EXTENDED REPORT

Influence of glucocorticoids and disease activity on total and high density lipoprotein cholesterol in patients with rheumatoid arthritis

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Background: Glucocorticoids induce hypercholesterolaemia, a cardiovascular risk factor, in patients with diseases other than rheumatoid arthritis (RA), but the data in RA are contradictory.

Objective: To determine the effects of antirheumatic treatment, including prednisolone (combination) therapy on total and high density lipoprotein (HDL) cholesterol levels in RA, taking disease activity into account.

Methods: HDL cholesterol and total cholesterol levels were determined in: (a) established RA (b) two cohorts with early active RA, (c) a previously conducted 56 week trial among patients with early RA comparing the value of intensive combination therapy (that included glucocorticoids) with sulfasalazine alone (COBRA trial).

Results: In established RA total cholesterol levels were only slightly raised, irrespective of disease activity. However, HDL cholesterol was significantly higher in patients in remission than in patients with active disease. In contrast, in active early RA at baseline total cholesterol was low normal: between 4.6 and 5.1 mmol/l in the different populations. The level of HDL cholesterol was highly dependent on the duration of storage. In both COBRA groups total cholesterol increased by a mean of 0.6 mmol/l. HDL cholesterol increased by more than 50% after treatment, leading to an improvement of the total cholesterol/HDL ratio (atherogenic index). This increase (and index improvement) was much more rapid in the group receiving combination treatment. A similar pattern was seen in the 2001 cohort with early RA. In all the groups with active disease HDL and total cholesterol levels correlated inversely with disease activity.

Conclusion: In established, but especially in early RA, disease activity is accompanied by atherogenic lipid levels. This dyslipidaemia can be rapidly reversed by aggressive antirheumatic treatment including glucocorticoids.

Mortality is increased in patients with rheumatoid arthritis (RA) compared with the general population, and cardiovascular disease is the most important cause of death. A theoretically, this increased cardiovascular risk in patients with RA could be caused by (1) an increased prevalence of (known) risk factors for cardiovascular disease such as dyslipidaemia, diabetes mellitus, hypertension, body mass index, physical fitness, and smoking habits; (2) RA itself by either (a) the underlying inflammatory process, or (b) decreased functional capacity; and (3) undertreatment of cardiovascular disease as a comorbid condition in patients with RA (Boers M, unpublished data).

In this investigation we focused on dyslipidaemia. Published reports are sparse and contradictory about the levels of total, high density lipoprotein (HDL) and low density lipoprotein cholesterol, and triglycerides in patients with RA, even though there is some evidence for increased Lp(a) lipoprotein levels and lowered lipid levels in patients with active disease.

Glucocorticoids are commonly used in patients with RA. Although it is well known that glucocorticoids induce hypercholesterolaemia, a well known cardiovascular risk factor, in patients with diseases other than RA, the effect of (long term) glucocorticoid administration on lipid profiles in patients with RA is uncertain. Thus far a limited number of small scale studies have dealt with this subject in patients with RA, indicating either an increase or no effect of total cholesterol levels during (long term) glucocorticoid administration.

Therefore, in stored serum samples we investigated total cholesterol and HDL cholesterol levels cross sectionally, in patients with early RA and in patients with longstanding, established disease. Moreover, we studied the course of lipid levels and the influence of antirheumatic treatment (including glucocorticoids), in a previously conducted, 56 week multicentre, randomised controlled trial among patients with early RA investigating the value of intensive combination therapy. Finally, we determined these levels in one year follow up samples of the 2001 cohort with early RA.

PATIENTS AND METHODS

This study is the result of an incremental process: the COBRA trial samples were determined first, followed by confirmation in patients with established active RA and in patients with RA in remission, and baseline samples of a cohort with early RA collected in 1996–97. All patients fulfilled the American College of Rheumatology (ACR) 1987 criteria for RA. The apparent effect of serum storage on HDL cholesterol led us to analyse “fresh” samples of patients with early RA collected in 1996–97.

Abbreviations: ACR, American College of Rheumatology; DAS, disease activity score; DMARDs, disease modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HDL, high density lipoprotein; RA, rheumatoid arthritis.

