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A study on thyroid, lipid profile and eGFR, protein-creatinine ratio, on assessing risk factor for renal failure

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***Abstract*---**Aim: To assess the risk factors for renal dysfunction in a heterogeneous population. To determine the age and sex wise distribution of eGFR and Urinary spot Protein- Creatinine ratio (UPCR) in a heterogeneous population. To estimate the lipid profile and thyroid profile and assess their role as risk factor in renal dysfunction. Introduction: Chronic Kidney Disease (CKD), is a major health problem in India. As per the Kidney Diseases Improving Global Outcomes (KDIGO) 2012, CKD is defined[1] as abnormalities of kidney structure or function present for more than three months. Thyroid hormones were also found to influence GFR, tubular secretion and absorption.[16,17]One study has shown that normal to high levels of Thyroid Stimulating Hormone (TSH) and normal to low levels of free triiodothyronine (FT3) were associated with increased risk of CKD in euthyroid subjects.[18] It is also said that high level of serum free thyroxine (FT4) was associated with increased risk of CKD rather than TSH and FT3.There was also associated rapid decline in eGFR.[19]Many studies have found that hypothyroidism is associated with dyslipidemia and renal dysfunction.[20,21,22] Methods: An overnight 12 hours fasting venous sample was collected for analysis of fastingblood glucose, fasting lipid profile [Total cholesterol (TC), Triglycerides(TGL), High Density Lipoprotein Cholesterol (HDLc), Low Density Lipoprotein(LDLc)],thyroid function tests [Thyroid Stimulating Hormone(TSH),Free thyroxine (FT4)], Renal Function test(serum urea, serum creatinine). A spot urine sample was collected

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in a clean 100ml urine collection container for spot UPCR. Results: In this cross-sectional study among a heterogeneous adult population in a tertiary care centre, 500 adults of both sexes were evaluated for their renal status. The study showed a prevalence of Chronic Kidney Disease (stage 3a-5) (based on eGFR < 60ml/min/1.73m^2) to be 22.6% and the prevalence of CKD stage 2 was 55.2%. With increase in age there was a significant decrease in eGFR. In this study male sex had a higher prevalence of CKD (stage 3a-5), as the age increased. In this study 60.4% of the study subjects had normal proteinuria and 13% had overt proteinuria. There was significant association between proteinuria and different stages of CKD. Conclusion: The prevalence of Chronic Kidney Disease was high in the study population. Hypertension, Diabetes mellitus, Cardiovascular disease and Proteinuria were associated significantly with different stages of CKD. Hypertension was the most common risk factor among CKD patients.

***Keywords*---**Ckd Patients, Hdl, Ldl, Creatinine, Tsh, T3 T4.

Introduction

Chronic Kidney Disease (CKD), is a major health problem in India. As per the Kidney Diseases Improving Global Outcomes (KDIGO) 2012, CKD is defined[1] as abnormalities of kidney structure or function present for more than three months. Presence of either of the following markers of kidney damage (one or more) present for > 3 months is considered as criteria for CKD.

1. Decreased Glomerular Filtration Rate (GFR) < 60 ml/min/1.73 m^2.
2. Albuminuria (Albumin Excretion Rate (AER) $\geq$ 30 mg/ 24 hrs, Albumin Creatinine Ratio (ACR) $\geq$ 30 mg/g).
3. Urine Sediment abnormalities.
4. Electrolyte and other abnormalities due to tubular disorder.
5. Abnormalities detected by histology.
6. Structural abnormalities detected by imaging.
7. History of Kidney transplantation.

As per the Screening and Early Evaluation of Kidney Disease (SEEK) India, study the prevalence of CKD in India is 17.2%(Stage1-5).[2] The prevalence of CKD globally remain up to 13.4%.[3]As per KDIGO 2012, CKD stages are determined according to estimated Glomerular Filtration Rate (eGFR) categories as G1-G5 and Albuminuria Categories as A1-A3, stressing the importance of albuminuria in predicting the prognosis of CKD.[1]

An upsurge in CKD has been attributed to the following risk factors age, sex, race, hypertension, diabetes mellitus, obesity, smoking, cardiovascular disease, exposure to nephrotoxic drugs, agrochemicals, herbal medication and food additives.[4,5] Serum elevation of excretory products like metabolites of purines, amino acid catabolism (urea and uric acid) has been attributed to decreased GFR.[6,7,8]

There is growing evidence that abnormalities in lipid metabolism may also contribute to progression of renal dysfunction.[9] High level of Triglycerides (TGL) and low High Density Cholesterol (HDLc) are identified as risk factors of renal dysfunction.[10,11] The ratio of TGL/HDLc and renal dysfunction is under study and a study among adult Koreans has stated that elevated TG/HDLc ratio is associated with renal dysfunction.[12] Injury induced by cellular TGL accumulation can cause disruption and damage to the cellular homeostasis. TGL accumulation caused renal tubular damage in both, in vivo and in vitro models.[13] HDLc promote TGL clearance from circulation and prevents lipid deposition in the arterial walls which may slow the progression of CKD.[14,15]

Thyroid hormones were also found to influence GFR, tubular secretion and absorption.[16,17]One study has shown that normal to high levels of Thyroid Stimulating Hormone (TSH) and normal to low levels of free triiodothyronine (FT3) were associated with increased risk of CKD in euthyroid subjects.[18] It is also said that high level of serum free thyroxine (FT4) was associated with increased risk of CKD rather than TSH and FT3.There was also associated rapid decline in eGFR.[19]Many studies have found that hypothyroidism is associated with dyslipidemia and renal dysfunction.[20,21,22] The association of thyroid dysfunction and dyslipidemia may play an important role in pathogenesis of renal dysfunction. Heat stress and dehydration are considered as risk factors for CKD. The pathophysiology is due to dehydration, decreased renal blood flow and increased level of uric acid.[23]

