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İRON METABOLISM İN PATİENTS WITH IMPAIRED THYROID FUNCTION

TİROİD FONKSİYON BOZUKLUĞU OLAN HASTALARDA DEMİR METABOLİZMASI

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ABSTRACT

We aimed in this study to determine the changes due to hyperthyroidism or hypothyroidism in serum ferritin, iron, transferrin, vitamin B_n and erythrocytic parameters and to investigate the interrelationships between these parameters .Serum ferritin, iron, total iron-binding capacity (transferrin), vitamin B_{12}, total andfree trüodothyronine (TT_3 and FT_3) , total andfree thyroxine (TT_4 and FT_4), thyroid-stimulating hormone (TSH) levels were measured in 30 patients (26 women, 4 men) with hyperthyroid; 30 patients (26 women, 4 men) with hyporthyroid and 25 healthy subjects (22 women, 3 men). Serum ferritin levels of hyperthyroid patients were higher than those of hypothyroid patients and healthy controls ($p<0.05$). Serum iron levels of hyperthyroid patients were only higher than those of hypothyroid patients ($p<0.05$). Transferrin levels were higher in ali of patients than healthy group ($p<0.05$). Vitamin B_{12} concentrations in hypothyroid patients were lower than those of hyperthyroid patients. Total and free T_3 and total and free T_4 levels in hyperthyroid patients were higher than those of hypothyroid patients and controls ($p<0.05$), but TSH levels were lower than only those of hypothyroid patients.

Statistical analysis between the groups according to erythrocyte count were insignificant. The differences between haemoglobin and hematocrit levels in group of patients were also insignificant. The effects of sex, smoking status, use of salt (with or without iodine), goitrogenic food on the serum parameters were statistically investigated.

Our data suggest that alterations in thyroid status produce changes in iron metabolism and vitamin B_{12} levels.

Key Words: hyperthyroidism, hypothyroidism, ferritin, iron.

ÖZET

Bu çalışmada hipertiroidizm veya hipotiroidizm nedeni ile serum ferritin, demir, transferrin, B_{12} vitamini ve eritrosit ile ilgili parametreler deki değişiklikleri saptamak ve birbirleri ile ilişkilerini araştırmak amaçlanmıştır. Serum ferritin, demir, total demir bağlama kapasitesi (transferrin), B_{12} vitamini, total ve serbest triiyodotironin (TT_3 ve ST_3), total ve serbest tiroksin (TT_4 ve ST_4) ve tiroid stimüle edici hormon (TSH) düzeyleri hipertiroidili 30 hastada (26 kadın, 4 erkek), hipotiroidili 30 hastada (26 kadın, 4 erkek) ve 25 sağlıklı bireyde (22 kadın, 3 erkek) ölçüldü. Hipertiroidili hastaların serum ferritin düzeyleri hipotiroidili hastalardan ve sağlıklı kontrollerden daha yüksekti ($p<0.05$). Hipertiroidili hastaların serum demir düzeyleri hipotiroidili hastalardan daha yüksekti ($p<0.05$). Transferrin düzeyleri hastalarda sağlıklı gruba göre daha yüksekti ($p<0.05$). B_n vitamini düzeyleri hipotiroidili hastalarda hipertiroidili hastalara göre daha düşüktü. Total ve serbest T_3 , total ve serbest T_4 düzeyleri hipertiroidili hastalarda hipotiroidili hastalara ve kontrollere göre daha yüksekti ($p<0.05$), fakat TSH düzeyleri sadece hipotiroidili hastalardan daha düşüktü.

Gruplararası istatistiksel değerlendirmede eritrosit sayısına göre anlamlı bir farklılık bulunamadı. Hasta grupları arasında da hemoglobin ve hematokrit düzeylerine göre anlamlı faklılık gözlenmedi. Cinsiyet, sigara içme, tuz kullanımı (iyotlu veya iyotsuz) ve guatrojen besin tüketiminin ölçülen serum parametrelerine etkisi istatistiksel olarak araştırıldı.

Bu çalışmada tiroid hastalıklarında demir metabolizması ile B_{12} vitamini düzeylerinde değişiklik olduğu gözlenmiştir.

