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Glutathione, glutathione-dependent enzymes and antioxidant status in gastric carcinoma patients

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Summary
Oxidative stress plays an important role in malignant transformation and is postulated to be associated with increased lipid peroxidation. The aim of this study was to determine the extent of lipid peroxidation with the antioxidant status in patients with gastric cancer. The study population consisted of fifty newly diagnosed gastric cancer patients and an equal number of age- and sex-matched healthy control subjects. Lipid peroxidation as evidenced by thiobarbituric acid reactive substances (TBARS), and also the status of enzymatic (superoxide dismutase – SOD, catalase – CAT, glutathione peroxidase – GPx, glutathione reductase – GR, glutathione S-transferase – GST) and non-enzymatic (reduced glutathione – GSH) antioxidants, were determined. Enhanced lipid peroxidation with concomitant depletion of antioxidants was observed in gastric cancer patients as compared to healthy control subjects. The present study highlights the occurrence of lipid peroxidation and possible breakdown of antioxidant status in patients with gastric carcinoma.

Key words: gastric cancer; lipid peroxidation; antioxidants; glutathione; GSH-dependent enzymes

INTRODUCTION
Gastric cancer is a leading cause of illness and death from cancer worldwide, with nearly a million new cases diagnosed each year. Indeed, it is the fourth most common cancer and the second leading cause of cancer death worldwide. The incidence of gastric cancer is different throughout the world and 60% of deaths from gastric cancer occur in developing countries (Forman and Burley 2006, Liu et al. 2008). In India, some earlier studies showed a relatively higher incidence of stomach cancer among males in Chennai during 1997 to 1998 (age-adjusted rate (AAR) = 13.2/105) and among women it is next to cancer of the breast (AAR = 7.0/105) (Parkin et al. 2005). The increase of gastric cancer and a relatively late diagnosis are serious clinical problems (Scibior et al. 2008).

Stomach cancer can develop in any part of the stomach and it may spread throughout the stomach and to other organs, particularly the esophagus and...
the small intestine (Kim et al. 2007). The etiology of gastrointestinal tract tumours is a multifactorial process and possible mechanisms leading to carcinogenesis have not yet been clarified. Growing evidence indicates that reactive oxygen species (ROS) and their reactive derivatives are associated with different stages of this process, either through structural DNA damage, interaction with oncogenes and tumour suppressor genes, or immunological mechanisms (Kireev 2002, Marnett 2002, Scibior et al. 2008).

ROS are continuously produced in aerobic organisms as byproducts of normal energy metabolism. These reactive species may react with a variety of biomolecules, including lipids, carbohydrates, proteins, nucleic acids and macromolecules of connective tissue, thereby interfering with cell function (Halliwell and Gutteridge 1986, Sies 1997). ROS have been found to be involved in a wide variety of cellular functions but they can be both essential to and highly toxic in cellular homeostasis. ROS in a controlled sphere are physiologically relevant in exerting a variety of biochemical reactions that regulate many important physiological functions including defense against microorganisms, cell signalling, vascular control, cell generation and degeneration, control of cellular homeostasis and presumably many other unknown essential functions (Mates et al. 1999, Johansen et al. 2005).

Antioxidants constitute the foremost defense system that limit the toxicity associated with free radicals. Cells have developed a comprehensive array of antioxidants that act co-operatively in vivo to combat the deleterious effects of free radicals. Superoxide dismutase (SOD) and catalase (CAT) are considered primary antioxidant enzymes since they are involved in the direct elimination of ROS. SOD scavenges the superoxide radical (O$_2^-$) by converting it to hydrogen peroxide (H$_2$O$_2$) and hence reduces the toxic effects due to this radical or other free radicals derived from secondary reactions. CAT subsequently reacts with H$_2$O$_2$, and decomposes it into water and molecular oxygen (Halliwell and Gutteridge 1986, Vattem and Shetty 2004).

