

# Acute Glucose Fluctuations and Chronic Sustained Hyperglycemia as Risk Factors for Cardiovascular Diseases in Patients with Type 2 Diabetes

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## Key words

- Type 2 diabetes
- chronic hyperglycemia
- acute glucose fluctuations

## Abstract

▼ Chronic hyperglycemia, usually assessed from HbA1c determinations, results in excessive glycation and generation of oxidative stress. As a consequence, chronic hyperglycemia has been identified as a risk factor for diabetes complications leading to accelerated atherosclerosis. Both fasting and postprandial hyperglycemia contribute to this process. However the acute glucose fluctuations that occur in diabetes have been recently described as an additional factor

that activates the oxidative stress. As a consequence, acute glucose swings, including upward (postprandial) and downward (interprandial) fluctuations can be considered as risk factors for cardiovascular events and should be included in the “dysglycemia” of diabetes in combination with fasting and postprandial hyperglycemia. As postprandial glucose is a contributor of both acute glucose fluctuations and chronic sustained hyperglycemia, it remains difficult to know whether these 2 mechanisms are equivalent or not equivalent risk factors for cardiovascular disease.

## Introduction

▼ To day, nobody can deny the role of diabetes in the development of specific microvascular complications and the high incidence of accelerated atherosclerosis [1]. Although a large number of studies have investigated and compared the roles of the many factors involved in diabetic vascular complications, an accurate assessment of their respective contributions is still difficult. However, as demonstrated by many trials, microvascular and macrovascular complications are mainly [2,3] or partly dependent on “dysglycemia”, which has two components: chronic sustained hyperglycemia (including fasting and chronic postprandial hyperglycemia) and acute glycaemic fluctuations from peaks to nadirs. Both components lead to diabetic complications through two main mechanisms: excessive protein glycation and activation of oxidative stress.

patients result in an activation of oxidative stress with an overproduction of superoxide by the mitochondrial electron-transfer chain [4] (○ Fig. 1). This activation in turn produces a cascade of such deleterious metabolic events as enhanced polyol activity, increased formation of advanced glycation end-products, activation of protein kinase C and nuclear factor  $\kappa$ B, and increased hexosamine pathway flux [4]. It is now well established that hyperglycemia both at fasting and during postprandial periods results in exaggerated and accelerated glycation. For instance, all the studies conducted in type 1 and type 2 diabetes have clearly shown a strong positive relationship between HbA1c levels and plasma glucose levels at fasting and over postprandial periods [5,6], the strongest correlation being observed between HbA1c and mean plasma glucose levels [7]. The latter relationship was considered sufficiently demonstrative to serve as a reference in the recent Standards of Medical Care in Diabetes that are published every year by the American Diabetes Association [8]. To day, HbA1c is unanimously recognized as a reliable marker for the overall glucose exposure and its direct consequence, an excessive rate of glycation [9,10]. The simplicity of this concept masks more complex phenomena because HbA1c is an integrator of both fasting

## The Brownlee theory or the theory of oxidative stress

▼ The two mechanisms which we have just evoked were unified in an elegant theory that suggested that the glycaemic disorders observed in diabetic

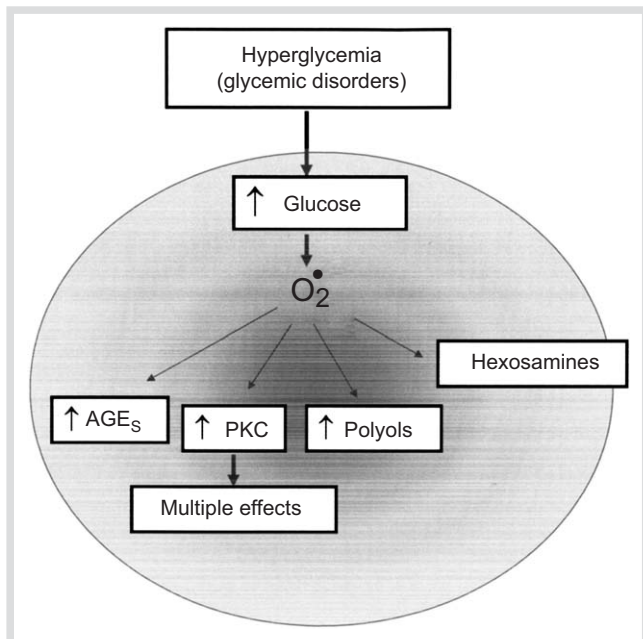
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**Fig. 1** Metabolic alterations activated by hyperglycemia in endothelial cells. Theory of oxidative stress for vascular damages in diabetes [4]. O<sub>2</sub>•: Superoxide anion AGEs: advanced glycation end products PKC: Protein kinase C.

