Urolithiasis Through the Ages: Data on More Than 200,000 Urinary Stone Analyses

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Purpose: The incidence and prevalence of urolithiasis are increasing but clinicians also have the impression that gender and age distributions of stone formers are changing. Moreover, regional differences in stone occurrence and composition have been observed. We analyzed such trends based on a large series of urinary stone analyses.

Materials and Methods: A total of 224,085 urinary stone analyses from 22 German centers were evaluated to determine the incidence of stone composition and identify age and gender distributions from 1977 to 2006. A subset of 58,682 stone analyses from 1993 to 2006 was available to identify regional differences in stone composition in Germany.

Results: Calcium containing calculi were most common in each gender. The overall male-to-female ratio of 2.4:1 increased from 1977 (1.86:1) to 2006 (2.7:1). The predominance of male calcium stone formers was even higher among elderly patients with a 3.13:1 ratio at ages 60 to 69. Since 1997, we observed a tendency toward an increasing incidence in middle-aged patients at ages 40 to 49 years. While the rate of infection stones constantly decreased, the incidence of uric acid calculi remained stable with an overall rate of 11.7% in males and 7.0% in females with a peak at higher ages. Cystine stones remained rare at 0.4% in males and 0.7% in females. In terms of regional analyses we noted great variation in stone composition in the 2 genders. Uric acid stones were more common in the eastern and southern regions but infection stones were mostly seen in eastern regions.

Conclusions: In what is to our knowledge the largest series of stone analysis reported to date we identified an age and gender relationship of stone formation and composition. Regional variations are common and underline the influence of living habits, diet and standard of medical care on urinary stone formation.

Key Words: urinary calculi, male, female, age groups, Germany

UROLITHIASIS is one of the most common diseases with approximately 750,000 cases per year in Germany. While most patients have only 1 stone episode, 25% experience recurrent stone formation. Thus, urolithiasis has a significant impact on life quality and socioeconomic factors.

Several groups have reported a worldwide increasing incidence and prevalence, which seems to be more pronounced in industrialized countries. Clinical observations indicate a changing incidence and composition of urinary calculi as well as a dynamic of gender and age related incidences.
Such observations seem to underline the impact of life and dietary habits, and access to better medical care on urinary stone formation. A nationwide evaluation of stone formation could provide valuable information on such issues. The individual German situation with the reunification of Western and Eastern Germany in 1990 had the consequence of merging 2 health systems. Thus, a comparison of the eastern and western parts of Germany as well as the northern and southern parts could be of interest due to different living habits. Therefore, we evaluated a large series of urinary stone analyses derived from 30 years with respect to regional, gender and age dependent variations in Germany.

MATERIALS AND METHODS

A total of 224,085 stone analyses from 22 German centers were collected prospectively from 1977 to 2006 at each individual center. The data were merged to build a database containing information on stone analysis, gender, age and laboratory site.

A subset of data on a total of 58,682 analyses from 1993 to 2006 was available to identify regional differences in stone composition by classifying participating regions into northern (Cologne, Aachen, Paderborn, Troisdorf and Münster), eastern (Jena, Dresden, Nordhausen, Halle and Berlin) and southern (Heilbronn, Erlangen, Tübingen, München, Augsburg, Weingarten, Weiden, Stuttgart and Coburg) Germany. Since data were collected in anonymous fashion, the database may include recurrent stones from the same patient that were counted as individual cases.

All stone analysis was done by infrared spectroscopy, x-ray diffraction or polarization microscopy. Due to different subclassifications at individual laboratories stone composition was classified into class 1—calcium oxalate and calcium phosphate, including whewellite, weddellite, brushite, apatite and whitlockite but excluding mixed compositions of 20% or greater uric acid, uric acid dihydrate, urate, struvite, newberyite or cystine, class 2—infection associated stones, including struvite, magnesium ammonium urate, newberyite and ammonium hydrogen urate, class 3—uric acid containing calculi, including uric acid, uric acid dihydrate, urate and those with less than an 80% mixture of calcium oxalate or calcium phosphate, and class 4—cystine stones. Rare stone compositions, such as xanthine, 2,8-dihydroxyadenine or drug induced stones, were excluded from analysis.

A subset of 111,196 stone analyses from 1980 to 2004 was available to evaluate chemical stone components. Stone components accounting for 20% or greater of the whole stone composition were counted.