Agrochemicals like 2,4 D and paraquat dichlorate, non-steroidal anti-inflammatory drugs(NSAID), heavy metal exposure are associated with acute kidney injury.[23,24,25] Studies suggest that in obesity, adipose tissue may contribute to renal damage by oxidative stress, abnormal plasma lipid, coagulation abnormalities, endothelial dysfunction, inflammation and insulin resistance.[26,27] Smoking is associated with CKD, the possible mechanism includes increased blood pressure and heart rate, cell proliferation, fibronectin, arteriosclerosis of renal artery and arterioles, increased production of growth factors like angiotensin II, endothelin-I, transforming Growth Factor-1, oxidative stress, tubular toxicity, increased aggregation of platelet and vasopressin mediated antidiuresis.[28,29]

There is not much of study in India to assess the risk factors and early detection of renal dysfunction in a heterogeneous group of population. Community based screening programs for early detection of renal dysfunction will prevent progression to CKD and decreases morbidity and mortality. Identification of novel risk factors can help in early detection of renal dysfunction.

Aim of The Study

To assess the risk factors for renal dysfunction in a heterogeneous population.

Objectives of The Study

1. To determine the age and sex wise distribution of eGFR and Urinary spot Protein- Creatinine ratio (UPCR) in a heterogeneous population.

2. To find out prevalence of various CKD stages based on eGFR.

3. To estimate the lipid profile and thyroid profile and assess their role as risk factor in renal dysfunction.

4. To find out the association between lipid profile and thyroid profile and different stages of CKD.

5. To find out the association between the risk factors like Obesity, Diabetes mellitus, Hypertension and Cardiovascular disease and different stages of CKD.

Materials and Methods

This was a Cross sectional Observational study, conducted with a total of 500 subjects who attended the medicine and allied out-patient department at Jagannath Gupta Institute of Medical Science & Hospital, Kolkata. Ethical clearance for the study was obtained from the Institutional Ethical Committee (IEC). All study subjects were explained about the study and informed written consent was obtained and the confidentiality of their results were maintained. I**nclusion criteria:** All adults of age 20 years and above, of both sex were included in the study. Exclusion criteria**:** Patients with Acute Kidney Injury (AKI) were excluded on the basis of oliguria and rapid increase in creatinine from previous recent records. Routine clinical examination of various systems was carried out. Blood Pressure (BP), Anthropometric measurements:

Biochemical Investigation (Estimated Parameters):

Sample Collection:

An overnight 12 hours fasting venous sample was collected for analysis of fastingblood glucose, fasting lipid profile [Total cholesterol(TC), Triglycerides(TGL), High Density Lipoprotein Cholesterol(HDLc), Low Density Lipoprotein(LDLc)],thyroid function tests [Thyroid Stimulating Hormone(TSH),Free thyroxine (FT4)], Renal Function test(serum urea, serum creatinine).

A spot urine sample was collected in a clean 100ml urine collection container for spot UPCR. The samples were processed within 30 minutes to1 hour of collection. Thyroid Hormone assay was done by Electro Chemiluminescence Immunoassay (ECLIA) using Roche, cobas e411 analyzer. All other tests were performed using auto analyser, Mindray BS 420.

Thyroid Function:

Euthyroid state was diagnosed with TSH – 0.4 – 4.2□IU/L and FT4 level 0.8- 2 ng/dl. Overt hypothyroidism was diagnosed with TSH □ 5□IU/L and Free T4 level < 0.8 ng/dl; Subclinical hypothyroidism was diagnosed when TSH □ 5□IU/L and with normal Free T4 levels. Hyperthyroidism was diagnosed when TSH□ 0.25□IU/L and Free T4>2 ng/dl. Subclinical Hyperthyroidism was considered when TSH□ 0.25□IU/L and Free T4 within normal range. Patients who were on treatment with Thyroxine supplementation were considered as hypothyroid.

Renal Function:

Serum Urea and Serum Creatinine were measured. Estimated Glomerular Filtration Rate (eGFR) :

Using serum creatinine Estimated Glomerular Filtration Rate (eGFR) was calculated using Chronic Kidney Diseases- Epidemiology Collaboration group (CKD-EPI) formula[49].

The CKD-EPI equation, expressed as a single equation

$$\mathbf{GFR = 141 * min\,(Scr/K,1)^{\infty} * max(Scr/K,1)^{-1.209} * 0.993^{Age} * 1.018[if\ female] * 1.159[if\ black]}$$

Scr is serum creatinine (mg/dl), K is 0.7 for female and 0.9 for males,∞ is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/K or 1, and max indicates the maximum of Scr/K or 1

Staging of CKD was done as per GFR category based on KDIGO 2012[39]

G1 - eGFR □ 90ml/min/1.73 m^2 – Normal or High

G2 - eGFR 60-89ml/min/1.73 m^2 – Mildly decreased

$G3_a$ - eGFR 45-59ml/min/1.73 m^2 – Mildly to moderately decreased

$G3_b$ - eGFR 30-44ml/min/1.73 m^2 – Moderately to severely decreased

G4 - eGFR 15-29ml/min/1.73 m^2 – Severely decreased

G5- eGFR <15ml/min/1.73 m^2 - Kidney failure

CKD was defined as eGFR <60ml/min/1.73 m^2

Urine Spot Protein- Creatinine Ratio (UPCR) Categorisation[35]

1. Normal, P1 - UPCR < 0.15

2. Moderate proteinuria, P2 - UPCR > 0.15-0.5

3. Overt Proteinuria, P3 - UPCR > 0.5

Cardiovascular disease was considered present or absent based on the diagnosis made by Physician or Cardiologist.

