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 glycemic 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 κ 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

received 27.02.2007

accepted 25.04.2007

Bibliography

DOI 10.1055/s-2007-985157

Horm Metab Res 2007;

39: 683–686

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Stuttgart · New York

ISSN 0018-5043

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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

Fig. 1 Metabolic alterations activated by hyperglycemia in endothelial cells. Theory of oxidative stress for vascular damages in diabetes [4]. O₂^{•-}: Superoxide anion AGEs: advanced glycation end products PKC: Protein kinase C.

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 $\pm$ 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

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)".

References

- 1 Laakso L, Lehto S. Epidemiology of macrovascular disease in diabetes. *Diabetes Rev* 1997; 5: 294–315
- 2 The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329: 977–986
- 3 Stratton IM, Adler AI, Neil HAW, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR, the UK Prospective Diabetes Study Group. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; 321: 405–412
- 4 Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001; 414: 813–820
- 5 Avignon A, Radauceanu 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
- 6 El-Kebbi IM, Ziemer DC, Cook CB, Gallina DL, Barnes CS, Philipps LS. Utility of casual postprandial glucose levels in type 2 diabetes management. *Diabetes Care* 2004; 27: 335–339
- 7 Rohlfing CL, Wiedmeyer HS, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA1c. *Diabetes Care* 2002; 25: 275–278
- 8 American Diabetes Association. Standards of medical care in diabetes-2007. *Diabetes Care* 2007; 30 (Suppl 1): S4–S41
- 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: 750–786
- 10 Gorus F, Mathieu C, Gerlo E. How should HbA1c measurements be reported? *Diabetologia* 2006; 49: 7–10
- 11 Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, Schmechel H, Ziegelsch HJ, Lindner J. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Interventional Study, 11-year follow-up. *Diabetologia* 1996; 39: 1577–1583
- 12 Ceriello A, Hanefeld M, Leiter L, Monnier L, Moses A, Owens D, Tajima N, Tuomilehto J. Postprandial glucose regulation and diabetic complications. *Arch Int Med* 2004; 164: 2090–2095
- 13 Cavalot F, Petrelli A, Traversa M, Bonomo K, Fiora E, Conti M, Anfossi G, Costa G, Trovati M. Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus, particularly in women: lessons from the San Luigi Gonzaga Diabetes Study. *J Clin Endocrinol Metab* 2006; 91: 813–819
- 14 Morrow JD, Hill KE, Burk RF, Nammour TM, Badr KF, 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
- 15 Roberts LJ, Morrow JD. Measurement of F(2)-isoprostanes as an index of oxidative stress in vivo. *Free Radic Bio Med* 2000; 28: 505–513
- 16 Basu S. Metabolism of 8-iso-prostaglandin F_{2α}. *FEBS Lett* 1998; 428: 32–36
- 17 Davi G, Falco A, Patrono C. Lipid peroxidation in diabetes mellitus. *Antioxid Redox Signal* 2005; 7: 256–258
- 18 Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol J-P, 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
- 19 Davi G, Ciabattini G, Consoli A, Mezzetti A, Falco A, Santarone S, Pennese E, Vitacolonna E, Bucciarelli T, Cotantini F, Capani F, Patrono C. In vivo formation of 8-Iso-Prostaglandin F_{2α} and platelet activation in diabetes mellitus. Effects of improved metabolic control and vitamin E supplementation. *Circulation* 1999; 99: 224–229
- 20 Sampson MJ, Gopaul N, Davies IR, Hughes DA, Carrier MJ. Plasma F₂ Isoprostanes. Direct evidence of increased free radical damage during acute hyperglycemia in type 2 diabetes. *Diabetes Care* 2002; 25: 537–541
- 21 Ceriello A. Postprandial hyperglycemia and diabetes complications. Is it time to treat? *Diabetes* 2005; 54: 1–7
- 22 Ceriello A, Quagliaro L, Catone B, Pascon R, Piazzola M, Bais B, Marra G, Tonutti L, Taboga C, Motz E. Role of hyperglycemia in nitrotyrosine postprandial generation. *Diabetes Care* 2002; 25: 1439–1443
- 23 Kilpatrick ES, Rigby AS, Atkin SL. The effect of glucose variability on the risk of microvascular complications in type 1 diabetes. *Diabetes Care* 2006; 29: 1486–1490