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Original Article

Seroprotection Status of Hepatitis B Vaccine in Children with Type 1 Diabetes Mellitus

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ABSTRACT

Background: "Type 1 diabetes mellitus [T1DM]" is the most common endocrine disease in the Pediatric population. It has been suggested that T1DM had inadequate immunological response to vaccines, including hepatitis B virus [HBV] vaccine.

Aim of the Work: To evaluate the immunological status against HBV vaccine among children with T1DM, and assess various possible risk factors for immunity failure.

Patients and Methods: A comparative cross-sectional study included 60 children [4-10 years] with T1DM [case group], and 60 healthy age- and sex-matched children [control group]. All included children had completed obligatory HBV vaccine. The evaluation of the immunological response was assessed through analysis of antibodies against HBV surface [HBsAB]. Seroprotection status to HBV vaccine was identified as plasma HBsAB of ≥ 10 mIU/ml.

Results: The mean duration of T1DM was 2.03 ± 1.73 years. The frequency of immunity failure to HBV vaccine [non-responders; HBsAB < 10 mIU/ml] was 51.7% among the case group, and 28.3% among the control group [P = 0.009]. Risk factors for immunity failure, as evaluated by regression analysis, were older age [P=0.002], and longer duration of T1DM [P=0.023].

Conclusion: Children with T1DM have a reduced level of HBV vaccine seroprotection when compared to the control group. Patients with older age and longer duration of T1DM showed a trend toward non-responding HbsAB titer. Long-term follow-up of responders is recommended to retest the level of immune response.

Keywords: Seroprotection; Hepatitis B; Vaccine; Type-1 Diabetes Mellitus.

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* Main subject and any subcategories have been classified according to the research topic.

INTRODUCTION

Type 1 diabetes mellitus [T1DM] is a frequent medical condition among children [1]. In 2017, it is estimated that more than one million children were diagnosed with T1DM worldwide, and these figures are expected to increase [2]. Type 1 diabetes mellitus has been associated with increased rates of infections [3]. Patients with T1DM are more vulnerable to HBV infection compared to the normal population [4]. It has been shown that T1DM had distinct effects on the immune system, involving both the humoral and cellular responses, which results in a less optimal reaction to vaccines compared to healthy controls [5, 6]. T1DM is associated with several immunologic abnormalities, which raise concerns about the long-term immunity to HBV vaccine [7]. Regarding cellular immune response, T1DM is linked to various abnormalities in the number and function of T cells, including a decreased percentage of CD4/CD8 lympho-cytes, decreased lympho-blastogenesis, and defective interleukin 2 production [8]. Other reported defects include downgraded primary T-cell response to protein antigens and suppression of T helper 1 [Th1] lymphocytes, decreased expression of Th1-related chemokine receptors, and reduced secretion of Th1 cytokines [5].

Hepatitis B virus infection remains a significant health issue in certain areas in the developing world including Egypt. The recombinant hepatitis B surface antigen vaccine is 80-100% effective in preventing HBV infection, and the inclusion of hepatitis B vaccine in the national immunization programs has been an important means to diminish the frequency of hepatitis B infection. However, the immune response to hepatitis B vaccination can be affected by several factors [9, 10]. The antibody response to HBV vaccine is primarily a T cell dependent. The sustained immune protection induced by the vaccine is attributed to the maintenance of immune memory through selective development and differentiation of clones of specific B and T-cell lymphocytes to the viral antigen [11]. Un-responsiveness to HBV vaccine has been associated with an alteration in T cell function, especially interleukins involved with Th1 functioning such as Interleukin-18 [IL-18] and Interferon-γ. These cytokines showed frequent aberrations among children with autoimmune diseases, including T1DM [12].

THE AIM OF THE WORK

Due to the high frequency of T1DM and susceptibility to HBV infection, the current study was conducted to analyze the seroprotective status of the HBV vaccine in T1DM children and assess the potential risk of immune failure.

PATIENTS AND METHODS

A controlled cross-sectional study conducted at "Al-Azhar University Hospital [Damietta]" from April 2020 to the end of March 2021. The study included 60 children [4-10 years old] with T1DM [case group] recruited from the Pediatric Outpatient Clinic as well as 60 healthy age- and sex-matched children [control group]. Children were diagnosed with T1DM according to the diagnostic criteria of the American Diabetes Association [13]. All included children had achieved HBV vaccine according to the "Egyptian compulsory vaccination program" at 2, 4, and 6 months of age. For the case group, the onset of T1DM had to be ≥ 2 months after the last dose of HBV vaccine. Children with a history of HBV infection, born to HBsAg carrier mothers, had other autoimmune disorders [e.g. celiac disease, thyroiditis], receiving immunosuppressive therapy, or developed comorbidities [e.g., hypertension, diabetic nephropathy and diabetic retinopathy] were excluded from the study. The onset and duration of T1DM was reported. Body mass index [BMI] was estimated by dividing the weight measured in kilograms by the height square in meters. All included children underwent assessment of hepatitis B surface antigen [HBs Ag] and hepatitis B core antibodies to exclude the hepatitis B infection, and results were negative for all children. The cut-off value for glycemic control was HbA1c level of 7.5% [14].

