TIA's during that period. This is in contrast to the present study where 12 out of 44 patients (27%) with distal VB stenosis developed VB ischemia (5 infarcts, 7 TIA) during follow-up. Angiograms were selected without knowledge of clinical history and it was notable that the main reason for angiography was VB symptoms in the group with distal disease as opposed to carotid or non-specific symptoms in those with proximal lesions. However, since the two groups probably differ in several ways affecting prognosis, strict comparisons are not possible.

References

Lipoprotein(a) as a Strong Indicator for Cerebrovascular Disease
Gerald Zanker, M.D.,* Peter Költringer, M.D.,† Gertrude Bone, M.D.,‡ Kurt Niederkorn, M.D.,† Karl Pfeiffer, Ph.D.,§ and Günther Jürgens, Ph.D.]

SUMMARY To evaluate the role of lipoprotein(a) (Lp(a)) in patients with cerebrovascular disease (CVD), lipid parameters were compared with a control group (CO). Additionally, the Lp(a) serum levels were investigated in a coronary artery disease (CAD) group. The CO was made up of 37 healthy persons (age: 54.5 ± 7.7, 26 males and 11 females), the CVD group included 46 patients with sustained transient ischemic attack (TIA) prolonged reversible ischemic neurologic deficits (PRIND) and cerebral infarction (CI) (age: 53.6 ± 9.7, 32 males and 14 females), and the CAD group was made up of 28 survivors of myocardial infarctions (age: 52.5 ± 8.1, 18 males and 10 females). The median values of Lp(a) in CVD were significantly higher than in the CO (p < 0.01) and did not differ significantly from the CAD. Total TC, HDL-C, TG, LDL-C and the ratio of LDL-C/HDL-C did not show any significant difference between the control and cerebrovascular disease group. For quantification of the vascular lesions of the carotid system, a Duplex Doppler score system was used. The score correlated with Lp(a) in patients between 40 to 65 years of age (r = 0.34, p < 0.01). Thus, we conclude that Lp(a) is not only a risk factor for CAD but also for CVD.

A NUMBER OF REPORTS have been published on the significance of dyslipoproteinemia for the development of cerebrovascular disease, but the results are conflicting.

While several groups observed elevated serum levels of cholesterol (TC) and/or triglycerides (TG) in survivors of attacks of ischemic cerebrovascular disease, epidemiological studies performed in Japan even showed that incidence of cerebral infarction was inversely related to levels of serum cholesterol and geometrical differences seemed to exist.

Lipoprotein(a) (Lp(a)), a cholesterol rich lipoprotein in human serum, has been considered to be an independent risk factor for the development of coronary artery disease (CAD). In patients under 56 years of age, Lp(a) was found to be a stronger indicator of CAD than total cholesterol (TC), triglycerides (TG) or decreased high density lipoprotein cholesterol (HDL-C) levels.

The aim of this study was to evaluate the role of Lp(a) in patients with cerebrovascular disease (CVD). The lipoprotein-parameters of a collective of patients suffering from CVD were compared to those of survivors of myocardial infarctions and of a control group of healthy subjects.
**Lipoprotein(a) and Cerebrovascular Disease**

**Zenker et al**

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**Table 1 Basic Characteristics of the Control and Patient Groups**

<table>
<thead>
<tr>
<th></th>
<th>Age (x ± SD)</th>
<th>IR&lt;sub&gt;25&lt;/sub&gt;</th>
<th>x</th>
<th>IR&lt;sub&gt;50&lt;/sub&gt;</th>
<th>C</th>
<th>D</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>54.4±7.7</td>
<td>50</td>
<td>57</td>
<td>60</td>
<td>10</td>
<td>(27%)</td>
<td>1</td>
</tr>
<tr>
<td>CHD</td>
<td>52.5±8.1</td>
<td>49</td>
<td>54</td>
<td>58</td>
<td>11</td>
<td>(39%)</td>
<td>2</td>
</tr>
<tr>
<td>CVD</td>
<td>53.6±9.7</td>
<td>50</td>
<td>56</td>
<td>59</td>
<td>10</td>
<td>(22%)</td>
<td>2</td>
</tr>
</tbody>
</table>

\( \bar{x} = \text{mean} \); SD = standard deviation; \( \bar{x} = \text{median} \); IR = quartiles; No = number of subjects; C = cigarette smokers; D = diabetes mellitus; H = hypertension; CHD = coronary heart disease; CVD = cerebrovascular disease.

