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Review

Epigenetic signatures and vascular risk in type 2 diabetes: A clinical perspective

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ABSTRACT

Risk of diabetic complications continues to escalate overtime despite a multifactorial intervention with glucose-lowering drugs, anti-hypertensive agents and statins. In this perspective, a mechanisms-based therapeutic approach to vascular disease in diabetes represents a major challenge. Epigenetic signatures are emerging as important determinants of vascular disease in this setting. Methylation and acetylation of DNA and histones is a reversible process leading to dysregulation of oxidant and inflammatory genes such as mitochondrial adaptor $p66^{Shc}$ and transcription factor NF-kB p65. Epigenetic modifications associated with diabetes may contribute to the early identification of high risk individuals. Ongoing epigenomic analyses will be instrumental in identifying the epigenetic variations that are specifically associated with cardiovascular disease in patients with diabetes. Here, we describe a complex scenario of epigenetic changes and their putative link with diabetic vascular disease. Pharmacological reprogramming of diabetes-induced epigenetic signatures may be a promising option to dampen oxidative stress and inflammation, and thus prevent cardiovascular complications in this setting.

Contents

1. Residual vascular risk in patients with type 2 diabetes

Diabetes Mellitus is associated with an increased risk of micro- and macrovascular complications and an approximate two-fold greater risk of mortality as compared with the general population [1]. Such disease burden in patients with type 2 diabetes continues to escalate. The incidence of diabetes has tripled between 1980 and 2006. Furthermore, recent predictions of the World Health Organization indicate a current worldwide estimate of 436 million patients with diabetes [1,2]. Evidence suggest that the rates of obesity and diabetes may be levelling off in Europe and the United States but continue to increase in Asia and Africa, making clear the global nature of the problem [2,3]. Advances in therapy have led to significant reductions in morbidity and mortality for patients with diabetes. However, cardiovascular risk is far to be eradicated and mechanism-based therapeutic approaches are in high demand [4]. Recent trials have shown that residual cardiovascular risk is high in patients with diabetes [5]. Despite current guidelines emphasize

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the importance of controlling blood glucose levels and hypertension, it is still unclear whether an adequate control of these risk factors may effectively reduce vascular complications [5]. In the ADVANCE trial [6] (*Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation*) intensive glycemic control led to a 21% reduction in the risk of nephropathy which was explained by a 30% decrease in microalbuminuria. However, restoration of normoglycemia did not affect the risk of retinopathy and, most importantly, did not reduce the occurrence of cardiovascular events. Similarly, blood pressure control with the combination of perindopril and indapamide reduced renal events without changing the risk of other microvascular and macrovascular complications [7]. Moreover, the ACCORD trial (*Action to Control Cardiovascular Risk in Diabetes)* was prematurely stopped because of an excess of cardiovascular events in the intensive blood glucose control arm, creating uncertainty about the safety of achieving HbA_{1c} levels within the non diabetic range [8]. The STENO-2 trial showed that an intensive multifactorial intervention with glucose-lowering drugs, anti-hypertensive agents and statins was beneficial [9]. Unfortunately, such benefit is negligible when compared with the residual risk of microvascular complications observed during follow-up [9–11]. Indeed, over the 7.8 years treatment period, 51% of intensively treated patients developed or showed progression of diabetic retinophathy, diabetic nephropathy (25%) and peripheral neuropathy (55%) (Fig. 1) [10]. New microvascular complications developed and progressed during the extended follow-up period [9], despite an optimal control of blood pressure values (131 ± 13 and 73 ± 11 mmHg vs. 146 ± 18 vs 78 ± 10 mmHg) and $Hb1_{Ac}$ (7.9 ± 1.2% vs 9.0 ± 1.8%) in the intensive as compared with conventional treatment group, respectively. Statin treatment in diabetic patients has shown clear benefits. In the 5963 diabetic patients of the HPS trial (*Heart Protection Study*), simvastatin significantly reduced the occurrence of non-fatal myocardial infarction or death, stroke and revascularization [12]. These benefit were also observed with atorvastatin in the lipid lowering arm of the ASCOT-LLA (*Anglo-Scandinavian Cardiac Outcomes Trial*) and CARDS (*Collaborative Atorvastatin Diabetes Study*) trials [13,14]. However, the residual risk in statin trials remains elevated also due to the large prevalence of atherogenic dyslipidemia in these patients [15]. Indeed, high triglycerides and low HDL cholesterol are important determinants of increased vascular risk in type 2 diabetic patients. In this regards, the usefulness of other lipid modification agents, alone or in addition to statins is not established in patients with diabetes [1]. The FIELD trial (*Fenofibrate Intervention and Event Lowering in Diabetes*) which randomized 9795 patients with type 2 diabetes to fenofibrate or placebo was unable to show a reduction in the primary outcome of coronary events [16]. In the recent ACCORD Lipid trial [17], 5518 patients on simvastatin treatment were randomized to fenofibrate or placebo. After a mean follow-up of nearly 5 years, despite a significant improvement of atherogenic dyslipidemia in the fenofibrate arm, there was no difference in the rate of major fatal or non-fatal cardiovascular events, stroke or death. Accordingly, niacin has yet to find a clear treatment indication when statins are in use. Indeed, the AIM-HIGH trial (Atherothrombosis Intervention in Metabolic Syndrome with Low/High Triglycerides: Impact on Global Health Outcomes) did not show any significant benefit of niacin on cardiovascular events [18].

