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THE ASSOCIATION BETWEEN CHRONIC VITAMIN D DEFICIENCY AND INCIDENCE OF TYPE 2 DIABETES MELLITUS IN ADULT POPULATION IN A TERTIARY HOSPITAL

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ABSTRACT

Vitamin D, commonly known as sunshine vitamin, is both indispensable and vital for human beings. The prevalence of vitamin D deficiency (VDD) is on the rise globally including the sunny regions such as in the UAE. The aim of this study was to examine the relation between the degree of chronic vitamin D deficiency as a risk factor of the incidence of type 2 diabetes mellitus among adult populations. This is a single-centre observational retrospective cohort study conducted in a tertiary hospital in the UAE. It was mainly based on reviewing the electronic data-base and medical records of all chronic patients that match the inclusion criteria. The inclusion criteria of this study included all adult patients aged between 18 and 55 years old, tested for vitamin D level, visited the practice at least three times in the past year. The exclusion criteria included renal failure patients, patients who had malabsorption disorders and those with T2DM risk factors. A sample size of 35,000 adult patients who were screened in a period of 12 months for vitamin D level was selected using the lab database. Patients were checked against the inclusion criteria and of them, only 391 patients met the inclusion criteria. Other diabetes risk factors such as obesity, family history, pre-diabetes, presence of co-existing hypertension and dyslipidemia were also reviewed and excluded. The results of this study showed that a total of 56 patients [14% (95% CI 10.56- 17.44)] had normal results compared to 335 patients [86% (95% CI 82.56-89.44)] who had a chronic vitamin D deficiency. In addition, the results showed that 17% (95% CI 13.28- 20.72) of the 391 patients had mild vitamin D deficiency (VDD), 31% (95% CI 26.42- 35.58) moderate VDD and 38% (95% CI 33.2- 42.8) severe VDD. A total of 32% of patients with severe vitamin D deficiency developed diabetes compared to only 16% from patients with normal vitamin D deficiency and statistically showed significant difference from all other VDD groups as to developing T2DM. This indicates that the more the severity of vitamin D deficiency, the more the susceptibility to develop T2DM. Of a note, in the prevalence of severe chronic VDD, female patients showed significantly higher percentage (61%) of VDD compared to their male counterparts (39%). According to the results of this study, there is a clear relation between severe vitamin D deficiency and incidence of type 2 diabetes mellitus, whereas, mild and moderate VDD showed no difference from normal.

Key Words: Vitamin D, Type 2 diabetes mellitus, relation between vitamin D deficiency and type 2 diabetes mellitus.

INTRODUCTION

Vitamin D, commonly known as sunshine vitamin, is both indispensable and vital for human beings. This vitamin can be obtained effectively upon exposure to sunlight and through balanced dietary intake [1]. The prevalence of vitamin D deficiency (VDD) is on the rise globally including the sunny regions such as in the UAE. Other studies carried out in Saudi Arabia, Turkey and India had shown a high prevalence of vitamin D deficiency [2, 3]. In many countries, vitamin D insufficiency exists in around 50% of the populations [3]. The reason for this phenomenon in warm countries may be attributed to avoiding

sunlight or clothing which prevents the exposure to ultraviolet B (UVB) irradiance from the sun. However, data is still inconclusive in terms of prevalence and consequences of severity of VDD. Root causes of vitamin D deficiency can be related to insufficient dietary intake and/or lack of UVB exposure; in addition to genetic factors which may also play a role in vitamin D deficiency. To diagnose and treat vitamin D deficiency, we need to understand different forms and metabolism of vitamin D and we also need to better understand the non-skeletal role of vitamin D [4].

Vitamin D exists in two forms, the plant source ergocalciferol (D2) and animal source cholecalciferol (D3). Vitamin D3 is considered the major source of vitamin D which is synthesized in skin upon exposure to sunlight. First hydroxylation of vitamin D is in the liver then in the kidneys which yields the active form of vitamin D (1, 25 (OH) 2D) [1]. Unfortunately very few foods naturally contain vitamin D and very few foods naturally contain vitamin D in significant amount like oily fish salmon, sardines and mackerel. Therefore, the extent of exposure to sun is critical to determine the level of vitamin D synthesized in the body. Vitamin D has an established role in calcium and bone metabolism. Low vitamin D levels have long been associated with bone disease such as rickets in children and osteomalacia in adults. For example, Hypovitaminosis D has been implicated as a risk factor for hip fracture in elderly (Determinants of vitamin D status in older women[1, 3].

