Importance of HDL-c for the Occurrence of Cardiovascular Disease in the Elderly

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Summary

Background: Studies on the impact of HDL-c and the occurrence of cardiovascular disease (CV) in the elderly are scarce.

Objective: To evaluate the clinical and laboratory variables and the occurrence of CV events in elderly patients stratified according to the behavior of HDL-c during an eight-year follow up.

Methods: We evaluated 81 elderly patients, mean age of 68.51 ± 6.32 years (38.2% male), in two stages (A1 and A2), with a minimum interval of five years. The subjects were divided into 3 groups according to HDL-c levels: normal HDL-c in both assessments (NG) (n = 31), low HDL-c in both assessments (LG) (n = 21) and variable HDL-c in A1 and A2 (VG) (n = 29). Main CV events were recorded: coronary heart disease (angina, myocardial infarction, percutaneous / surgical myocardial revascularization), stroke, transient ischemic attack, carotid disease, dementia and heart failure.

Results: The groups did not differ in gender and age in A1 and A2. Mean triglyceride levels were lower in the NG in A1 (p = 0.027) and A2 (p = 0.016) than in the LG. The distribution of CV events was as follows: 13 events in the NG (41.9%), 16 (76.2%) in the LG, and 12 (41.4%) in the VG ($\chi^2 = 7.149$, p = 0.024). The logistic regression analysis showed that the older the patient (OR = 1.187, p = 0.0230) and the lower the HDL-c (OR = 0.9372, p = 0.0102), the greater the occurrence of events CV.

Conclusion: Permanently low HDL-c during eight years of monitoring is a risk factor for the development of CV events in the elderly.

Key Words: Cholesterol HDL; Cardiovascular Diseases; Aging.

Introduction

Worldwide, the number of people aged 60 years or over has grown rapidly. 10.5% of the total population of Brazil are aged 60 years or over, according to data currently available on the IBGE website, and life expectancy at birth reached an average of 72.05 years. Furthermore, life expectancy for those reaching 60 years of age increased significantly, changing the epidemiological profile, with a high prevalence of cardiovascular diseases in this population.

Epidemiological data show that mortality from cardiovascular diseases (CVD) increases with age. These numbers reflect the importance of the atherosclerotic process in the elderly, and this makes its prevention and detection essential. However, studies in the field of geriatrics are still incipient and controversial as to the predictive value of risk factors (RF) for CVD in the elderly, especially after the age of 75 years.

Especially in the last four decades, RF for CVD were extensively studied. Aging, high blood pressure (HBP), dyslipidemia, type II diabetes mellitus (DM II), smoking habit, obesity and a sedentary lifestyle, for example, are some of the RF that can lead to endothelial dysfunction and, therefore, to vascular changes; also there is a clear association between these risk factors and atherosclerosis.

The presence of atherosclerotic lesions is associated, among other RF, with LDL cholesterol (LDL-c) ≥ 100 mg / dL (2.6 mmol / L) and HDL cholesterol (HDL-c) < 40 mg / dL (1.04 mmol / L). On the other hand, high levels of HDL-c have been recognized as having antiatherogenic effects. The role of HDL-c, though not yet fully established, is attributed to its ability to mediate reverse cholesterol transport.

Other protective HDL-c mechanisms have been proposed, such as inhibition of LDL-c oxidation, reduction in blood viscosity, regulation of prostaglandins and thromboxane synthesis and activation of fibrinolysis, influence on endothelial function and anti-inflammatory action.

The EPESE study suggested that, in the elderly population, HDL-c levels are a more specific and powerful predictor of risk of death from coronary artery disease (CAD) than total cholesterol. Corti et al concluded from the EPESE data that...
abnormal cholesterol levels are associated with CVD death in the elderly, and that their exclusion from studies that evaluate the relationship between cholesterol and CVD is improper. In “The Northern Manhattan Study”\(^a\), the authors infer that high HDL-c is associated with a reduced risk of ischemic stroke in the elderly, and they considered HDL-c as an important modifiable RF for stroke. Another study showed an association between low HDL-c and mortality risk from CVD and stroke in the elderly\(^b\). On the other hand, in the PROSPER study\(^c\), there was no highly significant reduction in vascular events, and there should be caution in the analysis of these data until other studies confirm these benefits. However, the HPS\(^d\) study found a greater reduction in vascular events in patients with high levels of HDL-c treated with simvastatin when compared to those treated with placebo.

Therefore, the objective of this study was to evaluate clinical and laboratory variables and the occurrence of fatal and non-fatal CV events, such as coronary artery disease (angina, myocardial infarction and percutaneous or surgical myocardial revascularization), stroke, transient ischemic attack (TIA), carotid artery disease, and heart failure (HF), in elderly patients stratified according to the behavior of the HDL-c during an eight-year follow up.

