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# ASSOCIATIONS BETWEEN THYROID DYSFUNCTION AND CHRONIC KIDNEY DISEASE

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## Abstract

***Background and Aims.*** *The interactions between kidney and thyroid functions are well established: thyroid hormones are necessary for the maintenance of electrolyte and water homeostasis and kidney is involved in the regulation of thyroid hormones metabolism. The aim of our study was to estimate the prevalence of thyroid dysfunction in patients with diabetes mellitus and chronic kidney disease (CKD).* ***Material and Method.*** *23 patients with diabetes mellitus and CKD in pre-dialysis phase were recruited for this study. All subjects were investigated with thyroid ultrasound and laboratory tests to determine thyroid function, including: serum triiodothyronine (T3), free thyroxine (free T4), thyroid-stimulating hormone (TSH) and antithyroid peroxidase antibodies (ATPO). Results were compared with the same measurements in 21 patients with diabetes mellitus but without CKD.* ***Results****. The prevalence of goiter (52.17% vs. 19.04%, p<0.05), subclinical hypothyroidism (23.80% vs. 9.52%, p<0.05), hypothyroidism (8.69% vs. 4.76 %, p<0.05) and low T3 syndrome (23.80% vs. 0.00% p<0.05) were significant high in diabetic patients with CKD compared with patients with diabetes mellitus but without CKD.* ***Conclusions.*** *We observed high prevalence of thyroid morphology abnormalities and thyroid function disorders in diabetic patients with CKD. Low T3 syndrome and subclinical hypothyroidism are the most frequently thyroid function disorders in CKD patients.*

**key words**: *chronic kidney disease, diabetes mellitus, thyroid disorders*

## Background and Aims

Thyroid hormones regulate growth, development, differentiation and metabolism of virtually all tissues of vertebrates. The kidney and cardiovascular system are some of the most important targets of the thyroid hormones [1]. Kidney and thyroid function are interrelated through several mechanisms. Thus, thyroid hormones are necessary for the maintenance of electrolyte and water homeostasis (directly by affecting the glomerular /tubular kidney function and the structure of the kidney itself and indirectly by affecting the cardiovascular system and the renal blood flow). Meanwhile, the kidney is involved in the regulation of thyroid

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hormones metabolism. The kidney contributes to the iodine clearance primarily by glomerular filtration. Serum iodine concentrations are elevated in patients with chronic kidney disease (CKD) but not correlated with the degree of kidney failure [2,3]. The excess of serum iodine has been linked to increased prevalence of goiter and hypothyroidism in patients with CKD [4,5].

Previous studies have shown that CKD patients have low triiodothyronine (T3), normal or reduced thyroxine (T4) levels, and consequently elevated thyroid-stimulating hormone (TSH) [6,7].

In an issue of the European Journal of Endocrinology, Iglesias P and Diez JJ published in 2009 a review article entitled: "Thyroid dysfunction and kidney disease " in wich they report that "*Serum TSH concentrations are usually normal or elevated in CKD. Free and total $T_3$ and $T_4$ concentrations are usually normal or low in patients with CKD. The reduction in $T_3$ levels (low $T_3$ syndrome) is the most frequently observed thyroid alteration in these patients. This reduction in $T_3$ concentrations has been linked to a decrease in the peripheral synthesis of $T_3$ from $T_4$. CKD is associated with a higher prevalence of primary hypothyroidism, both overt and subclinical, but not with hyperthyroidism*" [8].

The aim of this study was to explore the prevalence of thyroid dysfunction in a cohort of patients with diabetes mellitus and CKD from Bucharest, Romania.

