British Journal of Medicine & Medical Research
4(28): 4674-4694, 2014

SCIENCEDOMAIN *international*
www.sciencedomain.org

Hepatitis B Virus Seropositivity among Schistosomiasis and Diabetes Mellitus Patients in Sana'a City, Yemen

Ebtesam M. Al-Zabedi[1*], Mahmoud A. Ogaili[2,3], Mohamed T. Al-Maktari[4] and Mohamed S. Noman[5]

[1]Department of Biochemistry, Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, Yemen.
[2]Department of Medical Laboratories, Faculty of Medical Sciences, Hodeidah University, Hodeidah, Yemen.
[3]National Centre of the Public Health Laboratories (NCPHL), Sana'a, Yemen.
[4]Department of Medical Parasitology, Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, Yemen.
[5]Department of Internal Medicine, Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, Yemen.

Authors' contributions

This work was carried out in collaboration between all authors. Authors EMA, MTA and MAO designed the study, and wrote the protocol, authors EMA and MTA performed the statistical analysis, and interpreted the results, author EMA wrote the first draft of the manuscript. Author MSN managed the clinical examination. All authors read and approved the final manuscript.

Original Research Article

Received 8th May 2014
Accepted 10th June 2014
Published 20th June 2014

ABSTRACT

Hepatitis B virus (HBV) infection is a major public health problem worldwide, often coexisting with other illnesses like parasitic infections and other chronic diseases. Data on the association of HBV infection with schistosomiasis and diabetes mellitus (DM) is limited. This case-control study was conducted to investigate the seropositivity rate and potential risk factors of HBV, and to examine the association between HBV and schistosomiasis with or without super added DM.

Three hundred patients presented themselves to internal medical departments and diabetes centres at different public and private hospitals in Sana'a city, Yemen. Those

**Corresponding author: Email: somamzabedi@yahoo.com;*

recruited were then split in to six groups, those being type 1 DM, type 2 DM, schistosomal hepatic fibrosis (SHF), type 1 DM+SHF, type 2 DM+SHF and the control group. Overall, 20% (60/300) of the participants were positive when tested for hepatitis B core total antibody (HBcAb) by ELISA test. There were no significant differences in the positivity rate in terms of group, age or gender of the participants.
Univariate and multivariate analyses showed significant associations between HBV seropositivity and a history of jaundice, familial history of SHF, familial history of liver cirrhosis, personal history of schistosomiasisa and a history of using parenteral antischistosomal drugs. On the other hand, no significant association was reported between HBV seropositivity and any DM-related variables. It was also reported that no additional risk was added to the association between HBV seropositivity and SHF when the analysis stratified for DM.
In conclusion, HBV is still a highly prevalent infection and support is urgently needed in order to implement effective and integrated preventive measures among the people most likely to be affected. Further studies are required in order to investigate the epidemiology of HBV infection among various communities, and to evaluate its relationship with other diseases.

Keywords: Hepatitis B virus; schistosomiasis; diabetes; Yemen.

1. INTRODUCTION

Hepatitis B is a life threatining liver infection caused by the hepatitis B virus (HBV) which afflicts more than two billion people worldwide [1]. It is a major growing global health problem, with about 350 million people suffering from chronic liver infection, resulting in about 600,000 annual deaths due to acute or chronic complications of hepatitis B, including liver cirrhosis and hepatocellular carcinoma (one of the five major cancers worldwide) [2]. It is estimated that up to 60% of liver cancers can be attributed to HBV chronic infection, with about one million deaths worldwide annually [3]. About half of the world's population lives in chronic hepatitis B endemic areas in South East Asia, China, Africa, the Pacific region, the Amazon Basin, parts of the Middle East and across America [4].

Schistosomiasis, among the most prevalent of the neglected tropical diseases, is a major public health problem in many developing countries, with about 240 million infected people and 700 million people worldwide living in endemic areas at risk of infection [5]. Clinical manifestations of schistosomiasis are associated with the species causing the problem and the intensity of infection. Urinary schistosomiasis caused by *Schistosoma* haematobium is characterized by haematuria as a classical sign. In chronic infection, the patient may suffer bladder and uretral fibrosis, sandy patches in the bladder mucosa and hydronephrosis, while bladder cancer is reported as a late stage complication [6]. Similarly, intestinal schistosomiasis caused by *Schistosoma* mansoni or *Schistosoma* japonicum is usually associated with abdominal pain and appearance of blood flakes in the stool. In chronic infection, hepatosplenomegaly is commonly reported with ascites and other signs of portal hypertension [7].

Diabetes mellitus (DM), one of the largest growing threats to human health, is a clinical syndrome associated with a deficiency of insulin secretion or action. The disease is classified into two types, namely type 1 DM (previously called insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes) and type 2 DM (previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes). Type 2 DM, which is characterized by insulin resistance, pancreatic beta-cell dysfunction and excessive glucose

production by the liver, accounts for about 95% of all cases of diabetes. The other 5% of cases are of type 1 [8]. Besides the classical complications of the disease, DM has been associated with severe complications including heart disease, blindness, kidney failure and lower-extremity amputations. The disease also increases susceptibility to infections by reducing the immunity of patients through reduced response of T cells, neutrophil function and disorders of humoral immunity [9]. Recent estimates revealed that the total number of people with diabetes is expected to rise to 380 million in 2025, of those an estimated 3.4 million people will die as a consequences of high fasting blood sugar, with more than 80% of diabetes deaths occurring in low- and middle-income countries [10,11]. Many factors contribute to the increasing number of people with diabetes, such as urbanization, population growth, aging, as well as increasing prevalence rates of obesity and physical inactivity [12].

The concurrent presence of both HBV infection and schistosomiasis is of significant concern as patients with coinfections have been shown to have higher incidences of cirrhosis and hepatocellular carcinoma, as well as higher mortality rates than patients suffering from a single infection. Moreover, patients diagnosed with hepatosplenic schistosomiasis have increased susceptibilities to additional infections and medical abnormalities such as coinfection with HBV when compared to healthy controls [13]. Many studies have investigated the relationship between HBV and other diseases including DM and schistosomiasis, and have yielded a variety of results. Some studies have reported a higher prevalence of HBV infections among diabetic patients compared with healthy controls [14,15], while others have found no association [16]. Moreover, a higher prevalence of HBV infection have also been reported among diabetic patients who share a blood glucose meter, which has been attributed to a limited awareness of the high risk for HBV transmission during fingerprick blood glucose monitoring [17]. Some studies have suggested that schistosomiasis increases HBV and HCV morbidity and chronicity, and have identifyed hepatitis as a significant factor influencing the severity of schistosomiasis [18,19]. That said, other studies have found that schistosomiasis does not affect the outcome of HCV infection [20]. A recent study reported a higher prevalence of serological markers for HBV and a lower prevalence of anti-HCV among patients diagnosed with a hepatosplenic form of schistosomiasis [12]. HBV is a subject of some controversy when discussing its role as a risk factor for developing DM, as the disease is known have multiple etiologies and a pandemic image. Therefore, further studies are needed in order to clarify these questionable associations.

