Evaluation of lipid peroxidation and total antioxidant capacity in patients with uterine cancer

behrouz shademan
Ege University Faculty of Medicine: Ege Universitesi Tip Fakultesi
Soltan Ali Mahboob
Higher Education Institute of Rab-Rashid
Ghodsie Ravanbakhsh
Higher Education Institute of Rab-Rashid
Alireza Nourazarian (alinour65@gmail.com)
Khoy University of Medical Science: Khoy University of Medical Sciences https://orcid.org/0000-0002-2581-2676

Research Article

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Abstract

Oxidative stress has been associated with developing many female reproductive diseases, including uterine cancer. This study investigated lipid peroxidation levels and antioxidant enzyme activity in women with uterine cancer. Blood samples were collected from 50 patients with uterine cancer and 50 healthy subjects as a control group. All subjects gave their informed consent. The blood samples were measured for superoxide dismutase, catalase, glutathione peroxidase, total antioxidants, malondialdehyde, and lipid profiles. Hemoglobin levels of the control group and patients were also measured.

Serum levels of TG, LDL, and cholesterol were higher in the patients than in the healthy group but not statistically significant ($p > 0.05$). Serum HDL levels were lower in the patient group than in the healthy group. However, this decrease was not statistically significant ($p > 0.05$). The mean levels of glutathione peroxidase (GPx), catalase (CAT), and total antioxidant capacity (TAC) were increased in the patient group compared to the control group, but this increase was not statistically significant ($p > 0.05$). The mean serum levels of malondialdehyde (MDA) and SOD were increased in the patient group, which was statistically significant ($p < 0.05$). In addition, the hemoglobin level of patients with uterine cancer was decreased compared to the control group, which was statistically significant ($p < 0.05$). To develop treatment strategies for disease management. Increased serum levels of MDA and SOD and decreased hemoglobin in the blood of patients with uterine cancer can be considered diagnostic biomarkers. However, further studies are needed to confirm these findings.

Introduction

The uterus is divided into three layers: the endometrium (innermost layer), the myometrium (middle layer), and the serosa (outermost layer). Uterine cancer can occur in both the endometrium and the myometrium. Uterine sarcoma arises in the middle muscular layer. Endometrial cancer is the second most common cancer in developing countries after cervical cancer [1]. Postmenopausal bleeding (PMB) is common in women with endometrial carcinoma. In premenopausal women, bleeding between periods and irregular menstrual cycles may also be a sign of endometrial cancer [2]. According to available data from 2009 to 2015, women diagnosed with localized, advanced, and distant metastatic cancer had 5-year survival rates of 95%, 69%, and 17%, respectively [3]. For diagnosis, imaging techniques such as transvaginal ultrasound and magnetic resonance imaging (MRI) are used [4]. However, there is no agreement on what adenomyotic lesions are and how to classify them in histopathology and imaging, and the diagnosis is still complicated and not precise.

Oxidative stress is a state of imbalance between ROS-producing factors and the antioxidant defense system [5]. ROS at low concentrations can act as a message-transmitting molecule and mediator in regulating essential cellular activities such as cell growth. However, ROS can cause oxidative stress, cell damage, and apoptosis [6, 7]. Free radicals are involved in pathogenic processes and are implicated in carcinogenesis through DNA damage. There is evidence of an increase in TAC in the serum of cancer patients [8]. One of the essential effects of free radicals is the onset of lipid peroxidation, helping to

destroy cell membranes. The degradation of lipid endoperoxides containing at least three methyl groups helps to form malondialdehyde (MDA) [9]. MDA is the end product of the peroxidation of unsaturated fatty acids in cell membranes, which can widely diagnose oxidative stress [10]. The high MDA concentration can be attributed to the increased production of ROS due to the increased oxidative damage in patients with uterine cancer [11]. The antioxidant capacity of biological fluids can also assess oxidative stress. Because the body has a variety of antioxidants, it may be more reliable to use an indicator such as the TAC, which measures the total capacity of antioxidants in biological fluids [12].

