http://www.kidney-international.org

Ambient temperature as a contributor to kidney stone formation: implications of global warming

Robert J. Fakheri[1] and David S. Goldfarb[1,2]

[1]New York University School of Medicine, New York, New York, USA and [2]Nephrology Section, New York Harbor VA Medical Center and Department of Endourology, Lenox Hill Hospital, New York, New York, USA

Nephrolithiasis is a common disease across the world that is becoming more prevalent. Although the underlying cause for most stones is not known, a body of literature suggests a role of heat and climate as significant risk factors for lithogenesis. Recently, estimates from computer models predicted up to a 10% increase in the prevalence rate in the next half century secondary to the effects of global warming, with a coinciding 25% increase in health-care expenditures. Our aim here is to critically review the medical literature relating stones to ambient temperature. We have categorized the body of evidence by methodology, consisting of comparisons between geographic regions, comparisons over time, and comparisons between people in specialized environments. Although most studies are confounded by other factors like sunlight exposure and regional variation in diet that share some contribution, it appears that heat does play a role in pathogenesis in certain populations. Notably, the role of heat is much greater in men than in women. We also hypothesize that the role of a significant human migration (from rural areas to warmer, urban locales beginning in the last century and projected to continue) may have a greater impact than global warming on the observed worldwide increasing prevalence rate of nephrolithiasis. At this time the limited data available cannot substantiate this proposed mechanism but further studies to investigate this effect are warranted.

Kidney International (2011) **79,** 1178–1185; doi:10.1038/ki.2011.76; published online 30 March 2011

KEYWORDS: calcium oxalate; change, climate; greenhouse effect; nephrolithiasis; urolithiasis

Correspondence: *David S. Goldfarb, Nephrology Section/111G, New York DVAMC, 423 East 23 Street, New York, New York 10010, USA. E-mail: David.Goldfarb@va.gov*

Received 13 October 2010; revised 12 January 2011; accepted 18 January 2011; published online 30 March 2011

With the continued threat of global warming in the news, physicians have lately given much attention to the impact of climate change on human health and health care.[1] The hypothesis that global warming might also increase the rate of renal calculi dates at least as far back as 1989.[2] More recently, an article in the *Proceedings of the National Academy of Sciences* projected the effect of climate change on the incidence of nephrolithiasis (Figure 1).[3] Although the authors claim a 'well established dependence of nephrolithiasis on mean annual temperature,' the link between the two has never been proven unequivocally; in their paper, the authors later concede that 'the precise relationship between ambient temperature and stone risk remains unknown.' Our objective here is to review the medical literature regarding the relationship between temperature and stone formation.

Ambient temperature has been a putative risk factor for nephrolithiasis for quite some time, but distinguishing its effects from other complex factors has been impossible in individual epidemiologic studies. When comparing two different geographic locations, there are many possible confounding explanations for differences in stone incidence or prevalence such as humidity, exposure to sunlight, diet, and genetics. Each of these potential causes for nephrolithiasis can invoke a physiologically plausible effect.

HYPOTHESIZED MECHANISMS OF PATHOGENESIS

The mechanism for higher temperatures causing stone disease is attributed to heat-induced sweating. Loss of extracellular fluid leads to an increase in serum osmolality that in turn causes increased secretion of vasopressin (antidiuretic hormone) by the posterior pituitary, leading to increased urinary concentration and reduced urinary volume. As urinary concentration increases, the concentration of relatively insoluble salts, such as calcium oxalate, increases. When the concentration of these salts increases such that their activity exceeds their upper limit of solubility, the salts precipitate out of solution and form solid crystals that develop into stones. The mechanism for humidity contributing to stone formation is similar: when humidity is low and the air is dry, more water is lost through the skin and, again, urinary volume falls and urinary concentration increases. Whether these mechanisms cause stone formation regardless of where stones originate (renal interstitium or urinary space) is unknown.[4,5]

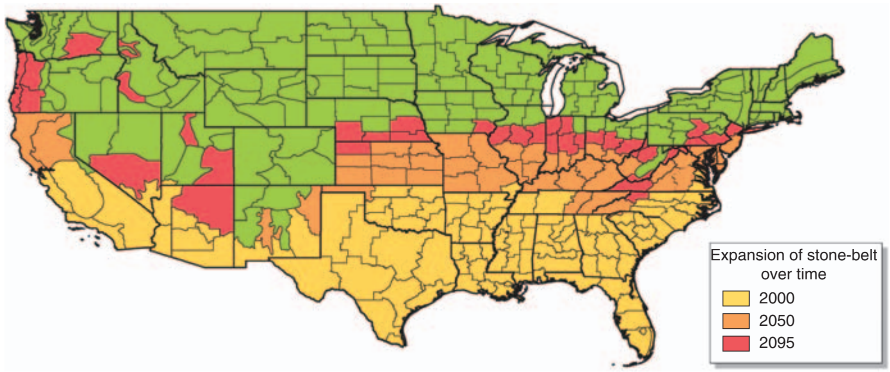

Figure 1 | Map of United States with current 'stone-belt' or high-risk stone area (risk ratio $>$1.2) in yellow. Computer model predicts expansion of stone-belt over time in orange (2050) and in red (2095). Currently, 41% of the population is within a high-risk zone. Computer model predicts 56% of the population will be in a high-risk zone by 2050 and 70% by 2095. Reprinted from Brikowski *et al.*[3] with permission.

