Prevalence of Subclinical Hypothyroidism in Chronic Kidney Disease

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Abstract

Introduction: *Subclinical primary hypothyroidism occurs in 5- 15% of the general population and frequency of subclinical hypothyroidism is even higher in females, old age and among population with high iodine intake. It has been suggested that primary hypothyroidism is more common in CKD population as compared to the general population.*

Objective: *To determine the frequency of subclinical hypothyroidism in patients with chronic kidney disease.*

Study Design: *Cross Sectional Study.*

Setting: *Department of Nephrology, PIMS, Islamabad.*

Duration of Study: *From 1st August 2018 to 31st January 2019.*

Subjects and methods: *A total of 128 patients of both gender with chronic kidney disease were included in study. Patients Venous blood from all participants were collected in the morning on fasting subjects (8 hours) and was sent to hospital laboratory. Subclinical hypothyroidism was noted.*

Results: *Age range in this study was from 18 to 60 years with mean age and duration 41.695±7.96 years & 12.015±3.41 months respectively. Males were 62.5% as compare to females 37.5%. Subclinical Hypothyroidism was present in 21.1% patients.*

Conclusion: *Sub-clinical hypothyroidism is a common issue in subjects with CKD found in 21.1% patients hence early detection may decrease the risk of cardiovascular events and progression of kidney disease.*

Keywords: *Chronic kidney disease, Subclinical hypothyroidism, Frequency*

1. INTRODUCTION

Progressive loss of renal mass leads to chronic kidney disease (CKD). It is characterized by decrease in GFR over months to years. [1] Numerous hematological, metabolic and endocrine abnormalities are likely to occur in CKD. [2] Subclinical primary hypothyroidism has drawn unprecedented and unparalleled attention of researchers to diagnose slight variation in thyroid function over last couple of decades. Subclinical thyroid disease is defined as "serum freeT4 and free T3levels within their respective reference ranges in the presence of abnormally high serum TSH level. It may be symptomatic or asymptomatic. [3] In routine clinical practice subclinical hypothyroidism have been seen in all age groups; however impact of subclinical hypothyroidism on CKD population is under discussion. [4] There are no guidelines available to diagnose and screen subclinical hypothyroidism.

There is difference of expert opinion regarding complications such as overt hypothyroidism, cardiovascular abnormalities and decreased GFR. Subclinical primary hypothyroidism occurs in 5- 15% of the general population with higher frequency of subclinical hypothyroidism in females, old age and population with high

iodine intake. [5] It has been reported that primary hypothyroidism is more common in CKD as compared to the general population. [6] "In subclinical hypothyroidism cardiac abnormalities are the main cause of increased mortality and this further increase in CKD patients with subclinical hypothyroidism." Cardiac complications of subclinical hypothyroidism include left ventricular systolic dysfunction, hypertrophy, and cardiomyopathy. [7]

In a study by Gupta A, et al has showed that frequency of subclinical hypothyroidism was 25% in patients with chronic kidney disease. [8] In a study by Chandramohan G, et al reported that frequency of subclinical hypothyroidism is 60% in out of 50 patients with chronic kidney disease, they suggest that subclinical primary hypothyroidism is a relatively common condition (60%) among persons with CKD not requiring dialysis, and it is independently associated with progressively lower estimated GFR in a small group of patients. [9] A local study form Karachi by Mal M, et al reported that frequency of subclinical hypothyroidism was 20% in out of 158 patients with chronic kidney disease. [10]

There is, however, limited quantitative evidence regarding the prevalence of subclinical hypothyroidism in Pakistani patients with chronic kidney disease. As far my research, only one study from Karachi is found so far. Moreover results of international studies have shown variability in results in different populations one study reported frequency of subclinical hypothyroidism by 25% while other reported by 60%, [8,9] therefore these results cannot be applicable on all population.

This prompted me to determine the frequency of subclinical hypothyroidism in patients with chronic kidney disease in our local population. Result of my study will help to measure the actual burden of this morbidity in our population. Early detection of SCH in CKD may decrease the risk of cardiovascular events and progression of kidney disease. My study will also pave the way to develop local guidelines for routinely screening for subclinical hypothyroidism in CKD patients.

1.1. Effects of Thyroid Hormone on Renal Development

Thyroid hormones influence protein synthesis and cell growth. Studies in neonatal rats have demonstrated the accelerating effect of thyroid hormones on renal development. Thyroid hormone affects the functioning renal mass (measured as the kidney to body mass ratio), with hypothyroidism reducing this ratio and hyperthyroidism increasing it.

However, severe hyperthyroidism results in protein breakdown and eventual renal atrophy. In addition, children with congenital hypothyroidism have a high incidence of congenital renal anomalies. Thyroid hormones also influence the neonatal renal function. Perinatal thyroid hormone status affects the mitochondrial energy metabolism enzymes in the cells of the proximal convoluted tubules (PCT). There is an increase in the activity of the Na – P co-transporter (NaPi), Na – H exchanger (NHE), as well as the Na/K ATPase in the PCT. Thus, thyroid hormones play an important role in renal development and early renal function.

