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Measurement of serum vitamin D3 levels in type 1 diabetes patients with and without Nephropathy in Iraqi patients

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Abstract---Background: a better understanding of the vitamin-D system's physiological role, particularly its potential effects on inflammatory and autoimmune conditions, insulin secretion, and possibly also resistance to insulin, interest in its potential role in the prevention and control of diabetes, both type 1 and type 2, has grown. Both of these diseases are linked to inflammation, with type 1 diabetes also having an autoimmune component. Indeed, animal and human research suggest that appropriate vitamin D supplementation may reduce the prevalence of type 1, diabetic microvascular complication and perhaps type 2 diabetes mellitus, as well as enhance metabolic control in people with diabetes. Aims: Evaluation of the role of diabetes mellitus type 1 on the level of vitamin D3 and comparison between patients of diabetes with and without Nephropathy in Iraqi. Method: This was across-sectional study of 120 subject,80 patients with type 1 diabetes mellitus (T1DM) with aging range between 18-40 years, they were divided into three groups group 1-DM without nephropathy consisted of forty (40) patients with type 1 diabetes only, group 2-DM with nephropathy consisted of forty (40) patient with type 1 diabetes having microalbuminuria group 3-control consisted of forty (40) healthy people, some clinical information and laboratory result were collected from the medical records (duration of DMT1

,FBS, urea ,Creatinine). Results: Statistically significant weak positive correlations were detected between vitamin D and both of BMI (r= 0.197, P= 0.031) and GFR (r= 0.321, P= 0.001); while significant moderate negative correlation was seen between vitamin D and HbA1c (r= - 0.494, P= 0.001) and weak negative correlation was seen with B. Urea (r= - 0.2, P= 0.028). No statistical significant correlations detected between vitamin D and all of age, DM duration, and s. creatinine.

Keywords---DMT1, VD, DNP, microalbuminuria.

Introduction

Type 1 diabetes (DMT1) is an organ-specific chronic autoimmune disease leading to immune-mediated destruction of insulin-secreting beta cells within the pancreatic islets, resulting in lifelong dependence on exogenous insulin. Insulitis is the inflammatory lesion considered as the histological hallmark of DMT1 [1]. In recent years, the extra-skeletal effects of vitamin D [25(OH) D] have raised considerable interest since specific receptors has been found in many tissues and systems, including pancreatic β cells and immune cells. The main extra-skeletal action of vitamin D is exerted into the cell nucleus which revealed its ability to regulate the transcription of approximately the 3% of the human genome. 25(OH)D deficiency represents a major health problem since it has been related to cardiovascular, inflammatory, autoimmune diseases, and cancer and development of DMT1 as well as diabetes-associated secondary osteoporosis [2,3]. The relationship between the bioavailability of vitamin D, its metabolism, and T1D development is multifactorial and is confirmed by genetic studies in humans. It has been established that 25OHD deficiency, associated with cytochrome polymorphism and inherited defects in vitamin D metabolism [4]. The patient of Diabetes nephropathy, a decrease in 25(OH)D2 concentrations is associated with an increased prevalence of albuminuria and there is an independent relationship between VD and DN deficiency. With progressive DN, the VD insufficiency becomes more severe [5].

Method and Criteria

Ethics approval

This study was approved by the Human Research and Ethics Committee of our hospital and was conducted according to the tenets of the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants.

Patients

This cross-sectional study evaluated 80 patients with DMT1 who attended the Diabetic control clinic of Endocrinology and Diabetes center \ Al Kindi Hospital, Baghdad Teaching Hospital / Medical City and Al shahed Al- Sader General Hospital during the period from October 2021 to March 2022. DM was diagnosed

according to the 2012 American Diabetes Association criteria [6]. the subject included in this study were divided into 3 groups, group A : included 40 patient had DM and NP, group B included 40 patient DM without NP, group C included 40 healthy subject .The exclusion criteria regarding group A and B were as follows: (1) type 2 DM or special types of diabetes, (2) acute complications of diabetes, only nephropathy (3) liver dysfunction, (4) parathyroid diseases, (5) severe cardiovascular and cerebrovascular diseases, (6) malignant tumors, (7) pregnant or lactating women, (8) cataract, glaucoma, and other eye diseases interfered with fundus photography, and (9) treatment with drugs or nutrition supplements about 6 month ago that affected vitamin D metabolism.

