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Functional Thyroid Disorders Are More Common in Patients on Chronic Hemodialysis Compared with the General Population

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ORIGINAL PAPER

SUMMARY

Introduction: Thyroid function disorders are common in patients with chronic kidney disease. **The aim** of this study was to compare thyroid function among patients on chronic hemodialysis (HD) and healthy participants and to assess duration of dialysis on thyroid disorders . **Material and methods:** Prospective study included 80 participants divided in two groups. Study group included 40 patients on HD who were divided in two subgroups, according to time on dialysis (under and over 72 months). Exclusion critheria were: previous thyroid disorders, systemic illnesses, criticaly ill patients and acute inflamatory diseases. Control group included 40 healthy participants. Blood samples were taken for standard laboratory analysis, total and free thyroid hormone levels. **Results:** In HD group we found statistycally significant lower mean values of T3 (1,36 ± 0.451, p<0.0001), T4 (80.33 ± 19.167, p= 0.0001), and higher mean values of TSH (3.16 ± 3.168, p= 0.01), higher frequency of low T3 syndrome in 12.5% (n=5) (p=0.01) and subclinical hypothyroidism in 17.5% (n=7) (p=0.021). In the subgroup of patients with time on HD <72 months, significantly, more frequent and low T3 syndrome was found in 19.23% (n = 5) (p = 0.01). In the subgroup of patients with HD >72 months subclinical hypothyroidism was found more frequently in 35.71% (n = 5) (p = 0.04) . **Conclusion:** Thyroid disorders are more common in patients on HD compared to general population. These findings suggest that thyroid function and morphology screening should be performed in HD patients.

KEY WORDS: Thyroid function, hemodialysis, TSH, CKD.

1. INDRODUCTION

Chronic kidney disease (CKD) influence hypothalamo-pituitary-thyroid axis. Secretion of hypophyseal thyroid stimulating hormone (TSH) is disturbed in uremia and the TSH response to the hypothalamic thyrotropin releasing hormone (TRH) is reduced (1, 2). CKD affects the thyroid function by lowering levels of circulating thyroid hormones, interfering with hormones binding to protein carriers, disrupting metabolism and elimination of thyroid hormones (3), and affect the storage of iodine in thyroid gland (1, 4). The concentration of serum iodine in patients with CKD is higher due to lower iodine clearance caused by reduced glomerular filtration. Elevated levels of serum inorganic iodine in patients with CKD may potentially block thyroid hormone synthesis (Wolf-Chaikoff effect), what canexplain higher prevalence of diffuse goiter and hypothyroidism in these patients (5).

More specifically, the prevalence of primary hypothyroidism, mainly in the subclinical form, increases with decreasing glomerular filtration rate (GFR) (6,7). Chronic hemodialysis (HD) is associated with abnormal concentrations of circulating thyroid hormones, mainly the reduction of total and free serum thyrotropin (T3) (3). Total and free T4 can be increased in haemodialysed patients due to lipolitic effects of heparin used in anticoagulant therapy during haemodialysis (8).

The aim of this study was to compare thyroid function among patients on chronic hemodialysis and healthy participants, and to assess if there is an association between the dialysis duration and thyroid disorders.

2. MATERIALS AND METHODS

Patients

A prospective single centar study lasting for 12 months included 80 participants divided in two groups. First group included 40 stabile patients on chronic haemodialysis program that lasted longer than three months, with a different etiology of renal diseases. Exclusion critheria were previous thyroid disorders, systemic illnesses, criticaly ill patients and acute inflamatory diseases. The control group included 40 healthy participants. The average time on dialisys was 60.32± 36.18 months (Table 1). There was no statistically

Variables	HD group (n= 40)	Control group (n=40)	P
Average age (yr; mean± SD)	53,28±11,76	49,43±7,80	0,088
Female gender (n[%])	22 (55%)	20 (50%)	0,654
Male gender (n[%])	18 (45%)	20(50%)	0,645
BMI (kg/m^2; mean ± SD)	23,15±2,07	25,13±2,29	< 0,001
Time on dialysis (mo; mean ± SD)	60,32±36,18	-	-
GFR mL/min/1.73m^2 ; mean ± SD)	12,35±1,981	63,14±51,926	0.0000

Table 1. Selected caracterisctics of study patients (data are presented as mean ± SD)

significant difference between genders and average age between two groups. The average body mass index was statistically significant lower in hemodialysed group.

To asses possible relation between thyroid function disorders and time on dialysis, participants of HD group were divided into two subgroups: subgroup A (patients on dialysis < 72 months), and B (patients on dialysis > 72 months). In table 2 wich shows selected caracterisctics of study subgroups (subgroup A patients with time on dialysis < 72 months, and B time on dialysis >72 months) is shown that there was no statistically significant difference between average age, genders, BMI and GFR between two subgroups, p> 0.05.

