Study of Hypothyroidism in Chronic Kidney Disease Patients

KEYWORDS
chronic kidney disease, GFR=glomerular filtration rate, RBF=renal blood flow, hypothyroidism.

Dr. CHADA RAMESH
ASSISTANT PROFESSOR, DEPARTMENT OF NEPHROLOGY, GANDHI MEDICAL COLLEGE, SECUNDERABAD-500002, TELANGANA, INDIA

Dr. M. PAVAN KUMAR
ASSISTANT PROFESSOR, DEPARTMENT OF MEDICINE, KAKATIYA MEDICAL COLLEGE, WARANGAL-506002, TELANGANA, INDIA

Dr. GANGHADHAR BATTINI
SENIOR RESIDENT, DEPARTMENT OF NEPHROLOGY, GANDHI MEDICAL COLLEGE, SECUNDERABAD-500002, TELANGANA, INDIA

ABSTRACT
BACKGROUND: The importance of understanding the impact of thyroid dysfunction on renal function is highlighted by recent studies indicating subclinical and clinical hypothyroidism is common in patients with estimated GFR, <60 ml/min per 1.73 m², petitioning the question of whether hypothyroidism might be contributing to the low GFR in some of these individuals.

AIM: The aim is to study the prevalence and trend of hypothyroidism as the renal impairment increases in CKD patients.

OBJECTIVE: 1. To estimate the glomerular filtration rate in chronic kidney disease patients and correlate with their thyroid levels

STUDY DESIGN: prospective observational study

MATERIAL AND METHODS: This study included 50 patients of chronic kidney disease from stage I to stage V and their thyroid profile was done to know the prevalence of clinical and subclinical hypothyroidism in the study population.

Statistical methods: Statistical analysis was performed using the GraphPad InStat software version 3.10 for Windows. Data are expressed as mean +/- SD. The Fisher's exact test was used for comparison of categorical variables. Student's unpaired t-test was used to compare continuous variables. P-value < 0.05 is considered as significant.

RESULTS: 1. Prevalence of hypothyroidism in chronic kidney disease patients is about 19%.

2. Prevalence of hypothyroidism increases as the severity of the renal impairment increases. Its prevalence in CKD Stage IV, V patients is 18%, 31% respectively.

CONCLUSION: This study 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.

INTRODUCTION:
The interactions between kidney and thyroid functions are known for years1,2,3,4. Thyroid hormones (TH) influence kidney function both during embryonic development and in the mature functioning of the kidney, indirectly by affecting the cardiovasculary system through its influence on renal blood flow (RBF), and directly by affecting glomerular function, the tubular secretory and absorptive capacities, electrolyte pumps and kidney structure. When the thyroid is either hyper- or hypo-functioning, changes in different clinical renal parameters such as glomerular filtration rate (GFR), urine specific gravity (USG), urinary protein/creatinine ratio (UPC) and markers of tubular function can occur. Vice versa, kidney disease influences circulating thyroid hormones. Although numerous contributing factors have been hypothesized, including altered iodine metabolism, decreased peripheral sensitivity to hormones, and autoimmune thyroiditis, the exact underlying mechanisms linking advanced CKD and primary thyroid dysfunction remain unclear.

GFR AND THYROID DYSFUNCTION:
Many case reports and small case series document increased levels of serum creatinine with hypothyroidism in humans13,14,15,16. Serum creatinine levels in excess of 6 mg/dl have been attributed to hypothyroidism, with a few patients even described as having ESRD, although in most reports, creatinine levels have been in the range 1.5–2.5 mg/dl.

Elevation of levels of serum creatinine can occur within as little as 2 weeks of significant hypothyroidism. These levels typically normalize rapidly with thyroid hormone replacement after short periods of hypothyroidism15, but slower and incomplete recovery has been noted with more prolonged periods of severe hypothyroidism. Similarly, multiple human and animal studies demonstrate a decreased serum creatinine in the setting of hyperthyroidism, which is similarly reversible upon treatment16. Most of these case reports, however, rely on estimations of kidney function using creatinine-based estimating equations, so the extent to which these changes reflect changes in true GFR as opposed to alterations in creatinine metabolism or tubular secretion or to an underlying myopathy has been unclear.

