Alterations in osmotic fragility of the red blood cells in hypo- and hyperthyroid patients

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ABSTRACT. ***Background:*** **Changes in concentration of thyroid hormones can affect Na^+-K^+-ATPase number and activity and phospholipid composition of the cell membranes leading to changes in the surface to volume ratio and strength of membrane.** ***Aim:*** **In this study, the osmotic fragility of the red blood cells from non-treated hypo- and hyperthyroid patients was compared to that of control subjects.** ***Material/subjects and methods:*** **After 3 washings with normal saline, red blood cells were placed in varying concentrations of sodium chloride (NaCl) (0-0.9%) and fragility was assessed with colorimetric method; to do this, after the incubation period, tubes were centrifuged and the optical density of the tubes was measured. Hemolysis percentage in tubes was calculated based on 100% hemolysis in the tubes containing no NaCl (0%).** ***Results:*** **Osmotic fragility of the cells from hyperthyroid patients in 0.45% NaCl was significantly lower than control subjects (74.6%±30.2** ***vs*** **93.8%±9.1, $p<0.01$). The osmotic fragility of red blood cells in 0.5% concentration of sodium chloride in hyperthyroid patients was significantly lower compared to that of controls (27.8%±26.0** ***vs*** **63.5%±27.5, $p<0.001$). No significant difference was observed between the osmotic fragility of the hypothyroid patients compared with control subjects.** ***Conclusions:*** **Alteration in osmotic fragility is seen in patients with hyperthyroidism; however, anemia reported in hypo- or hyperthyroid patients is not due to high osmotic fragility of red blood cells and other causes need to be investigated.**

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INTRODUCTION

Thyroid function disturbances are associated with changes in blood profile and anemia is prevalent in hypothyroidism (1). In a study (2), decreased synthesis of erythropoietin has been suggested to be one of the causes of the anemia. Hypochromic microcytic anemia along with iron deficiency and macrocytic anemia associated with folic acid and vitamin B_{12} deficiencies have been observed in hypothyroid patients (3). Shorter survival time due to faster hemolysis of the red blood cells (RBC) has also been reported (4). Although few studies have suggested the presence of hemolytic anemia in hypothyroid patients (5, 6), some other studies have failed to show any differences between the half life of RBC in patients with hypothyroidism as compared to controls (7, 8).

Abnormalities of blood profiles in hyperthyroidism have also been reported. Chronic anemia in hyperthyroidism (9) is usually reversed following the treatment of hyperthyroidism (10, 11).

Although thyroid hormones generally increase the number and the activity of the Na^+-K^+-ATPase in some tissues (12, 13) and cell culture (14) it appears that the effect on the activity of the pump in the RBC membrane is the opposite. A few studies reveal that the Na^+- K^+-ATPase activity in the membrane of red blood cells of hyperthyroid patients is decreased (15-17), while in hypothyroid patients it is increased (18, 19).

It is very well known that thyroid hormones can alter the lipid contents and as a result, the fluidity of the cell membrane (20, 21). The effect of thyroid hormones on the exchange of cholesterol between plasma and red cell membrane has been suggested, an effect which also influences the fluidity of the cell membrane (22, 23).

Since thyroid hormones can affect red cell volume by altering the Na^+-K^+-ATPase activity and can also influence the fluidity and strength of the membrane in the RBC through changes in the composition of the cell membrane, we attempted to investigate the osmotic fragility of RBC from newly diagnosed hypo- and hyperthyroid patients compared to that of control subjects.

MATERIALS AND METHODS

Subjects

Hyperthyroid (no.=26) and hypothyroid (no.=21) patients were selected from patients attending the outpatient department of a university teaching hospital using a simple sampling system. Patients were examined by an endocrine specialist and if suspected of being hyper- or hypothyroid, were referred for laboratory tests. If the results confirmed the primary diagnosis, data from the patients were included in the analysis. None of the patients was under thyroid-related or any other medications and they confirmed having had the symptoms of the disease for at least 1 month before attending the clinic. Age- and sex-matched control subjects were selected from hospital staff, none having any thyroid dysfunction or any other disease and all free of any medication; both the patients and controls were briefed regarding the purpose of the study and all gave written consent. The study was approved by the research Ethics Committee of the research institute for endocrine sciences, Shahid Beheshti University (M.C.).

Blood sampling

Ten ml of venous blood sample was obtained (08:00-10:00 h) from each subject which was then divided into two parts; 5 ml was kept at room temperature for 1 h, then centrifuged and sera separated and kept at –80 C until used for hormonal and biochemical measurements. EDTA (1.5 mg/ml blood) was added

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into the second 5-ml portion of the blood, which was then used for hematological studies including the osmotic fragility test.

