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Research Article

Renal Function Trajectories in Chronic Kidney Disease Patients With and Without Coexisting Hypothyroidism: A Prospective Observational Study from a Tertiary Care Nephrology Centre in South India

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ABSTRACT

Background: Hypothyroidism is a common but often under-recognised comorbidity in chronic kidney disease (CKD), and the two conditions are thought to influence one another through a bidirectional axis involving renal clearance of thyroid hormone and thyroid-dependent renal haemodynamics. Prospective data comparing renal function trajectories in CKD patients with and without hypothyroidism remain limited, particularly from South Asian nephrology settings.

Methods: In this prospective observational study conducted in the Nephrology department of a tertiary care hospital, 150 patients with CKD stage 3b-5 were enrolled and assigned to Arm A (CKD alone, n = 110) or Arm B (CKD with hypothyroidism, n = 40) according to their diagnosis at screening. Serum creatinine, urea, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), sodium, potassium and chloride were recorded at baseline and at three further visits spaced 28 ± 3 days apart over a 12-week follow-up. Between-arm comparisons used the unpaired t-test and chi-square test, within-arm change over time used repeated-measures one-way ANOVA, and associations with thyroid-stimulating hormone (TSH) and free thyroxine (T4) were assessed with the Pearson correlation coefficient. Significance was set at $p < 0.05$.

Results: Mean serum creatinine rose from 6.4 ± 1.5 mg/dL at baseline to 7.9 ± 2.3 mg/dL at week 12 in Arm B, while Arm A showed a modest decline from 6.2 ± 3.5 to 5.6 ± 3.4 mg/dL (within-arm $p = 0.0004$ and $p = 0.0483$, respectively). Mean eGFR fell from 9.3 ± 2.4 to 7.6 ± 2.4 mL/min/1.73m^2 in Arm B ($p = 0.0002$) but was essentially unchanged in Arm A (15.2 ± 12.3 to 15.6 ± 10.4 mL/min/1.73m^2, $p = 0.1839$). Between-arm differences in creatinine and eGFR reached significance by the second and third visits ($p \leq 0.02$ for both). Correlations between renal parameters and TSH or free T4 were weak and not statistically significant in either arm (all $|r| < 0.16$, $p > 0.10$).

Conclusion: Over a 12-week observation period, CKD patients with coexisting hypothyroidism showed a less favourable renal trajectory than those with CKD alone, despite the absence of a significant linear correlation between renal indices and circulating thyroid hormone levels. These findings support closer biochemical monitoring of thyroid status in patients with stage 3b-5 CKD, though the observational design and modest, unevenly sized comparison groups mean the results should be interpreted as hypothesis-generating rather than confirmatory.

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Introduction

Chronic kidney disease affects more than a tenth of the global population and ranks among the leading contributors to premature death worldwide, with a disproportionate burden in low- and middle-income countries.[1] Thyroid dysfunction, and hypothyroidism in particular, is increasingly recognised as a comorbidity of CKD rather than an incidental finding. The relationship appears bidirectional: reduced glomerular filtration slows the clearance and peripheral conversion of thyroid hormones, while thyroid hormone deficiency itself lowers cardiac output, renal plasma flow and glomerular filtration through several haemodynamic and tubular mechanisms. [2,3] Large population-based cohorts have reported a stepwise rise in hypothyroidism prevalence as eGFR declines, and some evidence suggests that CKD patients with coexisting hypothyroidism experience faster renal deterioration than euthyroid patients with CKD alone, although other cohorts have found no accelerated decline. [4,5] This inconsistency in the literature, together with the relative scarcity of prospective data from South Asian nephrology populations, motivated the present study.

This study aimed to compare renal function over a 12-week period in patients with CKD alone and patients with both CKD and hypothyroidism attending a tertiary care nephrology service. The primary objectives were to determine serum creatinine, serum urea, BUN and eGFR at baseline and at three subsequent visits in each group; secondary objectives were to determine serum sodium, potassium and chloride at the same time points and to examine their association with circulating TSH and free T4.

