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Anticardiolipin and anti-β2 glycoprotein I antibody concentrations in patients with type 2 diabetes mellitus

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Abstract

Anticardiolipin and anti-β2 glycoprotein I antibodies are associated with an increased tendency to thrombosis by various mechanisms. This study aimed to evaluate the association between micro and macrovascular complications of diabetes and anticardiolipin and anti-β2 glycoprotein I antibodies. Forty-six patients with type 2 diabetes mellitus (T2DM) were studied. Twenty-one patients had coronary artery disease as a macrovascular complication. Twenty-five age and sex matched healthy subjects formed a control group. Anticardiolipin IgM, IgG, anti-β2 glycoprotein IgM and IgG antibody levels were studied in both patient and control groups. Diabetic patients with ischaemic heart disease had significantly higher titres of anticardiolipin IgG antibody than patients without ischaemic heart disease ($P < 0.001$). However, none of these patients had an anticardiolipin IgG antibody level higher than 20 GPL, which is accepted as a clinically significant value, so this association may not be clinically important. There was no association with the microvascular complications. There was also no significant association between anti-β2 glycoprotein I antibodies in type 2 diabetic patients and micro and macrovascular complications. Anticardiolipin and anti-β2 glycoprotein I antibodies do not have a major role in the pathogenesis of diabetic complications in type 2 diabetic patients. Prospective studies of large populations are needed to explore this association further.

Keywords: Type 2 diabetes mellitus; Anticardiolipin antibody; Anti-β2 glycoprotein I antibody; Coronary artery disease

1. Introduction

The results of epidemiological studies indicate that the incidence of type 2 diabetes mellitus is doubling every 10 years [1]. Type 2 diabetes mellitus (T2DM) is also associated with a 3–4 times greater risk of

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coronary artery disease (CAD) [2]. As obesity, hypertension, dyslipidemia or genetic tendency are insufficient to explain this increase in CAD risk, research is focusing on investigating new risk factors.

There are significant changes in the hemostatic system of diabetic patients. There may be an activation of the intrinsic coagulation system, decreased fibrinolytic activity or alterations in platelet function in diabetic patients [3]. A procoagulant state has been found to exist in diabetes mellitus [4,5]. It has been suggested that these alterations in the hemostatic system may also play a role in the development of micro and especially macrovascular complications [6–8].

Vascular damage and endothelial cell dysfunction occur early in the course of diabetic microangiopathy [9]. Autoantibodies to endothelial cell surface antigens initiate vascular injury [10]. Anti-phospholipids are autoantibodies that target one or more phospholipids or phospholipid binding proteins present on cellular membranes [11]. One member of the anti-phospholipid antibody family, anticardiolipin antibodies (ACA), bind cardiolipin in the presence of their cofactor β2-glycoprotein I (β2 GPI) [12–13]. β2 GPI binds to negatively charged phospholipids [14] and inhibits the coagulation cascade and platelet function [15]. There are several mechanisms where by ACA and anti-β2 GPI (Aβ2GPI) antibodies may cause or promote ischemia and thrombosis including functional alterations of protein C [16,17], impaired fibrinolysis [18], altered antithrombin III level [19], inhibition of prostacyclin (PGI2) activity [20], platelet aggregability [21] and complement activation [22].

This study was designed to evaluate the association between the micro and macrovascular complications and the frequency and titre of anticardiolipin and anti-β2-glycoprotein I antibodies in diabetic patients with and without coronary artery disease and in a group of healthy controls.

2. Method

The study involved 46 patients with type 2 diabetes mellitus 23 men, 23 women; mean age: 59.8 ± 10 years and 25 healthy control subjects (12 men, 13 women; 57.7 ± 6.7 years). The study protocol was approved by the Ethics Committee for Human Studies of Kocaeli University Hospital, Turkey. Informed written consent was obtained from all subjects after explanation of the nature, purpose and potential risks of the study. The exclusion criteria were: uncontrolled hypertension (blood pressure $\geq$180/100 mmHg), a history of acute coronary syndrome within 3 months, auto-immune disease, infectious disease, malignancies, liver or kidney diseases (serum creatinine $\geq$117 μmol/L), proteinuria (dipstick positive proteinuria or albumin excretion rate $\geq$300 mg/24 h), any known acute or chronic disease other than diabetes, cigarette smoking and chronic alcohol consumption.

Twenty-one patients (13 men, 8 women) who had a history of acute myocardial infarction (AMI), coronary artery by-pass grafting (CABG), percutaneous transluminal angioplasty (PTCA) or angiographically documented CAD were considered as CAD(+). All other 25 patients (10 men, 15 women) had a normal 12 lead ECG and no history of AMI, angina pectoris (as defined by the Rose questionnaire), CABG or PTCA. A maximal treadmill exercise test according to Bruce protocol was used for screening, with exercise being continued until at least 90% of the maximal predicted heart rate for age was reached. The results of the test were evaluated by cardiologists and only patients with a maximal negative exercise test were included in the study as CAD(−) patient group. We also studied 25 age and sex matched non-diabetic control subjects. All were healthy and without any known vascular disease. Biochemical analyses, 12 lead ECG and maximal treadmill exercise test results were normal in this group.

An experienced ophthalmologist performed fundoscopic examinations by ophthalmoscopy and/or biomicroscopy. A neurological examination was performed by a neurologist and if necessary electromyelography was obtained. Three of the diabetic patients (6.5%) were controlled by diet only, 25 patients (56.5%) were receiving oral hypoglycaemic therapy, 15 patients (32.6%) were receiving insulin and 3 patients (6.5%) were receiving combined oral hypoglycaemic agents and insulin therapy. Thirty-six diabetic patients (78.2%) took anti-hypertensive therapy and 23 patients (50%) were using a cholesterol-lowering agent. Seventeen of the diabetic patients (36.9%) had established retinopathy, 30 patients (65.2%) had neuropathy and 13 patients (28.2%) had microalbuminuria. Twenty-one patients (45.6%) had two or more complications.