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CLINICAL STUDY

The evaluation of the metabolic and autonomic predictors of cardiovascular diseases in relation to prostatic hyperplasia symptoms

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ABSTRACT

OBJECTIVES: High prevalence of cardiovascular diseases (CVD) is present in benign prostatic hyperplasia patients. Risk prediction models were developed for early identification of these cardiovascular risks. We aimed to evaluate cardiovascular metabolic and autonomic predictors in relation to lower urinary tract symptoms' severity evaluated by the IPSS score.

METHODS: This study included 318 healthy individuals recently diagnosed with benign prostate hyperplasia (BPH). Laboratory tests including metabolic, hormonal and inflammatory markers were recorded. The cardiovascular risk indices like the atherogenic index of plasma and the triglyceride glucose index were calculated. The heart rate recovery after graded exercise was calculated.

RESULTS: There was a significant positive correlation between the IPSS score and both the atherogenic and the triglyceride glucose indices ($r=0.388$, $p<0.01$ and $r=0.109$, $p=0.032$, respectively). IPSS score was also significantly negatively correlated with heart rate recovery specially at the 3rd minute after exercise ($r=–0.547$, $p<0.01$). On the other hand, the IPSS score had a significant positive correlation with the inflammatory markers and a significant negative correlation with serum testosterone levels.

CONCLUSIONS: Our study results suggest the presence of a combination of hormonal and inflammatory changes in BPH patients affecting the severity of lower urinary tract symptoms (LUTS) which is correlated with metabolic and autonomic parameters that can predict an increased risk of CVD *(Tab. 3, Ref. 47)*. Text in PDF *www.elis.sk*

KEY WORDS: benign prostatic hyperplasia, atherogenic index of plasma, triglyceride glucose index, heart rate recovery.

Introduction

Benign prostatic hyperplasia (BPH) is one of the most common diseases of old males affecting their quality of life through the discomforts of lower urinary tract symptoms (LUTS) like urgency, high frequency of urination and nocturia (1). In these patients there is a considerably high prevalence of all cardiovascular diseases (CVD) compared to the general population (2, 3).

Although the underlying etiologies are still not clearly defined but considering the fact that the majority of BPH patients consist of old aged male appears to play an important role in this regard. In this group of patients, factors like decreased physical activity, obesity, cigarette smoking, blood pressure (BP) disturbances, and abnormal lipid profile can present frequently and are important in the development of CVD (4). On the other hand, factors like chronic inflammation and disturbances in serum sex hormones can also play an important role in the development of both BPH and CVD in this age group (1, 4–6).

Since CVD are the main cause of morbidity and mortality worldwide (7), the early identification of patients with increased risk of developing CVD has gained wide interest among the cardiovascular community in the past few decades. Clinical studies were conducted to develop prediction models to estimate such risks (8). Many serum laboratory biomarkers specially the metabolic markers have been identified as predictors for CVD like serum lipid parameters (9). A recent predictive model is the atherogenic index of plasma (AIP) which has been increasingly adopted as a low-cost, specific and quick non-invasive method to be used in clinical practice (10). Another important predictive index is the triglyceride glucose (TyG) index which has been recently suggested as a reliable marker of insulin resistance and proven to be associated with atherosclerosis (11–13). On the other hand, autonomic dysfunction is also considered as a predictor of CVD (14). For example, decreased vagal activity which is a powerful indicator for cardiovascular mortality can easily be evaluated by examining alterations in heart rate and blood pressure parameters during physical exercise (14–15).

In this study we aimed to evaluate the metabolic and autonomic predictors of CVD in BPH patients using previously recognized prediction models and examine its relation to LUTS severity evalu-

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ated by the international prostate symptom score (IPSS). We also examined the correlation of suggested pathophysiological factors that may lead to the development of both conditions.

Materials and methods

Study population and design

Between August 2020 and December 2021, 318 healthy individuals recently diagnosed with BPH and admitted to our cardiology out-patient clinic with non-specific symptoms were included in this prospective study. Exclusion criteria included having a history of any cardiovascular disease or the presence of any condition that could affect the normal function of the cardiovascular system like anemia or electrolyte disorder, having a chronic pulmonary or hepatic disease and having an abnormal thyroid function test. All patients had a detailed cardiac examination and investigations to exclude any clinical findings that indicate the presence of undiagnosed cardiovascular diseases. The severity of LUTS was assessed using the International prostate symptom score (IPSS) questionnaire (16).

