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Seroprevalence of hepatitis C virus: the first population-based study from Iran

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SUMMARY

Objective: Early studies on blood donors point to a seroprevalence of approximately 0.25% for hepatitis C virus (HCV) infection in Iran. However, the true prevalence in the general population is unknown. The objective of this study was to determine the prevalence of HCV infection in the general population of Iran.

Methods: We randomly selected 6583 subjects from three provinces in Iran for inclusion in the study. Subjects were aged between 18 and 65 years. Anti-hepatitis C antibody was tested by a third-generation ELISA test. A recombinant immunoblot assay (RIBA) test was used to confirm the results. Risk factors were recorded and a multivariate analysis was performed.

Results: A total of 5684 plasma samples were tested. After confirmatory tests, we found 50 cases of HCV. The overall weighted prevalence of anti-HCV was 0.5%. The rate was significantly higher in men (1.0%) than in women (0.1%). In multivariate analysis, male sex, history of intravenous drug abuse, and imprisonment were significantly associated with anti-HCV.

Conclusions: We found the prevalence of HCV infection in Iran to be higher than previous estimates. It appears that the rate is rising, and in the future, hepatitis C will replace hepatitis B as the most common cause of chronic viral liver disease in Iran.

1. Introduction

Hepatitis C is the second most common chronic viral disease in the world after hepatitis B.[1] With the mass hepatitis B vaccination programs now mandatory in many countries, it is predicted that hepatitis C will emerge as the most common chronic viral liver disease in the next few decades. Hepatitis C is already a major cause of cirrhosis and hepatocellular carcinoma (HCC) and is a leading cause of liver transplantation in the USA and many other Western countries.[2] The global prevalence of hepatitis C virus (HCV) infection is at least 2%, with over 120 million infected.[3] A precise estimate of HCV prevalence is required for all prevention and/or treatment programs. Most studies on HCV infection prevalence have been performed on specific populations such as blood donors, drug abusers, or cases of chronic hepatitis. Population-based studies of HCV prevalence are not available for many developing countries, including Iran.[3] The first study on HCV prevalence in Iran was on healthy blood donors in 1994, and showed a seroprevalence of 0.25%.[4] In that year, blood donors were unselected and anyone was allowed to donate blood. This number has always been stated as a rough estimate of the seroprevalence of HCV in Iran. A more recent study, again on blood donors, indicated an almost stable seroprevalence of 0.13% during the period of 2004–2007.[5] It should be noted that blood donors are now selected and that subjects with high risk factors are not allowed to donate blood. Studies on blood donors are seriously affected by selection bias and a male predominance. The male to female ratio is occasionally as high as 10:1 in such reports. Reports on the prevalence of HCV infection in special populations in Iran are as high as 11–25% for patients on hemodialysis,[6,7] 11–52% for intravenous drug abusers,[8] and 15–76% for hemophilia and thalassemia patients.[9–12] In the current study, we present the first population-based data on the prevalence of HCV infection in Iran.

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2. Methods

2.1. Study population

The general population of three provinces in Iran, Golestan (in the north-east of Iran), Tehran (north-center), and Hormozgan (south), was studied. Subjects between 18 and 65 years of age were included. Exclusion criteria were non-Iranian nationality, not being a permanent inhabitant of the household, or not consenting to the study. Some useful information on Iran and the three provinces studied is given in Table 1.

2.2. Sampling and randomization

The study was performed as part of a larger study evaluating common liver diseases in Iran during 2006. Clustered random sampling was used. One hundred clusters were selected from each province with a cluster size of 20 or 25. Postal code or family registry code was used to randomly select the first household for each cluster. Blood samples were obtained from each subject and a questionnaire was completed. The questionnaire included demographic and anthropometric data and risk factors for hepatitis. The details of sampling and randomization are available elsewhere.[13]

2.3. Laboratory tests

Blood samples from each participant were transferred to the Iran Blood Transfusion Organization (IBTO) Research Center where they were tested for anti-HCV antibody (anti-HCV) using a third-generation ELISA test (Ortho HCV 3.0 Enhanced SAVe ELISA, Ortho-Clinical Diagnostics, Amersham, UK and Hepanostika HCV Ultrakit, Beijing United Biomedical Co., Beijing, China). Positive samples were re-tested and those positive in repeated ELISA were confirmed by a recombinant immunoblot assay (RIBA) test (INNO-LIA HCV Score, Innogenetics, Ghent, Belgium). Subjects with a positive RIBA test were considered to have true anti-HCV and thus, exposure to the virus and active or past infection.