Vitamin D is a steroidal nucleus that has to be transformed to the 1, 25 hydroxylated form to show metabolic activity. This process happens in the liver and kidney successively.The lab uses 25(OH) form as the standard measure of vitamin D level and classified it as normal if it is >30 ng/ml, mildly deficient (30-20 ng/ml), moderately deficient (12-20ng/ml) and severely deficient (<12 ng/ml) [5], **Table 1**. In a community pharmacy, vitamin D exists as Vit D3 (cholecalciferol) which is driven from animal source and vitamin D2 (ergocalciferol) which is extracted from plant origins. Moreover, according to the literature, it is believed that vitamin D3 is more effective than vitamin D2 but clinical significance is uncertain [6, 7].

Table 1: Vitamin D range guidelines from various organizations [16].

Vitamin D Level	Vitamin D Council	Endocrine Society	Food and Nutrition Board	Testing Laboratories	Clinical symptoms
Deficient	0-30 ng/ml	0-20 ng/ml	0-11 ng/ml	0-31 ng/ml	Severe hyperparathyroidism, calcium malabsorption, rickets, osteomalacia, myopathy
Insufficient	31-39 ng/ml	21-29 ng/ml	12-20 ng/ml		Elevated PTH levels, low intestinal calcium absorption rates, reduced bone mineral density, subclinical myopathy
Sufficient	40-80 ng/ml	30-100 ng/ml	>20 ng/ml	32-100 ng/ml	No disturbances of vitamin D-dependent functions
Toxic	>150 ng/ml				Intestinal calcium hyper absorption, hypercalcemia

Vitamin D level screening test is usually performed in both out and inpatient settings. Patients with high risk (Geriatrics) or those with a positive history of fracture are mainly asked to do the test. Random screening is also performed through campaigns inside the hospital.

OBJECTIVES

The objective of this study was to explore the relation between Vitamin D deficiency and the incidence of type 2 diabetes in adult populations in a tertiary hospital in a warm region such as in the United Arab Emirates.

METHODS

This is a single-centre observational retrospective study using cohort patients from a tertiary hospital in the United Arab Emirates (UAE); the name of the hospital was kept anonymous to comply with the hospital's rules and regulations. This study was carried out in the Department of Biochemistry from November 2014 to May 2015 after obtaining the ethics approval from the hospital administration on

November 2014. The study was conducted by reviewing and collecting data of adult patients who met the inclusion criteria of all patients aged from 18 years to 55 years, had been tested for vitamin D and glucose level at least three times during the last year (2014). On the other hand, all patients with previous diabetes or other risk factors for type 2 diabetes mellitus or those receiving medications that may alter glucose homeostasis were excluded. The considered Type 2 diabetes mellitus risk factors in this study included obesity, family history, pre-diabetes, presence of co-existing hypertension, dyslipidemia and the history of gestational diabetes in females. According to the study protocol, vitamin D deficiency is classified as normal (>30 ng/ml), mildly deficient (30-20 ng/ml), moderately deficient (12-20ng/ml) and severely deficient (<12 ng/ml). Then the patients' medical records were reviewed for their status of glucose level and type 2 diabetes. In addition, obesity (a common risk factor for both T2D and VDD) was excluded in this study to enable isolating the two variables from other confounding factors.

A total of 35,000 adult patients with systematically random sampling technique were selected as the study subjects for screening of Vitamin D deficiency. Of them, a total of 391 patients met the inclusion criteria of this study. Then the medical records of these patients were collected and given a code number; the patients' names and codes were kept in separate sheet with the main investigator to retain patient's name anonymized. All medical records that complied with the inclusion criteria were reviewed and analyzed using a data-entry sheet by a health professional. The data was analysed using Microsoft Office Excel 2010 and Minitab 17 Statistical Software (made by "Minitab Inc.", Pennsylvania, USA) and chi-square test. P value of < 0.05 was considered to be statistically significant. In the absence of all other risk factors for diabetes, the incidences of new type 2 diabetes in each group of vitamin D deficiency – mild, moderate and severe- and in normal population were estimated.