Yemen is classified among areas of intermediate endemicity for HBV infection, with previous studies revealing that the prevalence of HBV chronic infection in different Yemeni cities ranges from 1.8% to 34% [21-25]. Moreover, schistosomiasis is considered as the second most frequent cause of death in Yemen, after malaria, with both urinary schistosomiasis due to *S. haematobium* and intestinal schistosomiasis due to *S. mansoni* being prevalent [26]. Recent estimates showed that more than 3 million people in the region are infected, with at least three-quarters of a million suffering from severe, chronic morbidity. A recent study revealed that 59% of the squamous cell carcinoma reported in 53 Yemeni patients with urinary bladder cancer was associated with chronic infection by *S. hematobium* [27]. With regards to diabetes, the prevalence of type 2 DM in Yemen ranges between 4.6% and 9.8% [28-30]. As such, the association between HBV and other diseases that affect a large sector of the Yemeni population is an important issue to address. Hence, the aims of the present study were to investigate the seroprevalence and potential risk factors of HBV infection, and to examine the possible association of HBV infection with diabetes mellitus, as well as looking at schistosomal hepatic fibrosis (SHF) with or without super added diabetes mellitus.

2. MATERIALS AND METHODS

2.1 Study Design

This hospital-based case-control study was carried out in Sana'a city, the capital of Yemen. All patients attending internal medical departments and diabetes centres in Sana'a city public and private hospitals between January and July 2012 were invited to participate in this study.

2.2 Study Subjects

The minimum sample size required for this study was calculated according to the formula provided by Lwanga and Lemeshow [31]. At a 5% level of significance and a 95% confidence level, the minimum number of participants required for the study was estimated at 288, assuming that the prevalence of HBV infection in Yemen was about 25% as previously reported [32]. Overall, a total of 300 individuals aged between 10 and 82 years of age (160 males and 140 females) agreed to take part in this study. The participants were recruited into 6 different groups based on final clinical diagnosis, with 50 individuals per group (Fig. 1). The groups were type 1 diabetes mellitus (Group 1), type 2 diabetes mellitus (Group 2), schistosomal hepatic fibrosis (Group 3), type 1 diabetes mellitus and schistosomal hepatic fibrosis (group 4), type 2 diabetes mellitus and schistosomal hepatic fibrosis (Group 5), and the control group (Group 6) which involved individuals apparently free from diabetes with no hepatitis B related history or schistosomal infection background.

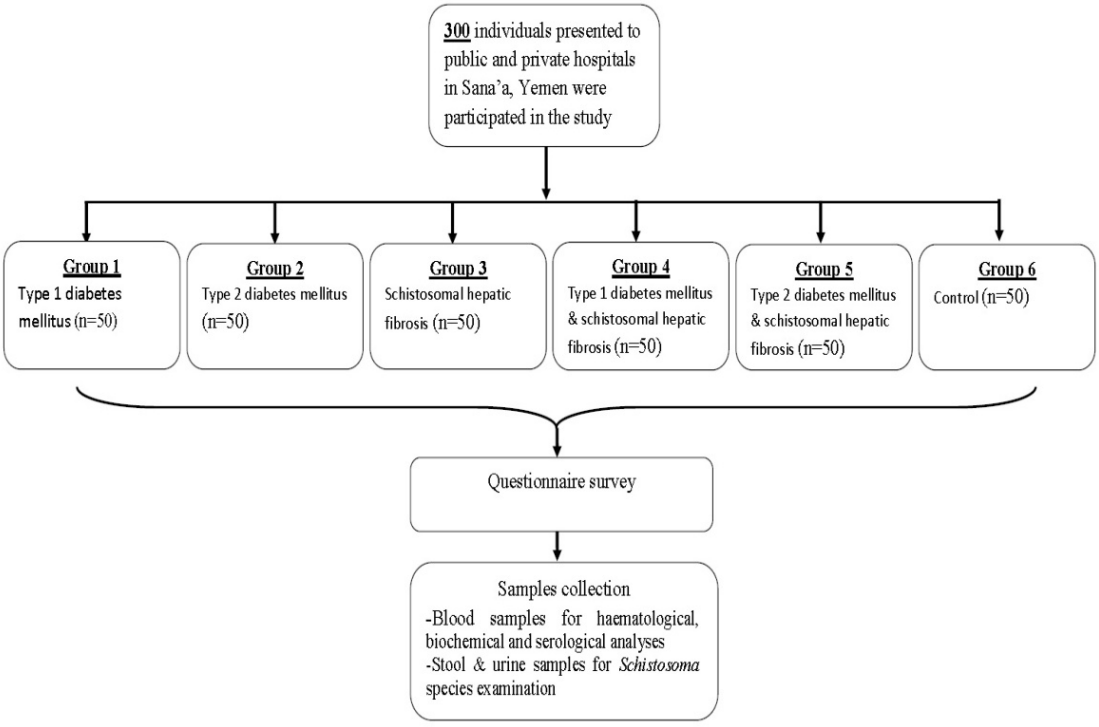

Fig. 1. Flow chart of the participation in the present study.

2.3 Questionnaire

All subjects of the present study were asked to fill out a questionnaire regarding their personal and demographic data (e.g. age, sex, and residence), socioeconomic data (e.g. marital status, occupation, educational level, income…etc), habitual information (e.g. smoking, alcohol intake, addiction…etc), health history related to diabetes mellitus (e.g. type, age of onset, complications, medications…etc), health history related to schistosomiasis (e.g. type, course, any complication, medications…etc), history of jaundice (e.g. probable type, duration, laboratory investigation results, complications, medications, history of jaundice affecting other household members…etc), and a complete history relating to the possible risk factors of hepatitis B virus infection (e.g. blood transfusion, surgical operations, tattooing, dental manipulations, type and frequency of parenteral injections, HBV infection among household members, history of hepatitis B vaccination…etc).

2.4 Clinical Examination

The participants underwent full clinical examination including examination of the heart, chest, abdomen, neurological, and dermatological systems. This was done to assess the presence of possible diabetic or schistosomiasis complications.

2.5 Urine and Stool Examination

Urine samples were collected from all participants and examined by microscopy for the presence of *Schistosoma haematobium* ova, and by dipstick (Auction sticks, A. Menarini Diagnostics, Florence, Italy) for the detection of glucose, acetone and proteinuria (Similarly, stool samples were collected and examined by using formalin ether sedimentation technique for the detection of *Schistosoma mansoni* ova and ova/cyst of other intestinal parasitic infections [33].

2.6 Haematological and Biochemical Analysis

Blood samples were collected between 8.00 and 10.00AM after an overnight fasting. For diabetic patients, 2 hours postprandial samples were also collected. About 10 ml of venous blood were obtained from each participant by venipuncture; 0.5ml of the blood was evacuated into a plastic tube containing EDTA for glyco-haemoglobin measurements. The rest of the blood sample was evacuated into a plain tube and allowed to clot at room temperature before serum was collected. The serum sample was divided into 2 portions; one portion was stored at –20°C to be used for ELISA test and the other portion was used for the other biochemical analyses. Moreover, the 2 hours post-prandial serum glucose level for the diabetic patients was measured by using Bio-Analytical Kit (enzymatic colorimetric method according to Trinder). The normal value is <180mg/dl. Furthermore, oral glucose tolerance test was done for all non-diabetic cases. A fasting blood sample was collected and then the subject was given a drink of 75gm glucose in 300ml water over a course of 5 minutes. Another blood sample was collected 2 hours after the test load. The patients with fasting blood sugar value of >126 mg/dl or 2 hours after glucose load value of >200mg/dl were considered diabetic while those with fasting blood sugar value of >110 and <126mg/dl or 2hours after glucose load value of >140 and <200mg/dl were considered having impaired glucose tolerance.