Anahtar Kelimeler: *Hipertiroidizm, hipotiroidizm, ferritin, demir.*

INTRODUCTION

Ferritin is an iron storage protein found in almost ali of the body tissues. in individuals, serum ferritin levels correlate well with body iron storage. Serum ferritin measurements have been widely used in clinical medicine as a diagnostic test for iron storage diseases or as a marker of some neoplastic diseases[1-3]. Serum ferritin levels also have been reported to be altered in patients with thyroid disease[4]. Recently, it has been reported that the serum level of ferritin is high in hyperthyroidism and low in hypothyroidism, and changes in the serum concentrations reflect thyroid function[5]. Thus, it has been suggested that serum ferritin measurement could be useful for the evaluation of thyroid hormone action on peripheral tissues. Several studies suggest that thyroid hormones may affect erythropoiesis and in these cases serum ferritin levels should be determined together with iron and transferrin measurements[1,4]. However the mechanism by which thyroid hormones al ter the ferritin concentration is not well known. Thyroid hormone therapy results in: lower serum iron, middle-high transferrin concentration and normal or slightly lower serum ferritin level. in hyperthyroidic patients, the greater turnover of plasma iron leads to changes in these parameters[6,7]. Either thyroid hormone or TSH level estimations serve as basic tests in suspected thyroid dysfunction. They are also used in determining the severity of thyroid hyper- and hypofunction and in monitoring known thyroid dysfunction, especially under thyrosuppressive or depressive therapy[8].

The thyroid is unique among the endocrine glands for its dependence on an essential micronutrient, iodine, for normal hormone production. Thyroid hormone production and metabolism is also influenced by a range of other goitrogenic substances found naturally in the environment and by cigarette smoking due to thiocyanate[910]. We evaluated statistically the effects of use of salt (iodine or iodine free), goitrogen intake and cigarette smoking on thyroid hormones and iron metabolism.

in this study, we aimed to investigate the changes in serum ferritin, transferrin, iron concentrations, vitamin B_{12}, erythrocytic parameters, thyroid hormones and TSH levels induced by thyroid function disorders.

MATERIALS AND METHODS

Thirty hyperthyroidic (26 women and 4 men) and thirty hypothyroidic patients (26 women and 4 men) were randomly chosen. None of the patients had anemia, liver diseases, malignancy, or inflammatory illness during the study period. The control group consisted of twenty-two women and three men who were ali healthy. Venous blood was taken from each patient at the time of initial diagnosis for measurement ferritin, transferrin, iron, B_{12}, erythrocytic parameters, both total and free thyroid hormones and TSH.

Serum ferritin levels were analyzed by the fluorescence polarization immunoassay method using Abbott Imx (Wess Baden-Delkenhim, Germany) [n]. The intra- and interassay coefficients of variation for ferritin were 4.25% and 3.25%, respectively. Serum iron and transferrin were measured at 560 nm by colorimetric methods using CL-770 Shimadzu spectrophotometer[1213]. Serum ferritin, iron and transferrin concentrations were determined using Sigma Diagnostic kits. The interassay coefficients of variation for iron and transferrin were 6.60% and 4.75%, respectively. Erythrocytic parameter analyses were done by hemocytometry. Total and free triiyodothyronine, total and free thyroxine, TSH and vitamin B_{12}were measured by Chiron Diagnostics ACS:180 automated chemiluminescence immunoassay system[14].

Ali data were expressed as the mean value ± SE. The statistical analysis of the results was performed using the SPSS for Windows package program. Mann-Whitney U, Kruskal-Wallis and Student's t-tests were used to compare the results between the patients and the control group. p-values less than 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

Table 1 shows the base-line characteristics of the study group. Table 2 shows mean values of iron, transferrin, ferritin, B_{12}, red cells count, haemoglobin, hematocrit, total and free thyroid hormones and TSH in patients vvith thyroid function disorders and healthy controls.

Table 1. Selected base-line characteristics for the study group.

			Patients		Controls
			Hyperthyroidy	Hypothyroidy	
N			**30**	**30**	**25**
Sex	Women		**26**	**26**	**22**
	Men		**4**	**4**	**3**
Body mass index (kg/m^2)			21.67 ±0.65	26.73 ±0.64	23.12 ±0.35
Age(X±S.E.) (years)			59.93 ±19.84	42.37 ±1.74	33.32 ±2.63
Goitrogen intake	consumer		**25**	**23**	**5**
	non-consumer		**5**	**7**	**20**
Smoking status	Non-smoker		**18**	**13**	**18**
	Current smoker (cigarettes per day)	**20**	**10**	**15**	**7**
		20	**2**	**2**	**---**
Salt consumption	Iodized		**13**	**9**	**16**
	iodine free		**17**	**21**	**9**

Table 2. Measured parameters in patients with thyroid function disorder and healthy individuals.

