The influence of metabolic syndrome and its components on the development of nephrolithiasis

Carter Boyd, Kyle Wood, Dustin Whitaker, Dean G. Assimos

Department of Urology, University of Alabama-Birmingham, Birmingham, AL, USA
University of Alabama-Birmingham School of Medicine, Birmingham, AL, USA

Received 16 November 2017; received in revised form 28 January 2018; accepted 18 April 2018

Available online 8 June 2018

KEYWORDS
Diabetes; Kidney stone; Metabolic syndrome; Obesity; Oxalate; Uric acid; Urolithiasis

Abstract The prevalence of kidney stone disease is increasing, afflicting 7%–11% of the United States population. Multiple systemic conditions, including obesity and diabetes, are also on the rise. Further, the literature has demonstrated a strong association between metabolic syndrome, its components, and kidney stone disease. In this article, we aim to review the associations of metabolic syndrome and nephrolithiasis, discussing the pathophysiology, urinary parameters, and clinical presentations. With this knowledge, urologists will have a more comprehensive understanding of this complex population of metabolic stone formers enabling improved patient management and treatment of stone disease.

© 2018 Editorial Office of Asian Journal of Urology. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Metabolic syndrome (MetS) is a constellation of systemic conditions that place an individual at risk for cardiovascular disease. In this paper, we will review the associations between MetS, its components, and the development of kidney stones. We will also discuss the metabolic factors that drive this risk. We performed a review of the literature using the PubMed Search database. The key terms which we queried were metabolic syndrome, kidney stones, obesity, hypertension, diabetes, hyperlipidemia/dyslipidemia, vascular disease, peripheral arterial disease, and coronary artery disease. We incorporated information from articles which examined the associations between MetS and kidney stone disease as well as the individual components of MetS and their associations.

Various parameters have been used to define MetS. While these definitions vary, the cornerstones include obesity, dyslipidemia, hypertension, and hyperglycemia [1]. Of the numerous guidelines in circulation, the United States National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) is used most frequently due to its
flexibility and reliance on basic metabolic laboratories that are widely available in clinics. The ATP III guidelines for diagnosis of MetS require the presence of three or more of the following five criteria depicted in Table 1. We recognize that some of the guidelines criteria used for defining MetS have limitations and, in these instances, alternative instruments may be utilized. For example, a disadvantage of the ATP III guidelines is the inability to apply them across different ethnic groups, especially in defining obesity and insulin resistance. To address this issue, the International Diabetes Federation (IDF) proposed new guidelines in 2005 with ethnic and racial specific cutoffs. Guidelines from the American Association of Clinical Endocrinologists (AACE), World Health Organization (WHO), and the European Group for the Study of Insulin Resistance (EGIR) are largely focused on insulin resistance determined by euglycemic hyperinsulinemic clamp studies, which are not routinely performed in clinical practice. Other methods of defining Mets are outlined in Table 2. It is important to note that based on these classification systems individuals who are under pharmacologic treatment for diseases such as hypertension, insulin resistance/diabetes, hypertension, and hyperlipidemia are still considered to have these entities even if they are controlled.

A separate discussion of each component of the Mets with respect to kidney stone risk follows. These include obesity, insulin resistance/diabetes, hypertension, and hyperlipidemia/insulin resistance. The interplay between these four factors defines MetS. Similarly, while MetS has overarching systemic effects, it also induces specific changes in body organs, some of which contribute to the development of kidney stones. Vascular complications which can develop are associated with the risk of developing uric acid and calcium oxalate stones. Kidney stone risk has also been shown to be positively correlated with the ratio of visceral to subcutaneous fat tissue and nonalcoholic fatty liver disease.

