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Effect of obesity and metabolic health on urolithiasis: A nationwide population-based study

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Purpose: To investigate the risk of symptomatic urolithiasis requiring surgical treatment according to obesity and metabolic health status using a nationwide dataset of the Korean population.

Materials and Methods: Of the 5,300,646 persons who underwent health examinations between the year 2009 and 2016, within one year after the health examination, 35,137 patients who underwent surgical treatment for urolithiasis were enrolled. Participants were classified as "obese" or "non-obese" using a body mass index (BMI) cutoff of 25 kg/m^2. People who developed ≥1 metabolic disease component in the index year were considered "metabolically unhealthy", while those with none were considered "metabolically healthy".

Results: Out of 34,330 participants excluding 843 missing, 16,509 (48.1%), 4,320 (12.6%), 6,456 (18.8%), and 7,045 (20.5%) subjects were classified into the metabolically healthy non-obese (MHNO), metabolically unhealthy non-obese (MUNO), metabolically healthy obese (MHO), and metabolically unhealthy obese (MUO) group, respectively. Mean BMI was 22.1±1.9 kg/m^2, 22.9±1.6 kg/m^2, 26.9±1.8 kg/m^2, and 27.9±2.4 kg/m^2 respectively. After adjusting the age and sex, the subjects in the MUNO group had an HR (95% CI) of 1.192 (1.120–1.268), those in the MHO group, 1.242 (1.183–1.305), and those in the MUO group, 1.341 (1.278–1.407) for either extracorporeal shockwave lithotripsy or surgery, compared to those in the MHNO group.

Conclusions: Metabolically healthy, obese individuals have a higher risk of developing symptomatic urolithiasis than non-obese, unhealthy, but have a lower risk than obese, unhealthy. It suggests that metabolic health and obesity have collaborative effects, independently affecting the development of symptomatic urinary stone diseases.

Keywords: Diabetes mellitus; Insulin resistance; Metabolic syndrome; Obesity; Urolithiasis

INTRODUCTION

The probability of developing urolithiasis during an individual's lifetime is estimated at 5% to 10% [1,2]. The rate of relapse after the onset of the first urinary stone is known to be as high as 50% for 5 years and 80% to 90% for 10 years [3]. Dietary and lifestyle factors play an important role in the epidemiological changes of urinary stone disease. In parallel to the epidemic increase of obesity and diabetes, the prevalence of urinary stone disease is also increasing [4]. In Korea, it is estimated that 6.0% of men and 1.8% of women will experience urolithiasis during their lifetime and the composition of commonly occurring urolithiasis was uric acid stones in men and struvite and calcium phosphate stones in

women [5,6]. The annual incidence of urinary stone disease is increasing, and the noninvasive treatment of symptomatic urinary stone disease is increasing every year [7]. Body mass index (BMI) is the most widely used measure of obesity, and higher BMI is associated with pathological physiology, which can lead to the development of various metabolic diseases and the symptomatic urinary stone diseases. Metabolic status and corresponding clinical outcomes in the same BMI group may vary depending on metabolic health status. Some obese patients are classified as having a metabolically healthy obese (MHO) phenotype because they exhibit low levels of insulin resistance and visceral fat and more favorable cardiovascular risk profile despite high BMI [8,9]. In contrast, people with a metabolically unhealthy non-obese (MUNO) phenotype are characterized by impaired insulin sensitivity, higher levels of abdominal adiposity, blood pressure (BP) and oxidative stress, lower physical activity energy expenditure, more atherogenic lipid profiles, and unfavorable adipokine profiles [10,11]. Several studies showed that people in the MHO or MUNO group have different risks in terms of the incidence of type 2 diabetes, cardiovascular diseases, and mortality [12,13]. There is a need for MHO and MUNO individuals to assess the risk of symptomatic urolithiasis that require active treatment. But there has been no large-scale study to date. For these reasons, we defined urolithiasis in patients who had undergone active treatment such as extracorporeal shockwave lithotripsy (ESWL) and surgery, as symptomatic urolithiasis and conducted this study. Therefore, we aimed to investigate the risk of symptomatic urinary stone diseases requiring surgical treatment according to BMI and metabolic health status using a nationwide dataset of the Korean population.

