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Original Article

Endocrinological Changes after Anamorelin Administration in Patients with Gastrointestinal Cancer

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Changes in hormone levels in patients with cancer cachexia after anamorelin administration have not been fully investigated. This study aimed to determine how anamorelin affects the endocrine system in patients with gastrointestinal cancer and cachexia. We prospectively enrolled 13 patients and comprehensively investigated their body weight and levels of serum albumin, hemoglobin A1c (HbA1c), and hormones before (week 0) and 3 and 12 weeks after anamorelin administration. The variables were evaluated at week 3 in 9 patients and at week 12 in 5 patients. At week 3, anamorelin administration resulted in body weight gain and increased the levels of growth hormone and HbA1c, as well as insulin-like growth factor-1 standard deviation scores (IGF-1 SD scores). At the same time, negative correlations were observed between Δ IGF-1 SD score and Δ thyroid-stimulating hormone (TSH) and between Δ IGF-1 SD score and Δ free testosterone. Δ Body weight and Δ IGF-1 SD score correlated positively at week 12. These results suggest that TSH and free testosterone levels can be affected 3 weeks after anamorelin administration; however, those variables tend to return to a state of equilibrium, and anabolic effects of anamorelin appear in long-term (≥ 12 weeks) users.

Key words: anamorelin, body weight, cancer cachexia, endocrine system

Cancer cachexia is a complex metabolic syndrome characterized by anorexia and cancer-related weight loss, particularly decreased muscle mass. Cancer cachexia has been known to have a substantial impact on patients' quality of life and is associated with poor survival [1-3]. Thus, treatment of cachexia is expected to improve the prognosis of patients with cancer. Anamorelin, a selective agonist of the ghrelin receptor, was developed as a novel drug for cancer cachexia and was first released in Japan in April 2021 [4,5]. Ghrelin, an orexigenic peptide primarily secreted from the stomach, stimulates multiple pathways that regulate body weight, muscle mass, appetite, and metabolism. Consequently, anamorelin increases appetite and body weight in patients with cancer cachexia [5-10].

Ghrelin acts as a growth hormone (GH) secretagogue that increases serum GH and insulin-like growth factor-1 (IGF-1) levels. Therefore, elevated levels of GH and IGF-1 have been reported in patients receiving anamorelin [7,8,10]. However, changes in other hormones have not been sufficiently investigated. This study aimed to prospectively determine endocrinological changes at 3 and 12 weeks after anamorelin administration in patients with gastrointestinal cancer.

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Patients and Methods

Patients. Serum hormone levels were prospectively measured in 13 patients with gastrointestinal cancer who started taking anamorelin between July 2021 and July 2022 at Okayama University Hospital (Okayama, Japan). Body weight, serum albumin, GH, IGF-1, hemoglobin A1c (HbA1c), free triiodothyronine (T3), free thyroxine (T4), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and bone-specific alkaline phosphatase (BAP) were measured before and 3 and 12 weeks after anamorelin administration. Testosterone and estradiol levels were measured in male and female patients, respectively. To reveal the effects of anamorelin, we compared (i) body weight and levels of HbA1c, serum albumin, and hormones before and 3 weeks after anamorelin administration, and (ii) body weight and levels of serum HbA1c, albumin, and hormones before and 12 weeks after anamorelin administration. Because of the strong dependence of serum IGF-1 on age and sex, the IGF-1 standard deviation score (SD score) was calculated and used as a variable in this study [11].

Statistics and ethics. Statistical analyses were performed using JMP 14.0.0 software (SAS Institute Inc., Cary, NC, USA). Numerical variables are expressed as means ± standard deviation. The Wilcoxon signed-rank test was used to compare body weight with serum albumin, HbA1c, and hormone levels. We performed a linear regression analysis to reveal possible relationships between the changes in IGF-1 and other variables. Because this was an exploratory study, the sample size was not estimated. Statistical significance was set at $p < 0.05$.

The patients were registered and analyzed prospectively in this study. Written informed consent was obtained from all the participants. This study adhered to the principles of the Declaration of Helsinki and was approved by the ethics committee of Okayama University Hospital. The study protocol was registered in the UMIN Clinical Trials Registry (UMIN000044653).

