

## Prevalence and risk factors of isolated anti-HBc antibody and occult hepatitis B infection in hemodialysis patients: a nationwide study

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### ABSTRACT

**Background.** Recent studies have demonstrated that prevention of hepatitis B virus (HBV) transmission remains a challenge in hemodialysis (HD) patients. The aim of this study is to explore factors which increase the possibility of occult HBV (OHB) infection in patients under HD in Iran. **Material and methods.** Among 2188 cases who spent an average of  $60.2 \pm 61.1$  months under HD, we selected 103 cases with isolated anti-hepatitis B virus core antibody (anti-HBc) and 231 controls without any HBV, hepatitis D virus (HDV) and hepatitis C virus (HCV) serologic markers. Socio-demographic data, past medical history, and clinical signs and symptoms were assessed. **Results.** The frequency of checking hepatitis B serologic markers was 15.3%. The rate of OHB infection in HD patients who were monitored for their HBV markers was 4.9%. Cases with isolated anti-HBc had significantly higher percentage of positive HBV DNA [odds ratio: OR (95% confidence interval: 95% CI) = 12.1 (1.4-105)], visual disturbances [OR (95% CI) = 1.8 (1.1-3.03)], history of diabetes mellitus [OR (95% CI) = 2.1 (1.3-3.5)], higher age, higher age when dialysis started and were mostly married, illiterate, disabled and retired. Diabetes mellitus was the only independent predictor of HBV DNA status in cases with isolated anti-HBc. **Conclusion.** In our region, OHB infection is prevalent among hemodialysis patients and displays a direct correlation with factors which are age related except diabetes mellitus. Thus, the presence of isolated anti-HBc should prompt the clinician to evaluate a possible OHB infection especially when it is detected in conjunction with a history of diabetes mellitus.

**Key words.** Renal dialysis. Hepatitis B antibodies. Occult HBV.

### INTRODUCTION

Occult hepatitis B virus (HBV) infection (negative hepatitis B surface antigen (HBsAg) with positive HBV DNA)<sup>1</sup> is different from isolated anti-hepatitis B virus core antibody [isolated anti-HBc: negative HBsAg, negative hepatitis B surface antibody (anti-HBs) and positive anti-HBc].<sup>2</sup>

HBV is a major problem especially in developing countries with limited facilities for hemodialysis (HD) patients and lower health standard precautions.<sup>3</sup>

HBV is the most important cause of transmitted infections by the parenteral route in patients on maintenance hemodialysis.<sup>4</sup> The prevalence of HBV infection in HD patients varies markedly around the world.<sup>5</sup>

The prevalence of HBV, anti-HBc and isolated anti-HBc in Iran is 2.14%,<sup>6</sup> over 35% and 5.13%,<sup>7</sup> respectively. The prevalence of HBsAg, anti-HBc and isolated anti-HBc is 2.6-6.72%,<sup>8-9</sup> 25.16%<sup>9</sup> and 6.2%<sup>10</sup> for HD patients in Iran, respectively.

The number of published studies available in the literature on occult hepatitis B (OHB) infection in hemodialysis patients is quite low.<sup>11</sup>

Despite a decline in HBV infection in the HD populations in Iran<sup>8</sup> and the world<sup>12</sup> over recent

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decades, the prevalence and possibility of infection is still considerably high.

Most other studies in Iran and even other countries are single center studies. Studies which are from more than one dialysis unit are mainly from a single state or city. Our study is from 14 provinces of Iran. The strength of our study lies in our nationwide sampling, better generalizability and larger anti-HBc positive samples.

This study evaluates the seroprevalence and risk factors of isolated anti-HBc and OHB infection in a large population of patients on HD.

## MATERIAL AND METHODS

Since 1975, Ministry of Health (MOH) of Iran introduced a treatment program for end stage renal disease (ESRD) patients. As a routine, all hemodialysis patients in Iran give biannual blood samples for assessment of serum HBsAg, anti-HBs and hepatitis C virus antibody (anti-HCV) [enzyme-linked immunosorbent assay (ELISA)]. The national data is collected in the related office in MOH.<sup>13</sup>

In this cross sectional study, we have analyzed the data from 14 provinces (from total 31 centers) in Iran constituting 43.1% of a 74,733,230 person target population in 2010.<sup>14</sup> The first phase of this work was done on 2,188 HD patients [mean age (standard deviation: SD): 51.2 (15.1) years, age range: 9-97 years, 1,299 (59.4%) males, mean (SD) duration of HD: 60.2 (61.1) months] who were assessed in December 2007 using a standardized questionnaire to collect data about sociodemographic, hemodialysis, hepatitis, other diseases, laboratory and clinical status. In this study what is referred to as visual disturbances is pertaining to any abnormalities of sight like diplopia, blurred vision, reduced visual acuity, reduced visual field and partial or total loss of vision, halos, blind spots, floaters, and other symptoms expressed by the patients.

