

## Hyposecretion of the adrenal androgen dehydroepiandrosterone sulfate and its relation to clinical variables in inflammatory arthritis

### ABSTRACT

Hypothalamic–pituitary–adrenal underactivity has been reported in rheumatoid arthritis (RA). This phenomenon has implications with regard to the pathogenesis and treatment of the disease. The present study was designed to evaluate the secretion of the adrenal androgen dehydroepiandrosterone sulfate (DHEAS) and its relation to clinical variables in RA, spondyloarthropathy (Spa), and undifferentiated inflammatory arthritis (UIA). Eighty-seven patients (38 with RA, 29 with Spa, and 20 with UIA) were studied, of whom 54 were women. Only 12 patients (14%) had taken glucocorticoids previously. Age-matched, healthy women (134) and men (149) served as controls. Fasting blood samples were taken for determination of the erythrocyte sedimentation rate (ESR), serum DHEAS and insulin, and plasma glucose. Insulin resistance was estimated by the homeostasis-model assessment (HOMAIR). DHEAS concentrations were significantly decreased in both women and men with inflammatory arthritis (IA) ( $P < 0.001$ ). In 24 patients (28%), DHEAS levels were below the lower extreme ranges found for controls. Multiple intergroup comparisons revealed similarly decreased concentrations in each disease subset in both women and men. After the ESR, previous glucocorticoid usage, current treatment with nonsteroidal anti-inflammatory drugs, duration of disease and HOMAIR were controlled for, the differences in DHEAS levels between patients and controls were markedly attenuated in women ( $P = 0.050$ ) and were no longer present in men ( $P = 0.133$ ). We concluded that low DHEAS concentrations are commonly encountered in IA and, in women, this may not be fully explainable by disease-related parameters. The role of hypoadrenalism in the pathophysiology of IA deserves further elucidation. DHEA replacement may be indicated in many patients with IA, even in those not taking glucocorticoids.

### INTRODUCTION

Introduction Decreased hypothalamic–pituitary–adrenal activity, particularly a blunted response to activation of the immune system, is strongly implicated in the onset and persistence of inflammatory arthritis (IA). Dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS) are the steroid hormones most abundantly produced by the human adrenal cortex, and therefore are probably of biological importance. Low serum concentrations of these weak androgens more sensitively confirm hypothalamic–pituitary–adrenal hypofunction than does glucocorticoid secretion. In young women with rheumatoid arthritis (RA), decreased DHEA and DHEAS levels are significantly correlated with low early-morning cortisol concentrations and high basal levels of interleukin-6. Both glucocorticoids and testosterone, of which DHEA is a precursor, attenuate cytokine production by synovial inflammatory cells. DHEAS concentrations before the onset of RA in pre-menopausal women were reported to be reduced in two studies by Masi et al and normal in a study by Heikilla et al, respectively. However, the findings in the latter report may have been related to a variation in the use of laboratory methods to assay DHEA levels or a genetically different type of RA in Finnish patients. The concentration of DHEAS in both serum and synovial tissue is decreased in established RA. The decrease is more pronounced in patients taking glucocorticoids. DHEA replacement in the latter circumstance has been recommended as a means of attenuating glucocorticoid-induced side

effects. Recently, the acute phase response and the severity of disease were reported to correlate with decreased basal DHEA levels in RA. Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) similarly attenuates hypothalamic–pituitary–adrenal axis function in RA. Also, insulin resistance, which may be a common disturbance in RA, is associated with loss of the diurnal rhythm and hyporesponsiveness of the hypothalamic–pituitary–adrenal axis to stress. In the present study, we compared serum DHEAS concentrations in 87 patients who had IA (RA, spondyloarthropathy [Spa], or undifferentiated inflammatory arthritis [UIA]) with the concentrations in controls matched for age and sex, and investigated whether decreased serum DHEAS concentrations in IA could be accounted for by the acute-phase response, previous glucocorticoid usage, current NSAID treatment, duration of disease, and insulin resistance.

## CONCLUSION

In a controlled study on patients with IA, we found that secretion of DHEAS is similarly reduced in RA, Spa, and UIA. After we had controlled for the acute-phase response, previous glucocorticoid usage, current NSAID therapy, duration of disease, and insulin resistance, the differences in DHEAS concentrations between patients and controls matched for age and sex were attenuated in women and were no longer present in men. The contribution of low DHEAS concentrations to the pathogenesis of IA deserves further study. Also, in view of the impaired health status associated with low DHEAS concentrations, the role of DHEA replacement therapy in IA needs to be investigated.