

Assessment of Decrease in Renal Function Associated with Hypothyroidism

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Abstract

Objective: Study was aimed to see the effects of hypothyroidism on GFR as a renal function.

Materials and Methods: Total of fifty eight patients was included in the study. Out of those forty eight patients were female and twelve were male. They were divided into 2 groups. Group 1 consists of Fifty three patients who were known case of thyroid cancer in which hypothyroidism was due to discontinuation of thyroxine before the administration of radioactive iodine for Differentiated thyroid cancer. Group 2 consists of five patients were post radioactive iodine treatment (for hyperthyroidism) hypothyroid.

Inclusion Criteria: All of the patients were above eighteen years of age with TSH value > 30 μ IU/ml. Pregnant and lactating females were excluded. Blood samples for urea, creatinine, creatinine clearance and serum electrolytes were taken followed by Tc-99m-DTPA renal scan for GFR assessment (GATES' method) were carried out in all subjects twice during the study, One study during hypothyroid state (TSH > 30 μ IU/ml) and other during euthyroid state (TSH between 0.4 to 4 μ IU/ml). The results of Student's t-test showed significant difference in renal functions (Urea, creatinine, creatinine clearance, GFR values) in euthyroid state and hypothyroid state (p-value < 0.05).

Results: In case of creatinine the paired t test reveal the mean 1.014 ± 0.428 , with standard error of 0.669 within 95% confidence interval, for creatinine clearance 80.11 ± 14.12 with standard error of 1.94 within 95% confidence intervals, for urea the mean 28 ± 12.13 with standard error of 1.607 within 95% confidence intervals and for GFR for individual kidney is 38.056 ± 8.56 with standard error of 1.3717 within 95% confidence interval.

Conclusion: Hypothyroidism impairs renal function to a big level and hence must be prevented and corrected as early as possible.

Keywords: Thyroid Dysfunction; G.F.R; Cancer Thyroid; Hyperthyroidism

Introduction

Thyroid gland is a master gland, thus it regulates majority of the human body's physiological functions. Thyroid gland exerts its effect through thyroid hormones (T3 and T4) on metabolism, body growth, directly affects cardiac myocytes by regulating genes important

for myocardial contraction, protein synthesis, and the regulation of many other important hormones [1,2]. If a dysfunction occurs in the thyroid gland leading to the defect in the production of thyroid hormones it can cause various pathologies throughout the body. Thyroid hormones have pre-renal and intrinsic renal effects by which they increase the renal blood flow and therefore the Glomerular filtration rate (GFR) [1].

Thyroid hormones are required for kidney growth and development, and thyroid deficiency leads to decreased renal plasma flow and glomerular filtration rate and in impaired urinary concentration and dilution [3]. Thyroid hormones also influence membrane transport and electrolyte metabolism, and alterations in mineral metabolism in hyperthyroidism frequently cause calcium nephropathy which affects renal function adversely [4]. Some are directly affecting the kidney while the indirect actions are a combination of the cardiovascular and systemic hemodynamic effects that influence kidney function [5]. These direct and indirect effects are illustrated in figure 1.

Thyroid hormone directly influences the expression and/or activity of variety of ion channels and transporters (Table 1). Examples of the effects of these changes can be seen clinically in both hyperthyroid and hypothyroid patients [5].

Sr.no	Transporters	Hypothyroidism	Hyperthyroidism
1	Na ⁺ -K ⁺ ATPase	↓	↑
2	H ⁺ -K ⁺ ATPase	↓	↑
3	Na ⁺ -HCO ₃ ⁻ exchanger	↓	↑
4	Na ⁺ -H exchanger	↓	↑
5	Na ⁺ -Pi Ila exchanger	↓	↑
6	Na ⁺ sulphate exchanger	↓	↑
7	Na ⁺ -K ⁺ -2Cl ⁻ cotransporter	↓	↑
8	Na ⁺ -Ca ²⁺ exchanger	↓	↑
9	Cl ⁻ channel	↓	↑
10	AQP 1 and 2	↑	↓

Table 1: Renal tubular ion transporters affected by thyroid hormone.