### 3. Insulin resistance and urolithiasis

In three large cohorts, type 2 diabetes mellitus was a risk factor for developing kidney stones; on multivariate analysis, the relative risk of stone disease in those with diabetes was 1.38 in older women, 1.67 in younger women, and 1.31 in men. Uric acid kidney stone formation has been linked to diabetes. For example, it has been reported that uric acid stone formers have a higher prevalence of diabetes as well as glucose intolerance. Furthermore, those with type 2 diabetes mellitus are at an increased risk of uric acid stone formation.

Fasting glucose levels assist in detecting insulin resistant diabetes mellitus, a disease with progressive negative systemic effects. Hyperglycemia secondary to insulin resistance leads to accumulation of advanced glycation end products (AGEs) inducing a pro-inflammatory state and vascular endothelial dysfunction. Insulin resistance is also associated with decreased ammonium production in the proximal tubule resulting in decreased urine pH, the major driver of uric acid stone formation.

### 4. Hypertension and urolithiasis

Hypertension, a component of MetS, has a bidirectional association with kidney stone risk. Patients with hypertension have been shown to possess a higher risk for stone development and stone formers are predisposed to develop hypertension compared to the general population. The risk of hypertension was higher after a first symptomatic kidney stone event when evaluating Olmstead County data from 2000 to 2011.

### 5. Dyslipidemia and urolithiasis

Elevated serum triglycerides and low high-density lipoprotein (HDL) levels, components of MetS, negatively influence cardiovascular health. Dyslipidemia has been suggested as an independent risk factor for nephrolithiasis as it is associated with lower urine pH. The specific derangements contributing to this increased risk have not been defined. Masterson and colleagues in a retrospective study of 52,184 patients demonstrated an association between dyslipidemia and nephrolithiasis, hazard ratio of 2.2. While low-density lipoprotein (LDL) and triglycerides were not individually associated with stone formation, low HDL

---

**Table 1** NCEP ATP III classification.

| Factors                        | Values                                      |
|--------------------------------|---------------------------------------------|
| Waist circumference (cm)       | >102 (males), >88 (females)                 |
| Fasting glucose (mg/dL)        | ≥100 or Rx                                  |
| Triglycerides (mg/dL)          | ≥150 or Rx                                  |
| High-density lipoprotein (ng/mL)| <40 (males), <50 (females), <40 (Rx)        |
| Blood pressure (mmHg)          | >130 (systolic), >85 (diastolic), or Rx     |

NCEP ATP III: United States National Cholesterol Education Program Adult Treatment Panel III; Rx, pharmacologic intervention for that element.
Metabolic syndrome and nephrolithiasis

Table 2

| Classification | Required elements | Other criteria |
|----------------|------------------|----------------|
| WHO            | MetS             | Microalbuminuria |
| EGIS           | MetS             | Other features of IR |
| IDF            | MetS             | Hypertension >140/90 |
| AACE           | MetS             | Hypertension >130/85 |

ACCE, American Association of Clinical Endocrinologists; BMI, body mass index; CO, central obesity; D, diastolic; EGR, European Group for the Study of Insulin Resistance; IR, insulin resistance; M, male; Rx, pharmacologic intervention for that element; S, systolic; T2DM, type 2 diabetes; TG, triglycerides; WC, waist circumference; WHR, waist-hip ratio.

MetS classifications.

Table 3

| MetS classification | Risk factor | Other criteria |
|---------------------|-------------|----------------|
| WHO                 | BMI > 25 kg/m² | Not part of criteria |
| EGIS                | WHR > 0.85 or WC > 80 cm | Fasting glucose > 100 mg/mL |
| IDF                 | WHR > 0.9 or WC > 94 cm | Fasting glucose > 100 mg/mL |
| AACE                | WHR > 0.85 or WC > 94 cm | Fasting glucose > 100 mg/mL |

