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Association between body mass index and hepatitis B antibody seropositivity in children

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Background: The seropositivity rate of hepatitis B surface antigen (anti-HBs) antibodies is known to be ≥95% after hepatitis B virus vaccination during infancy. However, a low level or absence of anti-HBs in healthy children is discovered in many cases. Recent studies in adults reported that a reduced anti-HBs production rate is related to obesity.
Purpose: To investigate whether body mass index (BMI) affects anti-HBs levels in healthy children following 3 serial dose vaccinations in infancy.
Methods: We recruited 1,200 healthy volunteers aged 3, 5, 7, or 10 years from 4-day care centers and 4 elementary schools. All subjects completed a questionnaire including body weight, height, and vaccine type received. Levels of serum hepatitis B surface antigen (HBsAg) and anti-HBs in all subjects were analyzed using electrochemiluminescence immunoassay. The standardized scores (*z* score) for each sex and age were obtained using the lambda-mu-sigma method in the 2017 Korean National Growth Charts for children and adolescents.
Results: Our subjects (n=1,200) comprised 750 males (62.5%) and 450 females (37.5%). The overall anti-HBs seropositivity rate was 57.9% (695 of 1,200). We identified significant differences in mean BMI values between seronegative and seropositive groups (17.45 vs. 16.62, respectively; $P<0.001$). The anti-HBs titer was significantly decreased as the BMI *z* score increased adjusting for age and sex (B=-15.725; standard error=5.494; $P=0.004$). The probability of anti-HBs seropositivity based on BMI *z* score was decreased to an OR of 0.820 after the control for confounding variables (95% confidence interval, 0.728–0.923; $P=0.001$).
Conclusion: There was a significant association between anti-HBs titer and BMI *z* score after adjustment for age and sex. Our results indicate that BMI is a potential factor affecting anti-HBs titer in healthy children.

Key words: Anti-HBs, Hepatitis B, Seropositivity rate, BMI *z* score, Child

Key message
Question: This study aimed to evaluate the association between BMI and anti-HBs level in healthy children following 3 serial dose vaccination in infancy.
Finding: After adjusting for age and sex, there was a significant association between anti-HBs titer and BMI *z* score.
Meaning: Our findings revealed that BMI may be a factor potentially affecting anti-HBs titer so that booster vaccination or range of vaccination dose based on BMI and age can be considered.

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Introduction

Hepatitis B virus (HBV) is a leading cause of acute or chronic hepatitis, and HBV infection continues to be a serious public health problem due to its high prevalence and association

with chronic liver disease including cirrhosis and hepatocellular carcinoma. Vaccination is important because no complete cure for HBV infection exists, other than conservative treatment.[1] With the availability of low-cost, unrestricted production of recombinant vaccines, vaccination in all age groups, including newborns, is expected to eradicate hepatitis B infection.[2] In Korea, the hepatitis B vaccine has finally been included in the National Mandatory Vaccination program since 1995 and the vaccination rate has reached 95%.[3] In the 1980s, the overall positive rate of hepatitis B surface antigen (HBsAg) in Korea was approximately 7.25%, which decreased to 4.38% in 2001 and 3.7% in 2005 after vaccination was initiated.[4] In a study conducted in 2008, the overall HBsAg seropositivity rate was found to have decreased to 2%.[5]

After the hepatitis B vaccine was included in the National Expanded Program on Immunization in Korea, all infants have been eligible for the basic course of HBV immunization, including 3 consecutive inoculations at 0, 1, and 6 months after birth.[6] The preventive effect of the hepatitis B vaccine as protection against infection is defined on the basis of the concentration of antibodies against hepatitis B surface antigen (anti-HBs) being ≥10 mIU/mL. The anti-HBs seropositivity rate is known to be ≥95% after 3 serial doses of HBV vaccination during infancy. However, 5%–15% of normal adults are reported to fail to produce anti-HBs after 3 inoculations, and there have been a few cases of HBV infection in such nonresponders, although with mild clinical courses.[1]

