Relationship of Vitamin D Deficiency to Glycemic Control in Type 2 Diabetes Mellitus

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Abstract

Introduction: Vitamin D deficiency and diabetes mellitus are two widely prevalent conditions across all ages and races.
Observational studies show a consistent association between low vitamin D status, and prevalence of type 2 diabetes mellitus.
Our study aims to explore the prevalence of vitamin D deficiency among diabetics compared to non-diabetics in the population of northern Jordan, and the impact of vitamin D deficiency on glycemic control.
Methods: Glycosylated hemoglobin (HbA1c) and serum vitamin D were measured in a group of 140 type 2 diabetic patients and 129 non-diabetics.
Vitamin D was measured by radioimmunoassay and glycosylated hemoglobin (HbA1c) was measured by high performance liquid spectrophotometric chromatography.
Results: 25(OH) vitamin D levels were significantly lower in the diabetes mellitus type 2 patients than in the non-diabetic subjects (control group), being 12.45 ± 9.36 nmol/L vs 14.85 ± 9.54 nmol/L respectively) (P-value 0.039). There was a significant difference in those with severe vitamin D deficiency (less than 20 nmol/L) between diabetics and non-diabetic subjects (control group) being 8.89 ± 4.65 vs 10.69 ± 4.68, (P-value = 0.001). Also, vitamin D deficient women had higher HbA1c levels.
Conclusion: Vitamin D deficiency is highly prevalent in our population and is more pronounced in patients with T2DM. Vitamin D deficiency's association with higher HbA1c level, although statistically not significant, raises the possibility that vitamin D replacement may improve glycemic control.

Keywords: Vitamin D, Glycemic control, Diabetes, glycosylated hemoglobin.

Introduction

Vitamin D deficiency and diabetes mellitus are two widely prevalent conditions across all ages and races. Epidemiologic studies have shown association of vitamin D deficiency and increased risk of cancer(1,2), cardiovascular disease(3–6), type 2 diabetes (7–10) and autoimmune diseases (11,12). Vitamin D deficiency is associated with impaired β-cell function and insulin resistance in animals and humans (13). Observational studies show a

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consistent association between low vitamin D status, and prevalence of type 2 diabetes mellitus or metabolic syndrome (9, 20, 27).

A prospective study by Pittas et al(14), examined the association between vitamin D and calcium intake and risk of type 2 diabetes, and the results suggest a potential beneficial role for both vitamin D and calcium intake in reducing the risk of type 2 diabetes.

Similar results were obtained by a 17-year observational Finish study (15); a high serum 25(OH)D concentration may reduce the risk of type 2 diabetes and the authors are contemplating the independent role of vitamin D versus the role of healthy dietary and lifestyle patterns in reducing the risk of type 2 diabetes. On the other hand, the women's Health initiative(WHI) study(16), reported that supplementation with calcium and vitamin D did not reduce the risk of developing diabetes over 7-years.

Our study aims to explore the prevalence of vitamin D deficiency among diabetics compared to non-diabetics in the population of northern Jordan, and the impact of vitamin D deficiency on glycemic control.

Methods

This is a retrospective study that included a total of 269 participants using their electronic medical records. Study subjects comprised of 140 diabetic patients and 129 non-diabetics. The age of participants ranged from 25 to 87 years, 199 were males and 70 were females. Patients visited the Endocrinology Clinic of King Abdullah University Hospital (KAUH) in Irbid, Jordan between July and December 2016. Patients were considered diabetics based on their history of diabetes and being on antidiabetic treatment, and non-diabetics were considered as controls if they lacked any

diabetic history and their HbA1c levels were below 6.5%.

Glycosylated hemoglobin (HbA1c) determination was based on the spectrophotometric non-enzymatic reaction of hemolyzed whole blood samples taken from patients. The HbA1c kit is a product of Roche Company. Regarding 25-Hydroxy Vitamin D3 serum concentrations, Roche Modular E170 Analyzer and a 25 OH Vitamin D Enzyme – Immunoassay kits were used to measure the patients' Vitamin D serum levels. The assay employs a polyclonal antibody directed against 25-OH vitamin D. Patients who had chronic diseases that affected Vitamin D levels such as kidney diseases, and patients taking steroids or vitamin D were excluded from the study. The study had the approval of the Institutional Review Board of KAUH.

