

Disorders in Thyroid Morphology Observed in ESRD Patients on Maintenance Haemodialysis

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ABSTRACT

Background: Chronic kidney disease has been associated with changes in thyroid gland morphology and thyroid hormone metabolism. Goiter and thyroid nodules have been reported with increased frequency in end-stage renal disease (ESRD) patients, however its frequency is not known in developing countries.

Aim: To study the thyroid gland morphology in our ESRD population and its correlation with patients' demographics.

Methods: We enrolled 74 patients with ESRD on maintenance haemodialysis (HD) at the dialysis centre of Jinnah hospital, Lahore. Two patients (3%) with pre-existing thyroid disease were excluded. Thyroid ultrasonography (USG) was done on all the patients to assess thyroid volume, nodules and its echotexture.

Results: A total of 72 patients were evaluated and forty six (64%) were male. Median age was 50 years (range 17-82 years). Twenty two (31%) patients had DM, 43 (60%) had HTN, 4(5%) patients had evidence of obstructive uropathy and 3(4%) patients had ADPKD as the cause of ESRD. Thirty two (44%) had HCV infection. Median duration on haemodialysis was 3.5 years (range 1-12 years). Sixty (83%) patients were on thrice weekly haemodialysis. Median thyroid volume was 8ml (range 3-24ml). Thyroid nodules were found in 31(43%) patients. Significantly higher number of females (57%) had thyroid nodules as compared to males (32%) [p-value 0.035, odds ratio 2.8 (95% CI 1.062-7.48)]. Twelve (17%) patients had single thyroid nodule, 14(19%) patients had 2-5 nodules, and 5(7%) patients had more than 5 nodules.

Conclusion: There is high prevalence of thyroid nodules in our dialysis patients' population. Higher frequency was observed in female patients. No correlation was found with PTH levels, pre-existing comorbidities, frequency and duration of haemodialysis and co-existing renal cysts. Ultrasound evaluation of thyroid gland morphology should be considered in patients on maintenance haemodialysis.

Keywords: Thyroid, End Stage Renal Disease, Haemodialysis, Pakistan

INTRODUCTION

The kidneys normally not only play an important role in metabolism, degradation and excretion of several thyroid hormones but also are a target organ of some of these hormones. Thyroid gland plays a vital role in human body and controls development, protein synthesis and metabolism of other hormones of body, by mainly T3 and T4. Thyroid hormones are necessary for growth & development of kidneys and for maintenance of water and electrolyte balance¹. Interactions between kidney and thyroid functions are known for many years. There is a clinical overlap between thyroid dysfunction and end-stage renal

disease. ESRD is a clinical situation in which patients depend upon dialysis continuously throughout their life span until they undergo renal transplantation. Impairment of renal functions disturbs thyroid gland morphology and physiology. Uraemia caused by ESRD affects thyroid hormones at the level of hypothalamic-pituitary-thyroid axis² as well as at the level of thyroid hormone peripheral metabolism.

The pituitary axis disturbance is explained by the finding that despite normal or raised levels of TSH, its effect on TRH is generally low and delayed due to increased half-life and decreased clearance of TSH by kidneys in patients with ESRD. In ESRD renal iodide excretion also diminishes due to marked reduction in glomerular filtration resulting in high levels of plasma inorganic iodide and initial rise in thyroid iodide uptake. This increase of intra-thyroidal iodide blocks further thyroid hormone production and this change in function explains well the higher

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prevalence of goiter and hypothyroidism in patients with ESRD³.

Chronic metabolic acidosis due to CKD results in reduced peripheral conversion of T4 to T3, also called as Low T3 Syndrome and this reduced level of T3 is also found to be associated with the duration on dialysis and markers of endothelial inflammation & damage [inflammatory markers are high sensitivity C-reactive protein (hs-CRP), IL 6, VCAM-1]⁴.