RESULTS

According to the result of this study a number of 56 patients [14% (95% CI 10.56- 17.44)] showed normal results compared to 335 patients [86% (95% CI 82.56-89.44)] who showed a chronic vitamin D deficiency. Based on the average of at least three readings of the 25 hydroxy vitamin D for each patient in a period of 3 to 4 months apart, the data showed that in addition to 14% normal patients, 17% (95% CI 13.28- 20.72) of the 391 patients had mild vitamin D deficiency (VDD), 31% (95% CI 26.42- 35.58) had moderate VDD and 38% (95% CI 33.2- 42.8) had severe VDD, **Figure 1**. The results of this study had also demonstrated that there is a clear relation between severe vitamin D deficiency and incidence of type 2 diabetes mellitus. All patients with chronic vitamin D deficiency were screened for type 2 diabetes (T2DM) and evaluating their medical records to detect any risk factor of T2DM. It was clearly indicated that patients with more severity of vitamin D deficiency showed higher risk to develop type 2 diabetes mellitus as shown in Table 2.

Table 2: The data showing the relation between vitamin D deficiency and diabetes.

vitamin D level	Number of vitamin D deficiency (n=391)	% of vitamin D deficiency	95% Confidence Interval (CI)	Number of diabetes cases (n=82)	% of diabetic cases	95% Confidence Interval (CI)
normal	56	14	(10.56- 17.44)	9	16	(6.31-25.69)
mild	65	17	(13.28- 20.72)	10	15	(6.32-23.68)
moderate	122	31	(26.42- 35.58)	16	13	(7.03- 18.97)
severe	148	38	(33.2- 42.8)	47	32	(24.48-39.52)

According to the result of this study, the highest number of newly diabetics was shown in patients with severe vitamin D deficiency. For example, out of 148 patients with severe vitamin D deficiency, 47 patients developed T2DM [32% (95% CI 24.48-39.52)]; compared to only 9 [16% (95% CI 6.31-25.69)] diabetic patients out of 56 patients with normal vitamin D. In addition, from a 65 patients [17% (95% CI 13.28- 20.72)] with mild vitamin D deficiency, 10 patients [15% (95% CI 6.32-23.68)] developed diabetes and from the 122 patients [31% (95% CI 26.42- 35.58)] with moderate vitamin D deficiency, 16 patients [13% (95% CI 7.03- 18.97)] developed diabetes. Where as, a total of 47 patients [32% (95% CI 24.48-39.52)] were found diabetics out of the 148 patients with severe vitamin D

deficiency. This indicates that the more severity of vitamin D deficiency, the more the susceptibility to develop type 2 diabetes mellitus as shown in

Moreover, the results of this study indicated that there are no clear differences between male and female patients in terms of mild and moderate vitamin D deficiency (VDD). A total of 51% (95% CI 42- 60) of the male patients showed moderate VDD compared to 49% (95% CI 40- 58) in their counterpart female patients. However, in the prevalence of chronic VDD, female patients showed significant much higher percentage of vitamin D deficiency compared to their counterpart male patients. A total of 61% (95% CI 57- 64) of female patients showed severe chronic VDD, compared to 39% (95% CI 35- 43) of their counterpart male patients **Figure 4**. This indicates that females are probably at more risk to develop type 2 diabetes as a result of developing severe vitamin D deficiency.