**Method**

In this study, 81 individuals were followed up during 96.68 ± 11.57 months in the outpatient clinic of Hospital Universitário Pedro Ernesto, and they were divided into three groups, which were formed according to HDL-c behavior, which was determined at the initial assessment (assessment 1) and at the second assessment (assessment 2), namely:

1. Normal group (NG), consisting of individuals with normal values of HDL-c, composed of 31 individuals, 10 males (32.3%) and 21 females (67.7%).

2. Low group (LG) with abnormal values of HDL-c (low), consisting of 21 individuals, 6 males (28.6%) and 15 females (71.4%)

3. Variable group (VG), with variable values of HDL-c at the two assessments, composed of 29 individuals, 15 males (51.7%) and 14 females (48.3%)

To form the groups, we considered the values of HDL-c in accordance with the recommendations of the IV Brazilian Guidelines on Dyslipidemia and Prevention of Atherosclerosis\(^e\), and HDL-c values greater than or equal to 40 mg / dl for males, and greater than or equal to 50 mg / dl for females were considered normal. The values below these cut-off points were considered low, corresponding to abnormal values.

Patients who agreed to participate were interviewed and underwent clinical examination and laboratory tests. From assessment 1, conducted about eight years in the past, we obtained demographic and epidemiological data, in addition to past medical conditions and medication in use. From assessment 2, the same data were obtained, with emphasis on the identification of fatal and non-fatal CV events, such as CAD (angina, myocardial infarction and percutaneous or surgical myocardial revascularization), stroke and TIA, carotid disease, dementia, and HF. In cases of death, the cause was established by analysis of the existing medical documentation.

The laboratory evaluation included obtaining the values of total cholesterol (TC), triglycerides (TG), HDL-c, and LDL-c. The following values were considered normal: TC <200 mg/ dl, LDL-c <130 mg/dl, and triglycerides <150 mg/dl.

For coronary artery disease characterization, surgical or percutaneous myocardial revascularization, positive myocardial scintigraphy and echocardiography\(^f\) with well-defined contractility changes for coronary disease were taken into account\(^g\). For TIA, an event of temporary loss of consciousness or motor deficit that was well documented by the hospital was taken into account. A cerebrovascular disease associated with two cognitive deficits, one of them involving memory, was considered as dementia according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Carotid disease was considered characterized when the echo-Doppler showed the presence of atherosclerotic plaques.

Any other complications, such as cancer, hypothyroidism, etc., were considered as events.

Resting blood pressure (BP) was measured twice during the consultation, with an interval of at least five minutes, with the patient in a sitting position, and the mean value of the readings was recorded. BP measurement and its classification were performed according to V Brazilian Guidelines of Arterial Hypertension criteria\(^h\).

Statistical analysis was performed using the program SPSS for Windows, version 8.0.0. The test of logistic regression was used to assess the probability of occurrence of an event.

**Results**

In reference to age and time of monitoring, the comparison of the mean values of the three groups showed no statistical significance, and the same was observed in reference to the distribution by gender (table 1).

The comparisons of anthropometric, metabolic and pressure variables of assessments 1 and 2 are described in tables 2 and 3, respectively. The only significant difference observed in both assessments was in the comparison of mean HDL-c and TG levels, in which group B had lower HDL-c levels and higher TG levels, when compared to other groups.

The comparison of mean systolic blood pressure (SBP) values and mean diastolic blood pressure (DBP) values, in both assessments (tables 2 and 3), showed no statistical difference among the three groups and the prevalence of high blood pressure.

Analysis of events in reference to HDL-c levels Table 4 shows the distribution of events in the three groups according to the behavior of HDL-c.

The group with low HDL-c in both assessments showed a significantly greater percentage of CV events than the other two groups. 13 CV events occurred in the normal group...
Table 1 - Epidemiologic variables: Age at A1, gender and time of monitoring.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal Group (n=31)</th>
<th>Low Group (n=21)</th>
<th>Variable Group (n=29)</th>
<th>Statistical test</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67.48 ± 4.70</td>
<td>68.82 ± 8.35</td>
<td>69.24 ± 5.93</td>
<td>F= 0.610</td>
<td>0.546</td>
</tr>
<tr>
<td>Gender</td>
<td>M</td>
<td>10 (32.3%)</td>
<td>6 (28.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>21 (67.7%)</td>
<td>15 (51.7%)</td>
<td>χ²= 3.532</td>
<td>0.171</td>
</tr>
<tr>
<td>Follow up</td>
<td>97.45 ± 11.21</td>
<td>97.90 ± 13.41</td>
<td>94.69 ± 10.09</td>
<td>F= 0.626</td>
<td>0.537</td>
</tr>
</tbody>
</table>

