ORIGINAL ARTICLE

# Frequency of Subclinical Hypothyroidism in Chronic Kidney Disease

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**ABSTRACT**

**Objective:** To determine the frequency of Subclinical hypothyroidism in patients with chronic kidney disease.

**Study Design:** Cross sectional study.

**Place and Duration of Study:** Department of Medicine Military Hospital Rawalpindi, from 20th July 2015 to 05th January 2016.

**Materials and Methods:** In this study 250 patients were included, 50 patients for each stage of chronic kidney disease (CKD) starting from stage II to stage V and 50 peoples were from normal control group. Serum Creatinine, Thyroid Stimulating hormone (TSH) and Free T4 (thyroxine) were measured. Data was analyzed by SPSS version 17. The quantitative variables like age, free T4 and TSH was presented in mean and standard deviation for each group. Qualitative variables such as sex and presence or absence of subclinical hypothyroidism was reported as frequencies percentages for each group. Comparison of TSH level in four stages of CKD and control group was performed by using Kruskal Wallis ANOVA. Mann Whitening U test was used for Post Hoc analysis if required. Comparison of frequency of Subclinical hypothyroidism among groups was performed by using Chi-Square likelihood ratio. P value lower than 0.05 was taken statistically significant.

**Results:** Frequency of Subclinical hypothyroidism was 04 % in normal control group. Frequency of Subclinical hypothyroidism was 06%,10%,12% and 16% in stage II, III, IV and V respectively. Frequency of Subclinical hypothyroidism was increases with decrease of GFR. Frequency of Subclinical hypothyroidism was slightly increased preponderance in female as compared to male.

**Conclusion:** Frequency of subclinical hypothyroidism is higher in CKD patients than normal population, but it is statistically not significant.

**Key Words:** *Chronic Kidney Disease, Hypothyroidism, Subclinical Hypothyroidism, Subclinical Primary.*

## Introduction

Progressive destruction of renal mass with irremediable and lasting sclerosis and loss of nephrons represent chronic kidney disease (CKD). It is characterized by decrease in GFR over months to years.[1,2] Numerous hematological, metabolic and other abnormalities like endocrine are likely to occur in CKD. [3,4]

Subclinical primary hypothyroidism, over last couple of decades has drawn unprecedented and unparalleled attention of researchers, capability to diagnose slight variation in thyroid is gradually upgraded.[5] Subclinical thyroid disease is defined as "serum freeT4 and free T3levels within their respective reference ranges in the presence of abnormally high serum TSH levels[6] It may be symptomatic or asymptomatic.[6,7] In routine clinical experience subclinical hypothyroidism have been seen in all age groups, however impact of subclinical hypothyroidism on population is under discussion.[8] There are no guidelines available to diagnose and screen subclinical hypothyroidism. Exact level of TSH to make diagnoses, is also under discussion. There is difference of expert view regarding complications of disease to develop, like Overt hypothyroidism, cardiovascular abnormalities and decreased GFR.[8,9] Subclinical primary hypothyroidism occurs in 5- 15% of the general population, and frequency of subclinical hypothyroidism is higher in females, old age group and among population with high iodine intake.[10] In addition, it has been suggested that primary hypothyroidism is more common in CKD population as compared to the general population.[9] However, little is known about the clinical features and implications of subclinical hypothyroidism in patients with CKD. In subclinical hypothyroidism

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cardiac abnormalities is the main cause of increased mortality and this further increases in CKD patients with subclinical hypothyroidism.[11] Cardiac complications of subclinical hypothyroidism are left ventricular systolic dysfunction, hypertrophy, and cardiomyopathy. Evidence of cardiomyopathy was confirmed by giving thyroxin therapy to these patients. There is evidence of improvement in cardiomyopathy with thyroxin therapy.[12] Left ventricular systolic dysfunction and LV hypertrophy are powerful predictors of death.[13]Various studies to diagnose the magnitude of problem have been done throughout the world both in pre dialysis CKD and ESRD patients and the estimated statistics ranges between 15-20% in different studies in different populations. This study was designed to measure the magnitude of problem in our population.

## Materials and Methods

This cross sectional survey was performed in Department of Medicine Military Hospital Rawalpindi, from 20th July 2015 to 05th January 2016. CKD was defined as GFR below 90 ml/min/1.73 m2 body surface areas for more than 3 months. Stages of CKD is defined as a decrease in GFR as described in Table I.

