# PROTEIN AND LIPID CONCENTRATIONS IN PATIENTS WITH DIFFERENTIATED THYROID CANCER TREATED WITH RADIOACTIVE IODINE-131

Olgica Mihaljevic[1], Snezana Radivojevic[2], Svetlana Djukic[1,2], Ljiljana Mijatovic Teodorovic[1,2], Irena Kostic[1], Ilija Jeftic[1], and Snezana Zivancevic Simonovic[1]
[1]Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia
[2]Clinical Centre Kragujevac, Kragujevac, Serbia

# KONCENTRACIJA PROTEINA I LIPIDA KOD PACIJENATA SA DIFERENTOVANIM KARCINOMOM ŠTITASTE ŽLEZDE KOJI SU LEČENI RADIOAKTIVNIM JODOM-131

Olgica Mihaljević[1], Snežana Radivojević[2], Svetlana Đukić[1,2], Ljiljana Mijatović Teodorović[1,2], Irena Kostić[1], Ilija Jeftić[1], and Snežana Živančević Simonović[1]
[1]Fakultet medicinskih nauka, Univerzitet u Kragujevcu, Kragujevac, Srbija
[2]Klinički centar Kragujevac, Kragujevac, Srbija

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## ABSTRACT

*Short-term, overt hypothyroidism in patients with differentiated thyroid cancer (DTC) before radioiodine (131-I) therapy might be accompanied by a number of metabolic changes, including altered protein and lipid metabolism. Protein concentrations and their relationship to lipids in the serum of DTC patients have not been fully elucidated. The aim of our study was to evaluate the protein and lipid concentrations in 24 DTC patients before and 3 and 7 days after 131-I therapy compared with those of 20 healthy control subjects. After radioiodine therapy, the mean protein concentration (78.71 ± 6.71 g/L vs. 87.16 ± 6.04 g/L; p = 0.003) and cholesterol level (8.12 ± 2.13 mmol/L vs. 8.84 ± 2.09 mmol/L; p = 0.001) were lower 3 days after therapy; this persisted up to 7 days after therapy, whereas triglyceride concentrations were higher 3 days after therapy (2.44 ± 1.07 mmol/L vs. 2.26 ± 1.08 mmol/L; p = 0.041) and returned towards the pretreatment values at 7 days after 131-I therapy. There was an indirect correlation between the protein and triglyceride concentrations 3 days after 131-I therapy in patients over 50 years old (Spearman's r = - 0.583, p = 0.048) but not in patients under 50 years old (Pearson's r = - 0.277, p = 0.384). Radioiodine therapy of DTC patients led to decreased serum protein and cholesterol concentrations, accompanied by increased triglyceride levels; these changes were especially evident in older subjects with metastases.*

**Keywords:** *cholesterol; differentiated thyroid cancer; proteins; radioiodine therapy; triglycerides*

## SAŽETAK

*Prolazna, manifestna hipotireoza koja se javlja kod pacijenata sa diferentovanim karcinomom štitaste žlezde (DTC) pre terapije radioaktivnim jodom (131-I) može biti udružena sa brojnim metaboličkim promenama, uključujući i promene u metabolizmu proteina i lipida. Koncentracija proteina i njihov odnos sa lipidima u serumu pacijenata sa DTC nakon terapije 131-I nedovoljno su ispitani. Cilj našeg istraživanja bio je da se ispita serumska koncentracija proteina i lipida kod pacijenata sa DTC pre, kao i tri i sedam dana posle terapije 131-I. Studijom je obuhvaćeno 24 DTC pacijenata i 20 zdravih ispitanika. Pokazano je značajno, progresivno smanjenje koncentracije proteina (78.71±6.71 g/L vs. 87.16±6.04 g/L; p=0.003) i holesterola (8.12±2.13 mmol/L vs. 8.84±2.09 mmol/L; p=0.001) tri dana nakon terapije 131-I, uz statistički značajno povećanje koncentracije triglicerida tri dana nakon terapije (2.44±1.07 mmol/L vs. 2.26±1.08 mmol/L; p=0.041) i povratkom na preterapijske vrednosti 7 dana posle terapije. Pri tom, indirektna korelacija između koncentracije proteina i triglicerida tri dana posle 131-I pokazana je u grupi pacijenata starijih od 50 godina (Spearman r=- 0.583, p=0.048), što nije bio slučaj sa ispitanicima mlađim od 50 godina (Pearson r=- 0.277, p=0.384). U zaključku, terapija radioaktivnim jodom prouzrokuje smanjenje koncentracije serumskih proteina i holesterola, koje je udruženo sa povećanjem koncentracije triglicerida i posebno je izraženo kod starijih pacijenata sa metastazama.*

