Increased fasting serum levels of growth hormone and gastrin in patients with gastric and large bowel cancer

J.K. Triantafillidis¹, V. Govosdis³, Evangelia Konstandellou², P. Cheracakis¹, C. Barbatzas¹, D. Tzourmakliotis³, Maria Sklavaina¹

SUMMARY
Background: Growth hormone (GH), Insulin-like growth factor-I (somatomedine, IGF-I) and gastrin seem to play a significant role in cell proliferation in mammalian and rat cells. The role of these factors in the etiology of gastric and large bowel cancer has not been completely elucidated. The aim of this study was to concurrently estimate the levels of GH, IGF-I and gastrin in a group of patients with gastric and colorectal cancer and to compare the results with those of a group of normal controls. Patients and Methods: In 33 consecutive patients with gastric (16 patients) and large bowel (17 patients) cancer, the serum levels of GH, IGF-I and gastrin were measured by radioimmunoassay. Fifty-four normal people served as controls. Results: Significantly higher levels of serum GH (3.16–3.12 ng/ml in gastric cancer patients vs 3.01–2.91 ng/ml in colorectal cancer patients vs 0.69–1.60 ng/ml in normal controls, \( \text{adjusted } P<0.001 \)) and gastrin (98.2–87.9 pg/ml in gastric cancer patients vs 95.3–85.4 pg/ml in colorectal cancer patients vs 47.5–32.4 pg/ml in normal controls, \( \text{adjusted } P<0.035 \text{ and } <0.05 \) respectively) were found in both groups of patients compared with normal controls. The levels of IGF-I in patients with gastric and colorectal cancer patients and normal controls did not differ significantly (Gastric cancer 98.2 pg/ml ± 87.9 vs 95.3 ± 85.4 vs 47.5 ± 32.4 respectively) (\( \text{adjusted } P=0.070 \)). Conclusion: It is concluded that in patients with gastric and colorectal cancer a significant increase of serum GH and gastrin can be found. This increase is likely to play a role in gastric and colorectal carcinogenesis.

Key words: Growth hormone, Somatomedine, IGF-I, Gastrin, Gastric cancer, Large bowel cancer

INTRODUCTION

Growth Hormone (GH) plays an important role in normal linear growth and regulation of metabolic processes¹-². The administration of GH to GH-deficient patients results in positive nitrogen balance, decreased urea production, decreased body fat stores and enhanced carbohydrate utilization. The acute effects of GH in isolated tissues include increased aminoacid uptake and incorporation into protein, stimulation of new RNA synthesis and enhanced glucose utilization. Delayed effects include enhanced triglyceride lipolysis, increased sensitivity to catecholamine lipolysis and inhibition of glucose uptake. Many GH effects are mediated by a group of GH-dependent growth factors that are synthesized in numerous tissues. The most important of these factors is Somatomedin C or Insulin-like Growth factor I (IGF-I), a peptide that has many similarities to insulin, including binding to insulin receptors³-⁴. IGF-I is a mitogen for both normal and neoplastic cells. It is believed that cell differentiation and growth require both GH and IGF-I with GH serving to commit a precursor cell to a specific pathway of differentiation and IGF-I to enhance growth and replication. GH has also been shown to exert a significant trophic effect on the intestinal tract and to stimulate wound healing. It is believed that GH predisposes to the development of benign or malignant lesions in the large bowel of patients with acromegaly⁵-⁷, although its exact role on the development of gastrointestinal malignancies is not known.
Gastrin also exerts a significant role as a trophic hormone on the entire digestive tract mucosa (small and large bowel). This may have implications on the nutritional status as well as on large bowel mucosal repair activities. It has recently been suggested that gastrin participates in the gastric carcinogenesis through its trophic result and positive proliferative action on gastrointestinal mucosa.

So far, there are no studies estimating concurrently the serum plasma levels of different hormones with known trophic effect on gastrointestinal epithelium in the same group of patients. Therefore, the aim of this study was to estimate in a cohort of patients with gastric and large bowel cancer the serum fasting GH, IGF-I and gastrin levels and to compare the results with a group of normal controls.

PATIENTS AND METHODS

Thirty-three patients with gastrointestinal malignancies (16 with gastric and 17 with large bowel cancer, as well as 54 normal controls (blood donors) were studied. Clinical details of patients and controls are shown in table 1. Serum GH levels were measured by a direct quantitative immunoradiometric assay (CIS biointernational - ELISA h GH Immunoradiometric assay). Serum IGF-I levels were estimated by a quantitative radioimmunoassay (Nichols Institute Diagnostics). Finally, serum gastrin levels were estimated by Gamma Dab Gastrin 125I Radioimmunoassay Kit (INCSTAR Corporation. Stillwater, Minessota, USA).