**Table I: Stages of CKD**

| Stage of CKD | GFR |
|---|---|
| Stage II CKD | 60 to 89 ml/min/1.73 $m^2$ |
| Stage III CKD | 30 to 59 ml/min/1.73 $m^2$ |
| Stage IV | 15 to 29 ml/min/1.73 $m^2$ |
| Stage V | Less than 15 ml/min/1.73 $m^2$ |

Subclinical hypothyroidism described as TSH more than5 mIU/L and T4 level is in normal range. Adult patients of CKD with either sex, age between 18-80 years, with different stages of pre dialysis CKD were included in the study. Healthy adults with GFR more than 100ml/min/m2 with no history of renal and thyroid disease were included as a control group. Patients of acute renal failure and CKD on dialysis were excluded from study. A sum of 250 patients, 50 for each stage II, III, IV, V and control group were selected by non-probability purposive sampling technique. Patients visiting Medical outpatient department, who fulfilled the inclusion criteria were included in the study after taking informed consent. Venous blood samples were taken from patients for serum TSH, serum creatinine and free T4 level estimation. An enzymatic method was used to measure serum creatinine on “Dimension” clinical chemistry system which employs a change of the kinetic Jaffe reaction given by Larsen. TSH and FT4 from a single lab were used in the diagnosis of subclinical primary hypothyroidism. ELISA kits from NETRIA UK were used to assess the thyroid status of the participants. Data for reporting was analyzed by Softmax Pro software using V Max from Nova Bio labs as plate reader. All information's obtained from patient were recorded on the predesigned performa. Data was analyzed by SPSS version 17. The quantitative variables like age, free T4 and TSH was presented in mean and standard deviation for each group. Qualitative variables such as sex and presence or absence of subclinical hypothyroidism was reported as frequencies percentages for each group. Comparison of TSH level in four stages of CKD and control group was be performed by using Kruskal Wallis ANOVA. Mann Whitening U test was used for Post Hoc analysis if required. Comparison of frequency of Subclinical hypothyroidism among groups were performed by using Chi-Square likelihood ratio. P value less than 0.05 was taken statistically significant.

## Results

The study included 250 patients, 123 (49.2%) were male and 127(50.8%) were females. Group wise gender distribution is given in Table II. Mean age was 56.33+ 15.06. Data of TSH, GFR, and T4 in all groups are given in Table III with mean and slandered deviation. Frequency and percentage of subclinical hypothyroidism is given in table IV.

Comparison of TSH level to find out difference in frequency of subclinical hypothyroidism among CKD stages and normal population was performed by Kruskal Wallis. P value calculated was 0.587 and 1.000 which were not significant statistically. There was no significant change among each stage of CKD and normal population and among male and female groups P value 0.617. For post hoc analysis we performed Mann Whitney U test. Significant statistical difference was only seen in Stage IV of CKD among males and females. Rest of the stages of CKD and normal population did not have statistical difference.

## Discussion

Our study showed that, frequency of subclinical hypothyroidism is higher in persons with decreased

**Table II: Gender Distribution of Study Subjects (N= 250)**

| Gender | CKDII | CKDIII | CKDIV | CKDV | Normal Patients | Total |
|---|---|---|---|---|---|---|
| Female | 28 | 23 | 24 | 29 | 23 | 127 |
| Male | 22 | 27 | 26 | 21 | 27 | 123 |
| Total | 50 | 50 | 50 | 50 | 50 | 250 |

