Plasma oxidized low-density lipoprotein levels and risk of Alzheimer’s disease

Jihad Murr a,b, Pierre-Hugues Carmichael a, Pierre Julien c,d, Danielle Laurin a,b,*

a Centre d’excellence sur le vieillissement de Québec, Santé des populations et pratiques optimales en santé, Centre de recherche du CHU de Québec, Quebec City, Quebec, Canada
b Faculty of Pharmacy, Laval University, Quebec City, Quebec, Canada
c Faculty of Medicine, Department of Medicine and CREMOCG, Laval University, Quebec City, Quebec, Canada
d Endocrinology and Nephrology Unit, CHU de Québec Research Center, Quebec City, Quebec, Canada

A B S T R A C T

This study examines the association of plasma oxidized low-density lipoprotein (OxLDL) levels with all-cause dementia, including Alzheimer’s disease (AD) and vascular dementia. Data are taken from the Canadian Study of Health and Aging, a population-based study of a representative sample of persons aged more than 65 years conducted from 1991 to 2002. The present study sample included 670 subjects of which, 155 developed all-cause dementia with 109 cases of AD and 32 of vascular dementia. In Cox regression models, no association between OxLDL and risks of dementia or subtypes was found. A triple interaction between OxLDL, sex, and history of cardiovascular disease (hazard ratio 1.11; 95% confidence interval 1.04–1.19) was found. Increased levels of OxLDL were significantly associated with an increased risk of AD in men with a history of cardiovascular disease (hazard ratio = 1.11; 95% confidence interval 1.04–1.19); no association in women was found. These findings suggest that increased levels of OxLDL are not associated with the risk of dementia, AD, and vascular dementia. The association of OxLDL with AD in men with a history of cardiovascular disease merits further investigation.

© 2014 Elsevier Inc. All rights reserved.

1. Introduction

The definite causes of Alzheimer’s disease (AD) are not well established yet. The 2 main hallmark pathologic features of AD are the abnormal accumulation of amyloid-beta (Aβ) peptides leading to senile plaques (Selkoe, 1993) and the hyperphosphorylation of the protein tau forming intracellular neurofibrillary tangles (Selkoe, 2004; Sobow et al., 2004). Aβ deposits and neurofibrillary tangles are important stimuli for the inflammatory mechanisms observed in the brains of AD patients. Cumulated over many years, the inflammatory mechanism is likely to exacerbate the pathogenic processes that gave rise to it (Akiyama et al., 2000).

In parallel to these processes, increased regional levels of oxidative stress (Markesbery, 1997; Zhu et al., 2005) and evidence of oxidative damage, mainly oxidized lipids, proteins (Smith et al., 1995), and nucleic acids (Mococci et al., 1993), can be found in neurodegenerative disorders. Whether oxidative stress plays a key role in the pathogenesis of AD or is just its pathologic manifestation is still controversial (Markesbery, 1997), but some studies indicate that the increase in oxidative stress is one of the earliest changes occurring several years before the disease (Nunomura et al., 2001). Similar signs like an increase in antioxidant levels in the cerebrospinal fluid (CSF) (Kankaanpää et al., 2009) and elevated indices of protein oxidation and lipid peroxidation (Picklo et al., 2002; Sayre et al., 2001; Subbarao et al., 1990) are detectable in AD patients and in cases of mild cognitive impairment (MCI) (Keller et al., 2005).

Low-density lipoproteins (LDL) are key molecules in the cholesterol transport mechanisms and are susceptible to oxidation into oxidized LDL (OxLDL). OxLDL are immunogenic and also cytotoxic to endothelial cells. Beside their highly atherogenic characteristics (Bhakdi et al., 1995; Steinberg, 1995; Young and McEneny, 2001), OxLDL are also associated with the development of coronary and vascular diseases (Holvoet et al., 2003; Toshima et al., 2000; Tsimikas et al., 2003; Zhu et al., 2007). The presence of atherosclerosis has been related to AD in postmortem studies (Jellinger, 2010; Jellinger and Mitter-Ferstl, 2001). It has been suggested that atherosclerosis, coronary heart disease, and AD may have certain risk factors in common including dyslipidemia, hypertension, oxidative stress, and elevated oxidation levels of LDL (Kivipelto et al., 2001; Pappolla et al., 2003; Sparks, 1997; Steinberg, 1997).

Unlike its links with coronary heart disease and atherosclerosis, the association between OxLDL levels and AD is still relatively novel and has been less often investigated in the literature. Koyama et al.
Among the 670 subjects that were retained for analysis, 115 were 1834
2.2. Blood samples
(Román et al., 1993). In all, 2914 subjects underwent the clinical
analyses. Finally, 31 subjects were excluded because they had no
before having any follow-up and 701 subjects were left for chemical
for a prospective analysis. Of these, 1219 nondemented subjects
were already demented and 500 were screened positive but refused
except for those who already did in a previous phase.

