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ORIGINAL PAPER

Role of Renal Anemia in the Functional, Morphological and Autoimmune Thyroid Disorders in Patients on Chronic Hemodialysis

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Thyroid disorders are common in chronic kidney disease. The aim of this study was to examine the role of renal anemia on thyroid function, morphology and autoimmunity in clinically euthyroid patients on chronic hemodialysis (HD). Prospective study during 12 months period included 40 stable patients on chronic HD treatment. Patients were divided into two groups according to the serum hemoglobin level (group A Hgb > 125 g / L and group B Hgb <125 g / L). Blood samples were taken for determination total and free thyroid hormones, thyroid antibodies and standard biochemical tests. Thyroid ultrasonography was performed with a 7.5 MHz transducer, 50 mm linear transducer. Thyroid wolume was calculated, echostructure assessed and presence of nodular changes. In group A, was found significantly lower levels of total T3 (1.29 ± 0469 vs. 1.55 ± 0352, p <0.1); higher prevalence of low T3 syndrome (17.24% (n = 5) vs. 0.00 (n = 0), p <0.05); ultrasound findings suggestive for Hashimoto thyroiditis (13.79 (n = 4) vs. 0.00% (n = 0), p <0.05) and multinodular goiter (13.79% (n = 4) vs. 0.00% (n = 0) , p <0.05). We found no statistically significant difference in the mean values of of thyroid antibodies levels, as well as in their percentage representation among groups. Morphological, functional and autoimmune disorders of thyroid gland are more common in patients on HD with Hgb level <125 g / L. These findings suggest a role of renal anemia in the pathogenesis of these, and need for periodical screening of thyroid function, morphology, and titer of thyroid antibodies in patients HD, as well as more effective diagnosis and more aggressive treatment of renal anemia.
Key words: Thyroid function, morphology, hemodialysis, TSH, autoimmunity, Hgb, renal anemia.

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1. INTRODUCTION

Chronic kidney disease (CKD) and hemodialysis (HD) are accompanied by numerous metabolic and hormonal disorders which include thyroid function, morphology and autoimmunity disorders (1). CKD effects both the hypothalamus-pituitary-thyroid axis and peripheral metabolism of thyroid hormones (2, 3, 4). Level of serum thyroid stimulating hormone (TSH) is usually normal or elevated in CKD, but has reduced response to its releasing hormone (TRH) (3, 4, 5). In CKD are also disturbed circadian rhythm of TSH and TSH glycosylation (6).

According to previous researches, the most common thyroid imbalance on chronic HD is a low T3 syndrome with FT3 levels generally within the normal limits (7). This reduction is associated with reduced peripheral conversion of T4 to T3, systemic acidosis, the length of dialysis and markers of endothelial dysfunction and inflammation (8, 9, 10). The reduction of total serum T3, but not FT3 is associated with increased cardiovascular mortality in euthyroid patients with CKD. Total and free T3 are acting as markers of survival in patients on HD (11). And finally there are reports to conclude that low serum T3 levels before kidney transplantation are associated with decreased graft survival (12). Although free and total T4 can be normal or slightly reduced, it can sometimes be increased due to the effect of heparin used in anticoagulant therapy during HD. Lipolytic activity of heparin leads to lipolysis of triglycerides in non–esterified free fatty acids which in high concentrations compete with T4 for proteins carriers (13). TSH levels according to several study results in patients with CKD are not uniform. In some studies was not found significant differences in mean TSH level in HD patients and healthy subjects (14, 15). In study Conchol et al. (16) there was examined 3089 adult patients with CKD who require dialysis treatment. It was concluded that subclinical primary hypothyroidism is relatively common in these patients (18%) and was correlated with decline in GFR.

Increased volume of the thyroid gland was found in about 50% of patients with CKD without clinically manifested goiter (14). Potential pathogenic factors are "capture" of iodine in the thyroid gland and possible accumulation of unidentified substances goitrogens in uremic plasma (10). Thyroid nodules and thyroid cancer are more common in patients with CKD and HD compared to general population. Patients on HD have a higher risk of oncogenesis, probably due to the impaired cellular immunity. Patients after kidney transplantation are under more risk of oncogenesis due to immunosuppressive therapy (17).

