Effect of a Complete Nutritional Supplement on Antibody Response to Influenza Vaccine in Elderly People

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Background. The impact of influenza infection on morbidity and mortality in the elderly population can be severe. Influenza vaccination is not very effective in this age group, which is potentially related to impaired nutritional status. We investigated the effect of a 7-month nutritional supplementation on antibody response to influenza vaccine in elderly people.

Methods. Nineteen subjects aged 65 years and older with a body mass index of 25 kg/m² or less were studied. Subjects received a complete liquid nutrition supplement containing energy, vitamins, and minerals, including enhanced levels of antioxidants or noncaloric placebo for 7 months. Antibody titers to influenza strains A/Sydney/5/97 (SY), A/Beijing/262/95 (BE), and B/Yamanashi/166/98 (YA) before and 28 days after vaccination were measured. Age, gender, weight, height, serum albumin, serum prealbumin, hemoglobin, and serum vitamin E at baseline were registered.

Results. Mean fold increase upon vaccination for SY was significantly larger in the supplement group (2.76 ± 0.66) compared to the placebo group (1.91 ± 0.66). These differences were not observed for YA (1.73 ± 0.31 vs 1.19 ± 0.18) and BE (4.40 ± 2.63 vs 5.76 ± 3.34). For all three strains, there was no significant difference between groups in protective antibody levels (HI titer ≥40) after vaccination.

Conclusions. We conclude that provision of a complete liquid nutrition supplement including enhanced levels of antioxidants may have a beneficial effect on antibody response to influenza vaccination in the elderly population. Further confirmation of these findings and their clinical consequences should be the subject of a larger study.

The impact of influenza infection on morbidity and mortality in the elderly population can be severe. Therefore, vaccination of elderly people (and other risk groups) is recommended. However, influenza vaccination has limited effectiveness in this age group (reviewed by Webster [1]) due to the fact that vaccination does not always result in protective serum antibody titers. An explanation for this is that, with aging, there is a decreased function of the immune system, mainly related to a decline in T-cell-mediated immunity. This is a multifactorial phenomenon affecting the number of T-cells, T-cell subset composition, and biological functions including lymphocyte proliferation and cytokine production (2). A strong correlation exists between the serum hemagglutination-inhibiting (HI) antibody titers to influenza viruses and clinical protection against infection (3). In healthy, well-nourished elderly people, only a small decline in immune function with aging is observed (4), which may mean that impaired immune function in elders is potentially related to comorbidity and/or impaired nutritional status. Therefore, it may be possible to improve the antibody response after influenza vaccination by nutritional intervention and reduce influenza-related morbidity and mortality.

The effect of a variety of nutritional supplements on antibody response to influenza vaccine has previously been investigated (5–10). Supplements contained either vitamins (7), minerals (9), or both (5,6,10), or were in the form of a complete liquid nutrition supplement (8). Most studies were performed either with elderly people living in nursing homes or long-stay hospital wards (7–10). Only two studies have been performed with noninstitutionalized elders (5,6). In some studies, positive effects were found (5,6,8,10), whereas other studies did not reveal effects on antibody response to influenza vaccination (7,9). It is of interest that, in the studies describing positive effects on the antibody response, a combination of nutrients was used. It seems that a combination of vitamins and minerals or a complete liquid nutrition supplement has the highest potential to improve the antibody response to influenza vaccination.

We, therefore, investigated the effect of a 7-month nutritional supplementation with a liquid nutrition supplement with enhanced levels of antioxidants on the HI antibody response to influenza vaccine in residents of homes for elderly people.

Methods
This randomized, double-blind, placebo-controlled study was part of a larger study performed from May through November 1999. Subjects aged 65 years or older with a body mass index (BMI; weight/height²) ≤25 were eligible to participate. Nineteen elderly people of this larger study (10...
supplement, nine placebo) could be included in the substudy as they consented to both influenza vaccination and blood draw and had adequate compliance with the supplement. The study was approved by the institutional review board of Wageningen University, and all subjects gave informed consent.

Subjects received nutritional supplementation with a supplement containing between 30 and 160% of the United States recommended daily allowance of vitamins and minerals, with enhanced levels of antioxidants and 250 kcal energy twice daily for 7 months. Per 100 ml, the supplement included 100 kcal (0.42 MJ), 3.5 g protein, 4.5 g fat, 11.4 g carbohydrates, 1.8 g fiber, 32 mg Na, 220 mg K, 16 mg Cl, 160 mg Ca, 160 mg P, 40 mg Mg, 3.6 mg Fe, 7.2 mg Zn, 1.2 mg Cu, 1.6 mg Mn, 0.3 mg F, 16 µg Mo, 34 µg Se, 14 µg Cr, 60 µg I, 96 µg RE vitamin A, 1.2 mg carotenoids, 100 mg vitamin C, 5.2 µg vitamin D, 28 µg-α-TE vitamin E, 32 µg vitamin K, 0.75 mg vitamin B1, 0.75 mg vitamin B2, 5.6 mg NE niacin, 1.8 mg pantothenic acid, 1 mg vitamin B6, 192 µg folic acid, 2.1 µg vitamin B12, 28 µg biotin, 1.2 mg coenzyme Q10, and 7.6 mg flavonoids. Influenza vaccine (Influvac®99, containing vaccine strains A/Sydney/5/97[H3N2] [SY], A/Beijing/262/95[H1N1] [BE], and B/Beijing/184/93-like [BYamanashi/166/98] [YA]) was administered in October, 6 months after start of the nutritional intervention. A fasting blood sample was taken after 6 months of supplementation immediately prior to vaccination and 1 month after vaccination (11). Antibody response to each strain was measured in serum by hemagglutination inhibition (HI) test following standard procedures using turkey erythrocytes and four HA-units of the virus (12,13) at key erythrocytes and four HA-units of the virus (12,13) at 2.4% hemagglutination. Antibody titers specific for the three vaccine strains were measured by hemagglutination inhibition (HI) test following standard procedures using turkey erythrocytes and four HA-units of the virus (12,13) and 4% hemagglutination.