Transporter function is decreased with hypothyroidism and increased with hyperthyroidism or hormone replacement with the exception of Aquaporin which has the other pattern. Correlation of thyroid hormone levels with CKD has been scarcely explored. Disorders in renal function are seen to coexist with specific levels of hormone [6,19]. Most of these case reports up till date published rely merely on, using creatinine as an estimation of kidney function. Karanikas and his colleagues performed 51Cr-EDTA isotopic renal scans in thyroidectomized patients with severe hypothyroidism (mean TSH 70 ± 23 µIU/ml) before and after hormone replacement. A fall in serum creatinine with hormone replacement (1.30 ± 0.44 versus 1.04 ± 0.32 mg/dl) was related to a rise in GFR by 51Cr-EDTA clearance (61 ± 18 versus 75 ± 23 ml/min) [6]. In another study of hypothyroid patients, estimated renal plasma flow, measured by 131I-hippuran clearance, increased from 542.8 ± 215.8 to 717.0 ± 140.6 ml/min per 1.73m², and GFR, measured with 52Cr-EDTA clearance, increased from 99.6 ± 32.2 to 125.7 ± 41.2 ml/min after hormone replacement [7], thus confirming that changes in levels of serum creatinine in patients with thyroid disorders do reflect actual changes in GFR. Only one case report has been published till date by Sanjay that showed in case of hypothyroidism there is decreased clearance of urea, creatinine and creatinine clearance and thus reduction in GFR and this condition was reverted by the use of levothyroxine. He used ^{99m}Tc DTPA as a renal isotope to measure GFR [8]. While in another study by Andrew Conner it is suggested that in patients of kidney diseases levels of TSH and FT4 must be taken into account for their treatment [18].

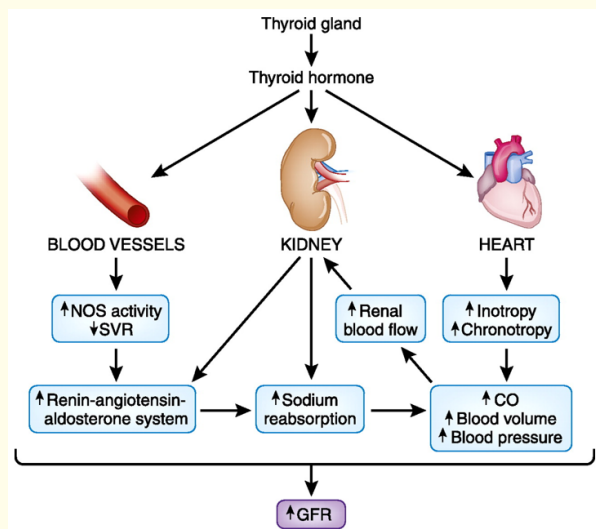


Figure 1: Multiple direct and indirect effects of thyroid hormones on *gfr*@ copy right from *jasn* from the renal manifestations of thyroid disease [20].

Aims and Objectives

To study the effect of hypothyroidism on renal function using camera based GFR assessment method.

Materials and Methods

The study was conducted at in Atomic Energy Cancer Hospital NORI. The study was approved by the ethical review committee of research training and monitoring cell RTMC of Atomic energy cancer hospital NORI. It was a prospective study. Total time duration was 6 months from January 2017 till June 2017. Informed consent was taken from the patients. Total of fifty eight patients were included in the study. Forty eight patients were female and the rest are male. Out of fifty eight patients, fifty three patients were known case of carcinoma of thyroid in whom hypothyroidism was due to discontinuation of thyroxin before the administration of radioactive iodine either for the whole body scan or for the ablation in the patients of differentiated thyroid carcinoma. The remaining five patients were those who were treated with radioactive iodine for hyperthyroidism.

Inclusion criteria

All of the patients were above eighteen years of age with TSH value > 30 Iu/ml.

Exclusion criteria

Pregnant and lactating females and those with the co morbid conditions such as hepatic or renal failure were excluded.

