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Review

Aging and dyslipidemia: A review of potential mechanisms

Hui-Hui Liu, Jian-Jun Li*

Division of Dyslipidemia, State Key Laboratory of Cardiovascular Disease, Fu Wai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China

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ABSTRACT

Elderly adults constitute a rapidly growing part of the global population, thus resulting in an increase in morbidity and mortality related to cardiovascular disease (CVD), which remains the major cause of death in elderly population, including men and women. Dyslipidemia is a well-established risk factor for CVD and is estimated to account for more than half of the worldwide cases of coronary artery disease (CAD). Many studies have shown a strong correlation between serum cholesterol levels and risk of developing CAD. In this paper, we review the changes of plasma lipids that occur in men and women during aging and the potential mechanisms of age-related disorders of lipoprotein metabolism covering humans and/or animals, in which changes of the liver sinusoidal endothelium, postprandial lipemia, insulin resistance induced by free fatty acid (FFA), growth hormone (GH), androgen (only for men) and expression and activity of peroxisome proliferator-activated receptor α (PPARα) are mainly focused.

Contents

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death in the western world, which is expected to remain the same during the foreseeable future (Turakhia and Tseng, 2007). It can happen in men and women, particularly at a later age. Aging is associated with multiple, systemic dysfunctions of the body and accompanied by lipid metabolism disorder and chronic inflammatory state which contribute to atherosclerotic CVD (ASCVD). According to recent report from the World Health Organization (WHO), the elderly population is the most rapidly expanding group, which meets or exceeds 10% of the total population in more than 60 countries. This aging population will endure more chronic medical conditions such as CVD, diabetes mellitus (DM) and chronic kidney disease. A great number of the aged will have morbidity and mortality related to CVD, with up to 85% of CVD patients over 65 years (Pohlel et al., 2006).

Dyslipidemia is characterized by increased triglyceride (TG) and/or low-density lipoprotein (LDL) levels, and also declined high-density lipoprotein (HDL) levels. Such an atherogenic lipid profile often predisposes an at risk individual to coronary artery disease (CAD) with incompletely understood mechanisms (Perdomo and Henry Dong, 2009). Of particular interest is the fact that plasma

* Corresponding author. Tel.: +86 10 88396077; fax: +86 10 68331730.
E-mail address: 13901010368@163.com (J.-J. Li).

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levels of total cholesterol (TC) and LDL cholesterol (LDL-C) are well known to increase with normal aging (Ericsson et al., 1991, 1997), while HDL cholesterol (HDL-C) is declining with age. Elevated plasma LDL-C levels represent one of the most important risk factors for the development of atherosclerosis and subsequent CVDs and are in fact a prerequisite for other risk factors such as smoking, inflammation, diabetes and hypertension to be active. The clustering of above factors has been demonstrated to steadily increase the incidence of CVDs (Ye et al., 2005). The Heart Protection Study (HPS) (2002) and the Cholesterol Treatment Trialists (CTT) (Baigent et al., 2010) meta-analysis demonstrated that a reduction in LDL-C of 1 mmol/L was associated with a 20% reduction in clinical cardiovascular events.

Although the mortality from CVD has declined dramatically, the number of patients with CVDs is increasing and the absolute risk associated with dyslipidemia rises substantially with advancing age (Gobal and Mehta, 2010). The association of aging-related dyslipidemia and CVD holds true for patients older than 65 years old, although much of the relevant data have been derived from large clinical research including middle-aged patients. Large population-based studies such as the Established Populations for Epidemiology Studies in the Elderly (EPESE) indicated that elevated TC levels, more specifically LDL-C and low HDL-C levels in older population, are associated with an increased risk of cardiovascular mortality. Moreover, dyslipidemia has also been treated as a risk factor for peripheral artery disease, stroke, and dementia in older adults (Shanmugasundaram et al., 2010). However, studies on the mechanisms underlying the age-related dyslipidemia are relatively insufficient. Additionally, several previous investigations reported on this issue were scattered. Thus, our understandings of age-related dyslipidemia are still unclear at present. Here we discuss mainly the potential mechanisms of dyslipidemia in aging, which may enhance our comprehension with regard to dyslipidemia with aging and be beneficial for the effective treatment and prevention of dyslipidemia for the purpose of further reducing CVDs in the future.

