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EFFECT OF SUBLINGUAL VITAMIN D3 ON CHRONIC KIDNEY DISEASE

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ABSTRACT

ORIGINAL RESEARCH ARTICLE

The present study was aimed to study the effect of Sublingual Vitamin D3 on Chronic Kidney Disease. This was a non-randomized clinical trial and interventional study. Total of 400 patients were enrolled for the study. All the subjects were screened for the serum 25(OH)D level. Subjects fulfilling the eligibility criteria with serum 25(OH)D level less than 20 ng/ml, having history of renal dysfunction were included in the study. At the end of the study, 49 patients (24 from Test and 25 from control group) dropped out of the study due to their personal reasons and finally 351 patients participated till the end of the study,176 patients in test group and 175 in control group. There was statistically significant difference in serum vitamin D3 level before 16.61±6.71 ng/ml and after 35.80±7.80 ng/ml after treatment with Sublingual Vitamin D3, whereas in the control group decreased from baseline 16.40±3.63ng/ml to 14.96±4.94 ng/ml. As per the information is taken from the patients, 38 participants in the test group (21.59%) and 41 in the control group (23.42%) had a history of renal dysfunction in our study. In our study there were no significant changes in the Renal Function Test on giving sublingual vitamin D3 further multicentred trials with large sample size are required to come to a conclusion. However, improvement in hypertension as a result of vitamin D3 could prove effective in treating CKD. further multicentred trials with large sample size are required to come to a conclusion.

INTRODUCTION:

Chronic kidney disease (CKD) is a major public health problem worldwide with regard to the number of individuals affected and therapeutic costs involved to treat it[1]. According to the results of the 2013 Global burden of disease study, CKD contributed to 956,200 deaths, a 134% increase from 1990[2]. In developed countries, CKD affects nearly 7% of all individuals more than 30 years of age, which translates to greater than 70 million individuals[3]. Furthermore, the prevalence of CKD increases with age and exceeds 20% in individuals aged more than 60 years and 35%

in individuals aged more than 70 years[4]. Globally, it has been estimated that more than 1.4 million individuals with end-stage renal disease receive renal replacement therapy with dialysis or transplantation2.In India, the incidence of CKD is rising, and as per estimates from 2006, the age-adjusted incidence rate of end-stage renal disease is 229 per million population. Further, the number of new patients entering renal replacement programs annually is >100,000[5]. The rising incidence of CKD in India is likely to burden health care and the economy in the future[6].Factors that predict the risk of CKD can be categorized into susceptibility factors, initiation factors, and progression factors. Susceptibility factors are those that increase the susceptibility to kidney damage and include older age, family history of CKD, reduced kidney mass, low birth weight, and low income or educational level. Initiation factors refer to factors that directly initiate kidney damage and include Diabetes mellitus, High blood pressure, Autoimmune diseases, Systemic infections, Urinary tract infections, Urinary stones, Lower urinary tract obstruction, and drug toxicity. Progression factors are those that worsen kidney damage and lead to a faster decline in kidney function after kidney damage has started. Examples of such factors include higher level of proteinuria, hypertension, poor glycaemic control in diabetes, and smoking6.The most common comorbidity associated with hypertension is CKD. Hypertension has been reported in 67% to 92% of patients with CKD, with increasing prevalence as kidney function declines. Rise in blood pressure observed associated with the decline of kidney functions with increasing age[7,8]. A probable mechanism may be, impaired kidney function leads to a blunted 1-alpaha hydroxylase production in the kidney and a reduction of appropriate conversion of 25-hydroxyvitamin D to *1,25*-(OH)2D8 Lower serum vitamin D levels are associated with prehypertension in a representative sample of US adults[9].Vitamin D and its active metabolites in a large number of tissues. This has been stimulated by the appreciation that most tissues in the body have receptors for the active form of Vitamin D,1,25di-hydroxyvitamin D[1,25(OH)2D] or "Calcitriol". These receptors are named appropriately as Vitamin D receptors (VDRs), and tissues with VDR are potential targets. Vitamin D receptors are found in most tissues, attributing to its classic and non- classic actions. Vitamin D receptors located on tissues such as bone, gut, and kidney are responsible for the known classic actions of Calcitriol. However, the discovery of vitamin D receptors in many tissues besides intestine and bone - including the brain, heart, pancreas, breast, prostate, lymphocytes, and other tissues implies that vitamin D supplementation might have applications for treating several disorders. These include Autoimmune diseases, Diabetes, cardiovascular disease, psoriasis, Hypoparathyroidism, Renal Osteodystrophy, and possibly leukaemia and cancers of the breast, prostate, or colon[10].Despite these findings, there is a lack of literature specific to the Indian scenario at present focusing on the management of hypertension in CKD.