Protocol:

Following investigations are carried out in each patient after informed consent:

1. Baseline renal dynamic study with ^{99m}Tc-DTPA with GFR calculation- when the patient is euthyroid.
2. Renal dynamic study with ^{99m}Tc-DTPA scan with GFR calculation- when patient has raised TSH value (> 30 IU/ml).
3. Renal function tests (urea/creatinine) before both studies.
4. Serum electrolytes were done base line for all of the patients, if at base line serum electrolytes were low, then after giving T4 and performing scan serum electrolytes were repeated.
5. Creatinine clearance in ml/min was performed as a baseline study in every patient and only repeated in those cases where there was a decrease in creatinine clearance.
6. For every patient ultrasound studies were also performed as a routine base line investigation.

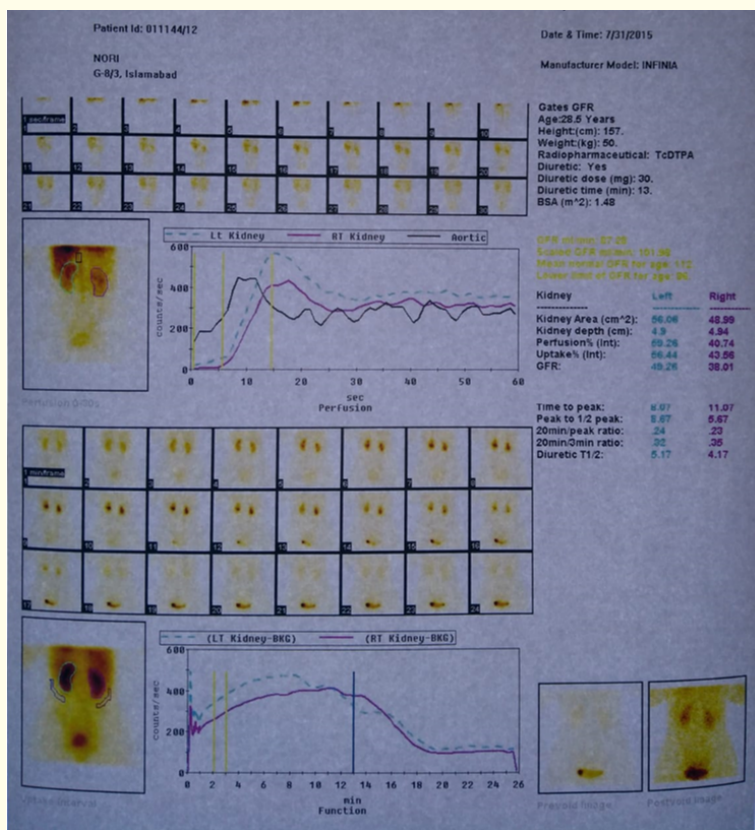


Figure 2: After withdrawal of thyroxine.

