The importance of HDL-C and CRP in cardiovascular risk evaluation in longevous elderly individuals

A importância do HDL-C e da PCR na avaliação do risco cardiovascular em idosos longevos

Renato Laks1, Lara Miguel Quirino Araújo1, Clineu de Mello Almada Filho1, Maysa Seabra Cendoroglo1

ABSTRACT

The association between total mortality, lipoproteinS, and inflammatory markers, and their implications with aging and longevity are often controversial. Among the most often studied markers are low HDL cholesterol and high C-reactive protein. Particularly in octogenarians, it is expected that the impact of the inclusion of HDL cholesterol and C-reactive protein will improve the stratification of absolute cardiovascular risk. In the present study, we performed a literature review in PubMed about the relation between HDL cholesterol, inflammation and longevity. Applying the inclusion and exclusion criteria adopted, we selected 30 studies, among which one systematic review on the relation between HDL cholesterol and stroke, one meta-analysis on the relation between total cholesterol and HDL cholesterol with mortality, 22 longitudinal studies, and six cross-sectional studies. The results show an inverse association between HDL cholesterol and total mortality, and between cardiovascular mortality and C-reactive protein, as well as a positive association between C-reactive protein and mortality in longevous individuals. C-reactive protein and HDL cholesterol displayed promising characteristics as predictors of cardiovascular mortality in longevous elderly persons.

Keywords: Longevity; C-reactive protein; Lipoproteins, HDL; Cholesterol, HDL; Mortality; Cardiovascular system; Lipids

INTRODUCTION

The prevalence of atherosclerotic cardiovascular disease increases exponentially with aging, and it is the main cause of morbidity and mortality in the aged. Risk stratification is fundamental for determining treatment goals. However, the predictive value of traditional risk factors decreases with age, while the identification of emerging risk markers shows greater importance, primarily for longevous elderly people.

Elevated levels of C-reactive protein (CRP) are a well-established biomarker in middle-aged adults. Albert et al., in a cross-sectional study conducted in 2003, showed a significant correlation between the levels of CRP and Framingham risk score(1).

In a prospective study, Danesh et al.(2) investigated the relation between CRP and coronary artery disease (CAD) in 2459 participants that developed coronary artery disease (CAD) and 3969 controls. The mean age was 56 years, and the odds ratio to develop CAD fell between the terciles with the greatest and lowest CRP levels ( > 2 mg/L and < 0.78 mg/L, respectively) of 1.45 (CI95%: 1.25-1.68). These authors also conducted a meta-analysis with the same objectives, involving 22 prospective studies and 7068 participants, resulting in an odds ratio for the development of CAD in the elevated CRP group of 1.58 (CI95%: 1.48-1.68). The Emerging Risk Factors Collaboration carried out...
a new meta-analysis in 2010 involving 54 prospective studies, with 160 thousand participants at a mean age of 60 years, and obtained a relative risk of 1.55 with an increase of one standard deviation in the CRP concentration log(3). We can also highlight the importance of the intervention study “Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin” - JUPITER, which demonstrated that treatment of inflammation, evaluated by means of CRP, was effective regardless of the LDL cholesterol (LDL-C) target. This clinical trial enrolled 17802 individuals, with a mean age of 66 years and average follow-up of 1.9 years, with LDL-C < 130 mg/dL and CRP > 2 mg/L, assessing the benefit of introducing rosuvastatin. The group that used the medication showed a reduction by 37% in CRP levels, with a relative risk for cardiovascular mortality or cardiovascular events > 0.56 (p<0.00001)(4, 5).

