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ORIGINAL PAPER

Regional and seasonal variation in the incidence of urolithiasis in Iran: a place for obsession in case finding and statistical approach

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Abstract The objective of the study is to measure the incidence rate of urolithiasis in a nationwide population-based study by a new methodology. A multi-stage stratified "epsem scheme" sampling was designed among imaging centres in 12 ecologic regions (composed of 30 provinces) while the regions were assumed as independent epidemiologic units. Four temporal phases were determined for sampling to represent four seasons. Imaging-proven positive cases for urinary stones were included and questionnaire filled out by interview. 2,955 new cases of urinary stone were included and the overall pooled yearly incidence rate was 136/100,000 (95% CI, 103–168). The whole positive group had a mean age of 41.5 years (SD = 16.3 years) and composed of 57.9% male. The most common season for presentation of disease was autumn. Geographically, the west and north of Iran, and seasonally, autumn have shown the highest incidence rates for the urinary tract stones. To establish the real burden of urinary stone disease, our study adds a little piece of information to the worldwide epidemiology of urolithiasis.

Keywords Urolithiasis · Epidemiology · Incidence · Seasonal variation

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Introduction

The urinary tract stone disease affects human beings of all ages. There are different epidemiological studies from different parts of the world with a variety of reported prevalence and incidence rates. Many studies have shown the rising prevalence [1–4]. All these studies are in agreement that urolithiasis is a common disease and has a great burden on health and economy. Therefore, the collection of accurate information about stone incidence rates has important health and economic implications for every country and demands a global concerted action.

The present study is based on a nationwide population study that includes imaging-proven cases of urinary calculi to identify incidence of urolithiasis in the Iranian population between 2007 and 2008. The goal was to define the disease occurrence in a complete illustrative population-based study along with consideration of the seasonal variations of the estimated incidence rates in different climatic regions across Iran.

Methods and materials

1. *Population and setting* The study was a nationwide multicentric epidemiological research in 787 imaging centres in 12 climatic regions (including 30 provinces). A multi-stage stratified "epsem scheme" sampling was designed while the regions were assumed as independent epidemiologic units. Of the 41 medical universities covering the whole nation for its health and medical services, 32 participated in this study. Consequently, the official population fractions covered by the non-participating universities were deducted from

the appropriate regional populations for estimating the related incidence rates.

2. *Recruitment and evaluation* Four temporal phases were determined for sampling to represent the four seasons of the year. The sampling was limited to the last month of each season, which restricts the intra-seasonal variations Among all referrals to the imaging centres for any medical problems, the imaging-proven positive cases for urinary stones were picked and detailed questionnaires were thoroughly filled in by educated well-oriented interviewers. The questioning was done under direct supervision of a physician. The diagnosis was established and confirmed by a radiologist. The interviewers all were medical staff. Based on the obtained information, "new cases" were identified as imaging-proven cases that were diagnosed incidentally or clinically for the first time.
3. *Diagnostic criteria* The imaging evidence for the diagnosis was obtained by one of the following methods: KUB, ultrasonography (US), IVP or a combination of these techniques. There were four different criteria for a positive diagnosis of a urinary stone:

   a. Any imaging evidence by any of the three techniques, regardless of the stone size (non-conservative approach)
   b. Of the above positive cases, inclusion of any stones equal to or greater than 3 mm in diameter found in ultrasonography, or any stones detected by KUB or IVP (semi-conservative approach) named as new cases.
   c. Of the above positive cases, inclusion of any stones equal to or greater than 5 mm in diameter found in ultrasonography, or any stones detected by KUB or IVP (conservative approach), named as new cases.
   d. Only symptomatic cases of the above population.

Consequently four sets of incidences were estimated.

