Original Article

Protocol and Methods: Role of Levothyroxine on the Progression of Chronic Kidney Disease in Subclinical Hypothyroid Populations (LP-CKD) – A Multicenter Randomized Controlled Trial

Narayan Prasad, Shivendra Singh[1], Vivek Kumar[2], Manisha Sahay[3], Arpita Ray Chaudhury[4], Manas Ranjan Behera, Ravi Shankar Kushwaha, Deependra Yadav, Sonam Gautam, Akhilesh Jaiswal

Department of Nephrology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, [1]Institute of Medical Science, Banaras Hindu University, Varanasi, Uttar Pradesh, [2]Institute of Medical Education and Research, Chandigarh, [3]Osmania Medical College, Osmania General Hospital, Hyderabad, Telangana, [4]Post Graduate Medical Education and Research, Kolkata, West Bengal, India

Abstract

Introduction: Subclinical hypothyroidism (SCH) is highly prevalent and associated with chronic kidney disease (CKD). However, it is still unanswered whether the restoration of euthyroid status in these patients will be beneficial in retarding a decline in glomerular filtration rate in early CKD patients. We aim to evaluate the efficacy of levothyroxine therapy versus placebo in slowing estimated glomerular filtration rate (eGFR) decline among CKD patients (stage 2–4) with SCH. **Methods:** This study will be a multicentric, double-blind, randomized, parallel-group, placebo-controlled study. A total of 500 CKD patients, 250 patients in the treatment group and 250 patients in the placebo group, will be randomized. The randomization between the treatment arm and placebo arm will be performed as per the computer-generated random number table in a 1:1 ratio. The sample size was calculated based on the assumed reduction in eGFR after 1-year follow-up in the treatment and placebo groups of 10% and 25%, respectively, at a minimum two-sided 99% confidence interval and 90% power of the study and considering 20% loss on follow-up. Each patient will be followed every 3 months for at least 1 year after randomization. Individuals completing 1-year follow-up visits will be considered for analysis. The baseline and follow-up data will be compared between the treatment and placebo groups. The study will evaluate the efficacy and safety of levothyroxine therapy versus placebo in slowing eGFR decline among CKD patients (stage 2-4) with SCH. The primary endpoint will be the end of follow-up of the patients, reduction of eGFR by ≥50% from a baseline of that patient, or development of ESKD or death of the patients. The secondary endpoint will be any cardiovascular event or arrhythmia after the institution of the drug.

Keywords: *Chronic kidney disease progression, estimated glomerular filtration rate, levothyroxine, subclinical hypothyroidism*

Introduction

Chronic kidney disease (CKD) affects more than 10% of the Indian population, and many progress to end-stage kidney disease (ESKD) or develop complications such as CVD and infections.[1-3] The kidney plays an important role in the metabolism, degradation, and excretion of thyroid hormones. CKD affects thyroid function in several ways, including low circulating thyroid hormone levels, altered peripheral hormone metabolism, insufficient binding to carrier proteins, reduced tissue thyroid hormone content, and altered iodine storage in the thyroid gland.[4,5] CKD is associated with a higher prevalence of overt and subclinical hypothyroidism (SCH).[6,7] Experimental studies revealed that deficiency of thyroid hormone lowers blood pressure,[8] increases vascular resistance,[9] and reduces renal sodium reabsorption,[10,11] which leads to volume contraction and reduced renal blood flow.[12] These events ultimately lead to a decline in the glomerular filtration rate (GFR).

Lo *et al*.[6] showed that the decline in GFR and CKD is associated with hypothyroidism with a higher prevalence of subclinical hypothyroidism up to the tune of 56%, which increases with a decline in GFR.[6] while another study revealed an 18% prevalence among the non-dialysis CKD population.[7] The beneficial impact of treating overt hypothyroidism on cardiovascular complications[12,13] and the decline in GFR are known.[14-16] The reduced GFR reverts to normal after treatment of hypothyroidism.[16-19] CKD patients are

How to cite this article: Prasad N, Singh S, Kumar V, Sahay M, Chaudhury AR, Behera MR, *et al*. Protocol and methods: Role of levothyroxine on the progression of chronic kidney disease in subclinical hypothyroid populations (LP-CKD) – A multicenter randomized controlled trial. Indian J Nephrol 2023;33:449-55.

