Anticardiolipin antibodies do not mediate macrovascular complications of type 2 diabetes

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ABSTRACT

The relationship of anticardiolipin antibodies (ACA), markers of the antiphospholipid syndrome, with vascular complications of diabetes mellitus is polemic. This cross-sectional study assessed the frequency of IgG, IgM, and IgA ACA in type 2 diabetics with and without history of vascular events for the last 5 years, and in healthy controls. ACA were detected by enzyme immunoassay. A total of 73 type 2 diabetics (33 with history of vascular events) and 54 healthy controls were tested. Most diabetics were female (p = 0.003), and older than controls (p < 0.001). Mean duration of disease was 10 years. The prevalence of a positive ACA test was 7.4% in controls and 9.5% in diabetics (p = 0.910).

Comparison of healthy controls and diabetics with or without history of macrovasculopathy, after adjusting for gender and age, showed no significant differences as to the presence of ACA (p > 0.09). ACA positivity rates were also similar when diabetics with and without history of vasculopathy were compared (p > 0.47). After adjusting for gender, age, hypertension, and smoking status, a weak but statistically insignificant association between IgM ACA and diabetes with vasculopathy was found (adjusted OR 2.7; 95% CI 0.2 - 34.2; p = 0.441). Overall, levels of IgG (r = 0.25; p = 0.005) and IgM (r = 0.23; p = 0.010) ACA were associated with increasing age. In short, the frequency of a positive ACA test in type 2 diabetics (with or without previous macrovasculopathy) was not significant as compared to healthy controls. There was no association of ACA with vascular events in patients with type 2 diabetes.

Keywords: Anticardiolipin Antibodies; Type 2 Diabetes Mellitus; Myocardial Infarction; Cerebrovascular Infarction

Anticardiolipin antibodies (ACA), as well as the lupus anticoagulant and antibodies to beta2-glycoprotein (beta2-gpl), are classical markers of the antiphospholipid syndrome (APS) [1]. The relationship of ACA with vascular complications of diabetes is rather unclear.

This cross-sectional study assessed the frequency of IgG, IgM, and IgA ACA in type 2 diabetics [2] with and without history of macrovascular events (myocardial and/or cerebral infarction) for the last 5 years, and in healthy controls. ACA were detected by enzyme immunoassay (ORGENTEC Diagnostika GmbH—Anti-Cardiolipin). Titers were considered as positive when above 10 GPL for IgG ACA, 10 MPL for IgM ACA, and 7 units for IgA ACA [3]. The study was approved by the local ethics committee.

Chi-square analysis were used for comparison of categorical variables, and the Student’s t test was used for comparison of continuous variables. A level of 5% (p < 0.05) was considered significant. Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated for univariate analysis. Logistic regression with 95% CI was performed to adjust the effects of gender, age, hypertension [4], and current smoking [5] in the OR. When needed, Agresti correction was employed to obtain non-adjusted OR. To co-relate quantitative variables, the Pearson coefficient was utilized. All analyses used procedures of the SPSS for Windows, version 11.5, Chicago, IL.

A total of 73 type 2 diabetics (33 with history of vascular events) and 54 healthy controls were tested. Most diabetics were female (p = 0.003), and older than controls (p < 0.001). Mean duration of disease was 10 years. The prevalence of a positive ACA test (any isotype) was 7.4% in controls and 9.5% in diabetics (p = 0.910).

Comparison of healthy controls and diabetics with or without history of macrovasculopathy, after adjusting for gender and age, showed no significant differences in ACA positivity (p > 0.09). ACA frequency rates were
also similar when diabetics with and without recent history of vascular events were compared (p > 0.47).

Females significantly predominated in diabetics without vasculopathy as compared to diabetics with previous vascular events. After adjusting for gender, age, hypertension, and smoking status, a weak but statistically insignificant association of IgM ACA and diabetics with vasculopathy was found. These data can be seen in Table 1.

Overall, levels of IgG (r = 0.25; p = 0.005) and IgM (r = 0.23; p = 0.010) ACA related to increasing age.

Type 2 diabetes comprise an independent risk factor for atherosclerotic disease. The etiopathogenesis of the micro and macrovascular complications of type 2 diabetics are not fully understood. Macrovascular obstructions affecting the coronary and cerebral arteries are the main cause of mortality in diabetics [6,7]. ACA and endothelial dysfunction might be synergistic for vasculopathy in insulin-dependent diabetes [8].