**Ključne reči:** *holesterol; diferentovani karcinom štitaste žlezde; proteini; radiojodna terapija; trigliceridi*

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**Correspondence to:** Olgica Mihaljevic, Faculty of Medical Sciences, University of Kragujevac
zara Markovica 69, 34000 Kragujevac, Serbia; Tel. +381 34 306 800; Fax. +381 34 306 800 ext. 112; E-mail. vrndic07@yahoo.com

## INTRODUCTION

Differentiated thyroid carcinomas (DTCs), or well-DTCs, are the most common tumours of the endocrine system (1). They represent approximately 85% of all thyroid carcinomas and include papillary and follicular types (2). As DTCs originate from thyroid follicular cells, which have the ability to concentrate iodine, the treatment of DTC patients with radioactive iodine (131-I) following thyroidectomy is the standard procedure for ablating remnant thyroid tissue and for treating iodine-avid metastases (3). The preparation of DTC patients for 131-I therapy involves two possibilities: thyroid hormone withdrawal (4-6 weeks) to increase the endogenous TSH level to above 30 IU/L or stimulation with exogenous, recombinant TSH (4). In the case of stimulating endogenous TSH secretion, short-term, overt hypothyroidism occurs and is manifested by abnormal thyroid tests (low free thyroxine (fT4) level, elevated thyroid stimulating hormone (TSH) level) and more or less pronounced symptoms and signs of hypothyroidism (impaired mental activity, including problems with concentration and memory, depression, chronic fatigue, muscle weakness, weight gain despite a diminished appetite, dry skin, sensitivity to cold, constipation, menstrual irregularities). Because thyroid hormones influence the rates of lipid synthesis, oxidation and mobilisation, as well as the synthesis and breakdown of proteins, overt hypothyroidism in DTC patients might be accompanied by a number of metabolic changes (5).

Iodine-131 administration and incorporation causes protracted and continuous internal whole body irradiation (gamma radiation of 0.38 MeV photons, beta radiation of 0.19 MeV electrons, half-life of 8.04 days). Part of the applied iodine specifically binds to and is retained in the residual thyroid tissue, whereas some persists in other parts of the body for days after 131-I therapy and might cause radiation damage. Therefore, the administration of large 131-I quantities provides ideal conditions for assessing the *in vivo* effects of prolonged irradiation by radionuclide incorporation and systemic exposure to radiation.

Some metabolic effects of short-term hypothyroidism, with a special focus on lipid metabolism, have been described in a number of earlier studies (6, 7, 8, 9), but the changes in protein and lipid concentrations in DTC patients treated with 131-I have not been fully elucidated. Hence, the aim of this study was to determine whether 131-I therapy leads to changes in serum proteins, as well as to analyse the relationship between the level of serum proteins and lipids during the first 7 days after the administration of radioactive 131-I.

## MATERIALS AND METHODS

### *Study population*

The study was approved by the Ethical Committee of the Clinical Centre Kragujevac. All patients and control subjects provided written informed consent according to the Declaration of Helsinki.

The study population included 24 well-DTC patients: 17 (70.8 % ) females and 7 (29.2 %) males with a mean age of 54.83 ± 15.17 years. Half of the patients were under the age of 50 (≤50 years), whereas the others were older (>50 years). Of the 24 DTC patients, 18 (75 %) had papillary carcinoma, 5 (20.83 %) had the follicular variant of papillary carcinoma, and one (4.17 %) had follicular carcinoma. Thirteen patients had no clinical evidence of metastasis, whereas 11 patients had metastases in the lymph nodes (9 patients) or in the lymph nodes and lungs (2 patients). None of the patients had been exposed to potentially confounding factors such as other ionising radiation (radiographic examination or scintigraphy) within 3 months before therapy. Patients with previously diagnosed or treated primary lipid metabolism disorders and those with type 2 diabetes mellitus, nephrotic syndrome, renal failure, chronic liver disease or obesity were not included in the study. The patients were released from the hospital 3 days after 131-I therapy or later when the residual activity had reached a value below 2 mR/h, measured at the distance of 1 m, which is equivalent to 20 μSv/h, or 400 MBq, in the patient's body.

