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Influence of Supplementary Vitamin D on the Prognostic Pathway of Type1 Diabetes among Children

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Diabetes is one of the commonest chronic diseases worldwide. Vitamin D deficiency showed to be increasing, and have a potential role in autoimmune diseases among which in type 1 diabetes. The aim of the study was to assess the impact of oral vitamin D supplementation on blood glucose (HbA1C) in T1DM patients and to find out the role of vitamin D as a biomarker for follow of T1DM patients compared to HbA1C. A randomized interventional clinical study was designed. The study enrolled 60 children patients with T1DM. Only 45 children continued to the end of study. Initial (pre-intake) assessment included history taking, clinical examination, and measurement of serum 25-OH vitamin D3 and serum HbA1C. These children received oral vitamin D supplements for 3 months then post-intake assessment were done again. The study showed that serum vitamin D was deficient among Egyptian children and adolescents with T1DM (mean 11.4±3.4 ng/ml). , 53.33% of the patients had vitamin D deficiency with a 35.6% had insufficiency and 11.11% were VD sufficient. Patients received oral vitamin D supplementation for 3 months after which marked improvement in the levels of serum vitamin D levels and HA1C, 87.5% and 86.5% respectively.

Keywords: Diabetes - Type1 diabetes mellitus (T1DM) -Vitamin D -Ultra-Violet Index.

Diabetes mellitus 'DM' is a multifactorial metabolic disorder characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism arising from defects in insulin secretion, insulin action, or both. The impact of DM comprises chronic damage, dysfunction, and failure of various organs[1].

Type 1 Diabetes Mellitus (T1DM) is a common endocrine and metabolic condition in childhood and adolescence. The patients require lifelong insulin injections for survival. The overall increase in the incidence of T1DM is around 3% and about 78,000 children under age 15 years develop T1DM worldwide[2]. The wide variation

in incidence can hardly be explained by genetic factors alone. Environmental factors have long been implicated in the pathogenesis of T1DM both as initiator and potentiator of pancreatic â-cells damage[3].

When using glycosylated hemoglobin (HbA1C) to diagnose DM, it is important to recognize that HbA1C is an indirect measure of average blood glucose levels and to take other factors into consideration that may impact hemoglobin glycation independently of glycemia including age, race and anemia/ hemoglobinopathies[4].

Vitamin D (vit D) is a multi-functional fat-solute metabolite required for human growth and health. The primary source of vitD in (80–90%) is from endogenous biosynthesis in skin cells, a critical step of which is hydroxylation of 7-dehydrocholesterol into cholecalciferol catalyzed by the ultraviolet radiation from sunlight[5]. During sun exposure, the ultraviolet B photons are absorbed by the cutaneous 7-dehydrocholesterol to form the split sterol pre-vit D3. However, a variety of factors limit the cutaneous production of vit D3. An increase in skin melanin pigmentation or the topical application of a sunscreen will absorb solar ultraviolet B photons and thereby significantly reduce the production of vit D3 in the skin. Latitude, time of day, and season of the year have a dramatic influence on the cutaneous production of vit D3. Lifestyle factors may also be associated with lower vit D concentrations, such as reduced physical activity, and increased body mass index (BMI) due to deposition of vit D in adipose tissue, where it becomes biologically inactive[6].

The role of vit D in innate immunity is postulated as deûciency can lead to autoimmune conditions, such as type 1 diabetes. Vitamin D and its metabolites as well as constituents of inûammation seem to have important effects on insulin synthesis, secretion and action[7]. At the level of the immune system, 1, 25(OH)2 D3 inhibits the differentiation and maturation of dendritic cells and promotes their apoptosis[8]. At the level of the pancreatic islets, 1,25(OH)2D3 decrease proinflammatory chemokine and cytokine expression, which are implicated in the pathogenesis of T1DM making â-cells less chemoattractive and less prone to inflammation[9].

