

# E-selectin, L-selectin, ICAM-1 and IL-6 concentrations changes in the serum of patients with hyperthyroidism in the early period of radioiodine I-131 therapy

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## Abstract

**BACKGROUND:** Among cytokines- interleukins: -6 and -8 (IL-6, IL-8) and E-selectin (E-sel.), L-selectin (L-sel.) and intercellular cell adhesion molecule-1 (ICAM-1) are the most important links in the initiation of the inflammatory process. Taking into account that the inflammatory process is the basic stage of effective radioiodine therapy, we tried to compare the behaviour of the initial inflammatory factors in the early period of I-131 therapy (RAI) of hyperthyroidism. The aim of the study was to estimate the behaviour of IL-6, ICAM-1, E-selectin and L-selectin concentrations in the serum of patients with hyperthyroidism before and during I-131 therapy.

**MATERIAL AND METHODS:** The groups of 26 patients with Graves' disease (GD) and 18 patients with toxic nodular goiter

(TNG), aged 34–77, were studied. Control group (C) consisted of 10 healthy volunteers.

For estimation of thyroid function serum concentrations of TSH, free T4 and free T3 were measured by IRMA or RIA kits (Pola-tom, Poland). IL-6, ICAM-1, E-selectin and L-selectin serum concentrations were determined using ELISA method by Bender kits (USA). Blood samples for all estimations were taken 10–12 days before and in 6<sup>th</sup> week after I-131 administration. Treatment dose of radioiodine was calculated, basing on modified equation for absorbed dose.

**RESULTS:** Compared to control, no statistical differences in the levels of E-selectin (C — 44.4 ± 11 ng/ml) and L-selectin (C — 842 ± 168.9 ng/ml) were observed before treatment in the patients with GD (E-sel. — 59.8 ± 19.6 ng/ml; L-sel. — 1288.2 ± 273.5 ng/ml) and with TNG (E-sel. — 61.5 ± 18.4 ng/ml, L-sel. — 1247.0 ± 273.5 ng/ml) as well as in the 6<sup>th</sup> week after I-131 administration; values in GD group were: E-sel. — 57.3 ± 19.5 ng/ml, L-sel. — 1142.4 ± 193.4 ng/ml; in TNG group: E-sel. — 62.1 ± 20.6 ng/ml, L-sel. — 1113.5 ± 236.3 ng/ml.

In comparison to control there was no difference in initial IL-6 levels either in GD or in TNG group, but a statistically important decrease was observed in the 6<sup>th</sup> week after I-131 administration in GD patients (C — 2.07 ± 0.2 ng/ml v. 1.79 ± 0.16 ng/ml). ICAM-1 serum concentrations before treatment were elevated compared to control group (C — 190.2 ± 34.7 ng/ml) in both groups (GD — 263.6 ± 24.6 ng/ml,  $p < 0.05$ ; TNG — 251.4 ± 36.1 ng/ml,  $p < 0.05$ ). In GD patients a statistically significant increase of ICAM-1 was observed in the 6<sup>th</sup> week (301.1 ± 33.2 ng/ml,  $p < 0.05$ ) of RAI whereas in TNG group there was no statistical difference compared to initial values (249.7 ± 42.6 ng/ml, N.S.).

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**CONCLUSION:** We conclude that ICAM-1 and IL-6 may be important factors in the estimation of the inflammatory processes in the thyroid gland during radioiodine therapy, especially in GD disease. E- and L-selectins seem to be not helpful in the monitoring of the thyroid inflammatory changes during the early period of I-131 therapy.

**Key words:** ICAM-1, L-sel., E-sel., IL-6, I-131, hyperthyroidism

## Introduction

I-131 therapy of thyroid gland diseases is the oldest and the most widely spread nuclear medicine radiotherapy procedure. The fifty-year-long history of I-131 treatment proved its safety and high effectiveness, but it can still be difficult to strictly predict the course and the outcome of the disease after radioiodine therapeutic dose application. It still happens that some patients are especially resistant to radiation, some have radiation-induced thyroiditis or exacerbation of ophthalmopathy concomitant with Graves' disease (GD). Late secondary hypothyroidism is the most frequent complication of isotope therapy and according to various authors it concerns from a dozen to more than fifty percent of patients after 20 years from the dose application. It especially deals with patients treated for hyperthyroidism during GD, which seems to ensue from the autoimmune character of the disease [1].

