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Study of Vitamin D3 Supplementation on Chronic Kidney Disease (Mineral Bone Disease (CKD – MBD) Parameters in Patients with Chronic Kidney Disease Stage 3)

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ABSTRACT

Background: Bone profile parameters are affected by decreased estimated GFR within chronic kidney disease stage 3. We aimed to investigate if bone profile parameters response to vitamin D3 supplementation , within this stage , became affected by the presence or absence of diabetic state. **Materials and methods:** 30 patients having chronic kidney disease (stage 3) were enrolled in the study. 19 patients constituted non – diabetic group I and 11 patients constituted diabetic group II . All of them have received vitamin D3 1000 IU daily for 3 months . For all patients the following measurements were performed before and after vitamin D3 use :CBC , ESR1 & ESR2 , blood urea , serum creatinine , estimated GFR , complete urine analysis , serum Na , protein / creatinine ratio , serum calcium , serum phosphorus , calcium – phosphorus product , serum albumin , serum alkaline phosphatase , and intact serum parathyroid hormone. **Results:** Serum calcium levels have increased, while intact parathyroid hormone has decreased within both groups , with a more obvious response within the diabetic group . Serum alkaline phosphatase , serum phosphorus , and calcium – phosphorus product did not show any significant change, they were within their level after vitamin d3 use .ESR 1 and ESR 2 levels were higher from the start of the study within the diabetic group. Their mean level values have significantly decreased in a highly significant way within this group . Kidney function parameters and proteinuria have been deteriorated within the two groups , being worse within the diabetic group . **Conclusion:** Vitamin D3 use within stage 3 chronic renal disease patients is effective for patients support against bone mineral disturbances occurring within this disease .

Keywords: Vitamin D3 - CKD-MBD – Bone profile – Diabetes Mellitus – CKD stage 3.

INTRODUCTION

Vitamin D is a steroid hormone which is required to regulate serum levels of calcium and phosphorus , as well as bone metabolism . Vitamin D can be obtained from dietary sources (D2 and D3) , together with exposure of the skin to ultraviolet (UV) light (D3)[(1)].

Chronic kidney disease leads to progressive derangement of vitamin D metabolism . Renal synthesis of 1,25 – dihydroxyvitamin D (1, 25 [OH]$_2$D) is reduced , due to decreased activity of 1 alpha – hydroxylase [(2)]. The decrease in vitamin D synthesis in chronic renal disease results in hypocalcemia , secondary hyperparathyroidism , and subsequent renal osteodystrophy[(3)]. The etiologies of hypo-vitaminosis D occurring in end- stage renal disease (ESRD) population are not only due to decreased renal ability to transform 1-alpha – hydroxyvitamin D to its active form , but also they include limited sunlight exposure , reduced ultraviolet – induced vitamin D synthesis in the skin , and disturbed vitamin D metabolism [(4)] . Replacement of active vitamin D has been considered an essential step in the management of secondary hyperparathyroidism and its associated disorders in chronic kidney disease [(5)] .

Most patients on dialysis are treated with vitamin D receptor agonists (VDRAs) , such as calcitriol , doxercalciferol , or paricalcitol , for management of secondary hyperparathyroidism . Supplementation with VDRAs without its nutritional vitamin D precursor may not optimize clinical benefits [(6)]. **Kovesdy *et al.*[(7)]** ,have reported increasing confusion as regards which type of vitamin D preparations (nutritional versus active formulas) , should be used within chronic kidney disease patients.

PATIENTS AND METHODS

This is a clinical trial which was carried out on 30 chronic kidney disease stage 3 patients , who attended the Benha Hospital for Health Insurance and the Benha University Hospital outpatient clinics , from April to August 2016 .All patients were above 18 years old .

Patients were divided into two groups : **Group I:** consisted of 19 patients who always had normal blood glucose levels (Non – diabetic group I).

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- **Group II:** consisted of 11 patients who had abnormal blood glucose levels (Diabetic group II).