The kidney plays an essential role in vitamin D metabolism in circulation [11].CKD is a condition characterized by a gradual loss of kidney function over time. The abnormalities in vitamin D metabolism contributes to the development of mineral and skeletal disorders, elevations in PTH, hypertension, systemic inflammation, and finally result in renal and cardiovascular damage [12]. The 2009 KDIGO (Kidney Diseases: Improving Global Outcomes) clinical practice guidelines recommended correcting 25(OH)D deficiency and insufficiencies for the general population [13].

The reasons for this marked vitamin D deficiency in CKD are multi-factorial. CKD can induce a progressive loss of the capacity of the kidney not only to convert 25(OH)D to

circulating calcitriol (the vitamin D hormone), but also to maintain serum 25(OH)D levels for non-renal calcitriol synthesis. The resulting calcitriol and 25(OH)D deficiency associate directly with accelerated disease progression and death [12,14]. Another interesting hypothesis is that urinary loss of 25(OH)D-VDBP (the main plasma carrier of vitamin D in circulation) associated with proteinuria and reduced megalin-mediated uptake might result in vitamin D deficiency[15]. the observational studies have demonstrated 25(OH)D deficiency is independently associated with impaired renal function in a cross-sectional analysis of the NHANES III data[16]. considering the effect of vitamin D3 on hypertension and subsequently on CKD we decided to undergo a study on the Effect of Sublingual Vitamin D3 on renal function test.

AIM:

To find out the effect of sublingual vitamin d3 on chronic kidney disease

OBJECTIVES:

1. To find out effectiveness of vitamin D3 therapy in renal dysfunction in terms of changes in Renal Function Test.
2. To compare the baseline serum Renal Function Test, Test & control group.
3. To compare mean serum RFT level of the test group from baseline to 6th follow up visit.
4. To compare the mean serum RFT level of the control group from baseline to 6th follow up visit.

MATERIALS &METHOD

This was a non-randomized clinical trial done in collaboration with Department Family and General Medicine. All the known cases of Essential hypertension coming to the Family and General Medicine department of PRH, Loni enrolled for the study. The study was registered with Clinical Trial Registry of India (CTRI), it is available on the Website: CTRI Website URL - http://ctri.nic.in; Registration number: CTRI/2017/03/008033 [Registered on : 07/03/2017].

STUDY DURATION: 2 Years

INCLUSION CRITERIA:

- Adult patients between age group of 18-60 Years.
- Patients of either sex
- All the patients of renal dysfunction.
- Patient ready to give written inform consent and willing to participant in the study.

EXCLUSION CRITERIA:

- Normal Vitamin D level of Hypertensive patients were excluded.
- The patient suffering from Gestational hypertension.
- Patients with a history of any tumours and Patients on medication which may lead to hypercalcemia.
- Patients suffering from genetic disorders, taking antiepileptic drugs.
- Patients on chronic medications other than antihypertensive.

STUDY GROUP:

All the patients satisfied with the inclusion and exclusion criteria were estimated of Serum Vitamin D3 below the normal (Deficiency = <20ng/ml) level taken grouped as under: following.

Group-I (n=200)

- Patients on add on Vitamin D3 60,000 IU sublingual

Group-II (n=200)

- Patients on only drugs without add on Vitamin D3 therapy

Vitamin D therapy:

Drug name: Dura D3(Cholecalciferol Vitamin D3)

Dose: 60,000 IU

- 1 Tablet/Every 15 days,
- 2 Tablets/One month,
- Total duration 3 months / 6Tab

Route: Sublingually

Investigated Profile:

- Estimated of Serum Vitamin D3 level at the baseline visit and at the 6th Visit (end of the study)
- Renal function test (RFT) at the baseline visit and at the 6th Visit (end of the study)

- ✓ Serum Urea
- ✓ Serum creatine
- ✓ S. Na+
- ✓ S. K+

DATA ANALYSIS:

- Data coding and entry was done in Microsoft Excel spread sheets and descriptive and inferential statistical analysis was done by using SPSS version 21 (Statistical Package for Social Sciences) software.
- Qualitative data analysis done by Chi-square test.
- Quantitative data analysis was done using, Mann Whitney U test, Wilcoxon matched pairs test.