Statistical Analysis:

Independent Chi-square test was used to examine baseline characteristics of diabetics and Non-diabetics, and baseline characteristics of controlled and uncontrolled diabetics. Further, the Independent T test was used to examine if a difference exists between diabetics and non-diabetics, and between controlled and uncontrolled diabetics regarding vitamin D serum levels. Diabetic patients were considered to have good glycemic control (controlled) if HbA1C levels were <7.0%, and poor glycemic control (uncontrolled) if HbA1C levels were >7.0% based on the guidelines of American Diabetes Association (17).

Vitamin D serum levels were divided into three categories: Severe Vitamin D deficiency (<20 nmol/L), Mild Vitamin D deficiency (20-30 nmol/L), and Normal Vitamin D levels (>30 nmol/L). The difference between Diabetics and non-diabetics across these three

categories was examined using a two-way ANOVA. A p-value less than 0.05 was considered significant. All statistical analysis was done using SPSS 20 software.

Results

The general demographic characteristics including age, gender and vitamin-D levels in diabetic and non-diabetic subjects are shown in table (1). In our sample, a total of 269 participants were included. 199 were males and 70 were females. 140 of the total participants were diabetic subjects (cases) and 129 non-diabetics (controls). Diabetics were significantly older than control subjects (57.71±9.18 vs 52.66±10.95years) respectively, P-value 0.003, table 1. Logistic regression analysis shows that there was no significant correlation between age and log vitamin-D concentration.

In the diabetic group, vitamin-D level was higher in females than males (14.28±12.53 vs 11.57±7.29 nmol/L), but in the non-diabetic group, vitamin-D level was lower in females than males (12.28±11.05 nmol/L vs 15.18±9.21 nmol/L), table 1.

The vitamin-D level was significantly lower in diabetics compared to non-diabetics (12.45 ± 9.36 nmol/ L vs 14.85± 9.54 nmol /L respectively) (P-value 0.039), table1.

Out of 140 diabetic patients, 23 were controlled and 117 non-controlled, figure 1. There was no age difference between controlled and non-controlled diabetics (57±9.34 vs 57±9.18 year), (P-value 0.838), table 2. Although vitamin-D level was lower in non-controlled compared to controlled diabetics (11.7±8.47 nmol/L vs 15.02±13.42 nmol/L), this difference was statistically not significant, (P-value = 0.296),table 2 and figure 1.

Females had significantly higher serum vitamin D concentrations than males in controlled diabetics (19.98±16.41 nmol/L vs 9.6±6.17 nmol/L) (P-value =0.0521). In uncontrolled diabetics, there was no significant difference in serum vitamin-D levels between females and males. (12.33 ± 10.46 vs 11.45 ± 7.52), (P-value =0.728), table 2.

Generally, vitamin-D deficiency (< 30 nmol/ L) prevalence was high in both groups in diabetics and non-diabetics (93.57% vs 90.69%), while severe vitamin-D deficiency prevalence (< 20nmol/ L) was 83% in diabetics compared to 78% in non-diabetics. On further analysis of severity of vitamin D deficiency in diabetics and non-diabetics, there was significant difference in those with severe vitamin-D deficiency between diabetics and non- diabetic subjects (8.89±4.65 vs 10.69±4.68), (P-value 0.001), table (3). In mild vitamin D deficiency, there was no significant difference between diabetics and non-diabetics, (24.87±2.86 vs 25.15±2.47), (P-value 0.871), table 3. Similarly, there was no significant difference between diabetics and non-diabetics in the group with normal vitamin-D levels (36.34±9.63 vs 36.05±6.94), (P-value 0.892), table 3.

