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Hypothyroidism in Patients with Chronic Kidney Disease: Treat or Leave Alone – a Burning Issue

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Abstract

Background: Chronic Kidney Disease (CKD) has been known to affect the pituitary thyroid axis and the metabolism of thyroid hormones, leading to two common thyroid abnormalities, low T3 syndrome followed by subclinical hypothyroidism. These hormones can also have a significant impact on kidney development and function; so it is important to consider the physiological association of thyroid dysfunction in relation to CKD.

Method: An observational study was performed in a tertiary care hospital in Delhi, India. Clinical and biochemical data was collected from 75 participants suffering from any stage of CKD to determine the prevalence of subclinical hypothyroidism in both dialysis and non-dialysis CKD patients.

Results: Significant correlation between TSH, serum creatinine, and eGFR was found in subclinical and overtly hypothyroid CKD patients.

Thyroid disease – particularly hypothyroidism – which is typically identified by biochemical tests including an elevated serum thyrotropin (TSH) level in conjunction with a low or normal thyroxin (T4) level defined as overt and subclinical hypothyroidism is highly prevalent among chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients[1-5]. It has been hypothesised that hypothyroidism is due to non-thyroidal illness, malnutrition, inflammation, iodine retention, metabolic acidosis, medications, mineral deficiencies (e.g., selenium) and exposure to dialysis procedures (i.e., peritoneal/effluent losses)[3,6-8]. Yet other data suggest that hypothyroidism leads to impaired kidney function through alterations in renal haemodynamics and structure[14,18]. Hypothyroidism is an under-recognised modifiable risk factor for the enormous burden of cardiovascular disease and death in CKD and ESRD, but this has been difficult to test due to the challenge of accurate thyroid function assessment in uraemia[2,3].

While a greater emphasis has been placed upon other endocrine disorders in CKD, e.g., secondary hyperparathyroidism and diabetes, large observational studies show that hypothyroidism is highly prevalent in kidney disease patients. For example, among 14,623 participants in the Third National Health and Nutritional Examination Survey (NHANES III), there was an incrementally higher prevalence of hypothyroidism (defined as TSH > 4.5 mIU/L or receipt of exogenous thyroid hormone) with increasing severity of kidney dysfunction: 5%, 11%, 20%, 23%, and 23.1% with estimated glomerular filtration rates (eGFR) of ≥ 90, 60 - 89, 45 - 59, 30 - 44, and < 30 ml/min/1.73 m^2 respectively[9]. Even after accounting for differences in age, sex, and race/ethnicity, participants with eGFR < 30 ml/min/1.73 m^2 had a 2-fold higher risk of hypothyroidism compared to those with eGFR > 90 ml/min/1.73 m^2. In a more recent study of 4,61,607 US veterans with stages 3 to 5 CKD who underwent serum TSH testing from 2004 - 2006 (84% of the cohort), 23% had hypothyroidism (defined as TSH > 5.0 mIU/L or receipt of exogenous thyroid hormone replacement)[10] (Table 1). Across these studies, a large proportion of cases have been due to subclinical hypothyroidism. In the aforementioned NHANES III study 56% of hypothyroid cases were due to subclinical disease[3]. In a study of 3,089 ambulatory adults in Italy, it was also found that there was an increasingly higher prevalence of subclinical hypothyroidism with lower levels of kidney function: 7% vs 18% with eGFR ≥ 90 vs < 60 ml/min/1.73 m^2, respectively[11]. In US and Asian haemodialysis and peritoneal dialysis cohorts, the prevalence of hypothyroidism has ranged from 13 to 25%[12-15].

Despite these data hypothyroidism remains under-recognised in many advanced CKD patients likely due to symptom overlap with uraemia, e.g., fatigue, cold intolerance, lethargy, malaise, cognitive and sexual dysfunction, oedema, poor appetite, constipation, intolerance to cold, goitre. However, periorbital puffiness, hoarseness, yellow or sallow complexion, delayed tendon jerks and constipation have been suggestive more of hypothyroidism, yet they are not definitive. The