Statistical analysis was performed using the statistical package SAS 8.1. (SAS Institute, Cary, NC, USA). The Wilcoxon Runk Sum Test and t-test were used in order to compare demographic and laboratory results between the different groups. Because it was necessary to perform multiple comparisons the p-values were adapted using the equation of Sidac. According to the equation the new values of p were: P sidac=1-(1-p)^n.

RESULTS

 Statistically significant differences were noticed between healthy controls and patients with gastric and colorectal cancer as far as the levels of serum GH were concerned (Table 2). Specifically significantly higher levels of GH were noticed in both groups of patients with gastric (adjusted P<0.001) or large bowel cancer (adjusted P<0.001) compared to normal controls.

As far as the levels of serum IGF-I were concerned, no statistically significant differences between patients with either gastric or large bowel cancer and normal controls were noticed (adjusted P=0.070) (Table 3).

Table 4 shows the results of serum gastrin estimation in both groups of patients and controls. As indicated in the table, statistically significantly higher levels of serum gastrin were found in patients with either gastric or large bowel cancer compared with normal controls (adjusted P<0.035 and <0.05 respectively).

DISCUSSION

Our study focused on the possible relationship between certain GI malignancies, namely gastric and colorectal cancer, and the levels of plasma GH, IGF-I and gastrin, three important hormones with well known trophic effect on gastrointestinal epithelium. We found that patients with gastric or large bowel adenocarcinoma exhibit concurrently significantly higher serum levels of GH and gastrin as compared with healthy controls.
controls. No significant differences between patients and controls were observed as far as the levels of IGF-I were concerned. Based on these results it could be supported that in the development of gastrointestinal cancer, among other factors, a synergistic effect of various hormones with trophic effect on gastrointestinal mucosa could be important.

**a) Gastric cancer**

Gastrin is an important hormone with significant trophic effects on gastrointestinal mucosa. Determinants of basal plasma levels in normal people include *Helicobacter pylori* infection, age, hazardous drinking and gender\(^{11}\). Preprogastrin, the gastrin precursor, gives rise to a variety of products with different biological activities. Progastrin itself stimulates colonic epithelial proliferation and C-terminally amidated gastrins stimulate acid secretion, as well as colonic proliferation and differentiation\(^{12}\). Similarly, increased plasma gastrin levels have been reported by others. Konturek\(^{13}\) showed that patients with gastric cancer are liable to release large amounts of gastrin into the gastric lumen to increase luminal hormone concentration. He found no correlation between plasma gastrin levels and luminal concentration of gastrin suggesting that the later originates from a different source than plasma hormone, most probably from cancer cells. The role of gastrin in the gastric carcinogenesis is further supported by a number of experimental work. Szabo et al\(^{9}\) found that gastrin-17 is a potent stimulating factor for gastric cancer cell lines and that the proliferation rate was in correlation with gastrin-17 concentration. It is of interest that gastrin and its receptor are expressed in the gastric mucosa of patients with the so-called premalignant lesions of the upper GI such as atrophic gastritis, intestinal metaplasia, dysplasia and intestinal type of carcinoma\(^{19}\). It has been suggested that preoperative hypergastrinemia is associated with unresectability and poor survival in patients with gastric cancer\(^{15}\).

*Helicobacter pylori*, a well known stimulating factor for gastrin secretion may well be equally important for the increased serum gastrin levels found in patients with gastric carcinoma. Wang et al\(^{16}\) described that chronic hypergastrinemia in mice can synergize with *Helicobacter pylori* infection producing gastric atrophy secretion of several growth factors, thus contributing significantly to the evolution to gastric cancer. However, the finding of increased levels of serum gastrin in patients with large bowel cancer suggests that infection by *Helicobacter pylori* is not the only important factor predisposing to gastric cancer evolution. This is further supported by a number of epidemiological studies showing that the rate of infection by *Helicobacter pylori* in patients with large bowel cancer is not higher compared to normal population\(^{17}\). The role of gastrin in gastric carcinogenesis is further supported by the well known relationship between hypergastrinemia present in low acid disease states and the development of gastric carcinoids\(^{18}\).

It is well established that GH plays a crucial role in stimulating and controlling the growth, as well as metabolism and differentiation of many mamalian cell types by modulating the synthesis of multiple mRNA species. The effects of GH are mediated by binding with its membrane-bound receptor and involve a phosphorylation cascade that results in the modulation of numerous signaling pathways\(^{19}\). GH receptors can be detected in isolated glands, gastric cell fructions and intestinal mucosa
lineages in normal people\textsuperscript{20}. Human GH receptor transcripts have also been observed throughout cancerous progression of the colonic and gastric mucosa from adenomas to colonic liver metastasis and gastrointestinal cancer cell lines at various stages of growth and differentiation. The widespread expression of the GH receptor transcripts in gastric and intestinal mucosal lineages, particularly in epithelia, suggests the regulatory role of GH on digestive growth and differentiation. The important role of GH is further supported by epidemiological data according to which patients with acromegaly have higher rates of colorectal cancer compared to the normal population\textsuperscript{7}.