For laboratory analysis, 3 ml of blood was drawn from each child. Samples were centrifuged at 3500 rpm for 8 min to immediately separate plasma, and stored at -30 °C until analysis. Assessment of serum HBsAb was done by "enzyme-linked immunosorbent assay [ELISA]", and the titer was reported in mIU/ml. To detect HBsAB, ELISA microplates were coated with 250 ng of commercial HBsAg. After blocking, serum was attached to the microwells along with horseradish peroxidase-conjugated commercial HBsAg. The well-bound HRP-HBsAg was proportional to the concentration of HBsAB in the sample. The cut-off value for a negative specific antibody response to hepatitis B vaccine was HBsAb of 10 mIU/ml. Children were classified as non-responders if having HBsAb titer < 10 mIU/ml, and responders if having HBsAb titer ≥ 100 mIU/ml [15].

Sample Size Calculation: The sample size was calculated using G-Power Software. A total sample of 120 children [60 in each group] is required to estimate an effect size of sample = 0.298 with a significance level of 5 % [two-sided test], that will provide a power of 90%.

Ethical considerations: The study was approved by the Ethical Research Committee of "Damietta Faculty of Medicine, Al-Azhar University". Written informed consent was obtained from parents or authorized legal

representatives of all included children.

Statistical analysis: Data were collected, and entered into "Statistical Package for Social Science [SPSS]" version 20. Qualitative data were expressed as numbers and percentages, while quantitative data were expressed as means and standard deviations. Chi-square test and Fisher's exact test were used to compare qualitative data. Student's T-test was used to compare the two groups with quantitative data. We used univariate linear regression analysis for studying various risk factors of immunity failure, and all variables with $p < 0.05$ were included in a multivariate regression model. For all tests, P values < .05 were considered significant.

RESULTS

The mean age was comparable between the study groups. Children with T1DM low BMI of < 5th percentile and had a more frequent low hemoglobin [P = 0.019]. The mean duration of T1DM was 2.03 ± 1.73 years, and the majority of children with T1DM had poor glycemic control [75%].

Regarding HBV seroprotection, there was no significant difference between the study groups regarding the mean level of HBsAB [35.07 ± 41.29 mIU/ml in the case group vs. 48.28 ± 45.99 mIU/ml in the control group; P = 0.108], while the frequency of non-responders to HBV vaccine was significantly higher among the case group [51.7%] compared to the control group [28.3%; P = 0.009] as shown in table [1].

Univariate and multivariate regression analysis revealed that older age of children and [P=0.002], and a longer duration of T1DM [P=0.023] were risk factors for immunity failure, while the sex of the child, BMI, hemoglobin and HbA1c levels did not show such significance [tables 2 & 3].

Table [1]: Demonstration of demographic and laboratory data among the study groups

Variables		Cases [n = 60]	Control [n = 60]	P value
Gender	Males Females	28 [46.7%] 32 [53.3%]	30 [50%] 30 [50%]	0.85
Age [years]	Mean ± SD.	8.07 ± 1.90	8.31 ± 2.20	0.52
BMI [percentile]	Underweight [<5 th] Normal [5 - 85] Overweight [>85 - <95] Obese [≥95]	6 [10%] 50 [83.3%] 4 [6.7%] 0 [0%]	1 [1.7%] 40 [66.7%] 18 [30%] 1 [1.7%]	**<0.001***
Hemoglobin [g/dl]	<11 ≥11 Mean ± SD	20 [33.3%] 40 [66.7%] 10.67 ± 0.76	9 [15%] 51 [85%] 11.24 ± 0.72	**0.019***
Duration of DM [years]	Min. – Max. Mean ± SD	0.20 – 7.0 2.03 ± 1.73	-	**-**
HbA1c	< 7.5 ≥ 7.5	15 [25%] 45 [75%]	-	**-**
HbsAb [mIU/ml]	Min–Max. Mean ± SD.	6.0 – 120.0 35.07 ± 41.29	6.0 – 150.0 48.28 ± 45.99	0.108
	Non Responder < 10 Responder ≥ 10	31 [51.7%] 29 [48.3%]	17 [28.3%] 43 [71.7%]	**0.009***

*: significant

Table [2]: Relation between response to HBV vaccine and demographic data in the case group