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**Subjects and Methods**

**Subjects**

All subjects gave their informed consent and the study was performed respecting the principles of the Declaration of Helsinki. Table 1 lists the basic characteristics of the different groups.

**Control group:** The controls were randomly selected from a consecutive series of out- and in-patient subjects, in the year 1984, by consulting the ambulance records of the Department of Psychiatry and Neurology and of the Department of Internal Medicine II of the Landeskrankenhaus Graz (26 males and 11 females). The criteria for inclusion in this group included (a) age between 40 and 65 years, (b) the non-existence of coronary artery disease (CAD) (CAD was excluded by an electrocardiographic examination during and after an exercise test), peripheral arterial disease and (c) history or signs of CVD.

**CAD group:** All patients between 40 and 65 years of age who had sustained a transmural myocardial infarction (TMI) and were admitted during 1984 to the coronary care unit of the Department of Internal Medicine II were included in the study (16 males and 12 females). TMI was diagnosed by the classic ECG changes and by a greater than two-fold elevation of serum creatine kinase with positive MB-fraction. Valvular heart disease and cardiomyopathy was excluded by means of two dimensional echocardiography and the patients had to have wall motion abnormalities of the left ventricle in the echocardiogram. Patients with a history or evidence of CVD were excluded.

**Cerebrovascular disease group:** All patients, between 40 and 65 years of age, with diagnosed transient ischemic attack (TIA), prolonged reversible ischemic neurologic deficits (PRIND) and cerebral infarction (CI), admitted during 1984 to the Department of Psychiatry and Neurology were included in this group. The neurological diagnosis was confirmed by history, clinical signs and symptoms, and computerized cerebral axial tomography (CT). TIA had been diagnosed in 13 patients, 8 patients suffered from PRIND, 17 patients from CI and 8 from multiple infarctions as proved by means of CT. This group included 32 males and 14 females between 40 and 65 years of age. Patients with a history of coronary artery disease or a positive stress test for CAD were excluded from this group.

The criteria of exclusion (concerning all groups examined) were inflammatory (0 patients), liver (5 patients), thyroid (2 patients), endocrine (1 patient) or renal (3 patients) disease. No one of the subjects was on a therapy known to cause changes of serum lipid and lipoprotein levels.

**Methods**

In both the control and the CVD group, a continuous wave Doppler examination of the extracranial brain arteries (Montages MX 300) with a 4 MHZ probe and duplex scanning of the extra-cranial carotid arteries was performed. A duplex sector scanner, with a frequency of 7.5 MHZ for imaging and 5 MHZ for the pulsed doppler (ATL Mark 500), was used.

With this combination of real time B scan-imaging it became possible to achieve a degree of resolution sufficient for the detection of even small ulcerated atherosclerotic lesions of the arterial walls of the extra-cranial arteries. 13-16 Quantification of the atherosclerotic lesions was performed using a score system, see table 2. The operator was without knowledge of the patient's history and the lipid parameters.

**Chemical Analysis:** The laboratory data were estimated after the subjects had been fasting for 12-14 hours. Serum concentrations of Lp(a) were determined using the Laurell technique 17 and our own monospecific antiserum, 18 calibrating the standard sera as described earlier. The assay allowed a highly reproducible determination of Lp(a) with a satisfying accuracy in the entire range of concentration. TC and HDL-C were determined enzymatically using the PAB-method (Merck, Darmstadt, West Germany) and TG with Testomar (Behringwerke AG, West Germany). LDL-C was calculated with the Friedewald formula.

