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RESEARCH ARTICLE

THE RELATION BETWEEN 25 HYDROXYVITAMIN D AND MMP9 PLASMA LEVEL AS SUGGESTED MECHANISM OF CARDIOVASCULAR DISEASES IN HEMODIALYSIS PATIENTS.

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Abstract

Background:- 25-hydroxyvitamin D [25(OH)D] concentration is inversely associated with cardiovascular disorders including coronary arterial disease and hypertension. Vascular remodeling may play a role in this association, however, few data relating vitamin Dlevel to specific remodeling biomarkers among ESRD patients is available. We investigated whether 25(OH)D levelis related to markers of vascular remodeling in ESRD patients.

Subjects & Methods:- It included a total number of 65 subjects. They were divided into three groups: Group 1 (29 subjects with severe vitamin D deficiency on regular hemodialysis), Group 2 (14 subjects with moderate vitamin D deficiency on regular hemodialysis) and Group 3 (22 subjects with normal vitamin D level on regular hemodialysis). All patients included in this study were subjected to the following: Full clinical assessment, Complete blood picture, alanine aminotransferase, aspartate aminotransferase, serum albumin, creatinine, blood urea, fasting plasma glucose, serum calcium, serum phosphorus, serum parathyroid hormone, lipid profile, 25 hydroxyvitamin D and MMP9 levels.

Results:- Among 65 patients, mean±standard deviation 25(OH)D concentration was 25.27±18.08, and was low(<20ng/ml) in 44.6% of patients. 25(OH) D concentration was inversely correlated withMMP-9 concentration ($r = -0.607$, $p < 0.001$). In multivariate analysis, MMP-9 concentration remained negativelyassociated with 25(OH) D concentration ($P = 0.001$).

Conclusion:- We detected thatplasma MMP-9 and circulating 25(OH) D concentrations are significantly and inversely associatedamong ESRD patients on hemodialysis. This finding may suggest a potential mechanism by which low circulating 25(OH) Dfunctions as a cardiovascular risk factor.

Introduction:-

The chronic inflammatory condition of end-stage renal illness (ESRD) is connected with expanded danger for cardiovascular disease and death (**1**).

Observational studies propose an inverse relationship between 25-hydroxyvitamin D [25(OH)D] concentration and serum inflammatory biomarkers. Low 25(OH)D levels are connected with increased tumor necrosis factor alpha (TNF-a) concentrations (**2**), and randomized controlled studies among basically sick patients and those with congestive heart failure report that vitamin D supplementation prompts noteworthy diminishments in interleukin 6 (

IL-6) and C-reactive protein (CRP) levels (**3**), and resulted in lower tumor necrosis factor alpha (TNF-a) and increased anti-inflammatory IL-10 levels (**4**).

However, few studies have documented the relationship between 25(OH)D level and increased levels of inflammatory biomarkers of vascular remodeling. Matrix metalloproteinases (MMP's) are essential in extracellular matrix remodeling, are significant effector molecules of inflammatory cells, and assume a key role in numerous vascular illnesses, including hypertension and aneurysm formation (**5**). In vitro studies show that vitamin D down-regulates MMP-9 generation by TNF-a (**6**) and suppresses creation of MMP-7 and MMP-9 (**7**).

Besides, MMP-2 and MMP-9 activation is connected with depositionof collagen and cardiovascular fibrosis (**8**). Past studies record the high pervalence of 25 (OH) D inadequacyamong the ESRD patients and overall public (**9**), and the relationship of 25(OH)D insufficiency with blood vessels disorders (**10**).
The aim of our work was intended to determine if circulating 25(OH)D level is associated with change of serum MMP-9 as a marker of vascular remodeling in ESRD patients on regular hemodialysis.

Subjects & Methods:-

This study has been carried out in the nephrology unit of Internal Medicine Department, Zagazig University Hospitals, during the period from October 2013 to October 2015.

Subjects:-

The study included 65 cases with end stage renal disease on regular hemodialysis three times per week. These patients were selected from hemodialysis unit of the internal medicine department, Faculty of Medicine, Zagazig University.

All subjects were divided into three groups according to their 25 (OH) vitamin D level:

- **Group 1:**
  This group included 29 patients (13 males and 16 females with age ranging from 20-60 years old with Mean ± SD 38.86±12.68 years old) with 25 (OH) vitamin D level <20 ng/ml ranging from 3 – 20 ng/ml and Mean ± SD is 9.68±5.49 ng/ml.
- **Group 2:**
  This group included 14 patients (7 males and 7 females with age ranging from 23-58 years old with Mean ± SD 40.14 ± 11.92 years old) with 25 (OH) vitamin D level from 21 – 29 ng/ml ranging from 22 – 28 ng/ml and Mean ± SD is 25.21±2.04 ng/ml.
- **Group 3:**
  This group included 22 patients (13 males and 9 females with age ranging from 22-58 years old with Mean ± SD 44.36 ± 9.23 years old) with 25 (OH) vitamin D level from >30 ng/ml ranging from 30 – 70 ng/ml and Mean ± SD is 45.86±13.22 ng/ml.