Evaluating cardiovascular risk predictors

Detailed laboratory tests including fasting blood glucose, serum lipid parameters, serum inflammatory markers and testosterone levels were obtained from patients' medical records. Atherogenic index of plasma (AIP) values were calculated using the [log10 triglyceride (TG)/high-density lipoprotein cholesterol (HDL)] formula (10). The triglyceride glucose index (TyG) was calculated using the [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2] formula (17). To evaluate the parameters of cardiovascular autonomic dysfunction, treadmill exercise test using the Bruce protocol was performed. The exercise testing procedures followed the guidelines set out by the American Heart Association (18). Participants abstained from heavy eating, coffee, alcohol, and smoking 2 days before the exercise test. Before the stress test, resting heart rate and blood pressure measurements were recorded. Blood pressure and 12-lead ECG recordings were obtained every 3 min over the course of stress testing and in the 1st, 2nd, and 3rd minutes of the recovery period. Both heart rate recovery (HRR) and systolic blood pressure recovery (SBPR) indices were calculated by extracting the measurements during the 1st, 2nd, and 3rd minutes of the recovery period from the measurements during maximum exercise.

Statistics

Continuous variables were defined as mean +/– standard deviation. Categorical variables were defined as percentages. Student's t-test was used to compare continuous variables and Chi-square test was used for categorical variables. Pearson correlation test was used to determine the correlation between the variables. $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 20.0 (IBM Co., Armonk, NY, USA).

Ethical statement

All procedures, including the informed consent process, were conducted in accordance with the ethical standards of the National Health and Medical Research Council of Turkey and with the Helsinki Declaration. The patients were informed about the study, and they were included after their informed voluntary consent forms were obtained. The study was approved by the ethical committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (No: 2020-07/714).

Results

The mean age of study participants was 68.1 ± 5.7 years. The mean AIP value was 0.66 ± 0.49 and the mean TyG was 0.69 ± 0.37. The mean IPSS score for study participants was 15.26 ± 5.67. All mean values of baseline clinical and laboratory parameters are listed in Table 1.

According to correlation analysis results there was a significant positive correlation between the IPSS score and BMI ($r = 0.088$, $p = 0.039$), but the correlation with fasting blood glucose was not significant ($r = 0.011$, $p = 0.059$). When the correlation was examined between the IPSS score and serum lipid profile parameters, there was a significant positive correlation between the IPSS score and total cholesterol, LDL, and triglycerides levels ($r = 0.117$; $p = 0.023$,

Tab. 1. The basal clinical and socio-demographic characteristics of the study participants.

Variables	Values
Age, years	68.1±5.7
Basal HR, b/min	82.76±11.4
BMI, kg/m^2	26.8±4.9
IPSS score	15.26±5.67
Systolic BP, mmHg	126.63±5.17
Diastolic BP, mm Hg	79.8±12.7
Fasting glucose, mg/dL	119.11±7.9
Hemoglobin, gr/dL	13.8±1.4
Total cholesterol, mg/dL	179.8±29.1
LDL, mg/dL	140.9±34.2
Triglyceride, mg/dL	181.4±32.6
HDL, mg/dL	29.9±4.1
Calcium, mg/dL	9.3±0.8
Sodium, mEq/L	142.1±1.6
Potassium, mEq/L	4.4±0.6
TSH, mIU/L	3.4±1.5

BMI – Body Mass Index, IPSS – International prostate symptom score, BP – Blood Pressure, LDL – Low-Density Lipoprotein, HDL – High-Density Lipoprotein, TSH – Thyroid Stimulating Hormone.

Tab. 2. The correlations of metabolic, hormonal and inflammatory markers with IPSS score.

Parameters	Values	Correlation with IPSS score	
		R	p
Body mass index (kg/m^2)	26.8±4.9	0.088	0.039
Fasting glucose (mg/dL)	119.11±7.9	0.011	0.059
Total cholesterol (mg/dL)	179.8±29.1	0.117	0.023
HDL (mg/dL)	29.9±4.1	–0.195	0.017
LDL (mg/dL)	140.9±34.2	0.091	0.042
Triglycerides (mg/dL)	181.4±32.6	0.341	<0.01
Atherogenic index	0.62±0.29	0.388	<0.01
Triglyceride glucose index	0.69±0.37	0.109	0.032
CRP, mg/dl	3.23±0.62	0.277	0.018
Fibrinogen, mg/dl	344.4±34.7	0.184	0.022
Testosterone, ng/ml	2.29±0.17	–0.221	0.037

LDL – Low-Density Lipoprotein, HDL – High-Density Lipoprotein

r = 0.091; p = 0.042, r = 0.341; p < 0.01, respectively) and a significant negative correlation with HDL levels (r = –0.195, p = 0.017). Regarding risk prediction indices, there were a significant positive correlation between the IPSS score and both AIP and TyG (r = 0.388, p < 0.01 and r = 0.109, p = 0.032, respectively) (Tab. 2).