Anthropometric and laboratory measurement

Information of sex, age, duration of diabetes, and medication was collected from the medical records with standardized questionnaires. The body mass index (BMI) was calculated as body weight (kg) divided by the square of height (m2) [6]. Fasting blood sugar (FBS) levels were measured using the quantitative determination of glucose in human serum on Roche/Hitachi cobas C311systems. Glycated hemoglobin (HbA1c) was measured via In vitro test is performed to determine mmol/mol hemoglobin A1C according to the International Federation of Clinical Chemistry (IFCC) and % hemoglobin A1C according to the National Glycohemoglobin Standardization Program (DCCT/NGSP) in whole blood and hemolysates prepared from whole blood on the cobas C111. serum urea and serum creatinine (scr) levels were measured In vitro test for the quantitative determination of urea and creatinine in human serum, on Roche/Hitachi cobas C 311 systems. Serum calcium and serum albumin were measured for the quantitative immunological determination of calcium and albumin in human on the cobas c 111 system. Serum 25-hydroxy vitamin D3 was detected by enzyme immunoassay technique for the quantitative in vitro diagnostic measurement using kit manufactured by (MyoBiosource,USA), Serum 25 (OH) D < 20 ng/mL was categorized as deficiency, 20-29 ng/ml as insufficiency in accordance with WHO definition [7]. measurement albumin in urine by using Immunoturbidimetric assay on Roche/Hitachi cobas C111systems.Measurement of GFR by using MDRD equation

MDRD equation: $1.86x\ (creatinine/88.4)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female})$ [8].

Statistical analysis

The data was analyzed using Statistical Package for Social Sciences (SPSS) version 26. The data presented as mean ± standard deviation and ranges. Categorical data presented by frequencies and percentages. Independent t-test and Analysis of Variance (ANOVA) (two tailed) was used to compare the continuous variables between study groups. Pearson's correlation test (r) was used to assess correlation between vitamin D and certain biological parameters. A level of P – value less than 0.05 was considered

Results

Patient characteristics

The distribution of study groups by general characteristics is shown in figure and table (4.1). Study participants' age was ranging from 18 to 40 years with a mean of 27.02 years and a standard deviation (SD) of ± 6.33 years. The highest proportion of study participants involved in groups A, B, and C was aged < 30 years (62.5%, 57.5%, and 75% respectively). In this study, proportion of males and females was approximately the same in all groups; the highest proportion of participants in groups A, B, and C had normal BMI level (65.0%, 60.0%, and 55% respectively). Regarding DM duration, it was > 10 years in 52.5% of group A and between 5 – 10 years in 55% of group B.