Materials and Methods

Study Design, Setting and Ethics

This was a prospective, observational, single-centre study conducted over 32 weeks in the in-patient and out-patient Nephrology department of King George Hospital, Visakhapatnam, India, an institution affiliated with Andhra University. The protocol, informed consent documents and case report form were approved by the Institutional Ethics Committee of King George Hospital prior to enrolment (Protocol No. AU/AUCoPS/M.Pharm/MPP/2021-2023/13), and written informed consent was obtained from every participant, or their legally acceptable representative, in the local language.

Participants

Adults aged 18 years or older with CKD stage 3b, 4 or 5, defined per Kidney Disease: Improving Global Outcomes (KDIGO) eGFR thresholds, were eligible. Participants were allocated by diagnosis, not randomised: those with CKD alone formed Arm A, and those with CKD together with a pre-existing diagnosis of hypothyroidism formed Arm B. Patients whose hypothyroidism preceded their CKD diagnosis, those with urinary tract obstruction, lupus nephritis, systemic lupus erythematosus or chronic pyelonephritis, those on long-term nephrotoxic agents (analgesics, aminoglycosides or immunosuppressants), and those enrolled in another concurrent clinical study were excluded.

Of 500 patients screened for eligibility, 150 met the inclusion criteria and were enrolled: 110 in Arm A and 40 in Arm B. The target sample size of 150 was derived from a population proportion of 0.09 for CKD admissions at the study site, using Cochran's formula at a 95% confidence level and 5% margin of error (n = 125.85), inflated by 10% to allow for anticipated dropout. Eight participants in Arm A and two in Arm B died during follow-up and were retained in the analysis up to their last recorded visit.

Follow-up and assessments

The enrolment visit was designated the baseline (day 0), and participants were reassessed at three further visits at 28 ± 3, 57 ± 3 and 86 ± 3 days. At each visit, serum creatinine, urea, BUN and eGFR (the primary renal indices) and serum sodium, potassium and chloride (secondary indices) were recorded, together with concurrent TSH and free T4 in participants with available thyroid function testing.

Statistical analysis

Continuous variables are presented as mean ± standard deviation. Within-arm change across the four visits was assessed by repeated-measures one-way ANOVA; between-arm comparisons at each visit used the unpaired t-test. Categorical variables (sex, CKD stage distribution) were compared using the chi-square test. Associations between each renal or electrolyte parameter and TSH or free T4 were quantified using the Pearson correlation coefficient, calculated separately within each arm. A two-sided p-value below 0.05 was considered statistically significant throughout; given the large number of comparisons performed, p-values close to this threshold should be interpreted with caution (see Section 5).

Results

Baseline characteristics

The overall mean age of the 150 participants was 51.1 ± 12.8 years (Arm A: 51.7 ± 13.2 years; Arm B: 49.5 ± 11.7 years). Males predominated in both groups (Arm A: 80/110, 72.7%; Arm B: 25/40, 62.5%; χ^2 p = 0.2268). No participant in either arm had stage 3a CKD. In Arm A, 15 participants were classified as stage 3b, 20 as stage 4 and 75 as stage 5; in Arm B, all 40 participants were classified as stage 5, consistent with reports that hypothyroidism prevalence rises as eGFR falls.

Serum Creatinine

In Arm A, mean serum creatinine changed little over follow-up (baseline 6.2 ± 3.5 mg/dL; visit 3, 5.6 ± 3.4

Table 1: Baseline demographic and disease-stage distribution

Characteristic	*Arm A (CKD alone) n = 110*	*Arm B (CKD + hypothyroidism) n = 40*	*p-value*
Mean age, years (± SD)	51.7 ± 13.2	49.5 ± 11.7	—
Male sex, n (%)	80 (72.7)	25 (62.5)	0.2268
CKD stage 3b, n	15	0	—
CKD stage 4, n	20	0	—
CKD stage 5, n	75	40	—

Table 2: Serum creatinine at each study visit. Arm A visit-1 value for Arm B was not separately reported in the source data and is marked accordingly; this should be confirmed against the original case report forms before submission

Visit	*Arm A, mg/dL (mean ± SD)*	*Arm B, mg/dL (mean ± SD)*	*Between-arm p-value*
Baseline	6.2 ± 3.5	6.4 ± 1.5	0.7297
Visit 1 (day 28 ± 3)	6.2 ± 3.4	—	0.2173
Visit 2 (day 57 ± 3)	5.9 ± 3.4	7.3 ± 1.7	0.0196
Visit 3 (day 86 ± 3)	5.6 ± 3.4	7.9 ± 2.3	0.0004
Within-arm change, p	0.0483	0.0004	—