Oxidative stress leads to an imbalance between prooxidant systems and antioxidants, reducing antioxidant levels and leading to DNA damage, dysfunction, and disease [13]. *Antioxidants* are substances that prevent the propagation of oxidation chain reactions by binding to free radicals and releasing electrons. These enzymes work in the mitochondria and cytoplasm of cells and provide for the degradation of H_2O_2, such as glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT), glutathione reductase (RG), and glutathione transferase (STG). SOD is a mitochondrial enzyme and the first line of defense against oxygen-free radicals. It catalyzes the superoxide anion into hydrogen peroxide and ordinary oxygen [14]. Increased lipid peroxides in patients with uterine cancer are associated with decreased SOD activity. The decrease in SOD activity may be due to an increase in endogenous production of ROS, indicating an increase in lipid peroxidation. The extent of oxidative damage induced by ROS may be exacerbated by a decrease in the efficiency of the antioxidant defense mechanism [15, 16]. GPx is a selenium-dependent enzyme found in erythrocyte membranes that regenerates lipid and non-lipid hydroperoxides besides hydrogen peroxide. GPx converts lipid hydroperoxides into alcohols, which pose less of a threat to the cell [17]. This enzyme converts hydrogen peroxide into water and oxygen. Therefore, it plays a vital role in inhibiting lipid peroxidation and preventing damage to DNA and RNA [17, 18]. In most mammalian cells, CAT is found exclusively in peroxisomes, which detoxify hydrogen peroxides produced by the long-term oxidation of fatty acids. GPx is probably used to detoxify H_2O_2 in the cytoplasm and protect CAT against H_2O_2 produced in peroxisomes [19, 20]. This antioxidant plays an essential role in protecting red blood cells from oxidative stress. When superoxide radicals are converted to hydrogen peroxide by the enzyme SOD, both CAT and Gpx can reduce superoxide, except their specific substrate and cellular position are different [21].

Our study aimed to evaluate the activity of total antioxidant capacity and the status of enzymatic antioxidants in the antioxidant defense of individuals and to determine the level of lipid peroxidation in the serum of patients with uterine cancer to diagnose the disease and apply treatment strategies.

Materials And Methods

Sample selection

This study was approved by the ethics committee of the Tabriz University of Medical Sciences. The case and control groups were selected from individuals admitted to Al-Zahra Hospital in Tabriz. All participants confirmed their informed consent to participate in the study. The control group consisted of women who

had no uterine tissue problems. Patients were sampled after the hospital pathology department confirmed that they had uterine cancer, including endometrial, sarcoma, cervical, etc., before chemotherapy and radiation therapy began. Blood samples were taken from 50 patients with uterine cancer and 50 as a control group aged 45–65. Systemic diseases (such as diabetes, liver disease, and rheumatoid arthritis), people who received chemotherapy and radiotherapy, people who took vitamin supplements, and smokers were excluded from the study.

Sampling

After 12 hours of fasting, five ml of blood was drawn from each subject, 0.5-1 ml of which was transferred to a test tube containing EDTA anticoagulant and placed in the freezer (-70°C) after the hemoglobin test. The blood was centrifuged at 35,000 rpm for 10 minutes, and the serum was separated from the rest of the blood. The serum was then stored in the freezer (-70°C).

Measurement of biochemical parameters in serum samples

Biochemical parameters such as total cholesterol (Chol), triglycerides (TG), and HDL-C were determined using the Alcyon Autoanalyzer (the USA, Model 300 Abbott). Serum cholesterol concentration was measured by enzymatic colorimetry (spectrophotometry) according to the Pars Azmoun Company kit (CHOD-PAP) at 492–550 nm wavelength. The Pars assay kits used the enzyme method GPO-PAP at 750–520 nm to determine serum TG concentration. Serum HDL-C concentration, like chol, was measured by an enzymatic colorimetric method according to the instructions of the Pars Azmoun Company (CHOD-PAP) kit. However, according to the formula of William Friedwald, LDL-C can be determined by the concentration of cholesterol, triglycerides, and HDL-C [22].

Measurement of hemoglobin in women with uterine cancer

To measure hemoglobin content in women with uterine cancer and control samples, one ml of blood was placed in an EDTA test tube, and the measurement was performed using the Sysmex XN-3100™ device.

