Urolithiasis (2016) 44:3–7
DOI 10.1007/s00240-015-0847-4

INVITED REVIEW

The exposome for kidney stones

David S. Goldfarb[1,2]

Received: 29 September 2015 / Accepted: 5 November 2015 / Published online: 28 November 2015

Abstract The exposome is the assembly and measure of all the exposures of an individual in a lifetime. An individual's exposures begin before birth and include insults from environmental and occupational sources. The associated field is called exposomics, which relies on the application of internal and external exposure assessment methods. Exposomics has not yet been thoroughly applied to the study of kidney stones although much is known about how diet and fluid intake affect nephrolithiasis. Some other novel exposures that may contribute to kidney stones are discussed including use of antibiotics, urbanization and migration to urban heat islands, and occupation. People whose school and jobs limit their access to fluids and adequate bathroom facilities may have higher prevalence of stones. Examples include athletes, teachers, heathcare workers, and cab drivers. Occupational kidney stones have received scant attention and may represent a neglected, and preventable, type of stone. An exposomic-oriented history would include a careful delineation of occupation and activities.

Keywords Kidney stones · Nephrolithiasis · Occupation · Urolithiasis

✉ David S. Goldfarb
dsgold@verizon.net

1 Nephrology Section, New York Harbor VA Healthcare System and NYU Langone Medical Center, New York University School of Medicine, New York, NY, USA

2 Nephrology Section/111G, New York DVAMC, 423 E. 23 St., New York, NY 10010, USA

Introduction

The suffix "-ome" has become rampant in biology and medicine and has been used to denote a complete accounting of molecular components. Wikipedia.com says that in cellular and molecular biology, the suffix is used to form nouns with the sense of "all constituents considered collectively". Success in mapping the human genome led that word to become a model for the proteome, the microbiome and the metabolome, as some prominent examples. A newer concept is that of the exposome, the assembly and measure of all the exposures of an individual in a lifetime [1]. Having then collected these exposures, one can apply a variety of new techniques utilizing large databases to try to determine how those exposures relate to health. Ideally, an individual's exposures begin before birth and includes insults from environmental and occupational sources.

This effort is leading to a field called exposomics, which relies on the application of internal and external exposure assessment methods. Disease (and health) is the result of how exposures are then filtered through the unique characteristics of each individual (Fig. 1) [1]. To a large degree, those unique characteristics constitute the genetics of individuals, their susceptibilities and resistances.

The exposome for kidney stone formation

Lithology, the study of kidney stones, has long been interested in risk factors for stone formation, both exposures and "unique characteristics" that determine whether the exposures have an effect. The "unique characteristics" of individuals include their genes and their contribution to kidney stone disease. The genetics of stone disease has yielded

Fig. 1 Exposures, constituting the exposome, are filtered by our unique characteristics (particularly heredity), to yield our individual disease states. Modified from (1)

much new information of late, and advanced rapidly, with a thorough understanding of rare genetic causes of kidney stones [2]. However, the genetic basis for the large hereditary component of stones in the general population remains unexplained [3].

As for exposures, a vast literature reporting on epidemiologic data has led to many notable advances in the science of stones. The conclusions of this body of work are that there are many exposures relevant to stone disease, which, unlike genetics, represent modifiable risk factors for stones, including fluid intake, diet, body habitus, exercise, and drug exposures. Diet and fluid intake have particularly been studied with regard to their effects on both urine chemistry (a surrogate for stone formation), as well as on the outcome of interest: clinically important kidney stones [4].

Ambient temperature and kidney stones

A recent exposure of interest leading to stone disease is that of ambient temperature. At warmer temperatures, perspiration advances via dermal losses and urinary concentration due to increasing vasopressin levels ensues. Urinary supersaturation supervenes and kidney stone formation occurs. The awareness of this association goes back to at least 1945 [5]. The extreme case of this phenomenon demonstrates the rapidity with which stones can form. In US service men deployed to the hot environment of Kuwait, the mean period of time before presentation with a kidney stone was 93 days [6].

The "stone belt" of the United States, the southern states, has a higher rate of stones than cooler, more northern, states [7]. Although diet and genetic variation may be alternative explanations, the warmer year-round temperatures are likely the important causative variable. Projections of global warming advancing northward suggest that every 1 °C increase in ambient temperature will cause a 4.2 % increase in stone risk [8]. In that case, by 2050, higher temperatures could cause an additional 1.6–2.2 million kidney stone cases in the US, representing up to a 30 % increase in some areas.