To correlate the stone analysis database with epidemiological data patients were age and gender stratified according to the format annually reported by the German Agency for Statistics to allow comparison with the whole population (due date December 31, 2007) (www.regionalstatistik.de/).

Statistical analysis was performed with SPSS®, version 14. The chi-square test was used for statistical testing. Regression analysis was done for trend calculation with results considered statistically significant at \( p < 0.05 \), very significant at \( p < 0.01 \) and highly significant at \( p < 0.001 \).

RESULTS

Stone Composition

Calcium containing calculi (class 1) were predominant in each gender with an overall prevalence of 84.1% in males and 81.3% in females \( (p < 0.001) \). During the observation period the incidence of class 1 calculi increased from 82% to 86% in males and from 79% to 84% in females \( (p \text{ not significant, fig. 1, A}) \). The male-to-female gender ratio changed from 1.86:1 in 1977 to 2.7:1 in 2006 \( (p < 0.05) \).

Infection associated calculi (class 2) were rare in males and common in females (3.8% vs 11.0%, \( p < 0.001 \)). Class 2 calculi showed a decreasing incidence that was more pronounced in females, including from 4.9% to 3.3% in males and 13.5% to 9.2% in females \( (p < 0.05, \text{ fig. 1, B}) \). The female-to-male gender ratio changed from 1.06 to 1.095 \( (p \text{ not significant}) \).

Uric acid containing calculi (class 3) were seen in 11.7% of male and 7.0% of female patients \( (p < 0.05) \). During the observation period the incidence decreased from 13% to 11% in males but remained stable in females \( (p \text{ not significant, fig. 2, A}) \). Class 3 calculi showed a significant predominance in males with a male-to-female ratio of 3.92:1 \( (p < 0.001) \).

Cystine calculi (class 4) were rare, noted in 0.4% of males and 0.7% of females for a total of 1,159 cystine calculi in 30 years. Regression analysis revealed a slight tendency toward a decreasing rate \( (p \text{ not significant, fig. 2, B}) \).

A subset of data were analyzed for stone components. We noted a tendency toward an increasing frequency of calcium phosphate relative to calcium oxalate stones \( (\text{fig. 3}) \). Hydroxyapatite became more common from 1988 to 1994 but the incidence decreased at the end of the observation period, comparable to that in 1980. In contrast, the incidence of brushite increased continuously.

Age Distribution

Children (ages 0 to 9 years) and adolescents (ages 10 to 19 years) showed the lowest incidence of stone formation for all compositions \( (p < 0.001) \). During the observation period class 1 stone formation started to become more common at ages 20 to 29 years \( (\text{fig. 4, A}) \). While stone formation in females had a peak from ages 60 to 69 years, representing 23.6% of all calcium stones, males showed a stone formation plateau at ages 30 to 69 years (19.6%). At greater ages class 1 calculi were 3 times more common in males than in females \( (p < 0.001) \). Since 2000, we observed a tendency of class 1 stones to become more common in the middle-aged group at ages 40 to 49 years in each gender compared to that
in 1990 to 2000 (data not shown, p not significant). Compared with the whole population distribution calcium stones affected patients older than 40 years old significantly more often than would be expected by their percent in the whole population (p < 0.05).

Infection associated class 2 calculi were relatively more common in young children with a higher rate in boys, followed by a decrease during adolescence and an increasing incidence in young adults (fig. 4, B). Female patients showed a constantly increasing rate starting at adolescence (ages 10 to 19 years). Infection stones were most common in each gender at greater ages from 60 to 69 years (vs other age groups p < 0.05). Class 2 stones were increasingly rare in adults and became a typical stone in elderly patients. However, the overall rate had decreased since 1977 (p < 0.05). Similar to class 1 calculi, class 2 calculi were most common in elderly patients (p < 0.01).

Class 3 calculi containing uric acid typically started to become more common at middle age, starting at ages 30 to 39 years (vs other age groups p < 0.05). Each gender showed a peak rate from ages 60 to 69 years but it was slightly pronounced in males (p < 0.01, fig. 4, C). During the last 10 years

Figure 1. Stone rate from 1977 to 2006. A, calcium containing calculi in 132,024 males and 54,615 females. B, infection stones in 5,891 males and 7,366 females.
uric acid stones tended to become more common at ages 60 to 79 years (p not significant).

