VITAMIN D STATUS AND METABOLIC ABNORMALITY PROFILE AMONG SIBLINGS OF PATIENTS WITH TYPE 2 DIABETES MELLITUS

DHIA J. AL-TIMIMI, MPhil, PhD*
SARAH H. HAZIM, MSc**
IDRIS H. AHMED, MD***

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ABSTRACT

Background: Cross-sectional data provide some evidence that circulating 25-hydroxyvitamin D is inversely associated with metabolic syndrome components. Reported data in populations at high risk for type 2 diabetes mellitus (T2DM), however, are contradictory. In this study we measured 25-hydroxyvitamin D [25(OH) D], glucose, triglycerides, HDL-cholesterol and insulin in siblings of patients with T2DM.

Methods: Body weight, height, waist circumference, blood pressure, glucose, insulin, triglycerides, HDL-cholesterol, and 25(OH) D were measured in 184 apparently healthy individuals, siblings of patients with T2 DM, with age range 20-40 years. Study participants were categorized into 2 groups: a metabolically obese, normal weight (MONW) group and non-MONW group. The association between components of metabolic syndrome and serum 25(OH) D levels was examined.

Results: Participants categorized as MONW group were 155(84.2%) ,exhibited lower serum 25(OH) D levels than did the non-MONW ($p<0.01$). Significantly higher prevalence of vitamin D insufficiency (36.1% vs. 20.7%, $p<0.05$) and severe deficiency (8.4% vs. 3.5%, $p<0.05$) were found in MONW compared to non-MONW group. MONW group had higher mean age, body mass index and waist circumference than non-MONW group. MONW had also higher mean values for HMOA-IR, triglycerides, but lower HDL-cholesterol concentrations. In MONW group, negative correlations of 25(OH) D were observed with waist circumference and triglycerides ($p<0.001$ and $P<0.01$, respectively) and a positive correlation was observed with HDL-cholesterol ($p=0.015$)

Conclusion: Our data showed a low vitamin D status among siblings of T2DM patients, particularly among MONW individuals, suggested that siblings of T2DM are at increased risk of future metabolic disease.

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Keywords: Vitamin D, siblings of diabetics, metabolic health status

Vitamin D deficiency and lower concentrations of serum 25(OH) D might be associated with a higher risk of diabetes and glucose intolerance[1,2]. The relationship between vitamin D and metabolic health status is controversial. Several studies have reported that vitamin D may have protective effects against metabolic syndrome (MS)[3,4], a condition that is highly prevalent in the world[5]. More

* *Professor of clinical Biochemistry; Department of Clinical Biochemistry, College of Medicine, University of Duhok, Duhok, Iraq.*
** *Specialist, Teaching Laboratories, Azadi Teaching Hospital, Duhok, Iraq.*
*** *Specialist, Duhok Diabetes Center, Azadi Teaching Hospital, Duhok, Iraq.*
Correspondence author: Prof. Dhia J. Al-Timimi. Email:altmimidj@yahoo.com

than 30 years ago, it was suggested that there are individuals who are not obese on the basis of body mass index, but who like people with overt obesity, are hyperinsulinemic with insulin-resistance (IR). They are predisposed to T2DM, hypertriglyceridemia, and premature coronary artery disease[6,7]. It is well established that first-degree relatives of T2DM patients are a high risk category for developing T2DM which may potentially be MONW individuals[8].

Vitamin D deficiency has recently been implicated as a possible risk factor in the etiology of numerous diseases, including diabetes[9]. Despite evidence suggestive of possible widespread vitamin D deficiency in Iraqi population[10], attempts to assess vitamin D status in the first degree relatives of patients with T2DM have been few. Given this existing data, it is reasonable to hypothesize that low vitamin D status in siblings of patients with T2DM may predispose them to insulin resistance and metabolically unhealthy status. Reports on this issue are limited and the prevalence of this entity has not been established in the siblings of patients with T2DM who are inherently at high risk for T2DM. Therefore this preliminary study aimed to investigate whether vitamin D status is associated with metabolic health status in a sample of siblings of patients with T2DM in Duhok Diabetes Center (Duhok, Iraq).

