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Comment on: Use of ^{99m}Tc-anti-CD3 scintigraphy in the differential diagnosis of rheumatic diseases: reply

SIR, We appreciate the comments of Garrood [1], regarding our manuscript recently published in *Rheumatology* [2]. The aim of our study was to assess the use of anti-CD3, labelled with technetium-99m scintigraphy, for evaluating the joints of patients with RA, JIA, OA and gouty arthritis (GA), and to establish the diagnosis parameters for each disease. We know that the diagnosis of such diseases (GA and OA) is primarily clinical, but in some cases, as we have shown, GA and RA can occur in the same patient. In these patients this method could be useful, and furthermore the establishment of scintigraphic diagnosis parameters in different diseases is needed. In our study, in some patients with RA ^{99m}Tc-anti-CD3 uptake was observed before clinical symptoms, which led to our conclusion that this is a promising tool in earlier diagnosis and also in the follow-up of these patients.

In our study, we first evaluated patients in different periods of time (30 min, 1, 2, 3, 6 and 24 h) and no significant changes were observed in the uptake pattern after 3 h of the injection of the radiopharmaceutical. Therefore, we verified that the uptake observed was probably due to a specific target in the inflamed synovium and not to non-specific extravasation into the hyperpermeable synovium. In this manner we used ^{99m}Tc-HIg scintigraphy as a negative control as it has non-specific uptake in affected joints and no uptake is observed in later images (after 1 h). These results were not shown as it was not the aim of the study, but only a complement. In ^{99m}Tc-anti-CD3 scintigraphy, the uptake pattern is maintained during later images (at least up to 24 h).

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Comment on: Alcohol consumption is inversely associated with risk and severity of rheumatoid arthritis

SIR, The recent article by Maxwell *et al*. [1] addresses a controversial issue that has already attracted considerable international media attention. Maxwell *et al*. [1] claim that drinking alcohol may reduce the risk and severity of RA. But does their evidence really support a protective effect of alcohol against risk and severity of RA?

Maxwell *et al*. [1] compared alcohol use in two groups of people. One group had a minimum of 3 years and a mean of 14 years of RA duration. The other group comprised healthy volunteers with no history of inflammatory joint disease. Both groups completed a questionnaire at study entry in which they recorded on how many days they had taken alcohol in the previous month. The relationship between alcohol consumption frequency and RA severity was explored by comparing alcohol consumption frequency against markers of disease severity, including anti-CCP antibodies, RF and radiographic scoring. The research design employed by Maxwell *et al*. [1] is a case–control study.

Maxwell *et al*. [1] are the first to demonstrate an inverse association between alcohol consumption and severity of RA, while inverse associations between alcohol consumption frequency and risk of RA have been observed in previous studies [2–5]. However, a well-known limitation

of case–control studies is that they cannot determine cause and effect. With such a study design, Maxwell *et al*. [1] cannot prove whether alcohol consumption affected RA risk and severity, or whether RA risk and severity affected alcohol consumption (or indeed whether an extraneous factor affected both alcohol consumption and RA risk and severity). In short, the cause–effect hypothesis postulated by Maxwell *et al*. [1] 'that the consumption of alcohol would reduce both the risk of RA and disease severity' cannot be answered by their case–control study.

An inverse association between alcohol consumption and RA risk and severity might simply reflect that patients with RA drink less alcohol after disease onset and that those with the most severe disease drink alcohol the least. Several aspects of the disease state in RA might plausibly cause a patient to drink less alcohol—for example, feeling unwell, being socially restricted and taking anti-inflammatory medications or DMARDs, which contraindicate alcohol use [6]. Indeed, Maxwell *et al*. [1] reported statistically significant inverse associations between alcohol consumption and both disease duration and the use of MTX. Multivariate analysis accounting for both radiological damage and specific DMARD treatment was conducted but due to the design of the study it cannot prove the cause–effect pathways.

Of particular concern is that age was a confounding variable in the case–control study, with the mean age of cases (61 years) statistically significantly older than controls (48 years). The age difference between the groups is a problem, as the severity and duration of RA and use of alcohol are unlikely to be independent of age. How can Maxwell *et al*. [1] be sure that case–control differences in alcohol consumption were related to differences in disease rather than in age? Although admitting that confounding with age is a weakness of their study, Maxwell *et al*. [1] did not adjust their conclusions.

The most convincing evidence to date that alcohol consumption might prevent the development of destructive arthritis comes from the laboratory studies on mice [7]. Epidemiological studies that have investigated relationships between alcohol consumption and RA in humans appear to have been limited to case–control studies [1–3, 5, 8], a prospective single cohort study [9] and retrospective single cohort studies [4, 10]. Only the prospective cohort study would have been capable of demonstrating a causal relationship between alcohol consumption and risk of RA: alcohol consumption was monitored in a cohort of older women, which was followed up to determine who would develop the disease [9]. However, the study authors found no association between alcohol consumption and the risk of RA. A review article published in this journal in 2002 [6] concluded that inverse associations between alcohol intake and the risk of autoimmune diseases are not well understood and require further research.

Of the epidemiological studies mentioned above, only those published in the past 4 years have claimed causal associations between alcohol consumption and RA [1–3]. Earlier studies did not infer causal relationships, in keeping with the limitations of their study designs. Could this reflect a recent slackening in the rigour of critical interpretation of observational studies?

In summary, the study by Maxwell *et al*. [1] and other recent case–control studies [2–3] do not prove a cause–effect association between alcohol consumption and the risk or severity of RA. More critical consideration should be given to the limitations of case–control studies in this area of research.

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