End-stage renal disease requires the renal replacement therapy (RRT). Various modalities of RRT include haemodialysis (HD), peritoneal dialysis (PD) and Renal transplantation. In our set up most frequently used modality is haemodialysis (HD). Patients with ESRD undergoing haemodialysis have generally low levels of total T4 but free T4 levels are raised. This change is due to Heparin used in HD that inhibits binding of T4 to plasma proteins resulting in elevated levels of free T4 and compensatory hypertrophy of thyroid gland forms thyroid nodules and goiter⁵. A study by G. Basu shows that TSH level was found to be raised in about 20% ESRD patients of his studygroup with range 20-50mU/L⁶. These transformations are considered as physiological mechanisms to conserve protein energy in response to uremic wasting by diseased kidneys.

Recent advancements in medical technology have enabled us to detect subclinical and asymptomatic nodules in all endocrine organs especially those of thyroid gland called as 'Thyroid Incidentalomas' (TI). These TI can be detected by using various imaging techniques including Ultrasonography (USG) as the most easily available technique'. Thyroid nodule is defined as 'any abnormal growth that forms a lump in thyroid tissue'. These are grossly differentiated in two main types

1. Functioning nodules- when they are producing thyroid hormones
2. Non-functioning nodules- when they are not producing thyroid hormones

These TNs can further be classified as benign or malignant, single or multiple and cystic or solid on basis of features and consistency of nodules⁸.

Thyroid nodules need removal when there is suspicion of malignancy or when they become symptomatic. Majority of nodules are asymptomatic and only 5%-10% are found malignant. Thyroid glands are larger in size and volume in uremic patients than the subjects having normal renal function and prevalence of goiter is more among women than men. Carcinoma of thyroid and thyroid nodules are also commonly found in patients with ESRD than healthy population.

ESRD is strongly associated with hypothyroidism but not with hyperthyroidism. As the GFR decreases, risk of developing hypothyroidism

increases exponentially. Chonchol M in his study found that hypothyroidism was present in 7% of patients with estimated GFR >90ml/min per 1.73m² that increased to 17.9% with GFR<60ml/min per 1.73m²(⁹).

In this study we have estimated the prevalence of disorders of thyroid morphology in ESRD patients on HD and their association with ESRD, haemodialysis, gender distribution and co-morbidities.

METHODS

We enrolled 74 patients on maintenance haemodialysis (HD) in a cross-sectional study conducted from May 2016 to June 2016, at the Dialysis Centre of Jinnah hospital, Lahore. Two (3%) patients were excluded from the study on exclusion criteria of pre-existing thyroid disorder, on medication (i.e., propranolol, amiodarone, lithium, steroids) affecting thyroid functions or detection of thyroid disease by thyroid function tests. Informed consent was obtained from all the patients included in this study. Baseline Demographic data about age, gender and medical history of diabetes, hypertension, hepatitis B & C and cardiovascular diseases were obtained on a standardized self-administered questionnaire for each patient. Thyroid ultrasonography was done by the expert sonologist to assess thyroid volume, echotexture and nodules. Strap muscle of neck was used as reference for echogenicity. Echogenicity more than that of strap muscle was considered normal and equal to or less than that of this muscle was considered hypo-echogenicity. Volume of both thyroid lobes was added up to calculate total thyroid volume and volume of each lobe was calculated individually by formula

Volume of each lobe = a × b × c × (π /6)

- a = anteroposterior dimension
- b = transverse dimension
- c = longitudinal dimension.

WHO classification was used for classification of thyroid gland according to the size on the basis of palpation and inspection¹⁰. Bilateral Renal USG was also conducted by the expert sonologist for number of renal cysts present in these patients.

The data generated from the study were entered and analysed by SPSS version 20 for windows software. Odds ratio was calculated with 95% Confidence Interval (CI) to assess different factors related to thyroid dysfunction in ESRD patients. P-values less than 0.05 were considered of statistic significance. Descriptive statistical analyses were also done to obtain clear picture of variables like age, gender and relevant clinical data. Qualitative

variables were represented with numbers and percentages while Quantitative variables were represented by mean±SD. Confidentiality of the patients was maintained at each step. At the end of the study, all patients were counselled about their illness and referred to Endocrinologist for the best possible management of the associated thyroid changes in them.