On the other hand, glycosylated haemoglobin (HbA_{1c}) for the diabetic patients was measured by using ion-exchange chromatography according to Stanbio-Glycohaemoglobin procedure No. 0350. The percentage of HbA_{1c} was determined and the values of 6.0-8.0%, 7.5-8.9%, 9.0-10.0% and >10.0% were considered as normal range, good control, fair control and poor control.

2.7 Serological Analysis

Detection of hepatitis B core total antibody (Anti-HBV) was performed using DETECT-HBV^{TM} (3rd generation) ELISA kits using Biochem Immuno Systems Detect-HBV (BioChem Immuno Systems Inc., Montreal, Canada).

2.8 Statistical Analysis

Statistical analysis of the collected data was done using SPSS (version 13, 2004; SPSS, Inc., Chicago, IL, USA) and EPI-Info for windows 2002 software (Centers for Disease Control and Prevention, Atlanta, GA, USA). The distribution of quantitative variables was examined using the Kolmogorov-Smirnov test. For descriptive analysis, a proportion was used to present the prevalence of categorical variables in the form of mean and standard deviation (SD). For inferential statistical analysis, a Chi-square test was used to assess the influence of different categorized variables on hepatitis B virus seropositivity. Unadjusted odd ratios (OR) with 95% confidence intervals (CI) were also computed. Moreover, a multiple logistic regression model was used to investigate the association between dependent variables and independent variables, taking into consideration the effects of potential confounding factors. All tests were considered significant at $P<0.05$.

3. RESULTS

3.1 General Characteristics of Participants

Three hundred participants (53.3% males and 46.7% females), with a mean age of 43.97years (±14.38), participated voluntairly in this study and were recruited into 6 different groups of equal sample size (n=50). The general characteristics of the subjects in different groups are shown in Table 1. The mean age was highest among the type 2 DM patient group with a mean age of 54.6 years (±10.23), the lowest was among the type 1 DM patient group with a mean age of 34.04 years (±11.62). The table also shows that females are predominant in the type 2 DM group, while males predominate the three schistosomiasis groups and the control group.

The majority of participants in groups 1 and 2 were from urban areas, while almost all participants in groups 3, 4 and 5 are from rural areas with the majority of them being either farmers or unemployed.

3.2 Seroprevalence of HBV Infection

Among the 300 serum samples collected from the participants, 60 (20%, 95% CI=15.9, 24.9) were positive for HBcAb. As shown in Table 1, the participants in group 2 showed the highest frequency of HBV positive patients at 14 (28%), while group 1 showed the lowest with only 6 (12%) cases. The frequency in most groups was higher than the control (reference) group, but the differences were not statistically significant (P>0.05). Higher

seropositivity rate was noted among participants aged >50(26.3%) when compared to their younger counterparts.

3.3 Risk Factors of HBV Seropositivity

The results of the univariate analysis for factors associated with HBV seropositivity are shown in Tables 2, 3 and 4.

3.3.1 Demographic, socioeconomic, past medical history and personal habit factors

Table 2 illustrates the evaluation of different socio-demographic characteristics as being possible risk factors for HBV seropositivity. Categorical representation of age into three ascending groups (≤30, 31-50, and >50) shows that there was an increased risk of HBV seropositivity with age. There was no significant association with gender, as both sexes had 20% anti-HBV positive enzyme immunoassay (EIA) results. With regards to residence, it is noted that the rural population is exposed to an increased risk for being HBV seropositive compared to those from urban areas (21.5% vs 16.8%; OR=1.35; 95% CI=0.69, 2.67). Similarly, socioeconomic class showed as having an influence on the risk of disease development, a step ladder pattern of increasing risk was noted when directed toward the poorer lower classes compared to individuals in the high class (33.3% vs 13.3%; OR=3.25; 95% CI=0.68, 15.83). However, these differences were not statistically significant (*P*>0.05). Other variables showed no remarkable signs of additional risk, as in general none of the other socio-demographic variables reached a statistically significant value (P>0.05).

The relationship between past medical history and the risk of developing a hepatitis B viral infection was also investigated. It is clear that a past history of clinically manifested jaundice was significantly associated with the risk of being HBV seropositive (OR=2.51, 95% CI=1.30, 4.85), as people who had previously suffered from jaundice showed a significantly higher seropositivity compared to individuals without such a history. In addition, a history of using glass syringes (OR=2.05; 95% CI=0.94, 4.50) doubled the risk of HBV seropositivity.

Other variables including a family history of jaundice, a past history of surgical intervention, repeated parenteral injections, occasional or infrequent dental manipulations, a history of blood transfusion, dental visits on a regular bases, as well as a host of medical illnesses (e.g. Rheuamtoid artheritis, systemic lupus erythematosus, renal insuffeciency, fascioliasis, amoebic dysentry…etc) showed no additional risk or significant association with HBV seropositivity.

Table 2 further shows the possible relationship between some personal habits and the risk of hepatitis B viral seropositivity. A higher risk of acquiring HBV was noted among 110 individuals who had a history of smoking when compared to non smokers (22.7% vs 18.4%). Similarly, those with a history of addiction (i.e. cannabis and/or alcohol) faced double the odds of being HBV seropositive (OR=2.47, 95% CI=0.45, 12.34). However, these differences were not statistically significant (*P* > 0.05).

Table 1. General characteristics of study participants according to study groups

Variables	Groups					
	Group 1	**Group 2**	**Group 3**	**Group 4**	**Group 5**	**Group 6**
Group name	**DM type 1**	**DM type 2**	**SHF**	**DM type 1+SHF**	**DM type 2+SHF**	**Control**
Sample size	**50**	**50**	**50**	**50**	**50**	**50**
Age (years) (Mean±SD)	34.0±11.6	54.6±10.2	40.3±14.4	42.2±12.4	51.5±10.0	44.5±16.1
Males	25 (50)	7 (14)	36 (72)	44 (88)	29 (58)	28 (56)
Females	25 (50)	43 (86)	14 (28)	6 (12)	21 (42)	22 (44)
Hepatitis B seropositivity	6 (12)	8 (16)	12 (24)	13 (26)	14 (28)	7 (14)
Working	9 (18)	2 (4)	1 (2)	5 (10)	4 (8)	6 (12)
Urban	34 (68)	34 (68)	1 (2.0)	0 (0.0)	2 (4.0)	24 (48)
Married	34 (68)	38 (76)	40 (80)	46 (92)	43 (86)	28 (56)
Low socioeconomic level	15 (30)	14 (28)	31 (62)	45 (90)	20 (40)	29 (58)
Smoking	12 (24)	8 (16)	26 (52)	26 (52)	23 (46)	15 (30)
Blood transfusion	8 (16)	1 (2)	13 (26)	5 (10)	7 (14)	5 (10)
Jaundice	7 (14)	1 (2)	15 (30)	11 (22)	13 (26)	6 (12)

DM: Diabetes mellitus; SHF: Schistosomal hepatic fibrosis

3.3.2 Aspects of schistosomal illness

Table 3 shows the association between the different aspects of schistosomal illness with the HBV seropositive EIA test. The results show that there are 82 cases that have a history of a household member suffering from schistosomal hepatic fibrosis (SHF), with 29 of them (35.4%) being anti-HBV EIA positive. The history of such illness was significantly associated with the risk of HBV seropositivity (OR=3.72; 95% CI=1.92, 7.23). Furthermore, liver cirrhosis doubled the odds of HBV seropositivity, but the association was not statistically significant (OR=2.91; 95% CI=0.90, 9.13).