Received: 31-05-2022
Revised: 05-08-2022
Accepted: 09-11-2022
Published: 05-06-2023

Address for correspondence:
Prof. Narayan Prasad, Department of Nephrology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India. E-mail: narayan.nephro@gmail.com

Access this article online

Website: https://journals.lww.com/ijon

DOI: 10.4103/ijn.ijn_188_22

Quick Response Code:

at higher risk of cardiovascular complications.[20] A few observational studies showed clear associations between SCH and an increased risk for heart failure, coronary heart disease, and mortality.[21,22] The association between SCH and lower renal function is poorly established.[23-25] Two studies from the same group showed that thyroid hormone replacement attenuates the decline in GFR in patients with SCH and CKD.[23,24] However, no association between thyroid hormone status and a decline in renal function was observed in a population-based study of elderly patients.[25] One recent study has shown that low thyroid function is not associated with a deterioration of renal function and has emphasized that the cross-sectional association may be explained by renal dysfunction causing thyroid hormone alterations. On the other hand, hyperthyroidism is known to accelerate the deterioration of renal function.[14,26] Levothyroxine (LVT) has a narrow therapeutic index and may pose the risk of iatrogenic thyrotoxicosis. LVT may also lead to increased protein catabolism and arrhythmia.[5,12] However, a very smaller dose of LVT (25–50 mcg/d) is required to treat SCH, and regular monitoring may obviate the side effects.

The multiple observational studies notwithstanding, there is a lack of randomized controlled trial (RCT) data on the effect of the progression of CKD with thyroid hormone replacement therapy for SCH in CKD patients. We plan to conduct a Randomized controlled trial (RCT) to look for the impact of LVT therapy, with the primary objective of finding its effect on the progression of CKD and the secondary objective of determining its effects on cardiovascular disease and mortality in SCH populations of CKD.

Materials and Methods

Study design: This study will be a multicentric, double-blind, randomized, parallel-group, placebo-controlled study. All patients of CKD (stages 2–4) with SCH visiting the outpatient clinics will be screened for evidence of SCH. Informed written consent will be obtained from each patient. All those patients who fulfill the criteria for the study will be allocated into two groups as per the computer-generated random number table in a 1:1 ratio. Patient enrollment will be stratified according to the CKD stage, aiming for at least 30% in each stage (stage 2, 3, and 4) of CKD. The total study duration will be 3 years, and patients will be recruited over 1½ years of the study. Each patient will be followed every 3 months for 1 year after randomization.

Participating centers: Department of Nephrology, Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS), Lucknow, is the principal coordinating center, with five participating centers across India [Figure 1]. SGPGIMS has all accountability regarding randomization, operational, financial, and quality control aspects of the study. Investigators from all the centers will be supervising trial progress, data collection, data analysis, and publication of study results. Every year, the progress report will be submitted to the Indian Council of Medical Research (ICMR), New Delhi. The present trial has received funding from the ICMR, New India (5/4/7-8/2019-NCD-II).

Study subjects: They include stage 2, 3, and 4 CKD patients with SCH, as per the inclusion and exclusion criteria given in Table 1. The randomized patients will be either receiving LVT or a matching placebo.

Definitions

Staging of CKD: CKD staging will be done as per the American National Kidney Foundation staging criteria as follows: stage 1: estimated glomerular filtration rate (eGFR) ≥90 ml/min/1.73 m^2; stage 2: eGFR 60–89 ml/min/1.73 m^2; stage 3: eGFR 30–59 ml/min/1.73 m^2; stage 4: eGFR 15–29 ml/min/1.73 m^2; and stage 5: eGFR <15 ml/min/1.73 m^2 or dialysis.[27] The eGFR will be calculated by the CKD Epidemiology Collaboration (CKD-EPI) equation 2012.[28]

SCH: SCH will be diagnosed based on biochemical parameters, including elevated serum thyroid stimulating

