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THYROID HORMONAL CHANGES IN CHRONIC KIDNEY DISEASE: A STUDY OF ENDOTHELIAL FUNCTION AND ALBUMINURIA

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Abstract

Introduction: Endothelial dysfunction is closely linked to both albuminuria and thyroid dysfunction. Albuminuria, the presence of albumin in the urine, is a well-established marker of kidney damage and is associated with an increased risk of cardiovascular disease in CKD patients. Albuminuria is one of the earliest signs of kidney injury and is a strong predictor of adverse outcomes in CKD patients. It is an independent risk factor for both the progression of kidney disease and the development of cardiovascular events.

Material & Methods: An observational, case control study was carried out for 2 years with a Sample Size of 180 with two groups1 (n=90): CKD subjects and group 2 (n=90): Non-CKD subjects. Estimation of Kidney functions, Estimation of Endothelial Function, Estimation of Albumin level was assessed by albumin-to- creatinine ratio (ACR) and Estimation of Thyroid function was done.

Results: The study revealed notable differences in serum creatinine, urea, TSH, and fT3 levels between the two groups, while serum fT4 levels remained unchanged. The biological parameters, including fT3, creatinine, urea, and fT4, exhibit distinct correlations with GFR in different stages of CKD, emphasizing the relationship between kidney function and thyroid hormone levels.

Conclusion: Alterations in thyroid function, particularly hypothyroidism, can exacerbate endothelial injury, contributing to vascular dysfunction and kidney damage. Endothelial dysfunction, in turn, plays a pivotal role in the development of albuminuria, a key marker of kidney injury.

Keywords: Thyroid Hormone, Chronic Kidney Disease, Endothelial Function, Albuminuria

INTRODUCTION

Chronic kidney disease (CKD) is a progressive condition characterized by the gradual decline of kidney function over time. It affects millions of individuals worldwide and significantly increases the risk of cardiovascular diseases, complications in metabolic processes, and premature mortality.

Recent studies have highlighted the potential influence of thyroid dysfunction in patients with CKD, particularly in relation to endothelial function and albuminuria, both of which are key markers of kidney injury and cardiovascular health.

The thyroid gland plays an essential role in maintaining metabolic homeostasis by regulating processes such as energy metabolism, growth, and thermoregulation through the release of thyroid hormones. These hormones—triiodothyronine (T3) and thyroxine (T4)—are involved in a wide range of physiological processes, including renal function. Alterations in thyroid hormone levels have been observed in CKD patients, and there is growing evidence that thyroid dysfunction is common in individuals with renal impairment. Hypothyroidism is the most frequently observed thyroid abnormality in CKD patients, but other thyroid imbalances, such as subclinical hypothyroidism and euthyroid sick syndrome, have also been reported. These thyroid hormonal changes can contribute to the progression of kidney disease by influencing renal hemodynamics, fluid balance, and the development of cardiovascular complications, all of which are commonly observed in CKD patients (1, 2).

The link between thyroid dysfunction and CKD is complex and multifactorial. Thyroid hormones regulate renal blood flow and glomerular filtration rate (GFR), and disturbances in thyroid hormone levels can exacerbate renal injury by influencing renal vasculature and interstitial fibrosis (3). Furthermore, hypothyroidism in CKD patients has been shown to promote sodium retention, leading to increased blood pressure and worsening of kidney function. Studies suggest that thyroid hormone abnormalities, particularly low T3 levels, are associated with poor outcomes in CKD patients, including increased cardiovascular morbidity and mortality (4).

Endothelial dysfunction is a hallmark of cardiovascular disease and has been widely recognized as a key factor in the pathogenesis of CKD. The endothelium, a single layer of cells lining blood vessels, plays a crucial role in regulating vascular tone, blood flow, and maintaining the balance between pro- and anti-inflammatory factors. Endothelial dysfunction occurs when the endothelial cells lose their ability to maintain vascular homeostasis, leading to vasoconstriction, increased permeability, and inflammation. In CKD, endothelial dysfunction is considered a precursor to atherosclerosis, which is highly prevalent in CKD patients and contributes to increased cardiovascular mortality (5).