RESULTS

The study population comprised of 72 patients with ESRD on maintenance HD. Forty six (64%) were male patients. Median age was 50 years (range 17-82 years). Twenty two (31%) had Diabetes mellitus, Forty three (60%) had hypertension, Four (5%) patients had evidence of obstructive uropathy, Three (4%) patients had ADPKD as the cause of ESRD and Thirty two (44%) had HCV infection. Thyroid nodules were seen in 31 (43%) patients. Twelve (17%) patients had single thyroid nodule, fourteen (19%) patients had 2-5 nodules, five (7%) patients had more than 5 nodules.

Significantly higher number of female patients had thyroid echotexture changes and thyroid nodules as compared to male patients [57% vs 43%; OR 2.8 (95% CI 1.062-7.48); p value 0.035]. The relation of mean number of thyroid nodules in male and female patients is shown by graph in figure 1.

No significant correlation was detected between co-morbidities like HTN, diabetes, HCV, obstructive uropathy, APKD and presence of renal cysts before dialysis (Table 1).

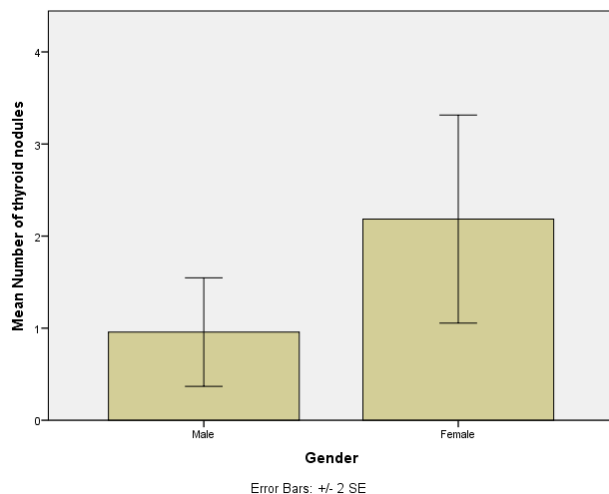


Fig. 1: Gender distribution of mean number of thyroid nodules.

Median duration on haemodialysis was 3.5 years (range 1-12 years). Sixty patients (83%) were on thrice weekly haemodialysis. No significant

correlation between duration & frequency of haemodialysis and presence of thyroid nodules was found.

Median thyroid volume was 8ml (range 3-24ml). Echotexture of thyroid gland was homogenous in 70 (95%) patients and heterogeneous in 4 (5%) patients.

Table 1: Association of co-morbidities with thyroid nodules in patients with ESRD on HD

Co-morbidities	Presence of Thyroid nodules			
	Yes	No	Total	P-value
Diabetes mellitus	11	13	24	0.756
No diabetes	21	29	50	
HTN	28	40	68	0.228
No HTN	4	2	6	
HCV	10	22	32	0.067
No HCV	20	20	42	
Obst-uropathy	3	1	4	0.185
No obst-uropathy	29	41	69	
APKD	0	3	3	0.062
No APKD	32	39	71	
Renal cysts before dialysis	0	2	2	0.129
No renal cysts before dialysis	32	40	72	

DISCUSSION

Our study identifies that there is high prevalence of disorders of thyroid morphology in patients with ESRD on maintenance haemodialysis. No such study in our patient population has been done so far. End-stage renal disease (ESRD) affects the functions and structure of thyroid gland in various forms including altered behaviour of thyroidal iodine storage, plasma levels of inorganic iodide, low levels of Thyroid hormones (TH) in circulation, increase in rT3, altered conversion in peripheral tissue, conspicuous augmentation in T3 sulfate concentration, decreased uptake by tissue and reduced binding to plasma proteins¹¹. Renal working status has high impact on function of thyroid gland like-wise thyroid gland influences renal functions. Children having hypothyroidism have high frequency of renal congenital anomalies¹². During perinatal period, levels of thyroid hormones affect enzymes involved in mitochondrial energy metabolism found in cells of proximal convoluted tubules of nephrons¹³. This results in altered renal function by altered activity of Na-P co-transporter (NaPi)¹⁴, Na-H exchanger (NaHE)¹⁵ and Na/K ATPase¹⁶ in PCT.

