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ORIGINAL ARTICLE

Oxidative stress in proliferative parathyroid lesions

Authors' Contribution:
A–Study Design
B–Data Collection
C–Statistical Analysis
D–Data Interpretation
E–Manuscript Preparation
F–Literature Search
G–Funds Collection

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Article history: Received: 06.09.2018 Accepted: 05.11.2018 Published: 07.11.2018

ABSTRACT:

Background: Primary hyperparathyroidism (PHPT) is one of the most common endocrine disorders and defined as excessive secretion of parathormone. PHPT is a risk factor of several cardiovascular diseases, which could be caused by alterations in the oxidant-antioxidant balance.

Materials and methods: Our study material constituted of blood serum collected from 52 consecutive patients with PHPT treated surgically, whereas 36 healthy volunteers were our control group. Oxidative stress was evaluated in both patients and control subjects by assessment of malondialdehyde (MDA) and lipid hydroperoxides (LHP). Antioxidants were evaluated by measurement of superoxide dismutase (SOD), ceruloplasmin (CER), catalase (CAT), sulfhydryl (SH) groups, glutathione (GSH), glutathione peroxidase (GSH-Px), Glutathione-S-transferase (GST) activity (GST) and glutathione reductase (GR). Moreover, total antioxidant capacity (TAC) and total oxidative status (TOS) were measured and oxidative stress index (OSI) was calculated.

Results: OSI was increased in patients with PHPT when compared to normal controls, whereas TAC was lower in PHPT. Levels of CER, MnSOD, GR, SH groups and MDA were significantly decreased in PHPT. Levels of LHP, catalase and SOD in serum were significantly higher in patients with PHPT than in healthy patients. Erythrocyte CAT activity and GST were significantly increased in patients after parathyroidectomy. Erythrocyte GR and GPx were upregulated postoperatively, whereas SOD activity decreased.

Conclusions: In PHPT, there are several alterations in the balance between production of reactive oxygen species and antioxidant defense system.

KEYWORDS: oxidative stress; primary hyperparathyroidism; parathyroid hyperplasia; parathyroid adenoma

INTRODUCTION

Primary hyperparathyroidism (PHPT) is one of the most common endocrine disorders; it isdefined as excessive secretion of parathormone (PTH) due to parathyroid hyperplasia (15%), parathyroid adenoma (80%) or parathyroid carcinoma (1-5%) [1]. The highest incidence of PHPT is seen between the age of 50 and 60, affecting 2% of the population aged 55 years or older, with a 2–3 times more frequent occurrence in females [1]. PTH is produced by the chief cells as a prohormone containing 84 amino acids and plays a role in upregulating the serum calcium concentration. PTH triggers bone resorption, promotes calcium absorption in the intestine, increases the production of vitamin D, which stimulates intestinal calcium absorption, and blocks secretion of calcium by the kidneys [1]. PHPT is a risk factor for several cardiovascular diseases, such as hypertension, dyslipidemia, left ventricular hypertrophy, calcification of the myocardium and heart valves, overweight and diabetes mellitus. This could be caused by hypercalcemia, low vitamin D level, osteoporosis, or hyperphosphatemia, which occur in patients with PHPT [1]. However, mechanisms leading to increased vulnerability to these diseases are not fully established.

Oxidative stress is a phenomenon, which could explain higher incidence of these illnesses in PHPT cases [2]. It is defined as excessive oxidation processes, which induce formation of reactive oxygen species (ROS), such as superoxide radical, hydroxyl radical and hydrogen peroxide. This may lead to damage of all components of the cell, including proteins, lipids, and DNA. Oxidative stress has been implicated in the pathogenesis of vascular diseases and renal failure, due to production of oxidized plasma proteins [2]. Nitrogen monoxide (NO), which maintains vascular tone, is synthesized by the endothelium. In disorders, such as diabetes, hypertension and hypercholesterolemia, higher levels of ROS are formed, which neutralize NO, causing atherotrombosis and atherosclerosis [2]. Walgenbach et al. demonstrated lower risk of cardiovascular diseases after surgery for primary hyperparathyroidism [3].

