Vitamin D level in patients with type 1 diabetes and its relation to tissue transglutaminase immunoglobulin A antibodies

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Received 14 February 2019
Accepted 17 February 2019

The Egyptian Journal of Internal Medicine
2019, 31:320–325

Introduction
Type 1 diabetes mellitus (T1DM) is a lifelong metabolic disorder, which accounts for ~10% of all cases of diabetes. Vitamin D deficiency is extensively studied in the pathogenesis of T1DM. Vitamin D regulates both innate and adaptive immunity, and this indicates its potential role in preventing and treating T1DM. T1DM is also associated with celiac disease which is an autoimmune-mediated, chronic inflammatory disorder of the small intestine. Vitamin D deficiency has been described in patients with celiac disease and T1DM.

Aim
The study's primary aim was to investigate the 25-hydroxyvitamin D [25(OH)D] level in patients with T1DM and relation between vitamin D level and the presence or absence of tissue transglutaminase immunoglobulin A [tTG (IgA)] antibodies.

Patients and methods
The study estimated 25(OH)D level in 75 patients with T1DM and 15 healthy participants. It also studied the relation between vitamin D level and the presence or absence of tTG (IgA) antibodies.

Results
Patients with T1DM had significantly lower level of 25(OH)D (82.7%) compared with control participants (46.7%) (P=0.003). In all, 5.3% of patients were positive for tTG (IgA) antibody, and antibody titer was significant higher in patients with T1DM, with mean of 1.57±3.38, compared with control participants, with mean of 0.31±0.07 (P=0.001). Vitamin D level was low in diabetic patients with positive tTG (IgA) antibody than diabetic patients with negative tTG (IgA) antibody, but this change did not achieve significant value.

Conclusion
Vitamin D deficiency is high in children and adolescents with T1DM. Its level was decreased in diabetic patients with positive tTG (IgA) antibody than diabetic patients with negative tTG (IgA) antibody.

Keywords:
celiac disease, tissue transglutaminase immunoglobulin A antibody, type 1 diabetes mellitus, vitamin D level

Egypt J Intern Med 31:320–325

1110-7782

Introduction

Type 1 diabetes mellitus (T1DM) is a metabolic disorder that accounts for ~10% of all cases of diabetes. There is a growing evidence that T1DM is increasing at a rate of ~3% per year in different countries around the world. T1DM is usually diagnosed in children, adolescents, and young adults, and it is associated with important psychological, familial, and social disorders [1]. The mechanism underlying the development of T1DM is insulin deficiency with autoimmune destruction of insulin-producing pancreatic β-cells. This organ-specific destruction is mediated by CD4+ and CD8+ T helper-1 lymphocyte and macrophages infiltrating the islets cells. This represent an interaction between susceptibility genes, environmental factors, and some other risk factors. The disease is irreversible once diagnosed, and patients need lifelong insulin treatment; moreover, it causes multiple disease-associated complications [2]. Vitamin D deficiency may have a role in the pathogenesis of T1DM, as it regulates both innate and adaptive immunity, thus indicating its potential role in preventing and treating T1DM. Vitamin D deficiency cannot be the sole determining factor for the development of T1DM, as genetic and environmental factors also determine the development of the disease [3].

Vitamin D increases pancreatic insulin secretion by a direct and indirect way. The direct effect occurs when 1,25-dihydroxyvitamin D binds to the nuclear vitamin D receptor, which is found in a variety of tissues, including the pancreatic islet β-cells. The indirect way appears through its effect in regulating extracellular calcium and calcium flux through

β-cells. Insulin secretion is a calcium-dependent process, so alterations in calcium flux can have adverse effects on insulin secretion by B cell. Vitamin D insufficiency through changing the balance between the extracellular and intracellular B-cell calcium pools may interfere with normal insulin release in response to glucose [4].

