

## Postprandial Hyperglycaemia and Cardiovascular Complications of Diabetes

a report by

**Antonio Ceriello**

Warwick Medical School, University of Warwick DOI:10.17925/EE.2006.00.01.23

There is increasing evidence that the postprandial state is an important contributing factor to the development of atherosclerosis. In diabetes, the postprandial phase is characterised by a rapid and large increase in blood glucose levels, and the possibility that the postprandial 'hyperglycaemic spikes' may be relevant to the pathophysiology of late diabetic complications has received recently much more attention.<sup>1</sup>

The Oral Glucose Tolerance Test (OGTT), although highly non-physiological, has been used mostly in epidemiological studies that attempt to evaluate the risk of cardiovascular disease. The main advantage of the OGTT is its simplicity: a single plasma glucose measurement two hours after a glucose load determines whether glucose tolerance is normal, impaired or indicates overt diabetes. The caveats of the OGTT are numerous because 75g or 100g 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. However, it has recently been demonstrated that the level of glycaemia reached at two hours after an OGTT is closely related to the level of glycaemia after a standardised meal (mixed meal in the form of wafers containing oat-fractionation products, soy protein and canola oil sweetened with oney: 345kcal, 10.7g fat, 12.1g protein, 8.9g simple sugars, 41.1g starch and 3.8g dietary fibre), suggesting that the OGTT may represent a valid tool to reveal altered carbohydrate metabolism during the meal.<sup>2</sup> Interestingly, the correlation is more consistent for the values of glycaemia in the impaired glucose tolerance range.<sup>2</sup>

From the epidemiological point of view, the Hoorn Study,<sup>3</sup> the Honolulu Hearth Study,<sup>4</sup> the Chicago Heart Study<sup>5</sup> and, more recently, the DECODE Study<sup>6</sup> have clearly shown that the glucose serum level two hours after oral challenge with glucose is a powerful predictor of cardiovascular risk. This evidence is confirmed by two important meta-analyses: the first, by Coutinho et al., examined studies on 95,783 subjects;<sup>7</sup> the second, on more

than 20,000 subjects, pooled the data of the Whitehall Study, Paris Prospective Study and Helsinki Policemen Study.<sup>8</sup> These findings have been supported also by the Diabetes Intervention Study (IDS), which showed how in type 2 diabetics postprandial hyperglycaemia predicts infarction,<sup>9</sup> and by another study, which associates postprandial hyperglycaemia levels with medio-intimal carotid thickening.<sup>10</sup> Intriguing evidence comes from a study that demonstrates how the medio-intimal carotid thickening is correlated not only with postprandial glucose serum level but particularly with the glycaemic spikes during the OGTT.<sup>11</sup> In this study post-challenge glucose spikes were defined as the difference between the maximal post-challenge glucose level during OGTT, irrespective of the time after glucose challenge and the level of fasting plasma glucose.<sup>11</sup>

Most of the cardiovascular risk factors are modified in the postprandial phase in diabetic subjects and directly affected by an acute increase of glycaemia.

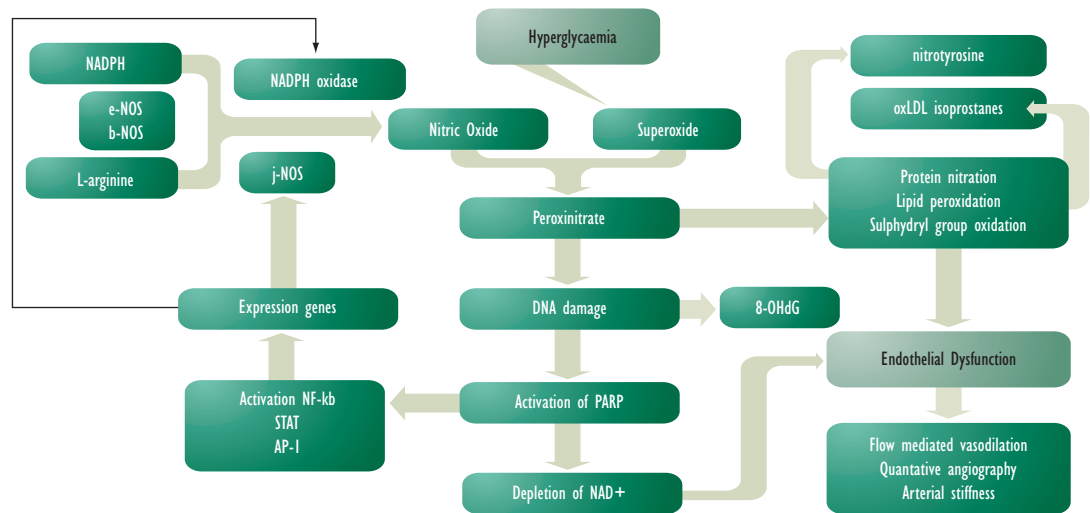
Post-prandial triglyceride level is a cardiovascular risk factor.<sup>12</sup> In non-obese type 2 diabetic patients with moderate fasting hypertriglyceridaemia, atherogenic lipoprotein profile is amplified in the postprandial state.<sup>13</sup> Triglycerides in diabetes are related to hyperglycaemia<sup>14</sup> and the control of postprandial glucose excursions reduces the postprandial triglyceride increase.<sup>15</sup> low-density lipoprotein (LDL) oxidation in diabetes is related to metabolic control,<sup>16-17</sup> and it has been shown in type 2 diabetic patients that after meals LDL oxidation increases<sup>18</sup> and that this phenomenon is in strict correlation with the degree of hyperglycaemia.<sup>19</sup>