Lipid oxidation is one of the most destructive effects of oxidative stress. During this process, electrons are transported from lipids to free radicals, which cause damage of lipids in cell membranes and in turn, cell destruction. Moreover, ROS inactivate transmembrane receptors and enzymes, upregulate tissue permeability and trigger several signal transduction pathways, such as activation of the epidermal growth factor receptor or fibronectin production [4]. The end products are lipid hydroperoxides (LHP) and reactive aldehydes, such as malondialdehyde (MDA) and 4-hydroxynonenal (HNE), which can be mutagenic and carcinogenic. One of the examples is the reaction of MDA with deoxyadenosine and deoxyguanosine in DNA leading to the production of DNA adducts. Levels of LHP and MDA are proportional to the production of ROS, therefore they are a useful marker used to measure oxidative stress. Lipid peroxidation has been linked with several diseases, such as atherosclerosis, ischemia-reperfusion injury, heart failure, Alzheimer's disease, rheumatic arthritis, cancer, and other immunological disorders [4].

Balance between production of reactive oxygen species and antioxidant defense mechanisms is maintained due to the presence of antioxidants, which are enzymes catalyzing the transformation of ROS into non-toxic products. One of the antioxidants is ceru-

loplasmin (CER), which inactivates reactive oxygen species such as singlet, superoxide, and hydroxyl radicals. Its roles in copper transport, iron turnover, ferroxidase, glutathione peroxidase and ascorbate oxidase activities have also been described. Its expression has been demonstrated in the liver, spleen, lung, testis, and brain [4]. Sulfhydryl (SH) groups, also denoted thiol or sulfur groups, are organic complexes that contain a sulfur and a hydrogen atom. They are involved in removal of free peroxidized fatty acids and hydrogen peroxide. Sulfur is an important component of many enzymes and antioxidants including thioredoxin and glutathione. Glutathione (GSH) is a tripeptide, which is present in all cell compartments. It plays a role in inactivation of hydrogen peroxide and lipid peroxides as a cofactor for glutathione peroxidase (GSH--Px). An electron from GSH is transported to H2O2 to reduce it into H2O and O2.

Oxidized glutathione (GSSG) is again reduced into GSH by GSH reductase. GSH-Px is also important for the protection of cell membranes from lipid peroxidation. Reduced glutathione donates protons to membrane lipids and protects them from oxidant attacks. Moreover, it transforms inactive vitamin C and E and has been implicated in iron metabolism, cell cycle and apoptosis [4]. Superoxide dismutase (SOD) takes part in the dismutation and decomposing of the superoxide (O2–) radical into either molecular oxygen (O2) or hydrogen peroxide (H2O2). Four families of SOD, depending on the protein fold and the metal cofactor, have been discovered including Fe-SOD, Mn-SOD, Ni-SOD and CuZn--SOD. CuZn-SOD comprises of copper and zinc and is present in the cytosol, however a small amount of this enzyme is localized in cellular organelles such as lysosomes, peroxisomes, nucleus, and intermembrane space of mitochondria. Mn-SOD contains manganese and is found in the mitochondria. Hyperoxia, irradiation or paraquat treatment upregulate the level of Mn-SOD. Several cancers showed decreased concentration of MnSOD and supply with this antioxidant inhibited cell growth in in vitro studies [5]. Catalase (CAT) is an enzyme, catalyzing the partitioning of hydrogen peroxide to water and oxygen, which is located mainly in peroxisomes. It is a tetramer of four polypeptide chains and contains four porphyrin heme groups that enable the enzyme to react with the hydrogen peroxide. Catalase is down-regulated in several diseases, such as obesity, fatty liver, and type 2 diabetes [4].

Other parameters used to assess oxidative stress are total oxidative status (TOS), total antioxidant capacity (TAC), and oxidative stress index (OSI). Total oxidative status (TOS) defines the total oxidant properties, whereas total antioxidant capacity (TAC) determines antioxidants' reducing potential of body fluids in organism and the capability to counteract ROS, resist oxidative damage and combat oxidative stress-related diseases [6]. Because there are differences in antioxidants' reducing potential, Trolox, which is analogous to vitamin E, is used to standardize antioxidants, therefore antioxidants are measured in Trolox equivalents. OSI is defined as the ratio of the TOS level to TAC level [6]. By measuring the activity of the antioxidant system, we can indirectly measure free radical activity [6].

Therefore, the aims of the study were to:

1. Assess the activity of antioxidant enzymes and free radical reaction products in patients with primary hyperparathyroidism according to the type of parathyroid lesion.