Table 2. Associations of hepatitis B virus seropositivity with demographic, socioeconomic, past medical history and personal habits factors (n=300)

Variables	Anti-HBV EIA		OR (95% CI)
	No. examined	Positive N (%)	
Socio-demographic factors			
Age in years			
≤30	49	8 (16.3)	1.0
31–50	152	26 (17.1)	1.06 (0.42, 2.77)
>50	99	26 (26.3)	1.83 (0.71, 4.85)
Sex			
Male	160	32 (20.0)	1.0
Female	140	28 (20.0)	1.00 (0.57, 1.76)
Residence			
Urban	95	16 (16.8)	1.0
Rural	205	44 (21.5)	1.35 (0.69, 2.67)
Marital status			
Single	45	10 (22.2)	1.0
Married	229	43 (18.8)	0.81 (0.35, 1.90)
Widowed	26	7 (26.9)	1.29 (0.37, 4.49)
Occupation			
Not farmer	219	43 (19.6)	1.0
Farmer	81	17 (21.0)	1.09 (0.55, 2.13)
Socioeconomic class			
High	45	6 (13.3)	1.0
Middle	154	28 (18.2)	1.44 (0.52, 4.21)
Low	86	21 (24.2)	2.10 (0.72, 6.40)
Very low	15	5 (33.3)	3.25 (0.68, 15.83)
Past medical history			
Blood transfusion			
No	261	53 (20.3)	1.0
Yes	39	7 (17.9)	0.86 (0.33, 2.18)
Surgery			
No	134	25 (18.7)	1.0
Yes	166	35 (21.1)	1.16 (0.63, 2.15)

Table 2 Continued……..

Parental injection			
No	104	16 (15.4)	1.0
Yes	115	55 (19.1)	1.30 (0.61, 2.80)
Glass syringes usage	81	22 (27.2)	2.05 (0.94, 4.50)
Dental manipulation			
No	101	18 (17.8)	1.0
Infrequent	136	33 (24.3)	1.48 (0.74, 2.96)
Regular	63	9 (14.3)	0.77 (0.29, 1.97)
Family history of jaundice			
No	221	42 (19.0)	1.0
Yes	79	18 (22.8)	1.26 (0.67, 2.35)
Personal history of jaundice			
No	247	42 (17.0)	1.0
Yes	53	18 (34.0)	2.51 (1.30, 4.85)*
Associated diseases**			
No	156	32 (20.5)	1.0
Yes	144	28 (19.4)	0.94 (0.53, 1.65)
Personal habits			
Smoking			
No	190	35 (18.4)	1.0
Yes	110	25 (22.7)	1.30 (0.70, 2.41)
Addiction			
No	292	57 (19.5)	1.0
Yes (Cannabis and/or alcohol)	8	3 (37.5)	2.47 (0.45, 10.66)

*OR: Odds ratio; CI: Confidence interval, *Significant association (P < 0.05), ** Associated diseases include rheumatoid artheritis, systemic lupus erythematosis, renal insufficiency, fascioliasis, amoebic dysentery …etc.*

One half (n=150) of the participants had a history of schistosomiasis with or without super added diabetes mellitus. Of those, 39 cases (26%) were anti-HBV EIA positive compared to only 21 (14%) positive cases among non-schistosomal individuals, with the difference being statistically significant (OR=2.16; 95% CI=1.20, 3.89). A past history of using the anti-schistosomal tartar emetic or potassium antimony tartrate drug significantly tripled the risk of anti-HBV EIA positive results (OR=3.22; 95% CI=1.16, 9.40) when compared to other schistosomal patients denied the intake of such medication.

The history of long standing schistosomal infection (10 years or more) was noted in most schistosomal patients (141 cases; 94%). This resulted in a higher risk of HBV seropositivity (OR=2.95; 95% CI=0.35, 64.99) when compared to other patients with a more recent relationship with their schistosomal infection (less than 10 years), although the difference was not statistically significant. Furthermore, complications with hepatosplenic types of schistosomiasis (e.g. organomegaly, oesophageal varices with or without haematemesis, ascitis …etc) were found to increase the risk of HBV seropositivity. Among these complications, ascitis was reported to have the highest risk (OR=1.91; 95% CI=0.85, 4.29), however it was not statistically significant.

3.3.3 Aspects of diabetes mellitus

Table 4 shows the association between diabetes mellitus and the risk of HBV seropositivity. The results reveal that the presence of either type 1 or type 2 DM apply no extra risk of

being HBV seropositive when compared with non-diabetic cases. Although a higher risk of acquiring HBV was reported in cases with poor control for blood glucose (OR=2.05; 95% CI=0.67, 6.71), among those with a history of gestational diabetes (OR=1.93; 95% CI=0.68, 5.42) and in those who developed DM after the age of 40 (OR=1.52; 95% CI=0.76, 3.02), the differences were not statistically significant. Likewise, associations of HBV seropositivity in terms of a family history of DM, duration of diabetic illness, the presence of secondary causes contributing to the development of DM, and the presence of diabetic complications were not statistically significant.

Table 3. Associations of hepatitis B virus seropositivity with factors related to schistosomiasis (n=300)

Variables	Anti-HBV EIA			OR (95% CI)
	No. examined	Positive N (%)		
Family history of liver Diseases				
No	195	25 (12.8)		1.0
Cirrhosis	20	6 (30.0)		2.91 (0.90, 9.13)
SHF	82	29 (35.4)		3.72 (1.92, 7.23)*
Others**	3	0 (0.0)		-
Personal history of schistosomiasis				
No	150	21 (14.0)		1.0
Yes	150	39 (26.0)		2.16 (1.20, 3.89)*
Schistosomiasis duration				
<=10 years	9	1 (11.1)		1.0
>10 years	141	38 (27.0)		2.95 (0.35, 64.99)
Schistosomiasis course				
Stationary	100	24	24.0	1.0
Progressive	50	15	30.0	1.36 (0.64, 2.90)
Ascitis†				
No	114	26 (22.8)		1.0
Yes	36	13 (36.1)		1.91 (0.85, 4.29)
History of IV anti-*schistosoma*l drugs‡				
No	47	6 (12.8)		1.0
Yes	103	33 (32.0)		3.22 (1.16, 9.40)*

OR: Odds ratio; CI: Confidence interval; SHF: Schistosomal hepatic fibrosis, Significant association (P <0.05), ** Two cases with family history of chronic hepatitis and one with HCC,† Ascitis was selected out of other complications of hepatosplenic schistosomiasis e.g. organomegaly, oesophageal varices with or without haematemesis … etc,‡ Past history of parenteral tartar emetic anti-schistosomal drug treatment.*

3.3.4 Multivariate Analysis for the Risk Factors of HBV seropositivity

The results of a multiple logistic regression analysis for the different possible risk factors that contribute to the development of HBV seropositivity revealed four variables that were retained in the final model as significant risk factors for HBV seropositivity. Those variables are a family history of a household member suffering with cirrhosis (OR=4.34; 95% CI=1.98, 6.94), family history of a household member suffering with SHF (OR=3.41; 95% CL=1.16, 11.23), a personal history of jaundice (OR=1.94; 95% CI=1.12, 5.57) and a personal history of schistosomal illness (OR=1.88; 95% CI=1.09, 12.14). Other factors including a personal

history of dental manipulations, multiple parenteral injections, diabetes and the subjects socioeconomic class were removed from the final logistic regression model.