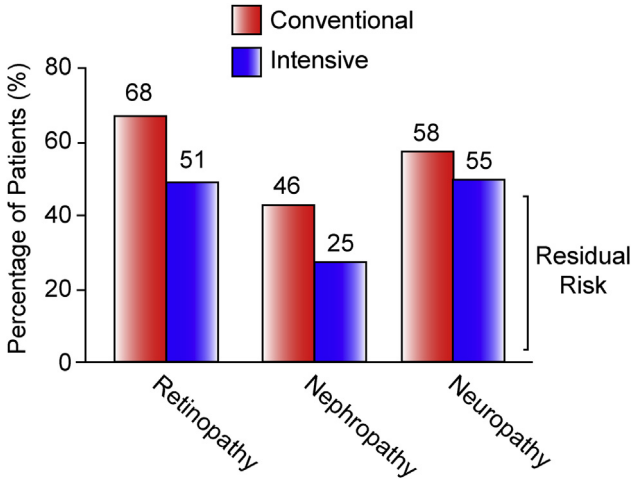

Fig. 1. Residual risk of retinopathy, nephropathy and neuropathy in patients with type 2 diabetes after conventional and intensive multifactorial intervention in the STENO-2 trial.

2. Understanding diabetic vascular disease

The results of recent clinical trials suggest that the constellation of risk factors associated with diabetes may have a legacy effect. Indeed, intensive control of glycemia, blood pressure and cholesterol may not be sufficient to abolish vascular risk in this setting [19,20].

In this perspective, understanding the mechanisms of vascular disease in diabetes represents a major challenge. In the diabetic vessels, hyperglycemia and insulin resistance activate signalling pathways favouring the unbalance between endothelial nitric oxide (NO) availability and accumulation of reactive oxygen species (ROS) [21]. Generation of ROS rapidly inactivates NO to form peroxynitrite ($ONOO^-$), a powerful oxidant triggering protein nitrosylation and dysfunction of key enzymes implicated in endothelial homeostasis. In patients with diabetes high glucose levels lead to excessive mitochondrial ROS generation and, in turn, to the activation of important biochemical pathways involved in the development of diabetic vascular complications [4,22]. Indeed, high oxidative stress levels lead to an increased synthesis of advanced glycation end products, activation of protein kinase C (PKC) and nuclear factor-kB (NF-kB) as well as polyol and hexosamine flux [4]. Given their importance for vascular disease, there is a growing interest in the regulation of endothelial redox state [23].

A recent study showed that PKC is highly activated in endothelial cells isolated from diabetic subjects and correlates with oxidative stress, impaired insulin signalling and, most importantly, endothelial dysfunction as assessed by flow-mediated vasodilation [24]. PKC is a cornerstone in the pathophysiology of diabetic vascular complications [25]. Activation of the enzyme by elevated diacylglycerol levels induces structural and functional changes in the vasculature including alterations of cellular permeability, inflammation, apoptosis and ROS generation [21]. In the diabetic endothelium PKC leads to increased ROS via activation of NADPH oxidase. Indeed, treatment with a PKCβ inhibitor blunts NADPH-dependent ROS generation [26]. More recently, it has been reported that glucose-induced activation of PKCβ2 isoform phosphorylates the adaptor $p66^{Shc}$ at Ser-36, favouring its localization to the mitochondria, oxidation of cytochrome *c* and subsequent ROS generation [27]. The mitochondrial adaptor $p66^{Shc}$ functions as a redox enzyme implicated in mitochondrial ROS generation and translation of oxidative signals into apoptosis [28]. Diabetic $p66^{Shc-/-}$ mice are protected against hyperglycemia-induced endothelial dysfunction and oxidative stress [29]. The relevance of $p66^{Shc}$ in the clinical setting of diabetes is supported by the notion that $p66^{Shc}$ gene expression is increased in peripheral blood mononuclear cells obtained from patients with type 2 diabetes and correlated with oxidative stress [30]. Despite these studies provided interesting insights into the role of $p66^{Shc}$ it remains unclear