MATERIALS AND METHODS

1. Data source and study population

The National Health Insurance System (NHIS) comprises a complete set of health information pertaining to 50 million Koreans, which includes an eligibility database (age, sex, socioeconomic variables, type of eligibility, income level, etc.), a medical treatment database (based on the medical bills that were claimed by medical service providers for their medical expense claims), a health examination database (results of general health examinations and questionnaires on lifestyle and behavior) and a medical care institution database (types of medical care institutions, location, equipment, and number of physicians) [14,15]. The source population for this system is the Health Insurance Review and Assessment (HIRA) service. Healthcare providers submit reports on medical services provided under the health insurance policies to the HIRA service for a review of the medical costs incurred. Therefore, the HIRA database contains all the insurance claims information of approximately 97.0% of the Korean population. For this study, we used a customized NHIS database that included about 10% of the Korean population. Subjects were selected using stratified random sampling to ensure that the sample was representative of the entire population. The year when subjects first participated in the health examination was considered as the index year. Of the 5,300,646 persons who underwent health examinations between 2009 and 2016, those with age <20 years (n=7,717) or subjects who diagnosed with urolithiasis before health examination (n=240,594) were excluded. Within one year after the health examination, 35,137 patients were properly treated with urinary stone diseases. Ultimately, the study population consisted of 34,294 subjects except for 843 patients with missing values (Fig. 1).

This study was approved by the Institutional Review Board of Hallym University Kangnam Sacred Heart Hospital of Korea (approval number: HKS 2017-04-004). Anonymized and de-identified information was used for analyses, and therefore informed consent was not obtained.

2. Measurements

BMI was calculated as the patient's weight in kilograms divided by the square of the subject's height in meters. The BMI cutoff of 25 kg/m^2 was adopted to define obesity for the Asian population enrolled in our study. Family histories of hypertension, stroke, heart disease, and diabetes in the first-degree relatives were obtained using a questionnaire. Subjects were categorized as non-smokers, ex-smokers, or current smokers, and as drinking alcohol 0, 1–2, or ≥3 times/week based on the information obtained using the questionnaire. Regular exercise was defined as strenuous physical activity that was performed for at least 20 minutes, and subjects were categorized as exercising 0, 1–4, ≥5 times/week. Income level was dichotomized at the lower 20%. Blood samples were drawn after an overnight fast and measured for serum levels of glucose and total cholesterol. Hospitals wherein these health examinations were performed were certified by the NHIS and subjected to regular quality control.

