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### Correlation between serum and synovial fluid estrogen concentrations: comment on the article by Sowers et al

*To the Editor:*

There is already substantial evidence for a role of estrogen in cartilage homeostasis (1), and the recent interesting report by Sowers and colleagues (2) adds further support for the existence of a link between estrogen deprivation and osteoarthritis (OA). Sowers et al observed that low serum estradiol ( $E_2$ ) concentrations in women were associated with an increased risk of knee OA.

Nevertheless, the mechanisms by which serum estrogen levels could influence cartilage homeostasis are still unclear. One of the important remaining questions is whether synovial fluid (SF) levels of estrogen parallel serum levels, because the potential effects of estrogen on avascular cartilage should be influenced mainly by local concentrations of the hormone.

To answer this question, we evaluated the estrogen concentrations in paired SF and serum samples from 21 premenopausal or postmenopausal women with knee OA. SF was obtained from the knee during therapeutic arthrocentesis and was stored at  $-80^\circ\text{C}$  until analyzed. Joint fluid samples were melted on ice and centrifuged at 10,000g for 15 minutes to remove cellular debris. Total  $E_2$  concentrations in SF and serum were determined by radioimmunoassay.

The mean  $\pm$  SD age of patients was  $59 \pm 11$  years.  $E_2$  concentrations in serum and SF were above the detection limit (10 pg/ml) in 14 of 21 patients. In these patients, the mean  $\pm$  SD serum and SF  $E_2$  concentrations were  $38.25 \pm 9.74$  pg/ml and  $18.83 \pm 5.70$  pg/ml, respectively. There was a high and positive correlation between serum and SF estrogen concentrations ( $r = 0.93$ ,  $P < 0.0001$ ). Age of patients was negatively correlated with serum ( $r = -0.79$ ,  $P = 0.0003$ ) and SF  $E_2$  levels ( $r = -0.62$ ,  $P = 0.03$ ).

These results show that estradiol is present in human SF from OA joints, at concentrations closely reflecting serum levels. The increased incidence of OA in postmenopausal

women might thus be explained by a decrease in local estrogen concentrations, because  $E_2$  has been shown to have antidegradative properties at physiologic levels (3–5).

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### Reply

*To the Editor:*

We thank Dr. Richette et al for their comments supporting our rationale for extending evaluation of the role of sex hormones and their metabolites in the development of OA. In our study, we assayed circulating serum estradiol concentrations to characterize the sex hormone status of individual women. Previously, it had been shown that estrogen receptors were present in joint tissues, including bone and cartilage (1–3), and we assayed serum under the assumption that the systemic estradiol levels reflected the local joint environment. Now, the data provided by Dr. Richette link the circulating serum estradiol concentrations with parallel values in the local synovial fluid environment.

These studies still do not identify what tissue (synovio-cytes, chondrocytes, or bone cells) might be directly impacted by the lower levels of estradiol or 2-hydroxyestrone, but these new data do justify the assumption that circulating hormones,

measured in a more accessible compartment, are a compatible surrogate for the hormonal environment of the knee joint.

This new information also does not yet establish whether our observed associations represent the response to a receptor-mediated process (as in the case of lower estradiol concentrations) or a cytokine-based response (as in the lower urinary 2-hydroxyestrogen concentrations), or potentially, both mechanisms. There is little evidence that 2-hydroxyestrogens have binding affinity to the estrogen receptor (4,5), but they appear to have additional important properties, including participation in oxidation/reduction actions (6), and may modulate arachidonic acid metabolism and the cyclooxygenase 1 (COX-1) and COX-2 enzymes.

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**Are the CIASsification criteria for Psoriatic ARthritis better than existing criteria for diagnosing psoriatic arthritis? Comment on the article by Taylor et al**

*To the Editor:*

We would like to congratulate Taylor et al for their proposed classification criteria for psoriatic arthritis (PsA), the CASPAR criteria (CIASsification criteria for Psoriatic ARthritis), which were devised based on a study of a large cohort of patients from several countries (1). We also appreciate the role of the authors in modifying our group's concept of PsA pathology (2) for the purposes of disease classification, where it fares rather well. Although the modified version of our group's criteria had the highest sensitivity of all diagnostic criteria, it appeared to have low specificity in the CASPAR study. We would like to point out the relevance of this for clinical practice and especially for the early diagnosis of disease, which does not come across in Taylor and colleagues' report.

The major argument proposed in favor of the CAS-

PAR criteria, as acknowledged by Taylor et al, is that this criteria set should be very useful for recruitment of patients into clinical trials. However, the vast majority of patients with PsA never participate in a clinical trial, and rheumatologists more commonly struggle to determine whether a patient with early inflammatory arthritis in fact has PsA. The specificity of the CASPAR criteria relies in part on radiographic changes that are a feature of late disease—hence their value for classification and trial recruitment. Unfortunately, bone changes, including spinal fusion and joint osteolysis, are irreversible at this stage. However, such radiographic features are generally absent at the time of clinical presentation early in the disease course (3). The criteria for PsA developed at our institution were based on events that take place in early PsA, when radiographic findings are usually normal (2). Therefore, our group's criteria may appear to have lower specificity than the proposed CASPAR criteria, but they are principally aimed at diagnosis of early disease, when magnetic resonance imaging (MRI) or ultrasonography could be useful.

While it is not yet economically feasible to use MRI to aid diagnosis, and the limitations of MRI for diagnosis of enthesitis in synovial joints have not been resolved, we believe the fact that our criteria demonstrated the highest sensitivity compared with the other criteria sets suggests that they are especially useful in the clinical setting for recognition and diagnosis of early PsA; that is, oligoarthritis, spinal disease, distal interphalangeal joint disease, and bone-based pathologies including sacroiliitis all point toward PsA in a patient with either current or past psoriasis or a strong family history of psoriasis. Furthermore, the presence of any of the above enthesitis/osteitis-related features in a patient with small joint polyarthropathy is also suggestive of PsA. This classification also allows one to conceptualize the coexistence of rheumatoid arthritis, a disease related to autoimmune mechanisms whereby the synovium is targeted, and PsA, a disease with a different immunologic basis and a different primary anatomic epicenter of disease. Therefore, our group's criteria may be useful during early disease in patients with small joint polyarthropathy without other enthesitis/osteitis-related features, in whom MRI changes, including diffuse bone edema or extra-capsular enhancement, would support the diagnosis of PsA (4,5).

Like the CASPAR criteria, our group's modified criteria do not rely on the presence of current psoriasis to aid diagnosis, but have the added advantage of allowing the classification of rarer features of PsA, including the SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis). It is clear that as therapies become more targeted and progressively move away from nonspecific immunomodulation, early accurate diagnosis could become increasingly important (6). For rheumatologists the greatest challenge with PsA remains its early recognition, especially in poor-prognosis groups. What is remarkably clear from the CASPAR analysis is that all of the criteria sets selected for study do indeed perform very well for the purpose of classification. Perhaps the greatest utility of the CASPAR classification criteria is that they clearly demonstrate that North American and European rheumatologists view PsA from a very similar perspective and that this international collaboration is contributing to significant advances in the clinical management of the disease.