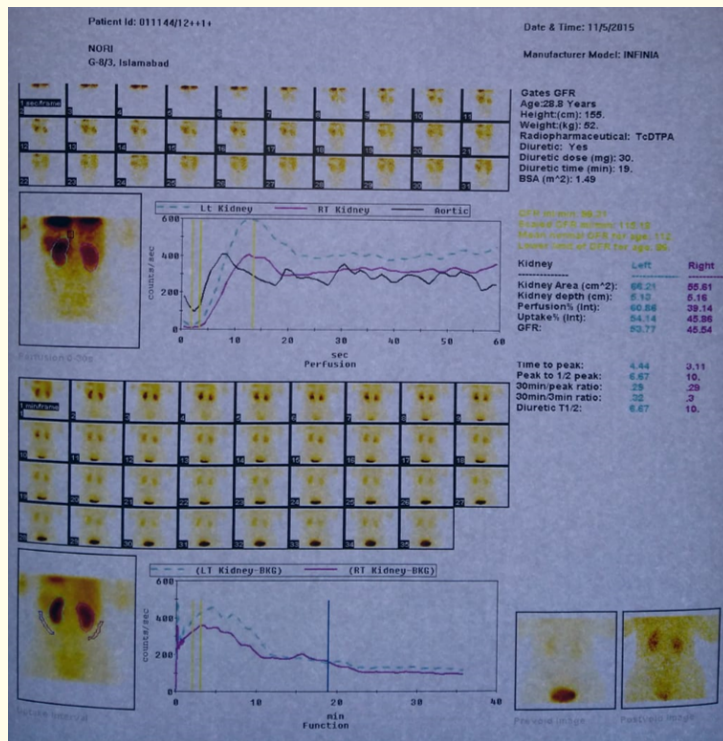


Figure 3: After starting thyroxine GFR of both kidneys in the bilateral good function.

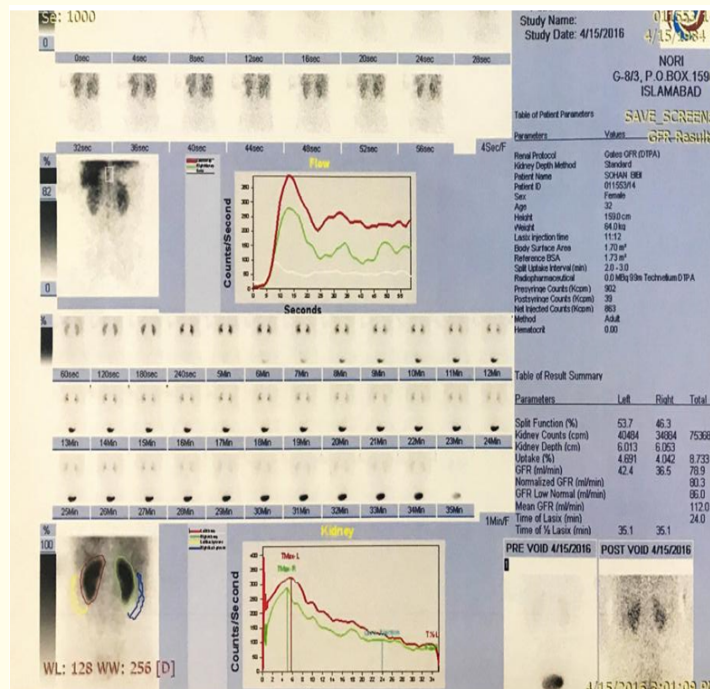


Figure 4: Patient in a state of hypothyroidism with reduction in GFR.

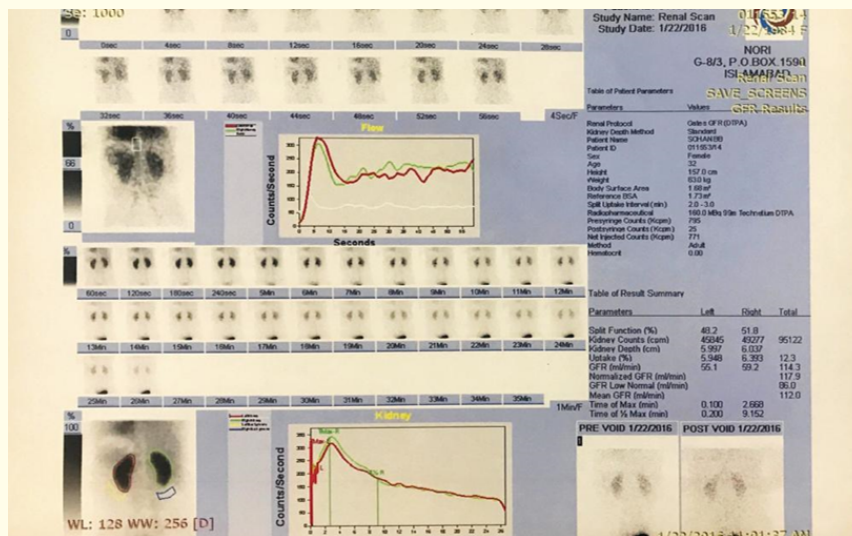


Figure 5: Renal scan performed after attaining the euthyroid status showing the normalization of GFR.

