The Effect of Vitamin D Supplementation on Metabolic Phenotypes in Thais with Prediabetes

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Objective: *To investigate the effects of vitamin D supplement for three months on anthropometric and glucose homeostatic measures in Thai adults with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT).*

Material and Method: *Forty-seven IFG and/or IGT subjects enrolled in the study. Subjects were randomized into three groups, control (n = 18), vitamin D_2 (20,000 IU weekly, n = 19) or vitamin D_3 (15,000 IU weekly, n = 10). Anthropometric variables were obtained at baseline and at 3-month. Oral glucose tolerance test was performed at baseline and at 3-month. Total serum 25(OH)D, 25(OH)D_3, and 25(OH)D_2 were measured by LC-MS/MS. Insulin resistance (HOMA-IR) and insulin secretion index (HOMA%B) were calculated by the homeostasis model assessment.*

Results: *The total 25(OH)D levels significantly increased from baseline in both the vitamin D_2 and the vitamin D_3 groups, while there was no change in the control group. D_3 supplementation raised 25(OH)D_3 significantly (+13.7±4.9 ng/mL, $p<0.01$) while D_2 increased 25(OH)D_2 levels (+25.9±4.2 ng/mL, $p<0.001$) but with a decrease in 25(OH)D_3 (-13.1±3.1 ng/mL, $p<0.001$). Subjects were classified into two groups, i.e., control (n = 18) and D_2 or D_3 supplementations (n = 29). After three months, waist circumference (WC) significantly decreased in subjects of vitamin D supplementation group. Body weight (BW, p = 0.05), systolic blood pressure (SBP, p = 0.05), body mass index (BMI, p = 0.06), and HOMA-IR (p = 0.09) also tended to decrease. Subjects with an increase of total 25(OH)D levels ≥10 ng/mL (23 of 29 subjects) had significant decrease in HOMA-IR and increase in disposition index. Using robust regression analysis, we found the use of D_3 was associated with a larger decrease in WC (coefficient = -3.5, $p<0.001$) independent of the change in total 25(OH)D and baseline BMI. No difference between D_2 and D_3 was observed for other metabolic measures.*

Conclusion: *Weekly supplementations of vitamin D_2 (20,000 IU) or vitamin D_3 (15,000 IU) improve metabolic phenotypes in subjects with prediabetes. D_3 supplement may decrease waist circumference more than D_2 supplement.*

Keywords: *Vitamin D, Vitamin D_2, Vitamin D_3, 25(OH)D, Prediabetes, Metabolic parameters*

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Increasing evidence suggested that vitamin D plays a role in many biological functions beyond the classical effect in calcium and bone metabolism[1,2]. With regard to glucose homeostasis, it has been demonstrated that vitamin D affects pancreatic beta-cell proliferation and survival[3]. Many studies reported that vitamin D improves glucose homeostasis and increases insulin sensitivity and insulin secretion[3,4]. At the population level, there is an association between 25-hydroxyvitamin D (total 25(OH)D; a marker of vitamin D status) and incident of type 2 diabetes (T2DM)[5,6]. A recent meta-analysis of prospective studies found 38% reduction in incident of T2DM in subjects who had 25(OH)D levels greater than 25 to 30 ng/mL when compared with subjects who had 25(OH)D levels of 8 to 20 ng/mL[5]. Corresponded to this finding in Caucasians, low vitamin D status was modestly associated with a small increased in the risk of diabetes in the urban Thai elderly[7]. These findings were disputed since there were inconclusive results in benefit of vitamin D supplement on glucose homeostasis from randomized controlled trials[8-11]. Some studies reported the benefit of vitamin D supplement in improving insulin sensitivity only in adults at high risk of T2DM, subjects with impaired fasting glucose (IFG), and/or impaired glucose tolerance (IGT), but not normal subjects[9,10]. Moreover, reports regarding this issue in Asian populations are scant.

In the present study, we investigated the effect of vitamin D supplement for three months on anthropometric and glucose homeostasis measures in Thai IFG and/or IGT.

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Material and Method

Study design

This open-label randomized controlled study was conducted at Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

Study population

One hundred twenty three healthy volunteers, aged 35 to 80 years were recruited by advertisement for the screening of type 2 diabetes between July and November 2012. A 75 g oral glucose tolerance test (OGTT) was performed in the morning after an 8-hour overnight fast to recruit subjects with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) according to American Diabetes Association Criteria[12]. Other inclusion criteria were adults with normal renal function, hepatic function, and calcium level. Exclusion criteria were adults who have been taking vitamin D supplements over 400 IU/day, and/or receiving medications that alter vitamin D metabolites (for example: glucocorticoid, phenytoin, phenobarbital, rifampicin). Fifty-one subjects with IFG and/or IGT were included in the present study. The Ethical Review Board of Ramathibodi Hospital, Mahidol University, approved this study; all participants provided written informed consents.