Aim

The aim of the study was to assess the impact of oral vitamin D supplementation on blood glucose (HbA1C) in T1DM patients and to find out the role of vitamin D as a biomarker for follow of T1DM patients compared to HbA1C.

Subjects and methods

Environmental recordings

Ultraviolet rays have a known impact on vit D metabolism. Therefore, ultraviolet index (UVI) was recorded throughout the period of the study (September 2019 till end of March 2020) – through daytime hours using website: https://www.accuweather.com/ar/eg/cairo/127164/weather-forecast/127164

Study design

A randomized interventional clinical study was designed using oral vitD supplements for 3 months.

Subjects

The study included 60 children and adolescents with type 1 diabetes (30 males and 30 females) with a final compliance of 45 patients, and an attrition of 15 patients (25% drop out percentage). The patients were attending the Pediatric and Adolescents Diabetes Clinic of Children's Hospital, Ain Shams University, Egypt, over 7 months period from September 2019 to March 2020. The study protocol was approved by the Medical Research Ethics Committee of National Research Center and patients were included after obtaining informed consents from their legal guardians after explaining the aim and steps of the study.

Criteria of inclusion

• Participants are children aged between 6-14 years old of both sexes.

• Diabetics with established diagnosis of T1D, according to the International Society For Pediatric and Adolescent Diabetes criteria (ISPAD Consensus Guidelines, 2018)

• The patients are otherwise free from any other health problems.

Criteria for exclusion

• Symptoms and signs of infection within 1 month of the study.

• Receiving vit D or calcium supplements via any route, one year previous to the study.

METHODS

All participants were subjected to 1- pre-

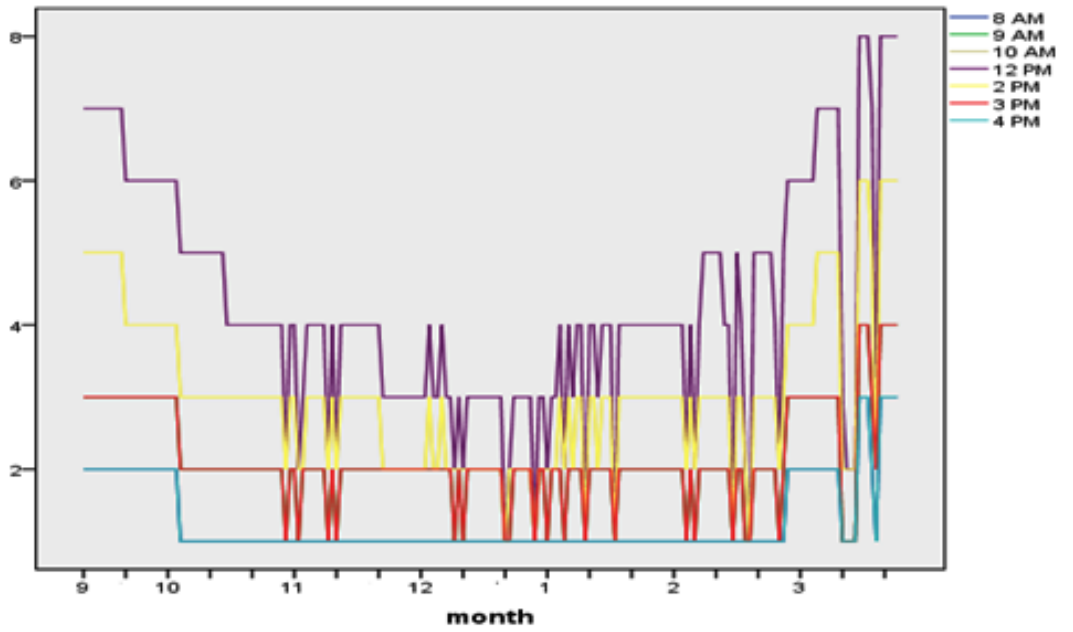
intake assessment: included detailed history taking, full clinical examination (including weight and height measuring and BMI Percentiles calculation), and laboratory assessments: included serum 25-OH vitamin D3 (using 25-OH vitamin D3 ELISA kit provided by ORGENTEC Diagnostika GmbH, Mainz Germany), and Hb A1C (Using Fine Care FIA meter apparatus for flurorescence immunoassay quantitative tests by Guangzhou Wondfo Biotech Co., China), 2- The patients were given vit D3 supplements in the form of oral drops (vidrops), 1ml per day orally that is equivalent to 2800 IU of cholecalciferol (for 3 months), 3-Follow-up assessment including (history follow up of symptoms and signs, clinical examination, serum vit D assessment and HbA1C measurement) were done after 3 months from the pre-intake assessment. Percentages of vit D categories in T1DM patients in the present study (vit D deficiency, < 12 ng/ml; insufficiency, 12 - 20 ng/ml; sufficiency, > 20 - 150 ng/ml)[10]

