COMPARATIVE STUDY OF THYROID ABNORMALITIES WITH SEVERITY OF CHRONIC RENAL FAILURE
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ABSTRACT: BACKGROUND: Patients with CRF often have signs & symptoms suggestive of thyroid dysfunctions. Prevalence of hypothyroidism in patients with terminal renal failure is 5%, in comparison with that in hospitalized patients with normal renal function. CKD is associated with higher prevalence of hypothyroidism, both overt and subclinical, but not with hyperthyroidism. In fact, the prevalence of primary hypothyroidism is mainly in the subclinical form, which increases as GFR decreases. OBJECTIVES: To estimate thyroid hormone levels i.e. T₃, T₄ & TSH in CRF. To estimate Serum urea & creatinine for selection and categorizing the study subjects in to different grades of CRF. To study the thyroid hormone levels and thyroid abnormalities as the severity of CRF increases.
MATERIALS AND METHODS: In this study 30 male patients of aged between 40-70yrs. with serum creatinine >5.5mg/dl & urea >55mg/dl and dipstick test positive for protein with symptoms of chronic renal failure are taken as cases. Age and sex matched normal healthy individuals are taken as controls. Serum Urea Estimated by DAM Method, serum creatinine is estimated by Jaffe’s method and Serum levels of T₃, T₄ & TSH were analysed by using CLIA method. Results: T₃, T₄ decreases and TSH increases significantly in cases compare to the controls as the severity of dices increases. In our study 10% of patients of CRF are hypothyroid and all these hypothyroid patients belongs to serum creatinine above 6 mg/dl category. CONCLUSION: Mean of T₃, T₄ decreases TSH increases significantly in cases compare to controls as the severity of CRF increases. The risk of hypothyroidism in chronic renal failure is very high if serum creatinine level are above 6 mg/dl.
KEYWORDS: Chronic renal failure, Hypothyroidism, Hyperthyroidism, Thyroid Stimulating Hormone (TSH).

INTRODUCTION: Chronic renal failure (CRF) is an irreversible deterioration of renal function, which results from diminished effective functioning renal tissue. Ensuing impairment of excretory, metabolic and endocrine functions of the kidney leads to development of clinical syndrome of uremia. CRF is accompanied by anemia, malnutrition impaired metabolism of lipids, carbohydrates and proteins & defective utilization of energy. With advancing renal disease, clear disturbances in electrolytes and endocrine functions takes place.

Thyroid hormones in the blood are almost entirely bound to plasma proteins. They are bound to a globulin named thyroid binding globulin (TBG), thyroxine binding prealbumin and albumin. Affinity of thyroxine is maximum for thyroid binding globulin and hence TBG is the major determinant of binding. Affinity for T₃ and T₄ are slightly different because T₃ is not bound significantly by thyroxine binding prealbumin and binds to TBG less firmly than T₄. The levels of free T₃ are 8 to 10 times more than T₄. As only the free hormone is available to tissues, metabolic state correlates closely with the concentration of free thyroxine.
Patients with CRF often have signs & symptoms suggestive of thyroid dysfunctions. Various Studies of thyroid functions in uremic patients have been carried out which have shown conflicting results. Hyperthyroidism, hypothyroidism & euthyroid state have all been reported by various Workers.1,2

Serum hormonal concentration may be altered by changes in the binding capacity of serum proteins. In CRF there is massive proteinuria mainly albuminuria. Globulin levels are not much altered. Hypothyroidism in CRF is mainly due to decreased level of albumin & thyroid binding pre-albumin.3

In CRF Circulating thyroid binding inhibitors are increased, which inhibits the binding of thyroid hormones to carrier proteins, it may be additional cause for hypothyroidism.4

In CRF hypothyroidism is observed but still many patients are euthyroid with normal T3, T4 and TSH, the chances of developing hypothyroidism is increases as severity of the disease increases.

MATERIALS AND METHODS:
Source of Data: The present study was undertaken in Al-Ameen medical college and hospital both in patients & outpatients and patients attending to dialysis unit.

Inclusion Criteria: The study subjects are divided in to 2 groups as cases & controls.

Cases: 30 Male patients aged between 40-70 years of having history of chronic kidney disease with serum creatinine >5.5mg/dl and urea >55mg/dl and dipstick test positive for protein with symptoms of chronic renal failure.

Controls: 30 Healthy men aged between 40 -70 years.

Exclusion Criteria: Patients with diabetic nephropathy, patients on treatment with estrogen, corticosteroids, Sulphonylurea, Phenobarbitones & β-blocker, Female & children's are excluded from the study.

Data Collection: All the subjects i.e. both cases & controls were subjected to medical examination as per a fixed proforma.

Biochemical Tests: -Morning sample blood was drawn after 12 hrs. Fasting. The samples of blood were allowed to stand to clot. Serum was separated by centrifugation, and analyzed by the following methods.