Responses to hepatitis B vaccine vary among vaccine responders and vaccine-induced anti-HBs levels may progressively decrease, as shown in several studies.[7-10] The factors associated with immunogenicity of the hepatitis B vaccine in healthy individuals include the number of injections, site of injection, type of vaccine, use of adjuvant materials, and storage conditions of vaccines.[11] It is also known that characteristics and health status of subjects such as immunosuppression, hemodialysis, female gender, older age, obesity, smoking, and drinking are associated with decreased antibody formation.[1] In particular, there have been studies in adults showing that a reduction in the rate of anti-HBs production is related to obesity.[1,12-14] However, there is a lack of studies addressing anti-HBs production or retention in obese children after HBV vaccination in Korea, even though the obesity rate is gradually increasing among the population, especially in children and adolescents.

The present study investigated whether BMI affects anti-HBs seropositivity in healthy children who received 3 serial doses of vaccination in infancy.

Methods

1. Subjects

We recruited healthy volunteers aged 3 (36–47 months), 5 (60–71 months), 7 (84–95 months), or 10 years old (120–131 months), with 300 in each group, from 4-day care centers and 4 elementary schools in Seongnam-si, Gyeonggi-do at 2016. All 1,200 subjects had received 3 serial doses of recombinant hepatitis B vaccine at birth, at one month of age, and at 6 months of age.

Exclusion criteria in the study were HBV-positive parents or a family history of hepatitis B infection; a history of hepatitis B infection; additional HBV booster vaccination other than the standard vaccination; HBsAg positivity; receiving blood transfusion; or immunocompromised status including congenital or acquired immune disorder, hemodialysis, liver dysfunction, or cancer.

2. Questionnaires and vaccination information

All parents of the subjects completed a questionnaire about their children's age, sex, medical history, body weight, height, and type of vaccine. In most cases, information about vaccine type was obtained from the National Immunization Program website of the Korea Centers for Disease Control.

3. Measurement of serum titer

Serum HBsAg and anti-HBs in all subjects were analyzed via electrochemiluminescence immunoassay using the Roche Cobas 8000 (Roche Diagnostics, Indianapolis, IN, USA).

The cutoff index value of HBsAg was 1.0. Samples were considered positive if the HBsAg level was >1.0, and negative if it was <1.0. The measurement range of anti-HBs was 2–1,000 mIU/mL, and seropositivity was defined as anti-HBs≥10 mIU/mL. Samples with anti-HBs≥1,000 mIU/mL were recorded as 1,000 mIU/mL and samples below the detection limit (2 mIU/mL) were recorded as undetectable.

4. BMI *z* score

We calculated the BMI of each subject based on their height and weight obtained via questionnaires. The standardized scores (*z* score) for sex and age were obtained using the LMS method in the 2017 Korean National Growth Charts for children and adolescents.[15]

5. Statistical analysis

All quantitative variables are presented as mean±standard deviation, and all qualitative variables are presented as percentage and number. Independent variables were analyzed using the chi-square test. T-test, Kruskall-Wallis test, or Mann-Whitney *U* test were used to compare mean values of independent variables. Multiple and logistic regression analyses were used to calculate the odds ratio (OR) and 95% confidence interval (CI), or the beta coefficients (B) and standard error (SE), after adjustment for age and sex. Statistical analysis was performed using the IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA) and statistical significance was defined as $P \leq 0.05$.

6. Ethical considerations

Written informed consent was obtained from the parents of all children or children enrolled in the study. The study was approved by the Institutional Review Board of CHA University (CHAIRB No.2015-196).

Results

1. Subject characteristics

A total of 1,200 subjects, 300 in each of the 4 groups of 3, 5, 7, or 10-year-olds, participated in the study. Of these, 750 were males (62.5%) and 450 were females (37.5%). The mean BMI value in each age group corresponded to the 50th percentile in each group. Euvax (recombinant DNA vaccine, LG Chemistry, Seoul, Korea) was the most commonly administered vaccine in all the groups (Table 1).

