

Original Research Article

Serum pepsinogen I and pepsinogen II levels and its ratio in patients with gastric cancer: a case control study

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ABSTRACT

Background: Cancer constitutes an enormous burden on society in more and less economically developed countries alike. The incidence of gastric cancer is found to increase in the developing countries like India due to change in the life style like having smoked food containing nitrates, smoking, alcoholism and consumption of large amount of red chillies. The objective of this study was to measure the serum pepsinogen I and pepsinogen II levels and its ratio in gastric cancer patients admitted in JSS hospital and Bharath Cancer Centre during the period October 2012 to October 2014 and to compare with controls.

Methods: 80 patients - 40 patients with gastric cancer and 40 patients control were studied. Serum pepsinogen I (PG I) and pepsinogen II (PG II) levels were measured using ELISA.

Results: The mean PG I levels for cancer patients and controls were 93.98 µg/dl and 82.156 µg/dl respectively, the mean PG II levels were 42.67 µg/dl and 18.79 µg/dl respectively. The PG I/II ratio in cancer patients is 2.75 and 5.73 in controls, the ratio was significantly lower in cancer patients (P value significant).

Conclusions: The ultimate aim in the management of carcinoma stomach is the early detection of the disease. At present endoscopy and biopsy is the gold standard of diagnosis. Different screening tools are under development for the diagnosis of the disease. Our study evaluates a test which can be recommended as an alternative to the diagnosis of gastric carcinoma at an early stage.

Keywords: Serum pepsinogen I, Serum pepsinogen II, Carcinoma stomach

INTRODUCTION

Cancer constitutes an enormous burden on society in more and less economically developed countries alike. The incidence of gastric cancer is found to increase in the developing countries like India due to change in the life style like having smoked food containing nitrates, smoking, alcoholism and consumption of large amount of red chillies. Strangely enough pan chewing is noticed as a high risk factor.¹ According to WHO estimation in

2012 almost one million cases were estimated to have occurred in 2012 (952,000 cases, 6.8% of the total) making it the 5th most common malignancy in the world after cancers of lung, breast, colorectum and prostate. Stomach cancer is the 3rd leading cause of cancer death in both sexes worldwide.²

Helicobacter pylori is one of the most common cause for chronic gastritis, which was detected many years before, increases the risk of gastric cancer.³ More than 75% of

cancers in India present in advanced stages. The 5 year survival rates for stage I and stage II gastric cancers are about 77% and 48% respectively. Stage IV tumors have very low survival rates around 4% for resectable and even lesser for unresectable tumors.

Primary prevention or early detection is the best strategy for prevention and cure of stomach cancer. Early diagnosis can improve the outcome of gastric cancer as this disease is curable in the early stage. Various biomarkers of gastric cancer are under study. Pepsinogen I (PG I) and pepsinogen II (PG II) as markers of atrophic gastritis in body. Gastrin17 as marker of atrophic gastritis in antrum and anti-helicobacter pylori are all under study in various populations.

Serum pepsinogen I and pepsinogen II levels can detect and diagnose gastric cancer at an early stage. Pepsinogen is the precursor of the proteolytic enzyme pepsin.⁴ PG I a precursor of pepsin which is synthesized in the chief cells and the neck cells of gastric corpus (oxyntic glands of gastric mucosa).⁵

The PG I levels correlates with the no. of chief cells. The decrease in the level of PG I may be due to destruction of chief cells due to gastric cancer. The detectable range is from 0 - 300 ng/ml using ELISA test. PG II is produced by the chief cells and mucosa neck cells of the gastric mucosa in pyloric glands in the gastric antrum and brunners gland in the proximal duodenum. As the severity of atrophy advances chief cells are replaced by pyloric glands and the concentration of PG II remains increased.^{6,7}

The detectable range is from 0 - 100ng/ml using ELISA test. The ratio of concentrate of PG I to PG II in plasma or serum of normal subjects about 4:1. When the atrophic gastritis is moderate or severe the PGI level decreases and the PG II remains constant. The ratio is <2.5 when the atrophic gastritis is advanced. A combination of the serum PG I level and PG I/PG II ratio have recently been recommended to screen for gastric cancer.