2.4. Statistical analysis

The prevalence of HCV infection was computed using a weight equal to the proportion of the population in each province. The same weights were used for evaluating frequencies for each risk factor. Weighted logistic regression analyses were used to calculate the odds ratio and 95% confidence interval (OR (95%CI)) for each risk factor. Then a final logistic model was developed by a backward model selection for age, sex, province, marital status, history of transfusion, addiction, and imprisonment. The final model was checked for outliers and goodness-of-fit.

2.5. Ethics

Written and informed consent was obtained from all subjects. Data were stored in the database with no reference to the subjects' names. The study protocol and the consent forms were reviewed and approved by the Institutional Review Board of the Digestive Disease Research Center, Tehran University of Medical Sciences.

Table 1
Census information—Iran and the three provinces studied[a]

	Area (km^2)	Population	Urban	Male	Literacy
Iran	1 648 195	70 495 782	68.5%	50.9%	84.0%
Tehran	18 814	13 422 366	91.3%	51.4%	91.3%
Hormozgan	70 697	1 403 674	47.1%	51.7%	82.4%
Golestan	20 367	1 617 087	49.2%	49.7%	82.1%

[a] Source: Iran national population and housing census, 2006; http://www.sci.org.ir/portal/faces/public/sci_en, reproduced from Merat et al.[13]

3. Results

A total of 6583 subjects were interviewed in the three provinces. The age criterion was not strictly observed in 381 subjects from Hormozgan and Golestan (age <18 or >65 years). These subjects were deleted from the database and not analyzed further. Another 518 subjects refused blood sampling or had inadequate samples and were excluded. A significantly higher number of exclusions, as compared to included subjects, were from Hormozgan Province (54.4% vs. 25.7%), lived in a rural area (94.4% vs. 81.8%), and were male (45.9% vs. 39.2%). A significantly lower number of exclusions were from Golestan Province (0.2% vs. 33.3%). There was no significant age difference between included and excluded subjects. A total of 5684 samples were analyzed. Demographic characteristics of the study population are given in Table 2. The frequency of all the risk factors studied was significantly different between the three provinces.

One hundred and forty-two study subjects were positive for anti-HCV by ELISA. Of these, 50 were confirmed by RIBA. The rate of positive RIBA tests (seroprevalence) in the three provinces and both sexes are given in Table 3. The age-specific seroprevalence of HCV for each sex is indicated in Table 4. It can be seen that the difference between the sexes is most prominent in the younger age groups.

In univariate analysis, Golestan and Hormozgan provinces had significantly higher rates of anti-HCV. Male sex, living in a rural area, unmarried status, history of transfusion, drug abuse (intravenous and non-intravenous), tattooing, and imprisonment were also correlated with higher HCV infection rates (Table 5). In multivariate analysis, only male sex, history of intravenous drug abuse, and imprisonment remained significantly associated with anti-HCV (Table 6). Golestan subjects were excluded from the multivariate analysis due to a high rate of missing data.

4. Discussion

This is the first population-based study on the prevalence of HCV infection in Iran. We observed an overall seroprevalence of

Table 2
Demographic data of the study population[a]

	Tehran	Hormozgan	Golestan	Total
Subjects interviewed	2561	1987	2035	6583
Number valid	2561	1745	1896	6202
Samples collected	2326	1463	1895	5684
Male	41.6%	44.9%	31.9%	39.2%
Age, mean ± SD (years)	35.6 ± 13.6	33.4 ± 11.9	38.7 ± 12.9	36.1 ± 13.0
Rural	5.2%	0%	48.2%	18.2%
Currently married	68.2%	72.9%	86.9%	73.3%
History of blood transfusion	9.2%	2.0%	8.2%	6.8%
Addiction	3.7%	0.5%	14.5%	4.9%
Intravenous addiction	1.0%	0.1%	N/A	0.7%
History of tattooing	7.8%	1.4%	N/A	5.3%
History of imprisonment	1.7%	0.3%	N/A	1.1%

[a] Percentages reported for subjects with available data. N/A, data not available.

