Journal of Advances in Medicine and Medical Research

33(20): 49-55, 2021; Article no.JAMMR.74261
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

High Normal Thyrotropin (TSH) is Associated with Higher Needed Dose of Erythropoietin in Hemodialysis Patients

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2021/v33i2031103
Editor(s):
(1) Dr. Emmanouil (Manolis) Magiorkinis, General Hospital for Chest Diseases "Sotiria", Greece.
Reviewers:
(1) Ayinbuomwan Ekiye, University of Benin, Nigeria.
(2) Ghulam Saqulain, Post Graduate Medical Institute, Pakistan.
Complete Peer review History: https://www.sdiarticle4.com/review-history/74261

Original Research Article

Received 13 July 2021
Accepted 23 September 2021
Published 29 September 2021

ABSTRACT

Background: Recombinant human erythropoietin demonstrated an impressive ability to improve hematocrit, raising hematocrit of hemodialysis patients, eliminating the need for transfusions, and in patients with iron overload, decreased serum ferritin. Thyrotropin could affect hematopoiesis by binding to a functional thyrotropin receptor, which is found in both erythrocytes and some extrathyroidal tissues. The aim of this study was to evaluate the relationship of Thyrotropin level within normal reference range (in euthyroid state) on erythropoietin dose in end-stage renal disease patients on hemodialysis.
Methods: Prospective cross-sectional study was carried out at the hemodialysis units. It included 60 patients who had end-stage renal disease on hemodialysis. The selected patients were classified into 2 groups: Group A: included 30 end-stage renal disease patients on hemodialysis with Thyrotropin level (0.4-<2.5 miu/L) and Group B: included 30 end-stage renal disease patients on hemodialysis with Thyrotropin level (2.5-4.2 miu/L).
Results: the hemoglobin level and the hematocrit level showed a highly statistically significant

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difference between both groups. The needed Erythropiotin dosage was higher in group B than in group A with highly statistically significant difference. Weighted Erythropiotin dosage was calculated (weighted Erythropiotin=Erythropiotin dosage/weight) and the mean required dose was less than the required dose in group B and there was a highly statistically significant difference between the two groups. There was a significant negative correlation between the Thyrotropin level and hematocrit level and that leads us to conclude that the higher the Thyrotropin, the lower hematocrit will be and subsequently the higher Erythropiotin dose needed.

Conclusions: There is a relationship between Thyrotropin level even within normal reference range (in euthyroid state) on erythropoietin dose in end-stage renal disease patients on hemodialysis. In other words, the higher Thyrotropin level is, the more Erythropiotin dose needed. The required erythropoietin stimulating agent dose can be predicted by measuring Thyrotropin level.

Keywords: Thyrotropin; erythropiotin; end-stage renal disease; hemodialysis.

1. INTRODUCTION

Chronic kidney disease (CKD) is considered as a risk factor that exists independently for cardiovascular disease. All phases of CKD are associated with an increased risk of cardiovascular morbidity and death, as well as a worse quality of life [1]. The burden of CKD is substantial. According to WHO global health estimates, this disease was responsible for 864 226 fatalities (or 1.5 percent of all deaths globally) in 2012. CKD was the fourteenth greatest cause of mortality, accounting for 12.2 fatalities per 100,000 persons [2].

Kidney disease improving global outcomes (KDIGO) organization classified CKD by the degree of kidney dysfunction, as resulted by the estimated glomerular filtration rate (eGFR) and by the presence or absence of structural abnormalities in the kidneys or other signs of chronic kidney disease, most notably albuminuria. This gives 5 levels of dysfunction defined by eGFR (G1–G5) and three by albuminuria (A1–A3) [3].

Only a small proportion of individuals with CKD develop end-stage renal disease (ESRD), kidney replacement therapy (dialysis or transplantation) poses a significant financial burden for health care companies and burden for patients [3]. ESRD is included under stage 5 of the KDIGO classification of CKD, where it refers to individuals with an estimated glomerular filtration rate less than 15 mL/min/1.73 m^2, or those requiring dialysis [4].