Celiac disease (CD) is an immune-mediated, chronic inflammatory disease of the small intestine. It occurs in genetically susceptible individuals by the ingestion of proline-rich and glutamine-rich proteins present in wheat, rye, and barley, although other factors seem to play a secondary role. There is a clear association of T1DM with CD [3]. The prevalence of CD among children and adults with T1DM is observed to range between 0.6 and 16.4% compared with 0.01–0.03% in the general population [5]. Vitamin D deficiency has been described in patients with CD [6] and in patient with T1DM [7].

The study aims to investigate the 25-hydroxyvitamin D [25(OH)D] level in patients with T1DM and its relation to tissue transglutaminase immunoglobulin A [tTG (IgA)] antibodies.

Patients and methods

This study was conducted at Minia University Hospital in the outpatient clinics of endocrine and metabolism from March 2014 to November 2014. It included 75 patients with T1DM and 15 control participants matched for age and sex after approval of hospital ethics committee and informed patient consents. The age of diabetic patients ranged from 9 to 30 years old. The study enrolled 15 control participants matched for age and sex. Patients were included in the study if they had no history suggestive of vitamin deficiency (rickets or osteoporosis) or undiagnosed or untreated CD. Patients were excluded if they have any of the following: taking multivitamin supplements including vitamin D; having past history of irritable bowel syndrome (for adults) or lactose intolerance (for children); having treated with systemic immunomodulatory agents in the prior 30 days, having complications of T1DM or CD; having treated with systemic immune-modifying biological agents, for example, infliximab in the prior 6 months; and known patients with CD. The 25(OH)D level was assessed by enzyme-linked immunosorbent assay. Vitamin D deficiency is defined as a 25(OH)D level less than 20 ng/ml, insufficiency is defined as a 25 (OH)D concentration of 20–30 ng/ml, and normal level of vitamin D is defined as a 25(OH)D concentration greater than 30 ng/ml [8]. tGA (IgA) antibody was estimated by Immunometric Enzyme Immunoassay (Chemux Bio Science, Inc company, USA) with cutoff value of 10 U/ml. Fasting and postprandial blood glucose, glycated hemoglobin (HbA_{1c}), lipid profile, renal function tests, and liver enzymes all were determined by automated chemistry analyzer. HbA_{1c} was also assessed, and the following levels were taken as a reference range: children<6 years old: <8.5%, children 6–12 years old: <8%, and teens 13–19 years old: <7.5%.

Results

Table 1 shows the baseline characteristics of the 75 enrolled diabetic patients with low BMI in diabetic patients in comparison with control group (P=0.03). The study revealed a significantly low level of vitamin D in diabetics patients, with mean of 17.6±17.2, than the control group, with mean of 44.4±31.8 (P=0.001) (Table 2 and Figs 1 and 2). Of the 75 diabetic patients studied, 5.3% (four patients) were positive for tTG (IgA) antibody and 94.7% patients (71 patients) were

Table 1 The demographic characteristics of diabetic patients and controls

Demographics	Cases (N=75) [n (%)]	Controls (N=15) [n (%)]	P
Age (mean±SD)	16.9±5.5	17.9±5.94	0.5
Sex			0.7
Male	34 (45.3)	6 (40)	
Female	41 (54.7)	9 (60)	
Weight	47.9±12.4	50.1±14.4	0.5
Height	146.2±14.8	152.8±10.3	0.1
BMI	22.1±3.01	24±3.07	0.03*
Underweight	7 (9.3)	0	
Normal	60 (80)	10 (66.7)	0.09
Overweight	7 (9.3)	4 (26.7)	
Obese	1 (1.3)	1 (6.7)	
Duration of diabetes mellitus (years)			
<5	53 (70.7)		
≥5	22 (29.3)		

*means statistically significant values.

Table 2 Vitamin D level in diabetic patients and controls

Vitamin D level	Cases (*N*=75) [*n* (%)]	Control (*N*=15) [*n* (%)]	*P*
Mean±SD	0.005–68	4–106	0.001*
Median	17.6±17.2	44.4±31.8	
Deficient	28 (37.3)	1 (6.7)	0.009*
Insufficient	34 (45.4)	6 (40)	0.3
Sufficient	13 (17.3)	8 (53.3)	0.02*

*means statistically significant values.

