THE EFFECT OF LOW DOSE PRAVASTATIN ON FIBRINOGEN, C–REACTIVE–PROTEIN AND C3 COMPLEMENT LEVELS

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SUMMARY

Aim: To investigate the effect of low dose pravastatin on C-Reactive-Protein (CRP), fibrinogen, and C3 complement levels in patients with hypercholesteremia.

Method: Fifty-seven patients with hypercholesteremia formed the study patients. Patients were divided into two groups. Group 1 (the study group) consisted of 37 patients (19 of them had hypercholesteremia and hypertension, 5 had previous myocardial infarction, 13 had hypercholesteremia). Mean age was 54.3 and mean cholesterol was 266 mg/dl. CRP levels were measured with nephelometric method and fibrinogen levels were measured with Clauss method. Those patients were initiated 10 mg pravastatin daily on top of a American Heart Association Step 1 diet therapy and CRP, fibrinogen and C3 levels were remeasured 2 months later. Group 2 (the control group) consisted of 20 patients (13 had hypertension and hypercholesteremia, 7 had hypercholesteremia). Mean age was 56.3 and mean cholesterol was 239 mg/dl. Group 2 had a American Heart Association Step 1 diet therapy and they had their CRP, Fibrinogen, and C3 levels measured at the beginning of diet therapy and two months later.

Results: Group 1 had their fibrinogen and CRP levels lowered statistically significantly (p<0.05 and p<0.001 respectively) but C3 levels did not change significantly (p>0.05). Group 2 also had some decreases in their C3 and fibrinogen levels which did not reach statistical significance. C3 levels also did not change significantly.

Conclusion: Low dose pravastatin therapy, in hypercholesteremic patients, decreased fibrinogen and CRP levels in quite a fast manner but did not have any effect on C3 levels.

Key Words: Pravastatin, C3 Complement CRP, Fibrinogen.

ÖZET

Düşük Doz Pravastatin Tedavisinin Fibrinojen, C-Reaktif Proteini, C3 Kompleman Düzeylerine Etkisi

Amaç: Hiperkolesterolemi olan hastalarda düşük doz pravastatin tedavisinin C- Reaktif Protein (CRP) , fibrinojen ve C3 kompleman düzeyleri üzerine etkisini araştırmak.


Sonuç: Grup 1’in fibrinojen ve CRP düzeyleri istatistik olarak anlamlı düştü (p<0.05, p<0.001) ancak C3 düzeylerinde anlamlı değişiklik saptanamadı (p>0.05). Grup 2’de ise istatistik anlama ulaşmayan bir miktar C3 ve fibrinojen değerlerinde düşme oldu. C3 düzeylerinde anlamlı değişiklik olmadığı söylenebilir.

Yorum: Hiperkolesterolemi hastalarında düşük doz pravastatin tedavisinin fibrinojen ve CRP düzeylerine oldukça hızlı bir şekilde düüyüşürcen C3 düzeylerine etki etmemektedir

Anahtar Kelimeler: Pravastatin, C3 Kompleman, CRP, Fibrinojen.
Despite ever-growing basic and clinical research, coronary artery disease remains the leading cause of death in the industrialised world. In the recent years, accumulating information explored atherosclerosis as an inflammatory disease (1,2). In this context, markers of inflammation, especially C-Reactive-Protein (CRP) has emerged as an important tool to risk-stratify patients for future cardiovascular events. CRP has been validated to predict future cardiovascular events in many clinical circumstances including acute coronary syndromes (3), chronic stable angina (4), recurrent stroke (5), risk of developing symptomatic peripheral vascular disease (6). Even apparently healthy men seem to be at increased cardiovascular risk with elevated levels of CRP (7).

Plasma fibrinogen critically influences platelet aggregation and blood viscosity. Fibrinogen interacts with plasminogen binding and together with thrombin mediates the final step in clot formation. Epidemiological studies found significant positive associations between fibrinogen level and future cardiovascular risk (8-10). Fibrinogen elevation may occur as part of an acute phase response and may thus be associated with risk owing to its role as a marker of systemic inflammation.

