

### Metabolic syndrome & Nephrolithiasis

Dr. Firouzeh Moeinzadeh Associate professor of Nephrology Isfahan Kidney Diseases Research Center Isfahan University of Medical Sciences

### Outline:

- What is the Metabolic syndrome?
- Common disease related to metabolic syndrome
- Obesity and kidney stone
- Studies on the Pathophysiology of Stone Formation
- Response of Obese Patients to Medical Therapy for Stone Prevention
- Weight Management and Treatment
- Bariatric surgery & kidney stone formation

### Metabolic syndrome definition

- $\rightarrow$  Elevated waist circumference ( $\geq$  88 cm for women;  $\geq$  102 cm for men)
- → Elevated triglycerides (≥ 150 mg/dL) or drug treatment for elevated triglycerides
- Low HDL cholesterol (< 40 mg/dL for men; < 50 mg/dL for women) or drug treatment for low HDL
- → Elevated blood pressure (systolic ≥ 130 mm Hg or diastolic ≥ 85 mm Hg) or hypertensive drug treatment
- → Elevated fasting glucose (≥ 100 mg/dL) or drug treatment for elevated glucose

# Common disease related to metabolic syndrome



# Obesity contributes to chronic disease development and progression:



Yang, M.; Liu, S.; Zhang, C. The Related Metabolic Diseases and Treatments of Obesity. *Healthcare* **2022**, *10*, 1616. https://doi.org/10.3390/healthcare10091616

### Obesity and kidney stone



#### Conclusion

MHO persons: higher risks of kidney stones, suggesting that obesity can independently contribute to kidney stones in the absence of metabolic abnormalities and insulin resistance

Chen W, Man S, Hong Y, Kadeerhan G, Chen L, Xu Q, Xiong L, Xu T, Wang B and Huang X (2023) Association between metabolically healthy obesity and kidney stones: results from the 2011–2018 National Health and Nutrition Examination Survey. *Front. Public Health*. 11:1103393. doi: 6 10.3389/fpubh.2023.1103393

### Obesity and kidney stone

- BMI, waist circumference, and weight are positively associated with the risk of developing incident kidney stones<sup>1.</sup>
- BMI was significantly higher in stone formers and may be associated with different types of urinary stone formation<sup>2</sup>
- 84,225 postmenopausal women: multivariate analyses showed an elevated BMI is associated with a 1.30-fold increased risk of incident kidney stones compared with women with a BMI in the normal range<sup>3</sup>

10/14/1402

1. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. JAMA. 2005;293:455–462.

2.Inci M, Demirtas A, Sarli B, et al. Association between body mass index, lipid profiles, and types of urinary stones. *Ren Fail*. 2012;34:1140–1143.
3. Sorensen MD, Chi T, Shara NM, et al. Activity, energy intake, obesity, and the risk of incident kidney stones in postmenopausal women: a report from the Women's Health Initiative. *J Am Soc Nenbrol*. 2014;25:362–369.

### Kidney Stones Composition and Prevalence

- Obese patients develop more calcium oxalate stones than uric acid stones
- Patients with uric acid stones have higher rates of obesity than patients with other types of stones

### Uric acid stones formation:

- low urinary pH: due to a **defect in the generation** of ammonia excretion in the nephron.
- Insulin resistance: may impair the transport of ammonia into the proximal tubular lumen as a consequence of attenuation of the Na<sup>+</sup>/H<sup>+</sup> exchanger 3.
- Defect in mitochondrial metabolism of glutamine to glutamate and subsequent conversion to alpha-ketoglutarate that generates ammonia in the proximal tubule cells

### Uric acid stones formation:

- low urinary volume: result in an increased concentration of substances that predispose patients to uric acid kidney stone formation
- Hyperuricosuria:
  - To be a result of nutritional indiscretion: consumption of high amounts of meat
  - Mutations in the URAT1 channel in congenital renal hypouricemia hyperuricosuria being another less common cause

- Inflammation and oxidative stress:
- Associated with: Obesity

Play a role in kidney stone inflammation.



renal crystal deposition in an obese mouse model of metabolic syndrome. J Urol. 10/14/1402

2015;194:1787-1796.

Ob/Ob (Ob) mice with leptin gene deficiencies and MetS-related characteristics

**Higher urinary** oxalate excretion (3.3-fold) when compared with control mice

Increase in inflammatory cytokines in obese mice Reduced the secretion of oxalate in the intestine

Increased net gastrointestinal oxalate absorption and augmented urinary oxalate excretion ultimately leading to stone formation

min R, Asplin J, Jung D, et al. Reduced active transcellular intestinal oxalate secretion contributes to the pathogenesis of obesity-associated hyperoxaluria. 10/14/1402

Kidney Int. 2018:93:1098–1107.

