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Determination of glutathione reductase activity and oxidized/reduced glutathione ratio in colon cancer patients

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Abstract

Colon cancer (CC) is the third leading cause of cancer-related mortality worldwide. Given the role of oxidative stress in carcinogenesis, this study investigated glutathione reductase (GR; EC 1.8.1.7) activity and oxidative stress markers, including reduced glutathione (GSH), oxidized glutathione (GSSG), and the GSH/GSSG ratio, in the etiopathogenesis of CC. Erythrocytes were isolated from 3 mL blood samples collected from volunteers aged 18–75 years. Hemoglobin concentration was determined spectrophotometrically at 540 nm by monitoring the conversion of methemoglobin to cyanmethemoglobin in the presence of cyanide. GR activity was measured at 340 nm by monitoring Reduced Nicotinamide Adenine Dinucleotide Phosphate (NADPH+H+) oxidation, whereas GSH and GSSG levels were determined at 412 nm based on the formation of 2-nitro-5-thiobenzoic acid. In patients with CC, GR activity was 1.41 ± 0.39 U/gHb, GSH concentration was 6.96 ± 1.45 nmol/gHb, and the GSH/GSSG ratio was 1.04 ± 0.49. In healthy individuals, the corresponding values were 0.86 ± 0.18 U/gHb, 11.43 ± 1.90 nmol/gHb, and 3.86 ± 1.30. Statistical comparison revealed significantly lower GSH levels and significantly higher GR activity and GSSG levels in CC patients, indicating elevated oxidative stress. These findings suggest that GR activity and the GSH/GSSG ratio may serve as useful biomarkers for CC diagnosis and prognosis overall.observed. This indicates that oxidative stress levels are significantly elevated in cancer patients.

Keywords: Colon Cancer; Glutathione; Reductase; Oxidative Stress

1. Introduction

Free radicals (FR) are highly reactive atoms or molecules that can be charged or neutral and can act as oxidants or reductants [1,2]. They are by-products of cellular metabolism in mitochondria, peroxisomes, the endoplasmic reticulum, and phagocytic cells [3]. Free radicals can also be generated by external sources such as pollution, radiation, chemicals, tobacco, and alcohol. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are the two most commonly studied classes of FR [1,4]. Living organisms possess antioxidant defense systems that counteract the adverse effects of these radicals. High ROS levels, in particular, can react with biomolecules such as lipids, nucleic acids, and proteins, disrupting their normal functions and contributing to the development of many chronic diseases, especially colon cancer [5-7]. Under normal physiological conditions, antioxidant systems and pro-oxidant systems are in equilibrium. Among the protective antioxidant mechanisms is the glutathione system. In cells, glutathione is primarily found in its reduced form. GSH acts as a coenzyme in antioxidant reactions and is converted to its oxidized form, GSSG, at the end of the reaction. GSSG must then be converted back to its reduced form, GSH, in order to be used again in antioxidant reactions. The enzyme responsible for this conversion is GR. GR is a homodimer flavoprotein composed of 52 kDa monomers. GR catalysis the conversion of GSSG to GSH, thereby maintaining high GSH levels and low GSSG levels within the organism and thus preserving a suitable reducing environment [8. 9]. Thus, GR plays an important role in the regulation,

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modulation, and maintenance of cellular redox homeostasis. Recent studies have highlighted the close relationship between GR levels in cells or blood and diseases such as liver cancer and colon cancer [10-14]. Oxidative damage cannot be prevented due to GR and GSH deficiency. Furthermore, numerous disorders, including Alzheimer's, Parkinson's, liver and lung diseases, sickle cell anemia, cancer, and diabetes, stem from GR and GSH deficiencies [15.16].

In this study, GSH, GSSG and GR were measured in erythrocytes obtained from colon cancer patients in order to evaluate the relationship between GR enzyme, which is responsible for GSH and glutathione regeneration, and colon cancer.

2. Materials and Methods

2.1. Patient and control groups

This study included 30 healthy subjects and 30 patients diagnosed with colon cancer Table 1.

