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ORIGINAL ARTICLE PEDIATRICS

Thiol disulfide homeostasis in ionizing radiation and chemotherapeutic drug exposure

Nilgun Eroglu,[1] Gurses Sahin,[1] Sule Yesil,[1] Ali Fettah,[1] Yasemin Tasci Yildiz,[2] Ozcan Erel[3]

[1]Department of Pediatric Hematology-Oncology, Sami Ulus Pediatrics Training and Research Hospital, Ankara, Turkiye
[2]Department of Radiology, Sami Ulus Pediatrics Training and Research Hospital, Ankara, Turkiye
[3]Department of Biochemistry, Yildirim Beyazit University, Ankara, Turkiye

ABSTRACT

OBJECTIVE: This study aims to reveal the oxidant and antioxidant status in nurses with chemotheropathic drug exposure and radiology unit workers exposed to ionizing radiation (IR).

METHODS: Nineteen radiology unit workers, 14 nurses, and 15 controls were included the study. All of the participants using antioxidants, vitamin supplements, smokers, any therapeutic drugs, and exposed therapeutic or diagnostic X-ray or chemotherapeutic drugs in 12 months were excluded from the study. Total and native thiols, disulfide/native thiol percent ratios (SS/SH), disulfide/total thiol percent ratios, disulfide amounts, and native thiol/total thiol percent ratios, ischemia-modified albumin (IMA) were determined.

RESULTS: Disulfide levels, disulfide/total thiol ratio, and disulfide/native thiol ratio of serum samples of both radiology unit workers and nurses were significantly higher and ratio of native thiol/total thiol was lower than the control group. The radiation dose in radiology unit workers was mean±SD: 0.02±0.009, median (min–max): 0.02 (0.001–0.04). Thiol-disulfide homeostasis was disturbed and the balance shifted in the direction of oxidant damage, even at low-dose IR exposure and normal range.

CONCLUSION: As far as we know, the current findings first demonstrate an apparent chronic oxidative stress in the subjects who were occupationally exposed to antineoplastic drugs and radiation even if annual radiation exposure dose measurements are normal.

Keywords: Chemotherapeutic drug; ionizing radiation; thiol disulfide homeostasis.

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Oxidative stress means the lack of balance between the removal and production of reactive oxygen species (ROS) [1]. ROS high levels can induce the mutation and damage in deoxyribonucleic acid (DNA). This is a risk factor of cancer and other disorders [2]. Free radicals are produced increasingly in the cells for different reasons, for example, when exposed to IR and antineoplastic drugs.

Radiation dose range considered normal in radiology unit staff is 1–5 mSv/year [3]. Radiology workers who are occupationally exposed to IR show that cancer incidence such as solid cancers and leukemia and frequencies of DNA breakage increased [3–8]. This phenomenon has been hypothesized to be due to the oxidative stress induced by reduced chronic dose ionizing radiation (IR), but no study has been done on the oxidative stress in radiology unit workers about thiol/disulfide homeostasis [9, 10].

ROS can be also produced by the antineoplastic drugs, leading to mutations and damage of DNA. Protein, lipids, and DNA of the cell can be affected by ROS overproduction, destroying the function, and structure of cells [9, 10].

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Correspondence: Nilgun EROGLU, MD. Sami Ulus Cocuk Sagligi ve Hastaliklari Egitim ve Arastirma Hastanesi, Cocuk Hematoloji ve Onkoloji Klinigi, Ankara, Turkiye.
Tel: +90 312 305 - 60 00 e-mail: dr-nilguner@hotmail.com

Preparation and administration of anticancer drugs make oncology nurses exposed to these drugs [11]. They may be exposed to antineoplastic drugs mainly through hands and sometimes through other body parts or through contact with those cured with anti-cancer drugs through their clothing and excreta [12].

The antioxidant defense system may inhibit the free radicals oxidative effects. There is sulfhydryl group in thiols playing a key role in coordination of the antioxidant defense system. There can be oxidation reaction in thiols throughout oxidant, forming disulfide bonds. The oxidative stress causes to convert sulfhydryl groups into disulfide bridges subsequently converted into thiols again. There is a balanced continuation of the cycle. Therefore, TDH is kept. TDH plays an essential role in apoptosis, detoxification, oxidative stress, cellular signal transmission, protection against antioxidants, and enzymatic activity [13].

