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Native Thiol, Total Thiol, and Dynamic Disulfide Profile in Patients with Gastrointestinal System Cancer

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Abstract: This study aims to evaluate the use of serum native thiol (NT), total thiol (TT), and dynamic disulfide (DD) levels as biomarkers in patients with gastrointestinal system (GIS) cancer with different cancer types by comparing with healthy controls. A total of 108 subjects consisting of68 patients with GIS cancer and 40 healthy individuals as a control group were included in the study. Serum NT, TT, and DD levels were measured by an automated method developed by Erel. There was a statistically significant difference between NT levels of GIS cancer and the control group ($P = 0.001$). However, there were no significant differences between male and female patients in terms of serum NT levels ($P = 0.08$). Similarly, no significant difference was observed when comparing serum NT levels among GIS cancer types ($P = 0.886$). The serum TT levels were statistically significant difference ($P = 0.013$) in GIS cancer, 141.82 ± 48.24 μmol/l (12.7-243.9) compare to the control group, 166.03 ± 56.23 μmol/l (12.7-326.8). When the serum TT and DD levels of the patients were compared according to gender, no significant difference was found ($P = 0.243$ and $P = 0.362$, respectively). In addition, the TT levels were not significantly difference among GIS malignancies ($P = 0.765$). When the patient and control groups were compared in terms of DD levels, no statistically significant difference was found ($P = 0.378$). In conclusion, it was determined that some parameters differ statistically between patients with GIS cancer and healthy controls. Therefore, there is a significant relationship between the thiol/disulfide balance with GIS cancer. This result suggests that oxidative stress may play a role in the development of the GIS cancer, consistent with the findings in this study, but not in terms of DD levels.

Keywords: Native thiol; Total thiol; Dynamic disulphide; Gastrointestinal system cancers

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1. Introduction

Cancer is an important public health threat worldwide[1]. In 2020, one in five people worldwide is expected to be diagnosed with cancer in their lifetime; therefore, emphasis should be placed on diagnosis, treatment, management, and palliative care as means of prevention to accelerate global cancer control[2]. Cancers have numerous types, depending on its location, the cell from which it originates, and the spectrum of genomic changes that

promote oncogenesis and affect the therapeutic response[3]. Although there are many known types of cancer and standards of care have been developed for certain types of cancers as much as possible, it is consider as an individualized disease[4]. Gastrointestinal system (GIS) cancers are among the most common cancers worldwide[5] and have poor prognosis[6], hence, GIS malignancies cause more deaths worldwide than cancer originating from any organ or system[7]. The poor prognosis of patients diagnosed with GIS cancer has turn primary prevention a potentially attractive approach[5].

Thiols are organic compounds characterized by a sulfhydryl group (–SH) consisting of a sulfur atom attached to a carbon atom and a hydrogen atom[8]. It clears free radicals physiologically and is the main component of the host antioxidant system[9]. Intracellular thiols are mainly reduced by the action of NADPH. In contrast, in extracellular environment, and especially in the plasma compartment, thiols are oxidized at a much lower concentration. A pool of plasma thiol is formed by albumin thiols, protein thiols, and small amounts of low molecular weight thiols such as cysteine (Cys), cysteinyl glycine, glutathione, homocysteine, and γ-glutamylcysteine[10].

Thiol-containing compounds are central to many biochemical and pharmacological reactions. Disulfide bonds have an important role in determining the tertiary structure of proteins. Molecules containing Cys residues are among the most easily metabolized compounds and are easily oxidized by transition metals, or participate in the thiol-disulfide exchange[11]. The disulfide bond is covalently bonded and the connection is also called SS-bond or disulfide bridge. The disulfide bonds formed can be reversibly reduced back to thiol groups, thereby maintaining dynamic thiol-disulfide homeostasis. It plays a critical role in dynamic thiol-disulfide homeostasis, antioxidant protection, detoxification, signal transduction, apoptosis, enzymatic activity regulation, transcription factors, and cellular signaling mechanisms[12].

Protein kinase B1 (AKT1) is activated by platelet-derived growth factor through phosphatidylinositol 3-kinase. Activation of AKT1 can suppress apoptosis in a transcription-independent manner. Mice lacking AKT1 are resistant to cancer due to slowing tumor growth initiated by the large tumor antigen or Neu oncogene[13].

Reducible polyethyleneimine/Akt1SH-siRNA complexes which involve in blocking Akt1 protein translation have been shown to reduce proliferation and increase apoptosis of mouse colon cancer cells *in vitro*, whereas, in an *in vivo* mouse tumor model, these complexes have been demonstrated to reduce tumor proliferation and downregulation of Akt1 compared to controls[14].