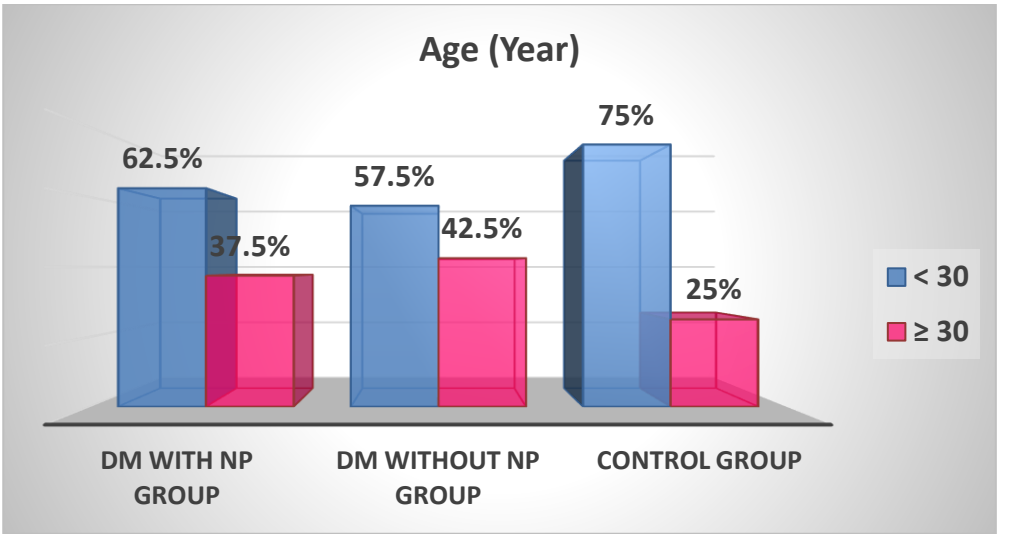

Figure 4.1. Distribution of study groups by age

Table 4.1
Distribution of study groups by general characteristics

Variable	Group A (%) n= 40	Group B (%) n= 40	Group C (%) n= 40	Total (%) n= 120
Gender				
Male	18 (45.0)	19 (47.5)	20 (50.0)	57 (47.5)
Female	22 (55.0)	21 (52.5)	20 (50.0)	63 (52.5)
BMI Level				
Normal	26 (65.0)	24 (60.0)	22 (55.0)	72 (60.0)
Overweight	14 (35.0)	14 (35.0)	13 (32.5)	41 (34.2)
Obese	0 (0)	2 (5.0)	5 (12.5)	7 (5.8)
DM Duration (Year)				
< 5	1 (2.5)	10 (25.0)	-	11 (13.8)
5 - 10	18 (45.0)	22 (55.0)	-	40 (50.0)
> 10	21 (52.5)	8 (20.0)	-	29 (36.2)

The comparison between groups had been don by certain characteristics as shown in table (4.2). Mean of BMI was significantly lower (23.03 kg/m2, P= 0.031), while mean of DM duration was significantly higher (13.82 years, P= 0.001) in group A than that in groups B and C. No statistical significant difference in age between study groups (P= 0.399).

Table 4.2
Comparison between study groups by certain characteristics

Variable	Study group			P - Value
	A Mean ± SD	B Mean ± SD	C Mean ± SD	
Age (Year)	27.42 ± 6.8	27.72 ± 7.0	25.92 ± 5.1	0.399
BMI (Kg/m^2)	23.03 ± 2.9	24.1 ± 3.9	25.04 ± 3.3	0.031
DM Duration (Year)	13.82 ± 8.0	7.42 ± 4.6	-	0.001

Investigation

Table 4.3 shows the comparison in investigation results between study groups. Means of FBS, HbA1c, B. urea, and albuminuria were significantly higher (P < 0.05) in group A than that in groups B and C. Means of S.Ca, S. albumin, and GFR were significantly low (P < 0.05) in group A than that in groups B and C. No statistical significant difference in mean of s. creatinine between study groups (P= 0.083).

Table 4.3
Comparison in investigation results between study groups

Investigation	Study group			P - Value
	A Mean ± SD	B Mean ± SD	C Mean ± SD	
FBS (mg/dl)	278.56 ± 122.4	262.07 ± 98.8	87.43 ± 6.3	0.001
HbA1c (%)	9.89 ± 1.9	9.49 ± 2.1	4.74 ± 0.31	0.001
S. Albumin (gm/dl)	40.38 ± 4.0	43.93 ± 3.7	47.6 ± 2.8	0.001
S. Ca (mg/dl)	8.71 ± 0.62	9.31 ± 0.5	9.57 ± 0.36	0.001
B. Urea (mg/dl)	30.38 ± 17.1	21.77 ± 6.2	23.12 ± 5.6	0.001
S. Creatinine (mg/dl)	1.01 ± 1.2	0.71 ± 0.08	0.72 ± 0.1	0.083
Albuminuria (mg/g)	5.73 ± 1.2	2.52 ± 0.56	2.61 ± 0.7	0.001
GFR	99.43 ± 21.4	114.97 ± 9.0	114.97 ± 8.5	0.001

Vitamin D

In this study, we noticed that 57.5% of diabetic patients with NP (Group A) had deficiency in vitamin D level; while 15% of diabetic patients without NP vitamin D deficiency (Group B); most of healthy subjects (Group C) had normal vitamin D level (80%) and 20%of them had vitamin D insufficiency as shown in figure (4.2).

