IS THERE ANY LINK BETWEEN A KIND OF THYROCYTE DYSFUNCTION, HYPOTHYROIDISM AND INFLAMMATORY HEMATOLOGIC PARAMETERS IN THE CASES HAVING THE BENIGN THYROID NODULES? A 5-YEAR SINGLE-CENTER EXPERIENCE

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Primljen/Received 02. 03. 2018. god.

Prihvaćen/Accepted 02. 04. 2018. god.

Abstract: Objective: Microscopically, the thyroid gland is composed of spherical follicles and thyroid parenchyma includes two major cell types, the thyrocytes releasing thyroid hormones and C cells secreting mature calcitonin. Hypothyroidism has been known as being associated with the various abnormalities of the coagulation system. In the present study, it had been purposed to investigate the relationship between inflammatory hematological parameters, RBC, Hb, Htc, RDW, WBC, neutrophil, lymphocyte, N/L, Plt, MPV, PCT, PDW and hypothyroid hormonal status in the cases possessing the benign thyroid nodules.

Material and Methods: A total of 313 cases, 202 with hypothyroidism and 111 with euthyroidism possessing the benign thyroid nodules, that was verified with the cytological evaluation after one-endocrine surgeon performed ultrasonography (US) guided fine needle aspiration (FNA) (US-g-FNA), at the Division of Endocrine Surgery, Department of General Surgery, Giresun University Faculty of Medicine, Giresun, Turkey, in conformity with the criteria, were enrolled into the study during the period, from April 2010 to April 2015. The documents that were used to follow consisted of laboratory tests of the cases including both the thyroid hormones, free T3, Free T4, and TSH, and the inflammatory hematological parameters were reviewed and scanned retrospectively. The upper limit of the normal Thyrotropin (TSH) reference range was determined as 4 mU/L in the present study.

Results: No statistically significant difference was found between the inflammatory hematological parameters, RBC, Hb, Htc, RDW, WBC, neutrophil,

lymphocyte, N/L, Plt, MPV, PCT, PDW, and hypothyroidism ($p > 0.05$).

Conclusion: Inflammatory hematological parameters may not be useful for estimating the hormonal status of the thyroid gland in the cases with the benign thyroid nodules verified with the cytological evaluation, TBSRTC.

Keywords: Thyroid neoplasms; Thyrocytes; Fine needle aspiration cytology (FNAC); Cytology; Thyrotropin (TSH); Hypothyroidism; Hematological parameters.

INTRODUCTION

The thyroid gland, weighing 10 to 20 grams in normal adults in the United States, is measured by ultrasonography (US) is a certain extent greater in men than women, increases with age and body weight, and decreases with increasing iodine intake (1, 2).

Microscopically, the thyroid is composed of the spherical follicles, each composed of a single layer of follicular cells surrounding a lumen filled with colloid (mostly thyroglobulin) and the thyroid parenchyma includes two major cell types, the thyrocytes releasing thyroid hormones and C cells secreting mature calcitonin (3). L-thyroxin (T_4) and to a much lesser extent of l-triiodothyronin (T_3), two main thyroid hormones, are synthesized by the follicular epithelial cells, thyrocytes, of the thyroid gland (4).

Electron microscopy demonstrates the normal flat to low cuboidal follicular cells, interdigitating and overlapping one another. They are intimately relevant to the capillaries, surrounding the follicle; microvilli on the apical surface are multiplexed near the cellular

margins. When stimulated, the follicular cells become columnar and the lumen is depleted of colloid; when suppressed, become flat and colloid, accumulating in the lumen (5, 6).

The thyroid hormones frequently have a worthy effect on the erythropoiesis by enhancing it via hyperproliferation of the immature erythroid progenitors and increasing the secretion of erythropoietin (EPO) by resulting in EPO gene expression (7-10). The erythrocyte mass is increased in the most hyperthyroid status, whereas the hypothyroidism have an attenuated erythrocyte mass due to the reduction of plasma volume and may undetectable by routine measurement such as hemoglobin (Hb) concentration (11, 12). The thyroid dysfunction also changes the other hematological parameters, hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), white blood cell (WBC) count and platelet count (Plt). However, all the mentioned alterations return to normal if an euthyroid state is sustained (9).