Dynamic thiol-disulfide homeostasis defines the healthy state of thiols (-SH) and disulfides (-S-S-) and must be present at certain levels in healthy people. Disruption of this homeostasis causes various pathologies that need to be carefully examined. Studies conducted so far have reported that disruption of this homeostasis causes chronic renal failure, diabetes mellitus, hypertension, cardiovascular diseases, various types of cancer, gestational diseases, chronic inflammatory diseases, and various neurodegenerative diseases[10,15,16]. Therefore, our study aims to elucidate the pathogenic mechanisms associated with GIS cancers and dynamic thiol-disulfide homeostasis and to evaluate its potential as diagnostic, prognostic marker, or therapeutic target in GIS cancers.

2. Materials and methods

2.1. Subjects

Patients who were admitted to the Medical Oncology Outpatient Clinic with GIS complaints at Medicalpark Gaziantep Hospital between 2019 and 2020 were included in the study. Sixty-eight patients aged 18 years and older with a histopathologically confirmed diagnosis of GIS cancer were recruited and 40 age- and sex-matched healthy individuals who were determined by systemic examination were included in the study as the control group. Patients under 18 years of age, with abnormal liver and kidney reserves, and who had previously been treated for cancer were excluded from the study. Patient files were scanned and information such as age, gender, routine laboratory tests, smoking, and alcohol use was obtained. This study was approved by Gaziantep University Clinical Research Ethics Committee dated January 15, 2020 and numbered 2019/493, and all participants were given written informed consent. All cancer patients were diagnosed for the first-time during enrollment and blood samples were taken before starting systemic drug therapy. Blood samples taken from patients diagnosed with GIS cancer were grouped according to the type of cancer (stomach, rectum, bile, liver, colon, pancreas, and anal). After sterilization by wiping the antecubital forearm area with 70% alcohol cotton from 68 patients diagnosed with GIS cancer and 40 age-sex-matched healthy volunteers, one tube (5 ml) of blood was collected for routine analysis. The blood samples taken for the study were kept at room temperature for 20 min, then the blood samples were centrifuged at 4000 rpm for 10 min and the serum was separated. The separated serum was divided into portions into labeled Eppendorf tubes and stored at −80°C before analysis. The samples were transferred from Gaziantep Medicalpark Hospital to Gaziantep University, Medical Biochemistry Department Laboratory, following the cold chain.

2.2. Measurement of serum native thiol (NT), total thiol (TT), dynamic disulfide (DD) profile, and other parameters

Parameters for thiol disulfide balance were measured by the spectrophotometric method using commercially available kits NT Assay Kit and TT Assay Kit (Rel Assay Diagnostics, Turkey). To measure thiol/disulfide blood

levels, reducible disulfide bonds were reduced to form free functional thiol groups. Formaldehyde was used to remove residual sodium borohydride and DTNB (5,5'-dithiobis-(2-nitrobenzoic acid)) products, to detect both reduced and native natural thiol groups. The number of DD bonds was recorded by detecting half the difference between the TT and NT groups. After calculating the native TT and disulfide amounts, disulfide/TT percentage ratios, NT/TT ratios, and disulfide/NT percentage ratios were calculated. Hematologic analyses were performed using XN-1000 Sysmex (Sysmex Corporation, Kobe, Japan) hematology analyzer. All biochemical parameters were analyzed using Abbott Kits (Abbott Laboratories, Chicago, IL, USA), which are manufactured for use with an Architect c16000 Auto-Analyzer.

2.3. Statistical analysis

Statistical analyses were performed using SPSS for Windows 15.0 software. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov–Smirnov test). In the Kolmogorov–Smirnov test, cases where the *P* value was above 0.05 were considered normally distributed. Since the NT and TT values were not normally distributed with *P*-value that was below 0.05 with the Kolmogorov–Smirnov test, the patient groups were compared using Mann–Whitney U test. Kruskal–Wallis test was used to determine the significant difference of the mean NT, TT, and DD serum levels between the patient and control groups.

3. Results

A total of 108 subjects, 68 of whom were in the patient group and 40 were in the control group, were included in the study. Forty-one (56.5%) of the patients were male and 27 (43.5%) were female. The mean age of the patients was 60.8 ± 12.6 (range 29 – 85-years-old). The laboratory values of the individuals are shown in Table 1.