2.2. Blood samples

3 ml of venous blood samples from the individuals in the patient and control groups were taken into tubes containing K3-EDTA, and the tubes were transferred to the laboratory at +4˚C. The erythrocyte isolation process was started immediately in the samples that reached the laboratory. Blood samples were centrifuged at 2500 xg for 10 minutes at +4˚C. After the supernatant was taken, isotonic NaCl solution 3 times its volume was added to the formed elements remaining in the tube. The erythrocytes were washed by gently inverting and centrifuged again at 2500 xg at +4˚C for 10 minutes. This process was repeated 3 times. Then, the erythrocytes were hemolyzed by the freeze-thaw method by adding distilled water at a ratio of 1:5 v/v. After this process, the hemolysate was centrifuged at 22,000 xg at +4˚C for 60 minutes to separate the cell membranes. The formed erythrocyte hemolysates were divided into 1.5 ml Eppendorf tubes to be used in all analyzes and stored at -20˚C [17].

2.3. Determination of glutathione reductase activity

Glutathione reductase activity in erythrocytes was determined according to the method described by Tietze and colleagues [18]. Enzyme activity was measured spectrophotometrically at 340 nm by monitoring the absorbance difference during the oxidation of NADPH+H+ to NADP+. Results were reported as U/gHb. Total hemoglobin concentration was determined in g/dl using the cyanomethemoglobin assay [19].

2.4. Measurement of oxidized and reduced glutathione

Glutathione measurement in erythrocytes was performed according to the principle defined by Beutler, et. al (1963). In the method, sulfhydryl groups form a chromogen compound with the DTNB (5,5′-dithiobis-(2-nitrobenzoic acid) reagent, and the yellow color formed is read against the reagent blank at 412 nm [20].

The calibration curve was plotted with 0.1, 0.2, 0.4, 0.8, 1.6, 3.2, 6.4 nmol/ml GSH solutions prepared from stock GSH solution (10 nmol/ml). The absorbance of the samples was converted to the concentration with the help of this curve, and quantification was made. Erythrocyte GSH values were expressed as nmol GSH/Hb by proportioning to hemoglobin values.

The amount of oxidized glutathione was determined by the method used to measure the amount of total GSH. Differently, only the amount of GSSG was measured by derivatizing the homogenate with 2-Vinylpyridine before use. Obtained absorbance values were converted into concentration values using the standard graph prepared for total GSH.

2.5. Statistical analysis

Results were analyzed using analysis of variance, Tukey test, Kruskal-Wallis test, Mann Whitney U test, and correlation analysis. $P<0.05$ was considered as the significance level.

3. Results

Thirty patients with colon cancer and 30 healthy control subjects were included in the study. The characteristic features of the patient and control groups are shown in Table 1. The means GR activity and GSH, GSSG, and GSH/GSSG values of the patient and control groups are shown in Table 2. Comparison of intra-group parameters according to smoking status Table 3 and Comparison of intra-group parameters according to gender Table 4 are showed.

When comparing the GR activities of the groups, it was found that individuals with colon cancer had statistically significantly higher GR activities compared to the control group ($p<0.05$), Table 2. When comparing the GSH values of the groups, it was found that the GSH levels of patients with colon cancer were lower than those of the control group, and this difference was statistically significant ($p<0.05$), Table 2. Similarly, when comparing the GSSG values of the groups, it was found that the GSSG level of individuals with colon cancer was significantly higher than that of the control group ($p<0.05$), Table 2. When comparing the GSH/GSSG ratios of the groups, as shown in Table 2, it was found that the GSH/GSSG ratio of individuals with colon cancer was statistically significantly lower than that of the control group ($p<0.05$).

In the control group, when the differences in GR activity and all other values were statistically evaluated between individuals who smoked and those who did not smoke, the differences were not statistically significant ($p>0.05$), Table 3. Similarly, in the CC patient group, when the differences in GR activity and all other values were statistically evaluated between individuals who smoked and those who did not smoke, the differences were not statistically significant ($p>0.05$), Table 3.

It was determined that the differences between all parameters according to gender were not statistically significant in both the patient and control groups ($p>0.05$), Table 4.