2. Anti-HBs seropositivity rate based on age group

The overall anti-HBs seropositivity rate in the subjects was 57.9% (695 of 1,200). In the 3-year-old group, the anti-HBs seropositivity rate was 79.7% (239 of 300). The seropositivity rates were 55.7% (167 of 300), 51.7% (155 of 300), and 44.7% (134 of 300) in the 5, 7, and 10-year-old groups, respectively. As age increased, the anti-HBs seropositivity rate was significantly decreased (P<0.001). There was no statistically significant difference in the anti-HBs seropositivity rate based on gender or type of vaccine in any of the age groups (Table 2).

Table 1. Baseline characteristics

Characteristic	Total	3-Year-old group	5-Year-old group	7-Year-old group	10-Year-old group
No. of patients	1,200	300	300	300	300
Male sex	750 (62.5)	216 (72)	189 (63)	193 (64.3)	152 (50.7)
Type of vaccine* (n)					
Euvax B[a]	577	130	148	156	143
Hepavax-gene[b]	514	134	110	132	138
Hepamun[c]	52	21	29	1	1
Others[d]	57	15	13	11	18
Weight (kg)		16.07±2.00	20.87±3.64	26.88±5.30	37.94±8.09
Height (cm)		99.16±4.56	113.54±5.49	125.50±5.95	142.52±8.91
Body mass index (kg/m^2)		16.29±1.16	16.11±1.92	16.95±2.33	18.52±2.62

Values are presented as number (%), number, or mean±standard deviation.
*First inoculation, if all 3 inoculations were not identical. [a]Recombinant DNA vaccine, LG chemistry, Seoul, Korea. [b]Recombinant DNA vaccine, Jassen Vaccine Corp., Seoul, Korea. [c]Recombinant DNA vaccine, SK Bio Science, Seongnam, Korea. [d]Heptis -BII, Hepa-B.

Table 2. Anti-HBs seropositivity rate based on age group

	Titer[a]<2	2≤titer<10	10≤titer<100	100≤titer	Seropositivity rate (%)	P value
Age						**<0.001**[b]
3 Years	27	34	133	106	79.7	0.116[c]
Male	19	20	100	77		
Female	8	14	33	29		
5 Years	97	36	107	60	55.7	0.667[c]
Male	57	25	68	39		
Female	40	11	39	21		
7 Years	92	53	96	59	51.7	0.063[c]
Male	65	36	59	33		
Female	27	17	37	26		
10 Years	108	58	91	43	44.7	0.366[c]
Male	64	24	42	22		
Female	44	34	49	21		

Values are presented as number of patients unless otherwise indicated.
Anti-HBs, antibody to hepatitis B surface antigen.
[a]Titer (mIU/mL); anti-HBs levels (min, 2 mIU/mL; max, 1,000 mIU/mL) were classified into 4 ranges: (1) titer <2; (2) 2≤titer<10; (3) 10≤titer<100; (4) 100≤titer; (3) and (4), seropositive. [b]P value for anti-HBs seropositivity rate based on age group. [c]P value for anti-HBs seropositivity rate based on sex.
Boldface indicates a statistically significant difference with P<0.05.

3. Difference in mean BMI based on immunogenicity

In all the subjects and in each age group, the mean BMI value in seronegative subjects tended to be higher than that in seropositive subjects. The mean BMI value in 505 seronegative subjects was 17.45±2.62 and that in 695 seropositive subjects was 16.62±1.93; this was a statistically significant difference (P<0.001).

There was a tendency for differences in BMI values based on immunogenicity in all 4 age groups. In particular, BMI values in seronegative subjects were statistically significantly higher than those in seropositive subjects in the 7-year-olds (17.34 vs. 16.58, respectively; P=0.005) and the 10-year-olds (18.85 vs. 18.11, respectively; P=0.016) (Table 3).

