Is There Any Association Between Type 2 Diabetes Mellitus and Biochemical Evidence of Vitamin D Deficiency?

Dr. Riyadh Mustafa Murtadha [MBChB, MD, FICMS (Medicine)]
Collage of Pharmacy / University of Kerbala

Key words: Vitamin D deficiency, Type-2 diabetes mellitus
(Received: Oct2013,Accepted: Dec2013)

Abstract

Background: Type 2 Diabetes Mellitus is a major public health problem, known to be multifactorial in origin. Over the last years, a number of observational studies have suggested an association between type 2 diabetes mellitus and vitamin D deficiency.

Objective: To identify any association between type 2 diabetes mellitus and biochemical evidence of vitamin D deficiency in our population.

Methods: This study was conducted at outpatient clinic in Karbala throughout the year 2011, with a cross-sectional design. The populations were patients with type 2 diabetes mellitus and non-diabetic subjects, who visited the clinic for treatment; all of them had normal renal function. Data collected including characteristics, such as age, sex & body mass index; and the laboratory data such as serum level of calcium, phosphorus, albumin and alkaline phosphatase. Statistical analysis was done by using Chi-Square test and multivariate analysis.

Results: A total number of 64 subjects (Age 45-75 years; 67% female); of them, 32 subjects with Type 2 diabetes mellitus, and 32 subjects without diabetes mellitus. The biochemical evidence of vitamin D deficiency was found in 22% (7 out of 32) of diabetic patients, while it was in 25% (8 out of 32) of non-diabetic subjects. So, there was no statistical difference between the two groups. Moreover, among diabetics, there was no effect of vitamin D deficiency on blood sugar control by measuring HbA1C level.

Conclusions: The association between type 2 diabetes mellitus and biochemical evidence of vitamin D deficiency cannot be proven statistically in this study.

هل توجد علاقة بين داء السكري/ النوع الثاني ودلائل نقص فيتامين د الكيموحياتية؟

الدكتور رياض مصطفى مرتضى (دكتوراه اختصاص الطب الباطني)
رئيس فرع الصيدلة السريرية - كلية الصيدلة / جامعة كربلاء

مفتاح البحث: نقص فيتامين (د)، من النوع 2 من داء السكري

الخلاصة :

خلفية البحث: يعتبر داء السكري/ النوع الثاني مشكلة رئيسية للصحة العامة ، وله عدة عوامل مسببة. عدد من الدراسات المشاهداتية خلال السنوات الماضية تقترح وجود علاقة بين داء السكري- النوع الثاني ونقص (فيتامين د).

الهدف: إيجاد أيّ علاقة بين داء السكري/ النوع الثاني ودلائل نقص (فيتامين د) الكيموحيوية.

الطرق: أجريت الدراسة في كربلاء في عام 2011، بتصميم مقطعي عرضي. قسّم الاشخاص الى مجموعتين؛ مرضى داء السكري/ النوع الثاني وأشخاص اصحاء. تضمنت البيانات خصائص مثل العمر، الجنس ومؤشر كتلة الجسم؛ وبيانات مختبرية مثل المستوى المصلي للكالسيوم ، الفسفور، الالبومين وانزيم الفوسفاتيز القلوي. التحليل الاحصائي اجري باستخدام مربع كاي والتحليل متعدد المتغيرات.

النتائج: كان العدد الكليّ 64 شخص (العمر 45-75 سنة ، 67% اناث)؛ منهم 32 شخص مصاب بداء السكري/ النوع الثاني ، و32 شخص غير مصاب بالسكري. وجدت دلائل نقص (فيتامين د) عند 22% من مرضى السكري بينما كانت عند 25 % من الأشخاص غير المصابين بالسكري. لذا لم يكن هناك اختلاف احصائي بين المجموعتين. كما أنه نقص (فيتامين د) لم يؤثر على السيطرة على سكر الدم عند مرضى السكري وذلك بقياس مستوى *HbA1C*

الا**ستنتاجات**: العلاقة بين داء السكري/ النوع الثاني ودلائل نقص (فيتامين د) الكيموحياتية لم تثبت إحصائياً في هذه الدراسة.