Our pilot study on 197 similar cases showed that our self administered questionnaire with 44 questions has a reliability of 0.715, according to the Cronbach's alpha coefficient. All of the questions had two choices (Yes-No).

All HBsAg positive patients were put on separate dialysis machines.<sup>13</sup> After identifying HBsAg positive patients prior to HD, each patient was assigned to his or her own machine to decrease the risk of spreading the infection.

Monthly blood samples were taken from all HD patients for assessment of serum levels of different

elements in the blood prior to the HD session. All samples were tested for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels by a colorimetric method. In addition to checking HBsAg and anti-HBs (Both by Hepanosticka Biomeieux, Boxtel, The Netherlands), the patients were also screened for human immunodeficiency virus (HIV) 1 and 2 (ELISA, MP Biomedicals, Illkirch, France), and anti-HBc by enzyme-linked immunosorbent assays (ELISA, Abbott Laboratories, US) every three months. ELISA generation III is the assay that is usually used to check for HCV antibody. Qualitative HBV DNA (Roche Diagnostics GmbH, Mannheim, Germany) was checked for cases with positive HBsAg or isolated anti-HBc. HCV RNA was ordered for all cases with positive anti-HCV (Biorad, Segrate, Italy).

To analyze the obtained data we used mean  $\pm$  SD, t-test, one way ANOVA, Kruskal-Wallis and chi-square (and fisher's exact) statistical methods. Odds ratio (OR) and its 95% confidence interval (CI) was used for assessing the strength of association of risk factors for positive anti-HBc or HBV DNA. Forward Wald logistic regression was used for determining the most important independent variables of being HBV DNA positive. Variables with p-value less than 0.2 (in univariate analysis) were entered into logistic regression analysis. Likelihood Ratio test was used to evaluate significant differences between logistic models. Cronbach's alpha was used for assessing internal consistency of the questionnaire. Authors considered differences and correlations with  $P < 0.05$  statistically significant. In our analysis, SPSS 16 software (SPSS Inc. Chicago, Illinois, USA) and Stata 10 (STATA Corp. LP) were used.

## RESULTS

Fifteen and three percent of the population is regularly checked for hepatitis B serologic markers. Of the 2188 HD cases, 103 cases were isolated anti-HBc, 231 cases were not. So, the rate of isolated anti-HBc in HD patients was 44.6%.

Percent of positive cases (among cases with determined status) for HBsAg, anti-HBs, anti-HBc, anti-HDV, anti-HCV, HBV DNA and HCV RNA were 18.2, 13.9, 36.7, 2.9, 40.8, 22.8 and 58.7, respectively.

Persons who had been monitored for HBV serological markers were significantly higher among high risk males who had more symptoms and a lower history of vaccination.

There were 103 cases with isolated anti-HBc, mean (SD) age: 60.5 (14.1) years old,