The period from surgery (total thyroidectomy) to the administration of 131-I was 4-6 weeks. During that interval, the patients did not receive thyroid hormone therapy and thus developed overt hypothyroidism: decreased free thyroxine and elevated TSH (>30 mIU/L) concentrations and more or less pronounced symptoms and signs of hypothyroidism. Ten days after receiving a low-iodine diet, the patients were treated at the Nuclear Medicine Department of the Clinical Centre Kragujevac according to EANM guidelines (10), with fixed nominal activities of 3.7 GBq (100 mCi) (15 patients) or 5.5 GBq (150 mCi) (9 patients) of sodium [131-I] iodide, administered orally.

The control group comprised 20 healthy subjects: 15 (75 %) females and 5 (25 %) males with a mean age of 46.76 ± 12.89 years. They were colleagues and relatives who were willing to participate and who had not been exposed to sources of ionising radiation for a minimum of 3 months before the study. Control subjects with previously diagnosed or treated primary lipid metabolism disorders and those with type 2 diabetes mellitus, nephrotic syndrome, renal failure, chronic liver disease or obesity were not included in the study. All control subjects were evaluated for thyroid function and thyroid antibodies. Their mean TSH concentration was 1.46 ± 0.72 mIU/L (range 0.4 – 3.5 mIU/L), and they tested negatively for thyroid antibodies.

Blood samples from control subjects were taken only once, whereas samples from DTC patients were collected before 131-I therapy, as well as 3 days and 7 days after 131-I therapy. Blood (5 mL) was taken by venepuncture, and the serum was separated out by centrifugation at 2000 rpm for 15 minutes. The sera were stored frozen at -20°C and were then thawed and assayed together.

| Patient no. | Age (y) | Sex (F/M) | Stage (TNM) | Histology (P/F) | fT4 (pg/ml) | TSH (mIU/l) | Dose (GBq) |
|---|---|---|---|---|---|---|---|
| 1 | 44 | M | pT2N0M0 | P | 1.4 | 282 | 3.7 |
| 2 | 77 | F | pT2N0M0 | P | 2.7 | 130 | 3.7 |
| 3 | 65 | F | pT1N0M0 | P | 1.8 | 31 | 3.7 |
| 4 | 43 | F | pT1N0M0 | P | 0.3 | 57.7 | 3.7 |
| 5 | 49 | M | pT2N0M0 | P | 0.4 | 168 | 3.7 |
| 6 | 72 | F | pT2N0M0 | P | 1.4 | 155 | 3.7 |
| 7 | 46 | F | pT1N1M0 | P/F | 0.8 | 65.7 | 3.7 |
| 8 | 45 | F | pT1N0M0 | P | 0.6 | 359 | 3.7 |
| 9 | 64 | F | pT1N0M0 | P/F | 1.0 | 262 | 3.7 |
| 10 | 21 | F | pT1N0M0 | P/F | 1.5 | 36.8 | 3.7 |
| 11 | 39 | F | pT1N0M0 | P/F | 1.9 | 145.1 | 3.7 |
| 12 | 59 | F | pT1N0M0 | P | 2.6 | 151 | 3.7 |
| 13 | 78 | F | pT1N0M0 | P | 2.2 | 68.6 | 3.7 |
| 14 | 48 | F | pT1N0M0 | P | 1.9 | 148 | 3.7 |
| 15 | 64 | M | pT3N1M1 | F | 1.5 | 175 | 5.5 |
| 16 | 78 | F | pT3N1M0 | P | 2.2 | 39.9 | 5.5 |
| 17 | 70 | F | pT2N0M0 | P | 0.9 | 37.2 | 5.5 |
| 18 | 39 | F | pT1N1M0 | P/F | 0.8 | 62 | 5.5 |
| 19 | 41 | M | pT1N1M0 | P | 4.7 | 71 | 5.5 |
| 20 | 67 | M | pT1N0M0 | P | 3.9 | 32.9 | 5.5 |
| 21 | 44 | F | pT1N1M0 | P | 0.5 | 170 | 5.5 |
| 22 | 65 | F | pT2N1M0 | P | 0.9 | 125.6 | 5.5 |
| 23 | 57 | M | pT3N1M1 | P | 2.9 | 306 | 5.5 |
| 24 | 41 | M | pT1N1M0 | P | 0.5 | 364 | 5.5 |

