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ORIGINAL ARTICLE

Effects of metabolic syndrome on renal stone progression

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Abstract

Purpose Studies on howmetabolic syndrome affects renal stone progression in untreated asymptomatic patients are lacking. Therefore, we investigated the effect of metabolic syndrome on changes in renal stone size.

Materials and methods We retrospectively analyzed 820 patients with renal stones incidentally detected on CT during regular health examinations and who underwent follow-up CT evaluations for > 1 year. The patients were divided into two groups according to the presence of metabolic syndrome. Changes in stone size during the follow-up were assessed, and differences were compared according to various factors. Predictors of stone size change on CT were assessed using linear regression analysis.

Results Overall, 820 asymptomatic patients without a history of stone treatments and with a mean follow-up of 52.4 months were included. Of these, 104 (12.7%) had metabolic syndrome and 335 (40.9%) showed stone size increase during the follow-up. The stone size at diagnosis was not significantly different between patients with and without metabolic syndrome (225.3 ± 332.6 vs. 183.9 ± 310.2 mm^3, $p = 0.159$); however, a significant difference was observed in the change in stone size at follow-up (148.5 ± 352.0 vs. 81.5 ± 222.4 mm^3, $p = 0.001$). Multivariable analysis showed that age ($\beta = -0.11$; -5.92 to -0.69; $p = 0.013$), fasting glucose level ≥ 100 mg/dl ($\beta = 0.11$; 9.78–99.73; $p = 0.017$), and metabolic syndrome ($\beta = 0.10$; 9.78–99.73; $p = 0.017$) were factors predictive of stone size changes.

Conclusion Metabolic syndrome, fasting glucose level ≥ 100 mg/dl and young age are positively related to renal stone size changes. Therefore, periodic follow-up and metabolic syndrome management are required in asymptomatic patients with renal stones, especially in young age.

Keywords Kidney calculi · Metabolic syndrome · Observation · Blood glucose · Mass screening

Introduction

Metabolic syndrome (MS) is a cluster of health problems that include abdominal obesity, high blood pressure, high triglyceride (TG) levels, elevated blood sugar levels, and low serum high-density lipoprotein (HDL)-cholesterol levels. The overall prevalence of MS in the US increased from 32.9% in the 2000s to 34.7% in the 2010s [1]. MS is also a common heath problem in Korea, with an overall prevalence of > 30% [2]. MS is known to be related to the development of cardiovascular diseases or type 2 diabetes, and evidence on the association between MS and renal stones is increasing [3]. Several studies have reported the association of MS traits (high waist circumference, increased serum triglyceride level, hypertension, impaired glucose tolerance, diabetes, use of antidiabetic agents, and decreased serum HDL-cholesterol level) and the prevalence of renal stones [4, 5].

Patients with renal stones may present with typical symptoms of flank pain, nausea, and voiding symptoms, whereas some patients show vague abdominal pain or have no symptoms at all. Although the indications for nephrolithiasis are well recognized, the management strategy for small, non-obstructing and asymptomatic renal stones remains unclear. The latest treatment guidelines for urolithiasis recommend active surveillance for asymptomatic calyceal stones [6, 7]. The prevalence of incidentally diagnosed asymptomatic renal stones is increasing owing to increasing use of radiologic imaging in the recent years [8]. The lifetime

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occurrence of renal stones in the US significantly increased from 8.7% in 2007–2008 to 10.1% in 2015–2016 [9]. With the Westernization of lifestyle in Asian countries, the prevalence of renal stones has also recently increased [10]. Various factors are involved in the occurrence of renal stones. In particular, many studies on the relationship between renal stones and obesity have been published [11, 12].

Obesity is a major component of MS, and several studies have proposed that MS is directly involved in renal stone formation [4, 13, 14]. Although the exact pathophysiologic mechanisms underlying the association between MS and renal stones are unclear, MS is known to be related to changes in urine composition, including low urine pH, decreased citrate excretion, and increased calcium and uric acid excretion, which lead to calcium and uric acid stone formation [15]. However, studies on how MS affects renal stone progression in untreated asymptomatic patients are lacking. Elucidating this issue not only can aid the prevention of renal stone development but also may confirm the importance of MS control in managing renal stones and preventing their recurrence. Therefore, we investigated the effect of MS on changes in renal stone size.