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development of goitre could be related to the failure to excrete iodides, but even without a goitre, dialysis patients often have subnormal plasma levels of total and free thyroid hormones, higher levels of thyroid stimulating hormone (TSH) and decreased conversion of T4 to T3 in non-thyroid tissues although the pituitary-hypothalamic axis appears to be intact. Thus, there appears to be evidence of abnormal thyroid metabolism at several levels in uraemia. Hence, it is important to recognise such symptoms early in their course which points towards the development of hypothyroidism in CKD patients. The main changes happening at the thyroid level are:

1. Increased thyroid volume
2. High prevalence of goitre, thyroid nodule, and carcinoma
3. Low or normal total T3 and total T4
4. Reduced or normal free T3 and free T4
5. Reduced T3 conversion from T4
6. Normal or high TSH
7. Altered TSH circadian rhythm
8. Reduced TSH response to TRH
9. Abnormal TSH glycosylation

Studies have shown that various thyroid functional abnormalities such as synthesis, metabolism, secretion and elimination are frequently seen in CKD[18-20,4] leading to decreased renal plasma flow, decreased GFR, increased serum creatinine, decreased sodium reabsorption, decreased renal ability to dilute urine and hyponatraemia. The earliest and the most common thyroid function abnormality in CKD patients is low T3 syndrome which occurs due to several reasons. However, the free T4 levels vary from being low to normal in CKD. This is primarily because of an impaired protein binding of T4 in CKD. The thyroid profile is similar to that observed in several non-thyroid illnesses (NTIs) such as severe infections, heart failure, malignancies, and in several hospitalised patients without renal disease. This led to the consideration of sick euthyroid state or non-thyroid illness (NTI) in CKD. However, unlike other NTI states, there is no increase in total rT3 levels in CKD[21,22]. Another difference from other NTIs is that the thyroid stimulating hormone (TSH) levels are elevated in CKD.

Though TSH has been found to be the best investigation for diagnosing hypothyroidism, yet T3 has been considered the best test to predict morbidity and mortality in CKD with underlying cardiovascular disease and/or proteinuria with low serum albumin level. In a study, Carrero *et al* showed that T3 levels appear to be an independent predictor of not only all cause but also CVD mortality in biochemically euthyroid patients, perhaps due to its intimate association with inflammation. Based on their study results, the use of T3 in studies assessing the relationship between thyroid dysfunction and mortality risk is recommended[23].

Studies have demonstrated that hypothyroidism is associated with higher risk of cardiovascular disease and death in this population[14,24]. The factors which could be associated with higher cardiovascular morbidity and mortality are; impaired systolic and diastolic function[25-28], altered blood volume and haemodynamics, decreased cardiac output[29-32], endothelial and vascular function, increased arterial stiffness and vasoreactivity[28,30], dyslipidaemia, atherosclerosis, vascular calcification[33-36] and arrhythmias[37-39]. However, the 4D study (Die Deutsche diabetes dialysis study) denies any such correlation of higher cardiovascular morbidity and mortality[40].

The effect of thyroid hormone replacement on renal function has not been widely investigated in hypothyroid CKD patients, especially in sub-clinical hypothyroidism. In an early study of HD patients with low T3 levels, administration of exogenous T3 resulted in increased protein degradation, suggesting that thyroid hormone repletion in hypothyroid ESRD patients exacerbates protein malnutrition[41]. However, in a placebo-controlled study of 39 euthyroid HD patients, exogenous T4 administration over 12 - 16 weeks reduced LDL cholesterol and lipoprotein (a) levels and did not lead to clinical symptoms of thyrotoxicosis[42].

Treatment with exogenous thyroid hormone has been associated with decreased progression or reversal of impaired kidney function in hypothyroid CKD patients[42-48].

Although these data suggest possible benefit and minimal risk, the narrow therapeutic-to-toxic window and catabolic properties of thyroid hormone treatment warrant more rigorous study in CKD and ESRD patients for two reasons: (i) Markers of protein-energy wasting (e.g., hypoalbuminaemia) are stronger mortality predictors than traditional cardiovascular risk factors in CKD and ESRD and (ii) CKD and ESRD patients may be more vulnerable to the risk of unwarranted treatment (i.e., atrial fibrillation, high output heart failure) given their high underlying cardiovascular risk[49,50]. Some experts suggest that concerns about adverse treatment effects in patients with underlying Coronary heart disease (CHD) are largely unfounded[51]. In the largest study examining the impact of exogenous thyroid hormone on CHD exacerbation conducted over five

decades ago, patients with atherosclerotic disease were more likely to improve than worsen with treatment[52]. Alternatively, thyromimetics (thyroid hormone synthetic analogues) are an emerging class of drugs with tissue-specific thyroid hormone actions that may selectively improve cardiovascular risk factors (e.g., dyslipidaemia) without adverse effects on the heart and other end organs (e.g., tachycardia)[53-55]. Further studies are needed to determine the longitudinal impact of thyroid hormone treatment and novel pharmacotherapies on hard outcomes in hypothyroid CKD patients.