1.2. Effects of Thyroid Hormone on Renal Physiology

Thyroid hormones affect renal function by both pre-renal and direct renal effects. Pre-renal effects are mediated by the influence of thyroid hormones on the cardiovascular system and the renal blood flow (RBF). The direct renal effects are mediated by the effect of thyroid hormones on glomerular filtration rate (GFR), tubular secretory and re-absorptive processes. Thyroid hormones affect renal clearance of water load by their effects on the GFR.

The primacy of Na/K ATPase in solute transport of the PCT is well known. Thyroid hormones influence Na reabsorption at the PCT primarily by increasing the activity of the Na/K ATPase and tubular potassium permeability.[11] Tubular reabsorption of calcium is affected in a similar manner, but not of magnesium. [12] Thyroid hormones also regulate the adrenergic receptors and dopaminergic activation of the renal tubular cells. [13] They have been shown to affect the renin – angiotensin – aldosterone axis by adrenergic regulation, [14] renin release, [15] as well as influencing the angiotensinase activity. [16]

1.3. Effects of Thyroid Dysfunction on the Kidney

Thyroid dysfunction affects RBF, GFR, tubular function, electrolyte homeostasis, and kidney structure. The various effects of hypothyroidism and hyperthyroidism on renal function have been summarized in Figure I.
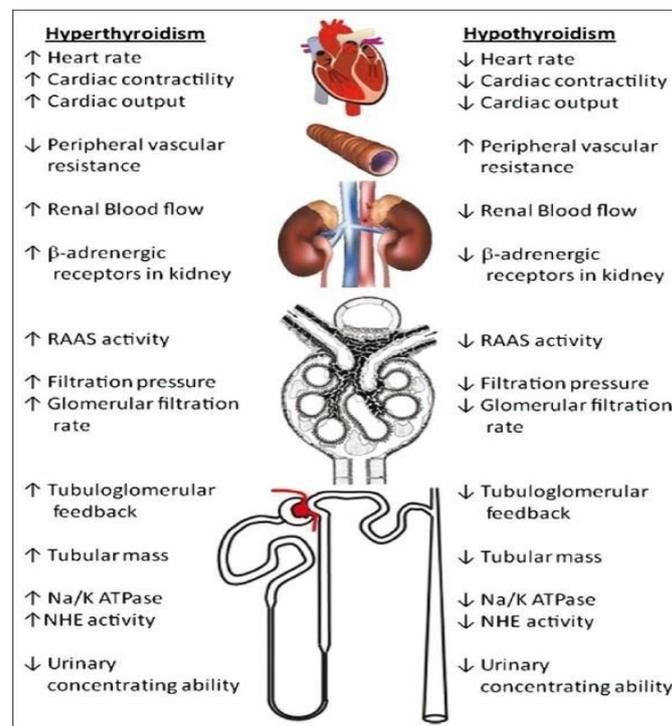
Figure1: *Effects of hyperthyroidism and hypothyroidism on renal physiology and function.*

1.4. Hyperthyroidism and Renal Function

Hyperthyroidism results in increased RBF and GFR. [17] The effect of thyroid hormones on RBF and GFR occurs at multiple levels. Among the pre-renal factors, thyroid hormones increase the cardiac output by positive chronotropic [18] and inotropic effects [19] as well as a reduction in systemic vascular resistance.[20] This indirectly contributes to an increase in RBF. There is an increased endothelial production of nitric oxide (NO) in the renal cortex and medulla by induction of nitric oxide synthase (NOS), [21] directly by the thyroid hormones and indirectly by high arterial pressure related endothelial shear stress. [22] This is accompanied by a reduction in renal vasoconstrictor endothelin. [23] Thus, an increased intrarenal vasodilatation and decreased vasoconstriction ensues, contributing to a net increase in RBF. The GFR increases by about 18–25% among hyperthyroid patients. [17] This improvement in GFR is not solely due to an increased RBF. The activation of renin – angiotensin – aldosterone system (RAAS) also contributes to the increase in GFR. Thyroid hormones stimulate the RAAS in a multifactorial manner. In hyperthyroidism, there is increased β-adrenergic activity, accompanied by increased density of β-adrenergic receptors in the renal cortex, resulting in increased stimulation of RAAS. [24] T3 increases the renin gene expression. Thyroid hormones increase the plasma renin, angiotensin II, and

serum angiotensin converting enzyme levels. In addition, there is an increase in angiotensinogen synthesis by liver and increased density of angiotensin receptors. [25] Thus, there is a net increase in the RAAS activity. This results in afferent arteriolar vasodilatation and efferent arteriolar vasoconstriction and a consequent increased filtration pressure. This adds to the magnitude of increase in GFR over and above that contributed by an increase in RBF. Efferent arteriolar vasoconstriction could result in hypoperfusion of the PCT and consequent avid sodium and chloride reabsorption in PCT. In addition, there is an increased activity of the basolateral NA/K ATPase, [5] apical Na – H exchanger (NHE),[7] and the Na – Pi co-transporter. [6]

Activation of these transporters increases the proximal sodium reabsorption. There is a simultaneous increase in the tubular mass, renal mass, and tubular reabsorptive capacity in hyperthyroidism. [26] The increase in basolateral sodium concentration feeds the basolateral sodium calcium exchanger. [27] The avid Cl reabsorption along with its transport through the basolateral chloride channel indirectly increases the calcium reabsorption, especially at the loop of Henle. Thus, there is a decreased Cl delivery to distal nephron. This is sensed by the macula densa which in turn increases the RAAS activity. Hyperthyroidism results in an increase in the sensitivity of macula densa, and therefore further RAAS activation.

