hour plasma glucose levels post 75 g glucose with the risk of cardiovascular disease starting well below the diabetic threshold (figure I); on the other hand, a non-significant relationship is found with fasting plasma glucose (FPG). In the DECODE study, the data show that subjects with IGT and newly-diagnosed diabetes, according to the 2-hour glucose criteria, are at increased risk for CV mortality. Whereas on the basis of FPG, neither impaired fasting glucose (IFG) (plasma glucose ≥ 6.1 and ≤ 6.9 mmol/L), nor newly-diagnosed diabetes is linked to increase mortality risk from CVD. Similar observations are made in the DECODA study [13,22] for Asian population (table II).

The relationship between post-load plasma glucose and CVD is present independently of glucose tolerance. This relationship is observed in subjects with normal glucose tolerance (NGT), IGT and diabetes [17]. Subjects with IGT have a survival rate in between that of normal and diabetic subjects. This relationship is absent, however, for fasting plasma glucose, and subjects with IFG have a survival curve similar to that of the subjects with normal fasting glucose (NFG) [17].

Though epidemiological evidence suggests that PPG is a risk factor for CVD, a cause-and-effect remains to be proven by prospective intervention studies targeting PPG whose primary objective would be the reduction of validated surrogates for CVD, CV events and ultimately CV mortality. This is of considerable interest, since over the age of 65 years, 40% of the population presents excessive PPG excursions [23]. In the last three years, three randomised controlled trials and one meta-analysis have addressed this issue [24-30].

**Intervention studies**

The first intervention study to test the hypothesis of postprandial hyperglycaemia as a risk factor for CVD was the STOP-NIDDM trial in subjects with IGT. The primary objective of the STOP-NIDDM trial was to assess the effect of the α-glucosidase inhibitor, acarbose, in preventing or delaying the conversion of IGT, a pre-diabetic state, to type 2 diabetes mellitus [24]. This study [24] showed that
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Treatment with acarbose in patients with IGT reduces the risk of type 2 diabetes by 36% over 3.3 years based on 2 oral glucose tolerance tests.

As secondary objective, the STOP-NIDDM trial also tested the effect of acarbose on pre-defined major CV events (coronary heart disease, CV death, congestive heart failure, cerebrovascular event, and peripheral vascular disease) and hypertension (defined by a blood pressure ≥140/90 mmHg) [25]. All cases of CV events were adjudicated by an independent committee blinded to treatment. Compared to placebo, acarbose treatment was associated with a relative risk reduction of 49% for any CV events and an absolute risk reduction of 2.5% in this population with IGT. Myocardial infarction (MI) was the major contributor to CVD risk reduction. Acarbose treatment also reduced significantly the mean systolic and diastolic blood pressure throughout the study period, and significantly decreased the risk of developing hypertension. However, the limitations of the study include the fact that the effect of acarbose on the incidence of CVD was a secondary objective. Therefore, this study is not powered to look at the effect of acarbose on the incidence of CVD. Secondly, the relatively small number of subjects with one or more events (n = 47) is another limitation of this study. Nevertheless, this is the first prospective interventional study supporting the postprandial hyperglycaemia hypothesis as a risk factor for CVD.

The electrocardiograms from the STOP-NIDDM trial were evaluated by two independent cardiologists blinded to treatment using the Minnesota code classification. They found 8 silent myocardial infarctions which had not been identified clinically, 7 in the placebo group and 1 in the acarbose group [27] (table III).

Furthermore in a subgroup of subjects from the STOP-NIDDM trial, the effect of acarbose on the progression of the carotid intima-media thickness (CIMT) was assessed using ultrasound technology [26]. The CIMT is a validated and well accepted surrogate for atherosclerosis.

<table>
<thead>
<tr>
<th>Table I</th>
<th>Epidemiological evidence supporting a relationship between elevated post-load plasma glucose and cardiovascular disease.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies</strong></td>
<td><strong>No. subjects</strong></td>
</tr>
<tr>
<td>The Honolulu Heart Program (1987) [4]</td>
<td>6,394</td>
</tr>
<tr>
<td>The Diabetes Intervention Study (1996) [5]</td>
<td>1,139</td>
</tr>
<tr>
<td>The Chicago Heart Association Detection Project in Industry Study (1997) [6]</td>
<td>12,220</td>
</tr>
<tr>
<td>The Rancho Bernardo Study (1998) [7]</td>
<td>1,858</td>
</tr>
<tr>
<td>Whitehall, Paris, Helsinki Study (1998) [8]</td>
<td>17,285</td>
</tr>
<tr>
<td>The Funagata Diabetes Study (1999) [9]</td>
<td>2,534</td>
</tr>
<tr>
<td>The Hoorn Study (1999) [10]</td>
<td>2,363</td>
</tr>
<tr>
<td>Pacific and Indian Ocean (1999) [1]</td>
<td>9,179</td>
</tr>
<tr>
<td>NHANES II (2001) [11]</td>
<td>3,092</td>
</tr>
</tbody>
</table>