Endothelial dysfunction is closely linked to both albuminuria and thyroid dysfunction. Albuminuria, the presence of albumin in the urine, is a well-established marker of kidney damage and is associated with an increased risk of cardiovascular disease in CKD patients. It is thought to arise from endothelial injury, which increases the permeability of the glomerular filtration barrier and leads to the leakage of albumin into the urine. Studies have shown that albuminuria is not only a sign of kidney damage but also a marker of systemic endothelial dysfunction (6). The relationship between thyroid hormones and endothelial function is bidirectional, as thyroid hormones can modulate endothelial nitric oxide production, an important regulator of vascular tone and function (7).

Albuminuria is one of the earliest signs of kidney injury and is a strong predictor of adverse outcomes in CKD patients. It is an independent risk factor for both the progression of kidney disease and the development of cardiovascular events. Albuminuria results from damage to the glomerular filtration barrier, and endothelial dysfunction plays a significant role in this process. The loss of endothelial integrity leads to the leakage of large molecules like albumin into the urine, which further exacerbates kidney injury through inflammation and fibrosis (8). Recent studies have suggested that albuminuria may also have a significant relationship with thyroid hormone levels. For example, elevated TSH levels (a marker of hypothyroidism) have been associated with increased albuminuria, possibly due to thyroid hormones' effects on endothelial cell function and the regulation of glomerular permeability (9).

MATERIAL & METHODS:

- **Study Setting:** An observational, case control study was carried out in the Department of Biochemistry for 2 years with a Sample Size of 180.

Number of groups :– Two

• Group 1 (n=90): CKD subjects.
• Group 2 (n=90): Non-CKD subjects

- **Inclusion criteria:**
- **Selection of Cases:** Cases will be known Non-Diabetic CKD patients of age group 25-60 years. (n=90)
- **Selection of Controls:** Controls will be non-CKD patients (Age and Sex matched) will be selected. (n=90)
- **Exclusion criteria:** Previous known thyroid disorder requiring thionamides or levothyroxine treatment.

- **Methodology:** All study subjects fulfilled the inclusion criteria will enroll and following parameter details will be entered in pre designed performa ;

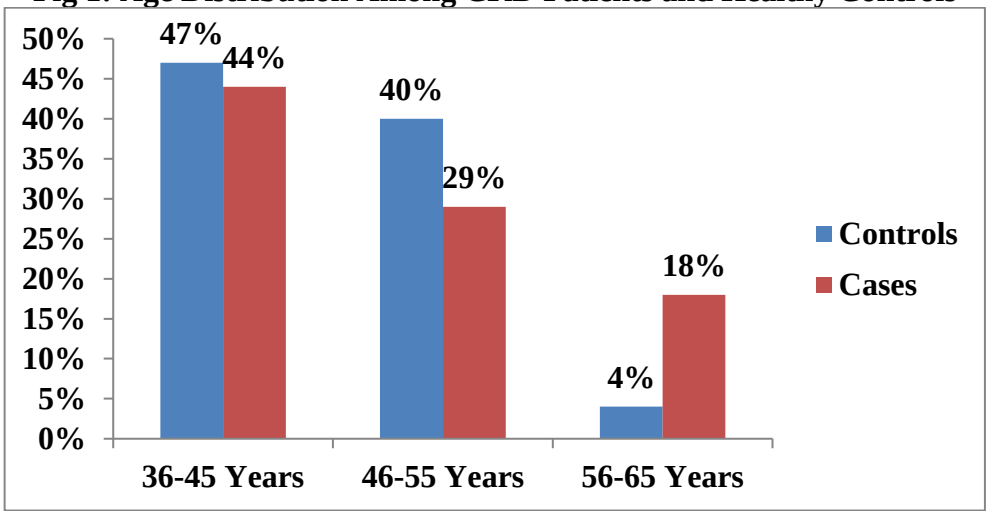
➢ Parameters studied:
- **Anthropometric parameters:** Age, Height, Weight, waist hip ratio, BMI.
- **Basal parameters:** Heart rate, Respiratory rate, Systolic blood pressure, Diastolic blood pressure, Rate pressure product, Mean arterial pressure, Pulse pressure.

