ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 04 | April - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A OBSERVATIONAL STUDY OF THYROID DYSFUNCTION IN THE PATIENTS OF CHRONIC KIDNEY DISEASE IN TERTIARY CARE HOSPITAL

General Medicine

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ABSTRACT

Introduction: The pathophysiological processes that make up chronic kidney disease are diverse, and they are all characterised by glomerular filtration rate declines and reduced kidney function. **Aims and objectives:** To determine the level of thyroid hormones in CKD patients and to estimate the prevalence of thyroid dysfunction and correlate between thyroid dysfunction with severity of renal disease. **Methodology:** This is a hospital based cross sectional study conducted in Department of Medicine (Medicine wards, Nephrology unit and OPD) in Tertiary Care Hospital, on 150 patients with or without CKD. **Results:** Low T3 syndrome, Sub-clinical hypothyroidism and Hypothyroidism was found in 21.33%, 13.33% and 42.66% cases respectively. High T4 was found in 2.66% patients and high T3 was found in 2.66% patients. **Conclusion:** Early diagnosis and treatment of these thyroid abnormalities may change the course of the condition and lower the morbidity rate in CKD patients.

KEYWORDS

Chronic Kidney Disease, Thyroid Dysfunction

INTRODUCTION

Several pathophysiological disorders are referred to as having chronic kidney disease [1] (CKD), which is characterised by decreased glomerular filtration rate and impaired kidney function (GFR). End-stage renal disease (ESRD) is a stage of chronic kidney disease (CKD) marked by an irreversible loss of endogenous renal function and accumulation of toxins, fluids, and electrolytes that are typically removed by the kidneys. This causes the development of uremic syndrome, which, unless the toxins are eliminated by renal replacement therapy, results in mortality.[2]

CKD is a significant global health issue. In the US, 20 million persons have CKD, either with or without a reduced glomerular filtration rate (GFR). With a population of over 1 billion, India's increasing prevalence of CKD is projected to cause significant issues in the coming years for both the healthcare system and the country's economy. In fact, it was recently determined that India has an age-adjusted incidence rate of ESRD of 229 per million people (ppm).[3]

India has a prevalence of CKD of about 0.785% [4] Obstructive uropathy, including calculus (2.9%), chronic glomerulonephritis (16–20%), chronic interstitial nephritis (5.4–12.7%), heredofamilial disease (8.4%), and diabetic nephropathy are the primary causes of these , with diabetic nephropathy accounting for 30–40% of cases. [5] According to several studies [6-9], the prevalence of thyroid dysfunction in CKD ranges from 13% in early CKD to 70% in ESRD.

Being an organ responsible for excretion, of waste body products, toxins (urea, ammonia, potassium, drug metabolites, water, protein filtration), metabolism (Vitamin D), homeostasis and production [10,11] of various hormones (Erythropoietin, Renin etc); diseases affecting kidney lead to a wide spectrum of metabolic derangements in body functions. All endocrine functions of the body are affected due to various mechanisms, from protein loss to effect of toxic waste products on hypothalamus-pituitary-thyroid axis. If reversible factors, like hypertension, urinary tract infection, autoimmune diseases are not taken care of, it can progress to ESRD. Despite successful treatment of reversible factors, not infrequently, many forms of renal injury may progress to ESRD.

Since kidney is the only organ that competes with thyroid for iodide clearance, they are closely related to each other. [12] It also plays an important role in thyroid catabolism, peripheral conversion of thyroid hormone, in storage and excretion of inorganic iodide. Thyroid functions are altered in CKD. Patients with CKD have many signs and symptoms in common with thyroid dysfunction like pedal oedema, puffiness of face, dry skin, cold intolerance, decreased BMR, asthenia and hyporeflexia. [13]

There is a wide open field for the investigation of effect of CKD on thyroid function and of its treatment on prognosis of CKD. Given the fact that, recent advances in management of CKD have improved survival and hence increased prevalence of ESRD; thyroid dysfunction is increasingly detected and treated. So to understand the effect of CKD on Thyroid function, the current study was conducted.

AIMS

- To determine the level of T3, T4 & TSH in CKD patients.
- To estimate the prevalence of thyroid dysfunction in patients with CKD.
- To correlate between thyroid dysfunction with severity of renal disease.

