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Research Article

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An Immune-modulating Diet Maintains Food Intake during Cancer Chemotherapy

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Abstract

An immune-modulating diet (IMD), an enteral diet enriched with immunonutrition and whey-hydrolyzed peptides, has been shown to bring an improvement of prognosis by suppressing inflammation after surgery or under stress. In this study, we have experimentally and clinically examined the effect of the IMD in cancer chemotherapy. In experiments using colorectal cancer cell-transplanted mice, the mice fed with the IMD in combination with anti-cancer agent significantly tended to maintain plasma body weight excluding tumor, and to reduce plasma interleukin-6 (IL-6) levels compared with the control group. Furthermore, normal mice fed with the IMD elevated the level of plasma ghrelin, in particular acyl ghrelin. An clinical trial for a patient with malignant lymphoma revealed that the acyl/desacyl ghrelin ratio and total calorie intake was increased when the patient was supplemented with the IMD in conjunction with chemotherapy. These results suggested that the supplementation of the IMD during cancer chemotherapy might enable to maintain the food intake of the patients through elevating plasma acyl ghrelin levels.

Keywords: Chemotherapy, Immunonutrition, Ghrelin, Calorie Intake, Diet

Introduction

There is a growing awareness of the relations between cancers and metabolism/ nutrition in various aspects. It is known as the Warburg Effect that cancer cells increase glucose uptake and enhance glycolysis system since they have vigorous proliferation activity [1]. This feature contributes to cancer diagnosis by 18F-fluorodeoxy glucose-positron emission tomography (FDG-PET) scan and drug development by the inhibition of the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of the rapamycin (PI3K-AKT-mTOR) pathway [2]. Cancers also cause a disorder of lipid metabolic pathways, *de* novo fatty acid synthesis in cancer cells, and the formation of inflammatory mediators such as prostaglandins by the activation of the arachidonic acid cascade [3]. It is considered that these disorders of various metabolic/ nutrition pathways accompanied with cancer progression lead to the decrease of ghrelin production or the increase of interleukin-6 (IL-6) production, which causes loss of appetite, malnutrition, and cancer cachexia. We have previously studied the body composition of advanced pancreato-biliary cancer patients and have reported the importance of maintaining body fat in order to continue cancer chemotherapy [4].

Ghrelin, consisting of 28 amino acids, is localized in the stomach and endocrine cells of the hypothalamus. It becomes the active form, acyl ghrelin when the side-chain of the third serine residue is modified by octanoic acid, while the inactive form is called desacyl ghrelin [5]. In the peripheral blood, the percentage of acyl ghrelin is only about 10 %, and metabolism is mostly conducted by inactive desacyl ghrelin. Acyl ghrelin is considered to have bioactivities such as the stimulation of the secretion of growth hormone (GH), food intake increase and body weight gain [6]. It has also been shown that administering ghrelin improves the cancer cachexia [7, 8].

Certain nutrients, classified as immunonutrients, such as L-arginine, glutamine, omega-3 fatty acids, and anti-oxidant molecules (vitamin A, C, E, zinc, selenium) have been shown to modulate the immune system. There has been developed an immune-modulating diet (IMD), which is liquid enteral diet with comprehensive nutrition mainly used for tube-fed patients. It has an excellent balance of essential nutrients and enriched with immunonutrients. Recently, an IMD enriched with whey peptides, fermented milk and immunonutrients was developed. It is expected to bring not only alimentation, which is its primary role, but also effects such as immunopotentiation and the suppression of excessive inflammatory response. It has been shown that

ingesting IMD under stress is effective in the experimental models of intestinal disorders and hepatitis, and in the clinical trials of liver transplantation. In this study, we have adopted IMD into cancer chemotherapy and experimentally/clinically investigated its effectiveness on controlling side effects such as weight loss caused by loss of appetite through production of acyl ghrelin.

Materials and Methods

Diets and Chemicals

The control enteral diet (SF) (Meibalance HP; Meiji Co., Ltd.) and the IMD (ME) (MEIN; Meiji Co., Ltd.) were obtained from Meiji Co., Ltd. The major differences between the compositions of the SF and the IMD are described in (Table I). These diets are iso-caloric and the same amount of protein per 100 mL. 5-Fluorouracil (5-FU) and sodium carboxymethyl cellulose were purchased from Wako Pure Chemical Industries (Osaka, Japan).

Table I Dietary composition (per 100 kcal)

	Control enteral diet (SF)	IMD (ME)
Protein (g)	5.0	5.0
Carbohydrates (g)	15.3	14.5
Lipids (g)	2.5	2.8
Vitamins		
Vitamin A (μg RE *)	60	150
Vitamin D (μg)	0.50	0.75
Vitamin E (mg)	3.0	5.0
Vitamin K (μg)	3.1	3.4
Vitamin B1 (mg)	0.15	0.25
Vitamin B2 (mg)	0.20	0.30
Niacin (mg)	1.6	3.0
Vitamin B6 (mg)	0.30	0.30
Vitamin B12 (μg)	0.60	0.60
Folic acid (μg)	50	50
Biotin (μg)	15.0	7.5
Vitamin C (mg)	16	50
Choline (mg)	1.7	9.2
Minerals		
Sodium (mg)	110	70
Potassium (mg)	100	80
Calcium (mg)	60	80
Magnesium (mg)	20	20
Phosphorus (mg)	60	70
Iron (mg)	1.0	1.0
Zinc (mg)	0.8	1.0
Copper (mg)	0.080	0.050
Manganese (mg)	0.20	0.18
Chromium (μg)	3.0	3.0
Molybdenum (μg)	2.5	2.5
Selenium (μg)	3.5	5.0
Iodine (μg)	15	9.7
Chloride (mg)	140	80