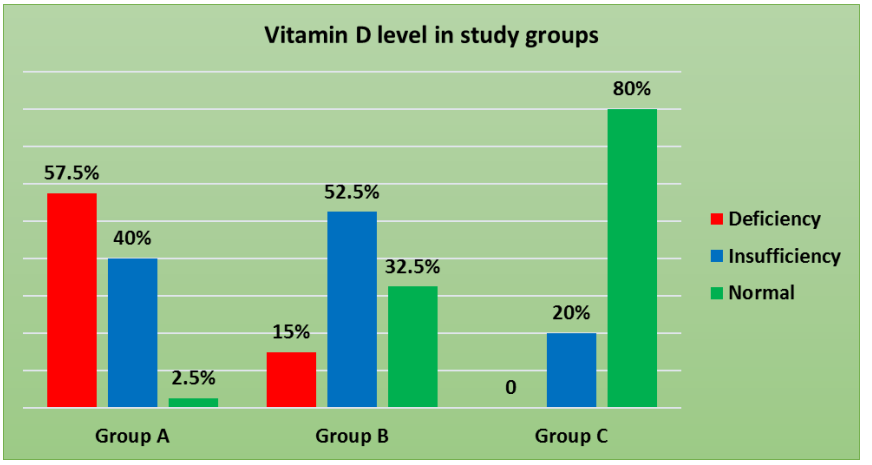

Figure 4.2. vitamin D level in study groups

As shown in table (4.4), Mean of vitamin D was significantly lower (19.13, P = 0.001) in diabetic patients with NP (Group A) than that in diabetic patients without NP (Group B) and healthy subjects (Group C).

Table 4.4: Comparison in vitamin D level between study groups

Vitamin D (ng/ml)	Study group			P - Value
	A Mean ± SD	B Mean ± SD	C Mean ± SD	
	19.13 ± 6.2	33.0 ± 16.1	51.88 ± 17.0	0.001

Post hoc tests (LSD) were run to confirm the differences occurred in mean of vitamin D between study groups and showed that mean of vitamin D was significantly lower ($P < 0.05$) in group A than that in groups B and C. Also, it was significantly lower ($P < 0.05$) in group B than that in group C as shown in table (4.5).

Table 4.5: Post hoc tests (LSD) to confirm the differences in mean of vitamin D between study groups

Vitamin D (ng/ml)	Study group			P - Value
	A Mean ± SD	B Mean ± SD	C Mean ± SD	
	19.13 ± 6.2	33.0 ± 16.1	-	0.001
	19.13 ± 6.2		51.88 ± 17.0	0.001
	-	33.0 ± 16.1	51.88 ± 17.0	0.001

Correlation between vitamin D and certain biological parameters

Statistically significant weak positive correlations were detected between vitamin D and both of BMI (r= 0.197, P= 0.031) and GFR (r= 0.321, P= 0.001); while significant moderate negative correlation was seen between vitamin D level and HbA1c (r= - 0.494, P= 0.001) and weak negative correlation was seen with B. Urea (r= - 0.2, P= 0.028). No statistical significant correlations detected between vitamin D and all of age, DM duration, and s. creatinine as shown in table (4.6) and figures (4.3, 4.4, 4.5, and 4.6).

Table 4.5: Correlation between vitamin D and certain biological parameters

Variable	Vitamin D (ng/ml)	
	r	P - Value
Age (Year)	- 0.102	0.269
BMI (kg/m^2)	0.197	0.031
DM Duration (Year)	- 0.102	0.368
HbA1c (%)	- 0.494	0.001
B. Urea (mg/dl)	- 0.2	0.028
S. Creatinine (mg/dl)	- 0.11	0.232
GFR	0.321	0.001