METHODS

This case control study was carried out in the department of General Surgery of JSS Medical College and Bharath Cancer centre, over a period from October 2012 to October 2014. Approval was taken from institutional ethics committee and JSS University, Mysore before commencing the study. The study was done after informed and written consent from the patient.

The study was done on 80 patients - 40 patients with gastric cancer and 40 patients were taken as control. The inclusion criteria were: proved gastric cancer patients. The exclusion criteria were as follows: underwent any gastric surgery and underwent any treatment for gastric cancer like chemotherapy or radiotherapy.

Sample collection

Patients should be fasting for 10 hours before blood sampling. Blood samples were collected by venipuncture into a plastic EDTA tube without additives. Plasma blood tubes should be then mixed immediately by turning them upside down 5-6 times and tubes for serum allowed to clot (for minimum 30 minutes) at room temperature (20-25°C). Serum after clotting was separated by centrifugation and stored frozen - 20°C. Samples were mixed thoroughly after thawing. Grossly hemolysed lipemic or turbid specimens were avoided and samples were not frozen and thawed.

The working principle of the pepsinogen kit is using ELISA.⁸ The pepsinogen kit is designed, developed and produced for the quantitative measurement of human pepsinogen I and II levels in serum sample. The assay utilizes the two site “sandwich technique” with two selected monoclonal antibodies that bind to different epitopes of human pepsinogen I without any cross - reaction to human pepsinogen I.

RESULTS

Forty patients who were diagnosed carcinoma stomach during the period from October 2012 to October 2014 were compared with forty controls. The observations found during the study were as follows

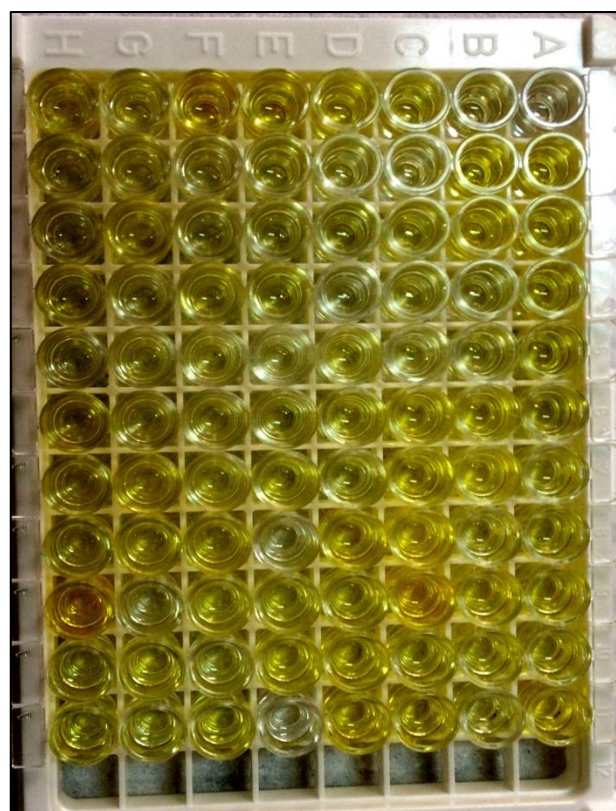


Figure 1: Micro plates at analysis.