Previous studies suggest that frequency of thyroid nodules is generally higher in females¹⁷ and prevalence of thyroid carcinoma is 3 times more in female population than male population¹⁸. In our study in ESRD patients prevalence of thyroid nodules was more among female patients (57%) than male

patients (32%). We used ultrasonography to detect subclinical and asymptomatic nodules. Thyroid ultrasound is preferred over other techniques because it is non-invasive, more accurate and cost effective modality. USG also helps to define characteristics of nodule like its consistency (cystic or solid), margins (regular or irregular) and echotexture¹⁹. Classification of thyroid nodules on the basis of their number has great significance as it tells about chances of developing thyroid malignancy. Zuberi LM reported in his study that risks of developing malignancy are more in multiple nodules than single nodules²⁰. As in our study we found that 17% patients had single thyroid nodule, 19% had 2-5 nodules and 7% had more than five nodules. This is concerning for the risk of development of thyroid malignancy and long-term follow-up studies are required to accurately assess and estimate this risk.

Subclinical hypothyroidism is very common among individuals with ESRD, worldwide. Recent studies show that almost 70% of patients with ESRD present with low levels of T3 and 20-25% present with asymptomatic subclinical hypothyroidism^{9,21}. A study conducted in Saudi Arabia showed that a significant fall in serum T3, T4 and elevation in TSH levels was found along with low levels of total proteins & serum albumin, in patients with ESRD as compared to the control group²². Reduced levels of serum T3, T4 and raised levels of TSH raise a possibility that the ESRD associated dysfunction of thyroid gland can be corrected by supplementation of thyroid hormones but it is still debateable among clinicians and no strong evidence is present supporting recommendation of thyroid hormone supplementation in patients with ESRD on HD⁶. Hypothyroidism can further deteriorate both systolic and diastolic functions of heart besides presence of traditional co-morbidities like hypertension and other cardiovascular diseases.

In our study the median age of the patients was 50 years (range 17-82 years). Increasing age also proves to be a co-morbid factor along with ESRD in causing thyroid dysfunction and enforces effects of ESRD on thyroid gland. Numerous morphological changes take place with aging in the endocrine system including subclinical changes in thyroid gland. Hypothyroidism and thyroid nodules are significantly more common in older age people than younger subjects and higher levels of free T4 & TSH have been observed²³. In present study there was no correlation found between the age of patients and thyroid illness neither with other comorbidities like DM, hypertension, HCV infection, APKD and pre-existing renal cysts. Moreover, low levels of thyroid hormones (T3, T4) have direct association with increasing mortality rate in patients with ESRD.

Zoccali *et al* were the first researchers who reported that direct association is present between low levels of T3 and all-cause mortality in stable ESRD patients on maintenance haemodialysis and similar result was found among those on peritoneal dialysis²⁴. In present study no correlation was found between frequency and duration of haemodialysis. Only two patients out of 74 patients were known cases of thyroid disease and were taking medication. All other patients were unaware of their co-existing thyroid disorder due to not having knowledge about ESRD and associated endocrine abnormalities.

Limitations of the study: The study was conducted at only one centre and limited number of patients was enrolled. The results of this study cannot be generalized to the whole population of ESRD patients on HD and larger prevalence studies are required. Use of 3-dimensional ultrasound would have provided us more accurate and precise information²⁵ about thyroid gland structure as compared to 2-dimensional ultrasound used by us. Thirdly FNAC, biopsy or radioiodine uptake studies of nodules were not carried out leading to limited information on status of hot and cold nodules.

CONCLUSION

There was high prevalence of disorders of thyroid morphology in our population of ESRD patients on HD. Majority of our ESRD patients had no prior knowledge of their co-existing thyroid disease and presented with single & multiple thyroid nodules. Higher prevalence of thyroid nodules was found among female patients. No correlation was found with PTH levels, pre-existing comorbidities, frequency and duration of haemodialysis sessions and co-existing renal cysts. Thyroid ultrasound should be included in routine investigations of patients with ESRD on HD for timely diagnosis and management of associated thyroid disorders.

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