Methodology

ESTIMATION OF PLASMA GLUCOSE
Method: Glucose Oxidase Peroxidase method (GOD-POD) (End point)

ESTIMATION OF SERUM UREA
Method: Urease –Glutamate Dehydrogenase ("Urease-GLDH")

ESTIMATION OF SERUM CREATININE
Method: Modified Jaffe"s kinetic method

LIPID PROFILE

ESTIMATION OF SERUM TOTAL CHOLESTEROL (TC)
Method: "CHOD-POD"–Cholesterol Oxidase Peroxidase.

ESTIMATION OF SERUM TRIGLYCERIDES (TGL)
Method: Colorimetric Enzymatic test using Glycerol-3- phosphate oxidase (GPO)

ESTIMATION OF SERUMLOW DENSITY LIPOPROTEIN CHOLESTEROL
Method: Direct enzymatic method

ESTIMATION OF SERUM HIGH DENSITY LIPOPROTEI CHOLESTEROL (HDLc)

Method: Direct enzymatic method

SPOT URINE PROTEIN ESTIMATION
Method: Photometric test using pyrogallol red.

ESTIMATION OF THYROID STIMULATING HORMONE (TSH)
Method: Electro Chemiluminescence Immunoassay (ECLIA)

ESTIMATION OF FREE THYROXINE (FT4)
Method: **Electro Chemiluminescence Immunoassay (ECLIA)**

STATISTICAL ANALYSIS

Data was entered in Microsoft Office Excel and data was analyzed by using Statistical Package for Social Sciences (SPSS) software, version 21.0.

Prevalence of CKD and other risk factors were expressed as percentage. Continuous variables like Body Mass Index (BMI), Blood Pressure (B.P), Blood glucose, estimated Glomerular Filtration Rate(eGFR), Serum Lipid Profile, free Triiodothyronine(FT3), free Thyroxine(FT4) which had normal distribution were presented as mean along with the standard deviation (SD). For continuous variables which had non normal distribution like Thyroid stimulating hormone(TSH), Serum Urea, Serum Creatinine and Urinary Protein Creatinine Ratio(UPCR) median and Inter Quartile Range(IQR) were used. Categorical variables such as gender were presented as percentage. Student „t" test was used to analyze the difference in the mean between two groups. Chi square test was used to analyze the presence of association between the outcome variable (Stage1-2 / Stage 3a-5, CKD) and other independent variables.

Results

A total of 500 individuals were included in the study. Of the study population there were 211(42.2%) females and 289(57.8%) males. The mean age of the study population was 48.31±12.76 years. There were 83(16.6%) participants who were farmers by occupation. Among the 500 study population 22(4.4%) gave a history of exposure to agrochemicals, 11(2.2%) had renal calculi, 68(13.6%) gave a history of smoking and 104(20.8%) were alcoholics.

The mean eGFR of the study population was 74.3± 23.88 ml/min/1.73 m^2.The study population was categorised based on their CKD stages, as CKD stage (1 and 2) whose eGFR was above 60 ml/min/1.73 m^2 and CKD (stages 3a, 3b, 4 and 5), whose eGFR was less than 60 ml/min/1.73 m^2.

Further results are presented under the following headings,

A) Age and gender wise distribution of eGFR among study population.

B) Prevalence of various UPCR stages among the study population and their association with different stages of CKD.

C) Prevalence of CKD stages based on eGFR.

D) Association of thyroid function and lipid profile with different stages of CKD.

E) Association of risk factors like BMI, DM, HT and CVD with different stages of CKD.

A) Age and gender wise distribution of eGFR among study population Table 3: Age and gender wise distribution of mean eGFR

Age	Male n (%)	Female n(%)	Number of patients n(%)	eGFR (Mean±SD) ml/min/1.73m²
20-29 years	21(48.8)	22(51.2)	43(8.6)	94.76±21.01
30-39 years	46(57.5)	34(42.5)	80(16)	87.40±19.13
40-49 years	67(53.2)	59(46.8)	126(25.2)	78.78±21.88
50-59 years	89(61.8)	55(38.2)	144(28.8)	68.24±22.45

60-69years	49(60.5)	32(39.5)	81(16.2)	60.88±20.42
>70 years	17(65.4)	9(34.6)	26(5.2)	53.73±16.25
Total	289(57.8)	211(42.2)	500(100)	74.30±23.88

Table 3, shows the distribution of mean eGFR of the study group by age and gender.

Among the study population there were 211 (42.2%) females and 289 (57.8%) males. The average eGFR among the age group of 20-29 years(n=43 patients) was 94.76 ± 21.01,which was normal. There was decreasing trend in eGFR as age increases. Among the individuals aged >70 years, the eGFR was 53.73±16.25 ml/min/1.73m^2 which was lowest among the study population. The mean eGFR of the males was 73.03±24.76 ml/min/1.73 m^2. The mean eGFR of females was 76.03±22.54 ml/min/1.73 m^2.