Patients and methods

Study participants

We retrospectively analyzed 2925 patients with renal stones incidentally detected on computed tomography (CT) among individuals who visited the health examination center of Ulsan University Hospital for regular health-screening examinations between January 2000 and December 2019. Of these 2925 patients, 1289 patients who underwent CT more than twice during a period of ≥ 1 year were considered eligible. A total of 469 patients were excluded because of missing imaging data ($n = 61$), misdiagnosis of renal stones, presence of calcifications or medullary nephrocalcinosis ($n = 242$), and a history of previous stone treatments ($n = 144$). The remaining 820 patients were included in this study.

Exposure measures

The health-screening program at our hospital includes not only CT imaging but also basic physical examinations and various blood tests that can confirm the presence of MS. The definition of MS followed that of the National Cholesterol Education Program-Third Adult Treatment Panel, with minor variations in threshold measurements [16]. Among the MS traits, abdominal obesity was defined as a waist circumference of > 90 cm for men and > 80 cm for women, according to the World Health Organization Asia–Pacific obesity criteria [17]. MS was diagnosed when three or more of the following five criteria were satisfied: (i) fasting glucose level (FGL) ≥ 100 mg/dl or undergoing treatment for hyperglycemia, (ii) blood pressure ≥ 130/85 mmHg or undergoing treatment for hypertension, (iii) triglyceride level ≥ 150 mg/dl or undergoing treatment for hypertriglyceridemia, (iv) HDL-cholesterol level < 40 mg/dl for men and < 50 mg/dl for women or undergoing treatment for low HDL-cholesterol level, and (v) waist circumference > 90 cm for men and > 80 cm for women.

Outcome measures

The sizes of renal stones were measured using the PACS (Picture Archiving Communications System) measurement tool. The measurements were reported in millimeters to one decimal place. The changes in stone size between the time of diagnosis and the follow-up examinations were measured by two physicians (M.C. Park and J.H. Yoon), and the mean value was used in the analysis. The maximum anteroposterior diameter on axial images and the length and width on mid-sagittal images were measured, and the stone volume was calculated using the prolate ellipsoid formula (0.524 × height × width × length) [18]. The side (right or left) and location (renal calyx or renal pelvis) of the renal stones were recorded.

Statistical analysis

The patients were divided into two groups according to the presence of MS. Continuous variables were compared using Student's *t*-test, and categorical variables were compared using Pearson's Chi-square test. Quantitative data are expressed as mean ± standard deviation. Changes in stone size during the follow-up period were assessed, and differences were compared according to various factors. Predictors of stone size change on CT were assessed using linear regression analysis. The multivariable linear regression model was fitted, and stepwise selection of the least significant factor was performed. All statistical tests were two-tailed, with $p < 0.05$ considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 24.0; IBM, Armonk, NY, USA).

Ethics statement

This study was approved by the Ulsan University Hospital Institutional Review Board (approval no. UUH-2020-04-047). Since all clinical data (patient information, laboratory

test results, and CT data) were retrospectively collected, informed consent was not required.

Results

Patient characteristics

A total of 820 asymptomatic patients with no history of stone treatments and with a mean follow-up of 52.4 months were included. A male predominance was observed (male-to-female ratio, ~ 4.7:1; 82.4% men vs. 17.6% women). Of the 820 patients, 104 (12.7%) had MS (satisfied at least three of the MS criteria) and 335 (40.9%) showed stone size changes during the follow-up. The average stone volume was 189.2 ± 313.2 mm^3 at the time of diagnosis and 278.7 ± 414.8 mm^3 at the last follow-up. The patients' characteristics according to the presence of MS are summarized in Table 1. No significant difference in the follow-up duration was observed between patients with and without MS (53.7 ± 40.4 vs. 52.2 ± 36.2 months, $p = 0.327$). The stone size at the time of diagnosis was not significantly different between patients with and without MS (225.3 ± 332.6 vs. 183.9 ± 310.2 mm^3, $p = 0.159$); however, a significant difference was found in the change in stone size at follow-up (148.5 ± 352.0 vs. 81.5 ± 222.4 mm^3, $p = 0.001$).