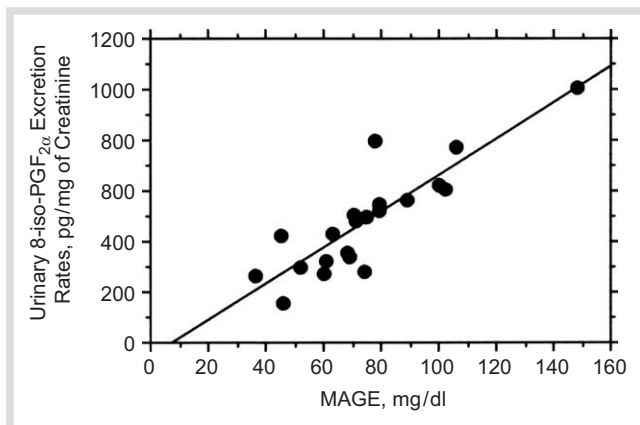
and postprandial glycaemic disorders. As a consequence, it is not surprising that either fasting or postprandial hyperglycemia were identified separately or concomitantly as major risk factors for diabetic complications. The UKPDS study pointed out HbA1c and fasting blood glucose levels as major predictors of diabetes-related complications. This study demonstrated that the risks for myocardial infarction and microvascular complications were diminished by 14 and 37%, respectively, for each 1% reduction in HbA1c [3]. On the other hand, in the Diabetes Intervention Study published in 1996 by Hanefeld [11], postprandial hyperglycemia was a better predictor of subsequent myocardial infarction and mortality than fasting hyperglycemia. These results, confirmed by other studies, suggest that postprandial hyperglycemia is an independent risk factor for macrovascular diseases [12,13]. However, risk factors are not limited to fasting and postprandial hyperglycemia. Other factors such as dyslipidemia, hypertension, and hemostasis dysfunction (all are at least partly associated with the insulin resistance of type 2 diabetes) can be involved in macrovascular complications. Furthermore, even though we consider only glycaemia alterations, fasting and postprandial hyperglycemia may be not the only components of diabetic complications. Another risk factor is probably the glucose variability within a day, especially the acute glucose fluctuations. This raises the following question: Are chronic hyperglycemia and acute glucose fluctuations equivalent risk factors for cardiovascular disease? In order to respond to this question, the first part of this review article is mainly devoted to the analysis of the contributions of the two components of the “dysglycemia”: sustained chronic hyperglycemia and acute glucose fluctuations to the activation of oxidative stress and thus to the respective impacts of these glycaemic disorders on diabetic complications. Several markers have been used to assess oxidative stress and the antioxidant status in patients with diabetes. The short plasma half-life of these markers is one of the limiting factors for the assessment of oxidative stress in plasma samples.

Thus, when available, urinary determinations provide a more reliable estimation of the activation of oxidative stress than plasma measurements [14,15]. Accordingly, the determination of such specific isoprostane isomers as the 8-iso-PGF<sub>2α</sub> in urine has been proposed. Isoprostanes are collectively formed from free radical-mediated oxidation of arachidonic acid [16]. As this fatty acid is ubiquitously distributed in cell membranes, measurements of urinary isoprostanes most likely provide an excellent reflection of the activation of oxidative stress in the whole body. In the different studies that have been conducted in diabetes, plasma and urinary metabolites have been alternatively or simultaneously used as oxidative stress markers.