Table 1: Inclusion and exclusion criteria of the LPCKD study

	Inclusion criteria
1.	CKD with eGFR 15–59 ml/min/1.73 m^2
2.	Any degree of albuminuria
3.	Subclinical hypothyroidism
4.	Stable renal function for 3 months
	Exclusion criteria
1.	Age <18 or >65 years
2.	GFR <15 or ≥60 ml/min/1.73 m^2
3.	Patients already on thyroid hormone replacement therapy
4.	Unstable renal course or acute kidney injury in the last 3 months
5.	History of recurrent UTI
6.	Obstructive uropathy or structural disease of kidney or renal tract
7.	History of analgesics abuse, alternative medication, and nephrotoxic agents in the past 3 months
8.	Patients on chronic or intermittent use of NSAIDs for the nature of diseases such as rheumatoid arthritis and so on
9.	H/O coronary artery disease, arrhythmia, structural heart disease, and congestive cardiac failure in the last 6 months
10.	Patients with acute and chronic liver disease
11.	Malignancy
12.	Brain disease – cerebrovascular accident, Parkinson's disease, Alzheimer's disease
13.	Serology positive for hepatitis-B, hepatitis-C, and retrovirus
14.	Kidney transplant recipients
15.	Pregnancy and lactation

CKD=chronic kidney disease, eGFR=estimated glomerular filtration rate, GFR=glomerular filtration rate, LPCKD=role of levothyroxine on the progression of chronic kidney disease in subclinical hypothyroid populations, NSAID=nonsteroidal anti-inflammatory drug, UTI=urinary tract infection

Figure 1: Participating centres in the study across India

hormone (TSH) concentration (4.0–10 μIU/ml) and a normal serum T4/free T4 (fT4) and T3 concentration. The tests will be performed two times within 4 weeks to confirm the diagnosis.

Adverse cardiac events

They are defined as new-onset acute coronary syndrome (ACS) and arrhythmia. Coronary artery disease is defined as a history of myocardial infarction or angina, angiographic evidence showing coronary artery disease, history of angioplasty, coronary artery bypass grafts, and any other investigations showing evidence of coronary artery disease. Arrhythmia will be labelled based on the history of palpitation and confirmation from an electrocardiogram (ECG).

Adverse effects to be monitored: Irritability, heat intolerance, excessive sweating, weight loss, diarrhea, tremor, muscle weakness (proximal myopathy), lid retraction, tachycardia, and palpitation.

Sample size calculation: With the assumed reduction in eGFR after 1 year follow-up in the treatment and placebo groups of 10% and 25%, respectively, at a minimum two-sided 99% confidence interval and 90% power of the study, the calculated sample size in each of the two groups came out to be 189. After considering the loss of follow-up of 20%, the minimum required targeted sample size in each of the two groups was 227. Thus, we will randomize 250 patients in the treatment group and 250 patients in the placebo group. The sample size has been estimated using software G*power version 3.1.9.2 (Dusseldorf, Germany).

Project Implementation plan: The **CONsolidated Standards of Reporting trials** (CONSORT) flow diagram of the study is shown in Figure 2. Patient screening will be done by the primary clinician from the outpatient clinic. Patients will be screened to satisfy the inclusion and exclusion criteria. The initial evaluation will include detailed clinical history, measurement of height, weight, body mass index (BMI), pulse rate, blood pressure, T3, T4/fT4, TSH, anti- Thyroid peroxidase (anti-TPO) antibody, serum creatinine, complete blood count, and lipid profile. Patients will be randomly assigned to the study drug LVT and placebo. Standard therapy for CKD will be continued in both groups. Both groups will continue antihypertensive medications, including angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), and other conservative treatments for CKD as before the study, unless there is a specific contraindication. Drugs and placebo will be continued throughout the study period.

Description of intervention: Patients will be randomly assigned to the study drug LVT and placebo. Allocation concealment will be done using sealed, sequentially numbered, opaque envelopes. They will be consecutively numbered, and medicine will be given out according to the number allocated to the participant. The investigator will be blinded to the allotment as the procedure will be carried out by a third person, a clinical coordinator, and a senior research fellow employed for this purpose. Patients in both groups will receive either LVT or placebo tablets once daily before breakfast. Drugs (LVT or placebo) will be delivered to the patient by hand on a visit to the center, which will be centrally regulated. Both LVT tablets and placebo will be provided as white tablets identical in appearance, taste, and packing. LVT tablets will be supplemented as 25 μg only.

