Male Lower Urinary Tract Symptoms/Benign Prostatic Hyperplasia and Metabolic Syndrome

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INTRODUCTION

Benign prostatic hyperplasia (BPH) was traditionally viewed as an organ-based anatomical disease. The contemporary concept of BPH commenced in 1976 when Cain [1] reported improvement of lower urinary tract symptoms (LUTS) and flow rates after using phenoxybenzamine, an alpha-blocker. It is now generally accepted that lower urinary tract symptoms suggestive of BPH (LUTS/BPH) has an important functional aspect due to alpha-1-receptor mediated smooth muscle contractions in the prostate.

In a recent report by the Third National Health and Nutrition Examination Survey (NHANES III) [2], positive correlations were demonstrated between markers of the metabolic syndrome and LUTS/BPH in 2,372 men older than 60 years. It was shown that those with history of diabetes and hypertension were positively associated with LUTS/BPH. The odds of the men having LUTS increased with increasing glycosylated hemoglobin. Moreover, men classified as having three or more components of the metabolic syndrome had increased odds for LUTS/BPH.

Thus the purpose of this review was to recapitulate relevant clinical and research evidence linking the two entities, LUTS/BPH and metabolic syndromes.

DEFINITION OF METABOLIC SYNDROME

The metabolic syndrome is a very common multi-component conditions characterized by insulin resistance, dyslipidemia, abdominal obesity and hypertension that is associated with a high risk of type 2 diabetes mellitus, cardiovascular diseases and atherosclerosis [3-5]. Furthermore in patients with type 2 diabetes and coronary heart disease, the metabolic syndrome identifies individuals at particularly high risk for cardiovascular events such as stroke, heart failure and myocardial infarction [6-8]. The most widely used criteria to define this syndrome were published as part of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III Guidelines (Table 1) [4]. The World Health Organization (WHO) and the American College of Endocrinology (ACE) have established criteria for the metabolic syndrome that requires insulin resistance and a combination of other metabolic factors [9]. Insulin resistance is the core metabolic perturbation of the metabolic syndrome whereby target tissues fail to respond effectively to normal circulating concentrations of insulin, impeding glucose disposal and utilization. On the other hand, obesity is the principal etiological factor that predisposes patients to insulin resistance [10].

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EPIDEMIOLOGICAL EVIDENCE LINKING LUTS/BPH AND METABOLIC SYNDROME

In addition to the NHANES III report, other epidemiological surveys have shown positive correlation between LUTS/BPH and metabolic syndrome risk factors. The Multinational Survey of the Ageing Male (MSAM-7) report [11] in 2003 demonstrated that BPH adversely affected sexual activity, erectile function and ejaculation in elderly male patients. The study investigated the association between LUTS and erectile dysfunction (ED) in 12,815 men aged between 50 and 80 years. The prevalence of ED in men without LUTS was 24.8%, compared with 43.3, 65.8 and 81.9% ED in men with mild, moderate and severe LUT symptoms, respectively. Ejaculatory problems were reported by 25.3% of the men without LUTS compared with 41.8, 61.4 and 76.0% with mild, moderate and severe symptoms, respectively. Associations between LUTS and sexual dysfunction have also been reported in other studies [12-14].

The relationship between BPH and hypertension has been controversial. Both diseases are highly prevalent in the elderly male population. Recently, Michel et al [15] reported that in 9,857 patients BPH symptoms were associated with being diagnosed as hypertensive or receiving antihypertensive medication. They concluded that: (1) each year of age increased the hypertension risk by 5.3%; (2) each International Prostate Symptom Score (IPSS) point increased the risk by 5.0%; and (3) the most logical explanation for the association between the two disease states was that they shared a common pathophysiological factor.