[28] On treating the hyperthyroidism, these effects are reversed and the GFR returns to normal. [17]

Serum creatinine, an inverse marker of GFR, is significantly decreased in hyperthyroid patients, not only due to an increase in GFR but also due to the reduction in overall muscle mass. [29] Cystatin C, a cysteine protease inhibitor constitutively secreted by all nucleated cells, is a new marker of renal function and indicator of future cardiovascular risk. In hyperthyroidism, increased cell metabolism and production of cystatin C results in increase in serum cystatin C levels despite an increase in GFR. [30] Serum cystatin C levels do not correlate well with GFR in hyperthyroidism. Treatment of hyperthyroidism results in a rebound increase in serum creatinine and decrease in serum cystatin C levels. [30] Urinary neutrophil gelatinase associated lipocalin (NGAL), a promising biomarker of reduced renal function, seems unchanged by the thyroid status. The 24-hour urine protein increase in hyperthyroidism is probably related to glomerular hyperfiltration, [3] which resolves on treating hyperthyroidism. Urinary *N*-acetyl-β- D-glucosaminidase (NAG) is increased in hyperthyroidism consequent to glomerular basement membrane disruption and tubular damage due to hyperfiltration, hypertrophy, and hyperplasia. [31] There is a decreased ability to concentrate urine, probably due to increased RBF and osmotic diuresis, rather than vasopressin insensitivity. [32] Hyperthyroidism is associated with a decrease in total body water and exchangeable potassium but not sodium. However, for most part, the serum concentrations of sodium and potassium remain normal. Occasionally, hyperthyroidism is associated with hypokalemia (thyrotoxic hypokalemic periodic paralysis of channelopathies) due to genetic mutation in either L-type calcium channel α1-subunit or potassium inward rectifier 2.6. [33]

Hypothyroidism and renal function The effects of hypothyroidism on the kidney are usually opposite to the effects of hyperthyroidism. The RBF is reduced in hypothyroidism by decreased cardiac output (negative chronotropic and inotropic effects), [34] increased peripheral vascular resistance ,[35] intrarenal vasoconstriction, [36] reduced renal response to vasodilators, [37] and a reduced expression of renal vasodilators such as vascular endothelial growth factor (VEGF) and insulin like growth factor-1 (IGF1). [38] In addition, pathologic changes in the glomerular structure in hypothyroidism, such as glomerular basement membrane thickening and mesangial matrix expansion, may also contribute to reduced RBF [39]. The GFR is reversibly reduced (by about 40%) in more than 55% of adults with hypothyroidism [40] due to several reasons. There is decreased sensitivity to βadrenergic stimulus and decreased renin release [3] along with decreased angiotensin II and impaired RAAS activity, resulting in loss of GFR. [25] There is a structural constraint imposed by limited glomerular surface area for filtration due to renal parenchymal growth retardation in hypothyroidism. [39] There is a reduced proximal tubular absorption of sodium, chloride, and water. [41] In addition, the renal basolateral chloride channel expression is reduced. Thus, reduced chloride reabsorption increases the distal chloride delivery, triggering the macula densa mediated tubuloglomerular feedback which reduces the RAAS activity. Consequently, the GFR falls. The tubular transport capacity is reduced and the activity of Na/K ATPase is reduced initially in the proximal tubules and later in almost all segments of the nephron. [42]

In addition, the NHE activity is also reduced in hypothyroidism. [43] Thus, there is a net reduction in sodium and bicarbonate reabsorption. An increase in sodium and bicarbonate loss in urine results in defective urinary acidification. Decreased tubular reabsorptive capacity also results in inability to maintain the medullary hypertonicity. Medullary hypertonicity is primary the driving force behind urinary concentration. Loss of medullary hypertonicity in hypothyroidism results in impaired urinary concentrating ability of the kidney [44].

However, hypothyroidism causes a reversible increase in vasopressin (antidiuretic hormone or ADH) sensitivity of the collecting ducts, thus increasing free water reabsorption. The increased fluid retention, however, is unable to maximally suppress ADH in hypothyroidism. [45] The resistance of pituitary response to increased fluid retention leads to continued ADH activity and further free water retention. Hypothyroidism results in low cardiac output which triggers the carotid bar receptors and consequently increases the non-osmotic ADH secretion. [46] In some patients, the urine sodium is not as low as would be expected with reduced cardiac output. In these patients, it is possible that the ADH secretion could be considered as inappropriate. The reduced GFR,

reduced sodium reabsorption, and relatively increased ADH secretion and renal ADH super sensitivity mediated impaired free water clearance, all contribute to hyponatremia in hypothyroidism. [40] Hyponatremia is twice as common among hypothyroid patients with raised serum creatinine as among those with normal serum creatinine.

