Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: a fieldwork TURHEP study

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Abstract

The present study was designed to determine the seroprevalence of hepatitis B and C virus (HBV, HCV) infections and risk factors in the Turkish general population. Participants were enrolled from urban and rural areas of the predetermined 23 EUROSTAT NUTS 2 region. A two-stage stratified sampling method was used to select participants from these regions (n = 5460; 50.9% females; mean (SD) age: 40.8 (14.7) years). Sociodemographics, clinical characteristics and risk factors were recorded at home visits. The seropositivity rates for hepatitis B surface antigen (HBsAg), anti-HCV, anti-HBs and anti-HBc total were 4.0%, 1.0%, 31.9% and 30.6%, respectively. Among HBsAg-positive cases, 94.5% were anti-HBe-positive, 70.2% were HBV-DNA-positive and 2.8% were anti-HDV total positive; 99.1% of HBV infections were of genotype D. Close contact with a hepatitis patient (OR 3.24; 95% CI 2.25–4.66; p < 0.001), living in the southeastern region (OR 2.74; 95% CI 1.7–4.45; p < 0.001), male gender (OR 1.77; 95% CI 1.28–2.46; p < 0.001), being married (OR 1.62; 95% CI 1.02–2.57; p 0.038), educational level less than high school (OR 1.53; 95% CI 1.04–2.26; p 0.03), orodental interventions (OR 1.54; 95% CI 1.01–2.35; p 0.047) and a history of non-disposable syringe use (OR 1.4; 95% CI 1.01–1.96; p 0.045) were significant determinants of HBsAg positivity. Age ≥50 years (OR 2; 95% CI 1.09–4.3; p 0.026) was the only significant predictor of anti-HCV positivity. In conclusion, our findings revealed an HBsAg positivity in 4% and anti-HCV positivity in 1% of the adult population and at least one-third of the population has been exposed to HBV infection in Turkey.

Keywords: Hepatitis B, hepatitis C, risk factors, seroprevalence, Turkey
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Introduction

An estimated 350–400 million people with chronic hepatitis B virus (HBV) infection and 170 million people with chronic hepatitis C virus (HCV) infection have been reported worldwide [1,2].

The prevalence of HBV infection varies widely by geographic region [3], ranging from 0.1% to 20% in different parts of the world [4], and from 2% to 8% in countries with intermediate endemicity for hepatitis B infection including Turkey [5,6].

Based mainly on studies in blood donors, the overall prevalence of chronic HBV infection has been reported to range from 4% to 5% [7] in Turkey with considerable regional differences [8] and a decline to 2% has been evident in recent years [10]. The Turkish Ministry of Health declared the incidence of hepatitis B infection to be 8.26 by 2002 and 4.2 by 2010 per 100 000 people [9]. A recent meta-analysis on viral hepatitis in Turkey reported 4115 new cases/year with a

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morbidity rate of 6.07/100 000 in 2000, and 2835 cases/year were associated with a morbidity rate of 3.79/100 000 in 2011 [10]. Significant geographic and temporal differences were noted in the epidemiology of HCV infection in Europe, with an overall prevalence between 0.1% and 1% in northern Europe, 0.2% and 1.2% in Central Europe and 2.5% and 3.5% in southern Europe [11].

Although epidemiological data on the general population are limited in Eastern European countries, a high prevalence of infection was documented among blood donors (0.9–5%), healthcare workers (1–10%) and high-risk groups (i.e. 50–92% in people with haemophilia) [11].

There is no national screening or reporting system for HCV in Turkey, and the epidemiological data are derived mainly from local studies [7,12–14] indicating anti-HCV positivity from 0.4% to 1.5% in community-based studies, from 0.19% to 0.68% in blood donors and from 2.2% to 2.4% in patients during routine outpatient visits. The current best estimate for the prevalence was reported to be approximately 1% [1].