Renal anemia in recent studies is cited as a possible cause of thyroid dysfunction (18). Chronic kidney disease leads to renal anemia, primarily by reducing the production of erythropoietin, which leads to extremely low concentrations of hemoglobin (19). Other mechanisms with which CKD can lead to anemia include blood loss during dialysis; shortened lifespan of red blood cells; inefficient transport iron; vitamin B12 deficiency and folate; inflamation. In early stage disease, renal anemia occurs in about 25% of patients with CKD, and increases up to 75-95% in HD patients in late stage disease (20, 21). It seems that for the initial steps in the synthesis of thyroid hormones is necessary incorporation of iodine into tyrosine residues of thyroglobulin and that the covalent bonds between these residues are catalyzed with iron containing thyroperoxydase. Other hem-containing enzymes such as cytochrome C and myeloperoxidase and succinate dehydrogenase were also highly sensitive to iron depletion. Severe iron deficiency may therefore interfere with thyroid hormone synthesis and reduce thyroperoxydase activity (22). Tomoda et al. (23) showed that the introduction of recombinant human erythropoietin (Rh EPO) in treatment of anemia in HD patients leads to improving function of hypothalamo-pituitary-thyroid axis and levels of thyroid hormones in the periphery.

The aim of this study was to investigate the role of renal anemia on the function, morphology and autoimmune thyroid disorders in clinically euthyroid patients on chronic hemodialysis.

2. MATERIALS AND METHODS

A prospective single center study in 12 months period included 40 stabile patients who were on HD treatment longer than three months. All patients are on treatment with Rh EPO. Patients are divided in two groups according to serum Hgb level (group A Hgb > 125 g/L and group B Hgb< 125 g/L). Exclusion criteria were previous thyroid disorders, systemic illnesses, critically ill patients, acute inflammatory diseases, and previous known other etiology anemia. The control group included 40 healthy participants.

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 and thyroid antibodies (TgAt, TPOAt) were assayed by RIA using commercially available kits.

The ultrasonographic examination of thyroid gland was performed with 7.5MHz probe, 50 mm linear transducer. Three consecutive measurements were taken for each thyroid lobe, than the thyroid volume each lobe was calculated with formula V=a x b x c x n/6, n/6 is correction factor 0.479 (24). A total thyroid volume was calculated as a sum of lobe volumes. After the thyroid volume measurement the thyroid echostructure was estimated. The thyroid gland was especially examined in respect of nodules presence.

We defined clinical features as:

Body mass index (BMI) was calculated according to the universal formula, as follows BMI = (weight in kilograms)/(height in meters) x (height in meters). Anemia was defined according to guidelines NKF-K/DOQI (19): Adult men and postmenopausal women with CKD Hgb ≤ 12.5 g/dL (125 g/L) (Hct <37%) of premenopausal women Hgb ≤ 11 g/dL (110g/L) (Hct<33%).

Subclinical hypothyroidism is defined as a mild elevation in (TSH) TSH> 4,4 mmol/L levels in patients with normal serum thyroxin level (25). Hypothyroidism is defined as elevation in TSH>10 mmol/L and reduced T3 and T4 (26). Low T3 syndrome is defined with reduced T3< 0.89 (27).

Simple goiter is defined with elevated thyroid volume > 20ml (28). Nodular goiter is defined with presence of one node in either of thyroid lobe, multinodular goiter is defined with two or more nodules in thyroid lobes (28). Autoimmune thyroid disease is defined with finding of elevated thyroid antibodies (TgAb,TPOAt) and irregular pathognomonic ultrasound echostructure (29).

Data are expressed as means ± standard deviations. Statistical differences between arithmetic means of variables of each parametters were assessed using parametric and non parametric tests. To test hypotheses about the relationship of two variables correlation coefficients were calculate. Values less than 0.05 were taken as significant. Data processing software package was used SPSS for windows.