Introduction:

Type 2 Diabetes Mellitus (T2DM) poses a worldwide major public health problem, affecting developed and developing countries [(1)]. While changes in obesity levels, diet and physical activity on the background of genetic risk factors appear to be fuelling this epidemic, other environmental factors may be important in the development of T2DM [(2)].

Interest in vitamin D and DM was stimulated by early animal studies identifying a vitamin D receptor in pancreatic tissue [(3)], and data showing that vitamin D deficiency affected insulin secretion [(4)]. A link between the development of type 1 diabetes mellitus and vitamin D deficiency has been well described, and a recent meta-analysis of five observational studies suggested that children supplemented with vitamin D have a reduced risk for the development of type 1 diabetes [(5)].

Vitamin D has been shown to have numerous non-skeletal effects, including an important role in pancreatic insulin secretion and insulin action [(6)]. Although several studies have reported a protective relationship between vitamin D and the risk of developing diabetes, the data are not consistent. A recent meta-analysis found that three of six observational studies found an association between low vitamin D status and increased risk of incident T2DM or metabolic syndrome [(7)]. In contrast, other clinical trials found vitamin D supplementation had no effect on glycemia or incident diabetes [(6,7)].

It is well known that vitamin D deficiency leads to impaired intestinal absorption of calcium, resulting in decreased serum total and ionized calcium levels. Hypocalcemia results in secondary hyperparathyroidism, a homeostatic response that initially maintains serum calcium levels at the expense of the skeleton [(8,9)]. Alkaline phosphatase levels are often increased because of the parathormone (PTH) -induced increase in bone turnover. In addition to increasing bone resorption, PTH decreases urinary calcium excretion, while promoting phosphaturia. This results in hypophosphatemia, which exacerbates the mineralization defect in the skeleton [(9)]. Since PTH is a major stimulus for the renal 25-(OH) D 1α- hydroxylase, there is increased synthesis of the active hormone, 1, 25$(OH)_2$ D. Paradoxically, levels of this hormone may be normal in vitamin D deficiency; therefore, the measurements of 1, 25$(OH)_2$ D do not provide an accurate index of vitamin D stores and should not be used to diagnose vitamin D deficiency in patients with normal renal function [(9)]. So, the biochemical evidence

such as hypocalcaemia, hypophosphatemia, and hyperphosphatasia (increased alkaline phosphatase level) may be used to indicate the presence of vitamin D deficiency.

The objective of this study was to answer the question; "Is there any association between type 2 diabetes mellitus and biochemical evidence of vitamin D deficiency in our population?" and also to see whether vitamin D deficiency affects blood sugar control in diabetic patients.

Patients and Methods:

This study was conducted at outpatient clinic in Karbala city throughout the year 2011, with a cross-sectional design. The populations were patients with type 2 diabetes mellitus (DM) and non-diabetic subjects, who visited the clinic for treatment; all of them had normal renal function by measuring the levels of blood urea and serum creatinine.

Data collected from both groups included persons' characteristics, such as age, sex and body mass index (BMI); and the laboratory data such as serum level of calcium, phosphorus, albumin and alkaline phosphatase, in addition to blood sugar and HbA1C.

Blood samples from all subjects were drawn without tourniquet and serum calcium level was measured by calorimetric method and corrected according to serum albumin level. Serum level of inorganic phosphorus was also measured by calorimetric method as well as serum albumin and serum alkaline phosphatase levels [(10)].

Statistical analysis

The statistical analysis used for continuous variables was paired Student's T-test, while for categorical variables was Chi-square test and multivariate analysis. P-value of < 0.05 was considered as significant. The values are presented either as percentage or means ± standard deviations (SD).

Results:

Table 1: Demographic Data of Diabetic & Non-Diabetic Subjects

Parameter	DM	Non-DM	p-value
Age (Mean± SD); yr	56.3 ± 8.2	55.6 ± 9.7	N.S.
Sex (Female %)	68.7 %	65.6 %	N.S.
BMI (Mean± SD)	26.7 ± 6.3	25.4 ± 6.9	N.S.