As most of the studies on the epidemiology of HBV and HCV infections in Turkey were conducted in blood donors and risk groups and limited nationwide data are available in the general population [7,8,12,15–19], the present population-based, large-scale field study was designed to determine seroprevalence of HBV, HCV and hepatitis delta virus (HDV) infections in relation to risk factors for increased seropositivity in the Turkish general population.

Materials and methods

Study population

In the present fieldwork, TURHEP Study, 5533 volunteers were screened through home visits in 2009–2010 living in urban and rural areas of 23 cities located in EUROSTAT NUTS 2 regions of Turkey and determined based on two-stage stratified sampling method. The participants were selected according to a randomized sampling method of the Statistics Institute of Turkey. Participants' sociodemographic features, anthropometrics, medical history, concomitant medications and presence of risk factors were recorded and blood samples were collected for serum HBV, HDV, HCV markers, and alanine transaminase (ALT) and aspartate transaminase (AST) were measured.

The inclusion criteria were, being $\geq$18 years of age, residing in predetermined locations and volunteering to participate. People who were visitors, lacked cognitive ability to respond to study questions, or refused to provide contact details were excluded from the study.

Before data collection, written informed consent was obtained from each participant following a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the Ministry of Health Primary Health Care Ethics Committee.

Blood tests and determination of risk factors

Blood samples (8–10 mL) were taken from all individuals for serological and biochemical tests including hepatitis B surface antigen (HBsAg), anti-HBs, hepatitis B core antibody (anti-HBc) total, anti-HCV, hepatitis B e antigen (HBeAg), anti-HBe, HBV-DNA, anti-HDV, ALT and AST measurements. Serum samples were transmitted to the central laboratory under cold chain with barcode labelling to be analysed.

Data on risk factors for HBsAg and anti-HCV positivity including close contact with a hepatitis patient, geographical region, gender, marital status, educational level, orodental interventions, previous use of non-disposable syringe, circumcision, unsafe sexual practices, intravenous drug use, blood transfusion, surgery, piercing/tattoo/acupuncture and dialysis were recorded on data collection forms by the physician using a face-to-face interview method.

Serological and molecular assays

Serological tests were performed by Cobas Roche Diagnostics using an electrochemiluminescence immunological assay. The extraction procedure was performed by QIA symphony (Qiagen, Hilden, Germany) automated extraction system. HBV-DNA quantification by real-time PCR was performed in a combination of Artus HBV RG PCR Kit (Artus™ GmbH, Hamburg Germany) and the real-time PCR instrument, Rotor-Gene Q (Qiagen). The analytical detection limit of HBV DNA is 10 IU/mL (linear range: 10–20 000 000 IU/mL).

Statistical analysis

At least 5000 volunteers were planned to be included in the TURHEP study based on representation of hepatitis C in the study sample with an expected prevalence of 0.8% and accuracy 0.2%. The statistical analysis included 5460 participants with data available on seroprevalence and risk factors for HBV and HBC infection.

Statistical analysis was performed using computer software STATA version 11.0 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP). Chi-square test was used for the comparison of categorical data, and Student's *t* test was used for numeric variables. One sample Z-test was used for the comparison of regional versus overall HBsAg positivity. Logistic regression was used for multivariate analysis to determine the predictors of HBsAg positivity and anti-HCV positivity. The potential risk factors for HBsAg positivity and anti-HCV positivity were included in the regression model.

Data were expressed as mean (standard deviation; SD), *n* (%) and OR (95% CI), where appropriate. A p value < 0.05 was considered statistically significant.

Results

Sociodemographic features and medical history

Mean (SD) age of the participants was 40.8 (14.7) years; 50.9% were women; mostly aged <50 years, at least primary school graduates, married and from urban areas (Table 1).

The HBsAg-positive and anti-HCV-positive participants were older than the HBsAg-negative and anti-HCV-negative participants (p 0.019 and p < 0.001, respectively). Among HBsAg positive participants, males, those with lower educational status and married participants were significantly more common (Table 1).

