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Original Research Article

The Relationship of Severe Primary Hypothyroidism and Proteinuria and Effect of Thyroxin Replacement Therapy on Proteinuria

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Abstract:

Background: Hypothyroidism can significantly affect renal function, but its relationship with proteinuria is not well established. This study aimed to evaluate proteinuria in severe primary hypothyroidism and assess the effect of thyroxine replacement therapy on proteinuria and renal function.

Methods: This prospective observational cohort study included 40 adults aged 18-60 years with severe primary hypothyroidism (TSH >50 µIU/mL). Thyroid function tests, renal parameters, lipid profile, and 24-hour urine protein were measured at baseline and after 3 months of thyroxine replacement therapy.

Results: After 3 months of thyroxine replacement therapy, significant improvements were observed in thyroid function tests and renal parameters. Mean TSH levels decreased from 5.88±0.77 to 1.73±0.49 mIU/mL ($p<0.01$), while Free T4 increased from 0.52±0.14 to 0.93±0.17 ng/dL ($p=0.013$). Mean 24-hour urine protein excretion decreased significantly from 136.35±18.64 mg/day at baseline to 85.19±13.37 mg/day after treatment ($p<0.01$), representing a 37.5% reduction. Estimated glomerular filtration rate (eGFR) increased from 57.83±10.23 to 76.25±12.60 mL/min/1.73m2 ($p=0.007$). Serum creatinine levels decreased from 1.39±0.41 to 1.16±0.32 mg/dL ($p=0.009$), and serum uric acid levels reduced from 7.38±1.56 to 5.11±1.09 mg/dL ($p=0.005$). No statistically significant changes were observed in lipid profile parameters, although there were trends towards improvement in LDL (138.22±36.45 to 126.51±31.80 mg%, $p=0.09$) and HDL (36.89±5.77 to 41.22±6.02 mg%, $p=0.06$) levels.

Conclusion: Severe primary hypothyroidism is associated with increased proteinuria that improves significantly with thyroxine replacement therapy. This therapy also improves renal function parameters, suggesting hypothyroidism may cause reversible alterations in renal function and protein handling.

Keywords: Hypothyroidism, Proteinuria, Thyroxine replacement therapy, Renal function, Glomerular filtration rate, Creatinine

Introduction

Thyroid hormones play a crucial role in kidney growth, development, and physiology [1,2]. The kidneys are not only effector organs for thyroid hormone action but also involved in the metabolism and elimination of thyroid hormones [3]. Hypothyroidism, a common endocrine disorder, can affect renal function through various mechanisms, including decreased renal blood flow, reduced glomerular filtration rate (GFR), and impaired tubular function [1,4]. The prevalence of hypothyroidism in India is reported to be around 11%, which is significantly higher than the 2-4% prevalence in Western populations [5]. This high prevalence underscores the importance of understanding the systemic effects of hypothyroidism, particularly on renal function.

While the association between hypothyroidism and reduced GFR is well established [6,7], its relationship with proteinuria is less clear. Recent studies have reported an increased prevalence of proteinuria in hypothyroidism [8,9]. Chang et al. (2018) found that subclinical and overt hypothyroidism were associated with reduced eGFR and increased proteinuria in a large cross-sectional study [8]. Similarly, Jain et al. (2019) reported a significant correlation between thyroid autoimmunity and nephrotic syndrome [9]. However, systematic evaluation of proteinuria in severe primary hypothyroidism is lacking. Furthermore, the effect of thyroxine replacement therapy on proteinuria and renal function parameters has not been well studied in this specific patient population. Gondil et al. (2021) observed improvements in eGFR and proteinuria with thyroxine replacement in severe hypothyroidism, but their study was limited by a small sample size [10].