West and associates [29] reported that 50.9% of patients with echographic evidence of nephrolithiasis had MetS. Furthermore, after adjusting for age, the occurrence of MetS was associated with echographic evidence of nephrolithiasis (odds ratio 2.0). Inci and associates [4] have reported significantly higher levels of total serum cholesterol and triglycerides in kidney stone formers. For total cholesterol, this relationship was accentuated in patients with uric acid and calcium oxalate stones also had significantly higher total cholesterol, lower HDL, higher systolic blood pressure, and elevated highly sensitive C-reactive protein (hsCRP). They also found that urinary calcium and oxalate were positively correlated with 10-year cardiovascular disease risk and 10-year cardiovascular mortality. Hamano and associates [23] also reported a positive association between several coronary artery disease risk factors and the development of calcium oxalate stones. These factors included smoking, hypertension, hypercholesterolemia, and obesity. Rule and colleagues [24] found kidney stone formers are at increased risk of myocardial infarction independent of some of these risk factors. Kidney stone risk is also associated with peripheral arterial vascular disease. In a longitudinal epidemiologic study (CARDIA) Reiner and associates [25] found that the kidney stone formers had greater carotid artery wall thickness. Patel and colleagues [26] demonstrated that the presence of abdominal aortic calcification found on CT was associated with uric acid stone formation, low urine pH, and hypocitraturia.

6. Cardiovascular disease and urolithiasis

The associations between cardiovascular disease and kidney stones have been well chronicled [21]. Aydin and colleagues [22] reported that cardiovascular disease and mortality were significantly higher in calcium oxalate kidney stone formers than non-stone formers. Those with calcium oxalate stones also had significantly higher total cholesterol, lower HDL, higher systolic blood pressure, and elevated highly sensitive C-reactive protein (hsCRP). They also found that urinary calcium and oxalate were positively correlated with 10-year cardiovascular disease risk and 10-year cardiovascular mortality. Hamano and associates [23] also reported a positive association between several coronary artery disease risk factors and the development of calcium oxalate stones. These factors included smoking, hypertension, hypercholesterolemia, and obesity. Rule and colleagues [24] found kidney stone formers are at increased risk of myocardial infarction independent of some of these risk factors. Kidney stone risk is also associated with peripheral arterial vascular disease. In a longitudinal epidemiologic study (CARDIA) Reiner and associates [25] found that the kidney stone formers had greater carotid artery wall thickness. Patel and colleagues [26] demonstrated that the presence of abdominal aortic calcification found on CT was associated with uric acid stone formation, low urine pH, and hypocitraturia.

7. MetS and urolithiasis

Studies of large patient cohorts have demonstrated the correlation with MetS and the development of kidney stones. West and associates [27] analyzed the United States National Health and Nutrition Examination Survey (NHANES III) and found that patients with MetS had 2 times the risk of developing a kidney stone based on self-reporting [27]. In a longitudinal study of 2132 patients in Southern Italy, Rendina and colleagues [28] reported that 50.9% of patients with echographic evidence of nephrolithiasis qualified for a diagnosis of MetS. Furthermore, after adjusting for age, the occurrence of MetS was associated with echographic evidence of nephrolithiasis (odds ratio 2.0). Inci and associates [4] have reported significantly higher levels of total serum cholesterol and triglycerides in kidney stone formers. For total cholesterol, this relationship was accentuated in patients with uric acid and calcium oxalate monohydrate-dihydrate stones (COM-COD). Additionally, LDL levels were found to be significantly higher in COM-COD stone formers than the COM cohort.

