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The 20210 G to A Prothrombin Polymorphism and Late Complications in Type 1 Diabetes Mellitus

Dear Sir,

The hypercoaguable state in diabetes mellitus and its association with late complications is discussed widely. Fibrinogen, Factor VII, Protein C and vWF showed significant positive correlation with the urinary albumin excretion rate (1). Intravascular thrombin generation, hyperactive platelets and reduced fibrinolytic capacity are also reflecting a prethrombotic situation in diabetes (2). This may relate to changes in the microcirculation resulting in diabetic nephropathy or retinopathy. The clinical appearance and progression of late complications of diabetes can only in part be explained by the quality of metabolic control. Ruiz reviewed the influence of the genetic factors on late complications in diabetes mellitus (3). He suggests that candidate genes affecting lipid metabolism, haemodynamics as well as the coagulation system might explain the excess risk for development of late diabetic complications not explained on the basis of hyperglycemia alone. The heterozygous 20210 G to A prothrombin polymorphism has been described as a risk factor for deep venous thrombosis, arterial disease and myocardial infarction in non-diabetic patients. This genetic variant is associated with elevated levels of prothrombin in plasma (4, 5). Apart from the known effect on macrovascular disease, elevated prothrombin concentrations might have an influence on the appearance or progression of microangiopathy in diabetes mellitus.

We screened 384 type 1 diabetic patients for the 20210 G to A prothrombin polymorphism using PCR amplification with the forward primer 5'-TGGGAAATATGGCTTCTACA-3' and the reverse primer 5'-CACTGGGAGCATTGAAGCT-3' followed by Hind III Restriction Analysis as described by Ferraresi et al. (6). The question was whether there is an association of the genetic prothrombin variant with late complications in type 1 diabetes mellitus. Patient data were available for duration of diabetes, nephropathy (persistent albuminuria >20 mg/l), retinopathy (diagnosis established by ophthalmologists) and cardiac events (diagnosed by stress ECG, a history of documented myocardial infarction or of persistent angina pectoris).

In 9 out of the 384 diabetic patients the 20210 A variant was detected. This results in a prevalence of 2.34 percent and is in line with earlier studies in which the carriership ranged from 0.7 to 4.0 percent in different groups representing the general population (7).

Groups with and without the 20210 G to A polymorphism were compared concerning the presence of diabetic complications (Table 1). Nephropathy was found in 3 out of the 9 (33%) carriers of the 20210 A-genotype and in 136 out of 375 (36%) patients showing the normal G-genotype [odds ratio (OR) = 1.14, 95% confidence interval (CI) 0.28-4.69, Fisher's Exact (FE) p = 1.0]. The results for retinopathy (OR = 2.87, 95% CI 0.7498-10.986, FE p = 0.172) and cardiac events (OR = 1.214, 95% CI 0.150-9.838, FE p = 0.592) also gave no significant correlation. Five (55%) out of the 9 carriers of the 20210 A-genotype showed no late complications at all, while 115 (31%) of the non-carriers had no late complications (OR = 0.35, 95% CI 0.10-1.27, FE p = 0.145). Similar results were obtained when only patients with a diabetes duration of over 10 years were analysed. Based on a calculation of the OR and their CI it is unlikely that even a tenfold larger study population would change the outcome.

Table 1 Late complications in type 1 diabetic patients with and without the 20210 G to A prothrombin polymorphism

	Nephropathy	Retinopathy	Cardiac Events	No late complications
20210 G - genotype n = 375	136 36%	221 59%	35 9%	115 31%
20210 A - variant n = 9	3 33%	3 33%	1 11%	5 55%

In summary: The 20210 G to A prothrombin variant does not seem to have a major influence on the occurrence of coronary heart disease, nephropathy or retinopathy in type I diabetic patients.

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