Results

Patient characteristics. The characteristics of the enrolled patients are summarized in Table 1. Thirteen patients (11 men and 2 women) were registered, who had been diagnosed with gastric (n = 7), pancreatic (n = 5), or colorectal (n = 1) cancer before enrollment in the study. The mean age was 73.5 years (60-82 years). One patient had been taking levothyroxine for hypothyroidism since before enrollment in this study and continued to take it throughout the study period. The other 12 patients had no endocrinological disorders. Five patients received anamorelin for more than 12 weeks; 2 discontinued anamorelin intake between 3 and 12 weeks, and 4 discontinued in less than 3 weeks after starting anamorelin. The reasons for cessation of anamorelin intake included ileus due to intestinal metastasis (n = 2), death due to pancreatic cancer (n = 1), cholecystitis (n = 1), inability to receive oral intake due to massive ascites (n = 1), and cancer progression (n = 1). In addition, 2 patients were transferred to other hospitals for palliative care 6 and 5 weeks after anamorelin

Table 1 Clinical characteristics of the study patients

No	Sex	Age	Underlying disease	Duration of anamorelin administration	Reason for discontinuation/observation of anamorelin treatment
1	M	60	Gastric cancer	> 12 weeks	–
2	M	71	Gastric cancer	> 12 weeks	–
3	M	73	Gastric cancer	> 12 weeks	–
4	M	82	Gastric cancer	> 12 weeks	–
5	M	74	Pancreatic cancer	> 12 weeks	–
6	F	73	Colorectal cancer	11 weeks	Ileus due to intestinal metastasis
7	M	72	Pancreatic cancer	6 weeks	Transferred to another hospital for palliative care
8	F	77	Pancreatic cancer	5 weeks	Transferred to another hospital for palliative care
9	M	68	Pancreatic cancer	4 weeks	Unable to receive oral intake due to massive ascites
10	M	77	Pancreatic cancer	2 weeks	Dead by pancreatic cancer
11	M	76	Gastric cancer	2 weeks	Unable to receive oral intake due to cancer progression
12	M	72	Gastric cancer	< 1 week	Ileus due to intestinal metastasis
13	M	74	Gastric cancer	< 1 week	Cholecystitis

administration, respectively, and could no longer be followed up in our hospital. Finally, the changes in body weight and levels of HbA1c, serum albumin, and hormones were evaluated at week 3 in 9 patients and week 12 in 5 patients (Fig. 1).

Changes in body weight and levels of HbA1c, serum albumin, and hormones. Figure 2 shows the body weight and levels of HbA1c, serum albumin, GH, free T3, free T4, TSH, FSH, BAP, and free testosterone, as well as IGF-1 SD score, measured before (week 0) and at 3 and 12 weeks after anamorelin administration. As this study included only 2 female patients, estradiol levels are not shown in Fig. 2; the estradiol levels were < 5.0 pg/mL at week 0 and 10.3 pg/mL at week 3 in one patient, and 8.9 pg/mL at week 0 and unchanged at week 3 in the other. Both patients discontinued anamorelin intake < 12 weeks.

The Wilcoxon signed-rank test revealed that the following were significantly higher at week 3 than at week 0: body weight (49.7 ± 9.6 kg vs. 47.3 ± 8.1 kg at week 3 vs. week 0, respectively) and levels of GH (7.5 ± 4.2 ng/mL vs. 3.5 ± 2.5 ng/mL), IGF-1 SD score (−2.4 ± 1.2 vs. −0.3 ± 2.0), and HbA1c (6.5 ± 1.2% vs. 6.2 ± 0.9%). There were no differences between the levels of serum albumin or other hormones between weeks 0 and 3. A comparison between the variables measured at weeks 12 and those measured at week 0 showed no significant differences in any items. However, mean body weight gradually increased (56.6 ± 9.5 kg at week 12). In contrast, mean levels of GH (5.2 ± 2.0 ng/mL), IGF-1 SD score (−0.8 ± 1.7), and HbA1c (7.0 ± 1.6%) were lower at week 12 than at week 3, despite the higher mean levels at week 12 than at week 0.

