ventricular or ventricular premature contractions, although they rarely become a serious clinical problem.[6]

The incidence of congestive heart failure (CHF) because of repeated anthracycline administration typically occurs within 1 year after completing the treatment, and depends on the cumulative dose. A report in 1981[9] showed that the incidence of doxorubicin-induced CHF was 0.14% with total doses less than 400 mg/m^2 body surface-area, whereas the incidence increased to 7% at a dose of 550 mg/m^2 and to 18% at a dose of 700 mg/m^2. In that early study, there was a clear dose-dependent response, with a rapid increase in cardiac toxicity at doses greater than 550 mg/m^2. Thus, cumulative doxorubicin doses of 550 mg/m^2 are empirically considered a limiting dose to avoid doxorubicin-induced cardiotoxicity. However, in some races, especially the Japanese, there are no data regarding the association of cumulative doses of anthracyclines and the incidence of CHF.

It is noteworthy that diastolic dysfunction, although generally asymptomatic and subclinical, is considered to start even at cumulative doxorubicin doses of 200 mg/m^2.[10] Several risk factors that potentially increase cardiac toxicity have been identified, including age, prior chest irradiation, the concurrent use of other anticancer drugs such as cyclophosphamide, trastuzumab, and taxanes, female sex, preexisting heart disease and hypertension.[6] Careful consideration must be given when treating patients with these risk factors, even when the patients have received low cumulative doses of anthracycline. Furthermore, anthracycline-mediated cardiotoxicity is not only a risk for elderly patients but also children.

Late-onset cardiac dysfunction, which manifests several years to decades after anthracycline treatment, has been increasingly recognized, often in patients who were treated for cancer during childhood or adolescence. Notably, it was reported that late-onset cardiotoxicity impaired the prognosis of 5–10% of cancer patients who received anthracycline-containing chemotherapy and would have otherwise been in remission.[11] In other reports, late-onset anthracycline-induced left ventricular (LV) dysfunction occurred in 18–65% of patients;[12,13] however, the incidence of severely reduced LV function increased with the duration of the follow-up period, suggesting that late-onset cardiac dysfunction is progressive. Aside from heart failure, it is noteworthy that life-threatening arrhythmias and sudden death have been reported in patients more than 15 years after they were treated with anthracycline.[14]

Although the mechanisms of late-onset cardiotoxicity remain unknown, progressive cardiomyocyte injuries that were initially caused by anthracycline must be involved in the delayed decompensation. Cumulative dose, higher rates of anthracycline administration, mediastinal irradiation, and female sex have been identified as risk factors for late-onset cardiac dysfunction. A recent study proposed that impairment of cardiac progenitor cells was involved in the pathogenesis of late-onset cardiotoxicity.[15]

Currently, early diagnosis and intensive treatment have greatly improved the prognosis of anthracycline-related cardiac failure. Nonetheless, certain patients with late-onset cardiomyopathy require cardiac transplantation.[13]

Taxanes

The taxanes, paclitaxel and docetaxel, are an important new class of anticancer agents that are widely used to treat breast and ovarian cancers. Interestingly, paclitaxel, which is introduced via a drug-eluting stent, has shown excellent clinical outcomes regarding in-stent restenosis. Taxanes exhibit their anticancer effects by promoting polymerization of tubulin, leading to the development of dysfunctional microtubules and disturbing cell division.

Although most cases of paclitaxel-induced cardiac side-effects are subclinical sinus bradycardia (approximately 30%), paclitaxel may induce heart block with syncope, supraventricular or ventricular arrhythmias, and myocardial ischemia through unknown mechanisms.[16] Importantly, taxanes potentiate anthracycline-induced cardiotoxicity by increasing the plasma levels of doxorubicin, and by promoting the formation of the toxic alcoholic metabolite, doxorubicinol, in cardiomyocytes.[17] Docetaxel shows less cardiac toxicity than paclitaxel.

Fluoropyrimidine

5-fluorouracil (5-FU) is widely used to treat many solid cancers, including gastrointestinal, gynecological, head and neck cancers. Although acute heart failure, arrhythmia, and ECG changes have been associated with 5-FU treatment, the most commonly described and severe cardiac side-effect is myocardial ischemia, which varies clinically from angina to acute myocardial infarction.[18] A previous report demonstrated that the frequency of cardiac events, including acute coronary syndromes, was 7.6% and the mortality rate was 2.2% after continuous intravenous infusion of a high dose of 5-FU.[18] Patients with a history of coronary artery disease had a higher incidence of ischemic adverse events.[19,20] Although the etiology is still unknown, it is thought that the cardiovascular toxicity is related to endothelial dysfunction and vasospasm of coronary arteries.[19]

Capecitabine, an oral prodrug of 5-FU, may also elicit myocardial ischemia and ventricular arrhythmias, although it appears to have less toxicity than 5-FU.[20]

Cyclophosphamide (CPA)

CPA is a common and classical alkylating agent that is widely used in the treatment of leukemia and many solid tumors, including lung, gastrointestinal, gynecological, skin and pharyngeal cancers. In addition, CPA is often used for the treatment of autoimmune diseases refractory to steroid treatments. Hemorrhagic cystitis is a well-known side-effect of cyclophosphamide administration.

CPA is generally well tolerated in terms of cardiovascular toxicity. However, high-dose rapid administration (eg, initial therapy for bone marrow transplantation) may induce lethal acute pericarditis and hemorrhagic myocarditis.[21] Although the etiology of this complication is not fully understood, direct oxidative cardiac injury has been implicated. Unlike the anthracyclines, the toxicity associated with CPA appears to be related to a single dose and not cumulative doses. In addition, patients who previously received anthracyclines or underwent chest irradiation are more likely to suffer from CPA-induced cardiotoxicity.[22]

Cisplatin

Cisplatin (CDDP) is a chemotherapeutic agent also used widely in the treatment of solid tumors, including lung, gastrointestinal, urinary, gynecological, head and neck cancers. The mechanism of the anticancer action of CDDP is not fully understood, although binding to DNA leads to the formation of inter- and intrastrand cross-links, resulting in impaired DNA synthesis and replication, further inducing cell death.

Dose-limiting side-effects of CDDP include ototoxicity, neurotoxicity, and nephrotoxicity because of renal tubular cell injury. With regard to cardiovascular complications, the

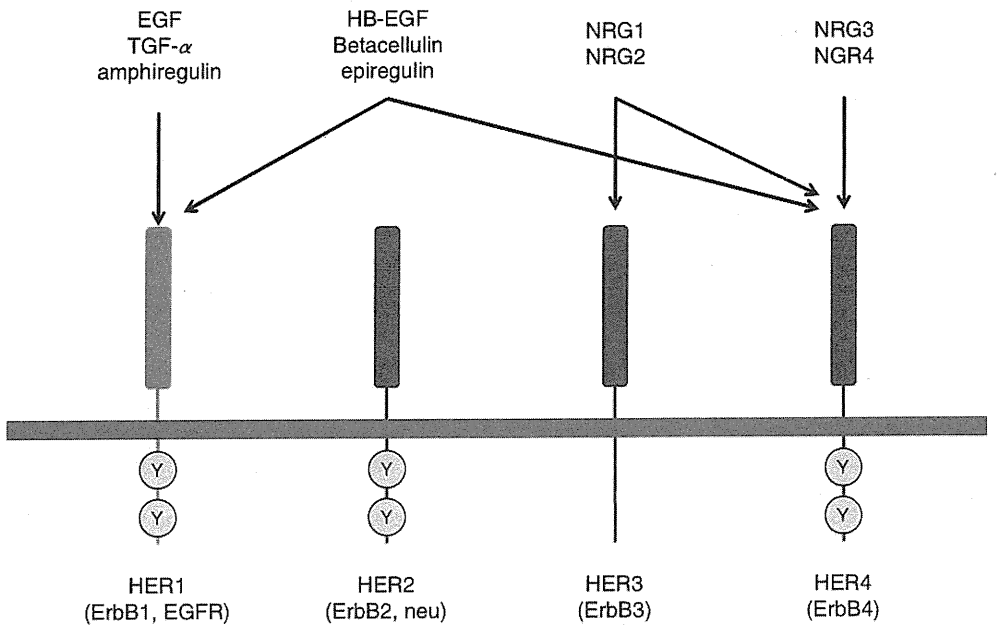

Figure 2. Epidermal growth factor (EGF) receptor ligands and their binding specificities for human EGF receptor (HER) family. Binding of these ligands to the HER family results in the formation of homodimers or heterodimers, leading to autophosphorylation of tyrosine residues in the cytoplasm and activation of downstream signaling pathways. Note that the specific ligand for HER2 is unknown. HER3 lacks a tyrosine kinase domain. TGF, transforming growth factor; HB-EGF, heparin-binding EGF-like growth factor; NRG, neuregulin.

pre- and post-therapy hydration that are necessary with CDDP administration to avoid the irreversible nephrotoxicity potentially induce hypertension, resulting in exacerbated heart failure. Major cardiac events, including myocardial ischemia, have been reported to occur more than 10 years after CDDP-containing chemotherapy.[23] In addition, CDDP-associated nephrotoxicity can lead to a serum electrolyte imbalance, such as hypokalemia or hypomagnesemia, and possibly induce cardiac arrhythmia.

