Orthostatic hypotension is a common condition in older people and increases exponentially with age. Among community-dwelling subjects aged >65 years, its prevalence is ≈ 20%, and in people aged >75 years, it is as high as 30%. Orthostatic hypotension is associated with significant cardiovascular morbidities, falls, fractures, and a higher mortality risk. Many factors are related to this condition, including age-associated changes in blood pressure regulation, rapid posture changes, autonomic insufficiency, cardiovascular diseases, or any acute illnesses involving fluid loss. Essential hypertension develops in ≈ 60% of individuals by the age of 60, but its characteristics in older people differ from those in the middle-aged, being associated more often with complications in the older-aged. Hypertension is one of the most common known risk factors for orthostatic hypotension in the elderly persons.

Among the less studied risk factors for this orthostatic hypotension, poor vitamin D status is increasingly attracting interest because of recent research showing a strong relationship between serum 25-hydroxyvitamin D (25OHD) and blood pressure. 25OHD levels have been correlated with both the prevalence and the incidence of hypertension, and low 25OHD levels were found to be associated with higher diastolic and systolic blood pressure levels. Vitamin D receptors are found in endothelial cells, suggesting a possible role for this vitamin in modulating vascular response during orthostatism. McCarron et al found a significant difference in 25OHD levels between individuals with and without orthostatic hypotension and suggested a possible role for vitamin D status in the pathogenesis of this condition in old people. Research on this association in the elderly persons is lacking, however, and although

**Abstract**—Interest in the association between serum 25-hydroxyvitamin D (25OHD) and blood pressure has increased because recent research showed a close relationship between them, but there is still little information on the possible association between 25OHD and orthostatic hypotension. The aim of this study was to explore the relationship of 25OHD levels with any presence of orthostatic hypotension in a large group of older people. This study was part of the Progetto Veneto Anziani (Pro.V.A.), an Italian population-based cohort study involving people aged >65 years. Orthostatic hypotension was identified as a drop of ≤20 mm Hg in systolic or ≤10 mm Hg in diastolic blood pressure <3 minutes of orthostatism. Orthostatic hypotension was identified in 32.2% of the sample. The prevalence of orthostatic hypotension was higher in individuals with 25OHD levels <50 nmol/L, but this trend was not significant (P=0.13). Individuals who had orthostatic hypotension had significantly lower 25OHD levels than those who did not (75.0±51.4 versus 82.6±54.0 nmol/L; P<0.0001). On logistic regression analysis, the greater likelihood of individuals with lower 25OHD levels having orthostatic hypotension was no longer statistically significant after adjusting for potential confounders (odds ratio, 1.08; 95% confidence interval, 0.77–1.51; P=0.67 for people with 25OHD levels ≤25 nmol/L; odds ratio, 1.01; 95% confidence interval, 0.78–1.32; P=0.92 for those with 25OHD levels between 25 and 50 nmol/L). In conclusion, vitamin D is not significantly associated with any orthostatic hypotension in older people.

**Key Words:** aged ■ hypertension ■ hypotension, orthostatic ■ vitamin D
the literature on younger people points to an association between these 2 factors, it has often consisted of studies on small samples.12

Based on the above considerations, we hypothesized that low vitamin D levels might be associated with orthostatic hypotension in older people. The aim of this study was to examine the relationship between 25OHD levels and any presence of orthostatic hypotension in a large group of elderly men and women, controlling for potential confounders typically related to age.

Methods

Data Source and Subjects

The data for this analysis came from the Progetto Veneto Anziani (Pro.V.A.), an observational cohort study on the Italian population aged 265 years. The study population included 3099 age- and sex-stratified white participants (1245 men and 1854 women), who were randomly selected between 1995 and 1997 using a multistage stratified method. Sampling procedures and data collection methods have been described elsewhere.13 Trained physicians and nurses examined participants at the local clinics. This cross-sectional study concerns the information on the prevalence of orthostatic hypotension and related hemodynamic parameters recorded at the baseline. Among the 3099 individuals enrolled in the study, details of their 25OHD levels at enrollment were lacking for 270 (8.7%). Another 37 participants with a diagnosis of Parkinson disease, 30 of them on oral vitamin D supplementation, were ruled out and so were 122 participants whose baseline hemodynamic parameters were missing. The sample considered in the present study thus comprised 2640 participants.