DISCUSSIONS

The results had clearly demonstrated that Vitamin D Deficiency can also be a chronic health problem in warm countries. It was illustrated that 86% of the patients included in the study showed a chronic vitamin D deficiency. The results of this study can be considered as additional evidence that there is a positive relation between severely chronic vitamin D deficiency and incidence of type 2 diabetes. As shown in this study the highest number of diabetic patients was found in the most severe vitamin D deficient patients. For example, out of 38% of patients who showed severe vitamin D deficiency, 32% were found diabetics. On the other hand, 16% diabetic patients were found in the 14% normal vitamin D level patients. In addition, from the 48% patients with mild and moderate vitamin D deficiency, about half of them (48%) developed diabetes. Moreover, a total of 45% of patients were found diabetics out of the patients with moderate to severe vitamin D deficiency. This indicates that the more severity of vitamin D deficiency, the more the susceptibility to develop type 2 diabetes mellitus. In addition, Moreover, the results of this study indicated that there are no clear differences between male and female patients in terms of the vitamin D deficiency (VDD). A total of 51% of the male patients showed moderate VDD compared to 49% of female patients. However, in the prevalence of chronic VDD, female patients showed significantly much higher level of vitamin D deficiency compared to their counterpart male patients. A total of 61% of female patients showed severe chronic VDD, compared to 39% (95% CI 35- 43) of their counterpart male patients **Figure 4**. This indicates that females are at more risk to develop type 2 diabetes as a result of developing severe vitamin D deficiency.

These results were concurred with many other observational studies reported in the literature [17-19]. For example, many studies indicated that vitamin D plays a critical role in the regulation of plasma calcium concentration via effects on intestinal absorption, bone metabolism and as a risk factor for type 2 diabetes [20, 21]. However, results from many other randomized controlled trials are with mixed conclusions [18, 22, 23]. Definitive conclusions may be limited in the context of the moderate degree of heterogeneity, variable risk of bias and short term follow up duration of the available evidence to date [23].

Other studies such as the Nurse' Health Study (NHS) found that vitamin D intake above 800 IU/day and more than 1200 mg of calcium per day were associated with a 33% reduction in the risk of developing type 2 diabetes mellitus compared with an intake of < 600 mg of calcium and < 400 IU of vitamin D [15]. Another meta- analysis study of largely observational studies concluded that there was a relatively consistent association between low vitamin D level and prevalent type 2 diabetes mellitus or metabolic syndrome [8]. Other evidence from interventional trials suggests that combined vitamin D and calcium supplementation may help prevent type 2 diabetes mellitus in only some populations at high risk for diabetes [8]. In addition, low vitamin D levels have been shown in many studies to correlate with the presence of cardiovascular disease in diabetics and more frequent cardiovascular complications [24]. On the other hand, other studies indicated that good intake of vitamin D by diabetic patients can be helpful in preventing complications of diabetes [25]. These data can suggest that vitamin D deficient patients are at greater risk of developing diabetes and be harmed by this deficiency.

In addition, vitamin D reduces inflammation which is commonly present in patients with insulin resistance syndrome and type 2 diabetes. It may also indirectly improve insulin production and its action by improving the level of calcium inside the cells. It also can prevent or delay complications like neuropathy, nephropathy, retinopathy and diabetes ulcers [10].

Other studies indicated that vitamin D is inversely associated with adiposity, glucose homeostasis, blood pressure and lipid profiles along with its classic role in calcium homeostasis and bone metabolism. For example, many systematic review studies suggested a possible inverse association between vitamin D and cardiovascular risks [28, 29]. One meta-analysis study showed that individuals with highest levels of serum vitamin D were associated with a 43%

reduction in cardio-metabolic disorders [30]. Other studies showed that vitamin D is associated with abdominal obesity which may be due to vitamin D being soluble in fat which is largely sequestered in adipose tissue and is therefore low in serum among obese individuals [31-33]. Furthermore, several epidemiological studies have shown an association between low serum vitamin D levels and increased risk for cardiovascular disease, stroke, hyperglycemic and hypertension [17-19, 28]. Therefore, vitamin D deficiency should not be considered only as a feature of osteo-mineral disorders, but also as a biomarker and a risk factor for metabolic derangements as well as cardiovascular disease.

