Serum lipid levels in Sjögren’s syndrome

B. M. Lodde1,2, V. Sankar1*, M. R. Kok1,2, R. A. Leakan1, P. P. Tak2 and S. R. Pillemer1†

Objectives. Altered lipid levels may occur in autoimmune diseases, for example low cholesterol levels have been described in rheumatoid arthritis (RA). Serum lipid profiles in patients with Sjögren’s syndrome (SS) have not been investigated. We hypothesized decreased lipid levels in SS patients and an inverse relationship with disease activity.

Methods. Serum lipid levels [total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides] and additional data regarding disease measures (clinical immunology parameters, focus score from labial salivary gland biopsy, salivary flow and ophthalmological measures) were available for 46 primary SS patients and 12 xerostomic controls.

Results. Significant differences between SS patients and controls means (s.d.) were seen for HDL (P = 0.04) and total cholesterol (P = 0.02). LDL (P = 0.12) and triglyceride (P = 0.08) levels were not different. In SS patients, but not in controls, total cholesterol (P = 0.003) and HDL cholesterol (P = 0.003) predicted immunoglobulin G levels. Anti-SSA antibodies were related to a lower total cholesterol (P = 0.02) and anti-SSB antibodies to a lower HDL cholesterol level (P = 0.0497).

Conclusions. Significant differences were seen in serum lipid levels of primary SS patients and these were associated with serological measures of inflammation. Our results are comparable to earlier findings in RA patients and raise questions related to adverse cardiovascular consequences in SS.

Key words: Sjögren’s syndrome, Cholesterol, HDL, Inflammation, Cardiovascular disease.

Altered lipid levels have been reported in patients with active autoimmune disorders. For example, several groups have reported on various changes in lipid levels in rheumatoid arthritis (RA) patients [1–9]. A decreased level of high-density lipoprotein (HDL) cholesterol with inflammation seems to be a consistent finding. Additionally, a higher risk of atherosclerosis and cardiovascular mortality is seen in RA [10]. Increased lipid levels were seen in patients with systemic lupus erythematosus (SLE), where disease activity may be related to increases in levels of triglyceride and very low-density lipoprotein (VLDL) cholesterol, while HDL cholesterol was decreased. Inflammatory proteins and autoantibodies in SLE are possibly associated with an increased risk of cardiovascular disease [11, 12].

Sjögren’s syndrome (SS) is a systemic autoimmune disease mainly characterized by ocular and oral dryness (keratoconjunctivitis sicca and xerostomia). There is a distinction between primary SS and secondary SS, the latter developing in the presence of other connective tissue diseases, like SLE or RA [13]. Sjögren’s syndrome occurs predominantly in peri- and post-menopausal women. Detailed investigations of serum lipid profiles or the prevalence of atherosclerosis in patients with SS have yet to be performed. One of the few studies related to this topic has concentrated on the distinction between pseudo-Sjögren’s syndrome in patients with hyperlipidaemia and genuine SS using magnetic resonance imaging (MRI) [14].

In the present study, we sought to compare serum lipid profiles in patients with primary SS and non-SS xerostomic patients. We hypothesized that serum lipid levels in SS patients would be lower than those in xerostomic controls. Additionally, we investigated the relationship between serum lipid levels and measures of inflammatory disease activity in patients with SS. Based on reports for other autoimmune diseases, we postulated an inverse relationship for such measures with lipid levels.

Patients and methods

We abstracted data from our database of SS patients in the National Institute of Dental and Craniofacial Research (NIDCR) Sjögren’s Syndrome Clinic. The database contains uniform and systematically collected information of all patients and is referral based. The selected patients were participants in research protocols, which had been approved by the Institutional Review Board of the NIDCR at the National Institutes of Health. The subjects’ written consent was obtained according to the Declaration of Helsinki. The diagnosis of primary SS was based on the 2002 American–European Consensus Classification Criteria [15]. The control group consisted of xerostomic patients, i.e. those who complained of a dry mouth and were screened for SS but did not meet the criteria. Patients with other connective tissue diseases, sarcoidosis, amyloidosis, diabetes mellitus, cardiovascular disease, thyroid disease, hereditary hyperlipidaemia or use of cholesterol-lowering medication were excluded. Lipid profile data, i.e. total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride serum levels (determined after at least 8 h of fasting), were available for 46 SS patients and 12 xerostomic controls seen at our clinic between 1997 and 2003.

Demographic information (age, gender and race) was collected. Data regarding disease activity were obtained at the...
We observed statistically significant differences in levels of certain measures examined in SS patients and xerostomic controls. The disease duration (duration between time of symptom onset and data collection) for SS patients of 12.0 (8.4) yr was greater than for xerostomic controls, which was 6.5 (5.2) yr (P = 0.04). Ethnicity did not differ between groups (P = 0.5). All subjects in this study were female.

