Original Article

Significant differences in struvite and cystine stone frequency seen among Chinese nephrolithiasis patients living in North America compared to those living in China

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Background: Interracial disparities in nephrolithiasis prevalence have been reported, but the interplay between genetics and the environment for urinary stone disease risk factors is poorly understood. To examine how environment may alter genetic predisposition for stone formation, we established the International Chinese Consortium on Nephrolithiasis (ICCON) as a multi-institutional collaboration to examine patterns of nephrolithiasis presentation between Chinese patients living in different countries.

Methods: Chinese patients undergoing percutaneous nephrolithotomy (PCNL) at six participating institutions in China and North America over 4 years were reviewed retrospectively. Patient demographics and clinical data were compared between Chinese patients living in China and North America.

Results: A total of 806 patients were included, encompassing 721 Chinese patients living in China and 85 living in North America. Nephrolithiasis patients living in China were more likely to be male (67% *vs.* 56%, P=0.02), present at a younger age (48.6±15.0 *vs.* 55.0±13.0 years, P<0.01), and have a lower BMI (24.6±4.0 *vs.* 25.9±5.7, P=0.04) but were less likely to form struvite stones (5.5% *vs.* 14.1%, P<0.01). No cystine stone patients were seen in North American Chinese patients, whereas 1.8% of nephrolithiasis patients living in China presented with cystine stones. Similar rates of calcium-based and uric acid calculi as well as urinary pH were seen among both groups.

Conclusions: Significant differences exist between Chinese nephrolithiasis patients living in China compared to those living in North America, highlighting the importance of environmental factors in addition to genetics in modulating risk for urinary stone disease.

Keywords: Asian Continental Ancestry Group; cystine; kidney calculi; struvite

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Introduction

Nephrolithiasis is a significant source of morbidity that crosses geographic boundaries. In the United States, kidney stones have a prevalence of 8.8% (1). It is estimated that the cost of their treatment may encompass up to $5 billion dollars across the out- and in-patient settings (2). Traditionally, kidney stones have been more prevalent in men than in women, and are largely thought to be increasingly influenced by environmental factors.

Worldwide, kidney stones affect 1 in 1,000 persons annually in industrialized countries (3). The prevalence of stones amongst the urban population in China has been estimated at 4% (4). In the past 20 years the average Chinese diet has changed dramatically, with an increase in total calories from animal fat and protein resulting in an increase in rates of obesity (5,6). As developing countries progress toward more Western diets and lifestyles defined by increased consumption of meat and processed foods, as well as an accompanying increased prevalence of obesity, rates of nephrolithiasis have increased in parallel (6-8).

Among patients presenting with nephrolithiasis, there exists a wide variation in frequency for different stone types. This phenomenon is well described in the United States but less so in China. In the United States, a recent analysis of 43,545 first time stone formers by Lieske *et al.* demonstrated that calcium oxalate stones represented 67% of the total presenting kidney stones, apatite 16%, uric acid stones 8%, struvite stones 3%, and cystine stones 0.35% (9). The overall prevalence of stone formation segregated by gender has been shown to be 10.6% in men and 7.1% in women (1). Data describing the distribution of stones in China is less well described. Rates of stone formation in men relative to women in urban centers in China have been published at 4.8% in men and 3.0% in women (4). Wu *et al.* recently detailed the stone composition of 507 patients from a single institution in Southern China. They found that calcium oxalate stones represented 78% of the stones analyzed, infection stones composed 15%, uric acid stones were 4%, calcium phosphate stones composed 3%, and there was one cystine stone present out of 507 stones (10). Sun *et al.* published another single institution experience looking at infrared spectroscopic analysis of 5,258 stones and found that the male to female ratio of stone frequency was 2.34:1. The composition of stones in their population was 53% calcium oxalate monohydrate, 22% carbapatite, 14% calcium oxalate dihydrate, 6% anhydrous uric acid, 1.7% struvite, and 1.1% cystine (11).