Many more studies in the literature indicated that low vitamin D concentration has been reported to be associated with decreased insulin sensitivity, particularly among the obese population. Therefore, vitamin D is believed to help improve the body's sensitivity to insulin and thus reduce the risk of insulin resistance which is often a precursor to type 2 diabetes [18]. Other large prospective studies concluded that there is a potential beneficial role for both vitamin D and calcium intake in reducing the risk of type 2 diabetes. The total calcium and vitamin D intake was inversely associated with incident type 2 diabetes after adjustment for age and BMI [8, 34]. Another study conducted using 320 healthy women indicated that vitamin D deficiency is a potential risk factor for obesity and development of insulin resistance leading to type 2 diabetes mellitus [4]. A study in Germany explored that vitamin D has been implicated in type 1 diabetes by genetic and epidemiological studies. It was found that people living in regions with low sunlight exposure have increased type 2 diabetes and vitamin D supplementation reduced the risk in human individuals and mouse models [5].

Another study opened up the issue of recognizing that severe vitamin D deficiency as a possible risk factor for diabetic foot infections and the need of vitamin D supplementation in such patients to lead to better clinical outcomes. It was concluded in this study that vitamin D deficiency was more prevalence and severe in patients with diabetic foot infection. It revealed that the patients with foot infection had comparatively higher prevalence of vitamin D deficiency than those who had no evidence of infection [35]. Although several studies have reported a protective association of vitamin D deficiency and type 2 diabetes mellitus, the current findings are not consistent. A systematic review and meta-analysis using a total of seventeen articles based on eighteen unique prospective studies and comparison of 210,107 participants with 15,899 metabolic events multiple databases was performed in a period of 10 years. It revealed that vitamin D status at baseline in healthy adults is inversely associated with future risks of type 2 diabetes [20]. Other current study demonstrated a strong association between low vitamin D status and the severity of arterial disease such as atherosclerosis, independent of traditional cardiovascular risk factors and irrespective of the type of vascular disease [36]. Another study showed that vitamin d deficiency was associated with a significant risk of cardiovascular disease such as diabetes mellitus and reduced survival. It was also found in the same study that vitamin D supplementation was significantly associated with better survival rate especially in patients with documented deficiency [12].

Many current epidemiological studies have reported that deficient or insufficient levels of documented vitamin D is associated with the increase in the rates of coronary heart disease, hypertension and diabetes [25, 37-40]. For example, recently, the relationship between low vitamin D levels and cardiovascular risk factors was explored among 15,088 subjects from the NHANES III national cohort registry. This cross sectional study had concluded that vitamin D levels were inversely associated with diabetes, hypertension, hyper triglyceridemia and obesity [41]. Other cross-sectional studies have confirmed the links between vitamin D deficiency and both diabetes and hypertension [42, 43]. Another study included 10,366 children who were given 2,000 IU of vitamin D3 per day throughout the first year of life experienced a 78% reduced risk of type 1 diabetes over the ensuing 31 years of follow up [21]. This result was also confirmed by another study in which vitamin D deficiency was more pronounced in children with newly diagnosed type 1 diabetes but not associated with progression of the disease [44].

A correlation between vitamin D deficiency and subsequent major adverse cardiovascular events was found among the 1,739 Framingham Offspring Study subjects who were free of cardiovascular disease at baseline. In this prospective study, vitamin D was measured at baseline and subjects were followed up for a mean of 5.4 years. The rate of a composite cardiovascular end point was 53% to 80% higher in people with low vitamin D levels [45]. A recent meta-analysis of 18 randomised controlled trials comparing 57,000 individuals showed that a vitamin D intake >500 IU/day improved all-cause mortality in part by decreasing CV deaths [16, 46]. According to the results of this study, female patients showed significant much higher level of severity of vitamin D deficiency compared to their counterpart male patients. This might indicate that females are at more risk of developing type 2 diabetes compared to their counterpart males. However, this unique finding is

not described or discussed in other studies in the literature; therefore, more studies are required to confirm these findings and to highlight this area of research.

Table 3: Distribution of Vitamin D levels among study subjects.