2. Age-related changes in lipid profile

Age and gender are physiologic factors that have a strong influence on plasma lipid levels in several species. The gender differences in lipid and lipoprotein levels are further affected by age. In human observations, the Framingham Study has demonstrated that aging is associated with a gradual increase in plasma LDL-C levels in men and women between 20 and 60 years (Abbott et al., 1983). After the age of 20 years, the plasma LDL-C concentrations increase progressively in men and women, but more rapidly in men, accounting for most of the overall gender differences in TC (Ericsson et al., 1991; Ferrara et al., 1997). However, menopause in women often causes an increase in their plasma LDL-C, and after the age of 50, women often have higher TC levels than men of the same age (Kreisberg and Kasim, 1987). Interestingly, the LDL-C levels have a plateau in men between the age of 50 and 60 years, and in women between the age of 60 and 70 years (Gobal and Mehta, 2010).

In addition, it has been reported that plasma HDL-C levels decrease in males during adolescence and early adulthood, but in elderly they are unchanged or increased slightly (Walter, 2009). In contrast, the HDL-C concentrations remain stable in women throughout their lifetime, however, menopause often causes a slight decrease in their HDL-C level (Kreisberg and Kasim, 1987). Besides, the TG concentrations increase progressively in men, reaching peak values between 40 and 50 years, and decline slightly thereafter. In women, the TG concentrations increase throughout their life, and are higher in those using estrogens all the time (Gobal and Mehta, 2010). Nevertheless, in a few studies including older persons, TC in the elderly has been reported to decrease with age (Table 1) (Gillum et al., 1982; Hershcopf et al., 1982). Most investigators consider that the decrease of TC as age increases may represent cohort, period, and/or survivorship effects rather than a true decline (Newschaffer et al., 1992).

Apart from the elevated plasma LDL levels, the decreased plasma LDL particle size has also been associated with increased risk of CAD (Campos et al., 1992). However, as for the changes of lipoprotein particle size with age, the related research is insufficient. Lemieux et al. (1999) once reported that middle-aged men (55.9 ± 6.2 years) were characterized by an increased concentration of LDL particles [reflected by increased LDL apolipoprotein (apo) B levels] but not by a reduced LDL peak particle size compared with young men (26.4 ± 4.2 years). It is therefore indicated that age per se is associated with an increased concentration of atherogenic LDL particles rather than a reduction of LDL particle diameter. In order to thoroughly understand the relationship between lipoprotein particle size and aging, we should make more efforts to investigate the specific situation of lipoprotein particle size in aging population.

3. Mechanisms of the age-related dyslipidemia

Plasma cholesterol levels increase with age, as does the incidence of CAD (Parini et al., 1999). The mechanisms responsible for the age-related hypercholesterolemia have not been well understood although there were a lot of studies aiming at explaining the mechanisms of aging and lipid disorders in humans. In this paper, we review the possible mechanisms that may explain the age-related changes of plasma cholesterol covering animals, humans or both, some of which need to be further demonstrated.

3.1. Age-related changes in the liver sinusoidal endothelium

The liver plays a pivotal role in the processing of physiological endogenous substances such as lipids, hormones, and different waste products. And also, it has been demonstrated that the age-related changes of liver sinusoidal endothelium is one of the important reasons of dyslipidemia in aging. In the past 10 years and more, many studies have reported that aging is associated with remarkable changes in the hepatic sinusoidal endothelium and space of Disse in the rat (Le Couteur et al., 2001), mouse (Ito et al., 2007; Warren et al., 2005), human (McLean et al., 2003), and the nonhuman primate, Papio hamadryas (Cogger et al., 2003). These changes were named pseudocapillarization since the aging sinusoidal endothelium had become more like capillaries seen in other nonfenestrated vascular beds (Le Couteur et al., 2001). On electron microscopy the researchers found a 40–80% increase in endothelial thickness and a 60–80% reduction in porosity and fenestrations, which was associated with basal lamina deposition in 25–40% of old livers. The presence of these changes in at least four species demonstrates this is a consistent change (Le Couteur et al., 2007). The age-related changes in the ultrastructure of the liver sinusoidal endothelial cells (LSECs, unique endothelial cells that line the hepatic sinusoids with no basal lamina or supportive connective tissue, whereas with pores called fenestrations) were associated with an increased expression of von Willebrand's factor (vWF, a capillary marker) in all species and laminin and collagen in rats and humans. Massive expression of vWF, not seen in LSECs of normal young livers, confirms that significant age-related changes are occurring in the endothelium. Changes were even apparent in the standard Masson's trichrome stain (a marker of connective tissue) in humans, consisting of obvious perisinusoidal staining. Major age-related changes in the liver were limited to the perisinusoidal regions.