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Original article

Circulating gastrin and ghrelin levels in patients with colorectal cancer: Correlation with tumour stage, *Helicobacter pylori* infection and BMI

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Abstract

Many studies have pointed out a possible role of gut peptides, including gastrin and ghrelin, in the pathogenesis and natural history of gastrointestinal malignancies, one of the most common death cause in the Western world. The objective of this work is to check gastrin and ghrelin serum levels in patients with colorectal cancer according to tumour's location, stage, *Helicobacter pylori* infection and BMI, in order to understand the two peptides' behaviour through the tumour's natural history and evaluate their assay's use in research and clinical practice.

Twenty-nine subjects affected by colorectal cancer and 50 healthy controls were studied. Circulating gastrin and ghrelin levels and *H. pylori* serum antibodies were assessed by radioimmunologic assay and ELISA method.

Gastrin and ghrelin serum levels were respectively slightly higher and significantly lower in colon cancer patients than in controls. Gastrin levels were higher in patients carrying left colon cancer and *H. pylori* infection while ghrelin levels were lower in both these groups. Both hormones' serum levels decreased from tumour earlier to later stages. Significant differences persisted in the correlation between BMI and ghrelin levels in controls but not in patients.

Additional studies are necessary to ascertain the significance of gastrin and ghrelin opposite behaviour in colon cancer probably linked with interferences in endocrine pathways involving other gut peptides in this compromised condition.
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Keywords: Gastrin; Ghrelin; Colorectal cancer

1. Introduction

Colorectal cancer is the third common cause of cancer-related death in the Western world. The annual incidence in Italy is of 40 new cases in every 100 000 inhabitants.

An early diagnosis and surgical treatment can assure a 70%–90% five-year survival while advanced tumours at the time of diagnosis, with lymphonodal involvement and metastatic disease, have a poor prognosis with a 35% five-year survival. It is, thus, essential to understand all the genetic factors and the molecular mechanisms that, together with life-style related risk factors (such as diet and with predisposing conditions like inflammatory bowel diseases and diverticulosis), cause the development of adenomatous polyps and their malignant transformation.

The gastrointestinal epithelium's endocrine secretion of peptides with hormonal activity such as gastrin and ghrelin has a fundamental role in the regulation of digestion's physiology and various metabolic pathways [1,7].

Gastrin is a 17-amino acid polypeptide, mainly produced by the antrum, duodenum and pancreas G-cells; it is responsible for gastric acid secretion and it is also implicated in the stimulation of pancreas enzymatic activity and of gastric emptying [1–6].

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Ghrelin is a 28-amino acid polypeptide produced, for the most part, by the X/A like cells of the stomach's *fundus*, with GH-realising activity. It has also an appetite-inducing activity, a stimulating action on the gut's motility, ant inflammatory and gastroprotective activity and endocrine interactions with numerous hormones such as insulin, ACTH, cortisol, aldosterone and prolactin [7,8].

Gastrin has been found to be involved in the tumour genesis in the gastrointestinal tract as a growth factor which increases the tumour's spread and angiogenesis and capable of imparting anti-apoptotic properties and activating the transcription of factors involved in the transformation of colon adenomas into malignant carcinomas [9–18].

Ghrelin, together with other hormones with appetite-related activities, such as leptin, can be involved in the pathogenesis of some gastrointestinal tumours and some of their predisposing conditions such as obesity, insulin-resistance and chronic inflammation due to *Helicobacter pylori* infection [19–21].

H. pylori infects nearly 70% of the world population and is responsible for chronic gastritis, peptic ulcer and gastric cancer.

The aim of our work is to study the serum levels of the two hormones in colorectal cancer according to tumour location, stage, *H. pylori* infection and BMI, in order to understand the possible role of the two peptides in the aetiology and the progression of this malignant disease and to evaluate the utility of circulating gastrin and ghrelin assay in research and clinical practice.

2. Materials and methods

2.1. Patient selection

Twenty-nine subjects, affected by colorectal cancer, hospitalized in the Department of Surgery, University Policlinic Santa Maria alle Scotte, University of Siena, between 2004 and 2005, were enrolled. The patients were 17 men and 12 women from 51 to 89 years of age. Forty-nine percent, 21% and 30% of the subjects were affected, respectively, by carcinomas of right colon, left colon and rectum. Nineteen percent of the adenocarcinomas were at stage I according to TNM staging system (Dukes A and B1), 38% at stage II (Dukes B2) and 43% at stage III (Dukes C).

Fifty healthy subjects, 39 men and 11 women, from 32 to 65 years of age (average 54–59years), were recruited as controls among blood donors at the Blood-transfusion Centre of the University Policlinic of Siena. Thirty percent of the controls were normal, 54% were overweight and 16% were obese according to BMI calculation through the following formula: weight (kg)/height (m^2).

Blood samples (5 cc) were collected from fasted subjects during routine screening test for blood donors as far as the controls were concerned, and the day before the operation for the patients. The samples were centrifuged for 5 min at 3000–3500× *g* and the sera were transferred to test tubes and frozen at −20 °C until the assays.

2.2. Circulating gastrin and ghrelin levels assay and assessment of H. pylori status

Circulating gastrin and ghrelin levels were assessed by radioimmunologic assay by MP Biomedicals (Orangeburg, New York, USA) and Linco Research (St. Charles, Missouri, USA), respectively. *H. pylori* serum antibodies, were detected through ELISA method by Genesis Diagnostics (Little Port, Cambridgeshire, UK).

2.3. Statistical analysis

Results were expressed as mean ± standard deviation (S.D.). In order to evaluate the difference in the mean values of the two groups, the data were analyzed using the ANOVA variance analysis or the Kruskal–Wallis analysis as a non parametric approximation; a P value less than 0.05 was considered statistically significant. Statistical analysis was performed through the software Prisma GraphPad Prism 4.

3. Results

Table 1 reports serum levels of gastrin and ghrelin in controls and in the total number of patients and according to tumour location. Ghrelin levels were statistically lower in patients compared to healthy subjects ($P < 0.01$ and $P < 0.05$), independently by the tumour location, while no significant differences were evidenced in gastrin levels between the two groups, even if the mean value of the patients was slightly higher, especially in patients carrying left colon cancer.

Fig. 1 shows circulating levels of the two hormones in the patients according to the tumour stage. Statistical differences ($P < 0.05$) were found in the case of ghrelin serum levels, showing a progressive significant decrease in serum levels from the earlier (I or II, Dukes A or B1) to the later stages.

Table 2 reports serum levels of the two hormones in controls and patients positive and negative for *H. pylori* infection. Statistical differences were evidenced only in ghrelin levels: patients HP+ and HP− respect to the corresponding healthy subjects ($P < 0.01$) and patients HP+ respect to patients HP− ($P < 0.05$). *H. pylori* infection did not interfere with gastrin levels both in normal and in cancer people, even if a quarter of patients HP+ was about six times higher than the other.

Table 1
Serum levels of gastrin and ghrelin in control and case groups subdivided by tumour location

	N° cases	Gastrin (pg/ml)	Ghrelin (pg/ml)
Healthy controls	50	51.62 ± 18	1708.00 ± 672
Total patients	29	68.49 ± 82	1137.00 ± 481**
Right colon tumours	14	41.73 ± 19	1110.51 ± 534**
Left colon tumours	7	105.58 ± 121	1030.00 ± 441**
Rectum tumours	8	79.67 ± 105	1159.90 ± 440*

Values represented as means ± S.D. *$P < 0.05$; **$P < 0.01$ vs healthy controls.

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