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Testosterone Levels in the Plasma of Normal Women and Patients with Benign Breast Disease or with Breast Cancer

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INTRODUCTION

THERE is a close relationship between the amounts of androgen metabolites in the urine and the clinical course of breast cancer. The majority of patients with widespread metastases who excrete subnormal amounts of androsterone and aetiocholanolone do not respond to adrenalectomy or hypophysectomy [1] or to pituitary destruction by yttrium-90 [2]. A similar abnormality in steroid excretion is found in about half the patients with the early disease (before metastatic spread is found) and these patients also have a poor prognosis [3, 4].

The urinary androgen metabolites are derived from at least four precursors (dehydroepiandrosterone and its sulphate, androstenedione, and testosterone) which means that deductions about the concentration of precursors in the blood cannot be made from measurements of urinary metabolites [5]. In an attempt to investigate the physiological meaning of the correlation between urinary steroid levels and the clinical course of breast cancer direct measurements of plasma 17-oxosteroids and 17-hydroxycorticosteroids have been made [6] and preliminary investigations of secretion rates have been carried out [7].

This paper is concerned with the levels of free testosterone in the plasma of normal women and patients with benign breast disease or early breast cancer.

METHODS

(a) *Subjects*

Blood (20 ml) was taken into heparinised syringes from the antecubital vein between 2 p.m. and 4 p.m. for normal women and between 10 a.m. and 11 a.m. for patients with breast disease. The time difference is unlikely to be important since there is no diurnal variation in plasma testosterone levels [8]. The plasma prepared from these samples was stored at -20° . Blood samples from premenopausal women were taken at random during the menstrual cycle. Minor variations in plasma testosterone levels have been reported during the cycle [9] but this variation would be unlikely to alter any of the conclusions in the present study since the proportion of premenopausal women in each of the three groups of subjects was approximately equal.

The patients with benign breast disease consisted of fourteen women admitted to hospital to await diagnosis and subsequent surgery. Their ages ranged from 24 to 59 years (mean 43.4). The patients with breast cancer were twenty-four women, in hospital awaiting radical mastectomy. The ages of these patients ranged from 25 to 84 years (mean 49.7). All diagnoses were confirmed eventually by histological examination. The normal women were nineteen volunteers, apparently healthy, who were housewives living in the North London

area. Their ages ranged from 25 to 76 years (mean 51.9).

(b) *Chemical*

Plasma testosterone was estimated by the method of Burger, Kent and Kellie [10]. Since there was the possibility of contamination of the testosterone fraction by epitestosterone [11] an additional purification step was introduced into the method. This was a preliminary purification of the plasma testosterone extract by paper chromatography (2:2:4 trimethylpentane:toluene/methanol:water. 450:50/400:100).

(c) *Precision*

Six estimations were carried out on pooled plasma from women. The mean value was $0.069 \mu\text{g}/100 \text{ ml}$ plasma with a standard deviation of $0.026 \mu\text{g}/100 \text{ ml}$. Similar experiments on plasma from males gave a mean value of $1.038 \mu\text{g}/100 \text{ ml}$ with a standard deviation of $0.071 \mu\text{g}/100 \text{ ml}$. Errors of this order have been reported previously [12] and are due mainly to the relatively large amounts of marker ^{14}C -testosterone added to the plasma. Since the mean level of testosterone found in this study was $0.12 \mu\text{g}/100 \text{ ml}$ the coefficient of variation would be of the order of $\pm 20\%$.

(d) *Specificity*

The ratio of tritium to ^{14}C in the last four chromatographic steps of the analytical method are shown in Fig. 1. The ratios are constant in the last two steps which implies that the testosterone acetate is radiochemically pure.

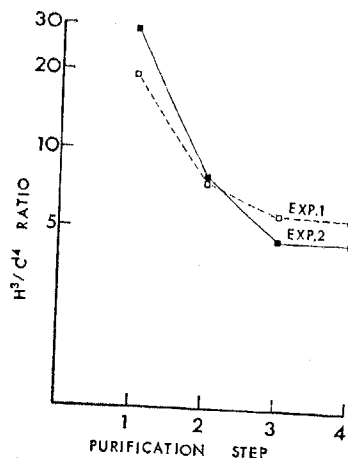


Fig. 1. Ratio of tritium to carbon-14 during purification of doubly labelled testosterone acetate.

RESULTS

The distribution of plasma testosterone levels with age are shown in Fig. 2 for normal women and for patients with benign breast disease or

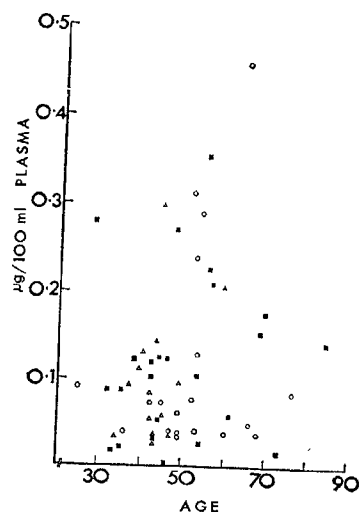


Fig. 2. Plasma testosterone levels and age in normal women, patients with benign breast disease, and patients with early breast cancer.

○ = normal women
△ = women with benign breast disease
■ = women with early breast cancer

breast cancer. There is no correlation with age in any of these groups of patients.

