ภาวะขาดวิตามินดีในคนไข้เบาหวานชนิดที่ 2

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บทคัดย่อ

บทนำ จากข้อมูลในปัจจุบันพบว่า การขาดวิตามินดี นอกจากมีผลต่อโรคทางด้านกระดูกและข้อแล้ว ยังส่งผลต่อการเกิดโรคต่างๆ ได้แก่ มะเร็งบางชนิด โรคหลอดเลือดแดง และ เบาหวาน เป็นต้น

วัตถุประสงค์ เพื่อศึกษาความสัมพันธ์ของภาวะขาดวิตามินดีกับโรคเบาหวานชนิดที่ 2

วิธีการศึกษา ทบทวนแฟ้มประวัติเวชระเบียนผู้ป่วยนอกคัดเลือกอาสาสมัครจากผู้ป่วยเบาหวานชนิดที่ 2 ที่มาตรวจรักษาที่ โรงพยาบาลมหาวิทยาลัยบูรพา จำนวน 360 คน โดยเก็บข้อมูลพื้นฐาน ข้อมูลสุขภาพ ข้อมูลทางห้องปฏิบัติการ ได้แก่ ระดับวิตามินดี (25(OH)D)

ผลการศึกษา ค่าวิตามินดี 25 (OH)D เฉลี่ยของอาสาสมัคร อยู่ที่ 25.0±7.7 ng/ml โดยพบว่ามีอุบัติการณ์ของภาวะขาดวิตามินดี ระดับ 25 (OH)D <20 ng/ml คิดเป็นร้อยละ 26.6 และมีภาวะพร่องวิตามินดีที่ระดับ 25 (OH)D 25-29 ng/ml คิดเป็นร้อยละ 48.8 และ พบ ดัชนี มวลกาย (BMI) (r = -0.123, p-value = 0.02) เส้นรอบเอว (waist circumference) (r = -0.0565, p-value = 0.28) HOMA-IR (r = -0.006, p-value = 0.91) ที่มากมีความสัมพันธ์ผกผันต่อระดับวิตามินดีหรือเพิ่มความเสี่ยงต่อภาวะขาดวิตามินดี ส่วนการทำงานของตับ (ALT) พบว่าประชากรร้อยละ 10.5 มีภาวะตับอักเสบจากไขมันพอกตับ (nonalcoholic fatty liver disease; NAFLD) โดยพบว่า ความดันโลหิต (DBP) (r = 0.159, p-value = 0.002) และ Fasting blood sugar (FBS) (r = 0.127, p-value = 0.016) มีความสัมพันธ์ไปในทิศทางเดียว กับระดับวิตามินดี ส่วน insulin sensitivity (r = -0.186, p-value < 0.001) ระดับ Triglyceride (r = -0.138, p = 0.009) และ Time to DM (r = -0.182, p = 0.001) มีความสัมพันธ์ผกผันต่อการเกิดภาวะตับอักเสบจากไขมันพอกตับ NAFLD

สรุป พบภาวะขาดวิตามินดีในคนไข้เบาหวานชนิดที่ 2 สูง โดยดัชนีมวลกาย (BMI) เส้นรอบเอว (waist circumference) และ HOMA-IR ที่มาก จะมีความสัมพันธ์ต่อการเกิดภาวะขาดวิตามินดีที่มากขึ้น นอกจากนี้ยังพบว่าระดับน้ำตาล Fasting blood sugar (FBS) ที่สูง insulin sensitivity ที่ต่ำ และระยะเวลาการเป็นเบาหวานที่สั้นกว่าเพิ่มอุบัติการณ์ของภาวะไขมันพอกตับ

คำสำคัญ เบาหวานชนิดที่ 2 ภาวะขาดวิตามินดี ภาวะดื้ออินซูลิน

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Vitamin D deficiency in diabetic patients

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Abstract

Introduction Current evidence suggests that vitamin D deficiency may contribute to an increased risk of type 2 DM.

Objective The aim of this study is to explore the relationship between vitamin D status and type 2 DM.

Material and Methods A cross-sectional study was conducted on 360 patients at the outpatient diabetes clinic of Burapha University Hospital. Patients were prospectively recruited, physically examined, submitted to laboratory investigations as well as given a vitamin D level assessment.