To determine the antioxidant capacity and status of oxidative stress in workers of radiology unit who were exposed to reduced dose IR and nurses who were exposed to antineoplastic drugs, their antioxidant status was investigated by measuring their thiol/disulfide homeostasis compared to a matched control group. As far as we know, this study is the first to provide the data that radiology workers and nurses oxidative stress status with thiol/disulfide homeostasis.

Highlight key points

- Disulfide levels, disulfide/total thiol ratio, and disulfide/native thiol ratio of serum samples of both radiology unit workers and nurses were significantly higher and ratio of native thiol/total thiol was lower than the control group.
- Thiol-disulfide homeostasis was disturbed and the balance shifted in the direction of oxidant damage, even at low-dose IR exposure and normal range.
- There should be attempt to eliminate the occupational exposure to these drugs and introduce the specific protective measures, for which some of the high-risk activities are automated and safety guidelines are required.
- The present findings were first to demonstrate an apparent chronic oxidative stress in subjects exposed to radiation even if annual radiation exposure dose measurements are normal.

MATERIALS AND METHODS

This prospective study was carried out at Sami Ulus Maternity and Children's Hospital, Ankara between January and June 2019. Approval from local Medical Ethics Review Committee (approval number: 2019-023). Written informed consent was obtained from all patients before the study.

Study was designed with 48 subjects. The first group included 19 subjects occupationally exposed to low-dose IR (X-ray) in the radiology unit. The radiology worker wears protective clothing for radiation and the radiation dose is checked once a year. The annual exposure dose of the employees was measured. All of the participants who used any therapeutic drugs, antioxidants, vitamin supplements, smokers, and those exposed to chemotherapeutic drugs or therapeutic or diagnostic X-ray in 12 months were excluded from the study. Second group included 14 nurses that work in pediatric hematology and oncology service. Working time of the nurses working in the chemotherapy unit was 6 months and 45 h per week. Demographic data including sex, age, chronic disease, and family history of cancer were collected. A control group including the gender and age matched 15 subjects were included in the study.

Measurement of Thiol/Disulfide Homeostasis

An spectrophotometric method which Erel and Neselioglu described was used to measure thiol/disulfide Homeostasis tests [14]. Disulfide bonds are reduced and combined with sodium borohydride, and then, thiol groups are formed. The reductant sodium borohydride which remained unused was consumed and removed with formaldehyde to prevent reducing DTNB (5.5'-dithiobis-(2-nitrobenzoic) acid), and after the reaction with DTNB, all of the thiol groups, including native and reduced thiol groups, were specified. If the natural thiols are subtracted from the total thiols, half of the difference represents the dynamic sulfur content. After native and total thiols were determined, disulfide/native thiol percent ratios (SS/SH), disulfide/total thiol percent ratios (SS/SH+SS), disulfide amounts, and native thiol/total thiol percent ratios (SH/SH+SS) were determined [15].

IMA (Ischemia-Modified Albumin) Measurement

Levels of IMA were measured within 1 h after the after acceptance of venous blood samples. Samples stored at room temperature for 30 min were centrifuged for 5 min at 3500 rpm, then taken to Eppendorf tubes and kept at -80°C for analysis. The presence of IMA was detect-

Table 1. Average and median values of measured values in radiology workers, nurses, and control group

	Radiology (n=19) Mean±SD	Nurses (n=14) Mean±SD	Control (n=15) Mean±SD	p
Age (year)	44.21±8.69	34.21±10.99	37.46±6.48	0.004
Height (cm)	165.94±7.64	163.07±5.66	161.60±6.51	0.236
Weight (kg)	71.63±12.23	71.50±8.60	63.80±7.93	0.077
BMI	25.99±4.09	26.92±3.38	24.39±2.40	0.129
IMA	0.65±0.06	0.70±0.06	0.67±0.05	0.052
Albumin	3.65±0.28	3.53±0.27	3.58±0.22	0.547
N thiol	289.11±44.34	292.96±34.24	302.46±30.49	0.754
T thiol	331.80±45.38	336.68±40.48	331.62±29.72	0.921
Disulfide	21.34±5.88	21.86±5.79	14,8±4.56	0.002
Index-1 disulfide/native thiol	7.57±2.72	7.45±1.81	4.90±1.74	0.002
Index-2 disulfide/total thiol	6.49±1.93	6.45±1.34	4.57±1.37	0.004
Index-3 native thiol/total thiol	87.01±3.87	87.10±2.69	91.14±2.87	0.002
Ionizing radiation dosage	0.02±0.009			

