EDITORIAL

Gone with the age(DL): high-density lipoprotein in senescence

Klaus Distelmaier, Georg Goliasch

Department of Internal Medicine II, Medical University of Vienna, Austria

Aging is a complex biological process characterized by a progressive decline of organ functions, leading to an increased risk of age-related diseases and death. Multifactorial processes are involved that are genetically predetermined and epigenetically influenced by the environment. Oxidative stress is considered as a key factor in promoting aging and inducing various age-related diseases including atherosclerosis, Alzheimer disease, diabetes, cancer, chronic obstructive pulmonary disease, and macular degeneration.[1] Oxidative stress results from an imbalance between the formation of reactive oxygen species (ROS) and a biological system's ability to neutralize their harmful effects by antioxidants. In a young and healthy body, intracellular ROS are maintained at low levels by a complex antioxidant defense system that includes enzymatic and nonenzymatic antioxidants. The major enzymatic antioxidants are superoxide dismutase, catalase, and glutathione peroxidase. Nonenzymatic antioxidants include small-molecule compounds such as α-tocopherol, ascorbic acid, β-carotene, and reduced glutathione. Oxidative damage occurs when ROS levels exceed antioxidant capacity and create a state of oxidative stress that may directly modify cellular DNA, proteins, and lipids or may trigger inflammation, apoptosis, and cell necrosis.[1]

Effects of oxidative stress on lipids are mainly the induction of lipid peroxidation. Oxidation of phospholipids within low-density lipoprotein (LDL) by oxidized lipids, such as fatty acid hydroperoxides, leads to the production of slightly modified LDL particles, which initiates a cascade of events that lead to vascular inflammation and progression of atherosclerosis. Lipid peroxidation products, such as isoprostanes and thiobarbituric acid-reactive substances, have been identified as indirect biomarkers of oxidative stress. In proteins, ROS may induce fragmentation of the peptide chain, alteration of electrical charge of proteins, and oxidation of specific amino acids. Particularly, cysteine and methionine residues in proteins are highly susceptible to oxidative stress.[2] Most of these oxidative modifications were found to be associated with aging and cardiovascular diseases.[1,3] A combination of both higher levels of oxidative stress as well as the inappropriate response to oxidative stress are suggested to be critically involved in pathophysiological processes during aging.[2]

High-density lipoprotein (HDL) is an effective component of the antioxidant system. HDL has the capacity to reduce oxidative burst in the plasma as well as the cellular compartment. Antioxidant properties of HDL are mediated in part by apolipoprotein A1 within the core lipoprotein particle and by a selection of HDL-associated proteins including apolipoprotein A1, haptoglobin, paraoxonase 1, and lecithin: cholesterol acyltransferase. Paraoxonase 1 has been found to prevent the formation of lipid hydroperoxides and oxidized phospholipids and hydrolyzes them once they are formed. A reduced systemic paraoxonase 1 activity correlates with the amount of systemic oxidative stress and predicts an increased risk for adverse cardiovascular events.[4] Consistent with this concept, individuals with low HDL cholesterol (HDL-C) levels are characterized by both the impairment of antioxidant activity and elevated systemic oxidative stress levels. This deficiency of antioxidant properties of HDL may result in attenuated atheroprotection and development of other oxidative-triggered diseases.[2]

With increasing age, serum HDL levels are decreasing. Moreover, there is strong evidence that not only plasma HDL concentrations but also HDL functions decline with age.[5] The influence of aging on HDL levels and function has not been fully understood but secondary effects of aging seem to be predominant. Insulin resistance and impaired lipolysis are more frequent in advanced age and may affect protective HDL activities. Furthermore, a reduction of physical activity, changes in dietary habits, and a modified hormonal balance have been reported to have adverse effects on

Correspondence to:
Klaus Distelmaier MD, PhD, Department of Internal Medicine II, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria, phone: +43 1 40400 46140, e-mail: klaus.distelmaier@meduniwien.ac.at
Received: October 17, 2016.
Accepted: October 17, 2016.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2016; 126 (10): 727-728
doi:10.20452/pamw.3594

HDL during aging.[5] The precise underlying mechanisms are unclear but changes in HDL protein composition and protein quality are known to critically alter the functional properties of HDL.[4] Even small changes in the microenvironment can unfavorably alter HDL structure and function. Modified HDL does not only lose protective capacities but may actually acquire prooxidant and proinflammatory properties.