4. *Incidence estimation* The number of the new cases and the duration of the screening (summation of all four phases for corresponding seasons) as well as the population reference (according to the most updated national census, and modified for the non-participant areas) in each region were considered for incidence estimation in the epidemiologic units. Due to the variations in the sample sizes, variance and distribution of the detected cases in each phase, a mere summing up of the values did not seem realistic. Therefore, the incidence rates were obtained for various regions based on each seasonal sampling and the national incidence was estimated by pooling the weighted incidences across the regions. Consequently, four values were obtained for each individual region as well as for Iran as a whole. The additions of the new cases and the screening duration in each region were considered in the estimation of the regional annual incidence rate, and then, the national annual incidence rate was calculated by adding up the individual regional values. All estimates were presented with 95% confidence interval. The pooling procedure was according to the following:

First, the weight for each regional estimate was obtained by its inverse variance. Afterward, the weighted pooled incidence was calculated by "Fixed Effect Model" (FEM):

$$P = \frac{\sum W_i P_i}{\sum W_i}$$

Prior to pooling, the regional incidence, a heterogeneity test was performed using Q statistics to ensure the homogeneity of the regions:

$$Q = \sum W_i (p_i - P)^2$$

The Q statistic follows Chi distribution with $(K-1)$ degrees of freedom. The significance level of $P < 0.10$ was considered for testing the null hypothesis of the homogeneity to avoid any considerable chance for heterogeneity. Since the test did not demonstrate any heterogeneity among the regions, the final pooling step was conducted according to the "Random Effect Model" (REM) as follows:

$$P^* = \frac{\sum W_i^* p_i}{\sum W_i^*}$$

When: $W^* = \frac{1}{\mathrm{var}(p_i) + D}$ and

$$D = \frac{Q - (k-1)}{U} \quad \text{if } Q > k - 1 \text{ or } D = 0 \text{ otherwise}$$

In the above formula, K is the number of strata (regions) and U was calculated as:

$$U = \sum W_i - \left(\frac{\sum W_i^2}{\sum W_i} \right)$$

Finally, the 95% confidence interval of the pooled estimate was obtained:

$$\left(P^* \pm \frac{1.96}{\sqrt{\sum W_i^*}} \right)$$

Results

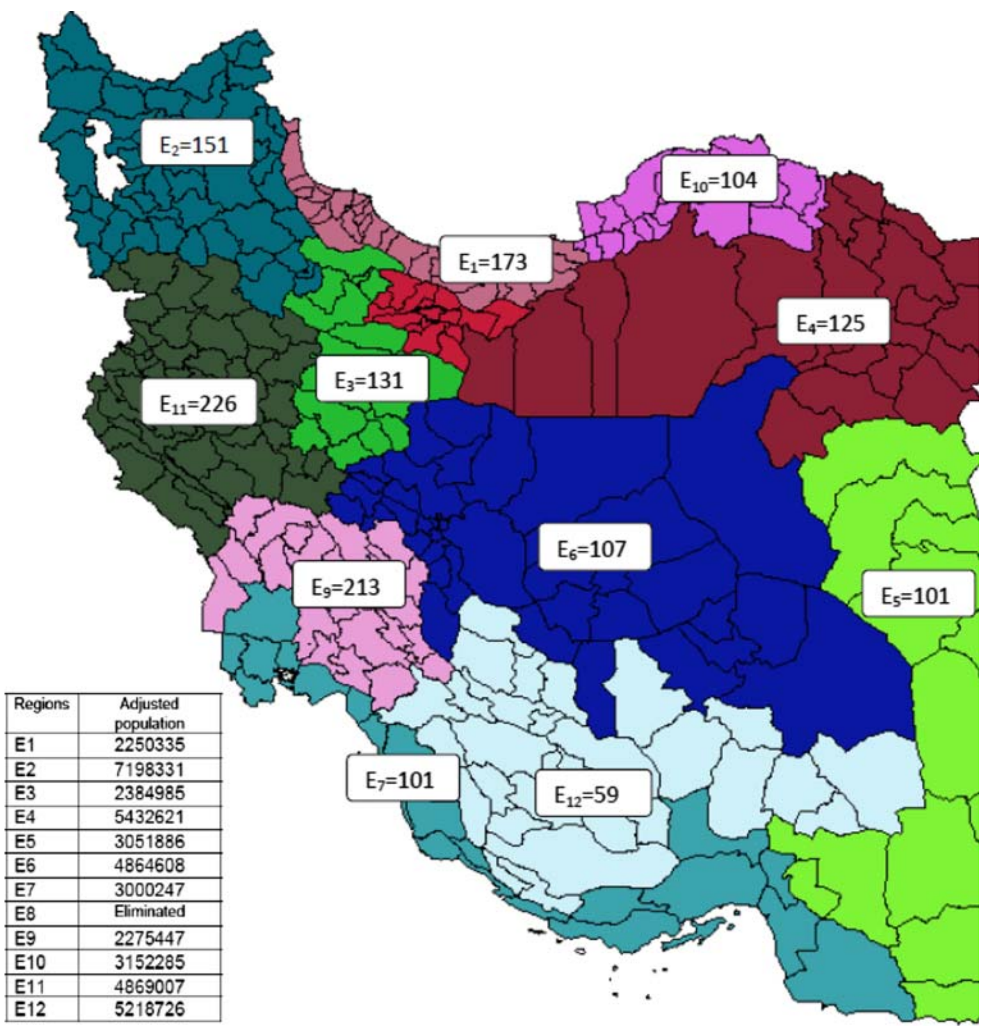
From 117,956 referrals to the imaging centers during the phases of study, namely, 31,765, 31,947, 30,600 and 23,644 for the various study phases, respectively, the positive stone cases were identified based on the above-mentioned four criteria: Totally 6,089 imaging-proven urinary stone patients were identified including new and old cases. 230 (3.8%) patients were excluded due to invalid questionnaire. The rest of the positive cases (5,859) were classified as 2,955 “new cases” (2,466 symptomatic and 489 asymptomatic), 2,202 as “symptomatic old cases” and 702 as “asymptomatic old cases”.