Influence of hypothyroidism on healthy mature kidney function Most of the effects of hypothyroidism on 19 kidney function are the opposite of the changes caused by...
hypothyroidism, and the decreased serum concentration of thyroid hormones slows many physiologic processes. Hemodynamic and vascular changes The increase of peripheral resistance in hypothyroidism is caused by intrarenal vasoconstriction. Although the plasma concentration of catecholamines is increased, the response to vasodilators in the kidney is reduced. Sensitivity to alpha- and beta-adrenergic stimulants such as norepinephrine, phenylephrine (PHE) and ATP is decreased; sensitivity to stimulants of G-protein coupled receptors, to nonspecific stimulants of receptors in vascular smooth muscle, to endothelium dependent vasodilatation, to NO in the kidney and to isoproterenol in the aorta and mesenteric vascular bed is also decreased. Reduced sensitivity of beta-adrenergic receptors to catecholamines and stimulation of the beta-adrenergic function decreases plasma renin release and activity, which, together with the decreased concentration of plasma AII and of the angiotensinogen synthesized in the liver, and with the decreased density of the beta angiotensinogen receptors, reduces RAAS activity.

Glomerular changes The glomerular filtration rate can be reduced up to 40% in hypothyroid humans and up to 30% in hypothyroid rats. The GFR is reported to have decreased in dogs after thyroidectomy, and to have significantly decreased in dogs diagnosed with thyroid deficiency. The decreased GFR is corrected after treatment with thyroid hormone in humans with normal renal function (den Hollander et al., 2005), which is suggestive of only functional renal changes that do not cause permanent histological damage.

The decreased GFR has several causes. Firstly, hypothyroidism is associated with decreased CO and circulating volume, impaired activity of the RAAS, and decreased ANF levels, which could lead to decreased renal perfusion (den Hollander et al., 2005). Secondly, the glomerular surface area can be decreased by growth retardation in the parenchyma of the kidney. Thirdly, a filtrate overload caused by deficient sodium and water reabsorption in the proximal tubule could lead to an adaptive preglomerular vasoconstriction (Zimmerman et al., 1988). Fourthly, renal expression of the chloride channel ClC2 is decreased in hypothyroid rats, and the tubule glomerular feedback mechanism decreases GFR when an increased chloride load is sensed in the distal tubules.

Finally, hypothyroidism causes a decrease in insulin-like growth factor 1 (IGF-1). However, in response to thyroidin replacement, the IGF-1 is increased, along with the vascular endothelial growth factor (VEGF). IGF-1 is known to increase creatinine clearance in humans and VEGF increases the activity of NOS, thereby improving the relaxing capacity of the renal vasculature.

Hence, both IGF-1 and VEGF could influence RBF and GFR in hypothyroidism before and after thyroidin replacement. The increase of serum creatinine in hypothyroidism is caused by the reduced glomerular function and creatinine generation from possible myopathy and rhabdomyolysis, though not from the impaired creatinine metabolism (Karanikas et al., 2004). It is reversible after treatment with thyroid hormone supplementation.

Tubular changes The influence of short-term hypothyroidism on the tubular functions is only modest, even though the tubular transport capacity is below normal and the phosphate reabsorption rate is reduced in the proximal tubule. The influence of hypothyroidism on Na+-K+-ATPase activity depends on the duration of the hypothyroidism. With short-term hypothyroidism, in rats the Na+-K+-ATPase activity is decreased in the proximal convoluted tubule, and in rabbits it is decreased in the proximal convoluted tubule as well as in the straight tubule and in the cortical and medullary collecting tubules, though not in other nephron segments. In long-term hypothyroidism, the Na+-K+-ATPase activity 23 is decreased in all segments of the nephron in the rabbit and in the proximal convoluted and straight tubules in the rat.

Sodium transport is restored after thyroid hormone supplementation, though Na+-K+-ATPase activity is delayed for more than 7 days, possibly by an additional effect of thyroid hormones on the potassium conductive pathways in the basolateral membrane of the tubules. Urinary acidification is impaired with increased sodium and bicarbonate excretion rates. Hypothyroidism causes a decreased back flux of H+ across the epithelium and H+ permeability with subsequent inhibition of bicarbonate reabsorption. It also causes decreased NHE activity and density in the apical membrane, and disturbances in the vacuolar H+-ATPase which are partly responsible for proximal H+ secretion.

