REDOX PARAMETERS IN BLOOD OF THYROID CANCER PATIENTS AFTER THE RADIOIODINE ABLATION

by

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The radioactive iodine (^{131}I) ablation is a well-accepted treatment modality for differentiated thyroid cancer patients. Unfortunately, the radiation induces the oxidative stress and damages cells and tissues, simultaneously activating the mechanisms of antioxidative defense. Since the mechanisms of those processes are not completely known, we wanted to examine the changes in the most important reactive oxygen species and antioxidative components, as well as their correlation and significance for lipid peroxidation. Our results showed that the level of thiobarbituric acid reactive substances was increased during the first 30 days after the radiotherapy. Among antioxidant components, superoxide dismutase was increased in the 3rd and 30th day; catalase in 7th and reduced glutathione in 3rd and 7th day after the radiotherapy. As regards the prooxidants, the reduction of hydrogen peroxide (H_2O_2) was recorded in 7th and 30th day, and superoxide anion radical (O_2) was unchanged after the exposure to ^{131}I. These results indicate that differentiated thyroid cancer patients are under constant oxidative stress despite the observed increase in antioxidative and reduction in prooxidative parameters. The understanding of these early processes is important since their progress determines the latter effects of ^{131}I therapy.

Key words: oxidative stress, antioxidant enzyme, lipid peroxidation, radiotherapy, thyroid cancer

INTRODUCTION

The cancer of the thyroid gland is the most common malignant tumor of the endocrine system and represents 1-2 % of all malignancies in the world [1]. Based on the US National Cancer Institute (NCI) 5-year data set for 2009-2013, the number of new cases of thyroid cancer was 13.9 and the number of deaths was 0.5 per 100 000 men and women per year [2]. The surgical resection (thyroidectomy), radioactive iodine ablation, and thyroid stimulating hormone (TSH) suppression therapy are all well accepted treatment modalities for differentiated thyroid cancers. The exposure to radiation (^{131}I is beta and gamma emitter) leads to the formation of the reactive oxygen species (ROS) and damages cells and tissues. Since the exact mechanisms of redox processes induced by the exposure to ^{131}I are not completely known, we wanted to examine the changes in the most important factors (ROS, enzymatic and non-enzymatic antioxida- tive components), and their correlation and significance for the formation of thiobarbituric acid reactive substances (TBARS), as the measure of lipid hydroperoxidation (LPO).

MATERIALS AND METHODS

Subjects

The study population included 45 differentiated thyroid cancer (DTC) patients of both genders (33 fe-

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males and 12 males, of average age 42.5 14.3 years) after the total thyroidectomy. Among them, 39 patients had papillary carcinoma and 6 patients had follicular carcinoma. After 10 days of a low-iodine diet, all patients were treated with a fixed dose of 3.7 GBq (100 mCi) or 5.55 GBq (150 mCi) of sodium-iodide administered orally, according to the EANM guidelines [3]. At the time of ^{131}I administration, all patients were hypothyroid (the concentration of thyroid-stimulating hormone in blood was TSH > 30 mIUL^{-1}). This was achieved by withdrawing the replacement therapy for at least three weeks. The patients were discharged from special premises dedicated to the radionuclide therapy to home treatment when the measured ^{131}I activity in the body was under 400 MBq (usually after 3 days, or later). Blood samples from DTC patients were obtained 4-times: before and 3, 7 and 30 days after the treatment with ^{131}I. The patients who were younger than 18 years, hypersensitive to iodine preparations, had bone marrow depression, with reduced lung function, with salivary gland dysfunction and patients with neurological impairments were excluded from the study. The following antioxidant parameters and parameters of oxidative stress were determined: superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), index of lipid peroxidation (TBARS), the concentration of superoxide anion radical (O_2), hydrogen peroxide (H_2O_2), and nitric oxide (NO).

The study was approved by the Ethical Committee of the Clinical Center Kragujevac. Also, all patients gave written informed consent to participate in the study according to the Helsinki Declaration.