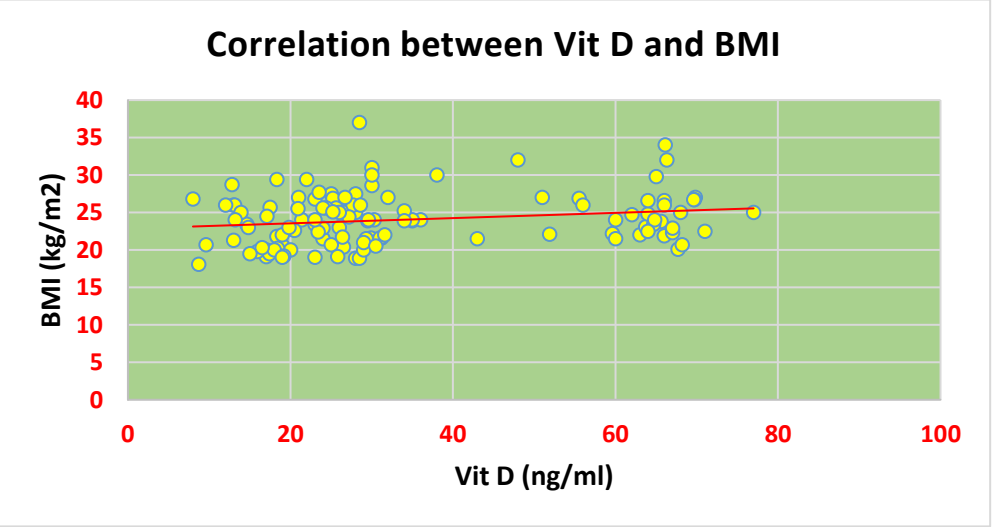

Figure 4.3. correlation between Vit D and BME

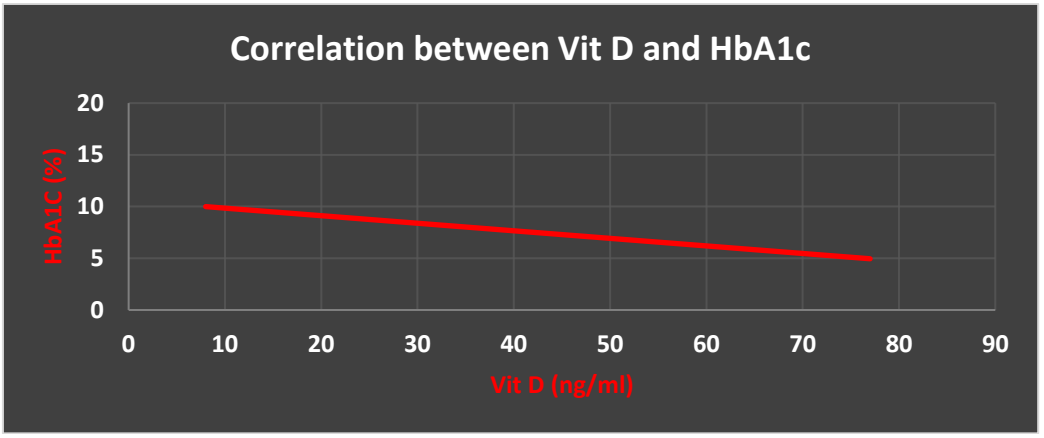

Figure 4.4. correlation between Vit D and HbA1c

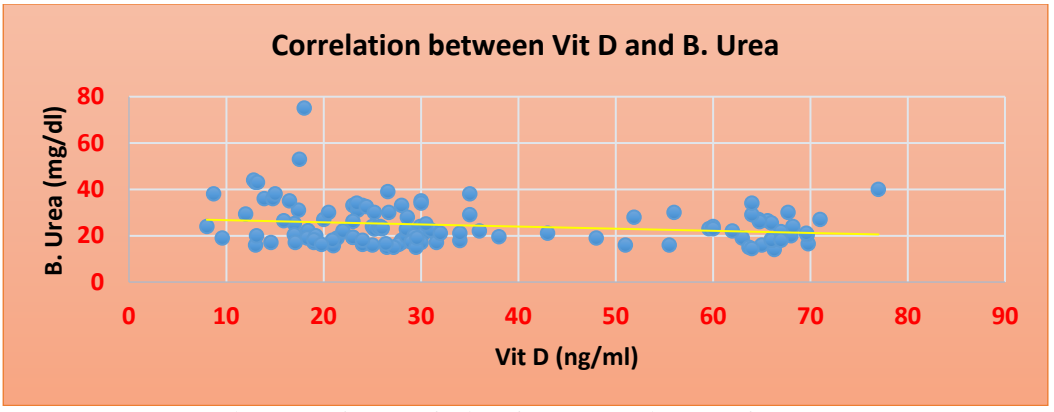

Figure 4.5. correlation between Vit D and Brera

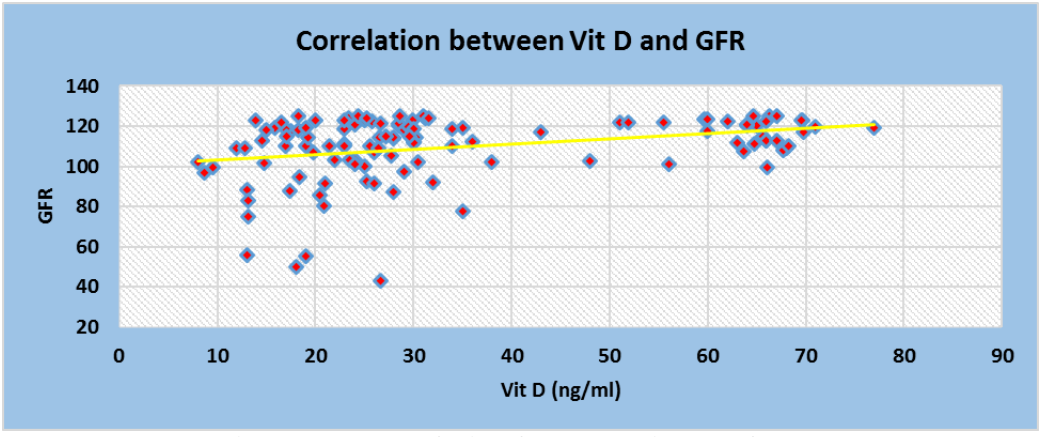

Figure 4.6. correlation between Vit D and GFR

Discussion

In this study, the 25OHD levels in DMT1 patients revealed correlation with several clinical parameters of diabetes, including HbA1c, albuminuria, GFR, and

calcium. Among diabetic macro- and microvascular complications, diabetic nephropathy was correlated with the 25OHD level. In particular, the 25OHD level remained an independent risk factor for diabetic nephropathy after exclusion other risk factors.

Table (4.2), the mean of BMI was significantly lower in group A(with nephropathy) than that in groups B(without nephropathy) and C (control) this result was consistent with recent studies conducted by Ghavam S *et al* ,[9] also in this study it was noticed that the mean of DM duration was significantly higher in group A than that in groups B and C these result were consistent with the recent studies conducted by Hong SH *et al*,[10] ,Besides there was no statistically significant difference in age between study groups .

Table (4.3), The current data showed the means of FBS, HbA1c, B. urea, and albuminuria were highly significant ($P < 0.001$)in group A than group B and C, the Means of S. Ca, albumin, and GFR were significantly lower in group A than that in groups B and C. high level of blood glucose is the reason behind this cumulative evidence that diabetic nephropathy is strongly associated with poor glycemic control, this result was consistent with recent researches conducted by Triozzi JL *et al.*, and Nandi-Munshi D *et al.* [11,12]. Hyperglycemia is not only causing but also aggravating glomerular lesions. Glomerular lesions may be prevented and if the lesions are present, delayed or stopped with better control of blood sugar. Indeed, hyperglycemia is the key of nephropathy creation. High glucose concentration causes impairment of cell growth and reduce secretion of growth factors and the occurrence of genes which will ultimately increase the extracellular matrix. Hyperglycemia may be causing toxic products which may lead to cell injury [13].

