



Metabolic Syndrome Is an Independent Risk Factor for Acquired Premature Ejaculation

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Purpose: To determine the role of metabolic syndrome (MetS) as a risk factor for acquired premature ejaculation (PE) after considering the various risk factors, such as lower urinary tract symptoms, erectile dysfunction, hypogonadism, and prostatitis.

Materials and Methods: From January 2012 to January 2017, records of 1,029 men were analyzed. We performed multivariate analysis to identify risk factors for PE, including the covariate of age, marital status, International Prostate Symptom Score, International Index of Erectile Function (IIEF) score, National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) score, serum testosterone levels, and all components of MetS. Acquired PE was defined as self-reported intravaginal ejaculation latency time ≤ 3 minutes, and MetS was diagnosed using the modified National Cholesterol Education Program Adult Treatment Panel III criteria.

Results: Of 1,029 men, 74 subjects (7.2%) had acquired PE and 111 (10.8%) had MetS. Multivariate analysis showed that the IIEF overall satisfaction score (odds ratio [OR]=0.67, $p < 0.001$), NIH-CPSI pain score (OR=1.07, $p = 0.035$), NIH-CPSI voiding score (OR=1.17, $p = 0.032$), and presence of MetS (OR=2.20, $p = 0.022$) were significantly correlated with the prevalence of acquired PE. In addition, the Male Sexual Health Questionnaire for Ejaculatory Dysfunction scores and ejaculation anxiety scores progressively decreased as the number of components of MetS increased.

Conclusions: MetS may be an independent predisposing factor for the development of acquired PE. Effective prevention and treatment of MetS could also be important for the prevention and treatment of acquired PE.

Keywords: Metabolic syndrome; Obesity; Premature ejaculation; Risk factors; Sexual dysfunctions; Type 2 diabetes

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INTRODUCTION

Premature ejaculation (PE) is the most common male sexual dysfunction, present in about 14.0% to 19.5%

of all adult men [1,2]. In 2014, the International Society for Sexual Medicine (ISSM) defined acquired PE as characterized by a the development of a clinically significant and bothersome reduction in ejaculation

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latency time, often to about 3 minutes or less, the inability to delay ejaculation on all or nearly all vaginal penetrations, and the presence of negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy [3]. PE affects not only the patient but also induces considerable emotional and sexual distress in the patient's partner; in severe cases, PE can cause secondary infertility. PE has a multifactorial pathogenesis involving a variety of organic and psychological factors. Previous studies have suggested a functional imbalance of serotonin receptors as one of the most notable organic causes of PE, popularizing the use of several selective serotonin reuptake inhibitors (SSRIs) as treatment. Several studies have also reported that age, lower urinary tract symptoms (LUTS), erectile dysfunction, prostatitis, and hypogonadism contribute to the pathogenesis of PE [4-7].

Metabolic syndrome (MetS) induces impairment in vascular endothelial function and may affect blood circulation to the penis as well as the formation and secretion of nitrogen oxide, a critical component in smooth muscle expansion in the corpus cavernosum [8-10]. Many researchers have examined the association between MetS and erectile dysfunction and recently reached a consensus that MetS is an independent factor for erectile dysfunction [11]. MetS induces not only erectile dysfunction but also may influence the onset of PE and other ejaculatory dysfunctions because it alters serotonergic function and induces psychological changes such as depression [12-16].

Although a recent study has reported a relationship between MetS and PE, the study did not consider the potential other risk factors, such as LUTS, erectile dysfunction, and prostatitis, thus limiting the role of MetS as an independent risk factor [17]. Therefore, we investigated the role of MetS as an independent risk factor for acquired PE after considering the various risk factors, such as LUTS, erectile dysfunction, hypogonadism, and prostatitis. Furthermore, this study presents a multivariate analysis factoring in various comorbidities as well as the effects of age, LUTS, erectile dysfunction, prostatitis, and hypogonadism, which could influence the presentation of PE.