Reduced glutathione (GSH) is known to have multifaceted physiological functions including antioxidant defence, detoxification of electrophilic xenobiotics, modulation of redox regulated signal transduction, storage and transport of cysteine, regulation of cell proliferation, synthesis of deoxyribonucleotide, regulation of the immune response and regulation of leukotriene and prostaglandin metabolism (Sen 2000, Pastore et al. 2003). Glutathione peroxidase (GPx) catalyses the reduction of H$_2$O$_2$ and organic hydroperoxides with the simultaneous oxidation of GSH (Jernstrom et al. 1993, Hayes et al. 1999). Glutathione S-transferase (GST) utilises GSH to detoxify reactive oxygen species and free radicals, as well as various other compounds with known mutagenic and/or carcinogenic activities, which are present in the human diet. GST catalyses their conjugation with GSH, making these compounds less biologically active and more water soluble, thus facilitating their excretion via urine and bile (Tsuchida and Sato 1992, Cotton et al. 2000). Glutathione reductase (GR) in the presence of NADPH catalyses the reduction of oxidized glutathione (GSSG) to reduced glutathione, and serves to maintain an appropriate level of, cosubstrate for GPx and GST (Hayes et al. 1999).

A delicate balance between the generation of free radicals and endogenous as well as exogenous antioxidants is of critical importance for the physiological functioning of the cell. It has been proposed that a net pro-oxidant state, which occurs when there is a loss of homeostasis between ROS generation and detoxification, i.e., oxidative stress, results in lipid peroxidation and DNA damage leading to carcinogenesis (Khanzode et al. 2003, Nishikawa 2008). Several reports have demonstrated that increases in the oxidant/antioxidant ratio are directly correlated with tumour progression, angiogenesis, and migration/invasion (Ho et al. 2001, Kumaraguruparan et al. 2002, Skrzydlewska et al. 2003, Storz 2005, Hwang et al. 2007, Nishikawa 2008, Pasupathi et al. 2008, Scibior et al. 2008). Low activity of SOD, CAT and GPx respectively is reported in a variety of tumour cells. Immunohistochemical studies have revealed that early lesions of human and animal cancers have low levels of antioxidant enzymes (Nishikawa 2008). Laurent et al. (2005) have reported that SOD and CAT activities were much lower in mouse colon carcinoma. Gupta et al. (2001) reported that the attenuation of CAT in malignantly transformed cell lines was mainly responsible for the elevated ROS levels in these cells. Scibior et al. (2008) have reported that GSH and enzymes cooperating with it, such as GPx, GST and GR, were lower in gastric carcinoma patients than in healthy subjects. These findings strongly suggest that ROS are not efficiently removed in most tumour tissues. The detection and measurement of lipid peroxidation is most frequently cited as evidence to support the involvement of free radicals in human diseases and toxicology. We therefore undertook the present study to assess the extent of lipid peroxidation and the status of enzymatic (SOD, CAT, GPx, GR and GST) and non-enzymatic (GSH) antioxidants in patients with gastric cancer and in their control counterparts.
MATERIALS AND METHODS

Drugs and chemicals
All the drugs and biochemicals used in this experiment were purchased from Sigma Chemical Company Inc., St Louis, USA. The chemicals were of analytical grade.

Study population
Fifty newly diagnosed gastric cancer patients (Mean age: 59.7 ± 9.4 years) and 50 healthy volunteers (Mean age: 55.2 ± 11.2 years) participated in this study were recruited from Kovai Medical Centre and Hospital (KMCH), and K. G. Hospital, Coimbatore, Tamil Nadu, India, during the period January 2006 to January 2008. All primary gastric cancers were diagnosed by histological examination (using gastric biopsy samples). The study population (age-matched male subjects) was selected on inclusion and exclusion criteria. The patients were not receiving chemotherapy or radiotherapy at the time of the study. Exclusion criteria for patients were other medical illnesses including endocrine, metabolic or autoimmune disorders that may reflect on free radical status. Informed consent was obtained from all the participants. General health characteristics such as age, sex, smoking status, alcohol consumption, and dietary habits, particularly as related to preference for spicy or salty foods, were investigated by a self-administered questionnaire.

