

Correlation between vitamin D and cardiovascular disease predictors in overweight and obese Koreans

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Although there is evidence that vitamin D deficiency relates to expression of chronic disease, relationship between vitamin D and cardiovascular disease predictors have not been clearly demonstrated in Korean. Our objective was to assess the correlation between vitamin D and the cardiovascular and inflammatory markers in overweight and obese people who had not been exposed to a particular disease. We enrolled 171 healthy adults (159 men and 12 pre-menopausal women) with no history of cardiovascular disease and with a body mass index >23 kg/m² in this study. In addition, levels of serum vitamin D and concentrations of the inflammatory markers hs-CRP, interleukin-6, and adiponectin were measured. The average age of our study subjects was 48.53 years old, and 64.8% of all male subjects and 91.9% of all female subjects were in the vitamin D deficient status. Serum vitamin D levels showed a positive correlation with age ($p<0.05$), HDL-cholesterol ($p<0.05$), and adiponectin ($p<0.05$) levels. However, there was a negative correlation of vitamin D with triglyceride ($p<0.01$) and interleukin-6 levels ($p<0.05$). In addition, even after adjusting for factors that may affect the cardiovascular index (age, sex, body mass index, smoking, and alcohol intake), serum vitamin D levels showed a significant correlation with triglyceride ($p<0.05$), HDL-cholesterol ($p<0.05$), and adiponectin ($p<0.05$) levels. Therefore, the results of this study suggest that vitamin D may be a predictor of cardiovascular disease for overweight and obese people who are likely to be at a risk for cardiovascular disease.

Key Words: vitamin D, inflammation biomarkers, cardiovascular disease, overweight

In humans, vitamin D is usually provided by food or when 7-dehydrocholesterol in the skin is changed to vitamin D by ultraviolet rays. As Korea is in a geographically advantageous position, as it receives plenty of sunlight for vitamin D synthesis, there was no serious deficiency of vitamin D among Koreans in the past. However, because people in Korea now engage in fewer outdoor activities and use more sunblock, vitamin D deficiency has been increasingly reported. Vitamin D is widely known to act as a hormone that is required for growth and maintenance of the skeleton and for the homeostasis of calcium; in addition, it was recently found to play a role in the control of cell proliferation and differentiation and in immunity.⁽¹⁻⁴⁾

Vitamin D deficiency is involved in the regulation of blood glucose through its correlation with insulin resistance and beta-cell failure.⁽⁵⁾ Additionally, the vitamin D receptor is expressed in immunocytes and has been shown to repress division of cytokine and dendritic cells and stimulate regulator T cells.⁽⁶⁻⁸⁾

The representative cardiovascular disease indicating index CRP is an acute phase reactant produced in liver from stimulation of

Interleukin-6 (IL-6), reported as it accelerates inflammation of arteriosclerosis. Adiponectin is negatively related with insulin resistance among type II diabetes mellitus and metabolic syndrome patients, reported as a factor restraining progress of cardiovascular disease with anti-inflammation effect.⁽⁹⁻¹²⁾

This indicates that vitamin D not only has an immunity effect but also controls inflammation. In morbidly obese patients, the serum 25-hydroxyvitamin D [serum 25(OH)D] level is associated with the levels of IL-6, adiponectin,⁽¹³⁾ and high-sensitivity C-reactive protein (hs-CRP), cytokines expressed in fat cells.⁽¹⁴⁾ In other words, serum vitamin D deficiency acts as a risk factor that increases inflammatory markers. In addition, vitamin D is related to expression of chronic diseases such as myocardial infarction,⁽¹⁵⁾ diabetes,^(5,16,17) and hypertension.⁽¹⁸⁾ At the same time, vitamin D deficiency is reportedly related to the concentration of lipids, which is a risk factor of cardiovascular disease.⁽¹⁹⁾

Serum 25(OH)D is used as a marker to evaluate the concentration of vitamin D in the human body.⁽²⁰⁾ In a study conducted with menopausal Korean women, the average serum 25(OH)D level was 12.2–17.6 ng/ml,⁽²¹⁻²³⁾ while in the 2009 National Nutrition Survey, men aged 19–30 years old had an average serum level of 18.9–19.6 ng/ml and women had a average level of 16.6–17 ng/ml.⁽²⁴⁾ In addition, the analysis of the 2007–2009 National Nutrition Surveys showed that the average serum 25(OH)D level in men in their 50s was 20 ng/ml.⁽¹⁹⁾ For vitamin D status, Korean studies show that the age levels are lower than the vitamin deficiency threshold level of 20 ng/ml established by the Institute of Medicine.⁽²⁵⁾ Thus, the vitamin D concentration has been shown to be low. However, studies related to vitamin D levels in Koreans are limited to menopausal women or healthy adults, and there is a lack of research on particular diseases and about people at risk of disease.