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**Table 2 Score system for Quantification of Atherosclerotic Changes of the Extra Cranial Carotid Arteries**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>no atherosclerotic lesions</td>
</tr>
<tr>
<td>1</td>
<td>discrete atherosclerotic lesions (ASL) on one side (&lt; 20% stenosis)</td>
</tr>
<tr>
<td>2</td>
<td>stenosis 20-50% on one side or discrete ASL on both sides</td>
</tr>
<tr>
<td>3</td>
<td>stenosis 50-70% on one side or stenosis 20-50% on both sides</td>
</tr>
<tr>
<td>4</td>
<td>stenosis &gt; 70% on one side or 50-70% on both sides or occlusion of one carotid artery on one side</td>
</tr>
<tr>
<td>5</td>
<td>stenosis &gt; 70% or occlusion of carotid artery on both sides</td>
</tr>
</tbody>
</table>
Results

Table 3 lists the median values of the Lp(a) levels we investigated in the control-, CVD- and CAD-group.

Lipoprotein profile of the different groups:
1. Lp(a) (table 3). The median of the Lp(a) serum levels was 5 mg/dl in the controls (range 0 to 138) versus 23 mg/dl in the CAD group (range 0 to 186) and differed highly significantly (p < 0.001). In the CVD group, the median of the Lp(a) was 11 mg/dl (range 0 to 129) and was significantly higher than in the control group (p < 0.01). However, there was no significant difference between the Lp(a) levels in the CAD and CVD group. Lp(a) correlated with Broca index (r = 0.36, p < 0.05), with TC (r = 0.35, p < 0.05), with LDL-C/HDL-C. These factors did not differ significantly between the control and cerebrovascular disease group (table 4).

2. Total TC, HDL-C, TG, LDL-C and the ratio of LDL-C/HDL-C. These factors did not differ significantly between the control and cerebrovascular disease group (table 4).

3. The carotid score system in the control and CVD group (table 5). The differences of the scores in the control versus CVD group were significant (p < 0.05).

4. Correlations of the lipid parameters with the carotid score system in the CVD group (table 6). In the group between 40 to 65 years of age, a positive correlation of Lp(a) concentrations to the carotid score (r = 0.36, p < 0.01) was received. All other lipid parameters measured had no significant correlation with our score system of the carotid arteries.

Discussion

The role of lipid and lipoprotein levels in atherogenesis is well established. Patients suffering from CAD and peripheral vascular disease had increased serum concentrations of TC, LDL-C, apolipoprotein B and very low density lipoprotein. On the other hand, the results of studies concerning lipoprotein levels in patients suffering from CAD and CVD are not uniform. In this study, the estimation of the risk of CVD by considering the significance of the differences between the median values of the controls and CVD, showed Lp(a) to be the most serious single risk factor, concerning serum lipids and lipoproteins for CVD. Various research projects agree in their findings that patients with CAD have obviously higher Lp(a) values than healthy controls and it was reported that Lp(a) is a stronger predictor for coronary arteriosclerosis than TC and decreased HDL-C levels.

Here we could show that Lp(a) serum levels were significantly higher in both, the CAD and CVD group and additionally, correlated significantly with the carotid score. Therefore, we conclude that Lp(a) is not only a risk factor for CAD, but also for cerebrovascular insufficiency. Furthermore, Lp(a) seems to be the only significant parameter for CVD among serum lipids and lipoproteins and must be considered an indicator for CVD at relatively very low concentrations.

However, the assumption that Lp(a) can act as an extremely atherogenic lipoprotein, cannot be clearly ascertained from studies with cell cultures. In fibroblasts, Lp(a) was shown to enter the cells via the LDL receptor pathway, but an uptake independent of the plasma membrane apo-B/E receptor was reported. Clear evidence for the accumulation of lipids and thus the formation of foam cells, when offering Lp(a) to cultured macrophages is lacking. Lp(a) prepared and isolated from the serum (protease protected and filtered) did not cause cholesterol ester deposition in macrophages, whereas an aggregated form of Lp(a) led to the formation of visible lipid droplets in murine peritoneal macrophages. So far, we are not able to establish if Lp(a) itself can be a cause of arteriosclerosis or is just a factor indicating an arteriosclerotic process. Lp(a) serum levels had been reported to be genetically determined, to be not significantly correlated