Sample preparation

Plasma and erythrocytes were separated from the whole blood in a procedure known as the 'washing' of erythrocytes. In the first step, the blood was centrifuged (10 min at 3000 rpm) for the extraction of plasma (usual volume 1-2 ml). The rest of the plasma was aspirated in order to keep only erythrocytes. In step two, the saline was added to erythrocytes (ratio 2:1) and vortexed. The mixture was centrifuged three times (10 min at 3000 rpm). After every centrifugation, the supernatant was aspirated. Following the last centrifugation, 1 ml of erythrocytes was taken and mixed with 3 ml of cold distilled water. In the final step, the solution was placed into the cold water jacket for 30 min.

Determination of oxidative stress parameters

Superoxide anion radical concentration

The concentration of O_2 was evaluated with the method of Auclair and Voisin [4]. The method is based on the reduction of nitroblue-tetrazolium (NBT) to monoformazan by O_2 in the alkaline nitrogen saturated medium. The yellow product of this reaction was measured spectrophotometrically at 550 nm. The concentration of O_2 was expressed in nmolml^{-1} plasma.

Hydrogen peroxide concentration

The determination of H_2O_2 concentration in blood plasma was done by the method of Pick and Keisari [5]. In reaction, the horseradish peroxidase converts the hydrogen peroxide into the water and the oxygen. This causes the oxidation of phenol red, thus forming the adduct with the dextrose, and has the maximum absorbance of 610 nm. The concentration of H_2O_2 was expressed in nmol/ml plasma.

Nitric oxide concentration

The nitrite, a stable NO oxidation product, was determined using the Griess reaction [6]. The samples were mixed with an equal volume of Griess reagent (1 % sulfanilamide, 0.1 % naphthylethylenediamine dihydrochloride, and 2 % phosphoric acid) and incubated at room temperature for 10 min. With the $NaNO_2$ to generate a standard curve, nitrite production was measured at 550 nm. The concentration of released nitrites was expressed in nmolml^{-1} extract.

Lipid peroxidation concentration

The TBARS was determined according to the Ohkawa *et al*. [7]. The TBARS measures the malondialdehyde, a product of lipoperoxidation caused mainly by free hydroxyl radicals. Firstly, plasma was deproteinised with the trichloroacetic acid (TCA) and then the precipitate was treated with the thiobarbituric acid (TBA) at 100 °C for 15 min. The TBARS was determined by the absorbance at 535 nm and calculated as nmol ml^{-1} plasma.

Determination of antioxidant parameters

SOD activity

The SOD activity was measured by the epinephrine method of Misra & Fridovich [8]. This method belongs to the „negative" type group of methods, since it monitors a decrease of autooxidation speed in alkaline medium, which is dependent on O_2 . The speed of epinephrine autooxidation to adrenohrom was detected spectrophotometrically as the change of the absorbance at 480 nm. One unit of SOD activity was defined as the amount of extract that inhibits the rate of adrenochrome formation by 50 %. The concentration of SOD was expressed in units of SOD activity per gram of hemoglobin (unit per gram Hb).

CAT activity

The activity of catalase (CAT) was assayed by the method of Beutler [9]. It was based on the measurement of hydrogen peroxide degradation speed in the presence of catalase (CAT) at 230 nm. The CAT activity was expressed in unit of mg^{-1} protein. One unit of CAT activity is defined as 1 μmol of H_2O_2 decomposed per minute under the assay conditions.

GSH level

The reduced glutathione (GSH) was measured at an absorbance of 412 nm according to the method of Beutler [9]. In this method, the reduced GSH present in the sample reacts with the di-thio-nitrobenzoic acid (DTNB) and the intensity of the color was measured at 412 nm, and calculated as nmol ml^{-1} plasma.