For the last decade, we have documented a defined association of IgA anti-beta2-gpI antibodies with cerebral ischemia [9], coronary disease [10], carotid disease [11], and peripheral artery disease [12]. Only in one of these studies [12], IgA ACA associated with the outcome. More recently, we demonstrated an association of the IgA anti-beta2-gpI antibody with metabolic syndrome; once more, the ACA prevalence was low [13]. We therefore infer that ACA do not relate to acute or chronic atherosclerotic disease, nor to metabolic syndrome. The relationship of ACA with type 2 diabetes and diabetic vasculopathy had not been so far evaluated in our research center.

In the current study, ACA positivity was similar in controls and type 2 diabetics (7.4% and 9.5%, respectively). There was no statistical difference as to the ACA prevalence in the two groups. The frequency of IgA ACA in our healthy controls (5.6%) was quite impressive, and this is an issue to be further addressed. Differently from our data, Hendra et al reported a significant frequency of IgG ACA in diabetics with or without coronary disease [14]. Gargiulo et al. described elevated levels of IgA anti-phosphatidylethanolamine, but not ACA, in type 1 or 2 diabetics as compared to controls [15]. Similarly to our findings, the prevalence of ACA in non-complicated diabetes was irrelevant in another previous study [16].

When our two groups of diabetics were compared, a weak association of IgM ACA with complicated diabetes was suggested by the adjusted OR, but this finding was statistically insignificant. Of interest, the frequency of ACA in type 1 or 2 diabetics with macroangiopathy and nephropathy was higher as compared to patients with non-complicated or well-controlled disease [16]. Another group of authors reported, in 1989, an increased positivity for IgG and IgA ACA in type 2 diabetics with macrovascular disease [17]. As seen, data concerning prevalence of ACA in diabetics are incongruent.

We herein documented a significant correlation of IgG and IgM ACA with increasing age. This is in accordance with the study by Fields et al., whereby IgG and IgM ACA were detected in 12% of the healthy elderly and in 2% of younger adults [18]. As opposed to that, ACA positivity in the elderly was reported to be insignificant and similar to younger populations [19].

In general terms, our results pointed to a insignificant positivity for ACA in type 2 diabetes. A low prevalence of ACA was seen in both complicated or non-complicated diabetic populations. These data, although limited by the small sample, do not favour a pathogenetic role for ACA in type 2 diabetes and diabetic macrovasculopathy. Our findings are corroborated by those reported by Tarkun et al., which desvinculated ACA from vascular complications of type 2 diabetes [20].

In summary, the frequency of a positive ACA test in type 2 diabetes (complicated or not by macrovasculo-

<table>
<thead>
<tr>
<th>Clinical variables and frequency of anticardiolipin antibodies (ACA) in both group of diabetics.</th>
<th>Diabetics with vascular event n = 33</th>
<th>Diabetics without vascular event n = 40</th>
<th>p</th>
<th>Non-adjusted OR (95% CI)</th>
<th>Adjusted OR*** (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) †</td>
<td>68.2 (±10.65)</td>
<td>65.9 (±9.1)</td>
<td>0.331‡</td>
<td>1.0 (0.9 - 1.1)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Females</td>
<td>16 (48.5%)</td>
<td>33 (82.5%)</td>
<td>0.005*</td>
<td>0.2 (0.1 - 0.6)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29 (87.9%)</td>
<td>33 (82.5%)</td>
<td>0.744*</td>
<td>1.5 (0.4 - 5.8)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>History of smoking</td>
<td>8 (24.2%)</td>
<td>11 (27.5%)</td>
<td>0.962*</td>
<td>0.8 (0.3 - 2.4)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>IgG ACA positive</td>
<td>0</td>
<td>1 (2.5%)</td>
<td>0.999*</td>
<td>0.6 (0.05 - 6.8)**</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>IgM ACA positive</td>
<td>3 (9.1%)</td>
<td>1 (2.5%)</td>
<td>0.475*</td>
<td>3.9 (0.4 - 39.4)</td>
<td>2.7 (0.2 - 34.2)</td>
<td>0.441</td>
</tr>
<tr>
<td>IgA ACA positive</td>
<td>0</td>
<td>2 (5.0%)</td>
<td>0.560*</td>
<td>0.4 (0.04 - 3.9)**</td>
<td>NC</td>
<td>NC</td>
</tr>
</tbody>
</table>

n: Sample number; †SD: Standard deviation; †Student t test; *Chi-square test; **Agresti correction; ***Adjustment for sex, age, hypertension and smoking; NC: Non-calculated.
pathy) did not significantly differ from controls. There was no association of ACA with vascular events in patients with type 2 diabetes. ACA do not appear to be relevant in the pathogenesis of vascular complications of type 2 diabetes.

REFERENCES


