Dissociation between Low Vitamin D Level and Hypertension in Coal Mine Workers: Evidence from the Kailuan Study

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Abstract

Objective The aim of this study was to evaluate the vitamin D status and the relationship between the vitamin D status and hypertension in a relatively large cohort in northern China.

Methods This study was a part of the Kailuan study, consisting of 3,788 coal mine workers (including 2,532 underground workers and 1,256 surface workers) who received periodic health examinations between September 13, 2012 and December 24, 2012. Information on demographic factors, personal history and medical history were collected. The height, weight, blood pressure and serum 25-hydroxyvitamin D [25(OH)D] level of each patient were measured.

Results The mean 25(OH)D level in this cohort was 21.73±15.82 nmol/L. The number (%) of patients with vitamin D deficiency, insufficiency, inadequacy and sufficiency were 2,509 (66.24%), 1,051 (27.75%), 201 (5.31%) and 27 (0.71%), respectively. In all the participants, after adjusting for the age, salt intake, physical activity, smoking status, alcohol drinking status, work type, work environment, body mass index, diabetes and hyperlipidemia, the odds ratios for hypertension with 25(OH)D level \( < 50\), \( 25-50 \) and \( < 25 \) nmol/L were 1.00 (reference), 1.44 (95% CI, 0.99-2.11) and 1.39 (95% CI, 0.97-1.99), respectively. Logistic regression models to evaluate the odds ratios and 95% CIs of hypertension for each quintile of the 25(OH)D level did not determine significant associations between the vitamin D status and hypertension. No significant associations were found in the underground workers or in the surface workers.

Conclusion There was a high proportion of coal mine workers with vitamin D deficiency and insufficiency in Kailuan. However, no significant association between low vitamin D levels and hypertension was found in this cohort. Further investigations are needed to determine the relationship between vitamin D levels and hypertension.

Key words: vitamin D deficiency, 25-hydroxyvitamin D, hypertension, Chinese

Introduction

The role of vitamin D as a key regulatory element in bone mineralization and musculoskeletal health is well established (1, 2). Vitamin D receptors are present in multiple tissue types, which has resulted in the exploration of the role of vitamin D in many other organs and tissues throughout the body (1, 3). Epidemiologically, although very severe vitamin D deficiency is no longer prevalent in recent decades, the deficiency and insufficiency, as well as the consequences of suboptimal vitamin D status have not received enough attention. Recent evidence has suggested that 25-hydroxyvitamin D[25(OH)D], widely accepted as the best biomarker of the vitamin D status, is inversely associated with cardiovascular and metabolic risk factors (4-9), though
the underlying mechanism has not been fully elucidated. Epidemiologic studies have linked vitamin D deficiency to the risk of hypertension in some Western populations (9-11). Given that both vitamin D deficiency and hypertension are global pandemics (12-14), whether vitamin D plays a role in the development of high blood pressure is of importance for the prevention of hypertension and hypertensive diseases. In mainland China, although there has been no national survey conducted to evaluate the overall vitamin D status, a recent review from scattered studies that measured circulating 25(OH)D levels revealed that vitamin D deficiency is widely prevalent in different age groups across the country (15).

Given the fact that (a) there is inconsistency in the previously reported relationship between vitamin D deficiency and hypertension (16, 17); (b) such investigation in Chinese populations is limited; and (c) there is reportedly ethnic differences in vitamin D metabolism between Eastern and Western populations (18, 19), the aim of the present investigation was to evaluate the vitamin D status and determine the correlation between the vitamin D status and hypertension in a relatively large cohort in northern China.

Materials and Methods

Study population

This study is a part of the Kailuan study which was designed to investigate the risk factors for chronic diseases such as stroke, hypertension, myocardial infarction, and cancers. The Kailuan study is a vocational cohort (n=101,510) consisting of the employees of the Kailuan Coal Group in Tangshan City (latitude 39.36° north). The employees of the Kailuan Coal Group received periodic health examinations. We randomly selected one of the 11 coal mines, and the current workers in the coal mine were enrolled in the study. After the exclusion of individuals with recent history of acute illness, any clinical evidence of cancer, secondary hypertension, liver cirrhosis or other chronic liver diseases, the final sample group consisted of 3,788 current workers (including 2,532 underground workers and 1,256 surface workers). Only 24 women were included in the surface worker group. The underground workers were defined as the staff members who worked in an underground coal mine for approximately 40 hours per week. The surface workers were defined as the staff members working on the ground) who received periodic health examinations between September 13, 2012 and December 24, 2012. The protocol and consent forms were approved by the ethics committees in the institution. Written informed consent was obtained from all participants.