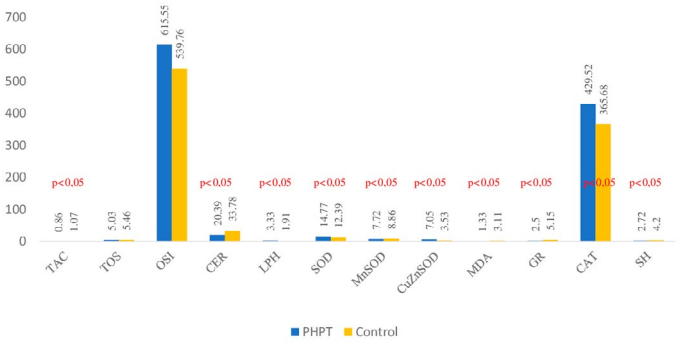

Fig. 1. Comparison of oxidative status between patients with PHPT and control group.

Notes: Mann–Whitney U-test was applied. The data were presented as median unless stated otherwise. Asterisk P-value shows the difference was statistically significant (p<0.05) Abbreviations: TAC -total antioxidant capacity; TOS- total oxidant status; OSI -oxidative stress index ,CER- ceruloplasmin, SOD- Superoxide Dismutase, MnSOD -mitochondrial form SOD, CuZnSOD- cytoplasmic form SOD, SH- sulfhydryl groups, LPH- lipid hydroperoxides, MDA- Malonic Dialdehyde, GR- Glutathione Reductase, CAT- Catalase

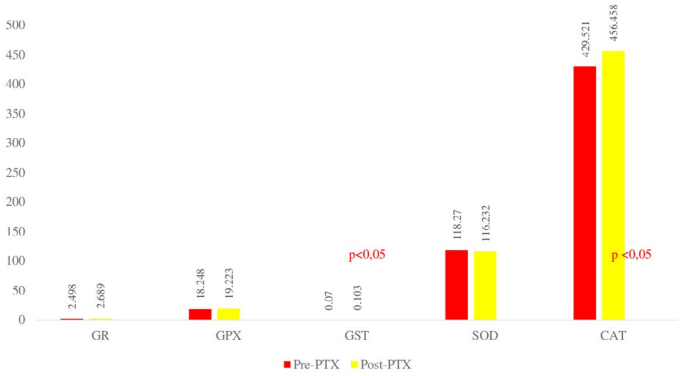

Fig. 2. Activities of antioxidant enzymes in erythrocytes before (pre-PTX) and after parathyroidectomy (post-PTX).

Notes: Mann–Whitney U-test was applied. The data were presented as median unless stated otherwise. Asterisk P-value shows the difference was statistically significant (P<0.05) Abbreviations: GR- Glutathione reductase, GPX- Glutathione peroxidase, GST- Glutathione S-transferase, SOD- Superoxide Dismutase, CAT- Catalase

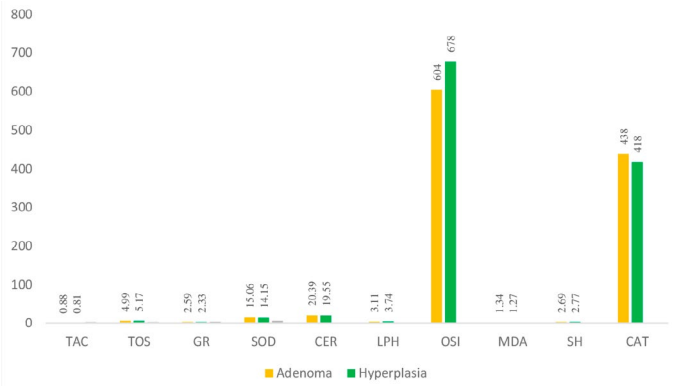

Fig. 3. Comparison of oxidative status between patients with PHPT according to histological diagnosis.

Notes: Mann–Whitney U-test was applied. The data were presented as median unless stated otherwise. Asterisk P-value shows the difference was statistically significant (p<0.05) Abbreviations: TAC -total antioxidant capacity; TOS- total oxidant status; OSI -oxidative stress index , CER- ceruloplasmin, SOD- Superoxide Dismutase, MnSOD -mitochondrial form SOD, CuZnSOD- cytoplasmic form SOD, SH- sulfhydryl groups, LPH- lipid hydroperoxides, MDA- Malonic Dialdehyde, GR- Glutathione Reductase, CAT- Catalase

2. Evaluate the activity of antioxidant enzymes and free radical reaction products in erythrocytes in patients with primary hyperparathyroidism.