In this study it is so evident that although the mean of HbA1c is higher in group A than group B and C but also the mean of HbA1c of group B is uncontrolled (group A: Mean ± SD= 9.89 ± 1.9\ group B: Mean ± SD 9.49 ± 2.1) long-term high glycated hemoglobin(HbA1c) is a sequel to renal impairment [14] It was suggested by the authors that the relationship between HbA1c and ESKD was stronger in patients with milder CKD as there may be a threshold of kidney function below which good glucose control alone in not enough to prevent progressive kidney loss.[14] so we noticed that there is positive correlation between HbA1c and albuminuria, this result was consistent with recent studies elicited by MacIsaac et al, [15], . In our study we noticed that albuminuria in group A is mor than group B and group C, the majority of patients with diabetes, albuminuria is one of the earliest and most common important markers of kidney disease [16,17]. The majority of diabetic patients with nephropathy in early stages do not have any symptoms, and microalbuminuria is picked up on routine laboratory testing that is carried out to evaluate systemic diseases, such as diabetes mellitus or hypertension and careful examination of patient must be conducted.

This result was consistent with recent studies conducted by Prasad RM, and Tikaria R [18] In the present study the Means of S. albumin, S calcium, and GFR were significantly lower in group A than that in groups B and C. The patient with diabetic nephropathy suffers from hypoalbuminemia, hypocalcemia and decrease

the rate of GFR. This result was consistent with previous studies conducted by Razip et al., [19]. In our study, patients with vitamin D insufficiency or deficiency exhibited lower serum calcium compared with patients with sufficient vitamin D3 this result was consistent with previous studies conducted by Mao L et al, [20]. In the intestine, the 1,25(OH)2D induced-calcium absorption which is mediated by the epithelial calcium channel TRPV6 (transient potential vanilloid type 6) and in the kidney,1,25(OH)2D mediates the active reabsorption of calcium via TRP5, in a mechanism similar to intestinal calcium absorption.