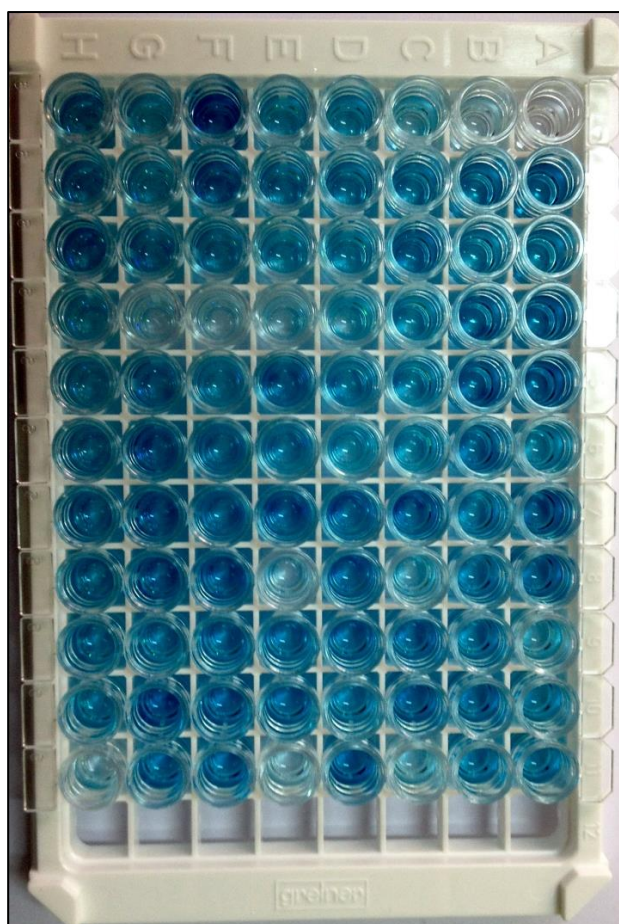


Figure 2: Micro plates after applying stop solution.

Table 1: Gender and mean age group.

Cases	Total number
Males	30
Females	10
Male:female	3 : 1
Mean age	55.45 (range 19 - 83 years)
More no. of cases of age group	56 - 65 years

The controls were taken randomly proved, who had undergone endoscopy with no significance.

Statistical analysis

The statistical analyses were done using SPSS software. The method used to calculate was 'T'-test and UNIANOVA.

There is statistical significance in the PG I:PG II ratio in case of cases and control.

The mean values of pepsinogen I was higher than pepsinogen II in cases, 93.98 µg /dl and 42.67 µg/dl and the mean paired difference was 51.27 and is statistically significant.

Table 2: Paired statistics of PG I:PG II ratio.

	Mean	N	Std. deviation	Std. error mean
Pair I PG I	93.9457	40	34.0611	5.38554
PG II	42.6732	40	26.73107	4.22655

Table 3: Paired mean difference of cases.

Paired differences				
	Mean	t	df	sig
Pair 1 PG I - PG II	51.2726	9.954	39	0.000

The mean values of pepsinogen I was found to be high when compared to pepsinogen II in control, 82.16 µg/dl and 18.79 µg/dl respectively with mean paired difference of 63.36 and is proved statistically significant.

The average levels of PG I is between 50 -150 g/dl and levels of PG II is 15- 20 g/dl. The normal serum PG I:PG II ratio is around 4:1 and this falls to below 2.5:1 in patients with gastric cancer or gastric atrophy according to literature. In our patients the rate of PG I:PG II in controls was 5.73:1 and in cases were 2.75:1 which is a significant study.

Age and gender are not making any changes in the pepsinogen values. More patients affected were male patients.

DISCUSSION

The 5-year survival rate of gastric cancer is low, and identification and a better control of risk factors seem to be the most effective means of prevention.

Screening for early detection of gastric precancerous changes may be helpful in diagnosis and treatment of cancer at curable stages. Many factors ascribe to the cause of gastric cancer, including the living habit, nutrition, microbe, and genetic predisposition. Recently, following the primary completion of Human Genome Project, the association of genetic polymorphisms with diseases came to the study frontier. Genetic polymorphisms are defined as variations in DNA that are observed in 1% or more of the population.

The study of genetic polymorphisms promises to help define pathophysiologic mechanisms, to identify individuals at risk for disease and to suggest novel targets for drug design and treatment. Family members of gastric cancer patients have been found to have a 1.5 fold to 3 fold increases in the risk of developing this cancer. This familial aggregation may be due to genetic or environmental factors shared by family members.

