Insulin resistance and hyperinsulinemia in non-diabetic non-obese benign prostatic hyperplasia patients.

Mohammed Mohsin Abdul-Aziz,*
*Nehad Nejris Helal***
**Dept. of Surgery, College of Medicine, Tikrit University*
*** Dept. of Pathology, College of Medicine, Tikrit University.*

Abstract

Benign Prostatic Hyperplasia (PBH) is the most common benign tumor in men, and its incidence is age related. Despite intense research efforts in the past five decades to elucidate the underlying etiology of prostatic growth in older men, cause and effect relationships have not been established. Insulin is a growth-stimulating hormone. Previous studies have reported the association between hyperinsulinemia and BPH in patients with metabolic disorders like diabetes. To assess insulin level and insulin resistance in non-diabetic non-obese BPH cases and correlated them with prostate size. 35 symptomatic BPH cases and 30 controls were included in this study. Fasting serum insulin concentrations were measured by enzyme-linked immunosorbent assay (ELISA). Insulin resistance was assessed by homeostatic model assessment (HOMA). Fasting glucose was quantified by glucose oxidase method. PSA was calculated by ELISA. Prostatic size was measured by ultrasonography. Fasting serum insulin and HOMA were significantly higher in BPH cases as compared to controls (P value < 0.01 and < 0.001 respectively). Hyperinsulinemia and accompanying insulin resistance were found to be risk factors of increased prostatic size, (P value < 0.001). Hyperinsulinemia associated with insulin resistance are risk factors of increased prostatic size**.**

Keywords: Benign prostatic hyperplasia; Insulin resistance; Hyperinsulinemia.

Introduction

Benign Prostatic Hyperplasia (PBH) is the most common benign tumor in men, and its incidence is age related. The prevalence of histologic BPH in autopsy studies rises from approximately 20% in men aged 41-50 years, to 50 % in men aged 51-60, and to > 90% in men older than 80. Risk factors for the development of BPH are poorly understood.[1] Previous studies have implicated the role of genetic [2], nutritional [3], immunological [4], and endocrine factors in their etiology. Among endocrine factors, the role of hormones like androgen [5], estrogen [6], growth hormone [7], prolactin [8], and growth factors like insulin-like growth factors [9], fibroblast growth factors [10], and transforming growth factors [11] have already been established.

The insulin-like growth factors (IGFs) are two protein growth factors, IGF1 and IGF2, related in sequence to insulin. These growth factors interact with two different types of receptors, type 1 and type 2. It was pointed out that there are aberration in the IGF associated with BPH including an increase in transcription of IGF, increased levels of the type 1 receptors, and an altered pattern of protease expression in the BPH stromal cells. [12]

Insulin is a growth-stimulating hormone [13]. In vitro experiments have demonstrated that there is a real need of insulin for prostatic growth [14]. Also insulin receptors have been identified on epithelial cells of prostate [15].

High serum concentration of insulin is associated with insulin resistance [13]. Among various tools to evaluate insulin resistance, homeostatic model assessment (HOMA) has been widely employed in clinical research [16, 17].

The relation between BPH and hyperinsulinemia has been reported in patients with metabolic disorders like diabetes and obesity [18]. But there is no report in Iraq – to our knowledge – that establish the relationship between BPH and insulin concentration and insulin resistance in non-diabetic non-obese BPH patients.

In this present study, serum insulin concentration and insulin resistance were evaluated in non-diabetic non-obese BPH patients and their association with prostatic size.

Patients and Methods

Thirty-five consecutive symptomatic newly diagnosed cases of BPH and thirty healthy controls with similar age group, who did not have lower urinary tract symptoms and their prostatic size and prostatic specific antigen (PSA) were < 25 g and < 4 μg/L, respectively, were included in this study. The study was conducted during the period form the 1st of February 2008 to the end of August 2008 in Tikrit city in Iraq.

The exclusion criteria were diabetes mellitus (Fasting serum glucose > 6.4 mmol/L), obesity (Body Mass Index (BMI) > 30), and those who were on drug that affect insulin metabolism. Patient who had serum PSA more than 4 μg/L, nodularity, or induration during digital rectal examination were subjected to prostatic biopsy to exclude prostatic carcinoma. Patients on BPH medical therapy also excluded from the study.

Prostatic size was measured by ultrasonography. PSA was quantified by ELISA (Microwell, Syntron Bioresearch). Fasting Insulin concentration was measured by ELISA (Diagnostic Automation). Fasting serum glucose was calculated by glucose oxidase method (Biocon Diagnostic). Insulin resistance was assessed by HOMA using the formula [19]:

HOMA= [fasting insulin(μU/ml) x fasting glucose(mmol/L)] / 22.5

Patients were considered as having insulin resistance when HOMA $\geq$ 2.6 [16, 20].

All variables were presented as mean values $\pm$ SD. Statistical analysis was performed with student's t test and ANOVA test as appropriate. Cox proportional hazard regression module was used to determine the risk factors of increased prostatic size. A P value of less than 0.05 was considered significant. Analysis was performed SPSS software, version 9.0 for windows (SPSS, Chicago, Illinois, USA).

Results

Table (1) shows mean and standard deviation of age, BMI, prostatic size and PSA level parameters in symptomatic BPH patients and controls. There was no statistical difference between the two groups regarding age and BMI (P value 0.24 and 0.37 respectively). Mean prostatic size was 43.57 g in BPH group and 18.8 g in control, with a mean PSA of 3.8 μg/L in BPH group and 1.5 μg/L in control group. BPH group had significantly higher prostatic size (P value < 0.001) and higher PSA level (P value < 0.001) compared to control group.