Imaging was performed on dual head 5 gamma camera within built option of SPECT. The processing and quantitative analysis was done using Xeleris model H2400PLJ and description Infinia GP3. ^{99m}Tc DTPA according to the weight of the patient was injected under the gamma camera and the dynamic study was performed in posterior mode for 25 - 30 minutes. Initially the perfusion images were taken for 2sec/frame for 1 minute to see the aorta blood flow and its relation to the renal artery flow and then the dynamic study in which 1frame/minute was taken for radiotracer uptake, corticopelvic radiotracer transit and then excretion. After the acquisition of the study region of interest were drawn on aorta, and on both kidneys. Relative renal uptake, renograms and Glomerular function rates were calculated. The same scan with same acquisition parameters were repeated after the continuation of thyroxine when the patient has attained the euthyroid status. Laboratory testing of TSH, FT4, urea, creatinine and creatinine clearance was performed on Cobas e 602 instruments, by Roche Diagnostics of, Penzberg, Germany).

The data was then statistically analyzed using Microsoft Excel 2010 and SPSS version illionos. The significance of difference in the scan results in between off Thyroxine and on thyroxine was calculated using nonparametric student T test at cut off value of 0.05 were considered significant.

Results

1	Total female pts	48
2	Total male pts	10
3	Mean age (yrs)	45.27 ± 13.9
4	Median height (cm)	155.22 ± 8.6
5	Median weight (kg)	55.72 ± 9.1

Table 2: Sr # characteristics of study population values.

The results of Student’s t-test showed significant difference in renal functions such as Urea, creatinine, creatinine clearance, GFR values in euthyroid state and hypothyroid state (p-value < 0.05). In case of creatinine the paired t test reveal the mean of 1.01 ± 0.42 , with standard error of 0.669 within 95% confidence interval, for creatinine clearance the mean of 80.11 ± 14.12 with standard error of 1.94 within 95% confidence intervals, for urea the mean of 28 ± 12.13 with standard error of 1.607 within 95% confidence intervals and for GFR for individual kidney the mean and S.D were 38.06 ± 8.56 with standard error of 1.3717 within 95% confidence interval.

Renogram analysis

Our study also depicts that in addition to the GFR values their is difference in the renal transit times, when given thyroxine there is reduction in time to peak, peak to half peak, 20 minutes to peak and also we can also see that renogram showed good uptake peak followed by satisfactory down slopes. Uptake occurs at 3 - 5 minutes with an average of 3.8 ± 0.56 in the euthyroid state and 7.89 ± 1.2 minutes in case of hypothyroidism. As renal function deteriorates, delayed transit of the radiopharmaceutical in the kidney results in an abnormal renogram curve, which can be quantitated by using this index that is 20 minute-to-peak count ratio (20 min/maximum count ratio). This is the activity measured in each kidney at 20 minutes and expressed as a percentage of peak curve activity and is often measured for whole kidney and cortical regions of interest. If there is no radiotracer hold up in the pelvicalyceal system or there only region of interest is drawn on the cortex, a normal 20-minute maximal cortical ratio was averages 0.185 ± 0.59 which is in correlation with our study in which we calculated it to be 0.19 ± 0.73 . While in case of hypothyroidism it can be seen that the uptake peak was after 8 minutes and peak was somewhat blunt and there is a plateau of hold up followed by down slope of excretion as noted in figure 2 and 4 20-minute maximal cortical ratio was averages 0.38 ± 0.54 [17]. Figure 8-10 showed almost linear correlation of TSH with urea, creatinine and G.F.R.

Blood test results

Hypothyroidism leads to retention of sodium in blood thus we can see in the blood assays that there raised TSH leads to raised serum urea, creatinine, serum sodium levels thus decreasing the creatinine levels. While these changes reverted to normal after achieving euthyroid status. Creatinine clearance was increased from 80.1 to 92, also had an impact on creatinine as its value decreased from 1 to 0.7 and to a lesser extent on urea as its value decreased from 30 to 19 and the value of Na was also restored from 136 to 139.

