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Editorial

Could Disease Activity Score in 28 Joints–Gamma-glutamyl Transferase Use Improve Cardiovascular Disease Risk Management in Rheumatoid Arthritis?

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Patients with rheumatoid arthritis (RA) experience a markedly increased risk of cardiovascular disease (CVD)[1,2,3]. Atherogenesis in RA remains poorly elucidated but traditional cardiovascular (CV) risk factors, systemic inflammation and their interactions, as well as genetic components certainly contribute[1,2,3]. In a recent 13-center study, the population-attributable CV event risk for disease activity as estimated by the Disease Activity Score in 28 joints (DAS28) and positive rheumatoid factor and/or anticyclic citrullinated peptide antibodies, were both as large as that for lipids in RA[4]. It is therefore not unexpected that current CVD risk stratification tools calculated based on major traditional CV risk factors, such as the Framingham score and Systematic Coronary Risk Evaluation (SCORE), perform suboptimally in RA[1,2,3].

Recently developed disease-specific CVD risk calculators may also not perform better than those developed for the general population in predicting CV events in RA[5]. In this regard, during the past 2 decades, many population studies revealed that circulating gamma-glutamyl transferase (GGT) concentrations within normal ranges relate to major traditional CV risk factors, systemic inflammation, and incident CV events[6,7,8,9,10,11,12]. In RA, GGT levels were also found to be associated with disease activity markers[13]. These reported observations suggest that serum GGT concentrations may be useful in the identification of patients with RA who are at increased CVD risk.

In this issue of *The Journal*, Vergneault and colleagues[14] explored the associations of circulating GGT levels with CV risk factors in 129 patients with RA. Only patients with unstable hepatic disease and manifestations of liver dysfunction or failure were excluded. GGT concentrations were weakly associated with C-reactive protein (CRP) concentrations (r_s 0.30, P = 0.002) but not with any other RA activity markers that are included in the DAS28 and comprise tender and swollen joint counts, global health or patient disease activity self-assessment, and the erythrocyte sedimentation rate (ESR). GGT levels were also not related to the Health Assessment Questionnaire–Disability Index, the presence of bone erosions, and ultrasound-determined synovitis.

In contrast, GGT concentrations were associated with the nonmodifiable CV risk factors of age and male sex, as well as metabolic features including body weight, fasting glucose levels and diabetes, and dyslipidemia. Also, smokers (41%) were more likely to experience increased GGT concentrations compared to nonsmokers (25%), although this difference did not reach significance (P = 0.1). In line with these findings, GGT levels were increased in patients with metabolic syndrome and associated with the number of CV risk factors and Framingham score.

Considering the reported associations of GGT concentrations with systemic inflammation and CV risk factors in non-RA persons, together with these current findings in RA, Vergneault and colleagues[14] constructed a DAS28 with inclusion of GGT concentrations instead of the ESR and named this new tool DAS28-GGT. In receiver-operating characteristic (ROC) curve analysis, the DAS28-GGT performed as well as the DAS28 in

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identifying patients with RA activity with a DAS28-CRP of > 3.2 or > 5.1. In addition, the DAS28-GGT identified patients with 2 or more modifiable traditional CV risk factors [ROC area under the curve (AUC) 0.70] and a Framingham score of > 10% that represents medium or high CV risk (AUC 0.74), whereas the DAS28 and DAS28-CRP did not discriminate between RA patients with and without an increased traditional CV risk factor burden. In further analysis, patients with a low DAS28-GGT (< 5.5) were all in RA remission and at low CVD risk as represented by a DAS28-CRP of < 2.6 and Framingham score of < 10%, respectively. By comparison, among patients with a DAS28-GGT of > 5.5, there were 64% who had active disease and 48% were at intermediate or high CVD risk. Taken together, the Vergneault study[14] suggests that the DAS28-GGT appears to be as reliable as the DAS28-CRP in assessing disease activity and may additionally help in identifying those patients with RA that require traditional CV risk factor evaluation (i.e., those with a value of > 5.5).