Since “inflammation hypothesis” gained widespread acceptance there has been research to evaluate the influence of complement activation on atherosclerosis. Basic research has shown that statins might have a novel cytoprotective action on vascular endothelium through enhanced protection against complement-mediated injury (11). Studies on animal models have indicated that maturation of atherosclerotic lesions beyond foam cell stage is strongly dependent on an intact complement system (12). A recent clinical autopsy study demonstrated evidence of complement activation in ruptured coronary plaques in acute myocardial infarction (13).

In this study we ought to search the effect of low dose pravastatin therapy, in a short term, on some markers of inflammation, namely CRP, fibrinogen, complement 3 (C3).

**Materials and Methods**

This was an open label prospective study. Patients were randomly drawn from outpatient clinics of our department. None of the patients were treated with any kind of drugs for hyperlipidemia prior to entering to our study. All patients required medications for their high cholesterol levels according to established guidelines (14), for either primary or secondary prevention. Age, sex, classical risk factors for atherosclerosis, body mass index, smoking status were collected. Clinical diagnosis of the patients ranged from hypercholesterolemia to documented prior MI. We collected data for 57 patients. Thirty-seven of the patients formed the study group and they were treated with pravastatin 10 mg daily in addition to an American Heart Association (AHA) Step 1 diet. Twenty patients formed the control group and they were put on AHA step 1 diet. Baseline levels of C3, CRP and fibrinogen were studied both at the beginning of the study and 2 months later for both groups. CRP levels were measured with nepholemetric method and fibrinogen levels were measured with Clauss method. All patients gave informed consent. Patient characteristics of the groups are given in table 1.
Before collecting laboratory data, so as to avoid potential misclassification because of any elevation of CRP and fibrinogen due to acute exogenous stimulus we decided not to analyse baseline and control values of > 3 standard deviation above the mean value. However, none of the patients both in the study group and control group fell into this category.

Hypertension was either defined to be on antihypertensive therapy or blood pressure readings of greater or equal to 140/90 mmHg on several occasions clinically judged to necessitate antihypertensive therapy. Hypercholestorelemia was defined to be positive according to requirement for therapy after risk assessment based on National Cholesterol Education Program-Adult Treatment Panel III recommendations (14).

Statistics

For continuos variables data are presented as mean ± standard deviation. Student’s t test was used to compare levels of baseline and 2 months’ inflammation marker levels and lipid parameters. Cathegoric variables between the study and control groups were compared with chi-square test. Data was analysed by using Statistical Programme for Social Sciences 8.0 version Results with a p value of < 0.05 were considered significant.

Results

As summarised in table 1 both groups were similar in terms of age, sex, risk factors, body mass index, cigarette smoking, use of medications that might alter level of inflammatory markers.

Laboratory analysis of the groups in terms of lipid profiles and inflammation markers at baseline and two months later after the treatment and diet or only diet are given in tables 2 and 3. Fibrinogen and CRP levels decreased significantly with pravastatin 10 mg/day therapy (p<0.05 and p<0.001 respectively). Complement 3 levels did not differ with pravastatin therapy.

<table>
<thead>
<tr>
<th>Table 1: Patient characteristics of the study and control group *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Group</strong></td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Female / Total</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>No. of Hypertensives</td>
</tr>
<tr>
<td>Smokers (Past or current)</td>
</tr>
<tr>
<td>Family history of premature CHD¶</td>
</tr>
<tr>
<td>Prior MI#</td>
</tr>
<tr>
<td>No. of patients on aspirin</td>
</tr>
<tr>
<td>No. of patients on ACEI§</td>
</tr>
<tr>
<td>Body Mass Index</td>
</tr>
</tbody>
</table>

*: All p values for the rows are greater than 0.05 when it was meaningful to calculate.
¶: CHD stands for Coronary Heart Disease
#: MI stands for Myocardial Infarction
§: ACEI stands for angiotensin converting enzyme inhibitors
In group 2 although there was a decrease in fibrinogen and CRP levels this did not reach statistical significance. Complement 3 levels also did not change with dietary therapy.

