Prostatic Fluid Free Insulin-Like Growth Factor-1 in Relation to Benign Prostatic Hyperplasia: A Controlled Study

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Purpose: Insulin-like growth factors (IGFs) have potent mitogenic and antiapoptotic effects on prostate tissue, whereas free IGF-1 is responsible for its metabolic effects but its role in benign prostatic hyperplasia (BPH) is unclear.

Material and Methods: Plasma and prostatic fluid levels of free IGF-I were determined from the fasting bloods of 35 BPH cases admitted for treatment and 35 randomly selected population controls.

Results: Prostatic fluid free IGF-1 concentrations did not differed significantly between two groups ($P = .23$). There was also no statistical difference in serum free IGF-1 levels between these groups. There was also no correlation between prostatic fluid free IGF-1 and serum prostate specific antigen (PSA) levels and prostate volume. When compared with control group, mean IPSS scores and prostate volumes of BPH group were significantly high, while mean maximum measured flow rate (Qmax) and international prostate symptom score (IPSS) and quality of life (QoL) scores were significantly low ($P < .05$).

Conclusion: Our study shows that free IGF-I is not associated with BPH risk. Further investigation is needed to elucidate the role of the free IGF-1 in BPH.

Keywords: prostatic hyperplasia; insulin-like growth factor; risk; humans; signal transduction.

INTRODUCTION

It has been suggested that insulin-like growth factor-1 (IGF-1) play a role in maintaining the replication of prostatic epithelial cells, and inhibits apoptosis.[1,2] In the circulation, 99% of IGF-1 is found in binding complexes.[3] However, a small, but important proportion (< 5%) of IGF-1 (free IGF-1) is not associated with IGF binding proteins[4-7] reported that free IGF-1 represented the biologically active fraction of IGF-1.

Insulin-like growth factor I (IGF-I) is the peptide functioning as both endocrine hormones and tissue growth factors.[8] The role of the IGF axis in benign prostatic hyperplasia (BPH) is suggested by studies showing that expression of IGF1 receptor is not only higher in periurethral than in intermediate and subcapsular regions of BPH tissue[9] but also higher in BPH cells than in normal or cancer cells.[10] In addition, in a recent study, men with BPH and increased levels of IGF-I and growth hormone (GH) due to acromegaly regained normal prostate volumes when they achieved GH/IGF-I control.[11]

Since this growth factor act primarily through autocrine and paracrine processes, circulating levels are not likely to serve as useful biomarkers. Prostatic fluid (PF) produced by prostatic epithelium provides a reliable reflection of the metabolic status of the prostate, and can be obtained repeatedly from most men by transrectal massage.[12] Prostatic fluid provides a unique medium for noninvasive evaluation of critical growth and differentiation signals in the prostatic microenvironment. Thus we investigated the patients with BPH to determine in quantity of biologically active free IGF-1 in PF and to compare it in patients with BPH and in control patients with no BPH.

MATERIAL AND METHODS

A total of 35 patients, who have been admitted to our outpatient clinic between May-2008 and May-2009 with lower urinary tract symptoms (LUTS) and considered to be BPH, were included to our study (Group-A). Patients with diabetes mellitus, prostate cancer, neurologic disease, previous operation due to infravesical obstruction and patients using drugs which affect lower urinary system functions were excluded from study.

The control group (group-B) was consisted of patients who were admitted to our outpatient clinic with some other urological problems (urolithiasis, hydrocele, etc.) except LUTS. All patients were selected prospectively. For all patients, after giving detailed information, written approvals were obtained. Detailed histories were taken from all the patients. The patients with diabetes, a prostate operation history and endocrinologic pathology (Acromegaly, Growth hormone deficiency, etc.) which can influence IGF-1 level were not included in the study. LUTS of each patient were scored by international prostate symptom score (IPSS). All patients were performed rectal examination and biochemical, hematological and urine analysis. Also serum total and free-PSA levels were determined. PSA levels above 4.0 ng/mL were considered as "high". All patients were evaluated with transrectal ultrasonography (TRUS) to detect prostatic volume and to perform prostatic needle biopsy, if necessary. As to calculate prostatic volume, ellipsoid formula was used (Ellipsoid formula: transverse diameter × anteroposterior diameter × cephalocaudal diameter × 0.52).

Expressed prostatic fluid samples, following digital massage of the prostate, obtained from 35 patients with BPH (group A) and an equal number of male controls were examined microscopically for cellular elements, sperm, and seminal vesicle globules. Two PF samples of at least 30 µL each were obtained on separate visits within 7 days. Uncontaminated PF samples were immediately placed in a refrigerator freezer and transported on ice to a –20 oC freezer within 4 hr. The mean prostatic fluid volume was approximately 64 µL. Prostatic fluid was diluted in a saline-Tris-BSA buffer (1/10, v/v) as provided in the kit for free IGF-1 (Diagnostic Systems Laboratories Inc, Free IGF-1 DSL-9400, Webster, Texas, USA). Free IGF-1 level in PF was measured in duplicated Direct Assay Immunoradiometric (IRMA) method which was described by Miles and colleagues.[13] The IRMA is a non-competitive assay in which the analytic to be measured is "sandwiched" between two antibodies. The first antibody is immobilized to the inside walls of the tubes. The other antibody is radiolabelled for detection. For the Direct Assay, the diluted sample was added directly to the assay tube. Unbound and readily dissociable IGF-1 was then captured by the antibody coating, the remaining sample was washed away, and the IGF-1 bound to the tube was then detected

Table 1. Age, free IGF-1 and PSA levels in distinguishing patients with benign prostatic hyperplasia (Group A) from those without (Group B).