**Table 1.** Clinical and pathological characteristics of the DTC patients treated with 131-I.

***Measurement of free thyroxine (fT4) and thyroid stimulating hormone (TSH)***

The free thyroxine (fT4) concentration was measured by radioimmunoassay (RIA, OCFD03-FT4, *Cis-Biointernational*, France), with a reference range of 7-18 pg/mL. The thyroid stimulating hormone (TSH) concentration was determined immunoradiometrically (IRMA TSH, INEP, Zemun, Serbia), with a reference range of 0.3-5.5 mIU/L. All measurements were made on a Wallac Wizard 1470 Automatic gamma counter (PerkinElmer Life Sciences, Wallac Oy, 2005, Finland).

***Determination of biochemical parameters***

Serum concentrations of total proteins, albumin, cholesterol and triglycerides were measured using commercially available enzymatic reagents (Makler d.o.o, Belgrade, Serbia) adapted to an autoanalyser (Olympus AU 400). The normal ranges are as follows: proteins: 64 - 83 g/L; albumin: 35 - 52 g/L; cholesterol: 3.10 – 5.20 mmol/L; and triglycerides: 0.10 – 1.70 mmol/L.

***Statistical analysis***

All values are expressed as the mean ± standard deviation (SD). The commercial software SPSS version 10.0 for Windows was used for the statistical analysis. The significance of the differences in the determined parameters between control subjects and DTC patients before therapy was analysed by the independent samples t-test or U-test (depending on the distribution), whereas differences within the group of DTC patients were evaluated by applying the paired samples t-test or Wilcoxon test in cases of non-normal distribution. Probability values less than 0.05 were considered to be statistically significant, and those less than 0.01 were considered to be highly significant.

## RESULTS

The study population comprised 24 DTC patients and 20 control subjects. The clinical and pathological characteristics of the DTC patients treated with 3.7 or 5.5 GBq of 131-I are given in Table 1. The TSH concentration ranged from 31 to 364 mIU/L, with a mean value of 132.9 ± 99.15 mIU/L, whereas the serum fT4 concentration ranged from 0.30 to 4.70 pg/mL, with a mean value of 1.55 ± 1.1 pg/mL.

The circulating protein and lipid concentrations of DTC patients and healthy controls are shown in Table 2.

**Table 2:** Concentrations of proteins and lipids in healthy controls and DTC patients before (0 day), three days (3 day) and seven days (7 day) after 131-I therapy

| parameter | healthy controls | DTC patients | | |
|---|---|---|---|---|
| | | 0 day | 3 day | 7 day |
| proteins (g/l) | 81.68 ± 4.71 | 87.16 ± 6.04* | 78.71 ± 6.71 ** | 82.54 ± 4.54*** |
| albumins (g/l) | 55.36 ± 5.25 | 57.42 ± 5.23 | 52.54 ± 5.23 ** | 53.83 ± 3.63 *** |
| globulins (g/l) | 26.32 ± 5.16 | 29.71 ± 5.48 | 26.16 ± 6.37 ** | 28.79 ± 4.23 |
| cholesterol (mmol/l) | 6.11 ± 1.56 | 8.84 ± 2.09* | 8.12 ± 2.13 ** | 8.41 ± 2.13*** |
| triglycerides (mmol/l) | 1.30 ± 0.62 | 2.26 ± 1.08* | 2.44 ± 1.07** | 2.14 ± 1.11 |

*Significant difference between DTC patients before therapy and control group
** Significant difference between DTC patients 3 days after therapy and before therapy
*** Significant difference between DTC patients 7 days after therapy and before therapy

