Skin changes in the neck and selenium content in patients with thyroid diseases

Dziemianowicz M.[1,2,3], Markiewicz-Żukowska R.[4], Socha K.[4], Soroczyńska J.[4], Borawska MH.[4]

[1.] Endocrinology Outpatients Clinic, Hospital MSWiA in Białystok, Poland
[2.] Endocrinology Outpatients Clinic, Hospital Zambrów, Poland
[3.] Endocrinology Outpatients Clinic Kętrzyn, Poland
[4.] Department of Bromatology, Medical University of Białystok, Poland

ABSTRACT

Purpose: Occurrence of skin changes, in the form of discolouration on neck and in form of a so-called ”thyroid shadow”, was observed in patients with: Hashimoto’s disease, Graves´ disease, struma nodosa euthyrotica or hyperthyreosis. Effects of selenium status and smoking on the risk of those skin changes were investigated.
Materials and methods: The study group consisted of 267 patients with different kinds of thyroid disease. The control group included 34 healthy people. Selenium concentrations in serum were determined by electrothermal absorption spectrometry method.
Results: Thyroid shadow was observed in 70 percent of the subject. Selenium levels in serum were lower in patients with thyroid disease (65.051±16.70 μg/L), especially in smokers (62.477±15.21 μg/L) than in the control group (75.162±19.92 μg/L).
Conclusions: Thyroid shadow syndrome would be the diagnostic signal of thyroid diseases, especially Hashimoto disease. Selenium status is important in the studied thyroid diseases. Cigarette smoking decreases the concentration of selenium in the serum of patients with thyroid diseases.
Keywords: Thyroid shadow, selenium, smoking

***Corresponding author:**
Maria H. Borawska
Department of Bromatology, Medical University of Białystok
Białystok 15-222 Mickiewicza 2D St.
Tel. /Fax.: +48 857485469
e-mail: bromatos@umb.edu.pl

Received: 30.06.2014
Accepted: 21.08.2014
Progress in Health Sciences
Vol. 4(2) 2014 pp 31-36

INTRODUCTION

There are numerous classifications of chronic thyroiditis, some of them based on clinical symptoms and immunological status and other related to microscopic criteria [1-3]. Hashimoto's thyroiditis and Graves' disease are different expressions of a basically similar autoimmune process. People with classic Hashimoto's thyroiditis have serum antibodies reacting with thyroglobulin and thyroid peroxidase [4]. Among various external and environmental factors, cigarette smoking seems to play a role in the pathogenesis of autoimmune thyroiditis, along with viral infections, excess of iodine and recently – also selenium deficiency. Some drugs, for instance Amiodaron, lithium salts, interferon-alpha, granulocyte growth factor or interleukin-2, may induce synthesis of thyroid antibodies in previously healthy subjects. Moreover, the aforementioned factors play a role in the manifestation of hypothyroidism and exacerbation of autoimmune process in patients with previously demonstrated thyroperoxidase (ATPO) and thyroglobulin (ATG) autoantibodies [5-9]. Currently more attention is being paid to the association between selenium supplementation and natural course of autoimmune thyroid disorders. The thyroid is the organ with the highest selenium content per gram of tissue. Selenium status appears to have an impact on the development of thyroid pathologies [10].

Recent studies revealed positive effects of several weeks of selenium administration. Results showed decreased titers of thyroperoxidase antibodies in patients with autoimmune thyroid diseases [11, 12]. Negro et al. [13] revealed that selenium supplementation during pregnancy and postpartum period inhibits progress of Hashimoto's thyroiditis and results in decreased ATPO titers and improved ultrasound thyroid echogenicity. Recent studies indicate a link between autoimmune disorders such as Hashimoto thyroiditis and the incidence of skin changes, for instance chronic spontaneous urticaria or vitiligo [14,15]. Effects of selenium status and smoking on the risk of skin changes were investigated.