Changes in renal stone size according to various factors

The changes in stone size according to various factors are shown in Fig. 1. During a mean follow-up duration of 52.4 months, the size of renal stones in the overall patients increased by 47.3% (from 189.2 ± 313.2 to 278.7 ± 414.8 mm^3). The size of the stones at the time of diagnosis was not significantly different between patients with and without MS (225.3 ± 332.6 vs. 183.9 ± 310.2 mm^3, $p = 0.159$); however, the size change after a mean follow-up period of 53.7 months for patients with MS and 52.2 months for patients without MS was statistically significantly different between the two groups (148.5 ± 352.0 vs. 81.5 ± 222.4 mm^3, $p = 0.001$). The stone size and the size change during the follow-up showed a significant difference according to location (renal pelvis vs. renal calyx, $p < 0.001$). FGL was one of the factors influencing the change in renal stone size. Patients with FGL ≥ 100 mg/dl showed significant differences in the size changes of renal stones from those with FGL < 100 mg/dl ($p < 0.001$).

Factors predictive of stone volume change

Age ($\beta = -0.11$; −5.92 to −0.69; $p = 0.013$), FGL ≥ 100 mg/dl ($\beta = 0.11$; 9.78–99.73; $p = 0.017$), and MS ($\beta = 0.10$;

Table 1 Characteristics of patients with and without metabolic syndrome

Variable	With MS	Without MS	*p* value
No	104	716	
Mean age ± SD, year	47.1 ± 6.7	48.0 ± 6.7	0.649
No. gender, *n* (%)			0.023
Male	94 (90.4)	582 (81.3)	
Female	10 (9.6)	134 (18.7)	
Mean BMI ± SD, kg/m^2	26.0 ± 3.1	23.8 ± 2.5	0.001
Mean total calcium level ± SD, mg/dl	9.4 ± 0.5	9.2 ± 0.4	0.260
Mean albumin level ± SD, g/dl	4.5 ± 0.2	4.4 ± 0.2	0.105
Mean uric acid level ± SD, mg/dl	6.4 ± 1.5	5.7 ± 1.4	0.225
Mean eGFR level ± SD, ml/min/1.73 m^2	104.8 ± 29.2	92.7 ± 21.2	0.001
No. stone location, n (%)			0.274
Pelvis	51 (49.0)	339 (47.3)	
Calyx	53 (51.0)	377 (52.7)	
Multiple stones, *n* (%)	15 (35.7)	90 (27.0)	0.237
Mean stone size (length) ± SD, mm	6.9 ± 2.9	6.6 ± 2.9	0.553
Mean stone size (volume) ± SD, mm^3	225.3 ± 332.6	183.9 ± 310.2	0.159
Mean follow-up period ± SD, month	53.7 ± 40.4	52.2 ± 36.2	0.327
Mean follow-up period in changed stone size	67.9 ± 49.3	57.4 ± 38.4	0.110
Mean follow-up period in unchanged stone size	43.7 ± 29.4	48.6 ± 34.1	0.294
No. stone size change, *n* (%)	43 (41.3)	292 (40.8)	0.913
Mean stone size change (length) ± SD, mm	1.3 ± 2.6	1.0 ± 1.9	0.005
Mean stone size change (volume) ± SD, mm^3	148.5 ± 352.0	81.5 ± 222.4	0.001

MS metabolic syndrome, *SD* standard deviation, *BMI* body mass index, *GFR* glomerular filtration rate