Exposure to sunlight is hypothesized to be an alternative explanation for the apparent relationship of ambient temperature to stone prevalence. We will explore whether data support this mechanism in the section on alternative hypotheses.

EVIDENCE FOR AND AGAINST THE ROLE OF TEMPERATURE IN THE PATHOGENESIS OF NEPHROLITHIASIS

The pertinent data that relate to the link between temperature and stone formation can be organized into three categories: (1) comparisons of stone incidence or prevalence in different regions of a single, contiguous geographic area; (2) comparisons of stone incidence over time in a single area—both by comparing seasons in a single year and comparing year after year changes; and (3) comparisons of specialized, thermally different environments to the normal environment of a given population.

Geographical variation in large epidemiological studies

In the United States, Soucie *et al.*[6] looked at data from nationwide surveys to map out the prevalence of kidney stones. The primary findings of the study were in stone prevalence based on geography. They found trends that stone prevalence increased from North to South and West to East. The North-to-South trend correlates well with temperature variation, but the role of climate in the West-to-East trend is much more ambiguous. In fact, the hottest states like Texas, Florida, and Louisiana had lower prevalence than cooler states like North Carolina and South Carolina. Differences in stone prevalence among different races were noted but whether they were accounted for by geographic, genetic, or dietary variation was not elucidated.

In a follow-up analysis by Soucie *et al.*[7], the relation between stone prevalence and specific risk factors such as mean temperature, sunlight index, and beverage consumption was examined. For males, sunlight exposure explained more of the regional variation than mean annual temperature or beverage consumption. For women, beverage consumption, average temperature, and sunlight index each explained

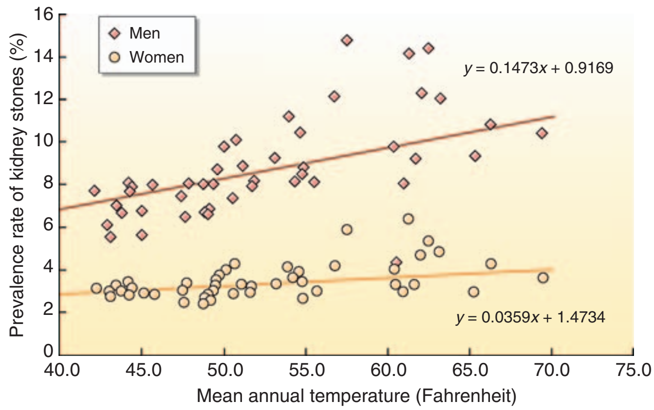

Figure 2 | Scatter plot of prevalence rates for kidney stones in the United States by state for each gender versus the mean annual temperature for that state. Prevalence data obtained from the CPS II study completed in 1982 (ref. 6). Temperature data obtained from the National Climatic Data Center's public database (temperature data presented from 1981 for relevant comparison with the prevalence data). Reprinted as permitted from Fakheri and Goldfarb.[8]

regional variation more or less equally, but even after adjustment for differences in all three risk factors, the regional variation in the odds of stones was still largely unexplained, unlike in males. It was speculated that some of the unexplained variation in the Southeast was because of an enriched gene pool that was prone to lithogenesis.

We reanalyzed the data and plotted the prevalence rates for each state against ambient temperature data corresponding to the time the data were collected (Figure 2).[8] There is clearly a correlation between temperature and stone prevalence rates for men, but a limited and questionable correlation, although a statistically significant one, for women.

We suggested that men had a much steeper effect of increasing ambient temperature on stone prevalence than women because men work outdoors more frequently than women; data supporting this conjecture are not available.[8] Changes in the proportion of women working outdoors may have increased since 1982 and changed the slope of the relationship between ambient temperature and stone prevalence.

These data are consistent with a study of stone-formers that showed that men, but not women, had lower urine volumes in summer, with higher calcium oxalate supersaturation.[9] Urine pH fell in men, but not in women, contributing to a difference in the risk of uric acid stones as well. No explanation to account for these differences was offered. The authors noted that men and women probably sweat to a similar degree as evidenced by their reduced urine sodium excretion, but women are better at replenishing losses. Perhaps, if men work outside more commonly than women, the mechanism, instead of relating to volume depletion from increased perspiration, could be from the limited access to water when working outdoors.

Another possible explanation for the different gender response to temperature is the different stone composition in men versus women. Although struvite stones are only $\sim$10% of all stones, women suffer from them proportionally more often than men: $\sim$3:1 female-to-male ratio.[10] As struvite stones are related to infection, rather than to the urinary supersaturation of calcium salts, one would not expect them to be associated with environmental factors. This may partially explain the gender difference in relation to changes in stone prevalence rates with respect to temperature. As struvite is a relatively infrequent component of stones even among women, the relative flatness of the relationship remains otherwise unexplained. Few data regarding any purported effects of ambient temperature on stone composition are available. One study from Australia showed a trend for both calcium oxalate and uric acid stones to increase in the summer, with only the latter reaching statistical significance.[11]

In Iran, a positive correlation between stone prevalence and both temperature and sunlight index was found for both men and women.[12] As in the United States, however, a stronger effect of temperature for men than for women was noted. The odds ratio for stones was almost twice as high in the hottest, most sunny parts of the country than in the coldest, least sunny parts.