METHODOLOGY

This is a hospital based cross sectional study conducted in Department of Medicine (Medicine wards, Nephrology unit and OPD) in tertiary care hospital, Pune from 1st November 2020 to 31st October 2021. The sample size was calculated using the formula

$n = z^2pq / d^2$ where —

n = sample size,

z = 1.96 (considering 0.05 alpha, 95% confidence limits and 80% beta)

p = assumed probability of occurrence or concordance of results q = 1 — p

d = marginal error (precession)

We assumed that 25% with 10% absolute precision (15-35%) prevalence of thyroid dysfunction among chronic kidney disease patients. This accumulates 72 subjects by using above given formula. Hence we considered a total of 150 patients (75 CKD (case) and 75 control (normal) patients).

Inclusion Criteria

- Patients willing to be a part of study.
- Patients with CKD were considered as cases.
- Patients without CKD were considered as controls.

Exclusion criteria

Individuals having a history of recent surgery, trauma, burns, a thyroidectomy, or a thyroid problem An ANC patient.

Patients who are unwilling to participate in the trial. Medications that affect the thyroid profile (like amiodarone, steroids, phenytoin, beta blockers, oestrogen pills, iodine containing drug)

Study Protocol

In each patient, relevant case history and clinical findings were recorded and necessary investigations were carried out to establish diagnosis of Chronic Renal Failure.

Criteria for CKD in our study

- Symptoms of Uremia for 3 months or more
- Elevated Blood Urea, serum Creatinine level and decreased creatinine clearance.
- USG evidence of CKD.
- ➢ Bilateral Contracted Kidneys :- < 8 cm in Males and < 7 cm in Females.
- ➢ Poor cortico-medullary differentiation.
- ➢ Type 1, 2 and 3 renal parenchymal disease.
- ➢ Laboratory evidence of CKD: Anaemia altered Serum electrolytes.

Investigations:-

Blood investigations such as Haemoglobin (Model Mindray), urine examination, blood biochemistry (serum Creatinine, blood Urea, blood sugar, serum proteins, serum sodium, serum Potassium, eGFR(Cockcroft Gault Formula), thyroid function tests) were conducted. USG abdomen was carried out for the determination of kidney size, echogenecity and corticomedullary differentiation as well as to visualize calculi if any. It was performed by Diagnostic Ultrasound equipment with colour Doppler (LogiQ-3 Expert) Model no. AY-15CUK.

Data analysis

An Excel spreadsheet was used to enter the data, which was then total. Statistics were deemed significant at P<0.05. Using SPSS and Microsoft Excel, the t-test, chi-square test, Fisher's exact test, and Karl Pearson's correlation were used to statistically analyse the data.

RESULTS

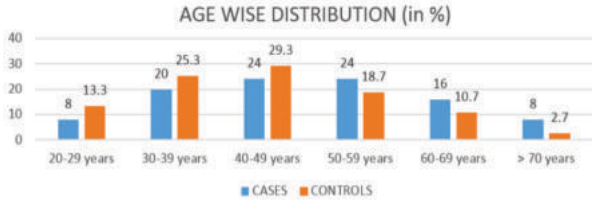

Figure 1: Age wise distribution of cases and controls

The mean age in the cases was 49.11 ± 13.20 years and in controls was 45.12 ± 12.34 years. The difference was found to be statistically not significant (p=0.61).

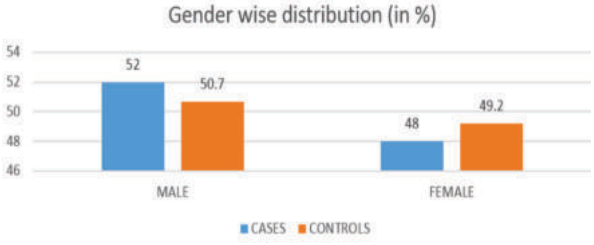

Figure 2: Gender wise distribution of cases and controls

In the cases, there were 39 (52.0%) males and 36 (48.0%) females, while in the controls, there were 38 (50.7%) males and 37 (49.3%) females. No statistically significant association seen between gender and subjects