Statistics		Vitamin D3 + D2 (Total)
Mean		18.85
Std. Error of Mean		.655
Median		16.00
Mode		8
Std. Deviation		12.610
Variance		159.013
Range		120
Percentiles	25	11.00
	50	16.00
	75	23.00

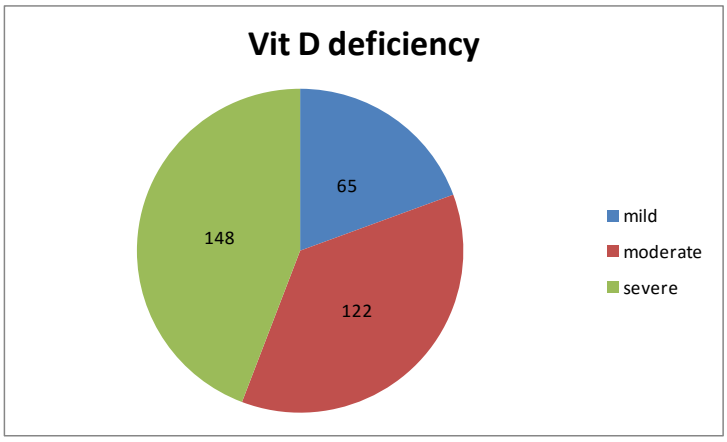

Figure 1: The cases of vitamin D Deficiency.

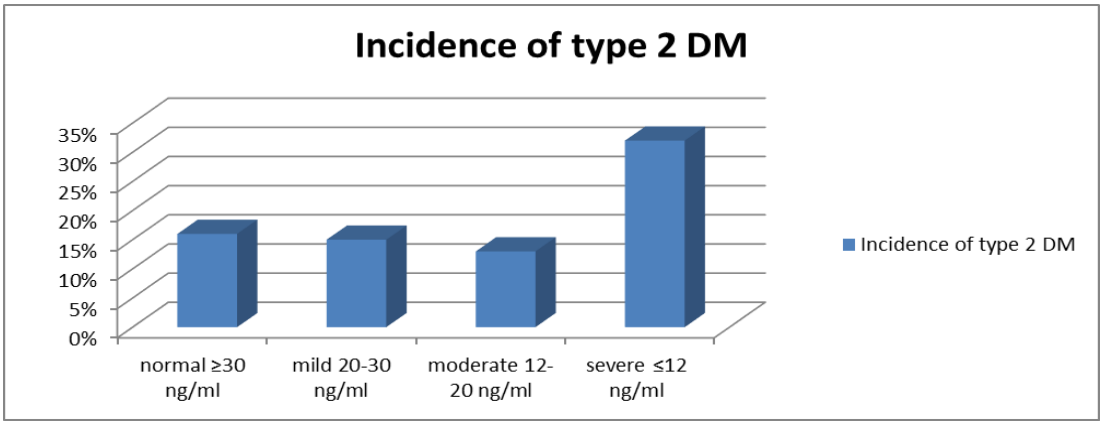

Figure 2: The correlations between Vitamin D level and type 2 Diabetes mellitus.

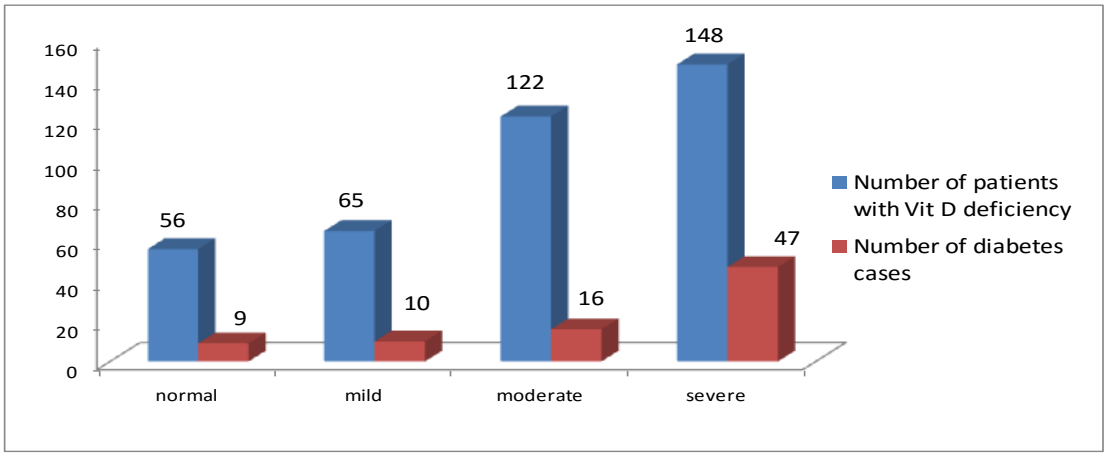

Figure 3: The correlations between Vitamin D deficiency and type 2 Diabetes mellitus.