There is a reversible reduction in the kidney to body weight ratio in hypothyroidism, where the renal mass almost doubles with treatment. Hypothyroidism results in a reversible elevation in serum creatinine due to the reduction in GFR as well as possible myopathy and rhabdomyolysis. There is a reduction in serum cystatin C levels in hypothyroidism due to reduced production, consequent to reduced cellular metabolism.[30] Both these changes are reversible with treatment of hypothyroidism. Hypothyroidism also results in increased glomerular capillary permeability to proteins. [47] The consequent proteinuria often precedes the reduction in GFR in hypothyroidism.[48]

1.5. Chronic Kidney Disease and Thyroid Dysfunction

Hyperthyroidism can result in/accelerate chronic kidney disease (CKD) by several mechanisms. Firstly, hyperthyroidism results in intra-glomerular hypertension (increased filtration pressure) and consequent hyperfiltration. Secondly, hyperthyroidism predisposes to proteinuria, which is known to cause direct renal injury. Thirdly, hyperthyroidism-induced increased mitochondrial energy metabolism along with down-regulation of superoxide dismutase contributes to the increased free radical generation and consequent renal injury. [49] Oxidative stress also contributes to hypertension in hyperthyroidism, which contributes to CKD progression.[3] The increased RAAS activity can accelerate renal fibrosis. In addition, hyperthyroidism contributes to anemia in CKD patients and is considered one of the causes of resistance to recombinant human erythropoietin (EPO). [50] For the abovementioned reasons, hypothyroidism does not contribute to progression of CKD except by the mild to moderate reduction in GFR. Treatment of hypothyroidism can result in improvement of GFR in CKD patients [51].

Primary hypothyroidism (non-autoimmune) is commonly observed in CKD patients. Especially, the prevalence of subclinical hypothyroidism increases consistently with

decline in GFR. [52] The earliest and the most common thyroid function abnormality in CKD patients is a low T3 level (especially total T3 than free T3). [53] This "low T3 syndrome" occurs in CKD due to several reasons. Fasting, chronic metabolic acidosis and chronic protein malnutrition affect iodothyronine deiodination, as well as protein binding of T3, reducing the peripheral conversion of T4 to T3 and its protein binding. In addition, inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1 inhibit the expression of type 1 5"-deiodinase, which is responsible for peripheral conversion of T4 to T3. [54] In addition, impaired renal handling of iodine increases serum iodine levels, causing a prolonged Wolff – Chaikoff effect. [55]

The clinical importance of this low T3 syndrome is controversial. The low T3 levels (especially total T3 and not free T3) in CKD patients have been correlated with higher levels of markers of inflammation [highly sensitive Creactive protein (hsCRP), IL-6, etc.], malnutrition (lower prealbumin, IGF-1), increased endothelial dysfunction, poorer cardiac function, poor survival, and higher all-cause as well as cardiovascular mortality in some studies. [54, 56] Some of these studies were underpowered to detect these associations or did not exclude confounders appropriately. [57] In some other studies, the low free T3 and not the total T3 level is associated with increased mortality. [58] However, recent studies have demonstrated that this association is not invariable, and the free T3 levels may not be associated with long-term mortality in CKD and dialysis patients. [59].

Subsequent studies also demonstrated a low T4 level in many CKD patients. 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-thyroidal illnesses (NTIs) such as severe infections, heart failure, malignancies, and in several hospitalized patients without renal disease. This led to the consideration of a "sick euthyroid state" in CKD, which is now called "non-thyroidal illness." However, unlike other NTI states, there is no increase in total rT3 levels in CKD. [60] This is due to an increased redistribution of rT3 into extra vascular and intracellular spaces. In some patients, due to an impaired renal clearance, free rT3 levels may be mildly elevated. Another difference from other NTIs is that the thyroid stimulating hormone

(TSH) levels are elevated in CKD. However, TSH is released in response to thyrotrophic releasing hormone (TRH) in CKD patients, indicating pituitary disturbances in uremia. [61] In addition, the circadian rhythm of TSH and its glycosylation is altered in CKD, compromising its activity. Thus, CKD patients have low T3 and normal or reduced T4 levels, and consequently elevated TSH and attendant increase in thyroid gland volume. [62–64]

These mechanisms are probably reflective of the physiological adaptation of the body to CKD to reduce the protein nitrogen turnover, reduce the protein catabolism and nitrogenous waste load. The reduced T3 levels and associated complications without increase in rT3, the reduced free T4 levels along with an elevated TSH, and hypo responsiveness of TSH to TRH question the "euthyroid" state and raise the possibility of benefit from thyroid supplementation CKD. However, three decades of research in this area have not been able to clarify the need for thyroid hormone replacement in CKD. Attempts at T3 replacement have often resulted in negative nitrogen balance by increased muscle catabolism, implying the prudence in not correcting the low T3 state in CKD.