MATERIALS AND METHODS

Out study material constituted of blood serum and parathyroid tissue specimens, collected from 52 consecutive patients with PHPT treated surgically. Thirty-six healthy volunteers were our control group. Blood samples for biochemical examinations were collected from patients 24h before surgery, as well as on postoperative day 15. At each time point, 5ml of blood were aspirated into both vacuum tubes and vacuum tubes with an anticoagulant (EDTA). In order to obtain a hemolysate, 0.9% NaCl was added to the remaining blood cells. The material was mixed and centrifuged for 10 min at 3000 revolutions/min. Supernatant was removed and again 0.9% NaCl was added. The procedure was repeated twice. Afterward, 0.4ml of blood was collected from the bottom of the test tube and 3.6 ml of double distilled water was added. After mixing, we obtained a 10% blood cell lysate. The material was frozen at –80 °C. After thawing, biochemical examinations were performed.

Biochemical analysis

Analysis of TOS and TAC

TOS and TAC were determined in the serum using the method described by Erel [6]. The spectrophotometric measurements were done at 560 nm after mixing the samples and reagents, and the results were expressed in hydrogen peroxide liter (μmol H2O2 equiv/l). The method is based on the oxidation of ferrous ion to ferric ion in the presence of various oxidant species in acidic medium and measurement of the ferric ion by xylenol orange. TAC was presented as mmol Trolox equiv/l. TAC measurements were performed by kinetic reading in the spectrophotometer 5 min after the sample and reagent were mixed.

Analysis of OSI

After TAC and TOS measurements, OSI levels, which allow us to make an exact comment on the oxidant and antioxidant balance, were calculated according to the following formula specified in the catalog of the kit (rel assay diagnostics): OSI = (TOS [μmol/l])/(TAC [mmol Trolox equiv/l] × 100).

Analysis of antioxidants

The method of Oyanagui was used to measure the activity of superoxide dismutase (SOD) and its isoenzymes: cytoplasmic Cu/Zn-superoxide dismutase (Cu/ZnSOD) and mitochondrial Mn--superoxide dismutase (MnSOD). In this method, xanthine oxidase produces superoxide anions, which react with hydroxylamine forming nitric ions. These ions react with naphthalene diamine and sulfanilic acid, generating a colored product. Concentration of this product is proportional to the amount of produced superoxide anions and negatively proportional to the activity of SOD. The enzymatic activity of SOD was expressed in nitric units. The activity of SOD is equal to 1 nitric unit (NU) when it inhibits nitric ion production by 50%. Activities of SOD were normalized to a milligram of protein in homogenates (NU/mg protein). Concentration of sulfhydryl groups (SH) in the serum was determined by Koster method using 5,5'-dithiobis (2-nitrobenzoic acid)—DTNB. Concentration was shown in mmol/l. Serum ceruloplasmin was determined spectrophotometrically using the Richterich reaction with p-phenyldiamine.