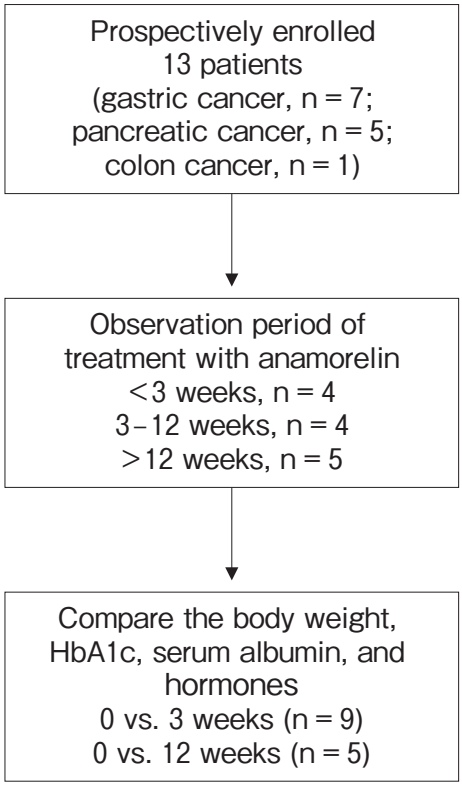

Fig. 1 Study flowchart.

We then performed linear regression analysis to investigate the possible relationship between the change in IGF-1 SD score [*i.e.*, Δ IGF-1 SD score (IGF-1 SD score at week 0 subtracted from that at week 3 or 12)] and changes in other variables. At week 3, there were significant negative correlations between the Δ IGF-1 SD score and Δ TSH and between the Δ IGF-1 SD score and Δ free testosterone (Fig. 3). Although the relationships were not statistically significant, Δ albumin ($p = 0.099$) and Δ FSH ($p = 0.066$) tended to correlate positively with the Δ IGF-1 SD score. At week 12, Δ IGF-1 SD score and Δ body weight showed a significant positive correlation (Fig. 4). In addition, Δ albumin tended to correlate positively with Δ IGF-1 SD score ($p = 0.055$).

Figure 5 shows the chronological changes in the 5 patients who continued to receive anamorelin for more than 12 weeks. One patient with hypothyroidism showed abnormally high levels of TSH throughout the study period. As shown in the line graph of IGF-1 SD scores, all patients showed arched lines; IGF-1 SD score was increased steeply at week 3 and decreased at week 12 in 4 patients, while in the remaining patient the score was highest at week 12. GH levels also showed arched lines, except for the same exceptional patient, whose lowest GH level was at week 3. In contrast, gradual weight gain was observed in 3 patients. Finally, all patients had gained body weight at week 12 compared week 0. There were no similarities among patients in the changes in other hormones or serum albumin levels.

Discussion

We conducted the present study to reveal endocrinological changes in patients with gastrointestinal cancer who were taking anamorelin. Although anamorelin is known to increase GH and IGF-1 levels as described