BMI: Body mass index; IMA: Ischemia-modified albumin; N thiol: Native thiol; T thiol: Total thiol; SD: Standard deviation.

ed using the Albumin Cobalt Binding Test. To perform this test, 50 mL 0.1% cobalt (II) chloride ($CoCl_2$, $6H_2O$) (Sigma-Aldrich Chemie GmbH Riedstrasse 2, Steinheim, Germany) was added to the patient serum. After it was mixed, 50 mL of 1.5 mg/mL dithiothreitol was added to allow cobalt to bind with albumin after a 10 min incubation. After it was mixed, the binding capacity was reduced before two minutes of incubation by adding 1.0 mL of a 0.9% sodium chloride solution. Distilled water was used instead of dithiothreitol to prepare the blank similarly. A spectrophotometer was used to measure the samples absorbance at 470 nm. The results were expressed as ABSU [16].

Statistical Analysis

SPSS 25.0 program is used for statistical analysis. Continuous variables with no normal distribution were expressed as median (min–max) and continuous variables with normal distribution were expressed as mean±SD. Categorical variables were expressed in percentage and numbers. The categorical variables were compared between groups using the Chi-square test. A normal distribution test was performed for numerical variables and the values were not distributed normally, the non-parametric test Kruskal–Wallis variance analysis was used to compare the groups. $P<0.05$ was regarded as statistical significance level.

Table 2. Distribution of some characteristics in radiology workers, nurses, and control group

	Radiology (n=19)	Nurses (n=14)	Control (n=15)	p
Systemic disease				0.192
Negative	68.4	71.4	93.3	
Positive	31.6	28.6	6.7	
Drug				0.097
Negative	73.7	85.7	100.0	
Positive	26.3	14.3	–	
Family disease				0.067
Negative	47.4	14.3	53.3	
Positive	52.6	85.7	46.7	

RESULTS

Of the participants in the study, 39.6% (n=19) were radiology unit workers, 29.2% (n=14) nurses, and 31.2% (n=15) the control group.

Radiology workers, nurses, and control group did not show statistically significant difference in height, weight, BMI, native thiol, albumin, IMA, and total thiol values ($p>0.05$) (Table 1). No significant difference was found in radiology workers, nurses and control groups in systemic disease, drug use, and familial disease ($p>0.05$) (Table 2).

