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KEY WORDS: Diabetic Nephropathy, Vitamin D3, Type2 Diabetes Mellitus

TO STUDY THE RELATIONSHIP BETWEEN SERUM VITAMIN D3 LEVEL AND DIABETIC NEPHROPATHY IN TYPE2 DIABETES MELLITUS SUBJECT

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ABSTRACT

Introduction & Objective: - To estimate & study the relationship between serum vitamin D3 level and diabetic nephropathy in type2 diabetes mellitus subject. The studies evaluating the role of vitamin D3 in Diabetic Nephropathy are few.

Material and Methods: - A total of 100 patients with type2 diabetes mellitus were enrolled from inpatients of our hospital. Out of which 50 patients with and 50 patients without Diabetic Nephropathy were considered. Serum vitamin D3 and 24 hour urinary albumin excretion rate were investigated and analysed. Nephropathy is defined as 24hour urinary albumin excretion >30 mg. Serum vitamin D3 levels were characterized as <20 ng/mL vitamin D3 deficiency, 20 to 29 ng/mL vitamin D3 insufficiency and >30 ng/mL normal vitamin D3.

Results: - Overall, the urinary albumin excretion rate was significantly higher in patients with vitamin D3 deficiency than with normal vitamin D3 level {(122+29.2)mg/24hr vs. (41.6+8.1)mg/24hr}. 48% of adults with type2 diabetes mellitus have vitamin D3 deficiency and 27% have vitamin D3 insufficiency. Higher proportions of individuals with nephropathy have vitamin D3 deficiency than individuals without nephropathy; 43% vs. 32% (odds ratio, 2.95; 95% CI, 1.14 –7.64, P= 0.0257). Logistic regressions demonstrate vitamin D3 deficiency and insufficiency are associated with the presence of nephropathy after adjustment for age, sex, hypertension, lipid profile, smoking and use of angiotensin-converting enzyme(ACE) inhibitors or angiotensin receptor Blockers(ARBs) (odds ratio, 3.60; 95% CI, 1.25 –10.23 for vitamin D3 deficiency; and odds ratio, 3.21; 95% CI, 1.01–10.22 for vitamin D3 insufficiency).

Conclusion: - There is a high prevalence of vitamin D3 deficiency in individuals of type 2 DM with Diabetic Nephropathy. Thus, evaluating vitamin D3 levels in people with Diabetic Nephropathy may be warranted. There is an independent association between vitamin D3 deficiency with the presence of nephropathy.

INTRODUCTION:-

Diabetic nephropathy (DN) is a common complication of diabetes mellitus (DM), usually accounting for chronic renal failure in many countries[1] The mechanism responsible for diabetic nephropathy remains incomplete, and thus the corresponding optimal therapy is undecided D3. Multiple agents have been used to delay the progression of diabetic nephropathy including beta-blockers, calcium channel blockers, diuretics, angiotensin converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (ARBs). In accordance with several large scale randomized controlled trials (RCTs), ACE inhibitors and ARBs have been proposed as the first line agents for treating diabetic nephropathy because of their role in reducing proteinuria[2]. However, these agents also contribute to elevated levels of potassium i.e. hyperkalemia and creatinine, finally limiting their actions to improve kidney function[3]. Therefore, additional interventions that are against diabetic nephropathy are needed.

Chronic hyperglycemia that affects especially the heart, kidneys, blood vessels, nerves and eyes[4].

Diabetes is an epidemic health problem. Diabetic nephropathy (DN) is a major microvascular complication of diabetes mellitus implicated in nearly 44% of end stage renal disease (ESRD) patients that requires hemodialysis[5]. The pathogenesis of Diabetic Nephropathy is multifactorial with contribution from several genetic and environmental factors. Diabetes induces various metabolic, biochemical and hemodynamic changes in kidneys. Major pathways leading to Diabetic Nephropathy include: intracellular activation of polyol pathway and protein kinase C, advanced glycation end products (AGEs) and oxidative stress by reactive oxygen species, and glomerular hyperfiltration and hypertension leading to shear stress and mechanical stretch. Hyperglycemia stimulates the production of Angiotensin II(Ang-II), which exerts hemodynamic, inflammatory and profibrogenic effects on kidney cells[6].