Statistical analysis

Due to a non-Gaussian distribution of values, to compare parameters level before and after the ^{131}I therapy, the Friedman's test was used, followed by Nemenyi's multiple pairwise comparisons with Bonferroni correction. The Spearman's rank coefficient was applied to investigate the SOD/$O_2^{\cdot-}$ and CAT/ H_2O_2 correlations. The automatic linear modeling (ALM) was used to estimate the predictive values of all examined redox parameters on LPO level. A 2-tailed $p < 0.05$ was considered statistically significant. All data were analyzed using IBM SPSS Statistics version 23 and GraphPad Prism 4 software.

RESULTS

When compared to the value before the ^{131}I therapy, the SOD activity after the therapy was increased in all three examined time points, but only the increase in days 3 ($p = 0.000$) and 30 ($p = 0.000$) was found to be statistically significant. The activity of CAT was unchanged in days 3 and 7 and increased in day 30 after the therapy with ^{131}I ($p = 0.003$). The level of GSH was found to be significantly increased in days 3 ($p = 0.000$) and 7 ($p = 0.003$), after which it returned to the base level on the day 30.

The level of H_2O_2 was significantly decreased on the 3rd ($p = 0.000$) and 7th ($p = 0.003$) day after the ^{131}I therapy. The post therapy level of $O_2^{\cdot-}$ reached its maximum in day 30, but this increase was significant only when compared with the $O_2^{\cdot-}$ levels on the 3rd ($p = 0.009$) and 7th ($p = 0.007$) day after ^{131}I therapy. The level of $^{\cdot}NO$ was not significantly changed in any of the three tested time points.

After the therapy with ^{131}I, the concentration of TBARS was increased in all three examined time points, but significantly only in day 7th ($p = 0.001$), (fig. 1 and tab. 1).

The correlation analysis showed that SOD activity was positively correlated to $O_2^{\cdot-}$ level at days 3 ($p = 0.01$) and 30 ($p = 0.01$) (fig. 2).