Discussion

The role of vitamin D in calcium and bone metabolism is well established. The extra-skeletal manifestations of vitamin D deficiency are currently the focus of interest in recent research. Several epidemiologic and cross-sectional studies have shown a link between vitamin D deficiency and increased risk of cancer (2), cardiovascular disease(4,5), type 2 diabetes(8,9) and autoimmune diseases (11,12). In our study we aimed to explore the prevalence of vitamin D deficiency among diabetics compared to non-diabetics in the population of Northern Jordan and the impact of vitamin D deficiency on glycemic control. In our study,

more than 90% of diabetics have low vitamin D level (< 30 nmol/l) and more than 80% of these patients have severe deficiency (< 20 nmol/l).

Similarly, in non-diabetic participants 83% were vitamin D deficient and 78% had severe deficiency. However, a significantly lower vitamin D level was observed in diabetics compared to non-diabetics, and a lower vitamin D level was observed in uncontrolled diabetics compared to controlled diabetics, but this difference was not significant.

Our results agree with those of Tromsø's Study (27), which showed a significant inverse association between serum 25(OH) D and HbA(1c). The association was most pronounced in subjects with risk factors for glucose intolerance/ type 2 diabetes. In a sub-analysis on subjects with diabetes the association between serum 25(OH) D and HbA(1c) appeared even stronger with a difference in HbA(1c) of 0.48 % between the highest and lowest serum 25(OH)D quartiles.

These findings imply that vitamin D deficiency may affect the incidence of diabetes as well as glucose control. Recently, vitamin D deficiency has shown to relate to metabolic syndrome and the development of type 2 diabetes mellitus(18,19). In a cross-sectional study of a general population in Finland(20), Hurskainen et al. found an inverse relationship between vitamin D levels and fasting insulin , glucose and glucose tolerance test. In a prospective observational study (10), Pittas et al. found that higher plasma levels of vitamin D were associated with a lower incidence of type 2 diabetes.

Also, in a study involving a large cohort of an adult population in USA from National Health and Nutrition Examination Survey III (NHANES III), significantly lower levels of vitamin D were observed in subjects with metabolic syndrome than in those without it (21).

Older patients had significantly lower vitamin D levels in our study, and the negative correlation between HbA1c levels and vitamin D levels remained significant after removal of age as an independent risk factor for vitamin D deficiency. Based on this study and previously mentioned studies linking vitamin D deficiency to increased prevalence of type 2 diabetes mellitus and impaired glycemic control in diabetics, one would suggest that vitamin D supplementation may prevent the onset of diabetes in patients at risk and improve glucose control in diabetics. However, studies involving vitamin D supplementation have not shown consistent results. In some studies, vitamin D supplementation was found to improve glucose control in type 2 diabetes mellitus (22,23), while in others, no such effect was observed(24–26).

Females had significantly higher serum vitamin D concentrations than males in controlled diabetics in our study. Similar results were observed in a study by Tahrani AA et al. (9), where they were studying the prevalence of vitamin D abnormalities in South Asians with type 2 diabetes mellitus in the UK. More studies are needed to illustrate this gender difference in vitamin D levels among controlled diabetics.

Conclusion

At present, a direct link between vitamin D and type 2 diabetes mellitus is not conclusively established. It is possible that people with poor glycemic control, also have unhealthy eating habits, poor exercise and less exposure to sunlight. Still larger scale, well designed and randomized trials are required to establish a protective role of vitamin D on glucose homeostasis.

Table 1: Baseline characteristics of Diabetics and Non-diabetics and Vitamin D levels

| Characteristic	Diabetics	Non-diabetics	P-value
Gender (n)			
Males	93	106	
Females	47	23	
Total	140	129	**0.003**
Age (Mean $\pm$ SD)	57.71 $\pm$ 9.18	52.66 $\pm$ 10.95	**<0.0001**
Vitamin D {nmol/L} (Mean $\pm$ SD)	12.45 $\pm$ 9.36	14.85 $\pm$ 9.54	**0.039**
Males	11.57 $\pm$ 7.29	15.18 $\pm$ 9.21	**0.003**
Female	14.28 $\pm$ 12.52	13.28 $\pm$ 11.05	0.745

