Association between Glutathione-S-Transferase and Gastric Carcinoma: A Case Control Study

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ABSTRACT

BACKGROUND

Gastric carcinoma is the fourth most common cancer type and the second leading cause of cancer deaths worldwide. Every year, around 1 million new cases and 0.7 million deaths are caused due to gastric carcinoma. Gastrointestinal tract is involved in absorption and metabolism of toxic or potentially carcinogenic compounds which may be present in the food we eat. In this context, digestive tract may be considered as a major site of cancer in humans. Glutathione-S-Transferase (GST) is an important metabolizing enzyme, present in the epithelial cells of human GIT. As nearly all reactive, ultimate carcinogenic forms of chemicals are electrophiles, GST is substantially important as a mechanism for carcinogen detoxification. The present study was conducted to evaluate the role of GST in gastric carcinoma and analyse the level of serum GST in patients suffering from gastric carcinoma.

METHODS

This is a case control study, conducted among 50 cases of gastric carcinoma and 50 age sex matched controls. Patients included in this study were diagnosed with gastric carcinoma, after clinical and histological examination. Circulating levels of GST were assayed in the in the serum of control group and in patients with gastric carcinoma, using standardized method.

RESULTS

Mean GST activity in serum was significantly higher ($p < 0001$) in gastric carcinoma patients (8.24 ± 1.94) as compared to control (5.47 ± 0.52). After chemotherapy (12.34 ± 1.05) the activity of GST was significantly higher ($p < 0001$) than before chemotherapy (10.23 ± 2.12). The generation of free radicals is as reflected by increased GST and GST-π activity in carcinoma cases.

CONCLUSIONS

Serum GSTs measurement in plasma may be a useful tumour marker in stomach cancer and serum GSTs activity might be helpful in predicting the response of chemotherapy in advanced stages of cancer. GST values are helpful in predicting the radiation response. Overexpression of GST in neoplasia may be causal, allowing replicative advantage, or casual, accompanying clonal expansion. The major limitation to its widespread use is the time needed for doing the assay and until this is overcome it will remain primarily a research tool.

KEY WORDS

Cisplatin, Gastric Cancer, Tumour Marker, Chemotherapy, Glutathione-S-Transferase, ROS, GIT

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BACKGROUND

Gastric carcinoma is currently the fourth most common cancer type and second leading cause of cancer deaths worldwide.[1] Every year, around 1 million new cases and 0.7 million deaths are caused due to gastric carcinoma.[2] Principal factors responsible for gastric carcinoma, are nutritional, genetic factors and infectious factors. Indeed, cigarette smoking has been a risk factor in development of gastric cancer. Carcinogens such as benzo [α] pyrene present in tobacco play vital role in gastric carcinoma.[3] Natural elements including dietary propensities are significant in its turn of events, utilization of salted, smoked, cured and safeguarded food wealthy in salt, nitrite and N-nitro mixes have been accounted for to be related with an expanded danger of gastric cancer.[4] Smoking and liquor utilization have been proposed as hazard factors for gastric disease in some epidemiological investigations however their job has been inconsistent.[5,6] Also dietary factors have been concentrated in some epidemiological investigations from India, however their job has not been reliably proven[6] certain substances in the eating routine may increase. GI carcinoma hazards for e.g. there have been proposals so far not all around demonstrated that an eating regimen high in prepared meat may expand the danger of GI carcinoma drinking extremely hot fluids often. In late year GSTs have pulled in enthusiasm for the field of malignant growth in light of the fact that their movement is promptly expanded in synthetically incited tumours.[7] There catalysts catalyse the conjugation of GSH to an assortment of electrophilic mixes, receptive compound for sure GSTs are one of the proteins by subterranean insect cancer-causing agents and in this manner can forestall tumour development GSTs have likewise been recommended to assume a significant job in various medication opposition in malignant growth chemotherapy[8] may expand the hazard for oesophageal carcinoma. This may be the aftereffect of long haul harm the fluids do to the cell covering the throat. Indulging which prompts stoutness, increments the danger of GI carcinoma. Then again, eating less carbs high in leafy foods have various nutrients and minerals that may help forestall carcinoma.[9]

