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RESEARCH ARTICLE

STUDY THE RELATION BETWEEN THYROID FUNCTION AND RENAL FUNCTION IN CHRONIC KIDNEY DISEASE AND THE EFFECT OF DIALYSIS IN THESE PATIENTS

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Key words:-

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Abstract

The aim of this work: Is to study the relation between thyroid function and renal function in chronic kidney disease and the effect of dialysis in these patients.

Materials and method: 60 participants of both sexes, were categorized into three groups, group I healthy control participants, group II Chronic kidney disease non dialysis patient and group III Chronic kidney disease (CKD) with dialysis. Last two groups are further subdivided into three subgroups: a) euthyroid, b) hypothyroid and c) hyperthyroid. Urine was collected for 24 hours and blood samples were analyzed for serum creatinine, serum urea, serum Total Tri-iodothyronine (T3), Thyroxine (T4), serum Thyroid Stimulating Hormone (TSH) and urine albumin. Glomerular filtration rate (GFR) will be measured as creatinine clearance

Results: GFR is significantly reduced in all group studied in CKD patients with and without dialysis compared to control. In hyperthyroid patients it is significantly increased compared to other groups without dialysis and also compared to hypothyroid patients with dialysis. Urea, creatinine and urinary albumin are significantly increase in all groups compared to control. TSH is significantly increased in hypothyroid and significantly reduced in hyperthyroidism and unchanged in euthyroid patients as compared to control. The opposite will be observe for T3 and T4 with exception of increase T4 in hypothyroid patients without dialysis

Conclusion: There are many remaining information with regards to the interaction between kidney disease and thyroid dysfunction. Thyroid function should be carefully monitored in persons with poor renal function. Further mechanistic studies are consider to understand the pathogenesis of thyroid functional disorders in kidney disease, and how CKD may affect thyroid dysfunction

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Introduction:-

Chronic kidney disease (CKD) is becoming a serious health problem; the number of people with impaired renal function is rapidly rising⁽¹⁾.

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Progression of CKD is associated with having a number of complications, including thyroid dysfunction, kidney and thyroid function and dysfunction are interrelated ⁽²⁾Epidemiologic data show that CKD patients have a substantially higher prevalence of hypothyroidism compared to their non-CKD counterparts⁽³⁾Limited information is available on the relationship between thyroid hormone levels and CKD⁽²⁾.The mechanistic link and associations between kidney and thyroid disease have not been fully elucidated ⁽⁴⁾No data to date are available about the relationships of thyroid hormone and GFR, and albumin, in CKD patients⁽⁵⁾

The aim of the work:

Is to study the relation between thyroid function and renal function in chronic kidney disease and the effect of dialysis in these patients.

Patients and Methods:-

60 participants of both sexes ranging between 19-64years,they were divided into three main groups:

Gp I: control group:10healthy participants

Gp II: (25 patients) chronic kidneydiseasenon dialysis patient were further subdivided into 3 subgroups:

GpIIa10 Patients with normal thyroid functions,GpII b 10 Patients with hypothyroid disorder. GpII c 5 patient with hyperthyroid disorder

Group III: (25 patients) Chronic kidney disease with hemodialysis three times weekly. They were further subdivided into three subgroups.

GpIIIa 10 Patients with normal thyroid functions, GpIII b10 Patients with hypothyroid disorder,GpIII c 5 patient with hyperthyroid disorder.

All participants were subjected to complete history taking and thorough clinical examination.Signs and symptoms of thyroid dysfunction were evaluated ^(6,7).

Inclusion Criteria:

The presence of albuminuria for 3 or more months

Exclusion Criteria:

Patients were younger than 18 years and older than 65, women who were pregnant.Patient clinically diagnosed not less than 3 months,subjects who were receiving concurrent treatment with drugs that could affect thyroid function (lithium, amiodarone, iodine, methimazole, or propylthiouracil), or steroids, or contraceptive pills or other medications containing hormones, such as androgens and oestrogens, Patients with urinary infection or acute kidney injury.

