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Research Article

Cardiolipin Antibodies in Biopsy-defined Adult Celiac Disease

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Abstract

Cardiolipin antibodies have been considered to be a hallmark or marker of the antiphospholipid syndrome, a disorder associated with an increased risk of cerebrovascular events and pregnancy loss. Prior studies have shown increased cardiolipin antibodies in celiac disease, and even higher in some studies of treated celiac disease with a gluten-free diet. Still, limited clinical follow-up in these studies did not permit exploration of an increased risk of cardiovascular events. This study explored this paradigm in 28 celiac disease patients, treated with a gluten-free diet, defined by histopathological evidence of normalization of small intestinal mucosa. Here, in celiacs on a lifelong gluten-free diet, no increased cardiovascular risk, as reflected in clinically evident thrombotic or embolic events, was identified despite follow-up for up to 34 years. Cardiolipin antibodies in gluten-free diet treated celiac disease could represent a marker of risk, but this was defined here despite long-term clinical follow-up over many decades.

Keywords: Anti-cardiolipin Antibodies; Celiac Disease; Antiphospholipid Syndrome; IgG and IgM Antibodies; Hypercoagulability in Celiac Disease

The antiphospholipid syndrome was first used to note the clinical association between antiphospholipid antibodies and a hypercoagulability state [1,2]. Over the past 20 years, terminology used to further define the disorder has been an evolving process. The initial antiphospholipid antibody was detected in syphilis patients, reported in 1906 [3]. The antibody was complement-fixing, mitochondrial in origin and reacted with bovine heart extracts [3]. In the past, thrombotic events or a complication during pregnancy with pregnancy loss were often associated with the antiphospholipid syndrome [1,2]. More recent information has led to the conclusion that specificity of anticardiolipin antibodies for the antiphospholipid syndrome is higher for the IgG than the IgM isotope [4], but there may be no definitive association with any specific clinical manifestation. Still, some believe their detection in serum is a risk factor for a thrombotic event but few studies have prospectively evaluated risk over a long period.

Antiphospholipid antibodies have been described in approximately 1 to 5% of young healthy controls and this percentage increases with aging and co-existent chronic disorders. In systemic lupus erythematosus (SLE), up to 30% may be positive for anticardiolipin antibodies. However, most with positive antibodies apparently have no clinical consequences, even if with repeated sampling over many weeks [1]. In long-term studies over 7 years, up to 30% of SLE patients lack any clinical evidence of an antiphospholipid syndrome [5] while prospective studies have reported an association between antiphospholipid antibodies and the initial episode of venous thrombosis [6], initial myocardial infarction [7] and recurrent stroke [8].

Celiac disease is an immune-mediated intestinal disorder that may have different circulating antibodies, eg., anti-tissue transglutaminase (tTG). In prior studies, cardiolipin antibodies

were recorded in children diagnosed with celiac disease (14%) [9], as in a later report from the same group compared to a control population [10]. In view of potential cardiovascular risk related to the presence of cardiolipin antibodies, long-term follow-up in treated celiacs was done here. A cohort of biopsy-defined adult celiacs positive for cardiolipin antibodies was followed, some for more than 20 years. No cardiovascular effects, including those specifically reported in the antiphospholipid syndrome, were detected.

Patients and Methods

A cohort of 28 celiac disease patients were randomly selected for this cardiolipin antibodies evaluation from a previously reported population of 182 biopsy-defined patients (122 females, 67%) [11]. As previously noted, this was a symptomatic population, initially referred from 1982 to 2011 and, after initial biopsy, treated with a strict gluten-free diet alone. No patient here was detected after serological screening (e.g., tissue transglutaminase antibodies). Diet compliance was regularly monitored with a trained dietitian. Up to 90% of all patients showed a mucosal biopsy response or complete healing on a second or later additional biopsy. Biopsies were reviewed by experienced endoscopic biopsy pathologists along with the author investigator. Most patients required at least 1 year to satisfactorily respond, although complete mucosal healing was still possible within 6 months. No patient in this celiac population was treated with corticosteroids or immunosuppressant medications. Added details of the overall study population have been described elsewhere [11].

In the 28 treated celiacs with measured cardiolipin antibodies, clinical follow-up with repeat endoscopic mucosal biopsy was done up to 34 years after completion of initial biopsies (mean, 15.0 years) and serological studies. Serum samples were collected and analyzed blinded to patient diagnosis. Antibody assays was performed as described elsewhere for IgG and IgM [12].

Biopsy results were classified according to the severity of architectural changes with differing degrees of villous atrophy: "flattening" or blunting (Marsh or Marsh 2, respectively), epithelial lymphocytosis with little or no architectural alteration (Marsh 1) and normal mucosa with intra-epithelial lymphocyte counts of less than 25 per 100 enterocytes (Marsh 0) [13-16]. In this celiac disease cohort, all patients had severe flattening of the mucosa (Marsh 3) on the initial biopsy. After gluten-free diet treatment, all patients showed a histopathological response in the mucosal architecture, even though 2 patients (patient 4, male; and patient 25, female) still had some persistently abnormal architectural changes. Although some had some intra-epithelial lymphocytosis, 7 patients had histopathological evidence of complete mucosal healing in subsequent biopsies.