Procedure

Subjects were randomized into three groups, vitamin D_3 (cholecalciferol), vitamin D_2 (ergocalciferol), or control (no vitamin D treatment). Some studies of vitamin D supplement demonstrated that vitamin D_2 is less effective than vitamin D_3 in raising total 25(OH)D levels[13-15]. We aim to raise total 25(OH)D levels to comparable levels with vitamin D_2 or D_3, thus different weekly dosage of vitamin D_2 (20,000 IU) or vitamin D_3 (15,000 IU) were used in the present study. Patients were randomly assigned (1:2:2) to receive vitamin D_3 (15,000 IU weekly, n = 11), vitamin D_2 (20,000 IU weekly, n = 20), or control (no vitamin D, n = 20) for three months. Four subjects were subsequently excluded from the analysis, two subjects were newly diagnosed as diabetes within three months of the study period and two subjects did not have the result of insulin resistance (HOMA-IR) and/or insulin secretion index (HOMA%B). Ultimately, data from 47 subjects were included in the final analysis (Fig. 1). Compliance was assessed by tablet-counting at 3-month, and was reported as percentage of medicine taken. All subjects had over 90% compliance for vitamin D_2 and vitamin D_3.

All study participants arrived at the research unit at 8-hour after at least a 12-hour overnight fast. Baseline characteristics, which included age, all medications, anthropometric variables, adverse events, and adherence to drug were recorded. The 75 g OGTT was performed at baseline and at 3-month. Fasting blood sample were additional measured for total serum 25(OH)D, 25(OH)D_3, 25(OH)D_2, HbA1c, and insulin levels. After randomization into three group of treatment, subjects were asked to return to the clinic three months after the first visit.

Biochemical measurement

Plasma glucose and HbA1c was measured using a Dimension® RxL Max® analyzer (Siemens Healthcare Diagnostics, Tarrytown, NY, USA). Serum 25(OH)D_2 and 25(OH)D_3 were analyzed by LC-MS/MS with an Agilent 1200 Infinity liquid chromatograph (Agilent Technologies, Waldbronn, Germany), coupled to a QTRAP® 5500 tandem mass spectrometer (AB SCIEX, Framingham MA, USA) using a MassChrom® 25-OH-Vitamin D_3/D_2 diagnostics kit (ChromSystems, Gräfelfing, Germany). The summation of serum 25(OH)D_2 and 25(OH)D_3 [total 25(OH)D] was used to reflect vitamin D status. Vitamin D deficiency was defined as having 25(OH)D levels of

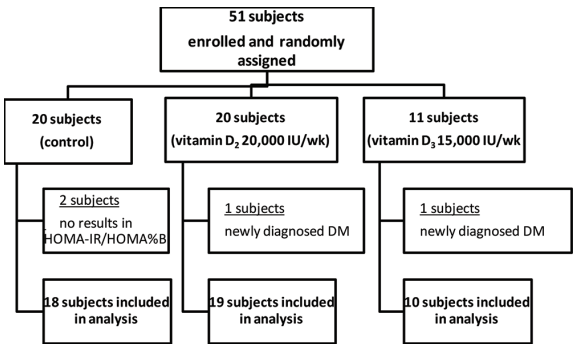

Fig. 1 Study design and patient flow. Fifty-one patients were enrolled and randomly assigned to receive vitamin D_3 (15,000 IU weekly, n = 11), vitamin D_2 (20,000 IU weekly, n = 20) or control (no vitamin D, n = 20) for 3 months. Four subjects were subsequently excluded from the analysis; two subjects of control group did not have the result of insulin resistance (HOMA-IR) and/or insulin secretion index (HOMA%B) and two subjects (1 subjects of vitamin D_2 and vitamin D_3 group) were newly diagnosed as diabetes within 3 months of the study period. Ultimately, there were 18, 19, and 10 subjects in control, vitamin D_2, and vitamin D_3 group, respectively, in the final analysis.

less than 50 nmol/L [20 ng/mL][16]. The inter-assay and intra-assay coefficients of variation of total serum 25(OH)D level were 6.3% and 5.0%, respectively. Computer-based homeostatic model assessment index of beta-cell function (HOMA%B) and computer-based homeostatic model assessment index of insulin resistance (HOMA-IR) were calculated using homeostasis model assessment-2 (HOMA-2) calculator (www.dtu.ox.ac.uk/homa)[17]. Disposition index was calculated as HOMA%B divided by HOMA-IR.

