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ORIGINAL RESEARCH

Elevated Glycated Hemoglobin Is Associated with Reduced Antibody Responses to Vaccinations in Children

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Background: Childhood obesity is a major health concern, and it is associated with an increased risk of infectious morbidity. Previous studies found a decrease in protective antibody titers in obese adults after hepatitis B, influenza, and tetanus vaccination.
Objective: We aimed at determining whether obesity or abnormal hemoglobin A1C (HBA1C) levels are associated with altered antibody responses in children.
Methods: Children (8–18 years) who have completed routine childhood immunization were recruited. Serum samples were tested by the enzyme-linked immunosorbent assay method for antibody levels to Diphtheria, Tetanus, *Haemophilus influenzae* type B (HIB), and *Streptococcus pneumoniae*, along with serum HBA1C levels. An electronic medical record review on the frequency of emergency visits for infection was conducted. Spearman rank correlation, Fisher-exact, and Pearson's Chi-squared tests were used for statistical analysis.
Results: There was an overall negative correlation between body mass index (BMI) percentile and the majority of pneumococcal subtypes, Diphtheria and Tetanus titers, although not statistically significant. There was a statistically significant negative correlation between HBA1C level and the *S. pneumoniae* serotype P9N ($P=0.037$), P4 ($P=0.017$), P12 ($P=0.023$), P19F ($P=0.050$), and HIB ($P=0.001$). On average, individuals with elevated HBA1C levels had more frequent emergency room visits for infection ($P=0.029$) and more viral infections ($P=0.023$) as compared with children with normal HBA1C.
Conclusion: Children with higher HBA1C levels were more likely to have lower pneumococcal and HIB titers and increased rates of emergency room visits for infection in a prospective, population-based cohort study. Although not statistically significant, there was an overall negative correlation between BMI percentile and titers for routine childhood vaccines.

Keywords: vaccination, obesity, HBA1C, vaccine titers

Introduction

Obesity is a major health epidemic affecting ~18.5% of the children in the United States.[1] Although the long-term complications of obesity, including hypertension, diabetes, and heart disease, have been studied extensively, the effect of obesity on immune function is less well established.

Obesity is known to have a negative impact on the immune system even in otherwise healthy obese individuals.[2,3] It is hypothesized that an increase in fat tissue and insulin resistance leads to a chronic inflammatory state, immune system dysregulation, and susceptibility to infections.[4] Elevated body mass index (BMI) has been correlated with increased susceptibility to various infections such as *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, *Helicobacter pylori*, *Candida albicans*, encephalomyocarditis, and influenza virus.[5] Animal studies have demonstrated a correlation between obesity and increased susceptibility to coxsackie virus B4 and encephalomyocarditis virus.[6,7]

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A small number of studies investigating the link between obesity and immune function have been conducted in adults. The first evidence of poor vaccine-induced immune response was reported in 1985 in obese adult hospital employees receiving the hepatitis B vaccine.[8] Similarly, a reduction in protective antibody titers in response to influenza, Tetanus, and rabies vaccines has been reported in adults, which can leave such individuals susceptible to disease-related complications.[9–11]

Less is known about childhood obesity and the immune system. To our knowledge, the data on the antibody response to vaccinations in otherwise healthy obese children come from 2 studies. One of these studies showed that obese children may have an impaired immune response to influenza vaccination, with a significant decrease in the CD4+T cell activation marker CD69.[12] The other earlier study compared overweight children with age-matched controls; specific IgG antibody levels to Tetanus were noted to be reduced in obese children.[13] However, none of the studies addressed the efficacy of other routine childhood vaccines in relation to BMI percentile and elevated glycated hemoglobin A1C (HBA1C) level or studied the effect of booster vaccines in obese children. In our study, we hypothesize that childhood obesity and elevations in HBA1C level will weaken the immune response to routine childhood vaccinations.

Materials and Methods

Study population

The study population was recruited from the general pediatric and the Allergy outpatient clinics at The Children's Hospital of Michigan in Detroit, Michigan. All children recruited were from ages 8 to 18 years. Only children who received their appropriate childhood vaccinations based on the Advisory Committee on Immunization Practices (ACIP) guidelines, confirmed by the Michigan Childhood Immunization Registry (MCIR) database, were included. Children with chronic medical illness (ex. autoimmune disorders, immunodeficiency disorders) or who were taking immunosuppressive medications that may affect the immune response were excluded. None of the participants had a known diagnosis of diabetes mellitus. We excluded children younger than 8 years of age to avoid potential immediate increases in antibody titers from recent booster vaccinations. The Wayne State University Human Investigation Committee (local Institutional Review Board) approved the study, number #061713MP2F. Written informed assent and consent were obtained for experimentation with human subjects from all participants and their parents, respectively, during the enrollment process. The privacy rights of human subjects were always observed.