**DISCUSSION**

In the last decade there has been a strong tendency to view atherosclerosis as an inflammatory disease (1,2). Markers of inflammation, especially CRP has been shown to predict future cardiovascular events (2). Several statin studies have documented that statin therapy, in different groups of patients (either primary or secondary prevention) lowered CRP levels (15,16). This effect could be seen rather quickly, namely in months, (17) and was in a lipid-independent manner (15-17). The present study, in terms of CRP levels reduction, confirms the current literature. The point with our study, to put some more, may be that, with such low levels of a statin, 10 mg pravastatin daily, we can still have the anti-inflammatory actions in a short time of two months. To the best of our knowledge (searching thorough the internet), the present study is unique to demonstrate a fast CRP reduction with a low dose of pravastatin. In a study with cerivastatin, CRP levels decreased with both 0.4 mg and 0.8 mg dose regimen, with a lipid independent manner in two month’s time (17). In another study pravastatin 40 mg/daily lowered CRP levels at 12 and 24 weeks, again with a lipid independent manner in both primary and secondary prevention patients (18).

The data about the effect of statins on fibrinogen levels are controversial. There seems to be inconsistency among the results. In a metaanalysis article reviewing the issue (19) some statins are noted to increase fibrinogen levels (atorvastatin, fluvastatin), some are stated to be neutral (simvastatin) and some are stated to decrease fibrinogen levels (pravastatin). Our data supports the findings in this analysis.

### Table 2: Laboratory data of the control group at baseline and 2 months after diet and drug treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>At two months</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>266.2 ± 29.6</td>
<td>228.9 ± 43.5</td>
<td>P&lt;0.005</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>3.54 ± 0.96</td>
<td>2.99 ± 0.79</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>5.7 ± 3.07</td>
<td>4.35 ± 1.77</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>C3 (mg/dl)</td>
<td>1.29 ± 0.42</td>
<td>1.13 ± 0.25</td>
<td>p&gt;0.05</td>
</tr>
</tbody>
</table>

### Table 3: Laboratory data of the study group at baseline and 2 months after dietary therapy

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>At two months</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>239.1 ± 23.7</td>
<td>225.2 ± 25.2</td>
<td>P&lt;0.005</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>3.87 ± 0.99</td>
<td>3.64 ± 0.82</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>4.52 ± 2.7</td>
<td>4.09 ± 1.63</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>C3 (mg/dl)</td>
<td>1.25 ± 0.34</td>
<td>1.24 ± 0.34</td>
<td>p&gt;0.05</td>
</tr>
</tbody>
</table>
Measuring plasma C3 levels as a possible marker of inflammation and looking for the possible effect of statins on C3 levels is probably a surrogate end point. Complement activation is shown to be present in ruptured plaques (13). Since complement activation is part of the inflammatory response of the body we tried search whether statins, as anti-inflammatory agents would alter the levels of serum C3 levels. However, we did not note any effect. This may be related with the low dose of the drug but even in this low doses we could document CRP lowering.

**Limitations of the study**

There are several limitations with the present study. First of all, for CRP analysis we did not use high sensitive CRP method which is superior. However, there are data to demonstrate that CRP is also valuable in terms of consistency of the laboratory results (17).

Another point may be that patients, in both study and control group, are a mixture of primary and secondary prevention patients (mainly primary prevention). However, arterial inflammation markers, especially CRP, seem to be capable of risk stratifying patients across a broad range of vascular diseases and apparently healthy man. Hence we can expect some degree of elevation of arterial inflammation markers in a population with cardiovascular risk and statins may act positively on these inflammatory markers.

The length of follow-up may be criticised to be too short but there is a large well-controlled study indicating cerivastatin to decrease CRP levels in two moth’s time.

**Conclusion**

Pravastatin, even with a low dose of 10 mg lowers arterial inflammation markers of CRP and fibrinogen in a short time interval but has no effect on serum C3 levels.
References