1. *Non-conservative approach* 2,955 patients out of 6,089 positive cases for urinary stone were labeled as “new cases”. The geographic and seasonal variations are illustrated in the Figs. 1, 2 and Table 1.
2. *Semi-conservative approach* 1,914 new cases were detected by this inclusion criterion.
3. *Conservative approach* Based on this approach, 1,697 new cases were identified.
4. *Symptomatic new cases* 2,466 new cases out of 2,955 patients in group 1 (non-conservative approach) were classified by this inclusion criterion.

Incidence estimation

There were seasonal as well as geographic variations for the urinary stone incidence.

1. *Non-conservative approach* Considering the first diagnostic criteria, the following was obtained and the annual pooled incidence was estimated being 136/100,000 (95% CI from 103 to 168 per 100,000 population). A geographic variation was observed in the estimated incidences across different regions such that the west and the northwest regions of Iran demonstrated the greatest incidence for the urinary stones (Figs. 1, 2). With respect to the seasonal variations, when the whole nation was taken into consideration, autumn season accounted for the highest number of detected new cases, and had the greatest incidence rate for the disease followed by spring, winter, and summer. Nonetheless, there were regional diversities in the seasonal patterns (Table 1; Fig. 3).



Regions	Adjusted population
E1	2250335
E2	7198331
E3	2384985
E4	5432621
E5	3051886
E6	4864608
E7	3000247
E8	Eliminated
E9	2275447
E10	3152285
E11	4869007
E12	5218726

Fig. 1 Yearly urinary stone incidence per 100,000 populations in the regions according to the non-conservative criteria. Region 8 was declined due to sampling problems

