Epidemiological data on postprandial glycaemia

B Balkau, E Eschwège

SUMMARY

There are few studies on the effects of postprandial hyperglycaemia, and usually it is assumed that its effects are the same as those of post-glucose-load hyperglycaemia, following a standard 75 g oral glucose tolerance test. There is some evidence from a study with blood drawn following ingestion of a standardised “diabetes screening product” or a 75 g oral glucose load, that the glucose concentrations during the 2-hour period of these two tests are highly correlated. There is epidemiological evidence that the 2-hour post-load-glucose is more predictive of cardiovascular mortality than fasting glucose, but it would appear that they are equally predictive of retinopathy. While hyperglycaemia is related with cardiovascular mortality, clinical trials lowering glucose levels in type 2 diabetic patients, have not succeeded in reducing cardiovascular disease rates, in contrast to the beneficial effects on micro-vascular disease. STOP-NIDDM, a clinical trial testing the prevention of type 2 diabetes, used the glucose lowering agent acarbose, a drug which lowers postprandial glucose. There was a beneficial effect on cardiovascular outcomes, however, the number of events was extremely small and the study was not designed to test this effect. Confirmatory studies are required before it is possible to conclude that acarbose is effective in cardiovascular prevention, and that indeed it is the treatment of postprandial glucose which is beneficial. The cardiovascular disease in diabetic patients may be due to the presence of other cardiovascular risk factors associated with diabetes.

Key-words: Postprandial glucose · Fasting glucose · Oral glucose tolerance test · Epidemiology · Cardiovascular diseases.

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RESUMÉ

Glycémie postprandiale : données épidémiologiques

Les études sur les effets de la glycémie postprandiale sont peu nombreuses. D’habitude, ces effets sont supposés être assimilables à ceux qui sont observés après une charge orale en glucose, test d’hyperglycémie provoquée par voie orale (HGPO). Cette hypothèse est en partie vraie : les comparaisons de la glycémie 2 heures après une charge en glucose ou après ingestion d’un « diabetes screening product » montrant des résultats très corrélés. Beaucoup d’études montrent que la glycémie 2-heures postcharge est plus prédictive de la mortalité cardio-sanguinaire que la glycémie à jeun. Cependant, il y a peu d’études sur les maladies microvasculaires, et il semble que pour la rétinopathie, les deux glycémies montrent des effets très parallèles. Bien que l’hyperglycémie soit liée à la mortalité et la morbidité cardio-vasculaire, les essais cliniques visant à diminuer la glycémie n’ont pas réussi à réduire vraiment le taux des maladies cardio-vasculaires : de manière contrastée, ils ont bien montré les résultats bénéfiques sur les maladies microvasculaires. STOP-NIDDM, un essai visant à prévenir et retarder la survenue du diabète de type 2 par l’acarbose, médicamente abaissant la glycémie surtout postprandiale, a montré un effet bénéfique sur les événements cardio-vasculaires. Toutefois, ceux-ci furent « très peu » nombreux et le protocole n’était pas prévu à cette intention. D’autres études sont nécessaires avant de conclure que l’acarbose est efficace pour la prévention des maladies cardio-vasculaires, et que c’est le traitement de la glycémie postprandiale qui est, en soi, bénéfique. Les maladies cardio-vasculaires chez les patients diabétiques peuvent être dues à la présence d’autres facteurs de risque des maladies cardio-vasculaires associées au diabète, mais pas à l’hyperglycémie proprement dite.

Mots-clés : Glycémie postprandiale · Glycémie à jeun · Hyperglycémie provoquée par voie orale · Épidémiologie · Maladies cardio-vasculaires.

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Epidemiological studies on true postprandial glucose, following a standardised meal – or even any meal are quite rare. Most of the information we have about the effects of non-fasting glucose have been extrapolated from studies using the glucose levels 2 hours after an oral glucose tolerance test (OGTT); a meal test would indicate the effects of carbohydrates (not only of a glucose load) and of other nutrients, for example lipids, which may alter the glucose metabolism.