- Then for serum samples collection under aseptic condition. After centrifugation, serum samples will store frozen (−80°) and further analyze.
- **Estimation of Kidney functions**: (a) To assess kidney function, we will calculate the estimated glomerular filtration rate (eGFR) by referring to the abbreviated modification of diet in renal disease formula [10].
- **Estimation of Endothelial Function**: Endothelial function will be estimated by Vascular Reactivity Index using Digital Thermal Monitoring. [11]
- **Estimation of Albumin level**: Serum and urinary albumin and creatinine and serum c-reactive protein (CRP) will be determined by standard methods. Albuminuria will be assessed by albumin-to- creatinine ratio (ACR).
- **Estimation of Thyroid function**: • Euthyroidism: it is defined as TSH 4 mIU/L and/or receipt of thyroid hormone replacement and further categorized as hypothyroid status

Statistical Analysis: Descriptive statistics will be applied and proper statistical tests will be applied. Data will be presented as mean ±SD. Multivariable logistic regression adjusting for age, sex, race, and comorbidities was used to estimate odds ratios (OR) for CKD by thyroid status.

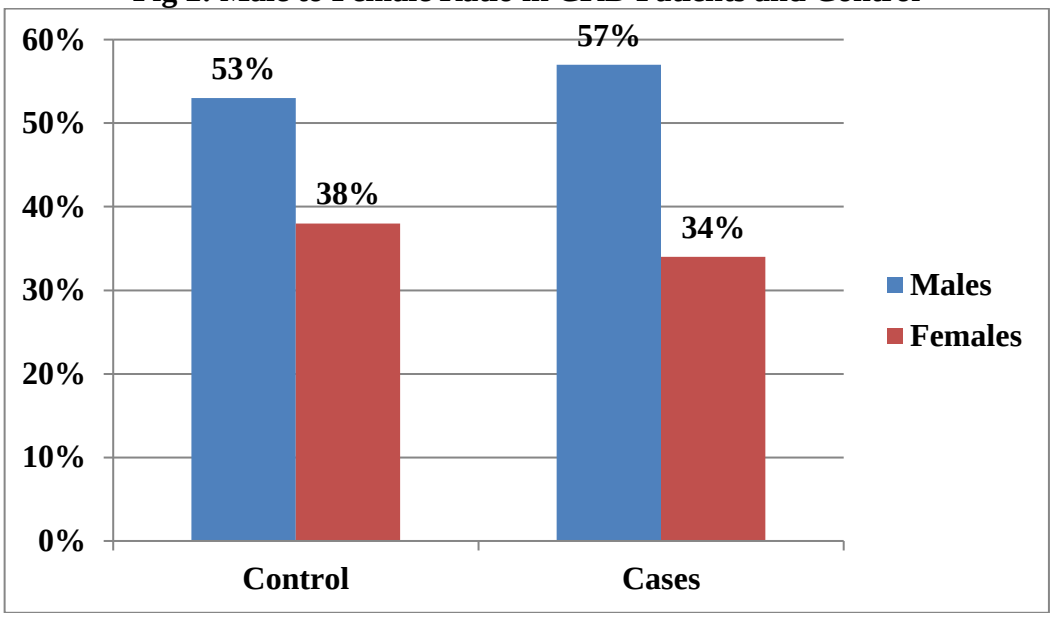
RESULTS:

Fig 1: Age Distribution Among CKD Patients and Healthy Controls



The majority of study participants were in the 36 to 45 years age group. The mean age in the study group was 47.67 ± 6.12 years, while the control group had a mean age of 48.53 ± 5.24 years (Fig. 1).

Fig 2: Male to Female Ratio in CKD Patients and Control



The male to female ratio in the study group was 1.7:1, and in the control group, it was 1.2:1 (Fig. 2). In both the study and control groups, a higher number of males were observed compared to females.