A recent study by Shin *et al*[48] demonstrated that thyroid hormone treatment not only preserved renal function but was also an independent predictor of renal outcome. Thus to clarify the direct impact of thyroid hormone treatment on the decline in renal function, it was imperative to compare decline in eGFR before and after L-thyroxin replacement in the same patient. The results of this study showed that thyroid hormone replacement significantly improved the renal function as evidenced by mean eGFR (ml/min/1.73 m^2) which increased from 13.7 ± 8.9 to 17.5 ± 6.8 and 22.4 ± 9.3 after 3 and 6 months of thyroid hormone replacement respectively ($P < 0.001$)[42]. Shin *et al* used a linear regression analysis to extrapolate how many patients would reach CKD stage 5, the stage requiring dialysis or kidney transplantation within 10 years on the basis of the pre- and post-treatment slopes of decline in eGFR. Based on the slope of decline in eGFR before L-thyroxin supplement 53 (46.9%) patients were supposed to reach CKD stage 5 within 10 years. However, the estimated number of patients decreased to 10 (8.8%) when the post-treatment slope of decline in eGFR was used indicating that thyroid hormone replacement delayed reaching CKD stage 5 within 10 years in 81.1% (43/53) of CKD patients with subclinical hypothyroidism. There are many remaining gaps in knowledge with regards to the interaction between thyroid and kidney disease. Further mechanistic studies are needed to understand the pathogenesis of thyroid functional disorders in kidney disease as well as how CKD may endanger thyroid dysfunction. Given that thyroid hormone receptors are present in nearly all tissues hypothyroidism may have pervasive effects on multiple end-organs (e.g., neuropsychiatric, haematologic, musculoskeletal); thus, further studies are needed to determine the underlying mechanistic pathways by which hypothyroidism is linked with mortality. Lastly rigorous studies of exogenous thyroid treatment, including dosing and biochemical targets, and kidney disease progression, cardiovascular disease, and mortality are needed to better understand the causal implications of hypothyroidism in CKD patients. There are however, only a few reports from India where various parameters of thyroid function were measured in patients with varying degrees of CKD. This study was aimed at gaining further insight into the parameters of thyroid function in patients of CKD.

Material and methods

The study was conducted in a tertiary care hospital of Delhi, India. The study enrolled 75 adult patients of CKD, defined as per NKF-K/DOQI guidelines[56] after written informed consent was taken with approval of ethics committee of the hospital and after fulfilling inclusion and exclusion criteria. Patients receiving concurrent treatment for thyroid disease (thyroxine and other antithyroid drugs), drugs known to affect thyroid hormone indices, such as glucocorticoids, salicylate, heparin, or lithium, amiodarone, iodine or iodinated contrast material and acutely ill patients were excluded. Glomerular filtration rate (GFR) was estimated by the Modification of Diet in Renal Disease (MDRD) equation. Enrolled subjects were further categorised into different stages of CKD (stage I toV), diabetic or non-diabetic subjects and dialysed or non-dialysed subjects for assessing thyroid function based upon these sub-categories. A detailed biochemical analysis, including thyroid function tests (comprising of total and free T3, total and free T4 and TSH), anti TPO antibodies was carried out. Competitive chemi-luminescent immune assay (CLIA) was employed for the measurement of total and free thyroid hormones [triiodothyronine (T3) and thyroxin (T4) while TSH was measured by an ultrasensitive sandwich CLIA. Subclinical hypothyroidism was characterised by a serum TSH above the upper reference limit in combination with a normal free thyroxin (T4) and normal hypothalamic-pituitary-thyroid axis and absence of recent or ongoing severe illness. This designation is only applicable when thyroid function has been stable for weeks or more[17]. Overt hypothyroidism was characterised as elevated TSH, usually above 10 mIU/L in combination with a subnormal free T4[17].