**Table 1.** Comparison of cases with isolated anti-HBc and cases with negative HBV and HCV markers.

Variables	Isolated anti-HBc positive n = 103	Normal cases with negative HBV and HCV markers n = 231	Sig.
Male gender, n (%)	66 (64.1)	134 (58)	0.296
Age, mean ± SD, years	60.5 ± 14.1	49.8 ± 17.8	< 0.001
Marital status, n (%)			
Married	85 (83.3)	159 (68.8)	0.006
Never married	6 (5.9)	44 (19)	
Divorced/widowed/left	11 (10.8)	28 (12.1)	
Literacy, n (%)			
Illiterate	61 (59.2)	97 (42)	0.009
Primary school	21 (20.4)	65 (28.1)	
Secondary school	20 (19.4)	53 (22.9)	
Bachelor or higher	1 (1)	16 (6.9)	
Job, n (%)			
Student	1 (1)	7 (3)	0.025
With job	4 (3.9)	23 (10)	
Retired	17 (16.5)	30 (13)	
Unemployed	45 (43.7)	121 (52.4)	
Disabled	36 (35)	50 (21.6)	
Positive HBV DNA, n (%)	5 (4.9)	0	0.003
Chronic fatigue, n (%)	54 (52.4)	102 (44.2)	0.162
Abdominal pain, n (%)	12 (11.7)	33 (14.3)	0.515
Bone pain, n (%)	53 (51.5)	99 (42.9)	0.145
Anorexia, n (%)	51 (49.5)	92 (39.8)	0.098
RUQ pain, n (%)	5 (4.9)	12 (5.2)	0.896
Weight loss, n (%)	41 (39.8)	77 (33.3)	0.253
Joint pain, n (%)	44 (42.7)	75 (32.5)	0.071
Muscular pain, n (%)	37 (35.9)	87 (37.7)	0.761
Muscular weakness, n (%)	46 (44.7)	95 (41.1)	0.546
Urine cloudiness, n (%)	19 (18.4)	25 (10.8)	0.057
Visual disturbances, <sup>†</sup> n (%)	35 (34)	51 (22.1)	0.022
Persistent pruritis, n (%)	19 (18.4)	32 (13.9)	0.281
Symptom free, n (%)	6 (5.8)	29 (12.6)	0.064
HIV positivity, n (%)	0	0	-
History of tattoo, n (%)	5 (4.9)	14 (6.1)	0.66
History of piercing, n (%)	25 (24.3)	62 (26.8)	0.621
History of Hejamat,* n (%)	4 (3.9)	17 (7.4)	0.227
History of multiple sexual partner, n (%)	0	3 (1.3)	0.555
History of sexual transmitted diseases, n (%)	1 (1)	0	0.308
History of drug abuse, n (%)	14 (13.6)	17 (7.4)	0.07
History of IV drug abuse with common syringe, n (%)	0	1 (.4)	0.692
History of use of common razor or toothbrush, n (%)	2 (1.9)	4 (1.7)	0.894
History of gum disease, n (%)	6 (5.8)	7 (3)	0.232
History of accidental exposure to blood or contaminated fluids, n (%)	0	4 (1.7)	0.316
History of blood transfusion, n (%)	61 (59.2)	121 (52.4)	0.246
History of daily drinking of alcoholic beverages, n (%)	0	5 (2.2)	0.329
History of alcoholic liver disease, n (%)	0	0	-
History of thalassemia disease, n (%)	0	1 (.4)	0.692
History of diabetes mellitus, n (%)	41 (39.8)	55 (23.8)	0.003
History of depression, n (%)	17 (16.5)	35 (15.2)	0.753
History of thyroid diseases, n (%)	1 (1)	5 (2.2)	0.671
History of chronic skin diseases, n (%)	2 (1.9)	5 (2.2)	0.629
History of kidney transplantation, n (%)	6 (5.8)	19 (8.2)	0.441

History of CAPD, n (%)	2 (1.9)	2 (0.9)	0.59
History of vaccination of family members against HBV, n (%)	16 (15.5)	44 (19)	0.44
Age when dialysis started, mean $\pm$ SD, years	58.1 $\pm$ 14.4	48 $\pm$ 18.4	< 0.001
Duration of dialysis so far, mean $\pm$ SD, months	27.9 $\pm$ 33.8	25.4 $\pm$ 34.4	0.531
Number of dialysis sessions per week, mean $\pm$ SD	2.75 $\pm$ 0.5	2.74 $\pm$ 0.47	0.866
Duration of each dialysis session, mean $\pm$ SD, hour	3.82 $\pm$ 0.42	3.79 $\pm$ 0.47	0.516
Session of dialysis, n (%)			
Morning or noon	87 (84.5)	176 (77.5)	0.147
Evening or night	16 (15.5)	51 (22.5)	

Since these numbers (percents) are calculated based on crosstabs; they are by considering that missing cases are deleted. Anti-HBs: hepatitis B surface antibody. CAPD: continuous ambulatory peritoneal dialysis. HBV: hepatitis B virus. HCV: hepatitis C virus. HIV: human immunodeficiency virus. IV: intravenous. RUQ: right upper quadrant. <sup>†</sup>In this study what is referred to as visual disturbances is pertaining to any abnormalities of sight like diplopia, blurred vision, reduced visual acuity, reduced visual field and partial or total loss of vision, halos, blind spots, floaters, and other symptoms expressed by the patients. \*A procedure in Iranian traditional medicine done by making shallow cuts on the trunk (upper back) and producing a suction effect that results in drawing blood from cuts (< 100 cc). It is usually done by a non-physician, using non-standard instruments (done for healing or cure purposes).