Table 3: Estimated glomerular filtration rate at each study visit

Visit	*Arm A, mL/min/1.73m² (mean ± SD)*	*Arm B, mL/min/1.73m² (mean ± SD)*	*Between-arm p-value*
Baseline	15.2 ± 12.3	9.3 ± 2.4	0.0028
Visit 1	14.6 ± 11.0	8.6 ± 2.3	0.0007
Visit 2	15.1 ± 10.7	8.0 ± 2.3	0.0001
Visit 3	15.6 ± 10.4	7.6 ± 2.4	< 0.0001
Within-arm change, p	0.1839	0.0002	—

mg/dL), though the overall change reached significance (repeated-measures ANOVA, p = 0.0483), driven mainly by the baseline-to-visit-3 and visit-1-to-visit-3 comparisons (p = 0.0211 and p = 0.0274). In Arm B, creatinine rose steadily from 6.4 ± 1.5 mg/dL at baseline to 7.9 ± 2.3 mg/dL at visit 3 (p = 0.0004), with significant increases already apparent by visit 2 (p = 0.0209). Between-arm comparisons showed no significant difference at baseline (p = 0.7297) or visit 1 (p = 0.2173), but significant divergence emerged at visit 2 (p = 0.0196) and visit 3 (p = 0.0004).

Estimated glomerular filtration rate

Mean eGFR in Arm A was essentially stable across follow-up (baseline 15.2 ± 12.3; visit 3, 15.6 ± 10.4 mL/min/1.73m^2; p = 0.1839), whereas Arm B showed a consistent decline from 9.3 ± 2.4 at baseline to 7.6 ± 2.4 mL/min/1.73m^2 at visit 3 (p = 0.0002). Between-arm differences were significant at every time point, including baseline (p = 0.0028), reflecting the more advanced disease profile of Arm B, and widened further by visit 3 (p < 0.0001).

Secondary renal and electrolyte parameters

Averaged across all disease stages and visits, serum urea (100.9 ± 33.3 vs 89.9 ± 43.6 mg/dL) and BUN (47.1 ± 15.5 vs 41.9 ± 20.4 mg/dL) were both higher in Arm B than Arm A, mirroring the creatinine and eGFR findings. Serum potassium was also higher in Arm B (4.7 ± 0.6 vs 4.5 ± 0.7 mmol/L). Serum sodium (138.2 ± 3.3 vs 138.7 ± 3.2 mmol/L) and chloride (102.0 ± 4.7 vs 101.4 ± 4.1 mg/dL) did not differ meaningfully between arms.

Table 4: Overall mean secondary renal and electrolyte parameters, pooled across visits and CKD stages

Parameter	*Arm A (mean ± SD)*	*Arm B (mean ± SD)*
Serum urea, mg/dL	89.9 ± 43.6	100.9 ± 33.3
Blood urea nitrogen, mg/dL	41.9 ± 20.4	47.1 ± 15.5
Serum sodium, mmol/L	138.7 ± 3.2	138.2 ± 3.3
Serum potassium, mmol/L	4.5 ± 0.7	4.7 ± 0.6
Serum chloride, mg/dL	101.4 ± 4.1	102.0 ± 4.7

Table 5: Pearson correlation coefficients between renal indices and thyroid hormones

Correlation	*Arm A, r (p-value)*	*Arm B, r (p-value)*
Serum creatinine vs TSH	-0.077 (0.421)	-0.086 (0.597)
Serum creatinine vs free T4	-0.139 (0.117)	-0.025 (0.902)
eGFR vs TSH	0.089 (0.352)	0.078 (0.632)
eGFR vs free T4	0.088 (0.378)	0.050 (0.806)

Correlation with thyroid function

Pearson correlation coefficients between renal indices and thyroid hormones were uniformly weak. For serum creatinine and TSH, r was -0.077 in Arm A and -0.086 in Arm B (p = 0.421 and p = 0.597); for creatinine and free T4, r was -0.139 in Arm A and -0.025 in Arm B (p = 0.117 and p = 0.902). For eGFR and TSH, r was 0.089 in Arm A and 0.078 in Arm B (p = 0.352 and p = 0.632); for eGFR and free T4, r was 0.088 in Arm A and 0.050 in Arm B (p = 0.378 and p = 0.806). None of these associations reached statistical significance.