Table 3 outlines these studies including the classification utilized.
| Reference                  | Country     | Study population | Mean age (years) | Female (%) | MetS criteria | MetS population | NL definition | NL population | Prevalence | Adjusted OR |
|----------------------------|-------------|------------------|------------------|------------|---------------|----------------|---------------|---------------|------------|-------------|
| West et al. (2008) [27]    | USA         | 14 870           | 50.1             | 52.4       | AHA/NHLBI     | 4949           | Self-reported history | 699         | History of NL in 8.8% of MetS patients vs. 4.3% in non-MetS patients | E: 1.52 |
| Rendina et al. (2009)      | Italy       | 2 132            | 63.8             | 51.3       | AHA/NHLBI     | 725            | US and self-reported history | 298         | 50.9% of patients with evidence of NL met criteria for MetS | E: 2.0 |
| Jeong et al. (2011)        | Korea       | 34 895           | 50.0             | 40.4       | NCEP ATP III  | 4 779          | CT and/or US | 839          | In MetS, 71% increased OR of kidney stone prevalence vs. non-MetS | E: 1.25 |
| Kohjimoto et al. (2013)    | Japan       | 11 555           | 52.5             | 26.1       | Obesity, BMI ≥ 25 kg/m²; hypertension, BP ≥ 140/90 mmHg; dyslipidemia, LDL ≥ 140 mg/dL, HDL < 40 mg/dL, or TG ≥ 150 mg/dL; diabetes, fasting ≥ 126 mg/dL, 2-h 75-g glucose test ≥ 200 mg/dL or HbA1c ≥ 6.5% | 6 306          | Previous radiologic diagnosis | 11 555      | Component number | E: 1.78 |

AHA, American Heart Association; BMI, body mass index; CT, computed tomography; E, entire study population; F, female; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HTN, hypertension; LDL, low-density lipoprotein; M, male; MetS, metabolic syndrome; NCEP ATP III, United States National Cholesterol Education Program Adult Treatment Panel III; TG, triglycerides; NHLBI, National Heart Lungs and Blood Institute; NL, nephrolithiasis; OR, odds ratio; US, ultrasonography.
8. Stone composition

Patients with MetS typically harbor calcium oxalate and uric acid stones. Kadlec and associates [31] analyzed nearly 600 patients for the involvement of MetS on kidney stone composition. They found that calcium oxalate stones were the most prevalent and uric acid was the next most common composition. Calcium phosphate stones were less prevalent. Relative to the generic stone forming population, the percentage of uric acid stones was significantly higher, and the percentage of calcium phosphate stones was significantly lower in patients with MetS. Cho and colleagues [32] found that the major discordance in composition between those with and without MetS was with uric acid stones, a higher prevalence of such stones in the MetS cohort.

Components of the MetS may also independently influence stone composition. Kadlec and associates [31] found that both hypertension and diabetes mellitus are independently associated with increased uric acid stone frequency and a lower prevalence of calcium phosphate stones. Li and colleagues [33] found that uric acid stone formers have a higher prevalence of obesity compared to other stone formers; 53.1% of uric acid stone formers, 34.3% for calcium phosphate, 42.7% for calcium oxalate, and 38.7% for mixed composition. Ekeruo and associates [34] 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 both cohorts. Nerli and colleagues [35] demonstrated that type 2 diabetic stone formers had a 30% prevalence of uric acid calculi compared to 11% in non-diabetic stone formers. Similarly, the prevalence of uric acid stones has been reported to be significantly higher in those with dyslipidemia, 12% vs. 5.1% [19]. It has been observed that stone composition tends to change with aging and that uric acid stones are more common in older age when compared to calcium oxalate stones [36,37]. This may explain why there is a high prevalence of uric acid stones in patients with MetS, as these patients are generally older.

9. Metabolic factors

The propensity for patients with MetS to form uric acid and calcium oxalate stones is influenced by certain changes in the urinary environment. We subsequently review these urinary stone risk factors and the potential mechanisms leading to stone development.

Uric acid stone formation is a disease of low urine pH which reduces the solubility of uric acid resulting in the generation of such stones. This is attributed to ineffective generation of ammonium in the proximal renal tubule, which is thought to be linked to insulin resistance. A reduction in ammonium generation results in decreased buffering capacity. Thus, there is an increase in titratable acidity and net acid excretion resulting in low urine pH. The lower urine pH provides a favorable urinary milieu for uric acid stone formation [38]. Experiments with the Zucker rat, a model for MetS, show that these animals have lower urine pH, lower urinary ammonium excretion and a higher net acid excretion as compared to lean rats. These differences may be related to an increase in renal fat depositions, fat content being significantly higher in the Zucker rat kidneys. Using an established cell line, this group demonstrated that fat exposure negatively impacts the generation of ammonium in proximal tubular cells [39]. These responses have been correlated to the number of components of the MetS. Maalouf and associates [15] reported that there was a negative correlation between component number and urine pH whereas this positively correlated with urinary ammonium.