Other countries have conducted similar epidemiological studies. Most are smaller in area than the United States and span fewer latitudes. Therefore, there may be some uncertainty as to whether the range of ambient temperatures is sufficient to detect changes in stone prevalence. In Taiwan, there are regional differences in stone prevalence rates but no correlation between stone prevalence and mean temperature.[13] In Turkey, a national study showed higher prevalence of stone formation in the hottest geographic areas, South and Southeast, but the differences in prevalence rates were not quantitated.[14]

In the United Kingdom, an analysis of hospital discharge rates found a trend toward higher incidence of stones in the southern regions of England.[15] But when this was further analyzed, no correlation was found. Regional variation was probably explained by patients of higher socioeconomic status in the south being admitted more frequently.[16] Whereas higher socioeconomic status could lead to stone formation via changes in diet (for example, higher intake of animal protein), an analysis of dietary variation in the United Kingdom found that consumption of fat, protein, and meat products was in fact inversely correlated with admission rates for stone disease.[17]

Similarly to the British study, in Sudan it was noted that urolithiasis is common in the northern region, farther from the Equator, but relatively rare in the southern region.[18] Statistical analysis did not demonstrate any correlation between mean annual temperature or relative humidity and incidence of calculi. The observed variation may have been because of sampling bias as the data were collected from surgical operations for urolithiasis. In Israel, the regional variation of urolithiasis was studied in the 1950s.[19] There was no simple association with climate. Interestingly enough, the country of origin of the inhabitants of the settlements seemed to play an important role. A later study in Israel of the hot, arid Negev region found similar results in terms of association with climate and country of origin.[20] Moreover, the average incidence rate of 2.4% was twice that of the previous study of northern and central Israel that has a milder climate.

Temporal variation in a single geographic area by season

Other evidence supporting the role of temperature in the pathogenesis of stone disease has been seasonal variation with higher incidence rates during the warmer summer months than the colder winter months. These studies cannot clearly separate effects of ambient temperature from those of sunlight exposure.

One of the first studies to analyze the relation between seasonal variation in temperature and stone incidence was done in Leeds, Great Britain.[21] The investigators analyzed 24-h urine samples from 246 male stone-formers. The data demonstrated statistically significant changes from the minimum value for both calcium and oxalate, with maximum values in the summer. No changes were observed in pH or volume. Rates of stone passage were also increased in the summer. The variation correlated with changes in both ambient temperature and hours of sunlight. A similar, but smaller, study was conducted in Finland.[22] Over the course of a year, the authors studied 11 normocalciuric stone-formers, 11 hypercalciuric stone-formers, 10 healthy subjects, and 14 long-stay hospital patients. The results showed that serum levels of 25-hydroxyvitamin D, urinary calcium, and urinary oxalate were all elevated in the summer for all groups except the hospitalized patients who showed no changes. Moreover, the levels of 25-hydroxyvitamin D were higher throughout the year in hypercalciuric stone-formers than normocalciuric stone-formers. These changes correlated temporally with increases in sunlight measured by units of ultraviolet light. Serum calcium was unchanged in all four groups. The limitations to this study include the small sample size and demographic differences between groups (for example, the long-stay hospital patients were mostly females, whereas the other groups were mostly or all males). Seasonal variation was also evaluated in Kuwait.[23] By looking at emergency room visits for renal colic, the authors found 980 cases of colic in the summer versus only 524 cases in the winter. These totals respectively corresponded to 7.0 and 3.8% of emergency room visits. Statistical analysis was not presented.

When comparing the incidence of stones in a given month to the mean temperature of the previous month, an Iraqi study found that temperature and stone incidence were correlated with threefold as many cases in the peak summer months compared with the trough winter months.[24] For comparison with other studies, the 200% increase corresponded to a difference of ~25 °C in mean monthly temperature. Conspicuously, females were excluded from this study.

Likewise, in Saudi Arabia, in a 3-year study of emergency room visits, regression analysis found a statistically significant correlation between the mean monthly temperature and the number of males presenting with urinary colic ($R=0.67$).[25] The difference between the peak and troughs was ~100% change in incidence, corresponding to ~12 °C, which is roughly consistent with the data from Iraq. Notably, this Saudi analysis failed to show any correlation with relative humidity, the fasting month of Ramadan or the pilgrimage festival. Again, females were not included in this study.

In Varmin, Iran, the incidence of hospital admission for renal colic in the summer months was higher than in the winter with statistical significance; regression analysis was not presented.[26] As in the Saudi Arabian study, the fasting month of Ramadan did not demonstrate a higher incidence of renal colic.

Studies in Japan found higher incidence rates in the summer months and lower incidence rates in the winter months in both Tokyo and in a rural area; however, quantitative statistical analysis was not performed.[27–29]

In Taiwan, there were similar findings with a cyclical pattern of urinary calculi attack rates.[30] As in most other studies, the male attack rate was significantly higher than that for females. Moreover, in the summer months, the attack rate went up on average ~100% for men whereas only up 30% for women even from the much lower winter baseline. The seasonal variation in the Taiwanese study correlated primarily with ambient temperature and additionally with hours of sunshine.