MATERIALS AND METHODS

1. Study population

A total of 1,337 men who visited the male health

screening center of Gyeongsang National University Hospital between January 2012 and January 2017 were assessed. Men with hyperthyroidism (n=19) or psychological disorders (n=6) who had undergone prostate surgery (n=27) or who were taking medications including SSRIs (n=6), testosterone (n=9), α blockers (n=197), 5- α reductase inhibitors (n=94), or phosphodiesterase (PDE)-5 inhibitors (n=37) were excluded. Those with lifelong PE (n=72) who had PE symptoms since their first sexual intercourse were also excluded. Finally, 1,029 patients (ages 27–70 years) were eligible.

2. Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board (IRB) of Gyeongsang National University Hospital (IRB No. 2017-03-015). Informed consent was waived by the IRB.

3. Measurement and definition of parameters

Routine laboratory and hormonal tests were performed between 08:00 AM and 9:00 AM in a fasting state. Waist circumference (WC) was measured just above the iliac crest at the level of the umbilicus using a standard tape measure with the patient standing. The diagnosis of MetS was made according to the most recent consensus report of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [18], which defined MetS as the simultaneous occurrence of at least 3 of the following 5 risk factors: abdominal obesity (WC greater than 90 cm or body mass index [BMI] greater than 25 kg/m²), blood pressure \geq 130/85 mmHg (or current use of antihypertensive medication), fasting blood glucose \geq 110 mg/dL (or current use of oral diabetes medication or insulin), triglyceride \geq 150 mg/dL, and high-density lipoprotein-cholesterol <40 mg/dL. We modified the definition of central obesity according to a new definition from the Western Pacific Regional Office of the World Health Organization instead of using the NCEP ATP III criterion of a WC greater than 102 cm [19]. Patients were asked to complete the International Prostate Symptom Score (IPSS) questionnaire and the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) to determine the severity of LUTS and chronic prostatitis (CP). The IPSS is the sum of scores on an 8-item questionnaire, ranging from 0–35; severity was categorized as mild (0–7), moderate (8–19), or severe (20–35). The NIH-CPSI is a 13-item questionnaire for

the assessment of symptom severity in men with CP/chronic pelvic pain syndrome. For each item, score ranges are 0–1 (6 items), 0–3 (2 items), 0–5 (3 items), 0–6 (1 item), and 0–10 (1 item). Patients were also assessed based on the International Index of Erectile Function (IIEF)-15 and Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD) scores for sexual function. The IIEF-15 is a widely used, multidimensional self-report questionnaire that assesses 5 domains of male sexual function, including erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction (OS). The MSHQ-EjD is a shortened version of the MSHQ that is designed to assess ejaculatory dysfunction. A testosterone level <3.5 ng/mL was defined as hypogonadism.

The incidence of PE was assessed with the patient self-reporting intravaginal ejaculation latency time (IELT) that included the following responses: within about 3 minutes or longer than 3 minutes. Acquired PE was defined as ejaculation within about 3 minutes based on the PE guidelines of the ISSM [20]. Additionally, ejaculatory disorder anxiety was assessed with the question (non-validated), “In the last month, how much anxiety did you feel about ejaculation during intercourse?” Answers were classified as 1=extreme, 2=quite a bit, 3=moderate, 4=a little, and 5=none.

4. Statistical analyses

Data were expressed as mean±standard deviation unless otherwise specified. Group differences of baseline characteristics were determined using independent t-tests for continuous variables and the chi-squared test for categorical variables. The odds ratios (ORs) and 95% confidence intervals were determined to evaluate the relationships between PE and risk factors including MetS from multivariate logistic regression models. All analyses were performed using IBM SPSS ver. 21 (IBM Co., Armonk, NY, USA). The $p < 0.05$ was defined as having statistical significance.