Control of the vascular tone is early altered in diabetes. *In vivo* studies have shown that hyperglycaemic spikes induce, in both diabetic and normal subjects, an endothelial dysfunction.<sup>20-21</sup> Furthermore, a rapid decrease of flow-mediated vasodilation has been shown in the post-prandial phase in type 2 diabetic patients and the decrease correlates inversely to the magnitude of post-prandial hyperglycaemia.<sup>22</sup>



Antonio Ceriello is Professor of Metabolic Medicine at the University of Warwick. He is an active member of numerous diabetes associations, including the American Diabetes Association (ADA), the American Heart Association (AHA), the International Diabetes Federation (IDF) and the European Association for the Study of Diabetes (EASD). Professor Ceriello has been invited as both chair and speaker to numerous conferences and congresses around the world. Professor Ceriello has published widely in the area of diabetes with over 180 original papers and several book chapters. Furthermore he is a regular reviewer for numerous journals including *American Journal of Physiology*, *Circulation*, *Circulation Research*, *Diabetes*, *Diabetes Care*, *Diabetic Medicine*, *Diabetologia* and *Lancet*. Professor Ceriello was also consultant of the National Institutes of Health (NIH) for the programme of research 2003–2005, related to cardiovascular disease and type 1 diabetes. He is also serving as Associate Editor of *Diabetes Care* and *Diabetic Medicine*. Professor Ceriello is the winner of 2004 Castelli Pedrolì Prize of EASD.

**Figure 1: Hyperglycaemia Determine an Overproduction of Superoxide by the Mitochondrial Electron Transport Chain and Favours Increased Expression of NADPH and iNOS by Activation of NF-kB**



Consequently, hyperglycaemia results in an overproduction of superoxide and nitric oxide (NO). This condition is related with overgeneration of a toxic reaction product, the peroxynitrite anion. Peroxynitrite is cytotoxic because it leads to oxidation of sulphhydryl groups in protein, peroxidation of lipids and nitrates amino acids. Moreover peroxynitrite is a potent initiator of DNA single-strand breakage, which is a stimulus for activation of poly (adenosine 5'-diphosphate-ribose) synthetase (PARP), that depletes the intracellular concentration of its substrates NAD<sup>+</sup>, slowing the rate of glycolysis, electron transport, adenosine triphosphate (ATP) formation and adenosine diphosphate (ADP) ribosylation of the glyceraldehyde-3-phosphate dehydrogenase (GAPDH). This process results in acute endothelial dysfunction in diabetic blood vessels, which contribute to the development of diabetic complications. Assessment of endothelial cell function is now possible with a consistent number of biomarkers: DNA damage can be detected with 8-OHdG, nitrotyrosine is a marker of protein nitration, while oxLDL and isoprostanes are markers of lipid peroxidation. Moreover is possible a direct measure of endothelial dysfunction with flow mediated vasodilation, quantitative angiography and arterial stiffness.

The mechanisms through which acute hyperglycaemia exerts its effects may be identified in the production of free radicals. It has been reported that, during a glucose oral challenge, a reduction of the antioxidant defenses is observed.<sup>23-24</sup> This effect can be observed even in more physiologic situations, that is, while eating a meal.<sup>25</sup> The role of hyperglycaemia is highlighted by the fact that giving two different meals, which will result into two different levels of postprandial hyperglycaemia, the greater drop in the antioxidant activity is linked with the higher levels of hyperglycaemia.<sup>19</sup> The evidence that in diabetics LDLs are more prone to oxidation in the

One of the major concerns about the role of postprandial hyperglycaemia in cardiovascular disease has been, until now, the absence of intervention studies. Evidence is now coming.