Variables	Subgroup A (n=26)	Subgroup B (n=14)	Total	P
Average age (yr; mean± SD)	54.35 ± 12.582	51.29 ± 10.194	53.28 ± 11,76	0.4396
Female gender (n[%])	15 (57.70%)	7 (50.00%)	22 (55.00%)	0.641
Male gender (n[%])	11 (42.30%)	7 (50.00%)	18 (45%)	0.641
BMI (kg/m^2; mean ± SD)	22.96 ± 1.949	23.50 ± 2.312	23.15 ± 2,070	0.4398
GFR mL/min/1.73m^2 ; mean ± SD)	12.35 ± 2.077	12.36 ± 1.865	12.35 ± 1.981	0.9869

Table 2. Selected caracteristics of study subgroups

Methods

Blood samples were taken fasting and before dialysis treatment and heparin administration. The following parameters were assessed: total protein, albumin, creatinine, urea, cholesterol, triglycerides, urea using Architect c 8000 Abbott. Hemoglobin, red blood cell count was assessed by standard laborathory measurements using SISMEX.T3, T4, and TSH were assessed using Architect i2000 Abbott TSH (IRMA) by means of standard laboratory methods. Free T4, free T3 were assayed by RIA using commercially available kits. Subclinical hypothyroidism was defined as a mild TSH serum elevation > 4,4 mmol/L in patients with normal serum thyroxin level (9). Hypothyroidism is defined as elevation in TSH>10 mmol/L and reduced serum T3 and T4 (10). Low T3 syndrome is defined as decreased serum T3 levels < 0.89 mmol/L (11).

Statistical analysis

Data are expressed as means ± standard deviations. Statistical differences in the variables were tested using parametric and non parametric tests where appropriate. The relationship between tested variables was asessed using Spearman correlation coefficients. P values less than 0.05 were considered statistically significant. Data processing software package was used SPSS for Windows.

3. RESULTS

Undefined renal disease was the most common underlying cause of CKD (47%), followed by chronic glomerulonephritis (25%). Diabetic nephropathy and polycistic renal disease was present in 15% and 13% of partients respectively. In HD group of patients mean serum triiodothyronine (T3) and thyroxine (T4) level was significantly lower, while mean serum TSH level was significantly higher compared to control group (p< 0.05) (Table 3). In HD group low T3 syndrome and subclinical hypothyroidism were significantly more prevalent compared to control group (p <0.05) (Table 4). Presence of thyroid functional impairment was not associated with underlying renal diseases (Figure 1).

As shown in Table 5, in subgroup A low T3 syndrome was observed more frequently (19.23%), and in subgroup B subclinical hypothyroidism was more frequent (35.71%) compared to control group, p<0.05. We did not found s statistically significant difference in mean values of total, free thyroid hormones and TSH between subgroups.

	HD group (n= 40)	Control group (n=40)	p-value
Triiodothyronine (T3) nmol/L	1.36 ± 0.451	2.24 ± 0.467	< 0.0001
Thyroxine (T4) nmol/L	80.33 ± 19.167	102.66 ± 28.837	0.0001
Thyroid stimulating hormone (TSH) mIU/ml	3.16 ± 3.168	1.83 ± 0.938	0.0131
Free T3 (FT3) pmol/L	5.21 ± 2.008	5.41 ± 1.409	0.6193
Free T4 (FT4) Free Free T4(FT4) pmol/L	14.19 ± 3.473	15.12 ± 4.059	0.2743

Table 3. Serum thyroid and thyroid stimulating hormones in patients on hemodialysis (HD group) and in healthy participants.

Thyroid function disorder	HD group		Control group		P
	(N)	%	(N)	%	
Without disorder	22	55.00	35	90.00	0.001
Low T3 syndrome	5	12.50	0	0.00	0.017
High T4 syndrome	0	0.00	1	2.50	0.311
Low T4 syndrome	3	7.50	0	0.00	0.072
Subclinical hypothyroidism	7	17.50	1	2.50	0.021
Clinical hypothyroidism	2	5.00	0	0.00	0.147
Subclinical hyperthyroidism	1	2.50	2	5.00	0.555

Table 4. Absolute and relative frequencies of thyroid functional disorders among groups

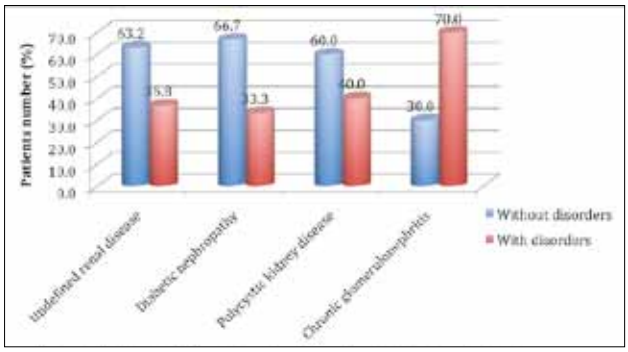

Figure 1. The ratio of thyroid function disorders

4. DISCUSSION

We aimed to assess spectrum of thyroid function disorders in patients on chronic hemodialysis and possibble conection between time on dialysis and thyroid disorders.