Gastrointestinal carcinoma aids to threatening states of the gastrointestinal tract (GIT) and adornment organ of assimilation and it incorporates throat, stomach, biliary framework, pancreas, small digestive system, internal organ, rectum and butt. The side effect identifies with the organ influenced and can incorporate block, strange draining or other related issues. The conclusion regularly requires blood test, pee test, stool test endoscopy and biopsy of dubious tissue. The tumour, just as the kind of threatening cell and whether it has attacked their tissues or spread somewhere else. These components likewise decide the visualization of sickness. Generally, the GI tract and the frill organs i.e., pancreas, liver and nerve bladder are answerable for additional malignancies and a larger number of passages from GI carcinoma than some other framework in the body. There is huge geographic variety in the paces of various gastrointestinal carcinomas.[10]

GI carcinoma is just one of the most widely recognized carcinoma yet in addition one of the most well-known reasons for carcinoma mortality. A brief glance at GLOBOCAN information 2012 demonstrated that out of evaluated 1.01 million new cases in the year 2012. In India, 227,000 were situated in GI tract. Out of around 682,000 carcinoma related deaths, 182,000 deaths were a direct result of GI carcinoma.[11] The six most basic GI carcinomas are associated carcinoma gastric, throat, liver, gallbladder and pancreas.[12] Gastric Carcinoma does not show any symptoms for long period of time. Symptoms include weight reduction, stomach torment, queasiness, heaving, changed bowel habits. Metastases to supraclavicular lymph nodes may be the first clinical sign.

Grouping of Gastric Carcinoma

The world wellbeing association and the Japanese grouping depict extravagantly a few histopathological kinds of gastric carcinoma and are helpful for the visualization dependent on the evaluation of the histological separation of early sore.[13] Adenocarcinoma adenosquamous carcinoma, squamous cell carcinoma, little cell carcinoma, undifferentiated carcinoma, other carcinoma.[14]

Gastrointestinal tract is involved in absorption and metabolism of toxic or potentially carcinogenic compounds which may be present in food we eat. In that context digestive tract may be considered as a major site for cancer in humans. GST is important metabolizing enzyme, present in epithelial cells of human GIT.[15]

Glutathione-S-Transferase is a dimer, divided into α, μ, π, θ are involved in detoxification of foreign toxic compounds. In an antioxidant defense system GST participates through several mechanisms including ROS and conjugation reactions which further results in synthesis of mercapturic acid and compels carcinogens toxins, and drugs to be excreted. It is also involved in binding of electrophiles to sulphydryl groups of GSH yielding less harmful and more water-soluble molecules which can be excreted via bile or via urine. As nearly all reactive, ultimate carcinogenic forms of chemicals are electrophiles, GSTs takes substantial importance as a mechanism for carcinogen detoxification.[16]

A various number of studies done on the effect of placental, serum and serum glutathione-s-transferase-pi from different regions have suggested that serum GST levels may be elevated in a wide range of gastrointestinal malignancies and thus the measurement of GST level might provide a useful tumour marker.[17-20]

Objectives

1. To evaluate GST in patients with gastric carcinoma.
2. To compare the role of serum GST activity in cases and controls.
3. To find out correlation of GST with severity of disease.

METHODS

This is a case control study conducted in a tertiary care hospital over a period of two years among 50 cases diagnosed with gastric carcinoma 20 - 50 years of age (Group 1 - Cases) and 50 age and sex matched controls (Group 2). Healthy control without diabetes, CAD, smoking habits were included in the present study as controls. Patients with other carcinoma were excluded. Around 20 patients were excluded as they were lost during follow-up. All patients underwent

chemotherapy treatment and drugs such as cisplatin and 5-Fluorouracil were administrated.

Collection and Processing of Blood Sample

5 ml blood samples were collected, samples were centrifuged for around 10 minutes at 4° c at 1000 x g. Yellow plasma layer was used for estimation of GST. Plasma was stored at -80° c as per requirement. The blood samples were processed by following standard protocol in the clinical biochemistry laboratory. Plasma GSTs activity was measured by using 1-chloro-2, 4 dinitrobenzene (Sigma-Aldrich) as substrate, was measured according to the procedure described by Habig et al.[21]

Statistical Analysis

All the collected data were submitted to excel worksheet in order to calculate mean and SD for linear variables, p value were calculated using SPSS version 10 with 95 % confidence interval.