From all participants urine was collected for 24 hours. To measure Urinary albumin concentration according to the method describe byBaureJD⁽⁸⁾Serum creatinine, will be measured by colorimetric method based on the Jafféreaction.Jaffe' colorimetric Procedure ⁽⁹⁾Serum urea, by Berthelot Enzymatic colorimetric Procedure ⁽¹⁰⁾.Serum Total Tri-iodithyronine (T3), Thyroxin (T4) Serum Thyroid Stimulating Hormone (TSH) concentration by ELISA from Sigma-Aldrich⁽¹¹⁾,were measured , GFR will be measured as creatinine clearance⁽¹²⁾

Statistical Analysis:

Collected data were statistically analyzed by SPSS software, version 23.0, using one-way ANOVA, followed by Tukey test. Also, Pearson's correlation analysis was performed. Statistical significance was considered at p-value ≤ 0.05, for all statistical tests.

Results:-

Table 1:- The mean values and standard deviation of measured parameters in control and CKD groups without dialysis.

Groups	Control Group	CKD Without dialysis		
		Euothyroid Group	Hypothyroid Group	Hyperthyroid Group
Parameters				
TSH	1.74	1.64	4.82 ab	0.47abc

(μ IU/ml.)	± 0.80	± 0.55	± 1.37	± 0.09
T3 (pg/ml)	114.00 ± 27.74	117.64 ± 11.18	36.67 a b ± 1.70	175.90ab c ± 20.83
T4 (ng/dl.)	9.40 ± 2.23	8.49 ± 1.59	10.06b ± 1.83	15.18abc ± 1.38
GFR (ml/min)	100.20 ± 9.99	36.90a ± 6.56	17.80ab ± 12.39	85.80abc ± 2.68
Urea (mg/ml)	25.30 ± 4.81	120.40a ± 37.07	125.60a ± 37.66	102.60a ± 14.54
Creatinine (mg/ml)	0.84 ± 0.12	5.29 a ± 1.99	4.14 a ± 1.94	4.16 a ± 0.97
U Albumin (mg/ml)	11.40 ± 3.44	172.60a ± 55.81	160.00a ± 41.63	136.40a ± 26.77

1. denote statistical significance vs control
2. denote statistical significance vs Euthyroid
3. denote statistical significance of vs Hypothyroid

Table 2:- The mean values and standard deviation of measured parameters in control and CKD groups with dialysis.

Groups parameters	Control Group	CKD With dialysis		
		Euthyroid Group	Hypothyroid Group	Hyperthyroid Group
TSH (μ IU/ml.)	1.74 ± 0.80	1.84 ± 0.62	6.70 ab ± 2.11	0.50 abc ± 0.18
T3 (pg/ml)	114.00 ± 27.74	78.68 a ± 13.97	74.27 a ± 12.96	185.00 abc ± 11.85
T4 (ng/dl.)	9.40 ± 2.23	6.39 a ± 1.05	6.37 a ± 1.37	14.72 abc ± 1.04
GFR (ml/min)	100.20 ± 9.99	9.80 a ± 4.08	6.80 ab ± 1.69	9.30 ac ± 1.64
Urea (mg/ml)	25.30 ± 4.81	147.60 a ± 22.97	111.10 ab ± 15.50	121.40 ab ± 19.27
Creatinin (mg/ml)	0.84 ± 0.12	7.88 a ± 1.06	7.41 a ± 0.98	6.10 abc ± 0.96
U Albumin (mg/ml)	11.40 ± 3.44	215.50 a ± 92.27	245.70 ^a ± 98.41	203.60 a ± 73.04

1. denote statistical significance vs control
2. denote statistical significance vs Euthyroid
3. denote statistical significance vs Hypothyroid

