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Abu-Amer Ahmed Mohamed
Hepatogastroenterology and Infectious diseases department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Zakaria Mohamed
Hepatogastroenterology and Infectious diseases department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Gamal Abdel-Hamid Mohammed
Department of Pathology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt,
mgamal198688@gmail.com

Ismail Bastawy Mahmoud
Hepatogastroenterology and Infectious diseases department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Abu-El Hassan Ahmed Abdel-Aleem Masood
Hepatogastroenterology and Infectious diseases department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

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ORIGINAL ARTICLE

Insulin Resistance and Level of Antibody to Hepatitis B Surface Antigen in Nondiabetic Healthy Adults

Mohammed Gamal Abdel-Hamid [a,*], Mohamed Zakaria Abu-Amer [a], Ahmed Mohamed Masood [a], Ahmed Abdel-Aleem Abu-El Hassan [a], Mahmoud Bastawy Ismail [b]

[a] Hepatogastroenterology and Infectious Diseases Department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
[b] Department of Pathology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Abstract

Background: **Hepatitis B virus (HBV) infection may last for a long time and eventually result in liver cirrhosis and hepatocellular cancer (HCC). The best approach for managing HBV infection is primary prevention through vaccination strategies. Anti-HBs concentrations may fall sharply within the first year following the primary HBV immunisation, and fall more slowly after that. The relationship between insulin resistance and Anti-HBs persistence, particularly in a nondiabetic population, has not been examined in any Egyptian studies.**

Aim of the work: **In this study, healthy nondiabetic Egyptian participants who received hepatitis B vaccines were examined to determine the relation between insulin resistance & the level of anti-HBs (post vaccination).**

Patients and method: **There were four groups, 25 participants per each one of them. Groups A (had insulin resistance) and B (had no insulin resistance), were born after 1992 (the year that compulsory baby vaccinations were introduced in Egypt), while groups C (had insulin resistance) and D (had no insulin resistance) were born before 1992. Hepatitis B vaccination (3- dose series on a 0-1- 6-month) was administered to these groups (C and D). One to four months following the initial course of three immunization doses, HBs antibody level was determined. Each participant received evaluations for metabolic syndrome, insulin resistance, and obesity.**

Results: ***P*** **value of anti-HBs of studied groups A & B was 0.04 and for groups C & D were 0.001. There was one patient of group A, anti-HBs less than 10.** ***P*** **value of fasting insulin of studied groups A & B was 0.001 and groups C & D was 0.001. There is inverse correlation between HBs- Abs titer & HOMA IR and Insulin level.**

Conclusion: **In seemingly healthy Egyptian, nondiabetic men and women, inadvertent loss of anti-HBs over time was correlated with insulin resistance.**

Keywords: anti-HBs, Insulin resistance, Nondiabetic healthy adults

1. Introduction

The Hepatitis B virus (HBV) has the potential to infect the liver for a long time and may eventually result in cirrhosis and hepatocellular cancer.[1]

A third or more of the world's population has experienced HBV infection at some point in their lives, according to World Health Organization (WHO) data. The vast majority of these persons acquired HBV as adults, experienced acute hepatitis B (AHB), a self-limited infection, and were able to successfully control the virus.[2,3]

Less than 5% of those who contract HBV as immune-competent adults go on to develop chronic hepatitis B (CHB), while the majority of infections picked up in utero or in the first few years of life do.[4]

More than 250 million people worldwide have CHB, and every year, about 1 million of them pass away from its consequences, including liver cirrhosis and hepatocellular cancer (HCC).

African, Asian, and portions of Central and Eastern European countries all have high CHB endemicities.[3,4]

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* Corresponding author.
E-mail address: mgamal198688@gmail.com (M.G. Abdel-Hamid).