We excluded from our study pregnant and breastfeeding women , patients who have previously performed parathyroidectomy operation , patients having liver cirrhosis , patients having phenytoin , phenobarbital , or primidone drug usage concurrently to study performance , and lastly patients suffering from either sarcoidosis or malignancies. All particpants to the study were subjected to complete physical examination . For all patients the following parameters were performed : Complete blood count (CBC) , ESR for first hour (ESR1) and ESR for second hour (ESR2) , blood urea (in mg / dl) ,serum creatinine (in mg / dl) , estimated glomerular filtration rate (e GFR in ml / min /1.73 m^2) , complete urine analysis , protein / creatinine ratio (in mg / mmol) , serum sodium (Na in m Eq / L)and other electrolytes as required , serum calcium (in mg / dl) , serum phosphorus (in mg / dl) , calcium – phosphorus product (Ca X PO4) , serum albumin (in g / dl) ,serum aluminium (in ng / ml) , serum alkaline phosphatase (in U / L) , and Intact serum Parathyroid hormone (in pg / dl) . All parameters were performed according to conventional methods used in Benha University Hospital Clinical Pathology Department .

All previous parameters were measured at the start of the study before administrating vitamin D3 to the studied patients .All patients have received a dose of 1000 IU per day of Vitamin D3 for 3 consecutive months, after which the same previously mentioned parameters were measured again at the end of these 3 months .

The study was done after approval of ethical board of Ain Shams university and an informed written consent was taken from each participant in the study.

STATISTICAL ANALYSIS

Data was collected , coded , revised and entered to Statistical Package for Social Science (IBM SPSS) version 20.

The data have been presented as numbers and percentages for qualitative data ,mean , standard deviations and ranges for the quantitative data with parametric distribution and median with interquartile range (IQR) for the quantitative data with non parametric distribution .

Paired t-test was used in comparing the two groups having quantitative data with parametric distribution and Wilxon Rank test was used to compare the two groups having quatitative data with non – parametric distribution.

Independent t – test was used in the comparison between the two groups with quantitative data and parametric distribution and Mann – Whitney test was used in the comparison between two groups with quantitative data and non - parametric distribution[8].

Spearman correlation coefficients were used to assess the significant relation between two quantitative parameters in the same group[9] .

Logistic regression analysis was used to assess the predictors of vitamin D3 effects on bone profile parameters .

Chi –square test was used to compare two groups having qualitative data .Fischer Exact test was used also to compare two groups having low number of qualitative data .

P value < 0.05 is considered to be significant , $P = 0.051 - 0.070$ is considered to be borderline significant , $P > 0.070$ is considered non-significant.

RESULTS

In the present study , gender distribution has shown a borderline significant difference among non diabetic group I (formed nearly equal male and female participants) as compared to diabetic group 2 (having a male gender predominance of 90.9 %) .

Table (1): Comparison of gender distribution between non – diabetic group I and diabetic group II

Variables		non diabetic group	diabetic group	Chi – square	
				X^2	p -value
Sex	Female	no. 8 /19 (42.1 %)	no. 1/11 (9.1%)		
	Male	no. 11/19 (57.9%)	no. 10/11 (90.9%)	3.616	0.057

Table (2) : Comparison of different characteristics between non diabetic group I and diabetic group II

Variable	non diabetic group	diabetic group	Independent t-test	
	mean ± SD	mean ± SD	t	p value
Age (years)	62.00 ± 7.20	64.82 ± 10.58	- 0.869	0.392
Duration of				
Renal disease	58.51 ± 51.26	79.11 ± 73.40	- 0.905	0.373
BMI	25.81 ±1.88	25.07 ± 2,51	0.918	0.366

There was no significant difference between the diabetic and the non diabetic groups as regards age , duration of renal disease , and BMI .