Patients were selected according to the following criteria:-

Inclusion criteria:-

- Age more than 18 years.
- ESRD patients on regular hemodialysis in hemodialysis unit in Zagazig university hospitals 3 times per week, each for 4 hours.
- Patients consent to enter the study.

Exclusion criteria:-

- Age < 18 years.
- Patients refuse to enter the study.
- Presence of known malignancy, active vasculitis or liver disease.
- Evidence of current infection or inflammation.
- Current or recent use of steroids, calcineurin inhibitors or antimetabolite medications (methotrexate, azathioprine, mercaptopurine, sulfadiazine). These exclusion criteria were chosen because they provide inflammatory or anti-inflammatory therapy that could alter the association between vitamin D and MMP 9 as an inflammatory marker.

Methods of Study:-

All subjects of the study were subjected to the following:-

1. **Thorough history and full clinical examination.**
2. **Blood samples were collected for :**

- Routine investigations including:
  - Fasting blood glucose.
  - Complete blood picture.
  - Serum creatinine and BUN.
  - Liver function tests.
  - Lipid profile.
  - Serum calcium.
  - Serum phosphorus.
  - Serum iPTH.

- Special investigations including:
  - Serum 25-hydroxyvitamin D.
  - Serum MMP-9.

We analyzed several covariates including the age, sex, smoking status, body weight, height and BMI. Comorbidities included diabetes (defined by use of diabetes medications), hypertension and cardiovascular insult during the study period which included cardiac event that required CCU admission in form of malignant hypertension or acute coronary syndrome in form of unstable angina or new myocardial infarction.

Results:-

Statistical analysis:-

All data were collected, tabulated and statistically analyzed using SPSS (Statistical Package for Social Science) version 20.0 for windows (SPSS Inc., Chicago, IL, USA), MedCalc 13 for windows and Microsoft Office Excel 2010 for windows.

Results:-

Table 1: Demographic data of the 3 groups.

Demographic data	All patients (N=65)	25(OH) vit D concentration			Test	p-value (Sig.)
		≤20 ng/ml (N=29)	21-29 ng/ml (N=14)	≥30 ng/ml (N=22)		
Age (years)						
Mean ± SD	41±11.54	38.86±12.68	40.14 ± 11.92	44.36 ± 9.23	2.807•	0.246
Median	40	39	40	45		(NS)
(range)	(20 – 60)	(20 – 60)	(23 – 58)	(22 – 58)	5.359‡	
20 – 29 years	11 (16.9%)	6 (54.5%)	4 (36.4%)	1 (9.1%)		0.499
30 – 39 years	17 (26.2%)	9 (52.9%)	2 (11.8%0	6 (35.3%)		(NS)
40 – 49 years	17(31.8%)	6 (35.3%)	4 (23.5%)	7 (41.2%)		
≥ 50 years	20 (30.8%)	8 (40%)	4 (20%)	8 (40%)		
Sex						
Male	33 (50.8%)	13 (39.4%)	7 (21.2%)	13 (39.4%)	1.022‡	0.600
Female	32 (49.2%)	16 (50%)	7 (21.9%)	9 (28.1%)		(NS)
Smoking						
Non smoker	54 (83.1%)	24 (44.5%)	10 (18.5%)	20 (37%)	2.313‡	0.315
Current smoker	11 (16.9%)	5 (45.5%)	4 (36.4%)	2 (18.1%)		(NS)

• Kraskall Wallis H test.‡ Chi-square test.p< 0.05 is significant.Sig.: significance.

Table (1) showing the demographic data of the patients, they were predominantly males (50.8%) with mean±SD age (41±11.54 years). It also shows no statistically significant differences between the three groups regarding age, sex and smoking distribution.

Table 2: Laboratory investigations of the 3 groups.