M– male; F– female

Table 2 - Anthropometric, blood pressure and metabolic variables of the three groups at assessment 1.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal Group (n=31)</th>
<th>Low Group (n=21)</th>
<th>Variable Group (n=29)</th>
<th>Statistical test</th>
<th>Level of significance (p)</th>
<th>2 by 2 Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>64.6839 ± 12.2831</td>
<td>66.0714 ± 10.4246</td>
<td>69.5034 ± 10.2623</td>
<td>F= 1.463</td>
<td>0.238</td>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.58 ± 0.0743</td>
<td>1.5976 ± 0.0612</td>
<td>1.6179 ± 0.0855</td>
<td>F= 1.886</td>
<td>0.158</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.0915 ± 4.0649</td>
<td>25.9275 ± 3.9813</td>
<td>26.4846 ± 3.9135</td>
<td>F= 0.134</td>
<td>0.875</td>
<td></td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>230.48 ± 44.10</td>
<td>231.38 ± 43.77</td>
<td>223.52 ± 63.37</td>
<td>F= 0.188</td>
<td>0.829</td>
<td></td>
</tr>
<tr>
<td>Abnormal TC</td>
<td>24 (77.4%)</td>
<td>16 (76.2%)</td>
<td>14 (48.3%)</td>
<td>χ²= 6.884</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td>HDL-c (mg/dL)</td>
<td>56.61 ± 12.12</td>
<td>38.57 ± 6.05</td>
<td>41.00 ± 7.47</td>
<td>F= 39.099</td>
<td>&lt;0.001</td>
<td>N&gt;B=V</td>
</tr>
<tr>
<td>Abnormal HDL-c</td>
<td>21 (100%)</td>
<td>22 (75.9%)</td>
<td>22 (75.9%)</td>
<td>χ²= 59.677</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>LDL-c (mg/dL)</td>
<td>146.05 ± 43.15</td>
<td>158.42 ± 40.35</td>
<td>149.78 ± 60.52</td>
<td>F= 0.308</td>
<td>0.673</td>
<td></td>
</tr>
<tr>
<td>Abnormal LDL-c</td>
<td>20 (64.5%)</td>
<td>15 (71.4%)</td>
<td>15 (51.7%)</td>
<td>χ²=2.167</td>
<td>0.338</td>
<td></td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>125.65 ± 56.45</td>
<td>171.33 ± 67.33</td>
<td>166.97 ± 80.95</td>
<td>F= 3.784</td>
<td>0.027</td>
<td>B&gt;N; N=V; B=V</td>
</tr>
<tr>
<td>Abnormal TG</td>
<td>10 (32.3%)</td>
<td>14 (46.7%)</td>
<td>13 (44.8%)</td>
<td>χ²= 5.987</td>
<td>0.049</td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>155.16±23.92</td>
<td>157.05±25.81</td>
<td>152.66±25.43</td>
<td>F= 0.195</td>
<td>0.823</td>
<td></td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>87.48 ± 9.09</td>
<td>86.76 ± 8.87</td>
<td>85.90 ± 8.46</td>
<td>F= 0.243</td>
<td>0.785</td>
<td></td>
</tr>
<tr>
<td>HBP</td>
<td>25 (80.6%)</td>
<td>21 (72.4%)</td>
<td>21 (72.4%)</td>
<td>χ²=0.567</td>
<td>0.753</td>
<td></td>
</tr>
</tbody>
</table>

BMI – body mass index; TC – total cholesterol; HDL – high-density lipoprotein; LDL – low density lipoprotein; TG – triglycerides; SBP – systolic blood pressure; DBP – diastolic blood pressure; HBP – high blood pressure.

(41.9%), 16 (76.2%) in the low group, and 12 (41.4%) in the variable group (χ² = 7.419, p = 0.0024).

Table 5 shows the distribution of types of events, showing that there was no difference among the groups as to the type of CV event.

In a logistic regression model the occurrence of events was considered as a dependent variable; in turn, age, SBP, DBP, cholesterol, HDL-c and triglycerides values obtained in the first assessment were considered as independent variables. In this model, only age and HDL-c had a significant correlation with the occurrence of CV events. We observed that the older the patient, the greater the occurrence of cardiovascular events (odds ratio = 1.187, p = 0.0230). We also observed that the lower the HDL-c, the greater the occurrence of cardiovascular events (odds ratio = 0.9375, p = 0.0102) (table 6).