Table 3
The weighted seroprevalence of hepatitis C virus in three provinces of Iran (*n* (%))

	Tehran	Hormozgan	Golestan	Total
Total	8 (0.3%)	24 (1.6%)	18 (1.0%)	50 (0.5%)
Male	8 (0.8%)	17 (2.6%)	8 (1.3%)	33 (1.0%)
Female	0 (0.0%)	7 (0.9%)	10 (0.8%)	17 (0.1%)

Table 4
The weighted seroprevalence of hepatitis C virus in male and female subjects in different age groups

Age group	Male	Female
18–29 years	1.2%	0.2%
30–45 years	0.9%	0.1%
46–65 years	0.4%	0.0%

Table 5
Risk factors associated with anti-HCV in univariate analysis

	Number (%)	OR (95% CI)	*p*-Value
Province			
Tehran	8 (0.3%)	1	
Hormozgan	24 (1.6%)	4.8 (2.2–10.8)	<0.001
Golestan	18 (1.0%)	3.0 (1.3–7.0)	0.011
Sex			
Female	17 (0.1%)	1	
Male	33 (1.0%)	10.2 (5.0–20.8)	<0.001
Location			
Urban	40 (0.4%)	1	
Rural	10 (1.3%)	3.4 (1.1–10.7)	0.040
Age group (years)			
18–29	20 (0.9%)	1	
30–45	21 (1.1%)	0.6 (0.2–1.8)	0.4
46–65	9 (0.6%)	0.2 (0.1–0.6)	0.002
Education[a]			
<5 years	13 (0.6%)	1	
5–12 years	14 (0.4%)	0.6 (0.2–1.8)	0.3
>12 years	4 (0.3%)	0.5 (0.1–3.0)	0.5
Marital status[a]			
Married	17 (0.2%)	1	
Not married	15 (1.0%)	6.9 (2.4–19.9)	<0.001
Transfusion[a]			
No	30 (0.5%)	1	
Yes	1 (0.1%)	0.1 (0.01–0.8)	0.028
Addiction[a]			
No	26 (0.2%)	1	
Yes	5 (5.8%)	27.4 (8.9–84.0)	<0.001
Intravenous addiction[a]			
No	28 (0.3%)	1	
Yes	3 (12.9%)	49.4 (12.7–192.5)	<0.001
Tattooing[a]			
No	27 (0.3%)	1	
Yes	4 (2.2%)	8.1 (2.5–26.2)	0.001
Imprisonment[a]			
No	26 (0.3%)	1	
Yes	5 (10.4%)	45.3 (13.6–151.0)	<0.001

[a] Data available for Tehran and Hormozgan Province only.

0.5% in the general population. However, as for hepatitis B virus (HBV), the rate for different provinces was significantly different. Considering the ethnic diversity and lifestyle variations among the different provinces of Iran, which is also discernible from Table 2, such a difference might be expected.[13] The difference is quite significant in the case of Hormozgan. This province is located on the northern littoral of the Persian Gulf and only a few hours of sailing from the Arab countries of the south. Much of the economy of Hormozgan is based on frequent travel to these countries, which might explain the greater exposure in this area. Another finding of interest is the significantly higher prevalence in males as compared to females. In the case of HBV, we observed that there was no significant sex preponderance after correcting for high-risk behaviors,[13] but the same does not appear to be true for HCV. This might be related to the fact that the transmission of HBV has been largely vertical, mother-to-infant, which is expected to infect male and female infants equally. Conversely, the transmission of HCV is through infected blood or blood products, needle sharing in intravenous drug abusers, and sexual promiscuity.[14] Male sex was an independent predictor of HCV infection in multivariate analysis. We have no explanation for this finding except that drug abuse, which is more common in men and was also found to be the strongest predictor in our study, might have been under-reported by our subjects. Alternatively, there might be other risk factors, more common in males, which we have not sought. An important finding is that the difference in sex is especially prominent in the younger age groups (Table 4), which is not only indicative of certain risk factors, but also indicates an important epidemiologic identity of HCV in Iranian young and middle-aged men. Unfortunately, previous reports from Iran have included very few women, so we cannot reliably comment on changes in prevalence in women. However, our data suggest that the rate in women is fairly constant in the different age groups and that the increased seroprevalence of HCV is mainly attributable to younger males.