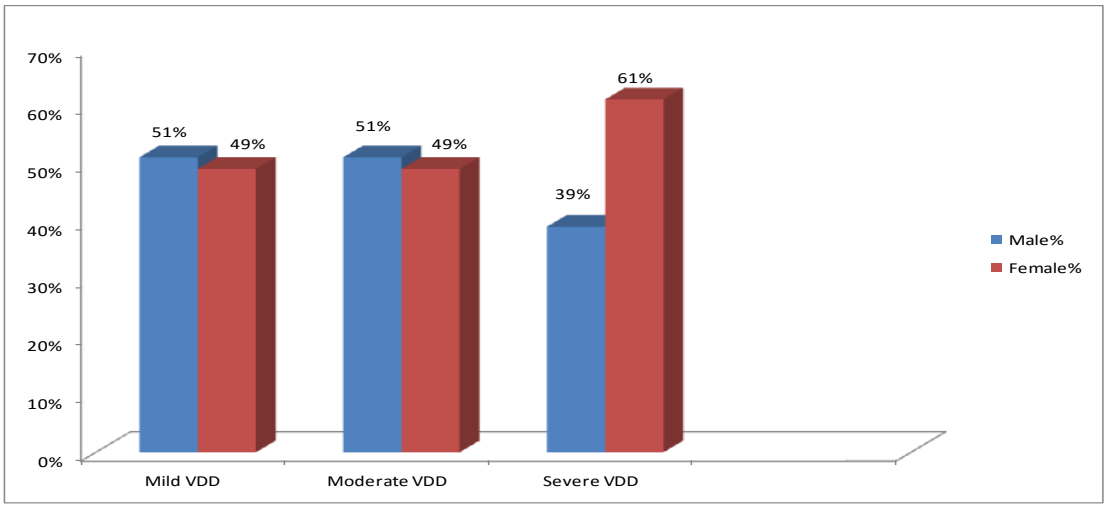

Figure 4: The differences between male and female patients in Vitamin D deficiency.

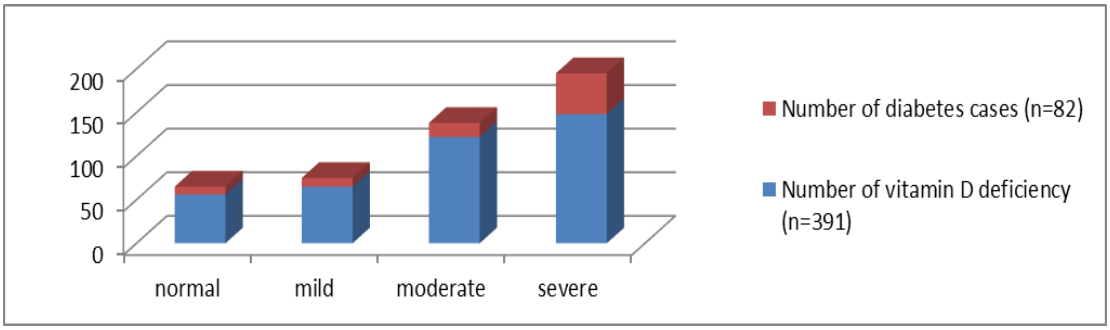

Figure 5: The relations between the number of patients with Vitamin D deficiency and type 2 Diabetes mellitus.