Table 2: Baseline characteristics of controlled and uncontrolled diabetics and Vitamin D levels

Characteristic	Controlled Diabetics (HbA1c $\leq$7%)	Uncontrolled Diabetics (HbA1c >7%)	P-value
Gender (n)			
Males	11	82	
Females	12	35	
Total	23	117	**0.039**
Age (Mean $\pm$ SD)	57.35 $\pm$ 9.34	57.78 $\pm$ 9.18	0.838
Vitamin D {nmol/L} (Mean $\pm$ SD)	15.02 $\pm$ 13.42	11.71 $\pm$ 8.47	0.296
Males	9.6 $\pm$ 6.17	11.45 $\pm$ 7.52	0.439
Female	19.98 $\pm$ 16.41	12.33 $\pm$ 10.46	0.067

Table 3: Comparison between non – diabetics and diabetics across the three categories of Vitamin D serum levels

Vitamin D Category	Diabetics		Non – Diabetics		P-Value
	Number	Mean $\pm$ SD	Number	Mean $\pm$ SD	
Total Vitamin D levels {nmol/L}	140	12.45 $\pm$ 9.36	129	14.85 $\pm$ 9.54	**0.039**
Severe Vitamin D deficiency {<20 nmol/L}	116	8.89 $\pm$ 4.65	101	10.69 $\pm$ 4.68	**0.001**
Mild Vitamin D deficiency {20-30 nmol/L}	15	24.87 $\pm$ 2.86	16	25.15 $\pm$ 2.47	0.871
Normal Vitamin D levels {>30 nmol/L}	9	36.34 $\pm$ 9.63	12	36.05 $\pm$ 6.94	0.892
Independent-Samples T test was used in the analysis of total Vitamin D levels Two-way ANOVA was used for the analysis of three categories of Vitamin D serum levels in Diabetics vs. Non-Diabetics P-value < 0.05 is considered statistically significant					
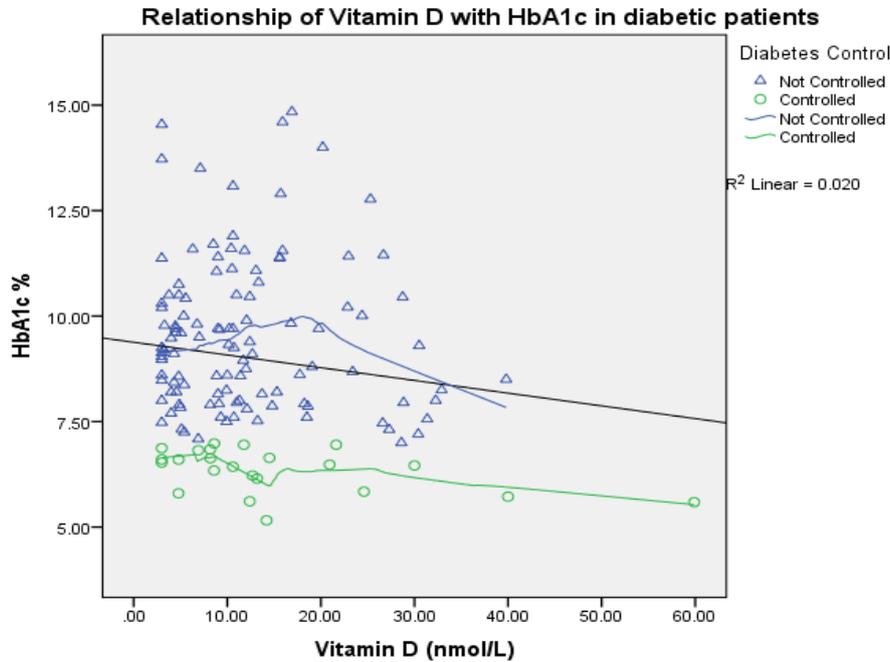
Figure1. Relationship between vitamin-D and HbA1c in diabetic patients.