Discussion

The two study groups diverged over follow-up in a pattern consistent with a less favourable renal course in patients with coexisting hypothyroidism. Serum creatinine and BUN rose progressively in Arm B while remaining broadly stable, or even falling slightly, in Arm A, and eGFR declined further in Arm B whereas it held steady in Arm A. This pattern is compatible with the proposed mechanism by which hypothyroidism reduces cardiac output and renal plasma flow, impairs glomerular filtration and slows tubular creatinine excretion, thereby raising circulating creatinine independently of any change in muscle mass.[2,6] A comparable prospective cohort by Meuwese et al. found that low thyroid function was associated with lower eGFR cross-sectionally but did not predict a steeper subsequent decline in renal function, a more cautious conclusion than the trajectory divergence observed here; the shorter follow-up and smaller hypothyroid subgroup in the present study limit any direct comparison of effect size.[5]

The absence of a significant linear correlation between renal indices and TSH or free T4 within either arm is a notable feature of these data. It suggests that any relationship between thyroid status and renal function in this cohort is unlikely to be explained by a simple dose-response effect of circulating hormone concentration, and may instead reflect the presence or absence of a hypothyroid diagnosis itself, duration of thyroid disease, adequacy of levothyroxine replacement, or unmeasured confounders such as comorbid diabetes, hypertension control or nutritional status. Jia et al. reported a comparable pattern of non-significant hormone-level correlations alongside between-group differences, which is broadly consistent with the present findings.[7]

Sex distribution favoured male participants in both arms, in keeping with reports that men more often receive nephrology follow-up even where population-level CKD prevalence is higher in women.[8] All 40 participants in Arm B were classified as stage 5 CKD, whereas Arm A included patients across stages 3b to 5; this imbalance mirrors epidemiological data showing that hypothyroidism becomes more prevalent as eGFR falls, but it also means that the between-arm comparisons in this study are confounded by disease stage and cannot be interpreted as reflecting the effect of hypothyroidism in isolation.[4] This point is addressed further as a limitation below, and the associations reported here are described accordingly as observed differences rather than causal effects of hypothyroidism on renal function.

Limitations

Several aspects of this study warrant caution when interpreting its findings. First, the 12-week follow-up is short relative to the natural history of CKD and cannot capture longer-term trajectories or hard renal outcomes such as progression to dialysis. Second, Arm B was both smaller (n = 40) and confined entirely to stage 5 CKD, which limits statistical precision, prevents separation of the effect of hypothyroidism from the effect of more advanced baseline disease, and restricts generalisability to patients with milder CKD and coexisting hypothyroidism. Third, participants were allocated to arms by existing diagnosis rather than randomised, so the study can identify associations but not causal relationships between hypothyroidism and renal decline. Fourth, a large number of statistical comparisons were performed across renal parameters, visits, stages and demographic subgroups without correction for multiplicity, so individual p-values close to 0.05 should be treated as exploratory rather than confirmatory. Finally, the study was conducted at a single tertiary care centre, and comorbidities, concurrent medications (including levothyroxine dosing and adherence) and nutritional status were not modelled as covariates, leaving residual confounding as a plausible alternative explanation for the observed between-arm differences.

Conclusion

In this prospective observational study, patients with CKD stage 3b-5 and coexisting hypothyroidism showed a progressive rise in serum creatinine and BUN and a further decline in eGFR over 12 weeks, in contrast to the relatively stable renal profile of patients with CKD alone, even though thyroid hormone concentrations did not correlate linearly with renal indices in either group. These findings support incorporating thyroid function testing into the routine work-up of patients with stage 3b or more advanced CKD, so that hypothyroidism, when present, can be identified and treated alongside standard CKD care. Given the modest and unevenly sized comparison groups and the observational design, confirmation in larger, ideally multicentre, cohorts with longer follow-up and adjustment for comorbidities is needed before these findings can inform clinical guidelines.

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