When a similar study of seasonal variation was performed in the United States, the change was not quite as dramatic.[31] The authors measured the percentage of renal colic visits out of total emergency department visits from 15 hospitals in New Jersey over a period of 7 years. The proportion of visits was 14% higher in the summer compared with the winter, which corresponded to approximately a 20 °C difference. With regard to gender, the ratio of visits in warmer versus colder months was significantly higher for males. Although these data are in line with previous reports, using percentage of emergency department visits may have confounded their results because of an increase in the number of emergency department visits in the winter for other reasons such as respiratory infections.

More recently, this question of seasonal variation was approached in Italy with more sophisticated computational methods.[32] The authors attempted to overcome the limitations of previous studies that either (1) compared stone incidence with month but did not correlate with temperature or (2) compared the incidence in a given month with only the average temperature of the month. Thus, this study took each individual subject and looked at the temperature of the preceding 15, 30, 45, and 60 days to better estimate the temperature exposure of each individual. The correlation with renal colic was statistically significant with a stronger correlation in the shorter time frames. Humidity was also studied by a similar computational analysis and this had an inverse correlation with renal colic. Given the trend of stronger correlation with shorter time periods, it is unclear if a time period <15 days would have had an even stronger correlation with colic.

Although all the above authors found some association between urolithiasis and seasonal variation, some other investigators found no appreciable association in their studied population. Most of these reports have come from studies of Scandinavian populations (for example, Sweden[33,34] and Finland[35]). In general, they lack rigorous statistical analysis and temperature data, and hence their value is limited. In Norway, it was reported that renal colic presented more commonly in the winter months than in the summer months.[36] In Mumbai, perhaps because of a range of mean temperature of only ~10 °F between summer and winter, no seasonal variation was evident.[37]

Another curious study was from Calgary, Alberta, Canada, that found a bimodal seasonal variation with peaks in September and January, but troughs in March and July (statistical analyses not presented).[38]

Temporal variation in a single geographic area over years

In addition to the seasonal variation in the incidence of stone disease, some authors have looked at changes in prevalence rates over many years. Although these increases in incidence may reflect hotter climates from global warming, changes in diet and other behaviors confound the role of temperature.

A report from the United Kingdom observed that in the summer months of 1989, there were more cases of renal calculi than in 1988 (58 vs 39).[2] They also reported that the average daily temperature and total hours of sunlight were increased in the latter year, 18.2 versus 16.1 °C and 1117 versus 726 h, respectively. Thus, a 53% increase in the hours of sunlight and a 2.1 °C increase in temperature were associated with a 48% increase in the incidence rate of kidney stones.

In the United States, an increasing prevalence of stones in the period of 1988–1994 compared with the period of 1976–1980 was observed.[39] In males, the increase was from 4.9 to 6.3%, a relative increase of 29%, with a similar increase in females from 2.8 to 4.1%, a relative increase of 46%. From the earlier to the later surveyed period, mean annual temperature in the United States rose 0.5 °C.[3] Although this

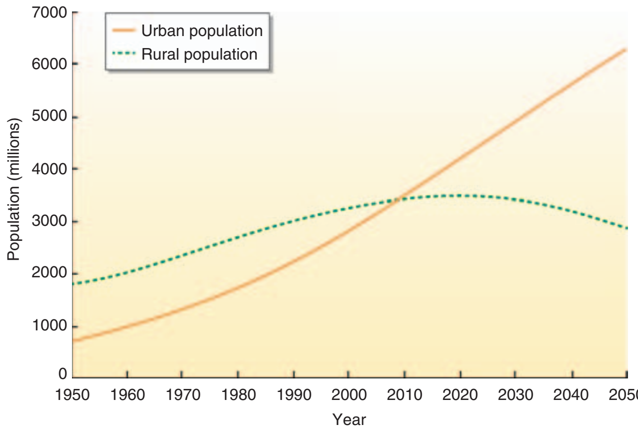

Figure 3 | Urban and rural populations of the world from 1950 to 2050 from the United Nations Population Division.[65] The graph shows that a greater proportion of people are living in urban areas and this trend is expected to continue in the future. Given that urban centers are hotter than surrounding areas, this could be a concern for climate-related conditions such as urolithiasis.

increase in ambient temperature might contribute to increasing stone prevalence, the relatively greater increase in female stone prevalence is not most consistent with a temperature-related change based on the evidence presented above. Studies in Italy, Japan, and Germany also show increases in stone prevalence over similar intervals, measured over the last 20–30 years.[40–44] These worldwide increases in stone prevalence are variously ascribed to improved detection rates and changes in diet such as 'Westernization' and increasing prevalence of diabetes, hypertension, and obesity, all associated with greater risk for stones.[45] Any contribution to increased prevalence of global warming is possible but not quantifiable.

Another possible explanation for increasing prevalence rates is population migration to warmer climates rather than changes in the climate itself. Although this topic does not garner as much attention as global warming, there is evidence from the United Nations Population Fund that the world's population is migrating in large numbers to urban centers (Figure 3). Urban centers, because of the phenomenon of 'urban heat islands,' tend to be hotter than surrounding suburbs and rural areas by 2 to 10 °F.[46] This migration could potentially increase stone prevalence rates more dramatically than global warming, although data supporting our hypothesis are currently lacking. One study in Iraq did show that the incidence of urolithiasis was higher in urban versus rural populations, 52.0 versus 30.2 per 100,000 inhabitants (no P-value presented).[35] Another recent study showed no difference in the increasing prevalence of stones in urban versus rural populations of children in South Carolina.[47] Without further research, this topic remains speculative.