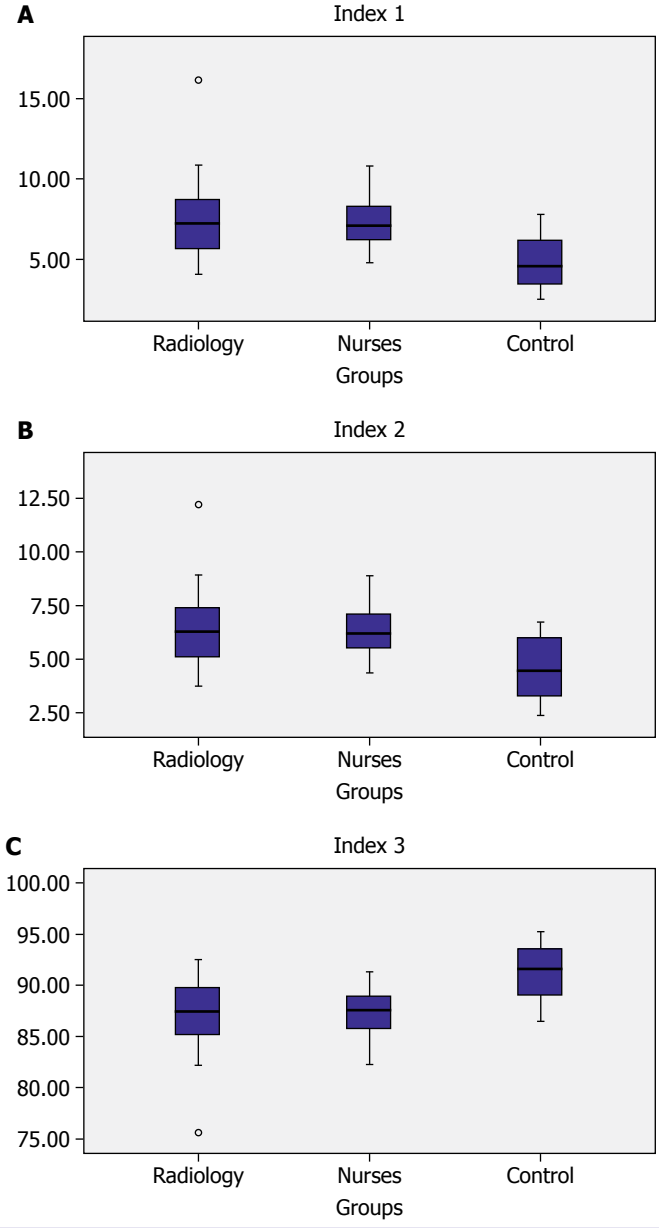

Figure 1. **(A)** Distribution of Index 1 disulfide-native thiol values in radiology workers, nurses, and control group. **(B)** Distribution of Index 2 disulfide-native thiol values in radiology workers, nurses, and control group. **(C)** Distribution of Index 3 disulfide-native thiol values in radiology workers, nurses and control group.

Doses and ratio are given in Table 1.

Disulfide levels, ratios of disulfide/total thiol and disulfide/native thiol in radiology unit workers, and nurses serum samples were significantly higher than the control group (p=0.002, p=0.002, and p=0.004) (Fig. 1A, B). Radiology and nurses groups had lower native thiol/total thiol ratio than the control group had (p=0.002) (Fig. 1C).

DISCUSSION

The present study investigated oxidative stress status in radiology unit workers and chemotheraphy nurses. Disulfide, disulfide/native thiol, and disulfide/total thiol ratios of both radiology workers and chemotherapy nurses' serum samples were significantly high. The excessive amount of free oxygen radicals is neutralized in the IR and antineoplastic drugs exposed groups to reduce the thiol levels. Thus, higher oxidants show that the oxidant-antioxidant balance is impaired.

Thiols, that is, mercaptans contain a sulfhydryl group consisting of hydrogen and sulfur atoms bound to a carbon atom as a class of organic compounds. The main components of plasma pool are albumin thiols, other protein thiols with contributions by thiols with reduced molecular weight such as cysteinylglycine, cysteine, homocysteine, γ-glutamylcysteine, and glutathione [14].

Cellular and tissue injury due to ROS is prevented through reaction between compounds of organic thiol and free radicals. Sulfhydryl groups are converted into disulfide bridges, consequently converted into thiols during oxidative stress again. There is a balanced continuation of the cycle. TDH plays an essential role in apoptosis, detoxification, oxidative stress, cellular signal transmission, protection against antioxidants, and enzymatic activity [14].

IR chronically exposed changes the gene expression patterns, cataract, cancer, cardiovascular disease, chromosomal aberrations, and DNA damage in radiology unit workers [17–21]. Workers in radiology unit are occupationally exposed to IR long-term low-level dose, affecting their antioxidant condition. The radiology workers have reported oxidative stress caused by chronic exposure to low-dose IR, leading to damage of DNA and mutagenicity [21–23].

Malekirad et al. [21] determined the status of oxidative stress in workers in radiology unit with occupational exposure to continual low-dose radiation. The plasma thiol groups were evaluated using DTNB in the present study. The group exposed to radiation showed significantly high thiol groups concentration in their study. However, disulfide/native thiol, disulfide, native thiol/total thiol ratios, and disulfide/total thiol were not determined by Malekirad et al. [21] This study found no significant difference between radiology unit workers and control group in total and native thiol values, but they had significantly higher disulfide levels, disulfide/total thiol, and disulfide/native thiol ratios than the control group had (p=0.002). The radiology group had lower native thiol/total thiol ratio than the control group had

(p=0.002). This may be due to increasing oxidant radicals in IR exposed group. Radiology workers, and control groups did not show any significant difference in the presence of systemic disease, smoking status, drug use, and familial disease (p>0.05)

Some studies show increased function of antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase and catalase, and glutathione peroxidase to protect them against the higher levels of free radicals during occupational exposure and some other studies find reduction of antioxidant defense in workers due to chronic oxidative stress and exposure to low level of IR for long term [24, 25]. As far as we know, this study was first to determine disulfide level, native thiol/total thiol, disulfide/total thiol, and disulfide/native thiol ratios in radiology unit workers compared with the control group.