The STOP-NIDDM Trial has presented data indicating that treatment of subjects with impaired glucose tolerance (IGT) with the  $\alpha$ -glucosidase inhibitor acarbose, a compound that specifically reduces postprandial hyperglycaemia, is associated not only with a 36% reduction in the risk of progression to diabetes,<sup>26</sup> but also with a 34% risk reduction in the development of new cases of hypertension and a 49% risk reduction in

*Triglycerides in diabetes are related to hyperglycaemia and the control of postprandial glucose excursions reduces the postprandial triglyceride increase.*

postprandial phase matches these data.<sup>18</sup> Even in this situation, higher levels of hyperglycaemia are matched with a greater oxidation of LDLs.<sup>19</sup> Figure 1 shows a detailed illustration of the pathways linking hyperglycaemia and oxidative stress.

cardiovascular events.<sup>27</sup> In addition, in a subgroup of patients, the carotid intima media thickness was measured before randomisation and at the end of the study.<sup>28</sup> Acarbose treatment was associated with a significant decrease in the progression of intima

media thickness, an accepted surrogate for atherosclerosis.<sup>28</sup> 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.<sup>29</sup> Finally, very recently, the effects of two insulin secretagogues, repaglinide and glyburide, known to have different efficacy on postprandial hyperglycaemia, on carotid intima-media thickness (CIMT) and markers of systemic vascular inflammation in type 2 diabetic patients, has been evaluated.<sup>30</sup> After 12 months,

treating postprandial hyperglycaemia may positively affect the development of cardiovascular disease.

The evidence described up to now proves that hyperglycaemia can acutely induce alterations of the normal human homeostasis. It should be noted that acute increases of glucose serum level cause alterations in healthy – normoglycemic – subjects, but also in diabetic subjects, that have also a basic hyperglycaemia.<sup>1</sup> On the basis of this evidence, it can be hypothesised that the acute effects of glucose serum level can add to those produced by chronic

*Correcting the postprandial hyperglycaemia can form part of the strategy for the prevention and management of cardiovascular diseases in diabetes.*

postprandial glucose peak was 148+/-28mg/dL in the repaglinide group and 180+/-32mg/dL in the glyburide group (p<0.01). HbA1c showed a similar decrease in both groups (-0.9%). CIMT regression, defined as a decrease of >0.020mm, was observed in 52% of diabetics 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 CIMT was associated with changes in postprandial but not fasting hyperglycaemia.<sup>30</sup> Therefore, evidence is emerging and suggests that

hyperglycaemia, 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, being the tendency to rapid variations of hyperglycaemia 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.

Correcting the postprandial hyperglycaemia can form part of the strategy for the prevention and management of cardiovascular diseases in diabetes. ■

**References**

1. Ceriello A, Hanefeld M, Leiter L et al., "Tuomilehto J. Postprandial glucose regulation and diabetic complications", Arch. Intern. Med. (2004);164: pp. 2,090–2,095.
1. Wolever T M S, Chiasson J L, Csima A et al., "Variation of postprandial plasma glucose, palatability, and symptoms associated with a standardized mixed test meal versus 75 g oral glucose", Diabetes Care (1998);21: pp. 336–340.
2. de Vegt F, Dekker J M, Ruhè H G, Stehouwer C D A, Nijpels G B L M, Heine R J, "Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study", Diabetologia (1999);42: pp. 926–931.
3. Donahue R P, Abbott R D, Reed D M, Yano K, "Postchallenge glucose concentration and coronary heart disease in men of Japanese ancestry. Honolulu Heart Program", Diabetes (1987);36: pp. 689–692.
4. Lowe L P, Liu K, Greenland P, Metzger B E, Dyer A R, 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 (1997);20: pp. 163–169.
5. The DECODE study group on behalf of the European Diabetes Epidemiology Group, "Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria", Lancet (1999);354: pp. 617–621.
6. Coutinho M, Gerstein H C, 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