While global warming has increased the temperature of the Earth by less than 1 °C in the last century, kidney stones have been increasing in prevalence for as long as there are reliable data, extending back about 30 years [9, 10]. A temperature-related explanation could be progressive urbanization, with more people exposed to urban heat islands (UHIs) [11]. Urbanization is the increase in the proportion of the Earth's population living in urban areas. Some of this increase in urban populations is due to migration and some due to reproduction. Lack of vegetation and effects of urban architecture lead to the formation of UHIs, areas in cities particularly warmer than more rural areas. To date, no studies have thoroughly examined data regarding the health effects of urbanization, though changes in diet, income, and activities may be relevant variables. Exposure to UHIs clearly has acute health effects, such as death from heat exposure, and may also have chronic effects, such as increased prevalence of stone disease.

Antibiotics and kidney stones

An additional novel exposure influencing stone disease could be the use of antibiotics. The protective effect of the colonic bacterium *Oxalobacter formigenes* (OF) has been proposed since the organism's discovery. Oxalate is the only substrate of this obligate anaerobe, so that its presence should reduce luminal oxalate available for absorption and excretion in the urine. Its presence is associated with fewer stones, though not all studies have shown that urinary oxalate is lower [12]. The organism also stimulates intestinal secretion of oxalate, suggesting that it has the ability to elicit movement of its substrate from blood to lumen, further reducing urinary oxalate excretion [13]. In the only longitudinal study of OF colonization following antibiotic use, in this case, treatment for *Helicobacter pylori*, OF colonization was substantially reduced at 1 and 6 months [14]. The continued overusage of antibiotics includes more widespread use of broad-spectrum macrolides to which OF is sensitive [15]. OF is present in significantly lower numbers of people in Western countries as compared with Amerindians, likely due to antibiotic use [16, 17]. If OF is truly protective against stones in humans as ample literature suggests, the observed increase in stone disease in the last 30 years may in part be due to exposure to antibiotics.

Occupational kidney stones

We note that one important exposure, however, remains relatively unexamined and not well surveyed or cataloged: occupation. In fact, the National Institute for Occupational Safety and Health (NIOSH) has identified the needs for the new field of exposomics in studying the occupational exposures that people undergo, though not from an interest in kidney stones specifically. NIOSH identifies a need

Table 1 Effect of work location on kidney stones in healthcare professionals: 3921 randomly selected Mayo clinic employees

	OR staff	Non-OR staff
History of stones	14.6 %	9.7 %
Mean # stones	1.8	1.3
Daily fluid intake <1.8 L	63.1 %	48 %
Physicians with stones	17.4 %	9.7 %

Hazard ratio for working in operating room (OR): 1.43 [30]

for investment in and exploration of new technologies and tools to measure internal and external exposures. Studying the associations between exposures and disease will require a new molecular epidemiology. This discipline will also need to develop and validate new methods for biomonitoring to measure both the exposures and the associated effects. That monitoring is further complicated given the need to have some measure of legacy, or past, exposures. In contemplating this new science, it is evident that our ideas about the data that need collecting and that will constitute the epidemiologic future of the study of disease is in flux and changing rapidly. Up until now, most epidemiologic databases used for assessment of kidney stone risk factors, such as NHANES, have not collected all the exposure data one might have liked.

Until these newer methodologies are developed, practitioners must account for occupation when seeing a patient with new onset of stone formation. A detailed understanding of a patient's access to water, access to bathroom facilities, exposure to ambient temperature, and liberties at work or school to attend to fluid and urination requirements are all mandatory.

The inadequacies of the current literature on this subject are clear from a search of the US National Library of Medicine's Pubmed.gov. I conducted a search, not intended to be systematic or all-inclusive, on September 29, 2015. The search was for titles containing "occupation" AND (kidney stones OR nephrolithiasis OR urolithiasis). The yield was four articles, with three actually dealing with the subject of interest [18–20]. If one searches for "work" instead of "occupation", the yield is at most 3 more relevant articles [21–23]. There are certainly others that I have collected that do not meet these narrow criteria, but not many. The practice of my stone clinic suggests this is a more common issue than is reflected in the literature.