3. RESULTS

The study included 40 patients on HD. Figure 1 shows that the most common cause of CKD is undefined renal disease (47%), followed by chronic glomerulonephritis (25%). Patients were divided into two groups according to serum hemoglobin level: group A (Hgb <125 g/L) and group B (Hgb>125 g / L). Table 1 shows that there is no statistically significant difference in the average values of age, gender participation, BMI and GFR between the groups. There is a significantly lower time of dialysis treatment in the group A.

Table 2 shows that there was no statistically significant differences in mean values between these groups in mean values of total and free thyroid hormones, p> 0.05. Testing with the significance level of 0.1 (10%) shows that in group A is statistically significant lower mean values of triiodothyronine (T3) level. Table 3 shows that in HD group is statistically significant more frequent low T3 syndrome and subclinical hypothyroidism (p <0.05).

In Figure 2 is showen that there is

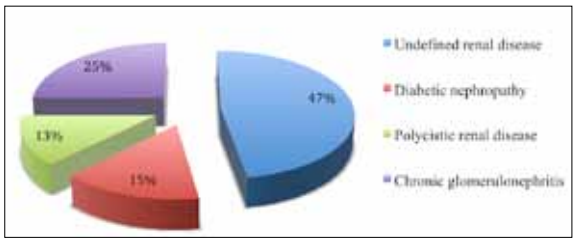

Figure 1. Percentage of underlaying diseases in HD group

a significantly higher frequency of the ultrasound findings suggestive for the Hashimoto thyroiditis in group A comparing to group B (13.79% (n=4) vs. 0.00% (n = 0), p <0.05). There was no statistically significant difference between the two groups in the incidence of nodular goiter (24,13% (n=7) vs. 27.27% (n=3), p>0.05), nor in the incidence of diffuse goiter (27.59 % (n=8) vs. 54.55% (n=14), p>0.05). Table 4 shows that by differentation nodular goiter to uninodular and multinodular we found statistically significant higher percentage of multinodular goiter in group A, p <0.05.

Table 5 shows that there is no statistically significant difference between mean values of thyroid antibodies (TgAt, TPOAT) between the two groups of patients, p> 0.05. In Figure 3 is showen that there is no statistically significant difference in the incidence of elevated levels of antibodies in the group A comparing to group B: TgAt (13.79% (n=4) vs. 18.18% (n=2), p>0, 05); TPOAt (24.13% (n=7) vs. 27.27% (n=3), p>0.05).

4. DISCUSSION

There are a limited number of studies in currently available literature which investigates the role of anemia in pathogenesis of thyroid function and morphology disorders in patients with CKD and HD. Tomoda at al. (23) examined the role of anemia on thyroid function in patients on chronic HD. The authors evaluated thyroid function before and after six months of treatment with rh EPO in 22 HD patients with a hematocrit level of 25%. Before rh EPO applications levels of thyroid hormones, particularly FT4 and FT3 were below the reference value, whereas after administration of rh EPO there was significant increase in the total and free hormones in a group of patients in which is caused an increase in hematocrit > 5%, while in the group of patients in which is caused an increase in hematocrit to <5% there was no significant increase in hormones levels. They found a significant correlation between hematocrit and fT3 in all subjects. According to a study Dabaganesha et al. (18) patients with iron deficiency in serum had significantly higher levels of TSH and lower FT4 levels compared with patients with normal serum ferritin level.

In our study, the group of patients with serum levels of hemoglobin under 125 g/L we found a statistically significant lower mean total T3 levels and consequently a significantly higher prevalence of low T3 syndrome in 17.24% (n=5). We found no statistically significant difference in mean total T4 , FT4, FT3 nor in mean TSH levels between groups.

Dabbaghmanesh at al. (18) investigated the role of iron deficiency anemia nonrenal causes in diffuse goiter pathogenesis. In their results, the presence or absence of goiter had nothing to do with a deficit of iron in serum. Azizi et al. (30) found a significant association with iron deficiency prevalence and diffuse goiter.