The lower urine pH has been linked to some of the components of the MetS. A negative correlation between BMI/body weight with urinary pH has been reported by several investigators. In a large group of stone formers, Maalouf and associates [40] reported a significantly negative correlation between urine pH and body weight [4]. Ekeruo and colleagues [34] demonstrated a similar negative correlation between BMI and urine pH in a similar cohort. Patients with increased BMI are known to have higher levels of visceral obesity and hepatic steatosis, both of which are associated with lower urine pH [41]. Wrobel and associates [42] reported a similar negative correlation between BMI and urine pH in a group of calcium oxalate stone formers. Insulin resistance has been found to be significantly correlated with low 24-h urine pH. Strengthening this association, severe insulin resistance was associated with recurrent uric acid stone formers [43]. Eiers and colleagues [44] demonstrated that patients with type 2 diabetes mellitus had more acidic urine. In addition, higher hemoglobin A1c (HbA1c) levels have been demonstrated to be inversely related to urinary pH [45]. Dyslipidemia is also reported to be associated with low urine pH [19].

Increased oxalate excretion appears to be a potential driving force for calcium oxalate kidney stone in those with MetS. Urinary oxalate excretion is influenced by various components of the MetS. For example, Lemann and associates [46] reported a positive correlation between urinary oxalate excretion and lean body mass. Taylor and Curhan [47] established a positive association between BMI and urinary oxalate in a large epidemiologic cohort study. Ekeruo and associates [34] found that obese kidney stone formers had higher urinary oxalate excretion than non-obese stone formers. In addition, a greater proportion of obese kidney stone formers had hyperoxaluria. Others have demonstrated this relationship between obesity and urinary oxalate excretion [48,49]. Urinary oxalate excretion has also been reported to be higher in diabetic kidney stone formers than those who do not form calculi [44,50,51]. A positive correlation between components of the MetS and prevalence of hyperoxaluria has been reported [52]. A number of yet undefined factors may be promoting increased urinary oxalate excretion including diet, renal and gastrointestinal oxalate transport, the fecal microbiome, and augmented endogenous oxalate synthesis.

Other urinary stone risk parameters have been associated with the MetS and its components. Ticinesi and colleagues [53] investigated the association of urinary calcium and urinary oxalate excretions in calcium stone formers with MetS traits. The only trait associated with increased urinary calcium was hypertension. No MetS traits were associated with oxalate excretion. Siener and associates [54] found a positive association between BMI and excretion of uric acid and ammonium in male and female calcium oxalate stone formers. However, there was only a positive correlation for calcium excretion in
males and oxalate excretion in females. Taylor and Curhan [47] reported a positive correlation between BMI and uric acid and phosphate excretion in a multivariate analysis. While they found a positive correlation with urinary calcium excretion and BMI in a univariate analysis, this was not present when adjustments were made for urinary sodium and phosphate excretion. Cupisti and associates [55] reported that insulin resistance was associated with lower urinary citrate excretion. Kohjimoto also demonstrated [52] a positive correlation between the number of MetS components and prevalence of hypercalciuria, hypocitraturia and hyperuricosuria.