Table 3 Tissue transglutaminase immunoglobulin A antibodies between diabetics and controls

tTG (IgA) antibody level	Cases (*N*=75) [*n* (%)]	Controls (*N*=15) [*n* (%)]	*P*
Mean±SD	1.4±3.07	0.3±0.06	0.1
Median	0.6	0.3	0.001*
Positive	4 (5.3)	0 (0.0)	0.001*
Negative	71 (94.7)	15 (100)	

IgA, immunoglobulin A; tTG, tissue transglutaminase. *means statistically significant values.

Table 4 Vitamin D level in diabetic patients with positive tissue transglutaminase (immunoglobulin A) antibody and negative one

Vitamin D level	Diabetic with negative tTG (IgA) (*N*=71) [*n* (%)]	Diabetic with positive tTG (IgA) (*N*=4) [*n* (%)]	*P*
Range	0.005–68	0.005–23	0.2
Mean±SD	18.02±17.3	6.7±10.9	
Deficient	25 (35.2)	3 (75)	0.05
Insufficient	33 (46.5)	1 (25)	0.2
Sufficient	13 (18.3)	0 (0.0)	0.1

IgA, immunoglobulin A; tTG, tissue transglutaminase.

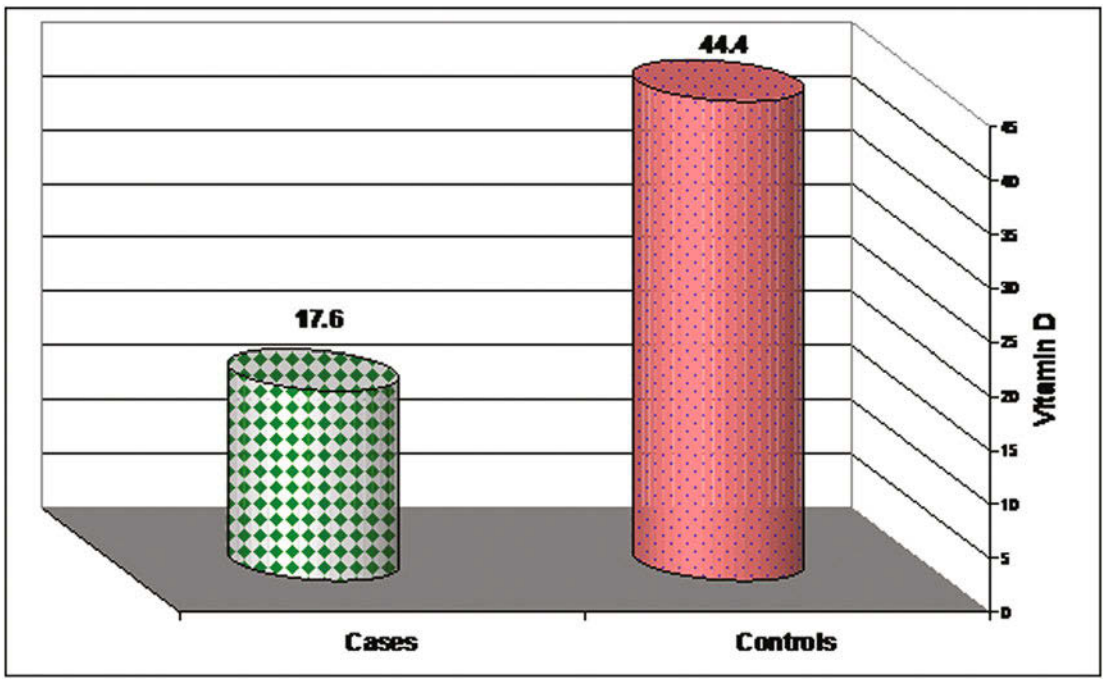
negative. These results showed significant difference regarding tTG (IgA) antibodies between patients with T1DM (5.3%) and control participants (0%) (*P*=0.001) and also revealed that tTG (IgA) antibody titer was significant higher in patients with T1DM compared with control participants (*P*=0.001) (Table 3). The study showed that vitamin D level was decreased in diabetic patients with positive tTG (IgA) antibodies, with mean of 6.7±10.9, than diabetic patients with negative tTG (IgA) antibody, with mean of 18.02±17.3, but this change did not achieve statistically significant value (Table 4).

