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Serum 25-hydroxyvitamin D and metabolic syndrome in a Japanese working population: The Furukawa Nutrition and Health Study

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ABSTRACT

Objective: Increasing evidence has suggested a protective role of vitamin D on metabolic syndrome (MetS). However, studies addressing this issue are limited in Asia and it remains unclear whether calcium could modify the association. We examined the association of serum 25-hydroxyvitamin D (25(OH)D) status with MetS, and the potential effect modification by calcium intake in a Japanese working population.
Methods: Study subjects were 1790 workers, ages 18 to 69 y, who participated in a health survey at the time of periodic checkup. MetS was defined according to the joint interim statement. Serum 25(OH)D was measured by a protein binding assay. Multilevel logistic regression was used to estimate the odds ratio (OR) with adjustment for potential confounding variables.
Results: An inverse trend was observed between 25(OH)D and MetS. Compared with those with a 25(OH)D of <20 ng/mL, multivariable adjusted OR (95% confidence interval) for MetS was 0.79 (0.55–1.15) and 0.52 (0.25–1.04) for those with a 25(OH)D of 20 to 29 ng/mL and ≥30 ng/mL, respectively (*P* for trend = 0.051). Similar association was observed in the analysis using quartile categories of 25(OH)D; the OR in the highest quartile of 25(OH)D compared with the lowest quartile was 0.61 (0.36–1.01) (*P* for trend = 0.046). This association was noted only in older subjects (≥44 y). The inverse association between serum 25(OH)D and MetS was more pronounced in subjects with high calcium intake. The inverse association between 25(OH)D and MetS appears to be linear according to restricted cubic spline regression. There was inverse, but statistically nonsignificant, associations between 25(OH)D and each component of MetS.
Conclusion: Our results suggest that higher circulating vitamin D is associated with decreased likelihood of having MetS among Japanese adults.

T.M. designed the research. M.E., K.K., T.K., I.K., R.I., H.T., K.K., and T.M. collected data. S.A. analyzed data and drafted the manuscript. M.E., K.K., T.K., I.K. R. I., K.K., H.T., I.K., and T.M. contributed to data interpretation and discussion. T.M. contributed to discussion, extensively reviewed, and edited the manuscript. The authors declare that they had no conflict of interest. M.E., T.K., R.I., H.T., and I.K. are health professionals in the Furukawa Electric Corporation. We are grateful to the study participants for their cooperation and participation. We thank Fumiko Zaizen (Furukawa Electric Corporation), as well as Ayami Kume, Sachiko Nishihara, Yuho Mizoue, Saeko Takagiwa, and Yuriko Yagi (National Center for Global Health and Medicine) for their help in data collection. This study was supported by JSPS KAKENHI Grant Number 25293146, 25702006; the Uehara Memorial Foundation; the Industrial Health Foundation; and the Health and Labour Sciences Research Expenses for Commission (Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus H26-005). The funding bodies had no role in the analysis or interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

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Introduction

Metabolic syndrome (MetS), a constellation of central obesity, hypertension, dyslipidemia, and impaired glucose homeostasis, increases the risk of type 2 diabetes, cardiovascular diseases, and cancers [1–3]. A worldwide increase in the number of people with MetS has taken place with a prevalence between 20% and 30% in the adult population [4]. Given the increasing prevalence of MetS and its strong link to many noncommunicable diseases, the prevention of this condition is important to public health.

Evidence from mechanistic and experimental studies suggests an important role for vitamin D in insulin response and glucose metabolism. Vitamin D can stimulate the expression of insulin receptors, and thereby, increase insulin responsiveness for glucose transport [5]. In animal models of vitamin D deficiency, vitamin D repletion improves insulin and glucose homeostasis [6,7]. Thus, higher vitamin D may have a protective effect on MetS. However, the association between MetS and serum 25(OH)D, a generally accepted indicator of vitamin D status, is not fully elucidated. Several studies [8–21] reported an association between blood 25(OH)D and MetS, but the results were inconsistent. In a recent meta-analysis [22], an association between vitamin D and MetS was observed in cross-sectional studies but not in longitudinal studies.

In spite of numerous studies conducted on this issue, several questions remain unanswered. First, we are aware of studies in Asia including Korea [16,18], China [15,17,21], Malaysia [20], and Iran [19], but no reports in Japan, whose population consumes larger amounts of fish (a rich source of vitamin D) compared with Westerners and other Asians [23]. Circulating 25(OH)D concentrations are associated with demographic, environmental, and life-style factors, including sun exposure and dietary intake [24]. The relationship between blood 25(OH)D and MetS in the Japanese population may, therefore, differ from that in other populations. Second, calcium is important for regulation of lipid metabolism and insulin-stimulated glucose uptake and storage, while vitamin D is essential for maintenance of intracellular calcium homeostasis [24]. Thus, the association between vitamin D and MetS may be modified by calcium intake, but no study has addressed this issue. Third, vitamin D deficiency is more prevalent among obese and older individuals [24]. A few studies suggested a stronger association between serum 25(OH)D and MetS among obese individuals than among normal-weight individuals [9,17], and a meta-analysis identified a stronger association among studies with a higher mean age ($\geq$60 y) than those with a lower mean age (<60 y) [22]. To elucidate these issues, we cross-sectionally investigated the association between serum 25(OH)D and MetS in a Japanese working population, while accounting for a large number of potential confounding factors.