RESULTS:

Table 01: Distribution of the participants according to H/O renal dysfunctions

Sr. No.	Groups	Renal		Total
		Yes	No	
1	Test	38	138	176 (50.14%)
2	Control	41	134	175 (49.85%)
	Total	79 (22.50%)	272 (77.49%)	351 (100.0%)
Chi-Square ($\chi 2$): 1.32 df:01 P 0.24 Non-Significant				

Graph No :01

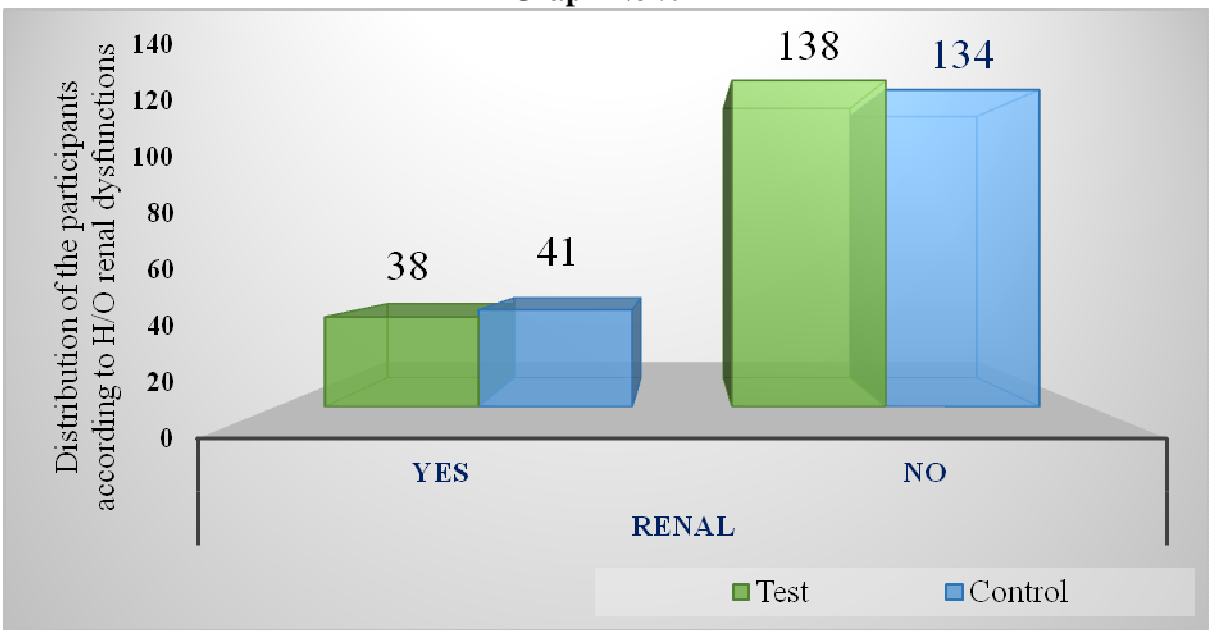

Table 01 and Graph No 01 shows 38 patients in Test group and 41 patients in Control group had history of renal dysfunction.