	Hyperthyroidy patients X±S.E. (n=30)	Hypothyroidy patients X±S.E. (n=30)	Healthy Controls X±S.E. (n=25)
Serum Iron (_g/dL)	89.03 ±8.52	49.22 ± 4.14[a]	84.12 ±4.35[b]
Serum Transferlin (_g/dL)	342.67 ±11.94	355.93 ± 10.73	285.12 ± 6.67[a,b]
Serum Ferritin (ng/mL)	93.41 ±20.26	26.69 ±3.81*	47.89 ± 7.04[a]
Serum B_{12} (pg/mL)	359.36 ± 59.00	225.60 ± 17.74[a]	521.92 ± 24.29[a,b]
Red cell count ($xl0^{12}$/L)	4.63 ± 0.09	4.35 ±0.13	4.60 ±0.19
Haemoglobin (g/dL)	12.93 ±0.48	12.64 ±0.25	14.58 ± 0.22[a,b]
Hematocrit (ratio%)	39.09 ±1.50	37.57 ±0.71	43.95 ±0.73"*
Serum TT_3 (ng/mL)	2.61 ±0.36	0.75 ± 0.11[a]	1.33 ±0.05"
Serum FT_3 (pg/mL)	6.92 ±1.06	1.91 ± 0.24[a]	3.27 ±0.14"
Serum TT_4 (μg/dL)	14.97 ±1.44	5.45±1.39[a]	9.14±0.41[a,b]
Serum FT_4 (ng/dL)	3.33+0.68	0.58 ±0.07[a]	1.24±0.06[a]
Serum TSH (μU/mL)	0.04 ± 0.01	71.91 ±8.08[a]	1.74 ±0.25[b]

[a] significantly different from hyperthyroid group ($p<0.05$).

[b] significantly different from hypothyroid group ($p<0.05$).

The mean serum iron level in hyperthroidic patients was higher than those of healthy individuals. There was no significant difference between hyperthyroidic patients and healthy individuals according to serum iron levels ($p>0.05$). The mean serum iron level in hypothyroidic patients was significantly lower than those of healthy individuals ($p<0.05$). In this study, the vitamin B_{12} level in healthy controls was significantly higher than those of all patients ($p<0.05$), Moreover there was a significant difference between patient groups ($p<0.05$). When red cells count were compared among the three groups of normal, hyperthyroid and hypothyroid, insignificant differences were found between the groups ($p>0.05$). Haemoglobin and hematocrit levels in controls were higher than those of patient groups ($p<0.05$), but there was no significant difference between patient groups ($p>0.05$). Thyroid hormone levels in patients with hyperthyroidism were higher, but thyroid-stimulating hormone levels were lower than hypothyroidic patients and normal subjects (Table 2).

Tables 3-5 summarize further observations. Serum ferritin level was compared among hyperthyroid patients according to cigarette smoking, there was a significant difference between heavy smokers and non-smokers and smokers ($p<0.05$) (Table 3). When serum free T_3 levels were compared in healthy subjects according to goitrogen intake, free T_3 level in non-consumer group was higher than those of goitrogenic food consumer group ($p<0.05$) (Table 4). Transferrin, red celll count, haemoglobin and hematocrit levels were compared in patients with hypothyroidism according to sex, there were significant differences between women group and men. In healthy group, ferritin and hematocrit levels of men were significantly higher than that of women ($p<0.05$) (Table 5).

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Table 3. Serum ferritin levels in hyperthyroid patients according to smoking.

Group	X±S.E.
Non-smoker	61.52+16.19[a]
Smokers (<20 cigarettes per day)	101.48±38.16[a]
Heavy smokers (>20 cigarettes per day)	340.00±52.00

* significantly different from heavy smoker group (2:20 cigarettes per day) ($p<0.05$).

Table 4. Serum free T_3 levels in healthy subjects according to goitrogen intake.

Group	X± S .E.
Goitrogenic food consumer	2.42±0.33
Non-consumer	3.48±0.12[a]

"significantly different from goitrogenic food consumer group ($p<0.05$).

Table 5. Measured parameters in hypothyroidic patients and healthy individuals according to sex.