Statistical analysis

SPSS (version 26) statistical package was used for analysis of data. Data was summarized as mean, standard deviation (±SD), count and percent. Shapiro-Wilk test was used for normality testing. Time series chart (sequence plot) of daily UVI recordings throughout study period was drawn. Paired t-test was used for compare means of measured parameters before and after vitamin D supplementation. Independent t-test test was used for comparisons between means of parameters between two different groups. Pearson's correlation (r) was done to detect the relation between the parameters. P-value is considered to be significant if $p < 0.05$.

RESULTS

The time series chart (figure 1) showed the variations in UVI on a daily/montly basis throughout 7 months (the period of the study from September 2019 till end of march 2020). The UVI was least on December (mean was 2.9±0.5), that increases gradually towards September and March (means were 6.9±0.3 and 5.9±2.1 respectively). Mean UVI was least at 8 am and 4 pm (1.3) and reaches a peak value at 12 pm with mean of 4.29.



[Data were obtained from https://www.accuweather.com/ar/eg/cairo/127164/weather-forecast/127164]; Mean UVI at 8am =4pm = 1.27±0.531; at 9am=3pm =2.15 ±0.673; at 10 am=2pm=3.06±1.111, peak at 12m= 4.29±1.648 .

Fig. 1. Time series chart of the UV Index in Cairo during the period from 20th September 2019 till 28th March 2020. Charts at various daytime hours were shown.

The patients who completed the study were 25 females (55.6%) and 20 males (44.4%). Those below 12 years constituted 67% (30 cases out of 45 enrolled cases).

It was found that 24 patients (53.3%) had vit D deficiency with a mean of 8.8±1.6 ng/ml, 16 patients (35.6%) had insufficiency with a mean of 14.4±2.4 ng/ml and only 5 (11.11%) had vit D sufficient serum levels with a mean of 24.6±1.5 ng/ml.

The sex and age groups did not seem to have an effect on pre- and post- intake serum vit D levels and pre- and post- intake HbA1C levels. There were no significant differences between males and females (table 1) and between younger (<12 years) and older (e"12 years) age groups (p>0.05) (table 2).

There was a highly significant improvement in the levels of serum vit D and HbA1C after the administration of vit D using paired t-test. Vit D increased from 11.4±3.4 to 29.9±8.5 ng/ml (p-value = 0.00001) and HbA1C dropped from 9.3±1.8 to 7.1±1.6 % (p-value = 0.00001) table (3). Results of correlation between

Table 1. Comparison between males and females as regards serum vit D and HbA1C at pre- and post-intake

Test	Sex	Mean	± SD	P-value
Serum vitamin D initial (ng/ml)	Males	11	2.9	0.59
	Females	11.6	3.8	
Serum vitamin D post-intake (ng/ml)	Males	29.3	8.4	0.72
	Females	30.2	8.8	
HbA1Cinitial (%)	Males	9	1.9	0.37
	Females	9.5	1.8	
HbA1C post-intake (%)	Males	6.8	1.7	0.26
	Females	7.3	1.4	