Yamaoka et al. [25] evaluated the higher activities of SOD and lower levels of TBARS (lipid peroxides) caused by reduced dose X-rays among rat organs. Their study indicated significant increases by 50–90% compared to the control groups after they were exposed to doses from 0.05 to 0.5 Gy, the activities of SOD in immune organs of the irradiated rats, 4 h after X-ray irradiation of the whole body. Moreover, we investigated the radiation dose in radiology unit workers mean±SD: 0.02±0.009, median (min–max): 0.02 (0.001–0.04). It was found that in this study, thiol-disulfide homeostasis was disturbed and the balance shifted in the direction of oxidant damage, even at low-dose IR exposure and normal range.

There has been growing concern over the safety of nurses handling chemotherapy drugs in the past decade. Nurses may be generally exposed to antineoplastic drugs when they inhale through vapors, creating aerosols, dermal exposure by touching contaminated surfaces when they prepare, administrate, or dispose drugs, generating dust when tablets are crushed, and oral exposure through hand to mouth contact. Although very uncommon, there has been evidence of accidental injection of antineoplastic drugs [26, 27]. Many studies have shown oxidative stress condition, genotoxic risk such as DNA damage, micronuclei frequency in exfoliated buccal epithelial cells, peripheral lymphocytes, cytogenetic effects, and so on in occupational workers handling antineoplastic drugs [28, 29].

Mahboob et al. [12] evaluated if the oxidative stress effect of antineoplastic drugs was common among the nurses routinely handling antineoplastic drugs. Lower glutathione content, malondialdehyde levels, and glutathione S-transferase activity were analyzed in their study. There were increased malondialdehyde levels in the exposed nurses' serum. However, glutathione S-transferase activity and glutathione content were reduced in these nurses. The nurses who were occupationally exposed to antineoplastic drugs were vulnerable to the oxidative stress in their study. However, no study has been done on the thiol-disulfide homeostasis in the literature. In the present study, the oxidant status of exposed nurses was determined by thiol disulfide levels and ratios.

In the present study, oxidant status of antineoplastic drugs exposed nurses was determined with increased disulfide levels and decreased native thiol/total thiol ratios. Balance of thiol/disulfide essentially affects the oxidative stress, and increasing oxidants show that oxidant-antioxidant balance is impaired. Serum disulfide levels were also increased, and so, TDH was shifted to the right side. We also calculated the three ratios such as disulfide/total thiol, disulfide/native thiol, and native thiol/total thiol to further evaluate TDH state. The ratios of disulfide/native thiol and disulfide/thiol increased, and the redox equilibrium was shifted toward disulfide bond formation. The data of this study have suggested that the change in TDH states in radiology workers and chemotheraphy exposed nurses may occur due to ROS-induced oxidation/reduction reactions.

Study Limitations

Our study has some limitation, sample groups were small. Oxidative stress could not be evaluated with different parameters such as lower glutathione content, malondialdehyde levels, and activity of glutathione S-transferase and not compared with thiol groups.

Conclusion

Our results indicate the possible condition of oxidative stress caused by exposure to the antineoplastic drugs among the nurses occupationally exposed, contributing to the effects of such drugs. Although nurses use personal protective equipment to handle the antineoplastic drugs, certainly reducing the risks, they cannot adequately prevent exposure. There should be attempt to eliminate the occupational exposure to these drugs and introduce the specific protective measures, for which some of the high-risk activities are automated and safety guidelines are required.

As far as we know, the present findings were first to demonstrate an apparent chronic oxidative stress in subjects exposed to radiation even if annual radiation exposure dose measurements are normal.

Ethics Committee Approval: The Sami Ulus Maternity and Children's Hospital Clinical Research Ethics Committee granted approval for this study (date: 18.02.2019, number: 2019-023).

Conflict of Interest: No conflict of interest was declared by the authors.

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