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Underlying Autoimmune Activation Rendering Paradoxical Non-Linear Relationship between Biomarkers and Cardiometabolic Risk

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Abbreviations

AF: Atrial Fibrillation; LDL: Low-Density Lipoprotein; apo: Apolipoprotein; Lp(a): Lipoprotein(a); CHD: Coronary Heart Disease; LpPLA2: Lipoprotein-Associated Phospholipase A2; CVD: Cardiovascular Disease; MetS: Metabolic Syndrome; HbA1c: Glycated Hemoglobin A1c; MIF: Migration Inhibitory Factor; HDL: High-Density Lipoprotein

Several chronic diseases share in our opinion a common pathophysiologic mechanism (what we designate as autoimmune activation), especially though not exclusively in elderly people prone to impaired glucose tolerance or metabolic syndrome (MetS). This process renders non-linear relationships between a biomarker and cardiometabolic risk.

Numerous observations have been reported which puzzled the observers in offering plausible explanation. These à priori paradoxical phenomena relate to circulating proteins (or polypeptides) and include lipoprotein a (Lp (a)), apolipoprotein B (apoB), lipoprotein-associated phospholipase A_2 (Lp-PLA_2, or PAF-AH), glycated hemoglobin A1c (HbA1c), creatinine, uric acid, thyroid stimulating hormone, acylation stimulating protein, asymmetric dimethyl arginine, macrophage migration inhibitory factor (MIF) and, possibly other serum proteins such as fibrinogen or apoCIII on high-density lipoproteins. We define autoimmune activation as a potentially reversible chronic (serologic) process developing under persistent pro-inflammatory state/oxidative stress rendering mild damage to one or more polypeptides or proteins which are thence perceived as foreign bodies, followed by aggregation to them of protective serum proteins.

Individual plasma proteins epidemiologically identified as having sustained oxidative damage

In the large prospective Women's Health Study [1], Lp(a) was found inversely associated to the development of type-2 diabetes, with roughly 25% higher relative risk in the bottom quintile compared with the remainder of the sample. This observation, confirmed in the Norfolk-EPIC study [2], can be explained by a mechanism of immune complex formation involving Lp(a) and interfered assay results due to failure by capture antibodies.

Elevated levels of apoB are a well-known risk factor for atherosclerosis complications but low levels of low-density lipoprotein (LDL)-cholesterol [3,4] have been reported to independently predict atrial fibrillation (AF). The large Women's Health Study [3] published analysis on predictive biomarkers for 795 of incident AF events. AF was predicted inversely by LDL-cholesterol yielding a 28% lower risk of AF per 1-SD increment in LDL-cholesterol, or *vice versa*. The number of small LDL particles was the driver of the stated association. This common arrhythmia is predicted by low apoB levels in an as yet unpublished work in the Turkish Adult Risk Factor study.

Lp-PLA_2, or PAF-AH, an enzyme concentrated on plasma lipoprotein(a), a major instigator of enhanced inflammation and autoimmune activation, is sensitive to enhanced pro-inflammatory state. The enzyme epitope may sustain damage, inducing aggregation and autoimmune complex formation with a protective protein. It partly escapes immunoassay, resulting in apparently "reduced" mass (and/or activity), and further fails to exhibit anticipated relationship to inflammation markers or cardiometabolic risk [5].

In a cross-sectional analysis of 825 patients with cardiovascular disease, Mayer Jr. and associates [6] observed inverse relationships of Lp-PLA_2 with high fasting glycemia, HbA1c and with quartiles of LDL-C/apoB ratio. Authors concluded that presence of diabetes was independently associated with lower likelihood of elevated Lp-PLA_2. Previously, in a cross-sectional analysis of about 1000 elderly Swedish subjects, Lp-PLA_2 activity was found not to be independently related to carotid atherosclerosis and to the amount of arterial stenosis [7]. Authors considered that Lp-PLA_2 levels may not constitute a good indicator of the activity within atherosclerotic lesions. We had documented in a population-based sample that circulating Lp-PLA_2 mass was independently associated with prevalent and incident coronary heart disease (CHD) in men, though being inversely associated only with diabetes in men, and only with MetS in women [8].

High-density lipoprotein (HDL)-apoCIII in 120 CHD patients using statins was significantly higher than in 80 control patients (not using) and was an independent predictor of CHD likelihood [9]. HDL-apoCIII significantly rose further in CHD patients after statin therapy. HDL-apoCIII correlated significantly with plasma triglycerides in both groups, but correlation in CHD patients was abolished after statin treatment. Total and LDL-cholesterol tended to be lower in the CHD group and LDL-cholesterol tended to be inversely associated with CHD, while apoB levels were significantly and positively associated with CHD likelihood. These findings suggest that HDL-apoCIII may assume atherogenic properties (just as it was shown in 2008 by us [10] to assume diabetogenic properties) in an environment of low LDL-cholesterol (and high apoB), consistent with autoimmune involvement of Lp(a) protein, but not of apoB. Moreover, of interest is the finding of

further elevation of HDL-apoCIII upon statin therapy (which might have damaged apo(a) of Lp(a)).