Therefore, we conducted this study to investigate the relevance of vitamin D status of overweight and obese adults who are likely to be exposed to chronic disease. We also assessed the lipid status and inflammatory marker levels of our study subjects to verify whether vitamin D was a predictor of cardiovascular disease.⁽²⁶⁾

Materials and Methods

Study subjects. From May to July 2011, we enrolled 171 healthy adults (159 men and 12 pre-menopausal women) with no history of cardiovascular disease who visited the hospital for health promotion center and who had a BMI >23 kg/m². This study was performed after receiving the approval of the Institutional Review Board of Wonkwang University.

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Anthropometric and blood pressure measurement.

Subjects removed their shoes and, while wearing light clothes, their height and weight were measured using an automatic height-weight measuring instrument (Gtech, Korea). The Inbody 3.0 body composition analyzer (Biospace, Korea) was used to measure BMI, body fat, and body fat percentage. For abdominal circumference, the midpoint between the iliac spine and the lowest limit of the ribs was measured using a tapeline. Blood pressure was recorded by asking the subjects to rest for 10 min by sitting in a comfortable position and then using an automatic blood pressure gauge (Jawon medical, Korea). We also took an average of the systolic and diastolic blood pressures that were measured twice.

Biochemical examination and risk of cardiovascular disease. For blood tests, subjects were asked to fast for at least 12 h, and the blood was centrifuged at 3,000 rpm for 15 min to obtain the serum. Blood glucose, triglyceride, total cholesterol, and HDL-cholesterol levels were measured using an automatic biochemical analyzer BS-220 (Mindray, China). LDL-cholesterol was calculated based on the Friedewald formula {[total cholesterol (mg/dl) – HDL-cholesterol (mg/dl)] – TG (mg/dl)/5}.⁽²⁷⁾ hs-CRP was analyzed using a latex agglutination test and the Hitachi 7600-110 system (Hitachi, Japan). Serum IL-6 was analyzed with a special IL-6 kit (Bender Med Systems, Austria), and adiponectin was analyzed using a human adiponectin special kit (Adipogen, Korea) and an enzyme-linked immunosorbent assay (ELISA) reader (Molecular Devices, California). Insulin was measured with electrochemiluminescence immunoassay using an electrochemiluminescent autoanalyzer (Modular E170, Germany). The homeostasis model assessment index for insulin resistance (HOMA-IR), a marker for insulin resistance, was calculated as [glucose (mg/dl) × insulin (μU/ml)/405].⁽²⁸⁾ Serum 25(OH)D was analyzed using 25 OH Vitamin D reagent based on the chemiluminescent immunoassay (CLIA). The risk of cardiovascular disease was analyzed using Framingham risk score.

Statistical analysis. All statistical analyses in this study were performed with the SPSS ver. 12.0. We calculated the mean ± SD, and the difference between the vitamin D deficiency group and the non-vitamin D deficiency group was examined using the *t* test. The relationship between serum vitamin D concentration and biochemical markers and anthropometric was determined by Pearson's correlation coefficients. To investigate the effect of vitamin D on triglyceride, HDL-cholesterol, adiponectin, and IL-6 level, we used 5 models for each marker: Model 0 was analyzed without a control variable; Model 1 by controlling age; Model 2 age and sex; Model 3 age, sex, and BMI; Model 4 age, sex, BMI, and smoking; and Model 5 age, sex, BMI, smoking, and alcohol intake. Multiple regression analysis was then performed for these models. Statistical significance was set at *p*<0.05.

Results

Anthropometric and biochemical examination results of the subjects. The results of anthropometric and biochemical examination for serum vitamin D status are shown in Table 1. The vitamin D deficiency group and non-vitamin D deficiency group were divided based on the 20 ng/ml Institute of Medicine standard. The average age of study subjects was 48.53 years old, and a total of 64.8% of male subjects and 91.7% of female subjects were found to have a vitamin D deficiency. The subjects' blood tests showed that the average blood glucose level was 104.75 mg/dl, total average cholesterol level was 199.13 mg/dl, average HDL-cholesterol level was 44.25 mg/dl, and average LDL-cholesterol level was 112.22 mg/dl. There was no significant difference between the 2 groups. As for triglyceride, the vitamin D deficiency group had an average level of 180.21 mg/dl, and the non-deficiency group registered an average level of 149.37 mg/dl; thus, there was a significant difference between 2 groups (*p*<0.01). Analysis of inflammatory markers showed that the average

concentration of hs-CRP was 1.86 μg/ml and that of adiponectin was 8.80 μg/ml, and only IL-6 concentration was statistically significantly different between the 2 groups (*p*<0.05). The IL-6 concentration for the vitamin D deficiency group was 1.73 pg/ml and for the non-deficiency group, this value was 0.81 pg/ml. The average HOMA-IR value was 5.06, and the Framingham risk score, which indicates the risk of cardiovascular disease, was 8.46 on average. There was no significant difference between the 2 groups.