Table 4, shows the baseline characteristics ofthe study population. Mean values of age, WC, SBP, TGL, LDLc, HDLc, FT4, Sr.Urea, Sr.Creatinine and UPCR, significantly differed between the different stages of CKD. The mean values of other parameters BMI, DBP, FBS, TC, TSH did not show any statistical significance between the different stages of CKD.

Table 4: Baseline Characteristics of the study population

Variables	**CKD stage 1-2 Mean±SD/Median(IQR)**	**CKD stage 3a-5 Mean±SD/Median(IQR)**	**pvalue**
Age(in years)	45.6±12.1	57.6±10.46	0.038*
BMI(kg/ m^2)	25.69±4.88	25.71±4.87	0.96
WC(cm)	93.23±11.19	93.99±12.72	0.02*
SBP(mmof Hg)	120.88±16.87	129.29±21.58	0.001*
DBP(mm of Hg)	78.24±10.32	80.21±12.32	0.088
FBS(mg/dl)	123.24±65.88	127.67±60.31	0.589
TGL(mg/dl)	125.75±71.30	149.17±79.23	0.003*
TC(mg/dl)	168.4±47.36	159.17±45.00	0.066
LDLc(mg/dl)	101.23±30.86	94.70±29.64	0.046*
HDLc(mg/dl)	39.71±9.48	37±11.01	0.010*
FT4(ng/dl)	1.28±0.50	1.31±0.74	0.046*
TSH(µIU/L)	2.54(1.9)	2.62(2.49)	0.268
Urea(mg/dl)	21.00(6)	33.00(20)	0.000*
Creatinine(mg/dl)	0.98(0.3)	1.5(0.84)	0.000*
UPCR	0.2(1.1)	0.12(0.14)	0.000*

*pvalue < 0.05 is statistically significant

B) Prevalence of various UPCR stages among the study population and their association with different stages of CKD.

B- 1) Table 5: Prevalence of UPCR stages among study population

Spot Urine PCR	Number of patient(n)	Percentage (%)
P1 (< 0.15)	302	60.4
P2 (0.15-0.5)	133	26.6
P3 (> 0.5)	65	13
Total	500	100

As seen in table 5, among the 500 study population 302 (60.4%) had a spot urine PCR of < 0.15 which was normal(P1), 133 (26.6%) study participants had a UPCR between 0.15 and 0.5 which was moderate proteinuria(P2), and 65 (13%) had UPCR more than 0.5 which was overt proteinuria(P3).

Table 6, shows the association between spot UPCR and different stages of CKD. In the CKD (stage1-2) 86.1% had normal protein excretion, 75.2% had moderate proteinuria and 41.5% had overt proteinuria. There were 13.9%, 24.8% and 58.5% of patients who had CKD(stage 3a-5) in spot UPCR category of less than 0.15, 0.15 to 0.5 and more than 0.5 respectively. As the proteinuria increased quantitatively the proportion of patients who had CKD (stage 3a-5) also increased, which was statistically significant (pvalue=0.000). There is significant association between proteinuria and different stages of CKD.

B-2) Table6: Association of UPCR with different stages of CKD

UPCR Category	CKD stage 1- 2 N (%)	CKD stage3a-5 n (%)	Chi-square value	P value
P1(< 0.15)	260(86.1)	42(13.9)	61.20	**0.000***
P2(0.15-0.5)	100(75.2)	33(24.8)		
P3(>0.5)	27(41.5)	38(58.5)		
Total	387(77.4)	113(22.6)		

*pvalue < 0.05 is statistically significant

C) Prevalence of CKD stages based on eGFR

Table 7: Prevalence of various stages of CKD based on eGFR

CKD Stages-G (eGFR ml/min/1.73m²)	**Number of Patients (n)**	**Percentage (%)**
G1 (≥90)	111	22.2
G2 (60-89)	276	55.2
G3a (45-59)	66	13.2
G3b (30-44)	19	3.8
G4 (15-29)	21	4.2
G5 (<15)	7	1.4

Table7; shows the prevalence of various stages of CKD among the study population, 22.2% (n= 111) of the study participants were in stage1(G1), 55.2% (n=276) were in stage 2 (G2), 13.2% (n=66) were in stage3a(G3a), 3.8% (n=19) were in Stage 3b(G3b), 4.2% were in stage4(G4)category and 1.4% (n=7) had stage 5(G5) or End stage renal disease(ESRD). The prevalence of CKD (eGFR of < 60ml/min/1.73 m², i.e. Stage 3a -5) among the study group was 22.6% (n=113). There were 387(77.4%) study participants in CKD (stage 1-2).

D) Association of thyroid function and lipid profile with different stages of CKD.

D-1) Prevalence of Thyroid Status:

Among the study population 406(81.2%) were euthyroid and 94(18.8%) had thyroid dysfunction. Among the 94 thyroid dysfunction patients, 51 had subclinical hypothyroidism, 38 had overt hypothyroidism, 3 had subclinical hyperthyroidism and 2 had overt hyperthyroidism.