3. Definition of metabolic health status and symptomatic urolithiasis

Three metabolic disease components (diabetes, hypertension, and dyslipidemia) were used to define metabolic health status. The presence of diabetes was defined according to the following criteria; (1) at least one claim per year for the prescription of antidiabetic medication under International
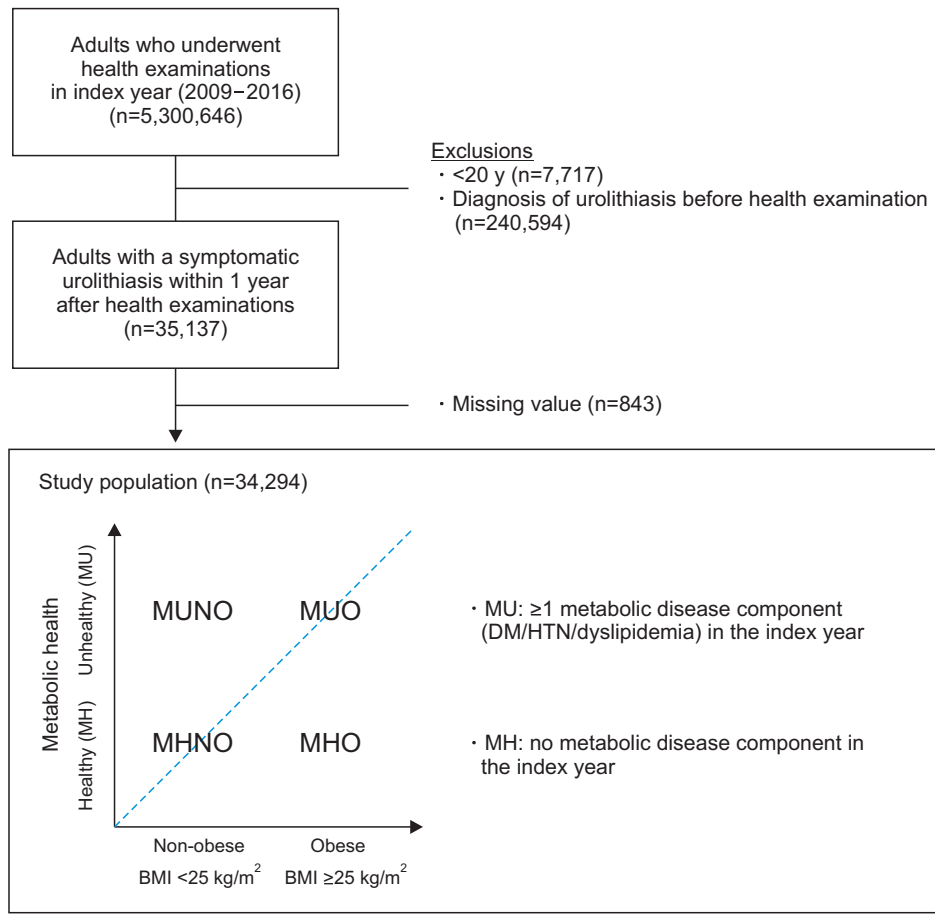
Fig. 1. Flow diagram of study subjects. MUNO, metabolically unhealthy non-obese; MHNO, metabolically healthy non-obese; MUO, metabolically un-healthy obese; MHO, metabolically healthy obese; BMI, body mass index; MH, metabolically healthy; MU, meta-bolically unhealthy; DM, diabetes mel-litus; HTN, hypertension.

Classification of Disease, 10th Revision (ICD-10) codes E10–14, or (2) fasting glucose level ≥7 mmol/L (obtained from the health examination database). The presence of hypertension was defined according to the presence of at least one claim per year for the prescription of an antihypertensive agent under ICD-10 codes I10–I15, or systolic/diastolic BP ≥140/90 mmHg. The presence of dyslipidemia was defined accord-ing to the presence of at least one claim per year for the prescription of an antihyperlipidemic agent under ICD-10 codes E78, or total cholesterol ≥6.21 mmol/L (obtained from the health examination database). Among subjects with BMI <25 kg/m^2, those who developed ≥1 metabolic disease component in the index year were considered MUNO indi-viduals, while those with none of the three metabolic disease components were considered metabolically healthy non-obese (MHNO) individuals. Similarly, among subjects with BMI ≥25 kg/m^2, metabolically unhealthy obese (MUO) and MHO were categorized according to the presence or absence of newly developed metabolic disease components in the index year, respectively. Symptomatic urolithiasis was defined as urolithiasis in adults who underwent active treatment such as ESWL and surgery (Table 1) or both within one year af-ter health examinations.

4. Statistical analyses

Data are expressed as mean±standard deviation, geomet-ric mean (95% confidence interval [CI]), or percentages. The characteristics of the 4 groups according to their BMI and metabolic health status were compared using one-way anal-ysis of variance or chi-squared tests. Hazard ratio (HR) and 95% CI values of ESWL, surgery, and both were analyzed using Cox proportional hazards models among 4 groups us-ing the MHNO group as a reference. The proportional haz-ards assumptions were evaluated by the logarithm of cumu-lative hazards function based on Kaplan–Meier estimates for each group. Multivariable-adjusted proportional hazards model were applied. p-value <0.05 was considered significant. Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

1. Baseline characteristics according to body mass index and metabolic health status

Out of 34,330 participants, 16,509 (48.1%), 4,320 (12.6%), 6,456 (18.8%) and 7,045 (20.5%) subjects were classified into the MHNO, MUNO, MHO, and MUO group, respectively (Fig. 2,

