Original Article

Prevalence Of Hypothyroidism In Chronic Kidney Disease Among Sample Of Iraqi Patients.

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Summary:

Background: Patients with chronic kidney disease have multiple alterations of thyroid hormone metabolism in the absence of concurrent thyroid disease. These may include elevated basal TSH values, which may transiently increase to greater than 10 mU/liter, blunted TSH response to TRH, diminished or absent TSH diurnal rhythm, altered TSH glycosylation, and impaired TSH and TRH clearance rates. In addition, serum total and free T3 and T4 values may be reduced, free rT3 levels are elevated while total values are normal, serum binding protein concentrations may be altered, and disease-specific inhibitors reduce serum T4 binding .

Objective:. To assess the prevalence of hypothyroidism and u/s abnormalities of thyroid gland in patients with chronic kidney disease at different levels of estimated glomerular filtration rate (eGFR) and their association with age , sex and duration of chronic renal failure .

cross sectional study.

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Patients and Method: a cross sectional study total of 50 patients who seek medical advice in Baghdad teaching hospital (29 male , 21 female) , the mean of their age was 60, with established chronic kidney disease were categorized into five groups according to the stages of chronic kidney disease . Full clinical, biochemical (includes blood urea , serum creatinine , total T3, total T4 , TSH) , thyroid ultrasonography studies were performed to all patients in this study. Risk factors such as hypertension, diabetes mellitus, smoking and family history of CKD were also recorded. Type of treatment of CKD whether conservative or renal replacement therapy (in form of peritoneal or hemodialysis) were also.

Results:- From a total of 50 patients with chronic kidney disease (CKD), eight patients had hypothyroidism (16 %) , three patients from stage 4 CKD and five patients from stage 5 CKD . Twelve patients from study sample had abnormalities in thyroid ultrasonography (24%) , one patient from stage 2 CKD , three patients from stage 3 CKD ,three patients from stage 4 CKD and five patients from stage 5 CKD . Thyroid ultrasound abnormalities includes six patients with simple goiter and six patients with multinodular goiter .From those eight patients with hypothyroidism , six patients were males (75%) and two patients were females (25%) .Regarding 12 patients with thyroid u/s abnormalities , five patients were male (41.6%) and seven patients were female (58.4%).Statistical analysis showed a significant association between drop in GFR and drop in thyroid function, from 13 patients in stage 4 CKD , three patients (23.07%) had hypothyroidism , and from 23 patients in stage 5 CKD , five patients (21.739%) had hypothyroidism .

Conclusion:- reduced glomerular filtration rate was associated with an increased prevalence of hypothyroidism, with many subclinical cases. Future studies are needed to determine the potential adverse effects of subclinical and clinical hypothyroidism in persons with chronic kidney disease.

Keywords: CKD, Hypothyroidism, Ultrasound of thyroid gland.

Introduction:

Abnormalities in thyroid function tests are frequently encountered in uremia. However, the overlap in symptomatology between the uremic syndrome and hypothyroidism requires a cautious interpretation of these tests. Nevertheless, it is ordinarily possible in the individual uremic patient to assess thyroid status accurately by physical diagnosis and thyroid function testing. Epidemiologic data suggests that predialysis patients with chronic kidney disease have an increased rate of hypothyroidism (1,2). Many cases are subclinical. The kidney normally contributes to the clearance of iodine, primarily by glomerular filtration. Thus, iodide excretion is diminished in advanced renal failure, leading sequentially to an elevated plasma inorganic iodide concentration and an initial increment in thyroidal iodide uptake. The ensuing marked increase in the intrathyroidal iodide pool results in diminished uptake of radiolabeled iodide by the thyroid in uremic patients (3). Increases in total body inorganic iodide can potentially block thyroid hormone production (the Wolff-Chaikoff effect). Such a change may explain the slightly higher frequency of goiter and hypothyroidism in patients with chronic kidney disease(4). Chronic kidney

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disease is associated with multiple disturbances in thyroid metabolism that are manifested low serum free and total T3 levels and normal rT3 and free T4 concentrations. The serum TSH concentration is normal and most patients are euthyroid(5).Free fatty acids and heparin also interfere with T4 binding to TBG. Thus, the routine use of heparin to prevent clotting in the dialysis tubing may explain the transient elevation in serum T4 levels that commonly occurs during hemodialysis(6). Low plasma free T3 levels may also be associated with decreased survival overall and the presence of the malnutrition-inflammation syndrome(7). The latter is a common chronic condition in dialysis patients associated with markedly increased cytokine levels(8).