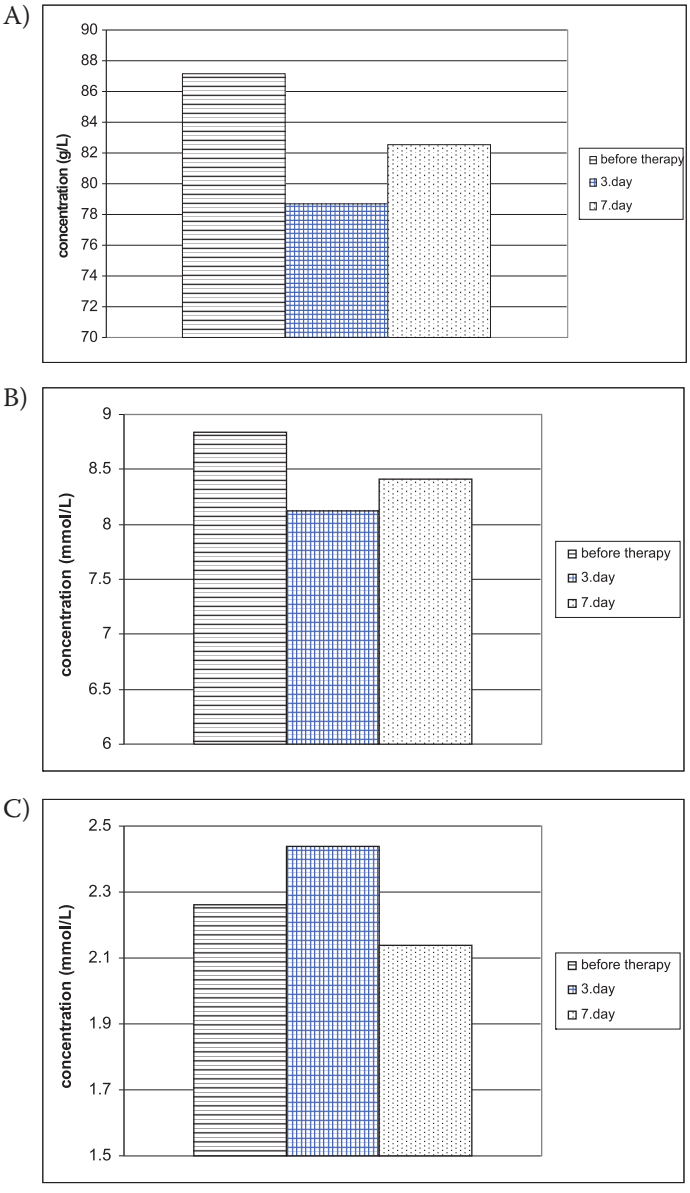


**Figure 1.** Changes in the concentrations of proteins (A), cholesterol (B) and triglycerides (C) in DTC patients after 131-I therapy.
* Significant difference between DTC patients 3 days after therapy and before therapy.
** Significant difference between DTC patients 7 days after therapy and before therapy.

There were statistically significant differences in the mean total protein concentrations (87.16 ± 6.04 g/L vs. 81.68 ± 4.71 g/L; independent samples t-test, t(42) = 3.453, p = 0.001), cholesterol concentrations (8.84 ± 2.09 mmol/L vs. 6.11 ± 1.56 mmol/L; independent samples t-test, t(42) = 4.642, p<0.001) and triglyceride concentrations (2.26 ± 1.08 mmol/L vs. 1.30 ± 0.62 mmol/L; U test, U = 108.0, z = -3.112; p = 0.002) between the DTC patients before therapy and the control subjects.

After 131-I therapy, the mean total protein concentration decreased from 87.16 ± 6.04 g/L to 78.71 ± 6.71 g/L (paired samples t-test, t(23) = 6.991; p = 0.003) at 3 days; this persisted up to 7 days after therapy (82.54 ± 4.54 g/L vs. 87.16 ± 6.04 g/L; paired samples t-test, t(23) = 4.610; p = 0.002). Similar decreases in the cholesterol concentrations were noted in DTC patients 3 days after therapy (8.12 ± 2.13 mmol/L vs. 8.84 ± 2.09 mmol/L; paired samples t-test; t(23) = 3.865; p = 0.001), followed by a gradual return towards the initial values before therapy. However, the difference between the concentrations 7 days after therapy and those before therapy (8.41 ± 2.13 mmol/L vs. 8.84 ± 2.09 mmol/L; paired samples t-test, t(23) = 2.285; p = 0.032) remained statistically significant. At the same time, the triglyceride concentrations rose after therapy from the initial value of 2.26 ± 1.08 mmol/L to 2.44 ± 1.07 mmol/L at 3 days (Wilcoxon test, z = -2.043, p = 0.041), followed by a return to the pretreatment levels 7 days after 131-I therapy (2.14 ± 1.11 mmol/L vs. 2.26 ± 1.08 mmol/L; Wilcoxon test, z = -1.214, p = 0.225). The serum concentrations of proteins (A), cholesterol (B) and triglycerides (C) in DTC patients before and after 131-I therapy are shown in Figure 1.