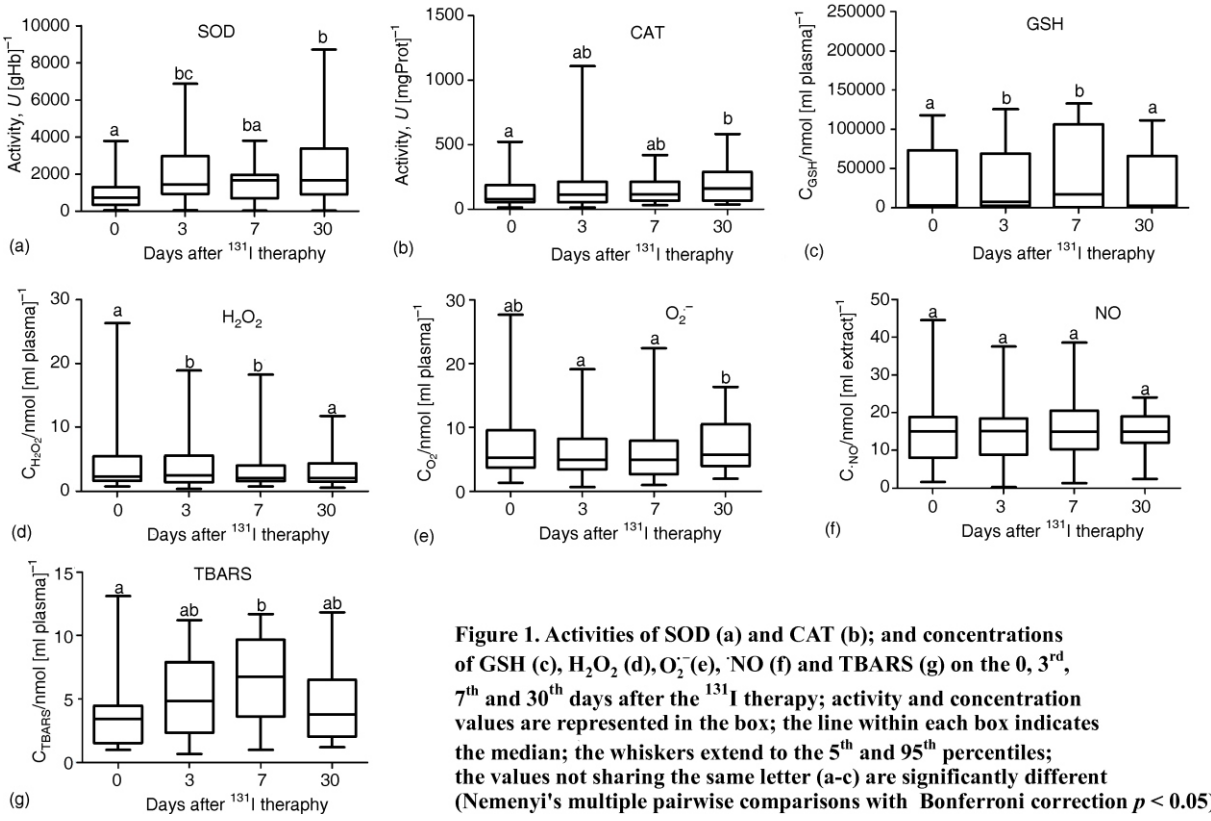

Figure 1. Activities of SOD (a) and CAT (b); and concentrations of GSH (c), H_2O_2 (d), $O_2^{\cdot-}$(e), $^{\cdot}NO$ (f) and TBARS (g) on the 0, 3rd, 7th and 30th days after the ^{131}I therapy; activity and concentration values are represented in the box; the line within each box indicates the median; the whiskers extend to the 5th and 95th percentiles; the values not sharing the same letter (a-c) are significantly different (Nemenyi's multiple pairwise comparisons with Bonferroni correction $p < 0.05$)

Table 1. Exact *p*-values for all pairwise comparisons (Nemenyi's multiple pairwise comparisons test with Bonferroni correction); Freidman's test *p*-values are also reported for all examined parameters

SOD	Freidman's test: $p < 0.0001$			CAT	Freidman's test: $p = 0.006$		
	0 days	3 days	7 days		0 days	3 days	7 days
3 days	0.000	1	0.066	3 days	0.447	1	0.960
7 days	0.330	0.066	1	7 days	0.198	0.960	1
30 days	0.000	1.000	0.060	30 days	0.003	0.198	0.447
GSH	Freidman's test: $p < 0.0001$			H_2O_2	Freidman's test: $p = 0.001$		
	0 days	3 days	7 days		0 days	3 days	7 days
3 days	0.000	1	0.896	3 days	0.000	1	0.896
7 days	0.003	0.896	1	7 days	0.003	0.896	1
30 days	1.000	0.000	0.003	30 days	1.000	0.000	0.003
O_2	Freidman's test: $p = 0.003$			NO	Freidman's test: $p = 0.017$		
	0 days	3 days	7 days		0 days	3 days	7 days
3 days	0.731	1	1.000	3 days	0.995	1	0.098
7 days	0.681	1.000	1	7 days	0.054	0.098	1
30 days	0.141	0.009	0.007	30 days	0.141	0.231	0.976
TBARS	Freidman's test: $p = 0.003$						
	0 days	3 days	7 days				
3 days	0.268	1	0.231				
7 days	0.001	0.231	1				
30 days	0.308	1.000	0.198				