MATERIALS AND METHODS

Two hundred sixty seven patients (260 women and 7 men) aged 49±14 years were treated in three endocrinology outpatients clinics in various towns of Poland (Białystok, Zambrów, Kętrzyn). Patients eligible for the study were not earlier treated for thyroid disorders. In the examined patients, levels of TSH, fT3, fT4 and titers of thyroglobulin and thyroperoxidase antibodies were evaluated. Thyroid disorder was confirmed by means of a standard ultrasound while histopathological examination of thin needle biopsy was performed whenever feasible. Patients qualified for the study were examined thoroughly with the visual inspection of the skin on the neck in daylight. Patients did not report any other skin problems. Moreover, they were asked about smoking. Control group was composed of 34 healthy volunteers – 33 women and 1 man (average age 43±13 years). Both subjects, patients and healthy individuals included in the study did not take dietary supplements of selenium. Protocol of the study was approved by the Local Ethical Committee. Patients and control group data are shown in Table 1.

Table 1. Patients and control group characteristic.

Variable	Patients with thyroid diseases (n = 267)	Control group (n = 34)
Gender (F/M)	260/7	33/1
Age (years) – Mean (range)	49 ± 14 (17-75)	43 ± 13 (19-65)
Smoking/ No-smoking*	150/117	14/20

F – female, M – male; *number of cigarettes: 5-20 daily

Samples of venous blood from patients and control group were drawn using the vacutainer system test tubes containing clot activator (Becton Dickinson, France). The samples were allowed to clot within 30 minutes then centrifuged within 10 minutes at approximately 1000 x g. Serum was removed and kept frozen at - 20°C. The concentration of selenium in the serum was analyzed by the electrothermal atomic absorption spectrometry technique with the Zeeman background correction on the Hitachi spectrometer of Z-5000 model. The accuracy of selenium determination methods was verified using the following certified standard materials MIO 181 (Seronorm Trace Elements, Serum Level 1, Sero AS, Norway). The samples were determined in the Department of Bromatology of the Medical University in Białystok, which is involved in a quality control program for trace elements analysis supervised by the Institute of Chemistry and Nuclear Techniques and the National Institute of Public Health National Institute of Hygiene in Poland.

Statistical analyses were performed using Statistica v.10.0 software. Differences between independent groups were tested by the Mann-Whitney U-test. P values less than 0.05 were considered statistically significant.

RESULTS

Skin lesions in the form of discolorations and disorder of pigmentations in the thyroidal region of neck (Fig.1) were observed in 70% of subjects with thyroid diseases (from 45% in struma nodosa euthyrotica to in ca 86% of Hashimoto's disease patients (Table 2). Their frequency and intensity increased with the disease progress. The content of selenium in serum in the control group was 75.162±19.92µg/L. The average levels of selenium in serum of patients with thyroid diseases were decreased in: Hashimoto's disease (63.026±17.31 µg/L), Graves´ disease (59.734±10.42 µg/L) and struma nodosa euthyrotica (67.593±15.88 µg/L); but not in struma nodosa hyperthyreosis (68.583±16.43 µg/L) (Table 2). The average content of selenium in serum of patients with Hashimoto disease with skin changes (64.998 ±16.93 µg/L; n=123) was significantly higher (p<0.0007) than in patients without skin lesion (50.776 ±14.72 µg/L; n=120). The concentrations of selenium in the smoking group of patients with Hashimoto's disease (59.632±13.58 µg/L) and all of patients with thyroid diseases (62.477±15.21 µg/L) were significantly lower than in the non-smoking group (68.620±21.30 µg/L and 67.994±17.77 µg/L, respectively) (Table 3).

