Prevalence and Determinants of Carotid Atherosclerosis in a General Population

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Background and Purpose: The aim of this study was to assess the prevalence of asymptomatic carotid atherosclerotic lesions and their relation to principal risk factors. The importance of the relation between asymptomatic carotid atherosclerotic lesions, stroke, and coronary atherosclerosis has been widely discussed, but there are few transversal and longitudinal studies on a general population.

Methods: A noninvasive examination was carried out using high-resolution B-mode ultrasonography, which has been shown to be a reliable tool for epidemiological studies. We examined 630 men and 718 women aged 18–99 years (participation rate, 74.9%).

Results: The global prevalence of carotid atherosclerosis was 25.4% in men and 26.4% in women. Intimal-medial thickening was found in 9.4% of men and 11.7% of women. Plaque prevalence was 13.3% in men and 13.4% in women; prevalence of stenotic plaques was 2.7% and 1.5%, respectively. Subjects aged <39 years showed a very low prevalence of any asymptomatic carotid atherosclerotic lesions. In the multiple logistic regression, the analysis of subjects aged ≥40 years showed a positive significant association between the severity of carotid atherosclerotic lesions (plaques and stenosis) and age (p < 0.001), systolic blood pressure (p < 0.01), cigarette smoking (p < 0.0001), and the protective effect of high density lipoprotein cholesterol (p < 0.037). This analysis did not provide evidence of a clear-cut association between risk factors and intimal-medial thickening.

Conclusions: This population study shows the high prevalence of asymptomatic carotid atherosclerotic lesions in a general population (approximately 25% of adults) and its relation with the classic risk factors. It emphasizes the value of ultrasonography in the detection of early atherosclerotic lesions. (Stroke 1992;23:1705–1711)

KEY WORDS • carotid artery diseases • epidemiology • risk factors • ultrasonics

The importance of carotid atherosclerosis has been widely recognized because of its relation to stroke, coronary atherosclerosis, and cardiovascular risk factors. Nevertheless, there are relatively few population studies on the prevalence and natural history of asymptomatic carotid lesions. This is certainly due to the lack of safe, noninvasive quantitative procedures, which have only recently become widely used, and to the high cost and organizational commitment required. High-resolution B-mode carotid ultrasonography has been shown to be a suitable tool for epidemiological research on a general population, allowing both the detection of minimal lesions and repeatable measurements at reasonable costs. One of the major issues in this kind of study has been the reproducibility of carotid morphological assessment.

Data reliability has been guaranteed by experienced physicians performing the scans. Up until now, the published studies on early extracranial carotid atherosclerosis in general populations have involved middle-aged people. The importance of a study involving a wider age range led us to choose a representative sample of men and women aged 18–99 years living in northeast Italy.

The subjects were tested to assess the prevalence and risk factors of asymptomatic carotid atherosclerosis through B-mode ultrasonography. Fibrinogen and lipoprotein(a) [Lp(a)] have been included among the risk factors, considering their importance in atherosclerosis research.

Subjects and Methods

Subjects and General Methodology

The San Daniele Project is a population study the purpose of which is to establish the prevalence, determinants, and natural history of asymptomatic carotid atherosclerosis in a representative sample of Italians living in the Friuli-Venezia Giulia region, located along the Austrian and Slovenian borders. This region is particularly interesting because the standardized cardiovascular mortality rates and risk factors are consistently above the national mean. Moreover, a Regional Register for Cardiovascular Diseases has been opera-
TABLE 1. Demographic Composition of Sample and Participation Rate

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>No.</td>
</tr>
<tr>
<td>18–29</td>
<td>130</td>
<td>127</td>
</tr>
<tr>
<td>30–39</td>
<td>101</td>
<td>112</td>
</tr>
<tr>
<td>40–49</td>
<td>135</td>
<td>127</td>
</tr>
<tr>
<td>50–59</td>
<td>112</td>
<td>124</td>
</tr>
<tr>
<td>60–69</td>
<td>90</td>
<td>104</td>
</tr>
<tr>
<td>70–79</td>
<td>48</td>
<td>91</td>
</tr>
<tr>
<td>≥80</td>
<td>14</td>
<td>33</td>
</tr>
<tr>
<td>Total</td>
<td>630</td>
<td>718</td>
</tr>
</tbody>
</table>

TABLE 2. Reproducibility of Assessment of Severity of Carotid Atherosclerosis

<table>
<thead>
<tr>
<th>First assessment</th>
<th>Second assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>IMT</td>
</tr>
<tr>
<td>Normal</td>
<td>105</td>
</tr>
<tr>
<td>IMT</td>
<td>1</td>
</tr>
<tr>
<td>NSP</td>
<td>...</td>
</tr>
<tr>
<td>SP</td>
<td>...</td>
</tr>
<tr>
<td>Total</td>
<td>106</td>
</tr>
</tbody>
</table>

IMT, intimal-medial thickening; NSP, nonstenotic plaque; SP, stenotic plaque.