RESULTS

1. Patient characteristics

Among 1,029 men, 74 subjects (7.2%) had acquired PE (IELT≤3 min) and 111 (10.8%) had MetS. The mean ages of the acquired PE and control groups were 48.64±8.79 years and 48.38±7.47 years, respectively, with no significant difference between the groups. Compared to

the non-PE group, patients with PE had an increased prevalence of MetS and significant differences in total IPSS and all NIH-CPSI subdomains ($p=0.019$ and $p<0.001$, respectively; Table 1). Patients with PE showed

Table 1. Demographics and laboratory findings of subjects according to the presence of acquired premature ejaculation

Characteristic	Acquired PE (n=74)	Non-PE (n=955)	p-value
Age (yr)	48.64±8.79	48.38±7.47	0.782
Marital status			0.006
Married	62 (83.8)	898 (94.0)	
Single	7 (9.5)	38 (4.0)	
Separate or divorced	5 (6.8)	19 (2.0)	
Comorbid conditions			
HTN	16 (21.6)	218 (22.8)	0.688
DM	7 (9.5)	85 (8.9)	0.871
IPSS	9.66±4.93	4.95±2.73	<0.001
IIEF			
EF subscore	17.65±9.20	23.86±6.89	<0.001
OF subscore	5.95±3.46	8.05±2.62	<0.001
SD subscore	5.57±2.07	6.92±1.87	<0.001
IS subscore	5.92±3.64	9.12±3.27	<0.001
OS subscore	5.04±2.05	7.09±1.77	<0.001
MSHQ-EjD	23.96±7.50	28.33±4.75	<0.001
PE anxiety score	4.23±1.04	4.59±0.73	<0.001
NIH-CPSI			
Pain subscore	3.72±4.63	1.96±3.27	<0.001
Voiding subscore	3.81±3.04	2.27±2.24	<0.001
QoL subscore	3.86±2.06	3.06±1.90	<0.001
Metabolic characteristics			
Waist circumference (cm)	88.08±10.31	87.49±10.87	0.653
Fasting blood glucose (mg/dL)	92.59±18.89	92.79±20.42	0.937
HDL (mg/dL)	52.57±14.13	52.21±13.35	0.824
TG (mg/dL)	151.05±152.84	138.30±91.64	0.278
Systolic BP (mmHg)	123.76±12.16	125.05±14.57	0.456
Diastolic BP (mmHg)	81.15±9.28	80.79±11.09	0.786
Metabolic syndrome (%)	14 (18.9)	97 (10.2)	0.019
BMI (kg/m ²)	24.51±2.84	24.44±2.83	0.851
Hypogonadism	14 (18.9)	179 (18.7)	0.970
Testosterone (ng/mL)	5.08±1.74	5.03±1.68	0.833

Values are presented as mean±standard deviation or number (%). PE: premature ejaculation, HTN: hypertension, DM: diabetes mellitus, IPSS: International Prostate Symptom Score, IIEF: International Index of Erectile Function, EF: erectile function, OF: orgasmic function, SD: sexual desire, IS: intercourse satisfaction, OS: overall satisfaction, MSHQ-EjD: Male Sexual Health Questionnaire for Ejaculatory Dysfunction, NIH-CPSI: National Institutes of Health Chronic Prostatitis Symptom Index, QoL: quality of life, HDL: high-density lipoprotein, TG: triglyceride, BP: blood pressure, BMI: body mass index.

significantly lower IIEF subdomain, PE anxiety, and MSHQ-EjD scores ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). In addition, there was a significant difference between the two groups in marital status ($p = 0.006$), with a greater proportion of married men in the control group (83.8% vs. 94.0%) and more single men in the acquired PE group (9.5% vs. 4.0%).

2. Univariate and multivariate analysis for premature ejaculation

To determine the correlations among acquired PE, MetS, and other conditions, a logistic regression analysis was performed including the covariates of age, total

IPSS, IIEF subdomains, NIH-CPSI subdomains, MetS, BMI, hypogonadism. Univariate analysis demonstrated that LUTS severity, all NIH-CPSI subdomains and MetS were positively correlated with the prevalence of acquired PE ($p = 0.004$, $p < 0.001$, and $p = 0.022$, respectively), while the IIEF subdomains were negatively correlated with acquired PE ($p < 0.001$; Table 2). After adjusting for the relevant factors, which were significant in univariate analysis, IIEF OS score (OR=0.67, $p < 0.001$), CPSI pain score (OR=1.07, $p = 0.035$), CPSI voiding score (OR=1.17, $p = 0.032$), and MetS (OR=2.20, $p = 0.022$) were significantly associated with the prevalence of acquired PE (Table 2). In particular, the presence of MetS