Methods and materials

Study procedure and participants

Data for the present study were derived from the Furukawa Nutrition and Health Study, the details of which have been described elsewhere [25,26]. In brief, a health survey was conducted at the time of periodic health checkup (April 2012 in factory 1 and May 2013 in factory 2) among workers of a manufacturing company of non-ferrous metal industry and its affiliated ones in Japan. Major occupational exposures (% workers exposed in the major company) were organic solvent (15%), heavy lifting (10%), laser (10%), noise (5%), and ionizing radiation (4%). We invited all employees undergoing the health checkup to take the survey and asked them to fill out two types of study-specific questionnaires: one for diet and another for health-related lifestyle. Of 2828 checkup attendants (women, 11%), 2162 agreed to participate in the survey with a response rate of 76%. On the day of the health checkup, research staff checked the questionnaire for completeness and, if necessary, participants were asked to clarify answers. We requested that participants donate 7 mL of venous blood for the study. We also obtained health checkup data containing anthropometric and biochemical data and medical history. The study protocol was approved by the Ethics Committee of the National Center for Global Health and Medicine, Japan. Written informed consent was obtained from each participant.

Study subjects

From the study participants, we excluded 58 subjects with a history of cancer (n = 20), cardiovascular disease (n = 25), chronic hepatitis (n = 2), chronic pancreatitis (n = 3), kidney disease (n = 11); some participants had two or more diseases. Of the remaining 2104 participants, we sequentially excluded those who lacked information on blood levels of vitamin D (n = 218) and blood glucose (n = 2), those without fasting condition (n = 64), and those missing covariates used in the analysis (n = 30). This left 1790 subjects (1620 men and 170 women), ages 18 to 69 y, for analysis.

Anthropometric and biochemical measurement

Waist circumference was measured at the umbilical level in standing position using a measuring tape. Systolic and diastolic blood pressures were measured with an automated sphygmomanometer (BP 103 i II for 2012 survey and HEM-907 for 2013 survey, Omron Health Care Co. Ltd., Kyoto, Japan). As part of the health checkup, the plasma glucose concentration was assayed enzymatically using Quick-auto-neo-GLU-HK (Shino-Test Corp., Tokyo, Japan). Venous blood donated for the study was drawn into a vacuum tube and centrifuged to separate the serum. After the measurement of insulin, the remaining serum sample was stored at −80°C until analysis. High-density lipoprotein (HDL) cholesterol level was measured by direct enzymatic methods using the Cholestest N-HDL (Sekisui Medical Co. Ltd., Japan) (for 2012 survey) and Metabolead-HDL-C (Kyowa Medex Co. Ltd., Japan) (for 2013 survey). Triacylglycerol level was measured by enzymatic methods using the Pureauto S TG-N (Sekisui Medical Co. Ltd., Japan) (for 2012 survey) and Determiner TG (Kyowa Medex Co. Ltd, Japan) (for 2013 survey). All laboratories involving health checkup in the participating companies have received satisfactory results (rank A or score >95 out of 100) from external quality control surveillance including those by Japan medical association, Japanese Association of Laboratory Medical Technologists, and National Federation of Industrial Health Organization. Serum 25(OH)D concentrations were determined at an external laboratory (LSI Medicine Corporation, Tokyo, Japan) using a competitive protein binding assay with an LSC-5200 liquid scintillation counter (Hitach-Aloka Co., Ltd.). The intraassay coefficients of variation were 10.9% at 13.3 ng/mL and 8.9% at 21.3 ng/mL.

Definition of metabolic syndrome

MetS was defined according to the joint interim statement of the International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute [27]. MetS was defined as the presence of any three or more of the following criteria: (1) high waist circumference for Asians: $\geq$90 cm in men and $\geq$80 cm in women; (2) high triacylglycerol: $\geq$150 mg/dL; (3) low HDL cholesterol: <40 mg/dL in men, <50 mg/dL in women; (4) high blood pressure: systolic blood pressure $\geq$130 mmHg or diastolic blood pressure $\geq$85 mmHg; and (5) high fasting glucose: $\geq$100 mg/dL. Participants currently receiving antihypertensive medication, those currently receiving the lipid-lowering drug, and those with a history of diabetes were also considered to meet the criteria for high blood pressure, high triacylglcerol, and high fasting glucose, respectively.

Other variables

Body height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, while the participants wore light clothes and no shoes. BMI was calculated as the body weight in kilograms divided by the square of body height in meters. Shift work, smoking status, alcohol consumption, work-related (work, domestic housework, and commuting to and from work) and leisure-time physical activities were assessed via a lifestyle questionnaire. Work-related and leisure-time physical activities were both expressed as the sum of the metabolic equivalent (MET) value multiplied by the duration of time engaged in activities of varying intensity. Dietary habits during the preceding one-month period were assessed via a validated brief self-administered diet history questionnaire, and dietary intakes for 58 food and beverage items, energy, and calcium intake were estimated using an ad hoc computer algorithm [28].

Statistical analysis

Although there is no consensus on optimal levels of circulating vitamin D, 25(OH)D levels of <20, 20 to 29, and $\geq$30 ng/mL are considered by most experts to be deficient, insufficient, and sufficient, respectively [24], and we divided participants according to this definition. We also classified participants according