H. pylori are considered a WHO class I carcinogen. Chronic *H. pylori* gastritis, in more than half of the affected subjects, could lead to a gradual loss of glandular structures with its specialized cells and a collapse of the reticulin skeleton of the mucosa, a condition of atrophic gastritis.⁹

As a result, the glandular layer of the mucosa became thinner, and glands were replaced by fibrosis and intestinal metaplasia. The major clinical importance of this condition was that it could significantly increase the risk for the intestinal type of gastric cancer.¹⁰ This risk might be elevated up to 90- fold in subjects with severe atrophic gastritis throughout the complete stomach.¹¹ The annual incidence of gastric cancer among patients with atrophic gastritis varied in cohort studies between 0.3 and 1.0%. This could explain the interest in the diagnosis of atrophic gastritis. At present, there is a wide circle of questions related to the diagnosis of critical stages of gastric carcinogenesis - gastric epithelial atrophy, intestinal metaplasia and dysplasia.

Therefore, it is extremely important to recognize dyspeptic patients who have very high risk of gastric malignant changes and require dynamic surveillance with the purpose of early revealing of the pre neoplastic changes in stomach mucosa. Atrophic gastritis is a serious disease, which often does not receive much attention. The relationship between gastritis, atrophic gastritis and other diseases of the stomach is based on the fact that infection and atrophy could alter the physiological functions of the stomach and influence the growth and growth control of epithelial cells in the stomach. These consequences varied depending on whether the changes of the gastric mucosa caused by gastritis were located in the antrum or the corpus or both.

H. pylori infection is known to be associated with a raised serum pepsinogen II level and a decreased PG I / II ratio. Expression of cytotoxin - associated gene A (*cagA*) which is known to be associated with more active mucosal inflammation and, hence higher levels of serum pepsinogen I and II than other strains. However the incidence of cancer is the same in *cagA* positive and negative patients. However not all cancers are associated with atrophic gastritis.

The most accurate diagnostic method of gastrointestinal tract diseases is endoscopy with subsequent biopsy, which should be made in all patients with the presence of clinical symptoms. However, because of patchy characteristics of atrophic changes in stomach mucosa, some histological researches could give false - negative results. Due to invasiveness of biopsy, it is expedient to make only for monitoring precancerous changes in stomach mucosa. For the selection of patients recommended to biopsy, the presence of a screening method is necessary.^{12,13}

Ohata et al. assessed *H. pylori*-negative subjects and found an increased risk of gastric cancer for those with a positive pepsinogen test level (pepsinogen I 70ng/ml and pepsinogen I/II ratio 3.0) compared with subjects with a negative level.¹⁴ It is reasonable that pepsinogen test positivity, a marker of chronic atrophic gastritis, is closely associated with this type of gastric cancer.¹⁵ On the other hand, diffuse-type gastric cancer is thought to be genetically determined, at least in part, and to be less associated with environmental factors. This type of cancer does not progress through severe atrophic gastritis; hence, no clear association with the serum pepsinogen test is seen.

In this study the pepsinogen values are coming in range as in literature and the ratio of PG I and PG II in cases are within the range and controls are a bit high, but significant decrease in the ratio in cases suggest that there is more of atrophic gastritis in our population leading to carcinoma stomach.

Noninvasive detection of gastric mucosal atrophy by means of enzyme immunoassay with assessment of G-17 and PG1 levels can be offered as the screening tool for gastric precancerous conditions. On the other hand, this method does not diagnose intestinal metaplasia and cancer development in stomach mucosa. Therefore, the results of serological screening indicating the stomach mucosal atrophy require carrying out the chromo endoscopy with subsequent mucosal biopsy, for revealing probable progressing of atrophic process with development of intestinal metaplasia, dysplasia or gastric cancer.¹⁶ The study has to be done in a large no: of patients before validating it.

CONCLUSION

The ultimate aim in the management of carcinoma stomach is the early detection of the disease. At present endoscopy and biopsy is the gold standard of diagnosis. Different screening tools are under development for the diagnosis of the disease. Our study evaluates a test which can be recommended as an alternative to the diagnosis of gastric carcinoma at an early stage. For validation of this test PG I, PG II and its ratio as a screening test for diagnosing carcinoma stomach, studies with larger numbers of patients are needed. This study can be used to detect carcinoma stomach patients earlier and cure disease once the study is validated.

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Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

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