Though it is clear that hypothyroidism would threaten the patient's well-being, it is not clear as to what level of thyroid dysfunction forms the threshold necessary for treatment by thyroxine replacement in CKD. In general, mild elevations of TSH (less than 20 IU/ml) with or without low T3/T4generally do not warrant thyroid hormone supplementation. One has to consider the dangers of hyperthyroidism as well as the teleological benefits of a hypothyroid state in CKD and the lack of clearly evident benefits of thyroid hormone replacement in the literature before deciding on therapy. A clinical decision of the treating nephrologists and endocrinologists should be made on an individual patient basis, after carefully considering the clinical features, possible hypothyroid manifestations, putative benefits, and possible risks of thyroid hormone therapy or the lack of it.

CKD results in reduced iodide excretion, which results in increased serum inorganic iodide level and the thyroid gland iodine content and consequent thyroid gland enlargement. Structural changes in thyroid among CKD patients include an increased prevalence of goiter (especially among women), thyroid nodules, and thyroid carcinoma, compared to general population [65].

There is no increase in the incidence of autoimmune thyroid disease in CKD patients. In fact, the incidence of positive thymoglobulin and thyroid microtonal antibodies is low in CKD patients. However, autoimmune thyroid disease may occur along with other autoimmune diseases associated with CKD, such as lupus nephritis, type 1 diabetes mellitus, etc. When elevated TSH is detected in association with other autoimmune disease, it is important to screen for antithyroid antibodies. Management strategy for autoimmune thyroid disease remains unaltered by the presence of CKD.

2. Thyroid Dysfunction in Dialysis and Kidney Transplantation

Patients on hemodialysis (HD) due to CKD have low thyroid hormone levels and elevated TSH. The minor increases in TSH levels (5 – 20 mU/l), observed in about 20% of uremic patients, are usually not considered to be reflecting "hypothyroidism" in this select group of patients. Though the total T4 levels are low, heparin inhibits T4 binding to protein, thereby increasing free T4 fraction in CKD patients after heparin dialysis. [66] Among the CKD patients on HD, there is a compensatory influence on cellular transport of thyroid hormones, which helps maintain the euthyroid state despite low serum thyroid hormone levels. [67] For all these reasons, despite low serum thyroid hormone profile, thyroid hormone supplementation should not be initiated without substantial elevation in TSH level and careful consideration.

Among patients on peritoneal dialysis (PD), there is a significant increase in prevalence of hypothyroidism (especially subclinical) and low T3 levels. [68] Thyroxine-binding globulin (TBG), T4, and T3 are lost in the PD effluent. Despite continuous and substantial protein loss, TBG levels are normal. The T4 and T3 losses are minor (10% and 1%, respectively) and easily compensated for. Thus, thyroid hormone replacement is not necessary in CKD patients on PD.

Kidney transplantation reverses the CKD syndrome and thus has an effect of CKD-mediated thyroid profile abnormalities. The low T3 and T4 levels recover after transplantation, although gradually, over the first 3–4 months. During the initial few months after transplantation, kidney transplant patients

predominantly exhibit a reduction in T4 levels lower than the pre-transplant level, before it gradually rises back to normal. [69] In general, post-transplant thyroid volume and free T3 levels correlate well with graft function. [70] Pre-transplant low T3 levels are associated with future risk of graft loss. [71] But therapy with T3 supplementation does not improve graft survival, negating the possibility of a causal association. [72] Thus, there is no need to supplement thyroid hormones for the low T3 levels noted in the first few months of renal transplantation. Thyroid carcinoma is the fifth most common malignancy among kidney transplant patients. [73]

2.1. Other Kidney Diseases with Thyroid Dysfunction

Several glomerulonephritides may occur in association with thyroid diseases.The most commonly were associated with membranous nephropathy, [74, 75] followed by IgA nephropathy, [76] membranoproliferative glomerulonephritis, [77] and minimal change disease. [78] There are several mechanisms for these associations. The presence of circulating immune complexes among patients with thyroid disease, [79] the association of Hashimoto's thyroiditis and membranous nephropathy with immune complex deposition in the glomerular as well as thyroid epithelial basement membrane, [80] and the common occurrence of thyroid and renal disease in association with other autoimmune diseases such as type 1 diabetes mellitus [81] suggest a common autoimmune pathogenesis or an autoimmune disorder (such as lupus or vasculitis) with associated thyroid and renal disease. Hypothyroidism could result in obstructive sleep apnea which is associated independently with minimal change disease.

Proteinuria, especially in nephrotic syndrome, often results in urinary loss of thyroid hormones bound to the various binding proteins such as TBG, albumin, prealbumin, and transthyretin. [82] This results in a reduction in the serum total thyroid hormone levels. Thyroid compensates for this by increasing the free fraction of the hormones and maintaining euthyroid state. However, patients with low thyroid reserve may develop hypothyroidism consequent to this urinary loss.

In patients on supplemental thyroxine, proteinuria can increase the dose requirement to maintain euthyroid state. [83] Primary hypothyroidism has also been described in congenital nephrotic syndrome, with urinary loss of thyroid hormones resulting in increased TSH level *in utero* [84]. In addition to the glomerulonephritides mentioned above, isolated cases of hyperthyroidism have been associated with tubulointerstitial nephritis and uveitis (TINU) syndrome. [85] The disease responds well to steroid therapy. Patients with acute kidney injury may develop an NTI (euthyroid sick syndrome), but without elevation of reverse T3 levels. [86] Hypothyroidism can result in rhabdomyolysis related acute kidney injury [87].

