REVIEW ARTICLE

The Dilemma of Subclinical Hypothyroidism in Chronic Kidney Disease

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Abstract

Thyroid hormones are important for growth and maintenance of kidney functions. Hypothyroidism has significant health consequences. Subclinical hypothyroidism has been less well defined clinically. Prevalence among women increases with age especially those with thyroid antibodies. Subclinical hypothyroidism carries the risk of developing overt hypothyroidism, subsequent cardiovascular health risks and renal dysfunction. Continuous clinical monitoring is recommended to evaluate the therapeutic response and possible adverse effects of over treatment requiring dosage adjustment. The present article reviews the complex interaction between subclinical hypothyroidism and kidney dysfunction.

Introduction

The definition of subclinical hypothyroidism (SH) is a biochemical one with elevated TSH levels (4.5- 10 mIU/l) but normal FT4 level. It may have subtle symptoms of hypothyroidism.[1] As against prevalence of subclinical hypothyroidism in general population of 4-10 %,[2-4] there is a higher prevalence in patients of chronic kidney disease not requiring dialysis, around 18%.[5] Moreover the prevalence gradually increases as the GFR falls further. This stands true independent of age, gender, fasting blood glucose levels, total cholesterol and triglyceride levels.[5] Multiple mechanisms have been cited to explain this association of SH and chronic kidney disease (CKD). This includes chronic inflammation[6,7] altered iodine metabolism, decreased sensitivity to hormones and autoimmune thyroiditis.[5]

Epidemiology

Thyroid autoimmunity and subclinical primary hypothyroidism are highly prevalent in CKD patients not requiring chronic dialysis treatment.[8] Higher TSH levels are seen with increasing age.[9] The percentage of individuals with positive antithyroid antibodies is roughly about 40% in over 80 yr. age group compared to 67.4% in 40-49 yr. age group.[9] Women have greater degree of anti TPO antibodies leading to higher number of cases of subclinical hypothyroidism.[10]

Those with elevated TSH and positive thyroid antibody have a wide prevalance of 20-78%[11] due to variation in method of selection of subjects. Seronegatives have a much lower risk of progression to overt hypothyroidism.[12,13]

17-50% of patients with TSH value between 5-10 mIU/L are thyroid antibody positive.[12,14,15] In euthyroids the seropositive state is about 10% which rises to 80% with TSH>10 mU/L.[3,12] Epidemiological studies have shown that a number of subjects especially males of patients with TSH value between 5-10 mIU/L may actually be euthyroid outliers (healthy population falling outside TSH reference range).[11]

Altered renal physiology in thyroid hormone deficiency

Various mechanisms are responsible for reduction of GFR in hypothyroidism. Reduced renal blood flow due to impaired left ventricular function, increased peripheral vasoconstriction,[17] intrarenal vasoconstriction,[18] decreased renal expression of various endothelium dependent vasodilators[19] like VEGF, IGF[18] are all responsible for a fall in GFR. Reduction in chloride reabsorption leads to tubuloglomerular feedback via macula densa causing fall in GFR. Apart from fall in GFR, rise in s. creatinine value in hypothyroidism can be due to decreased secretion in tubules[20] or release from muscles.[21] Rarely rhabdomyolysis as a part of thyroid myopathy can precipitate an acute worsening of GFR.[22]

By directly increasing the activity of Na/K ATPase activity in proximal convoluted tubule thyroid hormone increase sodium reabsorption.[23] They also have stimulatory effect on renin – angiotensin – aldosterone axis by adrenergic stimulation[24] promoting renal fibrosis.

Hypothyroidism is linked to decrease in calcium reabsorption similar in a fashion as that of sodium

In hypothyroidism there is reduction in sodium bicarbonate reabsorption owing to decreased activity of Na(+)/H(+) exchanger type 1 (NHE-1)[25] leading to defective urine acidification, loss of medullary tonicity subsequently causing poor urinary concentrating ability.[26] Hypothyroidism is also known to cause inappropriate increase in ADH levels causing fluid retention.[27] This leads to hyponatremia[28] whose incidence is all the more increased in presence of renal failure. Microscopically, there is glomerular basement membrane thickening, mesangial matrix expansion and renal parenchymal growth retardation.[29]

Intrathyroidal and intrapituitary defect is also seen in some, leading to decreased thyroxine response to thyrotropin and decreased s. thyrotropin response to TRH.[30]

Features of thyroid dysfunction in chronic kidney disease

Low T3 syndrome observed in CKD is possibly due to the state of chronic inflammation, malnutrition prevalent in CKD population. Impaired

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renal handling of iodine leads to Wolf Chaikoff effect.[31] There is also poor peripheral conversion of T4to T3 (decreased expression of type 1,5 deiodinase). However, the association of low T3 syndrome with endothelial dysfunction,[32] cardiovascular and all-cause mortality, is controversial.[7,33,34] Sometimes low T4 is seen probably due to poor protein binding.[35] Total rT3 is normal despite low renal clearance due to redistribution from vascular to extravascular space.[36] Free rT3 is mildly elevated due to poor renal clearance. TSH is often elevated in CKD in response to thyrotropin from pituitary as a result of uremic effect.[37] TSH also looses its circadian rhythm along with compromised bioactivity due to poor glycosylation.