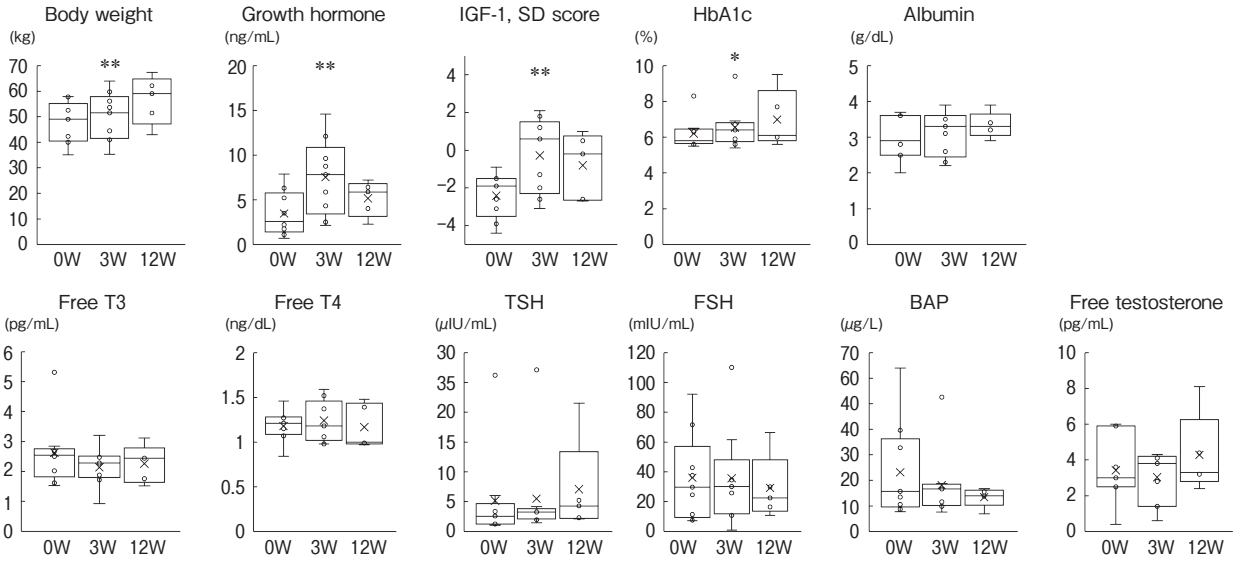

Fig. 2 Box plots before (week 0: 0W) and three (3W) and 12 weeks (12W) after anamorelin administration. Wilcoxon signed-rank tests were used to investigate differences.
*$p<0.05$ (vs. 0W); **$p<0.01$ (vs. 0W); IGF-1 SD score, standardized deviation score of insulin-like growth factor 1; HbA1c, hemoglobin A1c; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; FSH, follicle-stimulating hormone; BAP, bone-specific alkaline phosphatase.