Statistical analysis

All values were expressed as mean ± SD, frequency, and percentage. We used Mann-Whitney test and the Chi-square test to compare the difference of clinical characteristics at baseline and at 3-month between the three groups. Differences between anthropometric variables and laboratory results at baseline and at 3-month in each group were assessed by Wilcoxon test. Robust regression analysis was used to examine the differences in change in metabolic phenotypes after vitamin D_2 as compared to vitamin D_3. Statistical analysis was performed using SPSS software for Windows, version 18.0 (SPSS, Chicago, IL, USA).

Results

Forty-seven subjects (68% female) with a mean age of 60.3±11.2 years were included in the final analysis. According to the 75 g OGTT results, 6, 18, and 23 subjects were isolated IFG, isolated IGT, and combined IFG/IGT, respectively (Table 1). The mean total 25(OH)D in all subjects was 25.9±5.3 ng/mL. Eight subjects (17%) were classified as vitamin D deficiency [25(OH)D levels <20 ng/mL]. As expected, most of vitamin D deficient subjects were females (7 out of 8). When stratified subjects into three group; control, vitamin D_2, and vitamin D_3 groups. There was no difference in baseline characteristics of subjects. In addition, the prevalence of vitamin D deficiency was not different among groups (three subjects in control, four subjects in vitamin D_2, and one subject in vitamin D_3 group; p = 0.887). Total 25(OH)D levels significantly increased from baseline in both the vitamin D_2 and the vitamin D_3 groups (D_2: Δ total 25(OH)D = 12.8±3.6 ng/mL, p<0.001, D_3 13.1±4.1 ng/mL, p<0.01), while there was no change in the control group (Fig. 2, Table 1). Vitamin D_3 supplementation raised 25(OH)D_3 significantly (+13.7±4.9 ng/mL, p<0.01) while vitamin D_2 increased 25(OH)D_2 levels (+25.9±4.2 ng/mL, p<0.001) but decreased 25(OH)D_3 (-13.1±3.1 ng/mL, p<0.001) (Fig. 2, Table 1).

Subjects were then classified into two groups, i.e., control (n = 18) and vitamin D_2 or D_3 (n = 29) supplement. After three months of vitamin D supplement, waist circumference (WC) significantly decreased in subjects of vitamin D supplement group (Table 2). Body weight (BW, p = 0.05), systolic blood pressure (SBP, p = 0.05), body mass index (BMI, p = 0.06), and HOMA-IR (p = 0.09) tended to decrease (Table 2). Similarly, when considering subjects with

Table 1. Total 25(OH)D, 25(OH)D_2, and 25(OH)D_3 at baseline and at 3-month of subjects in control, vitamin D_2, and vitamin D_3 group

		Control (n = 18)	Vitamin D_2 20,000 IU/week (n = 19)	Vitamin D_3 15,000 IU/week (n = 10)	p-value*
Age (year)		57.9±13.3	61.2±7.6	63.0±12.9	0.51
F/M (n)		9/9	15/4	8/2	0.07
IFG/IGT/combined IFG and IGT		0/7/11	3/7/9	3/4/3	0.58
Total 25(OH)D (ng/mL)	Baseline	26.3±6.1	25.2±5.3	26.3±3.9	0.65
	3-month	25.6±5.8	38.0±5.0	39.3±5.7	<0.001
	p-value**	0.20	<0.001	<0.01	
25(OH)D_2 (ng/mL)	Baseline	0.6±0.2	0.9±0.9	1.3±2.1	0.35
	3-month	0.6±0.3	26.8±4.7	0.7±1.0	<0.001
	p-value**	0.16	<0.001	0.02	
25(OH)D_3 (ng/mL)	Baseline	25.8±6.0	24.3±5.3	25.0±4.3	0.66
	3-month	25.0±5.8	11.2±3.4	38.7±5.3	<0.001
	p-value**	0.17	<0.001	<0.01	

25(OH)D = 25-hydroxyvitamin D; F/M = female/male; IFG = impaired fasting glucose; IGT = impaired glucose tolerance
Data presented as mean ± SD
* p-value: between group, ** p-value: between baseline and 3-month