Results The mean level of 25(OH)D was 25.0 ± 7.7ng/ml. 26.6% of the patients had vitamin D deficiency; 48.8% had vitamin D insufficiency. After making adjustments for all variables, we found that body mass index (BMI) (r = -0.123, p-value = 0.02), waist circumference (WC) (r = -0.0565, p-value=0.28), and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) (r = -0.006, p-value = 0.91) had an inverted correlation to vitamin D levels. In terms of ALT levels, about 10.56% of the population had nonalcoholic fatty liver disease (NAFLD). In addition, we found that diastolic blood pressure (DBP) (r = 0.159, p-value = 0.002) and fasting blood sugar levels (FBS) (r = 0.127, p-value = 0.016) correlated with the presence of NAFLD. In contrast, insulin sensitivity (r = -0.186, p-value < 0.001), triglycerides (r = 0.138, p = 0.009), and Time to DM (r = -0.182, p = 0.001), had inversely correlated with NAFLD.

Conclusion High prevalence of vitamin D deficiency was observed in our diabetic type 2 patients. After multivarious adjustments for all variables, high WC, high BMI, and high HOMA-IR were associated with an increased risk of vitamin D deficiency; while high FBS, low insulin sensitivity and short duration of a type 2 DM were associated with an increased risk of NAFLD.

Keywords Vitamin D deficiency, NAFLD, Diabetic type 2, HOMA-IR

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Introduction

Type 2 diabetes mellitus (type 2 DM) has become a major public health problem in Thailand. Patients with type 2 DM have magnified the risk of developing cardiovascular disease. Several cardio-metabolic risk factors including obesity, dyslipidemia, diabetes and hypertension tend to be linked to insulin resistance.[1] In addition, evidence suggests a role of vitamin D in insulin resistance and cardiovascular disease. However, the relationship between vitamin D status and diabetes is unclear and has not been fully explored in Thai populations.

The major source of vitamin D is synthesized endogenously from the skin after exposure to sunlight. The contribu tion of diet and supplements are considered a minor source. Vitamin D plays a major role in maintaining calcium and bone metabolism. Additionally, vitamin D may play an essential role in a diversity of non-skeletal health activities, consisting of immune function and inflammation, as well as the proliferation, differentiation and apoptosis of the cell. Literature has found the association of vitamin D status and chronic disorders including cardiovascular diseases, diabetes mellitus as well as osteoporosis. Furthermore, altered calcium and vitamin D metabolism are associated with insulin resistance (IR), reduced cell function, metabolic syndrome (MS), glucose intolerance and diabetes.[2-5]

It has been discovered that type 2 diabetes relates to vitamin D status.[6,7] A number of studies have found an association between 25-hydroxyvitamin D (25 (OH) D) levels and type 2 diabetes. [8] However, since most of the data was collected from Caucasian populations, it is still inconclusive whether there is a relationship between vitamin D status and type 2 diabetes for populations living closer to the equator. Moreover, while it is generally known that heredity influences the risk of type 2 diabetes, environmental factors (for example, a modern and sedentary lifestyle), also increase the risk of type 2 diabetes.[9]

Additionally, vitamin D levels differ among different populations.[10] Similar with research done in Thailand, data from Soontrapa et al. have shown the percentages of vitamin D deficiency [25(OH)D <35 ng/mL] was 66.3%.[11] Another study has shown the prevalence of hypovitaminosis D [25(OH)D <30 ng/mL] at 82.4% in 80 patients with heart failure.[12]

In terms of non-alcoholic fatty liver disease (NAFLD), a few studies reported the prevalence of NAFLD between 28-55% in type 2 DM populations in Iran, Saudi Arabia, and Japan.[13-17] In previous studies, this condition has been associated with metabolic syndromes including truncal obesity, hypertension, diabetes and hypercholesterolemia.[14,16-24] In Thailand, an actual incidence and prevalence of nonalcoholic fatty liver disease in NIDDM patients is not known. Until now the relationship between vitamin D deficiency and NAFLD in Thai patients has not been investigated.