The relation between low HDL cholesterol (HDL-C) and cardiovascular risk is also well established in middle-aged adults. Gordon et al. evaluated the data of four large prospective American studies, resulting in 15252 participants, aged between 30 and 69 years, and obtained a significant protective relation between HDL-C and CAD. The increase by 1 mg/dL of HDL-C resulted in a CAD reduction by approximately 2% and 3% in men and women, respectively(6). Cooney et al. investigated the impact of the inclusion of HDL-C in the cardiovascular risk stratification of 104,961 adults at 47 years of age, from 12 European cohorts that originated the Systematic Coronary Risk Evaluation (SCORE), showing a statistically significant improvement of the index of risk reclassification, with a relative risk of 0.62 and 0.76 in women and men, respectively, and a slight modification of the absolute risk (6.5% of the participants increased risk by 1%)(). The same authors, in another study published in 2009, evaluated the effect of HDL-C in cardiovascular morbidity and mortality also by means of the SCORE study cohorts; this time, however, the age group of over 65 years was included. In these, an increase of 19.3 mg/dL resulted in a relative risk of 0.53 (CI95%: 0.42-0.8) and 0.79 (CI95%: 0.64-0.98) for women and men, respectively. These data become even more relevant because in longevous elderly relative risks are frequently attenuated, since age is an important risk factor, but reductions in absolute risk are generally greater, due to the high prevalence of cardiovascular diseases().

Nevertheless, in a systematic review performed in 2008, including 108 clinical trials, Briel et al. obtained no additional benefit with increased HDL-C relative to the isolated reduction of LDL-C, indicating that in middle-aged adults, possibly HDL-C fractions are more important than their total value(). In another prospective study with 89 adult individuals, CRP (24% presented with levels > 3 mg/dL) and low HDL-C (72% prevalence) were more prevalent and essential predictors compared to traditional risk factors in individuals with familial history of coronary disease().

Particularly in octogenarians, it is expected that the inclusion of HDL-C and CRP improve the absolute cardiovascular risk stratification. Therefore, the objective of this study was to investigate in literature data on the association between total mortality, lipoproteins, and inflammatory markers, and their implications with aging and longevity.

METHODS

This was a study of an exploratory and descriptive nature, based on the qualitative method of investigation.


Next, we applied the following inclusion criteria:
- systematic reviews;
- observational studies (cohort, cross-sectional, case-control, and ecological studies);
- languages: English, Portuguese, and Spanish;
- inclusion of individuals aged over 80 years.

The exclusion criteria were:
- specific population studies (for example, patients undergoing hemodialysis), due to the difficulty of applying data to the general population.

Based on the selection of studies that met these criteria, we initiated the detailed analysis, as per the level of evidence.

RESULTS

Using the PubMed search strategy, 2617 studies of potential relevance were identified for the combination of descriptors “C-reactive protein” and “lipids”; 519 publications combining the terms “lipoproteins, HDL” and “C-reactive protein”; 750 with the terms “lipoproteins, HDL” and “cardiovascular system”; 1191 combining “lipids” and “mortality”; 60 with “lipoproteins, HDL” and “mortality”; 290 with “C-reactive protein” and “mortality”; and 1423 with the combination of “C-reactive protein” and “cardiovascular system”.

---

(footnotes omitted for clarity)
Applying the inclusion and exclusion criteria adopted, we selected 30 studies, in which one was a systematic review on the relation between HDL-C and cerebrovascular accidents(11), one meta-analysis on the relation between total cholesterol and HDL-C with mortality(12), 22 longitudinal studies, and 6 cross-sectional studies(13-40). The description of these articles is displayed in chart 1.

Chart 1. Articles which analysed the importance of HDL-C and CRP in cardiovascular risk evaluation in longevous elderly individuals