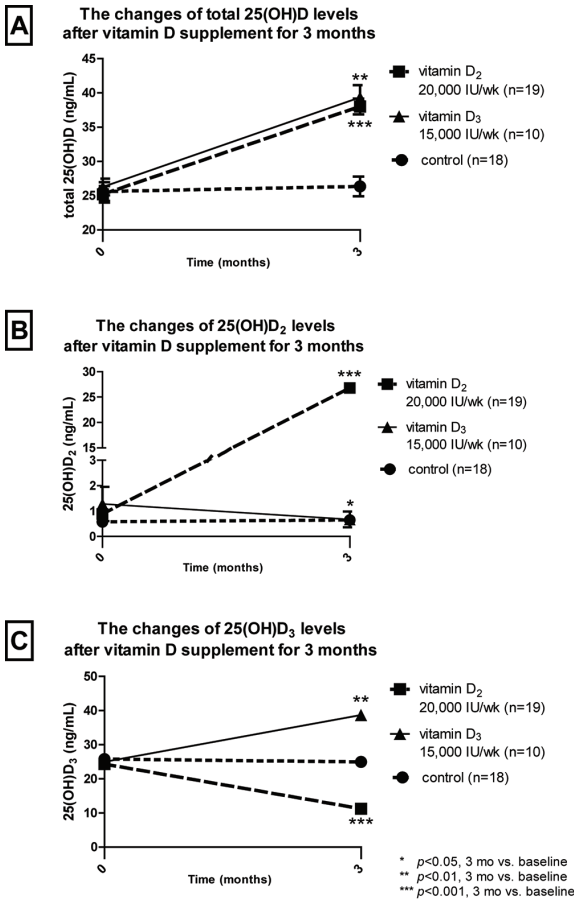

Fig. 2 The changes of total 25(OH)D, 25(OH)D_2, and 25(OH)D_3 at 3-month after vitamin D supplement in control, vitamin D_2, and vitamin D_3 group.

baseline total 25(OH)D <30 ng/mL (i.e., vitamin D deficiency and vitamin D insufficiency), WC significantly decreased, and BW, BMI and HOMA-IR tended to decrease after three month of vitamin D supplement (Table 3). On the other hand, there were no change in metabolic phenotype in subjects of control group (Table 2, 3). We further classified subjects who received vitamin D_2 or vitamin D_3 supplementations into two groups according to the change of total 25(OH)D levels: <10 or ≥10 ng/mL. Interestingly, 23 subjects with an increase of total 25(OH)D levels ≥10 ng/mL had significant decrease in HOMA-IR (-0.24±0.42, p<0.01) and increase in disposition index (+5.1±10.5, p = 0.03) (Fig. 3, Table 2). No changes of HOMA-IR and disposition index were observed in subjects with an increase of total 25(OH)D levels <10 ng/mL (n = 6) (Fig. 3). Nonetheless, the change in glucose tolerance status was not different between control and vitamin D_2 or D_3 group after three months of vitamin D supplementation (Table 4).

Using robust regression analysis to examine the differences in changes in metabolic phenotypes after vitamin D_2 as compared to vitamin D_3, the use of vitamin D_3 was associated with a larger decrease in WC (coefficient = -3.5, p<0.001) independent of the change in total 25(OH)D and baseline BMI. No difference between vitamin D_2 and vitamin D_3 was observed for other metabolic measures.

Discussion

Correspond with many studies, vitamin D_2 is less effective than vitamin D_3 in raising total 25(OH)D levels[13-15]. In the present study, 100 IU of

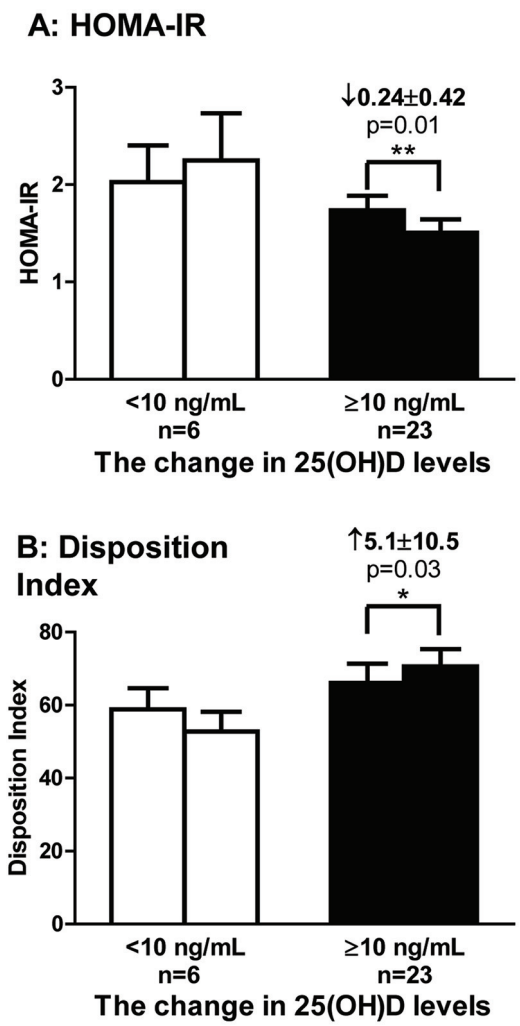

Fig. 3 The change of HOMA-IR (A) and disposition index (B) of subjects in vitamin D supplement group (n = 29) stratified by the change in 25(OH)D levels.

