Trends in Cardiovascular Medicine 29 (2019) 27–28

Contents lists available at ScienceDirect

Trends in Cardiovascular Medicine

journal homepage: www.elsevier.com/locate/tcm

Editorial Commentary: Oxidized LDL: The next "big thing"?

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The pathophysiology behind atherosclerotic vascular disease has been a constantly evolving area of active research. Since the discovery of LDL-C and its integral role in the development of coronary artery disease, the primary and secondary prevention of atherosclerosis has considerably improved especially after the widespread implementation of statin therapy [1]. However, despite these remarkable advances, cardiovascular disease and myocardial infarction remain among the leading causes of mortality worldwide [2]. It has become apparent that while reducing LDL levels mitigates cardiovascular risk, there is still a component of residual risk [3].

As this detailed review by Hartley et al. illustrates, our understanding of the pathophysiology has grown considerably beyond the accumulation of lipid particles in atheromatous lesions [4]. The process of plaque accumulation and rupture involves a complex interaction between the endothelial surface and various immune pathways, and oxLDL appears to play a central role in the early phases of an inflammatory cascade leading to plaque development and rupture [5]. Hartley et al. hypothesize that the ability to measure circulating oxLDL levels or their circulating antibodies (anti-oxLDL) would provide additional risk stratification in patients with coronary heart disease [4]. Both oxLDL and anti-oxLDL levels have been associated with increased rates of cardiovascular events independent of circulating LDL levels [6,7]. These may also have prognostic value for patients with cerebrovascular and peripheral vascular disease.

For practicing clinicians, a few questions remain. For instance, it is unclear if there exists a commonly accepted reference range for oxLDL and/or antibody levels and for which patients these should be sent? Additionally, the ability of non-coronary vascular beds to release oxLDL into the circulation may result in reduced specificity of this biomarker in risk stratifying patients for coronary events [8]. In our current era of primary and secondary prevention therapies, it also remains unknown how clinicians would manage elevated oxLDL levels in patients with traditional cardiovascular risk factors who are already on guideline directed medical therapy. Furthermore, the impact of novel LDL lowering agents such as the proprotein convertase subtilsin-kexin type 9 (PCSK9) inhibitors on oxLDL remains unknown and warrants further investigation.

There are certain populations not adequately captured in standard cardiovascular risk stratification tools that may additionally benefit. For example, the atherosclerotic cardiovascular disease (ASCVD) risk calculation tool is widely used in the United States for statin initiation, but does not account for inflammatory conditions that may predispose certain populations to coronary risk [9]. Patients with HIV, rheumatological disease such as systemic lupus erythematosus, or chronic kidney disease have all been shown to have accelerated rates of atherosclerotic disease which has been hypothesized to be secondary to the systemic inflammation with which these conditions are associated [10–13]. It would be interesting to see if oxLDL levels could be used to risk stratify these groups and guide recommendations for both anti-inflammatory and lipid lowering medications.

In the last several years, there has been considerable interest in the pleiotropic effects of statin therapy on plaque biology. Early studies identified C-Reactive Protein (CRP), a non-specific marker of inflammation, as a significant biomarker for identifying patients at an increased risk of future cardiovascular morbidity and mortality [14]. Building on these findings, JUPITER found that tailoring statin therapy to high-sensitivity CRP levels was able to reduce adverse cardiovascular outcomes [15]. Although the exact mechanism of these pleitropic effects and their clinical meaning have not been fully elucidated, it is possible that they be mediated through reductions in oxidized lipid particle levels. Small studies have shown that a dose-dependent relationship exists for statin therapy and circulating oxLDL particles [16]. There also appears to be a significant direct correlation between circulating oxLDL and hsCRP levels [17].

Similarly, canakinumab, an interleukin 1B monoclonal antibody, was shown to reduce cardiovascular events in patients with a history of myocardial infarction in the landmark CANTOS trial [18], independent of LDL levels. Interleukin 1B is just one of a whole host of cytokines that are released from immune cells within a coronary plaque [5]. As Hartley et al. outlined, oxLDL plays a more upstream role in activation of macrophages, and targeting oxLDL with antibody therapy has been proposed as a strategy to reduce cardiovascular event rates [4]. Canakinumab may similarly impact oxLDL. Although we do not have sufficient evidence at this time, the biological plausibility of investigation into this concept is robust and should be further investigated

The review also outlines the potential roles for oxLDL and anti-oxLDL antibodies as targets for molecular imaging of atherosclerosis. For instance, molecular probes to image the presence of oxLDL in arteries have been developed [19]. Non-invasive strategies using PET are also being explored [20]. Similarly, oxLDL antibody uptake may be a marker for plaque stability. These may have a role to play

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https://doi.org/10.1016/j.tcm.2018.07.005

in our quest to unearth one of the holy grails of atherosclerosis: the identification of vulnerable plaque, and ultimately, the vulnerable patient. Tantalizingly, the next step would be to study targeted therapies for these vulnerable plaques. Here too, oxLDL may be important by way of targeted nanoparticles with attached novel therapeutic agents that can be delivered directly to the plaque. This is a very exciting field of investigation and deserves close study.

From a therapeutic standpoint, the authors propose using the innate immune system to reduce levels of oxLDL through either immunization or via administration of anti-oxLDL antibodies. There appears to be an association between the pneumococcal polysaccharide vaccine and both reductions in oxLDL levels and reduced rates of acute coronary syndromes [21]. This finding may be mediated by cross-reactivity between the phosphorylcholine lipid antigens on the cell wall of *Streptococcus pneumonia* may cross react with oxLDL. The administration of anti-oxLDL antibodies has demonstrated safety in a small pilot study; however its efficacy in reducing oxLDL levels, downstream markers of inflammation, and hard clinical endpoints remains uncertain [22].

There is a growing body of literature that the biology of atheromatous plaques goes far beyond pure lipid accumulation. oxLDL and anti-oxLDL antibodies are promising candidates for identifying those patients at significant residual risk of coronary events as well as a possible plaque imaging and therapeutic targets. Thus, they are probably not quite ready for prime time, but hold great promise for the future as the next “big thing” in cardiovascular medicine.

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