Table (3) : Comparison of co- morbidities percentages between non – diabetic and diabetic groups

Co-morbity		nondiabetic group		diabetic group		Chi square test	
		No	%	No	%	X^2	P value
Hypertension	+ve	8	42.1%	2	18.2%		
	-ve	11	57.9%	9	81.8%	1.794	0.180
Ischemic heart	+ve	1	5.3%	2	18.2%		
Disease	-ve	18	94.7%	9	81.8%	1.292	0.256
Cerebro vas-	+ve	0	0.0%	1	9.1%		
cularinsuff.	–ve	19	100.0%	10	90.9%	1.787	0.181
LL edema	+ve	1	5.3 %	3	27.3%		
	-ve	18	94.7%	8	72.7%	2.921	0.087

There was no significant difference between the diabetic and the non diabetic group as regards different co – morbidities including : hypertension , ischemic heart disease , cerebro -vascular insufficiency and LL edema .

Table (4): Comparison of parameters levels within non – diabetic group I before and after vitamin D3 use

Variables	before ttt	after ttt	paired t – test	
	Mean ± SD	Mean ± SD	t	P value
Hb	11.12 ± 1.12	11.32 ± 0.90	-1.426	0.171
RBCs	4.00 ± 0.62	4.30 ± 0.50	- 2.644	0.016
ESR1	24.00± 11.37	22.95 ± 8.81	0.977	0.341
ESR2	42.68 ± 21.15	41.75 ± 8.65	0.871	0.395
Blood urea	71.00± 16.02	72.58± 14.33	- 1.297	0.211
S. creatinine	1.73± 0.27	1.81 ± 0.29	- 4.379	<0.001
e GFR	4379 ± 8.36	41.21 ± 8.15	4.576	<0.001
serum Na	139.05± 4.06	137.89± 3.97	2.480	0.023
prot/creat ratio	54.68± 11.87	69.95± 11.18	- 2.552	0.020
s. albumin	3.69 ± 0.57	3.71 ± 0.48	- 0.127	0.901
s. calcium	8.88 ± 0.46	8.97 ± 0.50	- 1.031	0.316
s. phosphorus	3.61 ± 0.42	3.63 ± 0.41	- 0.408	0.688
ca x po4	31.94 ± 2.92	32.48 ± 3.11	- 1.434	0.169
s. alkphos.	87.36 ± 15.51	87.53 ± 9.24	- 0.068	0.947
intact PTH	115.74 ± 32.13	76.48 ± 15.89	8.850	<0.001

Within non diabetic group I ,after vitamin D3 use : there was a statistically significant rise in the mean values of RBCs count , serum creatinine , and protein creatinine ratio . Also , we found a statistically significant decrease in the mean values of intact PTH , e GFR , and serum Na .

Table (5): Comparison of parameters levels within diabetic group II before and after vitamin D3 treatment

Variables	before ttt	after ttt	paired t – test	
	Mean ±SD	Mean ±SD	t	P-value
Hb	11.22 ± 1.07	11.41 ± 0.96	- 0.440	0.669
RBCs	4.19 ± 0.58	4.46 ± 0.58	- 1.717	0.117
ESR1	34.00 ± 9.26	29.91 ± 7.47	3.172	**0.010**
ESR 2	69.91 ± 19.58	65.91 ± 21.31	3.127	**0.011**
Blood urea	72.45 ± 13.74	69.82 ± 14.97	1.516	0.160
S. creatinine	1.87 ± 0.41	1.95 ± 0.42	- 3.105	**0.011**
e GFR	43.73 ± 10.50	40.91 ± 9.45	3.492	**0.006**
serum Na	136.45 ± 2.73	137.45 ± 3.88	- 1.581	0.145
prot/creat ratio	71.82 ± 16.94	113.00 ± 36.32	- 4.095	**0.002**
s. albumin	3.43 ± 0.40	3.86 ± 0.47	- 1.994	0.074
s. calcium	8.86 ± 0.60	9.02 ± 0.57	- 2.080	**0.064**
s. phosphorus	3.47 ± 0.51	3.45 ± 0.43	0.396	0.700
ca x po4	30.68 ± 3.85	31.01 ± 3.76	- 0.442	0.668
s. alkphos.	90.72 ± 11.86	89.06 ± 17.45	0.494	0.632
intact PTH	99.95 ± 29.07	66.50 ± 15.34	6.683	**<0.001**

