European Review for Medical and Pharmacological Sciences 2018; 22: 5077-5081

Correlations of glucose metabolism, insulin resistance and inflammatory factors with symptom score of patients with benign prostatic hyperplasia

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Abstract. – OBJECTIVE: To investigate the effects of glucose metabolism, insulin resistance, and inflammatory factors on International Prostatic Symptom Score (IPSS) of patients with benign prostatic hyperplasia (BPH), to explore their correlations and evaluate the clinical significance.

PATIENTS AND METHODS: 90 patients with BPH were selected and divided into normal blood glucose group and abnormal blood glucose group. The changes of indexes related to prostate function, prostate volume (PV), prostate-specific antigen (PSA), and IPSS in two groups were evaluated. The fasting blood glucose (FBS), fasting insulin (FINS), homeostasis model assessment of insulin resistance (HOMA-IR) index and inflammatory factors interleukin-8 (IL-8) and cyclooxygenase 2 (COX-2) levels in expressed prostatic secretion (EPS) were compared. The correlations of glucose metabolism, insulin resistance and inflammatory factors with IPSS were analyzed by Logistic regression. The changes of these indexes after treatment of BPH were observed.

RESULTS: The FBS, FINS, HOMA-IR, and inflammatory factors IL-8 and COX-2 levels were significantly different between high IPSS group and low IPSS group of patients with BPH. Moreover, the PV and PSA were higher in high IPSS group than those in low IPSS group. The FBS, FINS and inflammatory factors IL-8 and COX-2 levels were positively correlated with IPSS ($p<0.05$). All the indexes above of BPH patients were decreased after treatment.

CONCLUSIONS: The FBS, FINS, and inflammatory factors IL-8 and COX-2 levels are closely correlated with IPSS, which can reflect the severity and prognosis of BPH. It can effectively postpone the progression of BPH by lowering blood glucose, improving insulin resistance, and controlling the expressions of inflammatory factors in serum through a healthy lifestyle and clinical comprehensive treatment.

Key Words
Benign prostatic hyperplasia, Glucose metabolism, Insulin resistance, Inflammatory factors, Symptom score, Correlation.

Introduction

Benign prostatic hyperplasia (BPH) is a kind of progressive disease, common in middle-aged and elderly men, which can be gradually aggravated by age, seriously affecting male health[1]. Its pathogenesis involves hormone-endocrine, inflammation-immune, metabolic syndrome (including obesity, hypertension, insulin resistance, and hyperinsulinemia), and many other factors[2]. Recent studies have focused on the correlation between metabolic syndrome and BPH, of which hyperinsulinemia and insulin resistance are the main pathophysiological basis, and its clinical manifestation is in the chronic inflammatory state. Some cytokines in prostatitis microenvironment promote epithelial hyperproliferation, which can lead to prostatic hyperplasia and lower urinary tract obstruction[3]. Interleukin-8 (IL-8), as a potent chemotaxis of neutrophils, is increased in prostatic fluid of patients with BPH, which can collect and activate neutrophil aggregation and damage tissue cells. The expression of IL-8 can be detected to evaluate prostate inflammation[4]. Foreign studies have reported that cyclooxygenase 2 (COX-2) is up-regulated in the glandular epithelium of patients with BPH, which is found to be associated with the occurrence of BPH[5]. In this study, the international prostate symptom score (IPSS) was given, and the IL-8 and COX-2 levels in expressed prostatic secretion (EPS) were

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detected in patients with BPH, so as to investigate the correlations of glucose metabolism, insulin resistance and inflammatory factors with symptom score, and evaluate its clinical significance to guide the diagnosis and treatment.

Patients and Methods

Patients

A total of 90 patients diagnosed with BPH from March to October 2017 in Daping Hospital were enrolled. All the patients were in accordance with the diagnostic criteria of BPH in *Guidelines for the Diagnosis and Treatment of Urological Disease in China (2009)*. All the subjects were required to sign an informed consent before the study. Method for grouping: (1) high FPG group: FPG ≥6.1 mmol/L, normal FPG group: FPG ≤6.1 mmol/L, (2) high insulin group: FINS >15 Mu/L, normal insulin group: FINS <15 Mu/L. Exclusion criteria: patients with prostate tumor, severely abnormal lipid metabolism, a history of prostatic surgery or received hypoglycemic treatment recently, or patients whose EPS could not be collected. The study was approved by the Ethics Committee of Daping Hospital and written informed consents were signed by the patients and/or guardians.

