The role of lipoproteins and inflammation in cognitive decline: Do they interact?

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Received 8 January 2010; received in revised form 7 May 2010; accepted 22 May 2010

Abstract

The aim of this study was to examine the associations between high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides, and cognition and focus on the modifying effect of inflammation. Data were collected in the population-based Longitudinal Aging Study Amsterdam and analyzed with mixed linear models. The sample comprised 1003 persons ≥ 65 years with cognitive data on at least 2 occasions over 6 years of follow-up. Cognition was measured with the Mini-Mental State Examination (general cognition), Auditory Verbal Learning Test (memory), and Coding Task (information processing speed). We found an independent association between high HDL cholesterol and better memory performance. In addition, low LDL cholesterol was predictive of worse general cognitive performance and faster decline on information processing speed. Furthermore, a significant modifying effect of inflammation (C-reactive protein, α-antichymotrypsin) was found. A negative additive effect of low LDL cholesterol and high inflammation was found on general cognition and memory performance. Also, high triglycerides were associated with lower memory performance in those with high inflammation. Thus, a combination of these factors may be used as markers of prolonged lower cognitive functioning.

Keywords: Lipoproteins; Triglycerides; Inflammation; Cognitive decline; Older persons

1. Introduction

Both lipoproteins, lipids, and inflammation have been linked to dementia and cognitive decline, although their role is complex and mechanisms are still far from clear. In the current study, we focus on the additive effect of these biomarkers on cognitive decline in a population-based sample of older persons.

High levels of low-density lipoprotein (LDL) cholesterol, and low levels of high-density lipoprotein (HDL) cholesterol, both major transport lipoproteins of cholesterol, as well as high lipid levels of triglycerides have been shown to be independently associated with cardiovascular disease (CVD) (Boden, 2000; Morrison and Hokanson, 2009), which in turn is associated with an increased risk of dementia and cognitive impairment (Van Vliet et al., 2009). Inconsistent and even contrasting results have been found in studies focusing on the direct association between lipoproteins and dementia. While some studies have shown an association between high LDL cholesterol and increased dementia risk or worse cognitive functioning (Helzner et al., 2009; Lesser et al., 2009; Moroney et al., 1999; Yaffe et al., 2002), other studies found the opposite effect (Henderson et al., 2003; Packard et al., 2007), or failed to detect an independent association (Reitz et al., 2004; Romas et al., 1999;...
Yoshitake et al., 1995). High HDL cholesterol has been shown to be associated with better cognitive functioning (Atzmon et al., 2002; Merched et al., 2000; Van Exel et al., 2002) and has been suggested as a protective factor for dementia in most cross-sectional studies (Bonarek et al., 2000; Van Exel et al., 2002; Wolf et al., 2004), while longitudinal studies have not found a significant association with dementia, mild cognitive impairment (MCI), cognitive decline or functioning (Henderson et al., 2003; Reitz et al., 2004, 2005, 2008; Tan et al., 2003). In contrast, autopsy studies have shown that higher late-life levels of HDL cholesterol were associated with higher levels of Alzheimer’s disease (AD) pathology (Launer et al., 2001) and increasing pathological certainty of AD (Lesser et al., 2009). Some studies focusing on triglycerides have shown that higher triglyceride levels were associated with cognitive decline (De Frias et al., 2007) and poorer cognitive performance (Perlmuter et al., 1988; Sims et al., 2008), while several other studies showed no association with dementia or cognitive decline (Hall et al., 2006; Romas et al., 1999; Yaffe et al., 2002). Furthermore, the metabolic syndrome (MetS), which is defined as a cluster of low HDL cholesterol, high triglycerides, abdominal obesity, impaired fasting glucose, and/or hypertension (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001), has been linked to increased risk of dementia, cognitive decline, and poorer cognitive functioning (Dik et al., 2007; Kalmijn et al., 2000; Solfirizzi et al., 2010; Yaffe et al., 2004). Kalmijn et al. (2000) showed that a higher level of triglycerides during midlife was significantly associated with a higher risk of dementia 25 years later. A recent study focusing on MetS, found that higher triglycerides and also lower HDL cholesterol were associated with a higher risk of cognitive impairment in Apolipoprotein E (ApoE) ε4 carriers (Lee et al., 2010). Possibly, differences in sample characteristics (e.g., age, baseline cognition, outcome measure (AD, vascular dementia (VaD), cognition), level of lipoproteins, presence of CVD), and adjustment for possible mediating or modifying factors could explain the inconsistent results regarding the role of lipoproteins and triglycerides. Moreover, we hypothesize that inflammation plays a modifying role with respect to the association between lipoproteins and cognition.