The patients will be initially treated with l-thyroxine 25 μg/d or a placebo. After the start of the thyroid hormone supplement, serum TSH concentration will be remeasured every 12 weeks. If the level of TSH remains above the normal reference range, the dose of the trial drug (LVT 25 μg or placebo) will be increased by one tablet (25 mcg) in the next visit after 3 months. Thyroid hormones T3, T4, and TSH levels will be measured at each visit. The dose will be adjusted until the patient's serum TSH concentration is reduced to the normal reference range.

Apart from LVT, other renoprotective drugs such as ACEI, ARB, febuxostat, and other medicines for the conservative treatment will be continued in both arms as per clinicians' decision and standard indications.

Outcome parameters

The study will evaluate the efficacy and safety of levothyroxine therapy versus placebo in slowing eGFR decline among CKD patients (stage 2-4) with SCH. The primary endpoint will reduction of eGFR by ≥50% from a baseline of that patient, or development of ESKD or death of the

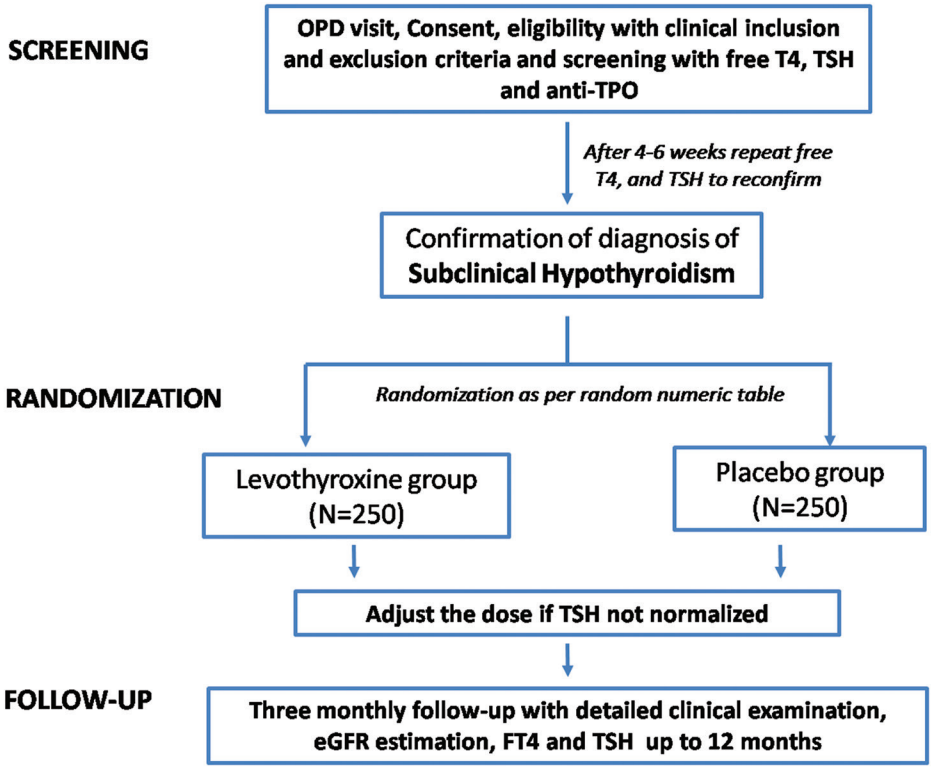

Figure 2: CONSORT flow diagram of the study

patient. The secondary endpoint will be any cardiovascular event or arrhythmia after the institution of the drug.

Follow-up and compliance monitoring: Patients will be evaluated at each visit for a detailed history, physical examination, assessment of any adverse events or endpoints, serum creatinine levels, complete blood count, lipid profile, T3, fT4/T4, and TSH, and any other tests as needed by the treating clinician. History will be taken from the patient by the treating physician, intending to inquire about a drug-related adverse event (as mentioned above), nonsteroidal anti-inflammatory drug (NSAID) abuse, and use of alternative medication. Compliance will be assessed at each visit by history taking and pill counting. On follow-up, if any patient converted into clean hypothyroid with TSH >10, the patient will be terminated from the study and LVT will be started.

