High-Density Lipoproteins

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The quantity of high-density lipoproteins (HDL) is represented as the serum HDL-C concentration (mg/dL), while the HDL quality manifests as the diverse features of protein and lipid content, extent of oxidation, and extent of glycation. The HDL functionality represents several performance metrics of HDL, such as antioxidant, anti-inflammatory, and cholesterol efflux activities. The quantity and quality of HDL can change during one's lifetime, depending on infection, disease, and lifestyle, such as dietary habits, exercise, and smoking. The quantity of HDL can change according to age and gender, such as puberty, middle-aged symptoms, climacteric, and the menopause. HDL-C can decrease during disease states, such as acute infection, chronic inflammation, and autoimmune disease, while it can be increased by regular aerobic exercise and healthy food consumption. Generally, high HDL-C at the normal level is associated with good HDL quality and functionality.

high-density lipoprotein (HDL)

1. Introduction: What Are HDL Quantities, Qualities, and Functionalities?

The general factors that are considered in terms of HDL quantity are the serum HDL-C level and the amount of cholesterol in the HDL, which can be detected by enzymatic determination. HDL quantity is expressed simply as a number alongside an mg/dL or mmol unit. In contrast, HDL quality is reflected by more diverse features of the particle morphology because HDL is a highly complex structure [1], consisting of many lipids (cholesterol, triglyceride, and phospholipid) and proteins (apolipoproteins and enzymes). HDL quality is related to the morphology of HDL particles, such as the shape, size, and composition of lipids and proteins in the particles. HDL quality also includes the extent of the oxidation and glycation of the components in HDL. The HDL functionality is represented as the antioxidant ability and cholesterol efflux activity for the prevention of LDL oxidation and the regression of atherosclerotic plaque, respectively [2].

The quantity and quality of HDL can influence the overall health status of blood vessels and the properties of LDL, such as an oxidized LDL (oxLDL), which is considered a major culprit of cardiovascular disease (CVD) to facilitate the growth of atherosclerotic plaque. More oxidized and glycated LDL can increase the incidence of cerebrovascular diseases, such as stenosis, thrombosis, embolism, hemorrhage, and CVD. OxLDL is a potent inflammatory trigger of atherosclerosis and vascular complications [3][4]. Native HDL can prevent LDL oxidation by removing oxidized lipid species via the neutralization of free radicals and reactive oxygen species (ROS). An impairment of the HDL quantity and quality is associated with the incidence of CVDs, cerebral diseases [5], and kidney diseases [6]. Therefore, increasing the HDL quantity and quality could be an appropriate tool to suppress

many heart and brain disorders. Regarding acute viral infections, such as coronavirus disease 2019 (COVID-19), a lower HDL quantity is associated with a high sensitivity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [7] and a high risk of death [8]. HDL functionality, particularly the paraoxonase (PON-1) activity, might be important for the suppression of a SARS-CoV-2 infection [9]. A previous study reported that native HDL with antioxidant and anti-atherosclerotic activities displayed a potent antiviral activity to suppress the replication of SARS-CoV-2, while glycated HDL lost their antiviral activity [10]. Accumulated studies reported many aspects of high-density lipoproteins (HDL) in human growth, human disease, and the aging process under different environmental changes, such as dietary patterns and an exposure to pathogens, smoking, and pollutants [1][2].

2. Change in HDL-C Quantity during One's Lifetime

HDL-C, usually expressed as mg/dL, can be measured directly from serum by enzymatic determination using the cholesteryl esterase and cholesterol oxidase method after precipitating apo-B containing lipoproteins. Unlikely total cholesterol (TC) and LDL-C, a low HDL-C level is one component of dyslipidemia and metabolic syndrome. Low HDL-C in men and women is defined as <40 and <50 mg/dL, respectively, according to the guidelines of the National Cholesterol Education Program Adult Treatment Panel III [11]. HDL-C can be applied to the expression of the lipid profile to indicate the risk of CVD and metabolic syndrome, such as the LDL-C/HDL-C ratio [12], triglyceride (TG)/HDL-C ratio [13], and HDL-C/TC ratio (%) [14][15]. Although the method of expression varies according to the disease (e.g., hypertension) and population cohort, HDL-C quantity is the critical factor affecting the risk of CVD and cholesterol-related disease. HDL-C quantity can change during one's lifetime, from one's teenage years to adulthood (approximately eighty years of age), particularly in the pubertal period, at a young age, middle age, menopausal age, and elderly age. HDL-C quantity can also be decreased as a result of individual lifestyle modifications, such as smoking, the consumption of trans fat, and intake of high fructose corn syrup.