The ethical committees of Padova University and of the Veneto Region’s Local Health Units Nos. 15 and 18 approved the study protocol, and participants gave their written informed consent.

Lifestyle Factors

Participants were examined at the city hospitals by trained physicians and nurses. Information was collected on their physical activities, disabilities, smoking status, and the number and types of drugs they were taking during a face-to-face interview. Regular physical activity was defined as ≥4 hours per week in the previous month of at least moderate physical activity (brisk walking, biking, gardening, dancing, or other physical exercise). Disability was assessed from participants' abilities in activities of daily living (bathing, transferring, dressing, eating, toileting, and continence). Smoking status was categorized as current versus never/former (for ≤1 year in the past) smokers. Body weight and height were measured by trained physicians, and the body mass index (kg/m²) was calculated. Any diseases at the baseline were assessed by the clinical information collected for each participant, including disease history, self-reported symptoms (using standardized questionnaires), medical and hospital records, blood tests, and a physical examination, as described elsewhere.14 The number and type of drugs currently taken were recorded at face-to-face interviews with participants and their relatives, also checking the medical documentation available. Previous major diseases recorded included any of the following: cardiovascular diseases (congestive heart failure, angina and myocardial infarction, stroke, or peripheral artery disease), diabetes mellitus, cancer, and hypertension. Cognitive function was assessed by administering the 30-item Mini Mental State Examination, and a score <24 was defined as cognitive impairment.

Definition of Orthostatic Hypotension

Every blood pressure measurement was taken by a trained nurse. The midpoint of the right upper arm was determined by measuring the length from the tip of the shoulder to the tip of the elbow, and the length was divided by 2. The tape was wrapped around the straightened arm at that midpoint and the tape inspected to ensure it was neither too tight nor too loose. The measurement was recorded to the nearest 0.1 cm and repeated 2 times if the measurements were <0.8 cm. The cuff was chosen based on this circumference among little (<24 cm), normal (24–32 cm), and big (33–41 cm) size. Clinostatic blood pressure was measured in both arms 3x with 30-second intervals between them with a mercury sphygmomanometer (Erkameter 300). Participants were in the lying position, and the highest value was taken for reference. Orthostatic blood pressure was then measured after 1 and 3 minutes of orthostatism. Heart rate was assessed from the radial pulse in both situations. According to the guidelines of the consensus committee of the American Autonomic Society and the American Academy of Neurology, orthostatic hypotension was defined as a drop of ≤20 mm Hg in systolic blood pressure, or ≤10 mm Hg in diastolic blood pressure <3 minutes of standing up.14

Laboratory Data

Serum 25OHD levels were measured by radioimmunoassay (RIA kit; DiaSorin). The intra-assay and interassay coefficients of variations for 25OHD were 8.1% and 10.2%, respectively. The value is given in nmol/L. In this work, we divided the sample using 75, 50, and 25 nmol/L of 25OHD as cut-offs indicative of mild, moderate, and severe vitamin D deficiency.15 Serum intact parathormone levels were measured using a 2-site immunoradiometric assay (N-tact PTHSP; DiaSorin): the intra-assay and interassay coefficients of variation for parathormone were 3.0% and 5.5%, respectively. Season of blood collection was defined as winter, spring, summer, or autumn.

Statistical Analyses

Participants' characteristics were summarized using mean±SD for continuous variables, and counts and percentages for categorical variables. Means and proportions were compared between study participants according to their 25OHD levels: ≤25, from 25 to 50, from 50 to 75, and >75 nmol/L. For continuous variables, normal distributions were tested using the Shapiro–Wilks test. Age- and sex-adjusted P values for trends were calculated, checking the differences between the means of the covariates by 25OHD category using ANOVA. Tukey correction was applied. Differences in categorical variables were examined using the χ² test.

