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Vitamin E, vitamin A, and zinc status are not related to serologic response to influenza vaccine in older adults: an observational prospective cohort study☆

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ABSTRACT

It has been hypothesized that micronutrient levels play a role in the immune response to vaccination; however, population-level research on the association between micronutrient levels and immune response to influenza vaccination is needed. In this study, we hypothesized that decreasing levels of nutrients would be associated with decreased hemagglutination inhibition (HAI) responses to influenza vaccination. Therefore, the purpose of this study was to determine whether serum vitamin A, vitamin E, or zinc levels are associated with influenza vaccine response determined by HAI titer in adults 65 years or older. Participants in this study included 205 community-dwelling adults 65 years or older who resided in Marshfield, WI, USA, from fall 2008 through spring 2009. Participants received trivalent influenza vaccine and donated blood samples before and 21 to 28 days after vaccination. Prevaccination levels of serum retinol, α-tocopherol, and zinc as well as prevaccination and postvaccination HAI titer levels were measured. No participants were vitamin A or vitamin E deficient; 20% had low serum zinc levels (<70 μg/dL). Continuous variables and categorical quartiles coding for vitamin A, vitamin E, and zinc levels were not related to prevaccination or postvaccination seroprotection or seroconversion for any of the vaccine components (influenza A [H1N1], A [H3N2], or B), after adjusting for age, sex, body mass index, and prevaccination HAI geometric mean titer. In conclusion, our study population showed no association between variations in levels of serum vitamin A, vitamin E, or zinc and influenza vaccine response as measured by HAI in adults older than 65 years. Thus, associations between micronutrients and other measures of vaccine response, such as cell-mediated immune parameters, should also be explored.

Abbreviations: BMI, body mass index; CI, confidence interval; GMT, geometric mean titer; HAI, hemagglutination inhibition; NHANES III, National Health and Nutrition Examination Survey III; OR, odds ratio; SD, standard deviation.

☆ The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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1. Introduction

Owing to the increase in average life expectancy in the last century, the proportion of the world population older than 65 years has increased greatly and will continue to increase [1]. This population of older adults has an increased risk of contracting infectious diseases and taking longer to clear those diseases [2], a phenomenon termed *immunosenescence* [3]. This effect is especially of concern with regard to respiratory illnesses because it is estimated that people older than 65 years account for most deaths and hospitalizations from influenza in the United States [2,4].

In older populations with increased risk of infection and longer disease clearance times, prevention is critical [2]. Vaccines are well suited to this task; influenza vaccines, for example, have been recommended by the World Health Organization [5] and the US Centers for Disease Control and Prevention [6] to reduce illness among the elderly. However, in addition to being at a higher risk for infectious disease complications, the immunologic response to vaccinations also declines in older populations [7]. Furthermore, the proportion of community-dwelling adults older than 65 years who receive the influenza vaccine may be healthier than those who are not vaccinated [8], meaning that the population most at risk and with a worse initial health status is the least likely to seek vaccination.

Variation in nutritional status (especially micronutrient status) is also apparent with increasing age [9]. Older populations have different nutritional requirements than the general adult population [10] and are at greater risk for both micronutrient and macronutrient deficiencies [11]. This is of special concern because evidence has shown that serum levels of vitamins [9] and minerals [12] can have an effect on the actions of the immune system and inflammatory response.

Although decreased vaccine response and increased nutritional deficiencies in the elderly have been separately documented, relatively little research has been devoted to investigating the concurrence of micronutrient deficiency and suboptimal vaccine response in older adults. Older adults supplemented with 200 mg/d of vitamin E have been shown to have a 6-fold greater antibody titer to hepatitis B compared with control subjects [13]. However, in 2 separate studies, influenza vaccine response was not improved by micronutrient supplementation providing the reference nutrient intake for all vitamins and trace elements [14] or by zinc supplementation alone [15].

In this study, we hypothesized that decreasing levels of vitamin A (retinol), vitamin E (α-tocopherol), and zinc would be associated with decreased hemagglutination inhibition (HAI) responses to influenza vaccination. Thus, we sought to determine the association between vitamin A (retinol), vitamin E (α-tocopherol), and zinc and the response to influenza vaccine as measured by HAI titer in an independently living population of individuals older than 65 years.

2. Methods and materials

2.1. Subjects and data collection

Research participants were recruited from September through October 2008 by sending letters to men and women 65 years or older who had received an influenza vaccine the year prior (fall of 2007) in Marshfield, WI, USA [16]. Potential participants were recruited from individuals who had previously received influenza vaccine because of the increased ease of contact as well as an increased likelihood of accepting the requirement to receive an influenza vaccine during the study year. Individuals were then contacted by telephone to assess interest in the study and schedule study visits. At baseline visits, which occurred in October and November 2008, an influenza vaccination (trivalent inactivated vaccine comprised influenza A/Brisbane/10/2007 [H3N2], influenza A/Brisbane/59/2007 [H1N1], and influenza B/Florida/4/2006 [B] virus strains) was administered by their primary caregivers, a special vaccine clinic, or trained study staff. All participants donated serum before and 21 to 28 days after vaccination. All participants provided informed consent before study enrollment, and all study procedures were reviewed and approved by the Marshfield Clinic Institutional Review Board (initial approval provided September 23, 2008).

2.2. Laboratory methods

Blood draws were performed on participants after a 12-hour fast by trained phlebotomists at the Marshfield Clinic Research Foundation and were processed. Blood was drawn into a tube without anticoagulant and left at room temperature for between 30 minutes and 2 hours. The samples were then centrifuged at 3000 rpm for 10 minutes at 4°C, aliquoted, and stored at –80°C. Hemagglutination inhibition testing was performed by Focus Diagnostics Inc (Cypress, CA, USA) [16]. For micronutrient assays, samples were collected in trace metal–free tubes (Becton Dickinson, Franklin Lakes, NJ, USA) and shielded from light. Samples were allowed to clot at room temperature for approximately 15 minutes and then were centrifuged at 2800 rpm for 15 minutes at 4°C. Aliquots of serum were stored upright at –80°C and shipped to the Nutrition Evaluation Laboratory, JM USDA Human Nutrition Research Center on Aging at Tufts University (Boston, MA, USA), for micronutrient assays. Serum retinol and tocopherol were measured by a modified high-performance liquid chromatography method of Bieri et al [17]. Serum zinc was measured by atomic absorption spectroscopy [18]. Aliquots of serum samples collected in serum separator tubes (Becton Dickinson) were shipped to Focus Diagnostics for HAI assays using protocols and reagents provided by the Centers for Disease Control and Prevention's Influenza Division.

2.3. Statistical analyses

Seroprotection was defined as having a geometric mean HAI titer of greater than or equal to 1:40; *seroconversion* was defined as a 4-fold or greater increase in geometric mean HAI titer level from prevaccination to postvaccination levels [19]. Geometric means of titers (GMTs) were calculated from 3 measurements each of prevaccination and postvaccination antibody titer levels of each of the 3 vaccine virus strains. *Vitamin A deficiency* was defined as less than 30 μg/dL; *vitamin E deficiency* was defined as less than 500 μg/dL; and *low serum zinc level* was defined as less than 70 μg/dL [18,20,21].