Nuclear receptors are found to be the negative regulators of inflammation, oxidative stress and fibrosis. Vitamin D receptor(VDR) is one such nuclear receptor involved in various inflammatory pathways[7]. Several observational studies have confirmed this pathophysiologic link between Vitamin D deficiency and Diabetic Nephropathy. The Third National Health and Nutrition Examination Survey (NHANES III) found an increase in the prevalence of albuminuria with decreasing 1-α, 25-dihydroxyvitamin D3 concentration[8]. A significant relationship between Vitamin D deficiency and nephropathy may exist, suggesting a possible role of Vitamin D in delaying the CKD progression.

However studies evaluating the role of vitamin D in Diabetic Nephropathy are few. There is a need to critically evaluate and establish any beneficial association of vitamin D or its analogues in Diabetic Nephropathy. The aim of this study is to estimate and evaluate the vitamin D3 relation in diabetic nephropathy in type 2 diabetic patients.

Material and method:-

- The prospective observational study was conducted at Department of Medicine, MBS hospital, Govt Medical College Kota, in 100 patients with Type 2 diabetes mellitus after obtaining informed consent from January 2018 to dececmber 2018.

INCLUSION CRITERIA

1. All Type 2 diabetic patients who fulfil the ADA criteria.
2. Albuminuria (> 30 mg/ 24 hours).
3. Vitamin D Deficiency (< 50 nmol/l OR <20ng/ml)

ADA CRITERIA FOR DIAGNOSIS OF DIABETES MELLITUS;

1. Symptoms of diabetes plus random blood glucose concentration more than or equal to 200 mg/dl or
2. Fasting plasma glucose more than or equal to 126 mg/dl or
3. HbA1C more than 6.5% or
4. Two hour plasma glucose more than or equal to 200 mg/dl during an oral glucose tolerance test.

The Diagnosis of Diabetic Nephropathy was made by an elevated uACR >30mg/mmol on at least two occasions and the exclusion of other etiologies for CKD by history, clinical, and laboratory examinations, including urine sediment and renal ultrasound. Patients were eligible for the study if they had type 2 diabetes mellitus treated with at least one anti-hyperglycemic medication within the 12 months before enrollment, and were on a stable

dose (that is, same type and regimen) of RAAS inhibition for at least 3 months before enrollment. Other criteria were uACR >30mg/mmol or history of macroalbuminuria (that is, previously uACR >30mg/mmol.

EXCLUSION CRITERIA

1. Prediabetes (impaired fasting glucose, impaired glucose tolerance) patients were excluded from both groups.
2. Diabetic patients other than type 2.
3. Nephrotic syndrome
4. Pregnant females
5. Age < 18 years
6. Etiologies of CKD other than diabetes & poorly controlled hypertension.
7. Treatment with vitamin D or active vitamin D analogs, steroid treatment.
8. Recurrent urinary tract infections, hepatitis B or C, or human immunodeficiency virus infection.

A detailed history was taken and examination was done as per the proforma in all cases. All the cases were investigated with CBC, lipid profile, liver function tests, renal function tests, electrolytes, fasting blood sugar, postprandial blood sugar, HbA1C. Study population was divided into two groups on the basis of proteinurea i.e. patients with and without diabetic nephropathy. The analysis was done separately and combined for patients with and without diabetic nephropathy and the serum vitamin D3 status of the individual patients.

Data obtained was tabulated using version 21 of the statistical package for social science (SPSS published SPSS Inc.). Qualitative variables were expressed as percentages. Association of various variables were assessed through chi square test and ANNOVA. P value less than 0.05 was considered for statistical significance.

RESULT:-

A total of 100 patients with type2 diabetes mellitus were enrolled from inpatients of our hospital. Out of which 50 patients with and 50 patients without Diabetic Nephropathy were considered. 59 patients were males in comparison to females which was 41. Age wise distribution is shown in the table 1.

Table 1:-Distribution Of Diabetic Patients (N=100) By The Age Of The Patients.

AGE OF THE PATIENTS (Year)	n	% of cases
<30	1	1
31-40	28	28
41-50	18	18
51-60	22	22
61-70	16	16
71-80	11	11
81-90	4	4

The mean level of serum vitamin D3 in the study population was 39.50ng/ml in patients with normal vitamin D3 and 17.76ng/ml in patients with vitamin D3 deficiency. Distribution of cases among vitamin d3 & diabetic nephropathy status is shown in table 2.