3.4 Further Analyses for The Association of Schistosomiasis and Diabetes with HBV Seropositivity

The distribution of the studied population according to their age group, their history of schistosomiasis and the results of the EIA anti-HBV seropositivity were analyzed further with the results being shown in Table 5.

It was found that the percentages of HBV seropositivity increased significantly with age among those who had a history of schistosomiasis, with the percentages among those aged <=30, 31-50, and >50 years being 12.8%, 35.9%, and 51.3%, respectively (P<0.002). On the other hand, the pattern of association between HBV seropositivity and age among the non schistosomal cases was not statistically significant (P=0.343).

Table 4. Associations of hepatitis B virus seropositivity with factors related to diabetes mellitus (n=300)

Variables	Anti-HBV EIA		OR (95% CI)
	No. examined	Positive N (%)	
Family history of DM			
No	176	38 (21.6)	1.0
Yes	124	22 (17.7)	0.78 (0.44, 1.40)
Personal history of DM			
No	81	19 (19.0)	1.0
DM type 1	81	19 (19.0)	1.00 (0.47, 2.15)
DM type 2	78	22 (22.0)	1.20 (0.57, 2.53)
Age of onset			
<= 40 years	94	20 (17.5)	1.0
> 40 years	65	21 (24.4)	1.52 (0.76, 3.02)
Duration			
<= 10 years	97	30 (23.6)	1.0
> 10 years	62	11 (15.1)	0.57 (0.25, 1.30)
Secondary cause of DM†			
No	153	40 (20.7)	1.0
Yes	6	1 (14.3)	0.64 (0.07, 5.45)
Gestational diabetes			
No	146	35 (19.3)	1.0
Yes	13	6 (31.6)	1.93 (0.68, 5.42)
Control of DM (Glycated Hb A_{1c})			
Good	32	5 (13.5)	1.0
Fair	46	10 (17.9)	1.39 (0.39, 5.23)
Poor	81	26 (24.3)	2.05 (0.67, 6.71)
Diabetic complications‡			
No	19	8 (29.6)	1.0
Yes	140	33 (19.1)	0.56 (0.23, 1.39)

OR: Odds ratio; CI: Confidence interval, † Secondary causes of DM e.g. steroids intake, ‡ Diabetic complications: (infection, microangiopathy, and macroangiopathy)

With regards to the diabetes illness aspects, the mean values of blood glucose among the studied population in relation to anti-HBcAb EIA results were compared (Table 6). Among non diabetic cases, the mean values of fasting blood glucose and glucose levels after 2 hours of 75gm oral glucose challenge were found to be lower in anti-HBV EIA positive cases than their negative counterparts, however the differences were not statistically significant (P > 0.05). Among 200 diabetic cases, almost similar levels of 2 hours post prandial mean glucose were found among HBV seropositive and negative cases (275.85 mg/dl vs 271.33 mg/dl).

When the 100 cases with a history of both schistosomiasis and diabetes mellitus illnesses were compared with the 50 individuals free from both diseases (control/reference), the results showed that 27 (27%) individuals were anti-HBV EIA seropositive in those with a history of both illnesses, compared to only 7 individuals (14%) in the control group. The risk of being HBV positive was higher in the illness group (OR=2.27; 95% CI=0.85, 6.29) compared to the control group, however the difference was not statistically significant.

Finally, the fraction attributable risk of the most influential risk factors for developing an HBV seropositive was calculated. It is evident that the highest values of attributable fraction were due to a family history of a household member with chronic liver disease (SHF or cirrhosis) (61.6%), followed by being a member of the very low socioeconomic class (60.0%), with a personal history of jaundice (50.0%) also being a significant indicator of risk. The lowest value of attributable fraction was due to the presence of diabetes mellitus (7.3%).

Table 5. Distribution of the studied population according to their HBcAb EIA seropositivity, history of schistosomiasis and age group

Age group (years)	Schistosomiasis			
	Negative (N=150)		Positive (N=150)	
	-ve HBcAb EIA N (%)	+ve HBcAb EIA N (%)	-ve HBcAb EIA N (%)	+ve HBcAb EIA N (%)
N	129	21	111	39
<= 30	29 (22.5)	3 (14.3)	12 (10.8)	5 (12.8)
31-50	52 (40.3)	12 (57.1)	74 (66.6)	14 (35.9)
> 50	48 (37.2)	6 (28.6)	25 (22.5)	20 (51.3)
χ^2	2.14		12.72	
P - value	0.343		0.002	

Table 6. Comparison of blood glucose levels between studied cases according to HBcAb EIA seropositivity

HBcAb EIA	FBG* (Mean±SD)	PGL** (Mean±SD)	2PPG*** (Mean±SD)
Negative (n=240)	89.47±19.49	140.27±30.12	271.33±100.69
Positive (n=60)	82.26±15.08	136.42±20.76	275.85±106.91
t-value	1.51	0.53	0.25
P-value	0.135	0.599	0.800

**Fasting blood glucose measurement done for non-diabetic cases; **Two hours after 75gm oral glucose challenge (Load) done for non-diabetic cases; ***Two hours post prandial serum glucose assessment done for diabetic patients*

4. DISCUSSION

Hepatitis B virus infection, schistosomiasis and diabetes mellitus are major global public health problems, especially in developing countries. The interactions between these diseases are still unclear and of great interest.

The findings of the present study show that 20% of the participants tested positive using the total HBcAb EIA test. Many previous studies conducted in Yemen revealed that the prevalence of HBV infection ranges between 1.8% and 34% based on the subjects being studied. A community-based study in Ibb, Gacche and Kaid found that the prevalence of HBV among 554 participants was 1.8% when examined for hepatitis B surface antigen (HBsAg) [34]. However, a recent community-based study conducted in the Taiz province showed a higher HBsAg prevalence at 16.9% [35]. A similar level of prevalence (16%) was reported by a hospital-based study in Aden city based on anti-HBV core antibodies (antiHBc) and HBsAg [23]. However, a comparable higher prevalence was reported among liver disease patients (33.6%) and among blood donors (28.8%) [36,37]. Moreover, a lower HBsAg prevalence was reported among schoolchildren in Taiz (10.6%), pregnant women in Sana'a (10.8%) and among mothers and their infants in Sana'a (13.2% and 4%, respectively) [21,26,38]. In agreement with previous studies, our findings confirm that Yemen is an area of intermediate endemicity for HBV infection (10%-60%). Moreover, only 5% of the patients recruited to the present study had declared prior hepatitis B vaccination.

The findings of the current study also show that the seropositivity of HBV based on total HBcAb was higher among participants aged >50 years when compared to younger participants, however the difference is not statistically significant. Previous studies from Yemen and other countries showed that the prevalence of HBV has an age-dependency factor, with infection patterns increasing with age, the highest prevalence being among subjects aged >40 years [23,24,35,39].

We found similar levels of HBcAb seropositivity among both male and female participants, which is in agreement with previous studies conducted in Yemen [34,35]. However, it is worth noting that some studies in Yemen and other countries have shown a significantly higher prevalence of HBV among males than females [24,40]. On the other hand, a WHO collaborative study on HBV in which 20 countries participated did not find a statistically significant difference in the prevalence of HBsAg between males and females [41].

