The link between plasma 25-hydroxyvitamin D and lung function in general and asthmatic children

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ABBREVIATIONS

25(OH)D – 25-hydroxyvitamin D

BMI – body mass index

CHMS – Canadian Health Measures Survey

FVC – forced vital capacity

$FEV_{0.75}$ – forced expiratory volume in 0.75 second

FEV_1 – forced expiratory volume in one second

FEV_1/FVC – ratio of FEV_1 to FVC

CDC – U.S. Center for Disease Control

ABSTRACT

Background: Vitamin D has been shown to play an important role in many bodily functions including the proper functioning of the respiratory system in adults. However, very little epidemiological evidence is available examining the relationship between vitamin D and pulmonary function among children. Our study will examine the association between plasma 25-hydroxyvitamin D (25(OH)D) and pulmonary function in children.

Methods: We used cross-sectional data from 1421 children aged 6-17 years who participated in the Canadian Health Measures Survey (CHMS) in 2007-09. Multiple linear regression analysis was used to examine the association in the general children population and children with asthma.

Results: The data showed that 20% of children had plasma 25(OH)D concentration below 50 nmol/L, which is classified as deficient. Linear regression analysis showed no significant association between 25(OH)D and lung function testing variables after adjustment for confounding factors in the general children population. However, data demonstrated a positive association of plasma 25(OH)D with $FEV_{0.75}$, FEV_1 and FEV_1/FVC among boys with asthma.

Conclusions: There was no significant relationship between plasma 25(OH)D and pulmonary function among children in general. In boys with asthma, plasma 25(OH)D had a positive relationship with respiratory function.

INTRODUCTION

Vitamin D insufficiency has become an important pubic health issue due to its widespread prevalence and health consequences. It not only affects the development of bone tissue, but also is associated with some chronic diseases including types 1 and type 2 diabetes, cancer, cardiovascular disease[1] and respiratory disease such as asthma in adults and children[2].

In adults, studies have demonstrated an association between low vitamin D status and lung dysfunction[3-5]. However, only a few epidemiological studies have explored the relationship between 25-hydroxyvitamin D (25(OH)D) and pulmonary function in children and they show differing results[6-7]. The objective of the current investigation was to determine the association between plasma 25(OH)D and pulmonary function among general Canadian children population and among children with asthma.

METHODS

Data on plasma 25(OH)D, pulmonary function measures and important covariates of children between the ages of 6 and 17 years were extracted from the Canadian Health Measures Survey (CHMS) conducted in 2007-09. Details about the study design and methodology can be found elsewhere[8]. There were a total of 1883 participants 6-17 years of age in the survey. After exclusion of children that had missing spirometric data or data with highly questionable reproducibility and quality or missing 25(OH)D data, 1421 were included in the current analysis.

All the necessary measurements including lung function testing and blood samples were collected on the same day for an individual. Information about how plasma

25(OH)D and pulmonary function were determined has been described previously[5]. Briefly, lung function testing was conducted using a Koko spirometer and followed procedures recommended by the ATS/ERS[9, 10]. Measurements were carried out while a participant was sitting in an upright position wearing a nose clip. A minimum of 3 trials were carried out up to a maximum of 8 and the best trial was selected. Plasma 25(OH)D concentration was determined via the LIAISON 25-Hydroxyvitamin D Total Assay (Diasorin SpA) with a Spearman's rank correlation of 0.95. The confounding factors that were adjusted for in the models included: age in years, height in meters, ethnicity (white, non-white), sex, body mass index (BMI), and asthma status. Asthma status was based on self-reporting and was determined by asking the following question: "Do you have asthma diagnosed by a health professional?"

Smoking was rare and did not significantly change the associations; therefore, it was excluded from final models. Passive smoking was also considered as a potential confounding factor; however, it had no significant effect on the relationships.

The means or frequencies of various demographic characteristics were compared between children with or without asthma using unpaired t-tests or Chi-square tests. A linear regression model was built for each of the following lung function testing variables: forced vital capacity (FVC), forced expiratory volume in 0.75 second ($FEV_{0.75}$) and in one second (FEV_1), and FEV_1/FVC. Plasma 25(OH)D concentration was included as a continuous predictor along with covariates such as age, height, ethnicity, sex, BMI and asthma status. Age- and height-squared terms were also tested and kept in the models if P-values were less than 0.10. Stratified analysis by asthma status and further by sex or BMI was also carried out. $P \leq 0.10$ was considered statistically significant for an

interaction. Linear regression analysis using 25(OH)D as a categorical variable (deficient or not) was also performed with all four lung function outcome measures. Vitamin D deficiency was defined as having plasma 25(OH)D concentration below 50nmol/L. Sampling weights and design effect associated with sampling were taken into account in all the analysis using a bootstrap approach. All the analyses were conducted using the SAS software package (SAS, version 9.3; SAS Institute; Cary, NC).

RESULTS

The demographics of the study population are shown in Table 1. There were 715 (52.1%) boys and 706 (47.9%) girls with mean age of 12.4 years. The majority of the sample consisted of white participants (86.6%). A total of 168 children were asthmatic (12.3%). The average BMI of all participants was 20.5 kg/m^2, with significantly higher mean BMI for children with asthma (p=0.013). About 13.5% (n=192) of the participants were classified as overweight and 12.9% (n=154) were categorized as obese based on the U.S. Center for Disease Control (CDC) BMI-for-age classification system. Overall mean plasma 25(OH)D was 70.8 nmol/L (standards error (SE) 1.61), and there was no significant difference between children with and without asthma even after taking into account season of blood collection. There were 270 children (20.4%) who had a plasma 25(OH)D concentration below the 50.0 nmol/L level. No significant difference in FVC, $FEV_{0.75}$, and FEV_1, was found between children with and without asthma while average FEV_1/FVC ratio was significantly lower in asthmatic children ($p<0.001$).