4. The association between BMI *z* score and the Anti-HBs titer

We investigated the association between BMI *z* score and anti-HBs titer using multiple regression and logistic analyses. These indicated statistically significant associations of anti-HBs titer with BMI *z* score. The anti-HBs titer was decreased significantly as the BMI *z* score increased, adjusting for age and sex (B=-15.73, SE=5.49, P=0.004). In addition, the probability of anti-HBs seropositivity based on BMI *z* score was decreased to an OR of 0.820 after controlling for confounding variables (95% CI, 0.73–0.92; P=0.001) (Table 4).

5. Anti-HBs titer in obese children

Based on 2017 Korean National Growth Charts for children and adolescents, we defined obesity as BMI greater than 95th percentile in each sex and age group.[15] According to this definition, 132 children were obese among the total 1,200 children. The anti-HBs seropositivity rate in this obese group was 48.5% (64 of 132). The difference between the seropositivity rate in obese and nonobese group was more pronounced in older age groups, for instance, the seropositivity rate in obese and nonobese groups of 10-year-old age group were 15.8% (3 of 19) and 46.6% (131 of 281), respectively.

Table 3. Difference in mean body mass index based on immunogenicity in the entire group of subjects and in each age group (n=1,200)

Anti-HBs titer	Body mass index (kg/m^2)	*P* value
Total (n=1,200)		**<0.001**
Seronegative[a] (n=505)	17.45±2.62	
Seropositive[b] (n=695)	16.62±1.93	
3-Year-old group (n=300)		0.260
Seronegative[a] (n=61)	16.44±1.60	
Seropositive[b] (n=239)	16.25±1.02	
5-Year-old group (n=300)		0.149
Seronegative[a] (n=133)	16.23±2.07	
Seropositive[b] (n=167)	15.97±1.78	
7-Year-old group (n=300)		**0.005**
Seronegative[a] (n=145)	17.34±2.37	
Seropositive[b] (n=155)	16.58±2.24	
10-Year-old group (n=300)		**0.016**
Seronegative[a] (n=166)	18.85±2.87	
Seropositive[b] (n=134)	18.11±2.21	

Values are presented as mean±standard deviation.
Anti-HBs, antibody to hepatitis B surface antigen.
[a]Anti-HBs titer<10 mIU/mL. [b]0 mIU/mL≤anti-HBs titer.
Boldface indicates a statistically significant difference with P<0.05.

Discussion

The Advisory Committee on Immunization, World Health Organization, and the international group of hepatitis experts have defined the preventive effect of the hepatitis B vaccine as the presence of anti-HBs concentration ≥10 mIU/mL, representing protection against infection.[7] The rate of protective anti-HBs formation is known to be 16%–40% after the first inoculation and 80%–95% after the second inoculation. The third inoculation is performed as the booster, raising the antibody production rate to 98%–100%.[16] However, there are many cases in which negative or low anti-HBs levels are found in healthy children. The highest concentration of anti-HBs level is known to be attained between 1 and 3 months after the last inoculation and subsequently, the anti-HBs level begins to decrease. The decrease in anti-HBs level is rapid after 1 to 2 years, but then slows down gradually.[16] In the present study, the seropositivity rate was found to be 79.7% at 3 years after vaccination, 57.7% after 5 years, 51.7% after 7 years, and 44.7% after 10 years. This is consistent with previous studies showing a statistically significant decrease in anti-HBs seropositivity rate with increasing age (Table 2).

It is known that the immune status of an individual is an important factor influencing antibody production. In addition, some studies have reported that several host factors in healthy individuals such as sex, age, obesity, smoking, and drinking are significantly related to immunogenicity of the hepatitis B vaccine.[1] In particular, obesity can be a notable risk factor for failure to produce anti-HBs, and it has been on the rise in both adults and children. In our study, we found significant differences in mean BMI values between seronegative and seropositive subjects (Table 3). Further, there was a significant relationship association between anti-HBs titer and BMI *z* score with age and sex adjusted (Table 4). These are similar to results

Table 4. Multiple regression and logistic analyses of the association of BMI *z* score with the anti-HBs titer (n=1,200)