General data collection

Information on demographic factors (e.g., gender, age, occupation), personal history (salt intake, physical activity, smoking status, alcohol drinking status), and medical history (medications prescribed by physicians, history of hypertension, cancer, liver diseases, diabetes, hyperlipidemia and other diseases) were collected by trained investigators who conducted face-to-face interviews to verify the accuracy of the information and collected the questionnaires on the examination day. Inactive, moderately active and very active physical activities were defined as performing weekly physical activities less than 3 times, 3-5 times and more than 5 times, respectively. Exercise per time was defined as vigorous-intensity aerobic activity for a minimum of 20 minutes or moderate-intensity aerobic activity for a minimum of 30 minutes (20). The salt intake was classified as low, medium, or high according to the responses to questions related to salt preferences, which is equivalent to the intake of salt less than 10 g/day, 10-20 g/day and more than 20 g/day, respectively (21, 22). Diabetes was defined as a history of using hypoglycemic agents, a clinical diagnosis or a fasting blood sugar of ≥7 mmol/L (23). Hyperlipidemia was defined as having either any history of cholesterol-lowering treatment, a clinical diagnosis, total cholesterol ≥220 mg/dL or low-density lipoprotein (LDL) cholesterol ≥130 mg/dL (24).

Weight and height were measured without outdoor clothing and shoes. The body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Blood pressure was measured two times for each subject according to a standardized protocol described previously (25). The first and fifth Korotkoff sounds were used to define the systolic and diastolic pressure, respectively. When the two readings differed by ≤5 mmHg, the mean value was recorded; otherwise an additional measurement was taken and the average of the three readings was used.

Laboratory measurements

Fasting (8-12h) blood samples were collected and centrifuged within one hour. The fasting serum glucose, total cholesterol and LDL cholesterol levels were measured using the Hitachi Modular 7600 Autoanalyzer (Hitachi, Tokyo, Japan). The serum samples for the determination of serum 25(OH)D were stored at -20°C until analyzed. Serum 25(OH)D concentration was determined via a direct enzyme immunoassay (25(OH)D Direct ELISA Kit; Immunodiagnostik AG, Ben- shheim, Germany). The intra-assay and inter-assay coefficients of variation were both 7%. For the present analysis, a serum 25(OH)D level <25 nmol/L was defined as deficiency, levels ≥25 to <50 nmol/L as insufficiency, levels ≥50 to <75 nmol/L as inadequacy, and levels ≥75 nmol/L as sufficiency (26).

Definition of hypertension

Hypertension was diagnosed when the systolic blood pressure was ≥140 mmHg or diastolic blood pressure ≥90 mmHg on at least 3 different visits to the hospital or if the patient was taking antihypertensive agents.
Table 1. The Characteristics of the Study Participants according to the Serum 25(OH)D Level.

| Variables | The level of serum 25(OH)D, nmol/L (n=3,788) | F/X² | p  |
|-----------|---------------------------------------------|------|----|
| n(%)      | <25 | 25-50 | ≥50       |       |       |
| Underground mine worker, n(%) | 1,777(70.8) | 627(59.66) | 128(56.14) | 54.22 | <0.001 |
| Age, y | 41.2±9.9 | 40.86±10.07 | 42.61±10.2 | 2.85 | 0.058 |
| BMI, kg/m² | 25.3±3.3 | 25.24±3.23 | 24.58±3.92 | 5.1 | 0.006 |
| SBP, mmHg | 127.04±14.86 | 126.96±13.93 | 126.56±14.4 | 0.11 | 0.892 |
| DBP, mmHg | 81.95±8.58 | 81.97±8.2 | 81.75±7.56 | 0.07 | 0.936 |
| Total cholesterol, mg/dL | 102.07±35.76 | 85.27±31.75 | 79.92±29.41 | 115.04 | <0.001 |
| LDL, mg/dL | 5.7±1.53 | 5.69±1.51 | 5.75±1.4 | 0.17 | 0.848 |
| Hypertension, n(%) | 1,777(70.8) | 627(59.66) | 128(56.14) | 54.22 | <0.001 |
| Diabetes, n(%) | 217(5.73) | 79(7.52) | 15(6.58) | 2.12 | 0.347 |
| Hyperlipidemia, n(%) | 727(29) | 177(20.6) | 35(15.4) | 70.1 | <0.001 |
| Salt intake, n(%) | 681(27.14) | 266(25.31) | 49(21.49) | 5.61 | 0.231 |
| Physical activities, n(%) | 1,427(56.88) | 627(59.66) | 144(63.16) | 5.12 | 0.006 |
| Smoking status, n(%) | 1,110(44.24) | 391(37.2) | 79(34.65) | 22.4 | <0.001 |
| Work type, n(%) | 1,210(48.23) | 561(53.38) | 123(53.95) | 5.12 | 0.006 |