In our study we have not found a statistically significant difference in mean values of thyroid volume between the two groups of patients. We found significantly more frequently multinodular goiter in patients with serum levels

Variables	Serum hemoglobin level			P
	Group A	Group B	Total	
	μ ± σ	μ ± σ	μ ± σ	
Average age (yr; mean± SD)	54,38 ± 12,388	50,36 ± 9,841	53,28 ± 11,760	0,341
Male gender (n[%])	11 (37,93%)	7 (63,64%)	18 (45,00%)	0,132
Female gender (n[%])	18 (62,07%)	4 (36,36%)	22 (55,00 %)	0,132
BMI (kg/m2 mean ± SD)	23,03 ± 2,179	23,45 ± 1,809	23,15 ± 2,070	0,573
Time on dialysis (mo; mean ± SD)	49,82 ± 33,64	88,00 ± 27,85	60,32 ± 36,18	0,002
HGB (g/L; mean± SD)	95,10 ± 14,94	133,24 ± 9,74	105,60 ± 21,96	< 0,001
GFR (mL/min/1.73m2)	12,31 ± 2,05	12,45 ± 1,86	12,35 ± 1,98	0,840

Table 1. Selected characteristics of study patients

Variables	Serum hemoglobin level			P
	Group A	Group B	Total	
	μ ± σ	μ ± σ	μ ± σ	
Triiodothyronine (T3) nmol/L	1,29 ± 0,469	1,55 ± 0,352	1,36 ± 0,451	0,1018
Thyroxine (T4) nmol/L	78,52 ± 15,850	85,11 ± 26,357	80,33 ± 19,167	0,3381
Thyroid stimulating hormone (TSH) mIU/ml	3,42 ± 3,538	2,47 ± 1,834	3,16 ± 3,168	0,4067
Free T3 (FT3) pmol/L	5,26 ± 2,194	5,10 ± 1,494	5,21 ± 2,008	0,8283
Free T4 (FT4) pmol/L	13,97 ± 3,244	14,78 ± 4,130	14,19 ± 3,473	0,5140

Table 2. Mean values and dispersion measures of total and free thyroid hormones and thyroid stimulating hormone

Thyroid function disorder	Serum hemoglobin level						P
	Group A		Group B		Total		
	f	%	f	%	f	%	
Without disorder	14	48,28	8	72,73	22	55,00	0,134
Low T3 syndrome	5	17,24	0	0,00	5	12,50	0,014
High T4 syndrome	0	0,00	0	0,00	0	0,00	———-
Low T4 syndrome	2	6,90	1	9,09	3	7,50	0,824
Subclinical hypothyroidism	5	17,24	2	18,18	7	17,50	0,945
Clinical hypothyroidism	2	6,90	0	0,00	2	5,00	0,143
Subclinical hyperthyroidism	1	3,45	0	0,00	1	2,50	0,309
	29	100,00	11	100	40	100	

Table 3. Frequency of thyroid functional disorders among the groups

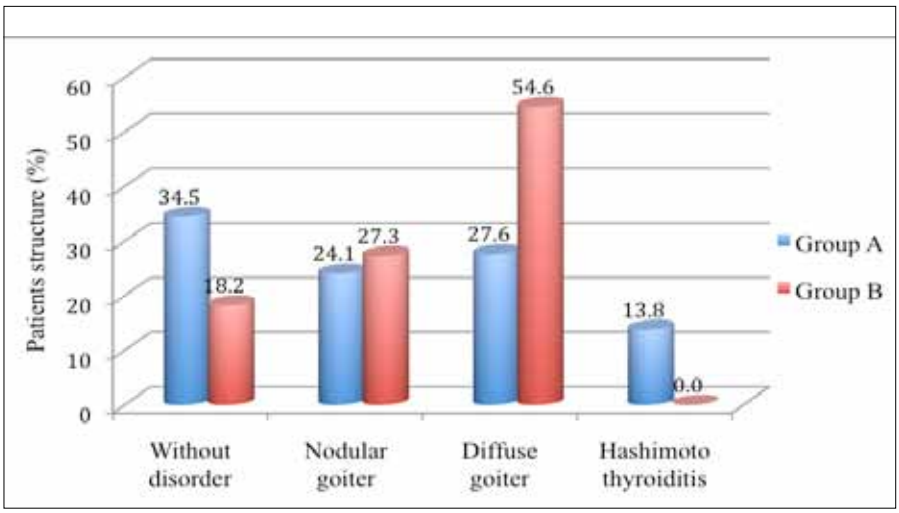

Figure 2. Thyroid morphology disorders among groups

of Hgb<125 g/L in 13.79% (n=4), p=0.03.