The analysis of the distribution of deaths showed no statistically significant difference (χ² = 1.359, p = 0.507).

Discussion

In addition to increased life expectancy at birth, chronic disability and institutionalization have also shown higher prevalence among the elderly, with a predominance in women. As a result of the increased prevalence of chronic degenerative diseases and their sequelae, functional dependence is an additional challenge. In 2005, the per capita expenditure of the hospitals of the Unified Health System (SUS) with men aged from 60 to 69 years was over four times higher than that spent with men aged from 30 to 39 years, but only half of the group had 80 years or over.
Table 5 - Occurrence of different types of CV events in the three groups stratified by the behavior of HDL-c

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal Group (n= 31)</th>
<th>Low Group (n= 21)</th>
<th>Variable Group (n= 29)</th>
<th>Statistical test</th>
<th>Level of significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Events</td>
<td>18 (58.1%)</td>
<td>5 (23.8%)</td>
<td>17 (58.62%)</td>
<td>χ² = 11.174</td>
<td>0.344</td>
</tr>
<tr>
<td>CAD</td>
<td>4 (12.9%)</td>
<td>8 (38.09%)</td>
<td>5 (17.24%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke-TIA</td>
<td>2 (6.45%)</td>
<td>2 (9.52%)</td>
<td>3 (10.34%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVD</td>
<td>3 (9.67%)</td>
<td>4 (19.04%)</td>
<td>3 (10.34%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF</td>
<td>3 (9.67%)</td>
<td>2 (9.52%)</td>
<td>1 (3.44%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>1 (3.22%)</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The magnitude of the demographic and epidemiological changes requires the urgent adoption of a health care policy for the elderly\textsuperscript{25-28}. Health expectation is even more important than life expectancy, and this is a challenge raised by the World Health Organization: “How to prevent and postpone disease and disability, and to maintain the health, independence and mobility of an aging population?”}\textsuperscript{26-27}.

CVD is the leading cause of death and disability among individuals aged 65 years or over, despite the gradual decline of CVD in the population since the 70’s. Therefore, CVD preventive measures have acquired special importance.\textsuperscript{1,24} CVD has a significant impact on life expectancy, and it contributes to a deterioration in quality of life, leading to loss of independence and institutionalization.

Numerous studies have addressed the influence of RF in the genesis of atherosclerosis\textsuperscript{25-28}. However, the literature presents controversial results regarding the predictive value of some risk factors for CVD in the elderly, especially after 75 years\textsuperscript{29,30}. The emergence of studies on risk factors for atherosclerosis, with appropriate design for the elderly, has revealed new facts\textsuperscript{31,32}, although the results still show some discrepancies among them.

Several articles have considered aging as one of the most important independent RF for morbidity and mortality from CVD, and the vascular endothelium is a clear body target\textsuperscript{25,28,31}. Luscher and Barton\textsuperscript{33} studied the influence of age, hypertension and lipids on the vascular endothelium, and observed that all three conditions were associated with functional changes in the endothelium and could contribute to vascular proliferation, thrombosis, vasospasm and ischemia. Within the context of risk factors, this study was designed to establish the importance of HDL-c for the occurrence of CVD in the elderly.

Initially, we compared the epidemiological variables of the three groups. An evaluation of the mean values for age, gender and follow-up time showed homogeneity among the three groups, with no statistically significant difference, and therefore no influence on the analysis of events.

The anthropometric indices used were weight, height and body mass index (BMI), which was used due to its good correlation with direct measurement of body fat. In this study, there were no differences among the groups regarding the average anthropometric variables analyzed, which is in agreement with the study by Price, in which BMI was not positively associated with CV mortality in men and women\textsuperscript{32}.

Mean SBP and DBP values showed no statistical differences among the three groups in both assessments, and they did not interfere with the results. A recent analysis of the Framingham Heart Study showed that the accumulation of RF, including high blood pressure, contributes to lower survival and greater inability in the elderly\textsuperscript{33}. The effects of BP on CV morbidity and mortality are well established\textsuperscript{34}. In this study, BP assessed by logistic regression model showed no statistically significant association with cardiovascular events.

The metabolic variables were determined in the initial phase of study, assessment 1, and reassessed after at least five years in assessment 2; these values were correlated with the events that occurred during the study.

High levels of total cholesterol and LDL-c have been shown to be important risk factors for the incidence of CVD and total mortality in middle-aged individuals in several studies, including the Honolulu Heart Program (HHP)\textsuperscript{35,36}. However, these findings in the elderly have been less consistent. In the HHP, the proportion of reduction in the rate of events was similar in young subjects and in the elderly over 70 years. In the results obtained in this study, there was no relationship among CVD, total cholesterol and LDL-c in the elderly.