As free radical production has been reported to be increased in patients with diabetes mellitus, it has been suggested that hyperglycemia may directly contribute to the generation of oxidative stress. There is cogent evidence from several studies that hyperglycemia is associated with an increased formation and urinary excretion rate of 8-iso-PGF<sub>2α</sub> [17]. The urinary excretion rate of 8-iso-PGF<sub>2α</sub> was found to be significantly increased in type 2 diabetic patients as compared with age-matched healthy subjects. Furthermore, significant correlations were observed between blood glucose and urinary 8-iso-PGF<sub>2α</sub> suggesting that the activation of oxidative stress may be, at least in part, related to the determinants of diabetic control. We have recently confirmed these results by showing that the mean urinary excretion rates of 8-iso-PGF<sub>2α</sub> were significantly higher ( $p < 0.01$ ) in patients with type 2 diabetes (mean  $\pm$  SD =  $482 \pm 206$  pg/mg of creatinine) than in nondiabetic healthy subjects ( $275 \pm 85$  pg/mg of creatinine) [18]. Improved metabolic control has been shown to be associated with a significant reduction in urinary excretion rates of both 8-iso-PGF<sub>2α</sub> and 11-dehydrothromboxane (TXM) by 32 and 48%, respectively, in 21 patients with type 2 diabetes. Vitamin E supplementation led to complete normalization of 8-iso-PGF<sub>2α</sub> excretion rates [19]. Moreover, changes in 8-iso-PGF<sub>2α</sub> excretion were accompanied by similar reduction in TXM excretion, consistent with a cause-and-effect relation between enhanced lipid peroxidation and persistent platelet activation. Increase of plasma 8-iso-PGF<sub>2α</sub> is an early event in the evolution of type 2 diabetes and could precede the development of endothelial dysfunction.

### Contribution of acute glucose fluctuations to the activation of oxidative stress

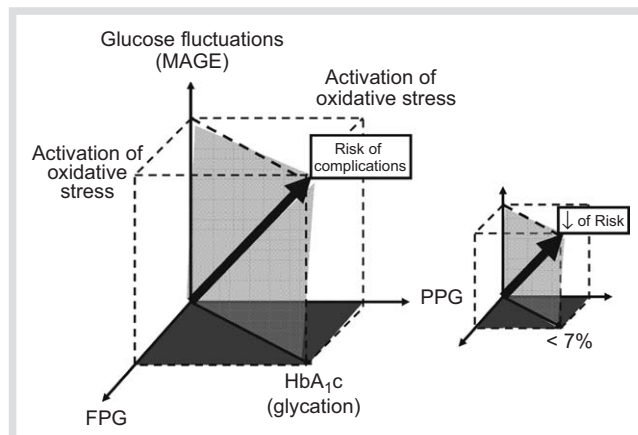
Postprandial glucose results in both acute and sustained hyperglycemia since postprandial periods have a 4-hour duration. Several interventional or epidemiological studies suggest that acute hyperglycemia after a meal or glucose load may be an independent predictor of risk for vascular event in type 2 diabetes [20]. Such a relationship results from an increased generation of reactive oxygen species during acute hyperglycemia, leading to acute oxidative damage to the vascular endothelium. For instance, acute hyperglycemia after a glucose load in type 2 diabetes is associated with an acute increase in plasma concentrations of 8-iso-PGF<sub>2α</sub>. The role of postprandial hyperglycemia in the generation of oxidative stress was particularly investigated by Ceriello et al., who demonstrated that the production of free radicals was increased during the postprandial period [21] and that this increment was proportional to the magnitude of the postprandial glucose excursions. For instance, fasting nitrotyrosine, a metabolite derived from nitrosamine stress, was



**Fig. 2** Linear correlation between 24-hour urinary excretion rates of 8-iso-prostaglandin F<sub>2α</sub> and Mean Amplitude of Glycemic Excursions (MAGE) in 21 patients with type 2 diabetes (from [18], printed with permission of JAMA).

significantly increased in the diabetic patients. An additional increase was observed during postmeal periods. Reduction of the postmeal glucose excursions by using a premeal bolus of rapid insulin analog (Aspart) resulted in parallel decrements in glycemic and nitrotyrosine responses [22]. This provides direct evidence for a link between acute rather than chronic hyperglycemia and free radical damage in diabetes.