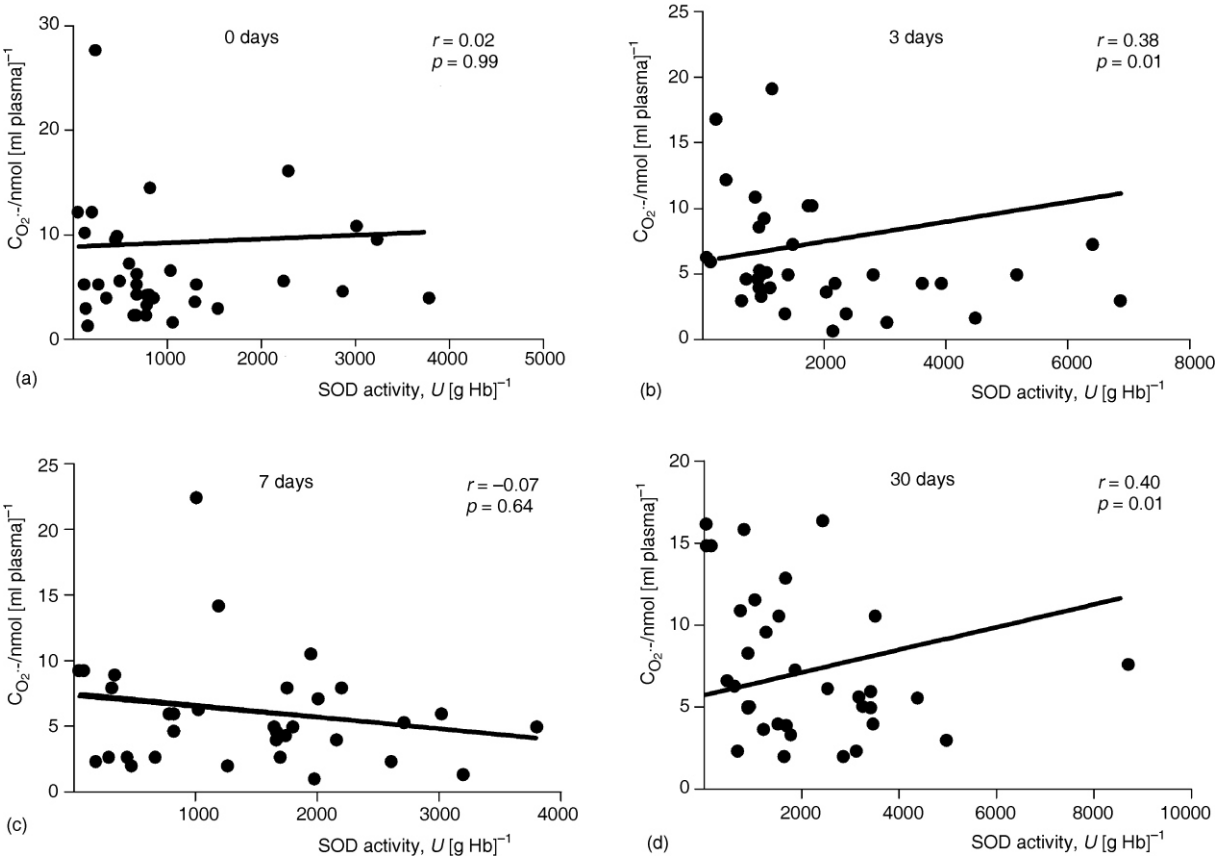

Figure 2. Scatter plot of SOD activity against O_2 level after 0 (a), 3 (b), 7 (c), and 30 (d) days following the ^{131}I therapy

The activity of CAT was positively correlated to H_2O_2 level on the 0 ($p < 0.001$), 3rd ($p < 0.001$) and 7th ($p < 0.001$) day, but n egatively correlated on day 30 ($p < 0.001$) (fig. 3).

The results of multiple linear regression analysis indicated that among all five tested parameters, only SOD activity, H_2O_2 and $O_2^{\cdot -}$ levels had the statistically significant importance on TBARS level (tab. 2).