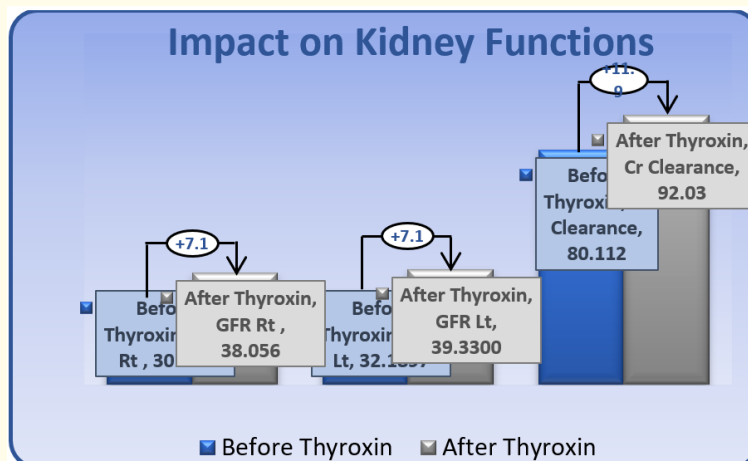


Figure 6: Showing changes in GFR and creatinine clearance in euthyroid state.

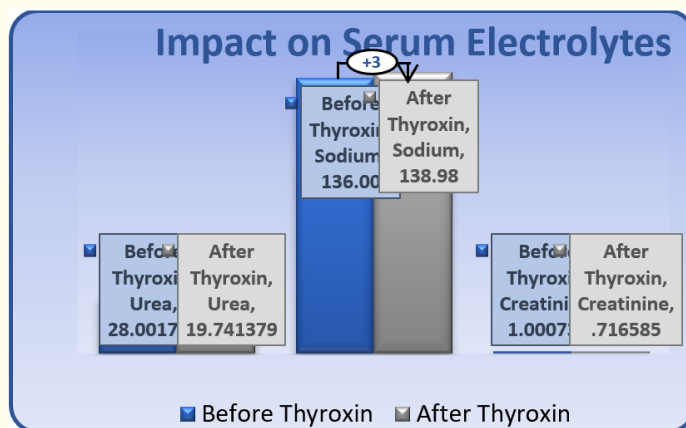


Figure 7: Showing changes in urea, creatinine and sodium after attaining the euthyroid state.

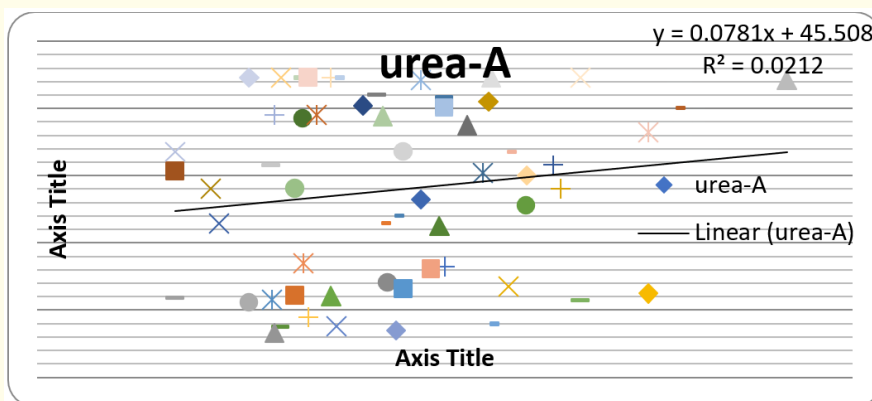


Figure 8: Showing linear fit curve for urea off thyroxine.