MATERIALS AND METHODS

Study population

Across-sectional study was carried out during the period from April to October 2014.One hundred and eighty four apparently healthy subjects, siblings of patients with T2DM were included (87 males and 97 females).. Protocol involved that: all patients diagnosed as T2DM or being treated as such who visited the Duhok Diabetes Center; during the period of the study (n=5783) were interviewed and informed about the nature of the study, and then asked to bring their siblings who are at the age range of 20-40 years in fasting state .At the beginning, a total of 286 were participated in the study. After exclusion of 102 responders who were with BMI >27 or <20 Kg/m2 , non-fasting ,and women with pregnancy, the reminders were enrolled in this study. The study protocol was approved by the ethical committee of the General Directorate of Health, and informed consent was obtained from all the participants at the start of study.

Data Collection: Data were collected from subjects interviewed by special questionnaire form. Included data were demographic information about the individual (age and sex), personal history of DM., coronary heart disease (angina,

myocardial infarction), hypertension, weight gain (after 18 years in women, 21 years in men), low birth weight (<2.5 Kg), and gestational DM. and menstrual irregularities (oligomenorrhea or amenorrhea) in women, and family history of T2DM, premature coronary heart disease (CHD), essential hypertension (<60 years) and hypertriglyceridemia.

Then physical activity was assessed by asking about the physical activity (work, leisure, and travel) in a typical week. History of hypertension was defined as blood pressure > 140/90 mm Hg or being on an antihypertensive medication. Family history of premature CHD was defined as definite MI or sudden death in a first degree relative before 60 years of ages. MONW or non-MONW individual was define according to the scoring method for identifying an MONW individual represented by Ruderman et al8. The proposed scoring value for identifying an MONW individual was > 7.

Anthropometric measurements

Waist circumference (WC) was checked by using a plastic metric tape applied midway between the lower costal margin and the iliac crest. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Resting systolic and diastolic blood pressure(BP) was measured by using random zero sphygmomanometer and cuffs appropriate for arm size.

Biochemical measurements

Biochemical blood measurements were determined by a standard laboratory procedure using Cobas 6000. Roche/Hitachi. Serum concentration of insulin and 25(OH)D were measured by enzyme linked immunosorbent assay (ELISA) method. The homoeostasis model assessment estimates insulin resistance (HOMA-IR) was calculated using the following formula (Glucose [mg/dl] × Insulin [uU/ml]) / 405.

Assessment of vitamin D status

Vitamin D status was assessed as follow: Severe vitamin D deficiency (serum 25(OH) D <10 ng /ml), insufficiency (10-29.9ng/ml), sufficient 30-150 ng/ml and toxic >150 µg /dl).A cut off point of < 25ng/dl of 25(OH) D was used to classify individuals as on low vitamin D status.

STATISTICAL ANALYSES

All data was analyzed using the statistical package for Social Sciences (SPSS); version 21.0. Independent t-test was used to assess differences in serum analyte among groups. Categorical variables were analyzed by Chi square tests.

RESULTS

Subjects consisted of 87 men (47.3%) and 97 women (52.7%), their mean age was 28.9±5.21year and BMI 20-27Kg/m^2 (23.9±1.56). The prevalence of MONW

among the study subjects was 84.2% . The vitamin D status of all study subjects was: severe deficiency (7.6%), insufficiency (33.7%) and sufficient (58.7%).

Table 1 shows the baseline characteristics of the study subjects. A significantly lower mean 25(OH) D level was found in the MONW group compared with non-MONW group (P<0.01). As expected, the comparison between MONW and non-MONW subjects showed higher frequency of some classical risk factors among siblings with MONW compared to non-MONW.

Table1- Baseline Characteristics of All Study Subjects

Characteristics	MONW (n=155)	non-MONW (n=29)	*P*-value
Age (years)	29.2±5.2	26.9± 4.7	<0.05
Systolic BP (mmHg)	113.1± 9.3	112.3± 6.1	0.199
Diastolic BP (mmHg)	74.3 ±7.7	72.5± 7.0	0.294
BMI (Kg/m^2)	24.0± 1.7	22.8 ±1.6	<0.01
Waist Circumference (cm)	87.2 ±7.6	75.8±8.7	<0.05
Fasting serum glucose (mg/dl)	102.1 ±17.8	99.2± 12.3	<0.05
Serum insulin (uIU/ml)	7.42±4.12	6.32±3.71	<0.05
HOMA-IR	1.87±0.42	1.54±0.08	< 0.01
Triglycerides (mg/dl)	146±39.9	78.6±35.7	< 0.01
HDL-Cholesterol (mg/dl)	43.5±12.0	47.8±13.1	<0.05
25(OH) D(ng/ml)	35.8±19.3	44.4± 22.3	< 0.05