2.1. Change in HDL-C Quantity between Gender during One's Lifetime

A low serum HDL-C level in middle-aged individuals is a hallmark of metabolic syndrome [16] and a risk factor of Alzheimer's disease [17], and vascular dementia [18] in old age. HDL-C quantity is not fixed during one's lifetime, and can change depending on age and gender [14][19][20]. In the Korean adult population, men and women showed the highest HDL-C quantity in their 20s (49.9 ± 11.1 mg/dL and 58.1 ± 11.3 mg/dL), respectively, with a gradual decrease until reaching the lowest levels of HDL-C in their 70 s (45.7 ± 11.6 mg/dL and 50.2 ± 11.4 mg/dL for men and women), respectively [19]. The female group had a significantly higher HDL-C level ($p < 0.001$) than the male group from their twenties to seventies at 8.2 mg/dL and 4.5 mg/dL, respectively [19]. These results raised the question of when women had a higher serum HDL-C level than men.

On the other hand, both groups showed a similar HDL-C level in their 80s, approximately 45.9 ± 10.9 mg/dL and 46.6 ± 10.9 mg/dL for men and women ($p = 0.656$), respectively. The male group from their 20 s to 80 s showed a 4.0 mg/dL difference in HDL-C, while the female group showed an 11.5 mg/dL difference in HDL-C, indicating that the female group experienced a more severe decrease during their lifetime from their 20 s to 80 s [19]. The same tendency was found in studies on the American population, such as the Rancho Bernardo Study 1984–1994 [20].

This study showed that the HDL-C levels decreased in older men and women with an increase in age. The HDL-C levels decreased gradually and dramatically in individuals older than 50 years, particularly in the female group.

The dramatic decrease in HDL-C after middle age is linked to the sharp increase in dementia in people in their 80 s. The female group showed a three-fold higher level than the male group [19]. Interestingly, both genders, men and women, showed a direct association between the income grade with the HDL-C level; the lower-income group showed a higher prevalence of low HDL-C levels [19][21].

2.2. Pubertal Change in HDL-C in Men

Why and when men have a lower HDL-C level than women in adulthood has been a mystery for a long time. A study on teenage subjects showed that the lowering of HDL-C in men is related to the remarkable decrease in serum HDL-C during the pubertal age, 14–15 years old [22]. The male group showed a sharper decrease in the HDL-C level from 10–11 years old (54.6 ± 11.1 mg/dL, $p < 0.001$) to 14–15 years of age (48.4 ± 9.0 mg/dL), while the female group showed a similar increase in the HDL-C level from 10–11 (52.8 ± 9.6 mg/dL) to 14–15 years of age (53.1 ± 9.7 mg/dL, $p = 0.001$). At 18–19 years of age, the HDL-C level in the male group decreased to 50.3 ± 9.3 mg/dL, whereas the female group showed an increase to 55.6 ± 10.5 mg/dL. HDL can cross the blood–testis barrier (BTB) to supply cholesterol for spermatogenesis in the male group, while LDL cannot. These results suggest that the dramatic gap between the HDL-C between males and females was initiated from the pubertal age, especially in the age range of 14–15 years. The male group has a remarkable demand for cholesterol for spermatogenesis in the testis, which explains the sharp decrease in HDL-C levels during the pubertal period for boys.

A higher HDL-C level is inversely associated with a lower incidence of cardiovascular disease [23]. Generally, women have a higher HDL-C than men between 20 and 50 years of age, particularly before experiencing the menopause. Other reports showed that women had a 5 mg/dL higher HDL-C level than men from the unadjusted mean difference in HDL-C [24], although it was unclear when and why men have a lower HDL-C level than women in adulthood.