Special investigations	All patients (N=65)	25(OH) vit D concentration			Test	p-value (Sig.)
		≤20 ng/ml (N=29)	21-29 ng/ml (N=14)	≥30 ng/ml (N=22)		
Calcium (mg/dl)						
Mean ± SD	8.74±0.82	8.78±0.87	8.64±0.81	8.75 ± 0.78	0.143*	0.867
Median (range)	8.80(7 – 11)	9(7 – 11)	8.75(7.23 – 10.2)	8.70(7.3 – 10.5)		(NS)
Phosphorus (mg/dl)						
Mean ± SD	4.94±1.54	5.31±1.69	4.67±1.41	4.63±1.34	1.534*	0.224
Median (range)	5(2.1 – 9.3)	5(2.1 – 9.3)	4.9(2.4 – 6.6)	4.85(2.6 – 7.4)		(NS)
iPTH (pg/ml)						
Mean ± SD	668.61±491.41	904.82±379.31	662.14 ±594.89	361.36±386.07	15.848•	<0.001
Median (range)	600(20 – 1600)	900(150 – 1500)	425(20 – 1600)	275(20 – 1400)		(HS)
MMP9 (ng/ml)						
Mean ± SD	700.80±605.34	1022.79±706.21	696.42±328.17	279.13±235.19	25.518•	<0.001
Median (range)	600(85 – 3600)	900(86 – 3600)	705(150 – 1200)	200(85 – 950)		(HS)

* One way ANOVA test.• Kraskall Wallis H test.p< 0.05 is significant.Sig.: significance.

Table (2) shows no statistically significant differences between the three groups regarding serum calcium and phosphorus. But there is highly significant difference regarding iPTH and MMP9 level.

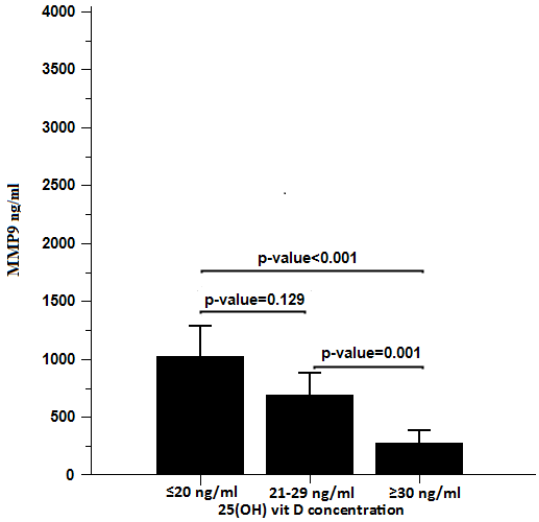

Figure1: Error Bar chart showing relationship between 25(OH) vit D concentration and MMP9 (ng/ml), bar represents mean, Y-error bar represents 95% confidence interval.

Table 3: Correlation between 25(OH) vit D (ng/ml) and study parameters.

Variables	25(OH) vit D (ng/ml)		
	r	p-value (Sig.)	r^2
Age (years)	+0.156	0.214 (NS)	2.4%
Weight (kg)	-0.078	0.535 (NS)	0.6%
Height (m2)	+0.061	0.630 (NS)	0.4%
BMI (kg/m2)	-0.171	0.174 (NS)	2.9%
SBP (mmHg)	+0.091	0.473 (NS)	0.8%
DBP (mmHg)	+0.026	0.836 (NS)	0.1%
MAP (mmHg)	+0.054	0.667 (NS)	0.3%
Hemoglobin (gm/dl)	-0.023	0.858 (NS)	0.1%
Albumin (gm/dl)	+0.089	0.481 (NS)	0.8%
ALT (U/L)	+0.228	0.068 (NS)	5.2%
AST (U/L)	+0.170	0.176 (NS)	2.9%
HDL (mg/dl)	+0.051	0.686 (NS)	0.3%
LDL (mg/dl)	-0.164	0.191 (NS)	2.7%
Triglycerides (mg/dl)	+0.094	0.455 (NS)	0.9%
Fasting blood glucose (mg/dl)	+0.057	0.654 (NS)	0.3%
Calcium (mg/dl)	-0.014	0.915 (NS)	0.0%
Phosphorus (mg/dl)	-0.152	0.227 (NS)	2.3%
iPTH (pg/ml)	-0.583	<0.001 (HS)	3.4%
MMP9 (ng/ml)	-0.607	<0.001 (HS)	36.9%

r Spearman rank correlation coefficientr^2 coefficient of determinationp< 0.05 is significant.Sig.: Significance.

Table (3): showing that 25 (OH) D is strongly correlated to iPTH and MMP9 levels but no significant correlation between 25(OH) vitamin D and other study parameters.

Table 4: Correlation between MMP9 (ng/ml) and study parameters.