The Prevalence of vitamin D and metabolic abnormalities in MONW and non-MONW subjects is presented in Table 2. Significantly higher prevalence of low vitamin D status [(25(OH) D <25 ng/ml] (29.6% vs. 17.2%; OR 2.81, p= 0.05) was observed in MONW group compared to those with non-MONW. MONW group showed a higher prevalence of vitamin D insufficiency (36.1% vs. 20.7%; OR 2.16, p<0.05), and severe vitamin D deficiency (8.4% vs. 3.5%; OR 2.56, p<0.05) than non- MONW group. MONW group had higher mean age, BMI, WC than non-MONW group. MONW had also higher mean values for HMOA-IR, triglycerides, but lower HDL-ch concentrations

Table 2- Prevalence of vitamin D and metabolic abnormalities in MONW and non-MONW subjects
MONW (n=155) non-MONW (n=29)

Variable	n (%)	n (%)	OR	*p*-value*
Waist Circumference (cm)				
male>86.4, female71.1	99(63.8)	3(10.3)	15.3	<0.001
Blood Pressure>140/90 (mmHg)	11(7.1)	3(10.3)	0.66	0.21
Glucose>110(mg/dl)	31(20.0)	3(10.3)	1.28	0.09
Triglyceride>150(mg/dl)	48(30.9)	1(3.4)	12.5	<0.001
HDL-ch <35(mg/dl)	39(25.1)	5(17.2)	1.60	<0.05
25(OH) D <25(ng/ml)	46(29.6)	5(17.2)	2.81	
Vitamin D status				
25(OH) D <10 (ng/ml)	13(8.4)	1(3.5)	2.56	<0.05
25(OH) D 10-29.9(ng/ml)	56(36.1)	6(20.7)	2.16	<0.05
25(OH) D 30-150(ng/ml)	86(55.5)	22(75.8)	0.39	<0.05

*Chi-square test

The relationship between 25(OH) D and metabolic syndrome components in MONW and non-MONW groups is presented in Table 3. On using the Spearman's correlation coefficient (P), the results in MONW group showed, 25(OH) D correlated negatively with WC and triglycerides ($p<0.001$, $p<0.01$).However, in the non-MONW group, no significant correlation was found.

Table 3: Spearman's correlation coefficient *(p)* between 25(OH) D and metabolic syndrome components in MONW and non-MONW subjects.

Variable	MONW		non-MONW	
	P	p	*P*	p
WC	**-0.612**	**<0.001**	**0.182**	**0.139**
BP	**-0.08**	**0.712**	**-0.131**	**0.351**
Glucose	**-0.075**	**0.682**	**0.193**	**0.146**
Triglycerides	**-0.551**	**<0.01**	**0.212**	**0.273**
HDL-cholesterol	**0.452**	**0.015**	**0.159**	**0.224**

DISCUSSION

This study has provided definitive evidence that siblings of patients with T 2 DM had low vitamin D status. The best relationship of low 25(OH) D levels was with obesity waist circumference, and hypertriglyceridemia. It is noteworthy that 41.3% appear at risk for vitamin D insufficiency or severe deficiency and most of them were MONW individuals. Several metabolic abnormalities are associated with vitamin D status. Of these, insulin resistance, T2DM and obesity are with the most marked negative effect on serum 25(OH) D concentrations 11 .Hence, vitamin D status may associate with metabolic unhealthy status in those with positive family history of DM.. In this study, lower concentrations of serum 25(OH) D and high prevalence of low vitamin D among MONW siblings is of potential concern and ever reported widely. In fact, this study confirms that low vitamin D status (serum 25(OH) D <25 ng/ml) is highly associated with the metabolically unhealthy status in siblings. It is noteworthy that the prevalence of MONW individuals among the siblings of patients with T 2 DM was 84.2 % and most of these individuals (63.8%) was with obesity waist circumference (>86.4 cm for males, and >71.1 cm for females). Moreover, they had higher means of HOMA-IR than non-MONW group, while the level of serum 25(OH) D was lower in those with high levels of triglycerides. Thus, this observation implied more susceptibility to low vitamin D status among MONW group, and reflect the association between vitamin D status and the high prevalence of MONW individuals among siblings of T2DM patients. This is in resonance with a study carried out by Liu,2005 3 as well as with a separate study, in which Reis and coworkers 12

reported a strong inverse relationship between 25(OH) D levels and prevalent metabolic syndrome that is independent of important confounders. The mechanism(s) by which low vitamin D could be associated with MS remain to be elucidated. A research among humans suggests that low 25(OH) D levels are associated with glucose intolerance and insulin resistance 13. However, our finding is a positive step towards further research to determine if vitamin D supplementation in siblings of patients with T2DM may reduce the risk of developing diabetes, this withstanding that 34/184(18.5%) of the study siblings was pre-diabetes or diabetes(FBG>110 mg/dl) and 26.6% had hypertriglyceridemia .

