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Vitamin D is not associated with serologic response to influenza vaccine in adults over 50 years old

Maria E. Sundaram[a,*], H. Keipp Talbot[b], Yuwei Zhu[b], Marie R. Griffin[b], Sarah Spencer[c], David K. Shay[c], Laura A. Coleman[a,d]

[a] Marshfield Clinic Research Foundation, 1000 North Oak Street, Marshfield, WI 54449, United States
[b] Vanderbilt University School of Medicine, D-3100, Medical Center North, Nashville, TN 37232, United States
[c] Centers for Disease Control and Prevention, 1600 Clifton Road, NE, Atlanta, GA 30329, United States
[d] Abbott Nutrition, 3300 Stelzer Road, Columbus, OH 43219, United States

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ABSTRACT

Vitamin D deficiency has been implicated in risk of respiratory illness. We determined whether serum vitamin D levels are related to influenza vaccine response measured by hemagglutination antibody inhibition (HAI) titer in adults aged ≥50 years old. The study was a prospective cohort study conducted over two influenza seasons (fall 2008–spring 2009 and fall 2009–spring 2010) in Marshfield, WI and Nashville, TN including 1103 community-dwelling adult volunteers ≥50 years of age. Pre-vaccination levels of serum vitamin D and HAI titer levels pre- and 21–28 days post-influenza vaccination were measured. Seroprotection was defined as HAI ≥40; seroconversion was defined as ≥4-fold rise in HAI titers from pre- to post-vaccination. More than 25% of participants were vitamin D deficient (<25 ng/mL). Vitamin D measured as a continuous variable was not related to pre- or post-vaccination seroprotection or seroconversion for any vaccine strain in any year. Vitamin D deficiency was associated with a greater frequency of post-vaccination seroprotection for seasonal H1N1 in the first year of the study, but was not related to seroprotection or seroconversion for any other strain in either year. No consistent association was found between vitamin D levels or vitamin D deficiency and serologic response to influenza vaccination in older adults. Cell-mediated immune parameters should also be explored in order to further investigate possible relationships between micronutrient status and influenza vaccine response.

1. Introduction

Influenza infects people of all ages, but causes higher rates of complications and deaths in older adults [1,2]. This is partly due to decreasing immune function with increasing age, a phenomenon termed "immunosenescence" [1,3]. The effects of immunosenescence on the immune system are complex [4]. However, recent evidence suggests that declining immune function is partly explained by increased antigenic stress and chronic inflammation in older adults [5].

Because of the increased risk of morbidity and mortality from influenza in older adults, it is especially important that influenza be prevented in this population [4]. To this end, the World Health Organization has recommended that older people be preferentially targeted to receive the yearly trivalent inactivated influenza vaccine (TIV) [6]. However, influenza vaccine supply may be limited, and even when supplies are adequate, not all adults are vaccinated [7]. Additionally, the serologic immune response to influenza vaccination is less likely to be less robust in older adults [8], suggesting that those who do receive the vaccine may not be optimally protected against influenza [9]; in fact, vaccine effectiveness against hospitalization in older adults is likely to be substantially lower than in younger adults [10]. This leaves a significant portion of the older adult population vulnerable to influenza [2]. It is therefore important to determine new methods to improve influenza vaccine response in older adults in order to ensure better protection against infection.

Although vitamin D has long been known to play an important role in calcium homeostasis and maintaining skeletal structure [11], it has also recently been linked to inflammation, immune response to influenza infection [12], and immune response to vaccines [13–15]. Furthermore, vitamin D is of particular interest in populations of older adults, who are at heightened risk for micronutrient deficiency [16]. The likelihood of vitamin D deficiency may increase with age [17].

Abbreviations: HAI, hemagglutination antibody inhibition; TIV, trivalent inactivated influenza vaccine.

* Corresponding author. Tel.: +1 715 221 6060; fax: +1 715 389 3880.
E-mail address: sundaram.maria@marshfieldclinic.org (M.E. Sundaram).

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Although suboptimal response to influenza vaccination and suboptimal vitamin D serostatus in older adults have been studied separately, few studies have focused on the connection between serum vitamin D and serologic response to influenza vaccine in older adults. Therefore, we investigated whether serum vitamin D levels predicted seroprotection or seroconversion to influenza vaccination in adults 50 years and older.

2. Materials and methods

2.1. Subjects and data collection

There were 1103 research participants ≥50 years old who were recruited from Marshfield, WI and Nashville, TN across two influenza seasons (season 1: 2008–2009; season 2: 2009–2010). The details of recruitment and data collection have been described in detail elsewhere [18]. Briefly, Marshfield participants were recruited from a pool of individuals who received the trivalent inactivated influenza vaccine the year prior; Nashville participants were recruited by using "snowball" sampling starting with a group of Vanderbilt University employees and also enrolling interested and eligible friends and family members. All participants received the trivalent inactivated influenza vaccine and donated serum before vaccination and 21–28 days post-vaccination; vaccinations and blood draws occurred before the start of the influenza season, in the fall of 2008 and fall of 2009. A demographic questionnaire was administered at enrollment. All participants provided informed consent prior to study enrollment and all study procedures were reviewed and approved by the Marshfield Clinic Institutional Review Board and the Vanderbilt University School of Medicine Institutional Review Board.