RESULTS

Table 1 reports baseline characteristics of the study participants. No differences between groups were observed in baseline parameters.

Antibody titers specific for the three vaccine strains after vaccination for placebo and supplement group before and after vaccination are given in Figure 1. Before vaccination, titers for BE were lower in the placebo than in the supple-

Table 1. Baseline Characteristics of Elderly Study Participants (Mean ± SD)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>84 ± 8</td>
</tr>
<tr>
<td>Male, %</td>
<td>42</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>22.3 ± 2.1</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>38 ± 4</td>
</tr>
<tr>
<td>Prealbumin (mg/l)</td>
<td>0.24 ± 0.06</td>
</tr>
<tr>
<td>Hemoglobin (g/l)</td>
<td>189 ± 25</td>
</tr>
<tr>
<td>Vitamin E (µmol/l)</td>
<td>26 ± 8</td>
</tr>
<tr>
<td>No. of Medications</td>
<td>2.8 ± 3.0</td>
</tr>
<tr>
<td>Chronic Diseases (%)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>53</td>
</tr>
<tr>
<td>Joint</td>
<td>21</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>16</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>16</td>
</tr>
<tr>
<td>Previous Vaccination (no.)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: BMI = body mass index.
*Weight/height².

Figure 1. Differences in mean titers (ln(titer) ± SD) for the influenza strains A/Sydney/5/97 (SY), A/Beijing/262/95 (BE) and B/Yamanashi/166/98 (YA) for placebo and supplement groups after vaccination in elderly people (p values for t test of changes between groups).
nation between treatment groups. The mean fold increase was significantly larger in the supplement group for SY ($p = .048$) but not for BE ($p = .780$) and YA ($p = .991$). A fourfold rise in titer, which is a criterion for an adequate effect of vaccination, could be detected only in a few subjects (SY: one placebo, one supplement; BE: one placebo, one supplement, YA: one supplement).

**DISCUSSION**

We have described that increased rises in influenza vaccine-induced antibody titer against two of the three influenza vaccine strains after nutritional supplementation. No significant differences in the number of protected individuals were observed between the supplement and placebo groups.

This report contains a per-protocol analysis of subjects who did not drop out of the larger study and who had adequate compliance with the supplementation for 7 months. This may have induced a selection bias leading to exclusion of subjects who were more frail (i.e., did not feel up to blood draw or vaccination or had intercurrent illness that led to cessation of participation in the trial). This observation is sustained by the fact that baseline characteristics of the subjects did not reveal a status of severe undernourishment. As a consequence, stronger effects may have been observed if a more frail and undernourished population had been studied. The high prevalence of adequate titers before vaccination reduced the potential for finding effects of supplementation. Explanations for this could be a study group without impaired antibody response or the vaccine composition for the study year, containing very similar strains to previous years, which led to high prevaccination antibody levels. The reason for the relatively small (50%) titer increases after vaccination in our study may be the fact that, in the previous year, a similar cocktail of strains was used. However, specifically for YA, the level of protection was largely adequate before vaccination. A bias in our results due to influenza infection circulating in the community cannot be expected, as no such epidemic was reported at the time of the study.

As the influenza vaccination substudy was dependent on the season of completion of the trial, we could study only a limited number of participants. The calculated required number of subjects per group needed for significance based on the observed effect sizes was 33, 25, and 85 for SY, YA, and BE, respectively.

The increase in titer rises found in our study was relatively small compared to studies with nutritional supplementation by Chandra and Puri (5,6). They used a supplement containing a range of micronutrients in levels comparable to our study and reported a fourfold increase in titer for a larger number of subjects in the supplemented group compared to the placebo group and an increase in geometric mean antibody titer (5). In a later study (6), the same authors found an increase in geometric mean titer after supplementation. However, Lesourd and colleagues (8) reported an increase of about 30% in antibody titer, which is similar to our study. Mean fold increases reported by Girodon and colleagues (10) after supplementation were even smaller than in our study (an increase of about 20%). In their study, the number of protected individuals remained low even after intervention, and the number of protected individuals before vaccination was not reported. In general, the data of studies on nutritional supplementation often report different calculations of titers, which complicates comparisons.

We conclude that provision of a complete liquid nutrition supplement containing enhanced levels of antioxidants may have a beneficial effect on antibody response to some influenza vaccine strains in the elderly population and, therefore, may improve the induction of protective immunity. Further confirmation of these findings and their clinical consequences should be the subject of a larger study.

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**REFERENCES**


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**Table 2. Mean Fold Increase in Antibody Titers and Number of Protected Individuals (Titer ≥40) Before and After Vaccination in Elderly People**

<table>
<thead>
<tr>
<th>Group</th>
<th>MFI Before</th>
<th>MFI After</th>
<th>Protected</th>
<th>Protective Antibody Titer Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo ($n = 9$)</td>
<td>1.91 ± 0.66</td>
<td>8</td>
<td>8</td>
<td>5.76 ± 3.34</td>
</tr>
<tr>
<td>Supplement ($n = 10$)</td>
<td>2.76 ± 0.66*</td>
<td>6</td>
<td>9</td>
<td>4.40 ± 2.63</td>
</tr>
</tbody>
</table>

Note: MFI = mean fold increase.

*p < .05 versus placebo group.

A/Sydney/5/97 (SY) A/Beijing/262/95 (BE) B/Yamanashi/166/98 (YA)


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