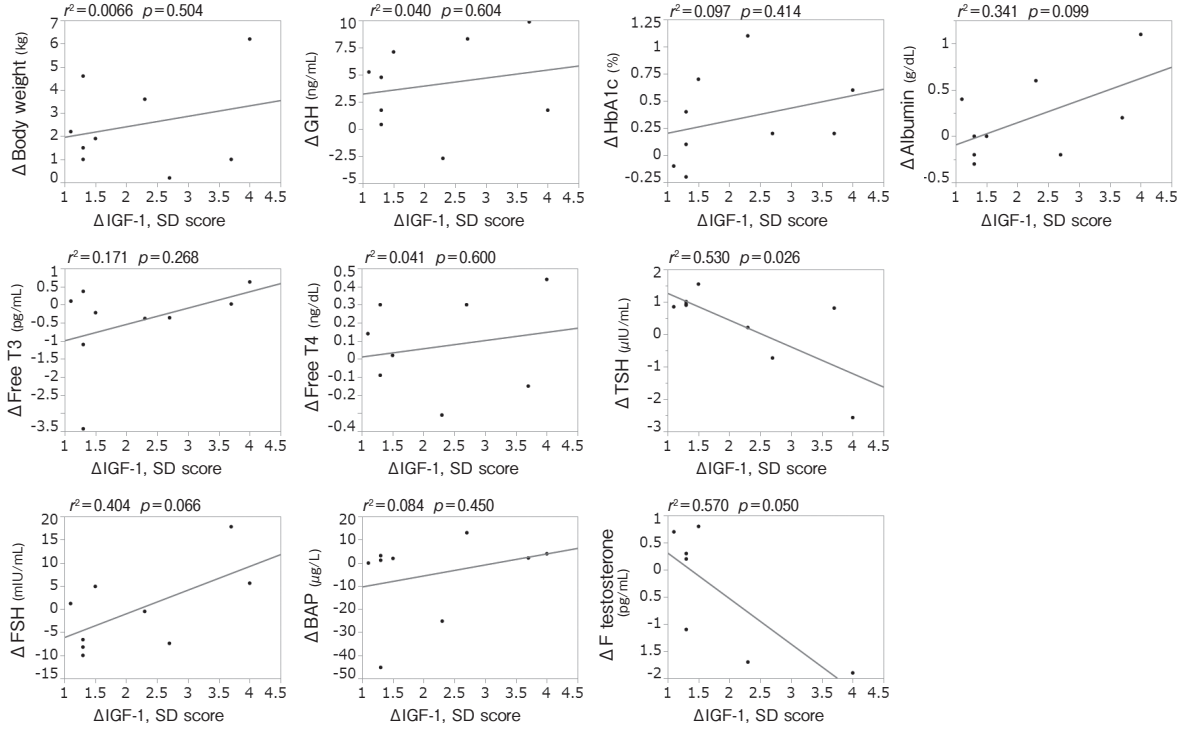

Fig. 3 Scatter diagrams and regression lines with respect to changes in standardized deviation score of insulin-like growth factor 1 (IGF-1 SD score) and other variables at week 3. Δ Values were calculated by subtracting the value at 0 week from that at week 3.
GH, growth hormone; HbA1c, hemoglobin A1c; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; FSH, follicle-stimulating hormone; BAP, bone-specific alkaline phosphatase; F testosterone, free testosterone.

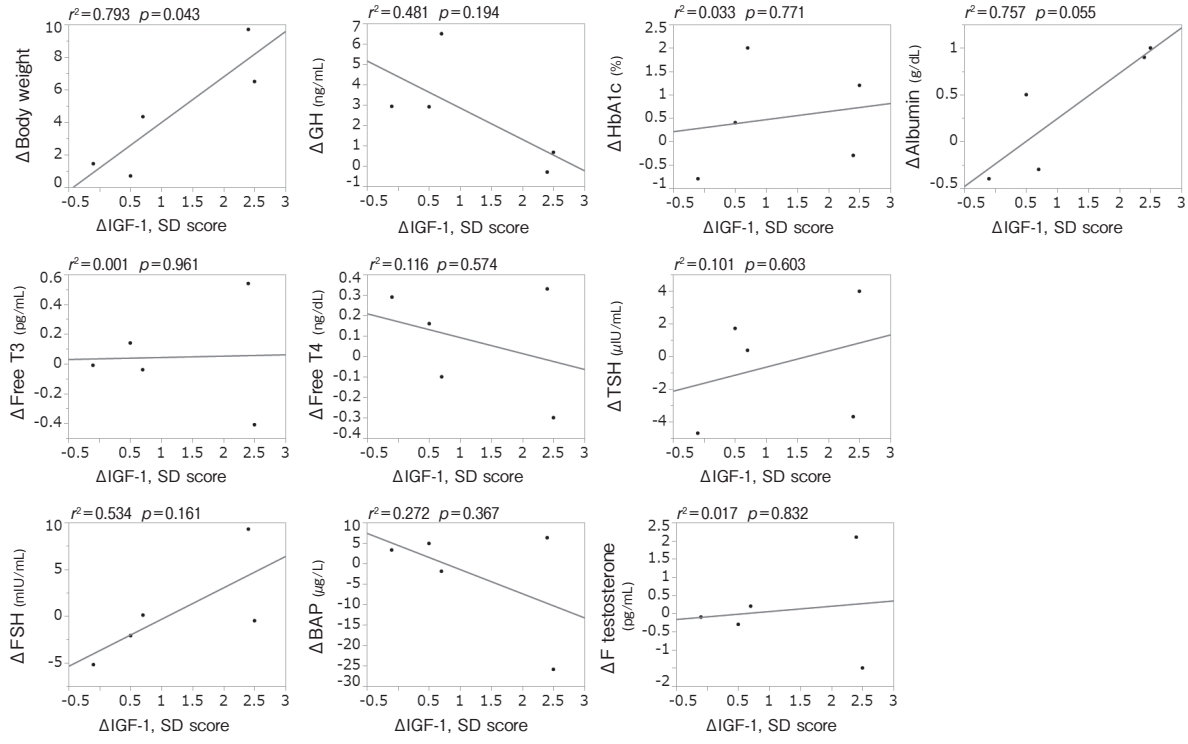

Fig. 4 Scatter diagrams and regression lines with respect to changes in standard deviation score of insulin-like growth factor 1 (IGF-1, SD score) and other variables at week 12. Δ Values were calculated by subtracting the values at week 0 from those at week 12.
GH, growth hormone; HbA1c, hemoglobin A1c; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; FSH, follicle-stimulating hormone; BAP, bone-specific alkaline phosphatase; F testosterone, free testosterone.