RESULTS

	Number of Subject (M / F)	Age (in Years)
Normal Control	50 (33 / 17)	40 - 55
Gastric Carcinoma Patients	50 (33 / 17)	25 - 75
Cases Stage 2 before Chemotherapy	25 (16 / 9)	25 - 69
Cases Stage 3 after Chemotherapy	25 (17 / 8)	25 - 75

Table 1. General Characteristics of Cases and Controls

Table 1 Depicts: Number of males were more in number as compared to females, all of the cases and controls were in between age group of 25 - 75.

	No. of Subjects (n)	Mean ± SD	P Value
GST Control	50	5.47 ± 0.52	p < 0.0001
GST Cases	50	8.24 ± 1.94	

Table 2. Comparison of GST Activity in Cases and Controls

Table 2 Depicts: Level of GST in control is 5.47 ± 0.52 and 8.24 ± 1.94 in cases. There is significant (p < 0.0001) increase in levels of GST in cases as compared to control.

	No. of Subjects (n)	Mean ± SD	P Value
GST Control	50	5.47 ± 0.52	p < 0.0001
GST Cases before Chemotherapy	25	10.23 ± 2.12	

Table 3. Comparison of GST Activity between GST Control and GST Cases before Chemotherapy

Table 3 Depicts: Enzyme activity of GST is increased in cases (10.23 ± 2.12) as compared to control (5.47 ± 0.52), and there is a significant (p < 0.0001) difference between cases and controls.

	No. of Subjects (n)	Mean ± SD	P Value
GST Cases before Chemotherapy	25	10.23 ± 2.12	p < 0.0001
GST Cases after Chemotherapy	25	12.34 ± 1.05	

Table 4. Comparison of GST Activity in Cases before and after Chemotherapy

Table 4 Depicts: Enzyme activity of GST is increased in cases (12.34 ± 1.05) after chemotherapy as compared to cases (10.23 ± 2.12) before Chemotherapy, and there is a significant (p < 0.0001) difference between cases and controls.

DISCUSSION

These findings amazed us that after cardiovascular disease malignancy is another cause of deaths in developing countries. Aetiology of malignancy is a result of genetic factors, environmental factors and behavioural factors.[22] GSTs are involved in protecting cells against a wide variety of xenobiotics. Thus, it stands as biomarker of both cancer susceptibility and chemo preventive activity.[23,24]

Present study observes more case of males as compared to females where total cases of males were 33 while females were 17 in number and all the cases were in between age group of 25 - 75 years of age. (Table 1) When all cases (8.24 ± 1.94) of gastric carcinoma (stage 2 before chemotherapy and stage 3 after chemotherapy) were compared with controls (5.47 ± 0.52), present study observed significant (p < 0.0001) high difference in activity of GST, in cases when compared to controls. (Table 2). G. S. Mohammadzadeh et al. study observed similar results as present study[25]. Study conducted by Pasupathi P et al[26] studied 100 patients of gastric carcinoma and observed a significant decrease in the activities of GPx, GST and GR in patients with gastric cancer. Increase in activity of GSTS may be due to overexpression of GST iso enzymes in tumour tissues. GSTs activity in plasma represents a biomarker of cellular protection.[27] however there is conflicts over considering GST as marker for all tissue.

Present study observed a significant increase (p < 0.0001) in activity of GSTs in stage III patients with gastric carcinoma after chemotherapy. (Table 3) The level of Glutathione s transferase were increased in group receiving chemotherapy (12.34 ± 1.05) as compared to stage 1 stage 2 group not receiving chemotherapy (10.23 ± 2.12). (Table 4) It may be due to improve in levels of anti-oxidant, which may lead tissue less susceptible to oxidative stress. Present study observation supports the literature of different studies, where the description states: GST s protects cells from lipid peroxidation and H_2O_2, as it is increased by cisplatin based chemotherapy drug.[28] Various studies have also observed progression in cancer and increase in GST levels has been associated with poor prognosis and drug resistance.[14-16]

Thus, progressive increase in levels of GST with progression of gastric cancer may be associated with drug resistance as well as poor prognosis.

Limitations

The chief limitation is the small sample size and period of time required for doing the assay.

CONCLUSIONS

Measurement of GST activity in plasma can predict gastric cancer as well as response of chemotherapy in advanced stages of cancer. GST values are helpful in predicting the radiation response. Over-expression of GST in neoplasia could

be causal, allowing replicative advantage, or casual, accompanying clonal expansion.

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