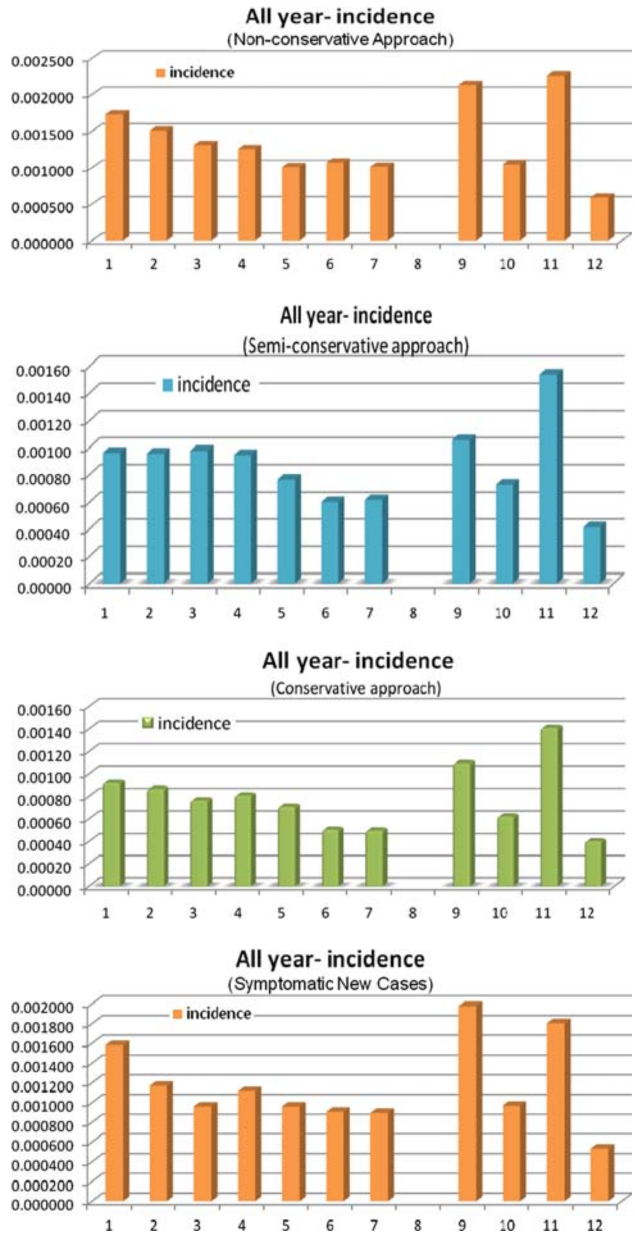


Fig. 2 Estimated incidence of urinary stone disease (per 100,000 per year) in regions across the country according to the four approaches (*X* axis represents the ecologic regions across the country; *Y* axis shows the incidence rates)

Table 1 The pooled incidence rates for the seasonal phases of the study, and the great pooled incidence rate in Iran (per 100,000) with the lower and upper limits of 95% confidence interval for the point estimation

	Spring	Summer	Autumn	Winter	Total
Pooled estimation	133	77	194	172	136
Lower limit	84	49	157	134	103
Upper limit	182	105	232	211	168

2. *Semi-conservative approach* The estimated pooled incidence rate was 87/100,000 (95% CI, 66–108) per year. The pattern of distribution remained constant compared to the non-conservative approach.
3. *Conservative approach* The pooled incidence rate was 78/100,000 (95% CI, 59–98) per year. No considerable change was observed regarding the pattern of stone distribution across the country compared to the two other estimates.
4. *Symptomatic cases* The pooled incidence rate was 117/100,000 (95% CI, 90–143). The regional pattern was almost the same.

Discussion

There are many epidemiologic studies on urolithiasis in different parts of the world. The extracted data from the most important studies are shown in Table 2. The existing literature presents conflicting evidences regarding the prevalence rate in various general populations. A number of possibilities could be brought into account for reasons of this issue. For instance, limitations in sampling and the data collection methods in studies are presumably some of the possible causes. Hospital records, general practice surveys or the selected group screenings are the sources of most epidemiologic studies. Hence, those differences make the comparison of the related incidence rates in various studies difficult.

Curhan et al. [5], in a longitudinal study of the etiology in cardiovascular diseases, cancer and the other diseases, included the health professional males older than 40 years of age and calculated the incidence rates, and therefore, there are age, gender, and population constraints in the samples.