		Women (X± S.E.)	Men (X± S.E.)
Hypothyroidic patients	Serum Transferlin (_g/dL)	350.08±11.83	394.00±14.38[a]
	Red cell count ($xl0^{12}$/L)	4.27±0.15	4.84±0.04[a]
	Haemoglobin (g/dL)	12.36+0.24	14.47+0.13'
	Hematocrit (ratio%)	36.85iO.72	42.25±0.48[a]
Healthy subjects	Serum Ferritin (ng/mL)	41.83+7.00	92.33+7.45[a]
	Hematocrite (ratio%)	43.43±0.76	47.77±0.96[a]

* significantly different from women group ($p<0.05$).

Elevated ferritin levels have been recently observed in patients with hyperthyroidism, but after implementing antithyroid therapy, serum ferritin levels decreased together with T_4 and T_3 levels[4,,615]. The link between T_3 and the regulation of ferritin expression suggest that a positive correlation exists between the levels of T_4/T_3 and ferritin in the serum[1617]. Some evidence suggests that ferritin plays a role not only in iron storage but also in iron transport, probably because of its carrying capacity of 4500 iron atoms compared with transferrin's carrying capacity of only 2 per transferrin. Thus, it may not be so suprising that, in some cases, a marked increase in ferritin can lead to an elevation of serum iron[3,518]. Significant difference was found

in serum ferritin levels between normal and hyperthyroid patients in this study. The increase in ferritin during hyperthyroidism has been attributed to the stimulatory effect of thyroid-stimulating hormone and thyroid hormone on ferritin synthesis and release, this may explain the elevation in the ferritin level.

Several groups have documented an association between T_3 levels and ferritin expression. In earlier reports, hypothyroidism produced by thyroidectomy was associated with increased rat hepatic ferritin content, which was found to be due to post-transcriptional changes in the ferritin synthetic rate. Administration of T_3 to hypothyroid individuals produce a significant increase in the serum ferritin level[16,19,20]. Our findings of decreased serum iron and ferritin levels and increased transferrin levels in hypothyroidism may be regarded as an indicator of decreased iron turn over in accordance with diminished erythropoiesis.

It is well known that thyroid and folate function are related in animals. In rats, hypothyroidism induced by thiouracil or thyroidectomy, leads to increased liver stores of folate and B_{12} and administration of thyroid powder leads to an increased dietary requirement for B_{12}[21]. In this study, B_{12} levels in patients with thyroid disorder were lower than healthy subjects, moreover in hypothyroidic patients vitamin B_{12} levels were lower than hyperthyroidic patients. These decreased levels may give support to the hypothesis previously described by Lewitt and Joffe. Another cause of the the decreased levels may be cigarette smoking. It has been reported that vitamin B_{12} levels are decreased in smokers[22]. In this study, in patients with thyroid disorder, especially hypothyroidism, the number of smokers was higher than that of non-smokers. Thiocyanate is a major metabolite of hydrogen cyanide which is present in high concentration in tobacco smoke. In cigarette smokers, serum and urinary thiocyanate concentrations are significantly increased by detoxification of cyanide which has been found in tobacco smoke[22,23]. Experimental studies in animals have demonstrated a goitrogenic effect of thiocyanate by a competetive inhibition on the recycling of thyroidal iodide[10]. Potantially important changes in thyroid function may occur in cigarette smokers, since thiocyanate in the smoke possess antithyroid activity.

It is generally accepted that nutritional status may interfere with endocrine functions, particularly thyroid function[24]. Since then other vegetables, predominantly of the genus Brassica, have been found to have goitrogenic properties. Plants in this group include cabbage, Brussels sprouts, cauliflower, broccoli, turnips, rape and rapeseed, horseradish and garden cress. These plants contain thiocyanates and isothiocyanates which are potent inhibitors of iodine uptake into the thyroid. They also stimulate the release of iodide from the thyroid gland[24,25]. In this study, free T_3 levels in healthy subjects consuming goitrogenic food was lower than in the non-consuming group.

It is known that serum ferritin concentrations in men are higher than in women, but there is no sex difference in infants, adolescents or in adults over fifty years of age[2]. This sex difference was found in the present study only in normal subjects.

Finally, our data suggest that alterations in thyroid status change serum iron metabolism and B_{12} concentrations. Measurement of this parameters before and after thyroid hormone therapy may provide useful information in the diagnosis of thyroid diseases.

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