Variables	MMP9 (pg/ml)		
	r	p-value (Sig.)	r^2
Age (years)	-0.130	0.302 (NS)	1.7%
Weight (kg)	+0.099	0.435 (NS)	0.1%
Height (m2)	+0.097	0.440 (NS)	0.9%
BMI (kg/m2)	+0.001	0.992 (NS)	0.0%
SBP (mmHg)	+0.130	0.304 (NS)	1.7%
DBP (mmHg)	+0.190	0.305 (NS)	1.7%
MAP (mmHg)	+0.136	0.282 (NS)	1.8%
Hemoglobin (gm/dl)	-0.224	0.073 (NS)	0.5%
Albumin (gm/dl)	-0.169	0.178 (NS)	2.9%
ALT (U/L)	+0.142	0.258 (NS)	0.2%
AST (U/L)	+0.191	0.127 (NS)	3.7%
HDL (mg/dl)	-0.024	0.846 (NS)	0.1%
LDL (mg/dl)	+0.097	0.440 (NS)	1.0%
Triglycerides (mg/dl)	-0.051	0.688 (NS)	0.3%
Fasting blood glucose (mg/dl)	+0.149	0.236 (NS)	2.2%
Calcium (mg/dl)	+0.057	0.654 (NS)	0.3%
Phosphorus (mg/dl)	+0.290	0.019 (S)	8.4%
iPTH (pg/ml)	+0.514	<0.001 (HS)	26.4%
25(OH) vit D (ng/ml)	-0.607	<0.001 (HS)	36.9%

r Spearman rank correlation coefficientr^2 coefficient of determinationp< 0.05 is significant.Sig.: Significance.

Table (4): showing that MMP9 level is significantly correlated to serum phosphorus and highly significantly correlated to iPTH and 25 (OH) D levels but no significant correlation between MMP9and other study parameters.

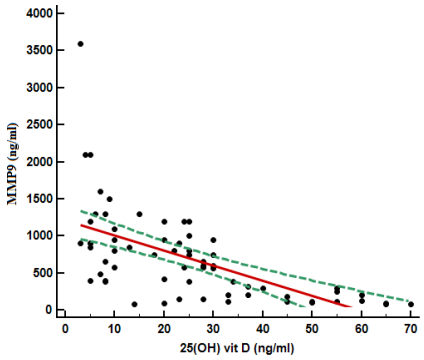

Figure (2): Scatter plot with regression line show a significant strong indirect correlation between 25(OH) vit D (ng/ml) and MMP9 (ng/ml) (r=-0.607, p<0.001). Continuous red line represent regression line, dashed green lines represent 95% confidence interval of correlation coefficient.

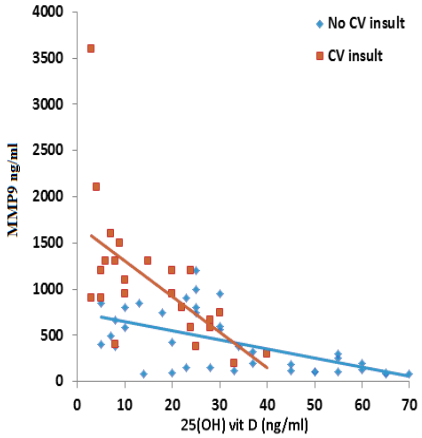

Figure (3): Scatter plot with regression line show correlation between 25(OH) vit D (ng/ml) and MMP9 (ng/ml) stratified by CV insult, (no CV insult: r = -0.594, p-value < 0.001; CV insult: r = -0.708, p-value < 0.001).

Table 5: Relation between laboratory investigations and CV insult.

Laboratory investigations	All patients (N=65)	CV insult		Test	p-value (Sig.)
		No (N=40)	Yes (N=25)		
HDL (mg/dl)					
Mean ± SD	43.92±2.77	43.67±2.75	44.32±2.80	-0.970•	0.332
Median (range)	44(40 – 49)	43.58(40 – 49)	44(40 – 49)		(NS)
LDL (mg/dl)					
Mean ± SD	114.38±12.54	113.50±12.46	115.80±12.80	-0.716*	0.476
Median (range)	115(90 – 140)	115(90 – 135)	110(95 – 140)		(NS)
Triglycerides (mg/dl)					
Mean ± SD	124.76±14.01	123.12±14.30	127.40±13.39	-1.160•	0.246
Median (range)	125(100 – 150)	122.50(100 – 150)	130(105 – 150)		(NS)
Fasting blood glucose (mg/dl)					
Mean ± SD	89.61±10.24	88.87±9.23	90.80±11.78	-0.912•	0.362
Median (range)	90(70 – 105)	90(70 – 105)	95(70 – 105)		(NS)
Calcium (mg/dl)					
Mean ± SD	8.74±0.82	8.74±0.72	8.74±0.97	0.011*	0.991
Median (range)	8.80(7 – 11)	8.80(7.3 – 10.5)	8.80(7 – 11)		(NS)
Phosphorus (mg/dl)					
Mean ± SD	4.94±1.54	4.62±1.46	5.46±1.54	-1.970•	0.049
Median (range)	5(2.1 – 9.3)	4.70(2.4 – 7.7)	5.40(2.1 – 9.3)		(S)
iPTH (pg/ml)					
Mean ± SD	668.61±491.41	542.25±421.01	870.80±535.47	-2.354•	0.019
Median (range)	600(20 – 1600)	400(20 – 1500)	900(20 – 1600)		(S)
25(OH) vit D (ng/ml)					
Mean ± SD	25.27±18.08	31.27±19.14	15.68±10.99	-3.375•	0.001
Median (range)	24(3 – 70)	28(5 – 70)	10(3 – 40)		(S)
MMP9 (ng/ml)					
Mean ± SD	700.80±605.34	442.55±327.41	1114±716.92	-4.587•	<0.001
Median (range)	600(85 – 3600)	380(85 – 1200)	950(200 – 3600)		(HS)