## Material and Method

A total of 23 patients with diabetes mellitus and CKD in the pre-dialysis phase were recruited for this study. The term pre-dialysis has not been defined in guidelines. The National Kidney Federation-Kidney Dialysis Outcomes Quality Initiative (K/DOQI) defines CKD as "*Glomerular Filtration Rate (GFR) less than≤60ml/min/1.73m$^2$ that is present for≥3 months with or without evidence of kidney damage or evidence of kidney damage with or without decreased GFR that is present for≥3 months as evidence by microalbuminuria, proteinuria, glomerular haematuria, pathological abnormalities, anatomical abnormalities*" [9]. In this classification, preparation for renal replacement therapy (RRT) has been recommended in the stage characterized by a reduction of the estimated GFR to <30 ml/min. In our study, pre-dialysis care was defined as CKD with a possible need for RRT. All subjects were investigated with thyroid ultrasound and laboratory tests. Laboratory tests to determine thyroid function include: serum triiodothyronine (T3), free thyroxine (free T4), thyroid-stimulating hormone (TSH) and antithyroid peroxidase auto-antibodies (ATPO). TSH, free T4 and T3 were measured by radioimmunoassay and ATPO by Enzyme-linked Immunosorbent Assay (ELISA) technique. Results were compared with the same measurements in 21 patients with diabetes mellitus but without CKD. The study protocol and informed consent were approved by the Institutional Ethics Committee. All subjects provided written informed consent before participating in this study.

### *Statistical analysis*

Data are presented as mean±SD. Clinical characteristics were compared using the t Student Test. Pearson's moment-product correlation coefficients were calculated to evaluate correlations between variables. Significance was defined at the 0.05 level of confidence. All calculations were performed using the Statistical Package for Social Sciences Software (SPSS) version 15.

## Results

The subjects were aged between 52 and 64 years (median age was 55±2 years in diabetic patients with CKD and 54±3 years in patients without CKD) and had an evolution of diabetes between 12 and 22 years. We observed a high prevalence of thyroid morphology abnormalities (diffuse or nodular goiter) in diabetic patients with CKD (12 patients - 52.17%: 7 patients with diffuse goiter and 5 patients with nodular goiter). Thyroid ultrasound aspects of nodular and diffuse goiter are shown in Figures 1 and 2.