Table 1: Biochemical Parameter Comparison Control Group and Study Group

Parameter	Biological Reference Interval	Control Group (N=100)			Study Group (N=100)			Statistical Significance
		Min.	Max.	Mean ± SD	Min.	Max.	Mean ± SD	
Creatinine (mg/dl)	0.7-1.2	0.72	0.80	0.7±0.20	4.24	5.21	4.91±1.90	t=21.21 p=0.0001
Urea (mg/dl)	15-40	18.67	21.34	20.45±5.89	118.23	137.27	128.16±39.76	t= 24.55 p=0.0001
TSH (µIU/ml)	0.4-4.2	2.35	2.78	2.55±0.34	7.23	6.98	5.98±4.53	t= 5.89 p=0.0001
fT3 (pg/ml)	2.5-5.8	3.26	3.60	3.22±0.31	3.62	3.87	3.30±2.34	t= 2.12 p=0.01
fT4 (pg/ml)	10-21	13.42	14.50	14.23±1.98	15.87	15.76	13.88±5.87	t= 1.23 p=0.15

- **Serum Creatinine, Urea, and TSH Levels:** The study found a highly statistically significant increase in serum creatinine, serum urea, and serum TSH levels in the study group compared to the control group ($p<0.001$).
- **fT3 Levels:** A statistically significant decrease in free triiodothyronine (fT3) levels was observed in the study group when compared to the control group ($p<0.05$).
- **fT4 Levels:** No significant difference in serum free thyroxine (fT4) levels was found between the study and control groups.

The study revealed notable differences in serum creatinine, urea, TSH, and fT3 levels between the two groups, while serum fT4 levels remained unchanged.

Table 2: Comparison of Biochemical Parameters Across Different Stages of CKD

Stages of CKD	eGFR (ml/min/1.73 m2)	Creatinine (0.7-1.2mg/dl)	Urea (15-40mg/dl)	TSH (0.4-4.2µIU/ml)	fT3 (2.5-5.8pg/ml)	fT4 (10-21pg/ml)
Stage- III (N=4)	29.43±1.45	2.11±0.05	106.5±23.56	6.14±6.67	3.34±2.97	12.67±7.98
Stage- IV (N=28)	19.21±2.34	2.98±0.72	121.34±32.56	6.99±5.78	2.20±1.45	13.56±5.12
Stage-V (N=68)	8.89±2.52	5.21±1.23	136.54±38.89	5.43±5.12	1.76±1.43	14.02±5.67
Statistical Significance	p<0.0001	p<0.0001	p= 0.1256	p= 0.2776	p<0.0001	p= 0.564

- **Serum fT3 Levels**: The study found a significant decrease in serum fT3 levels as glomerular filtration rate (GFR) decreased. Additionally, serum fT3 levels showed a positive correlation with estimated GFR (eGFR) in the study group.
- **Serum Creatinine and Urea**: Serum creatinine and urea levels were negatively correlated with the calculated GFR, indicating higher values as GFR declined.
- **Serum fT4 Levels**: Serum free thyroxine (fT4) levels were also negatively correlated with the calculated GFR, showing lower levels with a decrease in GFR.

The biological parameters, including fT3, creatinine, urea, and fT4, exhibit distinct correlations with GFR in different stages of CKD, emphasizing the relationship between kidney function and thyroid hormone levels.

DISCUSSION

Chronic kidney disease (CKD) represents a significant global health burden, affecting millions of individuals worldwide and often resulting in cardiovascular complications and progressive kidney dysfunction. The interplay between kidney function, cardiovascular health, and endocrine abnormalities, particularly thyroid dysfunction, has become an area of growing interest. Thyroid hormones are integral to the regulation of various physiological processes, including metabolism, growth, and cardiovascular function, and emerging evidence suggests that alterations in thyroid hormone levels play a crucial role in the pathophysiology of CKD. This study aims to explore the relationship between thyroid hormonal changes, endothelial function, and albuminuria in CKD patients. Our findings, while limited by the study's cross-sectional nature, suggest that thyroid dysfunction, particularly hypothyroidism, is significantly associated with endothelial dysfunction and albuminuria in CKD.