Because aging is accompanied by a decline in metabolism, we divided our DTC patients into two groups: the first group comprised patients under the age of 50, and the second comprised patients over the age of 50. There were no significant differences in total protein (87.58 ± 5.36 g/L vs. 86.75 ± 6.86 g/L; independent t-test, t(22) = 0.331, p = 0.744), cholesterol (8.97 ± 0.65 mmol/L vs. 8.72 ± 1.99 mmol/L; independent t-test, t(22) = 0.291, p = 0.774) and triglyceride (2.41 ± 1.29 mmol/L vs. 2.12 ± 0.85 mmol/L; U test, U = 64.0, z = -0.462; p = 0.671) concentrations between the two groups of DTC patients before therapy or

in the reduction rates of these parameters 3 and 7 days after treatment. An indirect correlation between the concentrations of total proteins and triglycerides was noted in patients over the age of 50 at 3 days after 131-I therapy (bivariate correlation test, Spearman's r = -0.583, p = 0.048) (Figure 2), which was not the case in patients under the age of 50 (Pearson's r = - 0.277, p = 0.384). In addition, there was a statistically significant correlation between the rate of cholesterol decline at both 3 and 7 days after therapy and TSH s in older patients (Bivariate correlation test, Pearson's r1 = 0.805, p1 = 0.002; r1 = 0.750, p1 = 0.005). No correlation was observed between the total decrease in protein and TSH in either group of DTC patients.

Because the trapping of 131-I by metastatic tissue is expected, the patients were divided into groups without (13 patients) and with (11 patients) metastases. Statistical analysis indicated no significant differences in the protein concentrations between patients without and with metastases before 131-I therapy (86.12 ± 6.09 g/L vs. 89.25 ± 5.72 g/L, p = 0.240), 3 days after 131-I therapy (78.00 ± 7.62 g/L vs. 80.12 ± 4.45 g/L, p = 0.477) and 7 days after 131-I therapy (83.43 ± 4.84 g/L vs. 80.75 ± 3.45 g/L, p = 0.177) (Table 3). Additionally, no significant differences were found in the triglyceride concentrations between the two groups before 131-I therapy (2.26 ± 1.23 mmol/L vs. 2.25 ± 0.96 mmol/L, p = 0.969), 3 days after 131-I therapy (2.60 ± 1.19 mmol/L vs. 2.13 ± 0.76 mmol/L, p = 0.327) and 7 days after 131-I therapy (2.46 ± 1.15 mmol/L vs. 2.30 ± 1.09 mmol/, p = 0.751). However, looking at the reduction in protein concentrations after 131-I therapy (before – after therapy), a highly significant difference was observed between DTC patients without (2.68 ± 3.32 g/L) and with (8.5 ± 5.47 g/L) metastases (independent samples t-test, t(22) = -3.249, p = 0.004) 7 days after therapy. This indicates a prolonged effect of 131-I in patients with metastases.

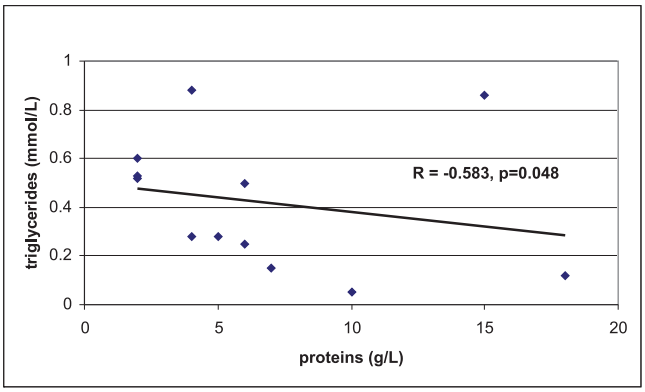


**Figure 2.** Correlation between the concentrations of proteins and triglycerides 3 days after 131-I therapy in patients over the age of 50.