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Since humans are the only known main reservoir for HBV, a comprehensive control plan based on HBV vaccination could result in the eradication of the infection.[5]

In terms of public health, vaccination is the primary method of infection prevention, notwithstanding significant research and advancements in antiviral medication. The most cost-effective strategy used to combat HBV infection is really global immunization.[6,7]

The prevalence of chronic HBV infection can be decreased with HBV vaccination. Numerous studies imply that immunologic memory may deteriorate with time. Anti-HBs concentrations fall sharply within the first year following primary immunization with the hepatitis B vaccine, and then fall more slowly after that.[8]

According to reports, The durability of detectable anti-HBs following vaccination in the absence of HBV exposure depends on the amount of post-vaccination antibody concentration and the characteristics of the vaccination (vaccine type, age at immunization, interval, etc.). Except for age and sex, the features of the vaccine recipients have not been extensively studied in the general population.[9,10]

Numerous studies have shown that obese or diabetic patients respond less favourably to the hepatitis B vaccine. Hyperinsulinemia and insulin resistance, two crucial factors in diabetes mellitus, are frequently linked to obesity.[11,12]

The relationship between insulin resistance and antibody persistence has not been investigated, particularly in the general nondiabetic population.[13]

In this study, healthy nondiabetic Egyptian participants who received hepatitis B vaccines were examined to determine the effect of insulin resistance on the level of anti-HBs (post vaccination).

2. Patient and methods

This cohort study was carried out at outpatient clinics of Gastroenterology, Hepatology and Infectious Diseases departments of Al-Hussein & Sayed Galal Hospitals, Al-Azhar University from June 2016 who meet the inclusion & exclusion criteria.

Inclusion criteria: Egyptian healthy participants more than 18 years old.

Exclusion criteria: Patients had positive serologic findings for HBsAg, anti-hepatitis B core (anti-HBc), or hepatitis C virus (HCV). Also, Chronic kidney disease (CKD) participants or on haemodialysis or whom had no glucose or insulin data. A fasting blood sugar (FBG) level of more than 126 mg/dL, an HBA1c level of more than 6.5%, self-report of a prior diagnosis, or current usage of blood glucose-lowering drugs were all considered to be eligible. Subjects decline to take part in the investigation.

Ethical approval: All subjects provided informed consent, and this study complied with the Helsinki Declaration and was approved by the Institutional Review Board at the Faculty of Medicine at Al-Azhar University.

All the subjects were submitted to: An individual's entire medical history, drug usage (with a focus on blood glucose-lowering agents), family history, physical activity, alcohol consumption, smoking habits, and socio-demographic characteristics were all gathered using a self-administered questionnaire. Measurements of body mass index (BMI), height, and weight were taken during a full physical examination. Trained personnel had taken anthropometric measures and blood pressure readings. Blood tests had been done such as CBC, ESR and CRP, liver function tests: (ALT, AST, Total Bilirubin, Albumin and INR), virological tests: HBsAg, anti-HBs titre, and anti-HBc antibodies for hepatitis B & antibodies to hepatitis C (HCV Ab), renal function tests (urea, creatinine, sodium and potassium), fasting blood insulin (lU/mL), fasting blood glucose (mmol/L), total cholesterol, triglycerides (TGs), low-density lipoprotein (LDL), high-density lipoprotein (HDL), glycated haemoglobin (HbA1c) and high-density lipoprotein (HDL). Insulin resistance had been assessed with a homoeostasis model of assessment of insulin resistance (HOMA-IR), according to the following equation:

$$\textbf{Fasting blood insulin}\,(\textbf{lU/ml})\,\textbf{x Fasting blood glucose}\,(\textbf{mmol/l})/\textbf{22.5}.$$

or

$$\textbf{Fasting blood insulin}\,(\textbf{lU/ml})\,\textbf{x Fasting blood glucose}\,(\textbf{mg/dL})/\textbf{405}.$$

All participants had been categorized into two groups:

Group (1): (A) 25 subjects with insulin resistance and were born after 1992 who received vaccinations for HBV (when compulsory HBV vaccination of infants was introduced in Egypt). (B) 25 subjects without insulin resistance and were born after 1992 who received vaccinations for HBV (when compulsory HBV vaccination of infants was introduced in Egypt).

Group (2): (C) 25 subjects with insulin resistance that were born before 1992 and not received vaccinations for HBV before. (D) 25 subjects without insulin resistance and were born before 1992 and not received vaccinations for HBV before.