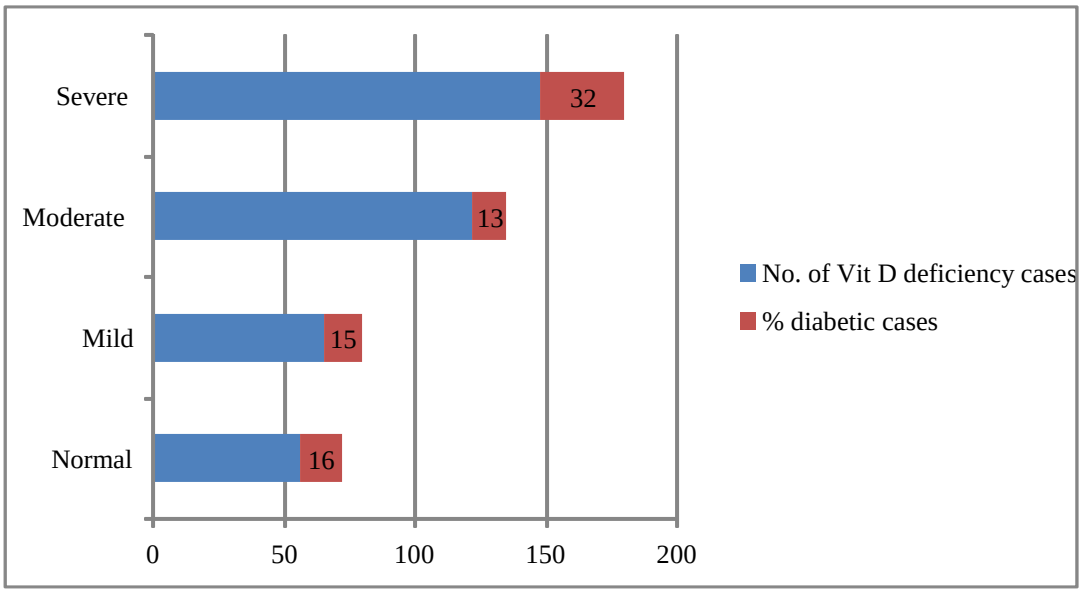

Figure 6: % **patients with Vitamin D deficiency and type 2 Diabetes mellitus**

CONCLUSIONS

Vitamin D deficiency is an alarming issue among adult patients and is a risk factor to many other diseases such as diabetes. This study is considered additional evidence that the prevalence of vitamin D deficiency is widespread among adult patients even in warm regions. Evaluating the relationship between VDD and diabetes mellitus revealed that there is a clear relation. Therefore, a step-wise approach should be developed in hospitals to address and control vitamin D deficiency among adult patients by direct intervention or through patients' education campaigns. Thus, include developing educational programs targeting primary care physicians, other healthcare professionals and patients. Strategies should also be defined to closely monitor adults who are diagnosed with severe vitamin D deficiency and are more susceptible to develop diabetes mellitus. This will increase the awareness of the magnitude of vitamin D deficiency phenomenon and its risk to develop diabetes mellitus.

Encouraging adults to adhere to lifestyles such as eating balanced diet, exposure to sunlight and indulging in outdoor recreational activities would help achieve optimal vitamin D level. Therefore, urgent measures needed to include the assessment of vitamin D status among the population and more particularly in females. Overall, more studies are required to establish the correlation of glycemic control and vitamin D status in different parts of the globe as vitamin D levels vary widely in different population groups. This can indicate that supplementation of vitamin D in diabetics may improve the glycemic control and can reduce the morbidity and mortality along with improving the quality of life. This conclusion will have important public health and economic implications since both of these interventions can be implemented easily and inexpensively to prevent type 2 diabetes. Vitamin D supplementation is simple, safe and inexpensive.

Limitations of the study: Limitations of this study include that the relation between vitamin D deficiency and incidence of type 2 diabetes mellitus was mainly assessed from reviewing patients' database and medical records retrospectively and not by following individual patients in cohort study but probable ethical issues may prohibit researchers from leaving study subjects without vitamin D correction in deficient people. In addition, since this study was conducted in a tertiary hospital, the results cannot be generalised, a community based study would have given more generalizable results. More prospective studies and systematic reviews are needed to better understand the importance of prevention of type 2 diabetes with vitamin D supplementation in deficient population.

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