1 IGT = post-load glucose < 8.9 mmol/L. All these results are observed in White men. Risk is similar though not significant in Black men.
2 Increased risk of fatal CVD only in women with isolated post-load hyperglycemia.
3 Hazard ratio for CVD death after adjustment for age, sex, race, education, smoking, physical activity, body mass index, systolic blood pressure and total cholesterol-to-HDL cholesterol ratio.

<table>
<thead>
<tr>
<th>Table II</th>
<th>Meta-analyses of the epidemiological observations on post-load plasma glucose as a risk factor for cardiovascular disease.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meta-analyses studies</strong></td>
<td><strong>No. of studies</strong></td>
</tr>
<tr>
<td>Coutinho et al. (1999) [12]</td>
<td>20</td>
</tr>
<tr>
<td>DECODE Study Group (1999) [2]</td>
<td>13</td>
</tr>
<tr>
<td>DECODA Study Group (2002) [13]</td>
<td>12</td>
</tr>
</tbody>
</table>

1 Data issued from Nakagami et al. about 5 prospective studies in 5 countries (n = 6817 subjects) [22].
Patients were treated with either placebo or acarbose for a mean of 3.3 years. CIMT was measured at baseline and at the end of the trial. A 50\% reduction in the progression of IMT mean was observed in the acarbose group compared to the placebo group (P < 0.02). Again, the major limitation of this single-centre substudy of the STOP-NIDDM trial is the relatively small number of participants.

To assess if acarbose would also reduce the risk of CV events in patients with type 2 diabetes, Hanefeld et al. [30] performed a meta-analysis of all double-blind, placebo-controlled, randomised trials with a minimum treatment duration of 52 weeks; they found 7 such studies for analysis. The Cox proportional hazard analysis shows that acarbose treatment was associated with a significant relative risk reduction of 35\% in the development of any CV event. As in the STOP-NIDDM trial, these results remain significant after adjustment for other classical CV risk factors. Again, this important effect was due mainly to the reduction of MI (relative risk reduction = 64\%; P = 0.012). However, this meta-analysis is subjected to criticism for inclusion bias since it is based on 7 studies including 2 that are not published, and 2 published as abstract only. But nevertheless, one must admit that the results are remarkably similar to those observed in the STOP-NIDDM trial.

The effect of treating post-prandial hyperglycaemia on CIMT was also tested in patients with type 2 diabetes by Esposito et al. [28] where they compare 2 secretagogues with different time-action, the short acting repaglinide (1.5 to 12 mg/day) and the long-acting glibenclamide (also called glyburide) (5 to 20 mg/day). The two experimental groups have similar baseline characteristics. The results showed similar reduction in HbA1c concentration during the study in both treatment groups. The fasting glucose concentration was significantly lower in patients treated with glibenclamide, whereas the reduction in post-prandial glucose peak was significantly greater in patients treated with repaglinide (figure 2). The reduction of interleukine-6, C-reactive protein and CIMT with repaglinide were related to the reduction in postprandial glucose peaks, but not to changes in fasting glucose or HbA1c. No significant change from baseline in lipid and blood pressure parameters occurred in either group. This study showed that progression of carotid atherosclerosis can be prevented by controlling postprandial hyperglycaemia rather than FPG in patients with type 2 diabetes. The limited one-year follow-up does not allow to evaluate the impact of this intervention on CV events. Nevertheless, this study has a strong methodological design which supports the hypothesis that targeting PPG can reduce atherosclerosis.

What is the pathogenetic relationship between postprandial hyperglycaemia and CVD?

Postprandial hyperglycaemia is therefore strongly related to the development of atherosclerosis in subjects with and without diabetes [32]. There is now growing evidence that oxidative stress resulting from hyperglycaemia could be involved in the development of diabetes as well as the micro- and macrovascular complications associated with the disease. Existing in vitro and in vivo data indicate that
reactive oxygen species (ROS) formation can be a direct consequence of hyperglycaemia. The different mechanisms that have been proposed to explain the pathogenesis of diabetes-related complications can be linked to a single hyperglycaemia-induced process: the overproduction of superoxide by the mitochondrial electron transport chain [19,33,34].