Table 1. Demographic data of all participants.

	Born after 1992		*P* value	Born before 1992		*P* value	Total *P*. value
	Insulin resistant A	Non-Insulin resistant B		Insulin resistant C	Non-Insulin resistant D		
Age	23.0 ± 1.5	22.7 ± 1.6	0.5	47.3 ± 5.7	42.9 ± 6.2	0.07	0.08
Sex							
Female	7 (28.0%)	8 (32.0%)	0.5	4 (16.0%)	4 (16.0%)	0.9	0.4
Male	18 (72.0%)	17 (68.0%)		21 (84.0%)	21 (84.0%)		
Resident							
Urban	15 (60.0%)	17 (68.0%)	0.2	20 (80.0%)	19 (76.0%)	0.7	0.2*
Rural	10 (40.0%)	8 (32.0%)		5 (20.0%)	6 (24.0%)		
Social status							
Single	16 (64.0%)	21 (84.0%)	0.01*	0 (0.0%)	1 (4.0%)	0.8	0.001**
Married	9 (36.0%)	4 (16.0%)		25 (100.0%)	24 (96.0%)		

0.01*: Correlation is significant at the 0.01 level. 0.001**: Correlation is significant at the 0.01 level.

This group was vaccinated with Hepatitis B vaccine (3- dose series on a 0-1- 6-month schedule to achieve immunity). One-four months had passed after the initial three immunization doses when a blood test was conducted to check the level of HBs antibodies.[14]

2.1. Statistical analysis

Data was calculated using the social science statistics programme, USA versions of Windows 10. (SPSS 21 software). Normal distribution-based variables were presented as mean and SD. The T test was used to determine any group differences in these variables. The median was used to express nonparametric data.

The data's normal distribution was examined using the Kalmogorove-Smirnov test. Spearman's correlation coefficients were determined for correlation analysis using a two-tailed P value. P 0.05 = Significant, $P > 0.05$ = Not Significant. If the data had a P value less than 0.05, it was deemed significant.

3. Results

The mean age of A, B, C and D groups of study participants at baseline were 23.0 ± 1.5, 22.7 ± 1.6, 47.3 ± 5.7 and 42.9 ± 6.2, years respectively. Regarding social status in group A 9 (36.0%) were married compared to group B where 4 (16.0%) only were married (Table 1). The median level of Weight of studied subgroups A, B, C and D were 65.0 ± 6.4, 58.7 ± 7.4, 67.4 ± 8.0 and 66.4 ± 5.0, respectively. The median levels of height of group A, B, C and D were 167.5 ± 5.5, 163.0 ± 5.4, 163.4 ± 3.3 and 162.5 ± 2.2. The

Table 2. Clinical and medical history data of all participants.

	Born after 1992		*P* value B vs. A	Born before 1992		*P* value D vs. C	Total *P* value
	Insulin resistant (A)	Non-Insulin resistant (B)		Insulin resistant (C)	Non-Insulin resistant (D)		
Weight	65.0 ± 6.4	58.7 ± 7.4	0.001[b]	67.4 ± 8.0	66.4 ± 5.0	0.6	0.001[b]
Height	167.5 ± 5.5	163.0 ± 5.4	0.01[a]	163.4 ± 3.3	162.5 ± 2.2	0.2	0.001[b]
BMI	23.2 ± 2.2	22.0 ± 1.9	0.03[a]	25.2 ± 2.6	25.1 ± 1.4	0.9	0.001[b]
Medications[a]							
No	18 (72.0%)	24 (96.0%)	0.01[a]	14 (56.0%)	19 (76.0%)	0.01[a]	0.013[a]
Yes	7 (28.0%)	1 (4.0%)		11 (44.0%)	6 (24.0%)		
Smoking							
No	19 (76.0%)	16 (64.0%)	0.2	13 (52.0%)	19 (76.0%)	0.08	0.2
Yes	6 (24.0%)	9 (36.0%)		12 (48.0%)	6 (24.0%)		
Alcohols							
No	23 (92.0%)	24 (96.0%)	0.7	22 (88.0%)	25 (100.0%)	0.1	0.3
Yes	2 (8.0%)	1 (4.0%)		3 (12.0%)	0 (0.0%)		
Family history[b]							
No	4 (16.0%)	6 (24.0%)	0.6	2 (8.0%)	5 (20.0%)	0.8	0.5
Yes	21 (84.0%)	19 (76.0%)		23 (92.0%)	20 (80.0%)		

