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Thyroid and parathyroid hormones in benign prostatic hyperplasia

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Benign prostatic hyperplasia (BPH) is an enlargement of the prostate gland characterised by overgrowth of the transitional and periurethral zones resulting from proliferation stromal and glandular elements. It is the most common non-malignant condition of the prostate occurring in ageing men, and is rarely seen in males less than 40 years of age. The incidence of BPH increases from 50% at 50 years and reaches 80% around 80 years.[1] Despite the magnitude of the public health impact of BPH, the aetiology remains obscure as it is a multifactorial disease. Previous studies have implicated family history, race/ethnicity and endocrine factors as risk factors.[2,3] Among endocrine factors, there are established roles for hormones such as androgen, oestrogen, growth hormone and prolactin in the pathophysiology of BPH.[2]

Thyroid hormones play an important role in cell differentiation, growth and metabolism.[4] Experimental studies have shown that thyroid hormones increase prostate cancer cell proliferation *in vitro* [5] and promote carcinogenesis by inducing angiogenesis.[6] Lehrer et al. have demonstrated association of recurrence of prostate cancer in patients with high tri-iodothyronine levels. [7] It has also been shown that men with hypothyroidism are at reduced risk for developing prostate cancer compared to euthyroid men.[8] Previous studies have reported high tri-iodothyronine in BPH patients when compared to controls.[9] Earlier studies have hypothesized that parathyroid hormone (PTH) stimulates normal prostate growth.[10] PTH receptors have been identified in normal and cancerous prostate cells.[11] Physiological levels of PTH promote the growth of prostate cancer cells in tissue culture and *in vivo*.[12] Clinical data have implicated PTH in the development of prostate cancer, and PTH has been found to predict prostate cancer mortality in men with advanced prostate cancer.[11]

To the best of our knowledge, there are only limited data available about the levels of thyroid and PTHs in BPH patients. We hypothesize that thyroid and PTHs are altered in BPH and are associated with prostate size. To test this hypothesis the present study was designed to assess the thyroid and PTHs and their association with prostate size in patients with BPH.

The study was conducted at the Department of Biochemistry, in collaboration with the Department of Urology, JIPMER, Puducherry from 2013–2014. This study was approved by Institute Ethics Committee (Human studies). Written informed consent was obtained from all subjects before participation. Forty consecutive BPH patients diagnosed on the basis of clinical findings, per rectal examination, ultra sound findings and confirmed by histopathological findings were included in the study. The results were compared with 40 age matched controls. Controls were recruited from the relatives and friends of the patients and staff working in the hospital. Subjects with prostate cancer, known thyroid and parathyroid disorders, other causes of lower urinary tract symptoms, diabetes, renal disease and inflammatory disorders were excluded from the study. Control subjects with lower urinary tract symptoms were excluded from the study. The International Prostate Symptom Score (IPSS) was calculated based on the answers to seven questions concerning urinary symptoms and one question concerning quality of life. Each question concerning urinary symptoms allows the patient to choose one out of six answers indicating increasing severity of the particular symptom. The answers were assigned points from 0 to 5. The total score ranges from 0 to 35 (asymptomatic to very symptomatic).

Five ml of venous blood samples were collected from the subjects. Serum was separated and used for the estimation of glucose, urea, creatinine, calcium and phosphorus immediately. The remaining sample was stored at –80 °C. Free tri-iodothyronine (FT_3), free tetra-iodothyronine (FT_4), thyroid stimulating hormone (TSH) and PTH were estimated by Chemiluminiscence (Advia Centaur Cp, Erlangen, Germany) using reagent kits from

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Siemens diagnostic Erlangen, Germany. Prostate specific antigen (PSA) was estimated by ELISA using reagent kits from DBC, Canada (Dorchester, Ontario, Canada). Glucose, calcium and phosphates were estimated using reagent kits from Aggappe diagnostics, adapted to an autoanalyzer (Olympus AU 400, Melville, NY, USA)

The sample size was estimated with an expected difference in the PSA levels between BPH and controls (mean difference of 3.3 µg/L, with a standard deviation of 2.9) at the 5% level of significance and 90% power, based on our previous studies.[13] It was calculated as 18 in each group. As we wanted to perform multivariate linear regression analysis (MVLRA), and measure additional molecules, we recruited 40 in each group to ensure adequate power for the study. The normality of the data was tested by Kolmogrov–Smirnov test. The data for the continuous variables were expressed as mean with standard deviation or as median with interquartile range. Independent student '*t*' test or Mann Whitney U test was used to compare the variables between cases and controls. Spearman correlation analysis was used to assess the relation between the parameters and their association with prostate size. Stepwise regression analysis was used to assess the predictors of prostate size in BPH patients. All statistical analyses were carried out for two tailed significance and *P* value <0.05 was considered as significant.