Table 2. Metabolic characteristic between baseline and 3-month of all subjects in control, all subjects in vitamin D group and subjects with Δ25(OH)D ≥10 ng/mL in vitamin D group

		Control (n = 18)	Vitamin D_2 or D_3 (n = 29)	*p*-value*	Vitamin D_2 or D_3 [Δ25(OH)D ≥10 ng/mL] (n = 23)	*p*-value**
Age (year)		57.9±13.3	61.8±9.5	0.33	62.5±9.9	0.31
F/M (n)		9/9	23/6	0.06	19/4	0.04
BW (kg)	Baseline	72.0±15.3	64.6±10.2	0.07	63.8±9.9	0.05
	3-month	71.9±15.0	64.1±10.4	0.05	63.3±10.1	0.04
	p-value***	0.91	0.05		0.12	
BMI (kg/m^2)	Baseline	29.0±5.0	27.1±3.2	0.33	26.7±3.4	0.22
	3-month	28.9±4.8	26.8±3.5	0.21	26.5±3.6	0.15
	p-value***	0.95	0.06		0.14	
WC (cm)	Baseline	97.7±11.7	94.7±9.8	0.30	94.2±9.5	0.34
	3-month	97.7±11.7	93.3±9.5	0.21	93.0±9.5	0.23
	p-value***	0.67	0.01		0.06	
SBP (mmHg)	Baseline	127.2±14.3	126.9±11.1	0.84	127.0±11.9	0.82
	3-month	124.3±11.3	122.3±13.0	0.55	121.1±13.6	0.39
	p-value***	0.44	0.05		0.04	
DBP (mmHg)	Baseline	82.6±8.8	76.9±8.9	0.07	76.9±8.7	0.08
	3-month	78.6±9.0	78.3±9.0	0.89	77.4±8.2	0.73
	p-value***	0.20	0.49		0.88	
FPG (mg/dL)	Baseline	104.5±11.2	104.1±11.2	0.99	103.6±11.8	0.96
	3-month	104.0±15.2	103.5±10.9	0.77	101.3±10.9	0.71
	p-value***	0.48	0.49		0.10	
PP 2-hour (mg/dL)	Baseline	161.4±13.9	149.5±29.3	0.34	149.7±29.3	0.32
	3-month	155.0±28.4	154.5±39.1	0.90	147.4±40.4	0.41
	p-value***	0.18	0.46		0.78	
HbA1c (%)	Baseline	6.1±0.3	6.0±0.4	0.62	6.0±0.34	0.42
	3-month	6.1±0.3	6.1±0.4	0.87	6.0±0.4	0.55
	p-value***	0.62	0.12		0.15	
HOMA%B	Baseline	112.1±61.5	104.3±31.2	0.71	102.9±28.9	0.77
	3-month	113.8±61.1	100.2±34.5	0.66	97.4±31.9	0.58
	p-value***	0.81	0.18		0.11	
HOMA-IR	Baseline	1.9±1.0	1.8±0.8	0.96	1.7±0.7	0.82
	3-month	1.8±0.8	1.7±0.9	0.35	1.5±0.7	0.13
	p-value***	0.81	0.09		0.01	
Disposition index (HOMA%B/HOMA-IR)	Baseline	62.0±14.4	64.3±22.9	0.79	66.0±24.3	0.97
	3-month	64.3±19.9	66.3±21.7	0.98	71.2±21.8	0.42
	p-value***	0.50	0.20		0.03	

BW = body weight; BMI = body mass index; WC = waist circumference; SBP = systolic blood pressure; DBP = diastolic blood pressure; FPG = fasting plasma glucose; PP = postprandial; HbA1c = hemoglobin A1c; HOMA%B = homeostatic model assessment of beta-cell function; HOMA-IR = homeostatic model assessment of insulin resistance

Data presented as mean ± SD

* *p*-value: between all subjects in control and vitamin D group, ** *p*-value: between all subjects in control and subjects with Δ25(OH)D ≥10 ng/mL in vitamin D group, *** *p*-value: between subjects in each group at baseline and 3-month

vitamin D_3/day increased total 25(OH)D level by 0.6 ng/mL whereas 100 IU of vitamin D_2/day increased 25(OH)D level by 0.45 ng/mL [Δ total 25 (OH)D) = 13.07±4.10 ng/mL and 12.82±3.58 ng/mL in vitamin D_3 (15,000 IU, weekly) and vitamin D_2 group (20,000 IU, weekly), respectively]. We also noticed that there was a concurrent decrease in 25(OH)D_3 after supplementation with vitamin D_2 and a small, but significant decrease in 25(OH)D_2 after supplement with vitamin D_3. This phenomenon is likely due to

Table 3. Metabolic characteristic between baseline and 3-month of subjects with baseline total 25(OH)D <30 ng/mL in control and vitamin D group