[a] Medications include proton pump inhibitors, NSAIDs, herbals. etc.).
[b] Family history of DM, HTN, coronary heart diseases, strokes, chronic liver & renal diseases, addiction, etc.).

Table 3. Laboratory investigations of all participants.

	Born after 1992		*P* value B vs. A	Born before 1992		*P* value D vs. C	Total *P* value
	Insulin resistant (A)	Non-Insulin resistant (B)		Insulin resistant (C)	Non-Insulin resistant (D)		
Hb	13.8 ± 0.7	13.9 ± 0.6	0.5	13.9 ± 0.7	13.5 ± 0.4	0.1	0.1
WBCs	7.9 ± 1.9	7.7 ± 1.7	0.8	8.1 ± 1.9	7.5 ± 1.3	0.2	0.7
Plat	271.6 ± 81.3	272.2 ± 79.0	0.9	306.0 ± 90.2	232.1 ± 59.0	0.001**	0.01*
ESR	22.6 ± 7.6	16.9 ± 5.7	0.001**	19.8 ± 7.0	15.6 ± 4.9	0.02*	0.001**
CRP	10.2 ± 5.2	9.4 ± 3.9	0.6	9.5 ± 4.0	8.9 ± 3.7	0.6	0.8
ALT	25.0 ± 6.4	23.6 ± 6.9	0.5	23.9 ± 7.3	27.3 ± 4.5	0.06	0.2
AST	25.4 ± 4.8	25.9 ± 5.6	0.7	26.9 ± 6.6	27.4 ± 4.7	0.8	0.6
Bili	0.9 ± 0.2	0.9 ± 0.2	0.4	0.9 ± 0.2	0.9 ± 0.1	0.3	0.6
Alb	4.1 ± 0.3	4.0 ± 0.3	0.3	4.1 ± 0.3	4.0 ± 0.2	0.5	0.7
INR	1.0 ± 0.1	1.0 ± 0.1	0.7	1.0 ± 0.1	1.0 ± 0.1	0.5	0.9
Creat.	0.9 ± 0.2	1.0 ± 0.2	0.9	1.0 ± 0.2	0.9 ± 0.1	0.4	0.8
Urea	28.6 ± 5.4	28.4 ± 4.6	0.9	28.4 ± 5.1	25.8 ± 3.7	0.06	0.1
Na	138.2 ± 2.3	138.9 ± 2.7	0.3	138.8 ± 2.3	138.1 ± 2.8	0.3	0.6
K	3.9 ± 0.2	3.9 ± 0.2	0.9	3.9 ± 0.2	4.1 ± 0.3	0.07	0.06
FBG	90.6 ± 11.0	93.5 ± 7.7	0.3	92.0 ± 10.1	92.6 ± 6.1	0.8	0.7
HbA1c	4.8 ± 0.4	4.9 ± 0.3	0.2	4.9 ± 0.3	4.9 ± 0.2	0.8	0.6
LDL	131.5 ± 12.8	135.9 ± 9.4	0.2	135.4 ± 12.5	140.6 ± 10.5	0.1	0.06
HDL	72.4 ± 11.6	72.4 ± 8.9	0.9	74.2 ± 10.6	74.4 ± 10.2	0.9	0.8
TG	165.7 ± 16.8	160.6 ± 11.5	0.2	175.5 ± 19.2	179.2 ± 15.8	0.8	0.6

Abbreviations: (**Alb**, albumin level); (**ALT**, alanine transaminase); (**AST**, aspartate transaminase); (**Creat**, creatinine); (**CRP**, C- reactive protein); (**ESR**, erythrocyte sedimentation rate); (**FBG**, fasting blood glucose); (**Hb**, Hemoglobin level); (**HbA1c**, glycated hemoglobin); (**HDL**, high-density lipoprotein); (**INR**, international normalized ratio); (**K**, serum potassium level); (**LDL**, low-density lipoprotein); (**Na**, serum sodium level); (**Plat**, platelet count); (**TG**, triglycerides) (**WBCs**, white blood cell count).
0.01*: Correlation is significant at the 0.01 level. 0.001**: Correlation is significant at the 0.01 level.