Table 8: Prevalence of Thyroid status among the different stages of CKD

Thyroid status	**CKD stage 1-2 n(%)**	**CKD stage 3a-5 n(%)**
Euthyroidism	318(82.2)	88(77.9)
Subclinical hypothyroidism	39(10.1)	12(10.6)
Overt hypothyroidism	28(6.5)	13(11.5)
Subclinicalhyperthyroidism	3(0.77)	Nil
Overthyperthyroidism	2(0.51)	Nil
Total	387(100)	113(100)

Table 8, shows the prevalence of thyroid status among different stages of CKD. Among CKD (stage 1-2) patients 318(82.2%) were euthyroid and in the CKD (stage 3a-5) patients 88(77.9%) were euthyroid. Among the CKD (stage1-2) participants 39(10.1%) had subclinical hypothyroidism and among CKD (stage 3a-5) patients 12(10.6%) had subclinical hypothyroidism. Among the CKD (stage 1-2) study individuals 25(6.5%) had overt hypothyroidism, in the CKD(stage3a-5)patients,13(11.5%) had overt hypothyroidism. Among the CKD (stage1-2) 3 patients had subclinical hyperthyroidism and overt hyperthyroidism was found among 2 patients and none of the CKD (stage 3a-5) patients had hyperthyroidism.

D-2) Table 9: Association between Thyroid status and different stages of CKD

Thyroid Status	**Total n**	**CKD stage 1-2 n(%)**	**CKD stage 3a-5 n(%)**	**Chi-Square value**	**pvalue**
Euthyroidism	406	318(78.3)	88(21.7)	4.612	0.202
Subclinical Hypothyroidism	51	39(76.5%)	12(23.5)		
Hypothyroidism	38	25(65.8)	13(34.2)		
Hyperthyroidism	5	5(100)	0		
Total	500	387(77.4)	113(22.6)		

Table 9, shows the association between thyroid status and different stages of CKD. Among the 51, subclinical thyroid patients 39(76.5%) had CKD (stage1-2) and 12(23.5%) of them had CKD (stage3a-5). Among the 38 hypothyroid patients, 25(65.8%) had CKD (stage 1-2) and 13(34.2%) patients had CKD (stage 3a-5). There were only 5 patients with hyperthyroidism and they had CKD (stage 1-2). There was no significant association between thyroid dysfunction and different stages of CKD (p value 0.202)

D-3) Prevalence of Dyslipidemia:

Among the study population 98(19.6%) had hypercholesterolemia, 121(24.2%) had hypertriglyceridemia, 272(54.4%) had low HDLc and 69(13.8%) had high level of LDLc.

Table 10: Prevalence of dyslipidemia among different stages of CKD

Lipid profile	**CKD Stage 1-2**			**CKD stage3a-5**		
	Normal n(%)	**Abnormal n(%)**	**Total n(%)**	**Normal n(%)**	**Abnormal n(%)**	**Total n(%)**
TC	309(79.8)	**78(20.2)**	387(100)	93(82.3)	**20(17.7)**	113(100

						)
TGL	305(78.8)	**32(21.2)**	387(100)	74(65.5)	**39(34.5)**	113(100)
HDLc	190(49.1)	**197(50.9)**	387(100)	38(33.6)	**75(66.4)**	113(100)
LDLc	329(85)	**58(15)**	387(100)	102(90.3)	**11(9.7)**	113(100)

Table 10, shows the prevalence of dyslipidemia among the different stages of CKD. Among the CKD (stage 1-2) individuals 78(20.2%) had hypercholesterolemia and among the CKD (stage 3a-5) patients 20 (17.7%) had hypercholesterolemia.

Among the CKD (stage1-2) subjects 32(21.2%) had hypertriglyceridemia and among the CKD (stage 3a-5) patients, 39(34.5%) had hypertriglyceridemia.

Among the CKD (stage1-2) persons 197(50.9%) had low HDLc and among the CKD (stage3a-5) patients 75(66.4%) had low HDLc.

Among the CKD (stage1-2) subjects 58(15%) had high LDLc and in the CKD (stage3a-5) patients 11(9.7%) had a raised LDLc.

D-4) Table 11: Association between Dyslipidemia and different stages of CKD

Parameter	Status	CKD stage 1-2 n(%)	CKD Stage 3a-5 n(%)	Total n (%)	Gross Total n(%)	Chi-square value	pvalue
TC	High	78(79.6)	20(20.4)	98(19.6)	500(100)	0.335	0.563
	Normal	309(76.9)	93(23.1)	402(80.4)			
TGL	High	82(67.8)	39(32.3)	121(24.2)	500(100)	8.465	**0.004***
	Normal	305(80.5)	74(19.5)	379(75.8)			
HDLc	Low	197(72.4)	75(27.6)	272(54.4)	500(100)	8.435	**0.004***
	Normal	190(83.3)	38(16.7)	228(45.6)			
LDLc	High	58(84.1)	11(15.9)	69(13.8)	500(100)	2.029	0.154
	Normal	329(76.3)	102(23.7)	431(86.2)			

* p value < 0.05 is considered significant

Table 11, shows the association between Lipid profile and different stages of CKD. Among the 98(19.6%) study subjects with raised total cholesterol levels, 78 (79.6%) had CKD (stage1-2) and 20 (20.4%) patients had CKD (stage3a-5). Among the 402(80.4%) participants with normal total cholesterol levels 76.9% had CKD (stage1-2) and 23.1% had CKD(stage3a-5). There was no significant association between total cholesterol and different stages of CKD (p value =0.563).

The Triglyceride level was raised in 121(24.2%) of the study subjects, among them 82(67.8%) had CKD (stage1-2) and 39(32.3%) patients had CKD (stage3a-5). There were 379(75.8%) subjects with normal triglyceridemia, among them 80.5% had CKD (stage 1-2) and 19.5% had CKD (stage3a-5). There was significant association between hypertriglyceridemia and different stages of CKD (p value= 0.004).