Discussion

T1DM is a chronic autoimmune disease that usually manifests during early childhood and puberty [9]. In Egypt, T1DM incidence and prevalence are increasing, being higher in females, and more cases are found to originate from rural areas [10]. Vitamin D deficiency is one environmental factor that has long been discussed to influence the risk of T1DM [11]. Suggested role of vitamin D in the pathogenesis of T1DM include the important functions of this hormone in immunoregulation and immunoactivation [12], the genetic association of vitamin D receptor with T1DM [13], and the results of epidemiological studies showing that lower serum vitamin D levels and inadequate supplementation during infancy increase the risk of T1DM [14]. In this study, vitamin D level was significantly low in patients with T1DM, with mean of 17.6±17.2, compared with control participants, with mean of 44.4±31.8 (*P*=0.001), and 37.3% of the patients with T1DM were deficient compared with 6.7% in control group. These results are similar to the results of Borkar *et al.* [15] in North India, as 58% of patients with T1DM were deficient in 25(OH)D compared with 32% of controls, but lower than the study of Bener *et al.* [16], in Qatar, as of 170 children with T1DM and 170 controls, 90.6% of children with T1DM versus (85.3%) of nondiabetic children had vitamin D deficiency. All these studies showed significantly lower mean 25(OH)D level in T1DM compared with controls [17]. These results are in disagreement with a study conducted in Florida, a solar-rich region in the USA, which demonstrated that there were no differences in 25(OH)D levels in diabetics (recently or more than 5 months diagnosed) compared with their first-degree relatives and controls [18].

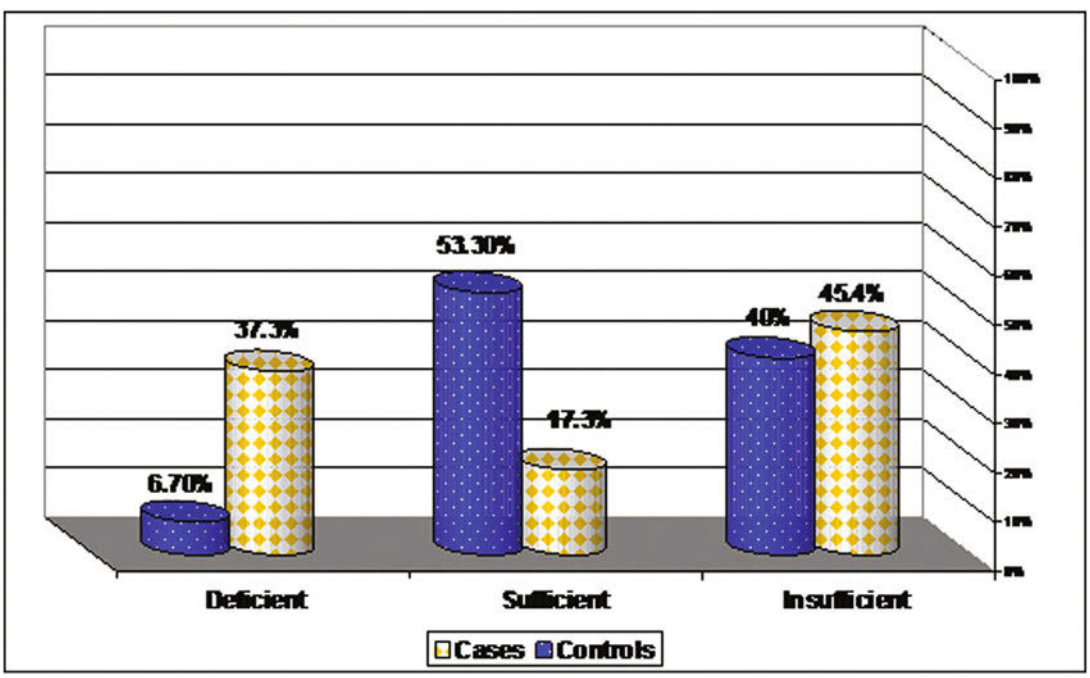
The range of prevalence difference might be explained by differences in geographical location, the age of patients, duration since diagnosis of diabetes, and glycemic control [19]. This can also be explained by the fact that variance in levels of 25(OH)D is related to the occurrence of malabsorptive state among patients with T1DM. It is evidently described that vitamin D

Figure 1



Vitamin D level between diabetic group and control.