Serum Urea Estimation by Diacetyl Monoxide Method (DAM, Method)
Principal: Urea reacts with diacetyl monoxide in presence of thiosemicarbizide, under acid conditions to form a coloured compound which is estimated calorimetrically at 520nm.

Estimation of Serum Creatinine by Jaffe’s method.
Principle: Creatinine in alkaline medium reacts with picric acid to form a red tautomer of creatinine picrate, the intensity of which is measured by colorimeter at 520nm.

Estimation of T3, T4 & TSH by Chemiluminesence immunoassay (CLIA)
Estimation of T3 & T4: The principle & procedure for estimation of T3 & T4 are similar
Principle: (Competition principle). The T₃, T₄ assay employs a competitive test principle with polyclonal antibodies specially directed against T₃, T₄. Endogenous T₃, T₄ released by the action of 8 anilino-1-naphthalene sulphonic Acid (ANS), competes with the added biotinylated T₃,T₄ derivate for the binding sites on the antibodies labeled with the ruthenium complex.

Estimation of TSH:
Principle: (Sandwich principle) The TSH assay employs monoclonal antibody specifically directed against human TSH. The antibodies labeled with ruthenium complex consist of chimeric construct from human & mouse specific components. As a result, interfering effects due to HAMA (Human anti-mouse antibodies) are largely eliminated.

RESULTS:
Study Design: A case control study with 30 controls and 30 cases is undertaken to study the thyroid hormone levels and thyroid disorders with severity of chronic renal failure.

| Study variables | Cases         | Controls      | P value |
|-----------------|---------------|---------------|---------|
| Blood urea (mg/dl) | 96.23±12.24 | 28.47±8.40    | <0.001**|
| S. creatinine (mg/dl) | 5.83±0.69   | 1.09±0.17     | <0.001**|
| T₃              | 81.67±15.07  | 111.96±10.17  | <0.001**|
| T₄              | 5.80±0.50    | 8.36±0.46     | <0.001**|
| TSH             | 4.81±0.38    | 3.02±0.79     | <0.001**|

Table 1: Comparison of study parameters in cases and controls (mean ±SD)

Comparison of study parameters in cases and controls is shown in table 1. Mean of blood urea among cases is 96.23±12.24 and in controls is 28.47±8.40 p value is <0.001 which is statistically significant.

Mean of Sr. creatinine in cases is 5.83±0.69 and in controls is 1.09±0.17 (mg/dl). P value is <0.001 which is statistically significant. Mean of T₃ among all 30 cases is 81.67±15.07 and in 30 controls is 111.96±10.17 (ng/dl). It means T₃ is decreases in cases compares to controls. P value is <0.001 which is statistically significant. Mean of T₄ also decreases in cases compare to controls. P value is <0.001 which is statistically significant. Mean of TSH in cases increases compare to controls. P value is <0.001 which is statistically significant.

| Pair                     | Correlation | P value   |
|--------------------------|-------------|-----------|
| Sr. creatinine vs T₃     | -0.791      | <0.001**  |
| Sr. creatinine vs T₄     | -0.631      | <0.001**  |
| Sr. creatinine vs TSH    | 0.479       | <0.001**  |

Table 2: Pearson correlation of Serum creatinine and thyroid hormones

Pearson correlation of Serum creatinine and thyroid hormones are shown in table 2 and graphically represented in graph 1, graph 2 and graph 3.

The levels of T₃, T₄ decreases and TSH increases as severity renal failure increases (i.e. Sr. creatinine levels increases, which is a marker for severity of renal failure). Even though the graph
thyroid hormones (T₃, T₄&TSH) levels against Sr. creatinine is not linear. P value is <0.001 which is statistically significant.

Graph – 1
Correlation of Serum T3 against Serum creatinine

Graph – 2
Correlation of Serum T4 against Serum creatinine
Table 3: Incidence of hypothyroidism and hyperthyroidism

| Hypo/Hyper Thyroidism | Cases       | Controls    |
|-----------------------|-------------|-------------|
| Normal                | 27 (90.0%)  | 30 (100.0%) |
| Hypothyroidism        | 3 (10.0%)   | 0           |
| Hyperthyroidism       | 0           | 0           |
| Total                 | 30 (100.0%) | 30 (100.0%) |

Graph - 3
Correlation of Serum TSH against Serum creatinine

Graph - 4
Incidence of hypothyroidism and hyperthyroidism
Incidence of hypothyroidism and hyperthyroidism are shown in table 3 and graphically represented in graph 4.