In this study, we aim to determine the correlation between vitamin D status and diabetes in Thai patients. Understanding this relationship may help to identify diabetic patients who have a long-term risk of developing cardiovascular disease.

Materials and methods

Study population

A cross-sectional study of outpatients at the Internal Medicine Department of Burapha University Hospital, Thailand, was conducted between October 2016 and September 2017. The study protocol was approved by the Human Subjects Research Committee of Burapha University. We prospectively recruited 360 patients, aged more than 18 years and less than 80 years, who met the criteria for the diagnosis of type 2 DM. All patients were informed about the study and were asked to sign consent forms. We excluded pregnant patients as well as any patients receiving medications or dietary supplements containing any vitamin D component, and requiring prescription drugs that would affect the level of vitamin D, e.g. Calcium-Sandoz forte D multivitamins. Likewise, patients with any disabilities, or those suffering from malignancy, were also excluded.

Data collection

Each subject supplied detailed demographic data such as age, gender, and medical data assessment. Physical examination was performed by physicians, except for body weight, height and waist circumference (WC) (which were measured by a nurse). Fasting blood samples were collected for glucose levels, HbA1C, lipid profiles, liver function tests (LFT), calcium, phosphorus, creatinine, insulin levels and 25-hydroxyvitamin D levels. Body mass index (BMI) was calculated as weight in kilograms, divided by the square of height in meters. Serum 25(OH)D were measured using a chemiluminescent immunoassay (Architect I 1000 SR Abbott). This immunoassay defined normal vitamin D levels as serum 25(OH) D levels from 30–100 ng/mL. Vitamin D insufficiency and deficiency were determined as serum 25(OH)D levels in the range from 21 to 29 ng/mL and ≤20 ng/mL, respectively.[25] Insulin resistance (IR) was defined as the homeostasis model assessment of resistance to insulin.

Statistical analysis

Statistical analyses were performed using a Statistical Package program. Data is presented as mean ± S.D. for normally distributed continuous variables (or median for the continuous variables that were not normally distributed). Categorical variables were presented as number and percent. Comparisons between patients' characteristics in each vitamin D group were performed using an unpaired t-test for normally distributed continuous variables (or a Chi-square test for the continuous variables that were not normally distributed). Pearson's correlation coefficient was used to calculate the linear

relationship between two variables. A 2-sided probability value of ≤0.05 was considered statistically significant.

Results

Baseline characteristics

The patient's baseline characteristics are shown in Table 1. The majority of the patients were elderly with an average age of 63.2 ± 9.6 years. 199 patients were female (55.2%) and 161 were male (44.7%). The mean BMI was 27.4 ± 5.1 kg/m2, meaning more than 64% of the population was obese (BMI>25), and more than 28.8% were morbidly obese (BMI > 35). The mean waist circumference was 97.0 ± 26.6 cm. 63% of the female population had waist circumferences more than 80 cm. 59% of the male population had waist circumferences more than 90 cm. Both group results are considered higher than the standard values of The US National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) guidelines.[26]

In terms of vitamin D levels, the mean of serum 25(OH)D levels in our population was 25.0 ± 7.7 ng/mL. The overall prevalence of hypovitaminosis D was 75.5%. Among these results, vitamin D insufficiency was 48.8%. The prevalence of vitamin D deficiency was 26.6%, as shown in Table 1.

Table 1 Baseline demographic data of the type 2 DM patients

Characteristics	Mean ± S.D.	Number	Percentage
Sex			
Female		199	55.2
Male		161	44.7
Average age	63.2 ± 9.6		
18-49 yrs		24	6.6
50-59 yrs		94	26.1
60-69 yrs		136	37.7
70-79 yrs		105	29.1
More than 80 yrs		1	0.2
Vitamin D level ng/ml	25.0 ± 7.7		
<20		96	26.6
20-25		107	29.7
26-29		69	19.1
≥30		88	24.4
BMI kg/m^2	27.4 ± 5.1		
≤25.0		126	35.0
>25		133	36.9
≥30		101	28.0
HbA1c %			
≤7		133	36.9
7-8		185	51.3
≥9		42	11.6
Waist circumference (cm)	97.0 ± 26.6		
Female ≤80		73	20.2
Female >80		127	35.2
Male ≤90		65	18.0
Male >90		95	26.3
SGPT/ALT U/L			
0-50		322	89.4
Female		186	51.6
Male		136	37.7
>50		38	10.5
Female		13	3.6
Male		25	6.9
HOMA-IR	4.8 ± 6.7		
<3		184	51.2
3-5		88	24.5
>5		87	24.2

BMI: Body Mass Index; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance.