2.3. Study sample
Of 10,263 subjects at the beginning of CSHA-1, 1132 subjects
were already demented and 500 were screened positive but refused
to be clinically evaluated; 8631 nondemented subjects were eligible
for a prospective analysis. Of these, 1219 nondemented subjects
provided blood samples and underwent a clinical evaluation either
at CSHA-1 or CSHA-2. Among these, 450 died, 68 went missing
before having any follow-up and 701 subjects were left for chemical
analyses. Finally, 31 subjects were excluded because they had no
whole blood available for another analysis (Kröger et al., 2009).
Among the 670 subjects that were retained for analysis, 115 were
from CSHA-1 and 555 from CSHA-2. Of the 115 subjects of
CSHA-1, 68 had only 1 follow-up and 47 subjects had 2 follow-ups.
There was no difference concerning age and sex between subjects
in the final study sample and those who were excluded; subjects
from the study sample had slightly fewer years of education than
those not included (mean [standard deviation]: 9.8 (4.1) and 10.3
(3.8) years, respectively; p = 0.01).

2.4. OxLDL dosage
OxLDL dosage was realized using frozen samples stored in
polypropylene microtubes. Plasma levels (U/L) of OxLDL were
measured in EDTA-treated plasma using a Mercodia Oxidized-LDL
Enzyme Linked Immunosorbent Assay containing mAb-4E6 anti-
body and has a detection limit of < 1 mU/L and a variation coeffi-
cient of 8%. The samples were analyzed in 2007 at the Lipid
Research Centre of the CHU de Québec, in Quebec City.

2.5. Statistical analyses
Comparison between the subjects who developed all-cause
dementia and those who remained cognitively normal were per-
formed using χ² tests for categorical variables and t tests or Wil-
coxon rank-sum test for continuous variables. Plasma OxLDL
concentration was treated as a continuous variable and in tertiles.
To examine the association between OxLDL levels and outcomes,
Cox proportional hazards regression models with age as the time
scale were used in 3 different models (basic; model 1), semi-, or
fully adjusted (models 2 and 3, respectively).

The proportionality and linearity assumption of the models
were tested and found to be satisfied. Age at the onset of disease
was defined as the midpoint between the last follow-up without
der dementia and the next one with dementia. Follow-up time was
calculated from time of blood provision and until the time of event,
loss of follow-up, or end of the study. When OxLDL concentration
was treated as categorical, the first tertile was used as the reference.
The semi-adjusted model included 2 covariates: sex and education
(continuous variable, in years) and the fully-adjusted model addi-
tionally controlled for apoE4 status (yes or no, defined as the
presence or not of at least 1 e4 allele), history of cardiovascular
disease (yes or no, defined as history of stroke or myocardial
infarction), history of diabetes mellitus (yes or no), hypertension
(Yes or no, defined as supine blood pressure > 160 mm Hg systolic
or 95 mm Hg diastolic, or a physician's diagnosis of hypertension),
ever smoking (yes or no), regular alcohol consumption (yes or no).
Information on these covariates was obtained from either the risk
factor questionnaire at baseline and/or from the clinical examina-
tion at the time of blood sampling. Effect modification of sex, his-
tory of cardiovascular disease, and apoE4 was tested in all-cause
dementia and AD according to model 2 and with OxLDL as a
continuous variable to test with the highest statistical power. Given
the small number of incident cases of VaD, effect modi-
cation at the time of blood sampling. Effect modification of sex, his-
tory of cardiovascular disease, and apoE4 was tested in all-cause
dementia and AD according to model 2 and with OxLDL as a
continuous variable to test with the highest statistical power. Given
the small number of incident cases of VaD, effect modification was
not tested. Statistical analyses were performed using SAS 9.1.3
software.

3. Results
Over 4.8 years of follow-up (range, 2.2–10.3 years), 515
remained cognitively normal and 155 developed dementia; this
included 109 cases of AD, 32 cases of VaD, and 14 cases of other
types. OxLDL levels were normally distributed with a mean (stan-
dard deviation) of 38.7 (11.2) U/L. No significant collinearity
was found between any of the independent variables. There was no
significant difference in the initial characteristics between subjects
who remained cognitively normal and those who developed
دریافت فوری متن کامل مقاله

امکان دانلود نسخه تمام متن مقالات انگلیسی
امکان دانلود نسخه ترجمه شده مقالات
پذیرش سفارش ترجمه تخصصی
امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
امکان دانلود رایگان ۲ صفحه اول هر مقاله
امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
دانلود فوری مقاله پس از پرداخت آنلاین
پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات