

Prevalence and features of dyslipidemia in different populations depending on race/ethnicity, gender and age

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Abstract

The increasing number of cardiovascular diseases (CVDs) in both developed and in the majority of developing countries emphasizes the importance of epidemiological research on cardiovascular disease risk factors (RFs) and their relationship, including dyslipidemia. Evidence from international randomized clinical trials suggests that elevated cholesterol levels are associated not only with atherosclerosis, but also with other chronic non-infectious diseases. These relationships are based on changes in lipid metabolism, increased concentration of free fatty acids, insulin resistance, and other mechanisms. Hypertriglyceridemia and decreased high-density lipoprotein cholesterol, being significant independent RFs of cardiovascular diseases, nevertheless show a weaker association compared to hypercholesterolemia, and the possibilities of their pharmacological correction are less bright. Many factors influence the prevalence of dyslipidemia, including certain racial-ethnic group with certain lifestyle, genetic and cultural differences. The same CVD risk factors may differ in males and females. The article

discusses the age-related aspects of dyslipidemia prevalence and mechanisms of cholesterol metabolism disorders with a regard to aging processes. We present the data of scientific research on the prevalence and characteristics of dyslipidemia considering race/ethnicity, gender and age.

Keywords: dyslipidemia, cardiovascular disease; racial/ethnic, age and gender differences.

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Introduction

Dyslipidemia is an established risk factor (RF) for cardiovascular diseases (CVD) and can be defined as: elevated serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) or reduced serum high-density lipoprotein cholesterol (HDL-C) concentration [1, 2]. These plasma lipid disorders can be primary, due to the interaction of genetic predisposition and environmental RF, or secondary, from other diseases (e.g., diabetes, hypothyroidism and nephrotic syndrome) [3, 4]. LDL cholesterol is a major modifiable risk factor for the incidence of revascularization, ischemic strokes, atherothrombotic process and CVD mortality [5-7]. The importance of the LDL cholesterol role is confirmed by numerous studies, including clinical trials of proprotein convertase inhibitors subtilisin/kexin 9 (PCSK9), which increase LDL cholesterol receptor expression in hepatocytes, as well as liver clearance of LDL cholesterol [8, 9]. It is known that elevated cholesterol (CH) levels (hypercholesterolemia), especially LDL cholesterol, contribute to the process of atherosclerosis, leading to the deposition of CH and fatty acids in the arterial wall, while HDL cholesterol is usually considered a protective factor [1]. However, while De Freitas E. et al. reported that low HDL cholesterol is a RF of CVD in the elderly [10], a systematic review and meta-analysis by Briel M. et al. showed that elevated HDL cholesterol was not associated with reduced CVD risk or mortality [11]. A National Health and Nutrition Examination Survey (NHANES) report from 2003 to 2006 indicated that 53% (105.3 million) of US adults had at least one lipid metabolism disorder: 27% (53.5 million) had high LDL-CH, 23% (46.4 million) had low HDL-CH, and 30% (58.9 million) had high TG levels. In addition, 21% (42.0 million) of adults in the United States have mixed dyslipidemia, defined as the presence of high LDL-CH in combination with at least one other lipid metabolism disorder [12]. The results of the relationship between the risk of CVD and its complications with dyslipidemia should consider various factors that may determine the intensity of the atherosclerotic process, which may determine the possibility of using medications with cardioprotective and angiorotective effect. Cromwell W. et al. adjusted their data regarding age, sex, BP, smoking and intake of hypolipidemic drugs [13], and Van den Berg M. et al. adjusted their data taking age, sex, BMI, smoking, alcohol intake, diabetes mellitus and intake

of hypolipidemic drugs into account [14]. A number of studies have found that elevated TG levels increase CVD risk in men to a greater extent than in women, although the role of TG in the pathogenesis of cardiovascular pathology and atherosclerosis is still unclear. Nevertheless, it may be related to the concentration of CH in TG-rich lipoproteins rather than to the role of TG particles themselves [15].