This process becomes weak in vitamin D3 deficiency [21]. It is well known that the glomerular filtration rate (GFR) is useful in staging chronic kidney disease. In comparison to microalbuminuria, GFR is a pure kidney damage marker. Several studies have demonstrated that there is a continuous correlation between microalbuminuria and developing end-stage renal disease. Therefore, when microalbuminuria presented in patient with a reduced GFR, renal damage is classified under stage 3 or 4, The patient with microalbuminuria should be considered to be a very high risk, instead of high risk as per the GFR. This classification ensures that real quick action must be taken to prevent further complications, such as macroalbuminuria, diabetic kidney disease and proteinuria [18]. Hypoalbuminemia is caused by an imbalance between albumin production and albumin degradation. Serum albumin has a half-life of 16 days. The degradation of albumin occurs at vascular endothelium. In acute illnesses, albumin shifts in to extracellular fluid and interstitial fluid due to increased vascular permeability. Glomerular filtration rate (GFR) depends primarily on glomerular perfusion pressure which is a result of hydrostatic pressure and serum oncotic pressure. Changes in these pressures may affect the GFR. This finding was consistent with recent studies conducted by Hansrivijit *et al.*, [22] In the present study no statistically significant difference in mean of s. creatinine between study groups because s. creatinine in stage 1 and stage 2 is not affected, while in the stage 3 is almost affected [13].

Figure 4.2, Mean of Vitamin D deficiency was significantly lower (19.13,p=o.oo1)in diabetic patient with NP (Group A) than that in diabetic without NP (Group B) and healthy subjects (Group C) ,vitamin D deficiency was high in patients with CKD, which was associated with albuminuria, faster progression of kidney disease and leading to increase rat of mortality [23]

Table (4.4), In this study, the rate of vitamin D deficiency (defined as less than 10 ng/mL) in groups A, B, C was 57.5 %, 15.0 %, 0%, respectively while that for insufficiency (less than 30 ng/mL) was 40 %. ,52.5 %, 20%, of the included adult male and female patients aged 18-40 years, respectively, Our data suggest that the result of vitamin D3 in control group is 80 % is normal, only 20% insufficiency, this could be attributed to the increase in health awareness of individuals after exposure to the corona viruses in 2019, and the demand of individuals to take vitamins to raise the body's immunity

Vitamin D3 (1,25(OH)2D3), which is the focus of our study is a fat-soluble steroid with endocrine function. In addition to its conventional role in calcium homeostasis, it exerts other biological effects, such as regulation of cell proliferation, differentiation, and apoptosis, in numerous types of cells and

tissues [24]. Recent studies in rodent models and humans had suggested that vitamin D may also plays a role in the glucose metabolism and the development of type 1 and type 2 diabetes mellitus (DM) [25]. also, that the vitamin D is a potential modifier risk of diabetes , Vitamin D enhances insulin sensitivity by stimulating the expression of insulin receptors and by activating peroxisome proliferator-activated receptor-δ (PPAR- δ) that results in the rise of intracellular calcium concentration via non-selective voltage-dependent calcium channels [26]. Vitamin D could promote β-cells survival by inactivation of nuclear factor-κB (NF-κb) and effects of cytokines. Vitamin D can affect insulin resistance indirectly through the renin angiotensin-aldosterone system (RAAS) [27].