Data collection, data and statistical analysis

Demographic data were collected and included age, sex, and ethnicity. BMI percentage was determined by using the Centers for Disease Control and Prevention (CDC) growth curves based on height and weight measurements. The definition for obese was at BMI ≥95th percentile as per the CDC guidelines. Serum samples were collected and tested by the enzyme-linked immunosorbent assay method for antibody levels to Diphtheria, Tetanus, *Haemophilus influenzae* type B (HIB), and *S. pneumoniae* (14 serotypes), along with serum HBA1C levels.

Data were also collected from medical record reviews on the frequency of emergency visits for common childhood infections, including sinopulmonary (pneumonia, otitis media) and viral infections. Visits with discharge diagnoses for other infections were excluded. The diagnosis code for the emergency room visit and the final impression recorded by the physician during the visit were used to determine the infection type. The total number of visits for infection and the final diagnosis for those found to have an infectious disease were recorded. This data collection was analyzed to determine whether there was an increased rate of vaccine-preventable disease in the study population.

All the laboratory tests were performed at a standardized commercial laboratory (ARUP® Laboratories, Salt Lake City, UT). Tetanus and Diphtheria IgG antibody titers, HIB Antibody IgG, and *S. pneumoniae* IgG antibodies (14 serotypes) were performed by quantitative multiplex bead assay. The pneumococcal serotypes were the following: serotype 1, 5, 6B, 3, 7F, 9N, 14, 8, 9V, 12F, 18C, 19F, and 23F. HBA1C level was performed by quantitative capillary electrophoresis. Per the ARUP Laboratories, a HBA1C level above 5.7 percent was considered abnormal. Age-appropriate reference values for all tests were standardized per ARUP Laboratories.

For analysis, antibody concentrations of ≥0.1 IU/mL were considered protective for Diphtheria or Tetanus IgG and antibody concentrations of ≥1.0 μg/mL were considered protective for HIB IgG, as per reference values set by ARUP Laboratories. Antibody concentrations of ≥1.3 μg/mL of at least 7 out of 14 pneumococcal serotypes were considered ''adequate'' against pneumococcal disease and they have been used extensively to reflect immunocompetence.[14] Participants with antibody concentrations <0.35 μg/mL in at least 7 out of 14 pneumococcal serotypes were considered ''non-protective'' against invasive pneumococcal disease and would require a booster vaccine.[14,15] Antibody concentrations from 0.35 to 1.2 μg/mL are considered protective against invasive pneumococcal disease, but inadequate against common infection and colonization from pneumococcus. As these individuals were protective against invasive pneumococcal disease, we did not give them a booster vaccine.

BMI percentile and HBA1C levels were used as a continuous variable versus the exact antibody titer values. We summarized the categorical variables by numbers and percentages. We analyzed normally distributed continuous variables by mean and standard deviation, and non-normally distributed continuous variables by median and interquartile range. Spearman rank correlation was used to study the relationship between variables. Pearson's Chi-squared test was used to analyze the distribution of categorical variable by groups, provided no expected frequency less than 1, and no more than 20% of the cell should have an expected frequency less than 5, otherwise Fisher's exact test was used for the analysis. We used SAS (version 9.4; SAS Institute, Inc., Cary, NC). Significance level was set at 0.05.

Results

A total of 81 participants were recruited, and their electronic medical records were reviewed. Nine participants were excluded due to a lack of clinic follow-up, the inability to

obtain blood work, or the loss of specimen by the laboratory. The remaining 72 participants were included in the final data analysis. These 72 participants were divided into an obese group (BMI percentile 95%–100%; $n=31$), a nonobese group (BMI percentile <95%; $n=41$), a high HBA1C group (HBA1C ≥ 5.7; $n=31$), and a normal HBA1C group (HBA1C < 5.7, $n=38$). Comparisons were made between the nonobese and the obese group and likewise, between the high HBA1C and the normal HBA1C group.

