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Editorial Comment

Dynamics shared by two related proinflammatory conditions, rheumatoid arthritis and metabolic syndrome

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Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease most frequently observed in middle-aged and elderly people and associated with increased risk for cardiovascular disease. Metabolic syndrome (MetS) is a cluster of risk factors, similarly driven by a pro-inflammatory state and predicts excess risk of metabolic and cardiovascular diseases. Thus the interrelationship between the two conditions in terms of various dimensions deserves to be studied, yet has been seriously under-investigated. In this issue of the Journal, Özmen et al. (1) attempt to contribute to the aspects of prevalence, as well as the disease-related factors, of this topic.

Authors enrolled in their study 52 consecutive RA patients meeting the ACR criteria, excluding those using anti-tumor necrosis factor (TNF)α or lipid-lowering agents or those with hypothyroidism. Age- and sex-matched subjects (n=30) free of RA served as a control group. Though the control group could desirably have been triple the current size and not insignificantly younger, significant differences between the two groups were related to RA patients harboring higher levels of low-density lipoprotein (LDL)- and HDL-cholesterol (presumably also of the unreported total cholesterol) and systolic blood pressure (BP). Wider waist circumference, the hallmark of MetS, higher fasting glycemia and thyrotropin levels suggestive of subclinical hypothyroidism commonly observed among Turkish adults are noted among RA patients than the controls, without reaching significance.

Abdominal obesity and elevated BP were the two components of MetS, defined by either ATP-III or modified WHO criteria, significantly more prevalent among cases than controls. Authors further examined the difference in risk factors among RA patients stratified to MetS, meeting the ATP-III definition. Higher systolic and diastolic BP and body mass index were distinct, both selection criteria for MetS. Smoking was regrettably reported in pack-years and presumably without categorizing to current and former smoking which hides the driving dynamics. Noteworthy was that, albeit a low number of individuals existed with RA and MetS, both HDL-cholesterol, the homeostasis model assessment (HOMA) index were similar in the subsets of RA and MetS suggesting that these MetS-related characteristics were harbored by RA patients, irrespective of the presence of MetS. Disease-related factors such as sedimentation rate, DAS-28 scores, HAQ and disease duration were likewise reported to be similar in patients with or without MetS.

In a previous report on 154 American patients with RA (2), MetS prevailed in a significantly (and by one-half) higher proportion of RA patients than in the control group. Circulating lipoprotein (Lp)(a) was reported to be 2.5-fold higher in the series of 87 Turkish female RA patients than in female controls (3), suggesting that a low proportion of patients had early RA. In 94 South African patients with RA, those with higher grade inflammation had higher ratios of triglycerides to HDL-cholesterol, increased insulin resistance and reduced ß–cell function (assessed by HOMA-B) (4). In another paper on patients with RA and systemic lupus erythematosus (SLE), Chung and coworkers (5) demonstrated in multivariable models that the major contributing factors to the HOMA index were IL-6 and TNFα levels in RA patients –contrasted to body mass index in SLE patients– concluding that the genesis of insulin resistance may vary in different inflammatory settings. What they also interestingly reported was that serum Lp(a) was significantly lower in individuals with –compared to without– MetS in the control group but only marginally lower among RA patients.

This leads to the consideration of Lp(a) levels in RA and MetS patients, crucial in the pathogenesis in each condition through immune processes which include the transformation of the atheroprotective apoA-I particles. In a total of over 1000 patients with RA and control groups from diverse studies originating from Western, Turkish, Korean and Japanese people, circulating Lp(a) in RA has been fairly uniformly higher than in the control groups, by about 1.5- to 2-fold in level (6). Yet LDL or total cholesterol levels, not associated

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with cardiovascular risk overall in RA (7), significantly decreased within 5 years prior to the diagnosis of RA in 577 patients that could not be attributed to medication or weight change (8) which may be related to Lp(a)-triggered autoimmune processes.

The above stated phenomenon highlights and supports the hypothesis on a pathogenesis fundamental not only to RA (6) and MetS, but also to type-2 diabetes, coronary heart disease, thromboembolism and other diverse chronic diseases (9). Autoimmune activation, defined as plasma polypeptides and proteins subjected to damage in their epitopes under oxidative stress, mainly though not exclusively due to increased adiposity, and perceived as foreign bodies by the organism, are insidiously aggregated to protective plasma proteins, primarily apoA-I. During intense autoimmune activation, Lp(a) levels are actually at an individual's peak, but the proportion of damaged Lp(a) protein escapes the specific immunoassay method, is not picked up and assayed as presenting a "reduced" level. Temporally, this autoimmune activation coincides with the new onset of diverse diseases including RA, MetS or diabetes. Indeed, lower Lp(a) concentrations have been reported in subjects with diabetes (by 11%) than without in a meta-analysis on over 120,000 participants (10). In the ensuing period, when RA or diabetes is recognized as established, the intensity of autoimmune activation becomes attenuated, Lp(a) no longer manifesting as apparently "reduced" but rather as non-significantly higher than the individual's average assays.

These dynamic alterations in "measured" Lp(a), resulting not in a linear but a J- or U-shaped association curve with the risk of respective outcome disorder, has been the reason why medicine has thus far failed to recognize the Lp(a)-triggered autoimmunity as a basic mechanism of diverse chronic diseases, which have over-extended worldwide health care costs.

The precipitous decline in circulating total and LDL cholesterol reported to precede the clinical RA incidence and the association of this development with higher cardiovascular risk (6) has also been observed In the Turkish Adult Risk Factor (TARF) study preceding the new-onset diabetes. This is possibly mediated by the autoimmune process inhibiting the expression of proprotein convertase subtilisin/kexin type 9 (PCSK9) gene on cell surface LDL receptor and suggests the inability to partly assay Lp(a) lipoprotein in immune processes via aggregation to apoA-I which may serve as a component of the autoimmune mechanism. Such impaired functionality of apoA-I recovered from human atheroma and oxidized by myeloperoxidase has recently been reported (11). The lipid-poor apoA-I particle displayed potent proinflammatory activity on endothelial cells *in vivo*. Elevated levels of such oxidized apoA-I in assayed subjects were associated with increased cardiovascular disease risk. In the TARF study over the past 5 years, we had prospectively shown among Turks that high compared with low circulating apoA-I nearly doubled the risk for incident diabetes, additively to confounders (12). The positive association of serum apoA-I with diabetes was independent of apoE genotype, obesity and apoB levels (13). Among plasma biomarkers enabling the detection of RA patients' response to the inhibition by anti- TNFα therapy, a good response was independently predicted by apoA-I and a poor one by platelet factor 4 (14), which may be interpreted as apoA-I pro-inflammatorily converted by TNFα activity to aggravate disease progression and then to mediate clinical improvement by resuming anti-inflammatory properties due to therapy.

Little is known on the origin of the development of MetS which has been considered by some workers as an arbitrary clustering of some components. As yet unpublished analyses in the TARF, however, suggest indirect evidence of Lp(a) aggregation and ensuing autoimmune activation, operating in each gender such that age-adjusted HRs for incident MetS increase parallel to the declining Lp(a) quintiles. This extends a previous report from the TARF, wherein the lowest Lp(a) tertile was inversely associated significantly with MetS likelihood; and the sex- and age-adjusted lowest Lp(a) tertile displayed higher mean fasting insulin or "plasma atherogenic index" (triglyceride/HDL-C) values (15).

It thus appears that longitudinal follow-up of patients with early (not long-standing) RA in each sex for circulating Lp(a), apoA-I, LDL- and total cholesterol is sorely required, if better understanding of this inflammatory disease and the associated autoimmune activation is aimed.

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