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, LDL: low-density lipoprotein, FBG: fasting blood sugar

Statistical analysis

The statistical package SPSS, version 17.0 (SPSS Inc., Chicago, USA) was used for all statistical analyses. A probability (p) value <0.05 (two-sided) was considered to be statistically significant. Continuous variables were presented as the mean values ± standard deviation (SD), and categorical variables were presented as the frequencies and percentages. Participants were examined by categories of serum 25(OH)D level using an ANOVA to compare the mean values or chi-square tests to compare the proportions of the baseline characteristics. Because the number of subjects with vitamin D sufficiency was relatively small, we divided all the subjects into three groups [≥50 nmol/L (as reference), 25-50 nmol/L, <25 nmol/L] according to the serum 25(OH)D level and used logistic regression models to evaluate the odds ratio (OR) and 95% confidence intervals (CI) of hypertension. To perform a sensitivity analysis, logistic regression models were also used to evaluate the ORs and 95% CIs of hypertension for each quintile of 25(OH)D compared with the highest quintile after adjusting for potential confounders.

Results

The mean age of the 3,788 men was 49.9±12.5 years and 1,067 (28.17%) participants were hypertensive. Antihypertensive therapy included the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers in 232 (21.7%) of the patients with hypertension, calcium channel blockers in 201 (18.8%) patients, diuretics in 165 (15.5%) patients, β-blockers in 7 (0.7%) patients, and α-blockers in 2 (0.2%) patients. Table 1 shows the characteristics of the study participants according to the serum 25(OH)D level. Subjects with lower 25(OH)D levels tended to be underground mine workers, have hyperlipidemia and consumed alcohol. The serum 25(OH)D level demonstrated a modest inverse association with the BMI and LDL. A higher proportion of subjects with lower 25(OH)D levels was engaged in mental work and were physically inactive.

Among our study participants, the mean 25(OH)D level was 21.73±15.82 nmol/L. The number (%) of subjects with vitamin D deficiency, insufficiency, inadequacy and sufficiency were 2,509 (66.24%), 1,051 (27.75%), 201 (5.31%) and 27 (0.71%), respectively. We examined the association between the 25(OH)D level and hypertension. The results of the multivariable regression analyses regarding the relationship between the 25(OH)D levels (3 groups) and hypertension are shown in Table 2. In all the participants, the 25(OH)D levels were inversely associated with hypertension after adjusting for age (Model 1), and the ORs for hypertension with 25(OH)D levels ≥50, 25-50 and <25 nmol/L were 1.00 (reference), 1.55 (95%CI, 1.09-2.22), and 1.57 (95%CI, 1.12-2.21), respectively. The 25(OH)D levels were not associated with hypertension after additionally adjusting for the
salt intake, physical activity, smoking status, alcohol drinking status, work type, work environment, BMI, diabetes and hyperlipidemia in Model 2, and the ORs for hypertension with 25(OH)D levels ≥50, 25-50 and <25 nmol/L were 1.00 (reference), 1.44 (95% CI, 0.99-2.11), and 1.39 (95% CI, 0.97-1.99), respectively. We further examined whether the different work environment affected the association between the 25(OH)D levels and hypertension. No significant associations were found between the underground workers and the surface workers. The ORs and 95% CIs of hypertension for each quintile of the 25(OH)D level are shown in Table 3. No significant associations between the 25(OH)D levels and hypertension were found.