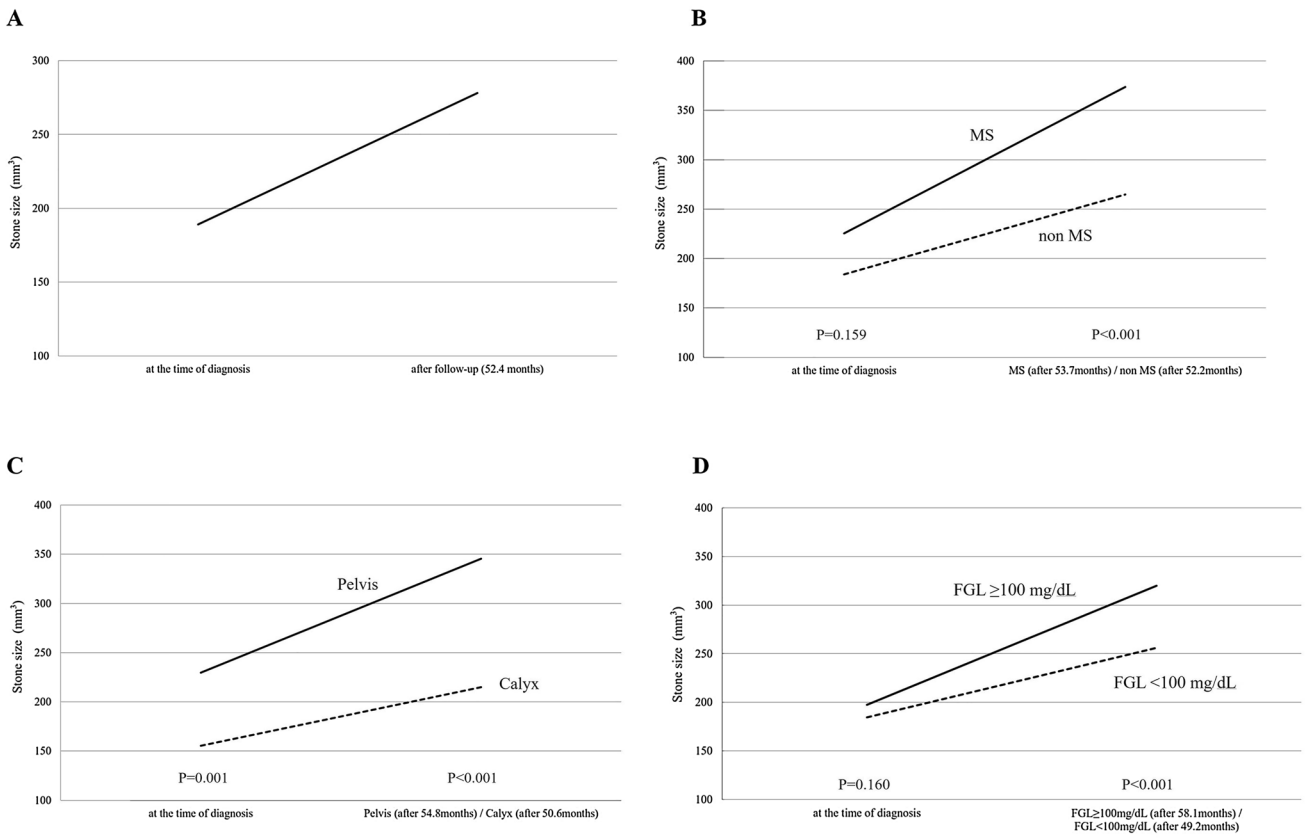

Fig. 1 Changes in renal stone size according to various factors

Table 2 Factors predictive of stone volume change

	Univariate analysis				Multivariable analysis[a]			
	Beta	95% CI		*p* value	Beta	95% CI		*p* value
Age	− 0.08	− 5.42	− 0.49	0.018	− 0.11	− 5.92	− 0.69	0.013
Gender (male)	− 0.51	− 76.47	11.18	0.144				
BMI (kg/m^2)	0.07	− 0.05	12.33	0.052				
eGFR	0.10	0.17	1.87	0.019	0.04			0.384
Stone location (calyx)	0.06	− 6.62	56.14	0.122				
Multiple stone (yes)	0.05	− 26.2	85.81	0.296				
Metabolic syndrome component								
WC (male > 90 cm, female > 80 cm)	0.03	− 55.78	124.97	0.453				
FGL ≥ 100 mg/dl or undergoing treatment	0.10	17.76	87.08	0.003	0.11	9.78	99.73	0.017
BP ≥ 130/85 mmHg or undergoing treatment	0.02	− 23.27	45.49	0.526				
TG ≥ 150 mg/dl or undergoing treatment	0.04	− 16.33	60.12	0.261				
HDL (male < 40 mg/dl, female < 50 mg/dl)	0.03	− 22.45	62.79	0.353				
No. metabolic syndrome component	0.08	4.13	34.60	0.013	0.11			0.384
Metabolic syndrome (yes)	0.09	16.96	116.8	0.009	0.10	9.78	99.73	0.017

Significant variables ($p < 0.05$) according to the univariate analysis were included in the multivariable analysis

[a]Linear regression model (stepwise selection)

9.78–99.73; $p = 0.017$) were factors predictive of stone volume changes (Table 2). Except for FGL, each of the other MS components alone, including waist circumference, blood pressure, TG level, and HDL level, was not a predictive factor of stone volume changes. Similar results were obtained when only patients with a change in stone size were analyzed (Table 3). Age ($\beta = -0.17$; -13.49 to -1.85; $p = 0.010$), FGL ≥ 100 mg/dl ($\beta = 0.15$; 11.06–192.26; $p = 0.028$), and MS ($\beta = 0.19$; 66.78–345.99; $p = 0.004$) were factors predictive of stone volume changes, whereas each metabolic component alone (e.g., waist circumference, blood pressure, and TG/HDL level) was not a predictor of stone size.

Discussion

The prevalence of incidentally detected asymptomatic renal stones is gradually increasing owing to the increasing use of radiologic imaging and the promotion of regular health screening in the recent years [8]. The prevalence of MS is also increasing because of increasing obesity, unhealthy dietary changes, physical inactivity, and genetic factors [1, 5, 14]. In this study, we investigated how MS and other