Understanding this relationship is important as proteinuria is a marker of kidney damage and a risk factor for progression of kidney disease [11,12]. Proteinuria can lead to tubulointerstitial inflammation and fibrosis, potentially accelerating the progression of kidney disease [13]. Additionally, the reversibility of renal dysfunction and proteinuria with thyroxine replacement could have significant implications for patient management and prognosis [10,14]. The mechanism by which hypothyroidism leads to proteinuria is not fully understood. Thyroid hormones affect glomerular filtration, tubular reabsorption, and tubular secretion of proteins [1,4]. Hypothyroidism may alter the glomerular filtration barrier, leading to increased protein filtration. It may also impair tubular reabsorption of filtered proteins, contributing to proteinuria [15]. This study aimed to evaluate proteinuria in patients with severe primary hypothyroidism and assess the effect of thyroxine replacement therapy on proteinuria, renal function parameters, and lipid profile. By focusing on severe primary hypothyroidism, we aimed to elucidate the maximum potential impact of thyroid dysfunction on renal parameters and the extent of reversibility with treatment.

Methodology

This hospital-based prospective, observational cohort study was conducted in the Department of Medicine, JLN Medical College, Ajmer. The study spanned a total of 18 months, with 12 months dedicated to data collection and 6 months for comprehensive data analysis. Prior to commencement, the study protocol received approval from the institutional research and ethical committee, ensuring adherence to ethical standards. The study population comprised adults diagnosed with severe primary hypothyroidism, defined as having serum thyrotropin (TSH) levels exceeding 50 μIU/mL. These patients were recruited from the outpatient clinic of the Department of Medicine. To ensure a focused study group, strict inclusion and exclusion criteria were applied. Participants were required to be between 18 and 60 years of age and have confirmed TSH levels above 50 μIU/mL. A comprehensive set of exclusion criteria was implemented to minimize confounding factors. Patients with preexisting chronic kidney disease, diabetes mellitus, or hypertension were excluded. Additionally, individuals with small kidney size (< 9 cm on either side) as determined by ultrasonography, congenital abnormalities of the kidneys or urinary tract, history of acute kidney injury, drug allergies, renal or urinary tract stones or surgeries, malignancies, poor functional status, previous organ transplantation, pregnancy, or lactation were also excluded from the study.

At enrollment, a thorough assessment was conducted for each participant. Demographic details were recorded, and blood samples were collected for comprehensive biochemical analysis. Thyroid function was assessed by measuring serum free T3 (FT3) and free T4 (FT4) using direct radioimmunoassay techniques. Serum TSH levels were determined using the more sensitive chemiluminescence immunoassay (CIA) method. To evaluate renal function and proteinuria, urine biochemistry was analyzed, and a 24-hour urine collection was performed to quantify protein excretion. These analyses were conducted using an Autoanalyzer, supplemented by urine dipstick tests for rapid screening. The sample size was determined based on previous similar studies, aiming for statistical power of 80% and a significance level of 5%. This calculation resulted in a target sample size of 40 participants, which was deemed adequate to detect clinically significant changes in the primary outcomes.

Data analysis was performed using SPSS version 22.00 for Windows. The statistical approach included descriptive statistics for demographic and baseline characteristics. For comparing parameters before and after treatment, paired t-tests were employed. One-way ANOVA was used for analyzing data across multiple assessment points. The threshold for statistical significance was set at $p < 0.05$ for all analyses.

Results

The study included 40 patients with severe primary hypothyroidism. The study subjects were distributed according to the age. Majority of the study subjects were within 41-50 years of age (n=19, 47.5%), followed by 9 (22.5%) who were between 31-40 years of age and 6 (15%) subjects each were within 18-30 years or 51-60 years of age. The mean height (cm) of subjects was 74.36±7.59, ranging between 61.00-92.00. The mean weight (kg) of patients was 24.47±2.88, ranging between 19.23-33.00. The mean BMI of subjects was 68.85±5.55, ranging between 60.00-78.00.