Results

Table 1 shows the ages and sex of each patient, along with duration of follow-up, biopsy results after gluten-free diet treatment as well as IgG and IgM cardiolipin antibody measurements. Ages ranged from 15 to 65 years at the time of initial biopsy and a similar percentage to the overall group were female (18 of 28, or 67%). Initial biopsies showed severe "flattening" of the mucosa in all 28 patients. Subsequent biopsies showed improved architecture in all 28 celiac patients, but in 2, the architectural changes showed only partial improvement. A total of 7 of these 28 celiac patients had complete healing of mucosal biopsies in response to a gluten-free diet.

	Age/Sex	Duration**	Biopsies	IgG	IgM
1	65/F	12	GFD Response	11.6	13.6
2	50/F	20	GFD Response	17.6	0.5
3	62/F	7	GFD Response	15.8	12.2
4	54/M	10	GFD Response***	13.1	2.9
5	61/F	21	GFD Response	14.9	2.2
6	44/M	28	GFD Response	5.2	1.6
7	25/F	14	GFD Response	4.3	3.3
8	54/M	6	GFD Response	4.0	3.7
9	28/M	6	GFD Response	2.2	2.7
10	40/M	10	GFD Response	3.4	2.6
11	55/F	12	Normal with GFD	3.3	0.8
12	43/M	20	Normal with GFD	12.2	6.0
13	51/M	12	GFD Response	11.3	2 .9
14	28/F	12	GFD Response	11.0	5.0

15	39/M	15	GFD Response	11.7	11.1
16	42/F	10	GFD Response	6.1	11.9
17	41/F	10	GFD Response	4.6	3.7
18	22/F	30	Normal with GFD	12.1	3.1
19	37/F	34	Normal with GFD	3.5	2.5
20	62/F	16	Normal with GFD	7.0	0.6
21	65/F	12	Normal with GFD	1.4	12.2
22	50/M	14	GFD Response	4.2	4.6
23	52/M	13	GFD Response	7.1	3.6
24	18/F	12	GFD Response	8.2	2.9
25	33/F	12	GFD Response***	9.9	2.6
26	26/F	30	GFD Response	13.1	0.4
27	29/F	15	GFD Response	6.6	2.3
28	26/F	6	GFD Response	13.4	0.9

Table 1: Celiac Disease and Cardiolipin Antibodies*.

*Normal range: IgG, 10.0-12.0; IgM, 0-10.0. Numbers in boldface, outside normal range. **Duration of follow-up, years. GFD, gluten-free diet, either histological response on repeated biopsy, or completely normal after GFD diet. ***Only partial architectural response.

In this celiac cohort of 28 patients, cardiolipin antibodies were present in all, with 12 patients having IgG and/or IgM levels above normal laboratory ranges. Of these, only 1 (patient 3, female) had increases for both IgG and IgM types of antibodies. In this celiac cohort, 8 (6 females, 2 males) of 28, or 28%, had increased levels of IgG antibodies and 5 (4 females, 1 male) of 28, or 18%, had increased levels of IgM antibodies. No significant differences in age at diagnosis, duration of treatment with a gluten-free diet or biopsy results were observed with either IgG or IgM antibody results.

None of the 28 patients suffered any subsequent vascular thrombotic or embolic event. No patient had a cerebrovascular or cardiac abnormality. No patient suffered loss of a pregnancy. At the time of last clinic follow-up, all patients, regardless of cardiolipin IgG or IgM antibody status, were well suggesting no evident increased cardiovascular risk.

Discussion and Conclusion

The antiphospholipid syndrome in celiac disease has been recorded, occasionally with other autoimmune disorders, including systemic lupus erythematosus [17,18]. Because of reported thromboembolic events, venous thrombosis and pregnancy losses, it was suggested that hypercoaguable autoimmune diseases may occur in celiac disease and may not be coincidental [19]. As a result, some have further explored the possible linkage with an anti-phospholipid syndrome in celiac disease. In an early study of 57 patients with antiphospholipid syndrome, celiac disease antibodies (i.e., anti-endomysial antibodies) were detected in 14% compared to 2% of 171 healthy controls [20]. Later studies in celiac disease patients showed increased antiphospholipid antibodies compared to control non-celiac populations [21-23]. Karoui., *et al.* [21] evaluated 50 celiac patients and 50 healthy controls. IgG, but not IgM, cardiolipin antibodies were found in only 2 celiacs and 1 control patient. Moreover, 2 patients with celiac disease had clinical features of apparent antiphospholipid syndrome but were cardiolipin antibody-negative. In a subsequent study, Mankai., *et al.* compared untreated celiac patients to healthy blood donors [22]. In this study, a significantly higher number, 12 of 63 (or, 19%) of celiac patients compared to 2 of 40 (or, 5%) healthy blood donors had cardiolipin or anti-beta2-glycoprotein I antibodies ($p = 0.04$). Although antibodies were often present in celiac disease patients, their clinical significance was not defined. In a large Finnish study of 179 biopsy-defined celiacs [23] showed that cardiolipin antibody levels, specifically IgG types, were higher in celiacs compared to controls and also higher in treated compared to untreated patients suggesting that increased cardiolipin antibodies were not gluten-dependent. Further studies appeared warranted to the investigators because of the apparent increased cardiovascular risk of cardiolipin antibodies.

In the present report, all 28 celiacs were treated with a gluten-free diet and showed a positive histopathological treatment response. However, the duration of long-term follow-up in this study up to 34 years demonstrated that there was no increase in risk of any cardiovascular event associated with the presence of either IgG or IgM cardiolipin antibodies.

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