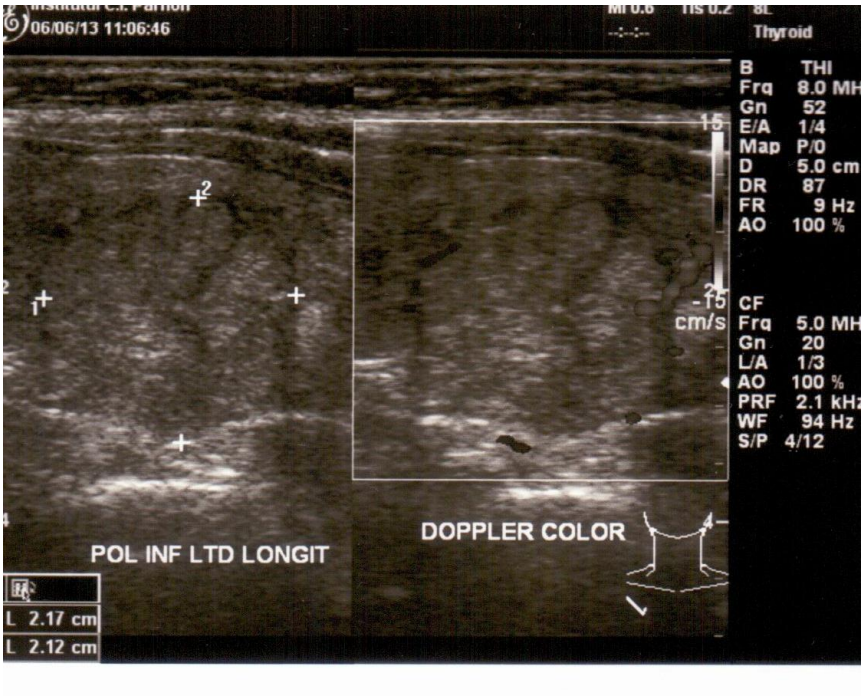


**Figure 1.** Thyroid ultrasound aspect of nodular goiter.

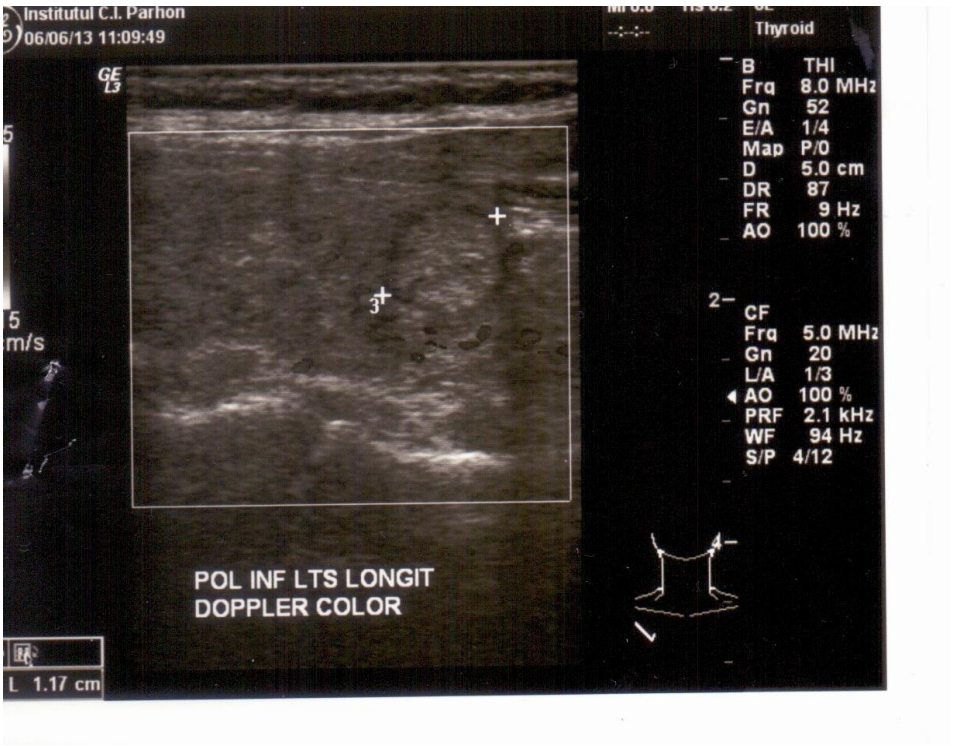


**Figure 2.** Thyroid ultrasound aspect of diffuse goiter.

Five diabetic patients with CKD (23.80%) had subclinical hypothyroidism (subclinical hypothyroidism is defined as a clinical syndrome of hypothyroidism associated with raised serum TSH but free T4 in the normal range), 2 patients (8.69%) had overt hypothyroidism (overt hypothyroidism is defined as a clinical syndrome of hypothyroidism associated with elevated TSH and decreased serum levels of circulating thyroid hormone) and 5 patients had low T3 syndrome (23.80%). In the control group the prevalence of goiter was 19.04% (4 patients). Subclinical hypothyroidism was present in 2 patients (9.52%) while one patient (4.76%) was diagnosed with overt hypothyroidism.

Statistically significant differences were recorded between diabetic patients with and without CKD for the prevalence of goiter (52.17% *vs.* 19.04%, $p<0.05$), subclinical hypothyroidism (23.80% *vs.* 9.52%, $p<0.05$), overt hypothyroidism (8.69% *vs.* 4.76%, $p<0.05$) and low T3 syndrome (23.80% *vs.* 0.00% $p<0.05$) as shown in Figure 3. The incidence of autoimmune thyroid disease was similar in both groups.