Multivariate logistic regression models were run using 25OHD categories as independent variables and orthostatic hypotension as the dependent variable. People with 25OHD levels >75 nmol/L were taken for reference. Known factors associated with 25OHD levels and orthostatic hypotension were examined for inclusion in the analyses as covariates, obtaining 2 models. Covariates were added sequentially to the logistic model to assess the associations at different adjustment levels. Model 1 included the covariates potentially influencing 25OHD levels, that is, age, sex, body mass index, physical activity level, activities of daily living score, and month of blood collection. In this analysis, month of blood collection was preferred because it better accounts for the inherent changes in 25OHD levels during the year compared with seasons. Model 2 included all variables considered in model 1 plus the factors that could influence any presence of orthostatic hypotension, that is, comorbidities such as cardiovascular diseases, cancer, hypertension, cognitive impairment, use of drugs associated with orthostatic hypotension (angiotensin-converting enzyme inhibitors, diuretics, β-blockers, calcium channel blockers, central antihypertensives, vasoconstrictors, nitrates, antidepressants, and benzodiazepines), diastolic and systolic blood pressure, and total number of drugs taken. Parathormone concentrations were also initially considered for inclusion in the analysis because they might act as intermediate factors of altered 25OHD levels, but they were subsequently removed from the models because of their high collinearity with 25OHD levels, as quantified by the variance inflation factor 3.59. Pearson correlations were
run on the sample as a whole and used to identify associations between 25OHD and clinostatic or orthostatic blood pressure values at 1 and 3 minutes.

All analyses were performed using SPSS 17.0 for Windows (SPSS Inc, Chicago, IL). All statistical tests were 2-tailed, and statistical significance was assumed for a \( P \) value <0.05.
Model 1 was adjusted for age, sex, body mass index, physical activity level, activities of daily living score, and month of blood collection. Model 2 was adjusted for the covariates in model 1 plus any presence of cardiovascular diseases, cancer, hypertension, β-blockers, calcium channel blockers, central antihypertensives, vasodilators, nitrates, antidepressants, benzodiazepines, which were significantly associated with orthostatic hypotension in the final model, the odds ratios (ORs) were no longer statistically significant (OR, 1.08; 95% confidence interval [CI], 0.77–1.51; P=0.67 for subjects with 25OHD levels ≤25 nmol/L; and OR, 1.01; 95% CI, 0.78–1.32; P=0.92 for those whose 25OHD levels were between 25 and 50 nmol/L). Adding parathormone serum levels in the model did not significantly change our findings, being the adjusted ORs (with 95% CI) of the 25OHD categories were as follows: 1.06 (0.75–1.52; P=0.85) for participants with 25OHD levels <25, 0.98 (0.75–1.28; P=0.74) for those with 25OHD levels between 25 and 50 nmol/L, and 0.98 (0.76–1.27; P=0.77) for those with 25OHD levels between 50 and 75 nmol/L. Joint results with 25OHD and parathormone did not substantially modify these results. As shown in Figure 2, the results of all our statistical analyses remained much the same after stratifying by sex or for use of antihypertensive medications.

Discussion

To our knowledge, this is the first study to explore the association between serum 25OHD levels and orthostatic hypotension in a large population of community-dwelling elderly people. Our findings identified no association between low vitamin D levels and orthostatic hypotension after adjusting for potential confounders (including serum parathormone levels) and after stratification for sex or use of antihypertensive medications. Low vitamin D status and orthostatic hypotension were both common conditions in our population, the former (defined as 25OHD levels <75 nmol/L) affecting 1 in 3 people in our sample, the latter 1 in 3. These findings are consistent with other studies on elderly people.1,16–20

Table 2. Adjusted OR (95% CI) for Orthostatic Hypotension by Baseline 25OHD Levels: The Pro.V.A. Study

