Circulating oxidised LDL lipids, when proportioned to HDL-c, emerged as a risk factor of all-cause mortality in a population-based survival study

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Abstract

Background and objective: the data concerning the predictive role of oxidised LDL (ox-LDL) in all-cause mortality are scarce. We investigated whether circulating ox-LDL would stand out as a risk factor of total mortality in the elderly.

Study subjects, design and methods: a total of 1,260 elderly inhabitants (533 men, 727 women) aged 64 years or more from Lieto, South-Western Finland participated the study in 1998–99. Medical records were re-examined approximately a decade later in January 2009. Circulating ox-LDL lipids were used as the main outcome measure. The comparisons were obtained by the Cox hazard ratio model.

Results: during the 10-year follow-up, 467 participants had died (37%), of whom 36% had died of atherosclerotic cardiovascular diseases. Ox-LDL was a significant predictor of all-cause mortality, when proportioned to low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c) or apolipoprotein A1 (apoA1). These findings were independent of age, sex, body mass index, smoking, blood pressure and diabetes (P < 0.05 for all).

Conclusion: circulating ox-LDL lipids, when proportioned to LDL-c, HDL-c or apoA1, stand out as a risk factor for all-cause mortality independent of major confounding attributes. In the prospective survival and increasing disease burden caused by accumulating age, oxidative stress may have a considerable role.

Keywords: oxidised LDL, mortality, survival, risk factors, elderly, population, older people

Introduction

Cardiovascular diseases (CVD) are the leading cause of death worldwide. Oxidised low-density lipoprotein (ox-LDL) and its ratios with some of the conventional lipids, such as LDL cholesterol (LDL-c) and high-density lipoprotein cholesterol (HDL-c), may be more potent biomarkers in the diagnostic and predictive procedures related to CVD than the conventional markers alone [1, 2]. Prospective research data concerning the relevance of in vivo oxidative markers in relation to all-cause mortality, particularly in the elderly, are very scarce.

The causal connection between a risk factor and a disease may become challenged not only by ageing but also by collateral phenomena such as co-morbidity or co-existence of several diseases [3, 4]. Therefore, we investigated whether ox-LDL lipids in the circulation would stand out as a risk factor with significance in all-cause mortality in comparison with serum lipids and apolipoproteins.
Circulating oxidised LDL lipids

Methods

Subjects consist of residents in Lieto, a semi-industrialised rural municipality in South-Western Finland. In 1998–99, all inhabitants born 1933 or earlier (aged 64 years or more at the time) were invited to join; 1,260 of 1,596 inhabitants participated (79%), whose mean age was 74 years. A more detailed description of the study protocol is provided elsewhere [5]. The death records, extending from the original inquiry in 1998–99 to 1 January 2009, were examined. This gave us a prospective view on the data, allowing us to investigate the possible contributing roles of different risk factors. The study protocol was approved by the Joint Ethics Committee of Turku University and Turku University Central Hospital and complies with the declaration of Helsinki. All participants gave their written informed consent.

In assessing the connections between a risk factor and mortality, we were particularly interested in a relatively new parameter, ox-LDL and its relation to HDL-c, LDL-c and apolipoproteins A1 (apoA1) or B (apoB) as more conventional risk factors. The analysis of ox-LDL was based on the determination of oxidative modifications, i.e. peroxidation of lipids, in LDL [6]. Appearance of conjugated dienes is characteristic of peroxidation of all polyunsaturated fatty acids. This method measures those circulating LDL particles that have undergone oxidative modifications in their lipid compartment [7]. Because of remaining in the circulation instead of being taken up by macrophages, their quantity can be measured. It has been shown that the scavenger receptor CD36 in macrophages recognises ox-LDL by its lipid components. This recognition is a key event in the formation of atherosclerotic plaque [8]. Furthermore, this binding event has been shown to increase the expression of the receptor, resulting in an uncontrolled lipid accumulation, foam cell formation and consequent arterial lesion formation [9]. Validation studies for the assay have ruled out interference by non-specific substances, and shown that the assay is able to detect oxidative modifications in all LDL particle classes [6, 7]. HDL cholesterol was measured enzymatically (直接, Boehringer Mannheim, Hitachi717). Apolipoproteins were measured immunonephelometrically (Dade- Behring BN II, Marburg, Germany).

Statistical analyses were performed using the SAS System for Windows, versions 9.1 (SAS Institute, Inc, Cary, NC, USA). Univariate Cox regression analysis, with and without controlling for major confounding factors, was used to examine the role of lipid concentrations in total mortality. P-values <0.05 were considered statistically significant.

Results

The mean (SD) age of death was 83 (7.2) years. Survivors by the end of 2008 were 81 (4.8) years old. Of the deceased participants, 36% had died of atherosclerotic and/or ischemic CVD. Demographic and biochemical data of the subjects are given in Table 1. The deceased were 7 years older and had 5% higher concentrations of fasting serum glucose but 3% less total cholesterol than the survivors (P<0.05 for all). The survivors had 7–10% less ox-LDL/LDL-c and ox-LDL/HDL-c and 5% more LDL-c and HDL-c than the deceased (P<0.01 for both, see Table 2). Ox-LDL/LDL-c, ox-LDL/HDL-c and ox-LDL/apoA1 were significant predictors of mortality, and these associations remained significant after controlling for age, sex, BMI, smoking, blood pressure and diabetes. HDL-c and apoA1 had a significant protective effect (P<0.05 for all).