Molecular-Target Agents

HER2 and HER1/EGFR: Antibodies

Trastuzumab Human epidermal growth factor receptor-2 (HER2) is a transmembrane receptor tyrosine kinase also known as ErbB2 or neu. Approximately 20–30% of breast cancers have augmented HER2 expression, which is associated with a poor prognosis.[24] Trastuzumab is an effective humanized IgG1 monoclonal antibody directed against the HER2 protein and is currently used as a central treatment for HER2-positive breast cancers.[25]

It is well documented that trastuzumab induces LV dysfunction and heart failure, especially when it is administered in combination with anthracyclines.[26] In the initial phase I–II studies, a single-use of trastuzumab resulted in a low incidence of heart failure or LV dysfunction (4–7% of patients).[25,27] However, a subsequent phase III study reported that administering trastuzumab in combination with anthracyclines and CDDP increased the overall incidence of cardiac dysfunction to 27%, with severe heart failure in 16% of patients[28] (8% and 3% of patients not treated with trastuzumab experienced cardiac dysfunction and heart failure, respectively). Likewise, paclitaxel and trastuzumab combination therapy resulted in symptomatic or asymptomatic cardiac dysfunction in 13% of patients, whereas paclitaxel alone resulted in overall cardiac dysfunction in 1% of patients.[28]

The mechanisms that lead to these complications are not fully understood, but HER2 signaling is thought to be pivotally involved in development of the embryonic heart and in maintaining postnatal cardiac function.[29] Although no specific ligand for HER2 has been identified, HER2 can heterodimerize with the HER4/ErbB4 receptors in the adult myocardium. Cardiac endothelial cells produce neuregulin-1 (NRG1), which binds to HER4 and promotes its heterodimerization with HER2 (Figure 2). The HER2/HER4 heterodimer subsequently activates various intracellular signaling pathways, including the PI3-kinase/Akt, MAP kinase, Ras, Raf and Grb2, which are essential for cell growth, glucose uptake, and the turnover of sarcomeric proteins.[30] Mice with targeted disruption of the *HER2*, *HER4* or *NRG1* genes are embryonically lethal because of aberrant cardiac development.[31–33] Additionally, ventricular-restricted HER2-deficient conditional mutant mice developed dilated cardiomyopathy, and cardiomyocytes isolated from these mice were susceptible to anthracycline-induced toxicity.[34] In addition, immune reaction contributes to trastuzumab-mediated cardiac dysfunction because trastuzumab facilitates antibody-dependent cell cytotoxicity.[35]

Aside from prior or concurrent exposure to anthracyclines, other potential risk factors are associated with trastuzumab-related cardiac side effects, including baseline LV ejection fraction (LVEF), prior cardiac diseases, elderly age and previous chest irradiation.[36,37] Patients predisposed to cardiovascular risk factors (eg, smoking, hypertension, dyslipidemia, diabetes, and obesity) are more likely to experience cardiac

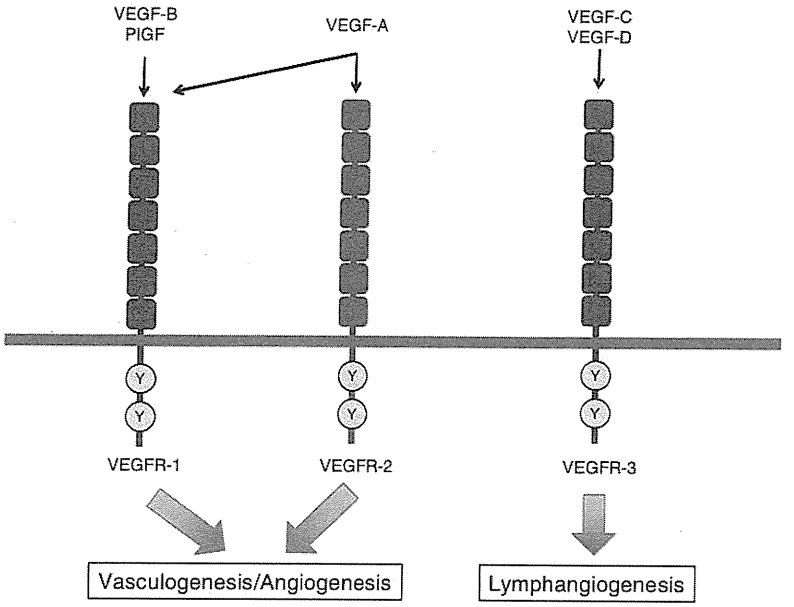

Figure 3. Vascular endothelial growth factor (VEGF) family and receptors. VEGF and VEGF receptor (VEGFR) signaling play pivotal roles in angiogenesis. PIGF, placenta growth factor.

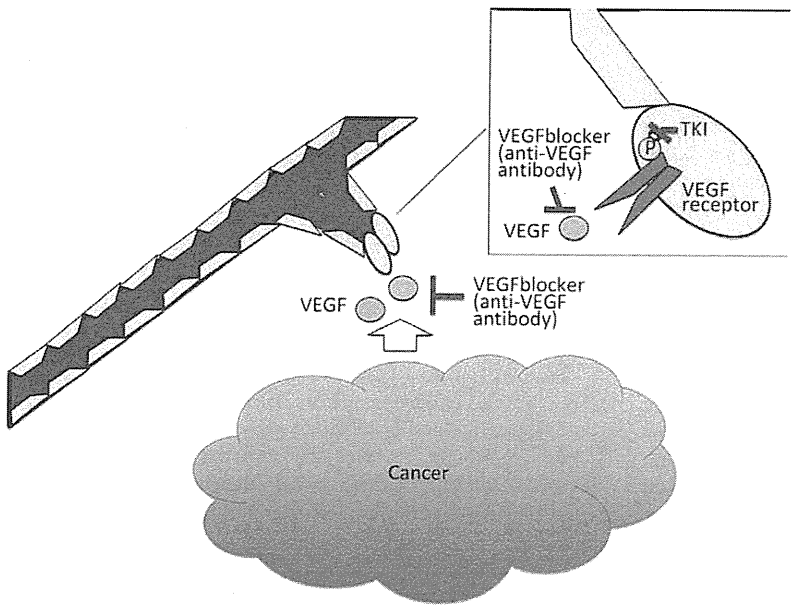

Figure 4. Anti-angiogenic inhibitors. Anti-vascular endothelial growth factor (VEGF) neutralizing antibody and tyrosine kinase inhibitor (TKI) of VEGF receptors inhibit tumor angiogenesis, which is essential for tumor growth and metastasis.

damage after trastuzumab treatment.[36]

Trastuzumab-induced cardiac dysfunction is often reversible. In the Herceptin Adjuvant Trial (HERA), withdrawing trastuzumab resulted in recovery of LVEF declines in 69% of patients with significant and confirmed cardiac dysfunction.[36] Myocardial biopsy specimens revealed that, unlike anthracycline, there were no ultrastructural changes after trastuzumab administration.[38] In addition, the recurrence of trastuzumab-mediated cardiotoxicity is inconsistent: among 25 patients with a history of LVEF reduction because of trastuzumab, after appropriate treatment and recovery of LVEF, only 3 patients had repeated cardiac dysfunction with trastuzumab rechallenge.[38]

Cetuximab Cetuximab, a human–mouse chimeric IgG1 monoclonal antibody that binds to the human HER1/EGFR, has recently been approved as a treatment for metastatic colorectal carcinoma. Cetuximab has been associated with thromboembolic adverse events, including myocardial infarction, pulmonary artery embolism, deep vein thrombosis and heart failure, although the incidence of those events was relatively low (2.5–4.8%).[39,40]

HER2 and HER1/EGFR: Tyrosine Kinase Inhibitors (TKI)

Lapatinib Lapatinib is an orally active, small molecule TKI that targets HER2 and HER1/EGFR. Lapatinib is a promising treatment for patients with trastuzumab-resistant,

progressive breast cancer because it is effective against HER2p95 (truncated form of HER2)-positive cancer. Phase I–III trials (3,689 patients enrolled) that examined the cardiovascular safety of lapatinib found that 1.6% of patients had reduced LVEF by at least 20%, and 0.2% experienced symptomatic heart failure. Furthermore, the incidence of cardiac complications increased in patients who had previously received anthracyclines or trastuzumab.[41]

Vascular Endothelial Growth Factor (VEGF): Antibody

Under pathological conditions, tumors promote angiogenesis, which is essential for supplying oxygen and nutrition for rapid growth and metastasis. The critical regulators of tumor angiogenesis are VEGF and its receptors (VEGFRs) (Figure 3). Anti-VEGF neutralizing antibody and the small molecules that block the TK activity of VEGFRs may be rational anticancer agents and have been proven effective in many human cancers (Figure 4).

Bevacizumab VEGF-A is highly expressed in most solid tumors, including colorectal, lung, breast and renal cancers. Bevacizumab, a humanized IgG1 monoclonal antibody that binds to human VEGF-A and inhibits downstream signaling, is used to treat colorectal and non-small-cell lung cancers.

Newly developed or exacerbated hypertension is a major side-effect of bevacizumab. In clinical trials, grade 3–4 severe hypertension occurred in 9.2% of patients,[42] with rare cases of hypertensive crisis, including encephalopathy or intracranial hemorrhage.