Blood collection and erythrocyte lysate preparation
Blood samples were collected by venous puncture in heparinized tubes and the plasma was separated by centrifugation at 1000×g for 15 min. After centrifugation, the buffy coat was removed and the packed cells were washed three times with physiological saline. A known volume of the erythrocytes was lysed with hypotonic phosphate buffer (pH 7.4). The hemolysate was separated by centrifugation at 2500×g for 15 min at 2 °C.

Biochemical measurements
Estimation of blood glucose and hemoglobin (Hb)
The blood glucose level was estimated by a fully automated clinical chemistry analyser (Hitachi 912, Boehringer Mannheim, Germany). Total hemoglobin and blood cell count (RBC and WBC) were determined using an automated hematology analyser (ABX Pentra XL 80, USA)

Estimation of lipid peroxidation
Lipid peroxides were estimated by the measurement of thiobarbituric acid reactive substances (TBARS) in plasma by the method of Yagi (1978) and in erythrocytes by the method of Donnan (1950). The pink chromogen produced by the reaction of thiobarbituric acid with malondialdehyde, a secondary product of lipid peroxidation, was estimated. Results were expressed as nmol/ml for plasma and pmol/mg Hb for erythrocytes.

Assay of superoxide dismutase (SOD) and catalase (CAT)
SOD was assayed utilizing the technique of Kakkar et al. (1984) based on inhibition of the formation of nicotinamide adenine dinucleotide, phenazine methosulfate and amino blue tetrazolium formazan. A single unit of enzyme was expressed as a 50% inhibition of NBT (Nitroblue tetrazolium) reduction/min/mg Hb. CAT was assayed colorimetrically at 620 nm and expressed as µmol of H₂O₂ consumed/min/mg Hb as described by Sinha (1972). The reaction mixture (1.5 ml) contained 1.0 ml of 0.01M phosphate buffer (pH 7.0), 0.1 ml of hemolysate and 0.4 ml of 2M H₂O₂. The reaction was stopped by the addition of 2.0 ml of dichromate-acetic acid reagent (5% potassium dichromate and glacial acetic acid were mixed in 1:3 ratio).

Estimation of reduced glutathione (GSH)
The GSH content was determined by the method of Ellman (1959). 1.0 ml of plasma was treated with 0.5 ml of Ellmans reagent (19.8 mg of 5,5'-dithiobisnitro benzoic acid – DTNB in 100 ml of 0.1% sodium nitrate) and 3.0 ml of 0.2M phosphate buffer (pH 8.0). The absorbance was read at 412 nm. The erythrocyte GSH content was determined with dithionitrobenzoic acid using the method described by Beutler and Kelley (1963). GSH content was expressed as mg/dl.

Assay of glutathione peroxidase (GPx) and glutathione reductase (GR)
GPx activity was measured by the method described by Rotruck et al. (1973) with modifications. Briefly, the reaction mixture contained 0.2 ml of 0.4M Tris-HCl buffer pH 7.0, 0.1 ml of 10mM sodium azide, 0.2 ml of hemolysate, 0.2 ml glutathione and, 0.1 ml of 0.2mM hydrogen peroxide. The contents were incubated at 37 °C for 10 min. The reaction was arrested by 0.4 ml of 10% TCA, and centrifuged. The supernatant was assayed for glutathione content by using Ellmans reagent. GPx activity was expressed as µmoles of GSH consumed/min/g Hb. GR activity was assayed using oxidized glutathione as a substrate according to the method described by Carlberg and Mannervic (1985). The method was based on the absorbance change at 340 nm due to oxidation/reduction of NADPH/NADP⁺. GR activity was expressed as µmol of NADPH oxidized/h/ml.
**Assay of glutathione-S-transferase (GST)**

GST activity was determined spectrophotometrically by the method of Habig et al. (1974). The reaction mixture (3 ml) contained 1.0 ml of 0.3mM phosphate buffer (pH 6.5), 0.1 ml of 30mM 1-chloro-2,4-dinitrobenzene (CDNB) and 1.7 ml of double distilled water. After preincubating the reaction mixture at 37 °C for 5 min, the reaction was started by the addition of 0.1 ml of hemolysate and 0.1 ml of glutathione as substrate. The absorbance was followed for 5 min at 340 nm. GST activity was expressed as µmol of CDNB–GSH conjugate formed/min/mg Hb.