The individual values for each group are shown in Fig. 3: the mean values are almost

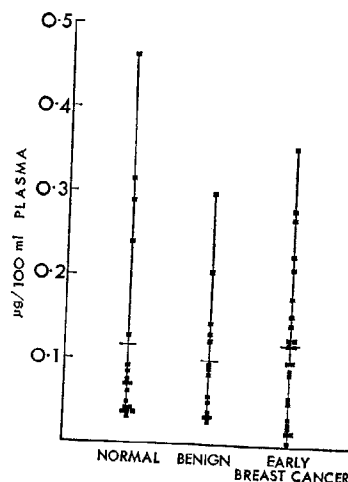


Fig. 3. Comparison of plasma testosterone levels in normal women, patients with benign breast disease, and patients with early breast cancer.

identical. The mean value for normal women is $0.12 \pm 0.12 \mu\text{g}/100 \text{ ml}$ (standard deviation). These values are in agreement with others in the literature [8, 12, 13]. The mean value for the breast cancer cases is $0.12 \pm 0.09 \mu\text{g}/100 \text{ ml}$ and is $0.10 \pm 0.08 \mu\text{g}/100 \text{ ml}$ for those with benign breast disease. There was no correlation between the plasma testosterone concentration and the amounts of androsterone or aetiocholanolone in the urine (see also [8, 9]).

DISCUSSION

It has been assumed that the subnormal excretion of urinary androgen metabolites by patients with breast cancer who have a poor prognosis after mastectomy or after endocrine ablation was a reflection of a deficient production of androgens [14, 15]. The present results showing normal plasma testosterone levels in both benign and malignant breast disease indicate that this interpretation of the results of assays of urinary androgen metabolites must be regarded with caution.

The abnormally low urinary excretion, found in some patients, of androsterone and aetiocholanolone is probably related to a deficiency in the secretion of dehydroepiandrosterone and its sulphate. This would be expected since the major portion of the urinary 11-deoxy-17-oxosteroids are derived from these two precursors [5]. Furthermore, a good correlation between the levels of plasma 17-oxosteroids (mainly the sulphates of dehydroepiandrosterone and androsterone) and those of the urinary 11-deoxy-17-oxosteroids has been reported [6].

The measurement of testosterone in plasma

has attracted much attention since it was supposed that this compound was the major androgen in women [5]. It has recently been shown [16, 17] that androstenedione is present in much higher concentrations than testosterone in the peripheral blood of normal women and that previous estimates of the amounts of testosterone secreted are probably over-estimates [5].

Before any statement can be made concerning androgenic status in women with breast cancer it would be desirable to obtain simultaneous measurements of both androstenedione and testosterone (and of the rates of their inter-conversion) in these patients. A more sensitive and precise method than that used in this study such as that employing ^{35}S -labelled thiosemicarbazide [18] would be essential in such an investigation. A second essential factor is the elucidation of the physiological roles of dehydroepiandrosterone and its sulphate in women. It seems unlikely that rapid progress can be made in the investigation of endocrinological aspects of human breast cancer until more is known about the androgenic stimulus in normal women.

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RÉSUMÉ

Chez les patientes atteintes de cancer du sein, il existe une corrélation entre le pronostic de l'affection et les taux urinaires des métabolites des androgènes. Afin de voir si ces données peuvent être étendues aux taux des androgènes dans la circulation périphérique, la testostérone a été dosée dans le plasma de trois groupes de sujets: des femmes normales, des patientes atteintes d'une affection bénigne du sein et des patientes atteintes de cancer du sein à un stade précoce. Aucune différence n'a été observée. Les valeurs moyennes (et la déviation standard) du taux de la testostérone plasmatique furent respectivement dans les trois groupes: $0.12 \pm 0.12 \mu\text{g}/100 \text{ ml}$; $0.10 \pm 0.08 \mu\text{g}/100 \text{ ml}$ et $0.12 \pm 0.09 \mu\text{g}/100 \text{ ml}$. On ne trouve aucune corrélation entre ces concentrations de testostérone et l'excrétion urinaire des métabolites des androgènes.

SUMMARY

The prognosis of patients suffering from breast cancer is related to the urinary levels of androgen metabolites. In an attempt to extend this finding, in terms of the levels of androgen in the peripheral circulation, plasma testosterone levels have been determined in three groups of women: normal, patients with benign breast disease, and patients suffering from early breast cancer. No differences in plasma testosterone levels were found between any of the groups, the values for them being $0.12 \pm 0.12 \mu\text{g}/100 \text{ ml}$ (standard deviation), $0.10 \pm 0.08 \mu\text{g}/100 \text{ ml}$ and $0.12 \pm 0.09 \mu\text{g}/100 \text{ ml}$, respectively. No correlation was found to exist between these testosterone levels and the urinary excretion of androgen metabolites.

ZUSAMMENFASSUNG

Bei den von einem Brustkrebs befallenen Patientinnen besteht ein bestimmtes Verhältnis zwischen der Krankheitsprognose und der Konzentration der im Harn ausgeschiedenen Androgenen Stoffwechselprodukte. Um zu bestimmen, ob diese Angaben auch bezüglich des Androgenen-Spiegels in dem zirkulierenden Plasma gültig sind, hat man den Plasma-Testosteronspiegel bei 3 Gruppen von Patientinnen bestimmt: bei normalen Frauen, bei

solchen, von einer gutartigen Brusterkrankung befallen, und bei Frauen an einem im Frühstadium Brustkrebs leidenden. Man konnte keinen Unterschied bezüglich des Plasma-Testosteronspiegels dieser 3 Gruppen feststellen. Die gefundenen Werte (mit der Standardabweichung) waren wie folgt: $0,12 \pm 0,12 \mu\text{g}/100 \text{ ml}$; $0,10 \pm 0,08 \mu\text{g}/100 \text{ ml}$ und $0,12 \pm 0,09 \mu\text{g}/100 \text{ ml}$. Es besteht kein Zusammenhang zwischen diesen Plasma-Testosteronwerten und der Konzentration der mit dem Harn ausgeschiedenen Androgenen Stoffwechselprodukte.

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