Methods

Fasting venous blood of the patients of two groups was collected in the morning before and after treatment. The blood was centrifuged to get the supernatant, and EPS was collected through prostate massage under aseptic conditions. The specimens were stored in a refrigerator at -80°C.

Observation Indexes

IPSS was given: mild and moderate: 0-20 points, severe: 20-35 points.

The levels of blood glucose (glucose oxidase method) and insulin (immunoturbidimetry) were measured by a full-automatic biochemical analyzer and the homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated.

IL-8 and COX-2 in EPS and prostate-specific antigen (PSA) in serum were detected by ABC ELISA method.

The prostate volume (PV) was measured by transabdominal ultrasound, and the volume of more than 12.5 mL indicated the prostatic hyperplasia.

Statistical Analysis

SPSS 20.0 software (IBM Corp. IBM SPSS Statistics for Windows, Armonk, NY, USA) was used for statistical analysis. Quantitative data were expressed as mean ± standard deviation, Student's *t*-test and analysis of variance were performed to compare two and multiple groups and the post-hoc test was SNK test. Pearson correlation analysis was used for correlation analysis. $p<0.05$ suggested that the difference was statistically significant.

Results

Comparisons of Prostate-Related Indexes Between Normal FPG Group and High FPG Group

Compared with those in normal FPG group, the PV was significantly increased and the IPSS was higher in high FPG group ($p<0.05$). There was no significant difference in PSA between the two groups (Table I).

Comparisons of Prostate-Related Indexes Between High Insulin Group and Normal Insulin Group

The PV in high insulin group was significantly increased and the IPSS was higher than that in normal insulin group ($p<0.05$). There was no significant difference in PSA between the two groups, as shown in Table II.

Comparisons of Levels of Inflammatory Factors IL-8 and COX-2, Blood Glucose and Insulin Resistance Between Low IPSS Group and High IPSS Group

Compared with those in low IPSS group, all the indexes including FPG, FINS, HOMA-IR, IL-8 and COX-2 were significantly increased ($p<0.05$ or $p<0.01$) (Table III).

Table I. Comparisons of prostate-related indexes between normal FPG group and high FPG group.

Index	PV (mL)	PSA (ng/mL)	IPSS (points)
Normal FPG group (n=48)	44.43±12.26	2.26±2.02	9.12±6.01
High FPG group (n=42)	52.26±13.73*	3.01±2.58	15.69±4.13*

Note: compared with normal FPG group, *$p<0.05$.

Table II. Comparisons of prostate-related indexes between high insulin group and normal insulin group.

Index	PV (mL)	PSA (ng/mL)	IPSS (points)
Normal FPG group (n=48)	44.96±13.23	2.09±1.77	8.98±5.12
High FPG group (n=42)	54.21±14.83*	2.63±2.05	15.23±6.79**

Note: compared with insulin-sensitive group, *p<0.05, **p<0.01.

Table III. Comparisons of levels of inflammatory factors IL-8 and COX-2, blood glucose and insulin resistance between different IPSS.

Index	High IPSS group	Low IPSS group
FPG (mmol/L)	5.89±0.76*	4.61±0.59
FINS (mU/L)	14.19±2.17*	24.25±3.50
HOMA-IR	4.8±1.1*	2.7±0.5
IL-8 (ng/mL)	16.31±1.25**	6.01±0.89
COX-2 (ng/mL)	366.09±17.23**	150.96±26.68

Note: compared with low IPSS group, *p<0.05, **p<0.01.

Correlations of Glucose, Insulin Resistance and Inflammatory Factors With IPSS of Patients With BPH

In this study, Pearson correlation analysis revealed that the FBS, FINS and inflammatory factors IL-8 and COX-2 levels were positively correlated with IPSS (r=0.5492, 0.7800, 0.8916 and 0.7604) (p<0.05), as shown in Figures 1-4.

Changes of the indexes in patients with BPH after treatment

The results of this study demonstrated that the FBG, FINS, IL-8, COX-2, and IPSS were decreased in patients with BPH after treatment (Figure 5).