**Table 2. Adjusted Odds Ratio of Having Hypertension according to the Serum 25(OH)D Levels (3 Groups).**

| 25(OH)D levels, nmol/L | quintile 1 | quintile 2 | quintile 3 | quintile 4 | quintile 5 | p trend |
|-------------------------|------------|------------|------------|------------|------------|--------|
| ≥50                     | 1.00       | 1.60       | 2.16       | 1.62       | 2.05       | 0.042  |
| 25-50                   | 1.00       | 1.44       | 2.23       | 1.72       | 2.81       | 0.105  |
| <25                     | 1.00       | 1.39       | 2.24       | 1.83       | 3.12       | 0.057  |

The main finding of the present study is the dissociation between a low vitamin D level and hypertension in a Chinese population, which is in contrast to most, but not all, observational studies conducted in Western countries. The data from the Third National Health and Nutrition Examination Survey (NHANES III) conducted in the United States demonstrated that the 25(OH)D levels were inversely associated with hypertension (5, 27). This inverse association is consistent with the findings from two other cross-sectional reports in Germany (10) and British adults (6) which were also performed in the general population, and several cohort studies (7, 11). A Mendelian randomization study also sug-

**Table 3. Adjusted Odds Ratio of Having Hypertension according to the Plasma 25(OH)D Levels (5 Quintiles).**

| Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 | p trend |
|------------|------------|------------|------------|------------|--------|
| ≥33.71     | 22.03-33.71| 14.34-22.03| 8.02-14.34 | ≤8.02      |        |
| 25(OH)D, nmol/L | 196(25.86) | 221(29.23) | 230(30.3)  | 214(28.27) | 206(27.18)| 0.342  |
| Model 1    | 1.00       | 1.09       | 1.22       | 1.06       | 1.06      | 0.765  |
| Model 2    | 1.00       | 1.06       | 1.19       | 0.91       | 0.95      | 0.427  |
| Hypertension, n(%) | 118(31.02) | 139(32.67) | 146(30.77) | 1.07(0.70-1.19) | 0.95(0.73-1.24) | 0.427 |
| 25(OH)D, nmol/L | 25-50     | 25.51-37.03| 17.34-25.51| 9.86-17.34 | ≤9.86     |        |
| Model 1    | 1.00       | 1.13       | 1.46       | 1.01       | 0.93      | 0.63   |
| Model 2    | 1.00       | 1.09       | 1.51       | 0.99       | 0.92      | 0.512  |
| Hypertension, n(%) | 118(23.27) | 121(21.75) | 121(21.62) | 1.00(0.71-1.67) | 0.92(0.58-1.46) | 0.512 |
| 25(OH)D, nmol/L | 25-50     | 25.51-37.03| 17.34-25.51| 9.86-17.34 | ≤9.86     |        |
| Model 1    | 1.00       | 1.20       | 1.13       | 1.26       | 1.10      | 0.499  |
| Model 2    | 1.00       | 1.12       | 1.07       | 1.12       | 0.98      | 0.852  |

**Discussion**

The main finding of the present study is the dissociation between a low vitamin D level and hypertension in a Chinese population, which is in contrast to most, but not all, observational studies conducted in Western countries. The data from the Third National Health and Nutrition Examination Survey (NHANES III) conducted in the United States demonstrated that the 25(OH)D levels were inversely associated with hypertension (5, 27). This inverse association is consistent with the findings from two other cross-sectional reports in Germany (10) and British adults (6) which were also performed in the general population, and several cohort studies (7, 11). A Mendelian randomization study also sug-
gested an inverse association between the vitamin D status and hypertension (28). However, in agreement with the present study, two large cross-sectional studies, the Amsterdam Longitudinal Aging Study and the Rancho-Bernardo Study, did not document a significant association (16, 17). To the best of our knowledge, there are a handful of studies that have focused on the relationship between vitamin D and hypertension in ethnic Chinese patients (29-31). In accordance with the present study, Li et al. found that the serum vitamin D levels were not independently associated with hypertension among 1,420 Chinese participants in Dali [25°N, mean serum 25(OH)D levels: 54.9 nmol/L] (29). In addition, Chan et al. found no significant association between the serum vitamin D level and blood pressure among 939 elderly Chinese men in Hong Kong [22°N, mean serum 25(OH)D levels: 77.9 nmol/L] (30). In contrast, an inverse association between the 25(OH)D levels and hypertension was found in the Shanghai Women’s and Men’s study [31°N, median 25(OH)D level: 34.7 nmol/L] (31). The inconsistency among the results of these Chinese studies may be partially due to differences in the study populations, geography and season.