GGT is expressed on the membrane surface of most cells[8,9,10]. It is best known for its role in glutathione metabolism. It hydrolyzes glutathione whereby cysteinyl-glycine and glutamate are released and subsequently transported across the cell membrane to provide substrates for intracellular glutathione synthesis; glutathione is the main intracellular antioxidant. Compared to cell membrane–bound GGT, circulating GGT derives from the liver and is bound to carriers including albumin and lipoproteins. It is produced in response to steatosis or secondary hepatic inflammation and its concentrations are best known as markers of alcohol intake and hepatobiliary disease. Determinants of serum GGT levels that are mostly within the normal range include metabolic CV risk factors and smoking[8,9,10,15]. Smoking may increase GGT production through heavy metal exposure[15]. Physical activity[16] and coffee consumption[17] are inversely associated with GGT concentrations. Coffee has antiinflammatory and antioxidant effects, and reduces metabolic risk[18]. Lipoproteins are thought to carry circulating GGT into atherosclerotic plaques where its extracellular effects on glutathione metabolism and the resulting production of cysteinyl-glycine may reduce Fe3+ to Fe2+, produce a free thiyl radical, and through subsequent reactions cause low-density lipoprotein oxidation and increased plaque vulnerability[8,9,10]. Thus, circulating GGT may accumulate in atherosclerotic plaque and act as a prooxidant[9].

Epidemiological studies support a potential role of circulating GGT concentrations in CVD risk. Indeed, in a large metaanalysis of prospective studies[6], serum GGT levels were associated with increased CV mortality risk in a dose-response manner. Interestingly, among patients with established coronary artery disease, coronary revascularization was shown to abolish the prognostic value of GGT concentrations in predicting cardiac death and nonfatal myocardial infarction[19]. This further supports an enhancing effect of GGT on plaque vulnerability.

A recent nationwide investigation among 16,624,006 Koreans again confirmed an independent relationship between GGT concentrations and CVD events and mortality[7]. However, in some studies, adding GGT concentrations to conventional CV risk factors did not improve CV mortality risk prediction[8]. This raises the possibility that the GGT-CVD risk association may be explained by concurrent CV risk factors and comorbidities, and not necessarily represent a causal relationship. In this context, within normal range increases in serum GGT concentrations and even more so, other liver enzymes, including alanine aminotransferase and aspartate aminotransferase levels, mostly reflect nonalcoholic fatty liver disease (NAFLD) that is driven by insulin resistance[7,20]. NAFLD comprises the hepatic component of the metabolic syndrome[20,21]. Serum aminotransferase concentrations are associated with atherosclerosis in the general population[7]. In methotrexate-naïve patients with RA, serum aminotransferase levels are independently related to both insulin resistance and atherosclerosis[21].

Current recommendations on CV risk management emphasize the need for overall CVD risk assessment in all patients with RA[1,2]. This should be performed at least every 5 years in those at low risk, and more frequently in those at high or very high risk[1,2]. This assessment merely involves smoking status recording, blood pressure measurement, and determination of glucose and lipid concentrations, which is an easy-to-perform and inexpensive undertaking. Yet, despite the increased CVD risk in RA, patients with this disease are less likely to have their modifiable traditional CV risk factors assessed and treated when compared to other persons[22]. Could the routine use of the DAS28-GGT as defined in the Vergneault study[14] assist in this regard?

The authors essentially propose that an elevated DAS28-GGT may be a useful indicator of the presence and therefore need for evaluation of major traditional CV risk factors. The limitations of the study are comprehensively covered. However, although the DAS28-GGT performed well in disease activity and CVD risk stratification in ROC curve analysis, the weak correlations of GGT levels with both CRP concentrations and traditional CVD risk factors remain a concern and call for further validation. More importantly in the present context, only 11 (8.5%) of included patients had a low DAS28-GGT and may therefore not have required formal traditional CV risk factor evaluation. Consequently, even if the findings of the Vergneault study[14] are confirmed in future larger and preferably longitudinal studies, the routine application of the DAS28-GGT is unlikely to significantly reduce the need for systematic formal CVD risk evaluation in RA. Moreover, besides the currently recommended need for consistent comprehensive traditional CVD risk factor recording in patients with RA, there is increasing evidence in support of a need for the complementary performance of noninvasive imaging, particularly carotid artery ultrasound, to optimize CV risk evaluation in many patients with RA[1,2,3,23]. This may be most important in RA patients from low or middle income populations such as black Africans in whom the Framingham score and SCORE are not useful in identifying high-risk atherosclerosis[2,24].

Nevertheless, the findings in the Vergneault study[14] indicate that serum GGT concentrations and the proposed DAS28-GGT may comprise reliable markers of particular metabolic CVD

risk in RA. Cardiometabolic risk is increased in patients with RA[25]. Hence, whether serum GGT concentrations and/or the DAS28-GGT independently predict subclinical and established CVD in RA merits further study. The potential usefulness of serum GGT concentration and/or the DAS28-GGT monitoring for CVD risk evaluation in RA will likely depend, at least in part, on whether GGT is or is not directly involved in the increased atherogenesis that is experienced by patients with this disease.

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