In contrast to other stone compositions, class 4 cystine stones were more common at younger ages. The highest rate was noted in females at ages 20 to 29 years and in males at ages 30 to 39 years (vs other age groups p <0.05, fig. 4, D). The stone incidence did not change significantly during the observation period and it correlated with the age distribution of the whole population.

**Regional Variations**

The incidence of class 1 calcium calculi showed wide regional variation. In eastern parts the class 1 stone rate was highly significantly lower than the overall mean, including 72.4% in eastern parts vs 83.2% in other regions in males and 62.1% vs 80.8% in females (each p <0.001). In contrast, class 1 stones were significantly more common in northern and western regions (86.6% and 85.1%, p <0.05). Again, class 2 infection calculi were highly significantly more common in eastern parts of Germany with a rate of 14% vs 2.9% in males and 26.7% vs 8.0% in females (each p <0.001). Infection associated calculi developed significantly less often in females in northern regions (6.0% vs 8.0%, p <0.001).

Class 3 calculi containing uric acid showed a highly significant increase in southern parts in males (15.3% vs 11.5), and in southern and eastern
parts in females (9.9% vs 6.0%, each \( p < 0.001 \)). The incidence was significantly lower in males and females in western regions (9.4% vs 13.4% and 5.0% vs 8.9%, respectively, each \( p < 0.001 \)). Class 4 cystine stones showed a slightly higher rate in southern parts of Germany in males and females (0.7% and 1.3%, respectively, \( p \) not significant). Figure 5 shows detailed data on regional variations.

**DISCUSSION**

Urinary stone formation is a common disease with a worldwide increasing incidence and prevalence.\(^8\)–\(^{12}\) While some groups suggest an impact of climate change,\(^{13}\),\(^{14}\) changing lifestyles and diet habits are the more probable causes. Taylor and Curhan noted that body weight correlated with urinary calcium excretion.\(^{15}\) From 2 large epidemiological series Taylor et al reported that diabetes is an independent risk factor for kidney stones.\(^3\) Siener confirmed such findings in studies in recurrent stone formers.\(^{16}\) Changing chemical stone compositions have been reported, possibly as the result of the described changes in habits.\(^{17,18}\)

Renal stone formation and the predominant chemical stone composition are age and gender dependent.\(^7\) Most stones are formed at older ages. However, many clinicians report the impression that patients are becoming younger when presenting with an initial stone event. Urinary stone disease remains rare in children with a stable overall incidence in most series.\(^{19}\) As in adults, factors of the metabolic syndrome complex such as obesity are risk factors for urinary stone formation in infants.\(^{20}\)

These observations underline the need for a large data collection encompassing a significant period. To our knowledge our study is the largest published series of stone analysis, including a 30-year period. Apart from evaluation of gender and age distribution as well as changes in stone composition the multicenter design allowed an analysis of regional differences.

Urolithiasis remains a disease with a clear predominance in males for all stone compositions except infection stones. In our series this difference increased during the observation period with a 2.7:1 male-to-female ratio for the most common calcium containing calculi. This was confirmed by Trinchieri et al, who reported an overall 1:0.76 male-to-female ratio but a 1:1.6 ratio for infection calculi.\(^{21}\)

We identified a clear correlation of different rates of stone composition with gender and age. In accordance with other reports calcium containing calculi were predominant in males and females.\(^7,22,23\) Daudon et al noted a male predominance of calcium oxalate and uric acid, and a female predominance of calcium phosphate and struvite stones.\(^7\) Approximately 15% of all stone formers produce calcium phosphate stones.\(^{24}\) Up to a quarter of those calcium phosphate stones contain calcium monohydrogen phosphate (brushite), a stone composition that is difficult to treat and prevent.\(^{25}\) Parks et al reported an increasing incidence of calcium phosphate calculi during the last 3 decades.\(^{26}\) Mandel et al performed a subanalysis of calcium phosphate stone formers and noted an increased prevalence of brushite.\(^{27}\) We analyzed a subset of our data in terms of stone composition components. While an
increased rate of hydroxyapatite was only temporary and normalized by the end of the observation period, our study confirms an increasing incidence of brushite.