Table 02: Distribution of participants according to estimate of serum Vitamin D level

	Baseline Visit		**Test Group**		**Control Group**	
	Test	Control	Baseline	6thF. P	Baseline	6thF. P
Mean ± SD	16.61±6.71	16.40±3.63	16.61±6.71	35.80±7.80	16.40±3.63	14.96±4.94
Median	15.60	15.90	15.60	36.00	15.90	15.16
test	Mann Whitney U Test: P:0.55 Non-Significant		Wilcoxon matched-pairs test P<0.0001 Significant		Wilcoxon matched-pairs test P<0.0001 Significant	

Graph No :02

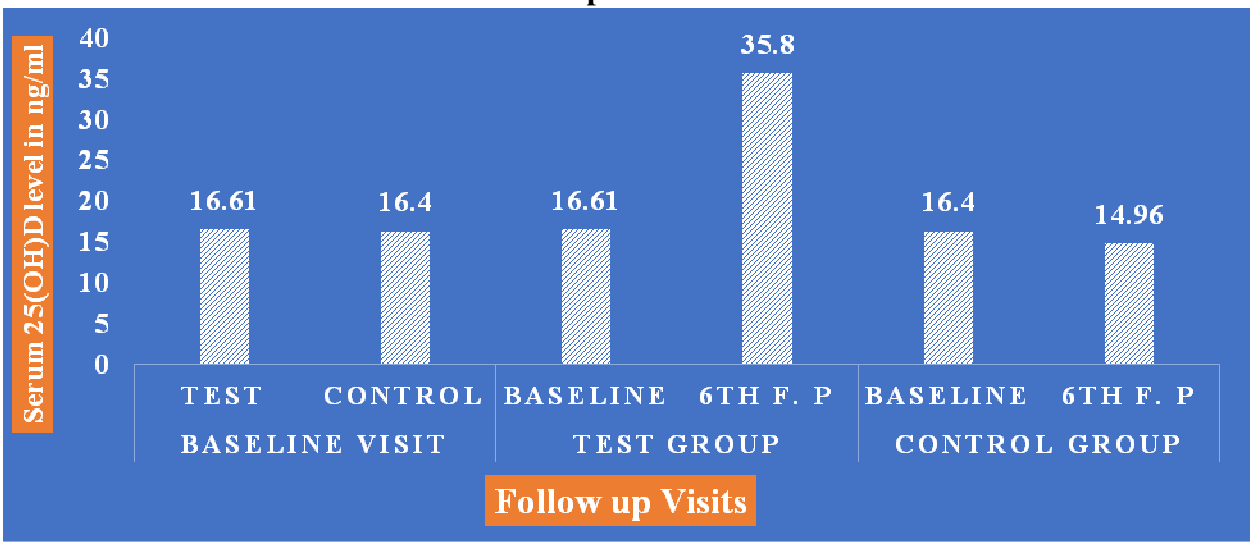

Table 02 and Graph No 02 shows significant increase in serum vitamin D level(ng/ml) was seen in test group whereas the vitamin D level was decreased in control group.

Table 03: Distribution of participants according to baseline serum Renal Function Test, Test & control group

RFT	**Sr. Creatinine**		**Sr. K+**		**Sr. Urea**		**Sr. Na+**	
	Test	Control	Test	Control	Test	Control	Test	Control
Mean ± SD	0.83± 0.14	0.84±0. 14	4.14± 0.36	4.16±0. 44	25.74± 4.92	25.23± 12.10	139.53 ±2.36	139.58 ±1.59
Median	0.81	0.83	4.10	4.20	25.00	23.80	139.10	139.00
Mann Whitney U Test	P:0.22 Non-Significant		P:0.12 Non-Significant		P:0.31 Non-Significant		P:0.86 Non-Significant	