Among the 272(54.4%) individuals who had low HDLc level, 197 (72.4%) had CKD (stage 1-2) and 75(27.6%) of the patients had CKD (stage3a-5).Among the 228(45.6%)participants with normal HDLc level, 83.3% had CKD (stage1-2) and 16.7% had CKD (stage3a-5). There was significant association between low HDLc and different stages of CKD (p value 0.004).

There were 69(13.8%) patients with raised LDLc level, among them 58(84.1%) had CKD (stage 1-2 and 11(15.9%) patients had CKD(stage3a-5).Among the 431(86.2%) of patients with normal LDLc level 76.3% had CKD(stage1-2) and23.7% had CKD(stage3a-5). There was no significant association between high LDLc and different stages of CKD(p value 0.154).

E) Association of risk factors like BMI, DM, HT and CVD and different stages of CKD

E-1) Prevalence of different categories of BMI:

Among the study population 190(38%) had normal BMI, 26(5.2%) were underweight, 206(41.2%) were overweight, 78(15.6%) were obese.

Table 12: Prevalence of BMI category among different stages of CKD

BMI Category	CKDstage1-2 n(%)	CKDstage3a-5 n(%)
Normal	147(38)	43(38.1)
Under weight	19(4.9)	7(6.2)
Over weight	160(41.3)	46(40.7)
Obese	61(15.6)	17(15)
Total	387(100)	113(100)

Table 12, shows the prevalence of various BMI categories among different stages of CKD. In the CKD (stage 1-2) subjects 38% had normal BMI, 4.9% were underweight, 41.3% were overweight and 15.6% were obese and in the CKD (stage 3a-5) patients 38.1% had normal BMI, 6.2% were underweight, 40.7% were over weight.15% were obese.

E-2) Table 13: Association between BMI and different stages of CKD

BMI	CKDstage1-2 n(%)	CKDstage3a-5 n(%)	Chi-square value	pvalue
Normal	147(77.4)	43(22.6)	0.315	0.95
Underweight	19(73.1)	7(26.9)		
Overweight	160(77.8)	46(22.2)		
Obese	61(78.2)	17(21.8)		
Total	387(77.4)	113(22.6)		

Table 13, shows the association between BMI and different stages of CKD. Among the participants with normal BMI, 77.4% had CKD (stage1-2), 22.6% had CKD (stage 3a-5);77.8% of overweight category had CKD(stage1-2), 22.2% of overweight category of study group had CKD(stage 3a-5). Among the obese, 78.2% had CKD (stage 1-2), 21.8% had CKD (stage 3a-5). There was no significant association between BMI and different stages of CKD (p value 0.95).

E-3) Prevalence of DM, HT and CVD:

Among the study population 179(35.8%) had DM, 217(43.4%) had HT and 29(5.8%) had CVD.

Table14:P revalence of risk factors, Diabetes mellitus, Hypertension and CVD in different stages of CKD

Risk factors	CKD stage 1-2 n(%)			CKD stage3a-5		
	Present	**Absent**	**Total**	**Present**	**Absent**	**Total**
DM	**116(30)**	271(70)	387(100)	**63(55.8)**	50(44.2)	113(100)
HT	**148(38.2)**	239(61.8)	387(100)	**69(61.1)**	44(38.9)	113(100)
CVD	**15(3.9)**	372(96.1)	387(100)	**14(12.4)**	99(87.6)	113(100)

Table 14, shows the prevalence of risk factors like DM, HT and CVD. Among the individuals in CKD (stage 1-2), 30% had DM and among the CKD (stage 3a-5) patients, 55.8% had DM. Among CKD(stage1-2) individuals, 38.2% were hypertensives and among the CKD (stage 3a-5) patients 61.1% were hypertensives. Among the subjects with CKD (stage 1-2) 3.9 % had CVD and in the patients with CKD (stage 3a-5) 12.4% had CVD.

E-4) Table15: Association between Diabetes and different stages of CKD

Diabetes	CKD stage 1-2 n(%)	CKDstage3 a-5 n(%)	Chi-square value	P value
Present	116(64.8)	63(35.2)	25.287	**0.000***
Absent	271(84.4)	50(15.6)		
Total	387(77.4)	113(22.6)		

*pvalue < 0.05 is statistically significant

Table 15, shows the association of diabetes with different stages of CKD. Among the 179 (35.8%) diabetic patients, 116(64.8%) had CKD(stage1-2) and 63 (35.2%)had CKD(stage3a-5). Among the 321(64.2%) of study individuals without diabetes, 271(84.4%) had CKD (stage1-2) and 50(15.6%) had CKD (stage3a-5).There was significant association between diabetes and different stages of CKD (p value 0.000).

E-5) Table16: Association between Hypertension and different stages of CKD

Hypertension	CKDstage1-2 n(%)	CKDstage3a-5 n(%)	Chi-square value	pvalue
Present	148(68.2%)	69(31.8)	18.54	**0.000***
Absent	239(84.5)	44(15.5)		
Total	387(77.4)	113(22.6)		

*p value < 0.05 is statistically significant

Table 16, shows the association between hypertension and CKD. Hypertension was present in 217(43.4%) of patients. Among the hypertensive patients 148(68.2%) had CKD(stage1-2) and 69(31.8%) had CKD(stage3a-5). Among the 283(56.6%) normotensive patients 239(84.5%) hadCKD(stage1-2) and 44(15.5%) had CKD (stage 3a-5). There was significant association between hypertension and different stages of CKD (p value 0.000).