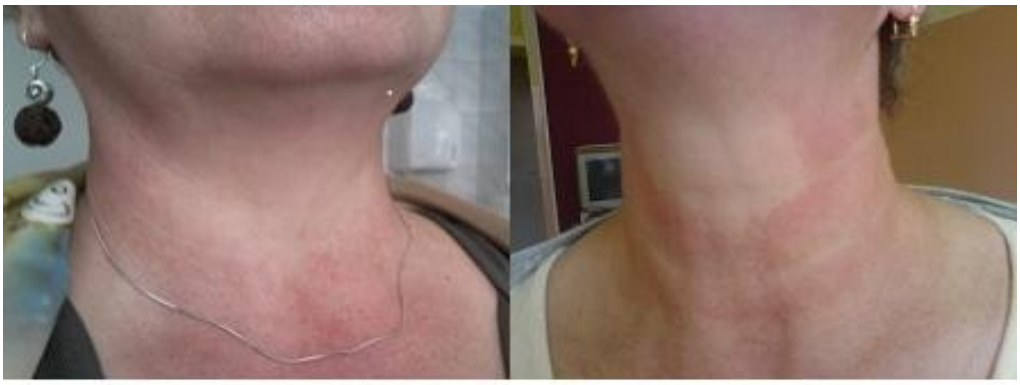

Figure 1A and 1B: Photo documentation of skin changes in patients with Hashimoto's disease.

Table 2. The concentration of serum selenium in patients with thyroid diseases and skin changes.

No.	Thyroid diseases	Concentration of selenium µg/L ± SD			$p_{A/B}$
		Without skin changes (A) (n)	With skin changes (B)(n %)	Total (C) (n)	
1.	Control	75.162±19.92 (34)	-	-	
2.	Hashimoto disease	50.776±14.72 (20) $P_{1/2A}$<0.00003*	64.998±16.93 (123 -86%) $P_{1/2B}$<0.004*	63.026±17.31 (143) $P_{1/2C}$<0.0007*	0.0007*
3.	Graves´ disease	63.467±13.80 (3)	57.686±9.21 (6 – 67%)	59.734±10.42 (9) $P_{1/3C}$<0.032*	0.485
4.	Struma nodosa hyperthyreosis	68.280±19.94 (12)	68.735±14.85 (25 – 67%)	68.583±16.43 (37)	0.939
5.	Struma nodosa euthyrotica	68.581±17.37 (43)	66.379±13.98 (35 – 45%)	67.593±15.88 (78) $P_{1/5C}$<0.004*	0.546
6.	All studied diseases	63.941±18.42 (77)	65.519±15.96 (183 – 70%)	65.051±16.70 (267) $P_{1/6C}$<0.002*	0.488

n - number of patients; p – significance level ; % - percent of total patients in studied group
SD - Standard deviation

Table 3. Smoking and concentrations of selenium in serum in patients with thyroid diseases.

No.	Thyreoidis disease	Concentration of selenium µg/L ± SD		$p_{A/B}$
		Smokers (A) (n)	Non smokers (B) (n)	
1.	Hashimoto disease	59.632±13.58 (95)	68.620±21.30 (48)	0.004*
2.	Graves´ disease	59.568±11.06 (4)	59.868±11.19 (5)	0.969
3.	Struma nodosa hyperthyreosis	68.312±16.68 (21)	68.962±16.64 (16)	0.909
4.	Struma nodosa euthyrotica	67.385±17.43 (30)	67.950±15.01 (48)	0.881
5.	Total	62.477±15.21 (150)	67.994±17.77 (117)	0.008*

n - number of patients; p – significance level; SD - Standard deviation

DISCUSSION

Skin of hypothyroid patients is usually dry, rough and cold. These changes result from the direct effects of thyroid hormones on the skin trophism and perfusion. Consequently, the measurements of skin perfusion by means of laser Doppler flowmetry [16, 17] revealed that such parameters as mean capillary flow velocity, capillary pulse wave amplitude, and capillary flow oscillation amplitude were decreased in non-treated hypothyroid patients compared to those with normal levels of thyroid hormones. The aforementioned changes were even more pronounced if compared to hyperthyroid subjects. In hypothyroidism, the reactive constriction of blood vessels, responsible for maintenance of proper body temperature under hypothermia, results in visible pallor and coolness of skin [17]. Lack of carotene metabolism in liver causes its accumulation in the stratum corneum of skin. Carotene is eliminated with sweat and reabsorbed through skin and its deposits are formed mostly in the regions rich in sebaceous glands. It is another factor responsible for the change in skin color to a characteristic, yellowish one, also known as carotenodermia. Hashimoto's thyroiditis is oligosymptomatic and its signs are mostly related to the consequences of that disorder, i.e. the initial hyper- and subsequent hypothyroidism. There are no pathognomonic symptoms for the condition besides the biochemical parameters.