In the current issue of *Polish Archives of Internal Medicine,* Dzięgielewska-Gęsiak et al[6] investigated the impact of HDL on the oxidant–antioxidant balance in healthy elderly individuals. Surprisingly, no differences in total antioxidant status were observed between patients with low and those with high plasma HDL-C levels. These data are in agreement with the current literature suggesting that HDL may lose its antioxidant capacities independently of serum HDL-C levels under certain conditions.[7-9] Furthermore, the study indicates that aging per se affects HDL function in this specific patient population of exclusively healthy elderly individuals, independent of other comorbidities. A disturbed turnover of damaged proteins in elderly individuals might explain this observation.[10] Protein homeostasis is critical for cellular function, organismal growth, and viability. An efficient degradation of damaged proteins by the ubiquitin-proteasome system or autophagy is critical for maintaining the integrity of the proteome of the whole organism. Aging is associated with impaired clearance of modified and damaged proteins, leading to an accumulation of damaged and aggregated proteins. Consequently, oxidative protein modifications are ubiquitously and dynamically involved in aging.[10] Considering that posttranslational modifications of HDL-associated proteins are critically involved in rendering HDL dysfunctional,[4] this age-related decline of protein turnover might explain a generally impaired antioxidant function of HDL in the elderly.

Nevertheless, the available data do not allow ignoring HDL as a risk factor in elderly individuals. Even though HDL-C levels of centenarians are 20% lower than those of 65-year-old individuals, their HDL-C levels are still much higher than their predicted HDL-C level according to an estimated decline of approximately 1% per year. The higher observed HDL-C concentrations in centenarians when compared to their predicted level may be caused by a survival bias, as an individual with a less privileged HDL profile may not become a centenarian.[5] Therefore, we conclude that HDL may serve as surrogate for general clinical condition in elderly people. However, the proof for a causal link between HDL functions and longevity is outstanding, and further molecular and cellular studies are needed to investigate this field in more detail.

REFERENCES

1 Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. Nature. 2000; 408: 239-247.

2 Birben E, Sahiner UM, Sackesen C, et al. Oxidative stress and antioxidant defense. World Allergy Organ J. 2012; 5: 9-19.

3 Smith LE, White MY. The role of post-translational modifications in acute and chronic cardiovascular disease. Proteomics Clin Appl. 2014; 8: 506-521.

4 Navab M, Reddy ST, Van Lenten BJ, et al. HDL and cardiovascular disease: atherogenic and atheroprotective mechanisms. Nat Rev Cardiol. 2011; 8: 222-232.

5 Walter M. Interrelationships among HDL metabolism, aging, and atherosclerosis. Arterioscler Thromb Vasc Biol. 2009; 29: 1244-1250.

6 Dzięgielewska-Gęsiak S, Bielawska L, Zowczak-Drabarczyk M, et al. The impact of high-density lipoprotein on oxidant–antioxidant balance in healthy elderly people. Pol Arch Med Wewn. 2016; 126: 731-738.

7 Distelmaier K, Schrutka L, Seidl V, et al. Pro-oxidant HDL predicts poor outcome in patients with ST-elevation acute coronary syndrome. Thromb Haemost. 2015; 114: 133-138.

8 Manjunatha S, Distelmaier K, Dasari S, et al. Functional and proteomic alterations of plasma high density lipoproteins in type 1 diabetes mellitus. Metabolism. 2016; 65: 1421-1431.

9 Schrutka L, Goliasch G, Meyer B, et al. Impaired high-density lipoprotein anti-oxidant function predicts poor outcome in critically ill patients. PLoS One. 2016; 11: e0151706.

10 Kevei E, Hoppe T. Ubiquitin sets the timer: impacts on aging and longevity. Nat Struct Mol Biol. 2014; 21: 290-292.