Change of the growth hormone–insulin-like growth factor-I axis in patients with gastrointestinal cancer: related to tumour type and nutritional status

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Changes in the growth hormone (GH)–insulin-like growth factor-I (IGF-I) axis, especially acquired GH resistance, develop in many severe illnesses, including cachexia. To study changes in the GH–IGF-I axis in patients with cancer cachexia, biochemical markers and body composition parameters were measured in eighty-eight gastric cancer patients, thirty colorectal cancer patients (subclassified according to the presence or absence of cachexia) and twenty-four healthy control subjects. Fifty-nine patients were defined as cachectic, based on the percentage of weight loss compared with their previous normal weight. The remaining fifty-nine patients were defined as non-cachectic. Measurements were repeated in twenty-seven patients (sixteen with gastric cancer and eleven with colorectal cancer) 3 months after radical operation. Compared with the controls, the cachectic gastric cancer patients had high GH levels (1·36 v. 0·32 ng/ml; P=0·001), a trend towards high IGF-I levels (223·74 v. 195·15 ng/ml; P=0·128 compared with non-cachectic patients) and a low log IGF-I/GH ratio (2·55 and 2·66 v. 3·00; P=0·002), along with a decreased BMI; the cachectic colorectal cancer patients showed the biochemical characteristics of acquired GH resistance: high GH (0·71 v. 0·32 ng/ml; P=0·016), a trend towards decreased IGF-I levels (164·18 v. 183·24 ng/ml; P=0·127) and a low log IGF-I/GH ratio (2·54 v. 2·99; P=0·005), with increased IGF-I levels following radical surgery (200·49 v. 141·91 ng/ml; P=0·046). These findings suggest that normal GH reaction and sensitivity occur in gastric cancer patients, controlled by nutritional status, whereas acquired GH resistance develops in cachectic colorectal cancer patients, which may be caused by tumour itself.

Growth hormone resistance: Insulin-like growth factor-I: Cancer cachexia: Gastric cancer: Colorectal cancer

One of the major complications of cancer is tissue wasting, also termed cachexia, which occurs in more than 80% of patients with advanced cancer and is a leading contributor to morbidity and mortality in these patients (Dunlop, 1996; Ma & Alexandar, 1998). Cancer cachexia is a complex, multifactorial syndrome that results from a reduction in food intake, a variety of metabolic abnormalities or more often a combination of the two (Fearon & Moses, 2002). Increased catabolism and decreased anabolism, partly caused by neuroendocrine disturbance, play an important role in the pathogenesis of various kinds of cachexia. Increased glucagon and cortisol, insulin resistance and leptin change in cancer cachexia have been discovered and profoundly studied in recent years (Yoshikawa et al. 2001; Aleman et al. 2002; Fearon & Moses, 2002). As a major mediator of metabolism, the growth hormone (GH)–insulin-like growth factor-I (IGF-I) system has attracted more and more attention in the research of cachexia associated with some other chronic illnesses, including congestive heart failure, acquired AIDS and chronic obstructive pulmonary disease. GH is secreted from the pituitary gland in a pulsatile manner and exerts a direct lipolytic effect, but its major mode of action is indirect and anabolic through the activation of somatomedins (Hartman et al. 1993). The main GH-dependent somatomedin is IGF-I. Acquired GH resistance is a feature of severe catabolism and malnutrition in conditions of sepsis, surgery and critical illness (Bentham et al. 1993, Ross & Chew, 1995). Biochemically, it is defined as the presence of a high GH but low IGF-I level. The GH–IGF-I axis, in particular the presence of GH resistance, has not been studied in detail in patients with cancer cachexia.

Our study, comprising two parts, focused on GH–IGF-I axis disturbance in patients with gastrointestinal cancer. In the first part of the study, we analysed the biochemical characteristics of acquired GH resistance in prospectively defined cachetic cancer patients, and compared them with those of non-cachetic patients and healthy subjects. In the second part, we compared the pre- and postoperative hormone levels in some selected patients enrolled in the first part of the study in an attempt to reveal the influence of cancer on the GH–IGF-I system.

Methods and materials

Patients and clinical characteristics

Included in this study were 118 patients (eighty-two males and thirty-six females), varying in age from 28 to 87 years with a mean age of 59·6 years, who had recently been diagnosed as having gastrointestinal cancer of various stages, including eighty-eight patients with gastric cancer and thirty with colorectal cancer. Of the 118 patients, thirty-one were inoperable because of local infiltration or distal metastasis, and the remaining eighty-seven patients received surgical therapy. Fifty-nine patients were defined as cachetic, based on the percentage of weight loss compared with their previous normal weight (≥5% within

Abbreviations: FM, fat mass; GH, growth hormone; IGF-I, insulin-like growth factor-I; LBM, lean body mass; MM, muscle mass; PM, protein mass.