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amanreco et al. 2008*(11)</td>
<td>10 prospective cohorts and 8 case-control studies analyzed the outcome of stroke. Six longitudinal studies and 36 cross-sectional studies were included to analyze carotid thickness.</td>
<td>Only 2 prospective studies did not show an association between HDL-C and stroke. Five studies showed a reduction by 11-15% of the risk for stroke for 10 mg/dL increase in HDL-C. Of the case-control studies, only 3 did not show an association, with a mean adjusted RR of 0.66 for each 10 mg/dL increase in HDL. As to carotid atherosclerosis, data show a tendency towards protective effect</td>
</tr>
<tr>
<td>Prospective Studies Collaboration 2007**(12)</td>
<td>61 observational prospective studies, with age range of 40 to 89 years, included 222 thousand longevous elderly persons per year. Information on HDL was available for 150,000 individuals. Average follow-up was 13 years.</td>
<td>Among the indices that assessed HDL-C, the TC/HDL ratio obtained the best positive predictive value for cardiovascular mortality. An increase of 0.33 mmol/L in HDL-C or a reduction of 1.33 in TC/HDL-C reduced by about 33% the mortality by CAD</td>
</tr>
<tr>
<td>Vliet et al., 2010***(25)</td>
<td>230 residents of a rural area, all aged between 85 and 94 years.</td>
<td>Among the markers studied, HDL-C and CRP increased during follow-up in those aged 85 to 90 years (p &lt; 0.001). The participants with the smallest increase in HDL-C presented the greatest mortality (p &lt; 0.001). CRP was analyzed along with TC, HDL-C, LDL-C, hemoglobin, blood glucose, albumin, and leukocytes, showing a significant association with total mortality and mortality by cancer (p &lt; 0.01)</td>
</tr>
<tr>
<td>Cesari et al., 2009**(21)</td>
<td>336 participants of the ilSIRENTE study aged over 80 years, with a mean age of 85.8 years.</td>
<td>CRP showed an inverse relation with HDL-C, but with statistical significance only in the group over 85 years of age. CRP was the only biomarker with a significant association with mortality after linear regression + D31</td>
</tr>
<tr>
<td>Krozit et al., 2009**(16)</td>
<td>227 participants of the Vitality 90 + study, age range of 90-102 years, and mean age of 93.9 years, 62.1% of them females</td>
<td>Elderly subjects with CRP ≥ 0.5mg/dL had a significant increase in mortality risk, with a HR: 1.7 (CI:1.2-9.7), whereas in individuals with the APOE4 allele the association + D15 was even stronger, with RR: 5.6 (CI:1.3-30.7)</td>
</tr>
<tr>
<td>Ruijter et al., 2009***(15)</td>
<td>302 participants of the Leiden-85 study, aged 85 years, 71.1% females. Follow-up was 5 years</td>
<td>The classic risk factors, including TC and HDL-C, were not predictors of cardiovascular mortality when used in Framingham’s risk score, with a relative risk of 1.2 (CI:0.51-2.6). CRP and IL6 were not cardiovascular mortality predictors, with p = 0.68 and 0.44, respectively</td>
</tr>
<tr>
<td>Carriere et al., 2008***(14)</td>
<td>1,441 participants with mean age of 70 years and standard deviation of 6.6 years. Of these, 134 were over 80 years old, 38% of them, males</td>
<td>Elevated CRP was associated with both, early, and late mortality in both genders, but with statistical significance only in males. HDL-C was not analyzed</td>
