Lipoprotein Subfractions and Particle Size in End-Stage Renal Disease

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Clin J Am Soc Nephrol 6: 2738–2739, 2011. doi: 10.2215/CJN.10281011

It is interesting to note that the most heavily relied upon measures in nephrology and cardiology are both derived from calculations based on laboratory and clinical values, that is, the estimated GFR and the estimated concentration of low-density lipoprotein cholesterol (LDL-C). The actual particles of LDL in the bloodstream represent the end product of multiple hydrolysis steps that allow the initial nutritional packet, very low-density lipoprotein (VLDL), to deliver fatty acids, as well as cholesterol esters, to tissues for cellular metabolism and maintenance. The half-life of LDL is approximately 3 days, and it is believed that LDL itself has no nutritional value (1). In an ideal situation, LDL would meet its catabolic fate by docking with the LDL receptor and clearance from the circulation. However, in most adults, there is an age-related increase in LDL-C due to impaired clearance and perhaps recirculation of particles via cholesteryl esterase transfer protein. Smaller LDL particles have a longer clearance time and are more densely packed with cholesterol ester than larger particles, giving them more opportunity for tissue deposition (Figure 1) (1). While LDL-C has served reasonably well as an estimate and a proxy for the pathogenic LDL particles, many have believed that measurement of either the number or concentration of particles according to size, or determination of the apolipoprotein B concentration (1:1 with the number of LDL particles) should bring us closer to appreciating ongoing deposition of LDL into the vessel wall, advancing atherosclerosis, and translation into binary events such as myocardial infarction and cardiovascular death (2,3).

In this issue of the journal, Noori and colleagues performed detailed LDL particle analysis on a random sample ($n = 235$) of hemodialysis patients who were part of a well established cohort followed for all-cause mortality (4). One of the most striking findings in this study is the influence of obesity, as stratified above and below a body mass index of 27 kg/m^2, which was associated with an approximately 20 to 40% increase in triglycerides, and statistically significantly higher LDL-C, total LDL particles, and very small to medium LDL particles. The very small LDL particles were only significantly correlated ($R = 0.21$) with one nonlaboratory measure: fat mass percent. This influence of excess adiposity on lipid subfractions in end-stage renal disease (ESRD) appear to be greater than those observed in the general population (5). These relationships are important to remember, as the detailed tables and figures in this article suggest that there are modest relationships between small LDL particle number and concentration with all-cause mortality, which is a relatively crude and diluted proxy for translated atherosclerotic events. Thus, this article indirectly brings into focus, perhaps, a special pathogenicity of excess adiposity in patients with chronic uremia that is related, in part, to greater numbers of smaller LDL particles. These nuances are fairly well concealed in the standard lipid profile, which features the calculated LDL-C.

Many articles suggest that chronic kidney disease (CKD), independent of other risk factors, appears to accelerate the atherosclerotic process, including the gradient dependent deposition of LDL particles, recruitment of monocytes, upregulation of adhesion molecules, ingress of monocytes and conversion to macrophages and foam cells, oxidation of lipid material, mobilization of vascular smooth muscle cells, breakdown of the elastic lamina, and development of an atheroma, which expands both toward the lumen and outward toward the adventitia (6–8). The most prominent component of atherosclerosis influenced by CKD is calcification, which, interestingly, is not associated with LDL particle size or number, nor is it influenced by lipid-lowering therapy (9,10). The present article by Noori and coworkers suggests that, beyond calcification, an atherogenic dyslipidemia is more prominently related to excess adiposity and is in the causal for pathway for earlier, more severe, and consequential atherosclerosis in patients with ESRD (11–13). Future research in ESRD using advanced clinical lipidology measures, including oxidized lipids and quantity, size, content, and circulatory time of particles, is warranted. More detail will be needed on the effects of adiposity, concurrent medications, and state of vascular disease determined by imaging. Finally, the end points of future studies will deserve to be more focused on atherosclerotic vascular events that experts can adjudicate and agree upon, including unstable angina, acute myocardial infarction, and ischemic stroke.

The clinical use of commercially available lipoprotein subfractionation or particle tests in patients with ESRD is premature at the present time, due to the

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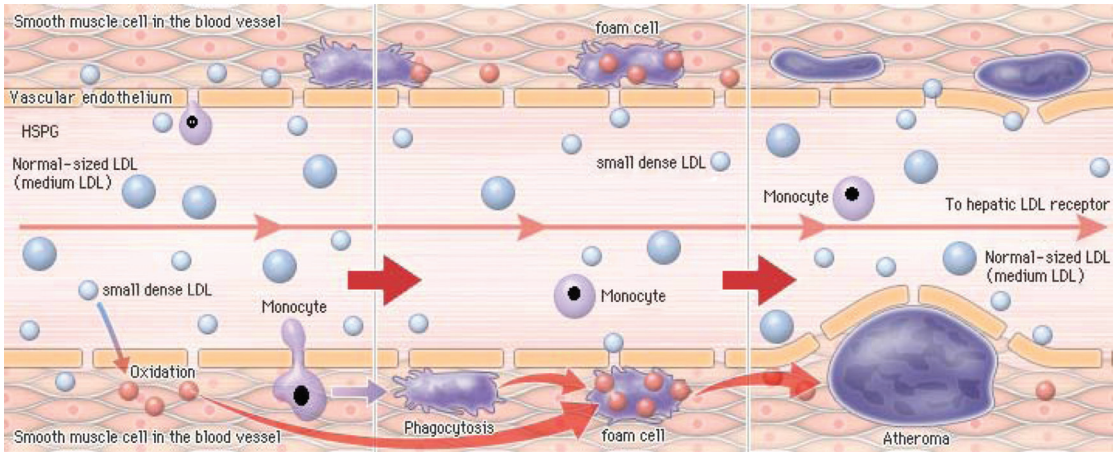

Figure 1. | Depiction of smaller dense LDL particles with ingress into the subintimal space initiating the pathogenesis of atherosclerosis. HSPG, heparin sulfate proteoglycans.

complexity of the biologic relationships in uremia, degree of uncontrolled confounding, lack of harmony between testing methodologies on the market, and the absence of a clear therapeutic mandate above and beyond what we currently have in the conventional lipid profile (14).

Disclosures

None.

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Published online ahead of print. Publication date available at www.cjasn.org.

See related article, "Novel Lipoprotein Subfraction and Size Measurements in Prediction of Mortality in Maintenance Hemodialysis Patients," on pages 2861–2870.