Table 1. Treatment procedures for urolithiasis used in the analyses

	Code	Procedure
ESWL	R3501 (≤2009) R3505 (≥2010)	Extracorporeal shockwave lithotripsy
Surgery	R3211	Percutaneous pyelolithotomy (including PCN)
	R3212	Percutaneous pyelolithotomy (except PCN)
	R3216	Ureteroscopic lithotripsy (upper ureteral stone)
	R3217	Ureteroscopic lithotripsy (mid ureteral stone)
	R3218	Ureteroscopic lithotripsy (lower ureteral stone)
	R3370	Nephrolithotomy
	R3375	Percutaneous nephrolithotomy (including PCN)
	R3376	Percutaneous nephrolithotomy (except PCN)
	R3390	Pyelolithotomy
	R3421	Ureterolithotomy (upper ureteral stone)
	R3422	Ureterolithotomy (mid ureteral stone)
	R3423	Ureterolithotomy (lower ureteral stone)
	R3424	Flexible ureteroscopic lithotripsy (kidney stone)
	R3425	Flexible ureteroscopic lithotripsy (upper ureteral stone)
	R3426	Flexible ureteroscopic lithotripsy (mid ureteral stone)
	R3427	Flexible ureteroscopic lithotripsy (lower ureteral stone)

ESWL, extracorporeal shockwave lithotripsy; PCN, percutaneous nephrostomy.

	MHNO	MUNO	MHO	MUO
Total	16,509	4,320	6,456	7,045
Male	9,632	2,494	4,637	4,742
Female	6,877	1,826	1,819	2,303

Fig. 2. Distribution of study population according to body mass index and metabolic health status. MHNO, metabolically healthy non-obese; MUNO, metabolically unhealthy non-obese; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese.

Table 2). Mean BMI was 22.1±1.9 kg/m², 22.9±1.6 kg/m², 26.9±1.8 kg/m², and 27.9±2.4 kg/m² in the MHNO, MUNO, MHO, and MUO group, respectively (Table 2). By definition, systolic and diastolic BP, fasting glucose, and total cholesterol levels were higher in the MUNO and MUO groups than in the metabolically healthy groups (p<0.001) (Table 2). Distribution of age groups and sex, prevalence of family histories, smoking, alcohol drinking, exercise, and income status also differed among the 4 groups (p<0.001) (Table 2).

2. Treatment methods for symptomatic urolithiasis according to body mass index and metabolic health status

After adjusting the age and sex, the patients in the MUNO group had an HR (95% CI) of 1.192 (1.120–1.268), those in the MHO group, 1.242 (1.183–1.305) and those in the MUO group, 1.341 (1.278–1.407) for either ESWL or surgery, compa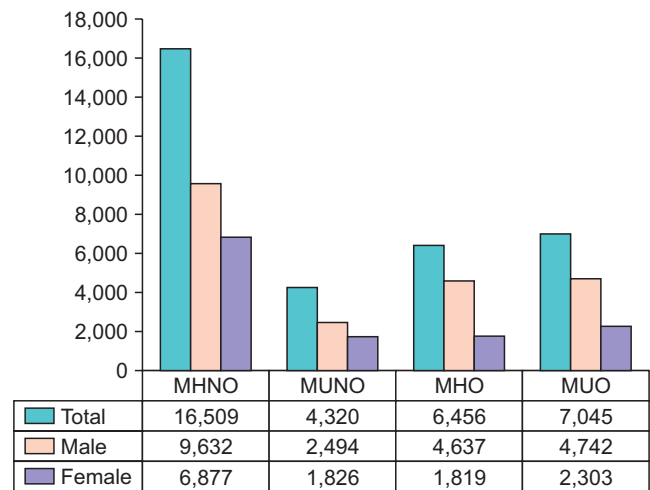red to those in the MHNO group (Table 3). For ESWL only, the subjects in the MUNO group had age and sex-adjusted HR (95% CI) of 1.182 (1.108–1.261), those in the MHO group, 1.250 (1.188–1.314) and those in the MUO group, 1.338 (1.273–1.406) compared to those in the MHNO group (Table 3). For surgery only, the subjects in the MUNO group had age and sex-adjusted HR (95% CI) of 1.178 (0.992–1.400), those in the MHO group, 1.091 (0.934–1.273) and those in the MUO group, 1.411 (1.230–1.619) compared to those in the MHNO group (Table 3). Among the patients receiving both SWL and surgery, and the recurred urolithiasis patients after receiving one of two, the subjects in the MUNO group had age and sex-adjusted HR (95% CI) of 1.195 (1.094–1.306), those in the MHO group, 1.192 (1.111–1.279) and those in the MUO group, 1.316 (1.229–1.410) compared to those in the MHNO group (Table 3). After adjusting for age and sex, the risk of treatment for symptomatic stone diseases was higher in the MUNO group and MHO group than in the MHNO group, and the risk was higher in MUO than in the MUNO group and MHO group, respectively.