Table 6
Risk factors associated with anti-HCV in multivariate analysis[a]

	OR (95% CI)	*p*-Value
Male sex	15.8 (4.8–51.7)	<0.001
History of intravenous drug abuse	29.6 (2.2–401.0)	0.001
History of imprisonment	20.3 (2.9–141.7)	0.002
Hormozgan vs. Tehran	10.3 (4.4–23.9)	<0.001

[a] Subjects from Golestan Province were excluded due to the large quantity of missing data.

We also observed an increased prevalence of HCV among rural subjects. A similar finding has also been reported for HBV.[13] We have no explanation for this finding other than the possible impact of lower socioeconomic status and standards of general health in these areas.

Our study confirms the correlation of intravenous drug abuse with HCV infection.[14] We also found a highly significant correlation with imprisonment. Intravenous drug abuse is illegal in Iran and addicts are imprisoned. Needle sharing, as well as introduction to drug abuse, frequently occurs in prisons, which might explain why imprisonment is an independent risk factor for HCV infection.[15] Realization of this fact by the Iranian Ministry of Justice has led to harm-reduction policies, including separation of intravenous drug addicts in prisons and the provision of free needles and syringes. These efforts are still in their early stages, but could reduce the transmission of HCV and other blood-borne infections in our prisons.[15]

In univariate analysis, not being married, living in an urban area, and history of transfusion or tattooing were also risk factors for HCV infection, but they lost their significance in multivariate analysis, indicating that they are somehow dependant on other factors. It should be noted that multivariate analysis was only performed on subjects from Hormozgan and Tehran.

An important strength of our study is that approximately 60% of our participants were women. Almost all previous studies, including those on hemophiliacs, drug abusers, and blood donors, have been performed on populations with an over 80% male preponderance, and a valid prevalence for the female population of Iran did not exist.

The seroprevalence of HCV among Iranian blood donors was 0.25% in 1994.[4] In the current study we observed a rate of 0.5%. Although our study is population-based and is not directly comparable to blood-donor studies, it strongly suggests an increase in the seroprevalence of HCV in Iran. The increasing seroprevalence of HCV indicates that hepatitis C is gradually replacing hepatitis B as the most common chronic viral hepatitis in Iran.[16,17]

In molecular phylogenetic analysis and PCR studies on a total of approximately 2500 patients presenting to various referral centers, 55–64% of Iranian patients were found to carry the so called difficult-to-treat genotypes 1 and 4.[18,19] Although alcohol consumption is not common in Iran, obesity, insulin resistance, and non-alcoholic steatohepatitis, all of which worsen the prognosis and render it more difficult to treat, are very common.[20,21]

A positive RIBA test confirms the presence of anti-HCV and exposure to the virus. But this is not necessarily equivalent to chronic hepatitis C infection, as only 60–85% of patients exposed to HCV progress to chronicity.[1,22] Reports from IBTO state that 70% of their RIBA-positive anti-HCV cases are positive for HCV RNA (unpublished data). We have not tested for HCV RNA in our study, but based on the reports from IBTO, it is safe to assume that at least 70% of our cases would be HCV RNA positive. Therefore, the prevalence of chronic hepatitis C in Iran would be 0.35% and the number of Iranians with chronic hepatitis C about 250 000. It is estimated that almost 16% of these patients will progress to cirrhosis over 20 years.[23] Thus, if not treated, we should expect at least 40 000 new cases of hepatitis C cirrhosis by 2028. The medical costs of a cirrhotic patient are very high and many would eventually require liver transplantation. The cost of transplant and the following life-long immunosuppression is tremendous. Even after transplant, the 100% recurrence rate of HCV requires further treatment and frequently re-transplant. Many studies point to the cost effectiveness of treating hepatitis C patients before they progress to cirrhosis.[24,25]

In conclusion, the seroprevalence of HCV in the population studied is 0.5%, which is higher than previous estimates for Iran. It appears that the prevalence of HCV is rising, especially among younger men, and in the future hepatitis C will replace hepatitis B as the most common cause of chronic viral liver disease in Iran.

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