Hypothyroidism Despite the negative influences of hypothyroidism on glomerular and tubular function described earlier, a hypothyroid state has been described as beneficial in CKD. Rats with induced renal insufficiency that underwent thyroidectomy showed reduced proteinuria and slower deterioration of renal function (Conger et al., 1989). This can be caused by alteration in proximal tubular protein reabsorption, prevention of oxidative stress with lower levels of the oxidant malondialdehyde (MDA) in renal tissue of hypothyroid rats, or changes in the glomerular hemodynamics. The same factors could account for the reduced renal compensatory hypertrophy subsequent to the subtotal nephrectomy seen in methimazole treated rats. On the 33 other hand, treatment of hypothyroidism in a patient with progressive renal failure can lead to significant improvement of renal function.

The effect of CKD on thyroid function Euthyroid sick syndrome The decreased serum thyroid hormone concentrations in patients with non-thyroidal diseases like CKD are referred to as the euthyroid sick syndrome. The lower serum concentration of TT4, fT4 and T3 is associated with increased severity of non-thyroidal illness, as well as increased mortality. Differentiation between hypothyroidism and non-thyroidal illness can be performed by evaluation of thyroidal 99mTcO uptake or TSH stimulation. Comitant non-thyroidal illness can suppress serum TT4 concentration into the reference ranges, even in a cat with hyperthyroidism (Peterson and Gamble, 1990). The decrease in thyroid hormones is caused by changes in peripheral hormone metabolism, thyroid hormone binding proteins and central effects. Extra thyroidal conversion of T4 to T3 is decreased due to decreased delivery of T4 to intracellular deiodinases and the activity of these deiodinases. At the tissue level there is decreased uptake of T4 and T3, impaired activity of nuclear receptors to T3, and post-receptor actions of T3. The production of thyroid hormone binding proteins (thyroxin binding globulin, transthyretine and albumin) and their affinity for thyroid hormones is decreased, which explains the normal serum concentration of freeT4 (fT4) in non-thyroidal illness. Thyrotropin (TSH) secretion is decreased, which causes decreased thyroidal secretion of T3 and decreased availability of T4 for peripheral conversion to T3. The hypothalamic–pituitary axis is intact in patients with CKD, because TSH can elevate in
patients with CKD and primary hypothyroidism, and TSH is sup- pressed in patients with CKD and hyperthyroidism. The decrease in TSH secretion despite the low level of circulating thyroid hormone explains the euthyroid sick syndrome as a host’s defence mechanism against protein wasting, and therefore treatment with thyroid hormone supplementation remains debatable due to the controversy in human medicine.

**PATIENTS AND METHODS**
The study was done in Gandhi Hospital, Secunderabad over a period of one year from December 2014-December 2015. 50 CKD patients were enrolled.

**INCLUSION CRITERIA**
The patients detected to have CKD Stage I to V.

**EXCLUSION CRITERIA**
1. Women who are pregnant
2. Subjects who are receiving drugs that could contribute to hypothyroidism (lithium, amiodarone, or iodine)
3. Subjects receiving antithyroid drugs (methimazole or propylthiouracil)

**METHODS**
Diagnosed patients of chronic kidney disease from stage I to stage V are advised to get thyroid profile done to know the prevalence of clinical and subclinical hypothyroidism in the study population. Parameters under the Study Thyroid profile – Sr. TSH, Sr.T3, Sr.T4 Blood urea, Sr.creatinine EGFR Patients with chronic kidney disease confirmed by : 1- Ultrasonography of kidneys. 2- GFR was measured by MDRD equation :- EGFR (mL/min/1.73m2) = 186 × (serum creatinine [mg/dL]) −1.154 × (age)−0.203 × 0.742( if female) × 1.21( if African American) 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, calcium and furosamide (40-160 mg/day) when indicated; and anti-hypertensive agents as required. Each patient was interviewed. Duration of CKD was reviewed carefully. Investigations (blood urea, serum creatinine, total T3, total T4, TSH) were done. The normal reference range for TSH – 0.35 to 5.5 μ IU/ml,

**DISCUSSION**
In the present study, all the patients selected are diag- nosed to have renal impairment of varying severity. Total number of patients studied - 50. Average age of the patients studied - 43.84 ± 15.22 years, of these 33.3% are women. Among the representative sample of patients with CKD, we found an increased prevalence of hypothyroidism in persons with reduced estimated GFR, independent of age and gender.