Inflammatory processes have been shown to be strongly associated with CVD (Stampfer, 2006) and may play a role in the development of dementia and cognitive decline (Peila and Launer, 2006). Furthermore, inflammatory markers including C-reactive protein (CRP), Interleukin-6 (IL-6), and α-antichymotrypsin (ACT), have been linked to increased dementia risk (Engelhart et al., 2004) and cognitive decline (Dik et al., 2005; Weaver et al., 2002). However, associations have not been found consistently between studies.

Some previous studies have focused on the association between lipids, lipoproteins, and inflammation in older persons. Both lower levels of HDL cholesterol (Arai et al., 2001; Lehtimäki et al., 2005; Zuliani et al., 2007), LDL cholesterol, and total cholesterol (Lehtimäki et al., 2005) as well as acquired hypocholesterolemia (Arai et al., 2001; Ettinger et al., 1995) have been shown to be associated with higher IL-6 (Arai et al., 2001; Ettinger et al., 1995; Lehtimäki et al., 2005; Zuliani et al., 2007) and higher CRP levels (Arai et al., 2001; Ettinger et al., 1995). Furthermore, it has been hypothesized that higher HDL cholesterol may diminish dementia risk by its anti-inflammatory effects (Cockerill et al., 2001). In addition, a synergistic effect of MetS and high inflammation has been shown with respect to increased risk of VaD (Solfirizzi et al., 2010), nonamnestic MCI (Roberts et al., 2010), cognitive decline (Yaffe et al., 2004), and worse cognitive function (Dik et al., 2007). To our knowledge, no study to date has focused on the modifying or mediating effect of inflammation on each of the associations between lipoproteins and triglycerides, and cognitive decline or dementia. In the current study, we focus on the interaction between HDL and LDL cholesterol, triglycerides, and the inflammatory markers CRP, IL-6, and ACT with respect to the trajectory of cognitive functioning in a population-based sample of older persons.

2. Methods

2.1. Study sample

For the present study, data were used from the ongoing population-based Longitudinal Aging Study Amsterdam (LASA). Procedures on sampling and data collection have been described in detail elsewhere (Deeg et al., 2002). In short, a random sample of men and women aged 55–85 stratified for age and sex according to the expected 5-year mortality, was drawn from the population registries of 11 municipalities in 3 areas of the Netherlands. Data collection started in 1992/1993, main and medical interviews in which structured questionnaires were completed and tests performed were repeated every 3 years. Respondents were interviewed at home by specially trained and intensively supervised interviewers. The study was approved by the Ethical Review Board of the VU University Medical Center (VUMc), and informed consent was obtained from all respondents.

In total, 3107 persons were enrolled during the first data collection of LASA. In total, 562 persons (18.1%) were lost to follow up of whom 416 died (13.4%), 90 refused (2.9%), 38 were ineligible (1.2%), and 18 could not be contacted (0.6%) for the second data collection (1995/1996). During the second data collection, 1509 persons aged 65 and older participated in the medical interview, of whom n = 1331 agreed to take part in the blood drawing procedure. Blood samples were obtained in the VUMc or a health care center near the respondents’ home. For respondents unable to come to the VUMc or health care center, blood samples were obtained in the home of the participant. Respondents who agreed to take part in the blood drawing procedure...
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