</tr>
<tr>
<td>Berbée et al., 2008***(18)</td>
<td>561 participants, all of them 85 years old</td>
<td>A high level of apoC1 was associated with mortality due to all causes. Both HDL-C and CRP showed a significant positive association with apoC1</td>
</tr>
<tr>
<td>Clarke et al., 2008***(20)</td>
<td>5,360 male participants, with a mean age of 76.9 years, range of 66-96 years</td>
<td>CRP and the TC/HDL-C ratio showed a significant positive association with vascular and non-vascular mortality</td>
</tr>
<tr>
<td>Landi et al., 2008***(21)</td>
<td>359 elderly subjects, all over 80 years of age, with a mean age of 85.9 years. 67% were females. Analysis was performed during a two-year period</td>
<td>HDL-C showed an inverse relation with mortality. Comparing the third with the highest HDL-C (&gt; 45.1mg/dL for men and 51.1 mg/dL for women) with that of the lowest HDL-C (&lt; 38mg/dL and &lt; 41mg/dL for men and women, respectively), the HR was 0.41, 0.21-0.79, similar between genders, and maintaining statistical significance after analysis of the indicators of fragility and albumin</td>
</tr>
<tr>
<td>Akerblom et al., 2008***(20)</td>
<td>2,556 subjects were analyzed, with a mean age of 77 years, range of 65 - 103 years. Of these, 27.6% were Caucasian, 31.2% Afro-American, and 41.2% Hispanic.</td>
<td>The highest levels of HDL-C were obtained among Afro-Americans, which also presented with highest mortality rates. However, there was no significant association between HDL-C and mortality</td>
</tr>
<tr>
<td>Kompoti et al., 2008**(22)</td>
<td>382 patients admitted to a ward during the period of 6 months. Mean age was 70.8 ± 15.7 years, and the main cause of hospitalization was stroke</td>
<td>CRP was greatest in patients that died, with p &lt; 0.001, increasing with age. Among those older than 80 years, CRP was predictive of hospital mortality, with a HR: 5.41 and p = 0.01</td>
</tr>
<tr>
<td>Shinkai et al., 2008**(24)</td>
<td>1,034 elderly-Japanese subjects, age range of 65-89 years, and mean follow-up of 7.9 years</td>
<td>Participants were divided into 3 groups as per level of CRP. The group with intermediate levels of CRP displayed HR for mortality of 1.39, with 95% CI 0.89-1.96, and the group with elevated CRP had a HR of 1.44, with a CI: 1.2-2.06</td>
</tr>
<tr>
<td>Spada et al., 2007**(25)</td>
<td>23 residents of a rural area, all aged between 65 and 94 years, 65% of them males, were analyzed for 2 years</td>
<td>Total cholesterol varied from 116 to 239 mg/dL. Assessing 4 variables (gender, BMI, age, and total cholesterol), only the low level of TC (&lt;160mg/dL) showed a significant relationship with mortality, with p &lt; 0.002.</td>
</tr>
<tr>
<td>Dupuy et al., 2007**(26)</td>
<td>1,709 participants with a mean age of 69.3 years, range of 60-92.9 years. Of these, 169 were over 80 years of age, and 38% were males</td>
<td>CRP showed no statistical difference between genders. Comparing the quartiles with the highest and lowest levels of CRP (&gt; 3.05 and &lt; 0.82mg/L), there was a significant relationship with metabolic syndrome. Analyzing HDL-C &lt; 40 mg/dL for men or &lt; 50mg/dL for women, the OR for the prevalence of the metabolic syndrome was 1.6 in women, with a CI: 1.03-2.48, and there was no statistical significance among the men</td>
</tr>
</tbody>
</table>