The relatively high prevalence of stones in a relatively younger population is well documented. What is less well known is to what extent the workplace contributes to the stone diathesis. As documented by the Urologic Diseases in America Project, more than 1 % of working-age adults were treated for nephrolithiasis in 2000 [24]. In addition, about one-third of employees treated for nephrolithiasis in 2000 missed work due to the condition, with an average work loss for the entire treated population of 19 h per person. If the employees received treatment, the incremental cost of nephrolithiasis was $3494 per person. The authors concluded that "the direct and indirect costs of nephrolithiasis are substantial among working-age adults." That study could have yielded useful information about the degree to which workers attributed low urine volume, as a potential risk factor, to workplace conditions.

Some examples might be useful to illustrate the sorts of cases one encounters. We first became aware of the potential magnitude of occupational kidney stones when we reported a 54-year-old professional driver who presented with polyuria and nocturia. He was not permitted to urinate on long drives made for his demanding employer [25]. The patient was found to have a hypocontractile and dilated bladder on urodynamic study. Ultrasound of the kidneys demonstrated multiple, bilateral, asymptomatic stones. No 24 h urine could be collected on a work day, but he had mild hyperoxaluria and hyperuricosuria on an off-day. After the death of his employer, he drove for the man's daughter, who was happy to stop frequently on the same long drives; the patient was completely more comfortable.

Inspired by that case, we recently reviewed the genitourinary pathology experienced by taxi cab drivers, which we coined "Taxi Cab Syndrome" [26]. There is a surprising amount of documentation that cab drivers suffer from increased prevalence of prostate, bladder and kidney disorders, including kidney stones. In addition, the popular press has repeatedly documented the problem with cab drivers' access to restrooms, with demonstration of the inadequate bathroom facilities in, for example, New York City [27, 28].

Another group that has received attention for low urine volumes, though kidney stones are not the primary pathology that develops, are healthcare workers. Nurses are said to have habitual suppression of the desire to void while working, resulting in overdistension of the bladder, and, like our chauffeur, an increase in the bladder capacity. Contributors to these habits are the hectic work schedule and poor access to adequate toilet facilities. In one study, nurses had a 16 % prevalence of self-reported cystitis compared to 6 % for other women [29]. In a more recent study, healthcare professionals at the Mayo Clinic who worked in an operating room had a hazard ratio of developing kidney stones of 1.43 (Table 1) [30]. OR workers had more stones and lesser fluid intake. One deficiency of this paper is that sex was not reported; it is possible that more OR workers are women (nurses and technicians), making the result that more remarkable. I myself had my first calcium oxalate stone as a house officer in internal medicine, a phenomenon that does not seem unusual, but about which no literature, other than my self-reported case, exists [31].

Similarly, the lay press frequently reports the development of kidney stones among baseball players. Yet, a search of Pubmed.gov for kidney stones and baseball yields nothing. Young men, who presumably have high animal protein diets, spend the summer baking in the sun. While adequate fluids are likely provided, it would appear an ideal situation for the development of stone disease. In a recent case, a player for the New York Mets developed "blood infection" as the result of a symptomatic kidney stone [32].

Implications for treatment

To some extent, most of these putative exposures and risk factors are potentially modifiable. But, to be modified they first need to be identified. After being identified, they also must be monitored. NIOSH has expressed interest in some of the areas where the scientific methods need to evolve. We already have the surrogate measures assayed in a 24 h urine collection. If kidney stone formation correlates with urinary chemistry, methods of reducing urinary calcium and uric acid and increasing urinary citrate excretion are well known and achievable [33]. New methods for reducing urinary oxalate may soon be available as well [34]. Recognition of the need to reduce wanton antibiotic use has led to antibiotic stewardship programs, though kidney stone prevalence obviously is not driving that trend [35]. Similarly, mitigation of urban heat islands has its proponents, again without reference to stone disease [36].

Can occupational kidney stones be mitigated? Lithologists can write letters to employers and principals urging that employees be given adequate liberties to have access to fluids during work and school. Most students of nephrolithiasis think they know the answer to the question "what is the treatment for low urine volume kidney stones?" "Drink more" is the usual advice. We have been oblivious to the fact that in many cases, this is not a reasonable prescription given the proscriptions our patients encounter every day. Those soldiers in Kuwait and those baseball players likely were increasing their fluid intake before they had stone disease, but failed to do so adequately. Of course there are also those who claim that the absence of thirst leads to a failure to drink.