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the previous month, $\geq 7.5\%$ within previous 3 months or $\geq 10\%$ within previous 6 months; (Nitenberg & Raynard, 2000). The remaining fifty-nine patients were defined as non-cachectic. Patients with abnormal liver or renal function, acute infection, gastrointestinal obstruction and chronic diseases such as diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease, AIDS or thyroid disease were excluded. The control group was composed of twenty-four healthy subjects (sixteen males and eight females) ranging in age from 32 to 74 years with a mean of 56-7 years, who were healthy hospital personnel without recent body weight loss or gain and who had no acute or chronic disease and were not taking any regular medication. The general data of the patients and healthy subjects are shown in Table 1.

Nutritional assessment

The patients were questioned carefully about their previous normal weight (the patient’s pre-illness weight or weight 6 months before diagnosis) and the weight loss they had experienced over the previous 6 months. The weight and height of all patients and healthy controls were measured on admission, and body composition was measured using a multiple-frequency bioelectrical impedance (MFBIA) model InBody 3·0 (Biospace, Seoul, Korea) at four different frequencies (5, 50, 250 and 500 KHz). Participants were instructed to fast and to avoid exercise for 8 h before measurement and to rest for at least 30 min before the measurement. Some selected parameters, including BMI, lean body mass (LBM), muscle mass (MM), protein mass (PM) and fat mass (FM), were analysed in this study.

Hormone determination

Venous blood samples (5 ml) were collected between 07.00 and 08.00 h from the patients, who had fasted for 12 h or more and rested in the supine position for 20 min or more. Aliquots were centrifugated and stored at $-80^\circ$C until analysis. IGF-I (Biocode S.A.; sensitivity 0·02 ng/ml by immunoradiometric assay, Biocode S.A., Liege, Belgium; sensitivity 0·12 ng/ml by RIA) and GH (Biocode S.A.; sensitivity 0·02 ng/ml by immunoradiometric assay) were measured in all patients and healthy controls. The intra- and interassay coefficients of variation were less than 7% and 10%, respectively.

Part 2 of the study

Twenty-seven of the eighty-seven surgical patients (sixteen gastric and eleven colorectal) repeated the measurements 3 months after operation. They all received radical surgery without any signs of relapse, confirmed by computed tomography examination and the detection of serum cancer markers at 3 and 9 months after operation.

Analyses

All results are presented as the mean value, or mean value with its standard deviation. The $X^2$ test, paired-samples Student’s $t$-test and non-parametric test, univariate ANOVA, post hoc test and analysis of covariance were applied, as appropriate. Forward stepwise multiple regression analyses were performed to control for potentially confounding covariates. A $P$ value of $<0.05$ was considered significant. Because of a skewed distribution, log-transformed values were used for statistical analyses of the ratio of IGF-I to GH (log IGF-I/GH), and rank-transformed values were used for the analysis of GH level. The study was approved by the Research Ethics Committee of Nanjing University, and written informed consent was obtained from all patients.

Results

Part 1

Measurements of GH–IGF-I axis. The results are shown in Table 2. According to the forward stepwise multiple regression analysis, both GH levels and log IGF-I/GH ratio were associated with age ($r$ 0.288, $P=0.001$ and $r$ 0.233, $P=0.005$, respectively). There was a significant negative correlation between GH level and BMI in all cancer patients and controls ($r$ 0.388, $P<0.001$). There was also a positive correlation between log IGF-I/GH ratio and BMI in all patients and healthy controls ($r$ 0.352, $P=0.002$), except for cachectic colorectal cancer patients ($r$ 0.359, $P=0.553$). When the patients with gastrointestinal cancer were subclassified according to the presence or absence of cachexia, major differences were found in the measures of the GH–IGF-I axis. Cachectic and non-cachectic gastric cancer patients had high GH levels (1.36 and 1.01 v. 0.32 ng/ml; $P=0.001$ and 0.047, respectively) and low log IGF-I/GH ratios (2.55 and 2.66 v. 3.00; $P=0.002$ and 0.022, respectively) compared with the controls. With regard to IGF-I level, no differences were found between the patients and the controls ($P=0.128$ and $P=0.524$ for the cachectic and non-cachectic group, respectively), but cachectic patients showed increased IGF-I levels compared with non-cachectic patients (223·74 v. 182·81 ng/ml; $P=0.012$).