As we compared the vitamin D deficiency group to the non-deficient group, we found that females had a significantly higher proportion of vitamin D deficiency, 70.8% vs. 49.6% ($p < 0.001$), especially in a female population with waist circumferences greater than 80 cm (35.3% vs. 29.2% $p < 0.001$), as shown in Table 2.

In addition, the patient group with vitamin D deficiency had a higher BMI mean (28.4 ± 5.9 vs. 27.1 ± 4.8, $p = 0.035$), higher use of the DPP-4 inhibitor (40.6% vs. 28%, $p = 0.023$), and lower albumin levels (4.2 ± 0.4 vs. 4.3 ± 0.3, $p < 0.001$) when compared with the non-deficient group. When we classified the population into different levels of vitamin D (as a vitamin D deficiency group, a vitamin D insufficiency group and a normal vitamin D group) we found higher waist circumferences in the vitamin D deficiency group, with statistical significance ($p = 0.001$), as compared with the other groups.

Table 2 Comparison of the numbers and percentages of demographic data between vitamin D ≤ 20 and vitamin D > 20, using a Chi-square test

	Vit D ≤ 20 (%) (n=96)	**Vit D > 20 (%) (n=264)**	*p - value*
Sex			<0.001*
Male	28 (29.2)	133 (50.4)	
Female	68 (70.8)	131 (49.6)	
Waist circumference (cm)			0.001*
Female ≤80	18 (18.8)	55 (20.8)	
Female >80	50 (52.1)	77 (29.2)	
Male ≤90	12 (12.4)	53 (20.1)	
Male >90	16 (16.7)	79 (29.9)	
DPP			0.023*
No	57 (59.4)	190 (72.0)	
Yes	39 (40.6)	74 (28.0)	

BMI: Body Mass Index; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance
DPP-4: Dipeptidyl peptidase-4 inhibitors; P-values < 0.05 were considered significant

The status and severity of diabetes type 2 and vitamin D

The average duration of diabetes treatment for the whole population was 10.1 ± 1.5 years, with a mean level of fasting blood sugar at 144.5 ± 39.9. The overall HbA1C level was 7.4 ± 1.3% (of this, 36.9% had HbA1C < 7%, and only 11.6% of the population had HbA1C > 9%). The level of HOMA-IR was 4.8 ± 6.7, with 24.2% having HOMA-IR > 5, indicating that about one-fourth of the population had very high insulin resistance. When we compared a

well-controlled diabetes group (HbA1C < 7%) with a poorly controlled group (HbA1C ≥ 7%), we found that the poorly controlled group had a longer duration of diabetes (10.9 ± 7.8 years vs. 8.1 ± 6.9 years, p = 0.001), higher triglyceride levels (149.9 ± 84.5 vs. 123.9 ± 55.6, p = 0.002), and higher HOMA-IR scores (5.8 ± 8.2 vs. 3.2 ± 3.5, p = 0.002) as compared with a good control group. In contrast, vitamin D, AST and ALT levels were not statistically significantly different between the two groups (see Table 3).

Table 3 Comparison of the mean of demographic data and laboratory data between HbA1C <7% and HbA1C ≥7 using a t-test method