2.2. Laboratory methods

Blood draws were performed by trained phlebotomists and processed according to methods described elsewhere [18]. Samples were processed within 24 h of collection and shipped to Focus Diagnostics (Cypress, CA) for HAI assays in season 1 and to Battelle (Frederick, MD) for HAI assays in season 2. Viruses used in the HAI assay for participants in year 1 were A/Brisbane/59/2007-like (H1N1), A/Brisbane/10/2007-like (H3N2), and B/Florida/4/2006-like. In year 2, the HAI assay included A/Brisbane/59/2007-like (H1N1), A/Brisbane/10/2007-like (H3N2), B/Brisbane/60/2008-like, and influenza A (H1N1)pdm09-like [A(H1N1)pdm09]. HAI assays were performed in triplicate in year 1 and duplicate in year 2. Vitamin D (25-hydroxyvitamin D) assays were performed at the Marshfield Clinic Core Laboratory using a Waters UPLC Acquity TQS mass spectrometer with the LC/MS/MS method. Both liquid and solid phase extractions were performed. The cut-offs for severe vitamin D deficiency (<10 ng/mL), mild to moderate vitamin D deficiency (10–24 ng/mL), optimum vitamin D status (25–80 ng/mL), and possible vitamin D toxicity (>80 ng/mL) were determined by the Marshfield Clinic Core Laboratory and were based on clinical data.

2.3. Statistical analysis

For each subject, seroprotection was defined as an HAI titer of ≥40 and seroconversion was defined as ≥4-fold rise in HAI from pre-vaccination to post-vaccination. If the pre-vaccination HAI was ≤10, seroconversion was defined as having a post-vaccination titer of ≥40. In season 1, three HAI measurements were taken for each sample and mean HAI was determined by the most frequently reported measure; in no case were all three measures different from each other. In season 2, two HAI measurements were taken for each sample and mean HAI for each subject was determined by geometric mean titer (GMT).

Logistic regressions determined the effect of vitamin D measured as a continuous variable and vitamin D deficiency on the odds of pre- and post-vaccination seroconversion and seroprotection, controlling for participant age, gender, and body mass index (BMI). Vitamin D deficiency was defined as <25 ng/mL; this cut-off was determined by Marshfield Labs, the clinical laboratories serving Marshfield Clinic, according to clinical decision values. Vitamin D deficiency was also assessed at levels of <15 ng/mL, <20 ng/mL and <30 ng/mL [19]. Pre-vaccination HAI titer levels were controlled for in outcomes of post-vaccination seroprotection or seroconversion, but not for pre-vaccination seroprotection. Due to differences in recruitment and data collection practices, data from each influenza season were analyzed separately. An alpha of 0.05 was considered to be statistically significant. Model fit statistics were calculated and assessed. All statistical analysis was done using SAS v. 9.2 TS (Cary, NC).

Table 1
Demographic and descriptive characteristics of the study population.

Year	Characteristic	Value	*n*
1	Age (mean ± SD)	64 ± 10 years	591
	Gender		
	Male	39%	233
	Female	61%	358
	BMI (mean ± SD)	29 ± 6 kg/m^2	425
	Vitamin D serostatus (mean ± SD)	31 ± 11 ng/mL	482
	Severely deficient (<10 ng/mL)	1%	6
	Moderately deficient (10–24 ng/mL)	28%	137
	Optimal range (25–80 ng/mL)	70%	337
	Possibly toxic (>80 ng/mL)	0%	2
2	Age (mean ± SD)	66 ± 10 years	509
	Gender		
	Male	38%	195
	Female	62%	314
	BMI (mean ± SD)	30 ± 7 kg/m^2	509
	Vitamin D serostatus (mean ± SD)	31 ± 10 ng/mL	506
	Severely deficient (<10 ng/mL)	1%	5
	Moderately deficient (10–24 ng/mL)	26%	133
	Optimal range (25–80 ng/mL)	73%	367
	Possibly toxic (>80 ng/mL)	0%	1

ng/mL = nanograms per milliliter; kg/m^2 = kilograms per meter squared; SD = standard deviation.

3. Results

A total of 591 participants in season 1 (2008–2009) and 512 participants in season 2 (2009–2010) were enrolled (Table 1). In season 1, the mean ± SD age was 64 ± 10 years old; 61% of participants were female; and the mean ± SD participant BMI was 29 ± 6 kg/m^2 (Table 1). In season 2, the mean ± SD age was 66 ± 10 years old; 62% of participants were female; and the mean ± SD BMI was 30 ± 7 kg/m^2 (Table 1). 33% of participants in year 1 and 20% of participants in year 2 seroconverted (defined as a ≥4-fold rise in HI titer from pre- to post-vaccination) to the seasonal H1N1 vaccine strains. 68% of participants in year 1 and 45% of respondents in year 2 seroconverted to the H3N2 vaccine strains; and 34% of participants in year 1 and 28% of participants in year 2 seroconverted to the influenza B vaccine strains (Table 2).

In unadjusted analyses, vitamin D measured as a continuous variable was not independently associated with the odds of pre- or post-vaccination seroprotection or seroconversion of any vaccine strain in season 1 or season 2 (data not shown). Vitamin D deficiency, assessed as a binary variable, was associated with increased odds of post-vaccination seroprotection for seasonal influenza A (H1N1) in season 1 (OR = 1.68, 95% CI = 1.13–2.49) but was not