Is this extrapolation from post-glucose-load to postprandial tenable?

A Canadian study provides fairly convincing evidence that the glucose and insulin levels post-glucose-load provide a reasonable surrogate measure for postprandial values [1]. In this study a “Diabetes Screening Product” was used for the meal: a 87 g, 345 kcal biscuit, with 10.7 g fat, 12.1 g protein 8.9 g simple sugars, 41.1 g starch, 3.8 g fibre, for comparison with a standard 75 g glucose load. Over the 2-hour test period, both glucose and insulin concentrations for the OGTT were always higher than for the Diabetes Screening Product, which is not surprising as the latter provided a lower glucose load (figure 1). Although there was an absolute difference in the glucose and insulin concentrations for the two tests at 2 hours, the correlations coefficients of 0.97 for both the 2 hour gluoses and the 2 hour insulins for the two tests were almost perfect.

A comparison of the 24-year cardiovascular mortality (figure 2), according to fasting and 2-hour post-glucose-load in the Paris Prospective Study of men not known as diabetic, aged 44-55 years at baseline, showed that high 2 hour glucose concentrations carried more risk than high values of fasting glucose [2]. This was corroborated by the meta-analysis of European studies, DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) [3] (figure 3).

For microvascular disease, there are very few studies which compare the effects of fasting and post-glucose-load hyperglycaemia. A study of 5,000 Pima Indians showed that the period prevalence of retinopathy for a fasting glucose ≥ 7.0 mmol/l (diabetes on fasting glucose) was 20.9% in comparison to 19.9% for a 2-hour post-glucose-load glycaemia ≥ 11.1 mmol/l (diabetes on 2 hour glucose) [4]. Thus post-load glucose does not appear to be more detrimental than fasting glucose.

**Figure 1**

Plasma glucose and insulin over 2 hours following a 75g glucose load, an OGTT (black dots) and following the Diabetes Screening Product (white dots) [From ref. 1, Copyright © 2005 American Diabetes Association. From Diabetes Care 1998; Vol. 21 : pp. 336-340. Reprinted with permission from The American Diabetes Association].

Lean Obese IGT Diabetes

<table>
<thead>
<tr>
<th>Plasma glucose (mmol/L)</th>
</tr>
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<tbody>
<tr>
<td>0 1 2 0 1 2 0 1 2</td>
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</table>

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<th>Plasmainsulin (mmol/L)</th>
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<td>0 1 2 0 1 2 0 1 2</td>
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</table>
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**Figure 2**
Cardiovascular death rates, over 24 years, in 7,000 men from the *Paris Prospective Study*, according to their fasting and their post-glucose-load glucose concentrations [Adapted from ref. 2].

**Figure 3**
Cardiovascular death rates from the DECODE meta-analysis, according to their fasting and their post-glucose-load glucose concentrations [Adapted from ref. 3].
DM: Diabetes Mellitus; IFG: Impaired Fasting Glucose; IGT: Impaired Glucose Tolerance.
What are the effects of hyperglycaemia for the patient with type 2 diabetes?

From the UKPDS (United Kingdom Prospective Diabetes Study), HbA1c (which is more related with fasting glucose than with the 2 hour post-load-glucose [5]) was more strongly related with microvascular than macrovascular complications [6]. Patients in the intensive treatment arm of the trial had consistently lower fasting glucose and HbA1c over the follow-up period, and in parallel a significantly lower risk of microvascular complications (p< 0.0099) whereas the lower rate of macrovascular complications was less convincing (p< 0.052) [7]. However, when the UKPDS was interpreted as an observational study, a higher HbA1c was significantly related with myocardial infarction (p < 0.0001) [6]. We cannot attribute these results to post-glucose-load or to postprandial hyperglycaemia.

