Does oxidized low-density lipoprotein occur in vivo?

Oxidation of low-density lipoprotein (LDL), the major cholesterol-carrying protein in human blood plasma, is now commonly implicated as an initiator of atherosclerosis [1]. Oxidation of the lipid moiety appears to be a key event in the process preceding the modification of apolipoprotein B-100, eventual uptake of the lipoprotein by macrophages and the formation of foam cells [2]. A key piece of evidence which has been lacking in support of this hypothesis has been the unequivocal demonstration that oxidized LDL exists in vivo. The paper by Jankowski et al. in this issue [3] appears to provide a relatively non-invasive and rapid technique which allows the quantification of oxidized LDL in serum using nuclear magnetic resonance (NMR) techniques. The work is potentially exciting in providing a further insight into the pathogenesis of this disorder and a novel means of assessing the risk of cardiovascular disease in individual subjects, but it is also surprising in apparently identifying oxidized LDL in serum, whereas current evidence suggests that oxidized LDL would only be generated in the arterial wall [4].

Despite the considerable potential of the work there are reasons to be cautious in interpreting the paper of Jankowski et al. [3]. They have not unequivocally identified the species present in serum which is responsible for the NMR spectra they have observed. Comparison with oxidized LDL prepared by copper-catalysed oxidation indicates that some unknown oxidation product(s) have the same NMR resonances, but the identity of the products has not been established. Future studies should aim to identify the compounds involved and firmly establish whether they are present in human serum in vivo. Assuming that this is eventually achieved, it will also be necessary to address the mechanism by which oxidized LDL might appear in blood serum. When LDL is subjected to oxidation in vitro (e.g. by copper), depletion of the sacrificial antioxidants (vitamin E, β-carotene etc.) must occur before LDL oxidation can be detected. Clearly an analogous situation does not occur in human serum in vivo and alternative mechanisms must be invoked. Jankowski et al. [3] hypothesize that lipoproteins might be lost from the arterial wall after oxidation, but given the difficulty of measuring oxidized LDL in tissue, this will be difficult to verify experimentally.

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REFERENCES