Stamatelou et al. [3] reported the prevalence of kidney stone from the United States national health and nutrition examination survey (NHANES II and III). They used a probability sample of the civilian noninstitutionalized American population between the ages of 20 and 74.

In a long-term community-based cohort study among the Rochester population, medical records of the samples were reviewed and incidence rates were reported [6].

Hesse et al. [2] and Safarinejad [7] carried out population-based cross-sectional surveys in Germany and Iran, respectively. Both of the studies excluded cases younger than 14 years of age. In their studies, they used telephone interviews and personal interviews, respectively.

In a Korean study performed in 1998, 65 cases of urolithiasis were selected for showing the prevalence rate [8]. It was a community-based study limited only to those

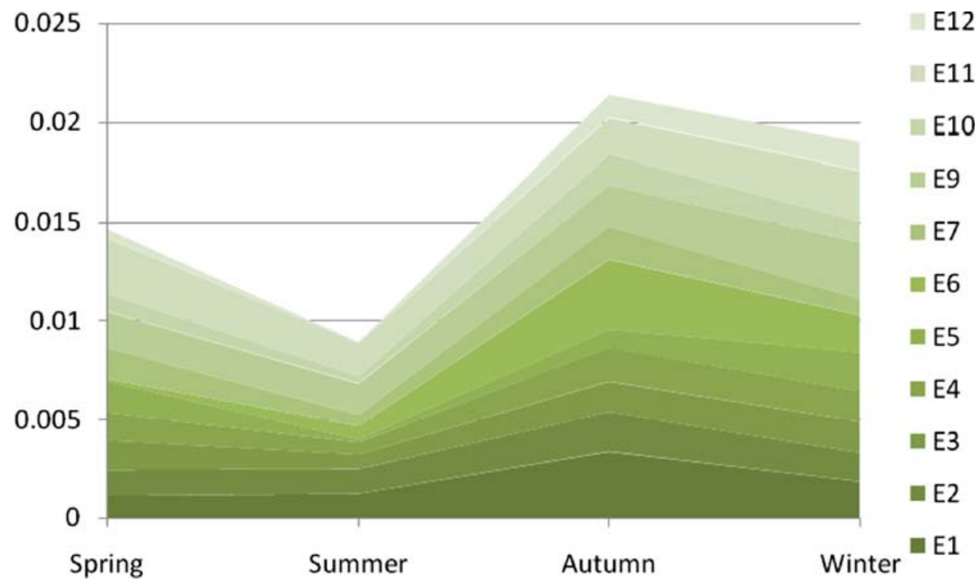


Fig. 3 Seasonal variation in urinary stone incidence as illustrated by cumulative incidence of ecologic zones across Iran, E8 is declined due to sampling problems. *X* axis represents seasons, *Y* axis demonstrates incidence rates

persons in the age range of 40 and 75. The method of sampling is shown in Table 2.

Trinchieri et al. [4] conducted a study between 1986 and 1998. All the adults of a village were asked whether or not they had experienced a kidney stone during their lifetime and requested to report any new stones in the period of the study.

Yasui et al. [1] reported a nationwide hospital survey conducted in Japan. They included all outpatients visited in 2005 who had the diagnosis of the first episode of upper urinary tract stones. Final responses were received from 430 of 1,218 institutions (35.3%), and 30,448 positive cases were included.

As we showed, in some of these studies, stone rates were determined by the self-reported surveys of the volunteer participants, and some studies obtained rates for all residents of a geographically defined population. Only in the Japanese's studies [1, 9] and a community-based study limited to three villages in Thailand, the completely imaging-proven cases were included. In the Lieske's study [6] in Rochester, 72% of cases had imaging proofs.

While some methodological differences might account for the differences in the ratio of urolithiasis in different populations, we believe that truly international differences in the rates of stone disease are possible.