Thromboembolic events, such as myocardial infarction, ischemic cerebrovascular diseases, and pulmonary arterial embolism, are infrequent but life-threatening side-effects of bevacizumab that have been reported to occur in 3.8% of patients,[42] and elderly patients (≥65 years) or those with prior arterial thromboembolic events may have a higher risk. Gastrointestinal perforation is also a rare (1–2%) but fatal adverse effect with bevacizumab treatment. Although the mechanisms are unclear, bowel ischemia is thought to play a part.[43]

Regarding LV dysfunction, increasing cardiac toxicity has been associated with bevacizumab-based therapies in patients with advanced or metastatic breast cancer, many of whom were previously treated with anthracyclines.[44] Although there is little evidence for toxicity in this patient population, cardiac safety should be carefully monitored because bevacizumab-containing regimens are currently used to treat HER2-negative breast cancer.

Multiple-Target TKI

Sunitinib Sunitinib, a multiple target TKI, has recently been approved to treat metastatic renal cell carcinoma and gastrointestinal stromal tumors (GIST). Sunitinib inhibits tumor growth, metastasis, and pathologic angiogenesis.

When the cardiovascular safety of sunitinib was examined in phase I–II trials,[45] 11% of patients who received repeated cycles of sunitinib experienced cardiovascular events, including acute myocardial infarction and heart failure; 28% of patients showed an asymptomatic but significant reduction in LVEF of at least 10%. In addition, approximately half of the patients (47%) developed hypertension during sunitinib treatment. Patients with a history of coronary artery disease, LV dysfunction, or prior exposure to anthracyclines have been shown to be at increased risk for sunitinib-related cardiotoxicity, indicating that the cardiac conditions of this high-risk patient population should be monitored carefully.[46]

Because it is unknown if LV dysfunction is reversible after sunitinib therapy ceases,[45,46] patients who experience significantly reduced LVEF should be monitored after they complete this therapy.

Sorafenib Sorafenib is a Raf kinase inhibitor that is also a multi-target TKI. The incidence of sorafenib-associated cardiac dysfunction is reportedly lower than that of sunitinib and appears to be reversible and responsive to general treatment.[47] In clinical trials of patients with renal cell carcinoma or solid tumors, severe hypertension occurred in 5.7% of patients treated with sorafenib and there was a 6.11-fold increase in hypertension in sorafenib-treated patients compared with controls.[48]

Other Biological Agents

Imatinib Imatinib binds to the TK domain of the BCR-ABL fusion protein that activates cell proliferation in chronic myeloid leukemia (CML). Despite the excellent clinical outcomes, especially in CML or GIST patients, recent reports show that imatinib may increase the risk of heart failure.[49] Although imatinib-induced LV dysfunction is largely reversible after discontinuing the treatment, persistent and irreversible heart failure has also been reported.[50] Other than LV dysfunction, imatinib typically induces periorbital or peripheral edema through a non-cardiogenic mechanism with an unknown etiology.

Rituximab Rituximab, a chimeric mouse–human monoclonal antibody against the CD20 antigen, is now widely used to treat NHL. Most of the side effects associated with rituximab are infusion-related hypotension, arrhythmia, angioedema, and bronchospasms, which occur within the first few hours of treatment. The addition of rituximab to doxorubicin-containing standard chemotherapy significantly improves the response to therapy and reduces the risk of death in NHL patients, although potentiation of anthracycline-induced cardiotoxicity by the addition of rituximab is not detected, at least within the first year following therapy.[51]

Clinical Follow-up and Monitoring of Patients

The clinical course of cardiovascular side-effects of chemotherapy may vary from a transient, asymptomatic reduction in LVEF to cardiac death. To date, the plasma concentrations of troponin I and N-terminal pro-B-type natriuretic peptide, both of which are released from the heart in response to myocardial overload, have been demonstrated to be specific and sensitive markers for chemotherapy-induced cardiotoxicity.[52–54]

Echocardiography is the most common and powerful tool to assess LV function. LVEF or fractional shortening is widely used and can definitively indicate cardiotoxicity associated with cancer chemotherapy. However, both of these methods depend on the preload and afterload at the time of evaluation, which can potentially lead to inconsistent values and assessments. Additionally, neither procedure is sufficiently sensitive to diagnose preclinical myocardial damage. From this perspective, Doppler echocardiography may be more powerful for detecting early cardiac toxicity.[10] Exercise or dobutamine stress echocardiography and strain echocardiography may also be useful for the early detection of subclinical, latent cardiomyopathy that is related to cancer treatment. LVEF can be measured non-invasively and more precisely by radionuclide ventriculography or cardiac magnetic resonance imaging.

Cancer patients must be routinely evaluated for ECG abnormalities, such as ST-segment and T-wave changes, decreased

QRS voltage, and a prolonged QT interval. Furthermore, arrhythmias and conduction disturbances must also be carefully monitored. In particular, "torsades de points" associated with a prolonged QT interval because of anticancer drugs could be life-threatening.

Currently, endomyocardial biopsy is not routinely performed because it is invasive and has a higher risk of complications and possible sampling error.

Treatment

Once cardiovascular side-effects occur, patients must be treated with the appropriate medication. It is important to consider ceasing the anticancer treatment in accordance with the severity of the complications.

Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type I receptor blockers (ARB), β-blockers, aldosterone antagonists, or diuretics should be administered as baseline CHF treatment. Although anthracycline-induced LV dysfunction is frequently irreversible, a recent clinical study indicated that enalapril (ACE inhibitor) and carvedilol (β-blocker; when possible) treatment resulted in a complete (42%) or partial (13%) recovery of LVEF, predominantly in patients in whom treatment was initiated at an early stage.[55] Similarly, for trastuzumab-related cardiotoxicity, administering an ACE inhibitor is currently recommended when LVEF declines to less than 50%.[56]

For other severe cardiovascular complications elicited by anticancer therapy, including hypertension, arrhythmias, and thromboembolism, it is important to consider intensive and appropriate treatments in addition to interrupting the cancer chemotherapy. The renin–angiotensin system (RAS) may play a key role in vasoconstriction and lead to hypertension.[57] Therefore, inhibiting the RAS with an ACE inhibitor or ARB may be an optimal approach to manage bevacizumab- and angiogenic inhibitor-induced hypertension.[42,58]

Prevention

To reduce the risk of anthracycline-induced cardiotoxicity, the cumulative dose should be limited and prolonged intravenous infusions should be considered instead of bolus administration. In addition, liposome-encapsulated anthracyclines have been developed to target cancer more preferentially and reduce the toxic effects on the heart. Some clinical trials have shown that liposomal anthracycline has less cardiotoxicity but provides similar antitumor efficacy.[59]

Many clinical trials have shown that dexrazoxane, an iron chelator, effectively prevents the LV dysfunction that is induced by anthracyclines.[60] The FDA has approved dexrazoxane for clinical use in metastatic breast cancer patients who have received a cumulative doxorubicin dose of 300 mg/m^2, although Japan has not yet approved this clinical therapy.

Conclusion

The impact of cardiovascular side-effects on modern cancer therapy is becoming greater in our aging society, together with the clinical use of novel anticancer drugs. In the current clinical setting, it is likely that every cardiologist will face cardiovascular complications in cancer patients. Cancer also occurs more frequently in elderly people, who are more likely to be predisposed to cardiovascular diseases and this means that additional cardiovascular risks will occur in patients with cancer, and an increasing number of patients will have both cancer and cardiovascular diseases.

Another point of consideration is cancer survivors. A recent retrospective cohort indicated that long-term survivors of childhood cancer have a 15.1-fold increased rate of CHF, a 10.4-fold higher rate of coronary artery disease, and 9.3-fold higher rate of cerebrovascular events compared with their sibling controls.[61] Notably, the susceptibility of these survivors to overall cardiovascular diseases is greater than their risk of a second malignant neoplasm (14.8-fold increased risk compared with controls). Certainly, cancer treatment increases the risk of cardiovascular diseases, which requires that the long-term cardiovascular condition of each patient be followed over an extended time period, even if the cancer has been cured. Cardiologists should be aware of the potent cardiovascular complications that are related to cancer chemotherapy, and closely collaborate with oncologists to further advance cancer treatment and overcome the associated cardiovascular diseases.

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フォーラム

臨床試験・治験被験者募集に関する多施設調査

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1．はじめに

臨床試験・治験を実施するうえで，被験者を試験期間内に登録することは重要なことである．しかしながら，実際には，しばしば被験者の登録に困難をきたすことがあり，被験者が不足した場合には試験結果の信頼性が損なわれたり，被験者の確保のため試験期間が延長される場合には試験の結果を診療に活かせる時期が遅れることになる．Campbellらは122の臨床試験のうち，目標症例数を達成できたものは31%にとどまり，45.1%の試験では実際に登録された被験者数が目標症例数の80%に満たなかったと報告している[1]．

海外では被験者募集をより効率的に行う方法が模索され，どの方法が最も費用対効果が高いかについて詳細に検討されている[2,3]．ダイレクトメールの配布やマスメディア（テレビやラジオでの治験の広告）は効果的で，最も汎用されている方法である．

本邦における治験の被験者募集においては，製薬企業では新聞や折り込みチラシを利用することが多い[4]．治験中核病院や拠点医療機関においては，被験者や一般患者に対して，治験への参加を促すために，「被験者募集中の治験情報の提供」「治験に関するパンフレット配布」「医療関係者が治験に関する一般的相談に応じる」などの対応を行っている[5,6]．このような取り組みにもかかわらず，本邦の2007年度終了の医薬品治験における実施率では，80%に満たない医療機関が全体の60%以上を占め，実施率の中央値は72.8%であったと報告されている[6]．また，京都大学医学部附属病院における2007年度終了の医薬品・医療機器治験の実施率は63.3%，2008年度では79.1%であった[7]．