In further research of the literature we have not found studies that investigates the role of renal anemia on thyroid autoimmunity in patients on HD and CKD.

Sibbilla at al. (31) examined the relationship between chronic anemia defined as unexplained anemia that is not related to occult bleeding and/or hematological disorders in patients with autoimmune thyroid disease (ATD) and in patients with nonautoimune thyroid disease (NAITD). Of 1643 patients with thyroid disease, ATD was diagnosed in 652 patients (of whom 71 patients had Graves disease, and 581 had Hashimoto's thyroiditis). In 145 patients, ATD was associated with other autoimmune disorders. Chronic unexplained anemia was diagnosed in 123 (7-5%) cases, 49 had talasemic characteristics (2-9%). Prevalence of chronic anemia was not significant differ in patients with ATD and NAITD, but the prevalence of anemia was higher in hypothyroid patients with ATD and ATD patients who have associated autoimmune disorders.

In our results, we have not found a statistically significant difference between mean values of thyroid antibodies nor the frequency of elevated antibody titer between the two groups. Morphological changes suggestive for autoimmune Hashimoto thyroiditis was significantly more frequently found in the group of patients with serum levels of Hgb <125 g/L in 13.79 (n=4) (p=0.031). Our results have a foothold in the research of Biondi et al. (32) according to whom irregular ultrasound echostructure may precede TPOAt positivity in autoimmune thyroid disease and TPOAt can be detected in only 20% of patients with ultrasound evidence of thyroid autoimmunity.

Thyroid morphology disorder	Serum hemoglobine level						p
	Group A		Group B		Total		
	f	%	f	%	f	%	
Multinodular goiter	4	13,79	0	0,00	4	10,00	0,031
Nodular goiter	3	10,34	3	27,27	6	15,00	0,245

Table 4. Frequency of nodular and multinodular goiter among groups

Variables	Serum hemoglobin level			p
	Group A	Group B	Total	
	μ ± σ	μ ± σ	μ ± σ	
Thyroglobulin antibodies (TGAt) IU/ml	21,14 ± 33,560	15,64 ± 10,305	19,63 ± 29,018	0,5993
Thyroid peroxidase antibodies (TPOAt) IU/ml	18,60 ± 14,644	18,12 ± 12,769	18,47 ± 13,994	0,9249

Table 5. Mean values and dispersion measures for TgAt and TPOAt

5. CONCLUSION

Considering that we are found in the HD patients a significant link of renal anemia with decreased level of T3 and higher incidence of low T3 syndrome, which are associated with increased cardiovascular mortality and morbidity, and acts as markers of survival in patients on HD, it is necessary to conduct a periodically measuring levels of T3 in these patients in order to assess the relationship between thyroid dysfunction and mortality risk in this population.

Also, our results relates renal anemia with greater frequency of multinodular goiter in these patients, who are already at greater risk of oncogenesis, so it is necessary to perform periodic ultrasound examinations of thyroid morphology. We are also found a significant link of renal anemia with morphological changes of the thyroid gland suggestive of Hashimoto thyroiditis. Considering that patients with this autoimmune thyroid disorder are at greater risk for subclinical and clinical hypothyroidism they requires periodic screening for thyroid antibodies and complete thyroid functional state assessment .

We found a significantly lower duration of dialysis treatment in patients with serum levels of hemoglobin <125 g/L, which may indicate the possibility that in patients who are shorter on HD anemia is not successfuly corrected compared with patients with longer duration of HD.

The results of our study suggest that anemia contributes to the pathogenesis of thyroid function, morphology and autoimmunity disorders in patients on HD and recommend more effective diagnosis, aggressive treatment of anemia, and introduction of Rh Epo without delay.

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