When exercise test results were evaluated, the mean pre-exercise heart rate was 88.76 ± 11.4/min and the mean systolic blood pressure was 136.63 ± 5.17 mmHg. There was a significant positive correlation between IPSS score and pre-exercise heart rate (r = 0.152, p = 0.019), but the correlation was not significant with pre-exercise systolic blood pressure (r = 0.076, p = 0.247). During the maximum exercise phase, the mean heart rate was 152.8 ± 10.8/min and the mean systolic blood pressure was 172.89 ± 20.34 mmHg and as it was in the pre-exercise period the positive correlation between IPSS score and heart rate was significant (r = 0.355, p < 0.01) but it was not significant with systolic blood pressure (r = 0.081, p = 0.098). Regarding the recovery indices, a significant negative correlation was observed between HRR and IPSS (for HRR 1st min r = –0.237, p < 0.01, for HRR 2nd min r = –0.288, p<0.01 and for HRR 3rd min r = –0.547, p < 0.01). Similarly, a significant negative correlation was observed between SBPR and IPSS (for SBPR 1st min r = –0.128, p < 0.01, for SBPR 2nd min r = –0.173, p < 0.01 and for SBPR 3rd min r = –0.288, p < 0.01). The negative correlation in both conditions was more prominent in the 3rd minute of the recovery period (Tab. 3).

Finally, the correlation analysis of the pathophysiological markers with IPSS score showed a significant positive correlation between the IPSS score and the inflammatory markers (for CRP r = 0.277, p = 0.018 and for fibrinogen r = 0.184, p = 0.022) and a significant negative correlation with serum testosterone levels (r = –0.221 and p = 0.037) (Tab. 2).

Discussion

In old males with BPH there is a high prevalence of CVD (19). Studies have been conducted to analyze the association between the two conditions. In this study we evaluated the risk of CVD in BPH patients by examining the changes in some metabolic and autonomic parameters in relation to LUTS. Study results showed that the severity of LUTS in BPH patients is correlated with many metabolic and autonomic risk predictors of CVD.

Many clinical trials investigated BPH and LUTS beyond the urinary system. A meta-analysis by Gacci et al showed that BPH patients with moderate to severe LUTS are at higher risk for major adverse cardiovascular events (20). Another study showed that the prevalence of coronary artery disease was significantly higher in BPH patients (2). Many pathophysiological changes present in BPH can also affect the risk of CVD. For example, Hammarsten et al reported in a prospective study a correlation between BPH and metabolic syndrome which is considered an important risk factor for the development of CVD (21, 22). Later on, many other studies also showed an increased prevalence of metabolic syndrome components in BPH patients (23–25).

Disturbances in lipid metabolism constitute a major part of metabolic syndrome (26). A study reported lower levels of HDL and higher levels of total cholesterol and LDL in patients with symptomatic BPH than in controls (27). In our study we evaluated the correlation between the IPSS score as an indicator of LUTS severity and serum lipid parameters. According to our study results, a significant positive correlation was observed between the IPSS score and all of total cholesterol, LDL, and triglycerides levels (r = 0.117; p = 0.023, r = 0.091; p = 0.042, r = 0.341; p < 0.01, respectively), and a negative correlation was observed with HDL levels (r = –0.195, p = 0.017). Obesity, which is another important component of metabolic syndrome (26), can increase the activity of the aromatase enzyme which increases the production of estrogen in the expense of testosterone and eventually deteriorates LUTS in BPH patients (28). A recent meta-analysis reported a positive association between body mass index (BMI) and LUTS associated with BPH (29). In our study, a significant positive correlation was also observed between the IPSS score and BMI (r = 0.088, p = 0.039). According to our results, there is a significant correlation between the severity of LUTS and components of metabolic syndrome which confirms a correlation with an increased risk of CVD.

Assessing individual's cardiovascular risk using the components of metabolic syndrome has been used for long time but recently numerous novel metabolic risk prediction indices were developed for better assessment of this risk. At the beginning of this century Dobiasova and Frohlich introduced the atherogenic index of plasma (AIP) which represents the logarithm of triglycerides to HDL ratio (30). Later on, many clinical studies have demonstrated AIP as predictor and prognostic biomarker for CVD (31–33). A more recent biomarker is the triglyceride glucose index (TyG) which can be calculated by a formula using fasting measurements of triglycerides and serum glucose levels. Studies proposed the TyG index as a marker of insulin resistance and it was proven to be associated with increased risk of atherosclerotic CVD (34).