Measuring serum concentrations of Total Antioxidant Capacity

TAC was measured according to the order of the TAC kit from Randox by a colorimetric method using the autoanalyzer (Alcyon). OD was measured at a wavelength of 600 nm.

Measuring serum concentrations of malondialdehyde

The thiobarbituric acid (TBA) method was used to measure MDA content in serum. 500 µl of serum was dissolved in 3 mL of 1% phosphoric acid for each sample. The test tube was placed in a boiling snake container. After vertexing, 1 ml of 0.67% thiobarbituric acid solution was added to the test tube. After complete vertexing for 45 minutes, the test tubes were cooled (to prevent evaporation of butanol in the next step) under cold water, and 3 ml of normal butanol was added to the test tubes and shaken for 1 to 2 minutes. In the final step, the tubes were centrifuged at 3000 rpm for 10 minutes, and the light absorbance of the isolated supernatant was measured at 532 nm against normal butane as a blank. The

MDA calibration curve and the resulting equation are shown in Fig. 1. By transferring the results to the standard curve, the concentration of MDA in the serum of the samples is determined.

Measurement of serum superoxide dismutase activity in serum

This method uses xanthine and xanthine oxidase (XOD) to generate superoxide radicals that react with 2-(4-idophenyl)-3-(4-nitrophenol)-5-phenyltetrazolium chloride (INT) to form a red furazan dye. SOD activity was measured spectrophotometrically using a commercial Randox kit (Randox, UK) and an Autoanalyzer (Alcyon300 Abbot). SOD activity was then measured by the inhibition of this reaction. A unit of SOD is the SOD that inhibits a 50% INT reduction rate under test conditions. The standard curve of the SOD enzyme is shown in Fig. 2.

Measuring the activity of glutathione peroxidase enzyme by UV method

The glutathione peroxidase activity was determined using the UV method and an Autoanalyzer by the Randox GPX kit. For this purpose, the microtubes containing blood samples were painted and melted after being in a freezer at 70 degrees for a few minutes. The steps of adding solutions and reagents and the other steps were performed automatically by scheduling the Alcyon Autoanalyzer.

Measurement of catalase enzyme activity by Hygo Aebi method

Measurement of CAT activity in blood samples was performed using the Hyogo Aebi method. In this method, hydrogen peroxide is degraded to water and oxygen by the enzyme catalase and measured by the Hygo Aebi Speed of H_2O_2 substrate rate at 240 nm wavelength of the spectrophotometer. The concentration of hydrogen peroxide is sensitive, and there is a direct relationship between the concentration of the substrate and its decomposition. To measure catalase activity, the average pH [5, 6, 8] is used. We have performed measurements at a pH of 7.

Statistical analysis

The XLSTAT 2010 software and SPSS version 20 were used for the statistical analysis and to obtain the research results. Due to the normal distribution of the data, the results were presented as mean ± SD. To compare the changes in the different variables before and after the intervention, the paired sample t-test was used, and the confidence level was set at 95% for all variables. To compare the groups and determine the significant difference between the experimental groups, the normal distribution of the data was first examined using the Kolmogorov-Smirnov statistical test. Then, the independent samples test was used to determine the significance of each group, and the values ($p < 0.05$) were assumed to be significant.

Results

Analysis of serum lipids in the desired samples

Based on the results, it was found there was no significant difference in cholesterol levels between the patient and control groups (p = 0.169). The mean cholesterol concentration in the patient group was 186.8 ± 58.6 mg/dl, and in the control group, it was 173.8 ± 30.8 mg/dl. The mean triglyceride concentration in the patient group was 142 ± 84.9 mg/dl and 118 ± 56.7 mg/dl in the control group. However, these results were not statistically significant (p = 0.095). The mean LDL-C level was 110.4 ± 50.5 mg /dL in the patient group and 102.4 ± 27.4 mg/dL in the control group. The difference between the mean LDL-C levels in the two groups was not statistically significant (p = 0.333).

The mean HDL-C level in the case group was 46.92 ± 18.7 mg/dL, and in the control group, it was 47.7 ± 15.1 mg/dL. The results of the t-test showed that the difference between the mean HDL-C levels in the two groups was not statistically significant (p = 0.817). The serum lipids of the patient and control groups are shown in Table 1. Serum levels of total cholesterol, LDL-C, and TG increased in the patient group compared with the control group. Serum levels of HDL-C decreased in the patient group. However, they were not statistically significant.