	Mean ± S.D.	HbA1C ≥ 7 (S.D.) (n=227)	HbA1C < 7 (S.D.) (n=133)	*p - value*
Age (yrs)	63.2 ± 9.6	63.1 (9.2)	63.6 (10.3)	0.616
Time to DM (yrs)	10.1 ± 1.5	10.9 (7.8)	8.1 (6.9)	0.001*
BMI (kg/m2)	27.4 ± 5.11	27.6 (5.0)	27.3 (5.3)	0.553
Waist circumference (cm)	97.0 ± 26.6	97.9 (26.7)	95.6 (26.8)	0.428
ALT (mg/dl)	26.0 ± 18.3	27.0 (19.2)	24.4 (16.8)	0.203
HOMR-IR	4.8 ± 6.7	5.8 (8.2)	3.2 (3.5)	0.002
Insulin sensitivity	0.4 ± 0.3	0.4 (0.3)	0.5 (0.4)	<0.001*
HDL (mg/dl)	47.5 ± 11.9	46.4 (10.2)	49.6 (14.1)	0.022*
Vitamin D	25.0 ± 7.7	24.9 (7.5)	7.5 (8.3)	0.702
FBS (mg/dl)	144.5 ± 39.9	124.0 (24.9)	156.7 (42.1)	<0.001*

BMI: Body Mass Index; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; FBS: Fasting Blood Sugar; HDL: High Density Lipoprotein, P-values < 0.05 were considered significant.

In this study, we found that BMI was inversely correlated with vitamin D levels (r = –0.123, p = 0.020). In addition, a significant positive correlation between ALT levels and DBP (r = 0.159, p = 0.002), FBS (r = 0.127, p = 0.016) and triglyceride levels (r = 0.138, p = 0.009) were observed. On the other hand, the data showed a negative correlation between ALT and time to DM (r = –0.182, p = 0.001) with insulin sensitivity (r = –0.186, p < 0.001), as shown in Table 4.

Table 4 Determinants of vitamin D deficiency using Pearson's correlation (n=360)

Parameters	Vitamin D r, *p - value*	Parameters	ALT (n=360) r, *p - value*
DBP	-0.031, 0.564	DBP	0.159, 0.002*
BMI	-0.123, 0.020*	BMI	0.054, 0.310
Time to DM	-0.043, 0.416	Time to DM	-0.182, 0.001*
Insulin sensitivity	-0.018, 0.729	Insulin sensitivity	-0.186, <0.001*
FBS	0.053, 0.315	FBS	0.127, 0.016*
triglyceride	-0.042, 0.432	triglyceride	0.138, 0.009*

BMI, body mass index; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; FBS, fasting blood sugar; p-values < 0.05 were considered significant, r = Correlation.

Table 5 Comparison of the mean of demographics data and laboratory data between ALT normal and ALT abnormal using a t-test method

	ALT Abnormal (S.D.)	ALT normal (S.D.)	*p - value*
Age (yrs)	60.4 (9.9)	65.0 (9.1)	<0.001
Time to DM (yrs)	8.6 (6.9)	10.7 (7.9)	0.013*
SBP (mmHg)	133.3 (13.3)	136.4 (16.0)	0.047*
DBP (mmHg)	77.0 (14.7)	74.3 (14.2)	0.091
BMI (kg/m^2)	27.7 (4.7)	27.3 (5.3)	0.528
Waist circumference (cm)	96.9 (27.9)	97.1 (26.0)	0.947
Hematocrit (%)	39.7 (5.5)	37.8 (4.7)	<0.001*
FBS (mg/dl)	152.9 (41.7)	139.6 (38.0)	0.002*
HOMRIR	5.7 (8.0)	4.3 (6.3)	0.079
Insulin sensitivity	0.3 (0.3)	0.5 (0.4)	0.001*
HbA1C (%)	7.6 (1.4)	7.3 (1.3)	0.086
Triglyceride (mg/dl)	152.9 (91.4)	132.6 (63.9)	0.014*
Vitamin D (mg/dl)	25.8 (7.2)	24.6 (8.0)	0.147
Albumin (mg/dl)	4.4 (0.3)	4.2 (0.3)	<0.001

BMI: Body Mass Index HOMA-IR: Homeostatic Model Assessment for Insulin Resistance FBS: Fasting Blood Sugar HDL: High Density Lipoprotein (P-values < 0.05 were considered significant)