CLINICAL EVIDENCE LINKING LUTS/BPH AND METABOLIC SYNDROME

Hammarsten and Hogstedt [16,17] showed that fast-growing BPH was a risk factor for type-2 diabetes, hypertension, obesity, dyslipidemia and hyperinsulinemia. In their long-term study, the annual growth rates of the prostate and metabolic profiles of 250 BPH patients were analyzed. The results showed that the median prostate growth rate was 1.04 mL/year. Men with fast growing prostates (>1.98 mL/year) had significantly higher prevalence of diabetes, hypertension, obesity, low HDL and hyperinsulinemia when compared with men with slow growing prostates (<0.51 mL/year).

The effects of diabetes on LUTS/BPH were reported by Michel et al in 2000 [18]. In their study, the severity of LUTS in BPH patients was significantly associated with diabetes. Additionally, alpha blocker (0.4 mg tamsulosin QD) treatment was effective in reducing LUTS in their

Table 1. Definitions of Metabolic Syndrome

(1) The World Health Organization (WHO) Definition of Metabolic Syndrome
The World Health Organization criteria (1999) require the presence of diabetes mellitus, impaired glucose tolerance, impaired fasting glucose or insulin resistance, AND two of the following:
- blood pressure: ≥140/90 mmHg
- dyslipidaemia: triglycerides (TG): ≥1.695 mmol/L and high-density lipoprotein cholesterol (HDL-C) ≤0.9 mmol/L (male), ≤1.0 mmol/L (female)
- central obesity: waist: hip ratio >0.90 (male); >0.85 (female), and/or body mass index >30 kg/m^2
- microalbuminuria: urinary albumin excretion ratio ≥20 mg/min or albumin: creatinine ratio ≥30 mg/g

(2) The European Group for the Study of Insulin Resistance (EGIR) Definition of Metabolic Syndrome
The European Group for the Study of Insulin Resistance (1999) requires insulin resistance defined as the top 25% of the fasting insulin values among non-diabetic individuals AND two or more of the following:
- central obesity: waist circumference ≥94 cm (male), ≥80 cm (female)
- dyslipidaemia: TG ≥2.0 mmol/L and/or HDL-C <1.0 mmol/L or treated for dyslipidaemia
- hypertension: blood pressure ≥140/90 mmHg or antihypertensive medication
- fasting plasma glucose ≥6.1 mmol/L

(3) The US National Cholesterol Education Program (NCEP) Definition of Metabolic Syndrome
The US National Cholesterol Education Program Adult Treatment Panel III (2001) requires at least three of the following:
- central obesity: waist circumference ≥102 cm or 40 inches (male), ≥88 cm or 36 inches (female)
- dyslipidaemia: TG ≥1.695 mmol/L (150 mg/dl)
- dyslipidaemia: HDL-C <40 mg/dL (male); <50 mg/dL (female)
- blood pressure ≥130/85 mmHg
- fasting plasma glucose ≥6.1 mmol/L (110 mg/dl)

patients. Berger et al [19] evaluated the relationship between clinical BPH and atherosclerosis using color Doppler ultrasonography and symptom scores. In diabetic patients and men with peripheral arterial occlusive disease, perfusion of the transition zone of the prostate was significantly lower and the resistive index of the transitional zone (TZ) was significantly higher than in healthy control subjects. In diabetics and men with peripheral arterial occlusive disease, the mean prostate volume was greater than in healthy controls. The IPSS in patients with vascular damage was significantly worse than in the control subjects. Parsons et al [20] examined the associations of serum lipids and lipoproteins with BPH in community-dwelling men. Among 531 participants, there were no significant associations of total cholesterol, HDL cholesterol or triglycerides with the risk of BPH. In a subset analysis in men with diabetes, those in the highest level (>133 mg/dL) of LDL cholesterol, compared with those in the lowest level (<110 mg/dL), were four times more likely to have BPH. The data suggest that diabetic men with increased LDL cholesterol are at greater risk of BPH. This observation is consistent with the concept that cardiovascular risk factors are involved with the pathogenesis of BPH.

