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AGE-RELATED CHANGES IN 11β-HYDROXYANDROSTENEDIONE CONCENTRATION IN NORMAL AND OSTEOPOROTIC WOMEN

R. SCHLAGHECKE,* D. BEUSCHER, H. K. KLEY and E. JULI
Department of Endocrinology and Rheumatology, Heinrich Heine University Düsseldorf, Moorenstr. 5, 4000 Düsseldorf, Fed. Rep. Germany

Summary—The secretion of dehydroepiandrosterone (DHEA) and its sulfate is known to decline gradually with advancing age. Furthermore DHEA is known to be significantly lower in osteoporotic subjects than in normals. Recently 11β-hydroxyandrostenedione (11-OHA) has been proposed as an important indicator of the adrenal source of hormone excess in different hyperandrogenic states. In the present study we measured 11-OHA in 224 normal women aged 20–79 yr and 130 osteoporotic women aged 40–79 yr. RIA of 11-OHA was performed with highly specific antiserum raised in rabbits.

The mean 11-OHA serum concentration was 2.20 ± 0.90 ng/ml in normal women and 1.75 ± 0.58 ng/ml in osteoporotic women. In contrast to DHEA there was no age-related decrease in 11-OHA serum concentrations in normal and osteoporotic women. Osteoporotic subjects showed statistically significantly lower 11-OHA serum concentrations than normal women. Therefore low serum 11-OHA might represent a further risk factor for osteoporosis.

INTRODUCTION

Sex steroid hormones play an important role in maintaining skeletal integrity. While the relationship of inadequate gonadal steroid production and declining bone mass is well established [1–6], little is known about the role of adrenal steroids in this context. Considerable evidence exists which suggest that the aging process involves not only the gonads but also the adrenal glands [7, 8]. Therefore a declining output of adrenal steroids might be a risk factor for developing osteoporosis.

The adrenal androgen dehydroepiandrosterone sulfate (DHEAS) is the most abundant steroid in the circulation and is known to decline with advancing age. Its concentration is significantly lower in osteoporotic subjects than in normals [7, 9, 10]. Besides the 5-ene-androgen DHEAS, the 4-ene-androgen 11β-hydroxyandrostenedione (OHA) is a specific marker of adrenal function [11, 12]. In this study we measured 11-OHA in 224 normal women aged 20–79 yr and 130 osteoporotic women aged 40–79 yr. The aim of the study was to obtain further information about age-related changes in adrenal androgens and to examine whether there is a correlation of 11-OHA concentrations with osteoporotic spine deformity.

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*To whom correspondence should be addressed.

SUBJECTS AND METHODS

Subjects

The study comprised 224 normal (20–79 yr, $\bar{x}$54.1 ± 14.4) and 130 osteoporotic women (40–79 yr, $\bar{x}$63.1 ± 10.0), presented to our osteoporosis ambulatory in 1986–1990. All subjects studied, were endocrinologically normal (based on normal serum assays for T4, T3, TSH, cortisol and PTH). Patients with osteomalacia, renal insufficiency, liver disease, or who had received long-term glucocorticoid therapy were excluded. The diagnosis of osteoporosis was made by X-ray (more than one wedged vertebrae, or one or more crushed vertebrae).

Laboratory analyses

The RIA system for 11β-hydroxyandrostenedione (11-OHA) has been described previously [11]. Highly specific antiserum was raised in rabbits. The synthesis of labeled 11-OHA was performed by the method of Appleby and Norymberski [13] with [1, 2-^{3}H]cortisol as starting substance. Thin-layer

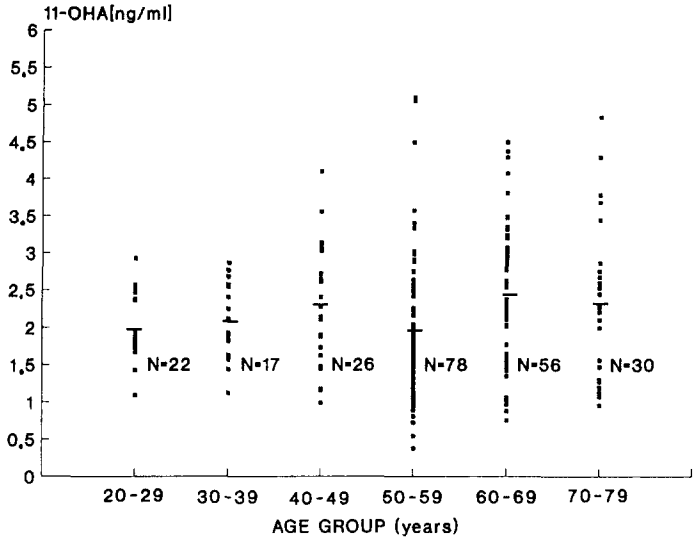

Fig. 1. 11-OHA concentrations vs age in normal female subjects.

chromatography was performed before RIA procedure. Each 11-OHA value reflects the average of duplicate analyses. The intra-assay coefficient of variation was 6.8%. The inter-assay coefficient of variation was 8.9%. Blood was taken for 11-OHA measurement between 08.00 and 09.00 h in all subjects. Data were analyzed by 10-yr age groups (20–29, 30–39, 40–49, 50–59, 60–69 and 70–79).