		Control (n = 12)	Vitamin D_2 or D_3 (n = 23)	*p*-value*
Age (year)		55.8±13.3	63.1±10.1	0.09
F/M (n)		7/5	18/5	0.26
BW (kg)	Baseline	72.8±10.9	65.0±10.9	0.06
	3-month	72.5±10.5	64.4±11.0	0.05
	p-value**	0.94	0.06	
BMI (kg/m^2)	Baseline	29.3±4.7	27.1±3.4	0.25
	3-month	29.2±4.5	26.9±3.6	0.18
	p-value**	1.00	0.07	
WC (cm)	Baseline	99.0±10.1	95.2±10.7	0.28
	3-month	98.7±9.8	93.9±10.4	0.27
	p-value**	0.94	0.04	
SBP (mmHg)	Baseline	129.2±13.6	126.3±11.1	0.72
	3-month	124.8±11.2	122.2±14.2	0.63
	p-value**	0.28	0.13	
DBP (mmHg)	Baseline	83.7±6.9	76.0±9.4	0.03
	3-month	79.6±7.5	78.7±9.3	0.87
	p-value**	0.17	0.25	
FPG (mg/dL)	Baseline	103.4±10.4	103.9±10.9	0.66
	3-month	105.0±16.1	103.4±11.12	0.97
	p-value**	0.86	0.53	
PP 2-hour (mg/dL)	Baseline	163.3±15.4	153.2±23.5	0.32
	3-month	158.9±33.1	159.0±35.9	0.93
	p-value**	0.39	0.46	
HbA1c (%)	Baseline	6.12±0.29	6.02±0.35	0.48
	3-month	6.13±0.39	6.08±0.35	0.51
	p-value**	0.70	0.44	
HOMA%B	Baseline	110.86±62.50	107.93±32.84	0.68
	3-month	106.73±50.01	101.85±33.75	0.89
	p-value**	0.48	0.10	
HOMA-IR	Baseline	1.82±0.99	1.89±0.85	0.79
	3-month	1.78±0.76	1.73±0.93	0.60
	p-value**	0.81	0.06	
Disposition index (HOMA%B/HOMA-IR)	Baseline	63.95±14.19	63.93±22.78	0.52
	3-month	64.72±23.24	66.19±22.01	0.92
	p-value**	0.70	0.22	

Data presented as mean ± SD

* *p*-value: between subjects with baseline total 25(OH)D <30 ng/mL in control and vitamin D group, ** *p*-value: between subjects in each group at baseline and 3-month

competition for the 25-hydroxylase enzyme by vitamin D_3 and vitamin D_2[18]. However, it is probable that enzymatic catalization by other enzymes with relatively minor roles, such as CYP24A1 and CYP3A4, may be different for vitamin D_3 and D_2, and thus be partially accountable for the observation[19]. As mention previously, because of using different weekly dosage of vitamin D_2 and vitamin D_3 in the present study, total 25(OH)D levels finally increased at the comparable levels at 3-month. Despite the fact that either vitamin D_2 or vitamin D_3 is believed to have comparable biological effects[20], statistical analysis might imply that vitamin D_3 relates to a larger decrease in WC. A larger clinical trial of vitamin D supplement is warranted before drawing any conclusion about the difference in biological effect between vitamin D_2 and vitamin D_3.

More important, this is the first study in Thais that either vitamin D_2 or vitamin D_3 supplement for three months in high-risk subjects (prediabetes and/or

Table 4. The change in the status of glucose tolerance at 3-month of subjects in control and vitamin D group stratified by the status of glucose tolerance at baseline (IFG, IGT, combined IFG/IGT)

Time	Glucose tolerance	Control (n = 18)	Vitamin D_2 or D_3 (n = 29)	*p*-value*
At baseline	IFG	0	6	
At 3-month	Normal		0	NA
	IFG		5	
	IGT		0	
	Combined IFG/IGT		1	
	DM		0	
At baseline	IGT	7	11	
At 3-month	Normal	1	3	0.786
	IFG	1	0	
	IGT	4	5	
	Combined IFG/IGT	1	2	
	DM	0	1	
At baseline	Combined IFG/IGT	11	12	
At 3-month	Normal	2	0	0.514
	IFG	3	2	
	IGT	2	2	
	Combined IFG/IGT	3	7	
	DM	1	1	

DM = diabetes mellitus; NA = not applicable; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; FPG = fasting plasma glucose; 2-h PG = 2-hour plasma glucose