(BMI) was computed as weight (kg) divided by height squared (m²). Blood pressure readings (by mercury sphygmomanometer) and cardiac frequency were measured twice according to WHO recommendations. The average of the two readings was considered. A nonfasting venous blood sample was drawn (tourniquet used only if necessary) and plasma separated for the assay of total cholesterol, high density lipoprotein (HDL) cholesterol, fibrinogen, and Lp(a). Bilateral ultrasonographic scanning of carotid and femoral arteries was then performed. All these steps were standardized and carried out by trained operators. Of the 1,348 participants, 140 (10.3%) were randomly reinvited, and all the procedures were performed again to evaluate ultrasonographic reproducibility (Table 2) and the regression toward the mean as a basis for the prospective part of the study.

Ultrasonographic Assessment

Ultrasonographic scanning was performed with the subject in the supine position. We were able to examine the common carotid, bifurcation, and internal carotid arteries bilaterally in every subject. A duplex ultrasound system (Angioview 600, Multigon Industries, Mt. Vernon, N.Y.) was used, with a mechanical sector transducer with 7.5-MHz scanning frequency in B-mode and 5-MHz scanning frequency in pulsed Doppler mode. The ultrasonographic examination was performed by a single trained physician, unaware of the subject’s characteristics, according to a standardized technique. The carotid arteries were explored with longitudinal (anterior, lateral, posterior) and transverse scans. The lesions were classified by a standardized scoring system into intimal plus medial thickening (IMT), nonstenotic plaques (NSP), and stenotic plaques (SP). If no lesion was detected, the subject was considered normal. The intimal–medial thickness, defined as the distance between the intimal–luminal interface and the medial–adventitial interface (measured on the posterior wall), was considered pathologic if ≥1 mm (IMT). The atherosclerotic lesion was defined as a plaque when a distinct area could be identified with either mineralization or focal protrusion into the lumen. The plaques were defined as NSP or SP according to the percentage of obstruction of the luminal diameter in the projection showing the greatest impairment (inferior or superior to 40%). In the case of SP, Doppler spectrum analysis quantification by continuous-wave and pulsed-wave Doppler was performed. The Doppler sonograms were recorded at the site of maximal stenosis. In the event of
pathological findings, other parameters such as site, echocentricity, plaque texture, and surface were evaluated. The site of carotid lesions was computed according to the distance from the flow divider (FD): above FD up to 1.5 cm, internal carotid artery; below FD down to 1.5 cm, bifurcation; below FD down to 3 cm, common carotid artery. The plaque texture was classified as homogeneous if the echo pattern was uniform or heterogeneous if complex. The surface characteristics were classified as smooth or irregular, according to the intimal surface. The scans showing the most advanced atherosclerotic lesions were recorded by a computerized system able to store and treat the images ("Mercurio" Stim), composed of an IBM-compatible AT PC, an acquisition and digitalization card, and original neurovascular software. This system digitalizes a video analog signal (8 bits) and memorizes an image with a resolution of 512×512 pixels and was particularly useful in assessing reproducibility. In fact, the second scanning of the 140 reexamined subjects was performed by the same sonographer, without access to the previous frames. The readings and the measurements were carried out by another observer for the two frames in two windows. The distribution of the carotid lesions by severity classes during the first and the second scanning is represented in Table 2. Only one normal finding of 106 was read as IMT in the second analysis, and two cases of IMT were considered normal in the second check. The global discrepancy between normal and pathological findings was 2.1%. There was generally an excellent correlation, with the exception of three cases: one IMT in the first assessment was considered a minimal plaque in the second, and the reverse situation occurred twice.

**Laboratory Methods**

Total cholesterol was assayed by the enzymatic CHOD-PAP method; HDL cholesterol was measured in the supernatant after precipitation of the other fractions by a polyethylene glycol reagent (PEG-6000). Fibrinogen was determined by the Von Clauss clotting test, using an MLA Electra 900 G automatic analyzer. Lp(a) was determined by radial immunodiffusion (Immuno Biochemical, Vienna). Considering the semiquantitative characteristics of this method, Lp(a) was discretized into two classes, <30 mg/dl and ≥30 mg/dl.