Figure 2



Vitamin D status between studied groups.

can prevent the death of islet cells [20]. Thus, there is a direct association of β-cell dysfunction, hypovitaminosis D, and insulin resistance [21].

The study revealed that vitamin D deficiency was predominant in female (64.3 vs. 35.7%). This result was in agreement with Al-Agha *et al.* [22] who demonstrated that 61.5% of the girls had inadequate amounts of vitamin D versus 38.5% of the boys. This result was inconsistent with the results by Littorin *et al.* [23] which showed lower levels of plasma 25(OH)D in men than in women with T1DM. Higher level of 25 (OH)D in men could be explained by the difference in sun exposure between the two sexes, as a higher sun

index score was shown in boys. In addition, faster growth spurt during puberty in girls and more vitamin D requirement for bones might be a further reason for the higher prevalence of vitamin D deficiency among girls than boys [24].

Our study showed that patients with low vitamin D level (deficient and insufficient) were overweight than vitamin D sufficient patients but without statistically significant changes, and this agrees with a study by Çizmecioglu *et al*. [25], which revealed that vitamin D deficiency and insufficiency were common in obese and overweight schoolchildren, especially in girls. Obesity could be a risk factor in terms of hypovitaminosis D in adolescent [26]. This result was in conflict with the results of Bin-Abbas *et al*. [27], which demonstrated no significant changes between vitamin D level and BMI.

The excess body fat may disrupt hormonal pathways important for skeletal health. For example, leptin, an adipocyte-derived hormone that binds to osteoblasts, appears to activate a pathway that inhibits renal synthesis of the active form of vitamin D [28].

Of 75 diabetic patients studied, 5.3% patients were positive for tTG (IgA) antibody and 94.7% were negative. A higher percentage of tTG (IgA) antibody-positive patients (17%) was reported by Abdulrahman *et al*. [29], as among the 106 children with T1DM who had been screened for CD over a 2-year period (2008–2010), tTG (IgA) ab assessment revealed 17% (19 children) of the children were positive for tTG (IgA) antibody.

The study revealed that 25(OH)D level was lower in diabetic patients with positive tTG (IgA) antibody than diabetic patients with negative tTG (IgA) antibody, but this change did not achieve significant value. This matched with the study by Setty-Shah *et al*. [30] (62 patients and 49 controls) which demonstrated a higher occurrence of vitamin D deficiency in children with T1DM+CD (27.3%) compared with the controls (18.4%), CD (22.2%), and T1DM (13.6%).

Patients with CD often present with nutritional deficiencies as a result of villous atrophy and subsequent malabsorption. Vitamin D is one such nutritional deficiency that has been noted in patients with CD [31].

Our study showed that patients with low vitamin D level (deficiency and insufficiency) had higher HbA_{1c} (25.8%). This result was in agreement with a study by Littorin *et al*. [24] and Janner *et al*. [32]; both demonstrated that there was no correlation between the concentrations of 25(OH) D and HbA_{1c}. This may indicate that the diabetic state *per se* is a reason for low 25(OH)D levels and is not secondary to any hyperglycemic or insulin-resistant state. This results was in disagreement with a study of Nahla Abdelkarim *et al*. [33] which showed that HbA_{1c} is higher in T1DM patients with low vitamin D level. Moreover, Tunc *et al*. [34] showed that children with T1DM had lower serum 25(OH)D concentrations and that these vitamin D-deficient children often require increased amounts of insulin to maintain normal glycemic control. A less likely explanation is the presence of altered dietary habits, or nutritional status in patients with worse glycemic control. Moreover, the relation between vitamin D status and HbA_{1c} may be explained by the effects of vitamin D on β-cell secretory function, on insulin action, and on systemic inflammation [35].