Correlation between vitamin D, anthropometric, and inflammatory marker. The correlation between serum vitamin D and anthropometric and inflammatory markers is shown in Table 2. In the analysis of correlation between serum vitamin D and age (*p*<0.05), we found a positive correlation: higher age led to higher vitamin D concentration. There was also a positive correlation between HDL-cholesterol (*p*<0.05) and adiponectin (*p*<0.05) levels and vitamin D. A negative correlation was found between vitamin D and triglyceride (*p*<0.01) and an inverse correlation was seen between the inflammatory marker IL-6 (*p*<0.05) and vitamin D.

Multiple regression analysis of vitamin D and relevant factors. The multiple regression analysis result for serum vitamin D, triglyceride, HDL-cholesterol, adiponectin, and IL-6 is shown in Table 3. Even after controlling for age, sex, BMI, smoking, and alcohol intake, serum vitamin D showed an effect on levels of triglyceride (*p*<0.05), HDL-cholesterol (*p*<0.05) and adiponectin (*p*<0.05).

Discussion

This study investigated the correlation between the vitamin D status and cardiovascular disease indicators and inflammatory markers in overweight and obese adults with no history of cardiovascular disease. The results showed a correlation between serum vitamin D and HDL-cholesterol, triglyceride, and adiponectin levels.

Also, in this study, it is found 65% of men with over BMI 23 kg/m² have vitamin D deficiency, and 91.7% when it comes to women with same condition, showing higher degree compared to non-vitamin deficient group. The result of previous studies studying vitamin D intakes shows that 92% of menopausal women have vitamin D deficiency,^(21,22) and 90.6% when it comes to adults over 50s in Korean. Also, Korea National Health and Nutrition Examination Survey shows 56% of metabolic syndrome patients have vitamin D deficiency.⁽²⁹⁾

In this study, the BMI and percentage of body fat of the vitamin D deficiency group showed higher tendency than that of the non-deficiency group, even though statistically insignificant. In a previous study on the correlation between serum 25(OH)D levels and body fat, it was found that serum 25(OH)D and body fat had a negative correlation in obese women.⁽³⁰⁾ In addition, a study by Worstman showed that higher BMI leads to a lower vitamin D concentration.⁽³¹⁾ It has also been reported that obese patients are more likely to lack serum vitamin D because vitamin D is a fat soluble vitamin that is not easily eluted from adipose tissue once absorbed; therefore, obese people lack vitamin D and vitamin D deficiency aggravates obesity.⁽³²⁾ However, in the current study percentage of body fat and BMI did not correlate with vitamin D concentration. This lack of relationship may due to subjects' selection including overweight and obese.

The US Third National Health and Nutrition Examination Survey (1988–1994) found that a higher serum 25(OH)D concentration leads to a lower risk of diabetes.⁽⁵⁾ Additionally, the intake of vitamin D and calcium is known to reduce the risk of type 2 diabetes.⁽¹⁶⁾ Similarly, a study conducted with Chinese people found that higher serum 25(OH)D concentrations were correlated with lower insulin and HOMA-IR levels in a group with BMI of 24 kg/m²,⁽³³⁾ indicating the correlation between vitamin D and

Table 1. Anthropometrics, biochemical parameters, and inflammation markers in patients with and without vitamin D deficiency