**Statistical analysis**

All data were expressed as mean ± SD. The statistical significance was evaluated by the Student’s t test using the Statistical Package for the Social Sciences (SPSS Cary, NC, USA) version 10.0 at the significance level $\alpha=0.05$.

**RESULTS**

Information about the parameters investigated is shown in Table 1. The study population consisted of 100 male subjects (age-matched) divided into two groups viz., healthy control subjects ($n=50$) and gastric cancer patients ($n=50$). The mean age limit was 59.7 ± 9.4 years in gastric cancer patients and 55.2 ± 11.2 years in healthy controls. The decrease in body mass index (BMI) in gastric cancer patients (31 ± 7.8 kg/m²) when compared to healthy control subjects (37 ± 9.2 kg/m²) was statistically significant. An increased number of hypertensives, smokers and alcoholics are observed in gastric cancer patients compared with health control subjects. Diabetic participants were defined as those with a fasting blood glucose concentration $\geq 120$ mg/dl.

Table 2 shows the levels of fasting blood glucose, total hemoglobin, hematocrit, and blood cell (RBC and WBC) count in gastric cancer patients and healthy control subjects. RBC count, hemoglobin (Hb) and hematocrit were significantly decreased in gastric carcinoma patients when compared with healthy control subjects. However, the levels of fasting blood glucose in gastric cancer patients and healthy control subjects did not differ significantly. In addition, WBC counts significantly increased in gastric carcinoma patients when compared to healthy control subjects.

Table 3 shows the levels of plasma and erythrocyte TBARS and GSH in gastric cancer patients and healthy control subjects. Lipid peroxidation indicated by TBARS level was significantly higher in both plasma and erythrocytes in patients with gastric cancer compared to healthy control subjects. The decrease in the levels of plasma and erythrocyte GSH in gastric cancer patients compared with healthy control subjects was statistically significant. The enzymatic antioxidant profile in the circulation of gastric carcinoma patients and healthy control subjects is presented in Table 4. A significant decrease in the activities of SOD, CAT, GPx, GR and GST in the erythrocyte lysate was seen in gastric cancer patients as compared to the healthy control subjects.

**DISCUSSION**

Previous studies performed in a variety of organisms have demonstrated that decreases in oxidant burden can prolong life span and prevent tumour development. Redox reactions can contribute to progression to malignancy by increasing mutagenesis, inhibiting differentiation, promoting mitogenesis, converting proto-oncogenes into oncogenes, and inactivating the tumour-suppressor gene (Dreher and Junod 1996, Hussain et al. 2003). In general, malignant cells exhibit enhanced production of ROS and an altered expression of cellular antioxidants that metabolize ROS (Codandabany 2000, Skrzydlewska et al. 2003, Hwang et al. 2007, Scibior et al. 2008).

The process of lipid peroxidation is one of oxidative conversion of polyunsaturated fatty acids to products known as malondialdehyde (MDA) or lipid peroxides, which is the most studied, biologically relevant, free radical reaction. It is suggested that MDA itself, because of its high cytotoxicity and inhibitory action on protective enzymes, acts as a tumour promoter and a co-carcinogenic agent (Bakan et al. 2002, Niederhofer et al. 2003). In addition to the deleterious effects of ROS on human cells, oxidative injury can lead to apoptosis. Dysregulation of apoptosis has a role in gastrointestinal diseases, including cancer. Oxidative stress can modulate the apoptotic programme and could cause gastrointestinal cancer (Bjelakovic et al. 2004).