Within diabetic group II , after vitamin D3 use : there was a statistically significant decrease in the mean values of ESR1 , ESR2 , e GFR , and intact PTH . Also , we found a significant rise in the mean values of serum creatinine , protein / creatinine ratio , and a borderline significant rise in the mean value of serum calcium .

Table (6): Comparison of different parameters between non – diabetic group I and diabetic group II before vitamin D3 use

Variable	non –diabetic group	diabetic group	Independent t –test	
	Mean ± SD	Mean ± SD	t	p-value
Hb	11.12 ± 1.12	11.22 ± 1.07	- 0.246	0.808
RBCs	4.00 ± 0.62	4.19 ± 0.58	- 0.807	0.427
ESR1	24.00 ± 5.37	34.00 ± 9.26	- 2.474	**0.020**
ESR2	42.68 ± 1.15	69.91 ± 19.58	- 3.488	**0.002**
Blood urea	71.00 ± 16.02	72.45 ± 13.74	- 0.252	0.803
S. creat	1.73 ± 0.27	1.87 ± 0.41	- 1.153	0.259
e GFR	43.79 ± 8.36	43.73 ± 5.50	0.018	0.986
serum Na	139.05 ± 4.06	136.45 ± 2.73	1.882	**0.070**
prot/creat ratio	54.68 ± 11.87	71.82 ± 16.94	- 1.900	**0.068**
s. albumin	3.69 ± 0.57	3.43 ± 0.40	1.378	0.179
s. calcium	8.88 ± 0.46	8.86 ± 0.60	0.079	0.938
s. phosphorus	3.61 ± 0.42	3.47 ± 0.51	0.801	0.430
ca x po4	31.94 ± 2.92	30.68 ± 3.85	1.020	0.317
salkphos	87.36 ± 15.51	90.72 ± 11.86	- 0.618	0.541
intact PTH	115.74 ± 32.13	99.95 ± 29.07	1.341	0.191

Before vitamin D3 use ,on comparing the diabetic and the non diabetic groups : diabetic group has shown a statistically significant higher mean values for ESR1 & ESR2 , and a borderline significant higher mean value for protein / creatinine ratio .While non diabetic group showed borderline higher mean value for serum sodium .

Table (7) : Comparison of different parameters between non –diabetic group & diabetic group after vitamin D3 use

Variables	non – diabetic group	diabetic group	Independent t-test	
	Mean ±SD	Mean ± SD	t	p – value
Hb	11.32 + 0.90	11.41 +0.96	- 0.253	0.802
RBCs	4.30 ± 0.50	4.46 ± 0.58	- 0.809	0.425
ESR1	22.95 ±8.81	29.91 ± 7.47	- 1.947	0.062
ESR2	41.74 ± 18.65	65.91 ± 21.31	- 3.248	0.003
Blood urea	72.58 ± 14.33	69.82 ± 14.97	0.500	0.621
s. creat .	1.81 ± 0.29	1.95 ± 0.42	- 1.159	0.256
e GFR	41.21 ± 8.15	40.91 ± 9.45	0.092	0.927
S. Na	137.89 ± 3.97	137.45 ± 3.88	0.295	0.770
Prot/creat ratio	69.95 ± 41.18	113.00 ± 56.32	- 2.410	0.023
s. albumin	3.71 ± 0.48	3.86 ± 0.47	- 0.875	0.389
s. calcium	8.97 ± 0.50	9.02 ± 0.57	- 0.250	0.805
s. phosphorus	3.63 ± 0.41	3.45 ± 0.43	1.183	0.247
ca x po4	32.48 ± 3.11	31.01 ± 3.76	1.155	0.258
s. alkphos	87.53 ± 19.24	89.06 ± 17.45	- 0.218	0.829
intact PTH	76.48 ± 15.89	66.50 ± 15.34	1.678	0.104

On comparing non diabetic and diabetic groups , after vitamin D3 use : the diabetic group has shown a statistically significant higher mean values for ESR2 and protein / creatinine ratio , and a borderline significant higher mean value for ESR2 .