Although the problem of vitamin D deficiency in patients with DMT1 is well known, the cause and effect relationship had not been fully explored. It is not fully clear whether an inadequate vitamin D concentration is a DMT1 trigger or a consequence of the disease. The available literature suggests these both possibilities; vitamin D status is a strong environmental risk factor for DMT1 as well as a consequence of physiological and behavioral changes that result due to disease [28]. Vitamin D deficiency also increases the level of parathyroid hormone, which contributes to increased insulin resistance and increases the risk of hyperglycemia and hypertension [29] Nevertheless, the potential mechanisms underpinning the renal protective effects of vitamin D are well described. Vitamin D receptors are highly expressed in the kidney, making the organ a major target site of vitamin D actions. Vitamin D primarily acts as an inhibitor of intrarenal RAAS activation, which occurs due to the effect of diabetes-induced hyperglycemia on the kidney. The RAAS pathway cascades through a sequence of events whose sequelae include renal fibrosis, glomerulosclerosis, inflammation, podocyte injury, endothelial dysfunction, and disruption of the glomerular filtration barrier. The latter contributes to various degrees of albuminuria seen in DKD. These pathological features constitute the essential components of DKD. In vitamin D deficiency, RAAS activation arising from hyperglycemia is unregulated: thus, creating the pathogenic pathway for DKD [29]. the recent studies showed that treatment with vitamin D3 causes better glycemic control in patients with type I diabetes mellitus. Moreover, vitamin D3 supplement causes the improvement of HbA1C in all degrees of glycemic control including poor, fair and good control. Increased level of 25OHD in all groups in this research including sufficiency, deficiency and insufficiency of vitamin D was observed this result was consistent with recent studies conducted by Ghavam et al, Hong SH *et al*, and Dehkordi EH *et al*, [9,10,30] in our study the Post hoc tests (LSD) were run to confirm the differences occurred in mean of vitamin D between study's groups and showed that mean of vitamin D was significantly lower ($P < 0.001$) in group A (microalbuminuria) than that in groups B(had no albuminuria) and C (control). Also, it was significantly lower ($P < 0.001$) in group B than that in group C as shown in table (4.5) this result was consistent with recent studies conducted by wu cc *et al*, sagi ps *et al*, [31,32].

Correlation between vitamin D and certain biological parameters

statistically significant weak positive correlations were detected between vitamin D and both of BMI ($r= 0.197$, $P= 0.031$) this result was consistent with recent studies conducted by Ghavam S *et al*, [9], and GFR ($r= 0.321$, $P= 0.001$); In this

research, vitamin D deficiency was found in all patients (in group A and B). A weak positive correlation (r=0.321, p = 0.001) between vitamin D and GFR was identified, indicating that circulating vitamin D concentrations were lower in patients of advanced stages and with lower GFR [33]. Vitamin D deficiency may be related to a decrease in intake from food, supplement, insufficient sunlight exposure, or generation of vitamin D3 from 7-DHC [22]. Due to the limitations of data collected in this study, it was difficult to confirm which of the above-mentioned reason is responsible for vitamin D deficiency.

While significant moderate negative correlation was seen between vitamin D and HbA1c (r= - 0.494, P= 0.001) this result was consistent with recent studies conducted by UWAEZUOKE *et al*, sagi ps *et al*, [27,30], and weak negative correlation was seen with B. Urea (r= - 0.2, P= 0.028). this result was consistent with recent studies conducted by Wang Y *et al*,[33]. No statistical significant correlations detected between vitamin D with creatinine this result was consistent with recent studies conducted by MacIsaac RJ *et al,* [16].in our study we find that No statistical significant correlations detected between vitamin D and age this result was consistent with recent studies conducted by Zhao WJ *et al*[34]. Also, we found in this study no statistically significant correlation between vitamin D deficiency and DM duration, Vitamin D status is influenced by a number of variables, including sun exposure, skin pigmentation (less pigment allows for the synthesis of more provitamin D), time of day, season, area of the body exposed to sunlight, body weight (only a 1% increase in body fat was linked to a 0.46 0.22 ng/mL reduction in circulating 25(OH)D, food-related vitamin D intake [35].

These variables it varies from person to person, so the duration of DM it has less impact on vitamin D deficiency, in addition, the individual's culture, how he deals with the disease, and his commitment to taking the nutritional supplements recommended by the doctor have a role in influencing vitamin D. As stated above, patients with DM in general and diabetic NP in particular have a higher probability to have suboptimal vitamin D levels: this condition can lead to a faster progression of both DM and CKD. This status for patients in both cases is often caused by inadequate dietary intake of vitamin D due to restrictions on foods and beverage as these aliments also have a relevant carbohydrate, phosphorus and/or potassium content.

Conclusion

our data suggest an association between reduced level of VD with presence of diabetes type one and diabetes nephropathy and it may be a potential predictor for both the occurrence and severity of DNP.

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