Hypothyroidism in Chronic Kidney Disease and Regular Hemodialysis Patients

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Introduction:

Chronic kidney disease (CKD) have evolved over time, but current international guidelines define this condition as decreased kidney function shown by glomerular filtration rate (GFR) of less than 90mL/min per 1.73 m^2, or markers of kidney damage, or both, of at least 3 months duration, regardless of the underlying cause. Diabetes and hypertension are the main causes of CKD in all high-income and middle-income countries, and also in many low-income countries. Incidence, prevalence, and progression of CKD also vary within countries [1].

Patients with end-stage renal disease (ESRD) have been found to have higher rates of goiter and thyroid dysfunction, and it has been hypothesized that these patients may also experience increased hypothyroidism. In addition, lower total and free triiodothyronine and other thyroid hormone abnormalities have been documented among ESRD patients [2].

Kidney function is significantly altered by thyroid disorders. Both hypothyroidism and hyperthyroidism have an impact on the kidney's structure, GFR, electrolyte homeostasis, tubular function, and renal blood flow. On the other hand, Increased serum creatinine levels decreased GFR and renal plasma flow (RPF), disruption of the ability to excrete free water, and hyponatremia are the most frequent kidney abnormalities linked to hypothyroidism [3].

In recent decades, there has been growing concern about the relationship between thyroid abnormalities and renal illnesses. The growth and development of the kidneys depend on thyroid

hormones. On the other hand, thyroid hormone metabolism, degradation, and removal are heavily influenced by the kidney [4].

It has been observed that people with kidney illnesses have a significant prevalence of thyroid issues. The specific explanation of this connection is unknown, although some ideas explain that it occurs when iodine reserves rise because of a reduction in renal iodine exertion, which leads to iodine retention and, ultimately, hypo- and hyperthyroidism [1]

Hypothyroidism, defined as elevated serum TSH without decrease of T3 and T4 and treated by Replacement of thyroid hormone that is fundamental not only relieves the symptoms of hypothyroidism, but also alleviates the deleterious effects of hypothyroidism on the kidney and heart and Normalization of RPF and GFR **[3].**

As few studies had been performed about the magnitude of thyroid dysfunction in CKD, to best of our knowledge few actual studies were performed in the Arab world and Egypt about the prevalence of thyroid dysfunction especially hypothyroidism in CKD patients with variable prevalance. But no studies were performed about the prevelance of Hypothyroidism in CKD with different treatment modalities including conservative treatment and those under regular hemodialysis.

Hypothyroidism in CKD and ESRD

Thyroid hormones influence renal development, kidney hemodynamics, glomerular filtration rate and sodium and water homeostasis. Hypothyroidism and hyperthyroidism affect renal function by direct renal effects as well as systemic hemodynamic, metabolic and cardiovascular effects. Hypothyroidism has been associated with increased serum creatinine and decreased glomerular filtration rate. The reverse effects have been reported in thyrotoxicosis [3].

Most of renal manifestations of thyroid dysfunction are reversible with treatment. Kidney disease may also cause thyroid dysfunction by several mechanisms. Nephrotic syndrome has been associated to changes in serum thyroid hormone concentrations. Different forms of glomerulonephritis and tubulointerstitial disease may be linked to thyroid derangements. A high prevalence of thyroid hormone alteration has been reported in acute kidney injury [5].

Thyroid dysfunction is highly prevalent in chronic kidney disease patients. Subclinical hypothyroidism and low triiodothyronine syndrome are common features in patients with chronic kidney disease. Patients treated by both hemodialysis and peritoneal dialysis, and renal transplantation recipients, exhibit thyroid hormone alterations and thyroid disease with higher frequency than that found in the general population [6].

Drugs used in the therapy of thyroid disease may lead to renal complications and, similarly, drugs used in kidney disorders may be associated to thyroid alterations. Lastly, low thyroid hormones,

especially low triiodothyronine levels, in patients with chronic kidney disease have been related to a higher risk of cardiovascular disease and all-cause mortality. Interpretation of the interactions between thyroid and renal function is a challenge for clinicians involved in the treatment of patients with thyroid and kidney disease [7].

Thyroid pathology and kidney:

Thyroid hormone contributes to renal development and physiology and participates in the development and increases de activity of many co-transport systems in the renal tubule, including the Na-P co-transporter, Na-H exchanger, and the Na/K ATPase in proximal convoluted tubule [8].

Pre-renal effects of TH are mediated by their influence on the CV system, the renin-angiotensin system and the renal blood flow. As an example, experimental investigations have shown that thyroid hormone produces up-regulation of beta-adrenergic receptor binding sites and their linkage to adenylate cyclase, thus regulating in this way the renin-angiotensin system [5].

Hypothyroidism and renal function:

Hypothyroidism may affect renal function through direct mechanisms on glomerular and tubular functions and also indirectly through modifications in cardiac and vascular function and derangements in the renin-angiotensin system [6].