* *p*-value: between group at 3-month

Glucose tolerance: normal (FPG <100 and-2 h PG <140 mg/dL), IFG (FPG = 100-125 and 2-h PG <140 mg/dL), IGT (FPG <100 and 2-h PG = 140-199 mg/dL), combined IFG/IGT (FPG = 100-125 and 2 h-PG = 140-199 mg/dL), DM (2 of the following: FPG ≥126 mg/dL, 2-h PG ≥200 mg/dL, HbA1c ≥ 6.5%)

overweight/obese) associated with a decrease in WC. A trend of reduction in BW ($p = 0.05$), SBP ($p = 0.05$), BMI ($p = 0.06$), and insulin resistance (HOMA-IR, $p = 0.09$) were additionally found. The beneficial effects of vitamin D supplement for several health-related issues, including the prevention of diabetes and obesity, reduction in blood pressure, are the topic of intense discussion[3,21]. The evidence from basic science suggested that vitamin D increases the synthesis of insulin, promotes beta cell survival, protects apoptosis cell death of beta cell, directly enhances insulin sensitivity in peripheral insulin-target cells (such as skeletal muscle and adipose tissue), suppresses the renin-angiotensin aldosterone system (RAS) and decreases the inflammatory cytokines[4]. All of these are potential mechanisms explain favorable effects of vitamin D supplement on promote insulin secretion and increase insulin sensitivity. Correspondingly, the present study demonstrated that vitamin D supplement tended to decrease insulin resistance (HOMA-IR). The benefit of reduction in insulin resistance was enhanced when the change of total 25(OH)D ≥10 ng/mL. Subjects with Δ25(OH)D ≥10 ng/mL had lower insulin resistance and higher disposition index than those with Δ25(OH)D <10 ng/mL. Thus, the optimum change in 25(OH)D might be needed to demonstrate the benefit of vitamin D supplement on glucose homeostasis in high-risk subjects. Nonetheless, the reduction in FPG was not found in the present study. On the other hand, a systemic review and meta-analysis by George et al demonstrated a small reduction in FPG (-5.76 mg/dL) after receiving vitamin D supplement[9]. The explanation of neutral effect of vitamin D on FPG in our study could be difference in study design, ethnicity, fat mass and duration of vitamin D supplementation. There were a small number of subjects who received relatively short duration of vitamin D supplement in our study. More important, most of the subjects (~83%) were relatively vitamin D sufficient. When vitamin D is sufficient in the circulation, increasing in vitamin D intake might not reveal significant benefit in either classical or non-classical effects of this vitamin[22].

There is evidence that vitamin D affects body fat mass by inhibiting adipogenic transcription factors and lipid accumulation during adipocyte differentiation[23] and influencing adipokine production and the inflammatory response in adipose tissue[24]. The mechanism implicating vitamin D with hypertension

is a negative regulator of vitamin D on the RAS[25,26]. Other notable hypotheses have suggested that vitamin D influences vascular endothelial function or vascular smooth muscle intra-cellular calcium concentrations[27]. Therefore, vitamin D deficiency may increase the risk of metabolic syndrome. Improvement in metabolic phenotype was demonstrated in the present study. As mention previously, there were significant decrease in WC and a trend of decreasing SBP, BMI, and BW.

Up to date, the issue of benefit of vitamin D on anthropometric measurements and glucose homeostasis is still inconclusive and this issue in Asian populations is scant. Our results suggested benefits of vitamin D on metabolic phenotypes in Asian. The strength of the present study is the study design that is randomized controlled trial in Thais. As mention previously, the limitation of our study was a small number of subjects and short duration of vitamin D supplement.

Conclusion

Weekly supplement of vitamin D_2 (20,000 IU) or vitamin D_3 (15,000 IU) improve metabolic phenotypes, including WC, SBP, HOMA-IR, and disposition index in subjects with prediabetes. Vitamin D_3 supplement may decrease waist circumference more than D_2 supplement.

What is already known on this topic?

Vitamin D_2 is less effective than vitamin D_3 in raising total 25(OH)D levels.

What this study adds?

Weekly supplement of vitamin D_2 (20,000 IU) or vitamin D_3 (15,000 IU) improve metabolic phenotypes in Thai subjects with prediabetes.

Vitamin D_3 supplement may decrease waist circumference more than D_2 supplement.

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Potential conflicts of interest

None.

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ผลของวิตามินดีต่อภาวะอ้วนลงพุงในประชากรไทยที่มีสภาวะเสี่ยงต่อโรคเบาหวาน

หทัยกาญจน์ นิมิตพงษ์, รัตนพรรณ สมิทธารักษ์, สุนีย์ แซ่ตั้ง, ณัฐพิมณฑ์ ภิรมย์เมือง, ละออ ชัยลือกิจ, บุญส่ง องค์พิพัฒนกุล

วัตถุประสงค์: *เพื่อศึกษาผลของการให้วิตามินดีเป็นเวลา 3 เดือน ต่อสัดส่วนของร่างกายและระดับน้ำตาลของผู้เข้าร่วมโครงการศึกษาที่มีภาวะเสี่ยงต่อการเป็นโรคเบาหวาน [impaired fasting glucose (IFG) และ/หรือ impaired glucose tolerance]*