In our study uric acid was the second most common composition in each gender, suggesting different living and diet habits between Germany and France when comparing our data with those in the series by Daudon et al. However, in contrast to those investigators, who reported a significant increase in the incidence of uric acid stones, the rate of this stone composition remained stable in our series. Since our series relied on stone analysis data derived from stones gathered after spontaneous passage or intervention, we may have missed a substantial number of uric acid stones that were treated with chemolitholysis.

Infection stones were rare in our series and that by Daudon et al with a clear decrease during the years that is most probably attributable to improved medical care. This was confirmed by others. Trinchieri et al reported a series of stone analyses from Italy during 15 years with a low number of infection stones. Marickar and Vijay reported a decrease in infection stones in females despite an overall increase in urinary stone formation. The decreasing number of staghorn stones in Europe underlines this observation since urinary tract infection is the most common cause of such large renal calculi.

Our investigation confirms the low rate of cystine stones. The higher peak at younger ages is in accordance with the first stone event, which typically occurs in the second decade of life, while the lower rate at older ages may be a result of preventive measures.

Although the observation that patients with stones are becoming younger is commonly reported, only sparse data are available to support such a change. In our series calcium containing calculi were most common at older ages, comparable to the 1996 series by Trinchieri et al. However, since 2000, a second peak occurred in each gender at ages 40 to 49 years, possibly suggesting the first effects of metabolic syndrome. Since our study is based on stone analysis, it lacks data on body weight and body mass index, and metabolic data. Curhan and Taylor reported an increased risk of calcium oxalate stone formation in patients with hypercalciuria. After adjusting for other urinary factors urinary uric acid was significantly associated with stone formation in men. Uric acid excretion is significantly increased when obesity
or diabetes is present. However, in contrast to other series, we did not observe an increasing incidence of uric acid calculi.

Interestingly even in a country with moderate geographic and climatic variation such as Germany, significant regional differences were present. While uric acid containing calculi were more present in southern Germany, we observed a significantly higher rate of infection stones in eastern Germany. We can only hypothesize to explain these findings. A diet that is based on more red meat may explain the higher rate of uric acid calculi in southern Germany. The higher incidence of infection stones in eastern parts, formerly the socialist German Democratic Republic, may result from patients coming from Eastern European countries with a lower standard of medical care. However, we cannot rule out that even in

\[ \text{Figure 5.} \quad \text{InterGerman comparison of calcium, infection, uric acid and cystine stones.} \quad \text{A, 7,246 male patients in north (blue bars), 12,905 in south (red bars), 5,149 in east (green bars) and 19,963 in west (purple bars).} \quad \text{B, 2,851 female patients in north, 5,187 in south, 2,607 in east and 8,149 in west.} \]
Germany differences in medical care exist. Further epidemiological studies must evaluate this topic of political impact.

We are aware that our study cannot reflect epidemiological data and, thus, we do not report real incidences. Only urinary stones that were sent for analysis could be analyzed. We definitely missed stones that passed spontaneously or were not collected after intervention. Especially uric acid stones treated with chemolitholysis may be underrepresented. Furthermore, detailed data on patient characteristics were not available and any recurrent stones from the same patients could not be identified due to the anonymous database. However, to our knowledge no series of comparable size, duration and regional distribution has yet been reported. Since stone analysis is standard at most German urology centers, we assume that including large stone laboratories ensured a reliable data set that provides valuable information on stone composition and formation.

CONCLUSIONS
We noted an age and gender relation of stone formation and stone composition. Regional variations are common and underline the influence of living habits, diet and probably the availability of good health care on urinary stone formation.

APPENDIX
Stone Laboratory Participants
St. Joseph Hospital, Troisdorf; Vivantes Medical Center Friedrichshain and University Hospital Benjamin Franklin, Berlin; St. Hildegardis Malteser Hospital and University Hospital, Cologne; Asklepios Hospital Pankow; University Hospital, Tübingen; University Hospital, Halle; Laboratory Schottorf, Augsburg; Laboratory Gärtner, Weingarten; University Hospital, Jena; Hospital Friedrichstadt, Dresden; Laboratory Buchwald, Weiden; University Hospital, Erlangen; Katharinenhospital, Stuttgart; St. Joseph Hospital, Paderborn; SLK Hospital, Heilbronn; Laboratory Becker, Munich; Südharz Hospital, Nordhausen; Central Institute of the German Defense Army, Kronshagen; Laboratory Krenz-Weinreich, Pilln; and University Hospital, Aachen, Germany.