Lipid peroxides were found in healthy subjects, suggesting that oxygen free radicals are also produced in the normal state probably as a consequence of normal metabolic processes. In our study we found an increased concentration of TBARS in plasma and erythrocytes from patients with gastric cancer, indicating that there is a non-specific over-production of free radicals in some phases of those diseases. This may also be due to the excessive generation of lipid peroxidation.
Table 1. **Demographic characteristics of gastric cancer and healthy control subjects.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy Control Subjects</th>
<th>Gastric Cancer Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of subjects</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>55.2 ± 11.2</td>
<td>59.7 ± 9.4*</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>37 ± 9.2</td>
<td>31.0 ± 7.8*</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>-</td>
<td>Gastric adenocarcinoma</td>
</tr>
<tr>
<td>Smokers</td>
<td>12.9%</td>
<td>25.0%</td>
</tr>
<tr>
<td>Alcohols intake</td>
<td>15.0%</td>
<td>29.7%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.5%</td>
<td>18.0%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.3%</td>
<td>5.0%</td>
</tr>
</tbody>
</table>

Values are given as mean ± S.D from fifty subjects in each group.
* statistically significant gastric cancer patients as compared with healthy controls

Table 2. **Blood characteristics of the subjects investigated.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy Control Subjects</th>
<th>Gastric Cancer Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>101.5 ± 9.0</td>
<td>99.3 ± 17.0</td>
</tr>
<tr>
<td>Total hemoglobin (g/dl)</td>
<td>14.8 ± 1.6</td>
<td>10.0 ± 1.3*</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>44.1 ± 4.2</td>
<td>23.0 ± 6.1*</td>
</tr>
<tr>
<td>RBC count (10⁶/µl)</td>
<td>5.5 ± 0.7</td>
<td>3.1 ± 0.6*</td>
</tr>
<tr>
<td>WBC count (10⁶/µl)</td>
<td>7.8 ± 2.0</td>
<td>11.3 ± 2.6*</td>
</tr>
</tbody>
</table>

Symbols as in Table 1

Table 3. **Plasma and erythrocyte TBARS and GSH in gastric cancer and healthy control subjects.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy Control Subjects</th>
<th>Gastric Cancer Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBARS (nmol/ml)</td>
<td>2.96 ± 0.21</td>
<td>7.12 ± 0.25*</td>
</tr>
<tr>
<td>GSH (mg/dl)</td>
<td>36.18 ± 1.67</td>
<td>25.09 ± 3.14*</td>
</tr>
<tr>
<td><strong>Erythrocyte</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBARS (nmol/ml)</td>
<td>3.26 ± 0.61</td>
<td>8.26 ± 0.93*</td>
</tr>
<tr>
<td>GSH (mg/dl)</td>
<td>56.27 ± 7.52</td>
<td>44.43 ± 6.65*</td>
</tr>
</tbody>
</table>

Symbols as in Table 1
Table 4. **Enzymatic antioxidant status in erythrocyte lysate of gastric cancer and healthy control subjects.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy Control Subjects</th>
<th>Gastric Cancer Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOD (U/\text{mg Hb})</td>
<td>3.21 ± 0.36</td>
<td>2.54 ± 0.17*</td>
</tr>
<tr>
<td>CAT (U/\text{mg Hb})</td>
<td>67.5 ± 7.60</td>
<td>50.7 ± 6.70*</td>
</tr>
<tr>
<td>GPx (U/\text{mg Hb})</td>
<td>8.15 ± 1.69</td>
<td>6.53 ± 0.85*</td>
</tr>
<tr>
<td>GR (U/\text{mg Hb})</td>
<td>35.40 ± 2.53</td>
<td>22.73 ± 3.00*</td>
</tr>
<tr>
<td>GST (U/\text{mg Hb})</td>
<td>2.10 ± 0.30</td>
<td>1.12 ± 0.35*</td>
</tr>
</tbody>
</table>