For analysing thyroid function, apart from a descriptive analysis, the data was categorised into normal, sub-clinical and overt hypothyroidism and its frequency described in percentage in various sub-groups defined in the study group (e.g., CKD stages, diabetic and non-diabetic, dialysed and non-dialysed groups). Further analysis of the data for categorical variables was done using the Chi-square test, after categorising the thyroid function into 3 categories (normal, sub-clinical and clinical hypothyroidism). The levels of statistical significance were taken as $P \leq 0.05$.

Observations

A total of 75 patients were enrolled for the study out of which 47 were males (63%) and 28 females (37%). The mean age of the group was 41.9 years with maximum members belonging to the age group 31 - 40 years (32%) and least in the age group 18 - 20 years (5.3%). The mean blood urea was 182.76 ± 83.35 mg/dl while mean value of serum creatinine was 8.46 ± 5.9 mg/dl. GFR was estimated by the MDRD equation and its mean value was 11.23 ± 7.6 ml/min/1.73 m². Out of 75 patients, maximum, i.e., 48 belonged to CKD stage 5 (64%), and 27 belonged to stage 4 CKD (36%). The various indices measured included total T3 and T4 (TT3, TT4), free T3 and T4 (FT3, FT4) and thyroid stimulating hormone (TSH).

Out of 75 patients of CKD, 51 (68%) reported a normal thyroid function status. 12 (16%) were found to have sub-clinical hypothyroidism and an equal number were found to be overt hypothyroid[39] (i.e., 52%) were non-diabetic while the remaining 36 (48%) were diabetic.

Mean TSH level in non-diabetics was 4.98 ± 6.93 µIU/ml while this value was 16.98 ± 34.51 µIU/ml in diabetics (P = 0.252). Though this difference was not statistically significant, mean TSH level in diabetics was considerably higher than non-diabetics and well above the higher limit of normal (0.3 - 5.5 µIU/ml). This indicates a perhaps higher prevalence of hypothyroidism in the diabetic CKD group as compared to the non-diabetic CKD group. It may be pointed out here, that all those patients who were found to have high TSH levels (and thus, hypothyroidism, whether sub-clinical or clinical) during the course of the study, also had TPO antibody measurements done to exclude an autoimmune aetiology to the hypothyroidism. 38 (50.7%) belonged to the non-dialysed group while 37 (49.3%) were in the dialysed group. It can be seen from these figures, that, all four hormonal indices (TT3, TT4, FT3 and FT4) show comparatively lower mean values in the dialysed group as compared to the non-dialysed group. Mean TSH level in the dialysed group (17.20 ± 34.25 µIU/ml) was observed to be higher than the non-dialysed group (4.45 ± 4.98 µIU/ml) and well above the upper limit of normal (0.3 - 5.5 µIU/ml).

This indicates a perhaps higher prevalence of hypothyroidism in the dialysed group as compared to the non-dialysed. Thus, it lent credence to our premise of expecting a greater likelihood of hypothyroidism in the dialysed group as compared to the non-dialysed group.

Discussion

In CKD patients, thyroid hormone physiology is known to be altered. Baseline TSH becomes elevated, reaching sometimes levels > 20 µIU/ml, response to exogenous thyrotropin-releasing hormone (TRH) gets blunted, diurnal rhythm of TRH gets disturbed, and there is an observed reduction in serum T_4 levels[3]. The Wolff-Chaikoff effect or increase in total-body inorganic iodide can block thyroid hormone production and hence may explain the higher frequency of goitre and hypothyroidism in CKD patients[18]. Further, chronic metabolic acidosis may cause hypothyroidism in these patients. The possible mechanisms were demonstrated by Brungger *et al*[57] in their experimental model. They showed that metabolic acidosis significantly decreased serum T_3 and T_4 levels, with a corresponding increase in serum TSH levels thereby resulting in hypothyroidism.