Racial-ethnic, gender, and age factors effect on dyslipidemia prevalence

One of the most important factors determining the prevalence of dyslipidemia is belonging to certain racial-ethnic groups. According to Pu J. et al. there are significant racial-ethnic differences in the prevalence of dyslipidemia, the mortality rate associated with dyslipidemia, and the response to hypolipidemic drugs [16]. Frank A. et al. found a significant heterogeneity in the pattern of dyslipidemia prevalence, its association with coronary heart disease (CHD) and stroke mortality, and response to hypolipidemic agents in racial-ethnic groups [17]. These differences in dyslipidemia provide important information that may partially explain the differences in the burden of CVD observed in different racial-ethnic subgroups, which is very important and necessary for the prevention, screening and treatment of cardiovascular pathology [7, 8]. Thus, according to Frank A. et al. among all racial-ethnic groups, Indians of Asian origin, Filipinos and Hispanics are at the highest risk of dyslipidemia development and progression, which is consistent with higher rates of mortality from CHD in these cohorts. According to the authors, these are risk groups that should receive more attention for timely detection and treatment of dyslipidemia [17].

U.S. scientists found differences in CHD mortality rates between different racial and ethnic groups. According to Enas E. et al. in the United States, mortality rates from CHD were the highest among African Americans, moderate among Caucasians and Hispanics, and the lowest in some Asian subgroups [18]. Although Asian subgroups traditionally have been referred to as a "model minority", Ye J et al. demonstrated a disproportionately high burden of CHD and stroke mortality in these cohorts of examinees, such as Asian Indians, Filipinos, and Japanese [19]. There are also racial-ethnic differences regarding lifestyle RFs such as unhealthy diet, obesity, and physical inactivity. According to the 2008-2010

National Health Interview Survey (NHIS), Asian adults are less likely to smoke or be obese [20]. Interestingly, both vegetarians and non-vegetarians in India have a higher prevalence of coronary artery disease, considered as “Indian paradox” [18, 21]. Black adults in the United States were more likely to be physically inactive, obese, and sleep-deprived. Hispanics were less likely than non-Hispanic adults to smoke cigarettes, to be sleep-deprived, but more likely to be inactive in terms of aerobic exercise and muscle-building activities [22]. Immigration and acculturation have a profound effect on the lifestyles of both Latinos and Asians in the United States [23]. For example, the Ni-Hon-San study showed an increased rate of CHD mortality and a decreased incidence of stroke among Japanese American men compared with those in Japan, indicating a differential effect of acculturation on Western lifestyles [24].

In 2013, NHANES data showed that the prevalence of high LDL cholesterol was the highest among Mexican men (40%) and women (30%), followed by non-Hispanic black men (33%) and women (31%). Non-Hispanic white men (30%) and women (29%) had the lowest prevalence of high LDL-C levels among these 3 racial/ethnic groups [25].

A study (SHARE) assessing health and health risk in ethnic groups was conducted in three Canadian cities. This study examined the prevalence of CHD in a multinational cohort. The researchers found that South Asians, mostly Asian Indians, had higher levels of CHD and LDL cholesterol compared with Europeans and Chinese [26].

There were mixed data regarding HDL cholesterol levels. According to the NHANES, 20% of black men and 10% of black women were found to have low HDL-CH (less than 40 mg/dL for both men and women), which was lower than in non-Hispanic white men (33%) and women (12%). It has also been demonstrated that Mexican-American men and women had higher prevalence of low HDL cholesterol (34% and 15%, respectively) compared with non-Hispanic whites [23]. According to NHANES data from 2011 to 2012, 25% of Asian American men and 5% of Asian American women had low HDL cholesterol levels. Asian Indian men (53%) and women (55%) had the highest prevalence of low HDL cholesterol among subgroups of Asian Americans; it was also higher than that of the Mexican American men (48%) and women (51%), non-Hispanic black men (34%) and