Hemoglobin A1c ($HbA1_c$) is a measure of glucose control in diabetic persons and a test recommended for diagnosing diabetes at a threshold ≥ 6.5% [11]. Though several studies demonstrated a linear relationship between $HbA1_c$ and several outcomes throughout the range of values [12,13], numerous recent studies showed that low $HbA1_c$ in nondiabetic [14,15] or diabetic individuals [16,17] is associated with increased mortality. Such association suggests the involvement of $HbA1_c$ levels in autoimmune activation and may be confined to one gender (e.g. to men among Turks). During a follow-up of 9.4 years in ~29,000, both low and high levels of $HbA1_c$ were associated with a higher risk of cardiovascular disease (CVD) in a Japanese non-diabetic general population [18]. Compared with $HbA1_c$ levels of 5.0 to 5.4%, HR for CVD in participants without known diabetes were 1.50 (95% CI 1.15-1.95) for $HbA1_c$ levels of <5.0%. This nonlinear relation persisted after excluding people with kidney dysfunction, liver dysfunction, anemia, body mass index <18.5 kg/m^2, or early events.

Low serum creatinine levels (<0.7/<0.8 mg/dl) may represent a clue to the existence of autoimmune activation [19,20]. This may again manifest itself in one sex in the general population. Increasing serum creatinine values were strongly associated with CHD risk in men but not in women in whom the risk curve was U-shaped [19]. In the prediction of incident type-2 diabetes risk by baseline estimated glomerular filtration rate in the Insulin Resistance Atherosclerosis Study, other than the bottom quintile, the top estimated glomerular filtration rate quintile disclosed excess multi-adjusted risk compared with the referent 4th quintile [21]. The phenomenon of low creatinine levels underlies some hitherto unexplained observations. Renal "hyperfiltrators" represent individuals with autoimmune activation (involving serum creatinine partly escaping assay) and are misclassified into a category of "optimal" renal function. By contrast, they are at significantly higher risk of cardiopulmonary events and death due to the underlying autoimmune process [20].

Chronic inflammatory processes can induce a chronic increase of interleukin-6 and thereby turn the acute phase reaction into a chronic perpetuating state with increased levels of fibrinogen [22]. A large prospective study on urban Chinese (n=6209) demonstrated that MetS was independently predicted in the female but not male [23]. Previously, it had been shown among Turks that independent prediction of MetS by plasma fibrinogen was confined to men [24]. These findings are consistent with the notion that ethnicity-specific sex-dependent prominent autoimmune activation may abolish the linear association of fibrinogen and render manifestation of MetS only in one sex. This forms an example also to prominent autoimmune activation predisposing the opposite sex in different races.

A large prospective study in Taiwan reported that sex- and age-adjusted hazard ratios of uric acid levels for all-cause and cardiovascular mortality were increased not only for elevated uricemia, but also for levels lower than 5 mg/dl [25]. An as yet unpublished work among Turks from applicants of a tertiary hospital showed inverse association of serum uric acid with adverse outcomes, consistent with involvement of uric acid mass in autoimmune activation.

Other serum proteins have also been reported to illustrate instances of autoimmune activation: these include thyroid stimulating hormone [26], acylation stimulating protein (as yet unpublished), asymmetric dimethyl arginine [27], cystatin-C [28], macrophage MIF [29].

Enhanced pro-inflammatory state and dysfunction of protective proteins

An important component of the autoimmune process with adverse outcomes is enhanced pro-inflammatory state to which gradual loss of protective properties of certain plasma proteins significantly contribute. ApoA-I, apoA-II, apoE, adiponectin, sex hormone-binding globulin constitute these protective plasma proteins [5]. As an illustration of this point may be given that, in a study on type-2 diabetes incidence in Finnish men, it was confirmed that apoA-I not only failed to significantly protect, but that apoA-I/HDL-C ratio was highly predictive of this outcome [30] suggesting that immature buoyant apoA-I had little insulin-sensitizing properties.

The presumed explanation to the non-linear relationship of a biomarker leading to "paradoxically" elevated cardiometabolic risk is that, plasma proteins sustaining epitope damage due to oxidative stress, partly escape immunoassay, are assayed lower than the actual mass, but have the capacity to render risk of cardiometabolic disease and death.

Autoimmune activation presumably mediates the outcome primarily *via* enhanced low-grade systemic inflammation and endothelial dysfunction. The link between the individual proteins involved in the autoimmune process and the specific cardiometabolic disease remains to be elucidated. Nonetheless, the huge public health issue requires better delineation in the future of damaged plasma proteins by new immunoassay methods or particle/mass measurement by MR spectroscopy.

We conclude that the practicing physician should best start to look for such clues in his/her patients, especially in elderly ones, with the ultimate aim of obtaining deeper insight into their longstanding health problems.

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