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SEX HORMONE CONCENTRATIONS IN POST-MENOPAUSAL WOMEN

RELATION TO OBESITY, FAT MASS, AGE AND YEARS POST-MENOPAUSE

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SUMMARY

Plasma sex hormone concentrations (testosterone, (T), androstenedione (A), oestrone (E1) and oestradiol (E2)) were measured in forty post-menopausal women more than 4 years post-normal menopause. Correlations between these and age, years post-menopause (YPM), degree of obesity and fat mass respectively were studied. T and A, as well as E1 and E2 were positively correlated ($P < 0.01$), but no statistically significant correlation between A and E1 was observed. Sex hormone concentrations in this group of postmenopausal women (> 4YPM) did not show any variation as a function of age, with the possible exception of E2 which showed a tendency to decrease in the late post-menopause. E1 and to a lesser extent E2 as well as the E1/A ratio were significantly correlated with degree of obesity or fat mass, suggesting a possible role of fat tissue in the aromatization of androgens. Neither the T/A nor the E2/E1 ratios were correlated with fat mass, suggesting that the reduction of 17 oxo-group does not occur in fat tissue. The E1/A ratio was significantly higher than the reported conversion rate of A in E1. This might suggest the existence of an additional precursor of plasma E1.

In post-menopausal women, plasma oestrogens seem to originate from peripheral conversion of androgens, mainly androstenedione (Grodin *et al.*, 1973; Siiteri & MacDonald, 1973; Longcope, 1971) and it has been reported that this conversion of precursors to oestrogens increases both with advancing age and with increasing weight (Hemsell *et al.*, 1974, Siiteri & MacDonald, 1973). It can be expected that variations in conversion will be reflected in variations in plasma oestrogen concentrations and/or in variations of the product/precursor ratio. In order to test this hypothesis, we measured plasma sex hormone concentrations (androstenedione, testosterone, oestrone and oestradiol) in forty normal post-menopausal women and studied the correlation between their hormone concentration and years elapsed since the menopause, age, weight, degree of obesity and fat mass.

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MATERIAL AND METHODS

As we had observed that in women less than 4 years after the menopause (YPM) sex hormone concentrations were significantly higher than later in the post-menopause, only women *more than 4 years post-natural menopause* were retained for this study. All were in general good health, and upon routine gynaecological examination a normal post-menopausal status was found. None of these women had been treated with hormonal steroids for the previous 2 years. Age varied between 56 and 87 years, with twelve women more than 4 but less than 10 YPM (group I); twelve women between 10 and 19 YPM (group II) and sixteen women more than 20 YPM (group III). Weight varied between 40 and 87 kg. Degree of obesity, expressed in kg, was defined as the difference between actual weight and normal weight (N.W.) as determined from the formula of Lorenz:

$$\text{N.W.} = \text{L} - 100 - \frac{\text{L} - 150}{4}$$

where L = length in cm (Vague *et al.*, 1969). Fat mass was derived using the formulae of Pace & Rathbun (1945) and of Hume & Weyers (1971).

Methods

Plasma samples were taken in the morning between 08.00 and 10.00 hours; at least two and generally three samples were taken with an interval of 20 min. Plasma steroid concentrations were determined using radioimmunoassay methods as previously described (Vermeulen & Verdonck, 1976; Verdonck & Vermeulen, 1974; Vermeulen *et al.*, 1977). At plasma oestradiol (E2) concentrations that occur in post-menopausal women (6–100 pmol/l), precision of measurement was relatively low, as expressed by an interassay coefficient of variation (C.V.) of 27% at a plasma concentration of 6 pmol/l and of 11% at a 50 pmol/l concentration. For plasma oestrone (E1) in the postmenopausal concentration range (75–250 pmol/l), interassay CV was 9.9%.

The correlation coefficient r was calculated using the method of least squares.

RESULTS

Frequency distribution analysis of steroid concentrations showed that in the entire group, values were normally distributed but due to the limited number of subjects, distribution in subgroups was best defined by the arithmetic mean and range of values. Therefore the non-parametric Wilcoxon rank sum test was used for analysing differences between groups. Neither mean androstenedione (A), mean testosterone (T) nor mean oestrone (E1) levels showed any significant variation in the different groups of post-menopausal women classified in respect of YPM (Table 1); the mean oestradiol (E2) in subjects more than 20 YPM was however significantly lower ($P < 0.05$) than mean levels in subjects less than 20 YPM. Taking all subjects together, no statistically significant correlation between A, T or E1 concentrations on the one hand, and either YPM or age on the other hand were observed. A borderline statistically significant negative correlation ($P < 0.05$) was however observed between E2 concentrations and age (Table 2). E1 showed a highly significant correlation ($P < 0.001$) with degree of obesity (Fig. 1) and fat mass respectively, the correlation with weight being somewhat weaker ($P < 0.01$), whereas borderline statistically significant ($P < 0.05$) correlations between E2 and either degree of obesity or fat mass, but not body weight, were observed (Table 2).