2.2. Thyroid and Renal Malignancy

There is an increased predisposition of patients with thyroid cancer to develop renal cell carcinoma (RCC)[88] due to genetic predisposition or treatment of disease. In addition, thyroid malignancy could metastasize to the kidney [89] and RCC is one of the common tumors metastasizing to the thyroid. [90] While clear cell carcinoma of thyroid, morphologically resembling the RCC, is described, some RCC may morphologically resemble thyroid follicular carcinoma. [91] Thyroid malignancies expressing EPO receptors have favorable prognosis, [92] while RCC expressing aberrant thyroid hormone receptors may contribute to carcinogenesis. [93]

2.3. Drugs in Thyroid Disease

Drugs used in thyroid or kidney disease may have adverse effects on the other organ's functions. Thionamides such as methimazole, carbimazole, propylthiouracil cause hypothyroidism as well as renal dysfunction by immune mechanisms resulting in various glomerular disease such as vasculitis, [94] lupus nephritis, [95] or necrotizing glomerulonephritis with pulmonary hemorrhage. [96] Alemtuzumab, used in renal transplantation, has been reported to result in autoimmune thyroid disease. [97] Interferon-α, used again in renal cell carcinoma as well as for treatment of hepatitis B and C virus infection pre-transplant causes hyperthyroidism. [98] Lenalidomide, used in renal cell carcinoma for its antitumor and antiangiogenic properties, results in a subacute thyroiditis and transient thyrotoxicosis. [99] Sunitinib, a new therapeutic agent against RCC, results in hypothyroidism, which some authors believe to be associated with better prognosis. [100]

Lithium use causes hypothyroidism as well as nephrogenic diabetes insipidus and CKD.

Amiodarone is associated with both hypothyroidism and hyperthyroidism as well as acute renal damage. [101] Rifampicin causes both a tubulointerstitial nephritis as well as hyperthyroidism. [102] an important consideration is the therapy of hyperthyroid patients with CKD. In general, CKD patients require lower doses of I for treatment of Grave's disease. Hyperthyroid patients on HD, due to I clearance by dialysis, require the usual therapeutic dose of I for treatment. [103] Patients on PD require a fivefold reduction in the I dose for treatment of thyroid carcinoma, to avoid excessive radiation [104].

2.4. Hypothyroidism

Hypothyroidism is the most common disorder arising from hormone deficiency. According to the time of onset it is divided in congenital and acquired, according to the levelof endocrine dysfunction in primary and secondary or central and according to the severity in severe or clinical and mild or subclinical hypothyroidism. The distinction between subclinical and clinical hypothyroidism is of major significance as in clinical hypothyroidism symptoms are more severe even coma may occur, while in subclinical hypothyroidism symptoms are less serious and may even be absent. The diagnosis may be easily performed by the measurement of blood levels of thyroid hormones. Therapy of choice is the administration of thyroxine and the prognosis is very good [105].

2.5. CKD Diagnosis

The first step in outlining an intervention strategy is to define which patients have early CKD. The publication of the first CKD guidelines in 2002 by the National Kidney Foundation, a US voluntary health organization, was an important step to bring policy attention to CKD. These guidelines, referred to as the KDOQI guidelines, were adopted by countries and institutions worldwide and form the basis for CKD classification [106]. Based on current prevalence estimates, 44.6 million people in the US – including 33.6% of people aged 60 years or older – have CKD. Over 95% of these individuals are classified as having stages 1–3, prompting some to call the current situation a "silent epidemic" and the "tip of the iceberg." A recent study suggested that a person born in the US today has a lifetime risk of developing CKD stages 3a+, 3b+, 4+, and ESRD of 59.1%, 33.6%, 11.5%, and 3.6%, respectively. The prevalence rates are based on eGFR readings – a proxy measure of renal function – usually calculated using the CKD-EPI (CKD Epidemiology Collaboration) or MDRD Study (Modification of Diet in Renal Disease) formulae. Albuminuria levels provide supplemental information. eGFR equations and age-related decline in renal function [106]. These high lifetime risks for CKD call into question whether there is a distinction between early CKD and normal age-related decline in renal function. Reductions in renal blood flow and mass, as well as increased glomerulosclerosis, are part of the normal ageing process, with eGFR falling by about 0.75 mL/min/1.73 m^2 per year from the age of 40. This rate of progression seems non-linear, with eGFR loss in elderly patients slowing below 45 mL/min/1.73 m^2. In population studies, the majority of patients assigned as having CKD are aged over 60 years, and most of these patients do not have significant albuminuria. It is therefore difficult to differentiate between age-related loss of kidney function and renal disease. The data suggest that, for a given reduction in eGFR, elderly patients are less likely to progress to ESRD. The role of the ageing process has long been recognized for other organ systems. For example, the natural decline in forced expiratory volume with age forms a referent for the identification of premature or accelerated loss of respiratory function. Meta-analyses of over 1.5 million patients performed by the CKD Prognosis Consortium, however, have shown almost identical risks for ESRD in patients above and below 65 years of age with an eGFR of 45–59 and an ACR of <10 mg/g. These data have been interpreted as evidence against the introduction of differing thresholds for defining CKD based on age, although the interaction between renal function and proteinuria does seem to differ with age, potentially due to the competing risk for death. It has also been argued that senescent changes in eGFR are due to other disease processes rather than pre-determined renal decline. The differing interpretations of the current data on eGFR loss in the elderly underscore the need to consider eGFR trends as part of a clinical assessment. Although it is unclear whether these eGFR changes reflect intrinsic renal disease or normal ageing, CKD and senility are associated with an increased risk for morbidity and mortality in an additive fashion. Comorbidity is common in CKD patients. In the UK, about 64% of patients aged over 65 years that are coded as having CKD have four or more additional morbidities. Whilst it is acknowledged that multi-morbidity leads to

