Editöre Mektup   ## Letter to the Editor

Autoimmune activation, a fundamental mechanism of coronary artery disease risk, missed by inadequate analysis

To the Editor,

Ertem and his colleagues[1] reported in one of your recent issues their study findings on the cross-sectional correlation between glycated hemoglobin (HbA1c) levels and the extent of coronary artery disease (CAD) in 65 predominantly male nondiabetic patients. The authors concluded that a relationship between the Gensini score and HbA1c levels was missing, though a significant relationship existed with obesity. The study was written with several inaccuracies and inconsistencies that should be brought to light. A definition of obesity was lacking, as were data on body mass index and a description of the statistical test used to delineate the relation with the Gensini score. More importantly, the coefficients of correlations with obesity and serum HbA1c correctly given in their table as inverse, were totally disregarded in their comments, and provided as positive in the abstract and Figure 2. This is crucial in interpreting their results, insofar as inverse associations are not equivalent to expected non-significant positive ones; any inverse correlation, irrespective of statistical significance, may well have pathophysiological meaning. The scatterplot in Figure 2 suggests, furthermore, a weak non-linear exponential association between the two variables, resulting in increasing scores, first with rising and then declining HbA1c. Both from this curve shape and the inverse direction of the overall correlation, one may deduce that relatively low levels of HbA1c with high Gensini scores represent cases with autonomic activation as a (or the) major pathogenetic underlying mechanism. The majority of patients were notably pre-diabetic, who are known to harbor autoimmune phenomena more frequently, and the significant inverse correlation of obesity (or metabolic syndrome) with Gensini scores may well be explained by the autoimmune process comprising concomitantly lipoprotein(a).[2]

Based on findings in the TARF study, we have recently reviewed our unifying hypothesis[3,4] regarding autonomic activation, indispensable for the understanding of chronic diseases, including CAD and diabetes. Under conditions of oxidative stress and pro-inflammatory state, a number of plasma polypeptides or proteins -such as HbA1c- may eventually sustain damage to their epitopes and escape partially from immunoassay. During formation also of a ß2-glycoprotein I-Lp(a) complex, part of the Lp(a) complex may escape immunoassay due to failure by capture antibodies to recognize oxidized epitopes interacting with ß2-glycoprotein I.[5,6] Proteins with damaged epitopes may be perceived as a foreign body, inviting the recruitment of protective plasma proteins such as apolipoprotein A-I, high-density lipoprotein (HDL), or adiponectin, rendering aggregation with the damaged proteins. This process of autonomic activation is a major mechanism for the development of diabetes, CAD, chronic kidney disease, inflammatory rheumatic diseases and, possibly, of chronic hepatitis or obstructive pulmonary disease.

As yet unpublished evidence on a large series of patients indicates that the coronary heart disease (CHD) risk curve of HbA1c is J-shaped, and values <4.5% are also associated with an increased risk, suggesting that apparently "reduced" HbA1c may underlie the increased CHD risk. This threshold might be higher in the study by Ertem and coworkers.[1]

Low plasma haptoglobin (Hp) protein concentrations were associated with increased risk for myocardial infarction in the AMORIS study.[7] Carriers of Hp-2 allele generally have lower plasma Hp concentrations and are associated with low low-density lipoprotein (LDL)-cholesterol concentrations.[8] Conceivably, of the two Hp genotype alleles, the 2-allele Hp protein is associated with higher HbA1c mass, but also with a greater tendency to aggregation to Lp(a) protein. The latter susceptibility may be critical regarding elevated CHD risk and explain concomitantly the overall lower Hp concentrations found associated with myocardial infarction.[8] Binding of the Hp2:Hb complex to HDL or its apoproteins[8] may additionally render HDL dysfunctional.

Instances of proteins [lipoprotein(a), creatinine, thyrotropin, asymmetric dimethylarginine (ADMA)]

involved in the autoimmune process were identified in the TARF study, but can also be identified in studies from other investigators. Cystatin C, normally expressed in vascular wall smooth muscle cells, was shown to be severely reduced in abdominal aortic lesions.[9] Moreover, an inverse correlation was found between cystatin C levels and ultrasonographically determined abdominal aortic diameter. It is highly likely that part of the circulating cystatin C was no longer detected by the immunoassay, yielding depressed concentrations, having concomitantly lost the property of counterbalancing cysteine proteases. Among 88 Turks who underwent elective coronary angiography in a case-control study,[10] those with (stable) CAD exhibited cystatin C levels lower than in normal individuals. Cystatin C and creatinine were each inversely associated with the presence of CAD in multi-adjusted logistic regression models.

Evidence is currently available that serum creatinine is commonly involved in autonomic activation, particularly but not exclusively in women, yielding a U-shaped CHD risk curve.[11] Such risk was observed even in the absence of metabolic disorders.[12] As yet unpublished analyses of data from applicants to a large cardiovascular center in Istanbul indicate that renal "hyperinflators" constitute about 1 of 3 such applicants and carry independent predictive ability of elevated risk for mortality and cardiopulmonary events. Similar findings were noted in the large Swedish AMORIS study[13] without offering a plausible explanation: when classified into estimated glomerular filtration rate (eGFR) quartiles, multivariable adjustment revealed, in the highest quartile, higher risk for all-cause mortality than in the optimal risk quartile and for incident myocardial infarction than in all the remaining eGFR quartiles.

In summary, autoimmune activation involving one or more damaged plasma proteins, including HbA1c, is a common process in individuals with a pro-inflammatory state, eventually resulting frequently in CAD or other chronic diseases.

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