Skin lesions in the form of discolouration, like carotenodermia, on neck, may be characteristic of the studied disease. Because of their shape, they are sometimes described as "thyroid shadow". This characteristic feature constitutes an important and easy to distinguish symptom and hence enables identification of the risk group among Hashimoto's thyroid patients. The symptom described, if widely recognized and understood by family physicians and dermatologists will facilitate referral of patients to endocrinology outpatient clinics and the implementation of proper treatment of Hashimoto's thyroiditis. Considering 70% incidence of the symptom, its clinical application is likely to reduce the redundant costs of diagnosis. These skin changes demonstrate direct positive correlation with smoking. Thyroid belongs to a group of organs with the highest concentration of selenium per mass unit. Selenoproteins participate in cellular antioxidative protection and redox control systems, such as glutathione peroxidase (GPX) and thioredoxin reductases (TxnRd). Consequently, they play a role in the protection of thyroid against the excess of hydrogen peroxide and reactive oxygen radicals synthesized by its follicles in course of hormonal biosynthesis [18]. In iodine deficiency, the excessive supplementation of selenium (selenium saturation) results in the increased activity of type 1 5'-deiodinase and subsequent enhanced metabolism of T4. That, in turn, exacerbates the existing hypothyroidism, since – deficient in iodine –thyroid is unable to compensate for the increased degradation of T4 [8,19-21]. Despite its role in thyroid metabolism, serum levels of selenium in patients with various thyroid disorders were decreased in all patients, without subjects with struma nodosa hyperthyreosis. Consequently, the study proved the importance of that element for the proper function of the thyroid. The reference level of selenium in the serum is 70 – 140 µg/L [22].

We observed decreased the mean selenium concentration in the serum of examined patients with thyroid diseases, whereas the average level of selenium was within the reference range in the control

group. Studies showed that selenium levels in subjects from different regions of Poland are low [23].

Our results indicate the need for selenium supplementation in patients with thyroid diseases. On the other hand, studies from the Austrain region showed no significant decrease in the concentration of selenium in patients with Hashimoto's thyroiditis, selenium concentrations in both the examined and control group were within the reference range [24].

Review of research [25] has demonstrated that currently there is no confirmed evidence of the benefits of supplementation in patients with Hashimoto's thyroiditis. The review highlights the need for randomised placebo-controlled trials to evaluate the effects of selenium in people with Hashimoto disease. Studies also indicate that the effect of selenium depends on the genetic background and the baseline level of selenium in the serum. Genetic polymorphism has a functional significance and it is associated with different response of Gpx1 activity to selenium [26,27].

It was revealed, however, that the serum selenium concentration in patients with thyroid disorders was not correlated with the skin changes in our study. Other studies have demonstrated that antioxidant supplements improve parameters related to skin structure in humans [28]. Selenium plays a role in immunotolerization, a cell-mediated process involved in many aspects of immune function. The consumption of yeast low in selenium induced energy in skin responses and increased counts of natural killer cells and T lymphocytes, but did not change them in the high-selenium supplementation group [29].