Table 1
Serum lipid profiles in case and control groups.

Variables	Control group (Mean ± SD)	Case group (Mean ± SD)	p-value
Cholesterol (mg/dl)	173.8 ± 30.8	186.8 ± 58.6	0.169
Triglyceride (mg/dl)	118 ± 56.7	142 ± 84.9	0.095
LDL-C (mg/dl)	102.4 ± 27.4	110.4 ± 50.5	0.333
HDL-C (mg/dl)	47.7 ± 15.1	46.92 ± 18.7	0.817
(HDL): high-density lipoprotein; (LDL): low-density lipoprotein.			

Changes in Hemoglobin levels in women with uterine cancer

Comparing the Hemoglobin (Hb) in women with uterine cancer with the control subjects showed that the Hb decreased significantly in women with uterine cancer; this decrease was also statistically significant (p = 0.00) (Table 2).

Table 2
Comparison of mean Hb concentrations in the blood of uterine cancer patients and healthy individuals.

Variables	Control group (Mean ± SD)	Case group (Mean ± SD)	p-value
Hemoglobin (g/dl)	13.4 ± 1.2	11.3 ± 1.3	0.00

Total Antioxidant capacity, Malondialdehyde concentration in case and control groups

The mean TAC in the case group was 1.2 ± 0.4 mmol/l, and in the control group, 1.3 ± 0.2 mmol/l. There was no statistically significant difference between the mean TAC concentration in the patient and control groups ($p = 0.370$). Figures (3. A) shows the mean TAC in the control and patient groups.

The mean MDA level in the patient group was 2.9 ± 0.6 nmol/ml and 2.5 ± 0.4 nmol/ml in the control group. The results of the t-test showed that the difference between the mean MDA levels in the two groups was statistically significant ($p < 0.05$). The results of the Kolmogorov-Smirnov test showed that the difference between the mean MDA values in the two groups was statistically significant ($p < 0.05$) (Fig. 3.B).

Evaluation of glutathione peroxidase, Superoxide dismutase, catalase enzyme activity in case and control groups

The serum levels of Gpx, SOD, and CAT of the patients and the control group are shown in Table 3. There was no statistically significant difference between the mean serum Gpx in the patient and control groups ($p > 0.05$). These results indicate no difference between the Gpx levels in the blood of uterine cancer patients and healthy subjects. There was a statistically significant difference between the mean serum SOD enzyme activity in the patient and control groups ($P = 0.001$). These results suggest that the enzyme SOD is more active in the blood of patients with uterine cancer than in healthy individuals. There was no statistically significant difference between the mean serum CAT enzyme activity in the patient and control groups ($p > 0.05$). Figure 4 shows the bar graph of mean Gpx, SOD, and CAT in the control and patient groups.

Table 3
Mean serum levels of Gpx, SOD, and CAT in patient and control groups.

Variables	Control group (Mean ± SD)	Case group (Mean ± SD)	p-value
Gpx (u/grHb)	37.4 ± 6.9	40.0 ± 10.4	0.146
SOD (u/grHb)	1190.4 ± 354	1482 ± 493.3	0.001
CAT (k/grHb)	193.5 ± 127.3	206.8 ± 114.7	0.583

Gpx: Glutathione peroxidase, **SOD**: Superoxide dismutase, **CAT**: Catalase

Discussion

Some neurologic, cardiovascular, and cancer diseases have been associated with alterations in serum lipid profiles [10, 23, 24]. The results of a study by Gibanananda Ray et al. [24], which investigated the role of lipids and lipoproteins in breast cancer patients, showed that high levels of TG may play a significant role in developing cancer. In addition, plasma LDL concentrations increase, which is more prone to oxidation and may lead to higher lipid peroxidation in cancer patients. In this study, HDL concentrations were reduced and may not adequately counteract the high ROS production. It has been reported that free radicals initially cause oxidative stress in breast cancer patients and lead to cell proliferation and malignant transformation [24]. In a study of cervical cancer patients, TG was higher in the patients than in the control group and was statistically significant. There was a significant decrease in serum HDL. TG is a consequence of cervical cancer, and as cancer progresses from stage 1 to stage 4, chol and LDL increase [25].