Graph No :03

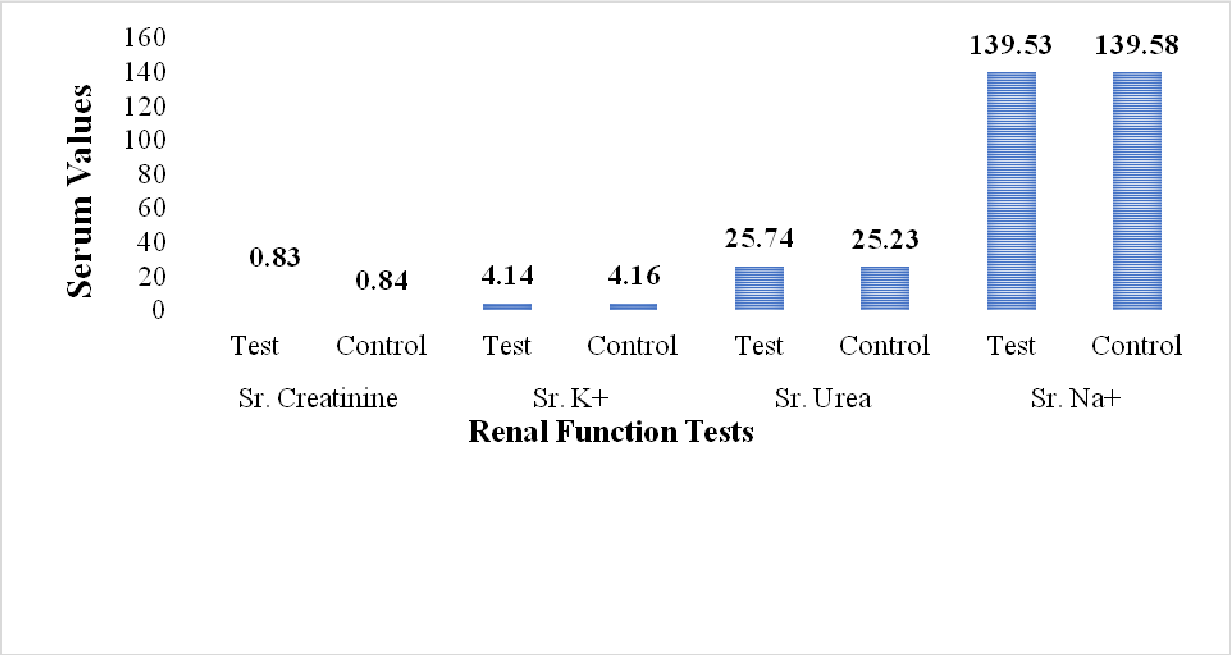

Table 03 and Graph No :03 baseline Sr. Urea(mg/dl), Creatinine(mg/dl), Na^+(meq/l), K^+ (meq/l), level in Test and control group was found to be non-significant.

Table 04: Test group of mean serum RFT level from baseline to 6th follow up visit

RFT	**Sr. Creatinine**		**Sr. K^+**		**Sr. Urea**		**Sr. Na^+**	
	Baseline	6th F. P	Baseline	6thF. P	Baseline	6th F. P	Baseline	6thF. P
Mean ±SD	0.83±0.14	0.82±0.09	4.14±0.36	4.17±0.01	25.74±4.92	24.29±4.30	139.53±2.36	137.74±1.11
Median	0.81	0.82	4.12	4.08	25.10	24.40	139.10	138.01
Wilcoxon matched-pairs test	P< 0.16 Non-Significant		P< 0.12 Non-Significant		P< 0.11 Non-Significant		P< 0.40 Non-Significant	