Table 1: Serum creatinine levels

Sr.no	Serum Creatinine (mg/dl)	No of patients	Percentage
1	1.5-2 mg/dL	1	1.3%
2	2.1-2.5 mg/dL	5	6.7%
3	2.6-3 mg/dL	7	9.3%
4	3.1-5 mg/dL	20	26.7%
5	>5 mg/dL	42	56%
	Total	75	100%

In the above table 1 (1.3%) patient were in the range 1.5-2.0mg/dl, 5 (6.7%) patients were in the range 2.1-2.5 mg/dl, 7 (9.3%) patients were in the range 2.6-3.0 mg/dL, 20 (26.7%) patients were in the range 3.1-5.0 mg/dL and 42 (56.0%) patients were having serum creatinine level more than 5 mg/dL.

Table 2: Distribution of patients in relation to eGFR

Sr.no	eGFR	No of cases	Percentage
1	<15	51	68%
2	15-29	18	24%
3	30-59	6	8%
4	60-89	0	0%
5	≥90	0	0%
	Total	75	100%

In table no.2 - 51 (68.0%) patients were having eGFR <15, 18(24.0%) patients were having eGFR between 15-29 and 6 (8.0%) patients were having eGFR between 30-59. Majority of the patients were having low eGFR.

Table 3: Ultrasonographic findings in CKD

Sr.no	USG finding	No of patients	Percentages
1	RPD grade I	31	41.3%
2	RPD grade II	35	46.7%
3	RPD grade III	9	12%
	Total	75	100%

In table no.3-31 (41.3%) patients were having RPD grade I, 35 (46.7%) patients were having RPG grade II and 9 (12.0%) patients were having RPD grade III. Majority of the CKD patients were having RPD grade II.

Table 4: comparison of thyroid function tests

Thyroid function	Cases	Controls	P value
Total T3 (ng/dl)	74.67±70.12	147.17 ± 38.54	0.001*
Total T4	5.29 ± 3.60	7.26 ± 2.11	< 0.001
TSH (IU/ml)	7.05 ± 5.15	1.77 ± 0.88	0.001*

Table 5: Comparison of thyroid function between cases and controls

S.no	Thyroid	Cases (CKD)		Controls (non-CKD)	
		Number	Percentage	Number	Percentage
1	Other*	41	54.7	75	100
2	Overt Hypothyroidism	32	42.7	0	0
3	Hyperthyroidism	2	2.7	0	0
	Total	75	100	75	100

*Other = Euthyroid/Subclinical hypothyroid/Low T3/High T3/ High T4

In cases, 41 (54.7%) had other type of thyroid disorder, hypothyroidism and 2 (2.7%) had hyperthyroidism. In controls, 75 (100%) had other type of thyroid disorder.

Table 6: Association between thyroid function and CKD stage

S.no	Thyroid function	CKD				
		1	2	3	4	5
1	Other*	0 (0%)	0 (0%)	4 (66.7%)	10 (55.6%)	27 (52.9%)
2	Overt Hypothyroidism	0 (0%)	0 (0%)	1 (16.7%)	7 (38.9%)	24 (47.1%)
3	Hyperthyroidism	0 (0%)	0 (0%)	1 (16.7%)	1 (5.6%)	0 (0%)
	Total	0 (0%)	0 (0%)	6 (100%)	18 (100%)	51 (100%)

*Other = Euthyroid/Subclinical hypothyroid/Low T3/High T3/ High T4

Chi-square value = 7.763, df=4, p value=0.101, Not significant

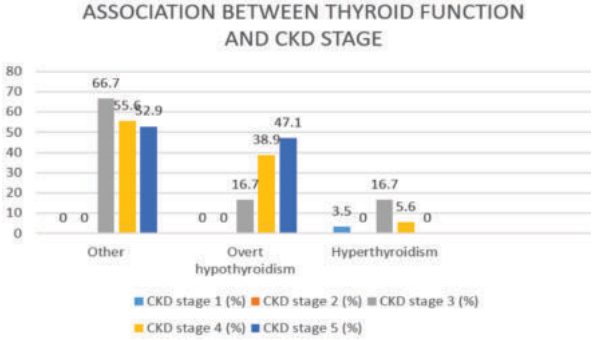

Figure 3: Association between thyroid function and CKD stage

Table 7: Thyroid function tests in cases

Sr. no	Thyroid function test	No of patients		
		Below normal range	Within normal range	Above normal range
1	TT3	50 (66.7%)	21 (28%)	4 (5.3%)
2	TT4	33(44%)	40 (53.3%)	2 (2.7%)
3	TSH	4 (5.3%)	29 (38.7%)	42 (56%