**Statistical Methods**

Subjects aged ≤39 years showed a very low prevalence pattern of any asymptomatic carotid atherosclerotic lesions and therefore were not taken into account in the statistical evaluation. Age standardization was performed by the direct method using the regional population in 1989 as standard. Logistic regression (PROC LOGISTIC, SAS, Cary, N.C.) was used to obtain the odds ratio and the confidence intervals of each risk factor (either quantitative or dichotomous variables), considering age and sex (male=1, female=0) as covariates, and to test significance. A first analysis was performed using this procedure to compare the NSP and SP groups with the normal group, considering a three-class dependent variable. Subsequently the same procedure was used to evaluate the relation between the NSP and SP groups and the IMT group, again considering a three-class dependent variable. Finally, a multivariate logistic regression was applied respectively to the two analyses, entering the previously significant risk factors as independent variables.

**Results**

The rough prevalence of any detectable carotid lesion was 25.4% for men and 26.6% for women in the San Daniele population. The prevalence of the three defined ultrasonographic categories (IMT, NSP, SP) is shown separately for men and women and for each age group in Table 3 and Figure 1. It must be taken into account that each lesion is classified according to its most severe degree and therefore it can be inclusive of minor pathological changes. This was true in all but three cases of plaques detected together with IMT. Among the 257 subjects (men and women) aged <30 years no carotid lesion was identified, and in the 30–39-year age group only two subjects with IMT were found. In contrast, no men and only one woman were lesion free in people aged ≥80 years. The prevalence of each kind of lesion increased progressively with age. The small decrease in IMT prevalence rate noted between men aged 60–69 years and those aged 70–79 years was not statistically significant. However, it is interesting to note the decrease in prevalence of stenotic plaques in men aged ≥80 years, even if this was not statistically significant. In regard to sex, the greatest difference in the prevalence of asymptomatic carotid lesions was recorded before the sixth decade, when the

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**Table 3. Prevalence of Ultrasonographic Findings in Carotid Arteries**

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Normal</th>
<th>IMT</th>
<th>NSP</th>
<th>SP</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–29</td>
<td>130</td>
<td>100.0</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>30–39</td>
<td>100</td>
<td>99.0</td>
<td>1</td>
<td>0.0</td>
</tr>
<tr>
<td>40–49</td>
<td>125</td>
<td>92.6</td>
<td>6</td>
<td>3.3</td>
</tr>
<tr>
<td>50–59</td>
<td>71</td>
<td>63.4</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>60–69</td>
<td>37</td>
<td>41.1</td>
<td>21</td>
<td>3.6</td>
</tr>
<tr>
<td>70–79</td>
<td>7</td>
<td>14.6</td>
<td>9</td>
<td>4.4</td>
</tr>
<tr>
<td>≥80</td>
<td>...</td>
<td>4.8</td>
<td>9</td>
<td>1.1</td>
</tr>
</tbody>
</table>

| Total | 470 | 74.6 | 59  | 9.4 |

IMT, intimal-medial thickening; NSP, nonstenotic plaque; SP, stenotic plaque.
prevalence of any lesion and of each category was almost twice as high in men as in women. In the sixth decade there was an excess prevalence of 10% in men. The various kinds of lesions contributed in a similar way (approximately 3% each). In the seventh decade and beyond, the overall prevalence of carotid lesions was similar in the two sexes, although the severity distribution was different. The mean±SD ages of men in the four categories of carotid findings were: normal, 40.1±13; IMT, 61.5±10; NSP, 66.1±10; and SP, 69.5±10 years. The mean±SD ages of women were: normal, 41.9±14; IMT, 67.8±11; NSP, 71.3±9; and SP, 76.0±6 years. In both sexes mean ages increased according to the degree of severity, and for each pathological category the mean age of men was 5–6 years younger than that of women.

Tables 4 and 5 show nonmetabolic and metabolic risk factors, respectively, according to the ultrasonographic carotid findings, in subjects aged ≥40 years. The normal group and the atherosclerotic groups (plaque and stenosis) were compared by means of logistic regression. Systolic blood pressure, cigarette smoking (expressed as number of packs smoked during the subject’s lifetime) and lifetime alcohol intake were significantly associated with the severity of the lesions after adjustment for age and sex. HDL cholesterol significantly decreased. These risk factors retained their statistical significance, sex excluded, when examined in a six-variable logistic model (Table 6), thus independently contributing to the prediction of the severity of the carotid atherosclerosis. A comparison between the IMT group and the atherosclerotic groups was then performed by means of logistic regression (Tables 4 and 5). Cigarette smoking (expressed as number of packs smoked during the subject’s lifetime) and lifetime alcohol intake were significantly associated with the severity of the lesion, after adjustment for age and sex. BMI significantly decreased. However, on entering these risk factors in a five-variable multiple regression model including age and sex (Table 7), alcohol intake lost its significance and cigarette smoking during the subject’s lifetime was only of borderline significance. Age and BMI retained their respective unfavorable and protective roles.