In a study by Abas AM et al. [26], cancer patients were found to have elevated plasma LDL concentrations, which are more sensitive to oxidation and may lead to higher lipid peroxidation in breast cancer patients and oxidative stress. This study is associated with lymph node metastases in men with colorectal carcinoma, LDL levels increase, and HDL levels decrease. Decreased HDL levels in premenopausal women may be a marker of increased breast cancer risk [26]. However, in this study, as in our study, TG levels did not differ significantly between the healthy and control groups. In our study, serum levels of TG, LDL, and cholesterol were higher in the patients than in the healthy group. However, statistically, no significant increase in their serum levels was observed. The serum level of HDL was also lower in the patient group than in the healthy group. However, this was not statistically significant. These changes may be due to people's diets or lifestyles.

According to the results of our study, the mean serum level of SOD and MDA was higher in the patient group than in the control group; this increase was statistically significant. However, the mean serum level of Gpx and CAT in the patient group was increased compared to the control group, but this increase was not statistically significant. The mean TAC level was lower in the patient group than in the control group,

which was not statistically significant and caused high toxicity and inhibition of protective enzymes, so MDA is approved as a mediator of tumor promotion and carcinogenesis [27]. Increased MDA levels and oxidative stress index are associated with a disturbed balance between oxidants and antioxidants, and these findings are supported by a decrease in antioxidant capacity [28]. The increase in MDA in cancer patients is due to the oxidation of membrane fatty acids stimulated by free radicals [29]. A study of patients with breast and cervical cancer found that lipid peroxidation increased in these patients, and MDA levels showed a statistically significant increase [30]. In Iraq, another 2011 study by Razooki et al. examined changes in lipid peroxidation and concentrations of certain elements in the serum and tissues of patients with uterine cancer. It concluded that MDA levels were significantly higher in patients than in the control group. This increase was also significantly increased in women close to menopause compared with other groups [31]. The mean serum level of MDA was higher than expected in the patient group due to increased lipid peroxidation in patients. The probable reason for the high lipid peroxidation level in cancer is decreased antioxidant capacity.

Low TAC levels may indicate oxidative stress or increased susceptibility to oxidative damage [8]. A study by Zińczuk et al. on colorectal cancer patients found that plasma TAC levels were significantly lower in cancer patients than in control subjects. In this study, it was reported that increased ROS formation or inadequate elimination leads to cancer. The results of this study support the increase in oxidative stress and the decrease in antioxidant defense in breast cancer patients [32]. In agreement with our study, Mahmood et al. investigated breast cancer patients. It was found that serum TAC levels were lower in breast cancer patients than in healthy women. These results may indicate increased oxidative stress in patients and a depletion of the body's antioxidant capacity [33]. Our results follow most previous findings suggesting that the increase in ROS may be due to decreased levels of antioxidants in the body, which significantly increases lipid peroxidation in serum.

A group in India studied lipid peroxidation, antioxidants, and red blood cell osmotic fragility in the blood of patients with cervical cancer. They found an increase in lipid peroxidation, insufficient levels of antioxidants, and an alteration in the ratio of cholesterol to phospholipids in the membrane of red blood cells. In addition, they discovered abnormalities in the structure, functioning, and operation of the Na-K-ATP-Ase pump. They examined the activity of SOD, CAT, and Gpx in patients and reported a decrease in SOD and an increase in CAT and Gpx [34]. One study investigated the expression of antioxidant enzymes in patients with uterine polyps, fibroids, hyperplasia, and adenocarcinoma. The results showed a decrease in SOD, CAT, and Nrf2 and increased GPx and glutathione reductase (GR) levels in hyperplasia. In patients with adenocarcinoma, the levels of CAT decreased, and GR increased compared with the benign groups [35]. To measure oxidative stress in the blood, a team examined lipid peroxidation levels and enzymatic antioxidant status in women with uterine conditions, including uterine tumors, endometrial polyps, and malignant endometrium.