In terms of NASH we found that the Hematocrit, hemoglobin, FBS and triglyceride levels were significantly higher in the NASH group compared with the non-NASH group: 39.7 ± 5.5 VS 37.8 ± 4.7 (p < 0.001), 13 ± 1.6 VS 12.2 ± 1.7 (p < 0.001), 152.9 ± 41.7 VS 139.6 ± 38 (p = 0.002)

and 152.9 ± 91.4 VS 132.6 ± 63.9 (p = 0.014), respectively. We also observed significant lower levels of age, time to DM, SBP and insulin sensitivity compared with the non-NASH: 60.4 ± 9.9 VS 65 ± 9.1 (p < 0.001), 8.6 ± 6.9 VS 10.7 ± 7.9 (p = 0.013), 133.3 ± 13.3 VS 136.4 ± 16 (p = 0.047) and 0.3 ± 0.3 VS 0.5 ± 0.4 (p = 0.001), respectively. In contrast vitamin D levels did not statistically significantly differ between the two groups: 25.8 ± 7.2 VS 24.6 ± 8 (p = 0.147). See Table 5

Discussion

The present study showed that only 24.4% of the patients had sufficient vitamin D levels, 26.6% were vitamin D deficient and 48.8% were vitamin D insufficient. This indicates that over 75% of our type 2 DM population had low vitamin D, even though Thailand is situated in a geographical area where the sun shines brightly all year. The high prevalence of vitamin D deficiency in our patients is owing to the lack of knowledge about how important it is to normalize vitamin D levels, and that vitamin D supplements can minimize or even prevent the severity of many chronic diseases, especially type 2 DM.

A study by Chailurkit et al. reported that the Thai population from the central region of the country had a prevalence of vitamin D deficiency around 6.5%, and a vitamin D insufficiency of 43.1%.[27] The results from Dr. Chailurkit's studies showed that diabetic type 2 patients had a much higher incidence of vitamin D deficiency and vitamin D insufficiency, when compared with the overall Thai population. Our data is consistent with the previous study showing that the prevalence of vitamin D deficiency was 24%, and vitamin D insufficiency was 73%.[28]

The high prevalence of vitamin D deficiencies in metabolic syndromes and diabetes type 2, presumably results from the effect of a high quantity of circulating vitamin D on subcutaneous fat.[29] Increased sequestration and low availability due to excess body fat, causes low levels of serum 25(OH)D. Persons with high BMI usually have higher body fat content, which acts as a reservoir for lipid-soluble vitamin D. It has been previously reported in an ambulant adult that the levels of vitamin D were inversely correlated with BMI and waist circumference. We observed similar results in our population. High BMI and increased waist circumference were negatively associated with both the prevalence of vitamin D deficiency and insufficiency. Part of the reason could be the vitamin D endocrine system is altered in high obese subjects, with increased production of 1,25(OH)2D, exerting negative feedback control on the hepatic synthesis of 25(OH)D.

Additionally, we found that age is inversely correlated with vitamin D levels. This result is in agreement with the observation that the capacity of vitamin D production in skin declines with age. Moreover, elderly people are less physically active (especially outdoor activities) and might therefore have less sun exposure. In contrast, a study by Rahman

SA et al. has found that vitamin D levels do not decrease with age.[30] They presumed that plenty of sunlight might conquer weaknesses of a decrease in dermal synthesis of vitamin D in the senile.

It has been found in several studies that there has been an inverse association between serum 25(OH)D concentration and insulin resistance, or T2DM prevalence, regardless of ethnic groups.[31] Lu L et al. reported a significant inverse association between vitamin D levels, fasting insulin levels and HOMA-IR scores in 3263 metabolic syndrome patients. A cross-sectional study from Beijing and Shanghai also observed a significant inverse association of 25(OH)D with fasting insulin levels and HOMA-IR scores in overweight and obese individuals (BMI of 24 kg/m2), but not in their normal-weight counterparts.[32] We found the same trend in our study, the average HOMA-IR was higher in the vitamin D deficiency group, although it did not reach statistical significance. It is plausible that vitamin D may regulate insulin action and enhance insulin responsiveness by direct stimulation of the insulin receptor gene.[31] Besides, vitamin D represses adaptive immunity by inhibiting the maturation of dendritic cells and differentiation of macrophages. As a consequence, it reduces their capacity to present an antigen to CD4+ T cells.[33] In addition, it hinders the proliferation and differentiation of CD4+ T cells into Th1 (T helper) and Th17 cells. These immunomodulatory effects of vitamin D enhance insulin sensitivity.