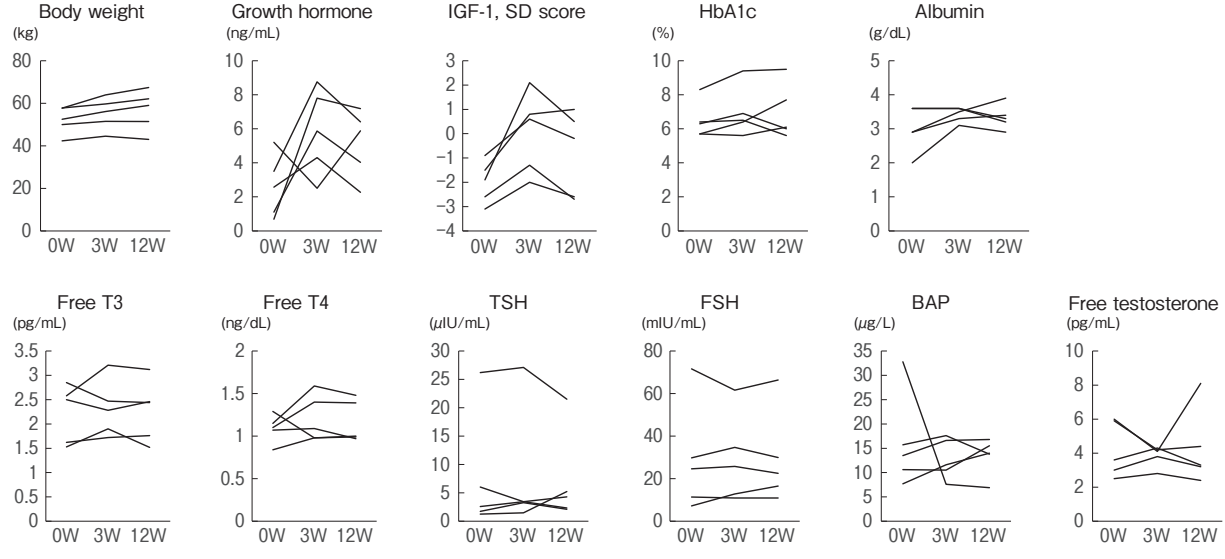

Fig. 5 Line graphs showing the chronological changes in 5 patients who continued to take anamorelin for 12 weeks or more.
IGF-1 SD score, standard deviation score of insulin-like growth factor 1; HbA1c, hemoglobin A1c; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; FSH, follicle-stimulating hormone; BAP, bone-specific alkaline phosphatase.

previously [7,8,10], to our knowledge this is the first comprehensive investigation of hormonal changes after anamorelin administration. Anamorelin was first released in Japan in April 2021, earlier than in other countries, for the treatment of cachexia in patients with gastric, pancreatic, colorectal, and non-small cell lung cancer [5]. Thus, there are insufficient data on the effect of anamorelin administration in actual clinical settings.

In the present study, body weight, GH levels, IGF-1 SD score, and HbA1c levels were significantly increased at week 3. Although the difference was not statistically significant, probably owing to the small number of patients who took anamorelin for 12 weeks, the mean body weight was higher at week 12, while the levels of GH and HbA1c, as well as IGF-1 SD scores, were lower at week 12 than at week 3. Elevation of IGF-1 and insulin-like growth factor binding protein-3 levels after anamorelin administration at week 3 or 4, followed by gradual decreases in both, have been reported [7,8,10]. Two of those reports showed increased body weight at week 3, which was maintained for 12 weeks [7,8]. Thus, our results agree with those of previous studies. We also revealed that the levels of GH and HbA1c may change in parallel with that of IGF-1.