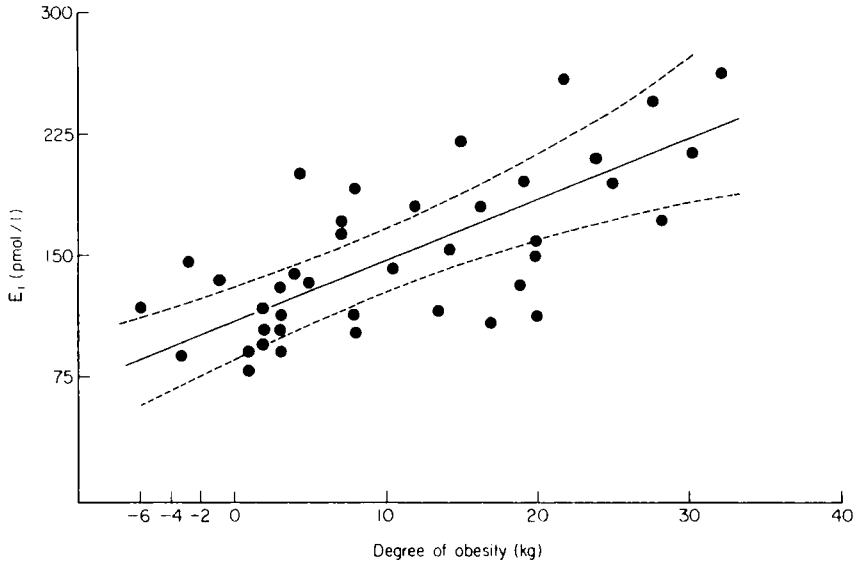

Fig. 1. Correlation between plasma E1 concentrations and degree of obesity in post-menopausal women (> 4 YPM). Regression line with 95% confidence limits. $r = 0.72$; $P < 0.001$.

Table 1. Mean plasma concentrations of sex hormones in post-menopausal women

	Time after menopausal (years)		
Years after menopause	4-9 ($n = 12$)	10-19 ($n = 12$)	> 20 ($n = 16$)
Testosterone (nmol/l)	1.00 (0.42-1.69)	0.97 (0.43-1.98)	0.76 (0.30-1.39)
Androstenedione (nmol/l)	2.52 (1.01-4.44)	2.03 (1.37-3.64)	2.45 (0.94-4.20)
Oestradiol (pmol/l)	55.1 (6.4-176.5)	58.8 (25.7-102.9)	33.1 (6.4-62.5)
Oestrone (pmol/l)	163.0 (103.7-259.3)	122.2 (77.8-192.6)	129.6 (74.1-255.6)

No significant correlation was observed between plasma E1 and A concentrations, but the E1/A ratio was positively correlated with degree of obesity and fat mass respectively ($P < 0.01$), whereas a borderline significant negative correlation ($P < 0.05$) between this ratio and age was observed. There existed a significant positive correlation between T and A ($P < 0.01$) but no significant correlations between the T/A ratio and either weight, degree of obesity or fat mass were observed.

Plasma E1 and E2 concentrations were significantly correlated ($r = 0.51$, $P < 0.01$); the E2/E1 ratio was rather variable, and no significant correlations with either age, YPM, degree of obesity or fat mass were found.

Finally no significant correlation was observed between either age or YPM and degree of obesity (Table 2).