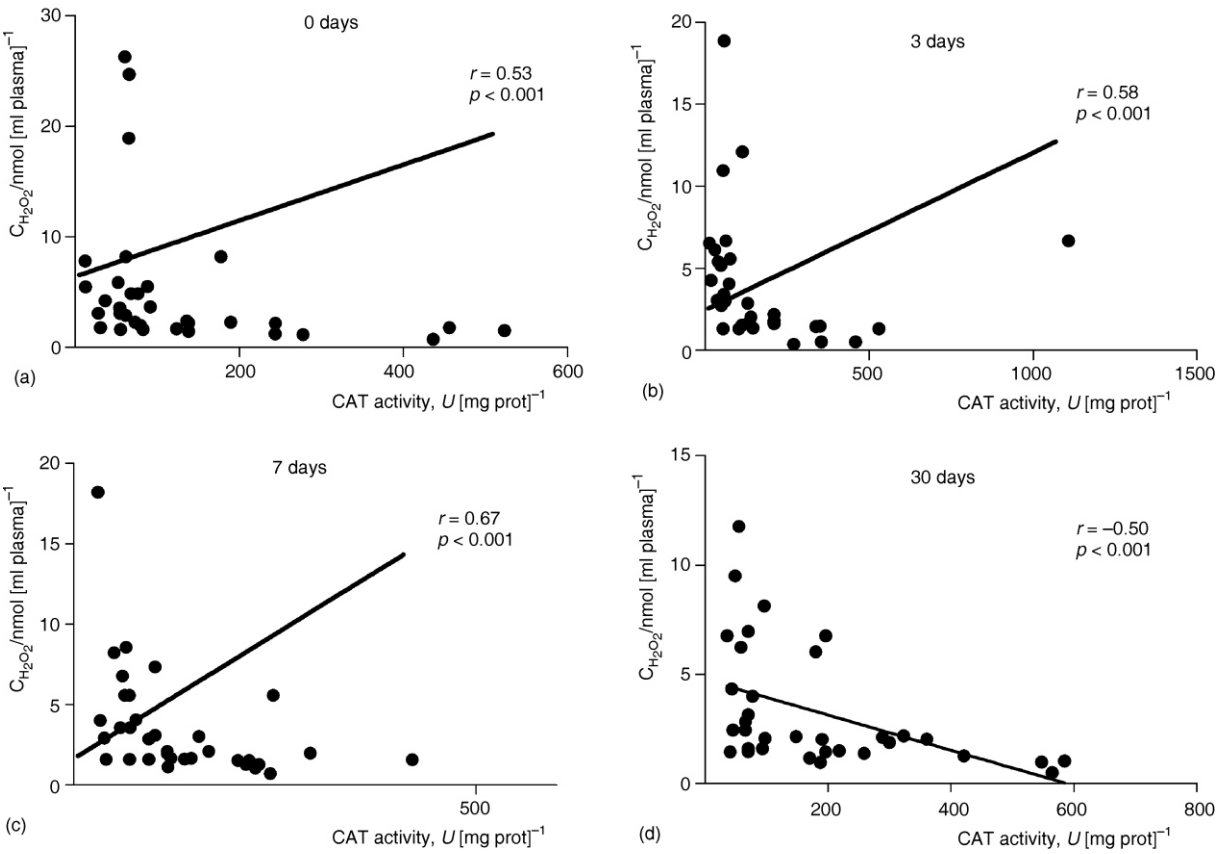

Figure. 3 Scatter plot of CAT activity against H_2O_2 level 0 (a), 3 (b), 7 (c), and 30 (d) days after ^{131}I therapy

Table 2. Multiple linear regression analysis using automatic linear modeling with TBARS as the dependent variable and activities of SOD and CAT; the levels of GSH, O_2 , H_2O_2, and NO as independent variables; only variables with significant predictive values are shown

Predictor	Coefficient	Std. error	*t*	*p*
SOD	0.000	0.000	3.134	0.002
H_2O_2	–0.148	0.055	–2.715	0.007
O_2	0.107	0.052	2.057	0.041

DISCUSSION

Despite the proven efficacy of ^{131}I administration in the treatment of differentiated thyroid cancer, there are several serious side effects associated with its use. They include salivary gland dysfunction, impairment of the lachrymal glands, reproductive disturbances and hematologic abnormalities [10-12]. The oxidative stress induced by the ^{131}I therapy of the thyroid gland is also not restricted to the area of administration but is detectable even in plasma, serum, and urine [13].