Discussion

Ultrasoundographic methods can certainly permit the evaluation of early carotid atherosclerosis in asymptomatic subjects.17–21 Epidemiological surveys have until recently had to deal with the major problems of reproducibility and skill. Thus relatively few population studies have estimated the prevalence of carotid atherosclerosis with this technique,12–19 and these are limited to middle-aged people. In the San Daniele Project we were able to evaluate a sample of the adult population of the Friuli-Venezia Giulia region of Italy, stratified by age and sex. In particular we decided to also include the geriatric age range, considering the high incidence of stroke in this population.35 Although different criteria have been adopted in the above-mentioned studies, there is a general agreement in categorizing carotid findings into three types of lesions: IMT, NSP, and SP. The last two categories have sometimes been considered together as "plaques."13–15,19 It is useful to compare our results with those of the published studies that adopted the same classification, taking into account the different criteria when necessary. The prevalence of any lesions is high in our asymptomatic population: 25.4% for men and 26.6% for women. It is similar to that reported by Gostomzyk et al,12 although these authors do not specify the criteria for defining the lesions and the German population is younger.

**Table 4. Age-Adjusted Nonmetabolic Risk Factors According to Ultrasonographic Carotid Findings in Subjects Aged ≥40 Years**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal (n=529)</th>
<th>Plaque (n=180)</th>
<th>Stenosis (n=28)</th>
<th>OR NO/ATHS (95% CI)</th>
<th>p*</th>
<th>IMT (n=141)</th>
<th>OR IMT/ATHS (95% CI)</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>159.5±24</td>
<td>165.6±29</td>
<td>175.1±30</td>
<td>1.11/10 mm Hg (1.02–1.21)</td>
<td>0.0110</td>
<td>162.4±23</td>
<td>1.05/10 mm Hg (0.96–1.14)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>92.3±12</td>
<td>93.3±12</td>
<td>95.1±15</td>
<td>1.08/10 mm Hg (0.93–1.26)</td>
<td>NS</td>
<td>93.4±12</td>
<td>1.03/10 mm Hg (0.88–1.20)</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.5±4.0</td>
<td>26.4±5.6</td>
<td>25.6±2.6</td>
<td>0.99/unit (0.94–1.04)</td>
<td>NS</td>
<td>27.2±4.1</td>
<td>0.93/unit (0.88–0.98)</td>
<td>0.0074</td>
</tr>
<tr>
<td>Cigarette packs (life)</td>
<td>32.5±63</td>
<td>65.6±72</td>
<td>111.7±85</td>
<td>1.007/100 packs (1.004–1.010)</td>
<td>0.0001</td>
<td>55.4±80</td>
<td>1.004/100 packs (1.001–1.007)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Alcohol (life) (kg)</td>
<td>496.8±647</td>
<td>916.2±907</td>
<td>596.8±660</td>
<td>1.005/10 kg (1.003–1.007)</td>
<td>0.0001</td>
<td>594.6±593</td>
<td>1.003/10 kg (1.001–1.006)</td>
<td>0.0160</td>
</tr>
</tbody>
</table>

Values are mean±SD. IMT, intimal-medial thickening; BP, blood pressure.

*Significance test obtained from logistic regression with three-class severity of carotid atherosclerosis as the dependent variable (Normal, Plaque, Stenosis) and age, sex, and each risk factor as independent variables. OR NO/ATHS, odds ratio from this logistic regression.

†Significance test obtained from logistic regression with three-class severity of carotid atherosclerosis as the dependent variable (IMT, Plaque, Stenosis) and age, sex, and each risk factor as independent variables. OR IMT/ATHS, odds ratio from this logistic regression.
In the 40–69-year age range, the overall prevalence in the San Daniele Project of 30.8% in men and 21.9% in women is quite similar to that found by Bucci et al\textsuperscript{16} in women (19.7%). We were able to compare the IMT (mg/dl) found in a central Italian population, both for men (29.8%) and women (11.2%). The difference between the Finns and the Italians and independently associated with the severity of atherosclerotic lesions (NSP and SP) is high in those aged 60–69 years (36% in men and 30% in women) and is particularly elevated in people aged ≥70 years (68% in men and 52% in women). In contrast, the prevalence of carotid lesions in those aged <39 years is very low both for men and women (1%).