Acknowledgements

The authors are very grateful to Minia University for their support.

This study was supported by a grant from Minia University Research Foundation, Minia, Egypt.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Rankin D, Cooke DD, Elliott J, Heller RS, Lawton J, The UK NIHR DAFNE Study Group. Supporting self-management after attending a structured education programme: a qualitative longitudinal investigation of type 1 diabetes patients' experiences and views. BMC Public Health 2012; 12:652.

2 Smart C, Aslander-van Vliet E, Waldron S. Nutritional Management. Global IDF/ISPAD guidelines for diabetes in childhood and adolescence. Diabetologica 2011; 100:66–69.

3 Harinarayan CV. Vitamin D and diabetes mellitus. Hormones 2014; 13:163–181.

4 Pittas AG, Lau J, Hu FB, Dawson-Hughes B. Review: the role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. J Clin Endocrinol Metab 2007; 92:2017–2029.

5 Marchese A, Lovati E, Biagi F. Coeliac disease and type 1 diabetes mellitus: epidemiology, clinical implications and effects of gluten-free diet. Endocrine 2013; 43:1–2.

6 Di Sabatino A, Corazza GR. Coeliac disease. Lancet 2009; 373:1480–1493.

7 Mager DR, Qiao J, Turner J. Vitamin D and K status influences bone mineral density and bone accrual in children and adolescents with celiac disease. Eur J Clin Nutr 2012; 66:488–495.

8 Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, *et al*. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2011; 96:1911–1930.

9 Mutlu A, Mutlu GY, Özsu E, Çizmecioğlu FM, Hatun Ş. Vitamin D deficiency in children and adolescents with type 1 diabetes. J Clin Res Pediatr Endocrinol 2011; 3:179–183.

10 Eisenbarth GS. Type I diabetes mellitus. A chronic autoimmune disease. Diabetologia 2014; 57:902–908.

11 El Ziny MA, Salem NA, El Hawary AK, Chalaby NM, Elsharkawy AA. Epidemiology of childhood type 1 diabetes mellitus in Nile delta and Northern Egypt – A retrospective study. J Clin Res Pediatr Endocrinol 2014; 6:9.

12 Chakhtoura M, Azar ST. The role of vitamin D deficiency in the incidence, progression, and complications of type 1 diabetes mellitus. Int J Endocrinol 2013; 2103:148673.

13 Badenhoop K, Kahles H, Penna-Martinez M. Vitamin D, immune tolerance, and prevention of type 1 diabetes. Curr Diab Rep 2012; 12:635–642.

14 Frederiksen B, Liu E, Romanos J, Steck AK, Yin X, Kroehl M, *et al.* Investigation of the vitamin D receptor gene (VDR) and its interaction with protein tyrosine phosphatase, non-receptor type 2 gene (PTPN2) on risk of islet autoimmunity and type 1 diabetes: the Diabetes Autoimmunity Study in the Young (DAISY). J Steroid Biochem Mol Biol 2013; 133:51–57.

15 Munger KL, Levin LI, Massa J, Horst R, Orban T, Ascherio A. Preclinical serum 25-hydroxyvitamin D levels and risk of type 1 diabetes in a cohort of US military personnel. Am J Epidemiol 2013; 177:411.

16 Borkar VV, Devidayal XX, Verma S, Bhalla AK. Low levels of vitamin D in North Indian children with newly diagnosed type 1 diabetes. Pediatr Diabetes 2010; 11:345–350.

17 Bener A, Alsaied A, Al-Ali M, Al Kubaisi A. High prevalence of vitamin D deficiency in type 1 diabetes mellitus and healthy children. Acta Diabetol 2009; 46:183–189.

18 Greer RM, Portelli SL, Hung BS. Serum vitamin D levels are lower in Australian children and adolescents with type 1 diabetes than in children without diabetes. Pediatr Diabetes 2012; 14:31–41.