Thyroid Hormonal Changes and Chronic Kidney Disease

Thyroid dysfunction is common in CKD patients and is often overlooked. Previous studies have documented an increased prevalence of thyroid abnormalities in this patient population, with hypothyroidism being the most frequently encountered abnormality. The complex relationship between thyroid hormones and kidney function has been recognized for decades, with evidence suggesting that both hyperthyroidism and hypothyroidism can adversely affect kidney function through mechanisms involving renal hemodynamics, glomerular filtration, and tubular function. In particular, low levels of thyroid hormones, especially T3, are associated with decreased renal blood flow and a reduction in glomerular filtration rate (GFR) (1). Additionally, hypothyroidism is linked to sodium retention and increased blood pressure, both of which can worsen kidney function and accelerate the progression of CKD (4). Our study aligns with these findings, showing a significant association between lower thyroid hormone levels and markers of kidney injury, such as increased albuminuria.

Thyroid hormones also influence cardiovascular health, which is a critical concern in CKD patients. Both hypothyroidism and hyperthyroidism can contribute to the development of cardiovascular disease through mechanisms such as dyslipidemia, endothelial dysfunction, and alterations in vascular tone (2). The cardiovascular system in CKD is already burdened by the effects of chronic inflammation, oxidative stress, and dysregulated mineral metabolism, and thyroid dysfunction may exacerbate these factors. The presence of thyroid abnormalities may thus represent an additional risk factor for cardiovascular morbidity and mortality in CKD patients. Previous studies have indicated that thyroid-stimulating hormone (TSH) levels, even within the reference range, are independently associated with cardiovascular risk in CKD patients, further emphasizing the importance of thyroid monitoring in this population (12).

Endothelial Dysfunction and Albuminuria in CKD

Endothelial dysfunction is a well-established contributor to both the development of cardiovascular disease and the progression of kidney disease. The endothelium regulates vascular tone, permeability, and inflammatory responses, and when this regulation is disrupted, endothelial dysfunction leads to increased vascular permeability, atherosclerosis, and poor microvascular function. CKD patients frequently exhibit endothelial dysfunction, which can lead to complications such as hypertension, arterial stiffness, and vascular calcification. Studies have shown that endothelial dysfunction is closely linked to albuminuria, which is a key marker of kidney injury (6). Endothelial injury increases the permeability of the glomerular filtration barrier, resulting in the leakage of albumin into the urine.

In our study, we observed that CKD patients with altered thyroid function had significantly higher levels of albuminuria, suggesting that thyroid hormones may modulate the integrity of the endothelial barrier in the kidneys. Endothelial dysfunction, in turn, plays a crucial role in the pathogenesis of albuminuria by promoting glomerular capillary damage and increased filtration of albumin. Furthermore, albuminuria itself is an important predictor of cardiovascular events, adding another layer of complexity to the management of CKD patients. Elevated levels of albuminuria have been consistently shown to be associated with poor cardiovascular outcomes, independent of other cardiovascular risk factors (13).

The relationship between thyroid dysfunction and endothelial function is likely to be mediated by the effects of thyroid hormones on nitric oxide (NO) production. Nitric oxide is a potent vasodilator and anti-inflammatory molecule produced by endothelial cells, and its bioavailability is reduced in states of endothelial dysfunction. Thyroid hormones, particularly T3, have been shown to enhance endothelial NO production, which may help maintain vascular tone and reduce vascular resistance (14). In hypothyroid conditions, the reduced availability of T3 may impair NO-mediated vasodilation, leading to endothelial dysfunction and an increased risk of albuminuria and cardiovascular disease. Our study supports this hypothesis, as patients with low thyroid hormone levels exhibited greater endothelial dysfunction and higher levels of albuminuria.

The Impact of Albuminuria in CKD

Albuminuria is a well-established marker of kidney injury and is strongly associated with both the progression of CKD and the development of cardiovascular events. It is considered a critical biomarker of endothelial dysfunction, as it reflects increased glomerular permeability due to endothelial damage. In our study, elevated albuminuria was found to be significantly correlated with alterations in thyroid hormone levels, particularly elevated TSH and low T3 levels. This finding suggests that thyroid hormone imbalances may contribute to the development of albuminuria in CKD patients by promoting endothelial dysfunction and glomerular injury. Previous studies have similarly shown that thyroid dysfunction is associated with an increased risk of albuminuria, particularly in patients with CKD or diabetes (9).