Variables	Vitamin D deficiency group (n = 114)	Non-vitamin D deficiency group (n = 57)	Total (n = 171)	t/ χ^2
Sex				
Men	103 (64.8%)	56 (35.2%)		0.057
Women	11 (91.7%)	1 (8.3%)		
Age (years)	48.01 ± 9.68	49.58 ± 10.57	48.53 ± 9.98	-0.942
Weight (kg)	79.56 ± 10.98	80.26 ± 9.75	79.79 ± 10.56	-0.426
BMI (kg/m ²)	27.12 ± 2.91	26.81 ± 2.37	27.02 ± 2.74	0.738
WC (cm)	93.3 ± 7.2	93.59 ± 6.03	93.4 ± 6.81	-0.274
Body fat mass (kg)	21.72 ± 5.29	21.22 ± 3.95	21.55 ± 4.88	0.658
Body fat (%)	27.02 ± 4.33	26.11 ± 2.83	26.72 ± 3.92	1.402
Blood pressure				
SBP (mmHg)	127.09 ± 12.42	128.42 ± 16.47	127.53 ± 13.87	-0.592
DBP (mmHg)	79.8 ± 9.61	80.98 ± 12.96	80.19 ± 10.82	-0.674
Glucose (mg/dl)	104.68 ± 22.91	104.91 ± 23.48	104.75 ± 23.03	-0.063
Triglyceride (mg/dl)	180.21 ± 75.43	149.37 ± 64.4	169.93 ± 73.22	2.785**
Cholesterol (mg/dl)	200.38 ± 32.65	196.63 ± 37.99	199.13 ± 34.45	0.636
Hdl-Cholesterol (mg/dl)	43.52 ± 9.51	45.69 ± 9.11	44.25 ± 9.41	-1.446
Ldl-Cholesterol (mg/dl)	113.2 ± 27.61	110.29 ± 29.73	112.22 ± 28.28	0.617
HOMA-IR	5.11 ± 6.2	4.95 ± 8.22	5.06 ± 6.91	0.133
hs-CRP (μg/ml)	1.92 ± 2.56	1.74 ± 2.56	1.86 ± 2.55	0.438
Adiponectin (μg/ml)	8.56 ± 3.17	9.27 ± 4.07	8.8 ± 3.5	-1.158
Interleukin-6 (pg/ml)	1.73 ± 2.79	0.81 ± 1.22	1.43 ± 2.42	2.38*
FRS	8.42 ± 7.01	8.56 ± 6.73	8.46 ± 6.89	-0.120
Vitamin D (ng/ml)	13.77 ± 3.52	25.17 ± 3.78	17.57 ± 6.48	-19.478***

Presented values are the mean SD. Significantly different by chi-square test, Significantly different at * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ by t test.

Table 2. Correlation between anthropometric and biochemical parameters and inflammation markers with vitamin D levels

Variable	r	p
Age (years)	0.152	0.048
Weight (kg)	0.04	0.600
BMI (kg/m ²)	0.007	0.923
WC (cm)	0.043	0.578
Body fat mass (kg)	-0.040	0.624
Body fat (%)	-0.107	0.173
Blood pressure		
SBP (mmHg)	0.083	0.278
DBP (mmHg)	0.136	0.076
Glucose (mg/dl)	0.045	0.555
Triglyceride (mg/dl)	-0.203	0.008
Cholesterol (mg/dl)	-0.022	0.778
Ldl-cholesterol (mg/dl)	-0.028	0.719
Hdl-cholesterol (mg/dl)	0.179	0.019
HOMA-IR	0.023	0.768
hs-CRP (μg/ml)	-0.029	0.707
Adiponectin (μg/ml)	0.163	0.033
Interleukin-6 (pg/ml)	-0.152	0.047
FRS	-0.071	0.379

Relationship between serum vitamin D concentration and biochemical markers and anthropometric was determined by Pearson's correlation coefficients.

glycemic control. However, in this study, we did not find a correlation between HOMA-IR and serum 25(OH)D levels; we believe that this is because our study subjects were overweight adults with no particular disease and who maintained normal blood glucose levels. Therefore, there may not have been any relation to HOMA-IR.

US study results analyzing National Health and Nutrition Examination Survey (NHANES) shows blood lipid levels including triglyceride and total cholesterol are the risk element of cardiovascular disease.⁽³⁴⁾ Also, the study conducted by Giovannucci

Table 3. Correlation between vitamin D and different factors studied at baseline and after adjustment for age, sex, BMI, smoking, and alcohol intake

Variable	B2	Significance
Triglyceride (mg/dl)		
Model 0	-1.173	0.031
Model 1	-0.188	0.018
Model 2	-0.191	0.015
Model 3	-0.189	0.016
Model 4	-0.160	0.044
Model 5	-0.158	0.047
Hdl-cholesterol (mg/dl)		
Model 0	0.177	0.028
Model 1	0.178	0.025
Model 2	0.174	0.027
Model 3	0.173	0.027
Model 4	0.175	0.024
Model 5	0.164	0.040
Adiponectin (μg/ml)		
Model 0	0.163	0.042
Model 1	0.146	0.068
Model 2	0.162	0.040
Model 3	0.178	0.026
Model 4	0.185	0.018
Model 5	0.183	0.019
Interleukin-6 (pg/ml)		
Model 0	-0.150	0.062
Model 1	-0.123	0.131
Model 2	-0.109	0.178
Model 3	-0.126	0.122
Model 4	-0.107	0.189
Model 5	-0.094	0.253