The radioactive iodine is considered to be related with the hematologic changes which persist for at least 1 year [14]. The results obtained in the current study indicated that a significant oxidative misbalance was present in the blood of DTC patients in the first 30 days after the ^{131}I therapy.

The early effects of radiation occur during the several hours to a few weeks after the exposure and typically include manifestations like cell death, inflammation, and oxidative stress [15]. The results of our study confirmed the existence of early redox imbalance on 3rd day after the treatment with ^{131}I. At this time point we observed an increase in TBARS (whose level was increased by 52 % although not statistically significant) and induction of AO system perceived as an increase in SOD activity and GSH level. The absence of increase in concentrations of H_2O_2, O_2 and NO indicated that AO defense system is sufficient to maintain the redox balance at the baseline level. Other authors also reported that SOD [16], CAT [17], GSH [18], and GSH synthesis-related proteins [19] are induced by irradiation.

In blood of DTC patients examined in this study, the SOD activity was statistically increased on the 30th day, but also more than doubled on the 3rd day after the ^{131}I treatment. These changes are significant for overall AO protection, since the SOD activity and the level of O_2 were among the three most important parameters for prediction of TBARS as an indicator of oxidative stress. Based on the positive SOD/O_2 correlation in the same time points, it seems that the SOD was, at least partially, inducted by its own substrate. It is most likely that this regulation is performed through the redox-sensitive transcriptional factors such as NF- B, AP-1, and Nrf2 [20].

The SOD activity protects against the free radical injury by converting O_2 to H_2O_2, thus disabling $O_2^{\cdot -}$ to combine with .NO and form peroxynitrite anion (ONOO), which initiates the lipid peroxidation. Our results showed that in the blood of DTC patients NO and O_2 levels were unchanged in all examined time points compared to the basal levels obtained before the therapy, so it seems that this path of formation of ONOO is not responsible for the observed increase of LPO.

The activity of CAT was increased in all three post therapy time points, although the increase was statistically significant only on the 30th day after the exposure. Such CAT activity was apparently sufficient to prevent the peroxide-induced oxidative stress, as the H_2O_2 level during the entire post radiation period was decreased in comparison to the value before the treatment. Our results also showed that on days 0, 3 and 7, the CAT activity was positively correlated with the level of H_2O_2, while on the 30th day this interrelation was negative. It seems that the expressional regulation of CAT activity observed in the first 7 days, shifted to a non-expressional mechanism in the 30th day after the exposure to the ^{131}I. This indicates that not only the mechanisms of AO protection after the ^{131}I therapy vary in patients with hyperthyroidism and cancer [21], but that in the DTC patients these processes change in the course of time.

The GSH level in blood of DTC patients was increased on the 3rd and 7th day after the exposure to ^{131}I, indicating that the non-enzymatic AO protection was also elevated in the first days after the radiotherapy. Similarly, Sadani and Nadkarni showed that in rats, the subablation doses of ^{131}I elevated GSH level for 16 % after 24 hours, but by the day 18th its concentration was declined by 15 % [22]. The GSH has multiple roles in the regulation of cellular homeostasis. In addition to its importance in enzymatic and nonenzymatic antioxidative processes, the GSH is required for cell proliferation and apoptosis, signal transduction, cytokine production and immune response [23]. Also, as the GSH can directly neutralize O_2 and OH, leading to the formation of oxidized glutathione [24], its increased amount in blood of DTC patients can help SOD in maintaining the basal level of O_2 after the exposure to ^{131}I.