A different answer to the question then is to prescribe potassium citrate for those who cannot increase fluid intake. A testable hypothesis is that administration of potassium citrate, regardless of urine chemistry, to those who are about to experience urinary concentration would be valuable. Examples of the appropriate situations include a surgeon before going to the operating room; a baseball player before the game; a teacher before a day of classes; a cab driver or a steel worker before their shifts. Even administration of potassium citrate at bedtime addresses the likelihood that stones form at night, as fluid intake and urine output wane. This latter strategy allows a less disturbed sleep for all stone formers, a condition with a demonstrable cardiovascular benefit [37].

Acknowledgments This paper is based in part on talks given at the annual meeting of the American Society of Nephrology on 11/10/13 and at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) on 4/1/15. I would like to gratefully acknowledge support of the Rare Kidney Stone Consortium (U54KD083908), a part of NIH Rare Diseases Clinical Research Network (RDCRN), funded by the NIDDK and the National Center for Advancing Translational Sciences.

Compliance with ethical standards

Conflict of interest Dr. Goldfarb is an owner of the Ravine Group and holder of US patent WO 2014152789 A1.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Centers for Disease Control and Prevention (2015) Exposome and exposomics. http://www.cdc.gov/niosh/topics/exposome/. Accessed 29 Sept 2015
2. Edvardsson VO, Goldfarb DS, Lieske JC, Beara-Lasic L, Anglani F, Milliner DS, Palsson R (2013) Hereditary causes of kidney stones and chronic kidney disease. Pediatr Nephrol 28(10):1923–1942. doi:10.1007/s00467-012-2329-z
3. Goldfarb DS, Fischer ME, Keich Y, Goldberg J (2005) A twin study of genetic and dietary influences on nephrolithiasis: a report from the Vietnam Era Twin (VET) registry. Kidney Int 67(3):1053–1061. doi:10.1111/j.1523-1755.2005.00170.x
4. Taylor EN, Curhan GC (2006) Diet and fluid prescription in stone disease. Kidney Int 70(5):835–839
5. Pierce LW, Bloom B (1945) Observations on urolithiasis among American troops in a desert area. J Urol 54:466–470
6. Evans K, Costabile RA (2005) Time to development of symptomatic urinary calculi in a high risk environment. J Urol 173(3):858–861
7. Soucie JM, Thun MJ, Coates RJ, McClellan W, Austin H (1994) Demographic and geographic variability of kidney stones in the United States. Kidney Int 46(3):893–899
8. Brikowski TH, Lotan Y, Pearle MS (2008) Climate-related increase in the prevalence of urolithiasis in the United States. Proc Nat Acad Sci USA 105(28):9841–9846
9. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC (2003) Time trends in reported prevalence of kidney stones in the United States: 1976–1994. Kidney Int 63(5):1817–1823
10. Scales CD, Smith AC, Hanley JM, Saigal CS (2012) Prevalence of kidney stones in the United States. Eur Urol 62(1):160–165
11. Goldfarb DS, Hirsch J (2015) Hypothesis: urbanization and exposure to urban heat islands contribute to increasing prevalence of kidney stones. Med Hypotheses 85(6):953–957. doi:10.1016/j.mehy.2015.09.003
12. Kaufman DW, Kelly JP, Curhan GC, Anderson TE, Dretler SP, Preminger GM, Cave DR (2008) *Oxalobacter formigenes* may reduce the risk of calcium oxalate kidney stones. J Am Soc Nephrol 19(6):1197–1203
13. Hatch M, Cornelius J, Allison M, Sidhu H, Peck A, Freel RW (2006) Oxalobacter sp. reduces urinary oxalate excretion by promoting enteric oxalate secretion. Kidney Int 69(4):691–698