The biochemical parameters, thyroid and PTHs in controls and BPH cases were shown in Table 1. Prostate size, PSA, serum FT3 and FT4 were significantly increased and TSH was significantly reduced in BPH when compared with controls. There was no significant difference in PTH, glucose, urea, creatinine, calcium and phosphorous levels between the two groups. Table 2 shows the correlation of thyroid and PTHs with prostate size. Prostate size was positively correlated with serum FT3, PTH and PSA and negatively correlated with TSH. There was no correlation between prostate size and FT4. A MVLRA was performed to assess FT3, FT4 and TSH as independent predictors of prostate size in BPH cases. This found that FT3 was an independent predictor of prostate size in patients with BPH (Table 3).

Several investigators have documented the role of thyroid hormones in the development of prostate cancer. Lehrer et al. have demonstrated association of recurrence of prostate cancer in patients with high FT3 levels.[7] In addition, it has been shown that men with hypothyroidism are at reduced risk for developing prostate cancer compared to euthyroid men.[14] But to date there are only limited data available regarding thyroid hormone levels in BPH. In the present study, we found significantly increased levels of FT3 and FT4 and reduced levels of TSH in BPH cases when compared with controls. These findings were in accordance with previous study which has reported significantly higher levels of FT3 in BPH when compared with the controls.[9] To test the hypothesis whether thyroid hormones are associated with the severity of BPH, we assessed the association between prostate size and thyroid hormones. FT3 was positively correlated and TSH was negatively correlated with prostate size. There was no significant association between free T4 and prostate size. There was no significant correlation between thyroid hormones and IPSS. A MVLRA found that FT3 was an independent predictor of prostate size in BPH.

These findings indicate that thyroid hormones are associated with the size of the prostate in BPH. Even though the mechanism through which thyroid hormones are associated, BPH is unclear, we speculated that the binding of thyroid hormones to plasma membrane receptor integrin avb3 might activate various pro-carcinogenic pathways, including PI-3 K and MAPK/ERK1/2, thereby increasing cell proliferation and angiogenesis. [15–17]

PTH is known to stimulate the normal prostate growth and promote prostate carcinogenesis,[10,11] but to date there are limited studies about PTH levels in BPH. In the present study there was mild but insignificant elevation in PTH levels in BPH patients compared to controls and PTH was positively correlated with prostate size. These findings are in contrast to a recent study form Korea which failed to find any association between PTH and prostate size.[18] The main limitation of the present

Table 1. General characteristics and biochemical parameters in controls and BPH.

Parameters	Controls (*n* = 40)	BPH cases (*n* = 40)	*P* value
Age (years)	57.3 ± 4.4	59.08 ± 4.6	0.091
Glucose (mmol/L)	5.82 ± 1.32	5.24 ± 1.31	0.055
Urea (mmol/L)	20.31 ± 6.13	23.83 ± 17.76	0.24
Creatinine (µmol/L)	1.20 ± 0.24	1.37 ± 0.97	0.282
Calcium (mmol/L)	2.17 ± 0.36	2.21 ± 0.23	0.573
Phosphates (mmol/L)	1.18 ± 0.30	1.24 ± 0.23	0.324
Serum PSA (µg/L)	0.85 (0.47 – 3.86)	2.56 (0.62 – 41.6)	<0.001
IPSS score		14.0 ± 5.37	NA
Prostate size (cm^3)	18 (12 – 22)	45.5 (23 – 116)	<0.001
Serum FT3 (ng/L)	2.72 (1.75 – 3.59)	3.14 (1.64 – 3.88)	0.001
Serum FT4 (ng/dl)	1.08 (0.77 – 1.67)	1.33 (0.57 – 1.78)	0.005
Serum TSH (mIU/L)	2.12 (0.2 – 17.2)	1.19 (0.15 – 5.02)	0.010
Serum PTH (ng/L)	22.7 (3.6 – 52.3)	45.5 (9.8 – 88.8)	0.356

Note. Data presented as mean and standard deviation or as median with interquartile range.

Table 2. Correlation of prostate size with thyroid and PTHs, IPSS and PSA in patients with BPH ($n = 40$).

Parameters	r	P
Serum FT3	0.341	0.031
Serum FT4	0.079	0.628
Serum TSH	–0.431	0.005
Serum PTH	0.353	0.026
PSA	0.532	0.001
IPSS Score	0.348	0.028

Table 3. MVLRA to show the predictors of prostate size in BPH.

Model	Adjusted R^2	β	P value
FT3	0.16	0.350	0.027
FT4		0.029	0.846

study was small sample size which precludes other analyses. Furthermore, our data do not reveal whether alterations in thyroid hormones are the cause or consequence of BPH.

This work represents an advance in biomedical science because it shows that elevated free T3 and reduced TSH may play a role in the development of BPH.

Disclosure statement

No potential conflict of interest was reported by the authors.

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