被験者の募集においては，被験者となりうる集団をどのように選び出すか，またその集団に対してどのような方法で募集を行うか，を工夫する必要がある．被験者となりうる集団を正確に把握することは現実的には困難であるので，被験者が高率で見込まれる集団を対象疾患ごとに想定し，募集を行うことが効率的である．また，利用できる設備，経費，スタッフは限られているので，実施できる範囲内で最良と考えられる方法を選択することになる．そこで，被験者募集の方法は，疾患あるいは医療施設ごとに適当な方法を模索する必要があると考えた．本研究では，医療施設で実施されている被験者募集の方法を収集し，疾患あるいは医療施設ごとにどのような方法が適当であるかを検討することを目的としている．

2．調査方法

多施設共同による記述疫学研究である．共同研究施設の選定に当たっては，相互交流がある3つの近隣の臨床試験実施施設に対して，メールにより協力依頼を行い，了解を得たうえで情報収集を行った．

2009年11月に筆頭著者は共著者の各施設〔国立循環器病センター病院臨床研究センター（現：国立循環器病研究センター臨床研究部），滋賀医科大学医学部附属病院治験管理センター，大阪市立大学医学部附属病院医薬品・食品効能評価センター〕を訪問し，被験者募集のためのインフラストラクチュア（被験者募集の広告手段や臨床試験にかかわる病院情報システムなど）を見学した．また，共著者からこれまで当該施設で実施した，被験者募集のより積極的な方法についてあらかじめ用意した質問用紙に基づき聞き取り調査を行った．質問内容は被験者募集で利用している手段（ポスターの掲示・マスメディアの利用・宣伝などについ

Key words：subject recruitment, multi-institutional descriptive study
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Table 1 被験者募集の方法

4つの臨床試験実施施設で聞き取り・実地調査を行い，調査で得た被験者募集の方法と適当であると考えられる対象疾患・医療施設を，被験者数の増加あるいは登録を促進する手段に分けた．

被験者募集の方法	適当と考えられる対象疾患や医療施設
1．被験者数の増加	
1-1. 自施設内での増加	
・電子カルテ，オーダーシステムなどから網羅的に被験者を探す	電子カルテやオーダーシステム，およびそれを閲覧または検索するシステムが導入されている医療施設
・分担医師，担当診療科の追加	対象疾患を診療している医師や診療科が多岐にわたる場合
・広告方法の工夫（美しいポスターやパンフレットの作成，視聴覚資料の利用）	対象疾患が不眠やうつなど，被験者の症状から診断できる疾患
・スタッフ用のわかりやすいマニュアルの用意	治験や臨床試験の専門のスタッフ（CRC など）が不足している医療施設
・“ボランティアの会”の設立・運営	健康な人を対象とする場合．また，会を設立・運営できる医療施設であることが必要
・1人の CRC が特定の疾患領域を専門的に担当する	対象疾患が慢性疾患の場合
1-2. 他の医療機関からの被験者の募集	
・同門会，学会，関連病院を通じての協力要請	他の医療機関との連携が活発な医療施設
・ネットワークの設立	他の医療機関との連携が活発な医療施設
1-3. 一般から被験者を募集	
・ウェブページの利用	対象疾患が難治性疾患で，患者自身（または家族）が積極的に治験参加を希望する場合
・患者会や学園祭などでの講演	対象疾患が若年者に多い疾患（学園祭での講演）
2．被験者の登録促進	
2-1. 開始前から被験者候補の患者を把握しておく	対象疾患が慢性，難治性で希少な疾患
2-2. 外来受診を待たずに試験の説明を行う	
・コールセンター，対応窓口の設置	対象疾患が不眠やうつなど，被験者の症状が主たる選択基準となる疾患
・説明会の実施	対象疾患における外来受診間隔が長い場合

て実施の有無），今まででとくに有効であった被験者募集方法，被験者のスクリーニングの方法，ネットワークやボランティアの会を運営している施設に対してはその詳細についてなどを含んだものとした．調査で得た被験者募集の方法と適当であると考えられる対象疾患・医療施設を，被験者数の増加あるいは登録を促進する手段に分けて記載し，海外での先行研究と比較した．また，各施設での被験者募集の具体的な例について筆頭著者と各施設の共著者が記載した．

3．結　果

1）被験者募集の方法（Table 1）

被験者募集の方法と適当であると考えられる対象疾患・医療施設を，被験者数の不足に対する手段と登録の遅れに対する手段に分けて記載したものを Table 1 に示した．

2）被験者募集方法の比較（Table 2）

本研究で収集した被験者募集の方法を海外での先行研究と比較したものを Table 2 に示した．

3）被験者募集の具体的な手順（Table 3）

各施設で実施した被験者募集の具体的な例を Table 3 に示した．

4．考　察

本研究では臨床試験実施施設の訪問・聞き取り調査にて得られた被験者募集に関する方法を収集し解析を試みた．

被験者が不足した場合にはまず自施設内で被験者を探し出すことを考えるべきである．CRC（Clinical Research Coordinator）が特定の疾患領域を専門的に担

Table 2 被験者募集方法の比較

本研究で得た被験者募集の方法を海外での先行研究と比較し，方法ごとに記載した．

本研究での結果	海外での先行研究
他の医療機関からの被験者の募集	
自施設以外の病院の医師に対し，被験者候補の患者を紹介してもらうよう依頼	自施設以外の病院の医師は試験の説明を行うのではなく，試験の紹介の手紙を対象者に出したり，対象者のリストを作成する[8,9]．
被験者募集の広告	
美しいポスターやパンフレットの作成，視聴覚資料を院内に設置	ダイレクトメールの配布やマスメディア（テレビやラジオでの治験の広告）の利用[2,3]
電子カルテの利用	
電子カルテ，オーダーシステムなどから網羅的に被験者を探す	条件に合致する患者の電子カルテを開いた際に，臨床試験の被験者候補であることを知らせるポップアップ画面が表示される[10]．

Table 3 被験者募集の具体的な例

共同研究施設において今までにとくに有効であった被験者募集方法について聞き取り調査を行い，その結果を医療機関・対象疾患・方法・倫理的配慮・結果について記載した．京都大学医学部附属病院における方法は，これまでに筆頭著者の所属する探索医療センターで実施した方法を記載した．

医療機関	国立循環器病センター（現：国立循環器病研究センター） 循環器関連の難病の診療を専門的に行っている．
対象疾患	慢性の難病指定疾患
方法	担当医師が被験者候補の患者60名程度に試験に関する説明会の案内を送付し，患者に対する集団説明会を実施（注）．
倫理的配慮	施設の倫理委員会に答申し，承認されたうえで，治験依頼者が用意したスライドを用いて説明を行った．
結果	患者十数名およびその家族が実際に説明会に訪れた．
医療機関	滋賀医科大学医学部附属病院 各診療科の待合にプラズマディスプレイを設置し，院内の各種案内や情報を放映している．
対象疾患	治験依頼者より要望があった場合
方法	プラズマディスプレイを利用して治験の広告を放映し，受診中の患者は診療の待ち時間等に鑑賞できる．作成，運用については，治験依頼者・病院の広報担当部門と相談し，実施している．
倫理的配慮	商品名・治験薬の名称を明らかにせず，患者を誘導するような内容にならないよう考慮して作成された映像が治験依頼者から提供され，治験審査委員会で募集広告として承認されている．
結果	プラズマディスプレイを見て治験を知り，問い合わせに至るケースがある．
医療機関	大阪市立大学医学部附属病院
対象疾患	ボランティアの会会員（健康な人および患者）
方法	ボランティアの会を運営し，医薬品や食品の機能性に関する，一般市民を対象とした講演会の案内や疾患についての情報，臨床試験についての情報を事務局から会員に対してメールマガジン等により配信・送付している．
倫理的配慮	会則に同意して申し込んだ，医薬品や食品などの試験にご協力いただける人を対象としている．
結果	現在会員は1,900人に達しており，ここから医薬品，医療機器ならびに機能性食品の臨床試験の被験者を募集し，効果的に収集した．
医療機関	京都大学医学部附属病院 医師主導治験を実施している．
対象疾患	他に有効な治療法がない重篤な疾患
方法	被験者募集の広告を探索医療センターのホームページに掲載した．
倫理的配慮	広告は「治験に係わる被験者募集のための情報提供要領」（日本製薬工業協会）に則り，センターで作成したものを，治験審査委員会の許可を得て掲載した．
結果	疾患を持つ患者のご家族が治療法を求めて情報を検索した際に，治験の広告を探し当て，センターに連絡，受診中の病院の医師とも連絡を取りながら試験に適格かどうかを確かめ，試験に組み入れることができた．

（注）国立循環器病センターでは集団説明会を実施したが，これは対象疾患の患者間での情報交換が活発で治験への関心も高く，一部の患者だけに対して治験の案内を行いにくいこと，および被験者候補の患者の外来受診間隔に対して治験の募集期間が短く，外来受診時に患者に説明する方法では，すべての被験者候補の患者に公平に治験の案内を行うことができなかったという理由からである．