12

- Enhanced systemic inflammation and increased inflammatory cytokines in the small intestine have been reported in murine models of obesity which might augment oxalate absorption<sup>1.</sup>
- Studies in mice and rats: the presence of *Oxalobacter formigenes* or its lysate within the GI tract can promote oxalate secretion<sup>2</sup>.
- Lower levels of oxalate: promote cell growth
- Higher oxalate levels: cell damage and death

#### 10/14/1402

Sakhaee K. Unraveling the mechanisms of obesity-induced hyperoxaluria. *Kidney Int.* 2018;93:1038–1040.
Canales BK, Hatch M. Kidney stone incidence and metabolic urinary changes after modern bariatric surgery: review10f clinical studies, experimental models, and prevention strategies. *Surg Obes Relat Dis.* 2014;10:734–742

- Administration of oxalate or its precursors: Calcium oxalate crystal deposition
- Inflammation and attracting many inflammatory cells including leukocytes, monocytes, macrophages, and multinucleated giant cells.
- This induces further crystal deposition via production of reactive oxygen species. Triggered : calcification and plaque formation in the body

Khan SR. Reactive oxygen species, inflammation and calcium oxalate nephrolithiasis. *Transl Androl Urol.* 2014;3:256–276 10/14/1402

• The mechanism whereby inflammatory cells enter the renal interstitium is not known but it is apparent that chemotactic factors and adhesion molecules are involved.

 Possibly explaining the increased incidence of kidney stones in obese patients who are chronically in an inflammatory state and are thus producing increased levels of reactive oxygen species.



Bobulescu IA, Dubree M, Zhang J. Effect of renal lipid accumulation on proximal tubule Na+/H+ exchange and ammonium 10/14/1402 secretion. *Am J Physiol Renal Physiol.* 2008;294:F1315–F1322. 16

- Renal lipid accumulation decreases the excretion of ammonium in the proximal tubule:
  - An important urinary buffer
- Decrease in pH due to defective ammonium secretion associate with an increased risk for uric acid stone formation.

Bobulescu IA, Dubree M, Zhang J. Effect of renal lipid accumulation on proximal tubule Na+/H+ exchange and ammonium 10/14/1402 secretion. *Am J Physiol Renal Physiol.* 2008;294:F1315–F1322. 17

- In human studies: A positive correlation between BMI and renal cortex TG levels as well as lipid accumulation has been shown.
- Lipid accumulation was most prominent in renal proximal tubular cells.

Bobulescu IA, Lotan Y, Zhang J, et al. Triglycerides in the human kidney cortex: relationship with body size. *PLoS ONE.* 2014;9:e101285. 10/14/1402 Response of Obese Patients to Medical Therapy for Stone Prevention

- Obese stone patients: more resistant to standard medication dosing regimens for kidney stone **prevention**.
- There was a **lower incremental increase in urine pH** and **urinary citrate excretion** in individuals with higher BMI receiving a similar dose of potassium citrate for management of hypocitraturia and urinary pH manipulation therapy for uric acid stones.

## Thus, more frequent adjustments in dosage or the addition of other agents may be necessary.

Astroza GM, Neisius A, Tsivian M, et al. Treatment response in patients with stones, and low urinary pH and hypocitraturia stratified by body mass index. J Urol. 10/14/1402 2016;195:653–657

### Weight Management and Treatment

• Several approaches used to promote weight loss may increase kidney stone risk, including orlistat, a lipase inhibitor



saponification Augment intestinal oxalate absorption, resulting in

increased urinary oxalate excretion.

### Weight Management and Treatment

- Phentermine-topiramate: FDA approved for weight loss
- Topiramate is a carbonic anhydrase inhibitor that promotes a reduction in urinary citrate excretion and increased urine pH

Generation of calcium phosphate stones

Symptomatic kidney stone: 10.7%

Asymptomatic kidney calculi: many

### Bariatric surgery & kidney stone formation

- Malabsorptive bariatric procedures: Roux-en-Y gastric bypass, duodenal switch
  - Increase the risk of developing kidney stones
- Restrictive bariatric operations have not.
- Kidney stones typically develop 2 years after malabsorptive procedures and this has been attributed to increased urinary oxalate excretion

### Bariatric surgery & kidney stone formation

 Increased GI oxalate absorption associated with fat malabsorption, the latter increasing urinary oxalate excretion



Laurenius, A., Sundbom, M., Ottosson, J. *et al.* Incidence of Kidney Stones After Metabolic and Bariatric Surgery—Data from the Scandinavian Obesity Surgery 10/14/1402 Registry. *OBES SURG* **33**, 1564–1570 (2023). https://doi.org/10.1007/s11695-023-06561-y

### Dietary Recommendations for Bariatric Patients to Prevent Kidney Stone Formation



<sup>10/14/1402</sup> Stone Formation. *Nutrients* **2020**, *12*, 1442. https://doi.org/10.3390/nu12051442

### Take home messages

- BMI, waist circumference, and weight are positively associated with the risk of developing incident kidney stones.
- Obese patients develop more calcium oxalate stones than uric acid stones.
- low urinary pH: in Uric acid stone
- More frequent adjustments in dosage or the addition of other agents may be necessary in obese patients.
- Kidney stones typically develop 2 years after malabsorptive procedures and this has been attributed to increased urinary oxalate excretion



10/14/1402