In CKD patients without and with dialysis TSH is significantly increased in hypothyroid and significantly reduced in hyperthyroidism and unchanged in Euthyroid patients as compared to control. The opposite will be observed for T3 and T4 with exception of increase T4 in hypothyroid patients without dialysis as compared to Euthyroid patients. As regard GFR it is significantly reduced in all group studied compared to control. In hyperthyroid patients it is significantly increased compared to Euthyroid and hypothyroid groups without dialysis and also compared to hypothyroid patients with dialysis. Urea, creatinine and urinary albumin are significantly increase in all groups compared to control. But CKD patients with dialysis urea level is significantly decreased in both hypothyroid and hyperthyroid patients as compared to Euthyroid patients Table (1) and (2)

Table 3:- The prevalence of hypothyroidism among Euthyroid Hypothyroid patients without dialysis.

	Without dialysis
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GFR ml/ minute	Euothyroid NO	Hypothyroid NO	Total NO	Prevalence of hypothyroid among hypothyroid & Euothyroid patients without dialysis	prevalence of Euothyroid among hypothyroid &Euothyroid patients without dialysis
>30	8	3	11	3/11 27.27 %	8/11 72.72%
<30	2	7	9	7/9 77.32 %	2/9 22.2 2%

The above table show the prevalence of hypothyroidism was increased in patients with reduced GFR, ranging from 27.27 % for persons with $\text{GFR} \geq 30 \text{ mL/min}$ to 77.32% in patients with $\text{GFR} < 30 \text{ mL/min}$.

However, the prevalence of euothyroid is very low amount to 22.22% in patients with $\text{GFR} < 30 \text{ mL/min}$ as compared to those of hypothyroid which amount to 77.32%.

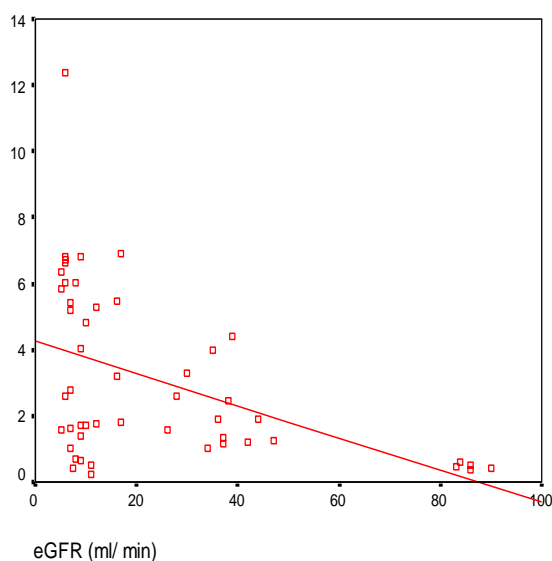


Figure 1:- Correlation between GFR (ml/ min) and T3.

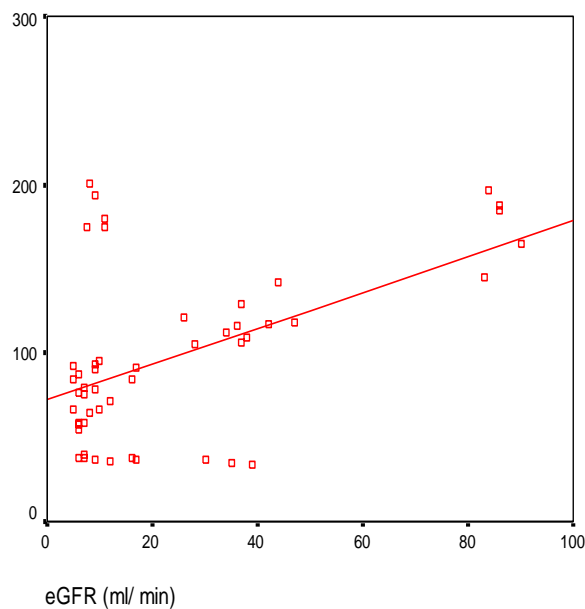


Figure 2:- Correlation between GFR (ml/ min) and TSH ($\mu\text{IU/mL}$).