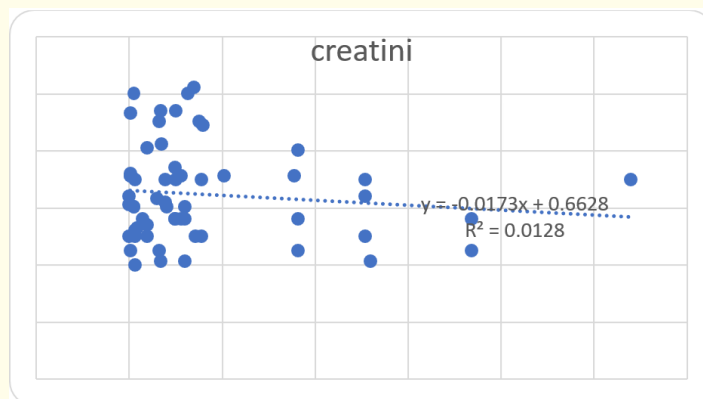


Figure 9: Showing almost linear correlation of TSH versus creatinine.

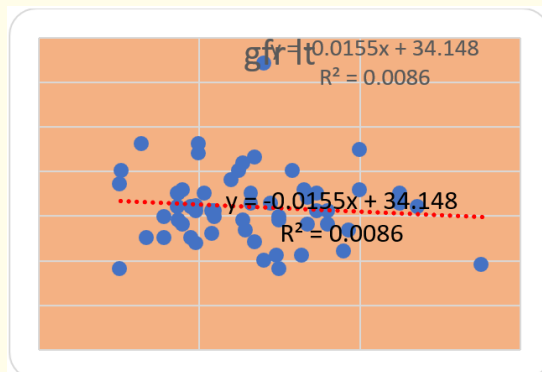


Figure 10: Showing almost linear correlation of TSH with GFR.

Discussion

Thyroid hormones mainly T4 and to a lesser extent T3 affects nearly every organ system within the body. It is produced and secreted by the thyroid under the control of the anterior pituitary gland hormone thyroid stimulating hormone (TSH), which is, in turn, regulated by hypothalamus [3].

Thyroid hormone influences the kidney size, weight, and structure both during development and in adults. Several Histologic studies document the consequences of hormone on cortical and outer medullary tubular segments, particularly involving the proximal tubule, distal convoluted tubule, and medullary thick ascending limb [4-6] it's been observed in neonatal rats, hypothyroidism is that the explanation for the decrease in kidney size and weight, tubule length and diameter, and, to a lesser extent, glomerular volume [9]. These changes invariably reverse with hormone replacement. Children with congenital hypothyroidism have reduced renal mass and a better prevalence of renal and urologic abnormalities, including dysplastic kidney, renal agenesis, ectopic kidney, hydronephrosis, posterior urethral valves, and hypospadias [10,11].

GFR and thyroid dysfunction

In a study conducted on 29 patients by S.H Kriessman he concluded that there's a uniform and reversible elevation of serum creatinine values within the hypothyroid state [12]. 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, begging the question of whether hypothyroidism could be contributing to the low GFR in a number of these individuals [12,13].

A minimum of 2 weeks is required for the elevation of levels of serum creatinine to cause significant hypothyroidism. These levels typically normalize rapidly with hormone replacement after short periods of hypothyroidism [12] 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 within the setting of hyperthyroidism, which is similarly reversible upon treatment [13].

One of the electrolyte imbalance caused by the hypothyroidism is hyponatremia and is due to impaired water excretion. Multiple studies in hypothyroid animals demonstrate reduced capacity to achieve maximal urinary dilution due to non-osmotic arginine vasopressin

release, as well as impaired urinary concentrating ability, increased urinary sodium excretion, increased fractional excretion of sodium, and impaired tolerance of sodium restriction [14,16]. Experiments have shown that these animals exhibit decreased Na⁺-H⁺ exchanger and Na⁺-Pi co transporter activity. A small study in five hypothyroid men given an acid load demonstrated a decreased ability to acidify the urine [15]. In our present study we also saw that within the absence of thyroxine there's increase within the level of serum creatinine that's restored after the attainment of euthyroid status.