Furthermore, the present study investigated the possible factors associated with HBcAb seropositivity among the participants and revealed that a personal history of juandice, a family history of schistosomal hepatic fibrosis (SHF), as well as a personal history of schistosomiasis and using IV anti-schistosomal drugs were key factors found to be associated with HBV seropositive results. Participants who had a history of juandice were at higher risk of HBV seropositivity than their counterparts. These finding are consistent with results reported previously in Thailand, Morocco and Bangladesh [40,42,43]. Juandice is a classical sign of liver diseases, therefore a history of juandice may indicate the high succeptablitity of individuals to these diseases.

In addition, our findings show that participants who live in houses with family members who have a history of SHF were at 3 folds higher risk of being HBcAb seropositive. This is in agreement with previous reports from other countries [44]. The results of the logistic regression also show that a history of household members having liver cirrhosis increases the risk of participants being infected with HBV. Although liver cirrhosis is present in the

majority of patients with HBV, an increased risk for hepatitis B-related liver cirrhosis in relatives of patients with hepatocellular carcinoma was reported in Taiwan, which may indicate familial clustering of hepatitis B-related liver cirrhosis [45].

An earlier serological survey for hepatitis B markers was carried out in Yemen among 654 individuals (243 pregnant females, 294 male blood donors and 108 patients with chronic liver disease), which found that the detection rate of HBsAg was significantly higher among patients with chronic liver diseases (including liver cirrhosis) compared to healthy individuals (24.1% vs 18.5%). There was also significantly higher evidence of HBV infection among the chronic liver diseases patients than their healthy counterparts (75.9% vs 59.8%) [46].

The findings of the present study show significant associations between the high prevalence of HBV seropositivity and several aspects of schistosomiasis, including history of schistosomiasis onset and the use of intravenous schistosomiasis treatment. We found that participants with a history of being infected with *Schistosoma* species are at double the risk of HBV seropositivity compared to those never infected with *Schistosoma*. Co-infection of HBV and *Schistosoma* is of significant concern, as patients with both infections have been shown to have increased histological activity, as well as higher incidences of liver cirrhosis and hepatocellular carcinoma (HCC), with a greater mortality rate when compared with patients suffering from only a single infection [47].

It has been previously reported that patients with hepatosplenic schistosomiasis were at an increased risk from other infections, including a 10-fold higher risk for co-infection with HBV, as well as an increased frequency of liver failure when compared to healthy individuals [12,48]. Similarly, Pereira et al. reported that co-infection of *Schistosoma mansoni* and other liver disease, particularly HBV or HCV infections, will trigger the progression of hepatic fibrosis into cirrhosis and hepatocellular carcinomacan, occuring within a few years [49]. Such co-infections were reported in Egypt and Brazil [47,50,51]. Furthermore, HCV but not HBV has been reported to influence the severity of schistosomiasis among Egyptian patients [52]. In Yemen, the only study on the co-infection of schistosomiasis and HBV was conducted in Taiz and reported that 10.6% of schoolchildren diagnosed as having schistosomiasis were also found to be positive for HBV, though it is worth noting that the percentage was as high as 22.2% in some areas [38].

In contrast, previous studies found no association between these two diseases [44,53]. Interestingly, when the association between HBcAb seropositivity and a history of schistosomiasis was stratified with age our findings revealed that the frequency of HBcAb seropositivity among participants with a history of schistosomiasis increased significantly with age. This might be attributed to the age-dependency pattern of both diseases.

Our findings also show that participants with a history of using intravenous schistosomal drug (tartar emetic or potassium antimony tartrate) were at 3-folds higher risk of HBV seropositivity compared to their counterparts. The underlying association could be attributed to the concomitant schistosomiasis or to the risk of HBV transmission due to contaminated needles. Using IV tartar emetic to treat schistosomiasis has been implicated as the primary factor behind the high prevalence rates of HBV and HCV in Egypt, where this drug was used by the schistosomiasis control programme between the 1950s and 1980s, the ultimate result of which was that the hepatitis viruses has now replaced schistosomiasis as the predominant cause of chronic liver disease [54,55].

With regards to diabetes mellitus, none of the diabetes-related factors showed a significant association with the HBcAb seropositivity. Many previous studies have examined the relationship between HBV and DM, but the results were not consistent. For instance, some studies have reported blood glucose abnormalities [13] while others have not [15]. An indirect explanation for the association between HBcAb seropositivity and DM was suggested as being because during the course of their disease diabetic patients would be subjected to frequent intravenous and subcutaneous injections (for the purpose of blood testing and insulin therapy), which may possibly increase risk of exposure to HBV.

A previous study among 210 Nigerian diabetics and 210 non-diabetic controls found a significantly higher detection rate of HBsAg among diabetic participants than controls, which was attributed to the common practice of injudicious administration of insulin injections among Nigerian diabetics [56]. In contrast, other reports showed no association [57,58]. On the other hand, the unexpected lower prevalence of HBsAg in diabetic patients than in controls was reported by a large-scale study of 2,465 individuals in Italy [59].

Our findings show that diabetic patients with poor control of blood glucose are at almost double risk of HBcAb seropositivity when compared to those with good or fair control levels. However, the difference was not significant. This is in agreement with a previous study from Nigeria [56]. We also compared the level of blood glucose between HBcAb seropositive and negative participants, and found no significant difference between both groups. In the present study, the results of the multivariate logistic regression analysis confirmed that a family history of a household member suffering cirrhosis, a family history of a household member suffering with SHF, a personal history of jaundice, and a personal history of schistosomiasis were the significant risk factors of anti-HBV EIA positive results among these participants.

The findings of the present study further revealed that the presence of concomitant schistosomiasis and DM did increase the risk of HBcAb seropositivity by more than 48%, and the increment was greatly attributed to the schistosomal impact of this association. We also found a higher anti-HBV EIA positivity (28%) among type 2 dieabetic participants who also had SHF (group 5), followed by those with type 1 DM and SHF (group 4), when compared with the lowest positivity rate of 12% among participants with type 1DM (group 1). However, these differences were not statistically significant when compared with the control group.

Although the interaction between schistosomiasis and DM is still unclear, previous studies revealed a protective role for *Schistosoma* infection, reporting a lower prevalence of diabetes and a better metabolic profile among Chinese participants with previous schistosome infection [60]. Moreover, a previous study showed that *S. mansoni* soluble egg antigens can profoundly regulate the immune system of the infected host and thus can be used to prevent type 1 diabetes in non-obese diabetic mice [61].

The findings of the present study should be interpreted with caution due to few limitations. First, this study had to rely on the results of total HBcAb while HBsAg was not examined. Data for HBsAg detection would be essential in order to identify positive patients as those with past or current HBV infection. Second, majority of the participants were from rural areas this could explain the absence of prior hepatitis B vaccination. Third, the hospital-based design limits the interpretation of our findings, and a community-based study is required.

5. CONCLUSION

The findings of this study revealed high HBV seropositivity among the participants. Schistosomiasis was found to be associated with HBV, particularly among individuals who are older in age, received parenteral anti-schistosomal treatment, have a history of clinical jaundice, and have a household member with a history of SHF. There was no association between HBV and DM among the subjects, with no additional risk being reported when DM was considered in examining the relationship between schistosomiasis and HBV. Large-scale community-based studies are needed to investigate the epidemiology of HBV infection and to evaluate its relationship with other diseases. Proper attention should be given to the high seropositivity rate of HBV, and effective measures should be implemented in order to reduce the prevalence of this life-threatining infection in Yemen.

