Original article:

Association between Insulin Resistance and Benign Prostatic Hyperplasia

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Abstract:

Introduction: Benign prostatic hyperplasia (BPH) is the most common benign disease in older men characterized by stromal and epithelial cell hyperplasia. Insulin is an independent risk factor and a promoter of BPH. Insulin resistance may change the risk of BPH through several biological pathways. **Aim and objective:** Aim of our study is to estimate the insulin resistance and prostatic specific antigen level in the patients suffering from benign prostatic hyperplasia and compare them with the control. **Materials and Methods :** Hospital based cross sectional case control study. 40 BPH-patients (aged above 50 years), clinically diagnosed and supported by serum PSA and USG findings were selected as case. **Results:** Insulin resistance was found to be elevated in the patients suffering from BPH. HOMA-IR score of cases was compared with the controls and found to be significantly elevated. A significant increase in fasting glucose level and PSA level were found in cases compared to controls. **Conclusion:** The insulin resistance was found to be significantly higher in patients. Further study regarding the relationships between metabolic syndrome and benign prostate diseases, including its underlying mechanisms is necessary.

Keywords: Benign prostatic hyperplasia, insulin resistance.

*International Journal of Human and Health Sciences Vol. 05 No. 02 April'21 Page : 240-245
DOI: <http://dx.doi.org/10.31344/ijhhs.v5i2.267>*

Introduction:

Benign prostatic hyperplasia (BPH) is that the commonest benign disease in older men. Autopsy studies have revealed histologic evidence of BPH in 42% of men aged 51–60 yr., rising to 85% among men older than 80 yr.¹. Severe BPH results in deterioration within the quality of lifetime of afflicted men, and its treatment associate with economic burden². Within the future as aging population is increase in most societies, it's inevitable that this disorder will become even more prevalent and a serious challenge for all health care facility³.

BPH may be a specific histopathologic entity characterized by stromal and somatic cell hyperplasia. Benign prostatic hyperplasia (BPH) is additionally characterized by the non-malignant overgrowth of prostatic tissue surrounding the urethra, ultimately constricting the urethral opening and giving rise to associated lower tract symptoms (LUTS) like urgency, frequency,

nocturia, incomplete bladder emptying, and weak urine stream serious complications can be occur in men with BPH, including acute retentiveness (AUR), insufficiency and failure, tract infection, and bladder stones⁴.

The exact etiology of BPH isn't known; however, the similarity between BPH and therefore the embryonic morphogenesis of the prostate has led to the hypothesis that BPH may result from a "reawakening" of embryonic induction processes in adulthood⁵. For over a century, there are two known etiologic factors for the pathogenesis of BPH: aging and testicular androgens⁴. Moreover case history, race/ethnicity, hypertension, type II diabetes, obesity, body height, cigarette smoking, low HDL-C, and high insulin levels were reported to be risk factors for the event of BPH.⁶⁻⁹ The main disorders in metabolic syndrome, which was characterized with insulin resistance and hyperinsulinemia, are localized in muscle, fat tissues, and therefore the liver¹⁰. The components

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of this syndrome are type II DM, hypertension, obesity, and dyslipidemia¹¹. These components are proposed as risk factors for the event of BPH; therefore, it's thought that metabolic syndrome may play a task in BPH etiology.

The major endocrine aberration in reference to the metabolic syndrome is hyperinsulinemia. Insulin is an independent risk factor and a promoter of BPH. Insulin resistance may change the danger of BPH through several biological pathways. Hyperinsulinemia stimulates the liver to supply more insulin-like protein (IGF), another mitogen and an anti-apoptotic agent which binds insulin receptor/IGF receptor and stimulates prostate growth. The amount of IGFs and IGF binding proteins (IGFBPs) in prostate tissue and in blood are related to BPH risk, with the regulation of circulating androgen and somatotropin. Stromal-epithelial interactions play a critical role within the development and growth of the prostate and BPH¹². Prior studies have demonstrated the connection between BPH and insulin-resistance syndrome. During insulin-resistance, hyperinsulinemia develops to combat the decreased responsiveness of the body towards insulin. Although, the compensatory hyperinsulinemia prevents development of fasting hyperglycemia in insulin-resistant individuals, the increased level of circulating insulin directly and/or indirectly affects different molecular signaling and may promote prostatic growth. Insulin-resistance syndrome includes group of disorders, like obesity, dyslipidemia, sympathetic overactivity, hyperinsulinemia and every individually reported as risk factor for the event of BPH¹³. Insulin-resistance associated secondary rise in insulin can stimulate prostatic growth through a) insulin-receptor mediated growth promoting effect and/or b) by augmenting the insulin like growth factor-1 receptor signaling. Recently, it's been reported that insulin/insulin like protein signaling activates androgen signaling through direct interaction of the Foxo-1 with the androgen receptor¹⁴. The hyperinsulinemia also can affect prostatic growth by affecting the androgen signaling within the prostate, which can involve i) increase within the androgen synthesis, ii) decrease within the expression of sex-hormone binding globulin, and iii) decrease within the inhibition of androgen signaling through direct interaction of Foxo-1 with the androgen receptors. Further, insulin can increase the conversion of testosterone into dihydrotestosterone, which has long been