There have been reports of prevalence of MONW in general population, which ranges from 5-45%. But, however none of these reports directly related the prevalence of MONW among siblings of patients with T2DM Thus, we carried out this cross-sectional study on three identities; MONW, vitamin D, and siblings of patients with T2DM. The prevalence of metabolic abnormalities for MONW was significantly higher than that of non-MONW. For example, MONW individuals had higher mean age, body mass index, obesity waist circumference than non-MONW group. MONW individuals had also higher mean values of serum triglycerides, but lower HDL-cholesterol and serum 25(OH) D concentrations. This finding agrees with trials performed in general population 14as well as in our population 15

This study has few limitations, first we conducted this present study in Duhok Diabetes Center which is a health facility and health facility based studies are more likely to be biased than population based randomized studies regarding sampling. Second, our study is a cross-sectional study and a cross-sectional analysis has limitations as research methodology as it lacks follow up so the data presented are less likely to be representative of the general population actual data and of the same individual at other times. Third, some of the variables present in the study were depending on history taking and this carries an inherent risk of bias. Despite these limitations, our descriptive study interpreted with suitable caution can offer some useful insight to complement the data from the forthcoming studies using randomization

CONCLUSIONS

A low vitamin D status is present in one third of the siblings of patients with T2DM, particularly among MONW individuals; this finding may have clinical implications due to the increased risk of future metabolic disease. A large prospective study is needed to confirm our

observation, and experimental data may further elucidate the biological mechanism of the associations.

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پوختە

ئاستێ ڤیتامین د و دوسیا شزوزا میتابولزمێ لدەف کەسوکارێن نەخوشین شەکرێ جورێ دووێ

ئارمانج: ڤەکولینا cross section پیزانینێن بەرجاڤ دان کو ئاستێ 25 (OH) D دناف خوینێدا پەیوەندیەکا هەڤدژ یا هەی دگەل پیکهاتێن ئێشا میتابولزمێ. پێزانینێن دیارکری لدەف جڤاکێن ڕێژەیا بلندتر یا مەترسیێ بو نەخوشیا شەکرێ جورێ دووێ، دگەل هندێ هەڤدژن. دڤێ ڤەکولینێدا پشکنینا D (OH) 25، گلوکوز، بەزێ سیانی، کولیسترولێ HDL، و ئەنسولین لدەف کەسوکارێن نەخوشێن شەکرێ جورێ دووێ هەی هاتنە ئەنجامدان.

ریکێن ڤەکولینێ: هەژمارتنا کێشا لەشی، بلندایی، درێژاییا دورماندوری سکی (WC)، فشارا خوینێ، گلوکوز، بەزێ سیانی وکولیسترولێ HDL و D (OH) 25 لدەف ١٨٤ کەسێن بسەرڤە دساخلەم، کەسوکارێن نەخوشێن شەکرێ جورێ دووێ هەی، دگەل ژیێ دناڤبەرا 40-20 سالان. بەشداربو هاتنە دابەشکرن ل سەر دوو گروپان: گروپێ MONW و گروپێ non-MONW. پەیوەندی دناڤبەرا پیکهاتێن ئێشا میتابولزمێ و ئاستێ 25 (OH) D دناف خوینێدا هاتە پشکنینکرن.

