The HDL dysfunction gains momentum: is it time for a new approach in rheumatic diseases?

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The lipoprotein levels have been the mainstay routine lipid analyses for 50 years. However, an increasingly growing number of studies suggest that, far from being simple cholesterol carriers, lipoproteins are complex, dynamic systems able to perform a number of functions, with effects beyond atherosclerosis development. Consequently, the actual role of lipoproteins cannot be totally appreciated by their levels alone. This has caused a major debate in Rheumatology, where lipoproteins have been the object of profound discussions during last decade, from the initial 'lipid paradox' mostly based on lipoprotein levels, to the more contemporary 'lipoprotein (HDL) dysfunction', related to compromised anti-oxidant and anti-inflammatory functionality. Although evidence is available especially in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), a knowledge gap exists in other chronic disorders. In this issue of Rheumatology, Bae *et al.* [1] addressed the analysis of the (altered) HDL antioxidant function in inflammatory myopathies, thus expanding this notion. So, where are we now in terms of lipoprotein functionality in Rheumatology and what does this study add?

First, although the altered lipoprotein anti-oxidant functionality was initially described in SLE and RA, recent studies have demonstrated this phenomenon in other rheumatic diseases, such as psoriatic arthritis, systemic sclerosis or antiphospholipid syndrome [2,3]. The study of Bae *et al.* reports a similar picture, with a lower HDL antioxidant capacity in myositis, without differences in HDL and LDL levels or in traditional risk factors. These findings further expand the HDL dysfunction across rheumatic diseases and again put into question approaches solely based on lipoprotein-cholesterol levels to account for the clinical relevance of lipoproteins, especially HDL. Current HDL dysfunction measurements rely on laboratory assays that are not easy to implement in a clinical routine setting and use isolated, exogenous LDL as the oxidative trigger. While this facilitates the standardization, it may also result in an underestimation of the actual HDL dysfunction since not only the patient LDL may be more altered than the reference LDL used in the assay, but also the influence of the surrounding modulating factors is lacking. Therefore, with the HDL dysfunction gaining ground, the development of novel, more reliable assays to capture the actual effect of the HDL dysfunction gains relevance

Second, the actual substrate(s) of this HDL dysfunction in Rheumatology is still to be elucidated, mainly due to the growing complexity of lipoproteins. In this sense, proteomic and high-throughput techniques have revealed that the lipoprotein fine composition is altered in rheumatic conditions, these changes being mainly related to their protein cargo [4]. However, it is not clear if these changes could fully account for the altered lipoprotein functionality. In the same way that lipoproteins are not only lipids, lipoprotein lipids are not only cholesterol. Lipoproteins also contain an amount of bioactive lipids, including

fatty acids and their derivatives, which are unrelated to cholesterol transport but may play a role in the modulation of the anti-oxidant properties, either by actively contributing to lipoprotein oxidation, by further impairing lipoprotein malfunction or by amplifying their effects. Bae *et al.* revealed a significant enrichment in oxidized fatty acids or oxylipins [5] derived from arachidonic and linoleic acid in HDL lipoproteins from myositis patients. Although potential limitations due to sample size and cross-sectional design need to be remarked, these findings add another layer of complexity to this setting by identifying novel potential contributors to the HDL dysfunction in rheumatic diseases. Now that alterations in another dimension of the lipid universe have been described, multi-level studies are needed not only to capture the full heterogeneity of this setting, but also to understand the connections with the surrounding factors. A more in-depth characterization of the lipoprotein fatty acid content with an untargeted analysis is to be included into the agenda.

Third, the role of autoantibodies as a potential 'missing link' between lipids and inflammation has also been debated in recent years. Although lipid disturbances were initially conceived as the result of chronic inflammation, current evidence suggest that inflammation may only account for a limited effect on lipid levels, and potentially function, and specific immune circuits seem to be involved [6]. In this scenario, the role of humoral immune response has emerged [7]. Several studies have demonstrated an association of lipid levels and/or functionality with disease-related autoantibodies. Bae *et al*. add to this notion, showing that autoantibodies-negative myositis patients exhibited the most preserved antioxidant capacity and those with anti-MDA5 or anti-synthetase antibodies showed the worst activity. Of note, the fact that different antibodies, with distinct cognate antigens which are not known to be present in lipoproteins, exhibit a similar effect may be an epiphenomenon. However, this association, again observed in several conditions, warrants further research. Novel studies have informed that autoantibodies directed against lipoprotein (mainly HDL) components can be detected in a wide range of rheumatic conditions [8,9]. These antibodies may account, at least in part, for the disturbed antioxidant HDL functionality [9]. Consequently, if confirmed in larger cohorts, the results observed for the first time in myositis patients strengthen the link between humoral response and lipoprotein outcomes, thus prompting the research into lipoprotein-related antibodies in systemic rheumatic diseases. Alternatively, whether dysfunctional HDL result in neo-antigen occurrence and thus, foster humoral responses leading to a breakdown in tolerance may be plausible. Prospective studies across all disease stages including the preclinical phase will be crucial to assess causality. In this regard, especially in the absence of direct evidence, an alternative role of type I

interferons (IFNs) may be also conceived. Immune-complexes are well-known triggers of type I IFNs, which have been linked to disease severity and vascular damage [10,11]. Type I IFNs can perpetuate and aggravate autoimmunity, leading to an over-activation of the humoral response which can in turn lead to higher levels of autoantibodies, thus closing the positive feedback loop. Since type I IFNs are a common trait in rheumatic diseases, its potential underlying role needs to be considered.

Taken together, the HDL dysfunction is becoming a popular 'main character' in rheumatology and appraising its added value for clinical management represents a major unmet need. This is also supported by the inclusion of lipid subparticles and novel biomarkers in the research agenda of the EULAR recommendations for cardiovascular risk management [12]. Expanding the scope of these and other clinical recommendations in view of the shared mechanisms needs to be evaluated. Finally, oxidative stress and vascular injury are common hallmarks of systemic diseases, related to both tissue-specific damage as well as systemic features, something that it is acknowledged by Bae *et al*. Therefore, we may have to start regarding changes in HDL dysfunction, and lipids in general, from a comorbidity issue on the side to a more prominent position in autoimmune disease. Future studies will have to investigate whether they in fact earn such centre stage.

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