14. Kharlamb V, Schelker J, Francois F, Jiang J, Holmes RP, Goldfarb DS (2011) Oral antibiotic treatment of *Helicobacter pylori* leads to persistently reduced intestinal colonization rates with *Oxalobacter formigenes*. J Endourol 25(11):1781–1785
15. Linder JA, Stafford RS (2001) Antibiotic treatment of adults with sore throat by community primary care physicians: a national survey, 1989–1999. JAMA 286(10):1181–1186
16. Clemente JC, Pehrsson EC, Blaser MJ, Sandhu K, Gao Z, Wang B, Magris M, Hidalgo G, Contreras M, Noya-Alarcon O, Lander O, McDonald J, Cox M, Walter J, Oh PL, Ruiz JF, Rodriguez S, Shen N, Song SJ, Metcalf J, Knight R, Dantas G, Dominguez-Bello MG (2015) The microbiome of uncontacted Amerindians. Sci Adv. doi:10.1126/sciadv.1500183
17. Barnett C, Nazzal L, Goldfarb DS, Blaser MJ (2015) The presence of *Oxalobacter formigenes* in the microbiome of healthy young adults. J Urol. doi:10.1016/j.juro.2015.08.070
18. Borghi L, Meschi T, Amato F, Novarini A, Romanelli A, Cigala F (1993) Hot occupation and nephrolithiasis. J Urol 150(6):1757–1760
19. Ferrie BG, Scott R (1984) Occupation and urinary tract stone disease. Urology 24(5):443–445
20. Burkland CE (1954) Causal factors in urolithiasis; role of possible interrelationship of stress, metabolism, and occupation. Stanf Med Bull 12(2):134–139
21. Pin NT, Ling NY, Siang LH (1992) Dehydration from outdoor work and urinary stones in a tropical environment. Occup Med (Lond) 42(1):30–32
22. Filikowski J, Renke W, Rzepiak M (1992) Observations on the conditions of work of Polish seafarers and their health. Bull Inst Marit Trop Med Gdyn 43(1–4):13–17
23. Laerum E, Aarseth S (1985) Urolithiasis in railroad shopmen in relation to oxalic acid exposure at work. Scand J Work Environ Health 11(2):97–100
24. Saigal CS, Joyce G, Timilsina AR (2005) Direct and indirect costs of nephrolithiasis in an employed population: opportunity for disease management? Kidney Int 68(4):1808–1814
25. Chang MA, Goldfarb DS (2004) Occupational risk for nephrolithiasis and bladder dysfunction in a chauffeur. Urol Res 32(1):41–43
26. Mass AY, Goldfarb DS, Shah O (2014) Taxi cab syndrome: a review of the extensive genitourinary pathology experienced by taxi cab drivers and what we can do to help. Rev Urol 16(3):99–104
27. Martin D (1995) Cabbies gain access to restrooms. New York Times, 12/20/1995
28. Gartland MH, R. (2014) Cabbies holding in their urine to a dangerous degree. New York Post, 10/30/2014
29. Bendtsen AL, Andersen JR, Andersen JT (1991) Infrequent voiders syndrome (nurses bladder). Prevalence among nurses and assistant nurses in a surgical ward. Scand J Urol Nephrol 25(3):201–204
30. Linder BJ, Rangel LJ, Krambeck AE (2013) The effect of work location on urolithiasis in health care professionals. Urolithiasis 41(4):327–331
31. Goldfarb DS (2013) A piece of my mind. Cocktail party nephrology. JAMA 309(24):2561–2562
32. Martino A (2015) NY Mets' Kirk Nieuwenhuis' harrowing staredown with mortality. New York Daily News, 03/26/2015
33. Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denu-Ciocca CJ, Matlaga BR, Monga M, Penniston KL, Preminger GM, Turk TM, White JR, American Urological A (2014) Medical management of kidney stones: AUA guideline. J Urol 192(2):316–324
34. Grujic D, Salido EC, Shenoy BC, Langman CB, McGrath ME, Patel RJ, Rashid A, Mandapati S, Jung CW, Margolin AL (2009) Hyperoxaluria is reduced and nephrocalcinosis prevented with an oxalate-degrading enzyme in mice with hyperoxaluria. Am J Nephrol 29(2):86–93
35. Patel SJ, Larson EL, Kubin CJ, Saiman L (2007) A review of antimicrobial control strategies in hospitalized and ambulatory pediatric populations. Pediatr Infect Dis J 26(6):531–537
36. Akbari H (2005) Energy saving potentials and air quality benefits of urban heat island mitigation. Lawrence Berkeley National Laboratory, http://escholarship.org/uc/item/4qs5f42s. Accessed 29 Sept 2015
37. Kim CW, Chang Y, Zhao D, Cainzos-Achirica M, Ryu S, Jung HS, Yun KE, Choi Y, Ahn J, Zhang Y, Rampal S, Baek Y, Lima JA, Shin H, Guallar E, Cho J, Sung E (2015) Sleep duration, sleep quality, and markers of subclinical arterial disease in healthy men and women. Arterioscler Thromb Vasc Biol 35(10):2238–2245