The distribution of GIS cancer was as follows: Colon cancer 20 (29.4%), stomach cancer 18 (26.5%), rectum cancer 11 (16.2%), liver cancer 7 (10.3%), gallbladder and bile duct 5 (7.4%) pancreatic cancer 5 (7.4%), and anal cancer 2 (2.9%). On the other hand, when considering the distribution of GIS cancer types of patients by gender: 6 (22.2%) colon cancer patients, 8 (29.6%) gastric cancer, 4 (14.8%) rectal cancer, 3 (11.1%) liver cancer, 3 (11.1%) bile duct cancer bladder and biliary tract cancers, 2 (7.4%) pancreatic cancer, and 1 (3.7%) anal cancer were detected in the female group. In male patients, 14 (34.1%) colon cancer patients, 10 (24.4%) stomach cancer, 7 (17.1%) rectal cancer, 4 (9.8%) liver cancer, 2 (4.9%) gallbladder and biliary tract cancer, 3 (7.3%) pancreatic cancer, and 1 (2.4%) anal cancer were detected. The distribution of cancer types of patients by gender is shown in Table 2.

Table 1. Mean age of the patients and their blood and biochemical parameters

	Patient (n = 68)	**Patient (n = 68)**
	Mean ± Standard Deviation	**Median**
Age (Years)	60.8 ± 12.6	62
BUN (mg/dl)	15.3 ± 6.5	14
CRE (mg/dl)	0.87 ± 0.27	0.84
AST (U/L)	19.5 ± 9.9	18
ALT (U/L)	26 ± 24.1	16
LDH (U/L)	171.6 ± 44.2	162.5
Albumin (g/dl)	3.8 ± 0.41	3.9
WBC ($10^3/mm^3$)	9.08 ± 3.36	8.67
Neutrophil ($10^3/mm^3$)	5.78 ± 3.08	4.99
Lymphocyte ($10^3/mm^3$)	2.22 ± 1.13	1.93
PLT ($10^3/mm^3$)	333 ± 134	304
HBG (g/dl)	12.5 ± 1.7	12.5
MCV (fl)	84.9 ± 7.81	86.1

The statistical difference between men and women in GIS cancer of different types was investigated and no significant difference was found (*P* = 0.921). In the patient group, mean serum NT levels were found to be 108.25 ± 36.81 μmol/l (10.5 – 201.3). In the control group, mean serum NT levels were 132.73 ± 6.05 μmol/l (10.5 – 281.3). When the NT levels of the patient and control groups were compared, a statistically significant difference was found (*P* = 0.001) (Figure 1). However, when the serum NT levels between male and female patients and the serum NT levels of GIS malignancies among themselves were compared, no statistically significant difference was found (*P* = 0.08 and *P* = 0.886, respectively).

The mean serum TT levels in the patient group were 141.82 ± 48.24 μmol/l (12.7 – 243.9) while the mean serum TT levels in the control group were 166.03 ± 56.23 μmol/l (12.7 – 326.8). A statistically significant difference was found when we compared serum TT levels between the patient and control groups (*P* = 0.013) (Figure 2). However, statistically significant difference was not observed when female and male patients were compared in terms of serum TT levels, (*P* = 0.243).

Serum TT levels in GIS malignancy of different types were as follow: Anal cancer 148.05 ± 59.18 μmol/l (106.2 – 189.9), stomach cancer 152.75 ± 46.16 μmol/l (35.8 – 215.2), colon cancer 133.365 ± 40.86 μmol/l (35.8 – 186.7), rectum cancer 143.78±62.8 μmol/l (12.7-243.9), liver cancer 146.75 ± 68.39 μmol/l (15.2 – 220.2), gallbladder and bile duct tract 134.48 ± 46.78 μmol/l (87.2 – 190.2), and pancreatic cancer 129.96 ± 28.9 μmol/l (96.9 – 159.1).

Table 2. Distribution of cancer types of patients by gender

Cancer Type	Female (N)	Female (%)	Male (N)	Male (%)	Total (N)	Total (%)
Colon cancer	6	22.2	14	34.1	20	29.4
Gastric cancer	8	29.6	10	24.4	18	26.5
Rectal cancer	4	14.8	7	17.1	11	16.1
Liver cancer	3	11.1	4	9.8	7	10.3
Gallbladder and bile duct cancer	3	11.1	2	4.9	5	7.4
Pancreatic cancer	2	7.4	3	7.3	5	7.4
Anal cancer	1	3.7	1	2.4	2	2.9
Total	27		41		68	