The analysis of cholesterol mean values in assessment 1 showed higher values in comparison to the values obtained in assessment 2 in all groups; therefore, lower values were obtained in older individuals. This observation is in agreement with the literature, which describes a reduction in the prevalence of abnormal lipid profile with age\textsuperscript{37}. Furthermore, the use of specific medication for the treatment of dyslipidemia could have contributed to the change observed. Also, some epidemiological studies suggest that the relationship between CAD and the levels of cholesterol undergoes a decline with age, which may have originated the belief that there would be less benefit in the treatment of cholesterol in the elderly\textsuperscript{24,35,36}. However, some studies show positive results in regard to the treatment, as occurred in the Heart Protection Study\textsuperscript{38}, in which there was a subgroup of patients aged over 70 years, most of them with less than 75 years, and there was a reduction in vascular risk in this group.

After using a logistic regression model in which the occurrence of events was considered as a dependent variable, and age, SBP, DBP, TC, HDL-c and TG as independent variables in assessment 1, we observed that cholesterol was not significantly associated with the development of cardiovascular events.

Mean triglyceride levels were significantly different in the two assessments. In this study, the highest triglyceride levels occurred in the group with the lowest HDL-c levels, both in assessment 1 and in assessment 2, in agreement with the close association among reverse cholesterol transport, HDL-c and triglycerides\textsuperscript{37,38}. However, in a logistic regression model, the variable triglycerides showed no significant relationship with...
CVD. While univariate analysis of epidemiological studies have shown that hypertriglyceridemia is associated with an increase in CAD in men and women, multivariate analysis have shown conflicting results for the characterization of triglycerides as an independent risk factor for CAD, which seems to be a more important factor for new events in women than in men.

The logistic regression model showed that the older the patient the greater the occurrence of CV events (odds ratio = 1.187, p = 0.0230), which is in agreement with the literature which describes a direct relationship between CV mortality and age.

The behavior of HDL-c showed statistical expression for the occurrence of events (χ² = 7419, p = 0024). In the analysis of logistic regression model, this relationship was maintained, showing that the higher the HDL-c levels the lower the occurrence of CV events.

HDL-c has been identified as a major and independent risk factor, with greater association with the development of CAD than total cholesterol and LDL-c. Another aspect that has been demonstrated is the predictive value of low HDL-c as a risk factor for CAD, which is higher in women than in men.

The antiatherogenic effects of HDL-c have been tentatively explained through its anti-inflammatory, antioxidant, antiplatelet, anticoagulant and pro-fibrinolytic properties, which promote the maintenance of endothelial function. Therefore, low levels of HDL-C would supposedly contribute to an increase in CVD by the loss of antiatherogenic effects, due to lower reverse cholesterol transport, lower anti-inflammatory action and loss of antithrombotic properties.

Low levels of HDL-c are frequently observed in CAD patients, and genetic syndromes that lead to high HDL-c are frequently associated with reductions in the incidence of CAD and greater longevity. The interest on HDL-c has become stronger, as is often found in association with high levels of atherogenic lipoproteins, including VLDL and small dense LDL-c, and also with the metabolic syndrome, including insulin resistance, glucose intolerance and high blood pressure. The complexity of the metabolism of HDL-c still needs further studies.

The high occurrence of events in the three groups could be related to a direct association between events and mortality with age and time of exposure to RF, so much so that in the low HDL-c group, only 23.8% of the patients did not show any event. However, there was no predominance of any specific type of CV event associated with the behavior of HDL-c.

It must be emphasized that this was a longitudinal study, with a prolonged follow-up — eight years — and that its main contribution was to demonstrate the significant correlation of persistently low HDL-c with the occurrence of CV events.

This study has limitations arising from the relatively small number of patients and it is not advisable to generalize its results, despite its important findings. The outcomes assessed are not all considered major; however, they may quite reasonably characterize the presence of significant atherosclerotic disease and cardiovascular events in a prospectively studied sample of elderly patients. Moreover, these conditions have great impact on the quality of life, which was one of the main objectives in the evaluation of this age group.

In conclusion, the occurrence of permanently low values of HDL-c in the elderly, during an eight-year follow up, was associated with higher levels of triglycerides in both assessments, but was not related to blood pressure, anthropometric indices and LDL-c. Aging and permanently low HDL-c levels were risk factors for cardiovascular events, whereas total cholesterol and blood pressure showed no significant relationship. Data from this study emphasize the need for a lipid profile assessment in the elderly, so as to identify patients with increased risk for CV disease.

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**Potential Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

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**Study Association**

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**References**