SD means standard deviation

Table 2. Comparison between cases <12 years old and cases ≥ 12 years old as regard levels of serum vit D and of HbA1C

Test	Age	Mean	± SD	P-value
Serum vitamin D initial (ng/ml)	< 12yrs	11.3	3.1	0.97
	≥ 12yrs	11.4	4.1	
Serum vitamin D post-intake (ng/ml)	< 12yrs	29.9	7.7	0.91
	≥ 12yrs	29.6	10.3	
HbA1Cinitial (%)	< 12yrs	9.1	1.8	0.39
	≥ 12yrs	9.6	1.9	
HbA1C post-intake (%)	< 12yrs	6.9	1.6	0.56
	≥ 12yrs	7.3	1.6	

SD means standard deviation

Table 3. Comparison between mean levels of pre- and post-intake serum vit D as regards serum vit D and HbA1C (oral vit D intake for three months)

	Mean	± SD	Paired T-Test	P_value
Serum vitamin D (ng/ml) (initial)	11.4	3.4	17.6	0.00001
Serum vitamin D (ng/ml) (post-intake)	29.8	8.5		
HbA1C initial (%)	9.3	1.8	16.8	0.00001
HbA1C post-intake (%)	7.1	1.6		

serum vit D and HbA1C confirmed results of paired t-tests as there was a highly significant negative correlation between HbA1C and serum vit D (r = -0.54, p = 0.00001).

DISCUSSION

The current study showed significant decline in serum vit D level among a group of Egyptian children and adolescents despite the sunny weather and moderate to high range of UVI, 24 patients (53.33%) had vit D deficiency with 16 patients (35.6%) had insufficiency and only 5 (11.11%) were vit D sufficient. This goes in hands with what Hafez *et al*[10] found that among 50 Egyptian children with T1D 70% of the patients had vit D deficiency, 24% had insufficiency and 6% were vit D sufficient. Also Hassan *et al* who conducted a study on 60 Egyptian children and adolescents with T1DM and found that 91.67% of were vit D deficient[11]. Similarly, another Egyptian studies revealed a prevalence of 84.9%[12] and 75%[13]. This concurs with Bin Abbas *et al*.,[14] and Bener *et al*.,[15] found that vit D deficiency was considerably higher in children with T1DM (84%, 90.67% respectively). Janner *et al*,[16] reported relatively lower prevalence (28%). This high prevalence of VDD in Egypt despite the presence of adequate sunlight and sunny weather most of the year can be attributed to the vit D receptor gene polymorphism[17] as well as the lack exposure to sunlight due to religious or cultural reasons. Or due to conducting the study during autumn and winter with the lowest UVI levels. Another possible cause as reported by Xiang *et al*.,[18] that pigmented skins are less effective than light skins at vit D production.

Our study showed highly significant negative correlation between levels of serum vit D and HbA1c (r = -0.54, p = 0.00001). Similarly, Al-Agha and Ahmad[19] identified a significant relationship between HbA1c and the status of vit D among diabetic patients. Soliman and his colleagues[12] also found a significant strong negative correlation between 25OHD levels and HbA1c%. This was in concur with what Aljabri et al[20] reported. On the other hand, Janner et al. [16] found no such significant correlation in the Swiss population. This could be explained on ethnic or genetic bases since most of the concurring studies were conducted in Egypt.

The current study shows improvement in the levels of serum vit D levels and HbA1C after the administration of vit D, 87.5% and 86.5%