Analysis of antioxidants is erythrocytes

CAT activity was measured using the method described by Aebi. The erythrocyte lysate was diluted in 0.05 M potassium phosphate buffer (pH=7), and the reaction was started by adding 10 mM hydrogen peroxide. The decrease in absorbance at 240 nm was measured for 30 seconds. Enzyme activity was calculated as a function of the rate constant of the first order reaction (k), and was expressed as k per gram of hemoglobin (Hb). Results were presented as units per g hemoglobin. The hemoglobin concentration of lysate was determined using the cyanmethemoglobin method. Glutathione peroxidase (GPx) was determined by a modified method of Paglia and Valentine. It was measured spectrophotometrically by coupling the oxidation of glutathione and NADPH using GR. Briefly, 1 mL of assay mixture contains optimized concentrations of the following chemicals: 0.5 M K2HPO4 (pH 7.0), 2.5 mM EDTA, 0.18 U/mL GR, 100 mM glutathione and 10 mM reduced NADPH and tissue extract (0.5 mL), which were added in the spectrophotometer cuvette along with 0.1 mL of 60 mM cumene hydroperoxide, a suitable substrate for GP. Glutathione transferase activity (GST) was spectrophotometrically determined at 340 nm by measuring formation of the conjugate of glutathione (GSH) and 1-chloro-2,4--dinitrobenzene (CDNB). The assay system consisted of CDNB prepared in absolute ethanol and hemolysate from the sample in 0.1 M potassium phosphate buffer with a 6.25 pH, to which GSH was added to initiate the reaction. The addition of GSH was done 3 minutes after the addition of CDNB. Formation of the S-conjugate was followed by measurement of the absorbance at 340 nm. Blanks obtained without the hemolysates were subtracted from each assay value. One unit of enzyme activity was defined as the amount of enzyme that catalyzed the formation of 1uM of the S--conjugate per minute under assay conditions. Calculations were done by using the molar extinction coefficient of 9.6mM l -1 cm -1 and taking into account the dilutions. Results were expressed relatively to hemoglobin content. Glutathione reductase (GR) activity was indirectly measured by oxidation of NADPH to NADP+. 24 μM GSSG and NADPH in 0.5 M TRIS-HCl buffer (pH 7.6) were added on the hemolyzed diluted erythrocytes. The enzymatic reaction was initiated by adding tert-butyl as a substrate. We followed the conversion of NADPH to NADP+ by a continuous recording of the decrease in absorbance at 340nm for 3 min.

Analysis of lipid oxidation products

Lipid hydroperoxide concentration in the serum was determined by Södergren et al. using xylene orange. Values were expressed in mmol/l. All these parameters were measured with the use of the Perkin Elmer spectrophotometer Victor X3. The malondialdehyde level was determined by the Ohkawa method using a Perkin Elmer LS45 spectrofluorometer. Concentration of MDA was expressed asmol/g of protein.

Statistical analysis

All statistical analyses were done with the use of STATISTICA 10 program. Normality of the results distribution was verified using the Shapiro–Wilk test. Due to the small size of the groups we used the non-parametric Mann-Whitney U test, and the data were presented as a median with the first and fourth quartiles. The results were considered statistically significant if $p < 0.05$. Lack of statistical significance was presented as NS (nonsignificant).

RESULTS

Our study demonstrated that OSI was increased in patients with PHPT when compared to normal controls, whereas TAC was lower in PHPT. Levels of CER, MnSOD, GR, SH groups and MDA were significantly decreased in PHPT. The level of serum LHP, catalase and SOD were significantly higher ($p<0.001$) in patients with PHPT than in healthy patients (Fig.1). Erythrocyte CAT ($p<0.05$) and GST ($p<0.05$) activities were significantly increased in patients after parathyroidectomy. Erythrocyte GR and GPx were upregulated postoperatively, whereas SOD activity decreased (Fig.2).

Patients with PHPT treated surgically were characterized by an increase of TAC, and decrease of OSI and TOS compared to the preoperative period. It was further found that the concentrations of serum MDA and LPH were decreased in patients with PHPT who underwent parathyroidectomy. When comparing the types of parathyroid lesions, parathyroid adenoma was characterized by increased CAT and down-regulated OSI compared to parathyroid hyperplasia, however, the results were not statistically significant (Fig.3).

DISCUSSION

In PHPT there are several alterations in the balance between production of reactive oxygen species and antioxidant defense system. Our study revealed that in PHPT, the oxidative stress, measured by OSI, was increased, whereas total antioxidant capacity was down-regulated. LHP, which are the products of lipid peroxidation, are proportional to the production of ROS and therefore, they are good markers of oxidative status. They can further trigger lipid peroxidation through prostaglandin synthesis and are cytotoxic and mutagenic. We showed that the LHP level was raised in PHPT. Previous studies also demonstrated an enhanced level of LHP in several neoplasms, such as oral cancer [7], head and neck squamous cell carcinoma [8], laryngeal cancer [9], benign and malignant prostatic lesions [10], breast cancer [11] and uterine cervical cancer [12]. Therefore, we hypothesized that in neoplastic lesions, there is an oxidant–antioxidant imbalance, which could be caused by at least two mechanisms. Firstly, neoplastic cells synthesize greater amounts of ROS than healthy cells. What is more, the antioxidant system in neoplastic cells is down-regulated and could facilitate ROS accumulation. It could also be due to the constant catalyzing activity of antioxidant enzymes for a prolonged time. Some enzymes, including GPx and SOD are vulnerable to oxidation by oxidative reactive molecules and lipid peroxides, and may be inactivated by their own substrates or due to lack of some ions, such as Cu, Zn and Se. Moreover, high levels of ROS have been implicated in developing several neoplasms, such as oral cavity cancer [7,9,12]. Formation of ROS results in damage to all components of the cell, including proteins, lipids, DNA and cell membranes and eventually leads to transformation of normal cells into malignant cells. ROS have been implicated in initiation and promotion of carcinogenesis [9,12].