In the present study, the laboratory tests of the patients having the benign thyroid nodules, verified with the cytological evaluation after one-endocrine surgeon performed ultrasonography (US) guided fine needle aspiration (FNA), had been evaluated retrospectively and purposed to investigate the relationship between the inflammatory hematological parameters, consisting red blood cell (RBC), Hb, Htc, red cell distribution width (RDW), WBC, neutrophil, lymphocyte, neutrophil lymphocyte ratio (N/L), Plt, mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW), and the hypothyroidism.

MATERIALS AND METHODS

The present study had been conducted on a total of 313 cases, from April 2010 to April 2015 in order to matching two groups, the patients with hypothyroidism, 202 cases, and the patients with euthyroidism, 111 cases, control group. In terms of the inflammatory hematological parameters we measured RBC, Hb, Htc, RDW, WBC, neutrophil, lymphocyte, N/L, Plt, MPV, PCT, PDW. The five years documents consisted of laboratory tests of the cases included both the thyroid hormones and the inflammatory hematological parameters were reviewed and scanned retrospectively.

An elevated serum thyroid stimulating hormone (TSH) was determined as a TSH concentration above the upper limit of the normal reference range, typically accepted as 4 to 5 mU/L in the most laboratories. Presently a considerable controversy exist over the appropriate upper limit of normal for serum TSH that some authors have suggested that the true upper limit is only 2.5 or 3 mU/L in healthy individuals without any thy-

roid disease, whereas the others argue that the serum TSH distribution shifts towards higher values with age, independent of the presence of antithyroid antibodies (13), or in obesity. It is recommended for these cases that the normal upper limit could be as high as 6 to 8 mU/L in healthy octogenarians, or as high as 7.5 mU/L in morbid obesity (14). The upper limit of the normal TSH reference range was determined as 4 mU/L in the present study. Hypothyroidism has known as being associated with the various abnormalities of the coagulation system, such as the modification of coagulation proteins and bleeding tendency.

The study was performed for the cases which had been undergone US guided FNA (US-g-FNA) cytology (US-g-FNAC) and all the US-g-FNAC results had been reported according the guidance of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), a 6-diagnostic-category system which was constituted through multidisciplinary formulation, proposed at the National Cancer Institute (NCI) Thyroid Fine Needle Aspiration State of the Art and Science Conference held in Bethesda, Maryland, 2007. TBSRTC is at present the most used and accepted reporting system for reporting FNA cytology (FNAC) worldwide (15). The use of TBSRTC also has been endorsed by 2015 American Thyroid Association (ATA) management guidelines (16) as 2009 ATA guidelines (17) which is a revision of 2006 ATA guidelines (18).

The criteria for including patients into the Study

The screening outcome revealed the 313 cases, 202 with hypothyroidism, 111 with euthyroidism, in conformity with the criteria, were incorporated into the study during the period, from April 2010 to April 2015. The exclusion criteria had been the hematologic disorders, cardiac disorders, autoimmune diseases, inflammatory or infective diseases, endocrinologic disease and diabetes, liver diseases, renal failure, recurrent diseases, thyroid malignancies and the previous or accompanying other malignancies, as well as those who had medical records as to the usage of steroids, anticoagulants, and alcohol along with those with a medical history of hepatitis and patients with the inappropriate samples.

Statistical Analysis

The statistical analyses were performed by using SPSS 23.0 computer program. Some descriptive statistics were calculated for control and hypothyroid groups. Some indexes of groups were compared by using Mann-Whitney U test due to the non-normality of the data sets.

Figure 1. The comparison of the inflammatory hematological parameters with the hormonal status of the thyroid

The results were expressed as mean $\pm$ standard deviation (SD) and $p < 0.05$ were considered as statistically significant.

Table 1. The comparison of the inflammatory hematological parameters between the patients with hypothyroidism and euthyroidism, control

