Urodynamic Evaluation of Female Patients with Metabolic Syndrome

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Abstract: *Objective*: In this study, our main objective is to show the connection between metabolic syndrome (MetS) and bladder functions by using urodynamic evaluation in female MetS patients.

Materials and Methods: 131 female patients referred to our clinic for urodynamic evaluation from April 2014 to December 2014 were included in our study. 85 of these patients were diagnosed with MetS (study group) meanwhile 46 patients did not meet MetS criteria (control group). MetS definitions were taken from National Cholesterol Education Program's Third Adult Treatment Panel criteria. SPSS 17.0 was used for statistical analysis of data and $p<0.05$ values were deemed as statistically significant.

Results: Urodynamic results of 131 patients were analyzed and patients were divided into study and control groups in accordance with their MetS profile. 85 patients were included in the study group and rest 46 were used as the controls. A statistically significant difference was detected when IPSS results were separated into low, intermediate and severe between study and controls ($p=0.007$). Moreover, urge-type incontinence was more frequent in MetS patients when compared with control group ($p<0.001$). However, there was no significant difference between groups in terms of SEAPI scores and IPSS. Patients with MetS had significantly higher detrusor, vesical and abdominal pressure in comparison with control group ($p<0.001$). No significant difference was found in uninhibited contractions, first urinary sense, strong desire to urinate, Valsalva leak-point pressure (VLPP) and abdominal leak-point pressure (ALPP) parameters between the groups

Conclusion: Our results showed that MetS and its components can be associated with neurogenic bladder symptoms due to peripheral neuropathy and urge incontinence. Female patients with MetS have significantly higher post-voiding residue and intravesical pressure in comparison with control group. Further clinical studies with longer and controlled series are necessary for clarification of the metabolic syndrome's effect on bladder dysfunction on a molecular level.

Keywords: Metabolic syndrome, urinary incontinence, urodynamic, neurogenic bladder, bladder dysfunction.

INTRODUCTION

Metabolic syndrome (MetS) is a growing health problem, especially in developed countries. Adult Treatment Panel (ATP) III report estimates the increase in the prevalence of MetS in USA as 6.7% in young adults (20-29 years) to 43.5% in the population aged 60-69 and 42% over 70 [1]. MetS is a common systematic disorder that is defined by frequent clustering of numerous metabolic abnormalities such as central (apple-type) obesity, dyslipidemia, hypertension, insulin resistance and glucose intolerance [2]. It is widely accepted that MetS develops from insulin resistance (IR). Therefore, an associated endothelial damage risk might lead to atherosclerosis, affecting the bladder by decreasing its blood supply, which results in bladder dysfunctions [3]. MetS can also cause "cystopathy" type of neurogenic bladder, which is also defined as "diabetic autonomic neuropathy" [4]. Metabolic syndrome-IR state can also be attributed to other pathological conditions such as sympathetic overactivity, pro-inflammatory status and increased oxidative stress [5].

Obesity is already established as a risk factor for incontinence in several ways. For example, adiposity can lead to chronic elevation of intra-abdominal pressure, weakening urethral support structures and effectively causing stress urinary incontinence (UI) [7]. In addition, neurologic complications of obesity such as type-II diabetes is also thought to be associated with urge UI [8].

Not all, but a large number of studies reported a connection between MetS and lower urinary tract symptoms (LUTS) [9-13]. Most of these studies were done about the connection between male LUTS and bladder functions. Our reason for including/performing this study on female patients is mainly because there are multiple factors such as benign prostate

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hyperplasia (BPH) and urethral stricture which might affect lower urinary tract symptoms in males. Another reason is that we already had an ongoing study on female MetS patients. Therefore, in this study, our main objective was to reveal the connection between MetS and bladder functions using urodynamic evaluation results of female patients previously diagnosed with MetS.

MATERIALS AND METHODS

131 female patients between April 2014 and December 2014 who were referred to our clinic for urodynamic evaluation were included in the study. Out of 131 patients, 85 of them were previously diagnosed with MetS (study group) and 46 were without MetS (control group). After recording the demographic and anthropometric properties of the patients, the patients were asked to fill out SEAPI incontinence life quality questionnaire, International Prostate Symptom Score (IPSS) in addition to their medical history, urodynamic parameters and parity status. Patients with neurological disorders such as Parkinson's, Alzheimer's, Multiple Sclerosis and such, with currently receiving medical treatment which affects bladder function, with history of previous pelvic surgery and with current urinary tract infections were excluded from the study. Urinalysis was done prior to urodynamic evaluation to ensure that the patients did not have an infection at the moment. Urodynamic test was done using Aymed DYNO urodynamic device.

MetS diagnostic criteria for females were defined as; Waist circumference ≥80 cm, Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg OR previously diagnosed hypertension, Fasting blood glucose levels ≥ 100 mg/dl or previously diagnosed Type 2 diabetes, Serum triglyceride levels ≥ 150 mg/dl or previously diagnosed with hyperlipidemia, HDL cholesterol levels ≤ 50 mg/dl or previous diagnosis of dyslipidemia. The simultaneous presence of 3 or more of these criteria was deemed as metabolic syndrome (MetS). The criteria list was taken from National Cholesterol Education Program's Third Adult Treatment Panel [14].