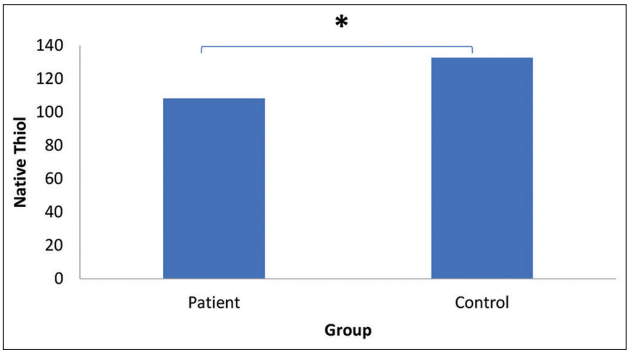

Figure 1. Native thiol (NT) levels of patient and control groups. Concentration of serum NT levels in patients (n = 68), and the healthy group (n = 40) (*P < 0.001).

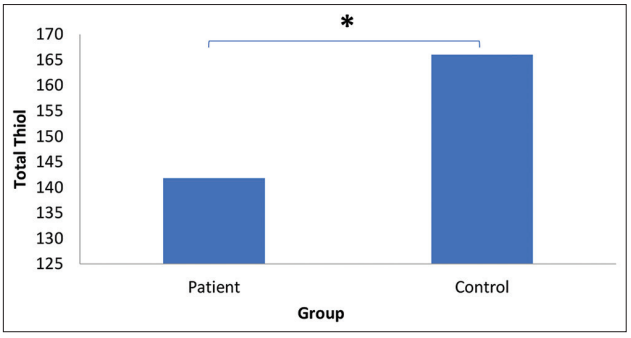

Figure 2. Total thiol (TT) levels of patient and control groups. Concentration of serum TT levels in patients (n = 68), and the healthy group (n = 40) (*P < 0.013).

Statistically significant difference was not found when serum TT levels were compared among GIS malignancy of different types (P = 0.765, Figure 3).

The mean serum DD levels in the patient group were 16.7 ± 16.2 µmol/l (0.4 – 38.35). In the control group, mean serum DD levels were 16.5 ± 15.65 µmol/l (0.4 – 43.1). DD levels of the patient and control groups were compared and no significant difference was found (P = 0.378, Figure 4). In addition, statistically significant difference was not found when the serum DD levels of female and male patients were compared (P = 0.362). Furthermore, statistically significant difference was absence (P = 0.865) when serum DD levels were compared between GIS malignancy of different types.

4. Discussion

Due to poor prognosis, high number of confirmed cases, and low survival rate of GIS cancers due to the delay in diagnosis and treatment, more studies are needed to identify new approaches in preventing, diagnosing, and treating GIS cancers. In this context, we investigated dynamic thiol-disulfide homeostasis in GIS malignancies, which is an essential biomarker in many types of cancer, to bring new insights on the role of these biomarkers in GIS cancers. In one of our previous publications, we investigated the relationship between prostate cancer and dynamic thiol-disulfide homeostasis and we found that homeostasis was impaired in these prostate cancer patients. This promising result prompted us to study the involvement of dynamic thiol-disulfide homeostasis in other cancer types[16-20]. The lack of studies on the involvement of dynamic thiol-disulfide homeostasis in GIS malignancies supports the originality of our research.

In this study, a statistically significant difference was found when the GIS patient and control groups were compared in terms of NT and TT levels. However, statistically significant difference was not found when serum NT and TT levels were compared in terms of GIS malignancies. On the other side, when the serum DD levels in our study were compared between the patient and control groups, no statistically significant difference was found.

It is known that oxidants modulate cell proliferation and apoptosis and induce the synthesis of growth factors that play an essential role in tumor growth and invasion. Antioxidant enzymes and thiol proteins, which regulate the cellular redox state, constitute the most critical cellular protection against oxidants. Consequently, they are also associated with both carcinogenesis and tumor

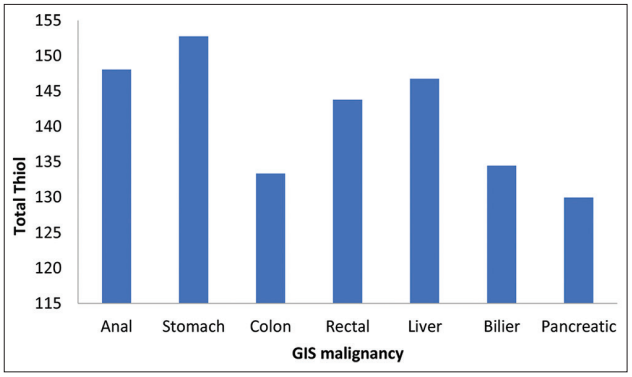

Figure 3. Total thiol levels of GIS malignancies.