Occupations and other special environments

A number of studies have reported higher prevalence rates of urolithiasis among certain occupations that expose workers to hotter ambient temperature. The hypothesis is that exposure to higher worksite temperatures results in lower urine volumes and more concentrated urine.

One of the first reports of this type was from 1945 regarding American troops in a desert area.[48] The authors reported a twofold higher incidence rate for troops deployed in desert areas versus those in cooler mountainous areas. Although of unclear statistical significance, the data are free of most confounding factors, as both groups were of similar racial background and consumed similar diets as provided by the US army.

In the 1960s, a study of the British Royal Navy analyzed the incidence of urolithiasis of its different occupations.[49] A higher incidence among cooks and engine room personnel than other occupational groups was attributed to the hot environment of the galley and engine room. However, 'officers' had a similar incidence rate for unclear reasons. Interestingly, the year-over-year stone prevalence declined in the engine room personnel, with the change attributed to the introduction of air conditioners. Incidence rates of 0.4, 0.8, 1.30, and 1.30 per 1000 were reported for personnel deployed at home, in the Mediterranean, in the Middle East, and in the Far East, respectively. No climate data were presented for comparison, nor was statistical analysis presented. Confounders such as race and weight were considered, with increasing weight associated with more urinary calculi. In another study, changes in urine calcium excretion occurred in British troops after transport from the United Kingdom to the Persian Gulf.[50] One group of soldiers was transported during the winter and a second group of soldiers was transported during the summer. Although the climate of the Gulf was very different than the climate of the United Kingdom in the winter (temperature 25.7 vs 13.7 °C, relative humidity 60 vs 88%, hours of daily sunlight 5.9 vs 4.17), increases in urinary calcium excretion were only observed in the Gulf summer (temperature 39.4 °C, relative humidity 34%, hours of daily sunlight 11.35). The summer months were associated with much higher temperatures, more hours of sunlight, and significantly decreased humidity. It is unclear which of these three factors contributed to the hypercalciuria and how the hypercalciuria correlated with stone formation.

In addition to military personnel, factory workers have been considered high risk for urolithiasis. As the potential for nephrotoxic metal exposure in factories might confound the effect of heat, Borghi *et al.*[51] conducted a study at a glass plant in Parma, Italy, of machinists working near blast furnaces compared with workers at the same factory who were assigned to locations with normal ambient temperatures. The authors found a prevalence of 8.5% in the hot temperature group (29 to 31 °C) compared with 2.4% in the normal temperature group (24 to 27 °C), a statistically significant difference ($P = 0.03$). Approximately 38.8% of the stones were composed of uric acid, higher than 26% observed in the studied geographic area.[52] Stone risk was measured in a random sample of 21 exposed and unexposed workers, without any evidence of stone disease, family history, or other predisposing factors and with similar diets and salaries. Urine was collected and fluid intake recorded during their 8-h work shift for 3 consecutive days. The authors found a statistically significant difference in intake of 1.5 l ($P<0.001$); urinary volumes were similar (P-value not reported). Uric acid concentration and specific gravity increased, and urine pH decreased. Calcium concentration was elevated in the heat-exposed workers, but was not statistically significant. Relative supersaturation of uric acid and calcium oxalate were elevated but only statistically significant for uric acid ($P<0.001$). These urine studies did not support greater transdermal fluid losses as the cause of the observed increased stone prevalence among the heat-exposed workers.

A Brazilian study investigated the prevalence rate of urolithiasis in a steel factory.[53] Heat-exposed workers, reportedly working in temperatures ranging from 50 to 150 °C, had a prevalence of 8.0% compared with 0.9% in the nonexposed workers ($P<0.001$). Unlike the Borghi study, a small decrease in urinary volume was found in the heat-exposed group: 1253 versus 1602 ml in 24-h urine collections ($P<0.01$). Urinary calcium and citrate levels were both decreased in the heat-exposed group but were not statistically significant ($P=0.16$ and $P=0.15$, respectively). However, 55.8% of the heat-exposed group, compared with 28% of the nonexposed groups, had urinary citrate <320 mg per 24 h ($P=0.03$).

In Singapore, indoor versus outdoor workers with similar age and incomes were compared.[54] The authors found increased prevalence among the outdoor workers compared with indoor workers (5.2 vs 0.85%, $P<0.05$). A frequently cited study of lifeguards on different beaches in Israel compared them with matched controls, both by prevalence rate of stones and by analysis of serum and urine.[55] The authors reported similar prevalence rates of 23.5% among lifeguards in northern beaches and 27.2% in the warmer southern beaches (no precise temperature data provided). The reported prevalence rate for the general population was only 1 to 2% in the northern regions and 3.8% in the south.[56] Urinary calcium was elevated in lifeguards at 308 mg per 24 h versus 168 mg per 24 h in controls ($P<0.001$) whereas urinary volume was decreased only in the southern lifeguards at 859 ml per 24 h versus 1180 ml per 24 h in controls ($P<0.001$). Serum 25-hydroxyvitamin D was also elevated in lifeguards at 53.4 versus 26.1 ng/ml in controls ($P<0.005$).