CONSENT

All participants agreed that their participation in the research is voluntary and they may withdraw from the research at any time without citing the reasons. Written and signed or thumb-printed informed consents were obtained from the participants.

ETHICAL APPROVAL

The protocol of this study was approved by the Medical Ethics Committee of the Faculty of Medicine and Health Sciences, Sana'a University, Yemen and permissions were also given from the related hospitals.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. World Health Organization. Hepatitis B vaccines: WHO position paper. Weekly Epidemiological Record. 2009;84:405-19.
2. Tillmann HL, Zachou K, Dalekos GN. Management of severe acute to fulminant hepatitis B: to treat or not to treat or when to treat? Liver Int. 2012;32(4):544-553.
3. Hayashi PH, Di Bisceglie AM. The progression of hepatitis B- and C-infections to chronic liver disease and hepatocellular carcinoma: epidemiology and pathogenesis. Med. Clin. North. Am. 2005;89(2):371–89.
4. Oakes K. Chronic hepatitis B, part 1: hepatitis B: prevalence and pathophysiology. Nursing Times. 2014;110(7):12-16.
5. Bruun B, Aagaard-Hansen J. The social context of schistosomiasis and its control: an introduction and annotated bibliography. Geneva: World Health Organization; 2008.
6. Gryseels B, Polman K, Clerinx J, Kestens L. Human schistosomiasis. Lancet. 2006;368(9541):1106-1118.
7. van der Werf MJ, de Vlas SJ, Brooker S, Looman CWN, Nagelkerke NJD, et al. Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa. Acta Trop. 2003;86:125–139.

8. Meyers JL, Parasuraman S, Bell KF, Graham JP, Candrilli SD. The high-cost, type 2 diabetes mellitus patient: an analysis of managed care administrative data. Arch. Public Health. 2014;72(1):6.
9. Muller LM, Gorter KJ, Hak E, Goudzwaard WL, Schellevis FG, Hoepelman AI, et al. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. Clin. Infect. Dis. 2005;41:281–288.
10. WHO. Global health risks. Mortality and burden of disease attributable to selected major risks. Geneva, World Health Organization; 2009.
11. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res. Clin. Pract. 2014;103(2):137-149.
12. Kelly T, Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. Int. J. Obes. 2008;32(9):1431-1437.
13. Aquino RT, Chieffi PP, Catunda SM, Araújo MF, Ribeiro MC, Taddeo EF, Rolim EG. Hepatitis B and C virus markers among patients with hepatosplenic mansonic schistosomiasis. Rev. Inst. Med. Trop. Sao. Paulo. 2000;42:313-320.
14. Demir M, Serin E, Göktürk S, Ozturk NA, Kulaksizoglu S, Ylmaz U. The prevalence of occult hepatitis B virus infection in type 2 diabetes mellitus patients. Eu. J. Gastroenterol. Hepatol. 2008;20:668–673.
15. Lao TT, Chan BC, Leung WC, Ho LF, Tse KY. Maternal hepatitis B infection and gestational diabetes mellitus. J. Hepatol. 2007;47:46–50.
16. Huang ZS, Huang TS, Wu TH, Chen MF, Hsu CS, Kai JH. Asymptomatic chronic hepatitis B virus infection does not increase the risk of diabetes mellitus: A ten-year observation. J. Gastroenterol. Hepatol. 2010;25:1420-1425.
17. Thomson ND, Perz JF. Eliminating the blood: ongoing outbreaks of hepatitis B virus infection and the need for innovative glucose monitoring technologies. J. Diabetes Sci. Technol. 2009;3:283–288.
18. Angelico M, Renganathan E, Gandin C, Fathy M, Profili MC, Refai W, De Santis A, Nagi A, Amin G, Capocaccia L, Callea F, Rapicetta M, Badr G, Rocchi G. Chronic liver disease in the Alexandria governorate, Egypt: contribution of schistosomiasis and hepatitis virus infections. J. Hepatol. 1997;26(2):236-243.
19. Mostafa K, Samar SY, Moataza HO, Ashraf AT, Wael T, Ahmed MS. Soluble egg antigen of *Schistosoma* haematobium induces HCV replication in PBMC from patients with chronic HCV infection. BMC Infect. Dis. 2006;6:6-91.
20. Allam WR, Barakat A, Zakaria Z, Galal G, Abdel-Ghafar TS, El-Tabbakh M, Mikhail N, Waked I, Abdelwahab SF. Schistosomiasis does not affect the outcome of HCV infection in genotype 4-infected patients. Am. J. Trop. Med. Hyg. In press; 2014.
21. Al-Shamahy H. Prevalence of hepatitis B surface antigen and risk factors of HBV infection in a sample of healthy mothers and their infants in Sana'a, Yemen. Ann. Saudi Med. 2000;20(5-6):464-466.
22. Al-Waleedi AA, Khader YS. Prevalence of hepatitis B and C infections and associated factors among blood donors in Aden City, Yemen. East. Mediterr. Health J. 2012; 18(6):624-629.
23. Bawazir AA, Parry CM, Hart CA, Sallam TA, Beeching N, Cuevas LE. Seroepidemiology and risk factors of hepatitis B virus in Aden, Yemen. J. Infect. Public Health. 2011;4(1):48-54.
24. Al-Nassiri KA, Raja'a YA. Hepatitis B infection in Yemenis in Sana'a: pattern and risk factors. East. Mediterr. Health J. 2001;7(1–2):147–152.