Collection, storage, and testing of samples: At baseline and at each visit, the sample will be collected for complete blood count, blood urea nitrogen(BUN), serum creatinine, T3, fT4/T4, TSH, and lipid profile (total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], and triglyceride). BUN, serum creatinine, T3, fT4/T4, TSH, and lipid profile will be done at individual centers if the same laboratory facilities are available. Otherwise, they will be done in the principal investigator's central lab identified for this purpose. Blood will be centrifuged; serum will be separated and will be stored at −80°C until final analyses will be carried out if required. Serum T3, fT4/T4, and TSH levels will be analyzed by chemiluminescence assay on a Roche Cobas E601 analyzer. Serum anti-TPO concentration will be analyzed by chemiluminescence assay on a Siemens Immulite 1000 analyzer. The reference ranges of T3, fT4/T4, TSH, and anti-TPO antibodies will be 1.2–2.1 nmol/l, 12–22 pmol/l, 0.4–4.0 μIU/ml, and <30 kIU/l, respectively.

Discontinuation of patients from the study: Patients who will develop adverse cardiac event or acute kidney injury or will need kidney replacement therapy (KRT) for a reason other than the natural course of the disease or who are lost to follow-up during the study period will be discontinued from the study. Any patient who will withdraw consent for the study will also be discontinued. The CO-PI of the respective centre will decide about the KRT and other clinical adverse events.

Ethical review: The study protocol has been approved by the Institutional Ethics Committee, SGPGIMS, Lucknow, India (IEC Code: 2019-52-EMP-108). The study is also registered in the Clinical Trials Registry-India (REF/2019/02/024293). Each participating center has obtained ethics clearance from the ethics committee of the respective institute. The study protocol and procedures are concordant with the principles of the Declaration of Helsinki. Informed consent will be taken from all patients before screening and inclusion in the study at all centers.

Data collection and statistical analysis plan: Data collection will be done through the specific website developed for this study purpose. The LPCKD study's website has been created with the domain name https://lpckd.com/. Separate login and passwords have been created for each center included in the study. The website includes registration, screening, randomization, and follow-up sections. The demographic, biochemical, medications, and events columns are given in the data entry section, and the data can be entered at each patient visit. The consent and prescription can also be attached separately. A specific user login name and password will be created for each participating center. Individuals completing 1-year follow-up visits will be considered for analysis. The baseline and follow-up data will be compared between the LVT and placebo groups. The normality of the continuous variables will be examined using the Kolmogorov–Smirnov test. Data will be presented as mean ± standard deviation for normally distributed variables and median (interquartile range) for non-normally distributed variables. Two-way repeated measures analysis of variance (ANOVA) will be used to test the changes in mean values on follow-up and their association with the study groups (treatment/control). Bonferroni corrections will be used for multiple comparisons. McNemar test will be used to determine the differences in dichotomous dependent variables between two related groups. Cochran's Q test will be used to test the changes in binary outcomes at different time points of follow-up in the case of more than three related variables. A P value <0.05 will be considered statistically significant. Statistical Package for Social Sciences version 20 (SPSS 20; IBM, Chicago, IL, USA) will be used for statistical analyses.

Discussion

The uremic milieu with inflammation and metabolic acidosis in CKD affects the functioning of the hypothalamic–pituitary–thyroid axis.[5] The peripheral conversion of T4 to T3 and its protein binding is reduced. Isolated low T3 level is the most common finding, followed by SCH.[26] It has been observed that as the GFR declines, the prevalence of primary hypothyroid, particularly the subclinical form, increases.[7] Hypothyroidism, both overt and subclinical, is a risk factor for incident CKD and a decline in GFR on follow-up.[29-31] Varied renal manifestations with proteinuria and defect in urinary acidifications had also been observed.[32-34] A linear trend between TSH elevation and CKD was observed in a case-control analysis.[35] The schematic diagram of complications and alterations in CKD with SCH is shown in Figure 3.