**Table 2.** Comparison of cases with positive (occult HBV infection) and negative HBV DNA in patients with isolated anti-HBc.\*

Variables	HBV DNA		Crude OR (95% CI)	Sig.
	Positive, n = 5	Negative, n = 98		
History of diabetes mellitus, n (%)	5 (100)	34 (35.8)	1.1 (1.02-1.3)	0.008
History of depression, n (%)	4 (80)	13 (13.7)	19.5 (2.3-164.1)	0.003
Visual disturbance, <sup>†</sup> n (%)	4 (80)	30 (31.6)	7.8 (0.9-66.8)	0.044

\*The remainder of the variables was not significant. <sup>†</sup>In this study what is referred to as visual disturbances is pertaining to any abnormalities of sight like diplopia, blurred vision, reduced visual acuity, reduced visual field and partial or total loss of vision, halos, blind spots, floaters, and other symptoms expressed by the patients.

64.1% (66 cases) male, 83.3% (85 cases) married at present, 59.2% (61 cases) illiterate, 43.7% (45 cases) unemployed, all supported by a health insurance, and 4.9% (5 cases) with HBV DNA positive test.

Considering all cases with negative HBsAg and anti-HCV tests, we analyzed cases with positive (103 cases) and negative anti-HBc (231 cases). Cases with isolated anti-HBc had significantly higher percentage of positive HBV DNA [OR (95% CI) = 12.1 (1.4-105)], visual disturbances [OR (95% CI) = 1.8 (1.1-3.03)], history of diabetes mellitus [OR (95% CI) = 2.1 (1.3-3.5)], higher age, higher age when dialysis started and were more likely to be married, illiterate, disabled and retired (Table 1). They did not have significant differences according to other basic characteristics and risk factors.

Cases with isolated anti-HBc who had positive HBV DNA result, had significantly more diabetes, visual disturbances and history of depression (Table 2). All cases with isolated anti-HBc and positive HBV DNA *vs.* 75.8% (72 cases) with negative HBV DNA had vaccination history against HBV. This difference was not statistically significant.

Forward Wald Logistic regression model showed that only history of diabetes mellitus has a signifi-

cant correlation with HBV DNA positivity in cases with isolated anti-HBc [P = 0.005, OR (95% CI) = 25.2 (2.6-243.7)]. This analysis was done on 100 cases and eight variables (with P-value < 0.2) were entered and the model was significant (P = 0.001).

## DISCUSSION

Our results verify the proposal given by earlier studies that while anti-HBc screening has little value in a low prevalence population, it can be useful in high prevalence populations.<sup>15-17</sup>

Routine blood donor screening for anti-HBc status has been implemented in some countries resulting in a decrease in the risk of post-transfusion HBV infection.<sup>18</sup> Hence, in our poor resource setting, inclusion of anti-HBc testing for donor screening will definitely remove possible HBV infected donations. Although this screening will result in the rejection of a large number of donations, it will constitute a valuable asset in reducing the risk of HBV transmission with its potential consequences, particularly among immunocompromised recipients. If our policy does not require that we reject all blood donated by anti-HBc infected people, we can at least

exclude donors who are high risk for being HBV DNA positive (persons with history of diabetes mellitus, depression or visual disturbance).

A similar paper on 289 patients on chronic HD from five dialysis units in Tehran with similar characteristics showed that 18 subjects (6.2%) had isolated anti-HBc. Positive HBV-DNA was detectable in 9 out of 18 patients (50%) who had isolated anti-HBc. Only one of them was anti-HCV positive. None of them were HIV infected. There was no significant difference between HBV DNA positive and negative patients regarding age, sex, ALT and AST levels or length of time on dialysis, maybe due to low sample size.<sup>10</sup>

Most studies have shown low copies/mL in viral load of HBV DNA positive cases. Therefore, a low HBV viral load seems the most likely explanation for our HBsAg negative/DNA positive samples.

An Iranian study on 90 HD patients found no one with positive HBV DNA and 30 cases with positive HCV RNA, 10 cases of which were positive for anti-HBc among HCV RNA positive subjects.<sup>19</sup>

A Brazilian study on 1476 HD subjects showed that positive anti-HBc, HBsAg and HBV DNA were 34.1%, 15.4% and 8.1%, respectively, while the incidence of HBV was null. This study suggests that employing more than one HBV marker and repeated follow-up evaluations may improve HBV screening in HD units.<sup>20</sup>

One Turkish study found that 9.1% (2/22) of non HD subjects with isolated anti-HBc have OHB infection.<sup>21</sup> Another Turkish study on 188 subjects on HD revealed that five (2.7%) cases have OHB. There was isolated anti-HBc in 12 (6.4%) patients, three (7.9%) of with anti-HCV and two (40%) with OHB.<sup>22</sup>