It is essential to compare the HDL-C level in teenagers (10–19 years old) between boys and girls to understand when and why women have a higher HDL-C level and a longer life span than men in adulthood and later life [25]. The HDL-C level rapidly decreases during the pubertal period (14 and 15 years old) in the male group. The lowest HDL-C level at 15 years of age was not restored at 19 years of age in the male group; it was almost fixed and remained at a lower level for the life expectancy of men compared to women. The decrease in HDL-C during the pubertal age occurred only in the male group, but the reason for this is unclear. One possible explanation is that the cholesterol from HDL is required to produce the male hormone and spermatogenesis in boys. Cholesterol is essential for spermatogenesis and steroidogenesis in the male reproduction system. Sertoli cells, which promote sperm production, block the passage of LDL at the blood–testis barrier (BTB), but permit the entry of HDL to the seminiferous tubules [26]. Cholesterol is an essential nutrient for spermatogenesis because it fuels spermatogenesis in Sertoli cells. The lower HDL-C during the teenage period in males might be associated with the

lower life expectancy of men in adulthood and remaining later life. Furthermore, the lower HDL-C in men might be correlated with the higher BP in men during adulthood [14].

2.3. Menopausal Change of HDL-C in Women

The menopause is a critical event in a woman's life in regard to the physical and emotional changes, accompanied by a decline in ovarian activity. Despite the conflicting data [27], many studies suggested that a decrease in HDL-C is associated with the menopause [28]. In a study on the Korean population, women showed a stable HDL-C level from 58 ± 11 mg/dL to 56 ± 12 mg/dL in their 20 s and 40 s, respectively, only a 2 mg/dL difference. On the other hand, women showed a sharp decrease in HDL-C from 55 ± 12 mg/dL to 46 ± 10 mg/dL in their 50 s to 80 s, respectively, a 9 mg/dL difference. A 12 mg/dL difference in the HDL-C was detected in the female group in their 20 s to 80 s [14][19]. On the other hand, men showed a more stable and smaller decrease in HDL-C with the increase in age; the male group showed only a 4 mg/dL difference from their 20 s to 80 s [19].

Generally, post-menopausal women have an elevated cardiovascular risk via increased hyperlipidemia [29], with a two-to-three-times higher CVD death rate than the premenopausal women of the same age [30]. A meta-analysis showed that the menopause effect was associated with around a 10–20% increase in TC, LDL-C, and triglycerides (TGs), while only HDL-C decreased by around 10% [27]. Interestingly, several studies suggested that post-menopausal women have an increased level of apoA-I (a 13% increase) [31], despite the decrease in HDL-C [32][33]. These discrepancies suggest that the HDL particle-formation ability of apoA-I in post-menopausal women might be impaired. Lipid-free apoA-I could be increased in post-menopausal women, despite the similar kinetic parameters of HDL and apoA-I in the two groups [34]. Post-menopausal women showed a greater decrease in large-sized HDL (~22%), with an increase in lipoproteins (Lps) containing apoA-II (LpA-II), than premenopausal women, while the LDL size was similar in the two groups [34]. These results suggest that the menopause is a critical event in a woman's life that changes the HDL quantity [27] and quality [35], similar to puberty playing a critical role in changing HDL-C in a man's life.

2.4. Exercise and Change in HDL

A sedentary lifestyle is associated with low HDL-C for all ages and genders [36][37]. A meta-analysis with 19 randomized controlled trials showed that exercise could improve the cardiometabolic risk factors, lowering the TC, LDL-C, and TGs in obese adolescents with sedentary behavior [37]. Interestingly, the increase in HDL-C as a result of exercise was prominent in studies on obese children [38]. Although short-term exercise (less than six months) could not sharply decrease the total cholesterol, HDL-C was increased as a result of exercise in healthy children [39]. Another report showed that the performance of resistance exercises for 14 weeks was not associated with improved HDL-C, even though the TC and LDL-C decreased in premenopausal women [40]. There are conflicting data concerning the effect of exercise on improving HDL-C quantity, depending on the type of sport [41]; aerobic exercise effectively improves HDL-C, but resistance exercise does not.

Aerobic exercise performed for 12–24 weeks can increase HDL-C more efficiently, by around 3.8–15.4 mg/dL from the initial level [42]. A recent meta-analysis also showed that aerobic exercise was the best option to increase HDL-

C [43]. In the same context, in Olympic athletes, aerobic exercise (runners and wrestlers) showed a 1.3-fold higher HDL-C level than anaerobic exercise performed by elite athletes [44]. They presented a larger HDL particle size, higher apoA-I content, and higher antioxidant enzyme (paraoxonase) activity. These results suggest that performing repetitive aerobic exercise can increase HDL-C quantity and the HDL quality.