In conclusion, skin lesions in the form of decolorations and discolorations on the neck were observed in 70% of patients with the studied thyroid diseases; mainly in 86% of cases with Hashimoto's thyroiditis patients. Serum levels of selenium in patients with thyroid diseases, without struma nodosa hyperthyreosis, were decreased and should be raised by supplementation of this trace element, after the initial determination the concentration of selenium in the serum. Despite being below the normal limit, selenium concentration in serum in Hashimoto's thyroiditis patients with skin lesions was higher, compared to those with the same disease, but unaffected skin. Cigarette smoking additionally decreases the concentration of selenium in the serum of patients with thyroid diseases; therefore, people diagnosed with thyroid disorders should stop smoking cigarettes.

Conflicts of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This work was supported by the Polish Ministry of Science (No 3-16587F).

Acknowledgements

M. Dziemianowicz would like to acknowledge Prof. Roland Gartner from Munich University for his interest in the role of selenium in thyroid diseases during his medical scholarship in Germany.

REFERENCES

1. Orell SR, Philips J. Fine-Needle Biopsy and Cytological Diagnosis of Thyroid Lesions, In: Orell SR, Ed., Monographs in Clinical Cytology, Karger, Basel, Freiburg, Paris, London, New York, New Delhi, Bangkok, Singapore, Tokyo, Sydney, The Thyroid, 14, 1997. p.66-72.
2. Mizukami Y, Michigishi T, Nonomura A, Nakamura S, Ishizaki T. Pathology of chronic thyroiditis: a new clinically relevant classification. Pathol Annu. 1994 Pt 1;29:135-58.
3. Słowinska-Klencka D, Sporny S, Klencki M, Popowicz B, Lewinski A. Chronic thyroiditis - current issue in the cytological diagnostics of the thyroid gland. Endokrynol Pol. 2006 Jul-Aug; 57(4):299-306.
4. Weetman AP. Autoimmune Thyroid Disease In: DeGroot LJ, Jameson JL Ed., Endocrinology 5th ed. Philadelphia: Saunders (Elsevier); 2006;p. 1979-95.
5. Padberg S, Heller K, Usadel KH, Schumm-Draeger PM. One-year prophylactic treatment of euthyroid Hashimoto`s thyroiditis patients with levothyroxine: is there benefit? Thyroid 2001 Mar; 11(3):249-55.
6. Iwatani Y., Hidaka Y, Matsuzuka F, Kuma K, Amino N. Intrathyroidal lymphocyte subsets, including unusual CD4+ CD8+ cells and CD3IoTCR alpha beta Io/-CD4-DC8- cells, in a autoimmune thyroid disease. Clin Exp Immunol. 1993 Sep;93(3):430-6.
7. Bogazzi F, Bartalena L, Dell'Unto E, Tomisiti L, Rossi G, Pepe P, Tanda ML, Grasso L, Macchia E, Aghini-Lombardi F, Pinchera A, Martino E. Proportion of type 1 and type 2 amiodarone-induced thyrotoxicosis has changed over a 27-year period in Italy. Clin Endocrinol. 2007 Oct; 67(4):533-7.