The results showed that changes in measured parameters differed according to the statute of enzyme and the type of disease diagnosed. Disturbances of antioxidants in the blood of patients with malignant endometrium are more pronounced than in other diseases. Although the activity of SOD was lower in the

blood of the patient group, the decrease in activity was greater in patients with hyperplasia and adenocarcinoma than in patients with polyps or fibroids. The decrease in SOD activity may be due to increased androgenic ROS production by lipid peroxidation. Lipid hydroperoxide levels are negatively correlated with SOD and Gpx and positively correlated with catalase. The ratio of lipid hydroperoxides to GPx also increased according to the statute of uterine disease. A significant increase in CAT activity was observed only in patients with hyperplasia. There was a significant increase in GPx activity in patients with polyps, whereas its activity decreased in the other groups [36]. The mean serum level of SOD was increased in the group of uterine cancer patients. Since cancer and oxidative stress are related, it was expected that the serum level of this antioxidant would decrease. However, based on previous studies and the direct effect of various factors such as cancer type, disease stage, monopoiesis status, and using various drugs on the changes in antioxidant status, this increase can be justified.

Conclusion

Oxidative stress is associated with many diseases, including atherosclerosis, chronic obstructive pulmonary disease, Alzheimer's disease, and cancer. Although many small molecules evaluated as antioxidants have shown therapeutic potential in preclinical studies, the results of clinical trials have been disappointing. It may be beneficial to better understand the mechanisms by which antioxidants act. Given the increasing incidence of uterine cancer, prevention of this deadly disease or its early detection could significantly reduce the number of deaths caused by it. It could be a rational approach that leads to the tremendous success of drugs.

Declarations

Acknowledgments

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Conflict of interest

The author’s state there is no conflict of interest in the present study.

Author contributions

AN, and **SAM** Study conception and design; **BS**, and **GR** Methodology and Data curation; **BS** Writing - original draft; **AN** Writing - review & editing.

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Figures

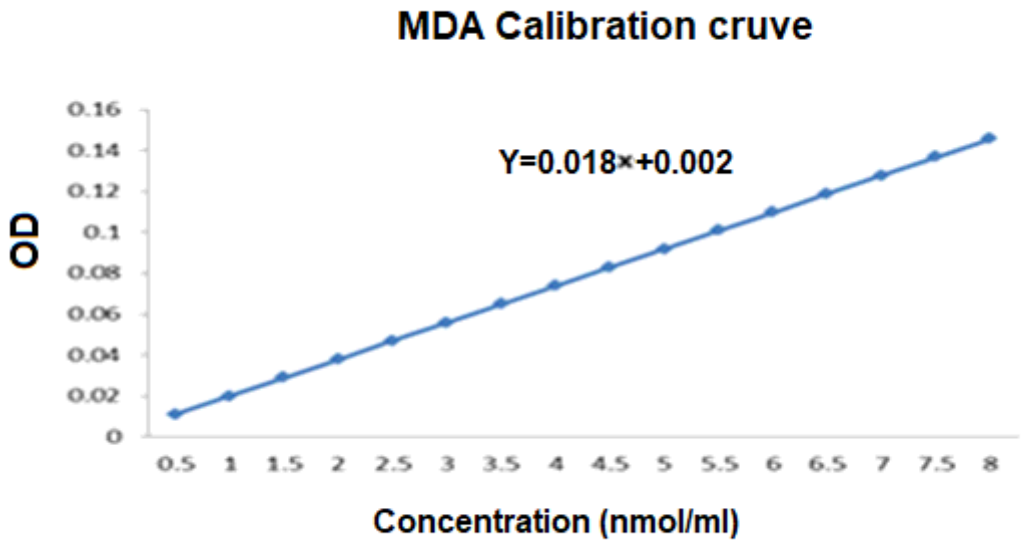

Figure 1

MDA calibration curve and its equation.