Table (2) shows mean and standard deviation of fasting serum glucose, fasting serum insulin, and HOMA parameters in BPH and control groups. No statistical difference observed between the two groups regarding fasting serum glucose (P value = 0.143).Mean fasting serum insulin was significantly higher in BPH group (11.8 μU/ml) compared to control (6.3 μU/ml), (P value < 0.01). Insulin resistance measured by mean HOMA was also significantly higher in BPH group (2.87) compared to (1.32) in control, (P value < 0.001).

When applying univariate analysis using Cox proportional hazard regression module, elevated fasting serum insulin and insulin resistance were found to be risk factors of increased prostatic size, (P value < 0.001).

Discussion

It is well known that benign prostatic hyperplasia is a pathologic process that contributes to, but is not the sole cause of, lower urinary tract symptoms in aging men. Despite intense research efforts in the past five decades to elucidate the underlying etiology of prostatic growth in older men, cause and effect relationships have not been established [21].

The data in this present study suggest that non-diabetic and non-obese patients with symptomatic BPH had significantly higher serum insulin level with insulin resistance compared to the healthy controls. The markedly raised insulin level in BPH patients can be attributed to the development of insulin resistance in those

patients, and insulin resistance can lead to secondary hyperinsulinemia.

A variety of mechanisms were instituted to explain the effect of insulin on prostatic growth. Insulin is claimed to be involved in pathogenesis of BPH through its action on sympathetic nervous system, sex hormones and IGF axis. It has been shown that insulin has a stimulating effect on the ventromedial hypothalamic nucleus that regulates the sympathetic nervous system [22]. Also hyperinsulinemia increases sympathetic nerve activity through its excitatory effect that enhances plasma catecholamine concentration [23]. Hammarsten and Hogstedt in 2001 stated that catecholamine might have a positive effect on prostatic cells growth by slowing down the apoptotic process, suggesting a link between hyperinsulinemia and BPH development [24], such a link has been established in this present study as hyperinsulinemia was found to be a risk factor for increased prostatic size.

Haffiner in 2000 proposed that insulin can induce BPH through its action on sex hormones by augmenting transcription of genes involved in hormones metabolism [25]. Hyperinsulinemia is associated with reduction of sex hormone binding globulin, which increases the amount of androgen entering the prostatic cells resulting in BPH [26].

Insulin can causes BPH via IGF axis. IGF1 has been shown to regulate prostatic epithelial growth [27]. Stattin et al in 2001 reported that IGF was linked with an increased risk of BPH development [9], given that insulin receptors share homology with IGF receptors, the insulin binding to it will activate the IGF signaling pathway and stimulate prostatic growth [27].

Carmena et al in 1986 identified that prostatic cells have insulin receptors [15]. Insulin can directly mediate its growth enhancing effect on prostatic cells by signal transduction mechanism. Insulin binds to its tyrosine kinase activity receptors on prostatic cells and encourages adenylcyclase to produce cyclic AMP [28].
Pretseva et al in 2003 found that cyclic AMP provokes mitogenic and anti-apoptotic activity in prostatic cells [29].

From the results of this study, insulin resistance and hyperinsulinemia were found to be risk factors of BPH development in non-diabetic and non-obese patients, such findings can be explained by the established growth enhancing activity of insulin on prostatic cells [23-30]. While an obvious relation has been documented between hyperinsulinemia and prostatic size in BPH patients, it is not easy to predict a direct cause and effect relationship between them. A prospective study with large number of non-diabetic BPH patients with sequential measurement of prostatic size and insulin level can appraise the direct relationship between BPH development and hyperinsulinemia.

From the present results of this study, it can be concluded that insulin resistance and hyperinsulinemia is significantly evident in non-diabetic non-obese BPH patients. Moreover insulin resistance and hyperinsulinemia were instituted to be risk factors of increase prostatic size and BPH development. Although an obvious relation has been documented between hyperinsulinemia and prostatic size in BPH patients, it is not easy to predict a direct cause and effect relationship between them due to the limited number of patients included in this study.

The present study recommend further studies involving large number of non-diabetic non-obese BPH patients with serial measurements of prostatic size and insulin level to ascertain a cause and effect relationship between insulin and pathogenesis of BPH.

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Table (1) Mean and standard deviation of age, BMI, prostatic size, and PSA parameters in BPH patients and controls.

Parameters	**BPH (n=35)**	**Control (n=30)**	**P value**	**Cut-off value**
Age (years)	63.12 ± 4.1	65.8 ± 3.8	0.24	
BMI	26.74 ± 2.1	25.83 ± 1.9	0.37	< 30
Prostatic Size (g)	43.57 ± 15.6	18.8 ± 4.5	<0.001*	< 25
PSA (µg/L)	3.8 ± 0.7	1.5 ± 1.2	<0.001*	< 4

Table (2) Mean and standard deviation of fasting serum glucose, fasting serum insulin, and HOMA parameters in BPH patients and controls.

Parameters	**BPH (n=35)**	**Control (n=30)**	**P value**	**Reference interval/ Cut-off value**
Fasting Serum Glucose (mmol/L)	5.2 ± 0.7	4.9 ± 0.63	0.143	< 6.4
Fasting Serum Insulin (µU/ml)	11.8 ± 1.6	6.3 ± 0.4	<0.01*	0.7 - 9
HOMA	2.87 ± 0.19	1.32 ± 0.15	<0.001*	< 2.6