* Independent samples Student's t-test.• Mann Whitney U test.p< 0.05 is significant.Sig.: significance.

Table (5) showing no significant relation between the lipid profile, FBG and serum calcium and the development of CV insult. But it shows a significant relation between hyperphosphatemia, hyperparathyroidism, hypovitaminosis D and the development of CV insult and a highly significant relation between increased MMP9 expression and the development of CV insult.

Table 6: Univariate logistic regression of potential independent predictors of CV insult.

Variables	β	SE	OR	95% CI	p-value (Sig.)
Age (years)	+0.037	0.023	1.038	(0.991 – 1.086)	0.114 (NS)
Male	+0.080	0.510	1.083	(0.399 – 2.944)	0.875 (NS)
Smoker	+0.348	0.668	1.417	(0.383 – 5.245)	0.602 (NS)
Hypertension	+0.553	0.534	1.739	(0.611 – 4.949)	0.300 (NS)
AV fistula	-0.485	1.438	0.615	(0.037 – 10.304)	0.736 (NS)
Weight (kg)	+0.035	0.016	1.036	(1.004 – 1.069)	0.029 (S)
Height (m^2)	+2.268	1.708	9.663	(0.340 – 274.806)	0.184 (NS)
BMI (kg/m^2)	+0.064	0.048	1.066	(0.970 – 1.170)	0.185 (NS)
SBP (mmHg)	+0.025	0.012	1.025	(1.002 – 1.049)	0.031 (S)
DBP (mmHg)	+0.044	0.017	1.045	(1.011 – 1.080)	0.010 (S)
MAP (mmHg)	+0.037	0.015	1.038	(1.008 – 1.069)	0.013 (S)
Hemoglobin (gm/dl)	-0.285	0.157	0.752	(0.552 – 1.023)	0.070 (NS)
Albumin (gm/dl)	-0.534	0.780	0.586	(0.127 – 2.705)	0.494 (NS)
ALT (U/L)	+0.006	0.039	1.006	(0.932 – 1.087)	0.871 (NS)
AST (U/L)	+0.030	0.040	1.031	(0.952 – 1.115)	0.455 (NS)
HDL (mg/dl)	+0.085	0.093	1.089	(0.907 – 1.307)	0.360 (NS)
LDL (mg/dl)	+0.015	0.021	1.015	(0.975 – 1.057)	0.470 (NS)
Triglycerides (mg/dl)	+0.022	0.019	1.023	(0.986 – 1.061)	0.231 (NS)
Fasting blood glucose (mg/dl)	+0.019	0.025	1.019	(0.969 – 1.071)	0.459 (NS)
Calcium (mg/dl)	-0.003	0.311	0.997	(0.541 – 1.834)	0.991 (NS)
Phosphorus (mg/dl)	+0.375	0.183	1.455	(1.017 – 2.082)	0.040 (S)
iPTH (pg/ml)	+0.001	0.001	1.001	(1.000 - 1.003)	0.011 (S)
25(OH) vit D (ng/ml)	-0.066	0.021	0.936	(0.898 – 0.976)	0.002 (S)
MMP9 (ng/ml)	+0.003	0.001	1.003	(1.002 – 1.005)	<0.001(HS)

β: regression coefficient; SE: standard error; OR: odds ratio; 95%CI: 95% confidence interval, $p< 0.05$ is significant.

Table (6)showing that there aresignificant correlations between the development of CV insult and each of the variables weight, SBP, DBP, MAP, serum phosphorus, iPTH, 25(OH) vit D and MMP9. While, it showed no significant correlations between the development of CV insult and each of the variables age, sex, smoking, hypertension, vascular access, height, BMI, hemoglobin, albumin, AST, ALT, HDL, LDL, triglycerides, FBG and calcium.