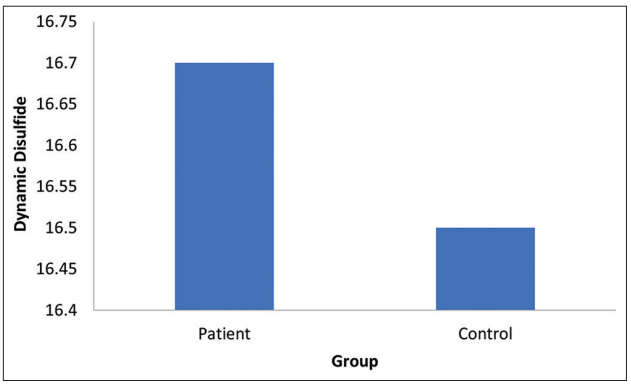

Figure 4. The mean serum dynamic disulfide levels.

progression[21]. The main antioxidant enzymes such as superoxide dismutases, catalase, peroxiredoxins, glutamate-cysteine ligase, thioredoxins, and thiol-disulfide regulatory pathways in cell proliferation and apoptosis were investigated on lung cancers. Thiol proteins not only increase cell survival and proliferation but also protect both non-malignant and malignant cells against oxidants, radiation, and chemotherapies. However, the functional significance of these thiol proteins remains unresolved and awaits future studies[22].

In another study, serum samples for thiol-disulfide were obtained from patients with gastric cancers and a healthy control group. Thiol-disulfide homeostasis was also measured according to clinical and laboratory characteristics. The patient group's natural thiol and TT levels were significantly lower than the controls. In conclusion, disturbances in thiol-disulfide homeostasis may play a role in the pathogenesis of gastric cancer[23]. In another study that evaluate the role of thiol-disulfide homeostasis in colorectal cancer using a new method, natural thiol, disulfide, and TT levels were found to be significantly lower in patients than in the control arm. This suggests that thiol and disulfide may play an important role in the pathogenesis of colorectal cancers[20]. Furthermore, one study reported that changes in the gene expression of matrix metalloproteinase genes, which play a role in tumor invasion, and β-catenin, which plays a role in oncogenic transformation in gastric cancer biopsy samples were completely dependent on oxidative stress[24].

Modulation of oxidative stress in cancer with anti-oxidants is promising strategies because of their zero toxicity and safety profile. The molecular pathways that activate or deactivate oxidative stress, and potential therapeutic interventions which target reactive oxygen species are suitable to treat GIS-related cancers. Therefore, these molecules may serve as a basis for future drug design to combat pancreatic ductal adenocarcinoma. On the other hand, in clinical trials, antioxidants are normally tested in combination with other chemotherapies, where their effects may be hindered by the other drug. However, limitations such as funding acquisition arise when testing antioxidants as single agents in clinical trials. It is believed that the significant potential use of antioxidants to increase the chemosensitivity of standard chemotherapy will promote the interest to use antioxidants and their combinations in the near future[25].

In a study that evaluate the relationship between NT, disulfide, and TT concentrations and serum biomarkers of corcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) in colorectal cancer patients. Thiol disulfide parameters showed no significant difference among CEA and CA 19-9 levels. According to the study, there was no significant relationship between NT, disulfide, and TT with colorectal cancer[26].

Although we compare the levels of all three types of biomarkers (NT, TT, and DD) with GIS cancer of different types in this study, we failed to obtain a significant association between them. One of the possible reasons is due to huge different number of subjects belonging to each cancer type. Therefore, evaluating more samples of cancer types of the same origin in future may help to reveal the true relationship between these biomarkers with GIS cancer of different types.

5. Conclusion

Our study revealed that some parameters differ statistically between patients with GIS cancer and healthy controls. This suggests a significant relationship between GIS cancer and thiol/disulfide balance. Our results highlight that oxidative stress may play a role in developing GIS disease. Changes in lifestyle that reduce oxidative stress may be beneficial in the prevention of this disease. However, GIS cancers are a very heterogeneous group of diseases, and investigation of individual cancer type in larger populations in terms of thiol/disulfide balance may yield more accurate results. Determining these parameters through non-invasive, easy, inexpensive, and reliable methods may help in the management of the disease.

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Conflict of interest

The authors declare that they have no competing interests.

Ethical approval

The approval was obtained from the Gaziantep University Faculty of Medicine Ethics Committee and it was studied following the Helsinki Declaration Rules. All patients participating in the study were informed about the study and their written consent was obtained.

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