Discussion

Various metabolic factors have been reported to affect the occurrence of BPH, in which insulin resistance and hyperinsulinemia are risk factors for the development of BPH[6,7]. In hyperinsulinemia, insulin acts on the endothelial cells of prostate tissues, and promotes cell proliferation to form atherosclerosis[8]. Arteriosclerosis can damage the supplying vessels of the prostate and reduce tissue perfusion, thus increasing blood flow resistance and aggravating ischemia and hypoxia, eventually leading to the progression of BPH[9,10].

Nickel et al[11] found that prostatitis has a significant impact on the lower urinary tract symptom (LUTS) score of BPH, both of which are reciprocal causation. The release of inflammatory factors can aggravate fibrosis and aggravate LUTS in patients with prostatic hyperplasia. Yoshimura et al[12] purified IL-8 from mononuclear epithelial cells for the first time, and proved that IL-8 is a multi-source pro-inflammatory factor, which enhances the proliferation of prostatic epithelial cells by stimulating the expression of cell growth factors[13]. Kaplan et al[14] reported that the expression of IL-8 is significantly increased in aging prostate epithelial cells. COX-2 is almost not expressed in normal prostate tissues, which, however, participates in the devel-

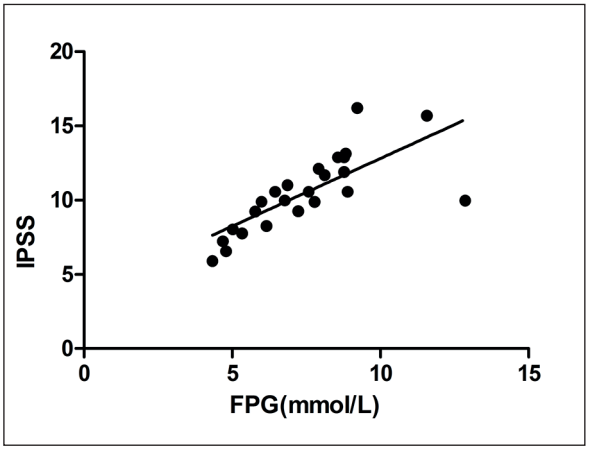

Figure 1. Correlation analysis between FPG and IPSS (r=0.5492).

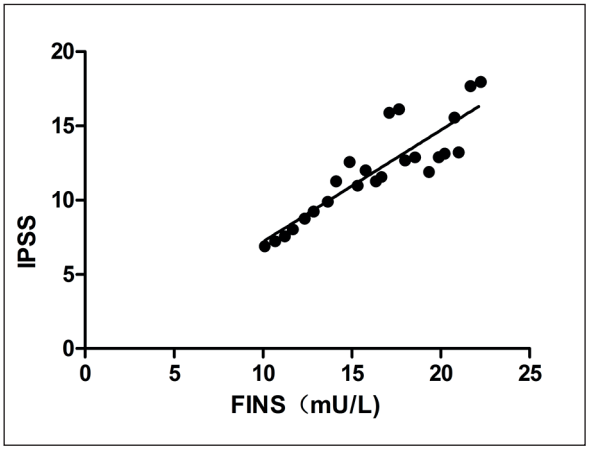

Figure 2. Correlation analysis between FINS and IPSS (r=0.7800).

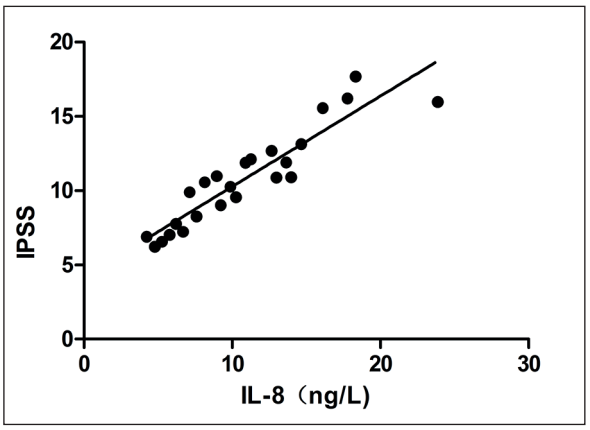

Figure 3. Correlation analysis between IL-8 and IPSS (r=0.8540).

opment of BPH as a local inflammatory mediator[15]. Animal experiments have demonstrated that the expression of COX-2 in the prostatitis group is significantly higher than that in the normal group[16].