Variable*	Group A (n = 35)	Group B (n = 35)	*P*
Age (years)	69.9 ± 1.18	62.7 ± 2.41	.12
Serum Free IGF-1 (nmol/L)	33.8 ± 2.6	31.4 ± 2.6	.21
Prostatic fluid free IGF-1(µg/L)	1.43 ± 0.02	1.38 ± 0.02	.23
Serum PSA (ng/mL)	3.8 ± 0.23	1.74 ± 0.14	.71

Key: IGF, insulin-like growth factor; PSA, prostate specific antigen;
* Variables are presented as mean ± standard error of measurement.

Table 2. The statistical correlation between QoL, IPSS, peak urine flow rate, and prostate volume through TRUS, in group A and group B.

Variable*	Group A (n = 35)	Group B (n = 35)	*P*
Prostate Volume (mL)	44 ± 2.4	22 ± 1.6	.034
Maximum Flow (mL/s)	13.0 ± 4.6	20.0 ± 5.4	.041
IPSS total	20.0 ± 1.7	12.6 ± 4.3	.041
IPSS QoL	1.5 ± 0.7	3.2 ± 0.4	.024

Key: QoL, quality of life; IPSS, international prostate symptom score; TRUS, transrectal ultrasonography.
* Variables are presented as mean ± standard error of measurement.

using a radiolabelled antibody directed to a second epitope. The absolute sensitivity of the assay used were 0.1 ng/mL for free IGF-1 and the usual amounts used for assay were 5 µl of prostatic fluid. Serum free IGF-1 immunoradioactivity was also measured by using duplicated IRMA method. The results were expressed as ng/mL.

Data were analyzed by using the Statistical Package for Social Sciences (SPSS). Pearson correlation analysis and Student's t test were used for statistical assessment and considered significant at $P < .05$.

RESULTS

The mean age of patients with BPH was 69.9 ± 1.18 standard error of measurement (SEM) and was 62.7 ± 2.41 SEM years in those without. The mean total PSA value in patients with BPH were significantly higher in those without BPH but free IGF-1 levels in PF and serum free IGF-1 contents were similar in both groups (Table 1). When compared with control group, mean IPSS scores and prostate volumes of BPH group were significantly high, while mean Qmax, IPSS, and QoL scores were significantly low ($P < .05$) (Table 2). The mean prostatic fluid free IGF-1 level was not correlated with serum PSA level (r = 0.11, P = .4). The mean prostate volume was also not correlated with free IGF-1 level ($r = 0.15$, $P = .15$).

DISCUSSION

Peptide growth factors such as IGF-1 and IGF-2 appear to be potent signaling factors for modulating the growth and differentiation of prostate cells and the growth of normal and malignant prostate cells in culture is dependent on the presence of IGF-1 and 2.[14] They are usually bound to an IGF-binding proteins which are found abundantly in prostate cells.[1,14] There are two types of receptors for the IGFs and the majority of the mitogenic effects of the IGFs appear to be mediated via the type 1 IGF receptor.[1,15] IGF-1 receptors are very sensitive to stimulation by IGFs.[16]

Involvement of the IGF axis in BPH etiology is biologically plausible. Prostate cells express IGFs, insulin-like growth factor binding proteins (IGFBPs), and the type I IGF receptor,[17] and prostate cell growth is stimulated by IGFs and inhibited by IGFBPs.[16,18-20] Furthermore, men with acromegaly induced GH/IGF-I hypersecretion have enlarged prostates, and among acromegalic men with BPH, prostate size and IGF-I levels were shown to return to normal after treatment.[11] A recent epidemiologic study among Scandinavian men revealed a nonsignificant upward trend in BPH risk associated with increasing circulating IGF-I (*P* trend¼ .10).[21] However, a study in Greek men found no association of IGF-I levels with BPH.[22] All these studies were concerned with the plasma levels of IGF-1. In this population-based study done in Turkey, the prostatic fluid levels of free IGF-1, which is biologically active form of IGF-1, were not associated with a significantly increased risk of BPH.[12] The prostatic levels of IGF-1 are better indicator than the plasma levels. They reflect the intraprostatic statement of IGF-1. It has been also showed that many different factors e.g. smoking, during waking hours, fasting, can alter circulating concentrations of IGF-1.[23,24,25] Thus, it is possible that circulating levels of IGF-1 may be influenced by various factors. In our study, we determined free IGF-1 levels in the prostatic fluid

which is responsible for the biological function of the IGF-1. The prostatic fluid levels of free IGF-1 were not significantly associated with increased risk of BPH. This is the first report showing the expression of free IGF-1 in prostatic fluids of BPH patients. However, larger prospective studies are needed to confirm our findings for free IGF-1 and BPH risk.

CONCLUSION

Our results showed that free IGF-1 can be accurately measured in prostatic fluid by radio immunoassay. Its levels were detectable in serum and PF samples. The mean prostate volume was not correlated with free IGF-1 level. The findings currently reveal the prostatic fluid level of this marker is not differed in patients with BPH in comparison to non-BPH individuals. The mean prostate volume was not correlated with free IGF-1 level.

CONFLICT OF INTEREST

None declared.

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