DISCUSSION

Obesity and metabolic syndrome interact with urolithiasis risk factors to produce a myriad of body responses that induce stone formation. Obesity is the leading cause of type 2 diabetes worldwide and fatty liver disease and cardiovascular disease. But of the obese, about one tenth had the metabolically healthy phenotype. These metabolically healthy but obese individuals are insulin sensitive, have normal BP, a favorable lipid profile, a lower proportion of visceral

Table 2. Characteristics of subjects according to body mass index and metabolic health status

Variable	MHNO	MUNO	MHO	MUO
Number of patients	16,509 (48.1)	4,320 (12.6)	6,456 (18.8)	7,045 (20.5)
Age (y)	46.4±13.5	57.6±11.8	46.4±12.2	52.5±12.5
20–39	5,170 (31.32)	298 (6.90)	2,049 (31.74)	1,211 (17.19)
40–64	9,572 (57.98)	2,745 (63.54)	3,860 (59.79)	4,527 (64.26)
≥65	1,767 (10.70)	1,277 (29.56)	547 (8.47)	1,307 (18.55)
Sex, male	9,632 (58.34)	2,494 (57.73)	4,637 (71.82)	4,742 (67.31)
Height	164.3±8.9	162.2±9.2	165.6±9.0	164.6±9.6
Weight	59.8±8.6	60.6±8.4	73.9±9.3	75.7±11.2
Body mass index	22.1±1.9	22.9±1.6	26.9±1.8	27.9±2.4
Systolic blood pressure	119.1±13.8	129.5±15.1	123.6±13.4	131.6±14.4
Diastolic blood pressure	74.5±9.4	79.7±10.2	77.6±9.3	81.9±10.0
Fasting glucose	92.8±17.2	111.8±34.4	93.5±14.9	110.3±31.1
Total cholesterol	191.6±42.4	200.3±42.8	201.8±42.7	205.8±48.8
Family history				
Hypertension	1,592 (9.64)	584 (13.52)	738 (11.43)	1,049 (14.89)
Diabetes mellitus	1,327 (8.04)	448 (10.37)	550 (8.52)	780 (11.07)
Heart disease	553 (3.35)	176 (4.07)	203 (3.14)	271 (3.85)
Stroke	947 (5.74)	363 (8.40)	396 (6.13)	519 (7.37)
Smoke				
Non	9,684 (58.66)	2,519 (58.31)	3,279 (50.79)	3,636 (51.61)
Ex	2,498 (15.13)	756 (17.50)	1,205 (18.66)	1,455 (20.65)
Current	4,327 (26.21)	1,045 (24.19)	1,972 (30.55)	1,954 (27.74)
Drink				
Non	8,550 (51.79)	2,629 (60.86)	3,018 (46.75)	3,617 (51.34)
1–2 times/week	5,882 (35.63)	1,100 (25.46)	2,509 (38.86)	2,266 (32.16)
≥3 times/week	2,077 (12.58)	591 (13.68)	929 (14.39)	1,162 (16.49)
Exercise				
Non	8,082 (48.96)	2,323 (53.77)	2,879 (44.59)	3,499 (49.67)
1–4 times/week	6,962 (42.17)	1,542 (35.69)	2,964 (45.91)	2,828 (40.14)
≥5 times/week	1,465 (8.87)	455 (10.53)	613 (9.50)	718 (10.19)
Income, lower 20%	2,841 (17.21)	746 (17.27)	1,033 (16.00)	1,121 (15.91)
Hypertension	3,731 (22.60)	3,009 (69.65)	1,830 (28.35)	4,734 (67.20)
By code/medication	2,927 (17.73)	2,630 (60.88)	1,297 (20.09)	3,862 (54.82)
By health examination	1,467 (8.89)	1,136 (26.30)	929 (14.39)	2,169 (30.79)
Diabetes	644 (3.90)	1,218 (28.19)	230 (3.56)	1,853 (26.30)
By code/medication	405 (2.45)	980 (22.69)	140 (2.17)	1,386 (19.67)
By health examination	435 (2.63)	771 (17.85)	167 (2.59)	1,188 (16.86)
Dyslipidemia	1,434 (8.69)	2,294 (53.10)	876 (13.57)	3,122 (44.32)
By code/medication	290 (1.76)	2,006 (46.44)	82 (1.27)	2,371 (33.66)
By health examination	1,274 (7.72)	779 (18.03)	825 (12.78)	1,337 (18.98)