Table 1. General data for healthy controls and gastrointestinal cancer patients

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls (n 24)</th>
<th>Cachectic (n 48)</th>
<th>Non-cachectic (n 40)</th>
<th>Cachectic (n 11)</th>
<th>Non-cachectic (n 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>16/8</td>
<td></td>
<td>39/9</td>
<td></td>
<td>26/14</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56.7</td>
<td>12.0</td>
<td>60.0</td>
<td>13.0</td>
<td>60.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.7</td>
<td>13.5</td>
<td>57.6</td>
<td>9.5</td>
<td>58.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165</td>
<td>8</td>
<td>166</td>
<td>7</td>
<td>163</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.1</td>
<td>3.8</td>
<td>20.8</td>
<td>3.3</td>
<td>22.0</td>
</tr>
<tr>
<td>Cancer stage (inoperable/operable)</td>
<td>–</td>
<td>22/28</td>
<td>5/35</td>
<td>3/8</td>
<td>1/18</td>
</tr>
</tbody>
</table>
Part 2

Pre- and postoperative hormone levels and body composition data are given in Table 3. All the patients showed higher GH (0.98 v. 0.42 ng/ml; P = 0.043) and IGF-I (198-19 v. 168-32 ng/ml; P = 0.009) levels postoperatively, along with significantly decreased BMI (20.5 v. 21.8 kg/cm²; P < 0.001) and body composition parameters, including FM (10.0 v. 11.7 kg; P = 0.003) and LBM (47.6 v. 49.8 kg; P = 0.016). In view of the significantly changed BMI (P = 0.012) and IGF-I/GH ratio (P = 0.011), the biochemical characteristics of acquired GH resistance improved in the cachectic colorectal cancer patients, with significantly increased postoperative IGF-I levels (200-49 v. 141.91 ng/ml; P = 0.046).

Discussion

This study showed that the GH–IGF-I axis underwent significant change in the gastrointestinal cancer patients, which was related to tumour type and nutritional status. The cachetic gastric cancer patients presented with normal reactions of the GH–IGF-I system to weight loss: high GH and IGF-I levels and a low log IGF-I/GH ratio, along with a decreased BMI. In contrast, the cachectic colorectal cancer patients presented with the biochemical pattern of acquired GH resistance: high GH but low IGF-I levels with a decreased log IGF-I/GH ratio, which might be corrected by radical surgery. These findings suggest that the cachexia caused by different cancers differs in terms of the characteristics of the neuroendocrine system.

Although the clinical features of cancer cachexia are apparent, its mechanism is complex and poorly understood (Hamerman, 2002). There is increasing evidence that the neuroendocrine system, especially some anabolic and catabolic hormones, plays an important role in the pathogenesis of cachexia. Insulin resistance, which may contribute to the disturbance of glucose metabolism and increased catabolism, has been widely studied in various kinds of cachexia, including congestive heart failure, AIDS, chronic obstructive pulmonary disease, sepsis and cancer (Tisdale, 2000). The GH–IGF-I axis, acting as the leading anabolic hormone system, may also be involved in the development of cachexia.

GH has several metabolic actions, including raising blood glucose and inducing protein anabolism and lipolysis. In addition, GH stimulates growth primarily through the regulation of the growth-promoting hormone IGF-I. IGF-I has a long serum half-life (up to 12 h), and its level is highly correlated with that of GH (Guyton & Hall, 2000). The principal physiological
Table 3. Pre- and postoperative (3 months) measurements of the growth hormone (GH)–insulin-like growth factor-1 (IGF-I) axis and body composition analyses

<table>
<thead>
<tr>
<th></th>
<th>Cachectic (n = 8)</th>
<th>Non-cachectic (n = 8)</th>
<th>Cachectic (n = 4)</th>
<th>Non-cachectic (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GH (ng/ml)</strong></td>
<td>0.32 (0.40)</td>
<td>0.60 (0.80)</td>
<td>0.25 (0.06)</td>
<td>0.41 (0.50)</td>
</tr>
<tr>
<td><strong>IGF-I (ng/ml)</strong></td>
<td>178.91 (71.42)</td>
<td>170.51 (57.28)</td>
<td>141.91 (36.45)</td>
<td>168.83 (26.47)</td>
</tr>
<tr>
<td><strong>log IGF-I/GH ratio</strong></td>
<td>2.89 (0.41)</td>
<td>2.78 (0.63)</td>
<td>2.75 (0.02)</td>
<td>2.92 (0.54)</td>
</tr>
<tr>
<td><strong>LBM (kg)</strong></td>
<td>46.4 (10.9)</td>
<td>51.0 (9.3)</td>
<td>43.7 (15.0)</td>
<td>51.8 (5.9)</td>
</tr>
<tr>
<td><strong>MM (kg)</strong></td>
<td>43.8 (10.4)</td>
<td>48.2 (8.9)</td>
<td>41.3 (14.4)</td>
<td>49.0 (5.7)</td>
</tr>
<tr>
<td><strong>PM (kg)</strong></td>
<td>11.7 (2.8)</td>
<td>12.9 (2.4)</td>
<td>11.0 (3.8)</td>
<td>13.1 (1.9)</td>
</tr>
<tr>
<td><strong>FM (kg)</strong></td>
<td>11.0 (4.1)</td>
<td>12.9 (4.9)</td>
<td>13.3 (7.9)</td>
<td>11.3 (1.8)</td>
</tr>
</tbody>
</table>