4. Discussion

It is known that free radicals (FRs) and the oxidative stress they cause have significant effects on cancer development. DNA damage caused by the effects of FRs can also alter the expression of radical scavenging enzymes. Changes in enzyme activity affect antioxidant defense [21]. Thanks to GSH's role in radical scavenging, damage caused by ROS is repaired. GSH, glutathione peroxidase, and glutathione S-transferase are common substrates of enzymes involved in ROS detoxification reactions. Oxidized glutathione must be reduced again to be able to show activity in antioxidant reactions [22]. This reaction is carried out by GR in the presence of $NADPH+H^+$ [23,24]. A decrease in GSH and GR activity, which play an important role in antioxidant defense, leads to insufficient antioxidant capacity in the body. One type of cancer in which FRs may play a role in the etiopathogenesis is colorectal cancer., which ranks third among causes of death worldwide [25,29]. Therefore, we sought to determine whether there was a change in oxidative stress levels (GSH/GSSG) and GSH levels, an important component of the antioxidant system, and GR enzyme activity in CC patients by comparing them with control group values.

Many studies conducted with cancer patients show differences in GR activity. In some studies conducted with CC and Colorectal cancer (CRC) patients, it was observed that GR activity in cancer patients was increased compared to healthy individuals [12, 30, 31]. While no significant difference was found in other studies [32]. Patel et al. (2005) observed in their study of patients with oral cancer that cancer patients had higher GR activity than healthy individuals [33]. Scibior et al. (2008), in their study with patients with gastrointestinal system tumors, reported that gastric cancer patients showed no significant change in GR activity compared to the control group, but colon cancer patients had significantly higher GR activity than the control group [34]. Once again, Saygılı et al. (2003) and Skrzydlewska et al. (2001), along with numerous other studies, have demonstrated that colon cancer patients have significantly higher GR levels than healthy controls [12, 35-39]. In our study, we also found that erythrocyte GR activity was significantly increased in colon cancer patients compared to healthy individuals, and our findings are consistent with many of the studies mentioned above Table 2.

Studies on the antioxidant system in CC patients have observed a decrease in erythrocyte GSH levels and an increase in GSSG levels in patients compared to healthy individuals [35, 40]. In a study conducted by Navarro et al. (1999) using mice with artificially created tumors, a significant decrease in blood GSH levels and a significant increase in blood GSSG levels were observed in tumor-bearing mice compared to pre-tumor formation values [41]. Another study showed that glutathione levels were significantly reduced in colorectal cancer tissue [12]. Similarly, Saygılı et al. (2003) and Skrzydlewska et al. (2001) found that GSH levels decreased while GSSG levels increased in their studies [35, 36]. Two separate studies conducted on CRC patients have demonstrated increased oxidative stress and antioxidant imbalance [28, 30]. Acevedo-Leon's research showed significant differences in GSH and GSSG levels in colorectal cancer patients compared to a healthy control group. In CRC patients, GSH levels decreased by more than 50%, while GSSG levels increased by more than 140%, leading to a significant increase in the serum GSSG/GSH% ratio. This indicates a significant change in the redox status of CRC patients, showing a shift towards oxidation [42. 43]. In this study, we also found that GSH levels in the erythrocytes of individuals with colon cancer were lower than in healthy controls, and that GSSG levels were increased Table 2. The GSH/GSSG ratio showed a significant shift towards oxidative stress in patients Table 2.

Table 1 Distribution of control and patient by mean age of groups, sex and smoking.

Parametreler	**Age**	**Sex**		**Smoking**	
		Male	Female	Yes	No
Control group (n=30)	41.4±2.60	12	18	13	17
Cancer group (n=30)	56.06 ±1.75	16	14	11	19

Table 2 GR activity, GSH, GSSG concentration and GSH / GSSG ratio of control and patient groups.

Parameters ($\bar{X}$ ±SD)	**GR (U/gHb)**	**GSH(nmol/gHb)**	**GSSG (nmol/gHb**	**GSH/GSSG**
Control group	0,86 ± 0,18	11,43± 1,9	3,09 ± 0,48	3,86 ± 1,3
Colon cancer	1,41 ± 0,39	6,96 ± 1,45	3,70 ± 1,17	1,04 ± 0,49
	*p=0.001	*p=0.001	*p=0.001	*p=0.001

*Statistically significant (p <0.05).

Table 3 Comparison of intra-group parameters according to smoking status.