Table 2. Univariate and multivariate logistic regression analysis of risk factors for acquired premature ejaculation

Variable	Univariate analysis			Multivariate analysis ^a		
	OR	(95% CI)	p-value	OR	(95% CI)	p-value
Age	1.00	(0.97–1.04)	0.782			
IPSS			<0.001			0.443
Mild	1			1	(Reference)	
Moderate	1.72	(0.99–3.00)	0.055	0.75	(0.37–1.52)	0.424
Severe	4.85	(2.51–9.35)	<0.001	1.11	(0.37–3.38)	0.853
IIEF						
EF subscore	0.92	(0.89–0.94)	<0.001	1.01	(0.95–1.07)	0.805
OF subscore	0.81	(0.76–0.87)	<0.001	1.12	(0.97–1.31)	0.130
SD subscore	0.71	(0.62–0.80)	<0.001	0.97	(0.82–1.15)	0.748
IS subscore	0.80	(0.76–0.85)	<0.001	0.86	(0.74–1.01)	0.064
OS subscore	0.61	(0.54–0.69)	<0.001	0.67	(0.53–0.83)	<0.001
NIH-CPSI						
Pain subscore	1.12	(1.06–1.18)	<0.001	1.07	(1.01–1.15)	0.035
Voiding subscore	1.28	(1.15–1.36)	<0.001	1.17	(1.01–1.36)	0.032
QoL subscore	1.24	(1.10–1.40)	<0.001	0.90	(0.75–1.09)	0.271
Metabolic characteristic						
Abnormal WC	1.16	(0.71–2.22)	0.101			
Abnormal BP	0.91	(0.56–1.46)	0.688			
Abnormal FBG	1.07	(0.48–2.40)	0.871			
Abnormal HDL	1.50	(0.85–2.66)	0.159			
Abnormal TG	1.02	(0.62–1.70)	0.930			
Metabolic syndrome						
Absent	1			1	(Reference)	
Present	2.06	(1.11–3.83)	0.022	2.20	(1.12–4.31)	0.022
BMI	0.85	(0.93–1.10)	0.851			
Hypogonadism						
Absent	1					
Present	0.99	(0.54–1.81)	0.970			

OR: odds ratio, CI: confidence interval, IPSS: International Prostate Symptom Score, IIEF: International Index of Erectile Function, EF: erectile function, OF: orgasmic function, SD: sexual desire, IS: intercourse satisfaction, OS: overall satisfaction, NIH-CPSI: National Institutes of Health Chronic Prostatitis Symptom Index, QoL: quality of life, WC: waist circumference, BP: blood pressure, FBG: fasting blood glucose, HDL: high-density lipoprotein, TG: triglyceride, BMI: body mass index.

^aEnter conditional method.

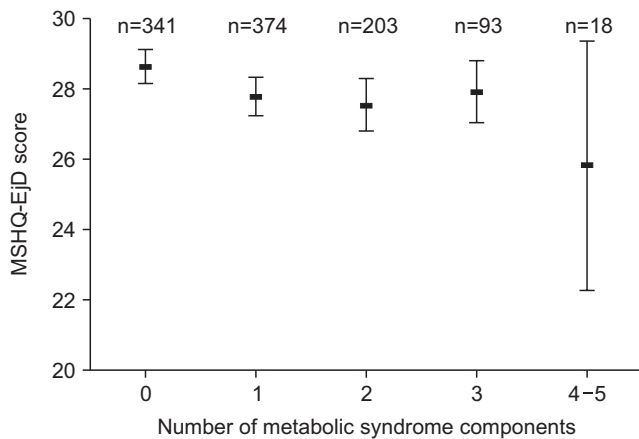


Fig. 1. The relationship between the number of metabolic syndrome components and the Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD) score (mean and 95% confidence interval).