当するというのは，とくに慢性疾患を対象とする場合，被験者候補の患者の状態を把握し患者との信頼関係を築くうえで手助けとなり，被験者登録に促進的に働くと考えられる．

自施設内で被験者が不足する場合には，他の医療機関あるいは一般の人々から被験者を募集しなければならない．他の医療機関から被験者候補を紹介していただくという方法は，実際には，自施設以外の病院の医師が，被験者候補の患者に対して外来受診などの限られた時間内で試験のことを説明し，自施設に紹介することは困難であることが多い．また，紹介されたものの選択基準に合致しない場合や試験終了後に紹介元の医療機関への通院をためらうなど，対応に苦慮する場合があり，紹介元の医療機関と事前に対応を協議する必要がある．Forster らは General Practitioner（一般医または家庭医）から対象者に試験の紹介の手紙を出した，または General Practitioner が研究者に対象者の名前と住所を渡し，研究者が紹介の手紙を出した，と報告している[8]．Dyas らも General Practitioner を通じて被験者を募集する際には，外来受診時に試験の説明を行う方法では成功しないとして，General Practitioner の代理でリストに基づいて手紙を出す方法を報告している[9]．海外で実施されている，ダイレクトメールの配布や電子カルテを応用した方法[10]も，今回の研究では認められなかったが，今後本邦においても実施される可能性がある．

被験者の登録を速めるには試験開始までに要する日程を短縮するとともに，試験責任医師・分担医師が試験の契約時に試験内容を理解し，臨床の場で対象となりうる候補者を把握し，試験開始後速やかに登録ができるよう配慮する必要がある．また，多忙な外来診療の場で試験の説明を行うことが困難な場合は，次回の外来受診を待たずに説明会を実施する，対応窓口を設置するなどの対策が必要である．

今回紹介した方法は，試験を実施する医療機関側が主体となって行いうる方法であるという点で，被験者を速やかに登録したい医療機関にとって有用であると考えられる．新たな治験活性化５カ年計画の中間見直しに関する検討会においても，症例集積性が必ずしも高くないことによる治験の効率化への障壁，医療機関が増えることによるコスト増への影響が懸念されている．症例集積性が低い背景は本邦の医療システムの影響が大きく，国民皆保険制度のもと，患者はどの医療機関でも受診できるフリーアクセス制であり，特定の病院に被験者候補の患者が集積しにくい可能性がある．しかし，治験管理センター等の臨床試験への積極的な取り組みにより，被験者の臨床試験への意識や理解度が変化し，試験への参加の見込みが変化する可能性があると考えられる．

本研究では積極的な被験者募集の方法を収集したが，その方法が実際に効率的であったかどうかについての検証は行っていない．Campbell らはどのような因子，たとえば臨床試験部門からの支援の有無や十分な資金などの因子が目標症例数の達成につながるのかについて検討し，因果関係を見いだすのは困難であるとしている．その原因として目標症例数がもともと限られた情報に基づいて定義されており，この達成を唯一の指標とすることは不十分であること，また，因子として取り上げられていない要素，たとえば研究者の特質がより重要である可能性があることなどをあげている[1]．むしろ，効率的であった方法を選択するということよりも，それぞれの試験の対象疾患や医療機関の状況に応じて取捨選択し，いくつかの方法を組み合わせて実施することが現実的であると考えられる．

また，被験者の登録が遅れているかどうかを早期に把握し，新たな被験者募集の手段を講じるためには，試験の進捗管理が重要である．Rubin らは被験者登録を支援する委員会を構成し，毎月，被験者の登録状況の報告を受け，３カ月に１度は被験者募集に関する戦略を協議し，登録が遅れている医療機関の手助けを行った[11]．とくに治験においては，被験者募集の方法の変更は治験審査委員会の意見を聴き倫理審査にはかったうえで実施することになるため，早めに対策をとる必要がある．

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FORUM

A Multi-institutional Descriptive Study on the Methods of Subject Recruitment for Clinical Trials

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Objectives：In this study, we surveyed the methods of subject recruitment used in medical institutions and investigated the appropriate methods for each type of clinical study or medical institution.
Methods：We conducted a questionnaire survey regarding the methods of subject recruitment used in four medical institutions (Department of Clinical Research, National Cerebral and Cardiovascular Center；Clinical Trial Center, Shiga University of Medical Science Hospital；Center for Drug & Food Clinical Evaluation, Osaka City University Hospital；Translational Research Center, Kyoto University Hospital) in November 2009. We listed the methods of subject recruitment indicated in the responses and determined the suitability for specific target diseases or medical institutions based on the possibility of increasing the number of subjects or promoting registration of subjects.
Results：Different methods aiming at facilitating recruitment were used depending on the target disease and the situation of the medical facility. These methods include advertising within the institution using audiovisual materials, putting information of the study on a web page, forming a volunteer group, and explaining the clinical study separately from outpatient consultation.
Conclusion：It is necessary to select and combine methods of subject recruitment depending on target disease and situation of the medical facility.

Key words：subject recruitment, multi-institutional descriptive study

Randomized phase II study of clinical effects of ghrelin after esophagectomy with gastric tube reconstruction

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Background. *Ghrelin is a peptide hormone with pleiotropic functions including stimulation of growth hormone secretion and appetite, and its levels decrease after esophagectomy. The aim of this study was to evaluate whether exogenous ghrelin administration can meliorate the postoperative decrease of oral food intake and body weight, which are serious complications after esophagectomy.*

Methods. *This prospective randomized, placebo-controlled, clinical trial assigned a total of 20 patients with thoracic esophageal cancer who underwent radical operation into either a ghrelin (n = 10) or placebo (n = 10) group. Synthetic human ghrelin (3 μg/kg) or 0.9% saline placebo was administered intravenously twice daily for 10 days from the day after the start of food intake. The primary end point was calories of food intake. Comparison of appetite and changes in weight and body composition were also made between the 2 groups.*

Results. *Intake of food calories was greater in ghrelin group than placebo group (mean 874 vs 605 kcal per day; P = .015). The appetite score tended to be greater in ghrelin group than placebo group (P = .094). Loss of weight was less in ghrelin group (−1% vs −3%; P = .019) and this attenuation was due largely to a decrease of lean body weight loss (0% vs −4%; P = .012). No side effects were observed in either groups.*

Conclusion. *These preliminary results suggest that administration of ghrelin after esophagectomy increased oral food intake and attenuated weight loss together with maintenance of lean body weight. (Surgery 2010;148:31-8.)*

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ESOPHAGEAL CANCER is associated with a dismal prognosis, even after curative resection[1]; however, recent improvements in operative treatment have improved markedly the prognosis of patients with esophageal cancer. Unintentional weight loss and malnutrition are serious postoperative complications, encountered frequently after esophagectomy.[2-4] The majority of patients (90%) lose >5% of body weight at 3 months postoperatively and 16% lose >15% of body weight.[2] These changes lead to deterioration of activity of daily living[5,6] and immune function.[7] Weight loss after esophagectomy is multifactorial and involves anastomotic stricture, reflux, disturbance of gastric emptying, swallowing dysfunction, and loss of appetite.[2,3,5,8] Martin et al[3] reported that appetite loss, eating difficulties, and odynophagia were linked to postoperative weight loss. In addition, large retrospective studies demonstrated that weight loss is a significant predictor of decreased survival in oncologic patients.[9-11] These results highlight the need for active nutritional intervention in patients with cancer. Surgeons have always tried to address this problem by parenteral or enteral nutrition[12]; however, these modalities are cumbersome for some patients, and the most effective means of delivering nutrition remains controversial. Moreover there are no guidelines for improvement of weight loss.

Our group has focused on ghrelin, a gut hormone known to increase appetite and regulate

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weight and body composition, and its potential role in postoperative weight loss. Ghrelin is a peptide hormone secreted mainly in the stomach and was identified as an endogenous ligand for the growth hormone (GH) secretagogue receptor of pituitary gland in 1999.[13] In a previous study, we examined the relation between weight loss after esophagectomy for esophageal cancer and postoperative ghrelin concentrations, and reported that the circulating concentrations of ghrelin decreased significantly by 50% at 3 and 7 days after esophagectomy; moreover, there was a significant correlation between ghrelin concentration and postoperative weight loss.[14]

Ghrelin plays a number of biologic functions, in addition to increasing GH secretion, such as regulation of energy balance and promotion of appetite signal in the hypothalamus and acts opposite to leptin.[15-20] A randomized, double-blind, crossover study in healthy volunteers demonstrated the safety and efficacy of stimulating food intake by ghrelin therapy.[21] The abovementioned functions of ghrelin led to a new concept of weight regulation and the role of the stomach. A number of studies have reported the clinical impact of ghrelin on patients with functional dyspepsia and cachexia owing to chronic obstructive pulmonary disease, cardiac disease, and malignancy; administration of ghrelin resulted in not only weight loss, but also in decreasing the exacerbation of primary disease.[22-27] These findings suggest that ghrelin may be effective for the treatment to weight loss after esophagectomy in patients with esophageal cancer. To elucidate this, we conducted a prospective, randomized, single-blind, placebo-controlled clinical trial.

PATIENTS AND METHODS

Study patients. The study protocol was approved by the Human Ethics Review Committee of Osaka University School of Medicine and was registered in University Hospital Medical Information Network (UMIN R000002483). A signed consent form was obtained from each enrolled patient. The study began in October 2007, and enrollment of patients ended in December 2008. The patients continued to be followed up until June 2009. The subjects of the study were patients with esophageal cancer. The following were the criteria used for study entry: (1) thoracic esophageal cancer, treated by radical esophagectomy with gastric tube reconstruction; (2) age 20–80 years; (3) ability of oral intake; (4) adequate function of major organs; (5) no other active malignancy; and (6) provision of written informed consent. Patients ineligible for inclusion were those with a severe pre-operative weight loss of >10% over the past 3 months, severe comorbid conditions, infectious diseases, and past history of drug allergy.