Diet can certainly influence kidney stone risk, and this has been strongly demonstrated in large epidemiologic cohort studies as well as carefully performed metabolic studies. The impact of calcium, sodium, oxalate, animal protein and fluid intake are well chronicled [56–67]. It is highly likely that patients with metabolic syndrome and kidney stones have dietary indiscretions that are highly likely that patients with metabolic syndrome and kidney stones have dietary indiscretions that are highly likely that patients with metabolic syndrome and kidney stones have dietary indiscretions that are highly likely that patients with metabolic syndrome and kidney stones have dietary indiscretions that are highly likely that patients with metabolic syndrome and kidney stones have dietary indiscretions that are highly likely that patients with metabolic syndrome and kidney stones have dietary indiscretions that are highly likely that patients with metabolic syndrome and kidney stones have dietary indiscretions that are highly likely that patients with metabolic syndrome and kidney stones have dietary indiscretions that are highly likely that patients with metabolic syndrome and kidney stones have dietary indiscretions that are highly likely that patients with metabolic syndrome and kidney stones have dietary indiscretions that are.

10. Conclusion

There is compelling evidence that MetS and its components are associated with the risk of developing kidney stones, particularly calcium oxalate and uric acid. Changes in urinary risk factors appear to be contributory. However, other processes such as systemic inflammation and oxidative stress, which are prevalent in this cohort, may also play a role. Reversing these conditions may also eradicate stone risk factors and should be considered a management strategy; an approach that has been demonstrated in animal models [68].

Author contributions

Study design: Carter Boyd, Dustin Whitaker, Kyle Wood, Dean G. Assimos.

Data acquisition: Carter Boyd, Dustin Whitaker, Kyle Wood.

Data analysis: Carter Boyd, Dustin Whitaker, Kyle Wood, Dean G. Assimos.

Drafting of manuscript: Carter Boyd, Dustin Whitaker, Kyle Wood, Dean G. Assimos.

Critical revision of the manuscript: Carter Boyd, Dustin Whitaker, Kyle Wood, Dean G. Assimos.

Supervision: Dean G. Assimos, Kyle Wood.

Conflicts of interest

The authors declare no conflict of interest.

References

[1] Gorbachinsky I, Akpinar H, Assimos DG. Metabolic syndrome and urologic diseases. Rev Urol 2010;12:e157–80.
Metabolic syndrome and nephrolithiasis

[24] Rule AD, Roger VL, Melton 3rd LJ, Bergstrahl EJ, Li X, Peyser PA, et al. Kidney stones associate with increased risk for myocardial infarction. J Am Soc Nephrol 2010;21:1641–4.

[25] Reiner AP, Kahn A, Elsner BH, Pletcher MJ, Sadetsky N, Williams OD, et al. Kidney stones and subclinical atherosclerosis in young adults: the CARDIA study. J Urol 2011;185:920–5.

[26] Patel ND, Ward RD, Calle J, Remer EM, Monga M. Vascular disease and kidney stones: abdominal aortic calcifications are associated with low urine pH and hypocitraturia. J Endourology 2017;31:956–61.

[27] West B, Luke A, Durazo-Arvizu RA, Cao G, Shoham D, Kramer H. Metabolic syndrome and self-reported history of kidney stones: the National Health and Nutrition Examination Survey (NHANES III) 1988–1994. Am J Kidney Dis 2008;51:741–7.

[28] Rendina D, Mossetti G, De Filippo G, Benvenuto D, Vivona CL, Imbroinise A, et al. Association between metabolic syndrome and nephrolithiasis in an inpatient population in southern Italy: role of gender, hypertension and abdominal obesity. Nephrol Dial Transplant 2009;24:900–6.

[29] Wong Y, Cook P, Roderick P, Somani BK. Metabolic syndrome and kidney stones: a systematic review of literature. J Endourol 2016;30:246–53.

[30] Jeong IG, Kang T, Bang JK, Park J, Kim W, Hwang SS, et al. Association between metabolic syndrome and the presence of kidney stones in a screened population. Am J Kidney Dis 2011;58:383–8.

[31] Kadlec AO, Greco K, Fridrici ZC, Hart ST, Vellos T, Turk TM. Metabolic syndrome and urinary stone composition: what factors matter most? Urology 2012;80:805–10.