However, a few studies did not reveal the same association.[25] Attempts to replace thyroid hormones may lead to increased muscle catabolism, and both overt hypothyroidism and SCH may lead to an increased risk of cardiovascular disease and death in CKD.[36,37] Randomized controlled trial evidence to treat SCH or not is limited to a specific group of patients and is small.[38-40] One study[39] in elderly SCH and two retrospective studies[23,24] showed a reduction in decline in GFR in CKD patients

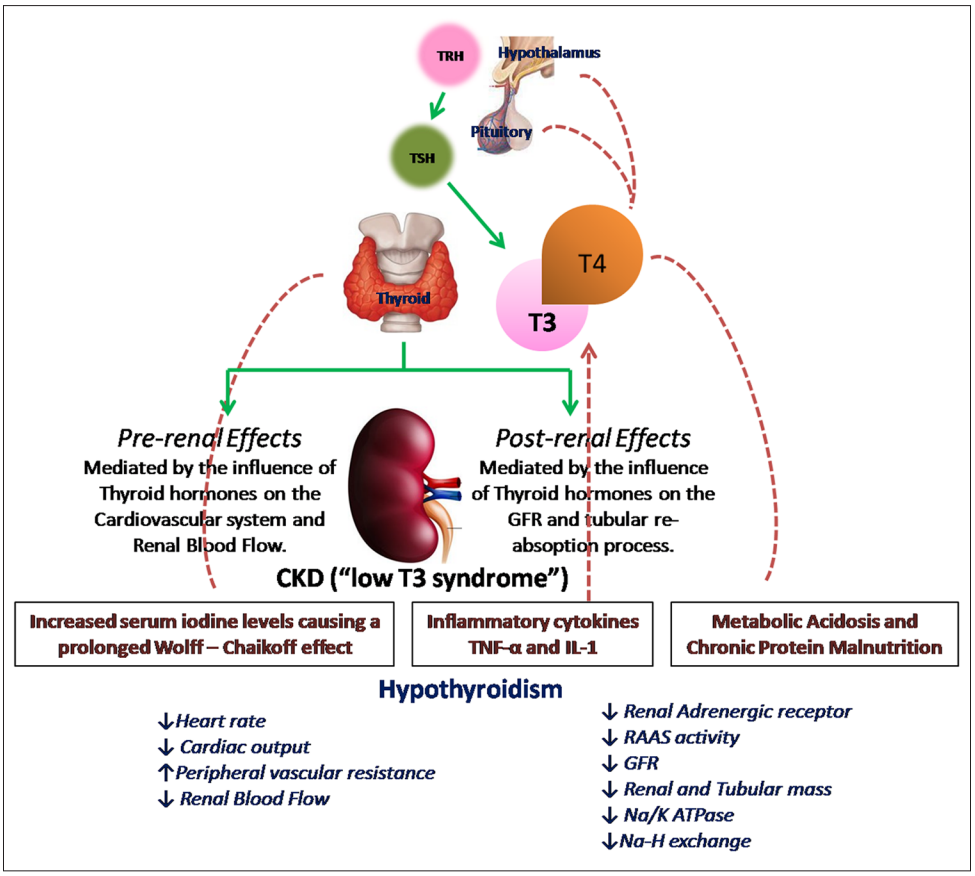

Figure 3: Schematic diagram of complication and alterations in CKD with subclinical hypothyroidism

with SCH. Biondi *et al*.[41] recommended LVT treatment for patients with SCH and TSH levels of 10 mU/l or higher, as well as those with mild hypothyroid symptoms. Recently, a retrospective database analysis on LVT treatment in CKD and SCH patients showed an absence of the overall benefit in eGFR; however, LVT use shortens the length of hospital stay.[42] There is possibly no association between low free thyroxine levels and CKD progression.[43] The progression of CKD was higher in the presence of proteinuria, with no effect on thyroxine levels. The present study is a large double-blind, placebo-controlled multicentric RCT. The design of the study is such that the study includes all early CKD patients This is the first large multicentric, well-powered study to resolve the issue of treating or not SCH in CKD patients.

Conclusion

SCH is prevalent in CKD patients. The association of SCH with the decline in GFR has been studied. However, whether achieving euthyroid status with LVT replacement will improve the GFR of the patients is unknown. This will be the first RCT to address the treatment of SCH in CKD patients.

Financial support and sponsorship

The study is funded by the Indian Council of Medical Research, New Delhi, India (5/4/7-8/2019-NCD-II).

Conflicts of interest

There are no conflicts of interest.