greater need for healthcare, the risk factors for multi-morbidity are ill-defined. Further work is required to determine whether renal impairment in elderly patients is associated with or causes other conditions. The formulae for estimating GFRs exhibit other well-documented limitations. The formulae were developed to identify patients with eGFR ≤60 mL/min/1.73 m^2 at risk for renal failure, and are not sensitive for stages 1 and 2. On their own, eGFR estimates are therefore of little value in early intervention efforts; some have even called for removing the first two stages from the KDOQI guidelines, while others have proposed alternative classification systems. The MDRD Study equation tends to underestimate true GFR in individuals with normal kidney function, while the CKD-EPI equation tends to overestimate it in individuals with CKD or at high risk for CKD. The two equations only generate eGFR figures that are within 30% of the true values. In 15.9% of CKD-EPI cases and 19.4% of MDRD Study cases, the estimated values are even less accurate. There are also gender and ethnic differences in GFRs that should be accounted for.

Epidemiologic studies have used different eGFR formulae, which limits direct comparison due to varying accuracies at higher levels of eGFR. Most national studies also rely on point estimates of eGFR, whereas a CKD diagnosis should only be made after multiple estimates over several months; results from point estimates tend to overstate prevalence rates. Moreover, not all studies consider AER when estimating prevalence rates.

3. MATERIAL AND METHODS

A total of 128 patients of both gender with chronic kidney disease were included in study. Patients Venous blood from all participants were collected in the morning on fasting subjects (8 hours) and were sent to hospital laboratory. Subclinical hypothyroidism was noted. It was a cross sectional study. The sample size was n=128 with 7.5 % margin of error, 95 % confidence level taking expected percentage of (subclinical hypothyroidism): 25%.[8] The sampling technique was non-probability consecutive sampling. Patients aged 18-60 both male and females with chronic kidney disease as per operational definition for more than 6 months were included in the study. Patients with family history of thyroid disorder, on thyroid medications, history of thyroid surgery or radiological intervention of thyroid

gland and history of drugd that affect thyroid metabolism were excluded from the study.128 patients fulfilling the inclusion criteria from Department of Nephrology, PIMS, Islamabad were included in the study after permission from ethical committee and research department of CPSP. Informed consent was taken from each patient/guardians, explaining the benifits while taking part in this study. Basic demographics (age, gender, type and duration of CKD) were noted.

Venous blood from all participants were collected in the morning on fasting subjects (8 hours) and was sent to hospital laboratory. Subclinical hypothyroidism was noted as per operational definition by researcher and noted on especially designed proforma.

Data was analyzed with statistical analysis program IBM-SPSS version-22. Frequency and percentage was computed for gender, stages of CKD and subclinical hypothyroidism. Mean±SD was presented for quantitative variables like age and duration of complain. Effect modifiers like age, gender, stages of CKD and duration of complain were controlled by stratification. Post stratification chi square test was applied p ≤0.05 was considered statistically significant.

4. RESULTS

Age range in this study was from 18 to 60 years with mean age of 41.695±7.96 years and mean duration of complain was 12.015±3.41 months as shown in Table-I.

Males were 62.5% as compare to females 37.5% as shown in Table-II.

Percentage and Frequency of patients according to stages of CKD are shown in Table-III.

Subclinical Hypothyroidism was present in 21.1% patients as shown in Table-IV.

Stratification of Subclinical Hypothyroidism with respect to age, gender, stages of

CKD and duration of complain are shown in Table-V, VI, VII and VIII respectively.

