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Review

Prevalence, determinants and clinical correlates of vitamin D deficiency in adults with inhaled corticosteroid-treated asthma in London, UK

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ABSTRACT

Vitamin D deficiency is common in children with asthma, and it associates with poor asthma control, reduced forced expiratory volume in one second (FEV₁) and increased requirement for inhaled corticosteroids (ICS). Cross-sectional studies investigating the prevalence, determinants and clinical correlates of vitamin D deficiency in adults with asthma are lacking. We conducted a multi-centre cross-sectional study in 297 adults with a medical record diagnosis of ICS-treated asthma living in London, UK. Details of potential environmental determinants of vitamin D status, asthma control and medication use were collected by questionnaire; blood samples were taken for analysis of serum 25 (OH)D concentration and DNA extraction, and participants underwent measurement of weight, height and fractional exhaled nitric oxide concentration (FeNO), spirometry and sputum induction for determination of lower airway eosinophil counts (n=35 sub-group). Thirty-five single nucleotide polymorphisms (SNP) in 11 vitamin D pathway genes (*DBP*, *DHCR7*, *RXRA*, *CYP2R1*, *CYP27B1*, *CYP24A1*, *CYP3A4*, *CYP27A1*, *LRP2*, *CUBN*, *VDR*) were typed using Taqman allelic discrimination assays. Linear regression was used to identify environmental and genetic factors independently associated with serum 25(OH)D concentration, and to determine whether vitamin D status was independently associated with Asthma Control Test (ACT) score, ICS dose, FeNO, forced vital capacity (FVC), FEV₁ or lower airway eosinophilia. Mean serum 25(OH)D concentration was 50.6 nmol/L (SD 24.9); 162/297 (54.5%) participants were vitamin D deficient (serum 25(OH)D concentration <50 nmol/L). Lower vitamin D status was associated with higher body mass index (P=0.014), non-White ethnicity (P=0.036), unemployment (P for trend=0.012), lack of vitamin D supplement use (P<0.001), sampling in Winter or Spring (P for trend<0.001) and lack of a recent sunny holiday abroad (P=0.030), but not with potential genetic determinants. Vitamin D status was not found to associate with any marker of asthma control investigated. Vitamin D deficiency is common among UK adults with ICS-treated asthma, and classical environmental determinants of serum 25(OH)D operate in this population. However, in contrast to

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studies conducted in children, we found no association between vitamin D status and markers of asthma severity or control.

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1. Introduction

Vitamin D deficiency has been reported to be common among children with asthma in diverse settings, and to associate with reduced forced expiratory volume in one second (FEV₁), poor asthma control and increased requirement for inhaled corticosteroids (ICS) [1–5]. Despite the high prevalence of both asthma and vitamin D deficiency among adults in the industrialised world, cross-sectional studies assessing the prevalence, determinants and clinical correlates of vitamin D deficiency in adults with asthma have not previously been performed in such settings to our knowledge. Moreover, despite evidence suggesting that genetic variation can influence vitamin D status in the general population [6], studies to quantify the relationship between single nucleotide polymorphisms (SNP) in the vitamin D pathway and serum 25-hydroxyvitamin D (25[OH]D) concentrations (the accepted biomarker of vitamin D status), or clinical correlates of asthma phenotype, have not previously been performed in patients with asthma.

We therefore conducted a cross-sectional study to assess the prevalence of vitamin D deficiency in a group of adults with ICS-treated asthma in London, UK, and to explore environmental and genetic determinants of vitamin D status in this group. We also conducted analyses to determine whether serum 25(OH)D concentration or genetic variation in the vitamin D pathway associated with markers of asthma control in this population, including symptom control, FEV₁, forced vital capacity (FVC), ICS requirement and fractional exhaled nitric oxide concentration (FeNO). Additional analyses were performed to determine whether serum 25(OH)D concentration and genetic variants in the vitamin D pathway interacted to influence asthma control.

2. Methods

2.1. Participants

Adult patients with a medical record diagnosis of asthma treated with ICS were identified by searching databases at 60

general practices and at asthma clinics in 2 Acute National Health Service Trusts in London, UK, and invited for screening as previously described [7]. The study was approved by East London and The City Research Ethics Committee 1 (ref 09/H0703/67) and written informed consent was obtained from all participants before enrolment.

2.2. Procedures

Respondents were asked to complete a lifestyle questionnaire detailing age, sex, ethnicity, self-reported Fitzpatrick skin-type [8], self-classified socio-economic position (SEP) using the National Statistics – Socio-Economic Classification (NS-SEC) method [9], daily hours spent outdoors, history of recent sunny holidays abroad (defined as a trip to any location within a latitude 51° North/South of the equator, during the local sunny season, 2 months prior to blood draw, for a duration of ≥1 week), smoking behaviour and consumption of alcohol and supplemental vitamin D. Respondents also completed the asthma control test (ACT) questionnaire [10], and underwent a baseline clinical assessment including the following: spirometry before and after inhalation of 400 µg salbutamol via a spacer device, performed using a MicroLab ML3500 desktop spirometer (CareFusion GmbH, Hoechberg, Germany) according to American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations [11]; FeNO measurement, performed using a NIOX MINO 09-1100 (Aerocrine, Solna, Sweden) according to ATS/ERS recommendations [12]; height measurement (using a Seca 220 Telescopic Measuring Rod, Seca, Hamburg, Germany), and weight measurement (using Marsden MMPS-250 column scales, Marsden, Rotherham, UK). A blood sample was collected for DNA extraction and determination of serum concentration of total 25[OH]D and parathyroid hormone (PTH). A sub-set of 35 participants underwent sputum induction with hypertonic saline, and their samples were processed to make cytosin slides according to methods described by Pizzichini et al. [13]. Differential cell counts were performed by one operator for all specimens throughout the study; a second operator repeated cell counts on a randomly selected sub-set of 20 slides: differential cell

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