



## The Role of Vitamin D in Metabolic Syndrome

Hwei-Fang Tsai\*

Taipei Medical University-Shuang Ho Hospital Department of Internal Medicine, New Taipei City, Taiwan

\*Corresponding author: Hwei-Fang Tsai, MD, PhD, Taipei Medical University-Shuang Ho Hospital Department of Internal Medicine, No291, Zhongzheng Rd. Zhonghe Dist, New Taipei City 235, Taiwan (Republic of China), E-mail: [hftsai8635@yahoo.com.tw](mailto:hftsai8635@yahoo.com.tw)

### Vitamin D is Associated with Insulin Resistance in Non-Diabetic Individuals in Cross Sectional Studies

The effects of vitamin D on bone and mineral metabolism were well known. Proper exposure under the sunlight to increase body vitamin D content was long well practiced. Still vitamin D deficiency was frequently detected in variable areas of the world. Vitamin D deficiency is not uncommon even in the tropical countries. Recently it was much appreciated that vitamin D status might be correlated with components of metabolic syndrome, such as insulin resistance, glucose intolerance, increased low density lipoprotein cholesterol, increased visceral fat and waist girth [1,2] Protective effect of vitamin D on glucose and lipid metabolism was implicated in a meta-analysis of 28 studies [3]. The highest levels of serum 25-hydroxy vitamin D [25(OH)D] were associated with a 43% reduction in cardiometabolic disorders. Since vitamin is further changed to biological active form of 1.25 dihydroxy vitamin D in human kidneys. Serum levels of 25(OH)D were measured in most studies. High levels of vitamin D among middle-ages and elderly populations are associated with a substantial decrease in cardiovascular disease, type 2 diabetes mellitus and metabolic syndrome. One large scale cross sectional data from the National Health and Nutrition Examination Survey 2003-2006 [4] studied 3206 U.S. adults with no physician diagnosed diabetes mellitus. This survey demonstrated that fasting and 2-hour hyperglycemia, high homeostasis model assessment-insulin resistance decreased linearly across quintiles of 25-hydroxy vitamin D [25(OH)D]. After extensive adjustment for potential confounders such as overall obesity and abdominal obesity, the relationship between 25(OH)D and the markers of insulin resistance and 2-hour hyperglycemia persisted. Low concentrations of serum 25(OH)D were associated with markers of insulin resistance. One study of the individuals in the diabetic prevention program showed higher plasma concentration of 25(OH)D was associated with greater insulin sensitivity and lower insulin secretion [5]. These individuals showed body mass index  $\geq 24 \text{ Kg/m}^2$  ( $\geq 22 \text{ Kg/m}^2$  in Asian American), fasting plasma glucose 5.3 to 6.9 mmol/L (95-125 mg/dl), and a 2-hour plasma glucose 7.8 to 11 mmol/L (140 - 199 mg/dl) after a 75-gram oral glucose tolerance test and are defined pre-diabetic. After multivariate adjustment, participants in the highest tertile of 25(OH)D (median [inter quartile range]) 30.6 [27.5-34.9] ng/ml had lower odds of prevalent metabolic syndrome, smaller waist circumferences, higher high-density lipoprotein, and lower fasting plasma glucose compared to participants in the lowest tertile of 25(OH)D (median [inter quartile range]) 12.1 [9.7-14.3 ng/ml. Another study measured plasma 25(OH)D concentrations in 808 non-diabetic participants

of the Farminghan offspring study [1]. After adjusting for age, sex, body mass index, waist circumference and current smoking status, plasma 25(OH)D concentration was inversely associated with fasting plasma glucose and insulin concentrations, and homeostatic model assessment-insulin resistance (HOMA-IR). The same correlation of vitamin D and metabolic syndrome has also been shown in recent years in nonwestern countries such as Japan and Korea [6,7]. Higher 25(OH)D concentration ( $\geq 36.3 \text{ nmol/L}$ ) was strongly correlated with lower homeostatic model assessment-insulin resistance (HOMA-IR) and insulin values independent of visceral fat area in Japanese men. Of all 301 subjects over 60 year old in Seoul, Korea, 76.6% were vitamin D deficient ( $< 50 \text{ nmol/L}$ ) and 16.9% were insufficient ( $< 75 \text{ nmol/L}$ ). The 25(OH)D levels were inversely associated with insulin, triglyceride, systolic and diastolic blood pressure. Vitamin D deficiency was found to increase risk of hypertriglyceridemia category of metabolic syndrome. The association between blood 25(OH)D levels and metabolic syndrome was analyzed further by Ju *et al.* [8]. The dose-response meta-analysis showed a generally linear, inverse relationship between 25(OH)D levels and metabolic syndrome in the cross-sectional studies. However the association was not demonstrated in longitudinal studies. It was much important that this study showed that 25(OH)D was associated with metabolic syndrome inversely in a linear dose-response relationship. The two cohort studies by Gagnon *et al.* and Amirbaigloo *et al.* showed follow up time for five years and seven years, respectively. It is highly probable that significant changes in parameters of metabolic syndrome might need longer time for development considering a substance with significant seasonal wax and wane.

### Association of Vitamin D with Insulin Resistance in Healthy Male Adolescents and Obese Adolescent Females and Obese Postmenopausal Women

In 135 male adolescents studied, every 10 ng/ml decrease in 25(OH)D level was associated with a 0.25 unit increase in homeostatic model assessment-insulin resistance (HMOA-IR). Male adolescents in the lowest 25(OH)D quartile were at significantly higher risk for insulin resistance. In 125 healthy female adolescents the 25(OH)D level, either in continuous or categorical measure, was not significantly associated with insulin resistance. Where as in obese female adolescent the association of 25(OH)D and insulin resistance was established [9]. In a series of eighty postmenarchal adolescents (53 African American and 27 Caucasian American) 25(OH)D was inversely associated with fasting glucose, and positively associated with low density lipoprotein cholesterol, independent of race and

body mass index. Fourteen vitamin D deficient female were subject to vitamin D treatment. Ten female with increasing vitamin D serum levels after supplement showed improved fasting glucose. Four individuals showed no improvement of serum vitamin D after supplement. The association of vitamin D and insulin resistance was also demonstrated in obese postmenopausal women [10]. A threshold effect of 25(OH)D on glucose-insulin metabolism was implied that 25(OH)D  $\geq$  26  $\mu$ g/ml (65.0 p mol/L) supports normal glucose homeostasis.

### No Difference in the Incidence of Diabetes Emerges between Groups of Different 25(OH)D Levels in Follow up Study and No Effect of Vitamin Supplement on a Double-Blind Controlled Trial

The effect of 25(OH)D supplements was studied in 2227 participants over a 4.4-year follow up. The incidence of onset of diabetes was studied. The onset of diabetes between four groups with different serum 25(OH)D levels ( $\leq$  25, 25-50, 50-75,  $\geq$  75 n mol/L) showed no difference [11]. In a case-control and randomized-controlled trial using hyperglycemic clamp technique, the effect of vitamin D supplement to 108 healthy subjects with insufficient serum 25(OH)D levels does not improve insulin sensitivity, insulin secretion and serum lipid profile [12].

In summary that vitamin D supplementation does not improve glucose metabolism universally in all persons. However vitamin D supplement is helpful to decrease insulin resistance and improve metabolic syndrome in pre-diabetic overweight adolescent females and postmenopausal women that are low in 25(OH)D levels.

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