Our study has used imaging-documented techniques to identify incidence of urinary calculi. It has been presumed that almost all of the incident cases of urinary calculi would be referred to imaging centres so rendering it comparable with incidence rates in the general population at the same time. We calculated the incidence rates for the urolithiasis patients, assuming that all of such patients were referred to the imaging centres. From the statistical point of view, while pooling by fixed effect model (FEM) and random effect model (REM) methods are usually applied in the meta-analysis of the separate results, they have been rarely used for pooling the incidence rates through studies. We applied same rationale for pooling the incidence rates across regions in a cross-sectional study that is the first to the best of our knowledge. This approach leads to a more accurate estimate of the incidence rate for the whole nation when compared to a simple adding up of the patchy results.

Thirty provinces in Iran were subdivided into 12 areas based on the geographic proximity, also the climatic and socioeconomic similarities. Therefore, the difference in incidences among various regions might be due to the difference in genetic/ethnic, environmental, dietary or occupational factors in populations. Furthermore, the samplings of the study were established in four seasons of a year; therefore, we were able to compare the statistics of a particular region in different weather conditions.

One feature of our study was that we defined incidence rates according to the newly diagnosed disease cases and could not comment on the prevalence rates because they were dependant on the frequency of imaging follow-ups in the cases of urinary stone disease. Moreover, we were unable to detect all of prevalent cases by this method, in particular the symptomless old cases.

A unique feature of our study was the sampling from all imaging centers in the regions during the screening periods; therefore, we almost included all inpatient and outpatient urolithiasis cases.

To increase the reliability of the diagnosis of urinary calculi, we also calculated incidence rates using conservative approach that in those cases ultrasonography was the only imaging modality, and stones with a diameter of less

Table 2 Epidemiologic studies on urolithiasis in different countries

Author	Date of study	Country	Type of study	Methods	Urolithiasis cases participant	Age	Prevalence (%)
Curhan [5]	1992	USA	Cohort	The health professional follow-up study: longitudinal study of the etiology of cardiovascular disease, cancer and other diseases, males, mailed questionnaires	753 incident cases in 6 years, 4,082 prevalent cases	≥40 males	8%
Stamatelou [3]	1976–1980, and 1988–1994	USA	Population-based, cross-sectional survey	The prevalence of kidney stone disease history from NHANES (II and III). a probability sample of the civilian noninstitutionalized American population, interviews	NR	20–74	1976–1980 = 3.8 1988–1994 = 5.2
Lieske [6]	1970–2000	USA	Community-based cohort	Incidental symptomatic stone in Rochester (72% imaging-proven) in a well-defined population, review of medical records	248	All ages	NR
Hesse [2]	2001	Germany	Population-based, cross-sectional survey	7,500 persons from all over Germany were questioned for the occurrence of urinary stones during their lifetimes (prevalence) and on acute urolithiasis in 2000 (incidence), telephone interviews	355	≥14	4.7
Safarinejad [7]	2006	Iran	Population-based, cross-sectional survey	8,413 persons from all over Iran were questioned on the occurrence of the urinary stones in their lives (prevalence) and for acute urolithiasis in 2005 (incidence), visit interviews	436	≥14	5.7
Serio [11]	1997	Italy	Population-based	A survey by ISTAT (Italian Statistics Institute)	9,5000 incident cases in 6 years, 974,000 prevalent cases	All ages	1.72
Kim [8]	1998	Korea	Community-based studies	Stepwise random sampling from inhabitants of the Seoul metropolitan area for the ages between 40 and 79 years old who were selected by the population census register in numbers consistent with the population distribution of each district and sex, questionnaires by interview	65	40–79	3.5
Trinchieri [4]	1986 and 1998	Italy	Community-based studies	All adult (age > 25 years) occupants of two random samples of households in the village. Participants were asked whether they had experienced a kidney stone during their lifetimes. The group was asked to report whether or not any new stones had formed in that time period of 12 years, questionnaire by interview	103	>25y	1986 = 5.9, 1998 = 9
Indridason [12]	1967–1991	Iceland	Cohort	Data were derived from the Reykjavik Study, a population-based cohort study carried out between 1967 and 1991. All subjects answered a thorough questionnaire concerning their medical history at each visit, questionnaires by interview	423 males and 307 females	30–80	4.1