women (40%), and non-Hispanic white men (36%) and women (31%) [17]. Similarly, data from the SHARE study showed that South Asians, including Asian Indians, had an increased prevalence of low HDL cholesterol compared to Europeans and Chinese [26]. Indians not only have low levels of HDL cholesterol but are also characterized by pro-inflammatory small dense dysfunctional HDL cholesterol particles. According to Radhika G. et al., the predisposition of South Asians to lower HDL cholesterol levels is due to a higher prevalence of insulin resistance and associated metabolic abnormalities, which may result from a combination of genetic predisposition, lack of physical activity and high carbohydrate content in the daily diet [27].

The results of studies examining the prevalence of hypertriglyceridemia have been very peculiar. NHANES data from 1999 to 2008 showed that 35% of Mexican Americans had high levels of TG, followed by 33% of non-Hispanic whites and 16% of non-Hispanic blacks [28]. Data from a Northern California clinical cohort from 2008 to 2011 showed that Filipino men (60%) and Mexican women (45%) had the highest prevalence of high TG compared to Mexican men (56%) and Filipino women (42%), Asian Indian men (55%) and women (37%), non-Hispanic white men (43%) and women (28%), and non-Hispanic black men (30%) and women (18%) [17]. Data from the SHARE study showed that South Asians had the highest prevalence of high TG [26]. In the Multi-Ethnic Study of Atherosclerosis (MESA), Goff D. et al. found that ethnic differences were significantly mitigated by providing an equal access to medical care [29].

Considering gender differences in the prevalence of dyslipidemia, according to Heidari S. et al. the risk of CVD in men increases after 40 years. In comparison, this risk in women group develops 7–10 years later [30]. Before the second half of the twentieth century, women were not included in experimental studies, so most of the current knowledge about the main diseases affecting public health comes from studies conducted exclusively in men, and their results were also applied to women [31]. Evidence from the current state of preventive cardiology indicates that health care delivery and outcomes continue to differ between women and men. Particularly alarming are the findings that women with the same CVD risk as men are less likely to receive treatment or preventive recommendations [32].

Despite the fact that CVDs are the main cause of death in women, they are still perceived as a male pathology [33]. Male gender can be a RF of dyslipidemia, which can be caused by excessive fat accumulation, significant increase in blood pressure (BP) and lack of exercise, although men constitute the main workforce in society. In addition, male lifestyle choices with the presence of smoking and alcohol consumption are associated with dyslipidemia, whereas female estrogen has some protective effect on lipid levels [34]. Although women and men tend to have the same CVD risk factors, they show different effects depending on gender. For example, in women, metabolic syndrome is the most important RF for the development of CHD at a young age; smoking more often causes CHD in women than in men; and arterial hypertension (AH) and dyslipidemia in women develop later, but are also worse controlled [35]. Poor control of dyslipidemia in both sexes may be related, on the one hand, to the limitations of the prognostic ability of the SCORE scale to detect CVD, and, on the other hand, to clinical inertia, defined by Phillips L. et al. as "the failure of physicians to start or increase treatment when it was indicated" [36]. This term was later reformulated as therapeutic inertia. Some studies have reported low control of LDL cholesterol in all patients, but especially in women, indicating less intensive treatment of dyslipidemia in women, thus, a greater therapeutic inertia in this group. The ESCARVAL-GENERO study examined 58,970 patients, including 27,311 (46.3%) men and 31,659 (53.7%) women with CVD RF but no CVD (CHD or cerebrovascular disease), who attended routine primary care between 2008 and 2012. The majority of those examined (81.9%, $n = 48,300$) had been diagnosed with dyslipidemia or had been treated for this pathology, and 18.1% ($n = 10,670$) had altered lipid levels and were neither diagnosed nor treated, indicating diagnostic inertia. This result was higher in women (20.1%, $n = 6358$) than in men (15.8%, $n = 4312$, $p < 0.001$). These differences may be related to gender stereotypes, which refer to a set of imposed and largely assumed perceptions about the characteristics, attitudes, and abilities of women and men [23].

