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Androgen concentrations in expressed prostatic secretions: no correlation with tissue levels

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Summary. In an attempt to determine whether the androgen profiles of the prostate fluid (EPS) mirror the concentrations in the prostate tissue, we have measured testosterone and dihydrotestosterone (DHT) in EPS and correlated their levels to the concentrations found in hyperplastic prostate tissue (BPH) obtained from the same 19 patients. Although androgen concentrations in EPS were very high (testosterone = 106.7 ± 81.9 ng/g dry weight; DHT = 54.2 ± 11.2 ng/g dry weight), they did not reflect the concentrations measured in BPH tissue (testosterone = 7.56 ± 1.54 ng/g dry weight; DHT = 10.54 ± 0.63 ng/g dry weight). Additionally the accumulation of tissular DHT usually associated with BPH was not mirrored in the EPS specimens which demonstrated a relatively higher concentration of testosterone when compared to DHT. In EPS, there was also a very strong correlation between testosterone and DHT concentrations ($r=0.89$; $P<0.01$). We have also measured zinc concentrations in EPS and BPH tissue but were unable to detect any relationship between the two parameters. Significantly, however, EPS zinc concentrations showed a close correlation with EPS testosterone ($r=0.73$; $P<0.01$) and DHT ($r=0.69$; $P<0.01$) concentrations.

Key words: Prostate fluid – Testosterone – Dihydrotestosterone – Zinc – Benign prostatic hyperplasia

The biochemical composition of the secretory products of the exocrine prostate have been extensively analyzed. However, the precise function and importance of most of the substances present is little understood and poorly characterized. Since prostatic secretions form a major part of the ejaculate, a supportive or nutritive function for spermatozoa has long been assumed. Split ejaculate studies using acid phosphatase and citric acid as markers for prostatic secretion and fructose as a marker for vesicular secretions suggest that the prostate contributes 15–30% of the ejaculatory volume [10]. Among the substances identified in seminal plasma and considered to be of prostatic origin are citric acid, acid phosphatase, phospholipid, zinc, zinc binding protein together with the aliphatic polyamines, spermine, spermidine and putrescine [10]. In seminal plasma the concentrations of free dihydrotestosterone (DHT) and its sulphate predominate over that of free testosterone and testosterone sulphate.

An inability to separate the prostatic fraction from semen without contamination by the vesicular component tends to invalidate the use of the ejaculate for the study of prostatic secretion. Therefore, studies of the secretory products have been based on the analysis of the fluid obtained by per-rectal massage of the prostate or on post-prostatic massage urine specimens [9].

Although the composition of expressed prostatic secretion (EPS) in respect of its zinc and inorganic constituents has been analyzed [8], there have been few studies performed to determine the androgenic content of EPS [11]. No attempt has hitherto been made to relate the androgen content of the EPS to the androgen levels in the tissue from the prostate gland in patients with benign prostatic fibro-adenomatous hyperplasia. If, perchance, the concentrations of androgenic steroids in the EPS were shown to reflect the metabolism of androgens and zinc levels in the diseased prostate, EPS might provide a useful probe for the diagnosis of pathological conditions of the prostate. The aim of this study, therefore, was to compare the concentrations of testosterone and DHT in EPS with androgen concentrations in the prostate tissue in patients undergoing transurethral resection of the prostate for benign prostatic hyperplasia (BPH). In view of the predominance of zinc in the prostate and its importance as a metallo-enzyme in the growth and function of the prostate an attempt was also made to examine the relationship between zinc concentrations and steroid hormone levels in both the EPS and BPH tissue.

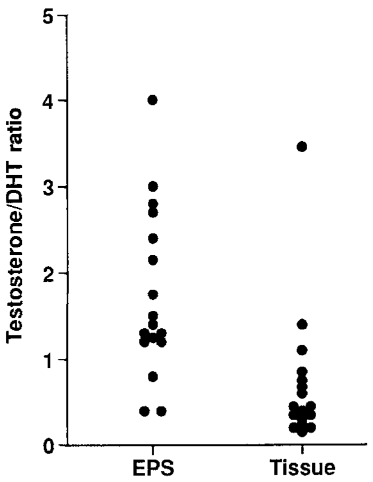

Fig. 1. The distribution of the ratio of testosterone/dihydrotestosterone *(DHT)* secretion *(EPS)* and tissue from 19 patients with benign prostatic hyperplasia

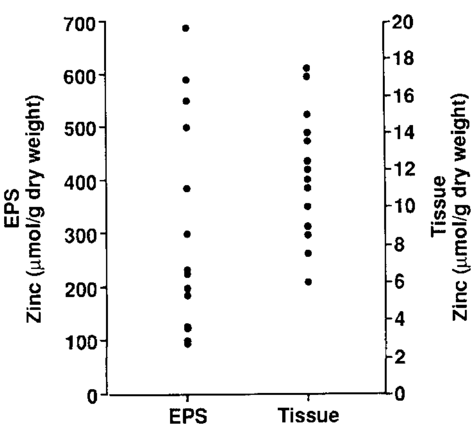

Fig. 2. A comparison of the concentrations of zinc in prostate tissue and expressed prostatic secretion *(EPS)* from 19 patients with benign prostatic hyperplasia

Patients and methods

Prostate tissue and EPS specimens

Prostate tissue was obtained at the time of transurethral resection from 19 patients with BPH. The tissue was transported immediately to the laboratory chopped into 1–3 g pieces, snap frozen in liquid nitrogen and pulverized in a microdismenbrator (Braun, Melsungen, FRG). The powdered tissue was then lyophilized to dryness and stored at −70°C until needed. For steroid analysis 50 mg of the lyophilized tissue was used, whereas only 10 mg was required for the zinc measurements.