In majority of the patients TT3 was below the normal range, TT4 in majority of the patients was within the normal range and TSH in majority of the patients was above the normal range

Table 8: Thyroid dysfunction

Sr. no	Type of thyroid dysfunction	No. of patients	% of thyroid dysfunction
1	Low T3 (Normal TSH)	16	21.3
2	Hypothyroidism (Low T3, high T4, high TSH)	32	42.7
3	Subclinical hypothyroidism (Normal T3, High TSH)	10	13.3
4	High T4	2	2.7
5	High T3	2	2.7
6	Hyperthyroidism (Low TSH, high T3 and T4)	2	2.7

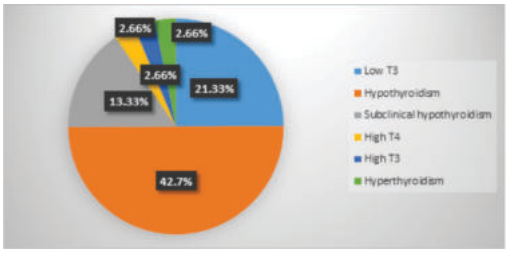

Figure 4: Thyroid dysfunction

Table 8: Correlation of eGFR and thyroid function tests

TFT	eGFR			P*1/2	P*1/3	P*2/3	Anova p-value
	<15 (51)	15-29 (18)	≥30 (6)				
TT3	61.29 ± 6.37	70.58 ± 33.09	116.05 ± 70.23	0.921	0.001*	0.014*	<0.05
TT4	10.15 ± 6.29	7.08 ± 3.36	8.79 ± 3.38	1.000	1.000	1.000	>0.05
TSH	8.17 ± 3.83	6.89 ± 4.26	2.02 ± 0.48	0.677	0.001*	0.025*	<0.05

P 1/2: Comparison between 1st group and 2nd group of eGFR.
P 1/3: Comparison between 1st group and 3rd group of eGFR.
P 2/3: Comparison between 2nd group and 3rd group of eGFR.

Table 12: Comparison of biochemical parameters between cases and controls

S.no	Parameters	Case	Control	Sig. (2-tailed) P-value
1	Urea (mg/dl)	238.87 ± 76.08	19.36 ± 9.51	0.001*
2	Creatinine (mg/dl)	4.78 ±1.52	0.92 ±0.57	0.001*
3	Total protein (g/dl)	5.81 ± 0.96	7. 27 ± 0.96	0.001*
4	Albumin (g/dl)	3.17 ± 0.53	3.97 ± 0.53	0.001*
5	Sodium (mcq/l)	137.00 ± 3.18	142.49 ± 3.17	0.001*
6	Potassium (mcq/l)	5.37 ± 0.53	4.27 ± 0.53	0.001*
7	Calcium (mg/dl)	8.47 ± 0.56	9.42 ± 0.56	0.001*
8	eGFR (ml/min/1.73 m2)	15.11 ± 9.63	101.17 ± 9.19	0.001*

Unpaired t test applied. P value <0.05 was taken as statistically significant

Serum urea, serum creatinine, serum potassium were found to be significantly higher in cases in comparison to the control group (p<0.05), while serum total proteins, serum albumin, serum sodium, serum calcium and eGFR were found to be significantly higher in the control group in comparison to the cases (p<0.05).

DISCUSSION

Our study was carried out from 1st November 2020 to 31st October 2021 at the Department of Medicine, in Tertiary Care Hospital, Pune, to investigate any potential links between chronic kidney disease (CKD) and thyroid dysfunction, to ascertain the prevalence of thyroid dysfunction in those with kidney disease, to assess how closely it relates to the magnitude of renal disease, and to compare the clinical profiles of those with and without thyroid dysfunction in those with CKD. Also, it assessed how kidney function was connected to changes in thyroid hormone levels throughout time (eGFR).