Other occupational studies have not supported an association with heat. A study in Japan compared stone prevalence rates in different occupations and found a statistically significant difference between the stone prevalence of administrative workers of close to 20% and of other workers whose prevalence varied from 0 to 10% ($P<0.01$).[57] Ironically, farmers and lumberman had no recorded stones, although they made up only a small part of the sample at 1.5%.

ALTERNATIVE HYPOTHESES

Regional differences in diet could account for regional differences in stone prevalence that appear to correlate with ambient temperature. Although data are lacking, there is some evidence that higher socioeconomic populations do have higher prevalence rates. It was postulated by Robertson[58] in 1990 based on previous epidemiologic studies that a population has to reach a moderate-to-high standard of living before ambient temperature plays a role in stone formation. In a study of the United States, the prevalence and incidence of nephrolithiasis in male health professionals between the ages of 40 to 75 were determined.[59] The prevalence was noticeably higher in the Southeast than the rest of the United States. The influence of regional dietary variation was considered using a semiquantitative questionnaire. There did not appear to be any significant difference between the Southeast and the rest of the United States, leaving climate as a possible explanation. Regional genetic variation could also play a role in explaining differences in regional prevalence of stones.[60] Our own classical twin study suggests that heredity accounts for >50% of stone prevalence, with 'environment' constituting the remainder of influences.[61] Sun exposure could contribute to stone formation as ultraviolet light causes increased production of 1,25-dihydroxyvitamin D, causing increased intestinal absorption of dietary calcium and potentially more calcium excretion by the kidneys. However, the net effect is not necessarily predictable. Vitamin D also increases reabsorption of calcium in the kidneys, which would decrease the calcium content of the urine. Sunlight exposure is well short of constituting 'vitamin D intoxication' that, along with calcitriol administration, is associated with hypercalciuria and stone formation. In one study, administration of 4000 IU per day resulted in serum concentrations of 38.6 ± 5.8 ng/ml, whereas a group of sun-exposed controls had serum concentrations of 18.7 ± 7.1 ng/ml; neither group had a change in urinary calcium. Other studies have shown increases in urinary calcium with vitamin D administration. Seasonal variation in urinary calcium in children[62] or adults[63] did not occur despite changes in ultraviolet index. We are also not currently aware of any data demonstrating that supplementation with vitamin D precursors in standard doses without calcium supplementation is associated with urolithiasis. Therefore, the role of sunlight exposure as an alternative causative factor to heat-induced kidney stones is equally unproven.

LIMITATIONS

There are several limitations to this review. Comparisons between studies are limited by age and gender discrepancies of the sample populations. For instance, some studies included subjects ⩾18 years old whereas others included subjects ⩾24 years old. Given the relatively low incidence for younger subjects in most populations, this will bias the measured incidence and prevalence rates. Gender also has an important role and, depending on the relative proportion of males and females, the measured stone rates will be affected. Moreover, the method of sampling of hospital admission rates, emergency room visits, clinic visits, and so on, makes comparisons between studies difficult. Studies from different time periods in different parts of the world with different technologies are subject to detection bias.[64]

CONCLUSION

The potential contribution of ambient temperature to increasing stone prevalence appears obvious if lacking supportive data. There is no doubt that greater transdermal fluid loss can reduce urine volume and increase urine supersaturation of stone-forming salts. Although the pathophysiology is clear and plausible, the data demonstrating causal links between climate or ambient temperature and stone prevalence are surprisingly sparse and complicated by other variables. Given the preponderance of evidence from different study designs across the globe, it seems undeniable that climate, whether it is through temperature, humidity, or sunlight, has at least some role in the development of urinary calculi, in at least some patients. The most consistently supportive data are the repeated demonstrations of seasonal variation in stone prevalence. However, the precise relationship of climate to stones in specific groups remains unclear. Even among heat-exposed workers, the simple measure of urine volume has not consistently demonstrated the expected effect. Limited access to water or other fluids in some populations or workers may be an additional variable. From our previous analysis, we found that in the United States, there is a dramatic disparity between males and females in their sensitivity to climate.[8] Although the reason for this varying response is unknown, it suggests that other factors such as age, race, and socioeconomic background may potentially augment or mitigate an individual's sensitivity to the effect of climate. Although the threat of continued global warming presents many dire risks, the risk of increased nephrolithiasis may be one of the more prevalent results, if one that cannot be reliably estimated.

DISCLOSURE

DSG is a consultant for Takeda and receives funding from NIDDK and ORDR. RJF has declared no competing interests.