Statistics

Hormone concentrations were given as the mean ± standard deviation ($\bar{x} \pm SD$). Data were processed statistically using the Wilcoxon rank test. Pearson correlation coefficients were estimated in a linear regression analysis.

RESULTS

The results on 11-OHA concentration in normal female subjects are shown in Fig. 1. The mean serum concentration was found to be 2.17 ± 0.90 ng/ml, range 0.5–4.0 ng/ml. There was no clear relationship between age and 11-OHA serum concentration ($r = 0.15$). The results on 11-OHA serum concentration in osteoporotic females are shown in Fig. 2. The mean serum concentration was found to be 1.75 ± 0.58 ng/ml, range 0.35–3.8 ng/ml. Again there was no clear relationship between age and 11-OHA serum concentration ($r = 0.17$). Osteoporotic subjects showed statistically significantly lower 11-OHA serum concentrations ($P < 0.01$) than normal subjects.

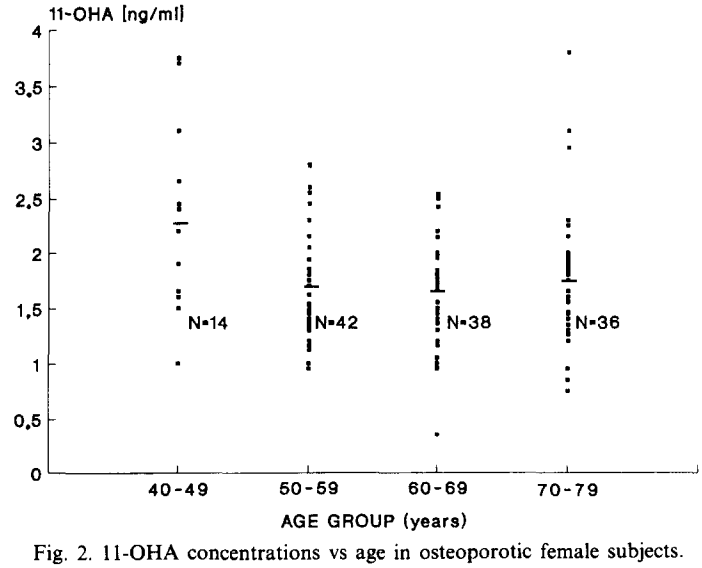

Fig. 2. 11-OHA concentrations vs age in osteoporotic female subjects.

DISCUSSION

Considerable evidence exists which suggests that there is a progressive modulation in adrenocortical function with advancing age [14]. However, the variability in the degree of modulation among species, strain and individuals is great [14]. The secretion of adrenal C 19 steroids, DHEA and its sulfate, has been known to decline gradually with advancing age, in contrast to that of cortisol, which is essentially unaffected by aging [7, 15]. In the present study we found no age-related changes in 11-OHA serum concentration. Together with above mentioned findings, the secretion of 4-ene-adrenal steroids seems not to be affected by age, whereas the secretory capacity of 5-ene-adrenal steroids seems to be impaired in elderly subjects. Therefore the site of the defect is not a decline in overall adrenal steroidogenesis as proposed recently [16], but a reduction in the activity of specific steroidogenic enzymes has to be assumed.

In postmenopausal women estrogens are known to be related to bone loss and risk of fractures [17]. Postmenopausal bone loss can be prevented by estrogen substitution therapy [18, 19]. After the menopause, when the ovarian estrogen production has ceased, adrenal androgens are the most important precursors of endogenous estrogen activity [20]. Moreover androgens may have a beneficial effect against osteoporosis in their own right [1]. In the present study, mean serum 11-OHA concentration was found to be statistically significantly lower in osteoporotic than in normal subjects. The difficulty to differentiate women with osteoporosis from those in control groups simply on the basis of steroid hormone levels is well known [2, 21]. Therefore our results cannot prove that adrenal androgens have an etiological basis in the development of the osteoporotic process. Nevertheless the results of our investigation encourage further study of the influence of endogenous adrenal androgen activity in relation to osteoporosis.

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