Baseline characteristics

Overall, African American males made up the majority of the participant population (64%, $n=46/72$), which reflected the patient population in our area. The median age was 10 years, the median BMI percentile was 94%, and the median HBA1C level was 5.6%. The age, sex, and ethnicity between the obese and nonobese groups were similar. Likewise, the age and sex between the high HBA1C and normal HBA1C groups were similar. African Americans were more likely to have a high HBA1C level in our study population ($P=0.003$). The median BMI percentile in the obese group was 99% with an interquartile range of 3 and in the nonobese group, 75% with an interquartile range of 44. The median HBA1C level in the elevated HBA1C group was 5.9% with an interquartile range of 0.30 and in the normal HBA1C group, 5.4% with an interquartile range of 0.30. Interestingly, there was no statistically significant correlation between HBA1C level and BMI percentile in our study population. This finding could be due to the small sample size our study population. Participant characteristics of the obese group (BMI percentile in the 95–100th percentile), the nonobese group (BMI percentile < the 95th percentile), high HBA1C group (HBA1C ≥ 5.7), and normal HBA1C group (HBA1C < 5.7) are summarized in Table 1.

Antibody response

There was no statistically significant correlation between BMI percentile and the titers for the 14 pneumococcal serotypes, Diphtheria, Tetanus, and HIB. However, there was an overall negative correlation between the BMI percentile and the majority of Pneumococcal subtypes, Diphtheria and Tetanus titers, but not with HIB titers (Table 2). There was an overall negative correlation between HBA1C level and all 14 Pneumococcal subtypes, Diphtheria, Tetanus, and HIB titers, with a statistically significant negative correlation with *S. pneumoniae* serotype P9N ($P=0.037$), P4 ($P=0.017$), P12 ($P=0.023$), P19F ($P=0.050$), and HIB ($P=0.001$) titers (Table 3).

Overall, the mean titer levels for Diphtheria, Tetanus, HIB, and all 14 pneumococcal serotypes were not statistically significant different between the obese participants and the nonobese participants. However, the overall mean titers were lower in the obese participants. This trend was also observed for Diphtheria, Tetanus, and HIB titers when comparing those with high HBA1C levels with those with normal HBA1C levels. There was no difference in the adequacy of pneumococcal titer levels (at least 7 out of 14 pneumococcal serotypes are ≥1.3 μg/mL) when comparing obese with nonobese individuals. However, the individuals with elevated HBA1C levels were more likely to have inadequate pneumococcal titer levels ($n=14/31$; 45%), where at least 7 out of 14 pneumococcal serotypes are <1.3 μg/mL, when compared with those with normal HBA1C ($n=8/38$, 21%; $P=0.05$). Those individuals with inadequate pneumococcal titer levels had, on average, 10 out of 14 pneumococcal serotypes less than 1.3 μg/mL. This was consistent between those individuals with high HBA1C and those with normal HBA1C. All individuals in our study, regardless of BMI percentile and HBA1C level, had antibody concentrations that were considered protective for invasive pneumococcal disease (antibody concentrations ≥0.35 μg/mL in at least 7 out of 14 pneumococcal serotypes) and did not receive a booster vaccine.

There was no statistically significant difference between the protective titer level of Tetanus, Diphtheria, and HIB titers in obese patients versus nonobese patients. This is also true for the high HBA1C group versus the normal HBA1C group.

A total of 16 individuals were found to have nonprotective Diphtheria/Tetanus titers, and 24 individuals were

Table 1. Participant Characteristics

	Obese[a] *(n=31)*	*Nonobese (n=41)*	P *value*	*Elevated HBA1C (n=31)*	*Normal HBA1C (n=38)*	P *value*
Sex, *n* (%)						
Men	17 (55)	30 (73)	0.11	21 (68)	24 (63)	0.69
Ethnicity, *n* (%)						
Caucasian	4 (13)	5 (12)	0.93	1 (3)	7 (18)	0.003
African American	21 (68)	25 (61)		27 (87)	17 (45)	
Hispanic	3 (10)	5 (12)		2 (6)	6 (16)	
Other[b]	3 (10)	6 (15)		1 (3)	8 (21)	
Age						
Median (range)	10 (8–15)	10 (8–17)	0.89	10 (8–17)	10 (8–15)	0.28
BMI percentile						
Median (range)	99 (95–100)	75 (25 -94)	<0.001	87 (25–100)	95 (25–100)	0.20
HBA1C						
Median (range)	5.7 (5.0–6.7)	5.6 (4.9–6.4)	0.95	5.9 (5.7–6.7)	5.3 (4.9–5.6)	<0.001

[a]Obesity as defined as BMI ≥95%tile.
[b]Unknown or undisclosed.
BMI, body mass index; HBA1C, hemoglobin A1C.