A coordinating center (a section of the Department of Gastroenterological Surgery, Osaka University Medical School) was responsible for creating the treatment allocation code using a computer-generated randomization table. Treatment allocation was arranged pre-operatively.

The study hypothesis combined existing data on administration of ghrelin to healthy volunteers[21] and our own clinical experience of patients after esophagectomy using standard regimens. We hypothesized that oral intake of food calories during the study period in placebo group were 800 ± 100 kcal/d. The power calculation based on a 20% improvement by ghrelin administration in oral food intake calories, with a power of 90% and α of 0.05, required 9 patients per study group; therefore, the initial proposal aimed to recruit 20 patients.

Preparation of synthetic human ghrelin. Synthetic human ghrelin (active form) was obtained from the Peptide Institute Inc. (Osaka, Japan). Ghrelin was dissolved in distilled water with 3.75% D-mannitol and sterilized by passage through a 0.22-μm filter. Ghrelin was stored as a 2 mL preparation (each containing 210 μg active ghrelin) in sterile vials at −50°C until handling for administration. The Department of Laboratory for Clinical Investigation, Osaka University Hospital, confirmed that there were no traces of endotoxin in ghrelin solution and that it was pyrogen negative.

Operative procedure and postoperative management. Enrolled patients underwent esophagectomy at the Department of Gastroenterological Surgery, Osaka University Hospital (Osaka, Japan). The thoracic portion of the esophagus was resected via right thoracotomy along the fourth intercostal space and the defect was repaired by a gastric tube with cervical anastomosis. Pyloroplasty was not performed, but finger bougie of the pyloric ring was performed in all patients. The posterior mediastinal route was used for the reconstruction. Enteral nutrition with a jejunostomy tube was not used in any enrolled patients. At the end of the operation, all patients were placed on mechanical ventilation and received postoperative care in the intensive care unit. All patients were weaned off mechanical ventilation on postoperative day 1 and received the same systematic and nutritional care via central venous infusion. The protocol of intravenous infusion before the start of

food intake included 2,100 mL of volume, containing 350 g glucose, 115.4 mEq sodium, 54 mEq potassium, and 115.4 mEq chlorine per day. Protein was administered intravenously, as needed in the intensive care unit. After 9–11 days fast postoperatively, oral food intake was started, after being certain there was no aspiration of water.

Study protocol. The study was performed in a single-blind manner. Only the person responsible for mixing study drugs knew the allocation, and the subjects and the individuals who collected data did not know about the allocation. Patients assigned into the ghrelin group received ghrelin treatment at a dose of 3 μg/kg body weight diluted in 50 mL saline given over 30 minutes and repeated twice daily (before breakfast and before dinner) for 10 consecutive days (days 1–10), beginning the day after the start of food intake (day 0). Patients in the placebo group received a corresponding placebo (saline) infusion in a similar fashion (Fig 1). All subjects received a similar nutritional therapy during the study period with the exception of administration of test treatment. The protocol of intravenous infusion during the study period was 1,500 mL of volume, containing 64.5 g glucose, 52.5 mEq sodium, 30 mEq potassium, 52.5 mEq chloride, and 30 mEq lactate per day. Protein infusion was not performed during study period. Alteration of food intake was the primary end point of this trial. The subjects were provided an adequate diet of 1,500 kcal of calories and could ask for additional diet if so desired. Calories of food intake beginning on day 0 (start of food intake) and for the next 10 consecutive days (days 1–10) were assessed by the national registered dietitian of Osaka University Hospital, by measuring the weight of each dish containing diet before and after every meal. Furthermore, the calories of all additional foods, snacks, and drinks were added to the measured food intake.

To evaluate the change in appetite, a visual analog scale (VAS) rating of hunger (possible scores 0–10 cm) was recorded by subjects immediately after administration of ghrelin or placebo before every meal during the study period (days 0–10). The average score was calculated each day. To determine the change in appetite score, the average appetite score of day 0 was considered 100%, and all values measured during the administration of the test drug (days 1–10) were expressed as a percent of day 0.

Measurements of plasma ghrelin, GH, and leptin concentrations. Blood samples were taken in the morning after an overnight fast on the preoperative day and day 10 of the study period. The

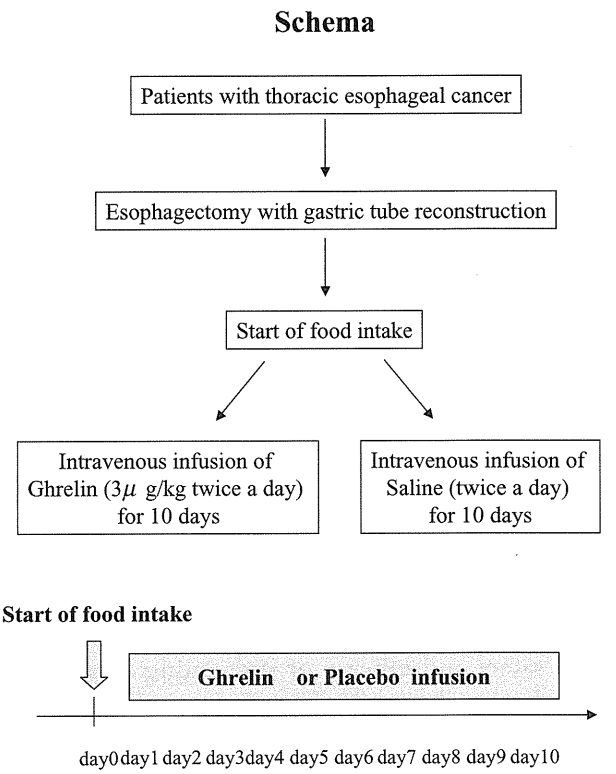


Fig 1. Study protocol.

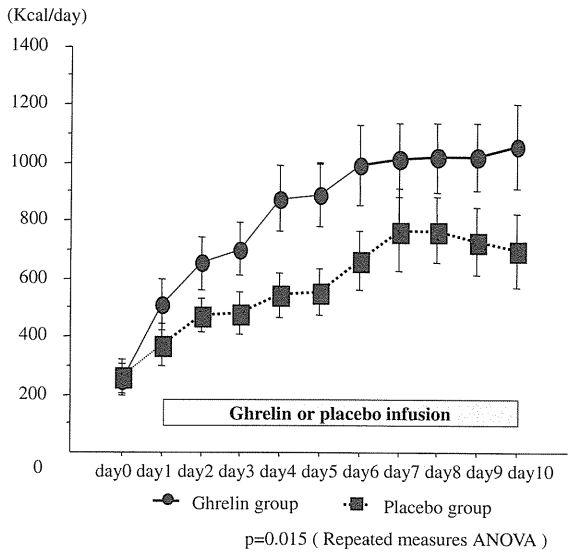
blood was transferred immediately into a chilled glass tube containing disodium ethylenediaminetetra-acetic acid for plasma sampling, and separating agent for serum sampling, and centrifugation at 4°C. The plasma samples were mixed with 10% volume of 1 N hydrochloric acid and stored at –50°C. Plasma active and desacyl ghrelin concentrations were measured with sandwich-type enzyme immunoassay kits for ghrelin according to the protocol supplied by the manufacturer (Mitsubishi Kagaku Iatron Inc., Tokyo, Japan).[28] Total plasma ghrelin concentration was calculated as active ghrelin concentration plus desacyl ghrelin concentration. Serum GH and leptin concentrations were measured by GH "Daiichi" Kit (TFB Inc., Tokyo, Japan) and Human Leptin RIA Kit (Linco Research Inc., St. Charles, MO), respectively.

Body composition. To analyze changes in body weight in detail, dual energy x-ray absorptiometry (Hologic QDR-2000 instrument; Hologic Inc., Waltham, MA) was performed to assess lean body weight and fat body weight of the enrolled patients.[29] The body composition measurement was performed before the start of food intake (day 0) and 10 days after the start of food intake (day 10).