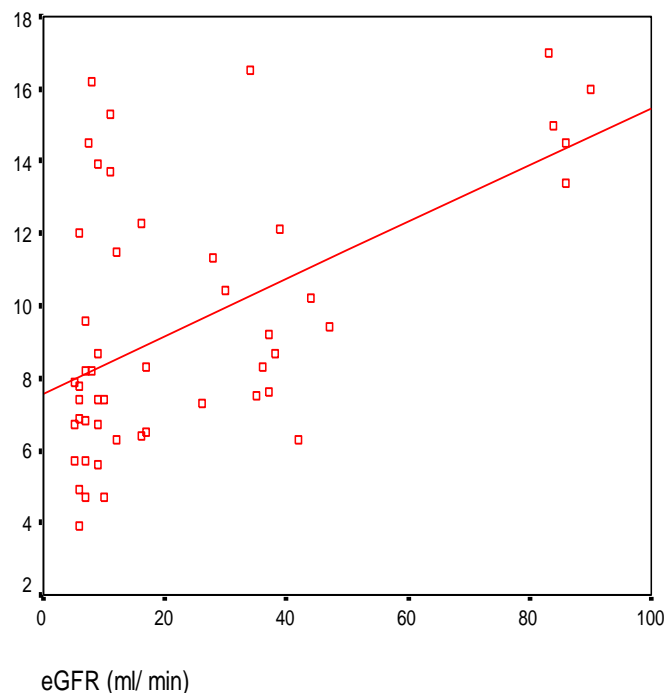


Figure 3:- Correlation between GFR (ml/ min)and T4 (ng/dl.).

It is evident from Figure (1), Figure (2) and figure (3) that there is significant negative correlation between (GFR ml/min) With TSH (μ IU/ml.) and significant positive correlation With T3 (pg/ml) and T4(ng/dl)

Discussion:-

The exact underlying mechanisms linking advanced CKD and thyroid dysfunction remain unclear⁽⁵⁾

It is evident that the prevalence of hypothyroidism among both hypothyroid and euthyroid patients was increased in patients with reduced GFR, amount to 27.27 % for persons with $\text{GFR} \geq 30 \text{ mL/min}$ to 77.32% in patients with $\text{GFR} < 30 \text{ mL/min}$. Gupta et al reported similar results⁽⁴⁾

It is clear that TSH is significantly increased in hypothyroid patients. without and with dialysis. One of possible mechanism for this increase impaired clearance of this hormone by the kidney⁽¹²⁾ or it could be due to blunted response of TSH to TRH in CKD⁽¹³⁾ Chandra et al concluded that the increase TSH level in CKD patients with hypothyroid may be due to resetting of central thyrostatetoward low level of thyroid hormone⁽¹⁴⁾. Or could be due to impaired sensitivity of Thyrotroph cells to negative feedback by the thyroid hormone⁽¹⁵⁾. Estrada et al reported that In chronic kidney disease there is decreased response to TRH feedback⁽¹⁶⁾. Rajagopalan et al observed that Circadian rhythm of TSH is disrupted in CKD suggesting that the nocturnal TSH surge is blunted in these patients resulting in increase TSH⁽¹⁷⁾, also The half-life of TRH was 16 min in CRF and 6.5 min in normal indicate that the pharmacokinetic properties of TRH are impaired in CKD. The kidney might be an important catabolic organ for TRH⁽¹⁸⁾.

The inverse correlation between TSH and GFR observed in this work could another explanation to the increase TSH in these patients. Lo et al reported similar results⁽¹⁹⁾. As regard Total T3 and T4 they are significantly reduced in patients with hypothyroidism both with and without dialysis as compared to normal. As regard T4 in patient without dialysis it is significantly increase in hypothyroid compared to euthyroid group.