Anemia is a frequent complication of chronic kidney disease that increases in frequency as GFR declines. It is a major complication of CKD & ESRD patients on dialysis either peritoneal dialysis or hemodialysis (HD) [2]. Anemia in chronic kidney disease and end-stage renal disease is primarily caused by erythropoietin (EPO) insufficiency, suppression of erythropoiesis by uremic solutes, and a decrease in RBC life span. Other possible reasons include a lack of iron, B12, or folic acid, or blood loss. Most patients with CKD can be effectively treated with erythropoiesis stimulating agents [5].

Thyroid hormones (THs) are critical regulators of metabolism, development, protein synthesis, and other hormone activities. Also, are necessary for metabolic function of the kidneys (Mohamedali et al., 2014). THs often have essential effect on erythropoiesis. They improve erythropoiesis through hyper proliferation of immature erythroid progenitors and increase secretion of EPO by inducing erythropoietin gene expression. Additionally, THs stimulate HIF-1 replication, which results in the development of erythroid colonies. (BFU-E, CFU-E) [6]. Since few data could be found on the effect of normal THs level on development of anemia in ESRD patients and the needed dose of EPO, we performed this study to shed the light on this important topic and to assess the connection between of Thyrotropin (TSH) level within normal reference range (in euthyroid state) on erythropoietin dose in ESRD patients on HD.

After searching the literature, we could not find any study to evaluate the association between low and high normal TSH levels with EPO dose in HD patients.

2. PATIENTS AND METHODS

A prospective cross-sectional study was carried out on 60 patients who had ESRD on HD for ≥ 6 months (3 sessions/week, 4 hours/session) at

the HD units at Internal Medicine Department, Tanta University Hospitals (University Student Hospital and Universal Educational Hospital), Cairo Fatemic Hospital and Nasr City Hospital for Health Insurance.

The selected patients were divided into 2 groups

Group (A): included 30 ESRD patients on HD with TSH level (0.4 - <2.5 miu/L).

Group (B): included 30 ESRD patients on HD with TSH level (2.5 - 4.2 miu/L).

Inclusion criteria: All patients participating in this study were older than 18 years, on maintenance HD for ≥ 6 months (3 sessions/week, 4 hours/session), efficiently dialyzed, and they received erythropoietin and Iron therapy to reach a hemoglobin target of (10-12g/dl). Those patients had normal thyroid function tests, with no history of thyroid diseases with.

Exclusion criteria: patients with any of the following were excluded from the study: acute kidney injury, acute infections, acute or chronic inflammatory diseases. other causes of poor response to EPO therapy (e.g.: chronic and advanced liver disease, malignancies, advanced heart failure, thalassemia, iron deficiency, gastrointestinal bleeding, pregnant patients, patients on drugs known to affect erythropoietin function).

3. METHODS

All patients were subjected to the following: full history taking, full Clinical Examination, laboratory Investigations in the form of: blood urea, serum creatinine and liver function tests (Kone Lab Prim 60 i), complete Blood count (ADVIA 2120 i), thyroid function tests including serum thyrotropin (TSH), free thyroxine (FT4), and free triiodothyronine (T3) levels, serum calcium and phosphate (Kone Lab Prim 60 i), serum Iron, Total Iron Binding Capacity "TIBC" (Kone Lab Prim 60 i) and Ferritin (TOSOH), C – Reactive protein "CRP" (Kone Lab Prim 60 i), dialysis efficiency was calculated for every patient by the equation: Urea reduction ratio (URR) = 100 × (1-$\frac{ureea\ post-HD}{urea\ pre-HD}$), weighted EPO was calculated as: EPO dosage/body weight.

3.1 Statistical Analysis

Analysis of the data was performed using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY, USA). Description of quantitative variables were in the form of mean and standard deviation (SD). Description of qualitative variables were in the form of numbers (N) and percentages (%). Comparisons between quantitative variables were carried out after data is explored for normality using Kolmogorov-Smirnov test of normality. Whenever the results of the test indicated that the data are normally distributed, the student t-test was used for the comparisons of means between groups, otherwise Mann Whitney was used.

Comparison between qualitative variables was carried out by Chi-Square test or Fisher's Exact Test. Linear Correlation Coefficient was used for detection of correlation between two quantitative variables in one group. P-value <0.05 was considered significant.