The prevalence of subclinical hypothyroidism in patients with eGFR >90 ml/min/1.73 m² is 7%. Whereas, in patients with an eGFR <60 ml/min per 1.73 m² the prevalence of hypothyroidism is 17.9%. (P < 0.0001 for trend).

The prevalence of hypothyroidism in different stages of CKD Include - 5.4% 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 <30ml/m²/1.73m² (P < 0.001 for trend). There is increased prevalence as the GFR declines. With progressively lower estimated GFR, there was a graded increased likelihood of hypothyroidism. Accordingly, there was a sign-ificant inverse association between estimated GFR and TSH levels throughout the normal and high TSH ranges.

There is increasing prevalence of hypothyroidism as the severity of renal impairment increases in the present study. Percentage of hypothyroidism in CKD stage III, IV, stage V patients is 10%, 18%, 31% respectively in our study.

In the present study, Hypothyroidism is more common in female patients with CKD compared with males. This finding is not statistically significant (P value - 0.2317, R.R – 2.719).

In the present study, hypothyroidism is more common in diabetic patients with CKD compared with non diabetic patients with CKD. This finding is not statistically significant(P value -0.413, R.R -1.575)

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.

**CONCLUSIONS**
1. Prevalence of hypothyroidism in chronic kidney disease patients is about 19%.
2. Prevalence of hypothyroidism increases as the severity of the renal impairment increases. Its prevalence in CKD Stage IV, V patients is 18%, 31% respectively.
3. Hypothyroidism is more common in female patients with CKD compared with males.
4. Hypothyroidism is more common in diabetic patients with CKD compared with non-diabetic patients with CKD.

**LIMITATIONS**
Our study has several limitations:
1. The overall sample size is small.
2. The definition of kidney function was based on estimated GFR rather than on more precise measurement of kidney function, such as iothalamate clearance.
3. Nonthyroidal (e.g., low T3 syndrome, which is typically seen in some ill patients, including those with end-stage renal disease) and thyroidal causes of hypothyroidism were not identified.
4. Given that only TSH and total T4 (rather than free T4) levels are tested, complete assessment of thyroid function is not possible. However, TSH concentration is considered the most sensitive indicator of hypothyroidism among individuals in the absence of acute illness.
5. GFR estimated using the MDRD equation, which may be less precise at higher GFR levels.

<table>
<thead>
<tr>
<th>CHARACTER</th>
<th>HYPOTHYROIDISM</th>
<th>NORMAL</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(Mean±SD)</td>
<td>55.5 ± 13.959</td>
<td>41.61 ± 14.565</td>
<td>0.0165</td>
</tr>
<tr>
<td>Female , N (%)</td>
<td>5 (62.5%)</td>
<td>14 (33.3%)</td>
<td>0.2317</td>
</tr>
<tr>
<td>TSH( μ IU/ml )</td>
<td>36.36 ± 39.72</td>
<td>3.03 ± 1.30</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Total T4 ( μg /ml )</td>
<td>4.38 ± 0.499</td>
<td>9.74 ± 1.96</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Total T3 ( ng /ml )</td>
<td>0.51 ± 0.11</td>
<td>1.10 ± 0.249812</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>EGFp(MDRD)</td>
<td>15.34 ± 9.70</td>
<td>24.74 ± 16.76</td>
<td>0.1326</td>
</tr>
<tr>
<td>Diabetis , N</td>
<td>3</td>
<td>10</td>
<td>0.413</td>
</tr>
<tr>
<td>R.R -1.575</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table1: characteristics of CKD patients**
Diagram 1:- patients in stages of CKD.

Diagram 2:- hypothyroidism in various stages of CKD