Patients and methods:

A total number of 50 randomly selected patients with chronic kidney disease attending nephrology and dialysis unit in Baghdad teaching hospital were studied between October 2010 to March 2011 . Study population consisting of 29 male and 21 female patients with different causes of chronic kidney disease . Age range was 22 years to 98 years . Patients had different durations of chronic kidney disease ranging from 6 months to 5 years .Twenty one patients in the study were on conservative treatments and the others were on renal replacement therapy(peritoneal or hemodialysis).Inclusion criteria are :

Patients with chronic kidney disease confirmed by : 1- ultrasonography of kidneys. 2-serum creatinine >2 mg/dl. 3- clinical features of uraemia of more than 6 months duration .In the study , the patients of stages 1 & 2 CKD (2 patients in stage 1 and 5 patients in stage 2) , they had not any features of uraemia but they had strong risk factors for developing CKD (these include polycystic kidney disease , diabetes mellitus , hypertension and nephrotic syndrome). 4- GFR was measured by Cockcroft and Gault equation :-

GFR = (140 – age$^{(years)}$) × lean body weight $^{(kg)}$/ serum creatinine × 72 .

If patient female , the result multiply by 0.85 .

Lean body weight (male)=(1.10×weight in kg)-128 (weight^2/(100×height in meter)^2).

For female =(1.07×weight in kg)-148(weight^2/(100×height in meter)^2).The study deals with adult patients, patients younger than 18 years were excluded from the study. We also exclude women who were pregnant (given potential pregnancy-related changes in thyroid function) and subjects who were receiving concurrent treatment with drugs that could contribute to hypothyroidism (amiodarone, or iodine).The treatment taken by patients included iron salts, vitamins, calicum and furosamide (40-160 mg/day) when indicated; and anti-hypertensive agents as required viz. ACE inhibitors , calcium channel blockers and beta blockers . Patients underwent haemodialysis (HD) each of 3-4 hours duration; twice a week, with heparin as anticoagulant during HD. Each patient was interviewed . For ethical considerations the goals of the interview were explained to the patients and they took their own decision to accept or refuse participation in the study. History , examination and vital signs were recorded .Duration of CKD was reviewed carefully with certification of the cause by nephrologists notes .Investigations such as blood urea , serum creatinine , total T3 , total T4 , TSH , thyroid ultrasound were done . The normal reference range for TSH was 0.39 to 4.60 mIU/L, for total T4, 4.5 to 13.2 mg/dL. Hypothyroidism was defined as a TSH level >4.5 mIU/L or treatment with thyroid hormone (levothyroxine). Subclinical hypothyroidism was defined by a TSH >4.5 mIU/L and total T4 ≥4.5 mg/dL (the lower limit of the normal range)(9). All variables were presented as numbers and frequency and arranged in tables and figures . Microsoft Excel computer program was used to analyze the data .

P value was measured by computer programs (EPI16).

Results:

Table 1: The prevalence of hypothyroidism &abnormal thyroid u/s in CKD

	Number of patients	percentage
Hpothyrodism	**8**	**16%**
Abnormal thyroid u/s	**12**	**24%**

Table 2: Relation between stages of CKD& abnormal thyroid u/s

Thyroid u/s abnormalities	Stage 1-4CKD	Stage5CKD	total
Simple goitre	5	1	6
multinodular goitre	1	5	6
total	6	6	12

P value <0.05 statically significant

Table 3: The prevalence of hypothyrodism in relation to the type of treatment in CKD

Type of treatment	hypothyroidism	percentage
HD	2	25%
PD	2	25%
Conservative	4	50%

Table 4: Relation of thyroid function test to abnormal thyroid u/s in CKD

	hypothyroid	Normal thyroid function test	total
Abnormal thyroid u/s	7	5	12
Normal thyroid u/s	1	37	38
Total	8	42	50

P value <0.05 stastically significant

Table 5: Gender percentage of hypothyrodism %abnormal thyroid u/s

gender	Hypothyroidism	percentage	Abnormal thyroid u/s	percentage
male	6	75%	5	41.6%
Female	2	25%	7	58.4%

Table 6: Percentage of hypothrodism in stage 4&5 CKD

Stages of CKD	Hypothyroidism	Percentage
patients in stage 4 CKD 13	3	23.07%
patients in stage 5 CKD 23	5	21.79%

Discussion:

Among a locally representative sample of adults , we found an increased prevalence of hypothyroidism in persons with reduced estimated GFR , independent of age and gender. In addition , with progressively lower GFR , there was an increased likelihood of hypothyroidism . It also showed that Total T3 and Total T4 levels were lower than normal specially among patients with stage 4 & 5 CKD and a progressive reduction in values of Total T3 and Total T4 were noticed as the severity of renal failure increased . TSH levels were however , within normal limits. In our study , the 8 patients (16%) with hypothyroidism were from stages 4 & 5 CKD only , that is why patients from earlier stages of CKD had no hypothyroidism may be related to the small number of patients taken in the study(table 1). In this study 24 % of our patients (12 patients) had thyroid U/S abnormalities (in the form of simple & multinodular goiter) approximately in all stages of CKD patients (from stage 2-5)(table 2). While numerous contributing factors have been suggested , including altered iodine metabolism and autoimmune thyroiditis , the exact mechanisms remain unclear .Previous study done by JOAN C LO, GLENN M CHERTOW, ALAN S GO and CHI- YUAN HSU used data from the Third National Health and Nutrition Examination Survey to examine the prevalence of hypothyroidism (clinical and subclinical) at different levels of estimated glomerular filtration rate (GFR)

in 16 June 2004 ; Revised 25 August 2004 ; Accepted 21 September 2004 . On 14,623 adult participants with serum creatinine and thyroid function test results, the mean age was 48.7 years , and 52.6% were women . The prevalence of hypothyroidism increased with lower levels of GFR (in units of mL/min/1.73m2) , occurring in 5.4% of subjects with GFR ≥90 , 10.9% with GFR 60–89 , 20.4% with GFR 45–59 , 23.0% with GFR 30–44 , and 23.1% with GFR <30 ($P < 0.001$ for trend)(10) . Overall , 56% of hypothyroidism cases were considered subclinical . Compared with GFR ≥ 90 mL/min/1.73m2, reduced GFR was associated with an increased risk of hypothyroidism , after adjusting for age , gender , and race /ethnicity (11).Previous studies have suggested an increased prevalence of hypothyroidism in patients with ESRD requiring maintenance dialysis, as well as an increased prevalence of goiter(12).Several investigators have studied thyroid hormone levels in CRF and obtained variable results . Low total T3(13), normal total T3(3), low Free T3(13), normal Free T3 in patients on HD(14), low Total T4 (low T4 syndrome), 11 normal Total T4(3), 11 levels have been reported.Basal concentrations of circulating TSH have been found at different levels in different studies . Normal levels of TSH were reported from previous Indian studies(15) . Thus a multitude of defects at all levels of hypothalamic-pituitary-thyroidaloeripheral axis does seem to exist in uremia (16).In the majority of studies , including our study , Total T4 concentrations were found to be low or low normal (table 6).However , Free T4 levels which is difficult to be obtained in our study, previous studies show its levels within normal limits and this is attributed to lowering of thyroxine binding globulin concentration as well as presence of inhibitors of thyroid hormone bindings to the thyroid binding proteins(17) .Levels of Total T3 and Free T3 suffer further reductions in CKD, which is thought to be due to impairment in deiodination of T4, a principal process by which T3 is produced at peripheral levels.Several factors are responsible for obtaining controversial results of thyroid hormone levels in CKD . The important amongst them are methodological variations and varying treatment .The drugs which could have influenced the thyroid hormone levels were furesamide and heparin . Other commonly used drugs known to suppress thyroid hormones like propranolol , glucocorticoids , and sulphonylurea . Heparin (which is used in hemodialysis) is known to acutely raise both total and free thyroxine levels in the blood(11) . Furesamide inhibits T4 and T3 binding to serum proteins at high levels and by a concentration dependent process resulting in artifactually low , percent Free T4 and estimated Free T4 concentrations .Our study had several limitations . Firstly , the overall sample was small . Second , GFR was estimated using serum creatinine concentrations in the Cockcroft and Gault equation , which may be less precise at higher GFR levels , albeit less so with the use of calibrated creatinine measurements. This is a cross-sectional study , so causality cannot be established.Information on the presence or absence of hypothyroidism-related symptoms was also not available .There is substantial clinical overlap between chronic kidney disease and hypothyroidism .There are a number of symptoms that are common to both conditions including cold intolerance , puffy appearance , dry skin , lethargy , fatigability , and constipation . Furthermore , the frequency of goiter is markedly increased in end-stage renal disease (18,19) . Given that only TSH and total T4 (rather than free T4) levels were available , complete assessment of thyroid function was not possible ; however , TSH concentration is considered the most sensitive indicator of hypothyroidism among individuals in the absence of acute illness . As random misclassification due to physiologic fluctuations in TSH and GFR levels would tend to bias toward the null , our observations may underestimate the true strength of association between hypothyroidism and CKD .

Conclusion:

A Low Total T3 And Total T4 Values In Clinically Euthyroid Ckd.TheReduction In Kidney Function Was Associated With IncreasedPrevalence Of Hypothyrodism Among Adults Patients.

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