Inverse association of serum cholesterol with plasma insulin in the elderly. Cross-sectional and prospective analyses

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ABSTRACT. Cross-sectional studies have suggested that high plasma insulin is associated with relatively low levels of low density lipoprotein (LDL)-cholesterol. The present study was aimed at re-testing this association in a 70-year-old age cohort (N=1023), and testing whether it could be caused by excessive mortality of hyperinsulinemic subjects with high LDL-cholesterol. A reverse U-shaped association between LDL-cholesterol and fasting plasma insulin was confirmed. LDL-cholesterol, HDL-cholesterol and total cholesterol were lowest in the highest insulin quarter. These associations remained after adjustment for diabetes, obesity and general health status. The combination of high LDL-cholesterol (>4.25 mmol/L, 75th percentile) and high insulin (>10 IU/L, 50th percentile) was not associated with excess 5-year mortality in this age cohort. Nor was it associated with excess mortality in four other elderly age cohorts (N=1188), in which similar associations of cholesterol and insulin have been demonstrated. Thus, the inverse association of LDL-cholesterol with fasting insulin in the elderly is not caused by selective over mortality.

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INTRODUCTION

High LDL-cholesterol is a well-established cardiovascular risk factor. Elevated levels of endogenous insulin have also been implicated as a cardiovascular risk factor, although these findings still remain controversial (1-3). In cross-sectional analyses of random subjects aged 65, 75, 80 and 85 years, we demonstrated that high fasting plasma insulin is associated with relatively low levels of LDL-cholesterol (4). A study of middle-aged subjects also found low LDL-cholesterol levels among those with high levels of insulin (5). These findings are new, as LDL-cholesterol has received minor attention in previous studies on hyperinsulinemia, or the insulin resistance syndrome.

The present study was aimed at re-testing the association of high insulin with low LDL-cholesterol in another elderly population, and evaluating whether it is caused by excessive mortality among hyperinsulinemic subjects with high LDL-cholesterol.

SUBJECTS AND METHODS

The birth cohort study of individuals aged 65, 75, 80 and 85 years (the Helsinki and Vantaa Ageing Studies, N=1188), and its methodology have been described previously (4). In brief, the study cohorts are representative of the entire age cohort, and there are no exclusions by design. The protocol comprises structured interviews, laboratory tests, and a physical examination by a general practitioner at baseline. In the present study, the entire 70-year-old community-dwelling population of Turku, Finland was targeted for examination according to a similar protocol (N=1023, participation rate 87%). In this cohort, data on insulin and lipids were available for 853 subjects of whom survival status was also confirmed for 822.

Fasting serum lipids (total and HDL-cholesterol and triglycerides), and fasting plasma insulin were analyzed as described earlier (4), and LDL-cholesterol concentrations were calculated according to the
Friedewald formula (6). Body mass index was calculated as weight (kg) divided by height squared (m²).

Diabetes mellitus was defined as follows: earlier diagnosis or medication for diabetes, or fasting blood glucose 6.7 mmol/L or more. At the end of the structured clinical examination, the general health status was scored on a visual analogue scale by the examining physician. For this estimate, the physician had at his disposal information from health records, nurses’ structured interviews, and laboratory tests (not fasting insulin).

The combination of hyperinsulinemia and high LDL-cholesterol was defined as follows: serum low density lipoprotein cholesterol >4.25 mmol/L (75th percentile) plus fasting plasma insulin >10 IU/L (50th percentile).

The prospective part of the present study pools the data of the Turku study with the 100% complete follow-up data of the Helsinki and Vantaa studies. Mortality data were collected from computerized registers of the Statistical Office of Finland.

Statistical analyses of the data were performed with the Biomedical Data Processing (BMDP) statistical software (7). The study was approved by the health care authorities of the participating communities, and by the Ethics Committee of the Department of Medicine. The informed consent of all subjects was obtained.

RESULTS

In the 70-year-old population, there was an inverse U-shaped association between fasting plasma insulin and LDL-cholesterol, as well as total cholesterol (Table 1). HDL-cholesterol decreased and triglycerides increased linearly with insulin quartiles. Moreover, the ratio of HDL to total cholesterol decreased linearly from the lowest to the highest insulin quartile.

Subjects in the top 75% of the insulin distribution had 7% lower LDL, 22% lower HDL-cholesterol, and 5% lower total cholesterol than all other subjects (p<0.001, p<0.001 and p=0.002, respectively). Their HDL to total cholesterol ratio was 23% lower (p<0.001). All these differences remained significant after adjustment for diabetes mellitus, body mass index, and the general health score.

The combination of high LDL-cholesterol (>4.25 mmol/L) with high insulin (>10 IU/L) was not associated with increased crude mortality in any of the age cohorts (Table 2). Analyses using a higher insulin cutpoint (e.g., 14 IU/L) yielded similar results.

DISCUSSION

The results from the 70-year-old cohort support our earlier finding from the cohorts aged 65, 75, 80 and 85 years, which indicated that high fasting plasma insulin is associated with low LDL-cholesterol in elderly subjects (4). Although that study did not provide an explanation for the association, it indicated that the association is not a consequence of diabetes, hypertriglyceridemia, the use of hypoglycemic drugs, or poor health. The presence of this association in a single large birth cohort, and its apparent independence of diabetes, obesity, and health status suggests that the association is a true phenomenon, and not a consequence of the aging processes or morbidity. The quantitatively rather small differences in LDL-cholesterol levels by insulin quartiles may explain why many previous studies have failed to demonstrate this association. The cross-sectional studies (4, 5) have not excluded excess mortality of subjects with combined hyperinsulinemia and hypercholesterolemia as a cause of this association. In fact, in view of the great cardiovascular risk attributed to LDL-cholesterol, and the risk possibly associated with high insulin, the combination of these two could be expected to impair survival prognosis. Therefore, the present results are new and quite surprising. We could not show that the combination of high LDL-cholesterol with high insulin was associated with any significant excess mortality in any of the five age

Table 1- Gender adjusted serum lipid concentrations, mean (SE), by fasting plasma insulin quartiles in random 70-year-old subjects.

<table>
<thead>
<tr>
<th>Serum lipid</th>
<th>Insulin quarter, IU/L</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 7.0</td>
<td>7.0 - 9.9</td>
</tr>
<tr>
<td>N=211</td>
<td>N=210</td>
<td>N=221</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.09 (1.10)</td>
<td>6.27 (1.24)</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L</td>
<td>1.56 (0.39)</td>
<td>1.43 (0.43)</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/L</td>
<td>4.06 (0.95)</td>
<td>4.23 (1.10)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.04 (0.49)</td>
<td>1.34 (0.65)</td>
</tr>
<tr>
<td>HDL-/ total cholesterol</td>
<td>0.26</td>
<td>0.24</td>
</tr>
</tbody>
</table>