<table>
<thead>
<tr>
<th>25OHD Categories</th>
<th>Crude OR (95% CI)</th>
<th>P Value</th>
<th>Model 1 OR (95% CI)</th>
<th>P Value</th>
<th>Model 2 OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;75 nmol/L</td>
<td>1.15 (0.93–1.42)</td>
<td>0.21</td>
<td>0.97 (0.70–1.24)</td>
<td>0.92</td>
<td>0.99 (0.77–1.28)</td>
<td>0.97</td>
</tr>
<tr>
<td>50–75 nmol/L</td>
<td>1.34 (1.08–1.66)</td>
<td>0.007</td>
<td>1.01 (0.81–1.21)</td>
<td>0.81</td>
<td>1.01 (0.78–1.32)</td>
<td>0.92</td>
</tr>
<tr>
<td>≤25 nmol/L</td>
<td>1.62 (1.23–2.13)</td>
<td>0.001</td>
<td>1.08 (0.74–1.42)</td>
<td>0.82</td>
<td>1.08 (0.77–1.51)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Unless otherwise specified, data are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Model 1 was adjusted for age, sex, body mass index, physical activity level, activities of daily living score, and month of blood collection. Model 2 was adjusted for the covariates in model 1 plus any presence of cardiovascular diseases, cancer, hypertension, cognitive impairment, use of drugs associated with orthostatic hypotension (angiotensin-converting enzyme inhibitors, diuretics, β-blockers, calcium channel blockers, central antihypertensives, vasodilators, nitrates, antidepressants, benzodiazepines), diastolic and systolic blood pressure, and number of drugs taken. 25OHD indicates serum 25-hydroxyvitamin D; and Pro.V.A., Progetto Veneto Anziani.
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azepines), and they had more comorbidities than participants (particularly antihypertensives, antidepressants, and benzodiazepines), and they had more comorbidities than participants with higher 25OHD levels. In addition, there were no differences in clinostatic and orthostatic hemodynamic parameters between the various 25OHD groups. Taken together, these findings indicate that the association between low 25OHD values and orthostatic hypotension is more likely to relate to the fact that individuals with a poor vitamin D status also had more of the factors known to be associated with orthostatic hypotension.

Our findings are consistent with a recent work by McCarroll et al demonstrating that 25OHD levels were significantly lower in patients with orthostatic hypotension, but these participants tended to be older, women, and more disabled, they used a larger number of drugs (particularly antihypertensives, antidepressants, and benzodiazepines), and they had more comorbidities than participants with higher 25OHD levels. In addition, there were no differences in clinostatic and orthostatic hemodynamic parameters between the various 25OHD groups. Taken together, these findings indicate that the association between low 25OHD values and orthostatic hypotension is more likely to relate to the fact that individuals with a poor vitamin D status also had more of the factors known to be associated with orthostatic hypotension.

Our study has its strengths and limitations. The main limitation was the cross-sectional design, which prevents any cause–effect relationship from coming to light. Another limitation lies in that we only measured orthostatic hemodynamic parameters at 3 minutes, whereas many cases of orthostatic hypotension in people aged >65 years are known to develop later on. The main strengths of our study include the large population considered, the use of 25OHD (which reflects total body stores of vitamin D better than other indicators), and the numerous potential confounders analyzed (including blood sampling season, use of drugs, and diseases potentially associated with orthostatic hypotension).

Perspective
Judging from our findings, serum 25OHD levels are not significantly associated with any presence of orthostatic hypotension in older people. Because poor vitamin D status might be considered a biomarker of frailty in the elderly persons, and frailty is strongly associated with orthostatic hypotension, the low vitamin D levels identified were probably simply part of a picture of frailty syndrome rather than having any biological significance per se. Nonetheless, given the high prevalence of low 25OHD levels and orthostatic hypotension in old people, further longitudinal and randomized controlled trials are warranted to further explore this association.

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Disclosures
None.

References
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Novelty and Significance

What Is New?

The literature about the association between vitamin D and hypertension in older people is wide, but no study about the relationship between vitamin D and orthostatic hypotension is available.

What Is Relevant?

• Our study confirmed that both orthostatic hypotension and hypovitaminosis D are 2 common characteristics of community-dwelling people aged >65 years.

• Even if the association between these 2 conditions exists, this is weak because it disappeared after adjustment for the potential confounders.

Summary

In old people, the association between hypovitaminosis D status, hypertension, and other cardiovascular diseases is known, but our study suggests that the link between hypovitaminosis D and orthostatic hypotension is not pathophysiological, but a result of the features shared by these 2 conditions. Other longitudinal and randomized trials are needed to check our finding.
Serum 25-Hydroxyvitamin D and Orthostatic Hypotension in Old People: The Pro.V.A. Study
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