Hemodynamic changes:

Hypothyroidism is associated with remarkable alteration in cardiac contractility and output, myocardial oxygen consumption, vascular resistance, blood pressure and electrophysiological conduction [3].

Decrease in systolic function and delay in diastolic relaxation and filling have been accounted for by hypothyroidism-induced alterations in the transcription of gene products which impact myocyte contractility. Synthesis of endothelial vasodilators is decreased in hypothyroidism, leading to arterial stiffness and increased systemic vascular resistance, and increased diastolic hypertension [8].

Thyroid hypofunction is associated with decreased sensitivity to beta-adrenergic stimulus, decreased renin gene expression, decreased renin release, and also with increased mean arterial pressure, resulting in reduction in the renin-angiotensin system activity. This reduction may result in impaired renal autoregulation. Other hemodynamic aftermaths of hypothyroidism include decreased levels of atrial natriuretic factor, decreased erythropoietin production and, therefore, decreased blood volume [7].

Glomerular changes:

Hypothyroidism may directly worsen kidney function through alterations in hemodynamics and structure. In experimental animals' hypothyroidism has been associated with reduction in kidney-to-body weight ratio and truncated tubular mass, as well as adverse changes in glomerular architecture [8].

A factor than contributes to the decrease in GRF in experimental animals is the adaptive pre-glomerular vasoconstriction mechanism in response to a filtrate overload due to deficient sodium and water reabsorption in the proximal tubule. The chloride load in distal tubuli of hypothyroid rats, caused by a disturbed activity of chloride channels ClC-2, activates the tubulo-glomerular feedback leading to decreased GFR. The intra-renal vasoconstriction may decrease renal blood flow and predispose to prerenal kidney injury [5].

A reduced expression of renal vasodilators such as vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1) has been reported in patients with hypothyroidism. Hypothyroid rats exhibited a significant decrease in the matrix Gla protein, with acts as a potent inhibitor of vascular calcification in vivo, as well as an increase in calcium content compared with that from the control euthyroid animals [3].

In humans, population-based studies have shown that higher TSH is associated with lower GFR and higher prevalence of CKD, independent of confounding factors such as age, sex, body mass index, smoking and comorbidities. Patients with hypothyroidism, both overt and subclinical, are characterized by a decrease in the GFR and renal plasma flow, resulting in increased serum creatinine [6].

The reduction in GRF in humans with hypothyroidism has been verified not only by using creatinine-based equations, such as the Modification of Diet in Renal Disease equation, but also with more precise GRF measurements methods using inulin or 51Cr-EDTA. The elevation of serum creatinine may occur within two weeks of significant hypothyroidism, and levels typically normalize rapidly after replacement therapy with levothyroxine [8].

Serum levels of cystatin C, a cysteine proteinase inhibitor freely filtered at the glomerulus and reabsorbed and metabolized by proximal tubular epithelial cells, is commonly decreased in hypothyroidism despite the increase in GFR. Nevertheless, cystatin C levels are not accurate indicator of GFR in patients with hypothyroidism [9].

Hypothyroidism also contributes to the reduction in GRF in patients with CKD. However, it has been shown that, in these patients, GFR increased rapidly over the first 6 months after thyroid hormone replacement therapy [10].

In patients with subclinical hypothyroidism and stage 2–4 CKD it has been shown that the overall rate of decline in GFR was significantly greater in subjects who did not take thyroid hormone therapy compared to treated subjects. Thyroid hormone therapy attenuated the rate of decline in renal function in CKD patients with subclinical hypothyroidism, suggesting that this therapy may delay reaching end-stage renal disease (ESRD) in these patients [5].

An increase in glomerular capillary permeability to proteins has also been reported in hypothyroidism. Hypothyroid patients exhibited a urinary albumin excretion rate significantly higher than in hyperthyroid and euthyroid subjects [7].

Tubular changes:

In animal models with long-term hypothyroidism, the activities of the Na/K ATPase and Na-H exchanger are reduced. The increase in sodium and bicarbonate loss in urine results in defective urinary acidification. A loss of medullary hypertonicity is also seen in hypothyroidism, resulting in impaired urinary concentrating ability. Hypothyroidism causes an increase in sensitivity of the collecting ducts to vasopressin, thus increasing water reabsorption [10].

The non-osmotic vasopressin release, impaired urinary concentrating ability, increased urinary sodium excretion, increased fractional excretion of sodium and impaired tolerance of sodium restriction have been advocated as causes for the reduced capacity to achieve maximal urinary dilution. A decreased Na-H exchanger and Na-Pi cotransporter activity has been demonstrated in hypothyroid animals [9].

A decrease urinary acidification with increased sodium and bicarbonate excretion rates has also been reported in hypothyroid rats. Therefore, hyponatremia and impaired free water excretion are common complications of clinical hypothyroidism. They may be accounted for by reduced GFR, reduced sodium reabsorption, relative increase in vasopressin secretion and renal vasopressin sensitivity [8].