Graph No :04

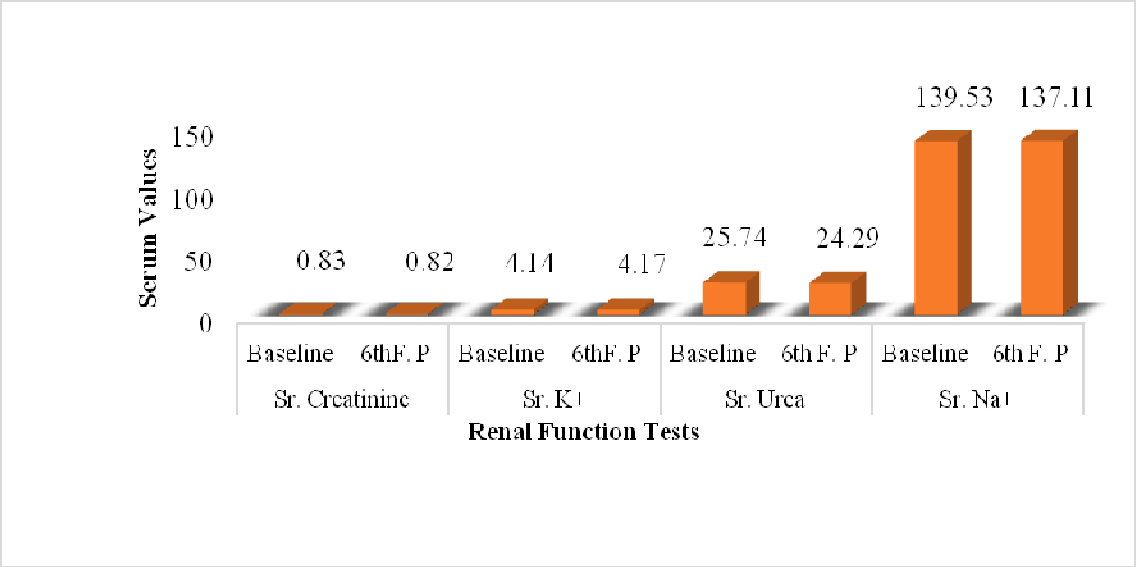

Table 04 and Graph No :04 shows changes in RFT of Serum Urea(mg/dl), Creatinine (mg/dl), Na^+(meq/l), K^+ (meq/l) level was found to be non-significant from baseline till the sixth follow up.

Table 05: Control group mean serum RFT level from baseline to 6th follow up visit

RFT	**Sr. Creatinine**		**Sr. K+**		**Sr. Urea**		**Sr. Na+**	
	Baseline	6thF. P	Baseline	6thF. P	Baseline	6th F. P	Baseline	6th F. P
Mean ± SD	0.84±0.14	0.86±0.13	4.16±0.44	4.18±0.43	25.23±12.10	24.89±04.76	139.58 ± 1.59	139.37 ±3.42
Median	0.83	0.86	4.20	4.10	23.80	23.20	139.00	140.00
Wilcoxon matched-pairs test	P: 0.05 Non-Significant		P: 0.001 Non-Significant		P :0.20 Non-Significant		P: 0.71 Non-Significant	

Graph No :05

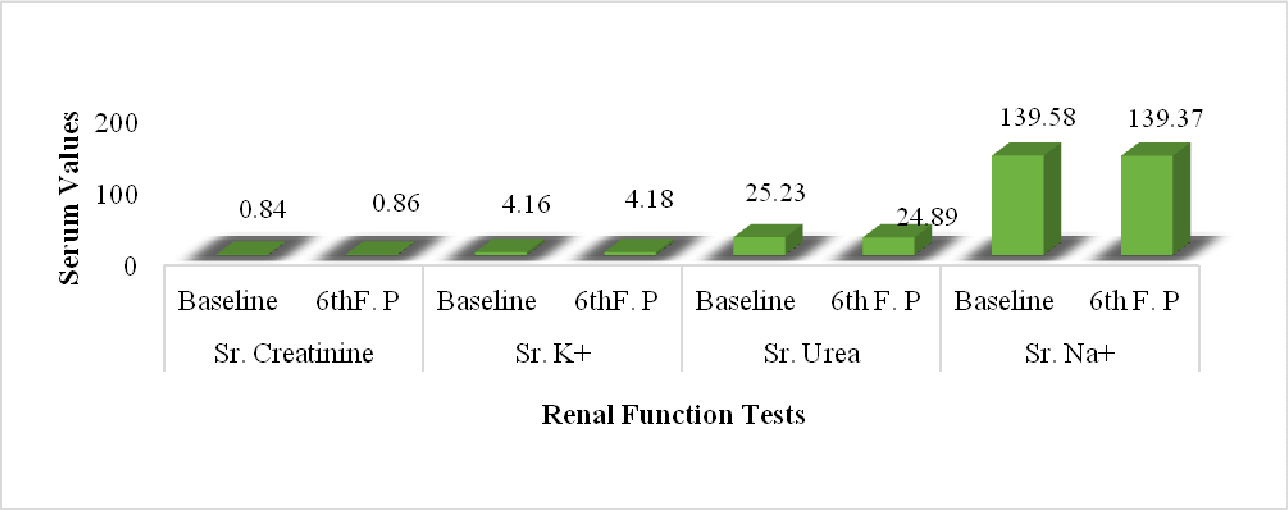

Table 05 and Graph No :05 changes in RFT of Serum Urea(mg/dl), Creatinine (mg/dl), Na^+(meq/l), K^+ (meq/l) level was found to be non-significant from baseline till the sixth follow up.