Symbols as in Table 1
A – One unit of activity was taken as the enzyme reaction, which gave 50% inhibition of NBT reduction/min/mg Hb
B – \( \mu \text{mol of H}_2\text{O}_2 \) consumed/min/mg Hb
C – \( \mu \text{mol of GSH} \) consumed/min/mg Hb
D – \( \mu \text{mol of NADPH oxidized} \)/h/ml
E – \( \mu \text{mol of CDNB–GSH conjugate formed} \)/min/mg Hb


The impaired antioxidant system may favour accumulation of free radicals. It has been found that low levels of essential antioxidants in the circulation are associated with an increased risk of cancer (Diplock 1991). Alternatively, it is possible that the antioxidant system is impaired as a consequence of an abnormality in the antioxidative metabolism due to the cancer processes. Decreased activity of SOD has been reported in pathological conditions including malignancies (Arivazhagan et al. 1997). Superoxide, a highly diffusible radical, can transverse membranes and cause deleterious effects at sites far from the tumour. It is possible that lipid peroxidation of erythrocytes in patients with gastric cancer is due to \( \text{O}_2^- \) produced by the tumour as well as to the low activity of SOD within red cells.

The antioxidant enzyme, catalase, is widely distributed in all animal tissues and is highly active in the red blood cells. It has been suggested that it plays an important role in the protection of erythrocytes against oxidative stress (Scott et al. 1991). Studies have shown that the administration of CAT results in protection against \( \text{H}_2\text{O}_2 \)-mediated lipid peroxidation. Several studies have shown a decrease in CAT activity in cancer as part of a severe impairment of antioxidant systems in cancerous tissues (Arivazhagan et al. 1997, Codandabany 2000). The increase in the erythrocyte lipid peroxidation levels in patients with gastric cancer can be correlated to the reduction in CAT activity.

Glutathione and glutathione dependent enzymes have been known to be of central importance in the detoxification of peroxides, hydroperoxides, xenobiotics and drugs. Oxidative stress may cause changes in the glutathione redox state in cancer tissues. It has been reported that MDA might react with amino acid residues of proteins and lead to their oxidative modification. This aldehyde also has the ability to increase oxidative stress by promoting cellular consumption of glutathione and by inactivating glutathione peroxidase (Gerber et al. 1996, Polat et al. 2002).

Glutathione, a widely distributed cellular reductant is a metabolic regulator and putative indicator of health. Blood glutathione levels are believed to be predicatoors of morbidity and mortality (Lang et al. 1992). GSH plays a key role in protecting cells against electrophiles and free radicals. GSH can act directly as a free radical scavenger by neutralising HO\(^{-}\), or indirectly by repairing initial damage to macromolecules inflicted by HO\(^{-}\). This is essential in the maintenance of the protein and non-protein SH groups in reduced form (Sies 1999, Della Rovere et al. 2000). A marked decrease in blood GSH in circulation has been reported in several diseases including malignancies (Abou-Ghalia and Found 2000, Estrela et al. 2006, Lin and Yin 2007, Scibior et al. 2008). The lower GSH levels in seen in gastric cancer patients support the hypothesis that glutathione...
status in inversely related to malignant transformation.

Glutathione peroxidase and glutathione-S-transferase that use GSH as a substrate play a crucial role in protection against the deleterious effects of oxygen free radicals and xenobiotics. The formation of GSSG during the reduction of peroxides, or as a consequence of free-radical scavenging, is potentially cytotoxic. Thereby, the activity of GR represents one of the most important determinants of cellular protection against oxidative stress (Boisio et al. 1990, Masella et al. 2005). Robinson et al. (1979) found a tendency for blood GPx to decrease with cancer progression. We also observed a significant decrease in the activities of GPx, GST and GR in patients with gastric cancer. The depletion of GSH may be responsible for the decreased activity of antioxidant enzymes in gastric cancer patients.

In conclusion, our present study suggests a very high production of ROS and oxidative stress in patients with gastric cancer with enhanced lipid peroxidation, and concomitant failure of both the plasma and erythrocyte antioxidant defense mechanisms. This causes changes in GSH concentration as well as in GSH dependent enzyme activities in patients with gastric cancer compared with control subjects.

REFERENCES