Increased amounts of LPO end products can be detected in many diseases, from multiple sclerosis [25] to cancer [26, 27], as damaged cells and tissues may peroxidase more rapidly than the normal ones [28]. In our experiment, the TBARS level in DTC patients was increased in all three time points after the irradiation. The increase was significant on the 7th, and enlarged by 52 % and 33 % on the 3rd and 30th day after the ^{131}I therapy. Similar results were reported by Konukoglu *et al*., who observed that the thyroidectomised patients had higher MDA levels in the erythrocyte membranes 2 days after the treatment with 3.7-5.55 GBq ^{131}I [29]. Gil *et al*. examined the later changes and found that a small initial increase in MDA level 1 month after the radiotherapy was followed by a significant decrease in MDA 6 months afterwards [30]. The excess of LPO in serum may result from the radiation induced apoptotic and mitotic cell death in the remaining thyroid tissue. Contrary to the radicals that attack biomolecules in their immediate surroundings, the lipid peroxidation products can easily diffuse across membranes and covalently modify biomolecules far from their site of origin [31]. Thus it seems that the elevated serum LPO level indicate increased free radicals production in tissues, as has already been observed by Arguelles *et al*. [32]. It should be noted that in DTC patients the extent of oxidative stress was probably wider than it could be concluded from our results, as serum LPO level before the ^{131}I therapy, which we used for comparison, is several times higher in cancer patients than in healthy subjects [33].

CONCLUSIONS

The increased TBARS level observed in this study indicated that the DTC patients are under the constant oxidative stress during the first 30 days after the radiotherapy. Also, the recorded changes of redox components and their dynamic indicated the most possible mechanisms that govern these processes. Understanding of these phenomena is important since there is no latent period for radiation exposure and the early oxidative stress can promote a cascade of downstream events that lead to late effects of ^{131}I therapy.

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AUTHORS' CONTRIBUTIONS

V. D. Spasojević performed the experimental work, analyzed the data, and wrote the manuscript. M. D. Matović participated in study design and editing. O. B. Mihaljević and S. T. Živančević-Simonović provided technical expertise and revision of the manuscript. M. Ž. Jeremić and V. Lj. Jakovljević contributed to data acquisition, and V. N. Todorović to critical revision of the article. I. Lj. Pavlović and S. A. Pejić performed final approval of the version to be published. A. U. Todorović participated in data analysis and in writing the manuscript.

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РЕДОКС ПАРАМЕТРИ У КРВИ ПАЦИЈЕНАТА СА ТИРОИДНИМ КАНЦЕРОМ НАКОН АБЛАЦИЈЕ РАДИОАКТИВНИМ ЈОДОМ

Аблација радиоактивним јодом (^{131}I) је третман избора за пацијенте са диферентованим карциномом штитне жлезде. Међутим, зрачење индукује оксидативни стрес и оштећење здравих ћелија и ткива, истовремено активирајући процесе антиоксидативне одбране. Како механизми тих процеса нису у потпуности познати, желели смо да испитамо промене најважнијих реактивних врста кисеоника и антиоксидативних компонената, као и њихову повезаност са пероксидацијом липида као показатељем оксидативног стреса. Наши резултати су указали на повећање нивоа пероксидације липида током првих 30 дана након радиотерапије Међу антиоксидативним компонентама супероксид дисмутаза је повећана у 3. и 30. дану; каталаза у 7. а глутатион у 3. и 7. дану након излагања ^{131}I. Што се тиче прооксидативних компонената, смањење нивоа водоник пероксида забележено је 3, 7. и 30. дана, а супероксид анјон радикала у 30. дану након радиотерапије. Приказани резултати указују да су пацијенти са диферентованим карциномом штитне жлезде третирани ^{131}I под константним оксидативним стресом упркос уоченом повећању нивоа антиоксиданса и смањењу нивоа прооксидативних компоненти. Разумевање ових раних пострадијационих процеса је важно, јер њихов развој одређује касније ефекте ^{131}I терапије.

Кључне речи: оксидативни стрес, антиоксидативни ензим, липидна пероксидација, радиотерапија, тироидни канцер