Table (8): Multivariate logistic regression analysis for the predictors of ESR2 level within non diabetic group I and diabetic group II before and after treatment

	B	S.E.	Wald	Sig.	ODDS Ratio (OR)	95% C.I. for OR	
						Lower	Upper
Before ttt							
ESR 2	0.131	0.066	3.894	0.048	1.140	1.001	1.298
After ttt							
ESR2	0.047	0.022	4.408	0.036	1.048	1.003	1.095

Multivariate logistic regression analysis performed for ESR 2 mean values , before vitamin D3 therapy , has shown that diabetic group had as much as 1.140 times chance of having higher level of ESR 2 than non diabetic group.

Multivariate logistic regression analysis performed for ESR2 mean values , after vitamin D3 therapy , has shown that diabetic group had as much as 1.048 times chance of having higher level of ESR2 than non diabetic group **.**

Table (9): Significant Correlations within non diabetic group before and after treatment

Variables	phosphorus		intact PTH	
Before ttt	**r**	**p-value**	**r**	**p-value**
age			**0.487**	**0.034**
ESR1			**0.539**	**0.017**
ESR2			**0.558**	**0.013**
Systolic blood				
Pressure	**- 0.438**	**0.061**		
Esinophils %	**- 0.451**	**0.053**		
Variables	**phosphorus**		**intact PTH**	
After ttt	**r**	**p –value**	**r**	**p- value**
ESR 1			**0.447**	**0.055**
ESR2			**0.563**	**0.012**

Before vitamin D3 therapy , within non diabetic group : intact PTH had a positive correlation to age , ESR1 , and ESR2 . Serum phosphorus has shown a borderline significant inverse correlation to systolic blood pressure and eosinophil % .

After vitamin D3 use , within non diabetic group :Intact PTH had a statistically significant positive correlation to ESR2 , and a borderline significant positive correlation to ESR1 .

TABLE (10) : Significant Correlations within diabetic group II before and after treatment

Variables	calcium		phosphorus		intact PTH	
Before ttt	**r**	**p – value**	**r**	**p – value**	**r**	**p-value**
Monocytes %	**0.606**	**0.048**	**- 0.663**	**0.026**	**- 0.671**	**0.024**
Variables	**calcium**		**phosphorus**		**intact PTH**	
After ttt	**r**	**p – vlue**	**r**	**p – value**	**r**	**p-value**
ESR1	**- 0.610**	**0.046**	**- 0. 616**	**0.044**	**0.651**	**0.030**
ESR2	**- 0.634**	**0.036**				

Before vitamin D3 use , within diabetic group : monocytes % has shown a statistically significant positive correlation to serum calcium , and a statistically significant inverse correlation to serum phosphorus and intact PTH .

After vitamin D3 therapy , within diabetic group : ESR1 has shown a statistically significant inverse correlation to serum calcium and serum phosphorus , and a statistically significant positive correlation to intact PTH .ESR2 has shown a statistically significant inverse correlation to serum calcium .

DISCUSSION

Decrease of vitamin D levels below normal values in human body takes place in the two extremes of age , in postmenopausal women , in the African – American subjects , and in chronic renal disease state [(10)] .

The gradually increasing levels of the phosphatonin FGF – 23 (fibroblast growth factor - 23), has a progressive inhibitory effect on the enzyme 1 α – hydroxylase (CYP27 B1). This results in a continuously decreasing level of the active 1,25 (OH)$_2$ vitamin D (1 , 25 dihydroxy – vitamin D) [(2)].