Hematologic Parameters	Hormonal Status	n	Min	Max	Mean	SD	p-value
N/L	Control	111	1,03	4,86	2,3022	1,38137	0,459
	Hypothyroid	202	0,00	5,57	1,8435	0,86573	
MPV	Control	111	101,00	122,00	107,3333	8,77876	0,137
	Hypothyroid	202	8,00	1114,00	177,8951	240,82600	
WBC	Control	111	157,00	762,00	544,6667	215,28090	0,395
	Hypothyroid	202	6,00	1662,00	621,9020	267,47184	
RBC	Control	111	412,00	492,00	442,3333	31,92909	0,155
	Hypothyroid	202	146,00	692,00	465,3333	49,48820	
Hb	Control	111	114,00	140,00	128,1667	8,30462	0,513
	Hypothyroid	202	11,00	841,00	135,6373	59,18326	
Hct	Control	111	343,00	438,00	388,5000	30,87880	0,302
	Hypothyroid	202	35,00	551,00	394,8693	69,99557	
Plt	Control	111	165,00	319,00	229,0000	57,00175	0,066
	Hypothyroid	202	131,00	452,00	272,3235	54,12551	
Neutrophil	Control	111	212,00	1209,00	493,8333	361,91956	0,756
	Hypothyroid	202	7,00	1216,00	381,6993	153,05536	
Lymphocyte	Control	111	172,00	266,00	211,0000	43,27586	0,623
	Hypothyroid	202	2,00	434,00	223,1373	81,44708	
RDW	Control	111	128,00	155,00	136,6667	9,58471	0,421
	Hypothyroid	202	13,00	288,00	131,0490	33,26398	
PCT	Control	111	202,00	321,00	243,3333	46,16781	0,61
	Hypothyroid	202	12,00	741,00	238,5869	93,00368	
PDW	Control	111	11,80	17,90	14,9500	2,55402	0,546
	Hypothyroid	202	8,70	279,00	15,9886	21,16918	

N/L; neutrophil lymphocyte ratio; MPV, mean platelet volume; RBC, red blood cell; Hb, Hemoglobin; Hct, Hemotocrit; Plt, platelet; RDW, red cell distribution width; PCT, plateletcrit; PDW, platelet distribution width

RESULTS

111 (35.46%) out of 313 cases were possessing the euthyroid state, whereas 202 (64.54%) had the hypothyroid condition. It had not been detected any statistically significant difference between the cases with hypothyroidism, Group 1 and cases with the euthyroidism, Group 2, Control, in terms of the inflammatory hematological parameters, RBC, Hb, Hct, RDW, WBC, neutrophil, lymphocyte, N/L, Plt, MPV, PCT, PDW ($p > 0.05$) (Figure 1). Therefore, in accordance with the statistical test results, no any difference between the inflammatory hematological parameters and hypothyroidism was detected (Table 1).

DISCUSSION

Thyroid, a crucial endocrine organ, has a notable effect on the erythropoiesis by inducing EPO secretion and also the proliferation of erythroid progenitors (8, 11, 19). Hypothyroidism reported as cooccurrence with some coagulation system abnormalities, the most rele-

vant one is expressed as acquired von Willebrand disease (20). The aim of the present study was investigate whether any commitment between a kind of thyrocyte dysfunction, hypothyroidism, and inflammatory hematologic parameters, consisting RBC, Hb, Hct, RDW, WBC, neutrophil, lymphocyte, N/L, Plt, MPV, PCT, PDW.

Geetha and Srikrishna (21) reported RBC indices, comparing in the cases with hypothyroidism and hyperthyroidism and the study revealed that RDW and MCV in these groups in comparison to the euthyroid individuals had statistically significant difference. However, the other RBC parameters, such as Hb and Hct, did not exhibit any significant difference in comparison with the euthyroid hormonal status. Kawa et al (9) reported that RBC, Hb in the cases with hypothyroidism attenuated, while Hct was increased. They also showed that MCH, MCHC were lower and MCV was increased in hypothyroid group in comparison with the control group.

In the present study, the upper limit of the normal TSH reference range was determined as 4 mU/L and the comparison of the cases with hypothyroidism and the euthyroid ones had been performed for investigating the prediction of the current hormonal status of the thyroid gland by means of their inflammatory hematologic parameters. However, it was not detected any significant difference between the inflammatory hematologic parameters, RBC, Hb, Hct, RDW, WBC, neutrophil, lymphocyte, N/L, Plt, MPV, PCT, PDW and a type of thyroid hormone disturbance, hypothyroidism.

CONCLUSION

The present study investigated just hypothyroidism, performed on the cases that had benign thyroid nodular diseases in the duration of five years. The limitations of the present study may be the retrospective design, studying on the cases with the benign thyroid nodular diseases and not analyzing the thyroid antibodies, like antithyroid peroxidase Ab (anti-TPO Ab) or antithyroid microsomal Ab, antithyroglobulin antibody (anti-Tg Ab), and thyroid stimulating immunoglobulin (TSI Ab).

In conclusion, the usage of the inflammatory hematological parameters may not be beneficial for estimating the hypothyroid hormonal status of the thyroid gland in cases with the benign thyroid nodules that was verified with the cytological evaluation, TBSRTC.