Continue...
Articles which analysed the importance of HDL-C and CRP in cardiovascular risk evaluation in longevous elderly individuals

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jyha et al., 2007**</td>
<td>285 nonagenarians were accompanied for a period of 4 years</td>
<td>Both HDL-C and CRP were greater in survivors, with an inverse relationship between HDL-C and CRP with statistical significance (p &lt; 0.001). CRP also presented a positive relationship with mortality, but with no statistical significance after adjustment for all D70 variables.</td>
</tr>
<tr>
<td>Mooijaart et al., 2006**</td>
<td>546 elderly individuals, all aged 85 years</td>
<td>HDL-C showed an inverse relation with APOE4 and with cardiovascular mortality. CRP also showed a significant positive relation with APOE4 and with cardiovascular mortality, with the risk of cardiovascular mortality related to APOE4 dependent on CRP &gt; D77.</td>
</tr>
<tr>
<td>Kistorp et al., 2005**</td>
<td>626 participants with a mean age of 67.9 years, range of 50-89 years, were evaluated for a period of 5 years</td>
<td>The group formed by 20% of the participants with highest levels of CRP showed a positive relationships with mortality, with a HR: 1.46, but no statistical significance, p = 0.14.</td>
</tr>
<tr>
<td>Schupf et al., 2005**</td>
<td>2,277 elderly subjects with no cognitive deficit and a mean age of 76 years, range of 65-98 years, 65.6% of them females. Mean follow-up of 3 years, with a standard deviation of 2.5 years</td>
<td>HDL-C displayed no statistical relation + D87 with mortality. Participants over 75 years of age had higher HDL-C levels than those younger than 75 years, with p &lt; 0.05.</td>
</tr>
<tr>
<td>Peaty et al., 2004**</td>
<td>4,885 elderly individuals, over 65 years of age, and mean age of 73 ± 5.7 years for men and 72.3 ± 5.3 years for women, 60% of them females. Mean follow-up was 7.5 years</td>
<td>The primary cause of death was cardiovascular, with results similar at all levels of LDL-C, but with relative risk for fatal cardiovascular disease of 2 for the group with lowest levels of HDL-C, a relative risk of 2 for CAD, and of 2.6 for cerebrovascular accidents.</td>
</tr>
<tr>
<td>Weverling-Rijnsburger et al., 2003***</td>
<td>599 participants of the Leiden 85-Plus study. All over 85 years of age, 67% of them females. Mean follow-up was 2.6 years.</td>
<td>The level of HDL-C varied significantly among the subtypes of cerebrovascular accidents, with a mean of 37.8 mg/dL for the embolic type, 40.2 mg/dL for the atherothrombotic type, 47.4 mg/dL in the lacunar type, and 48.2 mg/dL in the TIA, with p &lt; 0.05. Embolic cerebrovascular accident present with the worst prognosis, with the greatest disability and time of hospitalization. CRP showed no statistical significance.</td>
</tr>
<tr>
<td>Lloyd-Jones et al., 2003***</td>
<td>7,288 participants of the “Framingham Heart Study” in which 55% were females, age range of 40-94 years</td>
<td>HDL-C was significantly higher in women, while the thickness of the intima layer of the carotid was greater in men. There was no significant difference between the HDL-C of the group with less and with more than 1 mm of carotid intima layer thickness.</td>
</tr>
<tr>
<td>Shor et al., 2008**</td>
<td>204 patients hospitalized during the year 2005, were divided into two groups, as per HDL-C. Group 1 (HDL-C &lt; 20mg/dL)</td>
<td>Group 1 presented an OR: 17.5 for mortality (p &lt; 0.0001), OR: 15 for fever or SEPSIS (p &lt; 0.0001), and OR: 6.7 for the development of malignancies (p = 0.004).</td>
</tr>
<tr>
<td>Yokohawa et al., 2008**</td>
<td>171 patients diagnosed with stroke, ages 36 to 96 years. The patients were subdivided into 4 etiological subtypes and analyzed as to markers of fibrinolysis and atherosclerosis</td>
<td>Comparing the group without stenosis with the two other groups, HDL-C showed a significant association with carotid stenosis, but comparing the two groups with stenosis, there was no statistical significance. As to CRP there was a significant association with carotid stenosis, and statistical significance was lost only when compared to the groups with stenosis of less than 70% with the controls. There was a positive relationship between the CRP and the total cholesterol/HDL-C ratio in the group with stenosis &gt; 70%.</td>
</tr>
<tr>
<td>Fujisawa et al., 2008**</td>
<td>136 longevous elderly individuals aged over 80 years were evaluated for carotid atherosclerosis. Mean age was 84 years, and 39% were males. Factors related to atherosclerosis were analyzed by multiple regression</td>
<td>The primary cause of death was cardiovascular, with results similar at all levels of LDL-C, but with relative risk for fatal cardiovascular disease of 2 for the group with lowest levels of HDL-C, a relative risk of 2 for CAD, and of 2.6 for cerebrovascular accidents.</td>
</tr>
</tbody>
</table>

* Systematic review
** Meta-analysis
*** Prospective cohort
# Retrospective cohort
** Cross-sectional study
HDL-C: HDL cholesterol; TC: total cholesterol; CAD: coronary artery disease; CRP: C-reactive protein; HR: Hazard Ratio; CI: confidence interval; BMI: body mass index.
DISCUSSION

The objective of this review was to investigate in literature the studies that assess the relation between HDL-C, CRP, and longevity. We found a relatively small number of studies, and most of them show a strong association between low levels of HDL-C and high CRP with cardiovascular morbidity and mortality in this age group.

Data from the “Cardiovascular Health Study”, which included only individuals over 65 years of age, with a mean age of 72 years, showed that approximately 50% of women and 60% of men without clinical cardiovascular disease presented with subclinical disease, defined by alterations in the echocardiogram or electrocardiogram, carotid thickness or carotid stenosis upon Doppler ultrasound, and decreased ankle-brachial index\(^{41}\). In this way, the subclinical presentation of the disease and the factors that accelerate its progression or destabilize atherosclerotic disease seem to have greater relevance than atherogenic factors for this age group. HDL-C and CRP present different properties that influence the stability of plaque. HDL-C participates in the reverse transport of cholesterol and also presents antioxidant properties that are antioxidant, anti-inflammatory and antithrombotic, besides contributing to endothelial damage\(^{42}\). CRP sustains a status that is prothrombotic, proinflammatory and proatherosclerotic by means of its effects in regulation of endothelial cells, in vascular remodeling, in macrophage function, in increased migration, proliferation and production of oxygen free radicals by smooth muscle cells of blood vessels and in the increased activity of metalloproteinases, with resulting degradation of the biological matrix and instability of the atherosclerotic plaque\(^{43}\).