E-6) Table17: Association between CVD and different stages of CKD

Cardiovascular Disease	CKDstage1-2 n(%)	CKDstage3a-5 n(%)	Chi-square value	p value
Present	15(51.7)	14(48.3)	11.602	**0.001***
Absent	372(79)	99(21.0)		
Total	387(77.4)	113(22.6)		

*pvalue < 0.05 is statistically significant

Table 17, shows the association between patients with CVD and different stages of CKD. Out of 29 (5.8%) patients who had Cardio vascular disease, 15(51.7%) had CKD (stage1-2) and 14(48.3%) had CKD (stage3a-5). Among the 471(94.2%) study individuals without CVD, 372(79%) had CKD (stage1-2) and 99(21%) had CKD (stage 3a-5).There was significant association between patients with CVD and different stages of CKD (p value 0.001).

Discussion

The present study was conducted to assess the risk factors for renal dysfunction in a heterogeneous study population. The study was conducted to stress the need for early identification of risk factors causing CKD. The use of eGFR for CKD classification in this study will help in early diagnosis of CKD, because serum creatinine measurement alone will not determine the patients with stage 2 CKD. If CKD diagnosis is made early and treated, the progression of CKD can be prevented.

The prevalence of CKD (Stage 3a-5) based on the EPI eGFR (<60 ml/min/1.73m^2) in this study was 22.6%. The prevalence of different stages of CKD in this study were, stage1- 22.2%, stage2 - 55.2%, stage3a - 13.2%, stage3b - 3.8%, stage4 -4.2% and stage5-1.4%. In the Screening and Early Evaluation of Kidney disease (SEEK) study, Ajay.K.Singh et al[2] have done a population based study, among 5588 urban participants and have observed the prevalence as 17.2% (Stage 1- 5 and only 6% in CKD(stages3a-5), by using CKD-EPI formula for eGFR estimation. In another study by Narinder.P.Singh et al[233]. which had 5252 semi urban participants, the prevalence among CKD (Stage 3a-5) was 13.3%, eGFR was calculated using Cockcroft-Gault formula. A study done among the apparently healthy adult central government employees, among 3398 participants, in Agra by Varma et al.[234]the prevalence of CKD(stage1-3) was 13.12% (CKD-EPI). Sanjay Kumar Agarwal et al.[235] used serum creatinine more than 1.8 mg/dl on two occasions, 8-12 weeks apart as criteria for CKD diagnosis, and has found a prevalence of CKD(Stage3-5) as 0.785%. A US study done by Vassalotti et al,[236] the Kidney Early Evaluation Programme(KEEP) the prevalence of CKD was 28.7%.Compared to other studies conducted among Indian population, the present study showed a high prevalence of CKD. All these four Indian studies were population based study and in our study, more of diseased population is assessed and this may be attributed to the high prevalence of CKD. The very high prevalence of stage 3a-5 CKD, raises the possibility of CKD hot spot in the belt of rural and urban area of Trichy. To rule in and rule out the possible hot spot of CKD, a population based study should be performed in this geographical belt.

In this study 13% of the study population had overt proteinuria (Urine spot protein creatinine ratio more than 0.5), 26.6% had moderate proteinuria (UPCR 0.15 to 0.5). There was significant association between the proteinuria and CKD stages (p value 0.000). Many studies have found association between proteinuria and CKD. Inaguma Daijo et al.[237] in their recent study has found significant association between proteinuria and CKD and has identified proteinuria as a risk factor with CKD progressing to ESRD. KDIGO 2012[36] guidelines recommend urinary ACR as a better marker of diagnosis and progression of CKD, mainly in diabetic and hypertensive people and urinary PCR comes in the next order of preference. In this study we have analysed urinary spot PCR. Tracy Ying et al.[238] in a single centered prospective study of measuring proteinuria as the risk of progression of CKD has postulated that spot UPCR is equally good as the gold standard 24 hours proteinuria.

In this study there were 94 patients with thyroid dysfunction. Among the 500 study population, subclinical hypothyroidism was present among 10.2% of people, which was more than overt hypothyroidism (7. 6%).There were 5 (1%) hyperthyroid patients. There was no significant association between thyroid dysfunction and different stages of CKD in our study (p value0.202). In a large cross sectional study from a voluntary health examination program Yi-Cheng Chang et al.,[239] have documented a decrease in eGFR of 87.99, 83.46 and 72.22 ml/min/1.73 m^2 for euthyroid, sub clinical and overt hypothyroidism patients respectively. Similarly, Saroj Kathwada et al.[240] had found that hypothyroidism is associated with CKD progression. Xiaolin Huang et al.[19] in their prospective study had concluded that a high serum FT4 level is associated with increased risk of CKD and they have also found no association between T3 and TSH and incident CKD. In this study we had only 5 patients with hyperthyroidism and none of them had CKD(stage3a-5). Several studies have shown that there is increase in eGFR in hyperthyroidism. In hyperthyroidism an increase of 17-18% of eGFR has been noticed and this rise in GFR is due to increase in renal blood flow and activation of renin angiotensin aldosterone system.[118] Hyperthyroidism causes CKD by increasing the renal blood flow leading to intra glomerular hypertension and increased filtration pressure. Associated proteinuria in hyperthyroidism also causes renal injury.[241]