DECLARATION OF INTEREST

No any conflict of interest relevant to this article has been declared.

Acknowledgements

It has not been used any funding for the present work. DS had contributed in constituting the notion and hypothesis, intellectual planning and management of the study, collecting the data, performing the statistical analysis, writing the whole manuscript, its linguistic and academical revisions. IS had contributed in examining and follow-up of the patients, collecting the data, academical revision of the manuscript. All the authors finally approved the submitted and proof versions without any conflict of interest.

We would like to thank the resident and students of Department of General Surgery and all the staff and personnel of Department of Pathology and Biochemistry, Giresun University-Ministry of Health Prof. Dr. A. İlhan Ozdemir Education and Research Hospital, Giresun, Turkey.

Abbreviations

T₄ — L-thyroxin

T₃ — L-triiodothyronin

EPO — Erythropoietin

MCV — Mean corpuscular volume

MCH — Mean corpuscular hemoglobin

US — Ultrasonography

FNA — Fine needle aspiration

US-g-FNA — US guided FNA

FNAC — FNA cytology

RDW — Red cell distribution width

PDW — Platelet distribution width

N/L — Neutrophil lymphocyte ratio

MPV — Mean platelet volume

Plt — Platelet

TSH — Thyroid stimulating hormone

TBSRTC — The Bethesda System for Reporting Thyroid Cytopathology

ATA — American Thyroid Association

anti-TPO Ab — Antithyroid peroxidase antibody

anti-Tg Ab — Antithyroglobulin antibody

TSI Ab — Thyroid stimulating immunoglobulin

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Sažetak

DA LI POSTOJI VEZA IZMEĐU TIPRA TIREOCITNE DISFUNKCIJE, HIPOTIREOIDIZMA I ZAPALJENSKIH HEMATOLOŠKIH PARAMETARA U SLUČAJEVIMA SA BENIGNIM TIROIDNIM NODUSIMA? 5-GODIŠNJE ISKUSTVO JEDNOG CENTRA

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Uvod: Mikroskopski posmatrano, tireoidna žlezda je sastavljena od sferičnih folikula i tireoidnog parenhima koji uključuje dva glavna ćelijska tipa, tireocite koji oslobađaju hormone i C ćelije koje sekretuju zreli kalcitonin. Poznato je da je hipotireoidizam povezan sa mnogim abnormalnostima sistema za koagulaciju. U ovoj studiji, cilj je bio da se ispita povezanost između hematoloških parametara, RBC, Hb, Htc, RDW, WBC, neutrofila, limfocita, N/L, Plt, MPV, PCT, PDW i hipotireoidnog hormonskog statusa kod pacijenata sa benignim tireoidnim nodulima.

Materijal i metode: Ukupno 313 slučajeva, 202 sa hipotireoidizmom, 111 sa eutireoidizmom i benignim tireoidnim nodulima, koji su verifikovani citološkom evaluacijom nakon što je urađena ultrasonografijom (US) vodeća aspiracija tankom iglom (FNA) (US-g-FNA) od strane endokrinog hirurga na Odseku za endokrinu hirurgiju, odeljenja opšte hirurgije, Medicinskog fakulteta, Univerziteta Giresun u Turskoj je učestvovalo u studiji u periodu

od aprila 2010-te godine do aprila 2015-te godine. Peto-godišnji dokumenti su se sastojali od laboratorijskih testova za slučajeve koji su uključivali tireoidne hormone, slobodni T3, slobodni T4 i TSH i inflamatorne hematološke parametre koji su prikazani i analizirani retrospektivno. Gornja granica za normalni tireostimulirajući hormone (TSH) bila je 4 mU/L za potrebe studije.

Rezultati: Nije pokazana statistički značajna razlika između inflamatornih hematoloških parametara, RBC, Hb, Htc, RDW, WBC, neutrofila, limfocita, N/L, Plt, MPV, PCT, PDW i hipotireoidizma ($p > 0,05$).

Zaključak: Inflamatorni hematološki parametri verovatno nisu dovoljno korisni za procenu hormonskog statusa tireoidne žlezde u slučajevima sa benignim tireoidnim nodulima koji su verifikovani citološkom evaluacijom, TBSRTC.

Glavne reči: tireoidna neoplazma, tireociti; aspiracija tankom iglom (FNAC); citologija; tireotropin (TSH); hipotireoidizam; hematološki parametri.

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