Hematological tests

Hematological quantities were measured by an automatic cell counter (Sysmex, K 800, Japan). A slightly modified routine colorimetric method (24) was used to measure the osmotic fragility of RBC. In brief, cells were washed 3 times with 0.9% NaCl; for each washing, 1.5 ml of the blood sample was mixed with 8.5 ml of 0.9% NaCl and centrifuged for 5 min at 1000 rpm. After removing the supernatant of the last centrifugation, red cells were suspended in 1.5 ml of 0.9% NaCl and 50 µl of cell suspension was added in triplicate to the tubes containing 1 ml of different NaCl concentration (0-0.9%). Tubes were incubated for 30 min at 37 C in a water bath and then centrifuged for 10 min at 3000 rpm. Optical density (OD) of the supernatant was measured at 540 nm using an enzyme-linked immunosorbent assay reader (Sunrise, Tecan, Austria). Percent hemolysis was calculated from mean OD of triplicate for each concentration of NaCl considering OD for the tube zero (no NaCl) as 100% hemolysis.

Hormonal and biochemical assays

Hormonal and biochemical measurement for each patient was carried out in one batch. Total T_3 (TT_3), total T_4 (TT_4), and T_3 resin uptake were measured by radioimmunoassay (Kimiapakhsh, Tehran, Iran). TSH was measured using immunoradiometric method (Kimiapakhsh, Tehran, Iran). Intra-assay coefficients of variation (CV) for TT_3, TT_4, T_3 uptake, and TSH assays were 7.0, 6.3, 4.2, and 7.7% respectively. Enzyme-immunometric assay (DRG; Germany) was used to measure ferritin with CV of 8.4%; iron was measured using a kit from Parsazmoon Company (Tehran, Iran) with CV of 2.9%. Total iron binding capacity was measured using a kit from Darman kav Company (Tehran, Iran) with a CV of 2.4%.

Statistical analysis

The results are presented as mean±SE. To compare the findings, analysis of variance followed by Tukey *post-hoc* if necessary, was used. To compare the results for TSH, Mann-Whitney test was applied; *p*-values less than 0.05 were considered significant.

RESULTS

All subjects were female with no significant difference in ages of the controls (35.9±10.7 yr) hypothyroid (35.9±10.7 yr), and hyperthyroid (34.6±13.6 yr).

Hormone measurements

Table 1 shows TT_4, TT_3, TSH concentrations, and resin T_3 uptake in patients with hyper and hypothyroidism and control subjects confirming the status of the studied subjects.

Hematological measurements

The number of RBC in hyper- and hypothyroid patients was not significantly different from control subjects; it was however significantly higher in hyperthyroid patients, as compared to those with hypothyroidism ($p<0.01$). Hemoglobin concentration in hypothyroid patients was significantly ($p<0.05$) lower compared to control subjects. Mean hemoglobin content of the RBC in both groups of hyper- and hypothyroid patients was significantly lower compared to control subjects (Table 1).

Packed cells volume values were not significantly different in either group of patients as compared to the controls whereas mean corpuscle volume of the patient groups were significantly ($p<0.01$ and $p<0.001$, respectively) lower than controls (Table 1).

Lipid profiles

Triglyceride concentrations in hypothyroid and hyperthyroid patients did not differ significantly from controls; serum cholesterol level of hypothyroid patients was significantly ($p<0.01$) higher and in hyperthyroid patients significantly ($p<0.01$) lower as compared with the controls (Table 1).

Osmotic fragility

Percent hemolysis of the RBC from hypothyroid patients did not differ significantly from controls in any concentration of NaCl; however, RBC from hyperthyroid subjects showed significantly lower percentage of hemolysis as compared to controls. For RBC, the percentage of hemolysis in hyperthyroid patients in 0.45 and 0.5 g/100ml NaCl (74.5±5.9 and 27.7±5.0, respectively) was significantly ($p<0.01$) lower (93.8±1.8 and 63.5±5.6) compared with controls (Fig. 1, Table 2).