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Total and HDL cholesterol in patients with RA

RESULTS

Patients with established RA

The mean age of the patients with established active disease was 60 years, and their disease duration was 8 years (table 1). For patients in remission the mean age was 59 years and the disease duration 10 years. These patients with established disease had slightly raised levels of total cholesterol—that is, 5.5 (1.1) and 5.7 (0.8) mmol/l, respectively (table 2). However, HDL cholesterol levels were significantly lower in the patients with active disease than in those in remission, 0.94 (0.31) v

Table 2 Total cholesterol, HDL cholesterol and atherogenic index (cholesterol/HDL cholesterol) levels at baseline

<table>
<thead>
<tr>
<th></th>
<th>COBRA</th>
<th>Early arthritis clinic 1996–97</th>
<th>Early arthritis clinic 2001</th>
<th>Established disease active</th>
<th>Established disease remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol [TC] (mmol/l, SD)</td>
<td>4.7 [1.1]</td>
<td>5.1 [1.0]</td>
<td>5.1 [1.0]</td>
<td>5.5 [1.1]</td>
<td>5.7 [0.8]</td>
</tr>
<tr>
<td>HDL cholesterol [mmol/l, SD]</td>
<td>0.28 [0.11]</td>
<td>0.49 [0.13]</td>
<td>1.0 [0.33]</td>
<td>0.94 [0.31]</td>
<td>1.18 [0.13]</td>
</tr>
<tr>
<td>TC/HDL cholesterol ratio</td>
<td>16.7</td>
<td>10.4</td>
<td>5.4</td>
<td>6.4</td>
<td>5.1</td>
</tr>
</tbody>
</table>
In explanatory regression analysis, within the patients with active disease total cholesterol and HDL cholesterol levels correlated inversely with disease activity, as assessed by the disease activity index 28 joint score (DAS28).

**Early arthritis clinic 1996–97**

The mean age of the patients was 62 years (table 1). At baseline, total cholesterol was 5.1 (1.0) and HDL cholesterol 0.49 (0.13) in the 1996–97 group.

**56 Week randomised controlled trial (COBRA)**

The mean age of the patients was 50 years; median disease duration was four months (table 1). Disease activity improved more rapidly and effectively in the group receiving combination therapy at week 16, and this effect persisted until week 28. The clinical difference between the groups decreased and was no longer significant after prednisolone was stopped, and there were no further changes after methotrexate was stopped.

However, persistently lower yearly rates of radiological damage progression were observed at least four years after the trial ended in the (initial) combination group.

During the trial both groups showed a strong increase from low baseline cholesterol levels (fig 1), initially more pronounced in the combination group (week 16: 1.1 v 0.6; p=0.04). Likewise, for HDL cholesterol, both groups showed a strong increase from a very low baseline level (fig 1). At week 16 the increase in HDL cholesterol was much more pronounced in the combination group (0.18 v 0.05; p<0.001); this difference was still apparent at week 28 (0.16 v 0.10; p=0.02). Likewise, at week 16 the decrease in atherogenic index was more rapid in the combination group (–5.1 v –1.4; p=0.008). Thereafter, it decreased gradually in the sulfasalazine group, but remained stable in the combination group, resulting in similar values at week 28 and thereafter (fig 1). Of note, the changes in lipids were mirrored by the pattern of weight gain, initially greater in the combination group, but more than 3 kg in both groups at 56 weeks (data not shown).

Regression analysis on the changes at week 16 showed that changes in total cholesterol were only predicted by changes in ESR. The change in HDL cholesterol levels at week 16 could be partially predicted by the change in ESR and DAS at baseline. However, the treatment group was a more important predictor independently of the ESR or DAS. Similar findings were found for the ratio total cholesterol/HDL cholesterol.

**Early arthritis clinic 2001**

The mean age of the patients was 60 years (table 1) and at baseline the total cholesterol was 5.1 (1.0) and HDL cholesterol 0.49 (0.13) in the 1996–97 group.