REFERENCES

1. Wilson JF. Facing an uncertain climate. *Ann Intern Med* 2007; **146**: 153–156.
2. Curtin J, Sampson M. Greenhouse effect and renal calculi. *Lancet* 1989; **2**: 1110.
3. Brikowski TH, Lotan Y, Pearle MS. Climate-related increase in the prevalence of urolithiasis in the United States. *Proc Natl Acad Sci USA* 2008; **105**: 9841–9846.
4. Evan AP, Lingeman JE, Coe FL *et al*. Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. *J Clin Invest* 2003; **111**: 607–616.
5. Coe FL, Evan AP, Worcester EM *et al*. Three pathways for human kidney stone formation. *Urol Res* 2010; **38**: 147–160.
6. Soucie JM, Thun MJ, Coates RJ *et al*. Demographic and geographic variability of kidney stones in the United States. *Kidney Int* 1994; **46**: 893–899.
7. Soucie JM, Coates RJ, McClellan W *et al*. Relation between geographic variability in kidney stones prevalence and risk factors for stones. *Am J Epidemiol* 1996; **143**: 487–495.
8. Fakheri RJ, Goldfarb DS. Association of nephrolithiasis prevalence rates with ambient temperature in the United States: a re-analysis. *Kidney Int* 2009; **76**: 798.
9. Parks JH, Barsky R, Coe FL. Gender differences in seasonal variation of urine stone risk factors. *J Urol* 2003; **170**: 384–388.
10. Kristensen C, Parks JH, Lindheimer M *et al*. Reduced glomerular filtration rate and hypercalciuria in primary struvite nephrolithiasis. *Kidney Int* 1987; **32**: 749–753.
11. Baker PW, Coyle P, Bais R *et al*. Influence of season, age, and sex on renal stone formation in South Australia. *Med J Aust* 1993; **159**: 390–392.
12. Safarinejad MR. Adult urolithiasis in a population-based study in Iran: prevalence, incidence, and associated risk factors. *Urol Res* 2007; **35**: 73–82.
13. Lee YH, Huang WC, Tsai JY *et al*. Epidemiological studies on the prevalence of upper urinary calculi in Taiwan. *Urol Int* 2002; **68**: 172–177.
14. Akinci M, Esen T, Tellaloglu S. Urinary stone disease in Turkey: an updated epidemiological study. *Eur Urol* 1991; **20**: 200–203.
15. Barker DJ, Donnan SP. Regional variations in the incidence of upper urinary tract stones in England and Wales. *Br Med J* 1978; **1**: 67–70.
16. Power C, Barker DJ, Blacklock NJ. Incidence of renal stones in 18 British towns. A collaborative study. *Br J Urol* 1987; **59**: 105–110.
17. Barker DJ, Morris JA, Margetts BM. Diet and renal stones in 72 areas in England and Wales. *Br J Urol* 1988; **62**: 315–318.
18. Kambal A, Wahab EM, Khattab AH. Urolithiasis in Sudan. Geographical distribution and the influence of climate. *Trop Geogr Med* 1979; **31**: 75–79.
19. Frank M, De Vries A, Atsmon A *et al*. Epidemiological investigation of urolithiasis in Israel. *J Urol* 1959; **81**: 497–505.
20. Frank M, Atsmon A, Sugar P *et al*. Epidemiological investigation of urolithiasis in the hot arid Southern region of Israel. *Urol Int* 1963; **15**: 65–76.
21. Robertson WG, Peacock M, Marshall RW *et al*. Seasonal variations in the composition of urine in relation to calcium stone-formation. *Clin Sci Mol Med* 1975; **49**: 597–602.
22. Elomaa I, Karonen SL, Kairento AL *et al*. Seasonal variation of urinary calcium and oxalate excretion, serum 25(OH)D3 and albumin level in relation to renal stone formation. *Scand J Urol Nephrol* 1982; **16**: 155–161.
23. Salem SN, bu Elezz LZ. The incidence of renal colic and calculi in Kuwait. An epidemiological study. *J Med Liban* 1969; **22**: 747–755.
24. Al-Dabbagh TQ, Fahadi K. Seasonal variations in the incidence of ureteric colic. *Br J Urol* 1977; **49**: 269–275.
25. al-Hadramy MS. Seasonal variations of urinary stone colic in Arabia. *J Pak Med Assoc* 1997; **47**: 281–284.
26. Basiri A, Moghaddam SM, Khoddam R *et al*. Monthly variations of urinary stone colic in Iran and its relationship to the fasting month of Ramadan. *J Pak Med Assoc* 2004; **54**: 6–8.
27. Fujita K. Epidemiology of urinary stone colic. *Eur Urol* 1979; **5**: 26–28.
28. Fujita K. Weather and the incidence of urinary stone colic. *J Urol* 1979; **121**: 318–319.
29. Fujita K. Weather and the incidence of urinary stone colic in Tokyo. *Int J Biometeorol* 1987; **31**: 141–146.
30. Chen YK, Lin HC, Chen CS *et al*. Seasonal variations in urinary calculi attacks and their association with climate: a population based study. *J Urol* 2008; **179**: 564–569.
31. Chauhan V, Eskin B, Allegra JR *et al*. Effect of season, age, and gender on renal colic incidence. *Am J Emerg Med* 2004; **22**: 560–563.
32. Boscolo-Berto R, Dal MF, Abate A *et al*. Do weather conditions influence the onset of renal colic? A novel approach to analysis. *Urol Int* 2008; **80**: 19–25.
33. Almby B, Meirik O, Schonebeck J. Incidence, morbidity and complications of renal and ureteral calculi in a well defined geographical area. *Scand J Urol Nephrol* 1975; **9**: 249–253.
34. Ahlstrand C, Tiselius HG. Renal stone disease in a Swedish district during one year. *Scand J Urol Nephrol* 1981; **15**: 143–146.
35. Juuti M, Heinonen OP. Incidence of urolithiasis leading to hospitalization in Finland. *Acta Med Scand* 1979; **206**: 397–403.
36. Laerum E. Urolithiasis in general practice. An epidemiological study from a Norwegian district. *Scand J Urol Nephrol* 1983; **17**: 313–319.
37. Hussain F, Billimoria FR, Singh PP. Urolithiasis in northeast Bombay: seasonal prevalence and chemical composition of stones. *Int Urol Nephrol* 1990; **22**: 119–124.
38. Levinson AA, Mandin H. Seasonal variations in the incidence of kidney stones in Calgary, Alberta, Canada. *Clin Nephrol* 1985; **24**: 50–51.
39. Stamatelou KK, Francis ME, Jones CA *et al*. Time trends in reported prevalence of kidney stones in the United States: 1976-1994. *Kidney Int* 2003; **63**: 1817–1823.
40. Serio A, Fraioli A. Epidemiology of nephrolithiasis. *Nephron* 1999; **81**: 26–30.
41. Trinchieri A, Coppi F, Montanari E *et al*. Increase in the prevalence of symptomatic upper urinary tract stones during the last ten years. *Eur Urol* 2000; **37**: 23–25.