At the start of the study before the use of vitamin D3 , serum calcium was found to be within target range for stage 3 chronic kidney disease within the 2 studied groups . Serum calcium level rise within diabetic group after vitamin D3 use, did not occur within the non – diabetic group after therapy . This could imply that diabetic group was more responsive to vitamin D3 effect . **Respero and Arango**[(11)] have reported a positive significant relationship between vitamin D and serum calcium ($P< 0.05$) , within CKD patients stages 3 – 5 .**Adamasco *et***

al. [12] indicated that there was no change within serum calcium level after vitamin D3 use .

In our study , serum calcium and monocytes % recorded positive relationship within the diabetic group before vitamin D3 use ,but this relationship did not exist after treatment with vitamin D3 ,and this is could reflect vitamin D3 effect as a suppressor of inflammatory processes initiated via antigen - presenting cells activation , within an internal environment on its way to be a uremic milieu .

Lemiereet al. [13] have reported that the immunosuppressive effect of 1,25(OH)2D3 is correlated with a decrease in inflammatory cytokines such as IL -2 .

Serum phosphorus levels were within normal range within the 2 studied groups .Also serum phosphorus levels were not affected by vitamin D3 use within stage 3 CKD .

Respero and Arango[11] have reported an inverse significant relationship between vitamin D level and serum phosphorus , within CKD patients stages 3 -5 . **Adamasco *et al.*** [12] found that there was no change within serum phosphorus level after vitamin D3 administration , and this deduction is in agreement with our results .

The inverse relationship between mean serum phosphorus and each of systolic blood pressure and eosinophils % , within non diabetic group before vitamin D3 use , could be explained as a link existing between phosphate as a uremic toxin and cardiac performance as represented by systolic blood pressure .Also this uremic toxin could at least partially explain hypo-immune responses to agents initiating allergic or hypersensitivity reactions . Both relationships have disappeared after vitamin D3 use within the nondiabetic patients .

The inverse relation between serum phosphorus and monocytes % within diabetic group before vitamin D3 use , has shown an antigen - presenting cell offending action of serum phosphorus in chronic kidney disease .This relationship did not exist after the use of vitamin D3 , which implies the improvement of immune response to foreign antigens after its administration .

Calcium - phosphorus product (Ca X PO4) was very close to accepted level within the non-diabetic and the diabetic patients . Calcium - phosphorus product was not affected by vitamin D3 use within the 2 studied groups . **Respero and Arango**[11] have reported an inverse significant relationship between vitamin D level and Calcium – phosphorus product .

After the use of vitamin D3 , intact parathyroid hormone levels showed a significant decrease from above normal level to around normal level , within the 2 studied groups . The diabetic state in diabetic group II did not have any impact on intact PTH level before therapy and also after vitamin D3 use .**Adamasco *et al.*** [12] in their study showed mild decrease in PTH levels after vitamin D use in chronic kidney disease .**Respero and Arango**[11] recorded an inverse relationship between vitamin D and intact PTH .

The positive relationship between Intact parathyroid hormone and patients age mean value , within non diabetic group I before vitamin D3 use , was confirmed by the findings of a study conducted by **Khosla *et al* .** [14]. The steroid vitamin D3 has abolished this relationship , which did not exist after the treatment with vitamin D3 in non diabetic group I patients . The inverse relationship between Intact PTH and monocytes % in diabetic group II before treatment , has disappeared after vitamin D3 use , which could be due to normalization of the mildly elevated i PTH after the treatment with vitamin D3.

Serum alkaline-phosphatase was within normal limit in the non-diabetic and the diabetic groups before vitamin D3 use and it was not affected by vitamin D3 therapy . This could imply that our patients were on the low bone turnover side . Against our findings , **Respero and Arango**[11] found an inverse significant relationship between vitamin D level and serum alkaline phosphatase .