Within study by Karanikas., *et al.* 99mTc MAG-3 as an isotope was used. additionally, 51Cr-EDTA clearance and serum creatinine concentrations were also determined. The serum creatinine concentrations were significantly increased in hypothyroidism as compared with the concentrations after thyroxine substitution (1.30 0.44 vs. 1.04 0.32 mg/dl, $p < 0.05$). consistent with them, the glomerular filtration rate was significantly lower in hypothyroidism than after treatment (61 18 vs. 75 23 ml/min). In contrast, they didn't find any significant change within the renographic parameters for 99mTc-MAG [3] before and after treatment (total excreted activity 20 min after administration 51 12 vs. 54 14%; T(max) left:right 4.2 1.77 : 3.91 1.06 min vs. 4.1 1.66 : 4.4 1.96 min) [6]. In our study we also found that G.F.R of kidney before the starting of thyroxine was 32.067 ml/min 8.02 of a private kidney that was restored to 38.52 ml/min 8.37 for a private kidney. They didn't find any influence of thyroid hormones on the result of 99mTc-MAG [3] renography. As 99m Tc-MAG [3] reflects the tubular function, it seems that the renal hemodynamic changes in severe hypothyroidism mainly affect the glomerular function. Generally, the glomerular filtration rate reduction seems to be reversible after hormone substitution therapy; however, care has got to be taken in patients with insufficiency.

Within the study by Villibona., *et al.* they assessed blood volumes and glomerular filtration rate (GFR) in 17 patients with overt primary hypothyroidism and in 15 of those patients when in euthyroid state after substitutive therapy and therefore the same measurements in eight patients with subclinical hypothyroidism [7]. GFR increased after thyroxine therapy ($p < 0.05$). within the subclinical group, blood volumes and renal function were almost like those found within the other group of patients when within the euthyroid state.

In another study by Yuki Tanaka they found that e GFR gradually decreased with elevated serum TSH levels and that the significant linear correlation between serum TSH levels and e GFR values [19]. In our study we also saw that there is almost linear correlation between the TSH value and GFR values.

Increased levels of TSH have a direct effect on (GFR) and have an increased risk of developing chronic kidney disease. Effective hormone replacement therapy has been shown to postponed the progression to end-stage renal disease in sub-clinically hypothyroid patients with renal insufficiency. During a study conducted by Scharier he concluded that the a rise in TSH between 12 and 24 months after kidney transplantation results in a big decrease in eGFR, which strengthens the concept of a kidney-thyroid-axis [21].

In the case report by Sanjay he also showed it scintigraphically that there is reduction in GFR in the absence of thyroxine he also used ^{99m}Tc DTPA revealed a mildly compromised cortical function with adequate clearance of right kidney and adequate cortical function with adequate clearance of left kidney, showing a remarkable recovery of renal function with THRT.

But he did not comment about the values of the transit times. The uptake value is of 3 - 5 minutes normally. While in case of euthyroid state we found to have uptake values at with an average of 3.8 ± 0.56 and 7.89 ± 1.2 minutes in case of hypothyroidism. One of the reason of abnormal renogram is the delayed transit of the radiopharmaceutical in the kidney which can be measured in the form (20 min/maximum count ratio). This is the activity measured in each kidney at 20 minutes and expressed as a percentage of peak curve activity and is often measured for whole kidney and cortical regions of interest. In the absence of pelvic calyceal retention, or if only a cortical region of interest is used, a normal 20-minute maximal cortical ratio was averages 0.185 ± 0.59 , in our case of euthyroid it was calculated to be about the 0.19 ± 0.73 . While in case of hypothyroidism it can be seen that the uptake peak was after 8 minutes and peak was somewhat blunt and there is a plateau of hold up followed by down slope of excretion as noted in figure 2 and 4 20-minute maximal cortical ratio was averages 0.38 ± 0.54 [17].

Conclusion

Hypothyroidism impairs renal function to a big level and hence must be prevented and corrected as early as possible.

Conflict of Interest

There was no conflict of interest.

Funding Support

No grant/fund was taken for this project.

Ethical Approval

Ethical approval was granted by the Research Training and Monitoring Cell (RTMC) of NORI, in JUNE 2016, RTMC 3/1-74- 2016, and informed consent was obtained from the patients.

Informed Consent

Informed consent was taken from the patients.

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