Table 4. HBs Ab & HOMA IR and Insulin levels in the studied groups.

	Born after 1992			Born before 1992			Total *P* value
	Insulin resistant (A)	Non-Insulin resistant (B)	*P* value B vs A	Insulin resistant (C)	Non-Insulin resistant (D)	*P* value D Vs C	
HBs Ab	30.0 (18.5–57.5)	55.0 (21.5–84.0)	0.04*	55.0 (26.0–87.5)	93.0 (88.0–98.5)	0.001**	0.001**
Insulin	11.9 ± 1.7	7.8 ± 0.9	0.001**	12.1 ± 1.3	7.5 ± 0.8	0.001**	0.001**
HOMA IR	2.7 ± 0.5	1.8 ± 0.1	0.001**	2.7 ± 0.4	1.7 ± 0.2	0.001**	0.001**

Abbreviations (**HBs Ab**, hepatitis B surface antibody level); (**HOMA IR**, homoeostasis model of assessment of insulin resistance).
0.01*: Correlation is significant at the 0.01 level. 0.001**: Correlation is significant at the 0.01 level.

mean BMI of studied A, B, C and D groups were 23.2 ± 2.2, 22.0 ± 1.9, 25.2 ± 2.6 and 25.1 ± 1.4, respectively. The drug history of studied groups A, B, C and D were positive in 7 (28.0%) 1(4.0%), 11 (44.0%) and 6 (24.0%). *P* value of anti-HBs of studied groups A & B was 0.04 and for groups C & D were 0.001. There was one patient of group A, anti-HBs less than 10. *P* value of fasting insulin of studied groups A & B was 0.001 and groups C & D was 0.001 (Table 2).

The mean of platelets count of studied groups A, B, C and D were 271.6 ± 81.3, 272.2 ± 79.0, 306.0 ± 90.2 and 232.1 ± 59.0, respectively. The mean of ESR level at studied groups A, B, C and D were 22.6 ± 7.6, 16.9 ± 5.7, 19.8 ± 7.0 and 15.6 ± 4.9, respectively (Table 3). The median level of anti-HBs of studied groups A, B, C and D were 30.0 (18.5–57.5), 55.0 (21.5–84.0), 55.0 (26.0–87.5) and 93.0 (88.0–98.5). There was one patient of group A, anti-HBs less than 10. The median level of fasting insulin of studied groups A, B, C and D were 11.9 ± 1.7, 7.8 ± 0.9, 12.1 ± 1.3 and 7.5 ± 0.8. The median level of HOMA IR of studied groups A, B, C and D were 2.7 ± 0.5, 1.8 ± 0.1, 2.7 ± 0.4 and 1.7 ± 0.2 (*P* for group A vs. group B was 0.001) (P for group C vs. group D was 0.001) (Table 4)..

Table 5. Correlation between HBs Ab titer & HOMA IR and fasting Insulin level.

	HBs Ab	
	Pearson Correlation	Sig. (2-tailed)
INSULIN	−0.407	0.001[a]
HOMA IR	−0.410	0.001[a]

Abbreviations (**HBs Ab**, hepatitis B surface antibody level); (**HOMA IR**, homoeostasis model of assessment of insulin resistance).
[a] Correlation is significant at the 0.01 level.