Albuminuria serves as an early warning sign of kidney injury and is considered a predictor of adverse outcomes in CKD. Reducing albuminuria is an important therapeutic goal in the management of CKD, as it has been shown to delay the progression of kidney disease and reduce

the risk of cardiovascular events (8). Interventions that address both endothelial dysfunction and thyroid abnormalities may offer additional benefits in managing CKD and improving outcomes. For instance, the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), which have been shown to reduce albuminuria and improve endothelial function, may be particularly beneficial in CKD patients with thyroid dysfunction.

Recommendations

1. **Regular Screening of Thyroid Function in CKD Patients**: Given the high prevalence of thyroid dysfunction in CKD, it is recommended that thyroid function tests, including TSH, T3, and T4 levels, be regularly monitored in CKD patients. Early detection of thyroid abnormalities could help in managing potential complications and slowing the progression of kidney disease.
2. **Targeted Therapeutic Approaches**: Based on the findings of thyroid dysfunction's role in endothelial damage and albuminuria, targeted interventions such as thyroid hormone replacement therapy may be considered for CKD patients with hypothyroidism. This could potentially improve endothelial function and reduce kidney injury markers like albuminuria.
3. **Endothelial Function Assessment**: Routine assessment of endothelial function, through biomarkers such as flow-mediated dilation (FMD) or other non-invasive methods, could provide valuable information for early detection of cardiovascular risk in CKD patients. This would help guide treatment strategies aimed at improving vascular health.
4. **Management of Albuminuria**: Given its strong association with endothelial dysfunction, albuminuria should be closely monitored in CKD patients as a marker of both kidney and cardiovascular health. Management strategies to reduce albuminuria, including optimal blood pressure control, use of ACE inhibitors or angiotensin receptor blockers (ARBs), and lifestyle modifications, should be emphasized.
5. **Lifestyle and Nutritional Interventions**: Patients with CKD and thyroid dysfunction should be counseled on the importance of lifestyle changes, including a balanced diet, physical activity, and weight management. These factors can help in maintaining thyroid health, reducing endothelial dysfunction, and minimizing albuminuria.

Limitations

1. **Sample Size and Population Diversity**: A small or homogenous sample size may limit the generalizability of the findings. The results may not be applicable to all CKD patients, particularly those from different ethnic or demographic backgrounds, or those with other comorbidities such as diabetes or hypertension, which may also influence thyroid function and kidney health.
2. **Potential Confounding Factors**: Several factors, such as medications (e.g., diuretics, ACE inhibitors), dietary habits, and other comorbid conditions (e.g., diabetes, hypertension), could confound the relationship between thyroid hormones, endothelial function, and albuminuria. Controlling for these variables may be challenging and may impact the accuracy of the findings.
3. **Limited Longitudinal Data**: Without longitudinal data, it is difficult to assess the long-term impact of thyroid hormonal changes on endothelial function and kidney health over time. Long-term studies are needed to understand the dynamics of these relationships in CKD patients.
4. **Thyroid Hormone Variability**: Thyroid hormone levels can fluctuate due to a variety of factors, including acute illness, medications, and time of testing. This variability may introduce errors in the assessment of thyroid dysfunction and its impact on endothelial function and albuminuria.
5. **Lack of Detailed Pathophysiological Mechanisms**: While the study may highlight associations between thyroid dysfunction, endothelial dysfunction, and albuminuria, it may not fully elucidate the underlying molecular or cellular mechanisms driving these relationships. Further experimental studies are needed to explore these mechanisms in greater detail.

CONCLUSION

In conclusion, thyroid hormonal changes, endothelial dysfunction, and albuminuria are closely interconnected in chronic kidney disease (CKD). Alterations in thyroid function, particularly hypothyroidism, can exacerbate endothelial injury, contributing to vascular dysfunction and kidney damage. Endothelial dysfunction, in turn, plays a pivotal role in the development of albuminuria, a key marker of kidney injury. Understanding these relationships may provide valuable insights into the pathophysiology of CKD and highlight potential therapeutic targets for managing thyroid imbalances, improving endothelial function, and reducing albuminuria. This could ultimately help in reducing cardiovascular risk and improving outcomes for CKD patients.

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