It was not possible to find published data referring to the levels of serum GH and IGF-I in patients with gastric cancer. However the highly significant differences in the levels of GH between patients and controls found in our study suggest that GH plays could also play a role in gastric carcinogenesis. This matter should be further investigated.

\textbf{b) Large bowel cancer}

Both exogenous and autocrine gastrin have been demonstrated to stimulate growth of colorectal adenocarcinoma. Gastrin may well promote progression through the adenoma-carcinoma sequence\textsuperscript{21}. The majority of large bowel cancers produce their own gastrin which may act in an autocrine manner. The tumor cells also express gastrin receptors through activation of the Raf extracellular regulated kinase signal transduction pathway\textsuperscript{22}, a substance that mediates the proliferative action. Hyperproliferative colonic epithelium in the presence of hypergastrinemia has been recorded in humans\textsuperscript{23}. Moreover, it has been found that there is a wide expression of both gastrin and its receptors on colorectal polyps and that their activation occurs early in the adenoma-carcinoma sequence.

Despite the above mentioned clinical and laboratory data concerning the role of gastrin in gastrointestinal physiology, no clear data exist as far as its role in colorectal carcinogenesis is concerned. Siddheshwar et al\textsuperscript{24} found that only serum progastrin and not amidated gastrin is elevated in patients with large bowel cancer. In the same study no significant role of Helicobacter pylori infection was noticed. Increased (but not significant) levels of serum gastrin were noticed in patients with either large bowel cancer or polyps compared to normal people\textsuperscript{25}. The authors concluded that there is no significant role for circulating endogenous gastrin in patients with colorectal polyps or adenocarcinoma. Chen et al\textsuperscript{26} found that endogenous hypergastrinaemia does not induce trophic effects on rat colonic mucosa and does not promote growth of transplanted colon adenocarcinoma in the rat. Saurin et al\textsuperscript{27} found that gastrin-releasing-peptide receptor mRNA can be detected in most colorectal tumor specimens and suggest a link between high mRNA levels and both tumor differentiation and lymph vessel invasion, but not proliferation.

On the contrary, very recent data support the hypothesis according to which serum hypergastrinemia may promote the progression of existing premalignant lesions of the GI tract such as colonic polyps by increasing the rate of proliferation\textsuperscript{28}. Again the clear increase in the levels of serum gastrin of patients with colorectal carcinoma found in our study suggests that the role of gastrin in colorectal carcinogenesis is important and has to be further investigated.

In accordance with our findings, Tayek et al\textsuperscript{29} in their study reported a statistically significantly higher mean serum levels of GH in patients with large bowel cancer compared to normal people. The role of GH in large bowel cancer development is further supported by the findings of a number of clinical studies showing that the administration of octreotide reduced the proliferative activity of tumor cells and serum IGF-I levels in patients with large bowel cancer\textsuperscript{30}. Szapeshazi et al\textsuperscript{31} have demonstrated a significant inhibitory effect of growth hormone-releasing hormone antagonists on growth of human colon cancer both in vivo and in vitro, through a reduced production and secretion of IGF-II by cancer cells. Increased epithelial cell proliferation, most probably due to a direct stimulatory effect of IGF-I, contributes to the increased risk of colonic neoplasms in acromegaly\textsuperscript{3}.

In our study, no significant differences in the levels of IGF-I between patients with colorectal cancer and controls were noticed. Three studies also came to negative conclusions. Manousos et al\textsuperscript{32} found no statistically significant difference in the levels of serum IGF-I in patients with colorectal cancer compared to normal controls. Giovannucci et al\textsuperscript{33} found no statistically significant differences in the levels of IGF-I between women with colorectal cancer and normal controls, although an elevated risk in those women being in the high tertile was noticed. Exactly the same conclusion was reached by Kaaks et al\textsuperscript{34}. There are also some experimental data looking at the role of IGF-I in promoting dysplasia. Howarth et al\textsuperscript{35} found that twenty weeks’ administration of IGF-I to rats induced growth of the intestine but did not affect the severity of experimentally-induced colitis.
or the incidence of progression to colonic dysplasia. However, it seems that circulating IGF-I could be related to future development of large bowel cancer by predicting adenoma progression\textsuperscript{36,37}.

The results of the present study suggest that in the multifactorial process of gastrointestinal tract cancer development hormones producing a trophic result in the gastrointestinal mucosa such as GH and gastrin, play a significant role. In the light of these findings it would be of interest to see if a treatment targeting these hormones or their receptors (especially gastrin receptors) alone or in combination with other antitumor drugs could be of benefit to patients with gastric or large bowel cancer.

REFERENCES

29. Tayek JA, Bulcavage L, Chlebowski RT. Relationship of...
Increased fasting serum levels of growth hormone and gastrin in patients with gastric and large bowel cancer.