Although postprandial glucose is usually the major contributor of glucose variability, other fluctuations (especially downward fluctuations) must be taken into account. In a recent study [18], we have demonstrated that the urinary excretion rate of 8-iso-PGF<sub>2α</sub> was highly and positively correlated with the glycemic variability assessed from the mean amplitude of glycemic excursions (MAGE). For this purpose, the patients' glucose profiles were obtained over 48 hours from continuous glucose monitoring system (CGMS) data. The calculation of the MAGE was made by measuring the arithmetic mean of the difference between consecutive peaks and nadirs, provided that the difference was greater than the standard deviation (SD) around the mean glucose values. The relationship is indicated in **Fig. 2** ( $r=0.86$ ,  $p<0.001$ ). A statistically significant correlation was also observed with the mean postprandial glucose incremental area under the curve (AUC<sub>pp</sub>) but the relationship was less significant ( $p=0.009$ ). It thus appears that the triggering effect of acute glycemic excursions on oxidative stress should be integrated into glycemic disorders that are much broader than acute postmeal spikes. As a consequence, the concept that postprandial "hyperglycemic spikes" are "dangerous waves", should be extended to both upward (postprandial) and downward (interprandial) acute fluctuations of glucose around a mean value. This observation may provide an explanation for some of the epidemiological observations of the DCCT. For instance, in the subgroups with a sustained HbA<sub>1c</sub> of 9% for the entire study duration, the risk of retinopathy was reduced by more than 50% in the intensive control group compared with the conventional group, even though these two subgroups of patients had the same HbA<sub>1c</sub>. The difference might have been due to a lower intraday glucose variability in the intensive control group. However, this hypothesis was not confirmed by a recent analysis of the data sets collected in the DCCT. In this retrospective study, Kilpatrick et al. [23] reported that the mean blood glucose, i.e., sustained chronic hyperglycemia, was predictive of microvascular complications in patients



**Fig. 3** Model suggested for illustrating the pathophysiological impacts of excess glycation and activation of oxidative stress on the risk of diabetic complications (diagonal solid arrow). The contributions of the three components of dysglycemia, i.e., hyperglycemia at fasting (FPG), hyperglycemia during postprandial periods (PPG), and acute glucose fluctuations (MAGE) are indicated on the x, y, and z axis, respectively.

with type 1 diabetes while within-day glucose variability was not. It should be noted, however, that in this study the instability of blood glucose was calculated as the standard deviation (SD) around the mean of a seven-point glycemic profile measured at each patient's quarterly visit. With such a methodology, the authors probably selected not major fluctuations but rather a composite of both major and minor swings with a majority of minor ones. Furthermore, Kilpatrick et al. [23] probably blunted the contributions of major glucose fluctuations because there are many reasons to think that the four pre(inter)-prandial and the three postprandial glucose values included in the seven-point profile did not perfectly coincide with the glucose nadirs and peaks, respectively. The following example should be useful to explain the superiority of the MAGE index for assessing glucose variability compared with the SD of a seven-point glucose profile. Consider two patients with type 2 diabetes who have similar HbA<sub>1c</sub> and SD of glucose fluctuations around the mean. Assume that one subject has many minor glucose fluctuations and one or two major swings per day, while the other patient exhibits moderate glucose fluctuations over 24 hours. Despite similar SD of glucose around the mean, these two patients should exhibit very different MAGE values and thus Kilpatrick's use of SD as a definitive measure of glucose variability is questionable. Even though the MAGE determination requires continuous glucose monitoring, our opinion is that this index should be the "gold standard" for assessing glucose fluctuations in all prospective interventional trials designed to estimate glucose variability. Therefore, expanded use of continuous glucose sensors would certainly be useful for conducting such trials. In conclusion, the pathophysiology of diabetic complications can be considered as the result of two major deleterious metabolic alterations (excessive glycation and generation of oxidative stress) that are activated by three main glycemic disorders: hyperglycemia both at fasting and during postprandial periods and acute glucose fluctuations (**Fig. 3**). At present, there is no doubt that excessive levels of glucose at fasting and during postprandial periods activate the glycation process, which can be investigated as a whole by measuring the HbA<sub>1c</sub> levels. In addition to hyperglycemia at fasting, acute or sustained hyperglycemia over postprandial periods and more generally acute glucose

fluctuations around the mean glucose value activate oxidative stress. The resulting effect is the risk of complications depicted by the diagonal arrow of a geometric cube whose three-dimensional coordinates on the three axes are FPG, PPG, and glucose fluctuations. According to this model, a global antidiabetic therapeutic strategy should be aimed at reducing the values of the three coordinates, i.e., the volume of the cube, and therefore the magnitude of the diagonal arrow that illustrates the risk for diabetic complications (► Fig. 3). However, several questions remain to be solved. For instance and at present, it is not possible to know whether the famous Aristotle's aphorism can be applied to the dysglycemia of patients with type 2 diabetes or not: "The whole, i.e., the dysglycemia and its consequence – the risk of complication – is greater than the sum of its parts (FPG, PPG, and acute glucose fluctuations)".

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