The observational studies have shown an inverse association between HbA1c and vitamin D status in T2DM patients, suggesting a possible role of vitamin D in glucose control. In a study from Kostoglou-Athanassiou et al. 25(OH)D3 levels were found to be inversely associated with HbA1c levels in diabetic patients, and 25(OH)D3 levels were found to be inversely associated with HbA1c when the patient and the control groups were analyzed together.[34] In our study, we found the same results, indicating that 25(OH)D3 levels may affect glucose control in diabetes mellitus type 2. Several lines of evidence support the connection between vitamin D and insulin resistance. First, the secretion of insulin from pancreatic beta cells may be facilitated by vitamin D; thus, it appears to regulate insulin secretion.[35, 36] Second, insulin resistance may decrease due to vitamin D. In fact, it stimulates the expression of the insulin receptor.[37,38] Third, vitamin D also enhances the GLUT-4 receptor expression in myocytes, as well as improves insulin utilization by increasing adiponectin secretion from adipocytes.

The researcher's studies revealed the same incidence of NAFLD compared to the previous studies, which are around 25.8% vs. 28-55% in the populations of Iran, Saudi Arabia and Japan. However, the serum 25(OH) D3 concentrations were not significantly correlated with the prevalence of NAFLD in our study. We also found that age, HCT, waist circumference, BMI, DBP and triglycerides were significant determinants for NAFLD, as

previously reported.[39-41] Indeed, the findings in this study complied with those of other studies. There was a study involving 1,630 U.S. adolescents which, after adjusting the data for obesity, NAFLD was not associated with vitamin D status. Likewise, a study by Ashraf et al. also found no significant difference in LFT, when comparing adolescents with or without adequate concentrations of vitamin D. Nevertheless, ALT is not a specific or sensitive marker for NAFLD. As a result, further studies are needed to confirm similar findings in other non-Western populations.

In our study, we found that insulin sensitivity had an inverse correlation to NAFLD (r -0.186, $p < 0.001$*). In obese patients with metabolic syndromes, it is felt that high adipokines that promote proinflammatory cytokines contribute to the pathogenesis of NAFLD, suggesting that adipocyte is an important contributor to NAFLD.[42,43] Furthermore, diabetic patients with high waist circumference, high BMI and high triglycerides had high peripheral insulin resistance (a key pathogenesis of NAFLD, in agreement with our study). Important changes in lipid metabolism can occur owing to insulin resistance. The changes included enhanced peripheral lipolysis, increased triglyceride synthesis and increased hepatic uptake of fatty acids. Each may be the cause of hepatocellular triglyceride accumulation.[44] Thus, a significant increase in FFA levels has been observed in patients with NAFLD and type 2 diabetes mellitus compared with type 2 diabetics without NAFLD. We did not determine visceral fat and FFA levels in our patient cohort; however, we would predict that diabetic patients with NAFLD would have higher visceral fat and FFA levels. Future studies should examine these factors and their relationships to occurrences of NAFLD in Thai patients.

The strength of our study minimized seasonal variations of serum 25(OH)D concentrations thanks to its rapid completion. However, there were some limitations because of the following reason: first, our ability to examine the causal relationships between 25(OH)D levels and type 2 DM is limited because of the cross-sectional design of our study. Next, the participants were not randomly selected from the general population. Finally, the diagnosis of NAFLD was based on abnormality of LFT, which is not the gold standard. Future research should be conducted in many institutions and regions together. In addition, a study on the effects of vitamin D substitution, the delay of disease progression and severity of diabetes and metabolic syndromes, will provide a better understanding of the relationships between vitamin D levels and diabetes.

Conclusion

It was found in this study that there was a high prevalence of vitamin D deficiency in diabetic patients along the eastern seacoast of Thailand. After multivarious adjustments for all variables, high WC, high BMI and high HOMA-IR, were significantly associated with an

increased risk of vitamin D deficiency. However, these findings may not be generalized to all Thai patients with diabetes. Therefore, in order to clarify the relationships between vitamin D status, type 2 diabetes and the occurrence of NAFLD in non-Western populations, further intervention trials or longitudinal studies are required.

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