Past history of infective jaundice was confirmed by 7.6% (*n* = 414) of the participants; but the type of infection was known only by 42.0% (*n* = 174) and identified as HBV by 47.7% (*n* = 83) and as HCV by 5.1% (*n* = 9) of these participants. Among people recalling their previous immunization, 4.7 (*n* = 255) and 10.7% (*n* = 586) were vaccinated for hepatitis A and B, respectively.

Although a limited number of men could give information about their circumcision experience; the frequency of HBsAg positivity was significantly higher among those circumcised by a barber (11/99; 11%; p 0.006), compared to those circumcised by a circumciser (9/151; 6.0%; p 0.647), at a health centre (6/116; 5.2%; p 1.000) and by a health officer (29/720; 4%; p 0.072).

Serological findings

The overall HBsAg seropositivity was 4% (218/5460); whereas there was significant variability among geographic regions (p < 0.004): Aegean 2.3% (16/701; p 0.021 versus all regions), Black Sea 6.1% (18/294; p 0.062), Central Anatolia 4.3% (56/1301; p 0.566), Eastern Anatolia 3.4% (7/207; p 0.653), Marmara 3.8% (86/2258; p 0.655), Mediterranean 3.1% (12/383; p 0.390) and Southeastern Anatolia 7.3% (23/316; p 0.003).

Anti-HCV seropositivity was detected in 1% (52/5460) of all participants. Of 113 HBV-positive cases with genotype analysis, 99.1% were of genotype D. Among HCV-positive participants 92.1% were of genotype 1b.

In addition, HBsAg positivity was accompanied by anti-HDV positivity in 2.8% and by anti-HCV positivity in 0.9%. Among HBsAg-positive cases 94.5% were anti-HBe-positive and 4.1% were HBeAg-positive (Table 2). HBV-DNA level was non-detectable in 48 (22.0%), <2000 IU/mL in 88 (40.4%), 2000–20 000 IU/mL in 39 (17.9%) and >20 000 IU/mL in 43 (19.7%) of 218 HBsAg-positive participants.

Anti-HBs positivity was identified in 31.9% and anti-HBc positivity in 30.6% of participants; whereas anti-HBs positivity was accompanied with anti-HBc positivity in 22.0% and isolated anti-HBc positivity was evident in 4.6% of all participants (Table 2). None of these participants was HBV-DNA positive.

Risk factors for hepatitis B

Logistic regression analysis revealed that close contact with a hepatitis patient, living in the southeastern region, male gender, being married, educational level less than high school, orodental interventions and past use of non-disposable

TABLE 1. Sociodemographics of all participants according to HBsAg and anti-HCV positivity

	HBsAg (+) *n* = 218	HBsAg (−) *n* = 5242	p	Anti-HCV (+) *n* = 52	Anti-HCV (−) *n* = 5371	p	All participants[a] *n* = 5460
Age (years), mean (SD)	42.8 (13.8)	40.7 (14.5)	0.019	48.5 (16.0)	41.0 (15.0)	<0.001	40.8 (14.7)
Age group (years), *n* (%)							
18–29	42 (19.3)	1445 (27.3)	0.059	7 (13.4)	1483(28)	0.004	1490 (27.3)
30–39	54 (24.8)	1323 (25.4)		11 (21.0)	1364 (25)		1375 (25.5)
40–49	55 (25.3)	1080 (20.7)		9 (17.0)	1127 (21)		1136 (21.0)
50–59	41 (18.8)	706 (13.5)		10 (19.0)	738 (14)		748 (13.9)
60–69	14 (6.4)	400 (7.6)		9 (17.0)	405 (7.5)		414 (7.6)
≥70	11 (5.0)	247 (4.7)		6 (12.0)	242 (5.0)		248 (4.7)
Gender, *n* (%)							
Female	89 (40.8)	2692 (51.3)	0.002	33 (63.4)	2750 (51)	0.070	2783 (51.0)
Male	129 (59.1)	2550 (48.6)		19 (36.5)	2658 (49)		2677 (49.0)
Educational status, *n* (%)							
Less than high school	167 (76.6)	3647 (69.6)	0.027	43 (83.0)	3771 (70.0)	0.043	3814 (70.0)
High school or over	51 (23.4)	1594 (30.4)		9 (17.0)	1636 (30.0)		1645 (30.1)
High-risk profession, *n* (%)	*n* = 218	*n* = 5241					*n* = 5459
Healthcare workers	3 (1.4)	242 (4.6)	0.024	4 (8.0)	241 (4.6)	0.265	245 (4.5)
Marital status, *n* (%)							
Married	183 (84.0)	3979 (75.9)	0.006	39 (75.0)	4123 (76.0)	0.838	4162 (76.2)
Single (unmarried, widow(er) and divorced)	35 (16.0)	1263 (24.1)		13 (25.0)	1285 (24.0)		1298 (23.8)
Place of residence, *n* (%)							
Urban	147 (76.2)	3603 (75.0)	0.710	38 (73.0)	3949 (73.0)	0.989	3987 (75.0)
Rural	46 (23.8)	1202 (25.0)		14 (27.0)	1461 (27.0)		1475 (25.0)

HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.
[a]Number with available data.

TABLE 2. Serological findings in relation to HBsAg and Anti-HBs positivity

			n	%	N
HBsAg (+)			218	4.0	5460
+	HBeAg (+)		9	4.1	218
+	Anti-HBe (+)		206	94.5	218
+	HBV-DNA (+)		153	70.2	218
+	HBV-DNA (+)	+ ALT >1.5 UNL	6	2.8	218
+	HBV-DNA (−)		65	29.8	218
+	HBV-DNA (−)	+ ALT >1.5 UNL	1	0.4	218
+	Anti-HCV (+)		2	0.9	218
+	Anti-HDV (+)		6	2.8	218
Anti-HBs (+)			1746	31.9	5460
Anti-HBc (+)			1670	30.6	5460
Anti-HBs (+)	+ Anti-HBc (+)		1212	22.0	5460
Anti-HBs (+)	+ Anti-HBc (−)		463	8.4	5460
Isolated Anti-HBc (+)			251	4.6	5459

ALT, alanine transaminase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; UNL, upper normal limit.

syringes were significant predictors of HBsAg positivity (Table 3).

Risk factors for hepatitis C

Logistic regression analysis revealed that age >50 years was the significant predictor of anti-HCV positivity (Table 4). Educational level less than high school and transfusion of blood and blood products were significantly more frequent among anti-HCV-positive participants in the univariate analysis, whereas they were not confirmed to have a significant impact on anti-HCV positivity in the multivariate analysis, probably because of the small number of such participants (Table 4).

Discussion

This is the first and largest population-based cross-sectional screening on seroprevalence and risk factors associated with viral hepatitis in Turkey. Our findings of HBsAg (4.0%) and anti-HBs (31.9%) seroprevalence fall within the ranges provided for countries with an intermediate endemic profile [4,20] and are in agreement with past studies on epidemiology of hepatitis in Turkey, which indicated an overall prevalence of chronic HBV infection of 4–10% (3.5% in the western and 7% in the eastern regions), and of anti-HBs positivity of 20.6–52.3% [7,10,14,15,19,21,22]. This regional difference in HBV positivity, which is not observed in HCV infection, re-emphasizes the role of close contact and intrafamilial transmission in areas with crowded families and poor hygienic conditions in HBV seroprevalence.