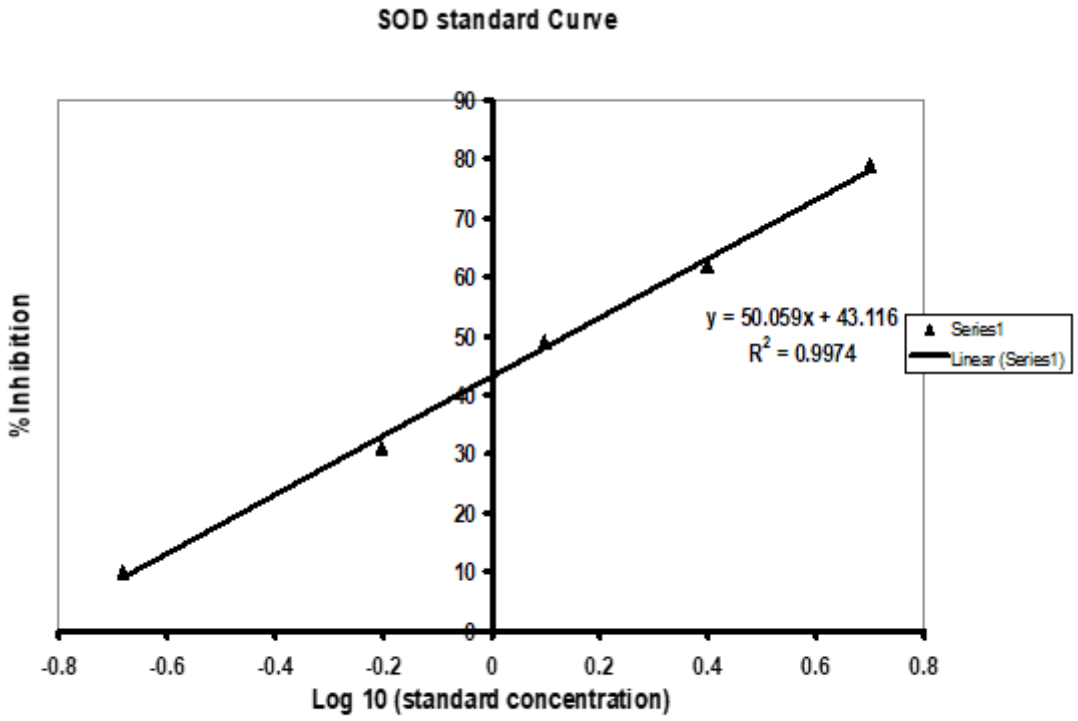

Figure 2

Superoxide dismutase calibration curve and its equation.

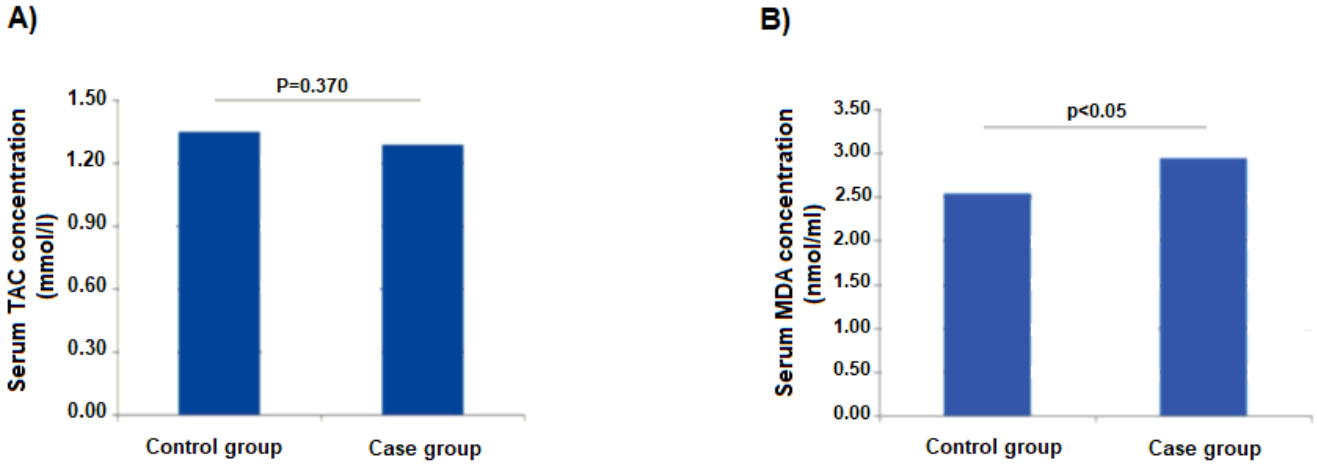

Figure 3

Mean serum level of TAC (A), and MDA (B) in the patient with uterine cancer disease and control groups