The mean age of cases in the current study was 48.21 ± 13.764 years while in the control group, it was 45.93 ± 12.03 years. 24% of the cases belonged to the age group of 40-49 years and 50-59 years in cases and controls respectively. The age of the patients of CKD in our study ranged from 26 to 80 years and in control group from 26 to 78 years. This difference in both the groups was statistically insignificant. Similar results were obtained by **Paudel et al** [14] with a mean age of 27.2 ± 15.6 years and **Lo JC et al** [15] with a mean age of 48.7 ± 18.9 years. **Abdel-Aziz et al** [16] conducted a study on 90 subjects having CKD and found the subjects to have a mean age of 40.17± 12.58 years.

In the current study, a male (52%) predominance was noted in the study group with the male to female ratio being 1.08:1. The control group showed comparable sex distribution with 50.7% male and 49.3% females. The male to female ratio was 1.02:1. The results of our study were consistent with studies of **Lo JC et al** [15] who observed 52% female population in their study and **Rajeev G et al** [17] who had sex matched case and controls.

The mean value of serum creatinine in our study group was 6.74 ± 3.84 mg % while in the control group, it was 0.701± 0.092 mg %. The blood urea levels in the cases and controls were 183.75 ± 85.53 mg/dl and 22.83 ± 5.06 mg/dl respectively. **Laddha M et al** [18] found mean blood urea level 151.7 ± 51.37 mg% and mean serum creatinine level 10.35 + 5.56 gm%. **Shivendra S et al** [19] found mean blood urea level 150.62 ± 55.75 mg/dl and mean serum creatinine level 8.13 ± 2.27 mg/dl in their study.

In our study the mean serum sodium level in case group was 133.2± 4.72 mEq/L and control group was 140.2±4.07meq/1. Mean serum Potassium level in case group was 5.33±0.62 meq/1 and control group was 4.23±0.3meq/1. Mean serum calcium level in case group was 8.62 ± 0.91mg/d1 and control group was 9.55 ± 0.67 mg/d1. Thus Sodium and calcium levels were significantly reduced in the CKD patients and potassium level significantly increase in CKD patients as compared to normal healthy control. **Shivendra S et al** [19] found mean serum calcium level 8.72 ± 1.16 mg/dl and **Foley RN et al** [20] found mean serum calcium level 8.4 ± 1.2 mg/d1. Thus results of our study were consistent with the above mentioned studies.

There was a significant decrease in serum T3 level (69.58 ± 38.28), T4 level (6.07± 2.55) and elevation of TSH level (7.42 ± 4.25) in cases as compared to controls where it was 113.96± 15.40, 7.54±1.38 and 2.13 ± 0.87 respectively. **Shamsuddin et al** [21] showed in their study that T3, T4 decreased and TSH increased significantly (P<0.05) in cases compared to controls. **Rakesh K et al** [22] observed that serum T3, T4 mean significantly decreased when compared to controls, but no significant difference was seen in TSH when compared to controls.

Among CKD patients and controls, overt hypothyroidism was discovered in 32 patients (42.66%) and overt hyperthyroidism in 2 patients (2.67%). Our investigation revealed that the stage of CKD is independent of the kind of thyroid dysfunction because we were unable to detect any meaningful correlation between thyroid function and CKD staging. Out of 75 patients, 53.33% patients had TT3 below normal range and 44% within normal range. TT4 in 66.66% patients was within normal limits and in 30.67% patients, it was below normal limit. So TT3 and TT4 were found to be reduced in CKD patients**. Horkek J et al** [23] observed that thyroid dysfunction and low T3 were particularly common (44.3 %) in HD patients. **Danciulescu et al** [24] also found significant subclinical hypothyroidism, low T3 and hypothyroidism in a group of 23 individuals with CKD. **Rajeev G et al** [17] showed that In 88% of CKD patients, the serum total T3 levels was below the normal limit. In addition, 33% of patients had lower total serum T4 concentrations than the controls, while 60% of people with CKD had higher serum TSH concentrations. **Abdel-Aziz et al** [16]**,** observed that there was significant fall in the serum levels of TT3 and TT4 as compared to normal individuals. **Rakesh K et al** [22] observed

that there was significant reduction of serum T3, T4 mean in comparison of controls.