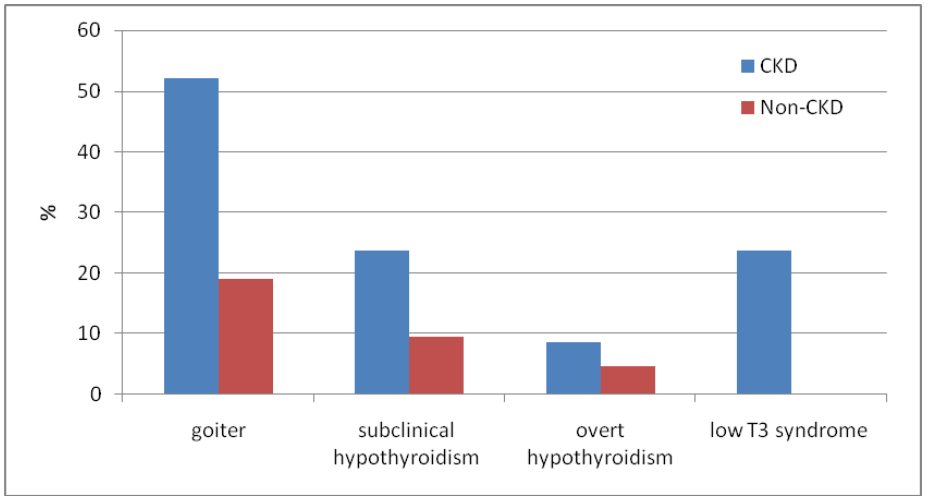


**Figure 3.** Prevalence of thyroid morphology abnormalities and thyroid function disorders in diabetic patients with and without CKD.

## Discussions

Previous studies have shown that patients with CKD have mild reductions in thyroid function, but these abnormalities could represent a risk factor for cardiovascular disease and might be also involved in kidney disease progression [5,6].

The low T3 syndrome and subclinical hypothyroidism are the most frequently thyroid function disorders in patients with CKD. In our study the prevalence of low T3 syndrome and subclinical hypothyroidism was 23.80% in patients with CKD. The clinical importance of low T3 syndrome is controversial. A reduction in total T3, concentrations was associated with increased cardiovascular mortality in euthyroid CKD patients [10] while low T3 syndrome before renal transplantation was associated with decreased survival of the graft [11]. The lowT3 syndrome in CKD patients has been also correlated with higher levels of inflammation markers, endothelial dysfunction and cardiovascular mortality [12-14].

Our findings add to data from other studies that report a high prevalence of low T3 syndrome and subclinical hypothyroidism in patients with CKD. Thus, Lim VS *et al*. reported that prevalences of low T3 were 80% in non-haemodialysis patients and 43% in

haemodialysis patients [15] while Lo JC *et al* reported that the prevalence of hypothyroidism in patients with GFR<30 ml/min/1.73m$^2$ was 23.1% [16]. A study performed by Chonchol M *et al* analysed the prevalence of subclinical hypothyroidism in 3089 adult outpatients with CKD. They found that "*subclinical primary hypothyroidism is a relatively common condition (approximately 18%) among persons with CKD not requiring chronic dialysis, and it is independently associated with progressively lower estimated GFR*" [17]. Kang EW *et al* analysed the prevalence of subclinical hypothyroidism in 51 stable patients in continuous ambulatory peritoneal dialysis. They found that subclinical hypothyroidism is present in 14 (27.5%) patients and might be involved in cardiac dysfunction [18].

Our data showed a high prevalence of thyroid morphology abnormalities (diffuse or nodular goiter) in diabetic patients with CKD which is concordant with data from a study conducted by Hegedüs L *et al* reporting that thyroid gland volume (ultrasonically determined) is increased in patients with CKD [19].

All patients with overt hypothyroidism should be treated with thyroxine, and the dose should be adjusted to normalize the serum TSH concentration. The role of therapy in patients with subclinical hypothyroidism and low T3 syndrome is more controversial. In a recent issue of of *Thyroid,* Shin DL *et al* published an article entitled: " *Thyroid hormone replacement therapy attenuates the decline of renal function in chronic kidney disease patients with subclinical hypothyroidism*". The authors evaluated 113 CKD patients with subclinical hypothyroidism treated with L-thyroxine. The treatment improves the GFR, suggesting that substitution therapy attenuates the decline of renal function [20].

A limitation of our study is represented by the relatively small number of patients enrolled. Future clinical and experimental studies should explore potential causal mechanisms linking low T3 syndrome, subclinical hypothyroidism and CKD.

## Conclusions

We observed a high prevalence of thyroid morphology abnormalities and thyroid function disorders in diabetic patients with CKD. Low T3 syndrome and subclinical hypothyroidism are the most frequently thyroid function disorders in CKD diabetic subjects.