[32] Cho ST, Jung SI, Myung SC, Kim TH. Correlation of metabolic syndrome with urinary stone composition. Int J Urol 2013;20:208–13.

[33] Li WM, Chou YH, Li CC, Liu CC, Huang SP, Wu WJ, et al. Association of body mass index and urine pH in patients with urolithiasis. Urol Res 2009;37:193–6.

[34] Ekeruo WO, Tan YH, Young MD, Dahm P, Maloney ME, Mathias BJ, et al. Metabolic risk factors and the impact of medical therapy on the management of nephrolithiasis in obese patients. J Urol 2004;172:159–63.

[35] Netri R, Jali M, Gunataka AK, Patne P, Patil S, Hiremath MB. Type 2 diabetes mellitus and renal stones. Adv Biomed Res 2015;4:180. https://doi.org/10.4103/2277-9715.e

[36] Knoll T, Schubert AB, Fahlenkamp D, Leussmann DB, Wendt-Nordahl G, Schubert G. Urolithiasis through the ages: data on more than 200,000 urinary stone analyses. J Urol 2011;185:1304–11.

[37] Krambeck AE, Lieske JC, Li X, Bergstralh EJ, Melton 3rd LJ, Rule AD. Effect of age on the clinical presentation of incident symptomatic urolithiasis in the general population. J Urol 2013;189:158–64.

[38] Ngo TC, Assimos DG. Uric acid nephrolithiasis: recent progress and future directions. Rev Urol 2007;9:17–27.

[39] Bobulescu IA, Dubree M, Zhang J, McIeroy P, Moe OW. Reduction of renal triglyceride accumulation: effects on proximal tubule Na+/H+ exchange and urinary acidification. Am J Physiol Renal Physiol 2009;297:F1419–26.

[40] Maalouf NM, Sakhaee K, Parks JH, Coe FL, Adams-Huet B, Pak CY. Association of urinary pH with body weight in nephrolithiasis. Kidney Int 2004;65:1422–5.

[41] Patel ND, Ward RD, Calle J, Remer EM, Monga M. Computer-ized tomography based diagnosis of vesicular obesity and hepatic steatosis is associated with low urine pH. J Urol 2017;198:1085–90.

[42] Wrobel BM, Schubert G, Hörmann M, Strohmaier WL. Overweight and obesity: risk factors in calcium oxalate stone disease. Adv Urol 2012;2012:438707. https://doi.org/10.1155/2012/438707.e

[43] Abate N, Chandalia M, Cabo-Chan Jr AV, Moe OW, Sakhaee K. The metabolic syndrome and uric acid nephrolithiasis: novel features of renal manifestation of insulin resistance. Kidney Int 2004;65:386–92.

[44] Elsner BH, Porten SP, Bechis SK, Stoller ML. Diabetic kidney stone formers excrete more oxalate and have lower urine pH than nondiabetic stone formers. J Urol 2010;183:2244–8.

[45] Torricelli FC, De S, Gebreelassie S, Li I, Sarkissian C, Monga M. Type-2 diabetes and kidney stones: impact of diabetes medications and glycemic control. Urology 2014;84:544–8.

[46] Lemann Jr J, Pleuss JA, Wrocławstum L, Hornick L, Schrab D, Hoffmann RG. Urinary oxalate excretion increases with body size and decreases with increasing dietary calcium intake among healthy adults. Kidney Int 1996;49:200–8.

[47] Taylor EN, Curhan GC. Body size and 24-hour urine composition. Am J Kidney Dis 2006;48:904–15.

[48] Tranchieri A, Croppi E, Montanari E. Obesity and urolithiasis: evidence of regional influences. Urolithiasis 2017;45:271–8.

[49] Curhan GC, Willett WC, Rimm EB, Speizer FE, Stampfer MJ. Body size and risk of kidney stones. J Am Soc Nephrol 1998;9:1645–52.