Aside from these single institution studies, there exists limited data examining stone demographics in Asia from a multi-institutional perspective. Additionally, few studies have compared ethnically similar stone formers living in different countries who are potentially exposed to varying environmental factors.

We established the International Chinese Consortium on Nephrolithiasis (ICCON) as a multi-institutional cross-continent collaboration in order to perform comparative studies between nephrolithiasis patients in the United States, Canada and China. The goal of this study was 2-fold: first, to examine the epidemiology of kidney stone formation among patients undergoing PCNL in China and second, to compare this with the frequency of stone formation amongst Chinese patients undergoing percutaneous nephrolithotomy (PCNL) in North America. We hypothesized that by comparing stone characteristics between two groups with different environmental exposures but a background of similar ethnicity, we could identify differences that would help define the interaction between environment and genetics in the formation of urinary stones.

Methods

Patients treated with consecutive PCNL between 2008 and 2012 at six endourology centers, including University of California San Francisco, University of California San Diego, University of British Columbia, Beijing Tsinghua Changgung Hospital, Renji Hospital Jiao Tong University and The First Affiliated Hospital of Xian Jiaotong University, formed the study cohort. Patients included in the North American cohort were those who indicated Chinese descent on their clinical intake, while all patients who underwent PCNL in China were included in the China cohort with the presumption that they were ethnically Chinese. Each institution provided appropriate IRB approval for chart review for data collection. Patients who did not self indicate Chinese descent in North America, as well as patients with incomplete peri-operative data, were excluded from this study.

All data had been collected prospectively at each institution. Demographics (age, gender, ethnicity) as well as body mass index (BMI) were reported. Pre-operative clinical data, including urinary pH, blood pressure, serum glucose, serum triglycerydes and serum HDL, was collected and reported. Stone composition analysis on stones removed at the time of PCNL was undertaken using Fourier transform infrared spectroscopy. All statistical analysess were performed using the student *t*-test.

Table 1 Chinese patient demographics and clinical characteristics

Patient characteristic	Value	North America (n=85)	China (n=721)	P value
Age, mean (SD)	Years	55.0 (13.0)	48.6 (15.0)	<0.01
Gender, n [%]	Male	48 [56]	480 [67]	0.02
	Female	37 [44]	241 [33]	
Urinary pH, mean (SD)	Number	6.35 (0.9)	6.16 (0.7)	0.10
Systolic blood pressure, mean (SD)	mmHg	135.3 (20.1)	130.4 (17.9)	0.08
Diastolic blood pressure, mean (SD)	mmHg	79.1 (10.8)	81.6 (12.1)	0.17
Serum glucose, mean (SD)	mg/dL	134.7 (57.6)	105.7 (47.8)	<0.01
Serum triglycerides, mean (SD)	mg/dL	124.5 (63.3)	159.4 (207.7)	0.86
Serum HDL, mean (SD)	mg/dL	73.5 (62.7)	41.8 (27.2)	<0.01
BMI, mean (SD)	kg/m^2	25.9 (5.7)	24.6 (4.0)	0.04

BMI, body mass index.

Table 2 Stone analysis results comparing Chinese living in China and North America

Stone type	North America, n (%)	China, n (%)	P value
Calcium oxalate	56 (65.9)	521 (72.3)	0.22
Calcium phosphate	3 (3.5)	49 (6.8)	0.25
Uric acid	14 (16.4)	98 (13.6)	0.47
Struvite	12 (14.1)	40 (5.5)	<0.01
Cystine	0 (0)	13 (1.8)	<0.01

