Lower Plasma Creatinine and Urine Albumin in Individuals at Increased Risk of Type 2 Diabetes with Factor V Leiden Mutation

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The factor V Leiden (FVL) mutation is the most frequent genetic cause of venous thrombosis in Caucasians. However, protective effects have been suggested to balance the disadvantages. We have recently observed protective effects of FVL mutation on experimental diabetic nephropathy in mice as well as an association with reduced albuminuria in two human cohorts of diabetic patients. In the present study we aimed to reevaluate these findings in an independent, larger cohort of 1905 Caucasians at risk of developing type 2 diabetes and extend possible associations to earlier disease stages of nephropathy. Carriers of FVL mutation had a significantly lower urine albumin excretion \((P = 0.03)\) and tended to have lower plasma creatinine concentrations \((P = 0.07)\).

The difference in plasma creatinine concentrations was significant after adjustment for the influencing factors: age, gender, and lean body mass \((P = 0.048)\). These observations at a very early "disease" stage are an important extension of previous findings and suggest that modification of glomerular dysfunction by FVL mutation is relevant during very early stages of diabetic nephropathy. This makes the underlying mechanism an interesting therapeutic target and raises the question whether FVL mutation may also exert protective effects in other glomerulopathies.

1. Introduction

The factor V Leiden (FVL) mutation is the most frequent genetic cause of venous thrombosis in Caucasians. The high frequency of the FVL mutation implies associated positive effects which balance the negative sequels of the FVL mutation [1]. Indeed, several protective effects associated with the FVL mutation and potentially conveying a positive selection bias have been proposed [2]. Thus, the presence of the FVL mutation has been associated with lower peripartal blood loss and reduced mortality in sepsis [2, 3]. Obviously the amelioration of these acute and potentially deadly health threats mediates a positive selection pressure, maintaining the FVL mutation in the gene pool despite the potentially negative effects associated with venous thrombosis. We have recently proposed that the protective mechanism(s) selected in FVL carriers may not only be relevant in acute diseases, but also modulate the course of chronic diseases, which pose the prevailing health threats in modern times. Thus, low but sustained thrombin generation associated with the
presence of the FVL mutation results in larger but more stable plaques in atherosclerosis prone mice, indicating a partial benefit [4]. Furthermore, in a second mouse model we observed a protective effect of the FVL mutation on experimental diabetic nephropathy [5]. The potential mechanisms include prevention of glomerular endothelial cell and podocyte dysfunction as well as reduction of extracellular matrix accumulation [5]. These results were supported by an association of FVL mutation with reduced albuminuria in two human cohorts of 200 type 1 and 350 type 2 diabetic patients [5]. In the present study we aimed to reevaluate these findings in an independent, larger cohort and extend the possible associations to earlier disease stages of nephropathy.

2. Materials and Methods

We investigated 1905 Caucasians who participated in ongoing studies on the pathogenesis of type 2 diabetes [6]. A written consent was obtained from all participants and the local ethics committee approved the study protocol. Unlike in the previous report, which included patients with established diabetes mellitus, inclusion criterion for the current study was an elevated risk of developing type 2 diabetes, that is, family history of type 2 diabetes, body mass index (BMI) > 27 kg/m², diagnosis of impaired glucose tolerance, or previous diagnosis of gestational diabetes. All participants underwent an oral glucose tolerance test (OGTT). After an overnight fast, 75 g glucose was ingested at 8:00 a.m.; plasma glucose and insulin concentrations were determined after 0, 30, 60, 90, and 120 min. Insulin sensitivity was assessed from glucose and insulin values during the five-point OGTT with the Matsuda index [7]. In 800 subjects urine samples were available for albumin measurements.

The HPLC method (Tosoh A1c 2.2 HLC-723, Tokyo, Japan, and Tosoh G8 HPLC A1c analyzer) was used for HbA1c measurements, plasma glucose was determined using a bedside glucose analyzer (glucose-oxidase method; YSI, Yellow Springs Instruments), urine albumin was determined on the BN Prospec nephelometer, plasma creatinine was measured enzymatically on the ADVIA 1800 clinical chemistry analyzer, and insulin was analyzed using the ADVIA Centaur XP immunoassay system (all from Siemens Healthcare Diagnostics, Eschborn, Germany). Lean body mass was measured by bioelectrical impedance (BIA-101; RJL Systems, Detroit). The Sequenom MassARRAY platform (Sequenom, San Diego) was used to genotype for FVL mutation (rs6025). For statistical analyses nonnormally distributed parameters were log transformed. Statistical analyses were conducted with JMP 8.0 (SAS Institute, Cary, NC).

3. Results and Discussion

Participant characteristics are supplied in Table 1. Based on a 75 g oral glucose tolerance test and/or HbA1c measurements performed at inclusion, 105 subjects were newly diagnosed with diabetes according to the criteria of the American Diabetes Association [8]. The frequency of newly diagnosed diabetes mellitus did not differ between FVL-negative and -positive individuals. To evaluate the impact of the FVL mutation on albuminuria and plasma creatinine a dominant model was used since only one homozygous FVL carrier was identified.

FVL carriers showed no significant differences in metabolic traits or blood pressure (Table 1). Carriers of FVL mutation had a significantly lower urine albumin excretion ($P = 0.03$) (Table 1). Even when the subjects with newly diagnosed diabetes were excluded, this trend was still present ($P =$...
diseases. For diabetic nephropathy and potentially other glomerular diseases, targeted answers may identify novel therapeutic targets. Hence, further studies evaluating the nephroprotective effect in other glomerulopathies. Providing answers to these questions may identify novel therapeutic targets for diabetic nephropathy and potentially other glomerular diseases.

Conflict of Interests

The authors state that they have no conflict of interests.

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