References

1. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr. 2007;85(6):1586–91.
2. Blazsek I, Farabos C, Quittet P, Labat M-L, Bringuier AF, Triana BK, et al. Bone marrow stromal cell defects and 1 alpha, 25-dihydroxyvitamin D3 deficiency underlying human myeloid leukemias. Cancer Detect Prev. 1995;20(1):31–42.
3. Bonakdaran S, Varasteh A-R. Correlation between serum 25 hydroxy vitamin D3 and laboratory risk markers of cardiovascular diseases in type 2 diabetic patients. Saudi Med J. 2009;30(4):509–14.
4. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation. 2008;117(4):503–11.
5. Scragg R, Jackson R, Holdaway IM, Lim T, BEAGLEHOLE R. Myocardial infarction is inversely associated with plasma 25-hydroxyvitamin D3 levels: a community-based study. Int J Epidemiol. 1990;19(3):559–63.
6. Forman JP, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, et al. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. Hypertension. 2007;49(5):1063–9.
7. Kayaniyil S, Vieth R, Retnakaran R, Knight JA, Qi Y, Gerstein HC, et al. Association of vitamin D with insulin resistance and β-cell dysfunction in subjects at risk for type 2 diabetes. Diabetes Care. 2010;33(6):1379–81.
8. Chiu KC, Chu A, Go VLW, Saad MF. Hypovitaminosis D is associated with insulin resistance and β cell dysfunction. Am J Clin Nutr. 2004;79(5):820–5.
9. Tahrani AA, Ball A, Shepherd L, Rahim A, Jones AF, Bates A. The prevalence of vitamin D abnormalities in South Asians with type 2 diabetes mellitus in the UK. Int J Clin Pract. 2010;64(3):351–5.
10. Pittas AG, Nelson J, Mitri J, Hillmann W, Garganta C, Nathan DM, et al. Plasma 25-Hydroxyvitamin D and Progression to Diabetes in Patients at Risk for Diabetes. Diabetes Care. 2012;35(3):565–73.
11. Weiss ST. Bacterial components plus vitamin D:

the ultimate solution to the asthma (autoimmune disease) epidemic? J Allergy Clin Immunol. 2011;127(5):1128.

12. Weinstock-Guttman B, Mehta BK, Ramanathan M, Karmon Y, Henson LJ, Halper J, et al. Vitamin D and multiple sclerosis. The neurologist. 2012;18(4):179–83.

13. Zeitz U, Weber K, Soegiarto DW, Wolf E, Balling R, Erben RG. Impaired insulin secretory capacity in mice lacking a functional vitamin D receptor. FASEB J. 2003;17(3):509–11.

14. Pittas AG, Harris SS, Stark PC, Dawson-Hughes B. The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults. Diabetes Care. 2007;30(4):980–6.

15. Mattila C, Knekt P, Männistö S, Rissanen H, Laaksonen MA, Montonen J, et al. Serum 25-hydroxyvitamin D concentration and subsequent risk of type 2 diabetes. Diabetes Care. 2007;30(10):2569–70.

16. De Boer IH, Tinker LF, Connelly S, Curb JD, Howard BV, Kestenbaum B, et al. Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative. Diabetes Care. 2008;31(4):701–7.

17. Association AD, others. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37(Supplement 1):S81–90.

18. Lim S, Kim MJ, Choi SH, Shin CS, Park KS, Jang HC, et al. Association of vitamin D deficiency with incidence of type 2 diabetes in high-risk Asian subjects. Am J Clin Nutr. 2013;97(3):524–30.

19. Kayaniyil S, Harris SB, Retnakaran R, Vieth R, Knight JA, Gerstein HC, et al. Prospective association of 25 (OH) D with metabolic syndrome. Clin Endocrinol (Oxf). 2014;80(4):502–7.

20. Hurskainen A-R, Virtanen JK, Tuomainen T-P, Nurmi T, Voutilainen S. Association of serum 25-hydroxyvitamin D with type 2 diabetes and markers of insulin resistance in a general older population in Finland. Diabetes Metab Res Rev. 2012;28(5):418–23.