	Anti-HBs titer			Anti-HBs titer[a]	
	B	SE	*P* value	aOR (95% CI)	*P* value
BMI *z* score	-15.73	5.49	0.004[b]	0.82 (0.73–0.92)	**0.001**

BMI, body mass index; anti-HBs, antibody to hepatitis B surface antigen; B, beta; SE, standard error; aOR, adjusted odds ratio; CI, confidence interval.
[a]Seronegativity was defined as anti-HBs<10 mIU/mL, seropositivity was defined as anti-HBs≥10 mIU/mL. [b]Factors were adjusted for age and sex.

of previous studies in Iran, Turkey, China, and Belgium involving adults.[11] This finding indicates a trend of decreasing anti-HBs with increasing BMI, beyond the simple fact that obese individuals (BMI≥25 kg/m^2) are significantly more likely to be nonresponders as reported in previous studies on adults.[1,12,17] In the present study as well, nonresponders accounted for 72% (18 of 25) of the group with BMI≥23 kg/m^2 and 100% (3 of 3) of the group with BMI≥25 kg/m^2. Other previous studies on adults have reported vaccine deposition into gluteal fat as a risk factor among obese people.[1,12,18-20] In the present study, however, injection site was not found to be a risk factor associated with obesity because all subjects were injected in the thigh or the deltoid muscle during the neonatal period.

There have been several previous studies reporting poor vaccine-induced immune responses in obese individuals against influenza/pH1N1, tetanus, or rabies,[21-23] and those reporting the effect of obesity on immune responses,[24] but the data were not of sufficient detail.[25] The mechanism via which obesity reduces antibody production is not clear, and it can be assumed that the relationship between obesity, inflammation, and vaccine immunogenicity is more complex than anticipated. It is currently a matter of discussion whether obesity should be regarded as a state of low-grade chronic inflammation which inhibits antibody production,[26] or whether dietary intake leading to obesity affects the gut leading to bacterial translocation and altered levels of immune activation.[17] Even if we cannot fully establish the mechanism currently, it is important to note that the proportion of obese individuals is increasing globally, particularly among adolescents.

Several studies have revealed that in individuals with the maximal anti-HBs level≥10 mIU/mL after a 3 serial dose vaccination, the anamnestic response rapidly elevates the anti-HBs level to a protective level upon further exposure to the virus and maintains such immune system memory for at least 15 years.[7,9,10] However, there is no clear evidence that normal responders continue to have an anamnestic response for more than 15 years. Further, the immune system memory status in individuals is unknown unless the maximum antibody level after vaccination is tested, which is not done in most cases.[7] Due to the above reasons, there is no precise consensus on the necessity or scheduling of revaccination, and there have been no claims that booster doses are unnecessary. However, if obesity directly affects the immune system outcome, the possibility that the anamnestic response does not occur in obese nonresponders should be considered. Therefore, further studies on the anamnestic response in obese nonresponders are needed. In addition, booster vaccination based on BMI or a range of vaccination dose based on body weight can be considered.

This study is the first in Korea to report the association between BMI and anti-HBs seropositivity in healthy children. This study also has strengths in that it offers some considerations in the interpretation of anti-HBs in children.

The present study does have some limitations. First, the study was limited to the Gyeonggi area and may not represent all regions. Second, we could not evaluate whether the anti-HBs-negative subjects were nonresponders from the beginning, or were initial responders who lost anti-HBs production. Third, height and weight values were obtained via parental questionnaires, and the accuracy of the BMI may have been low. Fourth, because samples with anti-HBs≥1,000 mIU/mL were recorded as 1,000 mIU/mL, the results of anti-HBs titer analysis considering it as a continuous variable may have been affected.

In conclusion, our results indicate that BMI may be a factor potentially affecting anti-HBs titer in healthy children. Our findings also revealed a significant correlation between anti-HBs titer and BMI in children and adolescents, beyond the simple observation that obese people are unlikely to respond to the hepatitis B vaccine.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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