HBsAg positivity was higher in the middle-aged compared with younger and older participants in our series. An 11-year retrospective analysis of epidemiological trends in HBV infections after the implementation of the nationwide vaccination programme in Turkey revealed a stable anti-HBs incidence (43.6%) and intermediate HBsAg seroprevalence of 6.0% with a significant decrease from 12.3% in 2000 to 5.0% in 2010 [19]. Despite the inclusion of older participants and the fact that only 10.7% of our participants recalled having been vaccinated against hepatitis B, HBsAg seropositivity prevalence (4.0%) was lower than previous reports [15,20,23]. Since 1998, HBV vaccine has been administered free of charge to all newborns. Furthermore, a catch up vaccination is offered for non-vaccinated children at primary school; and risk groups are also being vaccinated. The immunization coverage for HBV was 97% by the year 2013 [24]. Since 2012, hepatitis A virus vaccine has been included in the newborn immunization programme.

TABLE 3. Risk factors for hepatitis B surface antigen positivity

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Age ≥50	1.2	0.91–1.64	0.173	1.02	0.71–1.45	0.916
Close contact with hepatitis patient	1.82	1.53–2.17	<0.001	3.24	2.25–4.66	<0.001
Living in southeastern part (versus other regions)	1.99	1.27–3.12	0.002	2.74	1.7–4.45	<0.001
Male gender	1.53	1.16–2.01	0.002	1.77	1.28–2.46	0.001
Being married (versus single/unmarried, widow/widower, divorced)	1.66	1.14–2.39	0.007	1.62	1.02–2.57	0.038
Educational level less than high school	1.43	1.04–1.96	0.028	1.53	1.04–2.26	0.03
Orodental interventions	1.68	1.15–2.44	0.006	1.54	1.01–2.35	0.047
Use of non-disposable syringe	1.71	1.29–2.26	<0.001	1.4	1.01–1.96	0.045
Unsafe sexual practices	1.94	1.23–3.04	0.004	1.17	0.78–1.74	0.438

TABLE 4. Risk factors for anti-hepatitis C virus positivity

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p value	OR	95% CI	p value
Age ≥50	2.5	1.48–4.43	0.001	2	1.09–4.3	0.026
Close contact with hepatitis patient	1.8	0.86–4.06	0.109	1.9	0.86–4.3	0.109
Living in southeastern part (versus other regions)	2.1	0.9–5.06	0.081	1.4	0.42–4.73	0.565
Male gender	0.6	0.33–1.05	0.073	0.6	0.28–1.4	0.258
Being married (versus single: unmarried, widow/widower, divorced)	0.93	0.49–1.75	0.838	1.1	0.5–2.48	0.783
Educational level less than high school	2	1.01–4.26	0.047	1.3	0.56–2.94	0.552
Orodental interventions	1.5	0.72–3.08	0.275	1.3	0.54–2.97	0.575
Use of non-disposable syringe	1.7	0.35–19.51	0.071	1.07	0.53–2.15	0.849
Unsafe sexual practices	0.75	0.28–2.01	0.572	0.5	0.08–3.04	0.459
Transfusion of blood and blood products	2.2	1.14–4.39	0.018	1.3	0.55–3.16	0.519
Surgery	1.5	0.86–2.63	0.147	1.1	0.57–2.18	0.743
Piercing/Tattoo and/or acupuncture	1.5	0.83–2.61	0.175	1.1	0.55–2.49	0.667
Dialysis	(0%)	(0.2%)	0.768			

The trend in decline of HBV infection may also be related to the introduction of disposable syringes into clinical practice since late 1980s and implementation of more efficient preventive measures in the community within the scope of the Hepatitis B Control Programme in the country [22].

Likewise, a recent systematic review evaluating 129 studies published between 1999 and 2009 revealed that the estimated overall population prevalence was 4.57 (95% CI 3.58–5.76) with an estimated total number of HBV-positive cases of about 3.3 million [8].