Scholars[17,18] have shown that the increased fasting insulin level is an independent risk factor for the size of the prostate, and the higher level indicates the more obvious LUTS. In the present study, it was found that PV of the high FPG group and the high insulin group was higher than that of the normal FPG group and the normal insulin group, which were in accordance with conclusions in previous research. There was also a significant difference in the IPSS score between the two groups, suggesting that blood glucose and insulin level are important factors for the development and progression of BPH. The possible mechanisms are as follows: (1) Insulin increases the secretion of catecholamines by stimulating the sympathetic nerve, eventually slowing down

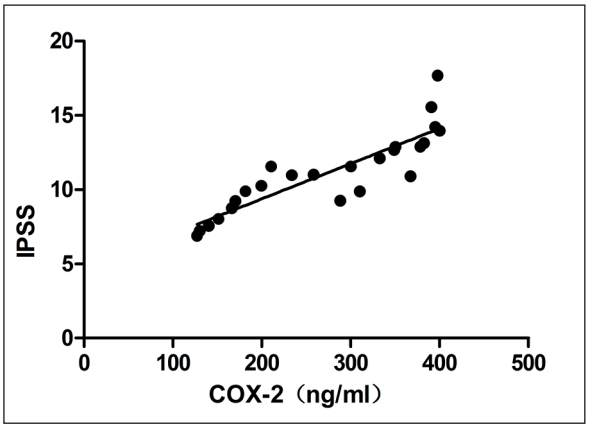

Figure 4. Correlation analysis between COX-2 and IPSS (r=0.7604).

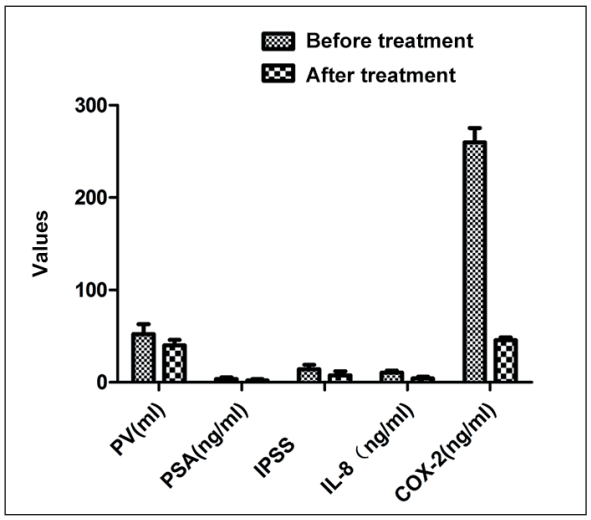

Figure 5. Comparisons of indexes before and after treatment.

the apoptosis of prostate cells, and (2) insulin promotes the proliferation of prostate tissues by releasing insulin growth factors[19]. Compared with those in low IPSS score group, FPG, FINS, HOMA-IR, IL-8, and COX2 of the high IPSS score group were significantly increased (p<0.05 or p<0.01). Further correlation analysis demonstrated that the IPSS score was positively correlated with the changes in blood glucose, insulin level and IL-8 and COX-2 in EPS (r=0.5492, 0.7800, 0.8916 and 0.7604, p<0.05). After a standardized, systematic and comprehensive treatment, the above indexes of the prostate were significantly improved. Moreover, clinical studies have revealed that the apoptosis rate of prostate hyperplasia cells is significantly decreased after the treatment of prostatic hyperplasia with COX-2 inhibitor and 5α-reductase inhibitor[20], indicating that monitoring and controlling inflammatory factors has an important reference value in the diagnosis and treatment of prostatic hyperplasia.

Conclusions

FBS, FINS, and inflammatory factors IL-8 and COX-2 are closely related to the IPSS score, and their levels can reflect the severity of BPH and evaluate prognosis. The reduction of the blood glucose, the improvement of insulin resistance and the control of expression of inflammatory factors in serum through a healthy lifestyle and a clinically comprehensive treatment can effectively delay the progression of BPH.

Conflict of Interests:
The authors declare that they have no competing interests

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