Table 2 continued

Author	Date of study	Country	Type of study	Methods	Urolithiasis cases participant	Age	Prevalence (%)
Yoshida [9]	1990 and 1995	Japan	Hospital survey	All outpatient visits to urologists that resulted in a diagnosis of the first episode of upper urinary tract stones between the years 1990 and 1995, enrolled all of the Japanese Board of Urology-approved hospitals covering nearly all urologists practicing in Japan, radiographic confirmations	56,798 incident cases	All ages	NR
Lee [13]	1994–1996	Taiwan	Population-based nationwide, cross-sectional survey	Questionnaires were mailed to 27,758 people, 0.2% of the adults in Taiwan	440	Adults	9.6
Yanagawa [14]	Not mentioned	Thailand	Community-based studies	Three villages in the rural areas of Khon Kaen province in the northeast Thailand. 367 persons were asked questions relating to urolithiasis and were examined by abdominal ultrasonography	62	All ages	16.9
Yasui [1]	2005	Japan	Hospital survey	Similar to O.Yoshida 's study records in 2005; final responses were obtained from 430 of the 1,218 institutions (35.3%)	30,448	All ages	NR

Author	Date of study	Incidence (per 100,000)	Male prevalence (%)	Female prevalence (%)	Male incidence (per 100,000)	Female incidence (per 100,000)
Curhan [5]	1992	NR	NR	NR	300	NR
Stamatelou [3]	1976–1980, and 1988–1994	NR	1976–1980 = 4.9 ± 0.42	1976–1980 = 2.8 ± 0.17	NR	NR
			1988–1994 = 6.3 ± 0.56	1988–1994 = 4.1 ± 0.27		
Lieske [6]	1970–2000	101.8 (±6.6)	NR	NR	140.6 (±11.4)	65.8 (±7.0)
Hesse [2]	2001	720	5.5	4	430	290
Safarinejad[7]	2006	138.4	6.1	5.3	147.2	129.6
Serio [11]	1997	168	1.84	1.61	NR	NR
Kim [8]	1998	NR	6	1.8	NR	NR
Trinchieri [4]	1986 and 1998	400	1986 = 6.8, 1998 = 11.9	1986 = 4.9, 1998 = 6.7	600	180
Indridason [12]	1967–1991	NR	4.7	3.2	545	202
Yoshida [9]	1990 and 1995	68.9	5.2	2.1	100.1	55.5
Lee [13]	1994–1996	NR	14.5	3.1	NR	NR
Yanagawa [14]	Not mentioned	NR	25.1	10.1	NR	NR
Yasui [1]	2005	134	NR	NR	192	79.3

All based on the first criteria

than 5 mm were excluded. This cutoff point for diagnosis of calculi has acceptable supporting evidence in the literature [10].

Since we had adequate number of samples from each region, we could analyze statistics in various regions separately in order to compare them properly.

The limitations of our study include: (1) We might have lost a few cases of urinary stone disease for simply not being referred to the participating imaging centers, though, because of the nature of the disease, it should be a rarity that would have caused an insignificant underestimation of the incidence rates. (2) We were unable to calculate the prevalence of stone disease in general population because of the type of sampling utilized. (3) There was no distinction on the types of stone composition.

Our data have important impacts on estimating the true burden of the disease and planning for the medical care and designing of the case–control and cohort studies.

Conclusions

The epidemiologic study and the incidence of the urinary calculi are highly dependant on the methodology of the study, the design of the study, and the strategy to prove the disease. Our study, by applying a superior meticulous method in sampling, statistical analysis and the disease establishing techniques could be a more reliable indicator of the disease incidence.

Geographically, the west and north of Iran, and seasonally, autumn have shown the highest incidence rates for the urinary tract stones.

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