SD= Standard Deviation, BMI = Body Mass Index, N.S. = Non Significant

Table 2: Serum Levels of Calcium, Phosphorus, and Alkaline Phosphatase in Diabetic and Non-Diabetic Subjects

Serum Levels (Mean± SD)	DM	Non-DM	p-value
S. Calcium (mg/dL)	8.6 ± 1.2	8.5 ± 1.3	N.S.
S. Phosphorus (mg/dL)	3.2 ± 0.5	3.4 ± 0.8	N.S.
S. Alkaline Phosphatase (U/L)	69.4 ± 21.9	68.7 ± 24.5	N.S.

Table 3: Diabetic and Non-Diabetic Subjects with Abnormal Serum Levels of Calcium, Phosphorus, and Alkaline Phosphatase

Abnormalities	DM	Non-DM	p-value*
Hypocalcemia	15 (47%)	16 (50%)	N.S.
Hypophosphatemia	7 (22%)	8 (25%)	N.S.
Hyperphosphatasia	6 (19%)	7 (22%)	N.S.

Table 4: Diabetic and Non-Diabetic Subjects with Biochemical Evidence of Vitamin D Deficiency†

Biochemical Evidences†	DM	Non-DM	Total No.	p-value*
Evidence of Vit.D deficiency	7 (22%)	8 (25%)	15(23.5%)	N.S.
No Evidence of Vit.D deficiency	25(78%)	24(75%)	49(76.5%)	N.S.
Total No.	32	32	64	

† Biochemical Evidence of Vitamin D deficiency =
Hypocalcemia + Hypophosphatemia ± Hyperphosphatasia (↑ S.ALP)

*N.S. = Non Significant

Table 5: Effect of Vitamin D deficiency on Blood Sugar Control in Diabetic Patients

Status	Controlled B.S.*	Uncontrolled B.S.	Total No.
Evidence of Vit.D deficiency	3 (43%)	4 (57%)	7
No Evidence of Vit.D deficiency	9 (36%)	16 (64%)	25
Total No.	12 (38%)	20 (62%)	32

* Controlled blood sugar: HbA1C <7%

Discussion:

The association between type 2 diabetes mellitus (DM) and vitamin D had been found by a lot of studies in some countries. A study conducted by Baynes et.al found that vitamin D_3 concentration has inverse correlation to blood glucose concentration in one hour period after glucose loading [(11)]. Another study by New Zealand Workforce Survey has identified that in patients with type 2 DM and glucose tolerance disorder; there was a lower level of vitamin D compared with control group [(12)]. Some other studies also find similar results [(13-17)].

However, this study suggests different results that after adjustment for BMI & other factors, there was no relationship between Type 2 DM and biochemical evidence of vitamin D deficiency. Although this finding may merit further investigation, it was supported by other recent studies conducted in Indonesia and America [(18,19)].

There are issues that may affect and explain why the results of our study different from most of similar studies in various countries. The first issue is the high prevalence of vitamin D deficiency in our population. The second issue may be the small sample size. The third is that this study measures the biochemical evidence of vitamin D deficiency unlike other studies.

The few small studies that have evaluated the association between circulating vitamin D and diabetes incidence have been conflicting, as have the larger epidemiologic cohort studies of dietary vitamin D intake [(20)]. The Women's Health Study found an inverse relationship between vitamin D intake and incident diabetes risk when adjusted for age [(21)]. In contrast, the even larger Nurses' Health Study found no relationship between vitamin D intake from supplements and incident type 2 diabetes after further adjustment for confounders [(22)], similar to the findings of this study.

In addition to that, this study had measured the effect of biochemical evidence of vitamin D deficiency on the control of blood sugar in diabetic patients which was not measured by other studies. It was found that there's also no association and no effect of vitamin D deficiency on the control of blood sugar in diabetic patients.

In conclusion, after adjusting for demographic factors, biochemical evidence of vitamin D deficiency was not proved to be associated with type 2 diabetes mellitus in this study, nor it was found to affect the control of blood sugar in diabetics.