ESR1 and ESR2 have shown higher values in the diabetic group , before and after use of vitamin D3 . This was confirmed by finding that ESR_2 had a chance of being higher within the diabetic group than non-diabetic group , before vitamin D3 use . This reflected the super-added inflammatory effect of diabetic state existence upon the chronic renal disease inflammatory state .Also , this result was supported by a significant O.R. (1.048) for diabetic group who had higher ESR2 than non-diabetic group after vitamin D3 use . O.R. value in itself has decreased after vitamin D3 use , but still the diabetic group had a higher chance of having higher ESR values than those of the non diabetic group . Our results

are comparable to those found by **Amina *et al.*** [15] who found higher ESR values within type 2 diabetic patients .

Within diabetic group II after vitamin D3 use , the inverse relationship between serum calcium level and each of ESR_1 and and ESR_2, reflected the direct inflammation suppressing effect of calcium and indirectly the inflammation inhibitory effect of vitamin D3 through increasing serum calcium levels and other pathways . **Al –Homrany**[17] stated that one of the important factors contributing to high ESR level in uremia was hypo-calcemia, but this was not the case in our study .In the diabetic group after treatment , the positive relationship of ESR_1 to each of serum phosphorus mean level and intact I PTH , has reflected the role played by each of serum phosphorus and intact PTH as toxins existing within the imbalanced uremic milieu .

Almqvist *et al.* [16] have found that , for patients having a state of hyper -parathyroidism for 1 year , it was enough to induce a rise in ESR .

Serum creatinine level rise in the diabetic and the non – diabetic groups , has occurred inspite of having a blood pressure figures around accepted values in both studied groups .Diabetic state did not play a role in making kidney function test worse within the diabetic group , whether before or after therapy .Our results are in agreement with those found by **Adamasco *et al.*** [12] who stated an increase in kidney function tests following vitamin D use .

Estimated glomerular filtration rate (e GFR) rise after vitamin D3 therapy within the 2 studied groups , which implied that vitamin D3 has lessened the filtration pressure and pressure gradient between afferent and efferent arterioles , may be through affecting blood flow auto-regulation within glomeruli by modulating renin – angiotensin system , which is necessary for maintaining filtration function within chronic kidney disease states . This assumption needs further studies at molecular mechanism level .Diabetic state did not affect the response of

eGFR to vitamin D3 therapy in diabetic patients . Our findings were confirmed by those found by **Adamasco *et al.*** [12] .

Protein / creatinine ratio has deteriorated within the 2 studied groups upon vitamin D3 use , being worse within the diabetic group .Against our results , **Yu –Hsien Lai and Te – Chao Fang** [19] stated that in the kidney , vitamin D exerts protective effects by inhibiting renal fibrosis , inflammation , and progression of proteinuria . Also , in controverse to our findings , **Respero and Arango**[11] have shown an inverse significant relationship between vitamin D level and 24 hour urinary protein .

Serum Na level decreased in non-diabetic group after vitamin D3 use , but not in the diabetic group . These findings confirmed the inhibitory effect of vitamin D3 on renin – angiotensin system , which is hyper-stimulated by the existence of diabetic state together with the chronic renal disease state in diabetic group .

Li [18] has reported that active vitamin D have shown a negative feedback on the renin – angiotensin system .

CONCLUSION

Bone profile parameters have shown a positive response to vitamin D3 use in stage 3 CKD , except for serum phosphorus, calcium – phosphorus product , and serum alkaline phosphatase levels .The response to vitamin D3 was more prominent in the diabetic group . Kidney function measurements and proteinuria have deteriorated within both groups upon vitamin D3 use , being worse in the diabetic group .Nutritional supplements of vitamin D3 is necessary to be considered in the formulation of the dietary regimen of the stage 3 CkD , in addition to other measures limiting the increase in serum phosphorus and calcium – phosphorus product levels .

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