Our study results are consistent with other studies that hypothyroidism is more common 32% (combined sub-clinical and clinical) in CKD and its prevalence increases with decreasing GFR. The individual prevalence of both sub-clinical as well as clinical hypothyroidism in our study was 16% each. FT3 mean level of 1.5461 ± 0.46 pg/ml (normal range 1.7 - 4.2 pg/ml), mean TSH level was 10.7375 ± 24.9872 µIU/ml (normal range 0.3 - 5.5 µIU/ml) which was found to be above the normal and hence, in the hypothyroid range. The prevalence of sub-clinical hypothyroidism was higher in stage 4 CKD (25.9% in stage 4 versus 10.4% in stage 5), while the prevalence of clinical hypothyroidism was higher in stage 5 CKD (16.7% in stage 5 versus 14.8% in stage 4). On the basis of this result, we speculate that as a patient worsens from stage 4 to stage 5 CKD, it is likely that he also progresses from sub-clinical to overt or clinical hypothyroidism[2,9,58].

The data of 14,623 adult participants from the third National Health and Nutrition Examination Survey, a national representative sample of the United States population, revealed that the prevalence of hypothyroidism increased with lower levels of GFR, occurring in 10.9% of patients with stage 2 CKD, 21.0% with stage 3 CKD, and 23.1% with stage 4 or 5 CKD[26]. Moreover, Chonchol *et al*[2] showed that the prevalence of sub-clinical hypothyroidism increased from 7% at an eGFR 90 ml/min/1.73 m^2 to 17.9% at an eGFR < 60 ml/min/1.73 m^2 in 3,089 unselected outpatient adults. Ghanshyam Palamaner *et al* has shown a 24.8% prevalence of sub-clinical hypothyroidism among a cohort of ESRD patients. Hence, it may be a good practice to routinely monitor thyroid functions in all ESRD patients[59].

It has also been seen that, as proteinuria increases, the intensity of CKD also increases which was observed in our study too. However, a cross-sectional, population based study by Yi-Cheng Chang involving 74,356 Taiwanese elderly adults found subclinical and clinical hypothyroidism is independently associated with reduced eGFR in a dose-dependent manner but less significant association was found with proteinuria[60].

Zhou, Jian-Bo *et al* showed that the prevalence of CKD increased with elevated TSH level, 4.78% in patients with TSH from 0.55 to 3.0 μIU/ml to 15.60% in subclinical hypothyroidism. This relationship between CKD and TSH level was independent of age, sex, duration of diabetes, A1C, BMI, blood pressure, and LDL cholesterol[62]. Decrease in renal blood flow associated with low thyroid function might be a factor[63].

Lo *et al*[9] found an increased prevalence of sub-clinical and clinical primary hypothyroidism in persons with reduced estimated GFR in a nationally representative cohort of US adults. In addition, they noticed that with progressively lower GFR, there was a graded, increased likelihood of hypothyroidism. Their study had a fairly large sample size (N = 14,623) as they used data from the third national health and nutrition examination survey (NHANES III) to examine the prevalence of hypothyroidism at different levels of estimated GFR. Our study had a much smaller sample size (N = 75) and included only CKD stage 4 and 5 patients. On comparison of thyroid hormone indices (total T3, total T4, free T3, free T4) between these two stages, the mean values of all these 4 hormonal indices were found to be lower in stage 5 CKD as compared to stage 4 though a significant difference was observed only with FT3 levels (P = 0.037). We observed an overall prevalence of hypothyroidism to be 32% (combined sub-clinical and clinical) in our study in CKD patients. Since NHANES is a national registry, Lo *et al* had persons with GFR ranging from ≥ 90ml/min/1.73 m² to < 30ml/min/1.73 m² in their ranks. However, their limitation was that while their overall sample size was relatively large the number of persons with reduced GFR levels was modest, particularly in the group with GFR < 30ml/min/1.73 m² (N = 65). This inherent difference in the demographic profile could have a bearing on the results obtained by us and those reported by Lo *et al*[9].

Despite previous studies consistently demonstrating the link between hypothyroidism and decreased eGFR, none of them showed any role of hypothyroidism in proteinuria. Our study showed the severity of proteinuria increase progressively from euthyroidism, subclinical to overt hypothyroidism. The risk of proteinuria is increased by 1.71-fold in patients with subclinical hypothyroidism and 2.35-fold in patients with overt hypothyroidism. The same albeit but less significant trend was observed after further adjustment for other risk factors. The less significant association may result from increased missing values when multiple covariates are incorporated in regression models. To our knowledge, this study is the first to examine the association between hypothyroidism and proteinuria in the general population. The causal relationship between hypothyroidism and proteinuria is also uncertain. In patients with nephrotic syndrome, the heavy urinary loss of thyroid hormone-binding proteins, including thyroxin binding globulin, trans-thyretin, and albumin, results in a reduction in total T4. However, the thyroid gland is able to compensate the loss so that most patients remained in euthyroid state since serum free T4 or free T3 levels remain normal.