FM, fat mass; LBM, lean body mass; MM, muscle mass; PM, protein mass.

Data are presented as preoperative vs. postoperative mean value with standard deviations. *P < 0.05, **P < 0.01 by paired-samples Student’s t-test or non-parametric test.
With respect to GH sensitivity, great differences exist between our results and previous findings. The IGF-I levels of the cachectic patients increased significantly compared with those of the non-cachectic patients ($P=0.012$; and $P=0.128$ compared with controls), suggesting that no abnormally decreased secretion of IGF-I occurred in cachectic gastric cancer patients. Unlike some other instances of chronic disease-related malnutrition, gastric cancer cachexia has normal GH sensitivity characterised by high GH and IGF-I levels. Unfortunately, normal GH sensitivity did not appear to protect the nutritional status of the gastric cancer patients in this study. Body composition measurements showed that high IGF-I levels did not prevent LBM, MM or PM from further decreasing significantly, indicating that IGF-I bioactivity may have been inhibited. Similar results have also been reported in the experimental cachexia model (Lazarus et al. 1996). The precise mechanisms involved in resistance to the anabolic actions of IGF-I are still unknown.

Colorectal cancer patients also have excess GH secretion stimulated by decreased body weight. But unlike the case with gastric cancer, acquired GH resistance developed in the cachexia patients. Univariate analysis of covariance with GH level as covariate showed decreased IGF-I levels in the cachectic patients compared with the controls ($P=0.019$), indicating that the secretion of IGF-I was beyond the control of GH. The log IGF-I/GH ratio also decreased sharply in the cachectic patients. These results agree with the typical features of acquired GH resistance: high GH and low IGF-I levels with a low log IGF-I/GH ratio. Furthermore, IGF-I levels increased significantly ($P=0.046$) in these patients following radical surgery, with no significant change in body weight, GH level and log IGF-I/GH ratio.

Taking all these facts together, acquired GH resistance, occurring in the cachectic colorectal cancer patients, is not adaptive to malnutrition but is caused by the tumour itself and may be corrected by complete removal of the tumour. It is recognised that acquired GH resistance represents a metabolic switch from the anabolic actions of GH, mediated through IGF-I, to its direct catabolic actions, such as anti-insulin actions (Ross & Buchanan, 1990). This switch may have a survival advantage in the fasted patient, with increased protein breakdown, lipolysis and reduced glucose utilisation maintaining circulating fuels, but may be harmful in the chronically diseased patients. Protein breakdown increased in sheep treated with IGF-I antibodies (Koea et al. 1992), and many studies showed that a partial reversal of GH resistance by GH treatment improved nitrogen economy (Wilmore, 1990; Vance & Maura, 1999). These studies support the theory that acquired GH resistance is ‘permissive’ for protein catabolism and involved in the development of malnutrition in some patients. In the cachectic colorectal patients in this study, body weight returned to almost the preoperative level 3 months after operation, which could have been due to a reversal of GH sensitivity.

Taking the common complaints of gastric cancer patients, including anorexia, dysphagia, abdominal distension, nausea and vomiting, into account, the disturbance of food intake and digestion may contribute to the cachexia associated mainly with gastric cancer. On the other hand, most colorectal cancer patients had no change in appetite or digestion, and therefore the disturbance of the neuroendocrine system may play an important role in the development of cachexia. We reviewed all 118 patients’ histories and found that thirty-six of the forty-eight cachectic gastric cancer patients complained of decreased food intake as a result of various factors: normal GH reaction and sensitivity in gastric cancer patients controlled by nutritional status; acquired GH resistance in cachectic colorectal cancer patients caused by the tumour itself. Furthermore, different cancer-related cachexias may be caused by different factors. Therefore, the treatment of cancer cachexia should be individualised for each patient.

References


Lieberman SA, Butterfield GE, Harrison D & Hoffman AR (1994) Anabolic effects of recombinant insulin-like growth factor-I in cachectic...