Results of the present work reveal significant direct correlation between the level of T3 and T4 with GFR Asvold et al reported similar results⁽²⁰⁾. Other reasons may explain the reduction of T3 and T4, is that increase oxidative stress

in CKD patients.⁽²¹⁾, ineffective clearance of inflammatory cytokines⁽²²⁾ kidney dysfunction decrease T3 can interfere with the activity of the 5'-deiodinase system resulting in decreased T3 production and may increase T4⁽²³⁾.

In addition, impaired renal handling of iodine inhibit thyroglobulin iodinations. Leading to decrease thyroid hormones⁽²⁴⁾ also rT3 concentrations are high in CKD patients due to a reduction in its renal clearance⁽²⁵⁾. increased rT3 is accompanied by decrease thyroid hormones⁽²⁶⁾, also impaired renal handling of iodine inhibit thyroglobulin iodinations. Leading to decrease thyroid hormones⁽²⁴⁾ also rT3 concentrations are high in CKD patients due to a reduction in its renal clearance⁽²⁵⁾. increased rT3 is accompanied by decrease thyroid hormones⁽²⁶⁾. It is evident that in hypothyroid CKD without dialysis there is significantly decrease in GFR and Significant increase in urea, creatinine and urinary albumin compared to the normal control patients secondary to decrease kidney functions

It is clear that in euthyroid patients there significant decrease in GFR, and significant increase in urea creatinine and urinary albumin as compared to those of normal control. However the TSH, Total T3 and T4 are insignificantly different from the normal control indicating that these patients suffering from CKD have a compensated thyroid function. The prospective association between thyroid hormones and kidney function in euthyroid individuals, is largely unexplored⁽²⁶⁾.

It is evident from the present results that the incidence of hyperthyroidism is very low in patients with chronic kidney disease. These results are previously reported by ⁽²⁷⁾Gupta et al found that hyperthyroidism is rare in CKD⁽³⁾. Also Mohamedali et al stated that Hyperthyroidism is usually not associated with CKD⁽²²⁾.

From the results of the present work it is clear that in patients with hyperthyroid without and with dialysis there is significant lowering of TSH and increase total T3 and total T4. This indicate that dialysis does not affect the thyroid indices in these patients. These results are similar to those reported by Lo et al, concluded that Among patients receiving hemodialysis thyroid indices were not significantly altered with dialysis⁽²⁸⁾

Hyperthyroidism results in increased GFR. compared to patient with all other studied groups with exception of insignificant change as compared to euthyroid patients with dialysis⁽²⁹⁾. The significant increase in GFR in these patients could be explained by its influence on cardiovascular system and systemic hemodynamic effects increasing renal blood flow which results in intraglomerular hypertension, leading to increased filtration pressure and consequent hyperfiltration⁽³⁰⁾

It is clear from table (2) that the mean level of urea in all patients of CKD with dialysis ranging between 111.10 and 147.60 mg/ml whereas the mean level of creatinine 6.10 and 7.88 mg/ml in spite of that they are on dialysis, this could be explained by marked reduction of GFR⁽³¹⁾

Most of these patient fall in grade V CKD with very low GFR⁽³¹⁾ The mean GFR ranges between 6.80 and 9.80 ml/min. Reduction in GFR, which in turn is associated with increased plasma creatinine concentrations⁽³²⁾ and urea.⁽³³⁾ As CKD progresses, plasma levels of both rises⁽³³⁾.

Similarly with dialysis there is micro albuminuria. Increased transcapillary leaking of the plasma proteins such as albumin. Lower GFR and greater albuminuria are both associated with an increased rate of progression and are synergistic⁽³⁴⁾

Conclusion:-

Thyroid and renal function should be carefully monitored in persons with poor renal function. Studies of exogenous thyroid treatment, including dosing and biochemical targets, in kidney disease progression are needed.

Clinicians, including nephrologists, must consider the dangers of thyroid disease and its appropriate treatment in conjunction to treating CKD.

Recommendation:-

Further studies, are necessary to clarify the interaction between kidney disease and thyroid dysfunction. For that reason, regular screening for thyroid function tests is so important and aggressively recommended.

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