DISCUSSION:

Total of 400 patients were enrolled for the study. All the subjects were screened for the serum 25(OH)D level. Subjects fulfilling the eligibility criteria with serum 25(OH)D level less than 20 ng/ml, having history of renal dysfunction were included in the study. At the end of the study, 49 patients (24 from Test and 25 from control group) dropped out of the study due to their personal reasons and finally 351 patients participated till the end of the study,176 patients in test group and 175 in control group.

Estimation of the Serum level of Vitamin D before and after the sublingual treatment of volunteers in Test Group and without add on therapy of Vitamin D in Control Group. 60,000IU dose of sublingual Vitamin D3 was prescribed at an interval of 15 days for 3 months, the mean serum Vitamin D levels raised from baseline 16.61±6.71 ng/ml to 35.80 ±7.80ng/ml in the test group which was found to be significant as analyzed by Wilcoxon matched-pairs test, whereas in the control group the mean serum Vitamin D levels decreased from baseline 16.40±3.63ng/ml to 14.96±4.94ng/ml after 3 months which was found to be non-significant as analyzed by Wilcoxon matched-pairs test **(Table number - 01 & Graph No :01)**.

This study is accordance with other studies done by Wei Ren Chen et al[17] , Hamid Nasri et al[18] and Miles D. Witham et al[19] where vitamin D was administered orally and was given for longer a duration of this studies vitamin D was given daily whereas in our study vitamin D was given at a duration of 15 days again here the results are showing the effectivity of sublingual administration of vitamin D and in fact this is the novelty of our study .

As per the information taken from the patients, 38 participants in the test group (21.59%) and 41 in the control group (23.42%) had a history of renal dysfunction in our study. This difference in both the groups was found to be nonsignificant as analysed by Chi square test **(Table number – 02 & Graph No :02)**. The rise of blood pressure observed with increase in age is also associated with the decline of kidney functions[20]. A probable mechanism for this may be that impaired kidney function leads to a blunted 1 α - hydroxylation production in the kidney and a

reduction of appropriate conversion of 25-hydroxyvitamin D to 1,25- (OH)2D[21]. This process seems to be important for overall vitamin D metabolism because recent data suggest that the decline of circulating 1,25(OH)2D in chronic kidney disease might be a consequence of increased inactivation (24-hydroxylation) rather than of reduced production (1 α -hydroxylation) of 1,25(OH)2D[22].In the study done by Triantafyllou et al[23], 60 (38.96%) patients out of 154 and in the study done by Aris D. Efstratopoulos et al[24] 1800(42.85%) patients out of 4200 were found to be associated with renal dysfunction.

Comparison between Sr. Urea, Sr. Creatinine, Serum Na^+ and K^+ level at the baseline in test and control group was found to be non-significant as analysed by Mann Whitney U Test in our study. This finding is in accordance with other studies done by Angela Yee-Moon Wang et al[25] and Miles D. Witham et al[19] , Michael Pfeifer et al [26].

Comparison between Sr. Urea, Sr. Creatinine, Sr. Na^+ and Sr. K^+ level at the baseline and at the end of the study (6^{th} visit) in the test group was found to be non-significant as analysed by Wilcoxon matched-pairs test in our study. Similarly, Comparison between Sr. Urea, Sr. Creatinine, Serum Na^+ and K^+ level at the baseline and at the end of the study (6^{th} visit) in the control group was found to be non-significant as analysed by Wilcoxon matched-pairs test in our study. Although the patients gave a history of previous renal disease at the start of the study but the changes in various parameters of renal function test were negligible and non-significant. This may be attributed to the efficacy of ongoing antihypertensive therapy like ARBs, ACE inhibitors etc. Our results do show similarity with the studies done by Davide Carrara et al[27], Angela Yee-Moon Wang et al[28] and Youssef Khaleel Ahmad et al[29]**(Table numbers – 03,04,05& Graph No:03,04,05)**.In our study there were no significant changes in the RFT on giving sublingual Vitamin D3 further multicentred trials with large sample size are required to come to a conclusion.

CONCLUSION:

In our study there were no significant changes in the RFT on giving sublingual vitamin D3 further multicentred trials with large sample size are required to come to a conclusion. However, improvement in hypertension as a result of Vitamin D3 could prove effective in treating CKD. further multicentred trials with large sample size are required to come to a conclusion.

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