Table 1 shows a summary of the various clinical measures examined in SS patients and xerostomic controls. We observed statistically significant differences in levels of certain serum lipids between SS patients and xerostomic controls. Thus, the mean (s.d.) level for total cholesterol in SS patients and controls was, respectively, 4.79 (0.97) vs 5.49 (0.69) mmol/l (P = 0.02) and for HDL cholesterol 1.41 (0.40) vs 1.72 (0.52) mmol/l (P = 0.04). There were no statistically significant differences in mean LDL cholesterol (P = 0.12), triglyceride (P = 0.08) or non-HDL cholesterol levels (P = 0.19) between the groups. Mean CRP levels showed significant differences: 1.75 (3.5) vs 0.00 (0.00) mg/l for SS patients and controls (P = 0.048), respectively. The total cholesterol/HDL ratio was not increased in SS patients compared with controls [3.66 (1.13) vs 3.43 (0.94), P = 0.55]. In the SS patients examined here, 39.0% had high-risk HDL cholesterol levels (ATP III criteria) compared with 18.2% of the xerostomic controls (P = 0.29). Additionally, 46.9% of patients with anti-SSA antibodies had high-risk HDL levels, while 15.0% of seronegative patients were at risk (P = 0.03) (not shown).

In SS patients, but not in controls, total cholesterol (P = 0.003), HDL cholesterol (P = 0.003), focus scores (P = 0.0006) and RF (P < 0.0001) predicted IgG levels by linear regression (Table 2). Total cholesterol levels were significantly lower in SS patients with anti-SSA (χ² = 5.37, P = 0.02), but not anti-SSB antibodies (χ² = 1.16, P = 0.28). Lower HDL cholesterol levels were seen in patients with anti-SSB (χ² = 3.85, P = 0.0497), but not anti-SSA antibodies (χ² = 3.21, P = 0.07). Focus scores, CRP, ESR, C3 or C4 levels were not predicted by either HDL or total cholesterol (P values between 0.08 and 0.9) in a linear regression model (data not shown).

Results

The mean (s.d.) age of SS patients was 53.5 (12.3) yr and 52.5 (7.8) yr for the xerostomic controls (P = 0.79). The mean (s.d.) disease duration (duration between time of symptom onset and data collection) for SS patients of 12.0 (8.4) yr was greater than for the xerostomic controls, which was 6.5 (5.2) yr (P = 0.04). Ethnicity did not differ between groups (P = 0.5). All subjects in this study were female.

Table 1 shows a summary of the various clinical measures examined in SS patients and xerostomic controls. We observed statistically significant differences in levels of certain measures including immunoglobulin levels [immunoglobulin G (IgG), IgA, IgM, IgG], autoantibodies [anti-nuclear antibodies (ANA), anti-SSA, anti-SSB, anti-deoxyribonucleic acid (anti-DNA), antinucleobase protein (anti-RNP), anti-Sm, antinuclear antigen (anti-DNA)] and C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were used. The analyses, performed at one time, included serologic tests, Fisher's exact tests, non-parametric analysis of variance (ANOVA) using the Kruskal-Wallis test, and linear regression models.

Discussion

This is the first report to examine the serum lipid profile of patients with primary SS. In the current study, HDL and total cholesterol levels were significantly lower in SS patients diagnosed using the new American-European Consensus Criteria than in xerostomic controls. In SS patients, low HDL and total cholesterol levels were associated with tissue inflammation and serological measures: serum IgG levels were predicted by both HDL and total cholesterol levels. Immunoglobulin G is an important disease marker in SS [19] and is positively associated with focus scores [20]. We were unable to find useful information in the literature on the association...
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TABLE 2. Predictors of focus score and IgG levels in SS patients (SS+) and xerostomia controls (SS−)

<table>
<thead>
<tr>
<th>Focus score</th>
<th>SS+ (n = 46)</th>
<th>SS− (n = 12)</th>
<th>IgG</th>
<th>SS+ (n = 46)</th>
<th>SS− (n = 12)</th>
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<tr>
<td>HDL cholesterol</td>
<td>−1.42 (0.16)</td>
<td>−0.25 (0.80)</td>
<td>−3.21 (0.003)*</td>
<td>−1.47 (0.18)</td>
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<tr>
<td>Total cholesterol</td>
<td>0.10 (0.92)</td>
<td>−0.25 (0.81)</td>
<td>−3.12 (0.003)*</td>
<td>−1.26 (0.24)</td>
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<tr>
<td>RF</td>
<td>2.25 (0.03)*</td>
<td>1.59 (0.14)</td>
<td>4.71 (0.0001)*</td>
<td>0.04 (0.97)</td>
<td></td>
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<tr>
<td>IgG</td>
<td>3.75 (0.0006)*</td>
<td>−0.06 (1.00)</td>
<td>−</td>
<td>−</td>
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T values (P values) in SS patients and controls. See Table 1 for abbreviations. *(Two-sided) P value ≤0.05.

discovered here between anti-SSA/B antibodies and cholesterol levels. However, the presence of these specific antibodies may reflect SS disease activity in general. Compared with the female adult US population of identical age [21], our xerostomic controls had similar total and LDL cholesterol, higher HDL cholesterol and lower triglyceride levels; SS patients showed lower mean total, LDL cholesterol and triglyceride, and similar HDL cholesterol levels. Previous investigations involved lipid infiltration of the major salivary glands of SS patients visualized by MRI and labial gland biopsies, but serum lipid levels were not studied [14, 22]. A study by Matsuo et al. [23] examined systemic disease activity in RA patients with ocular complications. The authors found that the presence of keratoconjunctivitis sicca in patients with secondary SS was related to higher titres of RF, higher levels of IgM and lower HDL cholesterol levels.