factors can affect the change in the sizes of untreated asymptomatic renal stones. Inci et al. prospectively reviewed 24 patients with asymptomatic renal stones with a mean follow-up of 52.3 months. They found that the 33.3% of the patients showed stone size increase during the follow-up [19]. Hubner et al. reported stone size increase in 45% of asymptomatic patients with renal stones during a follow-up period of 7.4 years [20]. Our study showed a similar result, with 40.9% of the overall patients showing stone size increase during the follow-up.

Many studies have shown that obesity is positively associated with the occurrence of renal stones. Powell et al. investigated 5924 patients and compared 24-h urine chemistry results between patients with and without obesity. Patients with obesity had higher excretion rates of uric acid, calcium, oxalate, sulfate, and cystine, as well as lower urine pH, all of which are contributors to renal stone formation [21]. Taylor et al. reported that body mass index (BMI), waist circumference, and weight gain from early adulthood were associated with an increased risk of renal stone formation [11]. However, in our study, BMI was not a significant predictor of stone volume change. The average BMI was lower and the proportion of patients with severe obesity was much lower in our study than in other studies. Thereby, it was difficult to identify the difference according to obesity in our study.

Several studies have reported the association between MS traits and the prevalence of renal stones. According to West et al., the presence of at least two MS traits was associated with significantly increased odds for renal stone disease compared with the absence of all traits. The presence of four or more traits was associated with an approximately two-fold higher odds for renal stone disease [4]. Kohjimoto et al. reported a significant and stepwise increase in the odds for recurrent or multiple stones. In patients with four MS traits, the odds were 1.8-fold greater than in patients with 0 traits [5]. In terms of stone size, however, our study showed that only high FGL was a predictive factor, whereas the effects of waist circumference, blood pressure, and lipid profile were not significant. According to Domingos and Serra, urine

Table 3 Factors predictive of stone volume change in patients with stone size change