Tab. 3. The correlations of autonomic parameters with IPSS score.

Parameters	Values	Correlation with IPSS score	
		R	p
Pre-exercise			
Heart rate	88.76±11.4	0.152	0.019
Systolic blood pressure	136.63±5.17	0.076	0.247
During maximum exercise			
Heart rate	152.8±10.8	0.355	<0.01
Systolic blood pressure	172.89±20.34	0.081	0.098
Heart rate recovery indices after exercise			
HRR 1st min	14.13±5.47	–0.237	<0.01
HRR 2nd min	22.37±8.11	–0.288	<0.01
HRR 3rd min	33.92±7.81	–0.547	<0.01
Systolic blood pressure recovery indices after exercise			
SBPR 1st min	17.3±5.53	–0.128	<0.01
SBPR 2nd min	26.8±7.46	–0.173	<0.01
SBPR 3rd min	39.64±8.23	–0.288	<0.01

HRR – heart rate recovery index, SBPR – systolic blood pressure recovery index

We evaluated the correlation between the IPSS score and the cardiovascular metabolic risk predictive indices AIP and TyG and observed a significant positive correlation between the IPSS score and both parameters ($r = 0.388$, $p < 0.01$ and $r = 0.109$, $p = 0.032$, respectively). These results also support the conclusion of a positive correlation between LUTS severity and the risk of CVD.

Apart from the metabolic disturbances, autonomic dysfunction can also be seen in BPH patients with LUTS as BPH patients usually have a status of sympathetic hyperactivity which can lead to decreased vagal responses (1). On the other hand, BPH patients suffer from night symptoms which causes disturbances of blood pressure and heart rate control during sleeping hours and hence impairment of the normal circadian rhythm and more dysregulations in the autonomic nervous system (19–35). Autonomic dysfunction is closely related with the development of CVD (36). One of the most common used techniques to evaluate the cardiovascular autonomic dysfunction is by measuring heart rate recovery indices after graded exercise (37). In our study both heart rate and blood pressure recovery indices after exercise were found to be significantly correlated with the IPSS score specially in the 3rd minute of the recovery period ($r = –0.547$, $p < 0.01$ and $r = –0.288$, $p < 0.01$, respectively). As it was with metabolic parameters, disturbances in autonomic nervous system control mechanisms also support the idea of a correlation between LUTS severity and the risk of CVD.

The exact etiological pathway causing the metabolic and autonomic disturbances and simultaneously aggravating LUTS is not clearly understood, but some common etiological factors can contribute to this pathogenesis. The first factor to mention is chronic inflammation, as many studies showed that it leads to disturbances in cardiovascular autonomic function, contributes to the development of metabolic syndrome and can increase the risk of CVD (38–42). Inflammation also induces the release of cytokines and growth factors which can stimulate prostatic cell proliferation leading to prostatic hypertrophy and aggravating LUTS (43). In our study, a significant positive correlation between the IPSS score and the inflammatory markers was observed (for CRP $r = 0.277$, $p = 0.018$ and for fibrinogen $r = 0.184$, $p = 0.022$). Another important factor to mention is the hormonal disturbances specially testosterone deficiency. Studies have shown that decreased serum testosterone levels can be associated with cardiac autonomic dysfunction and considered a risk factor for CVD (44–45). Studies also showed that low testosterone and high estrogen levels can stimulate prostatic cells hypertrophy and aggravate LUTS, a similar hormonal dysregulation is observed in metabolic syndrome (46,47). Similarly, in our study we observed a significant negative correlation between the IPSS score and serum testosterone levels ($r = –0.221$ and $p = 0.037$).

Conclusion

Our study results suggests the presence of a combination of hormonal and inflammatory changes in BPH patients affecting the severity of LUTS which is correlated with metabolic and autonomic disturbances that predicts an increased risk of CVD. In this case, following BPH patients with severe LUTS by a multidisciplinary teams that may include cardiologists and endocrinologists beside urologists can be beneficial in terms of the prediction and early treatment of possible cardiovascular risks.

The main limitation of our study is the lack of an asymptomatic control group. Another important limitation is the lack of long term follow up for study participants in terms of the development of cardiovascular diseases.

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