Another recent meta-analysis reported that globally the prevalence and number of people with anti-HCV has increased from 2.3% to 2.8% between 1990 and 2005 [25]. Overall, Turkey has a low prevalence of HCV infection. This might be related to the early introduction of screening of blood donors and the low rate of intravenous drug use in Turkey. Our finding of anti-HCV positivity (1%) seems in accordance with the data from community-based studies in Turkey (0.4–1.5%) [10,14,18]. In a previous epidemiological study, anti-HCV was detected in 21 (1.5%) of 1374 persons and was more common in residents >54 years of age [14]. Data from past studies on risk factors for HCV infections in Turkey revealed that a history of blood transfusion and nosocomial risk factors accounted for the majority of HCV cases, while intravenous drug use was reported in a small number of HCV cases (4% or less) [13,16,26,27]. Likewise, sexual transmission and mother-to-child transmission were low in Turkey [28,29]. The use of non-disposable medical devices and unsafe surgical interventions may have more impact on HCV seroprevalence than intravenous drug use in our group.

Identification of isolated anti-HBc positivity in 4.6% of the overall study population is compatible with the previously reported range of 3–5% for isolated anti-HBc positivity in Turkey [30]. This may indicate the likelihood of occult chronic hepatitis infection in these participants [31]; however, in none of these anti HBc-positive cases was HBV DNA positive.

Data from retrospective analysis of HBV-related epidemiological trends in Turkey revealed anti-HBe-positive infections to be more frequent than HBeAg-positive infections (77.1% versus 18.5%) [19]. Only 30–35% of patients were HBeAg positive in recent studies [15,32]. The fact that 94.5% of HBsAg-positive participants in our study were anti-HBe positive re-emphasized the role of mutant HBV infection in our region [33].

Overall, anti-HDV total seropositivity was reported to range between 2.9% and 33%, along with rates of 0–11.2% in asymptomatic HBsAg carriers and 6.8–53.4% in patients with chronic hepatitis [34–37]. Given the detection of anti-HDV positivity in 0.1% of the overall study population and in 2.8% of HBsAg-positive participants, our findings confirm a high rate of HDV infection compared with other countries, although a recent reduction in HDV prevalence has been reported in Spain, Taiwan and Turkey in the past three decades [35–39].

Regarding the risk factors, male gender, lower educational level, being married, living in the southeastern region, close contact with a hepatitis patient, orodental interventions and previous use of non-disposable syringes were indicated as the significant independent determinants of HBsAg positivity; the only risk factor associated with increased HCV prevalence was age >50 years in our cohort. This different pattern between the two viruses could be explained by a potential survival phenomenon.

The association between male gender and increased HBsAg positivity in our study may be linked to the fact that males tend to have less seroconversion and more progression to chronicity, easier access to medical care and more contact with the infection at their work or social life [40].

Another regional factor of interest is the custom of circumcision. As the majority of the inhabitants are Muslims and all Muslim men have been circumcised before reaching puberty [41] the higher HBsAg positivity among male participants who were circumcised by a barber in the past compared with those circumcised by health professionals in our study population may reflect the role of circumcision method as a risk factor for HBV transmission.

The identification of orodental practices as an independent determinant of increased HBsAg positivity in our study population is compatible with viral hepatitis being considered an important hazard in dental practice with risks of patient-to-patient and patient-to-doctor transmission [42].

In conclusion, the findings of this first population-based study in Turkey with respect to the epidemiology of HBV and HCV revealed HBsAg positivity in 4%, anti-HCV positivity in 1% and anti-HDV positivity in 2.8% of HBsAg-positive individuals. Male gender, lower educational level, being married, living in the southeastern region, close contact with a hepatitis patient and orodental interventions were identified as significant independent determinants of increased HBsAg positivity. Age $\geq$50 years was the only predictor of increased anti-HCV seroprevalence.

Prospective and long-term studies in younger and larger cohorts are needed to see the influence of the national vaccination programme and public awareness campaigns on the epidemiology of hepatitis B and C as well as morbidity and mortality related to their long-term complications in society. Due to a successful vaccination programme since 1998 HBV incidence has declined in younger age groups. However, immunization of risk groups and awareness campaigns for viral hepatitis still wait for more active and efficient organization by the authorities and related societies in the country.

Transparency declaration

The authors declare that they have no conflict of interest.

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