ئەنجام: گروپێ MONW (84.2%) 155 دیارکر ئاستەکێ نزمتر یێ 25 (OH) D بەراوردی کرن دگەل گروپێ non-MONW (P<0.01). هاتە دیتن بشێوەکێ بەرجاڤ ڕێژەیەکا بەربەلاڤبونێ یا بلندتر یا نە بەسیا 25 (OH) D (36.1% vs. 20.7%, P<0.05) و کێمبونا دژوار (8.4% vs. 3.5%, P<0.05) لدەف گروپێ MONW بەراوردی کرن دگەل گروپێ non-MONW. لدەف گروپێ MONW ڕێژەیا بلندتر یا تیکرایێ ئاستی هاتە دیتن دگەل ژیی، هیمایێ کێشا لەشی (BMI)، و WC. و هەروەسا ڕێژەیا بلندتر یا تیکرایێ ئاستی لدەف گروپێ MONW دگەل HOMA-IR، بەزێ سیانی، بەلێ ڕێژەیەکا نزمتر یا تیکرایێ ئاستی دگەل کولیسترولێ HDL. لدەف گروپێ MONW پەیوەندیەکا هەڤدژ هاتە دیتن دناڤبەرا 25 (OH) D و بەزێ سیانی و WC (P<0.001 وP<0.01 لدویف ئێك) و پەیوەندیەکا وەك هەڤ دگەل کولیسترولێ HDL (P=0.015).

دەرئەنجام: پیزانینێن مە دیارکر ئاستەکێ نزمتر یێ ڤیتامین د لدەف کەسوکارێن نەخوشێن شەکرێ جورێ دووێ و بتایبەتی لدەف کەسێن MONW هەی، پیشنیار دکەت کو کەسوکارێن نەخوشێن شەکرێ جورێ دووێ ڕێژەیەکا بلندتر یا مەترسیێ یاهەی بو ئێشێن میتابولزمێ دپاشەروژێدا.

الخلاصة

حالة الفيتامين د وملف الشذوذ الايضية بين اقارب مرضى السكري من النوع الثاني

الخلفية والاهداف: دراسة مقطعية زودت بمعلومات مشهودة بأن مستوى 25 (OH) D في الدم له علاقة عكسية مع محتويات المتلازمة الايضية. المعلومات المدونة في المجتمعات التي لديها نسبة خطورة اعلى للنوع الثاني من مرض السكري, مع ذلك, تناقضية. في هذه الدراسة تم قياس 25 (OH) D, الكلوكوز, الشحوم الثلاثية, كوليسترول الHDL والانسولين في اقارب مرضى السكري من النوع الثاني.

طرق البحث: تم قياس وزن الجسم، الارتفاع، محيط الخصر، ضغط الدم، الكلوكوز، الانسولين، الشحوم الثلاثية، كوليسترول الـHDL و25 (OH) D في ١٨٤ افراد أصحاء ظاهرياً، اقارب مرضى السكري من النوع الثاني، مع عمر يتراوح بين ٢٠-٤٠ سنة. المشاركين في هذه الدراسة تم تقسيمهم الى مجموعتين: مجموعة السمناء أيضياً، اوزانهم طبيعية (MONW) ومجموعة الـ(non-MONW). تم فحص العلاقة بين محتويات المتلازمة الايضية ومستوى الـ25 (OH) D في الدم.

النتائج: مجموعة الـ(MONW) كانوا (84.2%) 155، بينوا مستوى 25 (OH) D أقل من مجموعة الـ(non-MONW) (p<0.01). وجد بشكل ملحوظ نسبة انتشار أعلى من عدم كفاية الـ25 (OH) D (36.1% vs. 20.7%, P<0.05) والنقص الشديد (8.4% vs. 3.5%, P<0.05) في مجموعة الـ(MONW) مقارنة بمجموعة الـ(non-MONW). كان لدى مجموعة الـ(MONW) معدل قيمة اعلى من بمجموعة الـ(non-MONW) بالنسبة للعمر، مؤشر كتلة الجسم ومحيط الخصر، وكذلك معدل قيمة أعلى في مجموعة الـ(MONW) للـHOMA-IR، الشحوم الثلاثية، ولكن معدل قيمة اقل بالنسبة لكوليسترول الـ HDL. في مجموعة الـ(MONW) لوحظ علاقة عكسية للـ25 (OH) D مع الشحوم الثلاثية ومحيط الخصر (P<0.001 و P<0.01 على التوالي) وعلاقة طردية مع كوليسترول الـ HDL (P=0.015).

الاستنتاج: معلوماتنا وضحت حالة فيتامين د اقل بين اقارب مرضى السكري من النوع الثاني، وخصوصاً بين أفراد الـMONW، مما يقترح بأن اقارب مرضى السكري من النوع الثاني لديهم نسبة خطورة أعلى للامراض الأيضية مستقبلاً.