BASIC SCIENTIFIC RESEARCH EVIDENCE LINKING LUTS/BPH AND METABOLIC SYNDROME

During the last decade, our laboratory has made substantial contributions in prostate research related to metabolic syndrome. In 1996 [21], we reported increases of norepinephrine tissue concentration and neuropeptide-Y immunoreactivity in the prostate of spontaneously hypertensive rats (SHRs). Thereafter, it has been demonstrated that the SHRs are actually useful as animal models for the study of LUTS/BPH. Golomb et al [22] found that aging SHR prostates exhibited severe adenomatous hyperplasia characterized by piling-up of epithelial cells, papillary formations and increase of fibrocytes and smooth muscle cells in the stroma. Clemow et al showed that a positive correlation between blood pressure and voiding frequency existed in the first generation of offsprings between crossed SHRs and normotensive rats [23]. Thus the SHRs exhibited similar characteristics to human BPH patients, prostatic hyperplasia with LUTS.

More recently, we studied the diabetes-associated alteration in prostate alpha-1A adrenoceptor gene expression in the streptozotocin (STZ) induced diabetic rats [24]. RT-PCR results showed a 2.51-fold increase in the mRNA level of alpha-1A receptor. Western blotting showed a 2.23-fold increase in the receptor protein. Both insulin and phlorizin, a hypoglycemic agent, restored the normal levels of receptor mRNA and protein expression. The findings indicated an up-regulation of alpha-1A gene expression in the type-1 diabetic rat prostate, suggesting a state of "diabetic prostatopathy" which was similar to clinical BPH with respect to the involvement of an overactive autonomic nervous system. As McVary et al recently reported in BPH patients, the finding of autonomic hyperactivity was significantly associated with AUA symptom score and BPH impact index score [25]. Currently, we are using the fructose-fed obese rat as an animal model to study the effects of metabolic syndrome and type-2 diabetes on the prostate gland.

Different pathophysiological mechanisms linking metabolic syndrome and LUTS/BPH have been proposed [26]. These include:

1. The nitric oxide synthase (NOS)/NO theory; there is a reduction in NOS-containing nerves in the prostate and bladder/urethra in patients with bladder outlet obstruction. The theory is further supported by characterization and functional relevance of cyclic nucleotide phosphodiesterase (PDE) isoenzymes of the human prostate. The isoenzymes, PDE-4 and PDE-5, are most abundant in the ageing prostate, although the functional relevance in relaxing smooth muscles is still a matter of debate [27]. The use of PDE inhibitors presents an opportunity for PDE isoenzyme manipulation to improve both LUTS and ED.
2. The autonomic hyperactivity hypothesis: BPH is part of the metabolic syndrome, which includes cardiovascular diseases (e.g. hypertension, ischemic heart disease) and diabetes mellitus, both known risk factors for ED. Hypertension, obesity, and hyperinsulinaemia have all been shown to be associated with increased sym-

pathetic activity [25].

3. The Rho-kinase activation/endothelin pathway; there can be increased Rho-kinase activity in prostate smooth muscles in BPH, corpora cavernosa in ED and in the resistance vessels in hypertension. Noradrenaline, endothelin-1, as well as angiotensin II that regulate smooth muscle activity in the lower urinary tract and penis are dependent on Rho-kinase activity [28,29].
4. Pelvic atherosclerosis; animal models mimicking pelvic ischemia and hypercholesterolaemia show similar smooth muscle alterations of the detrusor and corpora [30]. Pelvic ischemia may induce the biological modifications described above and may thus represent a common link between LUTS and sexual dysfunction.

CONCLUSIONS

Recent scientific evidence has shown that BPH may be the tip of the iceberg and submerged underneath water is the metabolic syndrome. Further studies are needed to define the pathophysiological mechanism connecting these two entities. From a clinical perspective, it is advised that patients who present with LUTS/BPH should be screened for the co-existence of metabolic diseases, sexual dysfunction and hypertension. On the other hand, patients with chronic medical diseases such as hypertension and diabetes should be screened for the occurrence of LUTS or sexual dysfunction. Last but not least, treatment for BPH should aim not only to alleviate LUTS but also to improve sexual function and associated medical conditions.

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