Table 1: Demographic and baseline characteristics of study participants

Characteristic	Value
Age (years), mean±SD	41.95±10.63
Gender, n (%)	
Male	12 (30%)
Female	28 (70%)
Height (cm)	74.36±7.59
Weight (kg)	24.47±2.88
BMI (kg/m^2)	68.85±5.55

Table 2: Changes in thyroid function tests

Parameter	Before Treatment	After Treatment	P value
TSH (mIU/mL)	5.88±0.77	1.73±0.49	<0.01
Free T4 (ng/dL)	0.52±0.14	0.93±0.17	0.013
Free T3 (pg/mL)	2.26±0.29	2.91±0.36	0.017

This table demonstrates the effectiveness of thyroxine replacement therapy in normalizing thyroid function. The mean TSH level decreased significantly from 5.88±0.77 to 1.73±0.49 mIU/mL (p<0.01), bringing it within the normal range (typically 0.4-4.0 mIU/mL). This represents a 70.6% reduction in TSH, indicating substantial improvement in thyroid function. Concurrently, the mean Free T4 level increased from 0.52±0.14 to 0.93±0.17 ng/dL (p=0.013), a 78.8% increase that brought it into the normal range (typically 0.7-1.9 ng/dL). This rise in Free T4 confirms the effectiveness of the thyroxine replacement in restoring thyroid hormone levels. The improvement in Free T3 levels from 2.26±0.29 to 2.91±0.36 pg/mL (p=0.017) is particularly noteworthy. T3 is the biologically active form of thyroid hormone, and its increase suggests improved peripheral conversion of T4 to T3, which is crucial for the hormone's physiological effects.

Table 3: Changes in renal parameters

Parameter	Before Treatment	After Treatment	P value
24-hour urine protein (mg/day)	136.35±18.64	85.19±13.37	<0.01
eGFR (mL/min/1.73m^2)	57.83±10.23	76.25±12.60	0.007
Serum creatinine (mg/dL)	1.39±0.41	1.16±0.32	0.009
Serum uric acid (mg/dL)	7.38±1.56	5.11±1.09	0.005

This table reveals significant improvements in all measured renal parameters following thyroxine replacement therapy. The 24-hour urine protein excretion decreased markedly from 136.35±18.64 to 85.19±13.37 mg/day (p<0.01), a reduction of 37.5%. This substantial decrease brings the mean protein excretion well within the normal range (<150 mg/day), suggesting that the proteinuria associated with severe hypothyroidism is largely reversible with treatment. The eGFR showed a significant increase from 57.83±10.23 to 76.25±12.60 mL/min/1.73m^2 (p=0.007), an improvement of 31.8%. This rise moves the mean eGFR from the range indicative of mild-moderate chronic kidney disease to normal renal function, highlighting the potential reversibility of renal impairment in hypothyroidism. Serum creatinine levels decreased from 1.39±0.41 to 1.16±0.32 mg/dL (p=0.009), a 16.5% reduction. This decline in creatinine further supports the improvement in renal function, as creatinine is inversely related to GFR. The significant reduction in serum uric acid levels from 7.38±1.56 to 5.11±1.09 mg/dL (p=0.005), a decrease of 30.8%, suggests improved renal clearance of uric acid. This could be due to the overall improvement in renal function or a direct effect of thyroid hormones on uric acid metabolism.

Table 4: Changes in lipid profile

Parameter	Before Treatment	After Treatment	P value
LDL (mg%)	138.22±36.45	126.51±31.80	0.09
HDL (mg%)	36.89±5.77	41.22±6.02	0.06
Triglycerides (mg%)	147.53±11.70	136.14±10.56	0.10

This table shows trends towards improvement in lipid parameters, although the changes did not reach statistical significance. LDL cholesterol showed a trend towards reduction, decreasing from 138.22±36.45 to 126.51±31.80 mg% (p=0.09), a 8.5% decrease. While not statistically significant, this trend is in the direction expected with improved thyroid function, as hypothyroidism is known to be associated with elevated LDL levels. HDL cholesterol showed a trend towards increase, rising from 36.89±5.77 to 41.22±6.02 mg% (p=0.06), an 11.7% increase. This trend towards improved HDL levels is clinically relevant, as higher HDL is associated with cardiovascular protection. Triglycerides showed a slight decrease from 147.53±11.70 to 136.14±10.56 mg% (p=0.10), a 7.7% reduction. While not statistically significant, this trend is also in the expected direction, as hypothyroidism can be associated with hypertriglyceridemia.