Bando *et al*[1] showed in his study that the frequency of overt hypothyroidism in the diabetic group is significantly higher than in the non-diabetic group which matches our study.

Subclinical primary hypothyroidism has been identified as a strong predictor of all-cause mortality in chronic dialysis patients and a risk factor for nephropathy and cardiovascular events in type 2 diabetic patients[14,16,18]. T3 levels appeared to be an independent predictor of all-cause mortality as well as cardiovascular morbidity and mortality. Low T3 syndrome is the earliest and most common abnormality seen in CKD patients with hypothyroidism. There has been controversy over treatment of hypothyroidism in CKD patients as chances of going into negative nitrogen balance is high due to malnutrition and protein restriction ordered by doctors. However, the effect of increasing the GFR by thyroxin supplementation appears to be very encouraging as demonstrated by Shin *et al*[47,48]. Another study which has substituted that treatment with thyroxin in CKD not only increase the GFR but it prevented the decline in GFR[46]. As CKD advances from stage 1 to stage 5, there is increase in proteinuria and it is also evidenced by low T3, high TSH and high T4. Proteinuria is a known risk factor for deteriorating kidney function and treatment with thyroxin reduces proteinuria, therefore indicating that treatment with thyroxin is associated with improvement in GFR. Therefore more research is needed in the field of treatment of CKD which could raise the GFR or prevent the nephrons from dying. Future clinical and experimental studies should explore potential mechanistic and causal link between CKD and thyroid dysfunction. Finally, whether hypothyroidism should really be treated requires the light of scientific evidence and as of yet remains a matter of conjecture.

Our study had several limitations as well as strengths. An obvious limitation was the small sample size (N = 75) that could have a bearing on the results. Second, because this study is cross-sectional, the present analysis is limited in its ability to establish causal or temporal relationships between observed sub-clinical or clinical primary hypothyroidism and chronic kidney disease. Third, serum and urinary iodine measurements were not employed in order to study the effect of retained iodides on thyroid function, probably through a prolongation of the Wolff-Chaikoff effect. The strengths of our study lay in that our clinical laboratory used uniform methods to collect data on serum TSH and FT4 concentrations. Secondly, sub-clinical primary hypothyroidism was diagnosed according

to widely accepted diagnostic criteria (i.e., high TSH with normal FT4 levels). Third, free T3 and free T4 measurements were employed which are better indices than total T3 and total T4.

Conclusion

CKD is a cause of an irreversible death of nephrons. Anything that gives a hope of increasing GFR of CKD patient is definitely going to be encouraged. Some of the studies listed above have clearly demonstrated that treatment of thyroid dysfunction in CKD increases the GFR considerably. It was not associated with any detrimental effect on other systems also. Another study has shown that thyroxin supplementation not only increased the GFR but decreased the decline of nephron death also. Thyroxin has good effect on reducing proteinuria also which could be beneficial for both kidney and heart.

Given the cardiovascular risks associated with hypothyroidism and the excessive burden of cardiovascular disease and death in CKD and ESRD, hypothyroidism may be an under-recognised risk factor and a biologically plausible link to cardiovascular disease, and death in this population is a possibility. Therefore it is important to investigate all CKD patients meticulously for thyroid dysfunction and subsequent treatment. Identification of more sensitive and specific thyroid hormone assays will provide greater opportunity to distinguish hypothyroidism from nonthyroidal illness and to define corresponding risk in CKD and ESRD patients. Given the high prevalence of hypothyroidism and exogenous thyroid hormone use in CKD and ESRD patients, further research is needed to determine the prognostic implications of hypothyroidism and to more accurately define the risks and benefits of treatment in these populations.

Healthcare professionals caring for patients of CKD should be cognizant that CKD and hypothyroidism may exhibit overlapping symptom complexes. Future investigations are needed to determine the value of assessing or screening for clinical and sub-clinical hypothyroidism among persons of CKD. Finally, whether at all such hypothyroidism associated with CKD should be treated requires further clarification and scientific evidence. If it should be treated, then guidelines need to be defined for its screening, diagnosis, treatment, and follow-up.

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