## REFERENCES


1. **Klein I, Ojamaa K**. Mechanism of disease: thyroid hormone and the cardiovascular system. *N Engl J Med* 344: 501–509, 2001.

2. **Ramirez G, O'Neill W, Jubiz W, Bloomer HA**. Thyroid dysfunction in uremia: evidence for thyroid and hypophyseal abnormalities. *Ann Intern Med* 84: 672–676, 1996.

3. **Mariani LH, Berns JS**. The renal manifestations of thyroid disease, *J Am Soc Nephrol* 23: 22-26, 2012.

4. **Kaptein EM.** Thyroid hormone metabolism and thyroid diseases in chronic renal failure. *Endocr Rev* 17: 45–63, 1996.

5. **Singh PA, Bobby Z, Selvaraj N, Vinayagamoorthi R.** An evaluation of thyroid hormone status and oxidative stress in undialyzed chronic renal failure patients. *Indian J Physiol Pharmacol* 50: 279–284, 2006.

6. **Hegedus L, Andersen JR, Poulsen LR et al.** Thyroid gland volume and serum concentrations of thyroid hormones in chronic renal failure. *Nephron* 40: 171–174, 1985.

7. **Sato K, Okamura K, Yoshinari M et al**. Reversible primary hypothyroidism and elevated serum iodine level in patients with renal dysfunction. *Acta Endocrinologica (Copenh)* 126: 253–259, 1992.

**8. Iglesias P, Diez JJ.** Thyroid dysfunction and kidney disease. *Eur J Endocrinol* 160: 503-515, 2009.

**9. National Kidney Foundation.** K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 39: S1-266, 2002.

**10. Carrero JJ, Qureshi AR, Axelsson J et al.** Clinical and biochemical implications of low thyroid hormone levels (total and free forms) in euthyroid patients with chronic kidney disease. *J Intern Med* 262: 690-701, 2007.

**11. Rotondi M, Netti GS, Rosati A et al.** Pretransplant serum FT3 levels in kidney graft recipients are useful for identifying patients with higher risk for graft failure. *Clin Endocrinol (Oxf)* 68: 220-225, 2008.

**12. Zoccali C, Tripepi G, Cutrupi S, Pizzini P, Mallamaci F**. Low triiodothyronine: A new facet of inflammation in end-stage renal disease. *J Am Soc Nephrol* 16: 2789–2795, 2005.

**13. Carrero JJ, Qureshi AR, Axelsson J et al.** Clinical and biochemical implications of low thyroid hormone levels (total and free forms) in euthyroid patients with chronic kidney disease. *J Intern Med* 262: 690–701, 2007.

**14. Tripepi G, Zoccali C.** Low triiodothyronine and cardiovascular disease. *Circulation* 108: e29–30. author reply e29-30, 2003.

**15. Lim VS, Fang VS, Katz AI et al.** Thyroid dysfunction in chronic renal failure. A study of the pituitary-thyroid axis and peripheral turnover kinetics of thyroxine and triiodothyronine. *J Clin Invest* 60: 522–534, 1977.

**16. Lo JC, Chertow GM, Go AS et al.** Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. *Kidney Int* 67: 1047–1052, 2005.

**17. Chonchol M, Lippi G, Salvagno G, Zoppini G, Muggeo M, Targher G**. Prevalence of subclinical hypothyroidism in patients with chronic kidney disease. *Clin J Am Soc Nephrol* 3: 1296-1300, 2008.

**18. Kang EW, Nam JY, Yoo TH, Shin SK, Kang SW, Han SH**. Clinical implications of subclinical hypothyroidism in continuous ambulatory peritoneal dialysis patients. *Am J Nephrol* 28*:* 908-913, 2008.

**19. Hegedüs L, Andersen JR, Poulsen LR et al.** Thyroid gland volume and serum concentrations of thyroid hormones in chronic renal failure. *Nephron* 40: 171-174, 1985.

**20. Shin DH, Lee MJ, Lee HS et al.** Thyroid hormone replacement therapy attenuates the decline of renal function in chronic kidney disease patients with subclinical hypothyroidism. *Thyroid* 23: 654-661, 2013.