Table1: *Mean±SD of patients according to age and duration of complain n=128*

Demographics	Mean±SD
Age (years)	41.695±7.96
Duration of complain(months)	12.015±3.41

Table2: *Percentage and Frequency of patients according to gender n=128*

Gender	No of Patients	%age
Male	80	62.5%
Female	48	37.5%
Total	128	100%

Table3: *Percentage and Frequency of patients according to stages of CKD n=128*

Stages of CKD	No of Patients	%age
II	30	23.4%
III	35	27.3%
IV	36	28.1%
V	27	21.1%
Total	128	100%

Table4: *Percentage and Frequency of patients according to Subclinical Hypothyroidism n=128*

Subclinical Hypothyroidism	No of Patients	%age
Yes	27	21.1%
No	101	78.9%
Total	128	100%

Table5: *Stratification of Subclinical Hypothyroidism with respect to age*

Age (years)	Subclinical Hypothyroidism		p-value
	Yes	No	
18-40	11(20.8%)	42(79.2%)	0.937
41-60	16(21.3%)	59(78.7%)	
Total	27(21.1%)	101(78.9%)	

Table6: *Stratification of Subclinical Hypothyroidism with respect to gender*

Gender	Subclinical Hypothyroidism		p-value
	Yes	No	
Male	17(21.2%)	63(78.8%)	0.955
Female	10(20.8%)	38(79.2%)	
Total	27(21.1%)	101(78.9%)	

Table7: *Stratification of Subclinical Hypothyroidism with respect to stages of CKD*

Stages of CKD	Subclinical Hypothyroidism		p-value
	Yes	No	
II	1(3.3%)	29(96.7%)	0.000
III	1(2.9%)	34(97.1%)	
IV	13(36.1%)	23(63.9%)	
V	12(44.4%)	15(55.6%)	
Total	27(21.1%)	101(78.9%)	

Table8: *Stratification of Subclinical Hypothyroidism with respect to duration of complain*

Duration of complain (months)	Subclinical Hypothyroidism		p-value
	Yes	No	
6-12	22(30.6%)	50(69.4%)	0.003
>12	5(8.9%)	51(91.1%)	
Total	27(21.1%)	101(78.9%)	

5. DISCUSSION

Thyroid autoimmunity and subclinical primary hypothyroidism are highly prevalent in CKD patients not requiring long-term dialysis treatment [107]. In their study, Lo et al [108] reported a prevalence of hypothyroidism of 23.1% in CKD patients with an eGFR < 30 mL/min/1.73 m^2. In another study, subclinical hypothyroidism and clinically apparent hypothyroidism have been reported to occur in ∼18–20% of patients with CKD not requiring renal replacement therapy [109]. This study similar with these previous observations by demonstrating a prevalence of subclinical hypothyroidism (20.1%). In a study by Gupta A, et al has showed that frequency of subclinical hypothyroidism was 25% in out of 100 patients with chronic kidney disease, they concluded high prevalence of subclinical hypothyroidism in chronic kidney disease patients.[8] In a study by Chandramohan G, et al has showed that frequency of subclinical hypothyroidism was 60% in out of 50 patients with chronic kidney disease, they suggest that subclinical primary hypothyroidism is a relatively common condition (60%) among persons with CKD not requiring dialysis, and it is independently associated with progressively

lower estimated GFR in a small group of patients[9].In a local study form Karachi by Mal M, et al has showed that frequency of subclinical hypothyroidism was 20% in out of 158 patients with chronic kidney disease[10].An increased prevalence of subclinical hypothyroidism in persons with reduced eGFR independent of age and gender was seen in this study. This is in line with the observation made by Chonchol et al [109]. In this study, the absolute prevalence of hypothyroidism in the lower GFRs is higher than that reported in other studies, which may be due to the smaller sample size in the present study.

Majority of the patients in this study fell in the CKD stage IV/V category, which could be due to the fact that most of the CKD patients referred to this tertiary care center have a low GFR. A multicentric screening program for hypothyroidism in the CKD population can provide a better picture of its actual prevalence. Higher TSH levels are seen with increasing age [110]. The TSH level is often elevated in CKD in response to thyrotropin from pituitary as a result of uremic effect [111]. TSH also loses its circadian rhythm along with compromised bioactivity due to poor glycosylation. Chronic metabolic acidosis has also been labeled as one of the contributing factors in the rise of hypothyroidism cases in CKD population [112]. The Wolff–Chaikoff effect [113] has been cited as a causative phenomenon behind the rise of this disorder in diabetic kidney disease patients. Dyslipidemia is seen throughout the spectrum of thyroid dysfunction although it is of much milder degree with TSH levels between 5 and 10 mU/L compared to TSH > 10 mIU/L [114-116]. A few reports [117,118] have shown significantly elevated total cholesterol with TSH < 10 mIU/L in comparison to euthyroids. An increase in TSH levels may lead to increase in PTH levels either due to thyrotropin-releasing hormone stimulation or error in measurement by immunometric assays [119]. Our study followed the trend. Hypothyroidism leads to a reduction of osteoclast bone reabsorption and osteoblast formation, slowing the remodeling process and increasing the time taken in the remodeling cycle, mainly due to the prolongation of the mineralization phase. A slight increase in bone mass may occur, albeit not with a reduced risk of fracture.

Our study also had several limitations. This is a cross-sectional study, so causality cannot be established. In addition, our study lacks details about the possible etiology of SCH or a measure of antithyroid antibodies. A prospective study is desirable, which can throw light on the effect of thyroxine treatment on GFR and give a better picture of the true prevalence of hypothyroidism in CKD population.

6. CONCLUSION

Sub-clinical hypothyroidism is a common issue in subjects with CKD found in 20.1% patients. Early detection of SCH in CKD may decrease the risk of cardiovascular events and progression of kidney disease.

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