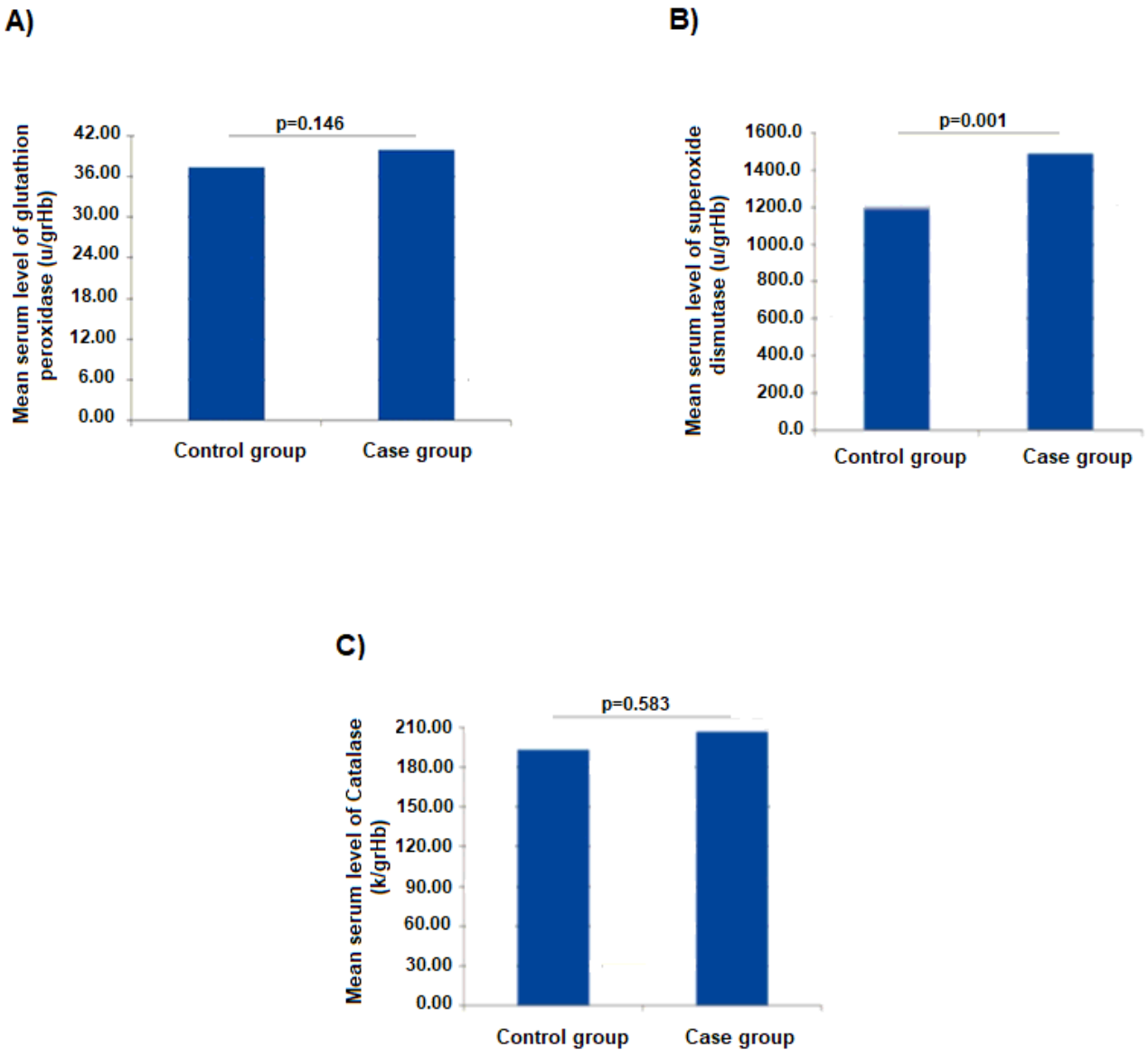

Figure 4

Mean serum levels of (A) glutathione oxidase, (B) superoxide dismutase, and (C) catalase in the patient and control groups.