		HbsAb		
		Non responder [<10] [n = 31]	Responder [≥10] [n = 29]	
Age [years]	4 – <6 6 – <8 8 – 10	0 [0%] 4 [12.9%] 27 [87.1%]	9 [31%] 6 [20.7%] 14 [48.3%]	**0.001***
Gender	Male Female	15 [48.4%] 16 [51.6%]	13 [44.8%] 16 [55.2%]	0.78
BMI [percentile]	Underweight [<5th] Normal [5 - 85] Overweight [>85 - <95] Obese [≥95]	3 [9.7] 27 [87.1] 1 [3.2] 0 [0]	3 [10.3] 23 [79.3] 3 [10.3] 0 [0%]	0.603

*: significant

Table [3]: Univariate and multivariate analysis for the parameters affecting responder cases among the case group

	Univariate		Multivariate	
	p	OR [95% C.I]	p	OR [95% C.I]
Age [years] ©	**0.002***	0.187*[0.065 – 0.540]	**0.046***	0.687*[0.475 – 0.993]
DM duration	**0.023***	0.666*[0.468 – 0.946]	**0.334**	0.823 [0.555 – 1.222]
Hemoglobin	**0.790**	0.913 [0.468 – 1.783]		
HbA1c	**0.694**	1.070 [0.764 – 1.498]		

*: significant

DISCUSSION

T1DT is associated with variable immunological abnormalities, which raise concerns about the immune response to hepatitis B vaccine [7, 11]. The mean age of children with T1DM in our study was 8.1 ±1.9 years, which was in agreement with two previous studies conducted for the same purpose in Iran [mean age of 8.6 ± 2.6 years] [16] and Italy [median age of 8 years] [17].

In contrast, many studies included relatively older children such as Elrashidy *et al*. [mean age was 10.29 ±3.04 years] [18], Hetta *et al*. [mean age was 10.36 ±3.51 years] [9], Onal *et al*. [mean age 12.63 ±3.9 years] [19], and Leonardi *et al*. [mean age of 13.67 ±4.9 years] [20].

For better evaluation of immunity failure, we suggest the employment of younger children as much as possible. Immunity to vaccines, including HBV vaccine, is waning with time. In an Egyptian study conducted on healthy children, protective antibody level was detected in 85.5% of the children aged up to 5 years, 71.6% of children aged between 5 and 10 years, and 47.7% among older children [21]. The main findings in our study are that children with T1DM had lower levels of HBsAb compared with healthy control children [35.07 ± 41.29 vs. 48.28 ± 45.99 mIU/ml]. Moreover, a higher percentage of children with T1DM [51.7%] had non-protective HBsAb levels [< 10 mIU/ml] compared with 28.3% of the healthy control children [P = 0.009]. Our results are in consonance with many previous studies, indicated that children with T1DM had lower specific antibody responses and seroprotection to HBV vaccination.

Leonardi *et al*. [20] included 110 children with T1DM and 100 healthy controls who received routine HBV vaccination. The mean HBsAb titer was significantly lower in children with T1DM [58 ±112.9 mIU/ml] than in healthy controls [266.49 ±335.85 mIU/ml], and 41% of children with T1DM had no protective levels of HBsAb, compared with only 16% in healthy controls. Likewise, Elrashidy *et al*. [18] measured the levels of HBsAb in 170 Egyptian children, 63 of which had T1DM, who had completed their routine vaccination against hepatitis 3 years before study beginning. This study found that 69.8% of children with T1DMdid not have protective anti-HBs levels [HBsAb levels < 10 mIU/ml], which was significantly higher than the healthy children group, in which 40% did not have protective HBsAb levels. Onal *et al*. [19] evaluated the antibody response to HBV vaccination in 201 children with T1DM and 140 healthy controls. In this study, 27.4% of children with T1DM had no protective levels of HBsAb, which was significantly higher than in healthy controls [17.9%].

In a recent Egyptian study, Hetta *et al*. [9] evaluated the immune response to HBV vaccine in 93 children with T1DM and 105 healthy controls as well as 22 university students with T1DM and 20 healthy controls. The mean HBsAb levels in children with T1DM [10.48 ±24.04 mIU/ml] were significantly lower than in healthy controls [67.53 ±143.1 mIU/ml], and the percentage of patients with DM having no protective HBsAb titers [73.1%] was significantly higher than controls [32.3%]. Even after in vitro activation of peripheral blood mononuclear cells with HBV vaccine, the levels of HBsAb were significantly lower among patients with DM compared with their counter-healthy controls.