A study on one group of HBsAg negative patients (n = 213) from a large cohort (n = 585) of Italian chronic dialysis patients showed that OHB infection was absent. Persistent HBsAg carriers were less frequent than anti-HBc positive patients in this study group [1.88% (11 of 585) vs. 36% (216 of 585), P = 0.0001]. No significant association between abnormal biochemical liver tests and serum anti-HBc was noted in our population. Nominal logistic regression analysis demonstrated an independent and significant relationship between anti-HCV and anti-HBc status in serum (P = 0.0001). The rate of patients seropositive for anti-HBc was higher among study patients than controls with normal renal function [36.9% (216 of 585) vs. 21.4% (59 of 275), P = 0.0001]; this difference partially persisted after correction for demographic parameters, and viral markers.<sup>23</sup>

A prospective study on 86 Spanish patients, prior to the start of a HD program in 2003 showed that 18.7% are anti-HBc positive. Logistic regression showed that only age (OR = 1.03), being born in the jungle area (OR = 13.1), and food consumption in restaurants (OR = 5.0) were related to total cases with positive anti-HBc.<sup>24</sup>

In the present study, there were only 5.3% who had checked their anti-HBs status. Among patients who had been tested for hepatitis B serologic markers, 44.6% were isolated anti-HBc. So, it is logical to vaccinate isolated anti-HBc cases.

Our present study found that persons who had been tested for their serological markers of HBV were higher risk males with more symptoms but lower history of vaccination. So, we have overestimated the prevalence of isolated anti-HBc in our patients tested for hepatitis B serologic markers. Total HD cases have a lower percent of OHB infection from that shown in our selected study group.

Table 3 summarizes the results of some relatively similar studies showing a wide range of isolated anti-HBc in various populations from 2.5% to 55.7%. However, some of these results are not reliable due to low sample size. One interesting finding is that different risk factors of isolated anti-HBc or OHB infection are not consistent among these papers and the present study. Another important issue is the different comparison groups in these studies which makes it hard to draw definitive conclusions. On the other hand, the different control groups in these studies give us valuable information pertaining to all possible risk factors in different nationalities.

One limitation of this study is that we only explored the situation of HBV DNA in anti-HBc cases and not all cases; while, OHB infection can be detected in anti-HBc negative cases as well. However, one similar study has shown that HBV DNA detection was more frequent when positive anti-HBc was detected in isolation (72%) than when associated with anti-HBsAg antibodies (31%).<sup>25</sup> In addition, other studies have found that isolated anti-HBc positivity was more frequent in patients with OHB than in those without (40% [2/5] vs. 5.5% [10/183], p = 0.002).<sup>22</sup> So, we should check the status of HBV DNA at least in anti-HBc positive cases for blood/organ donation or in immunocompromised patients like patients on HD in order to decrease the transmission risk of HBV infection. This is both "more cost effective" and a "minimum inevitable plan" which should be implemented.

**Table 3.** Characteristics and findings of similar studies about isolated anti-HBc in hemodialysis patients.

Study: country, year	Characteristics, sample size, percent of positive isolated anti-HBc		Risk factors of isolated anti-HBc/occult HBV infection	Reference
	Case group	Control group		
Egypt, 2009.	HD patients, . 143, 9	Healthy blood donor, 100, 8.	Multiple blood transfusion.	26
Egypt, 1995.	HD patients, 64, 51.8%	Healthy persons, 15, ND.* of anti-HCV positive patients.	ND.	27
Brazil, 1995.	HD patients, 185, 55.7.	Peritoneal dialysis patients, 124, ND.	ND.	28
Turkey, 2006.	HD patients, 188, 6.4.	No control group.	ND.	22
Hong Kong, 1989.	HD patients, 63, 19.	Personnel working in the dialysis unit, ND, ND. Healthy controls, ND, ND. transfusion requirement.	Higher incidence of repeated liver dysfunction, elevated alanine transaminase levels, and a higher	29
Italy, 2009.	HD patients, 128, 26.6 (occult HBV infection).	No control group.	HCV seropositivity and the positive anti-HBs, isolated anti-HBcAg.	25
Brazil, 2006.	HD patients, 1095, 2.5.	No control group.	ND.	30

\*Not determined.

Significant difference between persons who had checked hepatitis B serologic markers with others shows that we can only generalize our results to these patients.

In conclusion, our study underscores the high rate of OHB infection in hemodialysis patients in most parts of Iran. Except diabetes mellitus, factors correlated with anti-HBc status are age related (higher age, higher age when dialysis started, illiterate, disabled and retired, visual disturbances, and even being married). Diabetes mellitus was the only independent predictor of HBV DNA status in cases with isolated anti-HBc.

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### CONFLICTS OF INTEREST

There is no conflict of interest.

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