Results

A total of 806 patients were included in this analysis. Eighty five of those patients were treated in North America and formed the North America cohort, while 721 patients were treated in China and formed the China cohort. Fifty six percent (N=48) of North America cohort patients were male, while 67% (N=480) of China cohort patients were male (P=0.02). Mean age at time of procedure was significantly higher in the North America cohort compared to the China cohort (55.0 years, SD ±13 *vs.* 48.6 years, SD±15 respectively, P<0.01); other mean values that differed significantly among the North America and China cohort patients included preoperative serum glucose (134.7 *vs.* 105.7 mg/dL, P<0.05), serum HDL (73.5 *vs.* 41.8 mg/dL, P<0.05), and BMI (25.9 *vs.* 24.6 kg/m^2, P<0.05). While serum triglyceride levels were lower among North America cohort patients compared to China cohort patients (124.5 *vs.* 159.4 mg/dL, P=0.86) and urinary pH was higher among North America cohort patients compared to China cohort patients (6.35 *vs.* 6.16, P=0.097) these differences did not reach statistical significance. Mean systolic and diastolic blood pressure values did not significantly differ between the two groups. Patient characteristics are shown in *Table 1*.

Stone composition analysis showed significant differences between the frequency of struvite and cystine stones when comparing the North America and China cohorts (*Table 2*). Struvite stones comprised 14.1% of the total stones in the North America cohort, but only 5.5% of the China cohort (P<0.01). No cystine stones were seen in the North America cohort, while 1.8% of the stones in the China cohort were cystine (P<0.01). Calcium oxalate and calcium phosphate stones comprised similar percentages of both cohorts (65.9% *vs.* 72.3%, P=0.218, and 3.5% *vs.* 6.8%, P=0.247, respectively). Similar frequencies of uric acid stones also were seen between the two groups (16.4% *vs.* 13.6%, P=0.469). *Figure 1* summarizes these findings.

Discussion

This study represents the first to analyze a multi-national database consisting of ethnically Chinese patients with urinary stone disease. ICCON is a newly established research consortium in which we were able to compare data on Chinese patients from China with those living in North America. Our findings suggest that relative to ethnically Chinese nephrolithiasis patients living in China, Chinese living in North America experience higher rates of struvite stone formation, a greater incidence in women, and may have a younger age at the time of presentation. Interestingly, cystine stones were not present in the population of Chinese stone formers in North America, but among the Chinese

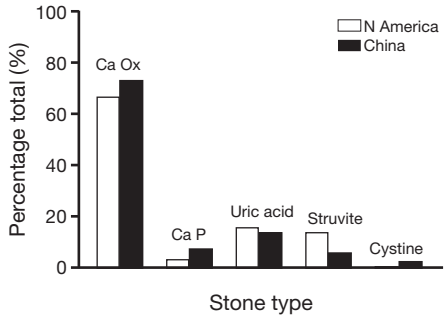

Figure 1 Stone analysis results comparing Chinese living in China and North America.

patients in China, a 1.8% prevalence of cystine stones was seen. This comparative study highlights differences between two patient populations in a background of ethnic similarity that raises several points of interest.

Cystine stone formation has been described amongst Chinese patients living in China (10-12). Cystine stones are caused by a single autosomal recessive defect (13). This genetic defect has been reported in 1/2,500 Libyan jews and 1/100,000 Swedish patients and there appear to be some areas of the world where the incidence appears to be unusually high (13). Cystinuria is responsible for 1–2% of adults and 6–8% of the pediatric population (13).

The presence of cystine stones amongst Chinese patients in China is striking since amongst the Chinese living in North America, no single case was seen during the study period. This may be explained by several possibilites. It is possible that the absence of cystine stones among our North American cohort may relate to an overall fewer number of nephrolithiasis patients captured here compared the China cohort. Perhaps with more Chinese patients in the North American cohort, cystine stones would be seen. Additionally, the autosomal recessive nature of cystinuria decreases its phenptypic expression likelihood in a smaller population such as the North American Chinese group compared to the inordinately larger population of China. Alternatively, genetic drift over time occuring either historically or in recent years may account for this difference, either introducing a cystine transporter mutation in the China cohort or eliminating it in the North American cohort. Another possiblility is that a new genetic mutation could be responsible for cystinuria amongst the Chinese poplation, particularly since, relative to other published studies, an incident rate of 1.8% is relatively high. In China the published rates of cystine stones has been demonstrated to be between 0.2–1.1% (10,11) in line with our findings, which pulled patients from three institutions within China.