Discussion:-

Chronic kidney disease (CKD) is identified as a risk factor for vitamin D deficiency, and many papers show that the frequency of deficiency is high among these patients **(11).**Vitamin D deficiency is not only associated with the increased risk of osteometabolic disease, but also to other relevant clinical issues, including different types of neoplasms,besides the risk of cardiovascular diseases **(12).**At the same time, low levels of vitamin D have been associated with the high mortality rates in the general population and in patients who undergo hemodialysis (HD) **(13).**

MMPs (matrix metalloproteinases) and TIMPs (tissue inhibitors of MMPs) are the main determinants of tissue remodeling in both physiological and pathological processes. Evidence suggests that MMP activity can change the structure of the ECM (extracellular matrix), leading to the loss of cardiac contractility through proteolysis **(14).**The remodeling of collagen fibers and the loss of myocytes is known to cause ventricular enlargement and progressive contractile dysfunction **(15).** LV (left ventricular) remodeling in HF patients is also stimulated by degradation of the ECM by MMPs **(16).**Gelatinases A and B (MMP-2 and MMP-9) are particularly active in degrading denatured collagen and have been the focus of pathological heart remodeling studies **(17).**

The aim of our studyisto determine if circulating 25(OH)D level is associated with change of serum MMP-9 as a marker of vascular remodeling in ESRD patients on regular hemodialysis.

In our study we found a highly significant difference between the three groups of the study as regards iPTH level with the highest value in group 1 and the least value in group 3; these results were in agreement with **Jean et al., 2009 (18)and Matias et al., 2010 (19).**This can be explained by the fact that low levels of calcitriol directly release the gene for PTH from suppression by the vitamin D receptor and allow increased PTH secretion. Continuous stimulation of the parathyroid glands by a combination of elevated extracellular phosphate concentration, decreased extracellular ionized calcium concentration, and markedly reduced serum calcitriol leads to increased PTH synthesis and release **(20).**

Our results also indicate that plasma MMP-9 expression is inversely and independently associated with circulating 25(OH) D concentration among ESRD patients; these results are consistent with the results of **Wasse et al., 2011 (21).** This may help to shed light on mechanisms by which vitamin D deficiency is associated with an increased risk of atherosclerosis and cardiovascular disease.Our results are consistent with previous data among non-ESRD populations that report a strong association between 25(OH) D deficiency and elevated markers of vascular remodeling: Vitamin D supplementation of vitamin D deficient, healthy British Bangladeshi adults resulted in significant reductions in plasma MMP-9 and serum CRP concentrations **(22).**MMP's promote the remodeling of connective tissue and basement membranes via degradation of collagen, and act as important regulatory molecules in inflammation and vascular diseases. MMP-9 is released by neutrophils and is a key effector molecule of inflammatory cells, aiding migration of inflammatory leukocytes through tissue barriers, lysing protein substrates, modulating smooth muscle cell migration, and promoting angiogenesis **(23).** MMP's also regulate inflammation by directly and indirectly acting on pro-inflammatory cytokines, such as TNF-α and TGF-β, to control chemokine activity. 25(OH) D may act to reduce MMP9 in several ways **(24).**

As regards the incidence of CV insult, there was significant relation between 25 hydroxyvitamin D deficiency and the development of CV insult during the study period; these results are in agreement with **Bouillon et al., 2008 (25), Pilz et al., 2010 (26)and Pilz et al., 2011 (27).** This was explained by the role of vitamin D in Ca handling and excitation-contraction coupling in the heart in addition to the antihypertrophic and antiproliferative effects of vitamin D and its metabolites, synergizing with natural and exogenous inhibitors of the renin-angiotensin system.Also in a subsequent meta-analysis of 4 prospective and 14 cross-sectional studies it was found that 25(OH)D level was inversely associated with hypertension with an odds ratio of 0.73 (95% CI, 0.63– 0.84) with a significant dose–response effect. The influence of vitamin D metabolites on both endothelial function and RAAS suggests an important role in physiological control of vascular tone and blood pressure and hence in the pathophysiology of hypertension**(28).**

Also in our study we found a highly significant relation between the incidence of CV insult and the increased expression of MMP9; these results are in agreement with **Hansson, et al., 2011 (29), Lindsey &Zamilpa, 2010 (30)and Yarbrough, et al., 2003 (31).**This can be attributed to the role of MMP9 in vascular and cardiac remodeling through cleaving several ECM proteins and as such modulating the outcome of various physiological and pathological processes including MI, atherosclerosis and congestive heart failure. In addition to structural ECM components, MMP substrates also include a multitude of substrates such as cytokines, chemokines, growth factors, and adhesion molecules that alter cellular migration, adhesion, and activation. MMPs, therefore, exert a strong influence on cardiac remodeling through multiple mechanisms **(32-33).**