4. RESULTS

The demographic and some clinical and laboratory data were mentioned in Table 1. Hemoglobin level, hematocrit and total iron binding capacity were significantly lower in group B in comparison to group A, while only serum ferritin was significantly higher in group B in comparison to group A Table 1.

When we compared the thyroid function between the two studied groups, we noticed significantly higher levels of fT3 and TSH but significantly lower level of fT4 in group B in comparison to group A. We also noticed significantly higher weekly needed doses of EPO and weighted EPO in group B when compared to group A. Table (2)

When we correlated the TSH level with the other studied parameters, we found significant positive correlations between TSH and ferritin level, weekly required EPO dosage and weighted EPO dose, while there were significant negative correlations with the hematocrit and creatinine. The correlation between TSH and hemoglobin was negative, but not reaching statistical significance.

5. DISCUSSION

THs perform a critical function in regulating hematopoiesis [7]. THs have a direct impact on erythroid precursor proliferation. and stimulation of bone marrow erythropoiesis. Besides, THs stimulate erythropoiesis by increasing EPO mRNA expression and EPO production in the kidney [8]. To treat anemia in individuals with

HD, a well-balanced combination treatment based on the use of Erythropoiesis Stimulating Agents and iron supplementation is recommended [9]. Numerous Previous studies have explored the relationship. Between baseline thyroid dysfunction, including subclinical hypothyroidism, overt hypothyroidism, subclinical hyperthyroidism, and overt hyperthyroidism, and the erythropoietin dose in patients with ESRD [10-11]. However, very few studies were performed to assess the effect of euthyroid status on anemia and EPO dose in ESRD, especially in Egyptian HD patients and hence comes the importance of this work.

In this study, 46.67% of group B patients were diabetics, while only 30% of group A patients were diabetics, while Meuwese et al. [12] found that out of his studied 64 euthyroid patients under HD, 22% of them were diabetics. On the other hand, Ng et al. [13] documented that 23.5% of included euthyroid patients were diabetics. Bichari et al. [14] on their study on 100 Egyptian HD patients, reported that 25% had diabetes mellitus. In agreement with Molitch et al. [15] the higher percentage of diabetic patients in our study may be attributed to the fact that 20-40% of cases with DM progress to diabetic kidney disease, and 40% also may progress to ESRD. Rodacki et al. [16] reported that not only subclinical hypothyroidism elevate the prevalence of diabetic kidney disease but also the high normal levels of TSH elevated the prevalence of diabetic kidney disease as compared to low normal levels in diabetes patients.

In our study, we noticed a negative correlation between TSH and hemoglobin level, but not reaching statistical significance, while a significant negative correlation was found between TSH and hematocrit.

Table 1. Demographic, clinical and laboratory data of the two studied groups

Parameter	Group A [N = 30]	Group B [N = 30]	T or X^2	P-value
Sex (male n, %)	16 (53.33%)	17 (46.67%)	0.066	0.7969
Age (years)	48.8 ± 11.8	51.6 ± 16.1	0.766	0.4467
DM (yes)	9 (30.0%)	14 (46.67%)	1.733	0.1880
HTN (yes)	22 (73.33%)	21 (70.0%)	0.081	0.7763
Weight (kg)	68.4 ± 9.4	69.3 ± 9.2	0.406	0.6862
Height (m)	1.74 ± 0.08	1.75 ± 0.08	0.394	0.6947
BMI (kg/m2)	22.51 ± 2.36	22.58 ± 1.71	0.133	0.8943
Calcium (mg/dL)	9.53 ± 0.53	9.40 ± 0.48	0.989	0.3268
Phosphorus(mg/dL)	5.01 ± 0.79	5.02 ± 0.64	0.030	0.9763
Kt/V	1.75 ± 0.15	1.69 ± 0.18	1.407	0.1647
Hb (g/dL)	11.3 ± 0.5	10.8 ± 0.4	3.581	0.0007**
HCT (%)	32.1 ± 4.9	27.0 ± 3.3	5.542	<0.0001**
WBCs (x103/µL)	5.4 ± 0.9	5.4 ± 1.0	0.230	0.8185
PLT (x103/µL)	205 ± 48	194 ± 58	0.794	0.4303
Fe (µg/dL)	83.38 ± 3.97	80.23 ± 2.75	3.581	0.0007**
Ferritin (ng/mL)	404.78 ± 248.88	637.80 ± 220.77	3.836	0.0003**
TIBC (µg/dL)	568.50 ± 27.09	546.97 ± 18.73	3.581	0.0007**

