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

C. Colette, L. Monnier

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 glycemic fluctuations from peaks to nadirs. Both components lead to diabetic complications through two main mechanisms: excessive protein glycation and activation of oxidative stress.

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 glycemic disorders observed in diabetic 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 κB, 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 and postprandial glucose levels.

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.
and postprandial glycemic 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 glycemia 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 glycemic 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-PGF2α 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-PGF2α [17]. The urinary excretion rate of 8-iso-PGF2α 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-PGF2α 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-PGF2α were significantly higher (p<0.01) in patients with type 2 diabetes (mean±SD=482±206 pg/mg of creatinine) than in nondiabetic healthy subjects (275±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-PGF2α 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-PGF2α excretion rates [19]. Moreover, changes in 8-iso-PGF2α 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-PGF2α 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-PGF2α. 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
显著增加在糖尿病患者中。额外的增加发生在餐后。餐后血糖浓度降低可以由用预设置的bolus的快速胰岛素（Aspart）结果在平行降低在血糖和血清素的反应 [22]。这直接证据为一个在急性期中超过慢性期的证据。

虽然餐后血糖是主要的决定因素的血糖变异性，其他波动（尤其是下降的波动）必须被考虑在内。在最近的研究 [18]，我们有证据显示尿液代谢率的8-ISO-PF2α在血糖浓度和正相关，而有证据显示的血糖变异性被测量从血糖波动幅度的平均值（MAGE）。对于这个目的，患者的血糖资料是在48小时以上的连续血糖监测（CGM）收集的。MAGE的计算被进行由测量的算术平均的血糖波动幅度的平均值。这种关系在图2中（r=0.86, p<0.001）被观察到。在有和没有血糖波动的患者中，这种相关性明显是强于标准偏差（SD）在血糖浓度的平均值。这种关系是不等的（p=0.009）。它表明了在餐前血糖波动的急性效应。为了评估血糖波动，其他波动（尤其是下降的波动）应被考虑在内。即使MAGE的确定需要连续血糖监测，我们的观点是这个指数应该被使用。

图2：线性关系为24小时尿液代谢率的8-ISO-PF2α和Mean Amplitude of Glycemic Excursions (MAGE)在21例患者中，他们有2型糖尿病（从[18]），用JAMA的许可。

图3：模型被用来说明生理病理影响的差异，过度糖基化和氧化应激在糖尿病并发症的风险。用7%的HbA1c作为标准的SD的差距和急性血糖波动的贡献。考虑到两种类型的2型糖尿病患者，他们的SD的血糖波动的贡献不同。可能出现两个重大血糖波动和一个或两个主要下降的波动，而另一患者可能有血糖波动的贡献每天超过24小时。相比相似的SD的血糖波动的平均值，这些两个患者应该有非常不同的MAGE值和Kilpatrick的使用SD的血糖波动的贡献。它可能被用来评估血糖波动的急性效应。虽然MAGE的确定需要连续血糖监测，我们的观点是这个指数应该被使用。

图3：模型被用来说明生理病理影响的差异，过度糖基化和氧化应激在糖尿病并发症的风险。用7%的HbA1c作为标准的SD的差距和急性血糖波动的贡献。考虑到两种类型的2型糖尿病患者，他们的SD的血糖波动的贡献不同。可能出现两个重大血糖波动和一个或两个主要下降的波动，而另一患者可能有血糖波动的贡献每天超过24小时。相比相似的SD的血糖波动的平均值，这些两个患者应该有非常不同的MAGE值和Kilpatrick的使用SD的血糖波动的贡献。它可能被用来评估血糖波动的急性效应。虽然MAGE的确定需要连续血糖监测，我们的观点是这个指数应该被使用。

图3：模型被用来说明生理病理影响的差异，过度糖基化和氧化应激在糖尿病并发症的风险。用7%的HbA1c作为标准的SD的差距和急性血糖波动的贡献。考虑到两种类型的2型糖尿病患者，他们的SD的血糖波动的贡献不同。可能出现两个重大血糖波动和一个或两个主要下降的波动，而另一患者可能有血糖波动的贡献每天超过24小时。相比相似的SD的血糖波动的平均值，这些两个患者应该有非常不同的MAGE值和Kilpatrick的使用SD的血糖波动的贡献。它可能被用来评估血糖波动的急性效应。
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 (see 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).

References
5 Avignon A, Radaudeau A, Monnier L. Nonfasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes. Diabetes Care 1997; 20: 1822–1826
9 Sacks DB, Bruns DE, Goldstein DE, Mac Laren NK, Mac Donald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus (position statement). Diabetes Care 2002; 25: 750–766
10 Gorus F, Mathieu C, Gerlo E. How should HbA1c measurements be reported? Diabetologia 2006; 49: 7–10
14 Morrow JD, Hill KE, Burk RF, Namour TM, BadrKF, Roberts LJ. A series of prostaglandin F2-like compounds are produced in vivo in humans by non-cyclooxygenase free radical-catalyzed mechanism. Proc Natl Acad Sci USA 1991; 87: 9383–9387
18 Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, Colette C. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 2006; 295: 1681–1687