**Table III: Data of TSH, GFR, and T4 in all Groups (N=250)**

| Variables | N | Minimum | Maximum | Mean | Standard Deviation |
|---|---|---|---|---|---|
| Stage II GFR | 50 | 60.00 | 89.00 | 74.0200 | 8.98636 |
| Stage II TSH | 50 | 0.02 | 12.10 | 2.2820 | 2.20674 |
| Stage II Free T4 | 50 | 6.25 | 28.64 | 15.6756 | 4.49573 |
| Stage III GFR | 50 | 31.00 | 60.00 | 46.5200 | 9.52170 |
| Stage III TSH | 50 | 0.16 | 10.68 | 2.6614 | 2.48296 |
| Stage III Free T4 | 50 | 8.71 | 23.80 | 16.4882 | 3.82532 |
| Stage IVGFR | 50 | 15.10 | 29.50 | 21.1106 | 4.17143 |
| Stage IV TSH | 50 | 0.45 | 9.61 | 2.5824 | 2.03005 |
| Stage IV Free T4 | 50 | 10.23 | 23.01 | 16.2269 | 3.89478 |
| Stage V GFR | 50 | 10.05 | 15.00 | 12.6394 | 1.62898 |
| Stage V TSH | 50 | 0.14 | 14.58 | 2.9642 | 2.89625 |
| Stage V Free T4 | 50 | 8.16 | 22.41 | 15.4818 | 3.88398 |
| Normal Populatio n GFR | 50 | 96.85 | 140.30 | 1.1638E2 | 11.43310 |
| Normal Populatio n TSH | 50 | 0.12 | 10.50 | 2.5347 | 1.92880 |
| Normal Populatio n F T4 | 50 | 9.05 | 23.00 | 16.5592 | 3.92824 |

**Table IV: Frequency Percentage of Subclinical Hypothyroid in Different Stages of CKD**

| Frequency of subclinical hypothyroidism in different stages of CKD and normal population | | |
|---|---|---|
| **Stages** | **Frequency** | **Percentages** |
| **Stage II** | 3 | 6 |
| **Stage III** | 5 | 10 |
| **Stage IV** | 6 | 12 |
| **Stage V** | 8 | 16 |
| **N.P** | 2 | 4 |

estimated GFR as compared to normal population but it was not statistically significant.

Previous studies have shown rising trend of frequency of hypothyroidism in ESRD requiring maintenance hemodialysis as well as peritoneal dialysis, and an increased prevalence of goiter. Only a few of the previous studies have examined the prevalence of hypothyroidism among patients with CKD not requiring dialysis. Bando et al in a small number study population with 32 diabetic and 31 no diabetic nephropathy (urinary protein excretion greater than 0.5 g/day), 24% of study subjects had overt or subclinical hypothyroidism, with a higher prevalence among patients with diabetes.[14] While in our study a large sample size was used. In our study we have compared normal population with diseased population. We also compared stage II, III, IV and V of CKD with each other. In another study, Lo et al. showed rising trend of frequency of subclinical and clinical primary hypothyroidism in population of deranged renal function in cohort of United States adults. In this study frequency of subclinical hypothyroidism was more than 20 % and in this study GFR was less than 60 ml/min.[15] In contrast, our study included only subclinical cases, those having clinical signs and symptoms of thyroid insufficiency were excluded from study. The criterion for CKD was same as in study. Our study did not adjust for the age, gender and ethnicity/race.

In a study by Chonchol et al subclinical primary hypothyroidism was found in 09 percent of study population and 09 percent of population were found with e GFR below 60 ml/mins. Frequency of subclinical hypothyroidism was 7 percent at GFR more than 90 ml/min and trend was on rising side with further decrease in GFR to 17.9 % ($P < 0.0001$ for trend).[5] This was a large study which used data base and analyzed the results. The study did not differentiate between those having abnormal thyroid function test with symptoms or those without symptoms. While our study excluded the patients with signs or symptoms of thyroid disease.

In our study it is shown that patients with chronic kidney disease have more percentage of subclinical hypothyroidism than normal population and frequency also increases with decline in GFR. Risk of cardiovascular events and atherosclerotic diseases and mortality is higher in those patients with CKD and subclinical hypothyroidism, so we should consider routine screening of subclinical hypothyroidism in CKD. It can lead to decrease mortality and improve patient's health.

Our study have certain limitations. The study did not adjust for the age gender, race, blood glucose levels, serum cholesterol and serum triglycerides levels.

The study was based on the estimation of GFR rather than more accurate methods to measure actual GFR. The study was cross sectional and limited in its ability to establish cause and chronological relationship between CKD and subclinical hypothyroidism.

In this study increased frequency of subclinical hypothyroidism was found in patients with reduced renal function not on dialysis as compare to normal population. Frequency of subclinical hypothyroidism also increases with decrease in GFR. Further studies are required to determine causes of decrease thyroid function in chronic kidney diseases. Studies are also needed to explore the potential benefits of screening CKD patients for subclinical hypothyroidism and possible role of the treatment to avoid cardiovascular risks.

## Conclusion

Frequency of subclinical hypothyroidism is higher in CKD patients than normal population, but it is statistically not significant.

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