21. Ford ES, Ajani UA, McGuire LC, Liu S. Concentrations of serum vitamin D and the metabolic syndrome among US adults. Diabetes Care. 2005;28(5):1228–30.

22. 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. 2003;57(4):258–61.

23. Al-Daghri NM, Alkharfy KM, Al-Othman A, El-Kholie E, Moharram O, Alokail MS, et al. Vitamin D supplementation as an adjuvant therapy for patients with T2DM: an 18-month prospective interventional study. Cardiovasc Diabetol. 2012;11(1):85.

24. Heshmat R, Tabatabaei-Malazy O, Abbaszadeh-Ahranjani S, Shahbazi S, Khooshehchin G, Bandarian F, et al. Effect of vitamin D on insulin resistance and anthropometric parameters in Type 2 diabetes; a randomized double-blind clinical trial. DARU J Pharm Sci. 2012;20(1):10.

25. Breslavsky A, Frand J, Matas Z, Boaz M, Barnea Z, Shargorodsky M. Effect of high doses of vitamin D on arterial properties, adiponectin, leptin and glucose homeostasis in type 2 diabetic patients. Clin Nutr. 2013;32(6):970–5.

26. Mitri J, Dawson-Hughes B, Hu FB, Pittas AG. Effects of vitamin D and calcium supplementation on pancreatic β cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. Am J Clin Nutr. 2011; 94(2):486–94.

27. Serum 25-hydroxyvitamin D levels are inversely associated with glycated hemoglobin (HbA(1c)). The Tromsø Study. Hutchinson MS, Figenschau Y, Njølstad I, Schirmer H, Jorde RSc and J Clin Lab Invest. 2011 71(5):399-406..

العلاقة بين نقص فيتامين د والسيطرة على نسبة السكر في الدم في داء السكري من النوع الثاني –نبذة مختصرة

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الملخص

المقدمة: نقص فيتامين د ومرض السكري هما وضعان منتشران على نطاق واسع في جميع الأعمار والأعراق تظهر الدراسات الرصدية وجود ارتباط ثابت بين انخفاض حالة فيتامين د وانتشار داء السكري من النوع الثاني وتهدف دراستنا لاستكشاف مدى انتشار نقص فيتامين د بين مرضى السكري مقارنة مع غير المصابين بالسكري في سكان شمال الأردن وتأثير نقص فيتامين د على السيطرة على السكر.

الأساليب: تم قياس الهيموغلوبين الغليكوزيلاتي ومصل فيتامين (د) في مجموعة من 140 مريض السكري من النوع الثاني و129 غير المصابين بالسكري. تم قياس فيتامين (د) عن طريق المناظير الإشعاعية المشيمائيمه وقياس الهيموجلوبين الغليكوزيلاتي بواسطة تحليل كروماتوجرافي سائل طيفي عالي الأداء.

النتائج: كانت مستويات فيتامين (د) أقل بشكل ملحوظ في مرضى السكري من النوع الثاني مقارنةً بالمرضى غير المصابين بالسكري (المجموعة الضابطة). كان هناك اختلاف كبير في أولئك الذين يعانون من نقص شديد في فيتامين د (أقل من 20 نانومول / لتر) بين مرضى السكري وغير المصابين بالسكري (المجموعة الضابطة) وكانت النساء اللواتي لديهن نقص فيتامين (د) لديهن أيضا أعلى مستويات الهيموغلوبين الغليكوزيلاتي.

الاستنتاج: نقص فيتامين (د) هو السائد في السكان لدينا أكثر وضوحا في المرضى الذين يعانون من النوع الثاني من السكري. إن ارتباط نقص فيتامين د بمستوى أعلى من الهيموغلوبين الغليكوزيلاتي على الرغم من أنه غير هام إحصائيًا إلا أنه يرفع احتمال أن يحسن استبدال فيتامين د التحكم في نسبة السكر في الدم.

الكلمات الدالة: فيتامين د، السكري.