Table 2. Correlation of Vaccine Titers and Body Mass Index

Pneumococcal antibodies														
	P3	*P7F*	*P9N*	*P14*	*P1*	*P4*	*P5*	*P6B*	*P8*	*P9V*	*P12F*	*P18C*	*P19F*	*P23F*
BMI	−0.22	0.05	−0.19	−0.15	−0.01	−0.12	−0.07	0.02	−0.07	−0.01	−0.12	0.05	−0.15	−0.20
P value	(0.059)	(0.657)	(0.111)	(0.200)	(0.937)	(0.327)	(0.564)	(0.896)	(0.576)	(0.918)	(0.311)	(0.654)	(0.202)	(0.100)
Spearman correlation coefficients Prob > |r| under H0: Rho = 0														

Diphtheria/tetanus and hemophilus antibodies			
	D	*T*	*H*
BMI	−0.10	−0.05	0.09
P value	(0.419)	(0.661)	(0.473)
Spearman correlation coefficients Prob > |r| under H0: Rho = 0			

D, diphtheria; H, hemophilus; T, tetanus.

found to have nonprotective HIB titers. Out of the 16 individuals with nonprotective Diphtheria/Tetanus titers, 9 of them returned for a booster dose (GSK; Boostrix Tdap; 0.5 mL dose) and 8 of these individuals followed up for repeat titers (repeat titers drawn between 28 and 64 days postbooster vaccination). Out of the 24 individuals with nonprotective HIB titers, 12 of them returned for a booster dose (Merck; Pedvax-Hib or ActHIB; 0.5 mL dose) and 9 of these individuals followed up for repeat titers (repeat titers drawn between 28 and 58 days postbooster vaccination; one individual had repeat titers 351 days postbooster vaccination). The individuals who received a booster vaccine dose and had repeat titers drawn showed an excellent titer response and were all in the protective range. None of the participants required a pneumococcus booster.

Frequency of emergency room visits and infections

Overall, the individuals with high HBA1C levels had a greater mean number of emergency room visits for infection compared with the individuals with normal HBA1C level ($P = 0.028$). On average, the high HBA1C group had more frequent emergency room visits for viral infections ($P = 0.022$) than their normal counterparts, but they had similar rates of emergency room visits for pneumonia ($P = 0.297$) and otitis media ($P = 0.199$). The obese individuals did not have a statistically significant higher number of emergency room visits for infection as compared with their healthy counterparts ($P = 0.2559$). These results are summarized in Table 4.

Discussion

Routine vaccinations to *S. pneumoniae*, HIB, Tetanus, and Diphtheria are given to children in the United States as an effort to prevent invasive disease. As childhood obesity is a leading health concern with previous data reporting the association between obesity and the increased risk of infection and infectious morbidity, we sought to identify the efficacy of routine childhood vaccines in relation to obesity and insulin resistance. Our study demonstrates that elevated HBA1C levels, but not obesity, were associated with lower antibody response to various routine childhood vaccinations. There was a strong negative correlation between HBA1C levels and antibody responses, specifically for HIB vaccine titer and the P9N, P4, P12, and P19F pneumococcal titer subtypes. A recent study characterizing invasive pneumococcal disease isolates through the CDC's Active Bacterial Core surveillance identified that among the serotypes detected, serotypes 3, 19A, and 19F accounted for 20.4% of the isolates from all ages.[16] In our study, individuals with HBA1C levels did have a strong negative correlation with the 19F pneumococcal subtype, perhaps placing them at higher risk for more invasive pneumococcal disease.

Table 3. Correlation of Vaccine Titers and Hemoglobin A1C

Pneumococcal antibodies														
	P3	*P7F*	*P9N*	*P14*	*P1*	*P4*	*P5*	*P6B*	*P8*	*P9V*	*P12F*	*P18C*	*P19F*	*P23F*
HBA1C	−0.02	−0.17	−0.25	−0.20	−0.15	−0.29	−0.23	−0.13	−0.13	−0.13	−0.27	−0.13	−0.24	−0.16
P value	(0.849)	(0.153)	(0.037)	(0.112)	(0.230)	(0.017)	(0.054)	(0.286)	(0.284)	(0.300)	(0.023)	(0.284)	(0.050)	(0.195)
Spearman correlation coefficients Prob > |r| under H0: Rho = 0														

Diphtheria/tetanus and hemophilus antibodies			
	D	*T*	*H*
HBA1C	−0.22	−0.23	−0.31
P value	(0.075)	(0.055)	(0.001)
Spearman correlation coefficients Prob > |r| under H0: Rho = 0			

D, diphtheria; H, hemophilus; T, Tetanus.