Great progress in understanding the mechanisms of the inflammatory and immunological processes has been made for the last ten years. The discovery of cytokines and adhesion molecules has drawn attention to the molecular mechanisms of the initiation and the course of immune and inflammatory processes [2]. The communication presents part of the study in which we attempt to estimate if and which factors could play an essential role in the proceeding radioiodine therapy of thyroid gland diseases.

The purpose of our study was to examine the effects of radioisotope therapy on the behaviour of E-selectin (E-sel.), L-selectin (L-sel.) and Intercellular Cell Adhesion Molecule-1 (ICAM-1) adhesion molecules and interleukin-6 serum concentrations of patients with hyperthyroidism. The enhanced levels of these molecules were seen in the serum of patients with various types of hyperthyroidism, i.e. GD, toxic multinodular goitre and toxic adenoma [3]. The influence of radioisotope therapy on the expression of these molecules is still being investigated [4, 5].

## Material and methods

The examinations were carried out on patients treated with radioisotope therapy for hyperthyroidism in the Nuclear Medicine Department of the Medical University in Białystok.

Groups of 26 patients with Graves' disease and 18 patients with toxic nodular goitre (TNG), aged 34–77, were studied. Control group (C) consisted of 10 healthy volunteers. Patients with any signs of infection or any concomitant other than thyroid diseases of autoimmune genesis were excluded from the study.

For estimation of thyroid function, serum concentrations of TSH, free T4 and free T3 were measured by IRMA or RIA kits (Polatom, Poland). Iodine scintigram of thyroid gland with the evaluation of 131-iodine uptake after 24 hours (U<sub>24</sub>) and after 48 hours (U<sub>48</sub>) from diagnostic I-131 dose application (4 MBq) was per-

formed in all patients before treatment [6]. IL-6, ICAM-1, E-selectin and L-selectin serum concentrations were determined using ELISA method by Bender kits (USA). Blood samples for all estimations were taken 10–12 days before and in 6<sup>th</sup> week after I-131 administration.

Therapeutic activities of 131-iodine were given in doses expressed in the units of radioactive activity calculated individually for each patient according to the Marinelli formula:

$$A \text{ [MBq]} = \frac{\text{thyroid mass [g]} \times \text{necessary absorbed dose [Gy]} \times 25}{\text{maksimal iodine-131} \times \text{I-131 effective half time (T}_{\text{eff}}\text{)} \times \text{thyroid uptake U}_{24} \text{ (I-131)}}$$

Mean therapeutic activity applied in GD was 280–400 MBq and in TNG — 400–600 MBq [7].

Patients were divided into groups with regard to the type of hyperthyroidism and the period in relation to the time of application of radioiodine therapeutic dose.

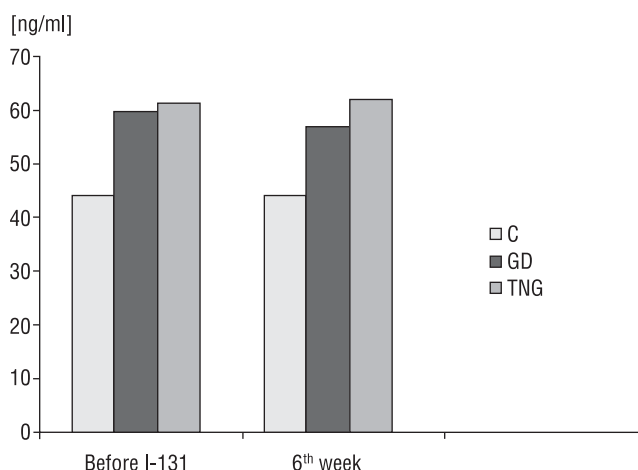
The permission of the Ethics Committee and the written consent of patients were obtained to determine the concentrations of adhesive molecules.

The statistical analysis of the results was performed by means of paired t-Student test and the coefficient of correlation — based on the Statgraphics computer program. The values of  $p < 0.05$  were considered as statistically significant.