Overall, our results for HDL and total cholesterol levels in SS patients are comparable to earlier findings in RA [1–9, 24, 25]. The acute-phase response in RA is thought to be at least partially responsible for the phenomenon of decreased HDL cholesterol levels [26, 27]. In RA, decreased lipid levels tended to predict cardiovascular morbidity and mortality [28, 29]. The hypothesized pathogenesis of this vascular damage in RA and SLE suggested by different authors [11, 29] is continuous endothelial activation due to several possible factors, including an up-regulation of adhesion molecules on endothelial cells by inflammatory cytokines and the presence of immune complexes and autoantibodies. This may lead to a prematurely aging, dysfunctional vasculature, rendering it more susceptible to traditional cardiovascular risk factors, such as cholesterol levels, than in the general population.

For example, Svenson et al. [1] suggested that the degree of inflammatory activity determined the lipoprotein alterations observed in their patients with untreated chronic inflammatory arthropitides. Furthermore, patients with untreated, active RA show altered lipoprotein patterns that may possibly expose them to a higher risk of atherosclerosis. Since we observed the same alteration in lipid profiles of SS patients, this raises questions about the prevalence of atherosclerosis and subsequent cardiovascular events in SS. However, this has not been studied thus far in SS.

Effective treatment of an inflammatory process may prove beneficial for dyslipoproteinemia and possibly the risk of cardiovascular disease (CVD) and related mortality. Both Svenson et al. [30] and Park et al. [25] investigated the effects of anti-rheumatic therapy on serum lipid levels in newly diagnosed and untreated RA patients. Active RA was associated with an adverse lipid profile that improved significantly upon effective treatment of RA with methotrexate, other disease-modifying anti-rheumatic drugs and/or prednisolone, suggesting it was the decrease in RA disease activity that reversed the altered lipid profiles.

Interestingly, several recent studies have tested whether HMG-CoA reductase inhibitors, such as atorvastatin and simvastatin, had pleiotropic immunomodulatory effects in RA patients [31, 32] and mouse models for multiple sclerosis [33] and inflammatory arthritis [34]. It appears that statins could inhibit developing and clinically evident disease through suppression of humoral and cellular immune responses, with no or only small changes in serum lipid levels. However, a new study indicated that increased glucocorticoid levels, induced by the statin treatment, could cause the perceived beneficial effect [35]. This raises the possibility that these drugs may have a role in the treatment of autoimmune diseases, including Sjögren’s syndrome; further research could lead to more insights.

Recently, it has been suggested that the CRP level was a stronger predictor of CVD than the level of LDL cholesterol [36]. Park et al. [5] found a negative correlation between HDL cholesterol and CRP in their study on lipid profiles in untreated RA patients, again suggesting an altered lipid profile during an inflammatory condition. In the current study we could not confirm this finding, which could be due to the relatively low mean CRP levels, with only six SS patients having an elevated CRP level, or an absence of an association between lipids and CRP levels in SS. In general, CRP levels tend to be a less useful marker of disease activity than ESR levels in SS [37]. Here, ESR did not correlate with cholesterol levels either. Although elevated non-HDL cholesterol has been shown to be a better predictor of cardiovascular mortality than LDL cholesterol [18], we found no differences between SS patients and xerostomic controls for LDL or non-HDL cholesterol. However, HDL and total cholesterol levels were significantly decreased in SS patients, suggesting that a lower total cholesterol reflects a low HDL cholesterol level. Non-HDL levels in rheumatological diseases have not been studied so far. Therefore, no conclusions can be drawn regarding the cardiovascular effects of altered non-HDL levels in SS or RA.

In conclusion, HDL and total cholesterol levels were significantly lower in primary SS patients than xerostomic controls, and in SS patients low total and HDL cholesterol levels were associated with serologically active disease. These results are comparable with earlier findings in RA. Since decreased cholesterol levels tended to predict cardiovascular morbidity and mortality in RA, the finding of an altered lipid profile in SS raises questions about the potential for adverse cardiovascular consequences in this disease.

Rheumatology

<table>
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<td>• In primary Sjögren’s syndrome patients show altered serum lipid levels compared with xerostomic controls.</td>
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<td>• These changes are associated with serologically active disease.</td>
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Acknowledgement

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The authors have declared no conflicts of interest.
References