DISCUSSION

The results of this study show that the osmotic fragility of RBC of hyperthyroid patients is lower compared with that of hypothyroid and control subjects. A search of available literature indicated that not too many studies have investigated the issue. Findings of this study show that, despite the presence of anemia in both groups of hyper- and hypothyroid patients, the cause of the ane-

Table 1 - *Hormonal and biochemical parameters in hypothyroid, hyperthyroid, and control subjects.*

Parameters	Control (no.=24)	Hypothyroid (no.=24)	Hyperthyroid (no.=26)
TSH (mU/l)	1.7±0.3	30±7[c]	0.1±0.03[c]
T_4 (nmol/l)	116±6	57±8[c]	203±9[c]
T_3 (nmol/l)	1.9±0.1	1.7±0.2	5.1±0.4[c]
T_3RU (%)	31.2±0.5	22.8±0.8[c]	32.7±1.5[c]
Ferritin (pmol/l)	89±15	83±10	128±27
Iron (nmol/l)	16±0.7	18±0.7	18±1
TIBC (nmol/l)	60±2	61±2	62±3
Triglycerids (mmol/l)	1.3±0.1	1.6±0.1	1.2±0.1
Cholestrol (mmol/l)	5.2±0.2	6.0±0.4[b]	3.8±0.1[b]
RBC (10^6/mm^3)	4.46±0.08	4.71±0.16	4.80±0.09[b]
Hemoglobin (g/l)	131±1	122±3[a]	124±2
HCT (%)	39.5±0.4	37.2±0.7	38.1±0.7
WBC (10^3/mm^3)	5.90±0.31	6.32±0.44	5.81±0.36
MCH (pg)	29.5±0.4	26.4±0.8[a]	25.9±0.4[b]
MCV (fmol)	89.0±1.4	80.7±2.6[a]	79.5±1.0[c]

[a]$p<0.05$, [b]$p<0.01$, [c]$p<0.001$ compared to control group. T_3RU: T_3 resin uptake; TIBC: total iron binding capacity; RBC: red blood cell; WBC: white blood cell; MCH: mean corpuscle hemoglobin; MCV: mean corpuscle volume.

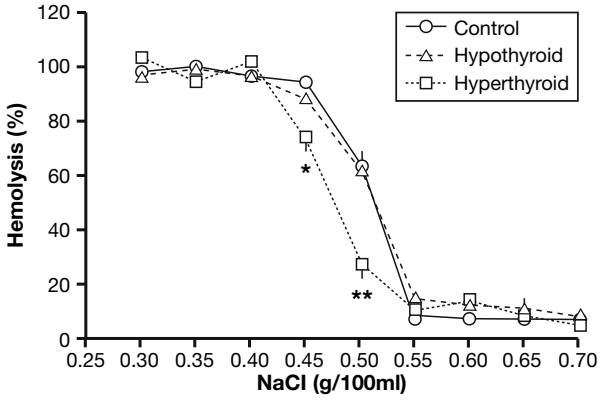

Fig. 1 - *Percent hemolysis of the red blood cells from hypothyroid, hyperthyroid and control subjects in NaCl concentrations of 0.3 to 0.7 g/dl. *p<0.05 and **p<0.001 indicate the significance of difference between hyperthyroid and control subjects.*

mia is not the altered resistance of the cells. One study has compared the osmotic fragility of hyperthyroid patients with controls and concluded that the osmoresistance of the RBC was significantly correlated with the degree of thyrotoxicosis (25); although in the abovementioned research the types of patients studied are different from the present, the findings of both studies are well matched. An *in vitro* study has shown that T_4 can directly decrease calcium concentration in RBC with doses not very different from the physiological range (10^{-7}-10^{-9} mol/l) (26), which may lead to an increase in the Na^+-K^+-ATPase activity (27). This effect of T_4 on Na^+-K^+-ATPase activity through intracellular calcium concentration is contradictory to the findings of some other studies showing that in hyperthyroid patients, the number of Na^+-K^+-ATPase in the RBC membrane is decreased (16, 19). Theoretically decreased Na^+-K^+-ATPase activity will lead to the accumulation of Na^+ inside the RBC causing increased cell volume (28). Not only was the size of the RBC not increased, but also mean corpuscle volume (MCV) was lower in hyperthyroid patients. Reduction in the size of RBC in these patients has been reported by others too (3, 22, 29, 30). Nevertheless, since the decreased RBC volume values were not associated with higher osmotic resistance in the hypothyroid patients, the possible involvement of other factor(s) must be explored.

Table 2 - *Percentage of hemolysis of red blood cells (RBC) in hypothyroid, hyperthyroid, and control subjects.*

NaCl (g/100ml)	Control (no.=24)	Hypothyroid (no.=25)	Hyperthyroid (no.=26)
0.05	102.02±1.19	102.61±1.95	106.65±4.30
0.1	101.85±1.30	100.51±1.84	106.31±4.20
0.15	100.40±1.51	101.22±1.59	107.55±4.17
0.2	97.81±1.96	98.86±1.45	102.10±3.29
0.25	97.53±1.56	99.11±1.39	105.06±4.86
0.3	97.85±2.00	97.00±2.06	103.53±4.52
0.35	100.29±1.81	99.87±1.44	95.42±5.21
0.4	97.35±1.90	98.37±1.51	101.66±3.84
0.45	93.82±1.86	89.69±3.62	74.55±5.92[b]
0.5	63.52±5.60	62.34±6.46	27.77±5.09[c]
0.55	8.63±0.40	14.99±3.36	10.50±3.66
0.6	7.89±0.26	12.25±3.68	13.93±5.64
0.65	7.71±0.24	11.38±3.22	8.99±3.77
0.7	7.60±0.29	8.19±0.39	5.59±0.68[a]
0.75	7.84±0.31	8.29±0.30	5.58±0.73[b]
0.8	7.66±0.22	8.22±0.35	5.46±0.67[b]
0.85	7.54±0.17	8.32±0.31	5.62±0.61[b]
0.9	7.58±0.21	8.32±0.34	5.70±0.66[a]