Table 2. Correlation coefficients and their statistical significance against zero

	Weight	Degree of obesity	Fat mass	YPM	Age	A
E1	0.55**	0.72***	0.66***	−0.24	−0.31	0.09
E2	0.26	0.38*	0.36	−0.30	−0.37*	0.16
A	0.28	0.28	0.21	−0.04	−0.02	–
T	−0.011	−0.09	−0.07	−0.19	−0.12	0.50**
100E1/A	0.46**	0.50**	0.50**	−0.30	−0.36*	–
T/A	0.22	0.27	0.20	−0.20	−0.21	–
E2/E1	0.06	0.12	0.13	−0.13	−0.13	–
Age	−0.21	−0.22	−0.17	–	–	−0.02

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

DISCUSSION

Few data are available in the literature concerning the evolution of sex hormone concentrations as a function of age or YPM. To our knowledge only Chakravarti *et al.* (1976) have reported such a study. Their date are, however, not in complete agreement with ours. Indeed, these authors found slightly lower A and significantly lower E1 concentrations, whereas they observed significantly higher T concentrations. More important however is the fact that these authors report an increase in T and E2 in the late post-menopause; as the number of women in each subgroup is not known however it is impossible to know whether these changes were statistically significant. Moreover no data are given concerning the weight of these subjects, an important variable among factors determining plasma oestrogen concentrations.

Our study, on the contrary, did not reveal any increase of sex hormone concentrations in respect of age or YPM; in fact oestrogen concentrations showed a trend towards a lowering with age or YPM. The most important finding however in our study is the highly significant correlation between plasma E1 and either degree of obesity and fat mass and the (less significant) correlation between these variables and E2 concentrations. This points to a probable role of fat tissue in the aromatization of androstenedione, as suggested by the *in vitro* work of Nimrod & Ryan (1975), and by the *in vivo* experiments of Siiteri & MacDonald (1973), Grodin *et al.* (1973), Rizkallah *et al.* (1975) and Longcope *et al.* (1976). Siiteri & MacDonald (1973) observed a significant correlation between the conversion of A in E1 and body weight in a group of normal post-menopausal women with a weight range between 80 and 360 lbs, whereas Rizkallah *et al.* (1975) confirmed this correlation in patients with endometrial carcinoma. Judd *et al.* (1976) in a study involving a combined group of post-menopausal women with and without endometrial cancer, observed a significant correlation ($r = 0.55$) between E1 and E2 concentrations and weight in a range between 80 and 220 lbs. That the correlation between E2 and degree of obesity we observed in this study is statistically less significant than the correlation between E1 and degree of obesity is not surprising. Indeed, the relative error on the low E2 concentrations in post-menopausal women is more important than on the significantly higher E1 concentrations, and might obscure an eventual correlation; moreover peripheral synthesis of E2 proceeds mainly by reduction of E1 (blood conversion rate of E1 to E2 = ±6.5%) (Longcope *et al.*, 1968) and for a very small part by

aromatization of T (blood conversion rate of T to E2 = 0.07%) (Longcope *et al.*, 1969); whereas the latter may be supposed to occur at the same site as the aromatization of A (fat tissue), the reduction of E1 might occur in another compartment.

Again we observed a significant correlation between the E1/A ratio and either degree of obesity or fat mass, supporting a role for fat tissue in the aromatization of these steroids.

Whereas the absence of an increase of the E1/A ratio with age is in accordance with the results of Rizkallah *et al.* (1975), Hemsell *et al.* (1974) in a study of twenty-three women, age 20-75 years reported an increase with age of the conversion of labelled A to E1; however when taking separately women over 50 years old, no such correlation is evident from published data. Moreover the conversion of A to E1 was measured in urine and when Grodin *et al.* (1973) compared this conversion rate to blood conversion rate, the latter was only half the urinary conversion; to our knowledge no study on the relation between age and blood conversion rates of A in E1 has been published.

In contrast to Marshall *et al.* (1977) we did not observe any correlation between A and E1 concentrations; this lack of correlation we attribute to the important influence of fat mass on E1 concentrations.

As expected, E2 and E1 concentrations were significantly correlated, ($P < 0.01$), E1 being the main precursor of E2. However, the E2/E1 ratio was not correlated with either fat mass, degree of obesity or age. Because of the important methodological errors involved in the determination of this ratio at low E2 concentrations, it may be hazardous to draw any conclusion from these observations, but they are compatible with the hypothesis that the conversion of E1 in E2 does not occur in the same compartment as the conversion of A in E1. Like Poortman *et al.* (1973) we observed a statistically significant correlation between T and A levels ($P < 0.01$), although only about half of T is derived from A in post-menopausal women (Poortman *et al.*, 1973, Vermeulen 1976).