Statistical analysis. Continuous variables are expressed as mean values ± standard deviation (SD)

Table I. Patients' characteristics

Characteristics	*Study group*	
	Ghrelin group	*Placebo group*
Age (yrs)	63 ± 6	65 ± 6
Gender (% male)	90	90
Body weight (kg)	56 ± 6	58 ± 13
BMI (kg/m^2)	20 ± 2	22 ± 4
Tumor localization (thoracic)		
Upper/middle/lower	2/4/4	1/6/3
cStage (UICC)		
I/II/III/IV	1/3/5/1	0/2/7/1
Pre-operative therapy		
None	3	1
Chemotherapy	7	8
Chemoradiotherapy	0	1



	Study group	
	Ghrelin group	Placebo group
Mean amout of energy of food intake (kcal/day) (Day 1-10)	874	605

Fig 2. Serial changes in food intake calories after esophagectomy. Changes in daily intake of food calories were compared between ghrelin group (*closed circles*) and placebo group (*closed squares*). In both groups, food intake calories increased with time, but the increase was greater in the ghrelin group than placebo group (repeated measure ANOVA; $P = .015$). Data are presented as mean values ± standard error of the mean.

unless stated. Statistical differences between groups were calculated by the Student *t* test, Mann-Whitney test, or Chi-square test. Comparisons of the time course of food intake calories and appetite score were tested by 2-way repeated measure analysis of variance (ANOVA). Statistical significance was

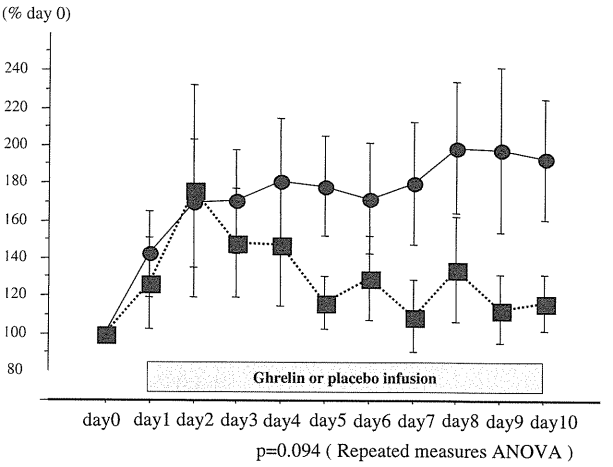


Fig 3. Serial changes in subjective appetite measured by VAS score. Percentage changes in VAS score (compared with score of day 0) were compared between ghrelin group (*closed circles*) and placebo group (*closed squares*). The VAS score of ghrelin group tended to be greater than placebo group ($P = .094$; repeated measure ANOVA). Data presented as mean values ± standard error of the mean.

set at $P < .05$. All calculations were performed using the StatView software package version 5.0 (SAS Institute Inc., Cary, NC).

RESULTS

Patient characteristics. A total of 20 patients were enrolled in the study. There were no significant differences in the background characteristics, including age, gender, preoperative weight, body mass index, localization of cancer, clinical cancer staging according to the International Union Against Cancer classification,[30] and pre-operative therapy such as neoadjuvant chemotherapy and chemoradiotherapy (Table I). Histologically, all patients had squamous cell carcinoma.

Peri-operative data. There were no significant differences in peri-operative data such as operative time and operative blood loss, time to food intake, or duration of hospitalization after esophagectomy. There were no severe postoperative complications or major adverse events in all enrolled patients. One patient (10%) of the ghrelin group developed grade 1 flushes and 1 (10%) patient of the placebo group developed grade 1 fever according to the CTC-AE version 3.0 (available at: http://www.cancer.gov), but there was no need to stop oral intake in either subject.

Food intake and appetite scoring. Changes in calories of food intake showed a similar pattern of increased intake in both groups; however, the increase in the ghrelin group was greater than

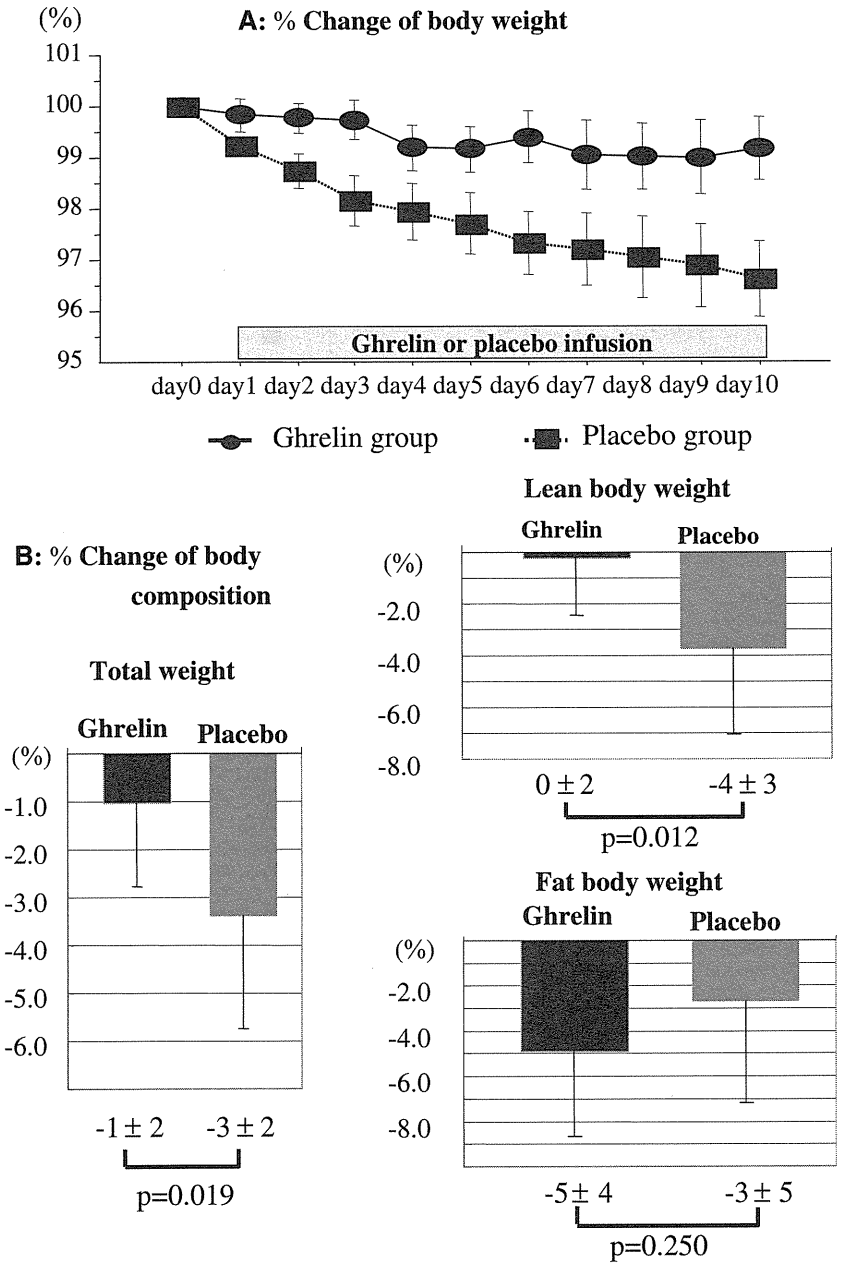


Fig 4. Changes in weight and body composition. Changes in postoperative weight (*A*) and body composition measured by dual energy x-ray absorptiometry before start of food intake (day 0) and after completing protocol treatment (day 10) (*B*). (*A*) Percent change in postoperative weight (compared with day 0) in the ghrelin group (*closed circles*) and placebo group (*closed squares*). (*B*) Changes in body composition between 2 groups. The decrease in total weight was less in the ghrelin group than placebo group (–1% vs –3%; $P = .019$). Ghrelin administration decreased lean body weight loss (0% vs –4%; $P = .012$). The loss of fat body weight was similar, but that of ghrelin group was greater than placebo group (–5% vs –3%; $P = .250$, by Student t test). Data are presented as mean values ± standard error of the mean.

that of the placebo group (repeated measure ANOVA; $P = .015$). On average, the intake of food calories were 44% greater in the ghrelin group compared with the placebo group (874 vs 605 kcal/d; Fig 2). These results suggest that administration of ghrelin after esophagectomy in esophageal cancer patients resulted in a successful increase of food intake postoperatively. At the beginning of oral food intake (days 0–2), the VAS score for appetite was similar in the 2 groups, patients in the ghrelin group tended to show a greater gradual increase in hunger sensation compared to patients of the placebo group ($P = .094$; Fig 3).

Table II. Results of laboratory tests

Test	*Pre-operative*			*Postoperative*		
	Ghrelin group	*Placebo group*	P *value*	*Ghrelin group*	*Placebo group*	P *value*
Hemoglobin (g/dL)	11.7 ± 1.8	10.9 ± 1.1	.25	10.2 ± 0.8	10.3 ± 1.3	.80
Albumin (g/dL)	3.6 ± 0.4	3.6 ± 0.5	.79	3.3 ± 0.1	3.2 ± 0.5	.44
Lymphocyte (/μL)	1,520 ± 491	1,629 ± 389	.58	1,283 ± 416	1,299 ± 265	.91
Choline esterase (IU/L)	245 ± 70	196 ± 58	.10	195 ± 28	164 ± 52	.12
Triglyceride (mg/dL)	94 ± 36	136 ± 79	.14	101 ± 28	111 ± 33	.48
Total cholesterol (mg/dL)	162 ± 46	189 ± 72	.32	159 ± 31	175 ± 49	.38
Rapid turnover protein						
Pre-albumin (mg/dL)	23 ± 9	24 ± 8	.74	19 ± 4	18 ± 7	.52
Retinal binding protein (mg/dL)	3.8 ± 1.4	4.4 ± 1.2	.30	2.8 ± 0.5	3.0 ± 1.2	.71
Transferrin (mg/dL)	192 ± 28	196 ± 28	.76	181 ± 18	162 ± 36	.15
Hormone						
Total ghrelin (fmol/mL)	74 ± 44	111 ± 111	.33	49 ± 31	78 ± 59	.19
Growth hormone (ng/mL)	2.3 ± 2.6	1.1 ± 1.6	.22	1.0 ± 0.8	0.8 ± 0.4	.51
Leptin (ng/mL)	2.6 ± 1.9	3.9 ± 2.5	.21	1.2 ± 0.4	2.9 ± 2.4	.035

Changes in weight and body composition. During the study period, changes in body weight were monitored as percent weight of day 0 (Fig 4, *A*). We compared body weight and body composition measured on day 0 (before start of food intake) and day 10 (after completion of the study period; Fig 4, *B*). The percent decrease in total weight was −3% ± 2% in the placebo group but only −1% ± 2% in the ghrelin group ($P = .019$). Body composition analysis by dual energy x-ray absorptiometry showed that percent decrease of body fat weight of ghrelin group (5% ± 4%) was greater than that of placebo group (3% ± 5%; $P = .250$). The percent decrease in lean body weight of the ghrelin group (0% ± 2%) was less than that of the placebo group (4% ± 3%; $P = .012$). These results suggest that the postoperative weight loss was less in ghrelin group, and this attenuation of weight loss was due to maintenance of lean body weight (Fig 4, *B*).

