Editorial

# Rheumatoid Arthritis and Diabetes Mellitus: Evidence for an Association?

There is now a large body of epidemiological evidence linking rheumatoid arthritis (RA) with the premature development of cardiovascular disease[1-4]. This relates, at least in part, to the systemic inflammatory burden in RA, which has been shown to predispose to the development of premature atherosclerosis in individuals with this condition.

Raised levels of systemic inflammation have also been shown to predispose to developing both insulin resistance[5,6] and type 2 diabetes mellitus (DM)[7-9]. In the case of the latter, Pradhan and colleagues reported that the development of type 2 DM in women was predicted by elevated levels of C-reactive protein (CRP) and interleukin 6, both markers of systemic inflammation[7]. The authors of 2 further longitudinal cohort studies found that markers of inflammation such as CRP, raised white cell count, and low serum albumin were associated with development of diabetes over prolonged periods[8,9].

The potential role of insulin resistance as a cardiovascular risk factor in patients with inflammatory arthritis has been examined by Svenson, et al, who reported impaired glucose handling in a sample of RA patients compared to controls[10]. These investigators also found evidence of an inverse relationship between insulin sensitivity and acute phase markers in RA. More recently, Dessein, et al reported significantly higher levels of insulin resistance in patients with inflammatory arthritis compared with controls, and an association between high CRP concentrations and insulin resistance[11,12]. Glucocorticoids, which are commonly used in RA therapy, would also be expected to contribute to insulin resistance[13].

Given that chronic systemic inflammation has been associated with both insulin resistance and type 2 DM, the question arises whether the prevalence of DM is increased in patients with RA. Although no studies to date have directly addressed this question, it has been indirectly examined in some of the studies addressing cardiovascular risk in RA.

The results of these studies have been conflicting. Han, et al, using a clinic-based population, found a significantly higher prevalence of type 2 DM in RA patients compared with matched controls[14]. However, contrasting findings were reported from 2 large cohort studies. Solomon and colleagues did not find evidence of an association between RA and DM in a prospective cohort of women[15]. Although del Rincon and colleagues noted a significantly higher frequency of diabetes in a cohort of patients with RA compared with that in a population-based cohort of persons without RA, this difference disappeared when the samples were stratified for age[16].

Simard and Mittleman's population-based study, in this issue of The Journal, is the first to directly address the question of an association between prevalent RA and DM[17]. These investigators used population-based data collected as part of the National Health and Nutrition Examination Survey (NHANES) III, which included 5302 study subjects aged > 60 years. A total of 144 of these subjects fulfilled criteria for RA, of whom 24 had prevalent diabetes. After controlling for a number of potential confounding factors, including demographic factors, body mass index, physical inactivity, and glucocorticoid prescription, a significant association between RA and DM was not found.

These findings must, however, be interpreted in light of the limitations of this study. In particular, the numbers of subjects with RA and DM are very small. This is reflected in the wide confidence intervals of the odds ratios, and suggests that the study may not have adequate power to pick up a moderate association between these 2 conditions. It is worth noting in this context that the adjusted odds ratios for DM in the subset of RA subjects not currently taking glucocorticoids and fasting for at least 8 hours prior to blood draw ranged from 1.29 to 1.57, although again, these findings were not statistically significant.

As an additional concern, included subjects with RA had

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very mild disease. Only 10% of RA cases were taking disease-modifying drugs, and mean CRP level was only 1.04 mg/dl. Further, the proportion of patients with positive rheumatoid factor was smaller than that seen in other population-based studies of RA[18,19]. Even given the community-based setting of this study, these results are surprising and suggest the possibility that patients in the community with more severe RA did not participate in NHANES due to disease-related disability. This would mean the sample of subjects with RA in this study is not representative of all patients with RA. Because DM might be expected to occur more often in patients with more severe RA, who have higher levels of inflammation, the noted prevalence of DM in these patients may be an underestimation.

Other factors that may have led to dilution of a true association between RA and DM include the cross-sectional design of the data used in this study. If patients with both RA and DM in the community had increased mortality, the number of survivors in this group would be lower, thus leading to underestimation of the concurrence of these 2 conditions. Further, due to missing data on fasting glucose in a large number of study participants, the prevalence of diabetes could have been underestimated due to asymptomatic patients with type 2 DM not having been included. Finally, the criteria used for definition of RA could have allowed inclusion of patients with other forms of inflammatory arthritis, thus diluting an association between RA and DM.

Given the limitations outlined above, an association between RA and DM has not yet been ruled out, despite the lack of a significant association noted in this study. Rather, these findings point to the need for further investigation of this interesting question. Future studies would ideally be prospective, use predefined criteria for diagnosis of both RA and DM, and include larger numbers than in the current study.

The study reported by Simard and Mittleman in this issue, along with most recent studies examining the association between RA and DM, have concentrated on type 2 DM. This is of particular interest at present due to the association of this condition with systemic inflammation. There are also, however, reasons for speculation about a possible association between type 1 DM and RA. These include evidence of familial clustering of autoimmune diseases, including RA and type 1 DM, and the common association of the HLA-DR4 allele with both DM and RA[20]. One study found that 13% of 295 RA patients had a first-degree relative with type 1 diabetes[21]. However, another study that examined a cohort of hospitalized RA patients found a prevalence of type 1 DM in the RA cohort similar to that in the general population[20]. Simard and Mittleman do not specify whether they included both type 1 and 2 DM, but given that all patients included in the study were over 60 years of age, it is likely that the majority of patients included in this study had type 2 DM.

Chronic systemic inflammation has been clearly shown to predispose to premature atherosclerosis and cardiovascular risk in patients with RA. Chronic inflammation also appears to predispose to development of both insulin resistance and DM. The important question remains whether there is an increased prevalence of DM in patients with RA. Ideally, large-scale, prospective studies are needed to gain a clearer picture of the true prevalence of DM in RA patients in the community.

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