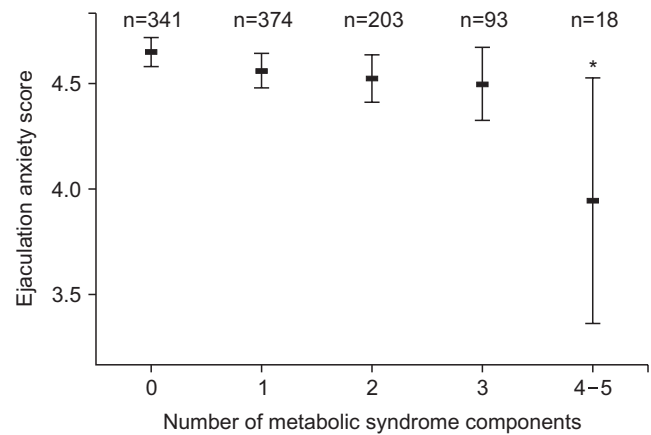


Fig. 2. The relationship between the number of metabolic syndrome components and the ejaculation anxiety score (mean and 95% confidence interval). * $p < 0.05$ vs. 0 metabolic syndrome components.

increased the risk of acquired PE up to 2.2-fold.

3. Metabolic syndrome and other ejaculatory dysfunction

The MSHQ-EjD score progressively decreased as the number of components of MetS increased (ANOVA test, $p=0.027$; Fig. 1). Furthermore, the ejaculation anxiety score significantly decreased as the number of MetS risk factors increased (ANOVA test, $p=0.001$; Fig. 2). After Bonferroni post hoc analysis, the mean ejaculation anxiety scores in patients with 4 or 5 MetS risk factors were significantly lower than in patients with no risk factors ($p=0.001$).

DISCUSSION

The aim of the present study was to investigate the association between acquired PE and various challenging factors that may affect ejaculatory function, such as age, LUTS, erectile dysfunction, prostatitis-like symptoms, testosterone, and MetS. The findings indicated that patients with MetS had a 2.2 times higher risk of acquired PE than controls. In addition, an increasing number of MetS components were associated with lower MSHQ-EjD and ejaculation anxiety scores, indicating that MetS may be associated with not only PE but also other ejaculatory dysfunction. Consistent with our results, a recent study by Bolat et al [17] showed that MetS and its component risk factors are significantly associated with acquired PE.

The underlying mechanism by which MetS contrib-

utes to the occurrence of PE has not been elucidated, but there are some hypotheses. First, MetS may induce psychological changes such as depression, which may precipitate or maintain PE. Previous studies have shown evidence of a bidirectional association between depression and MetS [12,13]. One of the largest studies of 1,598 patients with a risk of cardiovascular disease noted a positive association between depression and MetS [12]. In another study, the number of MetS components at baseline was significantly associated with the development of depression in subsequent years [21]. Second, MetS can influence the etiology of PE by inducing changes in serotonergic receptor function, which is the primary organic cause of PE [14]. Rosmond et al [15] examined 248 Swedish subjects to study the potential impact of *5-HT2A-1438G/A* promoter polymorphism on obesity and found that abnormal production of the *5-HT2A* gene can lead to obesity. In addition, Muldoon et al [16] reported that MetS and physical inactivity could impair central nervous system serotonergic responsivity by measuring prolactin responses induced by serotonin-releasing agents in 270 subjects with cardiovascular risk factors. Finally, MetS induced tissue inflammation such as prostatitis may contribute to the occurrence of PE. In general, the association of obesity and chronic low-grade inflammation has been evident for several years [22]. Recently, prostatic inflammation/infections have been reported to be associated with the prevalence of PE [6], and effective treatment of prostatitis improves IELT and ejaculatory control [23]. Such associations are consistent with the findings of the present study. The risk of acquired

PE statistically significantly increased with NIH-CPSI pain and voiding subdomain scores in this study (OR=1.07, $p=0.035$ and OR=1.17, $p=0.032$). However, it might be difficult to derive clinical implications from a study with a low OR, and more research will be needed in the future.