acknowledged because the major controller of prostatic growth. Supported the experimental and epidemiological evidences, hyperinsulinemia can play an important role in prostatic enlargement. The compensatory hyperinsulinemia might end in the over-activation of insulin signaling, to which different organs might show differential response either in nature and/or degree. In vasculature, over-activation of insulin signaling leads to the increased expression of the adhesion molecules, leading to the upper risk for hypertension and atherosclerotic plaque^{15,16}.

Aim of our study is to estimate the insulin resistance and prostatic specific antigen level within the patients affected by benign prostatic hyperplasia and compare them with the control.

Materials and Methods:

Our study was performed in Burdwan Medical College, Burdwan. Patients suffering from BPH Attending Outpatient Department of Burdwan Medical College and admitted for surgery in the surgical ward.

Sample:

(a) Case 40 BPH-patients (aged above 50 years), clinically diagnosed and supported by serum PSA and USG findings

(b) Control 40 Age matched normal subjects

Inclusion criteria: BPH patients with lower urinary tract symptoms (LUTS) and aged above 50 yr. who were seen in the outpatient clinic.

Exclusion criteria: Patients with a previous history of prostate or urethral surgery, medical treatment for BPH, diagnosed cases of prostate cancer and drastic change in body weight of more than 10 kg in the previous 6months, as well as diabetic patients using metformin or insulin, were excluded from the study.

Study Design: Hospital based cross sectional case control study.

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional) and with the Helsinki Declaration of 1964, as revised in 2013.

Parameters to be studied:

Estimation of fasting blood glucose: Quantitative estimation of blood glucose was done by Glucose oxidase / Peroxidase method¹⁷ from the separated plasma by using the autoanalyzer ERBA XL 600. Internal quality control was performed simultaneously. All test reagents were purchased from Ranbaxy RFCL, India and the quality control materials (Lyphochek, level 1 and 2) were

purchased from Bio-Rad laboratories, USA.

Insulin:¹⁸⁻²⁰ In a quantitative enzyme immunoassay, high affinity antibodies react with antigen to form an insoluble sandwich complex on the surface of a coated microplate. The antigen from the specimen gets sandwiched between the reactive IgG coated on the well and affinity purified antigen specific IgG conjugated with an enzyme. The unbound IgG is washed away by a washing step. The enzyme activity which is directly proportional to antigen concentration is measured by addition of the substrate. By utilizing calibrators of known antigen value, a dose response curve can be generated from which the antigen concentration in the sample can be found out.

Homeostatic model assessments (HOMA) of steady state β cell function (% β), insulin sensitivity (% S) and insulin resistance (HOMA IR) were calculated as percentages of a normal reference population of young people without diabetes mellitus. As a widely validated clinical and epidemiological tool for estimating insulin resistance and β cell function, the homeostasis model assessment (HOMA) is derived from a mathematical assessment of the balance between hepatic glucose output and insulin secretion from fasting levels of glucose and insulin^{21, 22}. This model requires only a single measurement of insulin and glucose in the basal state and so, in some conditions, is a suitable alternative for large-scale epidemiologic studies to the sophisticated -gold standard methods which usually require dynamic data via costly and invasive procedures. HOMA IR is computed with the formula: fasting plasma glucose (mmol/l) times fasting serum insulin (μ IU/l) divided by 22.5²³. The HOMA of β cell function (HOMA % β) index, is computed as the product of 20 and basal insulin levels divided by the value of basal glucose concentrations minus 3.5²⁴.

The HOMA indices in our present study were calculated with the help of HOMA2 Calculator v2.2 obtained from the website <http://www.dtu.ox.ac.uk/homa>.

Results:

The data obtained from the above tests were analyzed for difference between means and standard deviation. Independence t-test was used to determine whether differences between means and standard deviation were significant, with $p < 0.05$ taken as the significance level. All statistical analysis was carried out using SPSS software.

Insulin resistance was found to be elevated in the patients suffering from BPH. HOMA-IR score of cases was compared with the controls and found to be significantly elevated (Table 1 and Figure 1).

Table 1. The comparison of the HOMA-IR value of the cases and controls.

SUBJECT	N	Mean	Std. Deviation	Std. Error of Mean	'p' value
CASES	40	3.93	1.27	0.2006	<0.0001
CONTROLS	40	0.8	0.45	0.07089

Figure 1: Composite bar diagram showing the mean and standard deviation (S.D.) of the HOMA-IR value of cases and controls in the study population.

PSA level (Table 2 and Figure 2) and fasting glucose level (Table 3 and Figure 3) of cases were compared with those of controls. A significant increase in fasting glucose level and PSA level were found in cases compared to controls.