Chronic kidney disease causing hypothyroidism:

TSH is considered the most sensitive and specific single measure of hypothyroidism in general population. However, some TSH alterations may be observed in the absence of thyroid disease in uremic patients. These may include elevated basal TSH values, blunted TSH response to TRH, diminished or absent TSH diurnal rhythm, altered TSH glycosylation, and impaired TSH and TRH clearance rate [3].

CKD is also a widely recognized cause of nonthyroidal illness, characterized by alterations in TH in the absence of underlying intrinsic thyroid disorder. Recently, much interest has been focused on ESS, characterized by decreased serum T3 and/or T4 levels, accompanied by increased reverse

T3 (rT3) and no significant increase in TSH. Low T3 syndrome is the most common abnormality of ESS and appears frequently in CKD patients]5.[

This reduction in T3 concentrations has been linked to a decrease in the peripheral synthesis of T3 from T4 and has been reported to be a strong marker of adverse clinical outcomes in uremic patients [6].

Hyperthyroidism is typically not associated with CKD. However, it has been known that hyperthyroidism can accelerate the progression of CKD. It is likely that, somehow, hypertension associated with hyperthyroidism can intervene accelerating the progression of CKD [3].

The non-thyroidal illness syndrome (NTIS), also known as low T3 syndrome or euthyroid sick syndrome, reflects alterations in thyroid hormone levels that occur in almost every form of acute or chronic illness as CKD. The acute phase of critical illness, observed in a variety of clinical situations, is marked by low triiodothyronine (T3) and free T3 and high reverse T3 (rT3) levels [3].

As CKD progresses, additional decreases in T3 and further reductions in the T3/rT3 ratio are observed, whereas thyrotropin (TSH) levels typically remain within the normal range or slightly increased. The changes in serum thyroxine (T4) levels are more complex. At early stages, serum T4 tends toward normal levels but its fall is observed in severe or end-stage cases [11].

About 50% NTIS patients will also present decreased TSH levels, indicating concomitant changes in the hypothalamic/pituitary regulation. Whether these changes are due to adaptive physiological mechanisms to reduce the metabolic rate during stressful circumstances, or a consequence of the underlying process is still a matter of debate [5].

The changes in thyroid hormone levels are associated with duration and severity of CKD. An entire set of data obtained from critically ill patients demonstrated that the degree of reduction in thyroid hormone levels correlates with patient mortality and that serum rT3, T3/rT3 ratio, and free T4 levels are independent prognostic factors for survival. Low T3 levels are also an independent predictor of short- and long-term survival in patients with CKD as well myocardial infarction, heart failure, or acute stroke outside the ICU setting]11.[

End-stage renal disease (Stage 5) can overlap the symptoms of hypothyroidism, such as fatigue, lethargy and cognitive dysfunction, as the prevalence data previously known are on relatively small cohorts and there are little data about the severity of thyroid abnormalities in these patients. A relatively high prevalence of thyroid goiter and an increase in thyroid gland have been reported [3].

An increased prevalence of hypothyroidism and subclinical hypothyroidism has been suggested in patients with ESRD. Thyroid hormone dysfunction has been reported in ESRD patients, including low peripheral thyroid hormones and thyroid stimulating hormone]5.[

Dialysis and hypothyroidism:

Hemodialysis:

Although most HD patients are euthyroid, lower T3 and T4 values, higher TSH levels, higher frequency of low T3 syndrome and subclinical hypothyroidism are more frequent observed in HD patients compared with healthy subjects. Different studies have reported that hypothyroidism is a common condition that affects HD patients, although prevalence estimates vary across populations [5].

In the general population, hypothyroidism is associated with higher mortality, particularly in populations with underlying CV risk. Despite the main cause of mortality in HD patients is CV disease (CVD), the impact of hypothyroidism on the survival of these patients remains uncertain. Low serum free T3 (FT3) concentrations have been considered as an independent predictor of mortality in dialysis patients [7].

However, actually the optimal TSH range in dialysis patients remains unknown. Although some authors have suggested that the association between hypothyroidism and mortality may be ameliorated by thyroid hormone replacement therapy, additional studies are needed to confirm these findings [3].

Peritoneal dialysis:

The most common thyroid dysfunction observed in PD patients is primary hypothyroidism, especially subclinical hypothyroidism. PD patients frequently also display low T3 levels as an effect of impaired extra-thyroidal T4 to T3 conversion, or as a phenomenon secondary to peritoneal loss of thyroid binding globulin. The role of low T3 syndrome in these patients is uncertain and has been consider as a metabolic adaptation, marker of illness or even mediator of mortality [5].

It has been noticed that a high prevalence of thyroid disorders exists among patients of kidney diseases. The exact reason for this association is not well understood, and some theories explained that association as iodine stores increase due to a decrease in renal iodine exertion and subsequent iodine retention, in turn, cause hypo- and hyperthyroidism [10].

Few studies had been performed about the magnitude of thyroid dysfunction in CKD. And to our knowledge no actual studies were performed in Egypt about the prevalence between thyroid dysfunction especially hypothyroidism in CKD patients with different treatment modalities.

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