Immediately before the prostatic resection a specimen of EPS was obtained from the patient by firm, gentle per-rectal massage under general anaesthesia. The fluid was drawn up into a 1 ml insulin syringe, frozen without delay in liquid nitrogen, lyophilized overnight and stored at −70°C. Prior to the assays, the dry weight of the EPS was noted, and the powder reconstituted in 3 ml of distilled water and centrifuged at 1500 g. Two millilitres of the resultant supernatant was pipetted off for steroid extraction and the remaining 1 ml reserved for zinc assays.

Androgen measurement

Specific radioimmunoassays for testosterone and DHT were carried out after a single separation on Gelman ITLC plates using an antiserum against DHT (Guildhay Antisera, Guildford, UK). The androgen extraction from the tissue, chromatographic separation, radioimmunoassay and reliability of the method have already been described in detail [3, 6].

Measurement of endogenous zinc

The zinc content in the prostate tissue and EPS was measured by flame atomic absorption spectroscopy at 213.9 nm using zinc chloride in 0.1 M HCl as standard. Details of the procedure and the precautions taken to avoid contamination followed those described by Habib et al. [4].

A calibration curve was constructed from the absorbance of the standards, which was linear in the range of 0–6 μmol/l. Test samples with absorbance above this range were diluted and absorbance measured again.

Data analysis

All analysis were performed in triplicate and the data presented as mean ± SEM. Differences in androgen and zinc concentrations were tested for statistical significance by Student *t*-test. Correlation of the degree of association for any two parameters was determined by calculation of the correlation coefficient (r): r values presenting a probability of less than 0.05 were considered to be statistically significant.

Results

Androgen concentrations of EPS and prostate tissue

In the EPS the mean testosterone concentration was 106.7 ± 81.9 ng/g dry weight and the mean DHT concentration was 54.2 ± 11.2 ng/g dry weight mean ± SEM: $n = 19$) (Fig. 1). In most specimens the concentration of testosterone was significantly greater than that of DHT, with the ratio of testosterone to DHT being greater than 1 in 16 of the specimens. This clearly contrasts with the androgen levels measured in prostate tissues (testosterone = 7.56 ± 1.54 ng/g dry weight; DHT = 10.54 ± 0.63 ng/g dry weight), where the relatively higher concentrations of DHT compared to testosterone account for a testosterone: DHT ratio normally less than 1. No correlation was seen between the testosterone to DHT ratios of the EPS and prostate tissue derived from the same patients ($r = 0.5$; $t = -19$; $P > 0.5$). Analysis of testosterone and DHT content alone also failed to show any single relationship between levels in tissue and EPS (tissue testosterone vs EPS testosterone: $r = 0.04$, $t = 0.17$, $P > 0.5$; tissue DHT vs EPS DHT: $r = -0.24$, $t = 1.01$, $P > 0.5$).

Zinc concentration of EPS and prostate tissue

The zinc concentrations in EPS were variable and ranged from 0.08 to 0.7 mmol/g dry weight. The zinc concentra-

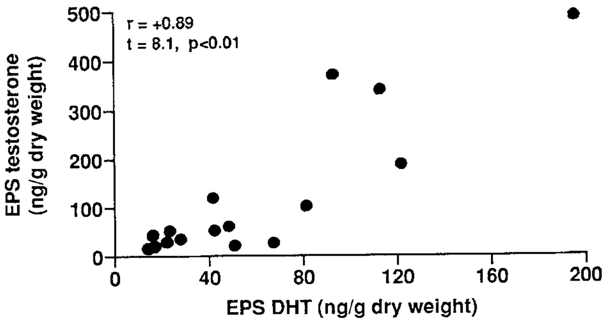

Fig. 3. The correlation between the concentrations of testosterone and dihydrotestosterone *(DHT)* as measured in expressed prostatic secretion *(EPS)* obtained from 19 patients with benign prostatic hyperplasia ($r = 0.89$, $P < 0.01$)

tion in prostate tissue showed less variability and was found to be present within a narrow range (6.5–14.9 μmol/g dry weight). The range and mean values of the zinc concentrations in EPS and BPH tissue are demonstrated in Fig. 2. No correlation was seen between tissue and EPS zinc levels ($r = 0.07$, $t = 0.28$, $P > 0.5$).