Table 3: Comparison of the Lp(a) Levels in the Controls (CO), Coronary Artery Disease (CAD) and Cerebrovascular Disease (CVD) Group

<table>
<thead>
<tr>
<th>Groups</th>
<th>IR25</th>
<th>x</th>
<th>IR75</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO</td>
<td>3</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>CAD</td>
<td>8</td>
<td>23</td>
<td>37</td>
</tr>
<tr>
<td>CVD</td>
<td>6</td>
<td>11</td>
<td>34</td>
</tr>
</tbody>
</table>

*p < 0.01; t > 0.001.

Table 4: Comparison of the Different Lipoprotein Parameters in the Controls (CO) and Cerebrovascular Disease (CVD) Group

<table>
<thead>
<tr>
<th>Lipid parameters (mg/dl)</th>
<th>IR25</th>
<th>x</th>
<th>IR75</th>
<th>IR25</th>
<th>CO vs. CVD</th>
<th>CO vs. CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>189</td>
<td>201</td>
<td>237</td>
<td>175</td>
<td>194</td>
<td>253</td>
</tr>
<tr>
<td>HDL-C</td>
<td>35</td>
<td>42</td>
<td>49</td>
<td>34</td>
<td>40</td>
<td>46</td>
</tr>
<tr>
<td>TG</td>
<td>99</td>
<td>151</td>
<td>178</td>
<td>100</td>
<td>156</td>
<td>214</td>
</tr>
<tr>
<td>LDL-C</td>
<td>103</td>
<td>128</td>
<td>145</td>
<td>99</td>
<td>124</td>
<td>161</td>
</tr>
<tr>
<td>LDL: HDL</td>
<td>2.1</td>
<td>3.1</td>
<td>4.7</td>
<td>2.5</td>
<td>3.0</td>
<td>3.8</td>
</tr>
<tr>
<td>HDL:TC</td>
<td>0.14</td>
<td>0.21</td>
<td>0.27</td>
<td>0.17</td>
<td>0.2</td>
<td>0.23</td>
</tr>
</tbody>
</table>

*x = median; IR = quartile; TC = total cholesterol; HDL-C = high density lipoprotein-cholesterol; TG = triglycerides; LDL-C = low density lipoprotein cholesterol; NS = not significant.
with age, sex, total cholesterol and triglycerides$^{34}$ and to be relatively resistant to pharmacological and dietary prohibition.$^{27,35}$ Thus, individuals with the genetic disposition to higher Lp(a) levels seem to be prone to cerebral arteriosclerosis too.

## References

27. Albers JJ, Cabana VG, Warnick GR, Hazzard WR: Lp(a) lipoprotein: relationship to sinking pre-Beta-lipoprotein, hyperlipoproteinemia and apolipoprotein B. Metabolism 24: 1047--1054, 1975

### Table 5 The Carotid Score System in the Control and CVD Groups

<table>
<thead>
<tr>
<th>Carotid Score</th>
<th>CO Groups (number of patients)</th>
<th>CVD Groups (number of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

CO = control group; CVD = cerebrovascular disease.
*p < 0.05.

### Table 6 Correlation Coefficients between Lipid Parameters and Carotid Score

<table>
<thead>
<tr>
<th>Lipid parameters</th>
<th>Correlation Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp(a)</td>
<td>0.36*</td>
</tr>
<tr>
<td>TC</td>
<td>0.25</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.07</td>
</tr>
<tr>
<td>TG</td>
<td>0.04</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.21</td>
</tr>
<tr>
<td>LDL-CHDL</td>
<td>0.04</td>
</tr>
<tr>
<td>HDL-TC</td>
<td>-0.03</td>
</tr>
</tbody>
</table>

*Years 40--65: 46 (number of patients).  
*p < 0.01.
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G Zenker, P Költringer, G Boné, K Niederkorn, K Pfeiffer and G Jürgens

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