References

1. Ene-Iordache B, Perico N, Bikbov B, Carminati S, Remuzzi A, Perna A, *et al*. Chronic kidney disease and cardiovascular risk in six regions of the world (ISN-KDDC): A cross-sectional study. Lancet Glob Health 2016;4:e307-19.
2. Varughese S, Abraham G. Chronic kidney disease in India: A clarion call for change. Clin J Am SocNephrol 2018;13:802–4.
3. Jha V. Current status of end-stage renal disease care in South Asia. Ethn Dis 2009;19 (1 Suppl 1):S1-27–32.
4. Kaptein EM. Thyroid hormone metabolism and thyroid diseases in chronic renal failure. Endocr Rev 1996;17:45–63.
5. Rhee CM. The interaction between thyroid and kidney disease: An overview of the evidence. Curr Opin Endocrinol Diabetes Obes 2016;23:407-15.
6. Lo JC, Chertow GM, Go AS, Hsu C-Y. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. Kidney Int 2005;67:1047–52.
7. Chonchol M, Lippi G, Salvagno G, Zoppini G, Muggeo M, Targher G. Prevalence of subclinical hypothyroidism in patients with chronic kidney disease. Clin J Am Soc Nephrol 2008;3:1296–300.
8. Wikström L, Johansson C, Saltó C, Barlow C, Campos Barros A, Baas F, *et al*. Abnormal heart rate and body temperature in mice lacking thyroid hormone receptor alpha 1. EMBO J 1998;17:455-61.