	Univariate analysis				Multivariable analysis[a]			
	Beta	95% CI		*p* value	Beta	95% CI		*p* value
Age	− 0.14	− 13.04	− 1.77	0.010	− 0.17	− 13.49	− 1.85	0.010
Gender (male)	− 0.09	− 181.99	7.47	0.071				
BMI (kg/m^2)	0.16	7.65	35.69	0.003	0.10			0.147
eGFR	0.20	1.02	4.69	0.002	0.07			0.356
Stone location (calyx)	0.08	− 14.79	104.29	0.140				
Multiple stone (yes)	0.12	− 22.45	203.23	0.116				
Metabolic syndrome component								
WC (male > 90 cm, female > 80 cm)	0.08	− 44.19	408.54	0.114				
FGL ≥ 100 mg/dl or undergoing treatment	0.15	29.91	179.66	0.006	0.15	11.06	192.26	0.028
BP ≥ 130/85 mmHg or undergoing treatment	0.04	− 49.90	101.22	0.505				
TG ≥ 150 mg/dl or undergoing treatment	0.09	− 12.55	158.34	0.094				
HDL (male < 40 mg/dl, female < 50 mg/dl)	0.08	− 24.37	167.90	0.143				
No. metabolic syndrome component	0.16	16.88	83.69	0.003	0.05			0.599
Metabolic syndrome (yes)	0.16	50.66	267.63	0.004	0.19	66.78	345.99	0.004

Significant variables ($p < 0.05$) according to the univariate analysis were included in the multivariable analysis

[a]Linear regression model (stepwise selection)

components in patients with MS play an important role in the formation of stones [22]. The mechanism is explained as follows: insulin resistance results in high uric acid levels in urine, which, in turn, increase the risk of formation of uric acid stones. Other studies suggested insulin resistance (leading to increased excretion of lithogenesis promoters and decreased excretion of inhibitors) and inflammatory damage to the renal epithelium caused by oxidative stress (leading to the development of Randall's plaques) as the mechanisms of calcium oxalate stone formation [22, 23]. This may explain why FGL, rather than the other MS components, was the significant predictor of stone volume changes.

In our study, age was an important predictor of stone size change. Patients with renal stones diagnosed at a younger age were more likely to show an increase in stone size. The association between age and stone formation in the pediatric population has been reported in several studies [24, 25]. This finding was attributed to the assumption that younger people consume more meat than elderly people and to the existence of a difference in 24-h urine parameters according to age [26]. Although no definitive data elucidating this apparent association are available, attention should be paid to patients with renal stones diagnosed at a young age.

This study had several limitations that should be considered when interpreting the results. First, because this study had a retrospective design, patients with spontaneous stone passage or those who underwent interventions were not included in this study. This might have affected our results on stone size changes. Moreover, stone component analysis was not performed. Second, our results showed that age was a factor related to the volume change of renal stones. However, this result is difficult to apply to the general population because the age distribution in our study was narrow because the patient group was limited to those who underwent health examinations. Most important, the MS exposure period was not considered. Nevertheless, our study is meaningful as the first large-cohort study to investigate how MS affects renal stone progression. Our study provides important information about the relationship between MS management and renal stone prevention, as well as about the importance of MS control in managing renal stones and preventing their recurrence.

Conclusions

In conclusion, we found that MS, especially FGL, is positively related to renal stone size changes. Periodic follow-up and MS management are required in asymptomatic patients with renal stones. In addition, the effects of MS are greater in younger patients. Therefore, attention should be paid to patients with renal stones diagnosed at a young age. Further studies on the prevention and management of renal stones through MS control are needed.

Author contributions MCP: data collection and manuscript writing. JHY: data collection. SP: data collection. SCK: data collection. SP: data collection. KHM: data collection. SHC: data collection. TK: protocol/project development, data analysis, and manuscript writing/editing.

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Declarations

Ethical approval All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Since clinical data, including patient information and laboratory test results, were retrospectively obtained and analyzed, the requirement for informed consent was waived.

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