The incidence of hypothyroidism is 10% in renal failure cases when compared to controls. P value is 0.237 which is positive correlation between CRF and hypothyroidism. There is no hyperthyroidism found in both cases and controls.

| Serum creatinine | Hypothyroidism |
|------------------|----------------|
|                  | No             | Yes            |
| <5.50 mg/dl      | 12 (44.4%)     | 0              |
| 5.50-6.0         | 13 (48.1%)     | 0              |
| >6.0             | 2 (7.4%)       | 3 (100.0%)     |
| Total            | 27 (100.0%)    | 3 (100.0%)     |

Table 4: Incidence of hypothyroidism in relation to severity of renal failure in cases

Incidence of hypothyroidism in relation to severity of renal failure in cases are shown in table 4 and graphically represented in graph 5. Incidence of hypothyroidism is significantly associated with Sr. creatinine >6.0mg/dl with p=0.002. Which is statistically significant.

DISCUSSIONS: A study of thyroid dysfunctions in chronic renal failure is done with 30 cases and 30 controls. Cases and control subjects are selected according to inclusion and exclusion criteria which are mentioned earlier. The cases and controls include different age groups. Among cases 6 patients are in age group 44-49 yrs., 9 patients are in age group 50-54 yrs., 8 patients are in age group 55-59 yrs. and 7 patients are ≥60 yrs. Control subjects are selected almost equal age distribution for comparison of study parameters. Only male subjects are selected as cases and controls for the study.
Mean of blood urea levels in cases are 96.23±12.24 mg/dl and in controls are 28.47±8.40 mg/dl. The mean of serum creatinine in cases are 5.83±0.69 mg/dl and in controls are 1.07±0.17 mg/dl. The mean of blood urea and serum creatinine is high when compared to the controls. All patients in cases are positive for frank proteinuria by urine dip stick test.

The mean of T₃ in all 30 cases is decreased when compared to controls. In this study the findings are comparable with the previous study showing decreased levels of T₃ in uremic and heamodialysis patients. This reduction in T₃ concentration has been linked to the decrease in the peripheral synthesis of T₃ from T₄. The mean of T₄ in all 30 cases is decreased when compared to the controls. The findings are comparable with previous study. The different studies mentioned various reasons to decreased levels of T₄. The decreased levels of T₄ may be secondary to the protein loss, which occur in CRF. Serum albumin and thyroid binding pre-albumin decreases. Decrease in T₄ is also attributed to the presence of circulating inhibitors, which impairs binding of T₄ to thyroxine binding globulin.

Mean TSH in cases is 4.81±0.38 μIU/ml which is high compare to controls of having 3.02±0.79 μIU/ml. Patients with low T₃, T₄ and free T₄ showed high TSH suggesting maintenance of pituitary thyroid axis. Studies conducted by G. Avasthi-et al, Joseph et. al shows increased TSH in those patients who had low T₃, T₄ & FT₄ suggesting maintenance of pituitary thyroid axis. Which is similar to this study.

In our study the levels of T₃, T₄ decreases and TSH increases as severity renal failure increases (i.e. Sr. creatinine levels increases) Even though the graph plotted thyroid hormone (T₃, T₄& TSH) levels against Sr. creatinine is not linear. The present study findings are comparable with Mehta H. J et. al Mean TT₃ & FT₄ levels reduced as the severity of renal damage increased. When the individual values plotted against their respective Sr. creatinine levels, no linear correlation was observed between those parameters.

The thyroid function studies on patients with CRF before & after hemodialysis resulted in only slight increase in TT₃ concentration without significant change in other thyroid function. Study conducted by Mehta H. J et. al thyroid function in uremic patients with conservative management & with regular dialysis they found that there is no change in thyroid profile except decrease in TSH in hemodialysates compare to normals. Restoration of renal function with renal transplant resulted in normalisation of all parameters of thyroid function with exception of blunted or absent TSH response to TRH. The latter may be a direct consequence of glucocorticoid administration.

In this study 3 patients (i.e. 10% of cases) among 30 cases have T₃, T₄ levels below normal range and TSH above the normal range. These 3 patients are hypothyroid, compared to none among control groups and all these 3 patients (i.e. 100%) belongs to serum creatinine >6mg/dl category. In this study 5 cases among 30 cases have serum creatinine of >6mg/dl. Among them 3 patients are hypothyroid (i.e. 60%) and 2 are euthyroid inspite of high sr. creatinine levels. In this study, findings are comparable with previous studies. Prevalence of hypothyroidism in patients with terminal renal failure is 5%, in comparison with that in hospitalized patients with normal renal function. CKD is associated with higher prevalence of hypothyroidism, both overt and subclinical, but not with hyperthyroidism. In fact, the prevalence of primary hypothyroidism is mainly in the subclinical form, which increases as GFR decreases.

CONCLUSION: In our study Mean of T₃, T₄ decreases TSH increases significantly in cases compare to controls. The levels of T₃, T₄ decreases and TSH increases as severity renal failure increases. The risk
of hypothyroidism in chronic renal failure is very high if serum creatinine level are above 6mg/dl. In our study 10% of patients of CRF i.e. cases are hypothyroid compare to 0% in controls and all these hypothyroid patients belongs to serum creatinine above 6mg/dl category.

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