There are several potential explanations for the lack of an association between vitamin D and hypertension observed in this study. First, the dissociation between the serum vitamin D levels and hypertension might be attributed to the relatively low levels of serum vitamin D in the patients enrolled in the present study. The distribution of the vitamin D levels in the present study was skewed toward the low-end. Similarly, in the NHANES III study, African American participants with the lowest levels of 25(OH)D exhibited little or no correlation between the 25(OH)D levels and hypertension (5). In addition, a study in southern California residents also did not show a significant association between 25(OH)D and metabolic syndrome, which might be attributed to extraordinary high levels of 25(OH)D (average: 108.9 nmol/L in men and 101.6 nmol/L in women) (16). These findings suggest that the relationship between vitamin D and hypertension may not be linear. The dissociation between the low vitamin D level and hypertension might be due to the lack of subjects with 25(OH)D sufficiency in the present study. A second possibility is that vitamin D may play an insignificant role in the regulation of blood pressure. Vuralet al. previously reported that there was no statistically significant difference in the genotype distributions and allele frequencies of the vitamin D receptor gene TaqI polymorphism between hypertensive patients and controls in Turkey (32). The largest randomized, double-blind, placebo-controlled trial (Women’s Health Initiative, n=36,282) failed to demonstrate an impact of vitamin D supplementation on blood pressure or incident hypertension over a 7-year follow-up period (33). A meta-analysis including 51 randomized trials that enrolled adults who received vitamin D supplementation and measured several cardiovascular outcomes found no significant association between the reduction in either the systolic or diastolic blood pressure and vitamin D level (34). A third possibility is that the effect of vitamin D on blood pressure may have population differences. Forman et al. recently reported that 3-month oral vitamin D supplementation significantly lowered the systolic pressure in Blacks (35). In contrast, such an effect was not observed in older patients with isolated systolic hypertension in the VitDISH randomized controlled trial (36). A fourth possibility is that the observational data were confounded by unmeasured factors, e.g., the data on the nutritional diet.

The present study revealed that the overall vitamin D status was poor among the study population. The serum 25(OH)D levels (average: 21.73 nmol/L) was relatively low and the prevalence of 25(OH)D <50 nmol/L (94%) was relatively high in our study participants, in comparison with the total population of the NHANES III study [average 25(OH)D level: 74 nmol/L; prevalence of 25(OH)D <50 nmol/L: 22%] (8). Our results were in accordance with the data from a review regarding the vitamin D status in mainland China, which suggested that in the Chinese population vitamin D deficiency/insufficiency is prevalent in nearly all areas and age groups (15). It is generally accepted that an adequate source of vitamin D is important for maintaining good bone health (37). Vitamin D deficiency can be an important risk factor for osteopenia, osteoporosis, falls and bone fractures (38-40). In our study participants, the general vitamin D status was poor and vitamin D sufficiency was rare. Taken together, vitamin D deficiency in China constitutes a significant, but modifiable public health risk. It deserves greater awareness and more efficient and timely management.

One major strength associated with our study is that the serum 25(OH)D levels were measured in a relatively short period, which minimized seasonal variation. Furthermore, the analyses were performed adjusting for several potential confounders, such as the salt intake, physical activities and BMI. However, there are some limitations associated with the present study. First, our study population was a vocational population and nearly all of the study subjects were men, thus our findings may not be generalizable to other populations. Second, as discussed above, the level of vitamin D was low and the range was in the lower-end, which made it challenging to explore thresholds or specific ranges for the association between the 25(OH)D level and hypertension. Despite these limitations, our findings confirmed and advanced the previous results of other studies conducted in China, which may further clarify the relationship between hypertension and vitamin D deficiency in Asian populations.

In conclusion, there was a high percentage of vitamin D deficiency and insufficiency in coal mine workers in the Kailuan Group. However, no significant association between low vitamin D levels and hypertension was found in this cohort. Further investigations are needed to determine the precise relationship between vitamin D and hypertension.

The authors state that they have no Conflict of Interest (COI).

Meng Peng and Shuohua Chen contributed equally to this study.
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