Weverling-Rijnsburger et al.\(^{32}\), in a study involving 599 elderly persons, all aged over 85 years, showed a relative risk of 2 for cardiovascular mortality in the group with the lowest levels of HDL-C, in which the cardiovascular mortality was independent of the levels of LDL-C. Ruijter et al.\(^{17}\) studied the same cohort of aged individuals with more than 85 years of age, but they excluded participants with past history of cardiovascular disease, resulting in 302 aged subjects. In these, the level of HDL-C was not a predictor of cardiovascular risk. However, in excluding the patients with heart diseases, also excluded were patients with lower levels of HDL-C, as HDL-C was around 42 to 62 mg/dL, with a mean of 50.2 mg/dL, while the tercile with the lowest HDL-C of the initial cohort showed values between 32 and 40 mg/dL.

The Prospective Studies Collaboration\(^{12}\) analyzed the relation between mortality and lipid profile by means of a meta-analysis of 61 prospective studies involving 900 thousand subjects, aged between 40 and 89 years, showing a 33% reduction in mortality by CAD with the increase of 12 mg/dL of HDL-C\(^{12}\). In this study, total cholesterol lost statistical significance to predict cerebrovascular accidents and vascular mortality in very old individuals, except for CAD, concluding that HDL-C was a more significant predictor for mortality than LDL-C and total cholesterol in longevous elderly individuals.

HDL-C is classified by its size and density into two primary fractions: HDL2-C, larger and rich in cholesterol, and HDL3-C, smaller and with less cholesterol. It is likely that HDL2-C is the fraction that best represents the reverse transport of cholesterol, and when its levels are low, there is an association with high cardiovascular risk. Ettinger et al., in a cross-sectional study in 1952 elderly persons over 65 years of age, showed that the higher HDL-C with aging probably is due to the increased fraction of HDL2-C\(^{44}\).

The relation between high CRP and vascular and non-vascular mortality suggests that the CRP gene is possibly one of those related to longevity\(^{45}\). Polymorphisms of the CRP gene are associated with the increase in its serum level. However, the association between these polymorphisms and increased mortality has not been established yet\(^{46}\). On the other hand, Mooijaart et al.\(^{28}\), in a cohort of longevous elderly people, showed that the apolipoprotein E gene is associated with lower HDL-C, higher levels of CRP, and increased mortality, and this effect on mortality is dependent on CRP levels.

The present study showed that in longevous aged, low levels of HDL-C are better predictors of cardiovascular mortality that the other cholesterol fractions, possibly substituting LDL-C as the main goal of treatment in this age group. Nevertheless, before altering the goals of prevention, more clinical trials are needed with the objective of increasing HDL-C in the population over 80 years of age.

A high level of CRP also proved an excellent predictor of cardiovascular mortality in longevous elderly individuals. On the other hand, despite the JUPITER study having shown benefits in its reduction with rosuvastatin, there is also a need for more clinical trials that include longevous individuals.

The identification of biological markers of longevity will enable the development of studies on the mechanisms that protect humans from common diseases and delay biological aging processes. Ideally, cardiovascular risk markers should provide prognostic information on various levels of risk, adding information to the traditional risk factors, and should be reproducible, with accessible costs and high prevalence in the population evaluated.
CONCLUSION

CRP and HDL-C present promising characteristics, although they still require greater evidence. Future research should explore the relations between them and cardiovascular disease in longevous elderly population, collaborating with their incorporation into traditional risk factors in the preparation of guidelines for this growing age group, which is still insufficiently studied.

ACKNOWLEDGMENTS

We thank Gabriel Seabra Cendoroglo for his collaboration in this project.

REFERENCES