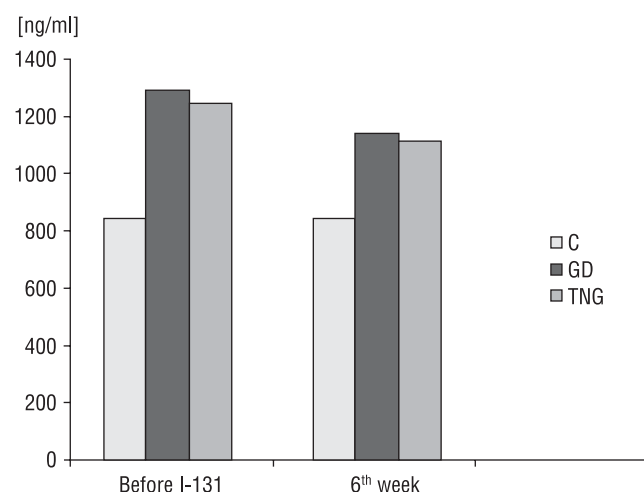
## Results

Serum E-selectin concentrations were higher than control in both untreated (GD —  $59.8 \pm 19.6$  ng/ml; TNG —  $61.5 \pm 18.4$  ng/ml) and radioiodine treated patients (GD —  $57.3 \pm 19.5$  ng/ml; TNG —  $62.1 \pm 20.6$  ng/ml) compared to control (C —  $44.4 \pm 11$  ng/ml), but no statistical difference either between the kind of hyperthyroidism or between the state before and after radioiodine application was seen (Fig. 1).

Analysis of the L-selectin serum concentrations in 6<sup>th</sup> week after radioiodine therapy shows similar results. Compared to con-



**Figure 1.** Mean values of E-selectin serum concentrations before and in 6<sup>th</sup> week after radioiodine administration in patients with GD and TNG treated for hyperthyroidism.

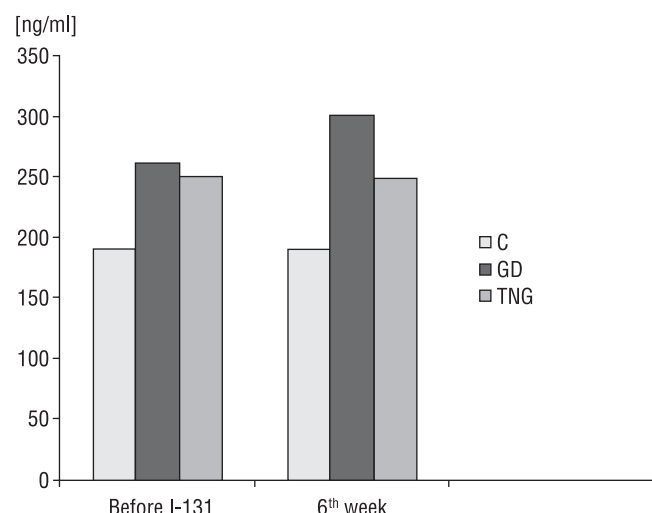


**Figure 2.** Mean values of L-selectin serum concentrations before and in 6<sup>th</sup> week after radioiodine administration in patients with GD and TNG treated for hyperthyroidism.

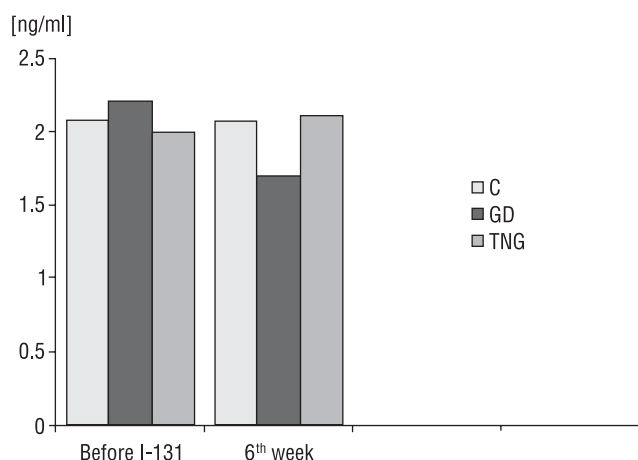
trol group (C — 842 ± 168.9 ng/ml) increased values of L-selectin were seen both in GD (1288.2 ± 273.5 ng/ml) and TNG (1247.0 ± 273.5 ng/ml) patients with hyperthyroidism before I-131 treatment dose administration as well as after 6 weeks (GD — 1142.4 ± 193.4 ng/ml; TNG — 1113.5 ± 236.3 ng/ml). A slight, but not statistically important, increase in values was observed (Fig. 2).

ICAM-1 serum concentrations were markedly elevated in all patients with hyperthyroidism compared to control (C — 190.2 ± 34.7 ng/ml; GD — 263.6 ± 24.6 ng/ml,  $p < 0.05$ ; TNG — 251.4 ± 36.1 ng/ml,  $p < 0.05$ ). Values of ICAM-1 concentrations increased in 6<sup>th</sup> week after I-131 administration in GD patients (301.1 ± 33.2 ng/ml,  $p < 0.05$ ) and stayed almost at the same level/with a very small drop in toxic nodular goitre patients (249.7 ± 42.6 ng/ml, N.S.) (Fig. 3).