Parameters ($\bar{X}$ ± SD)		**GR (U/gHb)**	**GSH(nmol/gHb)**	**GSSG(nmol/gHb)**	**GSH/GSSG**
Control group	Smoking	0.87 ± 0.19	11.61 ± 2.06	3.08 ± 0.52	3.98 ± 1.49
	No Smoking	0.84 ±0.17	11.30 ± 1.82	3.10 ± 0.46	3.77 ± 1.17
		p=0.630	p=0.851	p=0.950	p=0.818
Cancer group	Smoking	1.47 ±0.44	6.88± 1.55	7.22 ± 1.53	1.08± 0.73
	No Smoking	1.38 ±0.37	7.00 ± 1.43	7.18 ± 0.95	1.01 ± 0.32
		p=0.621	p=0.189	p=0.426	p=0.378

*Statistically significant (p <0.05).

Table 4 Comparison of intra-group parameters according to gender**.**

Parameters ($\bar{X}$ ± SD)		**GR (U/gHb)**	**GSH(nmol/gHb)**	**GSSG(nmol/gHb)**	**GSH/GSSG**
Control group	Male	0.86 ± 0.18	10.77 ± 0.75	3.22 ± 0.26	3.36 ± 0.38
	Female	0.85 ± 0.18	11.87 ± 2.30	3.00 ± 0.57	4.19 ± 1.58
		p=0.886	p=0.472	p=0.099	p=0.138
Cancer group	Male	1.43 ±0.43	6.71± 1.23	7.59 ± 0.63	0.89± 0.21
	Female	1.38 ±0.36	7.23 ± 1.67	6.74 ± 1.48	1.20 ± 0.67
		p=1.000	p=0.257	p=0.085	p=0.110

*Statistically significant (p <0.05).

In this study, when comparing GR activity, an important enzyme in the antioxidant defense system, the values of CC patients were found to be higher than those of the control group. While it was expected that GSH levels would also be higher than those of the control group, our study found that GSH levels were low. The reason for this was that we determined that FR production was higher in individuals with CC, and the evidence for this was that the patients' GSSG levels were much higher than those in the control group. Additionally, we obtained data showing that the GSH/GSSG level was low, indicating a low antioxidant defense and increased oxidation Table 2. Therefore, it demonstrates that excessive GSH is utilized in combating increased oxidative stress in CC individuals. Another reason for low GSH levels

may be that the amount of NADPH+H+ required for GSH regeneration is also insufficient. Ultimately, low GSH levels indicate that the oxidative load in CC individuals is significantly increased Table 2.

When comparing each group statistically with each other in terms of group-internal parameters based on smoking status, no significant differences were found between them Table 3.

In each group, the differences between all parameters based on gender were not statistically significant. Nevertheless, as shown in Table 4, GSH values were measured higher in women than in men in both the control and cancer groups, while GSSG and GR values were found to be higher in men than in women Table 4. These results indicate that antioxidant defense is better in women than in men.

5. Conclusions

In conclusion, this study compared erythrocyte GR enzymes in healthy individuals and CC patients, revealing that CC patients exhibited significantly higher GR enzyme activity. Nevertheless, the reason for GSH levels being lower than GSSG levels may be that the oxidative stress state exceeds antioxidant capacity. Disruptions in GSH homeostasis play a role in the etiology and progression of many human diseases, including cancer. GSH deficiency or a decrease in the GSH/glutathione disulfide (GSSG) ratio increases susceptibility to oxidative stress, which plays a role in cancer progression. Consequently, the adverse effects of oxidative stress may contribute to the development of colon cancer and a more severe prognosis of the disease.

Consequently, given the markedly reduced erythrocyte GSH levels observed in colorectal cancer patients and the increased levels of the GSH-metabolizing GR enzyme in colon tumors, these may be used as clinically useful biomarkers for colon cancer.

These findings support a possible role for GR in colon cancer development through changes in reduced GSH levels. Monitoring GSH/GR system and GSH/GSSG levels in cancer patients will provide information about the course of the disease. We believe that these parameters can be monitored as markers in healthy individuals to track cancer development processes.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Statement of ethical approval

Cumhuriyet University, Faculty of Medicine, Scientific Research Assessment Board has been working with the permission of decision 20120-04 / 10.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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