Finally, our results showed that the probability of CV insult by Univariate binary logistic regression was significantly greater with higher body weight [odds ratio (OR):1.036, 95% confidence interval (CI): 1.004 – 1.069, P = 0.029], higher SBP [odds ratio (OR):1.025, 95% confidence interval (CI): 1.002 – 1.049, P = 0.031], higher DBP [odds ratio (OR):1.045, 95% confidence interval (CI): 1.011 – 1.080, P = 0.010], higher MAP [odds ratio (OR):1.038, 95% confidence interval (CI): 1.008 – 1.069, P = 0.013], hyperphosphataemia [odds ratio (OR):1.455, 95% confidence interval (CI): 1.017 – 2.082, P = 0.040], hyperparathyroidism [odds ratio (OR):1.001, 95% confidence interval (CI): 1.000 – 1.003, P = 0.011], hypovitaminosis D [odds ratio (OR):0.936, 95% confidence interval (CI): 0.898 – 0.976, P = 0.002] and increased MMP9 [odds ratio (OR):1.003, 95% confidence interval (CI): 1.002– 1.005, P < 0.001].

Conclusion:-

In conclusion, the results of our study reveal a new finding of a significant inverse relationship between plasma MMP-9 and circulating 25(OH) D concentrations among ESRD patients, and suggest that there may a cardioprotective value in measuring 25(OH) D concentrations in ESRD patients and correction of vitamin D deficiency in these patients.

We recommend that more evaluation is needed by more studies on larger groups of hemodialysis patients.Because of the high prevalence of vitamin D deficiency and cardiovascular disease among ESRD patients, our findings suggest that future studies are warranted which further characterize the relationship between vitamin D therapy and vascular remodeling biomarker synthesis.

References:-

1. **Segarra A, Chacon P, Martinez-Eyarre C, Argelaguer X, Vila J, Ruiz P, Fort J, Bartolome J, Camps J, Moliner E, et al., (2001):** Circulating levels of plasminogen activator inhibitor type-1, tissue plasminogen activator, and thrombomodulin in hemodialysis patients: biochemical correlations and role as independent predictors of coronary artery stenosis. J Am SocNephrol, 12:1255-1263.
2. **Peterson CA, Heffernan ME (2008):** Serum tumor necrosis factor-alpha concentrations are negatively correlated with serum 25(OH)D concentrations in healthy women. J Inflamm (Lond), 5:10.
3. **Van den Berghe G, Van Roosbroeck D, Vanhove P, Wouters PJ, DePourcq L, Bouillon R (2003):**Bone turnover in prolonged critical illness: effect of vitamin D. J ClinEndocrinolMetab, 88:4623-4632.
4. **Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R (2006):** Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. Am J ClinNutr, 83:754-759.
5. **Friese RS, Rao F, Khandrika S, Thomas B, Ziegler MG, Schmid-Schonbein GW, O'Connor DT (2009):** Matrix metalloproteinases: discrete elevations in essential hypertension and hypertensive end-stage renal disease. ClinExpHypertens, 31:521-533.
6. **Bahar-Shany K, Ravid A, Koren R (2010):** Upregulation of MMP-9 production by TNFalpha in keratinocytes and its attenuation by vitamin D. J Cell Physiol, 222:729-737.
7. **Anand SP, Selvaraj P (2009):** Effect of 1, 25 dihydroxyvitaminD(3) on matrix metalloproteinases MMP-7, MMP-9 and the inhibitor TIMP-1 in pulmonary tuberculosis. ClinImmunol, 133:126-131.
8. **Rahman A, Hershey S, Ahmed S, Nibbelink K, Simpson RU (2007):** Heart extracellular matrix gene expression profile in the vitamin D receptor knockout mice. J Steroid BiochemMolBiol, 103:416-419.
9. **Melamed ML, Michos ED, Post W, Astor B (2008):** 25-hydroxyvitamin D levels and the risk of mortality in the general population. Arch Intern Med, 168:1629-1637.
10. **Giovannucci E, Liu Y, Hollis BW, Rimm EB (2008):** 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch Intern Med, 168:1174-1180.
11. **Gonzales EA, Sachdeva A, Oliver DA, et al. (2004):**Vitamin D insufficiency and deficiency in chronic kidney disease. A single center observational study. Am J Nephrol;24:503-10.
12. **Ewers B, Gasbjerg G, Moelgaard C, et al.** Vitamin D status in kidney transplant patients: need for intensified routine supplementation. Am J ClinNutr 2008;87:431-7.
13. **Holick MF.** VitaminD deficiency. N Engl J Med 2007; 357:266-81; PMID:17634462; http://dx.doi. org/10.1056/NEJMra070553
14. **Altieri, P., Brunelli, C., Garibaldi, S., Nicolino, A., Ubaldi, S., Spallarossa, P., Olivotti, L., Rossettin, P., Barsotti, A. and Ghigliotti, G. (2003)** Metalloproteinases 2 and 9 are increased in plasma of patients with heart failure. Eur. J.Clin. Invest. 33, 648–656
15. **D'Armiento, J. (2002):** Matrix metalloproteinase disruption of the extracellular matrix and cardiac dysfunction. Trends Cardiovasc. Med. 12, 97–101.
16. **Spinale, F. G. (2002)** Matrix metalloproteinases. Regulation and dysregulation in the failing heart. Circ. Res. 90,520–530
17. **Nagase, H., Visse, R. and Murphy, G. (2006)** Structure and function of matrix metalloproteinases and TIMPs. Cardiovasc. Res. 69, 562–573
18. **Jean G, Souberbielle J-C, Chazot C:** Monthly cholecalciferol administration in haemodialysis patients: A simple and efficient strategy for vitaminD supplementation. Nephrol Dial Transplant 24: 3799–3805, 2009.
19. **Matias PJ, Jorge C, Ferreira C, Borges M, Aires I, Amaral T, Gil C, Cortez J, Ferreira A:** Cholecalciferol supplementation in hemodialysis patients: Effects on mineral metabolism, inflammation, and cardiac dimension parameters. Clin J Am SocNephrol 5:905–911, 2010