Blood tests and hormonal assays. Rapid turnover protein (prealbumin, retinal binding protein, and transferrin), plasma total ghrelin concentration, and serum GH and leptin levels were measured preoperatively and postoperatively (after completion of study treatment; day 10) and compared between the 2 groups. Pre-operative plasma total ghrelin (active plus desacyl form) was 74 ± 44 and 111 ± 111 fmol/mL for the ghrelin and placebo groups, respectively. There were no significant differences between the 2 groups in the abovementioned blood proteins and GH levels (Table II). Postoperative leptin concentration was less in the ghrelin group than the placebo group (1.2 ± 0.4 vs 2.9 ± 2.4 ng/mL; $P = .030$). The difference in the latter hormone levels were considered due to larger decrease in body fat weight in the ghrelin group than placebo group.

DISCUSSION

Ghrelin is a 28-amino acid peptide hormone secreted mainly in the stomach and identified in 1999 as an endogenous ligand for the GH secretagogue receptor.[13] Various biologic functions have been described for ghrelin, in addition to increasing GH secretion, based on studies in animals and human. The pleiotropic functions include anabolic effects, stimulation of appetite, prevention of diabetes, improvement of cardiopulmonary function, and suppression of an excessive inflammatory response.[15,22-26,31-33] The effect of ghrelin on food intake and energy balance has received considerable attention, and several clinical studies have been conducted.[18] Furthermore, administration of ghrelin in patients with chronic obstructive pulmonary disease and cardiac disease improved cachexia and primary disease successfully.[23,24] In a previous clinical study of ghrelin by our group, we addressed the correlation between serum ghrelin level and weight loss after operations in patients with upper gastrointestinal cancer. We found that circulating concentration of ghrelin decreased immediately after total gastrectomy and esophagectomy by 10–20% and to 50% of the preoperative level, respectively.[14] A randomized, controlled, phase II study of ghrelin after total gastrectomy for gastric cancer patients has finished, and the preliminary results suggest that a 10-day administration of ghrelin is safe and improved successfully the postoperative loss of appetite, oral food intake, and weight loss (unpublished data). These results

correspond well with the results of previous animal experiments and other human clinical trials with other diseases or subjects.[15,22-27] We conducted the present clinical study to examine the efficacy of ghrelin after esophagectomy to improve the nutritional status. Unlike patients with esophageal adenocarcinoma triggered by Barrett esophagus in Western countries, the majority of patients in Japan with esophageal cancer have squamous cell carcinomas and are lean before esophagectomy[1,34]; therefore, postoperative malnutrition and body weight loss tend to be more serious complications. Because the decrease in circulating ghrelin concentration after esophagectomy is less than that after total gastrectomy, there was concern that exogenous ghrelin administration would not accomplish adequate clinical results. Nevertheless, exogenous ghrelin successfully improved postoperative oral food intake and attenuated weight loss after esophagectomy. Improvement of the postoperative nutritional status for esophageal cancer patients is important and beneficial, because long-term survivors after esophagectomy often develop malnutrition, and many of them die of pneumonia or malnutrition.[35] Furthermore, suppression of postoperative weight loss may improve their prognosis of cancer, because weight loss is a significant predictor of a decreased survival in oncologic patients.[9-11] Use of ghrelin in common clinical practice may be difficult. In the present trial, ghrelin was administered only for 10 consecutive days from the day after the start of food intake; moreover, the effect of ghrelin may disappear rapidly after the end of study period because of the short half-life of ghrelin (data not shown). Therefore, further studies with mid- to long-term administration are needed to confirm the effectiveness of ghrelin in attenuating body weight loss after esophagectomy. Because the serum concentrations of ghrelin show recovery at 2 years after esophagectomy,[14] compensation of ghrelin within 2 years after esophagectomy may be important. Further translational research would be expected to result in the development of a ghrelin agent that could be administered over a long period, such as an intranasal agent, an oral agent, or a long-acting subcutaneous injection.

Ghrelin has also been reported to suppress an excessive inflammatory response by inhibiting proinflammatory cytokine production, mononuclear cell binding, and nuclear factor-κB activation.[31,33] Esophagectomy is a very invasive operation comprising both thoracotomy and laparotomy, and may in some patients induce an uncontrolled inflammatory response owing to overproduction of proinflammatory mediators. Administration of ghrelin in the perioperative and early postoperative periods may attenuate such an operative stress-induced inflammatory response. We plan to conduct the next clinical trial designed to evaluate the efficacy of perioperative ghrelin administration. If the effectiveness is confirmed, ghrelin may be used to improve postoperative care of esophageal cancer patients.

In conclusion, the present study demonstrated that short-term administration of exogenous ghrelin at the start of oral intake after esophagectomy stimulated food intake and attenuated postoperative weight loss and lean body weight. Further studies are needed to evaluate long-term nutritional status, ghrelin administration for greater durations, and perioperative administration.

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Effects of Ghrelin Administration After Total Gastrectomy: A Prospective, Randomized, Placebo-Controlled Phase II Study

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BACKGROUND & AIMS: Body weight (BW) loss and reduction of blood ghrelin level are commonly observed after total gastrectomy (TG). A prospective study was designed to elucidate whether exogenous ghrelin administration prevents postoperative BW loss by improving appetite and oral food intake in patients with gastric cancer after undergoing TG. **METHODS:** In this randomized phase II study, 21 patients undergoing TG were assigned to a ghrelin (11 patients) or placebo group (10 patients). They received intravenous infusion of synthetic human ghrelin (3 μg/kg) or saline twice daily for 10 days after starting oral food intake following surgery. Changes in BW, appetite visual analog scale score, food intake calories, body composition, basal metabolic rate, and various blood test results were evaluated. **RESULTS:** Excluding one patient who developed profound diaphoresis during ghrelin infusion, 20 patients completed the study. Food intake and appetite were significantly higher with ghrelin compared with placebo (average, 13.8 vs 10.4 kcal/kg/day [$P = .030$] and 5.7 vs 3.9 cm [$P = .032$], respectively). BW loss was significantly lower in the ghrelin than in the placebo group (−1.4% vs −3.7%; $P = .044$). Fat mass, lean body mass, and basal metabolic rate decreased significantly in the placebo group; however, the reductions in lean body mass and basal metabolic rate were not significant in the ghrelin group, although that of fat mass was significant. **CONCLUSIONS: Short-term administration of synthetic ghrelin was safe and successfully lessened postoperative BW loss and improved appetite and food intake after TG.**

Keywords: Ghrelin; Total Gastrectomy; Gastric Cancer; Body Weight Loss.

Body weight loss is common and a serious outcome in patients with gastric cancer who have undergone total gastrectomy. It correlates well with decline in postoperative quality of life and is the most reliable indicator of malnutrition, which impairs immune function, infection susceptibility, and survival.[1–3] Although various mechanisms have been considered, such as perturbation of absorption due to reduced pancreatic excretion,[4,5] decrease of gastric acid level,[6] reflux esophagitis,[7] intestinal floral alteration,[8] and increased peristalsis and diarrhea,[9] reduced food intake[10,11] is the most conceivable explanation for body weight loss after total gastrectomy. Therefore, surgeons dealing with gastric cancers have tried to increase food intake by producing a gastric substitute, such as a jejunal pouch, but such procedures have not always been successful.[12] Another study indicated that the majority of patients with total gastrectomy could eat food as much as healthy subjects under a regulated program.[13] Our own experience indicates that some patients do not show significant body weight loss after total gastrectomy by resorting to small but frequent meals. These changes suggest that reduced food intake after total gastrectomy could not be simply explained by loss of storage volume due to gastrectomy, but rather reflect a disturbance of eating activity through an unknown mechanism.

The 28-amino acid peptide ghrelin is the endogenous ligand for the growth hormone (GH) secretagogue receptor 1a, which stimulates GH release from the pituitary gland.[14] The majority of ghrelin is produced by X/A-like cells of the oxyntic glands in the stomach, and a smaller amount is secreted from other organs, such as the intestine, pancreas, kidney, and hypothalamus.[15,16] Ghrelin has various physiologic functions in addition to secretion of GH, such as promoting the appetite signal in the hypothalamus (in contrast to leptin),[17] stimulating gastrointestinal activity (such as peristalsis, gastric acid secretion, and pancreatic excretion through the vagal nerves),[18] and regulation of fat metabolism.[19] In addition, ghrelin mitigates proinflammatory cytokine production and attenuates the stress signal.[20] Among the pleiotropic functions of ghrelin, this peptide is the only gastrointestinal hormone known to stimulate appetite. A randomized double-blind study of healthy volunteers

Abbreviations used in this paper: ANOVA, analysis of variance; BMR, body metabolic rate; GH, growth hormone; IGF, insulin-like growth factor.

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