Values are presented as number (%) or mean±standard deviation.
MHNO, metabolically healthy non-obese; MUNO, metabolically unhealthy non-obese; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese.

fat, less liver fat, and a normal glucose metabolism despite having an excessive amount of body fat [16]. Velho et al. [17] reported among obese (BMI ≥30 kg/m^2) participants, prevalence of MHO ranged between 3.3% and 32.1% in men and between 11.4% and 43.3% in women according to the criteria used. MHO participants had a lower prevalence of family history of type 2 diabetes. After multivariate adjustment, the odds ratio (OR) of presenting with MHO decreased with increasing age, whereas no relationship was found with gender, alcohol consumption or tobacco smoking using most sets of criteria. Physical activity was positively related, whereas increased waist was negatively related with BMI-defined

Table 3. Treatment methods for urolithiasis according to body mass index and metabolic health status

	Number of patients	Event	IR (per 1,000)	Crude HR (95% CI)	Age, sex adjusted HR (95% CI)
ESWL or surgery					
MHNO	16,509	4,880	52.6182	1 (ref.)	1 (ref.)
MUNO	4,320	1,370	59.6448	1.088 (1.025–1.155)	1.192 (1.120–1.268)
MHO	6,456	2,426	73.7307	1.319 (1.256–1.385)	1.242 (1.183–1.305)
MUO	7,045	2,674	75.5911	1.334 (1.273–1.399)	1.341 (1.278–1.407)
ESWL					
MHNO	16,509	4,558	47.9766	1 (ref.)	1 (ref.)
MUNO	4,320	1,254	52.6989	1.063 (0.998–1.131)	1.182 (1.108–1.261)
MHO	6,456	2,293	67.6412	1.330 (1.265–1.399)	1.250 (1.188–1.314)
MUO	7,045	2,488	67.8380	1.324 (1.260–1.390)	1.338 (1.273–1.406)
Surgery					
MHNO	16,509	539	4.33030	1 (ref.)	1 (ref.)
MUNO	4,320	187	5.89895	1.344 (1.138–1.588)	1.178 (0.992–1.400)
MHO	6,456	232	4.74804	1.101 (0.944–1.284)	1.091 (0.934–1.273)
MUO	7,045	349	6.64120	1.528 (1.335–1.748)	1.411 (1.230–1.619)
More than[a]					
MHNO	16,509	2,419	24.6124	1 (ref.)	1 (ref.)
MUNO	4,320	672	27.4543	1.075 (0.987–1.171)	1.195 (1.094–1.306)
MHO	6,456	1,152	32.1972	1.266 (1.180–1.358)	1.192 (1.111–1.279)
MUO	7,045	1,290	33.5542	1.300 (1.215–1.391)	1.316 (1.229–1.410)

IR, incidence rate; HR, hazard ratio; CI, confidence interval; ESWL, extracorporeal shockwave lithotripsy; MHNO, metabolically healthy non-obese; MHO, metabolically healthy obese; MUNO, metabolically unhealthy non-obese; MUO, metabolically unhealthy obese.
[a]:Urolithiasis patients receiving both SWL and surgery, or recurred urolithiasis patients after receiving one of two.