Moreover, women are less likely to receive intensified treatment or achieve optimal treatment effects. When these differences systematically lead to gender inequalities associated with established roles and stereotypes, this can be a determinant of

differences in health outcomes. In 2018, Aggarwal et al. concluded that the RFs of CHD should be stratified by gender [7]. Although recent studies show the deleteriousness of gender bias in terms of diagnostic delay and error in women, with no studies evaluating differences in the use of diagnostic criteria for dyslipidemia between men and women. The incidence of CHD in premenopausal women is 3 to 4 times lower than in men [37]. After menopause, due to the loss of vasodilatory properties of estrogen and increased sympathetic activity, the risk of CHD increases and is similar to that in men [38]. The RFs unique to women are the use of oral contraceptives, menopause, hormone replacement therapy, gestational AH and diabetes. Obesity and metabolic syndrome are also more common in women [39].

Age-related factors affecting the prevalence of dyslipidemia, CHD and its complications have been studied profoundly [1]. Plasma cholesterol levels and LDL cholesterol levels are similar in both sexes during infancy and adolescence. LDL cholesterol levels increase progressively in both men and women after the age of 20 years, but more rapidly in men. LDL cholesterol particle size decreases with age in men, whereas in women it remains stable until menopause, after which it becomes smaller [40]. Historically, it has been established that older age is the most contributing factor of dyslipidemia. Both cross-sectional and longitudinal studies have shown that concentrations of TC, LDL cholesterol, and TG rose with age, while the HDL cholesterol concentrations fell [41]. Thus, Chinese researchers studied age-related aspects of dyslipidemia in urban residents of southwestern regions of China. According to Huang C. et al. the prevalence of dyslipidemia decreases with age in men and increases in women. High TG concentrations were detected in men, where they reached their highest values in participants aged 45-54 years old compared with those aged 35-44 years old. Then they decreased in those 55-64 and 65-79 years old. In women, the prevalence of hypertriglyceridemia increased with age. High levels of TC in men did not change significantly with age, while in women hypercholesterolemia increased with age. The prevalence of high LDL cholesterol levels in men increased with age, reaching its highest level in participants aged 55-64 years, and then decreasing thereafter. In women, the prevalence of high LDL cholesterol levels fluctuated with age. The prevalence

of low HDL cholesterol in men was the highest among participants aged 35–44 years, and then decreased. Among women, there were no significant changes in HDL cholesterol with age [42]. This result was consistent with other studies, which may be related to changes in estrogen levels in women before and after menopause [43, 44].

The aging process is associated with an increase in both TC and LDL cholesterol. Ericsson S. et al. reported an increase of TC from 4.8 mmol/l in young (20–39 years), to 5.14 mmol/l in middle-aged (40–59 years) and to 5.44 mmol/l in elderly (60–80 years) healthy Scandinavian participants [45]. In addition, according to Abbott R. et al., LDL cholesterol levels increased with age from 3.37 mmol/L in the young to 3.76 mmol/L in the middle-aged and to 4.05 mmol/L in the elderly. In addition, the level of very low-density lipoprotein cholesterol either remains stable or increases with age, whereas the level of HDL cholesterol seems to be independent of the aging process [2].