Table 2 :- Distribution Of Cases Among Vitamin D3 & Diabetic Nephropathy Status. (N=100)

VITAMIN D STATUS	Patients without DN	Patients with DN
Patients With Normal Vitamin D3	18	7
Patients With Vitamin D3 Deficiency	32	43
Patients With Vitamin D3 Insufficiency	12	15
Patients With Vitamin D3 Severe Deficiency	20	28

The table 3 represent the distribution mean and standard deviation of serum vitamin D3 in relation to Diabetic Nephropathy. The P-value 0.0376 in relation to patient with and without Diabetic Nephropathy and serum vitamin D3 in the study population was noted to be statistically significant.

TABLE:-3 Statistical Analysis Of Serum Vitamin D3 Levels Of The Study Population

Parameter	Patients without DN (mean±SD) (n=50)	Patients with DN (mean±SD) (n=50)	P-value
Vitamin D (ng/dl) (min-max)	25.3504±11.5616 (7.56-49.37)	20.6848±10.5444 (5.79-47.41)	0.0376

DISCUSSION:-

In present study out of all 100 cases, males were 59 and females were 41. Males were outnumbering females with male:female ratio of 1.43:1. All the cases in the study were in age group of 30-90 years of age with mean age value of 53.62±15.34 years. Bonakdaran S Et Al[9] considered mean age of the study patients as 55.3 ± 11.2 years in their study. Maximum number of cases was in the age group of 31-40 years i.e. 28 cases (28%). In our study 44% of male were having vitamin D3 deficiency of which 15% having vitamin D3 insufficiency and 29% were having severe vitamin D3 deficiency as compared to females where 31% of female were having vitamin D3 deficiency out of them 12% having vitamin D3 insufficiency and 19% were having severe vitamin D3 deficiency. 15% of males and 10% of females were having normal vitamin D3 level. 44% of male were having vitamin D3 deficiency of which 15% having vitamin D3 insufficiency and 29% were having severe vitamin D3 deficiency as compared to females where 31% of female were having vitamin D3 deficiency out of them 12% having vitamin D3 insufficiency and 19% were having severe vitamin D3 deficiency. 15% of males and 10% of females were having normal vitamin D3 level. A study conducted by Del valle, Negri AL, Aguirre C[12], found that mean 25 (OH) D Levels were significantly higher in men that in women (28.6 ng/ml vs 18.9 ng/ml) whereas in our study The P-value in relation to normal and deficient vitamin D3 patient in male and female was noted to be statistically insignificant.

The distribution and relation between serum vitamin D3 level and Diabetic Nephropathy in our study population was that, out of 100 patients 18% of patients with normal vitamin D3 level and 32% of patients with vitamin D3 deficiency does not have DN, out of which those who have deficiency 12% and 20% respectively have insufficiency and severe deficiency of vitamin D3. On the other hand 7% of patients with normal vitamin D3 level and 43% of patients with vitamin D3 deficiency does have DN, out of which those who have deficiency 15% and 28% respectively have insufficiency and severe deficiency of vitamin D3. On conducting Chi-square with Yates correction test, the Chi squared equals 5.333 with 1 degrees of freedom.

The two-tailed P value equals 0.0209. The association between vitamin D3 deficiency and Diabetic Nephropathy is considered to be statistically significant.

The distribution of mean and standard deviation of various status of serum vitamin D3 in relation to Diabetic Nephropathy. The P-value in relation to patient with and without Diabetic Nephropathy and serum vitamin D3 in normal vitamin D3 level and patient with vitamin D3 deficiency, insufficiency and severe deficiency in the study population was noted to be statistically significant. These findings are in consistent with the study Bonakdaran S Et Al[9] Kim Mj, Frankel Ah Et Al[10] Momeni A Et Al[11].

CONCLUSION:-

It is concluded in our study that the serum vitamin D3 deficiency was more prevalent in type 2 Diabetes Mellitus patients with Diabetic Nephropathy. The serum vitamin D3 deficiency and its severity of the deficiency was associated with Diabetic Nephropathy in type 2 Diabetes Mellitus subjects.

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