SOD is the first enzyme induced in oxidative stress. In our study, the activity of SOD was increased in PHPT compared to normal controls, however, MnSOD activity was lower in the first group. Previous reports also showed higher SOD concentrations in lesions, such as gastric cancer or head and neck squamous cell carcinoma [8] compared to the control group. However, some authors observed lowered SOD levels [13]. Enhanced activity of SOD could be an adaptive response to raised levels of the superoxide anion and lipid peroxidation products, whereas absence of SOD leads to the deposition of superoxide anion [5].

Erythrocytes are particularly susceptible to oxidative destruction due to high oxygen pressure, great amount of polyunsaturated fatty acids and high concentration of iron. One of the most important antioxidant enzymes in erythrocytes is catalase, whose activity is decreased in neoplastic lesions [12]. It could be a result of enzyme overload by increased levels of ROS present in the blood and depletion of the enzyme caused by excessive neutralizing activity. In our study, erythrocyte CAT activity was significantly lower in patients with PHPT and raised in patients after parathyroidectomy. Similarly, GST, GR and GPx levels increased in patients after surgery. Nevertheless, previously GST activity was found to be increased [12], whereas GPx activity was lower in proliferative lesions compared to normal controls, which may be a result of is inactivation by superoxide anion and MDA [10]. GPx, GST and GR could modulate susceptibility of the neoplasm to chemotherapy, radiotherapy and cytokines; furthermore, down-regulation of GSH may increase vulnerability to chemotherapy and radiotherapy.

We found increased CAT and down-regulated OSI in parathyroid adenoma compared to parathyroid hyperplasia, however, the results were not statistically significant. Previous studies demonstrated several differences in oxidative status parameters when patients were grouped according to histological staging and grading. Increased level of ROS correlated with the stage of cancer [14]. SOD activity correlated with the stage in head and neck squamous cell carcinoma [8] and level of lipid peroxidation (MDA) was significantly elevated in patients who later manifested recurrence of cancer [8]. However, studies conducted by Gerber et al. are contrary to these reports; they showed that the MDA level decreased with tumor size and progression [15]. Erythrocyte glutathione peroxidase and superoxide dismutase activities were found to be significantly elevated in benign, rather than malignant lesions [10,14-15].

To sum up, there is an imbalance between the production of ROS and antioxidant defense system in proliferative lesions in parathyroid glands, as well as in other organs and tissues, and it could be one of the factors responsible for pathogenesis of neoplasms. ROS are implicated in the initiation and promotion of tumorigenesis. They lead to lipid peroxidation and DNA destruction, activate pro-carcinogens, and downregulate the cellular antioxidant defense system. Oxidative stress in cancer may result in a further mutation and chromosomal aberration, resistance to chemotherapy, and in tumor invasion and metastasis. Antioxidants could have a preventive effect and could be one of the anti-oncogenes. Inactivation of one of these genes during tumorigenesis may lead to neoplasm formation. Future studies regarding assessment of oxidant–antioxidant status in proliferative lesions should be conducted for better understanding of the pathogenesis of their development. Perhaps some of the oxidant–antioxidant factors could also become therapeutic targets.

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Word count: 3420 Page count: 6 Tables: – Figures: 3 References: 15

DOI: 10.5604/01.3001.0012.7258 Table of content: https://ppch.pl/issue/11803

Competing interests: The authors declare that they have no competing interests.

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Cite this article as: Deska M., Romuk E., Segiet O., A., Polczyk J., Buła G., Gawrychowski J.: Oxidative stress in proliferative parathyroid lesions; Pol Przegl Chir 2019: 91 (1): 29–34