Human data also suggest that hyperglycaemia is associated with oxidative stress production. Ceriello et al. [35] were the first to show that superoxide anion generation is increased in serum of subjects with diabetes and that it correlated with plasma glucose. Marfella et al. [36] demonstrated in healthy subjects that nitrotyrosine level, a marker of oxidative stress, rose 2.5-fold over baseline during a 2-hour hyperglycaemic clamp (15 mmol/L). Hyperglycaemia was shown to induce endothelial dysfunction probably through the production of oxidative stress [37,38], while the reduction in oxidative stress was associated with an improvement in endothelial dysfunction [39].

Excessive postprandial hyperglycaemia triggers a cascade of atherogenic events, leading to changes in endothelial, mesangial, pericyte, smooth muscle and macrophage cell function in a manner which can lead to micro- and macrovascular disease [40]. Most of the CV risk factors, which increase in the postprandial phase in normal subjects, have been shown to be significantly more increased in subjects with diabetes mellitus [41-44] and appear to be directly related to the degree of post-prandial plasma glucose peak.

More recently, Manzella et al. [29] have studied in a randomised, cross-over, parallel-group trial, the effect of repaglinide (1 mg twice a day) versus glibenclamide (5 mg twice a day) on oxidative stress and endothelial dysfunction. Repaglinide and glibenclamide administration were associated with a significant decline in fasting plasma glucose, HbA1c, triglycerides, and free fatty acids and with a significant increase in fasting and 2-hour plasma insulin, and HDL cholesterol levels. Repaglinide administration was associated with a larger reduction in 2-hour plasma glucose levels compared with glibenclamide administration (8.7 ± 0.2 versus 11.1 ± 0.9). Repaglinide but not glibenclamide showed a significant increase in plasma antioxidant power, and a decline of the degree of serum oxidative stress as well as a significant improvement in brachial reactivity, an index of endothelial function. After repaglinide treatment, changes in 2-hour plasma glucose levels significantly correlated with the changes in arterial diameter and flow. This study thus confirms the beneficial effects of decreasing postprandial glycaemic excursion on oxidative stress and endothelial function. The main limitations of this study are the lack of pharmacological washout between repaglinide and glibenclamide crossover and the fact that patients under repaglinide and glibenclamide have a significant reduction in fasting plasma glucose between baseline and the end of treatment period which could contribute to the improvement in brachial reactivity.

![Figure 2](image-url)


Table III
The effect of acarbose on the incidence of clinically overt and silent myocardial infarctions in The STOP-NIDDM Trial1.

<table>
<thead>
<tr>
<th>Myocardial infarction</th>
<th>Placebo (n = 686)</th>
<th>Acarbose (n = 682)</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically overt</td>
<td>12</td>
<td>1</td>
<td>0.09 (0.01 – 0.72)</td>
<td>0.02**</td>
</tr>
<tr>
<td>Silent</td>
<td>7</td>
<td>1</td>
<td>0.15 (0.02 – 1.2)</td>
<td>0.07**</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>2</td>
<td>/</td>
<td>&lt; 0.0010**</td>
</tr>
</tbody>
</table>

1 Adapted from Zeymer U. et al. [27].

* Cox proportional hazard. Cox proportional hazard model is adjusted for fasting and 2-hour plasma glucose and plasma insulin concentrations; HbA1c levels; total, high-density lipoprotein, and low-density lipoprotein cholesterol levels; triglyceride levels; systolic and diastolic blood pressure; heart rate; body weight; body mass index; waist circumference; concomitant medications (except for hypertension); and smoking status.

** Chi-square test.
Conclusion

The bulk of the observations strongly suggests that postprandial excursion of blood glucose is probably involved in the development of diabetes-related complications, particularly cardiovascular complications. This is further supported by intervention studies where the reduction in postprandial hyperglycaemia is associated with a reduction in CVD. Since CVD is the major cause of morbidity and mortality in patients with type 2 diabetes, confirming these beneficial effects of lowering post-prandial glucose per se on CVD events is crucial. This fundamental issue must be addressed in a well-designed sufficiently powered intervention trial whose primary objective would be the effect of reducing postprandial hyperglycaemia on cardiovascular events. A positive result would have a significant impact on the development of new strategies for the screening and the treatment of subjects with pre-diabetes as well as with diabetes. Under those conditions, postprandial hyperglycaemia would have to be treated aggressively, using the currently available antidiabetic medications affecting specifically postprandial plasma glucose such as acarbose, repaglinide, nateglinide, lispro insulin and insulin aspart. However, the optimal level of postprandial glycaemia remains to be determined.

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