9. Liu KL, Lo M, Canaple L, Gauthier K, Del Carmine P, Beylot M. Vascular function of the mesenteric artery isolated from thyroid hormone receptor-α knockout mice. J Vasc Res 2014;51:350-9.
10. Michael UF, Barenberg RL, Chavez R, Vaamonde CA, Papper S. Renal handling of sodium and water in the hypothyroid rat. Clearance and micropuncture studies. J Clin Invest 1972;51:1405-12.
11. Shah M, Quigley R, Baum M. Maturation of proximal straight tubule NaCl transport: Role of thyroid hormone. Am J Physiol Renal Physiol 2000;278:F596-602.
12. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001;344:501-9.
13. Cappola AR, Desai AS, Medici M, Cooper LS, Egan D, Sopko G, *et al*. Thyroid and cardiovascular disease: Research agenda for enhancing knowledge, prevention, and treatment. Thyroid 2019;29:760-77.
14. Basu G, Mohapatra A. Interactions between thyroid disorders and kidney disease. Indian J Endocrinol Metab 2012;16:204-13.
15. Huang CW, Li BH, Reynolds K, Jacobsen SJ, Rhee CM, Sim JJ. Association between hypothyroidism and chronic kidney disease observed among an adult population 55 years and older. Medicine 2020;99:e19569.
16. Rhee CM, Kalantar-Zadeh K, Streja E, Carrero JJ, Ma JZ, Lu JL, *et al*. The relationship between thyroid function and estimated glomerular filtration rate in patients with chronic kidney disease. Nephrol Dial Transplant 2015;30:282-7.
17. The Freeston J, Gough A. Reversible myopathy and renal impairment. J R Soc Med 2004;97:124-5.
18. Mooraki A, Broumand B, Neekdoost F, Amirmokri P, Bastani B. Reversible acute renal failure associated with hypothyroidism: Report of four cases with a brief review of literature. Nephrology (Carlton) 2003;8:57-60.
19. Connor A, Taylor JE. Renal impairment resulting from hypothyroidism. NDT Plus 2008;1:440-1.
20. Liu M, Li XC, Lu L, Cao Y, Sun RR, Chen S, *et al*. Cardiovascular disease and its relationship with chronic kidney disease. Eur Rev Med Pharmacol Sci 2014;18:2918-26.
21. Gencer B, Collet TH, Virgini V, Auer R, Rodondi N. Subclinical thyroid dysfunction and cardiovascular outcomes among prospective cohort studies. Endocr Metab Immune Disord Drug Targets 2013;13:4–12.
22. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA 2010;304:1365–74. Rhee CM. The interaction between thyroid and kidney disease: An overview of the evidence. Curr Opin Endocrinol Diabetes Obes 2016;23:407–15.
23. Shin DH, Lee MJ, Kim SJ, Oh HJ, Kim HR, Han JH, *et al*. Preservation of renal function by thyroid hormone replacement therapy in chronic kidney disease patients with subclinical hypothyroidism. J Clin Endocrinol Metab 2012;97:2732–40.
24. Shin DH, Lee MJ, Lee HS, Oh HJ, Ko KI, Kim CH, *et al*. Thyroid hormone replacement therapy attenuates the decline of renal function in chronic kidney disease patients with subclinical hypothyroidism. Thyroid 2013;23:654–61.
25. Meuwese CL, van Diepen M, Cappola AR, Sarnak MJ, Shlipak MG, Bauer DC, *et al*. Thyroid studies collaboration. Low thyroid function is not associated with an accelerated deterioration in renal function. Nephrol Dial Transplant 2019;34:650-9.
26. Mohamedali M, Reddy Maddika S, Vyas A, Iyer V, Cheriyath P. Thyroid disorders and chronic kidney disease. Int J Nephrol 2014;2014:520281.
27. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis 2002;39 (2 Suppl 1):S1-266.
28. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, *et al*. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.
29. Zhang Y, Chang Y, Ryu S, Cho J, Lee W-Y, Rhee E-J, *et al*. Thyroid hormone levels and incident chronic kidney disease in euthyroid individuals: The Kangbuk Samsung Health Study. Int J Epidemiol 2014;43:1624–32.
30. Montenegro J, Gonzalez O, Saracho R, Aguirre R, Martinez I. Changes in renal function in primary hypothyroidism. Am J Kidney Dis 1996;27:195–8.
31. Kim SH, Min HK, Lee SW. Relationship between thyroid and kidney function: Analysis from the Korea National Health and nutrition examination survey between 2013 and 2015. Kidney Blood Press Res 2020;45:442–54.
32. Vargas F, Moreno JM, Rodriguez-Gomez I, Wangensteen R, Osuna A, Alvarez-Guerra M, *et al*. Vascular and renal function in experimental thyroid disorders. Eur J Endocrinol 2006;154:197–212.
33. Asmah BJ, Wan Nazaimoon WM, Norazmi K, Tan TT, Khalid BA. Plasma renin and aldosterone in thyroid diseases. Horm Metab Res 1997;29:580–3.
34. Mariani LH, Berns JS. The renal manifestations of thyroid disease. J Am Soc Nephrol 2012;23:22–6.
35. Zhou J-B, Li H-B, Zhu X-R, Song H-L, Zhao Y-Y, Yang J-K. Subclinical hypothyroidism and the risk of chronic kidney disease in T2D subjects: A case-control and dose-response analysis. Medicine (Baltimore) 2017;96:e6519.
36. Rhee CM, Alexander EK, Bhan I, Brunelli SM. Hypothyroidism and mortality among dialysis patients. Clin J Am Soc Nephrol 2013;8:593–601.
37. Kang EW, Nam JY, Yoo T-H, Shin SK, Kang S-W, Han D-S, *et al*. Clinical implications of subclinical hypothyroidism in continuous ambulatory peritoneal dialysis patients. Am J Nephrol 2008;28:908–13.
38. Blackaller GN, Chávez-Iñiguez JS, Carreón-Bautista EE, González-Torres FJ, Villareal-Contreras M, Barrientos Avalos JR, *et al*. A pilot trial on the effect of levothyroxine on proteinuria in patients with advanced CKD. Kidney Int Rep 2021;6:110-9.
39. Lu Y, Guo H, Liu D, Zhao Z. Preservation of renal function by thyroid hormone replacement in elderly persons with subclinical hypothyroidism. Arch Med Sci 2016;12:772–7.
40. Liu P, Liu R, Chen X, Chen Y, Wang D, Zhang F, *et al*. Can levothyroxine treatment reduce urinary albumin excretion rate in patients with early type 2 diabetic nephropathy and subclinical hypothyroidism? A randomized double-blind and placebo-controlled study. Curr Med Res Opin 2015;31:2233–40.
41. Biondi B, Cappola AR, Cooper DS. Subclinical hypothyroidism: A review. JAMA 2019;322:153-60.
42. Hennessey JV, Weir MR, Soni-Brahmbhatt S, Duan Y, Gossain VV. Effect of levothyroxine on kidney function in chronic kidney disease with subclinical hypothyroidism in US veterans: A retrospective observational cohort study. Adv Ther 2021;38:1185–201.
43. de Souza ABC, Arantes MF, Zatz R, Elias RM, Lopes RI, Macedo E. Influence of low free thyroxine on progression of chronic kidney disease. BMC Nephrol 2020;21:36.