The results of our study revealed increased prevalence of functional disorders of the thyroid gland in HD patients, comparing to control group (45% vs. 10%). Mean values of serum T3 were significantly lower in HD patients (1.36 ± 0.451 vs 2.24 ± 0.467, p<0.0001). Mean values of free T3 did not satisticaly differ from those in control group and remained in normal limits. Low T3 syndrome was significantly more frequent in patients on HD treatment comparing to control group (12.5% vs. 0.00%, p< 0.05). Mentioned findings are similar with those found in recent literature. The most common thyroid imbalance in patients on hemodialysis was low T3 syndrome, while FT3 levels generally remain within the normal limits (12, 13, 14). Song et al. (15) examined the prevalence of decreased T3 in patients at different stages of CKD. This retrospective study included 2284 patients with normal TSH, and it was concluded that in these patients, there was a positive correlation between GFR and the level of T3. Zoccali et al. (16) in their study revealed that the decreased T3 and fT3 is connected with inflammation and cardiovascular damage in patients with end-stage CKD. These findings suggest that reduced T3 and fT3 may be a prognostic marker in patients with end-stage CKD. Rotondi et al. (17) has found link between low serum T3 levels before kidney transplantation and decreased incidence of graft survival.

Mean serum levels of T4 were significantly lower compared to controls (80.33 ± 19.167 vs. 102.66 ± 28.837, p < 0.0001). We found no statistically significant difference between groups in mean FT4 values. Low T4 syndrome was more common in patients on HD but without statistical significance.

The syndrome of high T4 and FT4 we did not observed in HD group. We believe that there was no increase in T4 and FT4 because we were taken blood samples for determining hormone before dialysis treatment and before heparin application.

For this interpretation, we found a foothold in the study of Bayer M (8). In this study author examined the correlation between changes in serum T4 and FT4, heparin application and post heparin lipolytic activity. In a significant number of patients, after application of heparin, there was an increase in mean T4 and FT4. These results suggest the possibility that the effect of heparin on T4 and FT4 is associated with heparin activation of lipases that act on non-esterified fatty acids, which in high concentrations compete with thyroxine for its carrier protein.

Thyroid function disorder	Subgroup A		Subgroup B		Total		p
	F	%	F	%	f	%	
Without disorder	15	57.69	7	50.00	22	55.00	0.641
Low T3 syndrome	5	19.23	0	0.00	5	12.50	0.013
High T4 syndrome	0	0.00	0	0.00	0	0.00	-
Low T4 syndrome	2	7.69	1	7.14	3	7.50	0.949
Subclinical hypothyroidism	2	7.69	5	35.71	7	17.50	0.043
Clinical hypothyroidism	1	3.85	1	7.14	2	5.00	0.674
Subclinical Hyperthyroidism	1	3.85	0	0.00	1	2.50	0.308
Total	26	100.00	14	100.00	40	100.00	

Table 5. Absolute and relative frequencies of thyroid functional disorders among subgroups

In our study, the mean values of TSH levels in HD group were significantly higher compared with the control group (3.16 ± 3.168 vs. 1.83 ± 0.938, p = 0.01). There was observed more frequent subclinical hypothyroidism in patients on chronic HD, compared to the control group (17.5% vs. 2.5 %, p = 0.021). We found no statistically significant difference in the frequency of clinical hypothyroidism between groups.

The results of recent studies regarding TSH levels in patients with CKD are not even. In some studies

authors did not found significant differences in mean TSH levels in HD patients and healthy subjects (18, 19). In a study Conchol et al. (7) was examined 3089 adult patients with CKD. It was concluded that subclinical primary hypothyroidism is relatively common in these patients (18%) and was correlated with decline in GFR.

In the subgroup of patients on HD < 72 months Low T3 syndrome was found significantly more frequently comparing to patients on HD > 72 months (19.23% vs. 0.00%, p = 0.013). We found no statistically significant difference between mean values of total and free thyroid hormones and thyroid volume, between these subgroups. Kutlay et al. (20) and Lebkovska et al. (19) in their studies found no relationship between duration of dialysis treatment and dysfunction of the thyroid gland and serum levels of TSH, FT4, FT3, T3, T4.

Considering the fact that clinical features of hypothyroidism are often masked with uremic state it is necessary to conduct periodic screening of thyroid function in all HD patients. In patients who are waiting for a kidney

transplant, early diagnosis and treatment of thyroid disease significantly reduce morbidity and mortality. Considering that low T3 and FT3 before renal transplantation is associated with decreased graft survival they should be diagnosed earlier and consider treatment.

5. CONCLUSION

Our study showed that functional thyroid gland disorders are more common among patients on HD compared with healthy subjects, and reveal their link with time on dialysis. Thyroid disorders on HD are known to be a strong risk factor for cardiovascular disease and a predictor for all-cause mortality, which represents a significant medical and financial problem.

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