19 Bierschenk L, Alexander J, Wasserfall C, Haller M, Schatz D, Atkinson M. Vitamin D levels in subjects with and without type 1 diabetes residing in a solar rich environment. Diabetes Care 2009; 32:1977–1979.

20 Svoren BM, Volkening LK, Wood JR, Laffel LM. Significant vitamin D deficiency in youth with type 1 diabetes mellitus. J Pediatr 2009; 154:132–134.5.

21 Riachy R, Vandewalle B, Moerman E, Belaich S, Lukowiak B, Gmyr V, *et al.* 1, 25-Dihydroxyvitamin D_3 protects human pancreatic islets against cytokine induced apoptosis via down-regulation of the Fas receptor. Apoptosis 2006; 11:151–159.

22 Lind L, Hänni A, Lithell H, Hvarfner A, Sörensen OH, Ljunghall S. Vitamin D is related to blood pressure and other cardiovascular risk factors in middle-aged men. Am J Hypertens 2015; 8:894–901.

23 Al-Agha AE, Ahmad IA. Association among vitamin D deficiency, type 1 diabetes mellitus and glycemic control. J Diabetes Metab 2015; 6:594.

24 Littorin B, Blom P, Schölin A, Arnqvist HJ, Blohmé G, Bolinder J, *et al.* Lower levels of plasma 25-hydroxyvitamin D among young adults at diagnosis of autoimmune type 1 diabetes compared with control subjects: results from the nationwide Diabetes Incidence Study in Sweden. Diabetologia 2006; 49:2847–2852.

25 Çizmecioğlu FM, Etiler N, Görmüş U, Hamzaoğlu O, Hatun Ş. Hypovitaminosis D in obese and overweight schoolchildren. J Clin Res Pediatr Endocrinol 2008; 1:89–96.

26 Razzaghy-Azar M, Shakiba M. Assessment of vitamin D status in healthy children and adolescents living in Tehran and its relation to iPTH, gender, weight and height. Ann Hum Biol 2010; 37:692–701.

27 Bin-Abbas BS, Jabari MA, Issa SD, Al-Fares AH, Al-Muhsen S. Vitamin D levels in Saudi children with type 1 diabetes. Saudi Med J 2011; 32:589–592.

28 Tsuji K, Maeda T, Kawane T, Matsunuma A, Horiuchi N. Leptin stimulates fibroblast growth factor 23 expression in bone and suppresses renal 1alpha,25-dihydroxyvitamin D_3 synthesis in leptin-deficient mice. J Bone Miner Res 2010; 25:1711–1723.

29 Abdulrahman A, Nimer S, Musa A, Ahmed A, Imad E. High prevalence of celiac disease among Saudi children with type 1 diabetes: a prospective cross-sectional study. BMC Gastroenterol 2012; 12:180.

30 Setty-Shah N, Maranda L, Nwosu BU. Increased risk for vitamin D deficiency in obese children with both celiac disease and type 1 diabetes. Gastroenterol Res Pract 2014; 2014:561351.

31 Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, Wellnitz B, *et al.* Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. Arch Intern Med 2008; 168:1340–1349.

32 Janner M, Ballinari P, Mullis EP, Flück CE. High prevalance of vitamin D deficiency in children and adolescents with type 1 diabetes. Swiss Med Wkly 2010; 140:13091–13091.

33 Salama NA, Ebian HF, Atteia HH. Assessement of vitamin D in Egyptian patients with type 1 diabetes mellitus. Int J Adv Res 2015; 3:570–576.

34 Tunc O, Cetinkaya S, Kizilgün M, Aycan Z. Vitamin D status and insulin requirements in children and adolescent with type 1 diabetes. J Pediatr Endocrinol Metab 2011; 24:1037–1041.

35 Devaraj S, Yun JM, Duncan-Staley CR, *et al.* Low vitamin D levels correlate with the proinflammatory state in type 1 diabetic subjects with and without microvascular complications. Int J Endocrinol 2013; 135:429–433.