Cho S. et al obtained interesting data regarding the association of age-related dyslipidemia prevalence with education level. In individuals with higher education in all age groups the prevalence of dyslipidemia was relatively lower than in the cohort with lower education level. The prevalence of hypercholesterolemia reached its peak in the 50–59 years old age group regardless of education level, and then declined in the elderly. Up to the fifth decade, the increase in cholesterol was more frequent in the group with low education, and its prevalence was higher in those with high education after 50 years of age. The prevalence of hypertriglyceridemia and hypoalphalipoproteinemia was consistently higher in the low-educated group in all age groups. Interestingly, the prevalence of hypercholesterolemia was lower in women in the fourth decade than in the third decade in both the low (11.8% versus 15.8%) and high (14.9% versus 18.6%) education groups. An important fact is that while the level of LDL cholesterol increased with age in the group of persons with high education, this indicator of dyslipidemia in persons with low education showed a decrease in prevalence from 10.4 % at the age of 50–59 years to 5.7 % in the group of examinees 60–64 years (5.7 %) [50].

Based on the laboratory studies of 63,606 different patients conducted in Slovenia between 2008 and 2019, Markovič R. et al. found an increase in the proportion of patients with high levels of TC in the

age groups 55–59 years, which then decreased. The proportion of patients with glucose levels above the norm increased until the age group of 75–79 years, and then began to decrease [41]. This decrease, according to the authors, does not mean that patients became healthier, but it indicates that patient survival depends on glucose and lipid levels. The proportion of male patients with elevated levels of TC and LDL cholesterol began to decline between 45 and 49 years of age. In women, this decrease was observed a decade later (age group 55–59 years). The proportion of male patients with normal serum HDL cholesterol levels was significantly lower than the proportion of female patients with normal serum HDL cholesterol levels in all age groups. Importantly, the mean level of TC increased more rapidly than glucose levels and peaked in the age group of 50–59 years. In this age group, mean serum cholesterol levels began to decline, while mean serum glucose levels continued to rise until the age group of 70–79 years. After that, both mean serum cholesterol and glucose levels began to decline. With age, women were characterized by lower glucose levels but higher levels of TC than men. Thus, women reached their highest serum cholesterol levels ten years later than men, with mean serum TC levels never returning to normal in women but remaining elevated. Laboratory results show that the peak proportion of patients with elevated serum cholesterol levels preceded the peak proportion of patients with elevated glucose levels by about 20 years.

According to Gobal F. and Mehta J. at the age of 50 to 60 years (men) and 60 to 70 years (women), serum LDL cholesterol levels remain at a plateau. Women have lower levels of LDL cholesterol than men throughout life, but levels increase sharply after menopause and are higher than in men over age 60 [47]. In addition, Mari A. et al. note higher LDL cholesterol levels in women and higher TG levels in men [48]. As for sex and age differences of serum HDL cholesterol levels, higher serum HDL cholesterol levels were found in female patients compared to male patients regardless of age [32]. According to Markovič R. et al. the decrease in the proportion of the population with abnormal lipid and/or glucose levels may be influenced by medication administration, and in older age by mortality [41].

Considering the pathogenetic mechanisms of age-related changes in the prevalence of dyslipid-

emia, it should be noted that with age there may be disorders of cholesterol metabolism. These include: decrease of LDL cholesterol clearance; potential increase of cholesterol absorption; decrease of bile acid synthesis; decrease of bacterial bile acids modification. According to Morgan A. et al., age-related dysregulation of cholesterol metabolism and accumulation of LDL cholesterol is associated with changes in several key mechanisms, including cholesterol absorption, LDL cholesterol clearance, bile acids synthesis, and subsequent bacterial modification. Several changes occur in the gut microflora with age, including a decrease in the number and species diversity of *Lactobacillus* and *Bifidobacterium*. Consequently, it is possible that the age-related de-

crease in the number of these bacterial species reduces bile acid deconjugation and, in turn, reduces the conversion of CH to bile acids. This may play a role in the accumulation of cholesterol with age [49].

Conclusion

Studies devoted to the role of certain dyslipidemia subtypes and other RFs should be continued, as this will help to explain the higher risk of CVDs in certain groups of subjects with a regard to racial-ethnic groups, sex and age, as well as allow clinicians to make personalized recommendations for the prevention and treatment of dyslipidemia.

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