A few epidemiologic studies have reported that patients with erectile dysfunction have high susceptibility to PE [5]. Through univariate analysis, we also found a significant association between acquired PE and all subdomains of IIEF. After adjustment for the relevant factors, however, only the OS subdomain was significantly associated with acquired PE. This suggests that acquired PE may be partially associated with erectile function. McMahon et al [24] conducted an experiment on patients diagnosed with PE and found that an 8-week administration of sildenafil did not produce significant improvement in PE but improved overall sexual satisfaction and the perception of ejaculatory control and reduced the refractory time before a second erection. However, Lee et al [25] reported that combined therapy of dapoxetine and mirodenafil in patients with lifelong PE improved IELT and overall sexual act time compared with that of dapoxetine alone. While it is evident that PE partially or closely linked to erectile dysfunction, PDE-5 inhibitors as first-line treatment in PE patients without erectile dysfunction are still controversial.

In this study, we also analyzed the association between acquired PE and age, severity of LUTS, and hypogonadism, but did not find a statistically significant association. In the literature, some studies have found age to be a predisposing factor for PE [26]. However, according to a multinational epidemiologic study, the prevalence of PE was similar across countries and age groups (21.0% in those aged 25–34 years, 23.6% in those 35–44 years, and 21.7% in those 45–54 years) [27]. Thus, the exact relationship between age and PE remains unclear due to conflicting study results.

LUTS are generally agreed to be closely associated with erectile dysfunction. Nevertheless, few studies have examined the effect of LUTS on PE. The Epidemiology of LUTS (EpiLUTS) study [4], which consisted of 11,834 men, demonstrated that the presence of terminal dribble, a split stream, incomplete emptying, and bladder area pain were significantly associated with PE (in the EpiLUTS study, the PE question was: “When you have sexual intercourse, how often do you

ejaculate before you wanted to?”). However, unlike our study, the EpiLUTS study did not consider IELT in defining PE and did not exclude patients with a history of using drugs that may influence PE or those who had a history of prostate surgery. Hence, more studies would be needed to identify the exact correlation between LUTS and PE.

While testosterone is known to have a central and peripheral action in the ejaculatory process [28], its association with PE is unclear. An epidemiologic study in 2008 reported that an increase in testosterone is associated with the prevalence of PE [7], but a recent study reported that salivary testosterone is not significantly associated with self-reported IELT [29]. The study also evaluated the association between androgen-related genetic polymorphisms and IELT but did not find a statistically significant association [29]. Such contrasting findings regarding the association between testosterone and PE may be due to the diurnal and day-to-day variation of testosterone. Thus, repeated measurements of testosterone would help to clarify the association between testosterone and PE, but this could not be done in the present study.

Another main limitation of this study is that we diagnosed PE based on a self-reported questionnaire for ejaculatory latency. Self-reported data may be quite different from stopwatch-measured ejaculatory latency. Although we had a relatively large sample size, the prevalence of PE was relatively low, presumably because the diagnosis was based on a self-reported questionnaire. Despite these limitations, our study is meaningful in that we comprehensively analyzed various factors that are known to play a part in the onset of PE and verified that MetS is associated with acquired PE and ejaculatory dysfunction.

CONCLUSIONS

MetS may be an independent predisposing factor for the development of acquired PE. ORs of MetS were higher than those of NIH-CPSI. Therefore, MetS may be an independent predisposing factor for acquired PE, and the effective prevention and treatment of MetS could also be important for the prevention of acquired PE or ejaculatory dysfunction.

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contribution

Research conception and design: Hyun JS, Jeh SU. Data acquisition: Yoon S, Choi JH, Do J, Seo DH, Lee SW, Choi SM. Data analysis and interpretation: Jeh SU, Kang HW. Statistical analysis: Lee C, Kam SC. Drafting of the manuscript: Jeh SU, Hwa JS, Hyun JS. Critical revision of the manuscript: Chung KH, Jeh SU, Hyun JS. Approval of final manuscript: all authors.

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