If plasma E1 is derived almost exclusively from peripheral conversion of A, one should expect that the E1/A ratio in plasma would reflect the blood conversion rate (CR) of A to E1. The mean ratio however was 0.074 ± 0.008, significantly higher than the CR (0.005-0.018) (Longcope *et al.*, 1969; Grodin *et al.*, 1973). It could be argued that the E1/A ratio as determined in this study, is not necessarily representative for the integrated ratio over 24 h, especially as A is released in pulses and conversion to E1 probably does not occur instantaneously. However, as several plasma samples were taken at 20 min intervals, the ratio is probably representative for the mean ratio during the period between 08.00 and 10.00 hours and as isotopic blood conversion rates are also generally determined in the morning, comparison with the latter seems warranted. Moreover, although conversion probably does not occur instantaneously, acute changes in metabolic clearance rate, as occurs when changing from the recumbent to the upright position, does not influence either blood conversion rate or plasma concentration (Flood *et al.*, 1973), whereas in post-menopausal women nycto-hemeral variations of plasma E1 concentrations roughly parallel variations in A concentrations (Vermeulen, 1976). Hence, notwithstanding its limitations, the E1/A ratio, as determined in this study, probably has a biological significance.

Among factors that might be responsible for the differences between this ratio and the blood conversion rate, one should consider first a possible lack of specificity of the E1 determination, yielding to high E1 concentrations. However, values reported in this study are similar to those reported by most authors, (Tulchinsky & Korenman, 1970; Rader *et al.*, 1973; Judd *et al.*, 1974; Maroulis & Abraham, 1976), only Chakravarti *et al.* (1976) reporting lower E1 concentrations. As far as A values are concerned, some authors have reported

slightly lower values (Maroulis & Abraham, 1976; Abraham & Maroulis, 1975; Chakravarti *et al.*, 1976), others slightly higher (Greenblatt *et al.*, 1976) or similar values (Judd *et al.*, 1974; Poortman *et al.*, 1973). Errors in the determination of conversion rates from radioactive precursors should also be considered as a possibility. The study of Rizkallah *et al.* (1975) showed that the mathematical model, upon which the urinary method of determining conversion rates is based, is inadequate. One of the requirements for obtaining valid blood conversion rates is attainment of a steady state isotope level in both precursor and product concentration. Recently (James *et al.*, 1977) it has been claimed that the metabolic clearance rate of A, like of other steroids with high MCR (Little *et al.*, 1966; Balikian *et al.*, 1968), may be subject to rapid variations, precluding steady state conditions. Moreover the possibility that radioactive product (E1) might be retained for a longer time in fat tissue, being released only slowly (eventually as E1 sulphate) or possibly recirculated, cannot be dismissed and might result in an underestimation of the conversion rate (Hembree *et al.*, 1969; Longcope & Tait, 1971).

If blood conversion rates of A to E1 as determined by isotopic infusions are a valid estimate of the real conversion rate, then, although absolute proof of method specificity is lacking, our high E1/A ratio points towards another source of E1 not involving A.

As in ovariectomized women E1 concentrations and the E1/A ratio are similar to those obtained in the natural menopause (Barlow *et al.*, 1969; Saez *et al.*, 1972; Vermeulen, 1976) and as the E1 concentration in ovarian venous blood is similar to the concentration in peripheral blood (Rader *et al.*, 1973; Judd *et al.*, 1974), an ovarian origin of E1 (either direct or indirect) seems unlikely. Therefore an adrenal source seems more probable; a significant secretion of E1 by the adrenal is however unlikely in the view of the findings in catheterization studies (Baird *et al.*, 1969; Greenblatt *et al.*, 1976). Data in the literature do not suggest oestrone sulphate to be a likely precursor, as constant infusion studies in males by Longcope (1972) and in males and females during reproductive age by Ruder *et al.* (1972) suggest that the conversion of plasma E1 and E2 accounts for all the circulating plasma E1 sulphate. However, the important inter-individual variations in MCR and conversion rates, the absence of steady-state conditions, as well as the nyctohemeral rhythms in oestrogen concentrations, make it hazardous to draw a final conclusion. Hence the postulated oestrogen precursor remains hypothetical. The development of endometrial carcinoma has been correlated with extra-glandular oestrone production (MacDonald & Siiteri 1974) and obesity has been reported to be a risk factor. Siiteri & MacDonald (1973) reported increased conversion of A in E1 in obesity; our data show a direct correlation between E1 concentrations and obesity. If long term exposure of the endometrium to oestrone is causally related to pre-malignant hyperplasia or endometrial carcinoma, then our findings give a direct explanation for an increased occurrence of the latter in obesity.

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