2.5. Nutritional Supplementation and the Change in HDL

2.5.1. Omega-3 Consumption

The elevation of HDL-C quantity by the consumption of omega-3 is still controversial, depending on a combination of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and the consumption period. The consumption of 2.8 g/d EPA and 1.7 g/d DHA for 6 weeks resulted in a selective increase in cholesterol in the subfraction of larger HDL (HDL_2) by up to 74%, with a concomitant 19% decrease in HDL-C [45]. However, the reason why only cholesterol in HDL_2 was increased, despite the lack of change in the TC, HDL-C, and TGs, is still unclear. A meta-analysis of the data from 33 randomized controlled trials reveals that dietary EPA supplementation on metabolic syndrome did not increase HDL-C (weighed mean difference, WMD = 0.02 nmol/L), while DHA supplementation increased HDL-C (WMD = 0.07 nmol/L) [46]. In contrast to the inconsistent results obtained from the combined supplementation, the supplementation of omega-3 (marine n-3) alone (1 g/d, *n* = 12,933) for 5.3 years did not reduce the risk of major cardiovascular events than the placebo without an increase in HDL-C, compared to the vitamin D3 (2000 IU/d) group (*n* = 12,938) as a placebo [47]. In the long-term and larger participant study, the high-dose consumption of icosapent ethyl (4 g/d) for 4.9 years decreased the risk of ischemic events and increased HDL-C [48].

The consumption of high-dose omega-3 fatty acids (4 g/d, *n* = 6539) for 12 months resulted in no significant changes in HDL-C (from 36 mg/dL at the baseline to 37 mg/dL at the follow-up in statin-treated participants with a high cardiovascular risk [49]). In comparison to the corn oil group (*n* = 6539) as a placebo, the geometric mean ratio between the groups was 1.01 (*p* = 0.002), indicating that HDL-C increased very slightly. Interestingly, the serum apo-B content was not changed between the groups, suggesting that the quality of HDL and LDL might not be changed. More recently, the consumption of omega-3 krill oil (4 g/d) for 26 weeks resulted in a decrease in the TG, but no significant improvement in HDL-C [50]. Therefore, despite the conflicting data, it can be concluded that the consumption of omega-3 did not increase the serum HDL-C in both long-term and short-term consumptions.

2.5.2. Consumption of Policosanol from Sugarcane Wax

Policosanol is a mixture of aliphatic alcohols, ranging from 24–34 carbon atoms, such as octacosanol, triacontanol, dotriacontanol, hexacosanol, and tetratriacontanol as the major components, which were purified from sugarcane (*Saccharum officinarum* L.) wax or various plants, rice bran, and beeswax. A meta-analysis of 22 studies reported that policosanol could lower the lipid content and is a safe drug used to elevate HDL-C levels [51].

Cuban policosanol in reconstituted HDL (rHDL) showed potent cholesteryl ester transfer protein (CETP) inhibition activity from HDL to LDL, as shown in previous reports [52][53], even though the policosanol in ethanol did not show

adequate activity. Policosanol in rHDL possesses a much higher CETP inhibitory ability, around 67% inhibition, than rHDL alone, which showed a 10% inhibition [52][53]. In the molecular structure, policosanol contains long-chain hydrophobic moieties, which can interact with the hydrophobic active site of CETP. The aliphatic chains can interfere with binding between CETP and HDL. The aliphatic chains bind to a putative CE-binding site in the C terminus of CETP to form a ternary complex, as previously suggested [54]. Other in vitro and animal studies reported that policosanol inhibits cholesterol synthesis by modulating 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, possibly by activating 5′ adenosine monophosphate-activated protein kinase (AMP-kinase) [55]. Other studies determined that the action of policosanol involves various pathways, such as the activation of AMP kinase, stimulation of the Akt signaling pathway to prevent lipopolysaccharide (LPS)-induced apoptosis [56], down-regulation of HMG-CoA reductase, and cholesteryl ester transfer protein inhibition [57][58][59]. In addition to the increase in HDL quantity and improvement of dyslipidemia, the consumption of Cuban policosanol also enhanced the HDL functionality [59] and the blood-pressure-lowering effects [60][61].

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