Table 2. The comparison of the PSA level of the cases and controls.

SUBJECT	N	Mean	Std. Deviation	Std. Error of Mean	'p' value
CASES	40	4.4337	2.1244	0.3359	<0.0001
CONTROLS	40	2.0155	0.9829	0.1554	

Table 3. The comparison of the fasting glucose value of the cases and controls.

SUBJECT	N	Mean	Std. Deviation	Std. Error of Mean	'p' value
CASES	40	117.48	23.08	3.6488	0.0254
CONTROLS	40	104.53	27.56	4.3577

Figure 2: Composite bar diagram showing the mean and standard deviation (S.D.) of the PSA level of cases and controls in the study population.

Figure 3: Composite bar diagram showing the mean and standard deviation (S.D.) of the fasting glucose value of cases and controls in the study population.

Discussion:

Metabolic syndrome may be a constellation of multiple metabolic and disorder risk factors, at the middle of which is insulin resistance (a state during which muscle, liver, and fat tissues have reduced sensitivity to insulin) and compensatory hyperinsulinemia. It's been reported a robust influence aged on the presence of metabolic syndrome, which affected 43.5% of these aged 60–69 yr²⁷. Similarly, BPH is seen frequently in males older than 50 yr and in 50% of males aged 60–70 yr with LUTS; 25% of the latter need surgical treatment²⁸. Despite the magnitude of the general public health impact of BPH, little is understood about its etiology²⁹. Recent studies suggest that hyperinsulinemia secondary to insulin resistance and therefore the components of metabolic syndrome are risk factors for BPH development^{30–33}. Furthermore, metabolic syndrome may play a task in BPH etiopathogenesis within the published literature. Hammarsten et al.³⁴ is that the first author to gauge the connection between metabolic

syndrome and BPH. In their study, annual TPrate of growth was significantly higher in BPH patients with metabolic syndrome versus BPH patients without metabolic syndrome (1.019 ml/yr vs 0.699 ml/yr, respectively). They also obtained similar leads to further studies^{35,36}. Insulin resistance and secondary hyperinsulinemia are important etiologic links between metabolic syndrome and increased BPH risk within the study conducted by Dahle et al.³⁰, increased serum insulin level was associated with increased BPH risk. In another study³¹, 138 patients with high insulin levels (9 μ IU/ml) were compared with 142 patients with normal insulin levels (<9 μ IU/ml); the median annual prostatic growth rate was significantly higher in hyperinsulinemic patients (1.16 ml/yr vs 0.93 ml/yr, respectively).

Similarly, in the present study, insulin resistance was found to be elevated in the patients suffering from BPH. HOMA-IR score of cases was compared with the controls and found to be significantly elevated (Table 1 and Figure 1). In a study by Kim et al., it has been found that prostate size correlates positively with age, PSA and fasting glucose level³⁷. In this study, PSA level and fasting glucose level of cases were also compared with those of controls. A significant increase in fasting glucose level and PSA level were found in cases compared to controls (Table 2, Figure 2 and Table 3, Figure 3).

Recent evidence suggests that BPH may be the tip of iceberg and submerged underneath water as the insulin resistance. The insulin level is interesting as a prognostic risk factor, because it is modifiable through lifestyle, nutritional and pharmaceutical interventions. Assuming a causative role of hyperinsulinemia in the development of BPH, an insulin lowering programme might slow down prostate growth. If this assumption is true, lifestyle modification factors or the use of medications lowering insulin levels and restoring insulin sensitivity might be an effective preventive and therapeutic measure, reducing the need for surgical therapy. Further studies are needed to define the pathophysiological mechanism connecting these two entities.

Conclusion:

The present study was started with the aim to assess insulin resistance among the patients, suffering

from Benign Prostatic Hyperplasia (BPH). For this, blood was collected from patients suffering from BPH and healthy controls after fulfilling the inclusion and exclusion criteria. Fasting serum insulin by ELISA method and plasma glucose by GOD/POD method were measured to obtain insulin resistance by HOMA method. It was observed that increased insulin resistance was present among the patients suffering from BPH. The insulin resistance was found to be significantly higher in patients. In addition, a significant increase in fasting glucose level and PSA level were found in cases compared to controls.

This work thus, reiterates a need for future investigations regarding the different genetic and environmental basis responsible for development

of BPH and insulin resistance in different population groups. Further study regarding the relationships between metabolic syndrome and benign prostate diseases, including its underlying mechanisms is necessary.

Conflict of interest: None declared.

Funding statement: No funding.

Ethical approval issue: The study was approved by the ethical comity of Burdwan Medical College, Burdwan, West Bengal, India.

Authors' contribution: Data gathering and idea owner of this study: AS; Study design: ID, AS, SS; Data gathering: AS; Writing and submitting manuscript: ID, AS, SS; Editing and approval of final draft: ID, AS, SS.

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