MHO [17].

The association between metabolic syndrome and nephrolithiasis is well documented, with several studies showing a dose-response effect of metabolic syndrome traits toward resultant stone disease [18,19]. Obesity, which is one of these traits, has itself been stated to increase the risk of nephrolithiasis up to 75% compared with normal weight patients [20]. Several large patient cohort studies have shown a correlation between metabolic syndrome and the development of kidney stones. West et al. [21] analyzed the United States National Health and Nutrition Examination Survey III (NHANES III) and found that patients with metabolic syndrome had 2 times the risk of developing a kidney stone based on self-reporting. Rendina et al. [22] reported that 50.9% of patients with sonographic evidence of nephrolithiasis qualified for a diagnosis of metabolic syndrome in a longitudinal study of 2,132 patients in Southern Italy. Jeong et al. [23] reported that among almost 35,000 residents of South Korea who were screened with ultrasonography or computed tomography, 2.4% had radiologic evidence of kidney stones, and 13.7% diagnosed with metabolic syndrome. The presence of metabolic syndrome had an OR of 1.25 (95% CI, 1.03–1.50) for kidney stone prevalence [23]. In this study, the metabolically unhealthy groups had a higher age distribution with or without obesity. After adjusting for age and sex, the risk of treatment for symptomatic stone diseases was higher in the MUNO group and MHO group than in the MHNO group, and the risk was higher in MUO than in the MUNO group and MHO group, respectively. Therefore, the key point we would like to argue in this study is that obesity and metabolic health status individually influence the occurrence of symptomatic stone diseases, and the combination of these two factors has a synergistic effect on the occurrence of symptomatic stone diseases. Our results also showed that ESWL was 8.1 times more than the surgery as a method of active treatment for symptomatic urolithiasis in Korean population.

Obesity is a multifactorial derangement of energy homeostasis causing a complex increase in nephrolithiasis risk, leading to the need for comprehensive metabolic evaluation in these patients. Obesity produces insulin resistance, abnormalities in acid-base handling, changes in urine chemistry, and is associated with dietary misadventures, producing an increased risk of nephrolithiasis [24,25]. Preventive medical therapy for the obesity-associated nephrolithiasis risk can be accomplished through a typical mix of dietary management, fluid intake, and common medical therapy, although physical activity and weight loss are additionally useful [26].

It is known that components of metabolic syndrome independently influence nephrolithiasis formation. West and associates reported that the kidney stone prevalence was 3.7% with no traits, 7.5% for three traits, and 9.8% for five traits [21,27]. Similar correlations have been reported in Japan and South Korea [27]. Patients with metabolic syndrome typically harbor calcium oxalate and uric acid stones. Kadlec et al. [28] found calcium oxalate stone was the most prevalent and uric acid was the next most common component in patients with metabolic syndrome. Ekeruo et al. [29] reported that, in obese stone formers, uric acid stones were more prevalent, apatite stones were less common, and calcium oxalate stones seemed to be equally distributed between the obese and the non-obese. Insulin resistance is associated with decreased ammonium production in the proximal tubule resulting in decreased urine pH, the major driver of uric acid stone formation [30]. Based on our data, metabolic health and obesity can be judged to have synergistic effects, independently affecting the occurrence of symptomatic stone diseases.

There are limitations in our study. First, because disease codes might not represent a participant's exact disease status and prescription of medications does not guarantee compliance, there might be errors in the classification of metabolic health status. Second, this study included symptomatic patients who received ESWL or surgery for urolithiasis, however did not include patients who received chemolysis or medical expulsive therapy. Third, because approximately 40% of subjects in customized NHIS database participated in the health examination, our dataset is not representative of the general population and a possibility of healthy user bias should be considered.

CONCLUSIONS

Metabolic health disorders and obesity individually affect the development of symptomatic urinary stone diseases. Because the combination of metabolic health disorders and obesity has a synergistic effect, metabolic unhealthy and obese patients have a higher risk for symptomatic urinary stone diseases.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

AUTHORS' CONTRIBUTIONS

Research conception and design: Jun Hyun Han. Data acquisition: Changil Choi and Jong Keun Kim. Statistical

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