The inter-relationship of androgen and zinc content in EPS and prostate tissue

Although there was no identifiable correlation between tissue and EPS androgen and zinc levels, there was a clear relationship between androgen and zinc concentrations within the prostatic secretion (EPS). A significant positive correlation was seen between testosterone and DHT concentration in the EPS ($r = +0.89$, $t = 8.1$, $P < 0.01$) (Fig. 3). A positive correlation was also seen between each of these androgen fractions and zinc in the EPS (Fig. 4a, b). By contrast, a similar relationship between the androgen and zinc concentrations was not demonstrated in BPH tissue.

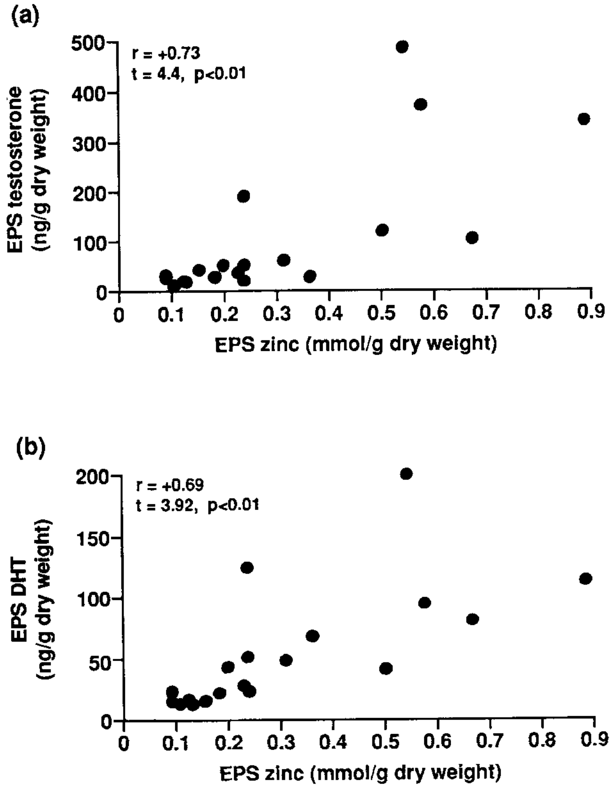

Fig. 4. The relationship between testosterone and zinc concentrations **(a)** and dihydrotestosterone *(DHT)* and zinc concentrations **(b)** in expressed prostatic secretions *(EPS)* obtained from 19 patients with benign prostatic hyperplasia

Discussion

Changes in the chemical, physical and enzymatic composition and characteristic of expressed prostatic fluid obtained by prostatic massage are widely employed in the diagnosis and management of prostatic inflammatory disease. However, there has not been any previous attempt made to correlate the androgen content of prostatic fluid and prostate tissue in pathological conditions of the prostate. Alterations in the concentrations of the two androgenic steroids, testosterone and DHT are well characterized in BPH [1–3, 5, 12]. A marked reduction in both zinc and androgen steroid concentration in prostate cancer tissue has been observed [5]; it is possible that some of these changes might pre-empt the development of clinically and histologically positive disease. If the androgen content of EPS were shown to reflect the expression of androgen metabolism in prostatic disease, prostatic fluid could provide a means of discriminating between benign and malignant disease and monitoring the response to hormonal treatment. The aim of this study was to determine whether the androgen profile of the prostatic fluid bore any relationship to the concentration of testosterone and DHT in BPH tissue, enabling EPS to serve as a diagnostic tool for differentiating diseases of the prostate.

It is well recognized that there is a considerable accumulation of DHT compared with testosterone in BPH tissue resulting in a testosterone to DHT ratio of less than 1. It is of interest that in this study the concentration of testosterone was significantly greater than that of DHT in the prostatic fluid. Thus, there appeared to be no relationship between either the androgen concentrations or zinc levels in the prostatic fluid and BPH tissue. Whilst the zinc concentration of prostatic fluid is well documented [7], there have been few reports on the presence of steroid androgens in EPS. The studies by Rose et al. [11] compared the levels of testosterone, oestradiol, oestrone and prolactin in EPS in prostate cancer with normal controls. However, the testosterone concentrations reported appeared to be considerably lower than the detection limits and sensitivity of the assay used. We found testosterone levels in EPS to be approximately 10 times higher than the concentrations measured by Rose et al. [11] in EPS from normal men. We are not aware of any previous reports of DHT levels in EPS. In view of the high concentrations of DHT in BPH tissue we were not surprised to detect its presence in the prostatic fluid, but an unexpected finding was the reversal in the ratio of testosterone to DHT from that of the prostate tissue and the close correlation found between the two steroids. An explanation for this may be that the high affinity binding of DHT to androgen receptors in BPH tissue results in a greater release of free testosterone into the prostatic secretions. Clearly the androgen profile of EPS does not appear to mirror the hormonal status of BPH tissue. The zinc concentrations of EPS were also shown to reflect tissue zinc levels poorly. The zinc content of EPS in prostate cancer has been shown to differ little from levels seen in other diseases, including BPH [8]. Nevertheless, this does not exclude the possibility that the hormone profiles of EPS may provide a diagnostic index for prostate cancer. In this regard further studies are in progress to determine the androgen levels in EPS in patients with carcinoma of the prostate.

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