BMI: body mass index. DM: diabetes mellitus. Hb: hemoglobin. HCT: hematocrit. HTN: hypertension. Kt/V: dialysis efficiency. PLT: platelets. Fe: serum iron. TIBC: total iron binding capacity. WBCs: white blood cells

Table 2. Comparison of the thyroid function and EPO dose in the studied groups

Parameter	Group A [N = 30]	Group B [N = 30]	T	P-value
fT3 (pg/dL)	2.23 ± 0.69	2.83 ± 0.46	3.988	0.0002**
fT4 (ng/dL)	1.26 ± 0.17	1.10 ± 0.21	3.345	0.0014**
TSH(µIU/mL)	1.51 ± 0.60	3.28 ± 0.49	12.689	<0.0001**
Weekly EPO dosage (units)	4000.00 ± 1819.44	9333.33 ± 1917.85	11.050	<0.0001
Weekly weighted EPO (unit/kg)	58.29 ± 22.43	136.74 ± 32.95	10.780	<0.0001

fT3: free triiodothyronine, fT4: free thyroxine. TSH: thyroid stimulating hormone. EPO: erythropoietin

Table 3. Correlation between TSH and the different studied parameters

Correlation between TSH and …	Correlation coefficient	P-value
Hb	-0.221	0.0903
Hct	-0.496	<0.0001*
PLT	0.051	0.6998
WBC	0.099	0.4528
Urea	-0.224	0.0860
Creatinine	-0.193	0.1401
Calcium	-0.007	0.9604
Phosphorus	0.030	0.8213
Dialysis Efficacy	-0.156	0.2337
fT3	0.516	<0.0001*
fT4	-0.174	0.1827
Fe	-0.221	0.0903
Ferritin	0.436	0.0005*
TIBC	-0.221	0.0903
Weekly EPO dosage	0.931	<0.0001*
Weekly weighted EPO	0.918	<0.0001*

BMI: body mass index. DM: diabetes mellitus. EPO: erythropoietin. fT3: free triiodothyronine, fT4: free thyroxine. Hb: hemoglobin. HCT: hematocrit. HTN: hypertension. Kt/V: dialysis efficiency. PLT: platelets. Fe: serum iron. TIBC: total iron binding capacity. TSH: thyroid stimulating hormone. WBCs: white blood cells

Our study was in agreement with the study performed by Gu et al. [17], lower serum fT3 and fT4 levels were found to be significantly associated with future anemia and decreasing annual changes in Hb concentrations in a euthyroid population.

Additionally, investigations in the general population of euthyroid individuals demonstrated that elevated normal TSH levels and low fT3 levels were linked with CKD [18-21).

When we studied the correlation between TSH and EPO dose, we found a significant positive correlation between them.

Bin Saleh et al. [10] as well, found that higher TSH levels were associated with higher resistance to EPO indicating that TSH level should be among the measured parameters when EPO resistance is observed. Ng et al. [11] demonstrated a substantially greater weighted mean monthly EPO dosage (1.22g/kg vs. 1.64g/kg) in the subclinical hypothyroidism group, corroborating earlier findings that euthyroidism is required for EPO to operate on bone marrow [22-24].

In patients with high normal TSH compared to those with low normal TSH, lower Hb and higher need for EPO highlight the importance of TSH level monitoring in the anemic CKD patients as well as in those having EPO resistance. Moreover, this work raises the question of the feasibility of thyroxin hormone supplementation in euthyroid CKD patients with anemia or EPO resistance, which will need further studies to answer this question.

After searching the literature, we could not find any study to evaluate the association between low and high normal TSH levels with EPO dose in HD patients.

6. CONCLUSION

High normal TSH was associated with lower hemoglobin levels and more EPO resistance. That might serve as a potential therapeutic option for anemia of CKD.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

ETHICAL APPROVAL

The approval of Tanta Medical Ethical Committee was obtained (approval number: 33269/7/19).

CONSENT

A written informed consent was signed by each participant.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/74261