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

Nesreen A Saadeh1, Rami A Saadeh2 Ashraf O Oweis1, Saeed Alghamri1

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
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), table 1.

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 extraskeletal 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 HbA1c. 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 HbA1c appeared even stronger with a difference in HbA1c 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diabetics</th>
<th>Non-diabetics</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>93</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>47</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>140</td>
<td>129</td>
<td>0.003</td>
</tr>
<tr>
<td>Age (Mean ± SD)</td>
<td>57.71 ± 9.18</td>
<td>52.66 ± 10.95</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vitamin D {nmol/L} (Mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>12.45 ± 9.36</td>
<td>14.85 ± 9.54</td>
<td>0.039</td>
</tr>
<tr>
<td>Female</td>
<td>11.57 ± 7.29</td>
<td>15.18 ± 9.21</td>
<td>0.003</td>
</tr>
<tr>
<td>Total</td>
<td>14.28 ± 12.52</td>
<td>13.28 ± 11.05</td>
<td>0.745</td>
</tr>
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</table>

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controlled Diabetics (HbA1c ≤7%)</th>
<th>Uncontrolled Diabetics (HbA1c &gt;7%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (n)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>11</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>12</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>117</td>
<td>0.039</td>
</tr>
<tr>
<td>Age (Mean ± SD)</td>
<td>57.35 ± 9.34</td>
<td>57.78 ± 9.18</td>
<td>0.838</td>
</tr>
<tr>
<td>Vitamin D {nmol/L} (Mean ± SD)</td>
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<td></td>
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<tr>
<td>Males</td>
<td>15.02 ± 13.42</td>
<td>11.71 ± 8.47</td>
<td>0.296</td>
</tr>
<tr>
<td>Female</td>
<td>9.6 ± 6.17</td>
<td>11.45 ± 7.52</td>
<td>0.439</td>
</tr>
<tr>
<td>Total</td>
<td>19.98 ± 16.41</td>
<td>12.33 ± 10.46</td>
<td>0.067</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Vitamin D Category</th>
<th>Diabetics</th>
<th>Non – Diabetics</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>Mean ± SD</td>
<td>Number</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Total Vitamin D levels {nmol/L}</td>
<td>140</td>
<td>12.45 ± 9.36</td>
<td>129</td>
</tr>
<tr>
<td>Severe Vitamin D deficiency {&lt;20 nmol/L}</td>
<td>116</td>
<td>8.89 ± 4.65</td>
<td>101</td>
</tr>
<tr>
<td>Mild Vitamin D deficiency {20-30 nmol/L}</td>
<td>15</td>
<td>24.87 ± 2.86</td>
<td>16</td>
</tr>
<tr>
<td>Normal Vitamin D levels {&gt;30 nmol/L}</td>
<td>9</td>
<td>36.34 ± 9.63</td>
<td>12</td>
</tr>
</tbody>
</table>

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
Figure 1. Relationship between vitamin-D and HbA1c in diabetic patients.

References

11. Weiss ST. Bacterial components plus vitamin D:
العلاقة بين نقص فيتامين D والسيطرة على نسبة السكر في الدم في داء السكري من النوع الثاني - نبذة مختصرة

نسرين سعادة1، رامي سعادة2، أشرف عيسى1، سعيد الغامري1

قسم الأمراض البدنية، كلية الطب، جامعة العلوم والتكنولوجيا الأردنية.
قسم الصحة العامة وطب المجتمع، كلية الطب، جامعة العلوم والتكنولوجيا الأردنية.

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

الأسلوب: تم قياس الهيموجلوبين الغليكوزيلاتي ومعدل فيتامين (D) في مجموعة من 140 مريض السكري من النوع الثاني و129 غير المصابين بالسكري.

نتائج: كانت مستويات فيتامين (D) أكثر للمحوز في مرضى السكري من النوع الثاني مقارنة بالمرضى غير المصابين بالسكري (المجموعة الضاملة). كان هناك اختلاف كبير في أولئك الذين يعانون من نقص شديد في فيتامين (D) (أقل من 20 نانومول / لتر) بين مرضى السكري وغير المصابين بالسكري (المجموعة الضاملة) وكانت النساء اللواتي لديهن نقص فيتامين (D) لديهن أيضاً أعلى مستويات الهيموجلوبين الغليكوزيلاتي.

الاستنتاج: نقص فيتامين (D) هو السائد في السكان لدينا أكثر ضعفاً في المرضى الذين يعانون من النوع الثاني من السكري. إن ارتباط نقص فيتامين D بمستوى أعلى من الهيموجلوبين الغليكوزيلاتي على الرغم من أنه غير هام إحصائيًا إلا أنه يرفع احتمال أن يكون استبدال فيتامين D بالتحكم في نسبة السكر في الدم.

الكلمات الدالة: فيتامين D، السكري.