8. Fountoulakis S, Philippou G, Tsatsoulis A. The role of iodine in the evolution of thyroid disease in Greece: from endemic goiter to thyroid autoimmunity. Hormones (Athens) 2007 Jan-Mar; 6(1):25-35.
9. Vestergaard P, Rejnmark L, Weeke J, Hoeck HC, Nielsen HK, Rungby J, Laurberg P, Mosekilde L. Smoking as a risk factor for Graves' disease, toxic nodular goiter, and autoimmune hypothyroidism. Thyroid 2002 Jan;12(1):69-75.
10. Drutel A, Archambeaud F, Caron P. Selenium and the thyroid gland: more good news for clinicians. Clin Endocrinol (Oxf). 2013 Feb;78(2):155-64.
11. Gartner R, Gasnier BC. Selenium in the treatment of autoimmune thyroiditis Biofactors 2003;19(3-4):165-70.
12. Mazokopakis EE, Papadakis JA, Papadomanolaki MG, Batistakis AG, Giannakopoulos TG, Protopapadakis EE, Ganotakis ES. Effects of 12 months treatment with L-selenomethionine on serum anti-TPO levels in patients with Hashimoto's thyroiditis. Thyroid 2007 Jul; 17(7):609-12.
13. Negro R, Greco G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. The influence of selenium supplementation on postpartum thyroid status in pregnant women with thyroid peroxidase autoantibodies. J Clin Endocrinol Metab. 2007 Apr; 92(4):1263-8.
14. Sugiyama A, Nishie H, Takeuchi S, Yoshinari M, Furue M. Hashimoto's disease is a frequent comorbidity and an exacerbating factor of chronic spontaneous urticaria. Allergol Immunopathol (Madr). 2014 Jul 31.
15. Prćić S, Djuran V, Katanić D, Vlaški J, Gajinov Z. Vitiligo and thyroid dysfunction in children and adolescents. Acta Dermatovenerol Croat. 2011; 19(4):248-54.
16. Torizuka T, Kasagi K, Hatabu H, Misaki T, Iida Y, Konishi J, Endo K. Clinical diagnostic potentials of thyroid ultrasonography and scintigraphy: an evaluation. Endocr J. 1993 Jun; 40(3):329-36.
17. Weiss M, Milman B, Rosen B, Zimlichman R. Quantitation of thyroid hormone effect on skin perfusion by laser Doppler flowmetry. J Clin Endocrinol Metab. 1993 Mar; 76(3):680-2.
18. Kohrle J, Gartner R. Selenium and thyroid. Best Pract Res Clin Endocrinol Metab. 2009 Dec; 23(6):815-27.
19. St Germain DL, Galton VA. The deiodinase family of selenoproteins. Thyroid. 1997 Aug; 7(4):655-68.
20. Beckett GJ, Arthur JR. Hormone-nuclear receptor interactions in health and disease. The iodothyronine deiodinases and 5'-deiodination. Baillieres Clin Endocrinol Metab. 1994 Apr;8(2): 285-304.
21. Stagnaro-Green A. Maternal thyroid disease and preterm delivery. J Clin Endocrinol Metab. 2009 Jan;94(1):21-5.
22. Neumeister B, Besenthal I, Bohm BO. Klinikleitfaden Labordiagnostik. Munchen: Elselvier Urban & Fisher Verlag; 2013.
23. Wąsowicz W, Gromadzińska J, Rydzyński K, Tomczak J. Selenium status of low-selenium area residents: Polish experience. Toxicol Lett. 2003 Jan 31;137(1-2):95-101.
24. Wimmer I, Hartmann T, Brustbauer R, Minear G, Dam K. Selenium Levels in Patients with Autoimmune Thyroiditis and Controls in Lower Austria. Horm Metab Res. 2014 Jun 30. [Epub ahead of print]
25. van Zuuren EJ, Albusta AY, Fedorowicz Z, Carter B, Pijl H. Selenium supplementation for Hashimoto's thyroiditis. Cochrane Database Syst Rev. 2013 Jun 6; 6:CD010223.
26. Jabłońska E, Gromadzińska J, Sobala W, Reszka E, Wąsowicz W. Lung cancer risk associated with selenium status is modified in smoking individuals by Sep15 polymorphism. Eur J Nutr. 2008 Feb;47(1):47-54.
27. Jablońska E, Gromadzińska J, Reszka E, Wąsowicz W, Sobala W, Szeszenia-Dąbrowska N, Boffetta P. Association between GPx1 Pro198Leu polymorphism, GPx1 activity and plasma selenium concentration in humans. Eur J Nutr. 2009 Sep;48(6):383-6.
28. Heinrich U, Tronnier H, Stahl W, Bejot M, Maurette JM. Antioxidant supplements improve parameters related to skin structure in humans. Skin Pharmacol Physiol. 2006 May;19(4):224-31.
29. Hawkes WC, Hwang A, Alkan Z. The effect of selenium supplementation on DTH skin responses in healthy North American Men. J Trace Elem Med Biol. 2009 Jun;23(4):272-80.