20. **Brown AJ, Ritter CS, Finch JL, Slatopolsky EA:** Decreased calcium sensing receptor expression in hyperplastic parathyroid glands of uremic rats: Role of dietary phosphate. Kidney Int 55: 1284–1292, 1999.
21. **Wasse H, Cardarelli F, De Staercke C, Hooper C, Veledar E, Guessous I.** 25-hydroxyvitamin D concentration is inversely associated with serumMMP-9 in a cross-sectional study of African American ESRD patients. BMC Nephrol. 2011;12:24.
22. **Timms PM, Mannan N, Hitman GA, Noonan K, Mills PG, Syndercombe-Court D, Aganna E, Price CP, Boucher BJ:** Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? QJM 2002, 95:787-796.
23. **Jorde R, Haug E, Figenschau Y, Hansen JB:** Serum levels of vitamin D and haemostatic factors in healthy subjects: the Tromso study. ActaHaematol 2007, 117:91-97.
24. **Parks WC, Wilson CL, Lopez-Boado YS:** Matrix metalloproteinases as modulators of inflammation and innate immunity. Nat Rev Immunol 2004,4:617-629.
25. **Bouillon R, Carmeliet G, Verlinden L et al.** Vitamin D and human health: lessons from vitamin D receptor null mice. Endocr Rev 2008; 29: 726–76. cardiomyocyte contractility. Endocrinology 2008; 149: 558–64.
26. **Pilz S, Tomaschitz A, Drechsler C, Dekker JM, Marz W.** Vitamin D deficiency and myocardial diseases. MolNutr Food Res 2010; 54: 1103–13.
27. **Pilz S, Tomaschitz A, Drechsler C et al.** Vitamin D deficiency and heart disease. Kidney Inter Suppl 2011; 1: 111–5.
28. **Burgaz A, Orsini N, Larsson SC, Wolk A.** Blood 25- hydroxyvitamin D concentration and hypertension: a meta-analysis. J Hypertens. 2011;29:636–645.
29. **Hansson J, Vasan RS, Arnlov J, Ingelsson E, Lind L, Larsson A, Michaelsson K, Sundstrom J.** Biomarkers of extracellular matrix metabolism (MMP-9 and TIMP-1) and risk of stroke, myocardial infarction, and cause-specific mortality: cohort study. PloS one. 2011; 6:e16185. [PubMed: 21283828]
30. **Lindsey ML, Zamilpa R.** Temporal and Spatial Expression of Matrix Metalloproteinases and Tissue Inhibitors of Metalloproteinases Following Myocardial Infarction. CardiovascTher. 2010
31. **Yarbrough WM, Mukherjee R, Escobar GP, Mingoia JT, Sample JA, Hendrick JW, Dowdy KB, McLean JE, Lowry AS, O'Neill TP, Spinale FG.** Selective targeting and timing of matrix metalloproteinase inhibition in post-myocardial infarction remodeling. Circulation. 2003; 108:1753–1759. [PubMed: 12975256]
32. **Lindsey ML.** MMP induction and inhibition in myocardial infarction. Heart failure reviews. 2004; 9:7–19. [PubMed: 14739764]
33. **Sternlicht MD, Werb Z.** How matrix metalloproteinases regulate cell behavior. Ann Rev Cell DevBiol 17: 463–516, 2001.