Overall, no statistically significant association was found between plasma 25(OH)D and lung function testing variables in general children population (Table 2). No

notable change in the results was observed upon exclusion of asthmatic children. Sex or BMI did not modify the association of 25(OH)D concentration with lung function parameters overall or in children without asthma (Table 3); therefore, combined analysis was performed in the total group and in the non-asthmatic children (Table 2). However, in children with asthma the data showed a significant or marginally significant interaction between sex and 25(OH)D on $FEV_{0.75}$ (p=0.106), FEV_1 (p=0.073) and FEV_1/FVC (p=0.094) (Table 3). Significant positive associations of 25(OH)D with $FEV_{0.75}$ (β=0.0048, p=0.016), FEV_1 (β=0.0050, p=0.023) and FEV_1/FVC (β=0.0011, p=0.046) were observed among boys with asthma (Table 2). Vitamin D was also tested as a categorical variable (deficient or not) with lung function measures in asthmatic and non-asthmatic groups (Table 4). No statistically significant associations were observed between vitamin D deficiency and pulmonary function parameters in either group.

DISCUSSION

Our investigation found no significant association between plasma 25-hydroxyvitamin D and pulmonary function among general Canadian children after adjustment for age, sex, height, ethnicity, BMI, and asthma status. Stratification also revealed no significant association between plasma 25(OH)D concentration and pulmonary function in non-asthmatic children and in asthmatic girls. However, amongst boys with asthma, significant relationships between 25(OH)D and respiratory function measures – $FEV_{0.75}$, FEV_1 and FEV_1/FVC were observed. An increase of 1 nmol/L in plasma 25(OH)D was associated with about a 4.8 ml increase in $FEV_{0.75}$, 5.0 ml increase

in FEV_1, and a 0.11% increase in FEV_1/FVC. We repeated the analysis after accounting for the season of blood collection and found very similar results.

Previously, vitamin D deficiency has been related to increased risk of atopy and asthma development especially among male children[11], and is also associated with asthma exacerbation[12-15]. In addition, vitamin D concentration has shown a significant positive correlation with FVC[15, 16], FEV_1[15, 16, 17, 18] and FEV_1/FVC[18] among asthmatic children. Moreover, a prospective study of asthmatic children found that vitamin D supplementation helped to reduce asthma exacerbation prompted by acute respiratory tract infection[19]. Maternal intake of vitamin D during pregnancy might also be associated with a reduced risk of asthma[20] and wheeze[21] among children. When exploring the relation between vitamin D and lung function among general children population, one cross-sectional examination based on data from the third National Health and Nutrition Examination Survey found a positive association between 25(OH)D concentration and FVC in 2446 children 12-19 years of age (β=0.035; 95% CI: 0.007-0.064)[6]. A cohort study of 436 children demonstrated no relation between 25(OH)D concentration and pulmonary function in children 6 to 7 years of age and no association between vitamin D supplementation during pregnancy or early childhood (1-2 years of age) and lung function at age 6-7 years[7]. The conflicting results among the above-mentioned studies could be due to the differing age ranges of the participating children.

A recent study[22] in mice has provided insight into a direct mechanism of action for modification of lung function by vitamin D that may help explain our findings. The study demonstrated that mice kept on a vitamin D-deficient diet had offspring with reduced lung function primarily exhibited by a smaller lung size. Therefore, it is plausible

that associations observed in childhood between vitamin D and lung function are merely a reflection of such early life events. Another possibility is that children with asthma become vitamin D deficient due to reduced outdoor activity resulting from their condition.

We found no association between the 25(OH) vitamin D metabolite and lung function in the general children population. Nor did sex or BMI modify this no association. In adults however, our previous study found that low 25(OH) vitamin D concentration was related to poor pulmonary function especially among overweight/obese individuals[5]. There are several possibilities, which may help explain the difference in the association between plasma 25(OH)D and pulmonary function between adults and children. First of all, the prevalence of 25(OH) vitamin D deficiency was lower in children compared to adults (20% versus 26%)[5]. There was also a notable difference in the prevalence of overweight/obesity (60% for adults versus 26% for children). Moreover, high BMI may result in improved lung function in children[23, 24]whereas in adults larger BMI is correlated with poor respiratory function[25, 26, 27]. BMI is more likely an indicator of body size for children but an indicator of adiposity for adults.

There are some limitations present in the current investigation, most important one being the cross-sectional nature of the data, which does not provide strong evidence for causal relationships. Another drawback is that the current study does not take into account whether participants have current symptomatic asthma versus a prior diagnosis. However, the same question for determining asthma status has been used in many previous Canadian studies[28, 29].

CONCLUSION

To the best of our knowledge, this is the first study to examine the relationship between 25 (OH) vitamin D concentration and respiratory function among the general population of Canadian children. Additional studies of longitudinal design in children are necessary to confirm if high body 25(OH) vitamin D concentration is associated with improved pulmonary function for boys with asthma.

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AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist for any of the authors.

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