Table 4. Frequency of Emergency Room Visits and Infections

	Obese[a] (n = *31*)	*Nonobese* (n = *41*)	P *value*	*Elevated HBA1C* (n = *31*)	*Normal HBA1C* (n = *38*)	P *value*
ED visits for infection (mean)	5.81	4.03	0.2559	5.97	3.54	0.0288
Pneumonia (mean)	0.13	0.25	0.9401	0.29	0.11	0.2968
Otitis Media (mean)	0.71	0.55	0.7692	0.74	0.51	0.1993
Viral Infection (mean)	3.77	2.60	0.3657	4.06	2.05	0.0225

[a]Obesity as defined as BMI ≥95%tile.

Further, our participants with elevated HBA1C levels showed a marginally significant difference in the adequacy of the overall pneumococcal titers when compared with their normal HBA1C counterparts. Individuals with elevated HBA1C levels were more likely to have inadequate pneumococcal titers (at least 7 out of 14 pneumococcal serotypes are <1.3 μg/mL) as compared with those with normal HBA1C. However, these individuals all have antibody concentrations that were protective for invasive pneumococcal disease (antibody concentrations ≥0.35 μg/mL in at least 7 out of 14 pneumococcal serotypes).

Our results highlight that the impairment of antibody responses to vaccines is broader than previously reported.[8–11,17] To the best of our knowledge, this is the first study to show a relationship between elevated HBA1C levels and impaired vaccine antibody levels. This suggests that insulin resistance itself, even before the diagnosis of diabetes, may alter the immune status in otherwise healthy individuals. The mechanism by which this occurs is not completely understood.

Based on proposed mechanisms linking obesity with immune impairment through the reduction in natural killer cell activity,[18] diminished $CD8^+$ T cell memory response with an altered CD4 T cell/CD8 T cell balance,[19–21] B cell exacerbated inflammation via autoantibodies and crosstalk with adipose resident macrophages and $CD4^+$ and $CD8^+$ T cells,[22] alterations in cytokine production leading to decreased IgG production,[23] we expected a more significant decrease in vaccine antibody levels in obese individuals. Our relatively small sample size could have limited us from reaching statistical significance for association between BMI percentile and antibody levels. A larger scale, multicenter study may help to clarity these associations.

To examine the clinical implication of having overall lower vaccine titers, we reviewed the medical record of our study individuals for the frequency of emergency room visits for an infectious disease (viral upper respiratory and bacterial sinopulmonary infections) over the course of the past 1 year. Obese individuals had a greater mean number of emergency room visits associated with infectious etiology as compared with nonobese individuals, although not statistically significant. Again, this may be due to our study's small sample size. Individuals with elevated HBA1C levels did have significantly more overall emergency room visits for infection ($P = 0.029$) and on average, more viral infections ($P = 0.023$), but not sinopulmonary infections, as compared with their normal HBA1C counterparts. The increased susceptibility for infections may be secondary to underlying insulin resistance. Insulin signaling modulates T cell activation and is also involved in promoting Th-2 cellular response and activation of JNK1 and IKKβ pathways, leading to a chronic inflammatory state.[24,25] Natural childhood infections themselves can generate antibodies. Our study did not investigate the timing of these natural infections and the development of antibodies, which was a limitation of our study. However, there was no difference in the overall frequency of common childhood infections (pneumonia and otitis media) that generate measurable antibodies between children with obesity or elevated HBA1C levels and healthy controls. The antibody titers against viral upper respiratory tract infections are not commercially available and were not tested, which is another limitation of our study.

Our study suggests that children with insulin resistance, even before the diagnosis of diabetes, could be at an increased risk for infectious morbidity due to their lower immunologic response to vaccines. Of the children with low vaccine response, administering one additional booster vaccine dose was enough to mount an adequate response regardless of BMI percentile or HBA1C levels. This indicates that the children with low vaccine antibodies in our study can adequately mount a response to vaccinations. However, the sustainability of these antibody levels is not known.

Given the prevalence of childhood obesity and insulin resistance, a greater understanding of their effects on immunity along with prevention and management strategies is important. Perhaps, we need to include active surveillance for antibody levels and include booster vaccine recommendations for children with abnormal HBA1C levels. The results from our study provide a platform to evaluate for earlier interventions to improve the efficacy of routine immunization and reduce infectious morbidity among obese children and those with insulin resistance.

Author Disclosure Statement

The authors have no financial relationships or potential conflicts of interest relevant to this article to disclose.

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