Discussion

We observed that ox-LDL, when proportioned to LDL-c, HDL-c or apoA1, maintains its predictive value as a risk factor in the late decades of life span. The protective roles of HDL-c and apoA1 appear to continue as well. These findings highlight the importance of lipid metabolism and balance in the circulation [10], which ultimately may, via oxidation, be connected to mortality and survival. In this sense, considering the health challenges pushed forth by accumulating age, the increasing burden of diseases at both the individual and population levels and the prominent contribution of atherosclerotic CVD’s to total mortality, circulating ox-LDL lipids seem to be a parameter of significance. Furthermore, from the context of the potential rearrangement of risk factor values by accumulating age [3], oxidation of lipids in circulating LDL particles may serve as an omen of oxidative stress including the progression of an atherosclerotic plaque via the scavenger receptor pathway. Hence, our results of total mortality indicate that ox-LDL,

Table 1. Demographic and biochemical data of study subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) survived (n = 793)</th>
<th>Deceased (n = 467)</th>
<th>P-value controlled for sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender distribution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men, n = 319; women, n = 474</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>71.0 (4.9)</td>
<td>77.7 (7.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.5 (8.9)</td>
<td>165.6 (9.6)</td>
<td>0.040</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.6 (13.5)</td>
<td>71.9 (16.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequency of LLT*</td>
<td>62/80</td>
<td>18/80</td>
<td>0.006</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.8 (1.1)</td>
<td>5.6 (1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.5 (0.7)</td>
<td>1.5 (0.8)</td>
<td>0.95, ns.</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>5.9 (1.6)</td>
<td>6.2 (2.3)</td>
<td>0.036</td>
</tr>
</tbody>
</table>

*LLT, lipid lowering therapy.

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proportioned to LDL-c, HDL-c or apoA1, is a useful discriminating clinical tool from the perspective of circulating lipid metabolism, oxidative stress and all-cause mortality. It is noteworthy that these ratios maintain their risk factor values independent of major confounding attributes.

Key points

- In the elderly, circulating ox-LDL lipids, when proportioned to LDL-c, HDL-c or apoA1, stood out as a predictor of all-cause mortality.
- This finding was independent of major confounding mortality attributes (age, sex, BMI, smoking, blood pressure and diabetes).
- Considering the known possibility of rearrangements in the predictive or protective values of risk factors by accumulating age and disease burden, this study suggests that circulating ox-LDL lipids maintain its predictive value in the late decades of the life span, when considered together with other circulating lipid components.

Conflicts of interest

None declared.

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References

Cognitive screening in the acute stroke setting

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Abstract

Background: current literature suggests that two-thirds of patients will have cognitive impairment at 3 months post-stroke. Post-stroke cognitive impairment is associated with impaired function and increased mortality. UK guidelines recommend all patients with stroke have a cognitive assessment within 6 weeks. There is no ‘gold standard’ cognitive screening tool. The Montreal cognitive assessment (MoCA) is more sensitive than the Mini-Mental State Examination (MMSE) in mild cognitive impairment and for cognitive impairment in the non-acute post-stroke setting and in a Chinese-speaking acute stroke setting.

Methods: a convenience sample of 50 patients, admitted with stroke or transient ischaemic attack (TIA), were screened within 14 days, using the MoCA and the MMSE.

Results: the mean MoCA was 21.80 versus a mean MMSE of 26.98; 70% were impaired on the MoCA (cut-off <26) versus 26% on MMSE (cut-off <27). The MoCA could be completed in <10 min in 90% of cases.

Conclusion: the MoCA is easy and quick to use in the acute stroke setting. Further work is required to determine whether a low score on the MoCA in the acute stroke setting will predict the cognitive and functional status and to explore what the best cut-off should be in an acute post-stroke setting.

Keywords: stroke, cognitive impairment, post-stroke dementia, older people

Introduction

Current literature suggests that 20–30% of patients will have dementia 3 months post-stroke [1] but up to two-thirds of patients will have cognitive impairment, if tested in the acute stroke period [2]. Post-stroke cognitive impairment results in impaired function, distress to patients and carers and is associated with increased mortality [3]. It is a hidden cost because if not specifically looked for it can be missed. A recent surveys by the Stroke Association (http://www.stroke.org.uk/information/our_publications/other_material/needs_survey.html) found cognitive impairment to be one of the silent unmet needs in >50% of stroke survivors at 1 year after stroke.

Recent Stroke Quality Standards from the National Institute of Excellence (NICE) state ‘All patients after stroke are screened within 6 weeks of diagnosis, using a validated tool, to identify mood disturbance and cognitive