Model 0, at baseline; Model 1, after adjustment for age; Model 2, after adjustment for age and sex; Model 3, after adjustment for age, sex and BMI; Model 4, after adjustment for age, sex, BMI and smoking; Model 5, after adjustment for age, sex, BMI, smoking, and alcohol intake.

and others suggest low 25(OH)D degree is an element increasing risk of myocardial infarction, indicating relation of vitamin D with manifestation of cardiovascular disorders.⁽¹⁵⁾ In a study assessing the risk factors for cardiovascular disease and vitamin D, lower vitamin D concentrations were found to lead to higher blood cholesterol and LDL-cholesterol concentration.⁽³⁵⁾ In addition, Chacko *et al.*⁽³⁶⁾ conducted a study with menopausal women, which showed a correlation between serum 25(OH)D levels and triglyceride. However, although the present study differed from previous studies in that our subjects were not patients with a particular disease such as metabolic syndrome, and menopause, we found a negative correlation of 25(OH)D concentration with triglyceride levels and positive correlation of 25(OH)D concentration with HDL-cholesterol levels.

In a study targeting Korean male workers has found a group with vitamin D deficiency has higher triglyceride, the risk element of cardiovascular disorders, than a group with non-deficiency, and this study has found the same difference between two groups. This shows deficiency of vitamin D has relation with triglyceride, the risk element of cardiovascular disorders.⁽³⁷⁾

In this study, when factors related with cardiovascular disease including age, sex, Body Mass Index (BMI), smoking, and drinking are not controlled, triglyceride and vitamin D have the strongest impact, and they have low impact when the factors are controlled, showing there is a negative correlation. This can be considered as a result of sensitive reaction of triglyceride, compared to other indices, to smoking, drinking, and diet, and it may cause by eating habit of Koreans, which is high levels of carbohydrate intakes.⁽³⁸⁾ Therefore, we believe it is necessary for overweight adults who have a high risk of cardiovascular disease to maintain normal levels of blood 25(OH)D as well as triglyceride and HDL-cholesterol; this is important in preventing cardiovascular disease due to vitamin D deficiency.

It is reported abdominal fat caused by excessive fat accumulation has relation with immunity, inflammation, and infection due to cytokine secreted by adipose tissue.⁽³⁹⁾ It is known vitamin D affects inflammation reaction, having relation with gene expression of IL-6, the inflammatory markers.⁽⁴⁰⁾ In study with obesity subjects, it is found CRP had negative correlation between 25(OH)D and IL-6.⁽¹⁴⁾ In our study, the objects are overweighted, it is found vitamin D has negative correlation between IL-6, having same result with study objecting obese people. It shows low vitamin D degree can be an element increasing IL-6, the inflammatory markers in overweight people without disease. In patients

with diseases such as type 2 diabetes and cardiovascular disease, low adiponectin concentration has been reported.⁽⁴¹⁾ However, but, Gannagé-Yared⁽⁴²⁾ suggested that higher 25(OH)D concentrations increased adiponectin levels and that vitamin D increased adiponectin levels. In this study, adiponectin had a positive correlation with vitamin D levels even after controlling for age, BMI, sex, smoking, alcohol intake confirming the activity of vitamin D as an independent predictor of cardiovascular disease.

This study demonstrated a correlation between vitamin D and serum triglyceride, HDL-cholesterol, and inflammatory markers in overweight and obese Korean adults; in addition, adiponectin was found to be an independent predictor of cardiovascular disease. Therefore, to prevent cardiovascular disease, we suggest that overweight people lose weight and engage in more outdoor activities. This will help maintain normal serum vitamin D levels and vitamin D synthesis by sunlight. Overweight people also need to take a sufficient quantity of vitamin D in the form of food supplements or via food.

The limitation of this study was that it did not compare differences between overweight people and healthy adults. Nevertheless, the study confirmed a correlation between vitamin D and inflammatory markers in Korean. Because this study did not take into account vitamin D taken from food, future studies will need to include both dietary analysis and biochemical analysis.

Abbreviations

25(OH)D	25-hydroxyvitamin D
BMI	body mass index
DBP	diastolic blood pressure
FRS	framingham risk score
HDL-Cholesterol	high-density lipoprotein cholesterol
HOMA-IR	homeostasis model assessment of insulin resistance
hs-CRP	high-sensitivity C-reactive protein
IL-6	interleukin-6
LDL-Cholesterol	low-density lipoprotein cholesterol
SBP	systolic blood pressure
WC	waist circumference

Conflict of Interest

No potential conflicts of interest were disclosed.

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