วัสดุและวิธีการ: *ผู้เข้าร่วมโครงการศึกษาที่มีภาวะ IFG และ/หรือ IGT จำนวน 47 ราย ถูกสุ่มแบ่งออกเป็น 3 กลุ่ม คือ กลุ่มควบคุม (จำนวน 18 ราย) ได้รับวิตามินดีสองขนาด 20,000 ยูนิตต่อสัปดาห์ (จำนวน 19 ราย) หรือได้รับวิตามินดีสามขนาด 15,000 ยูนิตต่อสัปดาห์ (จำนวน 10 ราย) มีการวัดสัดส่วนของร่างกายที่ 0 และ 3 เดือน และตรวจความทนต่อกลูโคส (75 g oral glucose tolerance test) ที่ 0 และ 3 เดือน ระดับของ total 25(OH)D, 25(OH)D_3 และ 25(OH)D_2 วัดด้วยวิธี LC-MS/MS ความดื้อต่ออินซูลิน (HOMA-IR) และความสามารถในการหลั่งอินซูลิน (HOMA%B) คำนวณด้วยวิธี homeostasis model assessment*

ผลการศึกษา: *ระดับ total 25(OH)D เพิ่มขึ้นจากค่าตั้งต้นในผู้เข้าร่วมโครงการศึกษาที่ได้รับวิตามินดีสองหรือวิตามินดีสาม และไม่มีการเปลี่ยนแปลงของค่าดังกล่าวในกลุ่มควบคุม (ไม่ได้รับวิตามินดี) ผู้เข้าร่วมโครงการศึกษาที่ได้รับวิตามินดีสาม มีระดับ 25(OH)D_3 เพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ (+13.7±4.9 ng/mL, $p<0.01$) ในขณะที่ผู้เข้าร่วมโครงการศึกษาที่ได้รับวิตามินดีสองมีระดับ 25(OH)D_2 เพิ่มขึ้นอย่างชัดเจน (+25.9±4.2 ng/mL, $p<0.001$) ร่วมกับมีระดับ 25(OH)D_3 ลดลงด้วย (-13.1±3.1 ng/mL, $p<0.001$) ผู้เข้าร่วมโครงการศึกษาถูกแบ่งกลุ่มใหม่เป็น 2 กลุ่ม คือ กลุ่มควบคุม (จำนวน 18 ราย) หรือ กลุ่มที่ได้รับวิตามินดี (วิตามินดีสองหรือวิตามินดีสาม จำนวน 29 ราย) เมื่อครบ 3 เดือน พบว่าผู้เข้าร่วมโครงการศึกษาที่ได้รับวิตามินดีมีเส้นรอบเอวลดลงจากค่าตั้งต้น นอกจากนี้น้ำหนักตัว ($p = 0.05$) ความดันตัวบน (systolic blood pressure, $p = 0.05$) ดัชนีมวลกาย ($p = 0.06$) และค่าความดื้อต่ออินซูลิน ($p = 0.09$) มีแนวโน้มลดลงด้วย ผู้เข้าร่วมโครงการศึกษาที่ได้รับวิตามินดีและมีการเพิ่มขึ้นของ total 25(OH)D levels ≥10 ng/mL มีภาวะดื้ออินซูลินลดลงและการหลั่งอินซูลินดีขึ้น การวิเคราะห์ทางสถิติด้วยวิธี robust regression analysis พบว่าการได้รับวิตามินดีสามส่งผลลดเส้นรอบเอวได้มากกว่าการได้รับวิตามินดีสอง (coefficient = -3.5, $p<0.001$) โดยไม่ขึ้นกับระดับ total 25(OH)D ที่จุดตั้งต้นและค่าดัชนีมวลกาย อย่างไรก็ตามเมื่อทำการเปรียบเทียบระหว่างผู้เข้าร่วมโครงการศึกษาที่ได้รับวิตามินดีสามและวิตามินดีสอง พบว่าการเปลี่ยนแปลงของดัชนีชี้วัดของภาวะอ้วนลงพุงตัวอื่นไม่มีความแตกต่างกัน*

สรุป: *การให้วิตามินดีสองขนาด 20,000 ยูนิตต่อสัปดาห์ หรือ วิตามินดีสามขนาด 15,000 ยูนิตต่อสัปดาห์ เป็นเวลา 3 เดือน ส่งผลให้ metabolic phenotypes ในคนที่มีความเสี่ยงต่อการเป็นเบาหวานดีขึ้น และการได้รับวิตามินดีสามอาจส่งผลลดเส้นรอบเอวได้มากกว่าการได้รับวิตามินดีสอง*