[a]$p<0.05$, [b]$p<0.01$, [‡]$p<0.001$ compare to control group.

Thyroid function status can alter the lipid composition of the red cell membrane (31). Lipid composition of the red cells was not measured in this study; however, serum cholesterol level was lower in hyperthyroid patients. This decrease may reflect partly the increased free cholesterol of the red cell membrane (22) which might affect membrane fluidity and, as a result osmotic resistance of the cell (20-23). About two-thirds of the cholesterol in human circulation is incorporated into LDL and uptake of it by different cells occurs through specific receptors (32). The number of these receptors is well correlated with thyroid function (33). The altered dynamic of a recently discovered protein named ATP binding cassettes transporter A1 (ABCA1) on the shuttle of cholesterol between RBC and plasma could not be ruled out since the involvement of this transporter on the trafficking of the substrates including cholesterol in several tissues has been established (22, 23, 34). The role of ABCA1 activity on the cholesterol content of RBC and RBC membrane and its status related to thyroid function has not been reported.

One other explanation for the increased osmotic resistance of RBC in these patients is the possible change in the number of water channels. The RBC membrane contains a tetramer protein called aquaporin 1 (35). The impact of hyperthyroidism on the profile of these proteins on RBC membrane has not been studied, but it has been shown that hypothyroidism can increase the number of aquaporin 2 in the cell walls of the collecting tubules of the rat's kidney (36). Although the type of aquaporin in the RBC membrane is different from the collecting tubule cell, if the thyroid status acts similarly in both tissues, then one might expect an alteration in the osmotic resistance due to altered thyroid function. Study of the time course of volume changes and hemolysis and the measurement of the aquaporin contents of the RBC membrane from the patients may answer some of the raised questions.

Despite normal numbers of RBC and the hemoglobin concentrations of hyperthyroid patients, considering the mean corpuscle hemoglobin and MCV values, the patients had been anemic as in other reports (24, 30, 37). Evidence suggests that the abnormality of hemopoiesis is not seen in all hyperthyroid patients. In the study by Hambsch et al. (37) only 34% of patients had anemia and Firvida et al. (9) suggest that hyperthyroidism likely to be causing anemia is rare.

In this study, the osmotic resistance of RBC from hypothyroid patients was not significantly different compared with the controls. In one report, it has been shown that the fragility of RBC of hypothyroid patients might be increased (5). Findings of our study do not confirm the

report by Nomura et al. (5), which was found in hypothyroid patients under regular dialysis. It has been shown that the number and activity of Na^+-K^+-ATPase in RBC membrane is increased in hypothyroidism (19). Increase in Na^+-K^+-ATPase activity is expected to reduce cell size (28) leading to increased cell resistance. The cell volume was significantly lower in our study suggesting that either the increased osmotic resistance in hypothyroidism was not significant or the changes on the other effective parameters have masked the altered resistance due to changes of cell volume.

Anemia seen in this study confirms the finding of some other studies (5) although we have not been able to show significant changes of ferritin, total iron binding capacity, and iron concentration in patients with hypothyroidism. Franzese et al. (38) too, were unable to show any alterations in these parameters of infants with congenital hypothyroidism despite established anemia in the subjects. Nevertheless, it has been suggested that anemia in hypothyroid patients may be due to deficiencies of hemopoietic nutrients such as iron, vitamin B_{12}, and folate (39). Differences in these findings may reflect the variations in the type of the subjects, severity and duration of the disease.

One limitation of this study is the low number of subjects due to the fact that the patients were newly diagnosed and had had no prior treatment; it was therefore not possible to categorize them according to varying severity and duration, which could explain differences with other studies.

From the results of this study, it appears that osmotic resistance of RBC in hyperthyroid patients is increased, which may reflect the alteration in the structure of the cell membrane toward longer life span of RBC, which in hyperthyroid patients with high metabolic demand would be to their advantage. The results also indicate that anemia observed in hypothyroid patients is not due to alteration in the fragility of RBC and other possible causes should be explored.

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