Particular differences in the behaviour of levels of interleukin-6 concentration were seen during radioiodine therapy. In compari-



**Figure 3.** Mean values of ICAM-1 serum concentrations before and in 6<sup>th</sup> week after radioiodine administration in patients with GD and TNG treated for hyperthyroidism.



**Figure 4.** Mean values of IL-6 serum concentrations before and in 6<sup>th</sup> week after radioiodine administration in patients with GD and TNG treated for hyperthyroidism.

son to control (C — 2.07 ± 0.2 ng/ml) there was no difference in initial IL-6 levels either in GD or in TNG groups, but a statistically important decrease was observed in the 6<sup>th</sup> week after I-131 administration in GD patients (1.79 ± 0.16 ng/ml) (Fig. 4).

## Discussion

The changes of adhesion molecule concentrations were found in the course of radioisotope therapy of both GD and TNG. Although some authors showed statistical changes in E- and L-selectin concentration during hyperthyroidism, our results showed only a slight increase with no statistical importance. The changes of ICAM-1 concentrations were different in the groups of patients examined. The enhanced ICAM-1 concentrations both before and in the 6<sup>th</sup> week of therapy were observed in patients with TNG in comparison to controls. However, the slight increase in concentrations was of no statistical significance. In patients with Graves' type of hyperthyroidism the ICAM-1 concentrations tended to increase after therapeutic capsule administration and a statistically significant increase was observed. Many authors describe the increased levels of ICAM soluble form in the serum of patients with thyroid diseases [3, 5, 7, 8]. Zheng et al. showed ICAM-1 expression on the thyrocytes in Graves' disease [9], whereas Bagnasco et al. discovered it only in Hashimoto disease [7]. De Bellis et al. observed an increase of sICAM-1 and of E-selectin concentrations in patients with Graves' disease and found no increase in patients with TNG [8]. Our results have also shown that changes of adhesion molecule behaviour both before and during radioiodine therapy take place mainly in GD.

Serum interleukin-6 concentration changes have been reported in patients with different thyroid gland disorders. Siddigi et al. demonstrated that compared with control untreated patients with GD and TNG had elevated IL-6, but these levels fell after carbimazole treatment [10]. In patients treated for hyperthyroidism caused by toxic adenoma, Bartalena et al. showed a dramatic increase 10 minutes after percutaneous intranodular ethanol injection and 24 hours after radioactive iodine administration suggesting that this cytokine may be a marker of thyroid-destructive processes

[11]. Nygaard et al. showed no change at day 0, 4, 7, 21 and after 3 months during follow-up GD and TNG after I-131 treatment, whereas Jones et al. demonstrated transient increase on day 17 with a return to normal, pre-treatment level on day 59 [4, 6]. In our study we observed no statistical changes in IL-6 levels during TNG treatment but a decrease on day 42 in GD patients compared to slightly increased initial values. It is in contrast with the increase of the concentration of ICAM-1. The proper explanation may be then that the elevation of IL-6 before I-131 is connected with the metabolic action of an excessive amount of thyroid hormones and/or reflects the morphological rather than functional destruction of thyroid cells. In our study we observed a statistically significant decrease in values of IL-6 in the 6<sup>th</sup> week after I-131 administration, which can mean that the peak increase after RAI had taken place earlier. The diminishing then might reflect the extinction of the inflammatory processes in the thyroid after the destructive influence of beta radiation of I-131. This decrease is bigger in GD than in TNG, because in Graves' disease the whole gland, not only the autonomously functioning part, is being destroyed.

## Conclusions

Summing up, both E- and L-selectin levels were elevated in all patients with hyperthyroidism, but their values did not differ among the patients with GD and TNG and did not change during radioiodine therapy, which suggests that the increase of these selectins is the effect of humoral reactions in hyperthyroidism rather than processes occurring strictly in the thyroid gland.

E- and L-selectin seem then not to be useful in the monitoring of the thyroid inflammatory changes during the early period of I-131 therapy.

With changes of ICAM-1 levels during early period of radioiodine therapy occurring only in GD patients, we came to the conclusion that these cytokines may be an important factor in the estimation of the immune inflammatory processes in the thyroid gland during radioiodine therapy. IL-6 changes seem to reflect the morphological rather than the functional death of thyroid cells after radiation.

To estimate the usefulness of the determination of ICAM-1 and IL-6 in clinical practice a comparison with the clinical outcome of hyperthyroidism would be essential. That is why we plan to continue the study over a longer period after I-131 treatment dose administration.

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