Statistical analysis was made using SPSS 17.0 statistical software. Frequencies and percentages were used for categorical variables and continuous variables were demonstrated using means and standard deviation. Chi-square test was used to show the relationship between two categorical variables. The relationship between two continuous variables was shown using Pearson's correlation test. Comparison of two independent variables was done using Student-t test or Mann-Whitney U test. Statistical significance was defined as $p<0.05$.

RESULTS

Our study included 131 female patients with 85 with MetS and 46 patients as control group. Table **1** summarizes the demographic values, body mass index (BMI), lipidemic status (Cholesterol, trigliserid, HDL and LDL levels) and MetS criteria presence of both groups. In the study group, 49(57,6%) patients have diabetes mellitus and 23(27,1%) patients have hypertension. In the control group, 9(19,6%) patients have diabetes mellitus and only 2(4,3%) patients have hypertension. All patient's hypertension was under controlled in both study and control groups. Mean SEAPI score was 11.9±6.9 and mean IPSS score was 12.5±7 in the study group (MetS patients). The same results were calculated as 12.2±9.9 and 10.2±3.5 respectively in control group. No statistically significant difference was detected in those terms between the groups. When IPSS scores were classified as low (0-7), moderate [8-19] and severe (>20); 26 (30.6%) of patients in study group had low, 45 (52.9%) had moderate and 14 (16.5%) had severe IPSS scores. In control group, this was 12 (26.1%) low and 34 (73.9%) moderate scores with no severe score patient in that group. The difference in IPSS classification was significant between the groups ($p=0.007$). Moreover, there was also a significant difference in terms of incontinence type, with urge-type incontinence being more frequent in MetS patients as with 38 (44.7%) in the study and 15 (32.6%) in control group ($p<0.001$). No statistically significant difference was detected between the groups for cystocele and rectocele ($p=0.08$ and $p=0.3$ respectively).

In urodynamic evaluation, mean post-voiding residue (PVR) amount was 474.3 ± 210 cc in study and 404.2±230.8 cc in control group. Patients in study group had significantly higher detrusor, vesical and abdominal pressure in urodynamic test when compared to control group ($p<0.001$). There were no significant differences in terms of uninhibited contractions, first urinary sense, strong urination desire, Valsalva leak-point pressure (VLPP) and abdominal leak-point pressure (ALPP) parameters between groups (Table **2**). PVR was significantly correlated with bladder capacity, strong urinary desire and SEAPI scores in the study group ($p<0.001$). Likewise, detrusor pressure was also strongly correlated with bladder capacity

Table 1: Patient Characteristics

	MetS(+) (n=85)		MetS(-) (n=46)		p
AGE *(Mean, SD)*	54.6	11.5	52.3	14.7	0.359
BMI	30.0	3.7	21.0	1.5	<0.001
WC	119.8	10.8	99.5	3.1	<0.001
GLC	130.0	44.3	97.7	13.4	<0.001
CHOL	196.1	39.0	179.1	56.3	0.006
TG	151.1	63.0	112.4	44.0	<0.001
HDL	39.5	10.2	54.4	8.4	<0.001
LDL	134.8	37.9	121.1	40.6	0.015

Table 2: Urodynamic Parameters

	MS(+) (n=85)		MS(-) (n=46)		p
BLADDER CAPACITY (Mean, SD)	474.3	210.0	404.2	230.8	0.078
PVR (Mean, SD)	57.8	71.2	49.4	39.7	0.425
PDET (Mean, SD)	18.1	14.4	12.2	10.1	0.002
PVES (Mean, SD)	27.1	18.4	15.9	11.7	<0.001
PABD (Mean, SD)	12.6	13.0	5.9	4.9	<0.001
UNHIBITED CONTRACTION (n, %)					
PRESENT	7	8.2	5	10.9	0.752
ABSENT	78	91.8	41	89.1	
FIRST URINARY FEELING (Mean, SD)	155.7	121.8	158.7	104.9	0.619
STRONG URINARY DESIRE (Mean, SD)	343.3	186.6	313.4	206.1	0.257
VLPP (Mean, SD)	33.1	30.3	32.4	31.2	0.817
ALPP (Mean, SD)	30.5	30.0	27.6	31.6	0.477

($p<0.05$). Moreover, there was also a significant correlation between detrusor pressure and VLPP and ALPP ($p<0.001$). Finally, vesical pressure was also found to be significantly correlated with VLPP and ALPP ($p<0.001$).

DISCUSSION

In our study, our main objective was to show the correlation between MetS and urge incontinence in addition to neurogenic bladder. Patients with MetS have significantly higher PVR and urge continence. There are limited studies in the literature on the relationship between MetS and bladder functions. A number of studies showed that MetS, especially in form of Type-II diabetes, can cause urge-type incontinence or LUTS. Some other studies reported that increased BMI or waist circumference can cause elevated abdominal pressure, causing UI. Our results were also similar to these previous studies.