The impaired antibody response to HBV vaccination emphasizes the need for a population-based strategy for the detection and management of patients without HBsAb protection levels after routine vaccination [9, 19]. However, in a cross-sectional study included 90 children < 15 years of age with T1DM as well as 90 healthy control children, the mean levels of HBsAb in children with T1DM were 45.9 ± 66 mIU/ml compared to a mean level of 63.7 ± 83.2 mIU/ml in the healthy control group. In addition, 45.46% of children with T1DM had no protective levels of HBsAb compared to 53% in the healthy control children. However, the differences were not statistically significant [16]. On the other side, some studies showed an adequate antibody response to HBV vaccine in patients with T1DM. Marseglia *et al*. [22] investigated HBsAb titers in 54 young adults with T1DM and 70 healthy controls 4 years after HBV vaccination. Protective antibody levels were found in 92% of diabetics and in 96% among healthy controls. In the systematic review, Schillie *et al*. [23] concluded that children and young adults with DM generally have immune responses to HBV vaccination, as do people of a similar age without diabetes. The elderly respond less, and the elderly with diabetes, especially those with kidney diseases, seems to have a more impaired vaccine response.

The inconsistent findings among studies may be attributed to the disparity in the designs of the study, type of vaccine, method for antibody assessment, interval between vaccination and testing, ethnic and genetic discrepancies among the studied populations. The reduced immune response of children with T1DM to HBV vaccine may be attributed to impaired cellular response with less beneficial antibody production after HBV vaccination. This may be related to a reduced quantity of moving helper T cells and defects in the uptake and processing of antigen [6]. In addition, many patients with T1DM demonstrate particular human leukocyte antigen [HLA] haplotypes such as DR3/DQ2 and DR4/DQ8. The presence of specific haplotypes [DR3/DQ2 and DR7/DQ2] has been associated with poor response to HBV vaccines. This HLA profile may explain the poor response to HBV vaccination in patients

with T1DM [12, 20]. However, the clinical significance of lower HBsAb levels in T1DM has not been clearly justified. Despite having lower HBsAb levels, HBsAg and anti-HBc are not detected among vaccinated children with T1DM. Even in the absence of HBsAb, immune memory appears to persist after vaccination in children with T1DM [24].

Our study showed no significant association between levels of HbA1c and HBsAb. These findings agree with previous studies, which showed no significant association between HbA1c levels and antibody response to hepatitis B vaccination [18, 19, 20, 22]. Moreover, a systematic review concluded that no significant association between impaired response to HBV vaccination in children with T1DM and glycemic control [23]. Compared to healthy controls, patients with T1DM showed impaired primary antibody response to both T-cell-dependent vaccines [e.g. hepatitis A vaccine and diphtheria toxoid], and T-cell-independent pneumococcal poly-saccharide vaccine. In contrast, patients with T2DM show a normal antibody response to immunization, indicating that hyperglycemia is not implicated in the abnormal immune response to vaccination among patients with T1DM [25].

In the present study, there was no significant association between BMI and HBsAb levels in children with T1DM. Of note, a recent meta-analysis revealed that obesity is significantly related to poor immune response to HBV vaccine, but this was not specific to obesity among diabetic patients [26].

In the present study, higher age was associated with increased percentage of non-responders [HBsAb level < 10IU/L] with a statistically significant threshold in children with T1DM. In univariate analysis, increasing age was significantly associated with lower HBsAb levels. Our results agree with previous studies that reported a decrease in HBsAb levels over time. Arefkhah *et al*. [27] displayed that 88.7% of children 0–5 years were seropositive, which decreased to 84.3% in children aged 6–10 years, and 78.1% in children > 10 years [P= < 0.05]. In Salama *et al*. [21] study that included 902 Egyptian children with an age range from 9 months to 16 years, the number of those with non-protective HBsAb titers was significantly higher among children > or = 10 years [64.8%] compared with children < 5 years [11.1%]. In the study by Hetta *et al*. [9], there was a significant association between serum levels of HBsAb and time elapsed since the last dose of hepatitis B vaccination. However, some studies showed no significant association between age and achieving protective levels of HBsAb in children with T1DM [18-20].

Following the primary administration of HBV vaccine, HBsAb titer will drop quickly during the first year and then slowly. After five to fifteen years from primary vaccination, 15% to 50% of initial responders will have low concentrations of HBsAB [28].

This study was not devoid of limitations. First, the somewhat small sample size might reduce the study power to detect some significant changes between the study groups; future studies on a larger number are recommended. Second, the cross-sectional design can indicate only associations; establishing causal-relationship requires long cohort studies since an early age. Third, the assessment of HBsAb was done at a single point in time; repeated measures at later ages may better elucidate the antibody response to HBV vaccine. Last, some other factors that may affect the immune response to HBV vaccination were not evaluated, including gestational age, the dose and type of the vaccine, needle length, breastfeeding, micro-nutrients status, and co-administered vaccines.

Conclusion: We concluded that children with T1DM have a reduced level of HBV vaccine seroprotection when compared with controls. Patients with older age and longer duration showed a trend toward lower HBsAB titer.

Financial and Conflict of interest disclosure

"Authors declare no conflict of interest"

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