[50] Hartman C, Friedlander JJ, Moreira DM, Elsamra SE, Smith AD, Okeze Z. Differences in 24-h urine composition between nephrolithiasis patients with and without diabetes mellitus. BJU Int 2015;115:619–24.

[51] Taylor EN, Curhan GC. Determinants of 24-hour urinary oxalate excretion. Clin J Am Soc Nephrol 2008;3:1453–60.

[52] Kohjimoto Y, Sasaki Y, Inouchi M, Matsumura N, Inagaki T, Hara I. Association of metabolic syndrome traits and severity of kidney stones: results from a nationwide survey on urolithiasis in Japan. Am J Kidney Dis 2013;61:923–9.

[53] Ticinesi A, Guerra A, Allegri F, Nouvenne A, Cervellin G, Maggio M, et al. Determinants of calcium and oxalate excretion in subjects with calcium nephrolithiasis: the role of metabolic syndrome traits. J Nephrol 2018;31:395–403.

[54] Siener R, Glatz S, Nicolay C, Hesse A. The role of overweight and obesity in calcium renal stone formation. Obes Res 2004;12:106–13.

[55] Cupisti A, Meola M, D’Alessandro C, Bernabini G, Pasquali E, Carpi A, et al. Insulin resistance and low urinary citrate excretion in calcium stone formers. Biomed Pharmacother 2007;61:86–90.

[56] Curhan GC, Willett WC, Speizer FE, Spiegelman D, Stampfer MJ. Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. Ann Intern Med 1997;126:497–504.

[57] Sorensen MD, Kahn AJ, Reiner AP, Tseng TY, Shikany JM, Wallace RB, et al. Impact of nutritional factors on incident kidney stone disease: a systematic review of literature. J Urol 2012;189:1645–9.

[58] Borghi L, Meschi T, Amato F, Briganti A, Novarini A, Giannini A. Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis. Urolithiasis 2017;45:271–8.

[59] Remer EM, Monga M. Association of metabolic syndrome traits and severity of kidney stones. Adv Biomed Res 2012;2012:438707. https://doi.org/10.1155/2012/438707.e

[60] Rule AD, Roger VL, Melton 3rd LJ, Bergstrahl EJ, Li X, Peyser PA, et al. Kidney stones associate with increased risk for myocardial infarction. J Am Soc Nephrol 2010;21:1641–4.
[62] Taylor EN, Curhan GC. Dietary calcium from dairy and nondairy sources, and risk of symptomatic kidney stones. J Urol 2013;190:1255–9.

[63] Sakhaee K, Harvey JA, Padalino PK, Whitson P, Pak CY. The potential role of salt abuse on the risk for kidney stone formation. J Urol 1993;150:310–2.

[64] Nouvenne A, Meschi T, Prati B, Guerra A, Allegri F, Vezzoli G, et al. Effects of a low-salt diet on idiopathic hypercalciuria in calcium-oxalate stone formers: a 3-mo randomized controlled trial. Am J Clin Nutr 2010;91:565–70.

[65] Breslau NA, Brinkley L, Hill KD, Pak CY. Relationship of animal protein-rich diet to kidney stone formation and calcium metabolism. J Clin Endocrinol Metab 1988;66:140–6.

[66] Knight J, Easter LH, Neiberg R, Assimos DG, Holmes RP. Increased protein intake on controlled oxalate diets does not increase urinary oxalate excretion. Urol Res 2009;37:63–8.

[67] Taylor EN, Curhan GC. Oxalate intake and the risk for nephrolithiasis. J Am Soc Nephrol 2007;18:2198–204.

[68] Sasaki Y, Kohjimoto Y, Iba A, Matsumura N, Hara I. Weight loss intervention reduces the risk of kidney stone formation in a rat model of metabolic syndrome. Int J Urol 2015;22:404–9.