Does postprandial blood glucose matter and why?

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Type 2 diabetes is characterized by a gradual decline in insulin secretion in response to nutrient loads; hence, it is primarily a disorder of postprandial glucose (PPG) regulation. However, physicians continue to rely on fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c) to guide management. There is a linear relationship between the risk of cardiovascular (CV) death and the 2-hour oral glucose tolerance test (OGTT), while a recent study confirms postprandial hyperglycemia as independent risk factor for CVD in type 2 diabetes. At the same time, several intervention studies show that treating postprandial hyperglycemia may reduces the incidence of new CV events. Evidence supports the hypothesis postprandial hyperglycemia may favour the appearance of the CV disease trough the generation of an oxidative stress. Furthermore, clinical data suggest that postprandial hyperglycemia is a common phenomenon even in patients who may be considered in "good metabolic control". Therefore, physicians should consider monitoring and targeting PPG, as well as HbA1c and FPG, in patients with type 2 diabetes.

Over the last several years, diabetes organisations around the world have begun to recognise that prandial glucose regulation (PGR) leads to improved outcomes in patients with diabetes. As a result, they have strengthened their recommendations for monitoring and treating postprandial glucose (PPG)[1] (reviewed in reference 1).

These recommendations are supported by an increasing body of evidence.

Many epidemiological data support this concept, showing that the value of glucose after 2h during an oral glucose tolerance test (OGTT) is an independent risk factor for cardiovascular disease, while fasting glucose is not[2-7].Clearly, the OGTT is highly non-physiological and can not be considered as a meal. However two studies have confirmed that PPG is an independent risk factor for CVD in type 2 diabetes in the clinical setting: "The Diabetes Intervention Study", which showed that in type 2 diabetics 1h PPG predicts myocardial infarction[8], and, more recently, a prospective study, with a mean follow-up of 5 years, able to show that PPG is an independent CVD risk factor, particularly in women, in patients with type 2 diabetes[9].

Intervention studies are also coming and support the relevance of PPG in the development of CVD.

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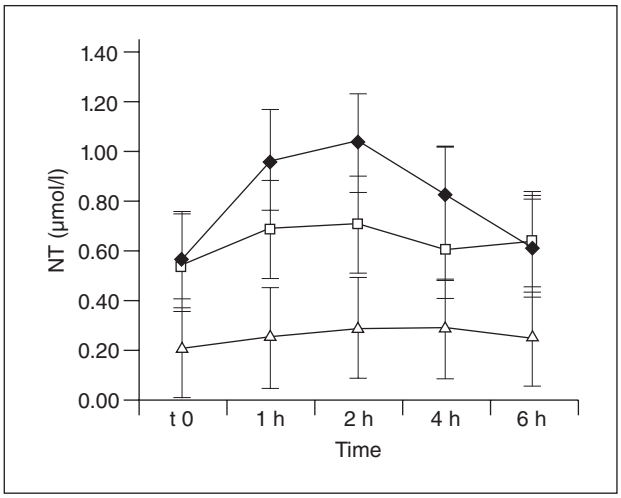

Fig. 1. Nitrotyrosine (a marker of oxidative stress) before and after a mixed meal: regular insulin, insulin aspart and control. From: Ceriello et al[18].

The STOP-NIDDM Trial has shown that treatment of subjects with IGT with the ·-glucosidase inhibitor acarbose, a compound which specifically reduces postprandial hyperglycemia, is associated not only with a 36% reduction in the risk of progression to diabetes[10], but also a 34% risk reduction in the development of new cases of hypertension and a 49% risk reduction in cardiovascular events[11], particularly of silent myocardial infarction[12]. In addition, in a subgroup of patients from this study, carotid intima media thickness was measured before randomisation and at the end of the study[13]. Acarbose treatment was associated with a significant decrease in the progression of intima media thickness, an accepted surrogate for atherosclerosis[13]. Furthermore, in a recent meta-analysis in type 2 diabetic patients, acarbose treatment was associated with a significant reduction in cardiovascular events relative to placebo treatment, even after adjusting for other risk factors[14]. Finally, the effects of two insulin secretagogues, repaglinide and glyburide, known to have different efficacy on postprandial hyperglycemia, on carotid intima-media thickness (CIMT) and markers of systemic vascular inflammation in type 2 diabetic patients has been evaluated[15]. Although a similar reduction in A1c was observed in both groups (–0.9%), CIMT, interleukin-6 and C-reactive protein decreased more in the repaglinide group than in the glyburide group. The reduction in CIMT was associated with changes in postprandial but not fasting hyperglycemia[15].

The mechanisms through which PPG exerts its effects may be identified in the production of free radicals, which, in turn, can induce an endothelial dysfunction and the production of an inflammation[16] (revised in reference 16). Studies confirm that after a meal an oxidative stress is generated[17,18] (fig. 1) and that it is related to the level of hyperglycemia reached[19], and, particularly, as very recently demonstrated, to the level of glucose fluctuations[20]. In parallel, the production of this oxidative stress induces an endothelial dysfunction and the release of cytokines[21,22], convincingly related to the activation of the transcription factor NF-kB, which plays a key role on endothelial function and inflammation[23]. Therefore, it is not surprising that controlling PPG with various different compounds specifically working on PPG, such as, fast acting insulin analogues, hypoglycaemic agents improving the first phase of insulin secretion, an amylin analogue and acarbose, is accompanied by a significant improvement not only of the oxidative stress[18,24-26], but also of endothelial dysfunction[26-29], myocardial blood flow[30], inflammation[15] and NF-kB activation[31].