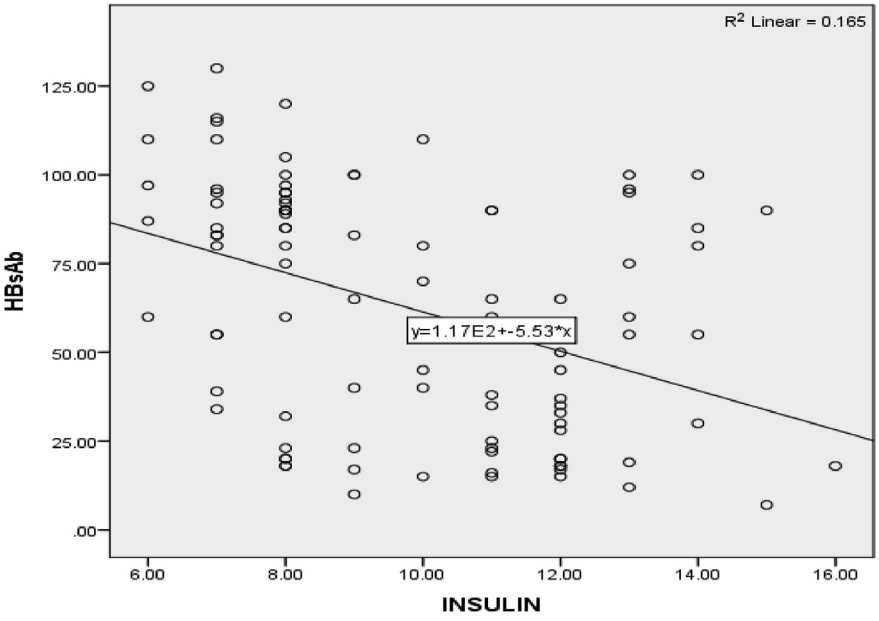

Fig. 1. Pearson correlation between HBs Ab and Insulin.

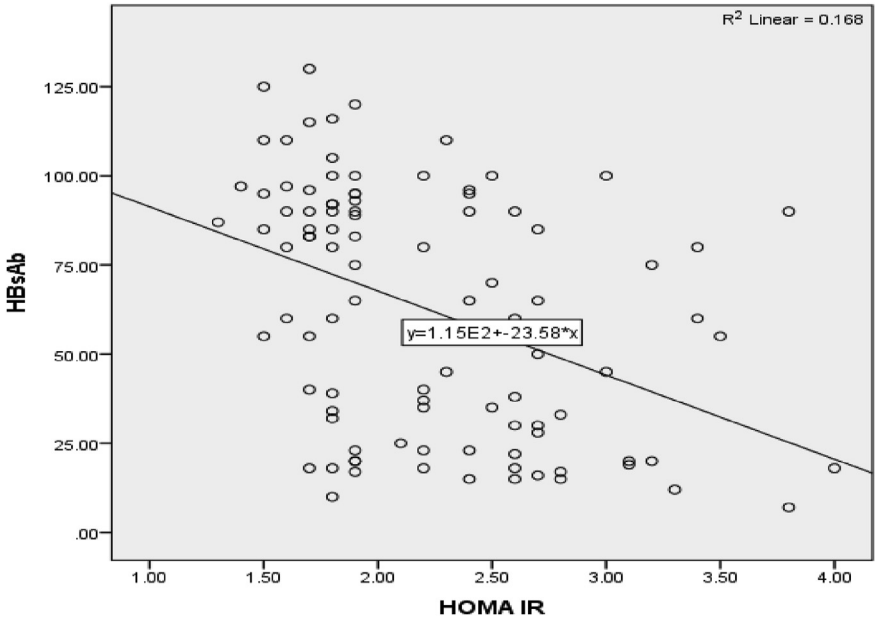

Fig. 2. Pearson correlation between HBs Ab and HOMA IR.

There is inverse correlation between HBs- Abs titer & HOMA IR and Insulin level (as described at Table 5).

Figs. 1 and 2.