42. Hesse A, Brandle E, Wilbert D *et al.* Study on the prevalence and incidence of urolithiasis in Germany comparing the years 1979 vs. 2000. *Eur Urol* 2003; **44**: 709–713.
43. Yasui T, Iguchi M, Suzuki S *et al.* Prevalence and epidemiological characteristics of urolithiasis in Japan: national trends between 1965 and 2005. *Urology* 2008; **71**: 209–213.
44. Matsushita T. [Statistical observation of urolithiasis at the Hokkaido University Hospital (1959–1975) (author's transl)]. *Hokkaido Igaku Zasshi* 1978; **53**: 322–327.
45. Obligado SH, Goldfarb DS. The association of nephrolithiasis with hypertension and obesity: a review. *Am J Hypertens* 2008; **21**: 257–264.
46. Harlan SL, Brazel AJ, Prashad L *et al.* Neighborhood microclimates and vulnerability to heat stress. *Soc Sci Med* 2006; **63**: 2847–2863.
47. Sas DJ, Hulsey TC, Shatat IF *et al.* Increasing incidence of kidney stones in children evaluated in the emergency department. *J Pediatr* 2010; **157**: 132–137.
48. Pierce LW, Bloom B. Observations on urolithiasis among American troops in a desert area. *J Urol* 1945; **54**: 466–470.
49. Blacklock NJ. The pattern of urolithiasis in the Royal Navy. *J R Nav Med Serv* 1965; **51**: 99–111.
50. Parry ES, Lister IS. Sunlight and hypercalciuria. *Lancet* 1975; **1**: 1063–1065.
51. Borghi L, Meschi T, Amato F *et al.* Hot occupation and nephrolithiasis. *J Urol* 1993; **150**: 1757–1760.
52. Borghi L, Ferretti PP, Elia GF *et al.* Epidemiological study of urinary tract stones in a northern Italian city. *Br J Urol* 1990; **65**: 231–235.
53. Atan L, Andreoni C, Ortiz V *et al.* High kidney stone risk in men working in steel industry at hot temperatures. *Urology* 2005; **65**: 858–861.
54. Pin NT, Ling NY, Siang LH. Dehydration from outdoor work and urinary stones in a tropical environment. *Occup Med (Lond)* 1992; **42**: 30–32.
55. Better OS, Shabtai M, Kedar S *et al.* Increased incidence of nephrolithiasis (N) in lifeguards (LG) in Israel. *Adv Exp Med Biol* 1980; **128**: 467–472.
56. Frank H, Graf J, mann-Gassner U *et al.* Effect of short-term high-protein compared with normal-protein diets on renal hemodynamics and associated variables in healthy young men. *Am J Clin Nutr* 2009; **90**: 1509–1516.
57. Iguchi M, Umekawa T, Katoh Y *et al.* Prevalence of urolithiasis in Kaizuka City, Japan—an epidemiologic study of urinary stones. *Int J Urol* 1996; **3**: 175–179.
58. Robertson WG. Epidemiology of urinary stone disease. *Urol Res* 1990; **18**(Suppl 1): S3–S8.
59. Curhan GC, Rimm EB, Willett WC *et al.* Regional variation in nephrolithiasis incidence and prevalence among United States men. *J Urol* 1994; **151**: 838–841.
60. Stechman MJ, Loh NY, Thakker RV. Genetics of hypercalciuric nephrolithiasis: renal stone disease. *Ann NY Acad Sci* 2007; **1116**: 461–484.
61. Goldfarb DS, Fischer ME, Keich Y *et al.* A twin study of genetic and dietary influences on nephrolithiasis: a report from the Vietnam Era Twin (VET) Registry. *Kidney Int* 2005; **67**: 1053–1061.
62. Hilgenfeld MS, Simon S, Blowey D *et al.* Lack of seasonal variations in urinary calcium/creatinine ratio in school-age children. *Pediatr Nephrol* 2004; **19**: 1153–1155.
63. Barger-Lux MJ, Heaney RP. Effects of above average summer sun exposure on serum 25-hydroxyvitamin D and calcium absorption. *J Clin Endocrinol Metab* 2002; **87**: 4952–4956.
64. Bansal AD, Hui J, Goldfarb DS. Asymptomatic nephrolithiasis detected by ultrasound. *Clin J Am Soc Nephrol* 2009; **4**: 680–684.
65. Department of Economic and Social Affairs, Population Division. *World Urbanization Prospects: The 2009 Revision*. United Nations: New York 2010.