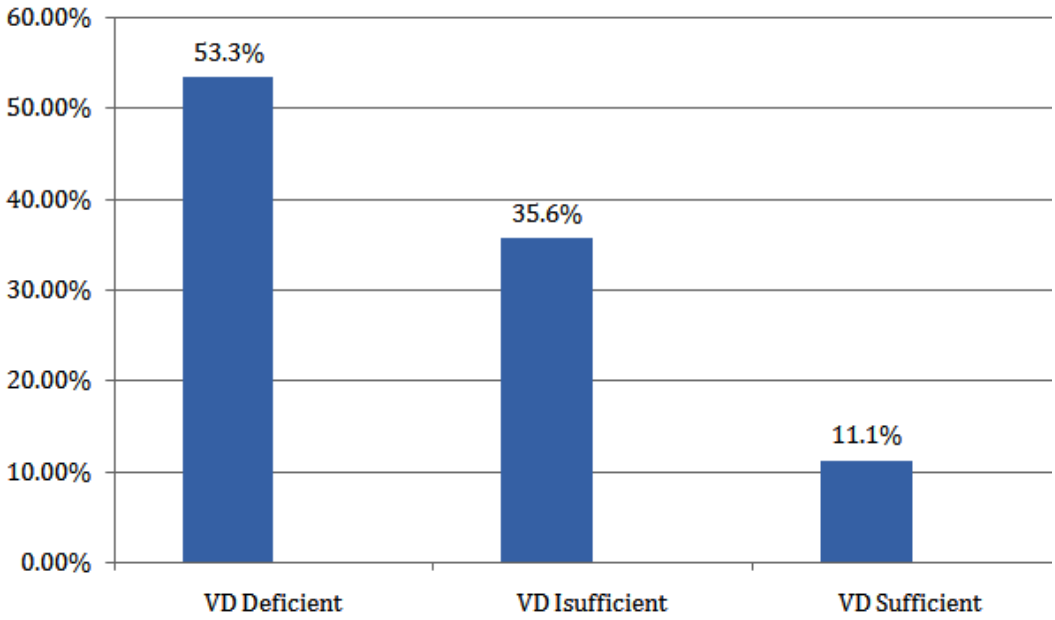


Fig. 2. Percentages of vit D categories (vit D deficiency, < 12 ng/ml; insufficiency, 12 - 20 ng/ml; sufficiency, > 20 - 150 ng/ml)

respectively and statistical analysis shows that, the improvement was statistically highlysignificant (p-vales < 0.05). in concur with that, Hafez *et al*[10] reported that VIT D supplementation was associated with a significant improvement in HbA1c% mean values. Similarly, Parildar and his co-workers[21] found a significant reduction in HbA1c following vit D supplementation in patients with prediabetes favoring the improvement in glucose metabolism. Aljabri et al.[21] concluded that vitD supplementation might improve the glycemic control of patients with T1D as there was significant reduction in HbA1c% levels following a supplementation given to 80 patients with T1D aged over 12 years. Walter and his colleagues[22] as well as a meta-analysis conducted by George et al[23] in Scotland, observed no significant improvement in HbA1c% or fasting blood glucose in those receiving vit D supplementation compared with those who received placebo concluding that there was insufficient evidence of the beneficial effect of vit D supplementation as a means of improving glycemic control in children and adolescents with T1D.

Our study showed no significant statistical difference between comparable groups (either sex difference or age difference) regarding the levels of serum vit D and HbA1c% initially or post vit D intake. That was also reported by Branco et al.[24] and Mutlu et al[25] who found no significant difference between males and females regarding 25OHD and their glycemic control. In contrast, Hafez *et al*[10] found no significant sex difference regarding HbA1c% but males had higher mean 25OHD levels. That was also the case in the study conducted by Al-Agha and Ahmad[19] where the boys had higher levels of vit D. This could be attributed to females covering their head and body due to cultural and religious reasons. In addition to the fact that, more vit D is required for bone growth during faster pubertal spurt in females[26].

CONCLUSIONS

The study showed that serum vit D was deficient among Egyptian children and adolescents with T1D (mean 11.4±3.4 ng/ml). , 53.33% of the patients had vit D deficiency with a 35.6% had insufficiency and 11.11% were vit D sufficient. Patients received oral vit D supplementation for 3 months after which marked improvement in the levels of serum vit D levels and HA1C, 87.5% and 86.5% respectively.

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Conflict of interest

No conflict of interest

Funding Source

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