References:

1- Roglic G, Unwin N, Bennett PH, et al. The burden of mortality attributable to diabetes realistic estimates for the year 2000. Diabetes Care; 28: p2130, (2005).
2- Riste L, Khan F, Cruickshank K. High prevalence of type 2 diabetes in all ethnic groups, including Europeans, in a British inner city: relative poverty, history, inactivity, or 21st century Europe? Diabetes Care; 24: p1377, (2001).
3- Christakos S, Friedlander EJ, Frandsen BR, et al. Studies on the mode of action of calciferol. XIII. Development of a radioimmunoassay for vitamin D-dependent chick intestinal calcium-binding protein and tissue distribution. Endocrinology; 104: p1495, (1979).

4- Norman AW, Frankel JB, Heldt AM, et al. Vitamin D deficiency inhibits pancreatic secretion of insulin. Science; 209: p823, (1980).
5- Zipitis CS, Akobeng AK. Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. Arch Dis Child; 93: p512, (2008).
6- Song Y, Manson JE. Vitamin D, insulin resistance, and type 2 diabetes. Curr Cardio Risk Rep; 4: p40, (2010).
7- Pittas AG, Chung M, Trikalinos T, et al. Systematic review: Vitamin D and cardiometabolic outcomes. Ann Intern Med; 152: p307, (2010).
8- Fraser DR. Vitamin D. The Lancet; 345: p104, (1995).
9- Bringhurst FR, Demay MB, Krane SM, Kromenberg HM. Bone and mineral metabolism in health and disease. In: Harrison's principles of internal medicine, 16th ed. New York: McGraw Hill; p.2248 (2005).
10- Tietz NW. Clinical guide to laboratory tests, 3rd ed. Philadelphia: WB Saunders; p444 (1995).
11- Baynes KC, Boucher BJ, Feskens EJ, Kromhout D. Vitamin D, glucose tolerance and insulinemia in elderly men. Diabetol.; 40(7): p870, (1997).
12- Scragg R, Holdaway I, Singh V, Metcalf P, Baker J, Dryson E. Serum 25-hydroxyvitamin D3 levels decreased in impaired glucose tolerance and diabetes mellitus. Diab Res Clin Pract.; 27(3): p181, (1995).
13- Chiu KC, Chu A, Go VLW, Saad MF. Hypovitaminosis D is associated with insulin resistance and β cell dysfunction. Am J Clin Nutr.; 79: p820, (2004).
14- Boucher BJ, Mannan N, Noonan K, Hales CN, Evans SJ. Glucose intolerance and impairment of insulin secretion in relation to vitamin D deficiency in east London Asians. Diabetol.; 38(10): p1239, (1995).
15- Borissova AM, Tankova T, Kirilov G, Dakovska L, Kovacheva R. The effect of vitamin D3 on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. Int J Clin Pract.; 57(4): p258, (2003).
16- Scragg R, Sowers M, Bell C. Serum 25-Hydroxyvitamin D, diabetes, and ethnicity. The Third National Health and Nutrition Examination Survey. Diab Care.; 27: p2813, (2004).
17- Pittas AG, Hughes BD, Li T, VanDam RM, Willet WC, Manson JE, Hu FB. Vitamin D and calcium intake in relation to type 2 diabetes in women. Diab Care.; 29(3): p650, (2006).
18- Hidayat R, Setiati S, Soewondo P. The Association Between Vitamin D Deficiency and Type 2 Diabetes Mellitus in Elderly Patients. Indones J Intern Med.; 42(3): p123, (2010).
19- Robinson JG. et al. Lack of Association Between 25(OH)D Levels and Incident Type 2 Diabetes in Older Women. Diab Care; 34: p628, (2011).
20- Song Y, Manson JE. Vitamin D, insulin resistance, and type 2 diabetes. Curr Cardio Risk Rep; 4: p40, (2010).
21- Liu S, Song Y, Ford ES,Manson JE, Buring JE, Ridker PM. Dietary calcium, vitamin D, and the prevalence of metabolic syndrome in middle-aged and older U.S. women. Diabetes Care; 28: p2926, (2005).
22- Pittas AG, Dawson-Hughes B, Li T, et al. Vitamin D and calcium intake in relation to type 2 diabetes in women. Diabetes Care; 29: p650, (2006).