Karoli *et al*'s. study reported that 102 out of 153 female patients (67%) have LUTS, attributable to bladder dysfunctions secondary to diabetes. Storage and voiding symptom scores were significantly higher in females with diabetes in comparison with controls. Chronic implications of diabetes such as peripheral neuropathy and nephropathy were significantly associated with moderate LUTS. 46 patients were evaluated by urodynamic studies and 22 (48%) had an evidence of stress urinary incontinence, meanwhile 10 (23%) had detrusor overactivity and 5 (11%) had detrusor underactivity [15].

Uzun *et al*'s. study argued that MetS correlated highly with overactive bladder in female patients. Risk factors for MetS such as larger waist circumference,

greater BMI, low high-density lipoprotein levels and incidence of hypertension were significantly higher in overactive bladder group in comparison with controls [5]. However, we found no significant difference in terms of uninhibited contractions between MetS and control subjects.

In another study, Pinggera *et al.* showed that chronic ischemia of urinary bladder could be detected as lower perfusion seen in transrectal color Doppler ultrasonography in elder LUTS patients, as opposed to younger control patients who are asymptomatic. Therefore, they argued that decreased perfusion of urinary bladder and/or prostate can be responsible for LUTS development in patients with advanced age [16].

Rohrmann *et al.* conducted a large population-based survey and found that some MetS components were likely to be associated with LUTS in older males, and recently, in a population-based sample of African-American males between 40-79 [17]. However, this study is not compatible with our study results since our study includes only female patients.

In a number of studies, LUTS pathogenesis is currently considered as a sex-independent, multifactorial process involving structural changes in urinary bladder, infections, comorbidities, medications, neurological factors and hormones [18].

Kupelian *et al*'s. study showed significant associations between urological symptoms and type-II diabetes or increased blood sugar levels [19]. Insulin resistance affects ventromedial nucleus regulating the sympathetic nervous system of hypothalamus. It increases blood and tissue catecholamine levels, stimulates peripheral sympathetic nervous system and increases sympathetic nervous system activity. Likewise, prostate or bladder neck, with a wide distribution of sympathetic nervous system, also becomes stimulated, causing LUTS [20].

Brown *et al*'s. study reported a higher prevalence of urge incontinence in females with higher BMI and waist-to-hip ratio. In addition, the same prevalence was also higher in older women, diabetic women and women with frequent (2 or more in 1 year) urinary tract infections.

Lee *et al*'s. study in 2004 included 328 male patients. Out of 328, 187 (57.0%) had MetS and 135 (41.2%) had no/mild, 130 (39.6%) had moderate and 63 (19.2%) had severe LUTS. MetS was not found to be associated with moderate/severe LUTS presence [21].

Gao *et al*'s. study done on 3103 male patients concluded that the presence of MetS was not associated with LUTS severity, on the contrary, moderate or severe storage symptom subcategories were inversely related with MetS [22].

There is a limited number of studies which tries to explain the possible molecular mechanism of MetS in rat models. Basically, it is thought to be related with neurological control of detrusor muscle, detrusor mucosal changes in addition to direct myogenic cell damage due to MetS-related soluble toxins and increased oxidative stress in the tissue. Lee *et al.* reported that sensory receptor and enzyme alterations in the bladder mucosa can precipitate the emergence of bladder phasic contractions and oversensitivity through activation of C-afferents during acidic ATP solution stimulation in experimental rat bladder *in vitro* studies. They argued that down-regulation of bladder mucosa and detrusor overactivity (DO) caused by MetS are main factors to eliminate bladder oversensitivity to certain urothelium stimulus. This hyposensitivity and DO can be explained by C-afferent fiber activation and MetS related toxin build-up in the bladder [23]. Same group also showed loss of bladder muscle cells and a decrease in antiapoptotic protein and bcl-2 in experimental fructose-fed rat models due to increased nitrosative stress. Up-regulation of post-synaptic receptors and dysregulation of smoothelin are also other possible mechanisms which causes detrusor dysfunction in rats with MetS [24].

Another experimental rat study with alterations in peripheral purinergic and muscarinic signaling of rat bladder caused by MetS reported the main responsible molecular factors for bladder dysfunction in MetS as those [25].

CONCLUSION

MetS is still an increasing health problem in developing countries and some of its components can cause serious health complications. One of these severe complications is peripheral neuropathy, and as a consequence thereof, bladder storage and voiding function deterioration. For this reason, MetS patients should be closely followed up for changes in bladder function. During follow-up, urodynamic evaluation can be considered in necessary situations in order to

protect the urinary system and to increase the life quality of patients.

In this study, the connection between MetS and its components with neurogenic bladder caused by peripheral neuropathy and urge incontinence was shown. Female MetS patients have significantly higher post voiding residue and intravesical pressure in comparison with controls. Risk factors such as incomplete glycemic control, ischemia of pelvic organs such as bladder, diabetes duration and abdominal obesity can all impair bladder functions in MetS patients. Further clinical studies with longer and controlled series are necessary for clarification of the metabolic syndrome's effect on bladder dysfunction on a molecular level.

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