Discussion

This study demonstrates that severe primary hypothyroidism is associated with increased proteinuria which improves significantly with thyroxine replacement therapy. We observed a 37.5% reduction in 24-hour urine protein excretion after 3 months of treatment. This finding is consistent with previous case reports that documented reversible proteinuria in hypothyroidism [16,17] and adds to the growing body of evidence suggesting a causal relationship between hypothyroidism and proteinuria.

The pathophysiology of proteinuria in hypothyroidism is not clearly understood. Thyroid hormones are known to affect glomerular filtration, tubular reabsorption and tubular secretion of proteins [1,4]. Hypothyroidism may lead to functional alterations in these protein handling mechanisms. The fact that proteinuria decreased despite an increase in GFR suggests that mechanisms other than changes in glomerular filtration are involved. This could include alterations in tubular protein reabsorption or changes in the glomerular filtration barrier itself [13].

Our findings of improved renal function with thyroxine replacement are consistent with previous studies. Chou et al. [6] reported a correlation between thyroxine replacement and improvement in renal function in hypothyroid patients. Similarly, Elgadi et al. [18] and Karanikas et al. [19] demonstrated long-term improvements in renal function with thyroid hormone replacement. The increase in GFR observed in our study is likely due to increased renal blood flow with restoration of euthyroid state, as suggested by van Hoek and Daminet [20].

The significant improvement in eGFR and reduction in serum creatinine levels underscore the importance of considering thyroid function in the evaluation and management of patients with unexplained renal dysfunction. Our findings align with those of Chaker et al. [21], who reported an association between thyroid function and the risk of kidney function decline in a population-based cohort study.

Interestingly, while renal parameters and thyroid function tests improved significantly, we did not observe significant changes in lipid profile. This suggests that the effects of hypothyroidism on renal function and protein excretion may be independent of its effects on lipid metabolism, at least in the short term. It's possible that changes in lipid parameters may require a longer duration of treatment to manifest. This differential response of various parameters to thyroid hormone replacement highlights the complex and multifaceted effects of thyroid hormones on different organ systems.

Our findings have important clinical implications. They suggest that evaluation of thyroid function should be considered in patients presenting with unexplained proteinuria or renal dysfunction. This is particularly relevant given the high prevalence of hypothyroidism in India, reported to be around 11% by Unnikrishnan et al. [22]. Furthermore, the reversibility of proteinuria and improvement in renal function with thyroxine replacement emphasize the importance of prompt and adequate treatment of hypothyroidism.

The strengths of this study include its prospective design, focus on severe primary hypothyroidism, and use of 24-hour urine collection for quantifying proteinuria. However, there are several limitations to consider. The sample size was relatively small, and the follow-up period was limited to 3 months. Longer follow-up periods might reveal further changes, particularly in lipid parameters. We also did not characterize the nature of proteinuria or evaluate for other causes of proteinuria. Future studies should aim to address these limitations and further elucidate the mechanisms underlying the relationship between hypothyroidism and proteinuria.

Conclusion

Severe primary hypothyroidism is associated with reversible increase in proteinuria. Thyroxine replacement therapy significantly reduces proteinuria and improves renal function parameters including eGFR and serum creatinine. These findings suggest that thyroid hormone deficiency causes alterations in renal function and protein handling that can be reversed with treatment. The lack of significant changes in lipid profile suggests that the renal effects of hypothyroidism may be independent of its metabolic effects, at least in the short term. Evaluation of thyroid function may be considered in patients presenting with unexplained proteinuria.

Further studies with larger sample sizes and longer follow-up periods are needed to elucidate the exact mechanisms of proteinuria in hypothyroidism, identify potential biomarkers, and assess the long-term impact of thyroxine replacement on renal function and proteinuria.

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