4. Discussion

Hepatitis B virus affects 240 million individuals globally on a long-term basis, raises the risk of cirrhosis and HCC.[15]

Despite the HBV vaccine's efficiency, certain populations fail to produce defence mechanisms. Immunosuppression and end-stage renal disease dependent on dialysis are risk factors for a poor response. But 5% of the general population does not respond.[16]

Insulin resistance is thought to reduce the persistence of the level of protective anti-HBs. The relationship between insulin resistance and the persistence of HBV antibodies has not yet been

examined in published Egyptian studies, particularly in non-diabetics (all studies related to HCV or DAAs). Additionally, no published studies from Arabia or Africa have addressed the connection between insulin resistance and the persistence of HBV antibodies, particularly in non-diabetics. This study looked at healthy, nondiabetic persons in Egypt to see how insulin resistance affected their levels of anti-HBs. (10 mIU/mL is the protective level of anti-HBs concentration).[13]

38 473 Korean men and women with anti-HBs at concentrations ≤10 mIU/mL were included in a cohort research. When anti-HB levels fell below 10 mIU/l during the follow-up, it was determined that protective anti-HBs had been lost. Over the course of 180522 person-years of follow-up, 20826 incidences of anti-HBs antibody depletion were found (incident rate 11.5 per 100 person-years). Incident loss of anti-HBs was strongly associated with rising HOMA-IR. When compared to persons aged 35 or older, these links were more strong in younger adults under the age of 35 (P for interaction = 0.004). Additionally, patients with greater titres of anti-HBs had a stronger correlation compared to those with lower titres (100 mIU/mL) (P for interaction 0.001). Since insulin resistance was associated with a higher risk of losing anti-HBs acquired through vaccination in a sizable sample of the general population without diabetes, they came to the conclusion that it may play a role in vaccine-induced immunity.[13]

According to Lee *et al.*[17] 7880 persons (3851 men and 4029 women) were divided into three groups: those with negative, recovering from, or chronic viral hepatitis B (CVHB). They came to the conclusion that CVHB and insulin resistance are related. It could be necessary to monitor CVHB for the development of IR and diabetes mellitus. Should adults with diabetes mellitus get vaccinated against the hepatitis B virus? This is the question that Younossi *et al.*[18] respond to it. In order to find publications (from January 2000 to January 2017) describing the course of liver disease among patients with HBV by DM status, researchers conducted a systematic literature search. Risk variables including the connection between HBV and non-alcoholic steato-hepatitis were evaluated (NASH).

Al-zahaby *et al.*[19] showed that there was significant difference in positive HBs Ab titer between non-diabetic HCV patients compared to diabetics (50.44 ± 25.24and126.61 ± 70.48 respectively $P < 0.01$), but there was insignificant difference with negative HBs Ab titer & the response in diabetic patients was lower than non-diabetics. Also there was significant difference in positive HBsAb titer in non-diabetic controls compared to diabetics (47.82 ± 33.42 and 108.16 ± 65.08, respectively $P < 0.01$). This was attributed to the immune compromization state in diabetic patients. There was one patient of group A, anti-HBs less than 10 mIU/l. Our findings showed that insulin resistance was associated with episodic loss of anti-HBs over time in Egyptian non-diabetic men and women who appeared to be in good health.

It's noted that this study had some **limitations**. The participant history of vaccination was not available all though the study. The exact timing, age and types of primary hepatitis B vaccination in the study population were not evaluated. Also, incidental loss of anti-HBs does not necessarily mean a lack of protection against HBV.

4.1. Conclusion

In conclusion, insulin resistance was linked to incidental loss of anti-HBs over time in healthy men and women from Egypt. These results may support the hypothesis that insulin resistance contributes to the maintenance of a protective level of anti-HBs and that insulin resistance can impair immunological, metabolic, and cardiovascular function. Despite the limitations of the study, our findings provide critical insights into the variables influencing the unintentional loss of anti-HBs acquired through vaccination and the effect of insulin resistance on vaccine-induced immunity. Hepatologists and internists should be alert for these dangerous patients since obesity, alcoholism, and acanthosis nigricans may enhance the likelihood of immunity loss against HBV vaccinations. To evaluate our findings, additional research including sizable populations from various backgrounds is required. Further research will be required to determine the precise function of insulin resistance in protective immune memory.

Authorship

All authors have a substantial contribution to the article.

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Conflicts of interest

There are no conflicts of interest.

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