However, also dyslipidaemia is a recognized risk factor for cardiovascular disease in diabetes[32] and today the contribution of postprandial hyperlipidaemia to this risk is well-recognized[33].

In non-obese type 2 diabetic patients with moderate fasting hypertriglyceridaemia, atherogenic lipoprotein profile is amplified in the postprandial state[34]. These evidences have frequently raised the question that being postprandial hyperglycemia accompanied by a concomitant increase of postprandial hyperlipidaemia, the latter was the true risk factor[35].

It is today well recognized that endothelial dysfunction is an early factor involved in the development of cardiovascular disease[36]. Evidence suggests that both postprandial hypertriglyceridemia and hyperglycemia induce an endothelial dysfunction, through an oxidative stress[21,37].

Finding shows an independent and cumulative effect of postprandial hypertriglyceridemia and hyperglycemia on endothelial function, suggesting oxidative stress as common mediator of such effect[21,22]. Therefore, evidence exists to support a specific and direct role of posprandial hyperglycemia, independent from lipids, in favouring cardiovascular disease.

The production of an oxidative stress in postprandial state, due to postprandial hyperglycemia, is of particular relevance because recent studies demonstrate that a single hyperglycemia-induced process of overproduction of superoxide by the mitochondrial electron-transport chain seems to be the first and key event in the activation of all other pathways involved in the pathogenesis of diabetic complications[38] (fig. 2). Interestingly enough, it has very recently been shown that hyperlipidemia works in generating an oxidative stress in the mitochondria through the same pathway of hyperglycemia[39].

The evidence described up to now proves that hyperglycemia can acutely induce alterations of normal human homeostasis. It should be noted that acute increases of glucose levels cause alterations even in healthy —normoglycemic— subjects[16]. Diabetic subjects also have basal hyperglycemia and it can be hypothesized that the acute effects of mealtime hyperglycemia can exacerbate those produced by chronic hyperglycemia, thus contributing to the final picture of complicated diabetes. The precise relevance of PPG in the daily life of diabetic patients has recently been quantified[40].

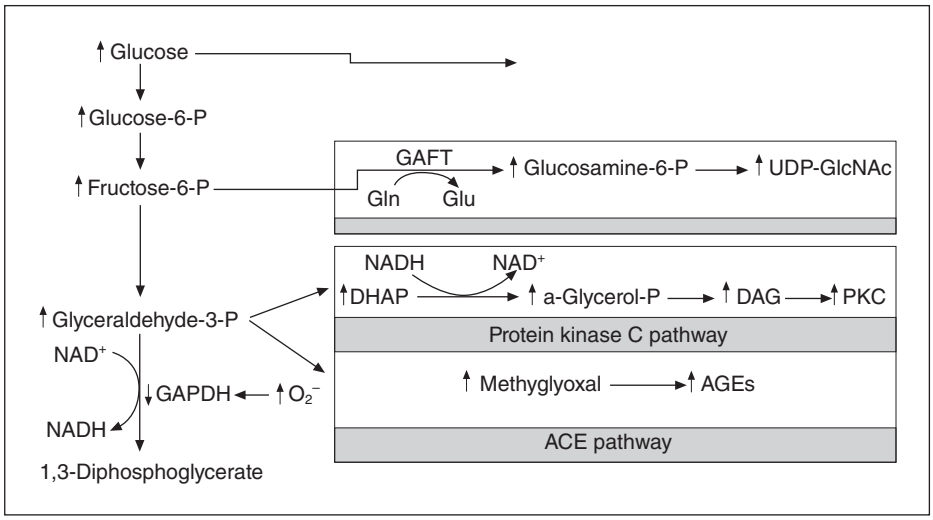

Fig. 2. Superoxide formation and its relationship to other key mechanisms of hyperglycemia-induced damage. From: Brownlee M[38].

Three self-assessed daily blood glucose profiles over a 1-week period, including 18 glucose readings before and 2 h after meals, were obtained from 3,284 unselected outpatients with non-insulin-treated type 2 diabetes mellitus attending 500 different diabetes clinics operating throughout Italy. A PPG blood glucose value > 8.89 mmol/l (160 mg/dl) was recorded at least once in 84% of patients, and 81% of patients had at least one deltaglucose (the difference between pre and postprandial glucose) ≥ 2.22 mmol/l (40 mg/dl). Among patients with apparently good metabolic control, 38% had > 40% of PPG blood glucose readings > 8.89 mmol/l, and 36% had > 40% deltaglucose ≥ 2.22 mmol/l. These results indicate that PPG is a very frequent phenomenon in patients with type 2 diabetes mellitus on active treatment and can occur even when metabolic control is apparently good[40].

Therefore, at the present time, given the tendency to rapid variations of hyperglycemia throughout the life of diabetic patients —above all in the postprandial phase—, it is proper to think that this may exert an important influence on the onset of complications. Thus correcting postprandial hyperglycemia should form part of the strategy for the prevention and management of cardiovascular diseases in diabetes.

Conflict of interest

The author declares he has no conflict of interest.

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