The PROACTIVE (PROspective pioglitAzone Clinical Trial in macroVascular Events) trial in type 2 diabetic patients with existing macrovascular disease, showed that patients treated with pioglitazone, in addition to their usual glucose lowering drugs, had a lower HbA1c than those with placebo, over the entire time of the trial [8]. Subsequent macrovascular events, showed a lower event rate in patients on pioglitazone, with results being more or less significant, depending on the trial end-points chosen.

The conclusion that can be drawn from the trial data, is that for the type 2 diabetic patient, HbA1c does not seem to determine the cardiovascular event rate, and that other risk factors play a more major role. The role of hyperglycaemia, either post-prandial or post-glucose-load is not reported in either study.

Hyperglycaemia and type 1 diabetes

The long-term 17 year risk of cardiovascular disease was studied in the DCCT/EDIC (Diabetes Control and Complications Trial/Epidemiology of Interventions and Complications) trial population [9]. In the intensively treated group, cardiovascular risk was reduced by 42% in the intensively treated group in comparison with the conventionally treated group (p< 0.02). Further, the updated glycosylated haemoglobin value during the trial period (6.5 years on average) was significantly related with the cardiovascular outcome. This provides solid evidence of the cardiovascular benefits of glucose control in type 1 diabetes.

Studies with acarbose

Most of the information we have about postprandial glucose comes from treatment with acarbose, with its specific effect on lowering postprandial glucose. The STOP-NIDDM (Study TO Prevent Non Insulin Dependent Diabetes Mellitus) trial was designed to study the effect of the drug on the incidence of type 2 diabetes in subjects with impaired glucose tolerance, and as a secondary analysis, cardiovascular events were also investigated [10]. Indeed, in the patients treated with acarbose, the risk of myocardial infarction was significantly reduced, with a hazards ratio of 0.09 [95% CI: 0.01-0.72 ; p= 0.02] (table I). However, there was only one event in subjects treated with acarbose, 12 events in those treated with placebo. For all cardiovascular events, the hazards ratio was 0.51 [95% CI: 0.28-0.95; p= 0.03].

Table I

Hazard ratios associated with various cardiovascular outcomes in the STOP-NIDDM trial [Adapted from ref. 8].

<table>
<thead>
<tr>
<th>Cardiovascular event</th>
<th>Number (%) experiencing event</th>
<th>Hazards ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>1 (0.2)</td>
<td>0.02 (0.01-0.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Angina</td>
<td>5 (0.7)</td>
<td>0.4 (0.1-1.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Revascularisation</td>
<td>5 (0.7)</td>
<td>0.6 (0.2-1.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>1 (0.2)</td>
<td>0.6 (0.05-6.2)</td>
<td>0.7</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0</td>
<td>...</td>
<td>0.5</td>
</tr>
<tr>
<td>Cerebro-vascular event or stroke</td>
<td>2 (0.3)</td>
<td>0.6 (0.1-3.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1 (0.15)</td>
<td>1.1 (0.07-19)</td>
<td>0.9</td>
</tr>
<tr>
<td>Cardiovascular event</td>
<td>15 (2.2)</td>
<td>0.5 (0.2-1.0)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Further evidence for the effects of acarbose come from a sub-study of the STOP-NIDDM trial on progression of the intima-media thickness (IMT) – after almost 4 years of follow-up, the mean IMT increased by 0.02 mm in the acarbose group, by 0.05 in the placebo group (p=0.027) [11].

Finally a meta-analysis of seven studies using acarbose in close to 2,000 type 2 diabetic patients, showed that those treated by acarbose had a lower overall event rate (table II) [12]. For the individual events, there was only a lower risk for myocardial infarction.

### Conclusion

In conclusion, we can state with certainty that hyperglycaemia is associated with an increase in cardiovascular disease, but in clinical trials that lower glucose levels, there has not always been a significant decrease in cardiovascular events. Is the cardiovascular disease associated with diabetes due to hyperglycaemia itself or to other factors associated with diabetes? A second question is whether postprandial glucose is more influential in macro- and micro-vascular disease progression than fasting glucose?

### References