- (1999);22: pp. 233–240.
7. Balkau B, Shipley M, Jarrett R J et al., “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* (1998);21: pp. 360–367.
  8. Hanefeld M, Fischer S, Julius U et al., “The DIS Group. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up”, *Diabetologia* (1996);39: pp. 1,577–1,583.
  9. 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* (1999);144: pp. 229–235.
  10. Temelkova-kurktschiev T S, Koehler C, Schaper F, Leonhardt W, Henkel H, Hanefeld M, “Post-challenge plasma glucose and glycemc spikes are more strongly associated with atherosclerosis than fasting glucose and glycosylated hemoglobin level”, *Diabetes Care* (2000);23: pp. 1,830–1,834.
  11. Hamsten A, Björkegren J, Boquist S et al., “Postprandial lipaemia and coronary heart disease”, *Atherosclerosis* (1998);11: pp. 141–149.
  12. Cavallero E, Dacht 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* (1994);43: pp. 270–278.
  13. Howard B V, “Lipoprotein metabolism in diabetes mellitus”, *J. Lipid. Res.* (1987);28: pp. 613–628
  14. Hanefeld M, Fischer S, Schulze J et al., “Therapeutic potentials of Acarbose as first-line drug in NIDDM insufficiently treated with diet alone”, *Diabetes Care* (1991);14: pp. 732–737.
  15. Tsai E C, Hirsch I B, Brunzell J D, Chait A, “Reduced plasma peroxyl radical trapping capacity and increased susceptibility of LDL to oxidation in poorly controlled IDDM”, *Diabetes* (1994);43: pp. 1,010–1,014.
  16. Jenkins A J, Klein R L, Chassereau C N, Hermayer K L, Lopes-Virella M F. “LDL from patients with well-controlled IDDM is not more susceptible to in vitro oxidation”, *Diabetes* (1996);45: pp. 762–767.
  17. Diwadkar VA, Anderson J W, Bridges S R, Gowri M S, Oelgten P R, “Postprandial low density lipoproteins in type 2 diabetes are oxidized more extensively than fasting diabetes and control samples,” *Proc. Soc. Exp. Biol. Med.* (1999);222: pp. 178–184.
  18. Ceriello A, Bortolotti N, Motz E et al., “Meal-induced oxidative stress and low-density lipoprotein oxidation in diabetes: the possible role of hyperglycemia”, *Metabolism* (1999);48: pp. 1,503–1,508.
  19. Kawano H, Motoyama T, Hirashima O et al., “Hyperglycemia rapidly suppresses flow-mediated endothelium-dependent vasodilation of brachial artery”, *J. Am. Coll. Cardiol.* (1999);34: pp. 146–154.
  20. Giugliano D, Marfella R, Coppola L et al., “Vascular effects of acute hyperglycemia in humans are reversed by L-arginine. Evidence for reduced availability of nitric oxide during hyperglycemia”, *Circulation* (1997);95: pp. 1,783–1,790.
  21. Shige H, Ishikawa T, Suzukawa M et al., “Endothelium-dependent flow-mediated vasodilation in the postprandial state in type 2 diabetes mellitus”, *Am. J. Cardiol.* (1999);84: pp. 1,272–1,274.
  22. Ceriello A, Bortolotti N, Crescentini A, “Antioxidant defenses are reduced during oral glucose tolerance test in normal and non-insulin dependent diabetic subjects”, *Eur. J. Clin. Invest.* (1998);28: pp. 329–333.
  23. 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.* (1999);54: pp. 541–545.
  24. Konukoglu D, Hatemi H, Ozer E M, Gonen S, Akcay T, “The erythrocyte glutathione levels during oral glucose tolerance test”, *J. Endocrinol. Invest.* (1997);20: pp. 471–475.
  25. Ceriello A, Bortolotti N, Motz E et al., “Meal-generated oxidative stress in type 2 diabetic patients”, *Diabetes Care* (1998);21: pp. 1,529–1,533.
  26. Chiasson J L, Josse R G, Gomis R, Hanefeld M, Karasik A, Laakso M, “STOP-NIDDM Trial Research Group: Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial”, *Lancet* (2002);359: pp. 2,072–2,077.
  27. Chiasson J L, Josse R G, Gomis R, Hanefeld M, Karasik A, Laakso M, “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* (2003);290: pp. 486–494.
  28. Hanefeld M, Chiasson J L, Koehler C et al., “Acarbose slows progression of intima-media thickness of the carotid arteries in subjects with impaired glucose tolerance”, *Stroke* (2004);35: pp. 1,073–1,078.
  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.* (2004);25: pp. 10–16.
  30. Esposito K, Giugliano D, Nappo F, Marfella R, “Regression of Carotid Atherosclerosis by Control of Postprandial Hyperglycemia in Type 2 Diabetes Mellitus”, *Circulation* (2004);29: pp. 2,978–2,984.