Linear regression analysis revealed that ΔTSH correlated negatively with ΔIGF-1 SD score at week 3. TSH levels are known to be susceptible to dietary consumption of carbohydrates, iodine, and other micronutrients [12]. For instance, frequent intake of foods with a high glycemic index reportedly decreases TSH levels [13]. TSH levels also decreased by approximately 30% even after breakfast, compared to those measured without eating [14]. It is likely that anamorelin improves appetite and increases food intake, leading to decreased TSH levels. Meanwhile, 6-day administration of recombinant human GH has been reported to reduce TSH levels in anabolic-androgenic steroid-dependent patients [15]. Thus, GH or IGF-1 may directly or indirectly affect TSH levels, respectively.

ΔFree testosterone also correlated negatively with ΔIGF-1 SD score at week 3. Contradictory results have been reported on the relationship between testosterone and GH levels. In dog experiments, a 6-day infusion of very high doses of recombinant human GH reduced testosterone levels significantly [16]. In humans, daily administration of GH for 2 weeks did not alter testosterone levels [17]. In comparison to gonadotropin injection alone, combined therapy with recombinant human GH and gonadotropins increased testosterone levels significantly [18,19]. Another hypothesis is that sex hormone–binding globulin concentrations and/or albumin levels were altered after anamorelin administration, thus affecting free testosterone levels [20]. The possible interactions between testosterone and IGF-1 levels in anamorelin users should be investigated henceforth.

Although ΔTSH and Δfree testosterone levels correlated significantly with the ΔIGF-1 SD score at week 3, these values were not significant at week 12. Instead, Δbody weight and ΔIGF-1 SD score were correlated positively (Fig. 4). ΔAlbumin also tended to have a positive correlation with ΔIGF-1 SD score. These results suggest that anamorelin administration generates a surge in GH and IGF-1 secretions, which may influence TSH and free testosterone levels at week 3. However, these hormone levels tend to be balanced by week 12, and the anabolic effects of anamorelin appear at week 12.

Our study has several limitations. First, the number of patients enrolled was small. In particular, only 5 patients took anamorelin for 12 weeks, which is the most significant limitation hampering sufficient statistical analysis in this study. There were two major reasons why participants dropped out: cancer deterioration (n = 5) and intestinal obstruction (n = 2). Patients with gastrointestinal cancer accompanied by cachexia are prone to debilitating conditions and deteriorate rapidly because of disease progression [21]. In addition, gastrointestinal cancer, metastatic lesions in the gastrointestinal tract, and peritoneal dissemination often cause impairment or complete arrest of the passage of contents through the intestine. Although anamorelin is covered by insurance only for patients with weight loss > 5% in Japan [5], interventions in patients predisposed to or in the early stages of cancer cachexia probably improve adherence to the therapy. The second limitation is the lack of a control group. Because the levels of various hormones fluctuate during cancer treatment due to the use of anticancer drugs, cancer progression, and deterioration of the nutritional condition, a comparison of levels between patients with and without anamorelin administration would be ideal for investigating the true nature of this medication. The third limitation is selection bias due to loss to follow up. As described above, 7 participants dropped out because of cancer deterioration (n = 5) or intestinal obstruction

(n=2). Since the nutritional statuses of these patients were likely to be worse than those of the patients who completed the 12-week course of anamorelin, hormone levels may have been over- or underestimated. Thus, further investigations with larger numbers of patients and control groups are necessary.

In conclusion, our comprehensive analysis of hormonal changes in patients with cancer cachexia revealed: (i) increased body weight and levels of GH and HbA1c, as well as IGF-1 SD scores, 3 weeks after anamorelin administration; (ii) negative correlations between ΔIGF-1 SD score and ΔTSH and between ΔIGF-1 SD score and Δfree testosterone at week 3; and (iii) a positive correlation between Δbody weight and ΔIGF-1 SD score at week 12. Although the levels of hormones other than GH and IGF-1 in patients with cancer cachexia should be monitored and investigated in further studies with large numbers of participants, our results imply that the levels of several hormones can be altered 3 weeks after anamorelin administration, while they tend to return to a state of equilibrium in long-term (≥12 weeks) users.

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