It has been established that urinary tract infections are more common among adult women relative to men and struvite stones are thought to form from infected urine (14). In the United States, struvite stones are found with greater frequency in women relative to men (4.6% *vs.* 1.8%) (9), and infectious stones occur more often in younger patients. These previously published associations may explain why more struvite stones were found in the North American Chinese patients in our study, who were more often women and significantly younger in age.

Alternatively, another possible explanation accounting for the differences in this study could be a discrepancy in access to care between patients in North America versus China. If Chinese patients in our North America cohort were recent immigrants to the United States or lived in underserved communities, they may be less likely to seek care for urinary tract infections due to a language barrier or limited access to care. In fact, state-assisted insurance has been linked to increased rates of infectious stones as well as female gender and younger age amongst nephrolithiasis patients living in the United States (15). This might subsequently explain the increased incidence of infectious stones among the North America patients seen in our study. This finding that Chinese stone formers living in North America were more likely to be struvite stone formers relative to Chinese stone formers living in China may in this instance highlight the relatively higher impact of environmental factors over genetic factors in struvite stone formation.

Our study demonstrates that rates of calcium oxalate, calcium phosphate, and uric acid stones did not differ between Chinese patients from North America versus China. Because these stones can be largely influenced by diet and lifestyle, it is not a surprising finding given China's changing lifestyle, dietary habits, and obesity rates trending towards those of Western nations (5,6).

However, there are examples in the literature that demonstrate that for immigrant populations there is an acculturation process that does have health-related consequences. Disease prevalence for illnesses such as diabetes mellitus have been shown to drift toward those of the adopted county in within one generation as Zheng *et al.* was able to demonstrate in a study of Indian immigrants in Singapore. Their study found that rates of type 2 diabetes and diabetic retinopathy among those with type 2 diabetes was significantly higher in second-generation immigrants relative to first generation immigrants (16).

In our study population, Chinese nephrolithiasis patients were more likely to have an increased BMI and blood glucose in North America relative to China. In a similar fashion, our results suggest that a significant impact of Western diet and lifestyle may exist on urinary stone formation amongst Chinese patients living in North America.

This study cohort only included patients who underwent percutaneous nephrolithotomy as an intervention for stone formation and does not include all stone formers presenting for care. This represents a potential study weakness as the nephrolithiasis characteristics and prevalence rates seen in our study may not be representative of all stone formers but rather only those that required percutaneous intervention. In addition, we did not have access to self-identifying ethnicity data for the patients among the Chinese consortium. The presumption made for this study was that these patients were all Chinese in ethnicity. We also recognize that North American Chinese may more commonly represent certain provinces of China that introduces a selection bias. Likewise, the China cohort lacks detailed province demographics that perhaps limits our comparative analysis. In addition, there was a large difference in the number of Chinese patients in each cohort since, not surprisingly, Chinese patients living in China are more abundant and thus more likely to present with stone disease. These limitations withstanding, our results represent a first multi-center study performed by a newly formed consortium and raises several comparative points of interest that warrant additional study.

Conclusions

The etiology of urinary stones is represented by a multifaceted assortment of dietary, environmental, and genetic factors. This study allowed for a unique comparison between two assumedly genetically similar patient populations exposed to two different environments, highlighting several important differences. Our data demonstrated a statistically significantly increased prevalence of struvite stones in patients in North America relative to China as well as an increased frequency of female stone formers and a younger age at presentation. Living in the North American environment appeared to confer a significant impact on patients as seen by their higher BMI and blood glucose levels, but this did not significantly affect rates of calcium oxalate, calcium phosphate, or uric acid stone formation. Lastly, Chinese patients with cystine stones were documented in China, but not in North America. This is the first study to identify such a difference. Such comparisons point out areas that could be explored for improving our understanding of the interplay between the environment and genetics and how it influences urinary stone formation.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: IRB approval was obtained for this study (IRB #14-14533). The Internal Review Board deemed this study appropriate for waiver of consent since data was gathered in a retrospective fashion.

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