Patients on haemodialysis can have high free T4 levels due to heparin induced poor protein binding of T4.[38] TSH is also mildly elevated although mostly below 10mU/ml indicative of non-thyroid disorder rather than thyroid dysfunction.[39] Dose of erythropoietin is also higher in subclinical hypothyroidism than in euthyroids.[40] Peritoneal Dialysis (PD) is associated with continuous loss of heavy amount of protein in PD fluid including tyrosine binding globulin (TBG) and minor losses of T4 and T3 which is easily compensated.[35] Among PD patients there is a significant increase in subclinical hypothyroidism (up to 27.5%)[41] and it continues to increase with duration of PD.[40] However, indication of hormonal therapy initiation remain the same as in CKD population not on dialysis. Low t3 syndrome is seen in 16 percent[42] of this group of pts. This has been correlated with poor cardiac function status.[41] Overall, dialysis therapy has minimal effect on thyroid hormone metabolism.

Thyroid hormone affects nearly all organ systems in the body. The risk of nephropathy, cardiovascular events increases in type2 diabetes mellitus with SH.[43] The Wolf Chaikoff effect[31] has been cited as a causative phenomenon behind rise of this disorder in diabetic kidney disease patients. Restriction in dietary intake of iodine[44] is often considered before initiation of thyroxine replacement therapy.

Dyslipidemia is seen throughout the spectrum of thyroid dysfunction although it is of much milder degree withTSH levels between 5-10 mU/L compared to TSH>10mIU/L.[15,46,47] Few reports[2,45] have shown significantly elevated total cholesterol and LDL with TSH<10mIU/L in comparison to euthyroids. Renal failure patients have increased apoC-III, increased triglycerides, decreased levels of mature HDL, accumulation of small dense atherogenic LDL. These can stimulate oxidative stress and inflammation contributing to endothelial dysfunction and progression of atherosclerosis. Dyslipidemia has been linked to progression of renal failure.[48] Studies have given conflicting results regarding improvement in lipid profile with use of thyroxine.[49-53] Mostly treatment has not shown any significant effect on lipid profile in SH. However, in context to renal failure it needs further trials before any conclusive statement is derived.

Subclinical and overt hypothyroidism have been found to be associated with atherosclerosis,[54] myocardial infarction particularly in elderly females[55] and total mortality.[56] On the other hand some studies have not supported this association.[49,57,58]

Hypothyroidism has been found to be associated with polymyositis like weakness and elevation in creatine kinase.[59]

Effect of Treatment

One rationale given behind treatment of subclinical hypothyroidism is the prevention of progression to overt hypothyroidism. As per 20-year Wickham survey the progression occurs in 2-4.3% per year, more in cases with elevated TSH and presence of thyroid antibodies.[13]

Treatment of elevated TSH (4.5-10 mIU/L) has not found equivocal approval from all the societies as per available evidence.[60] However, TSH>10 mIU/L has found more acceptance with regards to thyroxine treatment.[2,9,12,13]

Few studies that have shown improvement in cardiovascular profile after thyroxine mostly had TSH>15 mIU/L.[61-64] Some uncontrolled studies have shown improvement in neuromuscular and cardiovascular parameters(cardiac systolic interval) after thyroxine replacement in subclinical hypothyroidism.[61-63,65] But most of these improvements occur at a higher exercise intensity or at a higher baseline TSH levels (>15 mIU/L). Data from Framingham heart study has demonstrated that after adjustment of known risk factors, elderly people with ≥ 60 yrs. of age with low TSH have a 3.1 fold higher risk of atrial fibrillation over a 10 yr. period compared to normal TSH levels.[66] This phenomenon may assume importance in the CKD population as it carries a higher risk of arrhythmias compared to the general population.

Cognitive and affective scores are also insignificantly affected by thyroxine replacement in SH.[67,68] Improvement in quality of life or symptoms with thyroxine treatment has been reported in few studies.[69,70]

The impact of thyroid hormone replacement has not been extensively studied in CKD patients with SH. In particular, it still needs to be conclusively evaluated whether the restoration of euthyroidism is beneficial in terms of preserving renal function in these patients.

Between 10-53% of individuals on thyroxine treatment have TSH values less than normal[2,70-74] and approximately 1/3-1/2 of these are less than 0.1mIU/L.[74,75]

The risk of overzealous treatment of subclinical hypothyroidism are many like iatrogenic hyperthyroidism, arrhythmias, decreased bone mineral density, requirement of dose adjustment as per TSH levels (low TSH quite common). On the positive side the treatment is simple, cheap and effective when used appropriately. Possible indications of treatment in subclinical hypothyroidism can be: TSH>10 mIU/L on repeated measurements,[11] clear symptoms and signs of thyroid failure, strong family history, pregnancy, severe degree of hyperlipidemia, associated with smoking[76] and rapid worsening of renal functions.

Given the high incidence of oversupressed TSH levels, the negative effect on poor nitrogen balance because of increased protein catabolism can worsen the existent malnourished status in CKD population. The desirable level of TSH in this group of population is also not clear making clinical decision all the more complicated. The overlap in the symptomatology between symptoms of hypothyroidism and uremia makes evaluation challenging. The treating physician has to carefully

balance the positive and negative effects of hormone replacement therapy.

The prediction of transition to overt hypothyroidism can be made to some extent on baseline value of TSH. However, waiting period for spontaneous resolution of subclinical hypothyroidism is far from clear. Presence of anti TPO antibody decreases the possibility of its spontaneous resolution.

Conclusion

To achieve optimisation it is important to relate TSH levels to clinical outcomes measures including renal functions, osteoporosis, coronary artery disease and overall mortality. One may follow individuals with antithyroid antibodies, subtle clinical symptoms at 6-12 month interval for their progression to full blown hypothyroidism. Ones with rapid worsening of renal functions possibly deserve a trial of thyroxine treatment.

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