**Effect of storage duration on lipid levels**

Overall, storage duration of baseline samples did not influence total cholesterol levels. However, the estimated decrease for HDL cholesterol was 0.15 for each storage year (fig 2).

**DISCUSSION**

This study shows that patients with early RA with active disease present with low concentrations of cholesterol and HDL cholesterol. Although both total and HDL cholesterol levels appear to be only moderately decreased the total cholesterol/HDL ratio is at least 5.1 at baseline. This so-called atherogenic index is an important prognostic marker for future cardiovascular disease; the desirable ratio is four or lower. A higher index implies an increased cardiovascular risk, and lowering this ratio has been shown to decrease this risk—for example, lowering the ratio from 6.0 to 4.5 halves the five year rate of coronary artery disease in women. Our longitudinal investigations indicated an improvement of the atherogenic index by antirheumatic treatment, which might result in a lower
(future) cardiovascular risk, provided that the improvement is maintained over a longer period.

In the COBRA trial the rapidity of response was faster in the group receiving combined treatment. Owing to the design of the trial, we are unable to answer the question as to whether this is the result of better disease suppression, specific to one of the components or even their combination. However, we did find a linear relationship between the DAS28 score and the atherogenic index in both early and established RA. Regression analyses of the COBRA data showed that changes in total cholesterol were best predicted by changes in ESR, but the model for changes in HDL cholesterol also contained disease activity at baseline and treatment group as additional factors. These findings suggest that changes in total cholesterol are the result of effective RA treatment, but changes in HDL are more specific to glucocorticoid (or combination) treatment.

To our surprise, and not reported before, HDL cholesterol (but not total cholesterol) levels were strongly influenced by storage duration of the samples. Hence, the absolute values of the atherogenic index in all except the latest (early arthritis clinic 2001) samples, should be interpreted cautiously, as they are too low. However, the differences between the trial groups, and the changes over the year (and their determinants) can still be studied validly.

Therefore, comparisons between the patients with established RA whose disease is active and those in remission of and of both groups with the COBRA group remain valid.

It is well known that physical activity has beneficial effects on the total cholesterol/HDL cholesterol ratio. In the transverse comparisons of patients with established RA who have active disease and those in remission such an effect cannot be excluded. However, the similarity in Health Assessment Questionnaire scores makes this explanation for the lipid findings less likely. In the trial COBRA patients with RA improved much more rapidly than patients receiving sulfasalazine, and the former may well have increased their physical activity. However, it seems unlikely that this would have such major effects on blood lipids in such a short period of time.

The lipid profile may be also influenced by weight/body mass index or drugs such as antimalarial drugs or statins. In the transverse comparisons there were no significant differences in body weight. In the trial, both groups gained weight, (about 3 kg in 56 weeks, difference NS), but the COBRA group gained weight more rapidly in the first 28 weeks. Only a very few patients were receiving antimalarial drugs and/or statins. Moreover, these drugs were equally distributed between the several groups. In the COBRA trial such drugs were not used. Altogether, the combination of cross sectional and longitudinal evidence appears strong. Our findings indicate an atherogenic lipid profile in active RA, especially in untreated patients with early RA, which improves on treatment. The concomitant changes in body weight suggest a state of rheumatoid cachexia at baseline.2 This is supported by a recent uncontrolled investigation in 42 patients with early RA which also indicated improvement of the lipid profile in the 27 patients who responded to antirheumatic treatment.18

Thus far published reports are contradictory about the effect of glucocorticoids in RA, and data of properly designed studies are lacking. The controlled COBRA data indicate that glucocorticoid (combination) treatment increases total cholesterol and HDL cholesterol more quickly, with a concomitant faster improvement of the atherogenic index, than sulfasalazine alone. Whether or not this favourable influence on the cardiovascular risk is ultimately offset by adverse cardiovascular effects of long term glucocorticoid administration—for example, hypertension and insulin resistance,19 remains to be established.

Thus far increasing awareness that patients with RA have an enhanced cardiovascular risk, which appears to be, at least partly, caused by inflammation.1 Our study shows that inflammation (disease activity) has a negative influence on the lipid profile and that effective treatment can ameliorate this.

**REFERENCES**


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