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

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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 criteria were: previous thyroid disorders, systemic illnesses, critically ill patients and acute inflammatory 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 statistically 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. INTRODUCTION

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 can explain 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 stable patients on chronic haemodialysis program that lasted longer than three months, with a different etiology of renal diseases. Exclusion criteria were previous thyroid disorders, systemic illnesses, criticaly ill patients and acute inflammatory diseases. The control group included 40 healthy participants. The average time on dialysis was 60.32± 36.18 months (Table 1). There was no statistically
significant difference between genders and average age between two groups. The average body mass index was statistically significant lower in hemodialysed group.

To assess 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, it is shown that there was no statistically significant difference between average age, genders, BMI and GFR between two subgroups, p>0.05.

### 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 i2000 Abbott. Hemoglobin, red blood cell count was assessed by standard laboratory 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 assessed using Spearman correlation coefficients. P values less than 0.05 were considered statistically significant. Data processing software package was used SPSS for Windows.

### Results

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 find statistically significant difference in mean values of total, free thyroid hormones and TSH between subgroups.

### Table 1: Selected characteristics of study patients (data are presented as mean ± SD)

| Variables               | HD group (n=40) | Control group (n=40) | P  |
|-------------------------|----------------|----------------------|----|
| Average age (yr; mean ± SD) | 55.28±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/m²; 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/1.73m²; mean ± SD | 12.35±1.981  | 63.14±51.926         | 0.0000 |

### Table 2: Selected characteristics of study subgroups

| 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/m²; mean ± SD) | 22.96±1.949       | 23.50±2.312       | 23.15±2.070      | 0.4398 |
| GFR ml/min/1.73m²; mean ± SD | 12.35±2.077       | 12.36±1.865       | 12.35±1.981      | 0.9869 |

### 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  |
|---------------------------|----------|---------------|----|
| 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
4. DISCUSSION

We aimed to assess spectrum of thyroid function disorders in patients on chronic hemodialysis and possible connection 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 statisically 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.

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 transplantation.
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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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