25. Murad EA, Babiker SM, Gasim GI, Rayis DA, Adam I. Epidemiology of hepatitis B and hepatitis C virus infections in pregnant women in Sana'a, Yemen. BMC Pregnancy Childbirth. 2013;13:127.
26. Sady H, Al-Mekhlafi HM, Mahdy MAK, Lim YAL, Mahmud R, Surin J. Prevalence and associated factors of schistosomiasis among children in Yemen: Implications for an effective control programme. PLOS Negl. Trop. Dis. 2013;7(8):e2377.
27. Al-Samawi AS, Aulaqi SM. Urinary bladder cancer in Yemen. Oman Med. J. 2013;28(5):337–340.
28. Al-Habori M, Al-Mamari M, Al-Meeri A. Type II diabetes mellitus and impaired glucose tolerance in Yemen: Prevalence, associated metabolic changes and risk factors. Diabetes Res. Clin. Pract. 2004;65(3):275-281.
29. Badran M, Laher I. Type II diabetes mellitus in Arabic-speaking countries. Int. J. Endocrinol. 2012;902873.
30. Gunaid AA. Prevalence of known diabetes and hypertension in the Republic of Yemen. East Mediterr Health J. 2002;8(2-3):374-385.
31. Lwanga SK, Lemeshow S. Sample size determination in health studies: A practical manual. Geneva: World Health Organisation; 1991.
32. Bajubair MA, Elrub AA, Bather G. Hepatitis B virus infection in the Republic of Yemen between 2000-2005. Saudi Med J. 2008;29(6):871-874.
33. Cheesbrough M. District Laboratory Practice in Tropical Countries: Part 1, 2nd ed. Cambridge University Press, London; 2005.
34. Gacche RN, Kaid AS. Epidemiology of viral hepatitis B and C infections in Ibb city, Yemen. Hepat. Mon. 2012;12(7):460-462.
35. Sallam TA, Raja'a YA, Bahaj S, Al-Shami AM, Lu M, Roggendorf M, Tong CY. Hepatitis B virus carrier rate, prevalence and susceptibility and impact of immunization program among households in the city of Taiz, Yemen. Vaccine. 2012;30(37):5564-5568.
36. Al-Moslih MI, Al-Huraibi MA. Prevalence of hepatitis C virus among patients with liver disease in the Republic of Yemen. East Mediterr Health J. 2001;7(4-5):771-778.
37. Sallam TA, Tong CY, Cuevas LE, Raja'a YA, Othman AM, Al-Kharsa KR. Prevalence of blood-borne viral hepatitis in different communities in Yemen. Epidemiol. Infect. 2003; 131(1):771-715.
38. Al-Shamiri AH, Al-Taj MA, Ahmed AS. Prevalence and co-infections of schistosomiasis/hepatitis B and C viruses among school children in endemic areas in Taiz, Yemen. Asian Pac. J. Trop. Med. 2011;4(5):404-408
39. Daw MA, Siala IM, Warfalli MM, Muftah MI. Seroepidemiology of hepatitis B virus markers among hospital health care workers: Analysis of certain potential risk factors. Saudi Med. J. 2000;21(12):1157-1160.
40. Chiarakul S, Eunumjitkul K, Vuttiopas S, Vorapimol AR, Kaewkungwal J, Poovorawan Y. Seroprevalence and risk factors of hepatitis B virus infection among health care workers at the Institute of Neurology. J. Med. Assoc. Thai. 2007;90(8):1536-1545.
41. Sobeslavsky O. Prevalence of markers of hepatitis B virus infection in various countries: a WHO collaborative study. Bull WHO. 1980;58(4):621-628.
42. Baha W, Foullous A, Dersi N, They-they TP, El alaoui K, Nourichafi N, Oukkache B, Lazar F, Benjelloun S, Ennaji MM, Elmalki A, Mifdal H, Bennani A. Prevalence and risk factors of hepatitis B and C virus infections among the general population and blood donors in Morocco. BMC Public Health. 2013;13:50.

43. Ashraf H, Alam NH, Rothermundt C, Brooks A, Bardhan P, Hossain L, Salam MA, Hassan MS, Beglinger C, Gyr N. Prevalence and risk factors of hepatitis B and C virus infections in an impoverished urban community in Dhaka, Bangladesh. BMC Infect. Dis. 2010;10:208.
44. Berhe N, Myrvang B, Gundersen SG. Intensity of *Schistosoma mansoni*, hepatitis B, age, and sex predict levels of hepatic periportal thickening/fibrosis (PPT/F): A large-scale community- based study in Ethiopia. Am. J. Trop. Med. Hyg. 2007;77(6):1079-1086.
45. Yu MW, Chang HC, Chen PJ, Liu CJ, Liaw YF, Lin SM, Lee SD, Lin SC, Lin CL, Chen CJ. Increased risk for hepatitis B-related liver cirrhosis in relatives of patients with hepatocellular carcinoma in northern Taiwan. Int. J. Epidemiol. 2002;31(5):1008-1015.
46. El Guneid AM, Gunaid AA, O'Neill AM, Zureikat NI, Coleman JC, Murray-Lyon IM. Prevalence of hepatitis B, C, and D virus markers in yemeni patients with chronic liver disease. J. Med. Virol. 1993;40(4):330-333.
47. Van-Lume DS, Albuquerque Mde F, Souza AI, Domingues AL, Lopes EP, Morais CN, Montenegro SM. Association between *Schistosomiasis mansoni* and hepatitis C: systematic review. Rev. Saude. Publica. 2013;47(2):414-424
48. Kamal SM, Turner B, He Q, Rasenack J, Bianchi L, Al Tawil A, Nooman A, Massoud M, Koziel MJ, Afdhal NH. Progression of fibrosis in hepatitis C with and without schistosomiasis: correlation with serum markers of fibrosis. Hepatol. 2006;43:771-779.
49. Pereira LMMB, Spinelli V, Lacerda C, Mies S, Massarolo PCB, McFarlane IG. Hepatite B e C na esquistossomose mansoni. Gastroenterol. Endosc. Dig. 2001;20(3):71-77.
50. El-Sayed HF, Abaza SM, Mehanna S, Winch PJ. The prevalence of hepatitis B and C infections among immigrants to a newly reclaimed area endemic for *Schistosoma mansoni* in Sinai, Egypt. Acta Trop. 1997;68(2):229-237.
51. Strickland GT, Elhefni H, Salman T, Waked I, Abdel-Hamid M, Mikhail N, et al. Role of hepatitis C infection in chronic liver disease in Egypt. Am. J. Trop. Med. Hyg. 2002;67(4):436-442.
52. Manal MH, Ashraf SZ, Hashem B, Osama MS, Yehuda ZP, Cynthia LC, et al. The role of hepatitis C in hepatocellular carcinoma: A case control study among Egyptian patients. J. Clin. Gastroenterol. 2001;33(2):123-126.
53. Mudawi HMY, Smith HM, Rahoud SA, Fletcher IA, Babikir AM, Saeed OK, et al. Epidemiology of HCV infection in Gezira state of central Sudan. J. Med. Virol. 2007;79:383-385.
54. Frank C, Mohamed MK, Strickland GT, Lavanchy D, Arthur RR, Magder LS, El Khoby T, Abdel-Wahab Y, Aly Ohn ES, et al. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. Lancet 2000;355:887–891.
55. Strickland GT. Liver disease in Egypt: Hepatitis c superseded schistosomiasis as a result of latrogenic and biological factors. Hepatol. 2006;43(5):915-922.
56. Oli JM, Okafor GO. The prevalence of hepatitis B surface antigen in Nigerian diabetics. Trop. Geogr. Med. 1980;32(1):40-44.
57. Kew MC, MacKay ME, Mindel A, Joffe BI, Kusman B, MacNab GM, Seftel HC. Prevalence of hepatitis B surface antigen and antibody in white and black patients with diabetes mellitus. J. Clin. Microbiol. 1976;4(6):467-469.
58. Mekonnen D, Gebre-Selassie S, Fantaw S, Hunegnaw A, Mihret A. Prevalence of hepatitis B virus in patients with diabetes mellitus: a comparative cross sectional study at Woldiya General Hospital, Ethiopia. Pan Afr. Med. J. 2014;17:40.

59. Bedarida G, D'Agostino F, Bianchi M, Susani G, Sangalli F, Fattorini A, Sterza G. Unexpected lower prevalence of HBsAg in diabetics than in controls. (A study on 2,465 patients). Ric. Clin. Lab. 1982;12(2):409-415.
60. Chen Y, Lu J, Huang Y, Wang T, Xu Y, Xu M, Li M, Wang W, Li D, Bi Y, Ning G. Association of previous schistosome infection with diabetes and metabolic syndrome: a cross-sectional study in rural China. J. Clin. Endocrinol. Metab. 2013;98(2):E283-287.
61. Cooke A, Tonks P, Jones FM, O'Shea H, Hutchings P, Fulford AJ, Dunne DW. Infection with *Schistosoma mansoni* prevents insulin dependent diabetes mellitus in non-obese diabetic mice. Parasite Immunol. 1999;21(4):169-176.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=579&id=12&aid=5025