The main question is the nature of IMT: independently of other lesions, it is present in 70% of people aged ≥60 years, and its prevalence as a single finding is 52% in women (1%). The prevalence of carotid atherosclerotic lesions (NSP and SP) is high in those aged 60–69 years (36% in men and 30% in women) and is particularly elevated in people aged ≥70 years (68% in men and 52% in women). In contrast, the prevalence of carotid lesions in those aged <39 years is very low both for men and women (1%).

The main question is the nature of IMT: independently of other lesions, it is present in 70% of people aged ≥60 years, and its prevalence as a single finding is 26%. IMT increases with age and hypertension in hypercholesterolemic patients.\textsuperscript{37} Salonen and Salonen\textsuperscript{15} consider IMT an early form of arteriosclerosis; IMT, like other carotid plaques according to these authors, has a predictive value for future coronary events. On the other hand, other authors maintain that IMT may be an adaptive change associated with age.\textsuperscript{38} Moreover, definite proof is lacking for a progression of carotid lesions from IMT to plaque.

In the logistic regression analysis performed on subjects aged ≥40 years, systolic blood pressure, the number of cigarette packs smoked during the subject's lifetime, and lifetime alcohol intake were significantly and independently associated with the severity of atherosclerotic lesions (plaques and stenosis) after adjustment for age and sex. On the other hand, HDL cholesterol is roughly twice as high in men as confirmed by other population studies. As far as we are aware, the San Daniele Project is the first study to include a noninstitutionalized asymptomatic geriatric population. The prevalence of carotid atherosclerotic lesions (NSP and SP) is high in those aged 60–69 years (36% in men and 30% in women) and is particularly elevated in people aged ≥70 years (68% in men and 52% in women). In contrast, the prevalence of carotid lesions in those aged <39 years is very low both for men and women (1%).

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terol was significantly lower, in agreement with other population studies. The age-standardized mean cholesterol and BMI levels found in the SP group (Table 4) can be partly explained by the small number in the group and by its elevated mean age. (The nonstandardized values are cholesterol, 214.3±43.0 mg/dl; BMI, 25.9±3.3.) In addition, it is well known that cholesterol and BMI levels tend to decrease in the older population. Considering the relation between IMT and the atherosclerotic groups (plaque and stenosis) to establish whether they share the same risk factors, age proved a worsening variable, together with the absolute number of cigarette packs smoked, although the significance of age was borderline in the multivariate analysis. BMI showed an inverse pattern, which may be attributed to the marked decrease of this factor with age, an effect only partially corrected by the standardization procedure. These results are difficult to explain, considering also the multiple logistic model (Table 7) in which the chances of a carotid finding being plaque compared with IMT were not significant. Thus the problem of IMT is still unresolved, and its role cannot be determined from the cross-sectional part of this study. The lack of effect of Lp(a) in this study may be attributed to the assay method used, which does not allow quantitative estimates. The different results obtained by Koeltinger and Jurgens may depend on their quantitative assay and their different inclusion criteria.

In other population studies, it is evident that age and cigarette smoking are the most concordant independent risk factors for carotid atherosclerosis severity, confirming previous reports in selected subjects. Systolic blood pressure seems to be a risk factor only in the San Daniele Project and in the French study, but diastolic blood pressure is significant only in the French study. The question is widely debated because the results of other studies in selected subjects are discordant: probably a more accurate identification of the role of blood pressure will emerge from longitudinal observational population studies. The precise role of blood lipids, in particular total and HDL cholesterol, in the development and severity of carotid atherosclerosis is not known at present because findings are also discordant in regard to these factors in both population and selected studies. Although total cholesterol is not an independent risk factor in the multivariate analysis in the San Daniele Project, it is noteworthy to consider the protective effect of HDL cholesterol.

Conclusions

The huge human and economic costs of cardiovascular diseases in affluent industrial societies emphasize the need for effective prevention. The predictive validity of ultrasonographic assessment of asymptomatic carotid atherosclerosis has recently been evaluated, confirming the role of even minimal lesions such as IMT in the development of major coronary events. On the other hand, the risk of stroke is particularly high in those with asymptomatic severe carotid lesions. The San Daniele Project data show that the prevalence of asymptomatic carotid atherosclerosis is high (approximately 25% of the adult population) and is related to the classic risk factors.

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