In our study the relationship between dyslipidemia and different stages CKD was assessed, serum levels of total cholesterol, HDLc, TGLc and LDLc were analysed and their relationship with CKD was studied. Among the study population 19.6% had hypercholesterolemia, 24.2% had high triglyceride level, 54.4% had low HDLc and 13.8% had high LDLc levels. There was significant association between CKD and high TGL levels (pvalue= 0.004) and low HDLc (p value=0.004). But there was no significant association between CKD and high levels of totalcholesterol (p value=0.563) and LDLc (pvalue=0.154). Saroj Khatiwada et al[240] in their cross sectional study, conducted among 360 CKD patients have stated that hypercholesterolemia, low HDLc, hypertriglyceridemia and undesirable LDL cholesterol were significantly associated with presence of cardiovascular disease in CKD. But did not find significant rise in dyslipidemia cases during CKD progression. Our study also did not show significant association for total cholesterol and LDLc and CKD. Zhongshang Yuan et al[102] in a large scale multicentric cross-sectional study (National community based program) has concluded that TG/HDL ratio was associated with renal dysfunction and also exhibited a significantly strong association between increase in serum creatinine and CKD in hypothyroidism and euthyroidism.

In this study, 38% the study subjects had normal BMI, 41.2% were overweight and 15.6% were obese. There were more participants in the overweight category. There was no significant association between obesity and CKD in our study (pvalue 0.95). A study done by Zaman et al., [242] has shown a negative association between BMI and CKD in a study done among Type 2 DM. Similarly, Narinder P Singh et al.[233] has found an inverse association between BMI and renal impairment. The BMI assess both the central and peripheral fat, muscle mass and fluid. As it is the central obesity that determines the cardiovascular and the renal risk, BMI might not have accurately shown the association with CKD. A lot of studies have stated obesity as an important risk factor for CKD. Christiana Aryee et al.[144] had stated that in their study higher anthropometric were recorded among hypertensive nephropathy patients. Andrzej Jaroszynski et al.[243] had demonstrated that central obesity (waist circumference and waist hip ratio) showed higher discriminative ability for CKD than BMI. In this study we found a significant difference between the mean values of waist circumference between the CKD (stage1-2) and CKD (stage 3a-5) (p value=0.02). In early stages of obesity there will be increased GFR. The mechanism for early rise in GFR in obesity may be due to macula densa feedback mechanism, the visceral obesity causes compression of kidneys which may cause an increase in sodium reabsorption in loop of Henle hence less sodium in the macula densa and causes a tubulo glomerular feedback and increases renin secretion, increased blood flow and GFR. The glomerular hyper filtration then gradually subsides and there will be a gradual decrease in GFR.[153]

The prevalence of Diabetes mellitus among our study population was 35.8%, and among the CKD patients 47.8% had diabetics. There was significant association between diabetes and CKD stages (p value 0.000). Diabetes is the second most common risk factor for CKD in our study. In a study done by Wu Bingcao et al.[244] the prevalence of CKD in T2DM was 38.3%, which is similar to that of our study. The study by Justin Gatwood et al, [245] also had reported a prevalence of 40%, which is nearly similar to our study .In a retrospective hospital based study done in Assam, Manjuri Sharma et al,[246]have identified diabetes mellitus(44.2%) as a leading cause of CKD. Sajith Kumar Soman et al, [247] have concluded in their study that CKD was highly prevalent among diabetics and the duration of diabetes, urinary protein levels and RBS value had a strong association with CKD in diabetes.

The prevalence of Hypertension was 43.4% and the prevalence of hypertension among CKD (stage 3a-5), patients was 61.1% and there was significant association between hypertension and different stages of CKD (p value=0.000). In our study hypertension was the most common risk factor for CKD. A lot of studies have stated hypertension as a common risk factor for CKD. The SEEK study done by Ajay.K.Singh et al.[2]showed a high prevalence of hypertension(65%) and identified hypertension as one of the most common risk factor for CKD. Kayori Hayashi et al[5], in their study of metabolic factors associated with CKD have found that hypertension was associated with rapid decline in eGFR and hence need to be monitored for prevention of occurrence of CKD. Narinder.P.Singh et al[233]. in a population based study have found a CKD prevalence of 17.1% among hypertensives and have stated that hypertension plays an important role as risk factor in CKD development.

In our study population cardiovascular disease (CVD) was found in 29 (5.8%) patients. Among the CKD (stage 3a-5) patients in our study 12.4% had CVD.

There was a significant association between CVD and different stages of CKD (p value=0.001). Several studies have shown association between CKD and CVD. Luis .M.Ruilope et al[248] in their HOT study has stated that patients who had renal insufficiency as identified by a baseline creatinine of >1.5 mg/dl or eGFR< 60 ml/min/1.73 m^2 had an increased risk of CVD. In the HOPE randomized trial Johannes.F.E.Mann et al,[249] have concluded that in patients with pre-existing vascular disease or diabetes combined with cardiovascular risk, mild renal insufficiency significantly increased the risk of CVD. Bruce. F. Culleton et al.[250] in a community based cohort have found that mild renal insufficiency is common in the community and those with mild renal insufficiency were associated with high prevalence of CVD. This may be because many traditional CVD risk factors like hypertension, hypertriglyceridemia low HDLc etc. are themselves risk factors for CKD.

Conclusion

- The prevalence of Chronic Kidney Disease was high in the study population. The prevalence of CKD was more among males than females in our study population. Hypertension, Diabetes mellitus, Cardiovascular disease and Proteinuria were associated significantly with different stages of CKD. Hypertension was the most common risk factor among CKD patients. There was significant association between high triglyceride levels and low HDLc levels and different stages of CKD.

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