TSH was found to be above normal in 56% cases. So TSH was increases in CKD patients. Results of our study were consistent with studies by **Rajeev G et al** [17] who observed increased serum TSH levels in 60% cases with CKD. **Danciulescu et al** [24] showed, substantially raised levels of TSH (30.43%) in diabetic CKD patients, as compared to those without CKD. **Allawi A et al** [25] conducted a cross sectional study of 50 patients of CKD and found 16% patients having raised TSH with a significant change as compared to controls. **Kim EO et al** [26] also observed elevated TSH levels in 24.4% CKD patients.

While studying effect of CKD, it was found that, any long term disease or stress is responsible to cause alteration in function, production or action of thyroid hormones (called as Non thyroidal Illness.) We attempted to know the prevalence of such illness in patients of CKD. We found 80% cases to be having some sort of thyroid dysfunction i.e. changes in concentrations of thyroid hormones. **Prajapati P et al** [9] in their study observed 70% of CKD cases to be having abnormal thyroid functions.

The fact that thyroid dysfunction was more common in our study than it had been in previous ones could be attributed to the smaller sample size. The majority of the study participants had CKD stages 4 or 5, which may be related to the fact that many CKD patients are admitted to this tertiary care facility with low eGFR levels.

In our study, Low T3 syndrome, Sub-clinical hypothyroidism and Hypothyroidism was found in 21.33%, 13.33% and 42.66% cases respectively. High T4 was found in 2.66% patients and high T3 was found in 2.66% patients. Studies done by **Mehta et al** [27], **Kayima et al** [28], **Avasthi et al** [29] **and Song et al** [30] found various degrees of thyroid dysfunction, but none had reported prevalence of different thyroid dysfunctions which could be observed in a patient of CKD

Mean T3 in 1st group (eGFR< 15 ml/min/1.73m2) was 61.29 ± 26.37 while in 2nd group (eGFR 15 — 29 ml/min/1.73m2) it was 70.58 ± 33.09 and in 3rd group (eGFR> 30 ml/min/1.73m2) it was 116.05 ± 70.23. Significant difference was observed between 1st and 3rd group and 2nd and 3rd group of eGFR in T3 value. Mean TSH in 1st, 2nd and 3rd group was 8.17 ± 3.83, 6.89 ± 4.26 and 2.02 ± 0.48 respectively. A negative, significant correlation was seen with the fall in eGFR and the level of TSH. Mean T4 in 1st.2nd and 3rd group was 10.15 ± 16.29, 7.08 ± 3.36 and 8.79 ± 3.38 respectively. Thus, in our study a positive significant correlation was seen with the fall in eGFR with the level of T3 and a negative significant correlation was seen between TSH and eGFR.

Kim EO et al [26] showed that unresolved subclinical hypothyroidism and the rate of eGFR decline may be predicted directly by multivariate linear regression. The rate of renal function decline was independently correlated with both the initial renal function and the degree of proteinuria. Consequently, a decline in eGFR was directly related to a decrease in thyroid hormones and an increase in TSH.

As thyroid hormone has multiple effects on the kidney, heart, and vascular system, thyroid malfunction can cause significant changes in renal and cardiovascular performance. Primary hypothyroidism is known to cause symptoms such as decreased RPF, increased creatinine levels, reduced GFR, impaired renal salt resorption, and decreased renal ability to dilute urine. As was already mentioned, there are still contradicting results. As a result, extensive follow-up research involving a big population is necessary.

CONCLUSIONS

When cases were compared to controls, there was a significant decrease in serum T3 and T4 levels and an increase in TSH levels. 60 individuals had altered thyroid function, of whom 42.7% had overt hypothyroidism, 21.3% had low T3 syndrome, and 13.3% had sub-clinical hypothyroidism. The decrease in serum TT3 level and the rise in TSH level were found to have a strong negative association, but not with the level of TT4. Hence, prompt detection and treatment of these thyroid anomalies may change the course of the condition and aid in lowering CKD patients' morbidity.

Conflict of interest

The Authors have no conflicts of interest that are directly relevant to the content of this clinic-pathological case

Financial Resources

There are no financial resources to fund this study

Informed Consent

Informed Consent was obtained from the patient.

Author's Contribution

All the authors contributed equally to the case report.

Data and materials availability

All data associated with this study done at PCMC'S PGI YCM hospital are present in the paper.

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