## DISCUSSION

In this study, we analysed the effects of short-term, overt hypothyroidism on the protein and lipid concentrations in DTC patients before and within a week after 131-I therapy. We observed the well-known effect of decreased thyroid function on cholesterol metabolism, but our main finding was the combined decline in serum protein and cholesterol concentrations 3 days after 131-I therapy, which was accompanied by increased serum triglyceride levels. There was an indirect correlation between the concentrations of proteins and triglycerides in patients over the age of 50.

Iodine-131 is used for the ablation of remnant thyroid tissue or for the treatment of iodine-avid metastasis (11). For the optimal accumulation of 131-I in differentiated thyroid tissue, an elevated TSH concentration is required (12). In clinical practice, high TSH levels can be achieved by exogenous TSH administration or by endogenous TSH stimulation (13). To increase the accumulation of 131-I, short-term hypothyroidism was induced in our DTC patients. At the time of 131-I administration, all patients had very high TSH concentrations with significantly elevated levels of cholesterol and triglycerides compared with the control group of healthy subjects. Our results are in agreement with those of previously published studies, in which the associations between the thyroid status and serum lipid concentrations were analysed (14, 15, 16). They are also consistent with the findings of Regalbuto and co-workers (17), who reported an increase in cholesterol levels in DTC patients before therapy. This is not surprising if one takes into account that thyroid hormones affect the synthesis, mobilisation and degradation of lipids (18). It is assumed that the primary mechanism for hypercholesterolemia is the accumulation of LDL cholesterol due to a reduction in the number of its cell surface receptors (19), whereas decreased lipoprotein lipase activity might be responsible for the elevated triglyceride levels (20).

Interestingly, three days after 131-I administration, decreased total serum protein and albumin concentrations and decreased serum cholesterol concentrations were simultaneously recorded in our DTC patients. We assume that this decrease in protein concentrations could be explained by either oxidative stress or decreased liver function. It has been shown that protein oxidation (21) and oxidative damage (22) might be responsible for decreased protein levels in cancer patients. In our DTC patients, the levels of MDA were increased 3 days after 131-I therapy (data not shown). Because liver tests were not performed, we cannot exclude the possibility that radiation damage to the liver led to the decreased serum protein concentrations. Namely, diffuse hepatic uptake of 131-I was shown on post-therapeutic scans in DTC patients (23), and it is well known that the liver synthesises most plasma proteins. The highly significant difference in the reduction of protein concentrations between DTC patients with and without metastases 7 days after the therapy might indicate a prolonged effect of 131-I in patients with metastases.

Unlike cholesterol, triglyceride levels were significantly increased after 131-I therapy, likely as an attempt to compensate for the decline in protein concentrations to preserve the colloidal osmotic pressure. A direct relationship

between hypoalbuminemia and hyperlipidaemia has been reported, but in these studies, more profound decreases in albumin concentration were caused by nephritic syndrome (24, 25, 26), peritoneal dialysis (27) or hepatic dysfunction (28). Because the decline in protein concentration found in our 131-I-treated DTC patients was not as great as in the other specified conditions, the changes in lipid concentrations were also less pronounced.

It is well known that the aging process causes a number of functional and metabolic changes, which are reflected by increased concentrations of serum lipids (29). Slightly impaired thyroid gland function might contribute to the changes in lipid metabolism (30, 31). Therefore, we divided our patients into two groups according to age: one group of patients under the age of 50 and the other over the age of 50. However, there were no significant differences in the serum levels of proteins, cholesterol or triglycerides between these two groups of DTC patients before 131-I therapy. Moreover, hypothyroidism produced similar increases of cholesterol and triglycerides in both groups. Nevertheless, in patients over the age of 50, we found an indirect correlation between the rate of total protein decline and the increase of triglycerides 3 days after therapy.

Despite the limitations of this study (small sample size, the possible existence of clinical conditions not diagnosed or previously treated that might affect lipid metabolism), it is the first study to demonstrate decreased protein and cholesterol concentrations accompanied by increased serum triglyceride levels in DTC patients after radioactive 131-I therapy.

In conclusion, radioiodine therapy in DTC patients leads to decreased serum protein and cholesterol concentrations and increased triglyceride concentrations, which are especially evident in older subjects with metastases.

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