* RE; retinol equivalent, 1 IU = 0.33 μg RE

Animals

All animal experiments reported herein were approved by the Animal Experiment Committee of Meiji Co., Ltd. (Tokyo, Japan) (approval #2011_3871_0177, approval date 3 Aug 2012, and approval #2014_3871_0158, approval date 17 Sept 2014). The experiments carried out from Mar 2012 to Oct 2014 in strict accordance with the guidelines of this committee. Six-week-old male BALB/c mice and six-week-old male C57BL/6 mice were purchased from Japan SLC (Hamamatsu, Japan). The mice were housed in plastic cages under controlled temperature and humidity with a 12-h light/dark cycle and fed commercial chow with water *ad libitum* for 1 week prior to use in the experiments. All surgery was performed under isoflurane anesthesia, and all efforts were made to minimize animal suffering.

Effects of IMD Ingestion on Tumor Transplanted Mice

Six-week-old male BALB/c mice had been acclimated for one week. After acclimation, they were divided into three groups of eight mice whose average weights were equal; tumor bearing control group (TB; SF fed without 5-FU administration group), SF fed with 5-FU administration group (FU/SF), and IMD fed with 5-FU administration group (FU/ME). $1x10^6$ of colon-26, cells were implanted subcutaneously in the flank. After implanting colon-26 cells, mice were fed the freeze-dried SF or the IMD ad *libitum*. With regard to anti-cancer agent administration, 5 mL/kg (60mg/kg) of 5-fluorouracil (5-FU) suspension that was suspended into 0.5% carboxymethylcellulose solution to make its concentration 12mg/ml was orally administered three times a week from the next day to 14th day after implant (Day 2, 5, 7, 9, 12, 14) by reference to prior experiments [9, 10]. The body weight and food intake were measured twice a week, and mice were sacrificed on the 21st day to collect their blood, muscle and fat. The plasma IL-6 was measured with Cytometric Bead Array (CBA) Inflammation Kit (BDTM, San Diego, CA, USA).

Change of Level of Serum Ghrelin after IMD Administration in Normal Mice

Six-week-old male C57BL/6 mice were divided into two groups; SF group and ME group. SF mice ingest the SF and the ME group ingest the IMD *ad libitum* for two weeks, and fasting them for one night, their blood was taken from abdominal aorta under isoflurane anesthesia. Plasma acyl ghrelin and desacyl ghrelin levels were measured by ELISA (Sceti K.K. Tokyo, Japan).

To investigate the effect of medium-chain fatty acid (MCT) which is contained in the IMD, we divided mice into two groups, and one group was fed with powdered form of rodent purified diet (AIN-93G) and the other group was fed with the diet whose fat was partially replaced with MCT (AIN-93G+MCT) *ad libitum* for two weeks. Fasting them for one night, their blood was taken from abdominal aorta under isoflurane anesthesia. The plasma ghrelin levels were measured under the same protocol. The differences of the compositions of AIN-93G and AIN-93G+MCT are shown in (Table II). AIN-93G+MCT substitutes for a fat ingredient of AIN-93G in MCT.

Table II Dietary composition and sources

	AIN-93G	AIN-93G +MCT
Dietary Composition (per 100kcal)		
Protein (g)	5.0	
Carbohydrates (g)	18.4	
Lipids (g)	1.8	
Dietary sources (per kg)		
Casein (g)	200	
L-cystine (g)	3.0	
α-cornstarch (g)	532	
Sucrose (g)	100	
Soy bean oil (g)	70	51.7
Medium chain triglycerides (g)	0	23.5
Cellulose (g)	50	
Vitamin mix (g)	10	
Mineral mix (g)	35	
Total energy (kcal)	3958	

Effects of IMD Supplementation during Chemotherapy Treatment in patients with malignant lymphoma

Before starting clinical trials, we got approval from the Ageo central general hospital Ethics Committee (No.174) and received a written form of informed consent from a patient after explaining that it is a clinical trial of nutritional supplement. A single-arm controlled trial was conducted with a 43-year-old woman with malignant lymphoma under R-CHOP treatment. From the 5th course, we alternated Course A that she supplemented the IMD during treatment and Course B that she ingested ordinary meal only. During Course A, she had orally ingested daily three bottles of the IMD (equivalent to 600 kcal.) with meal from three days to one day before chemotherapy treatment, and ingested daily one bottle (equivalent to 200 kcal.) for four days from the treatment. She recorded her meal and physical condition in the diary. In the morning of the very day of treatment after overnight fasting, we measured body composition and measured serum Prealbumin, IL-6 and acyl/desacyl ghrelin. The calorie intake and the nutritional component were calculated based on her meal record and the Japanese Standard Tables of Food Composition [11].

Data Analysis

Data are presented as means ± standard deviations in the animal experiments. Differences between the control group and the other groups were assessed using Bartlett's test for variance. In the case that we can assume homoscedasticity, we conducted Dunnett's test. But in the case that we cannot assume it, we conducted Steel's test. The patient's calorie intake comparison was tested with paired t-test. Differences were considered significant at $P < 0.05$.

Results

IMD affects the body weight and inflammatory cytokine on Tumor Transplanted Mice

No significant difference in whole body weight was observed among three groups (Figure 1A). On day 21, tumor weight was significantly higher in TB group, but no difference was observed between FU/SF group and FU/ME group (Figure 1B). The body weight excluding tumor in FU/ME group showed significantly higher than that in TB group (Figure 1C). Plasma IL-6 levels were significant lower in only FU/ME group compared with TB group, but not in FU/SF group (Figure 1D).

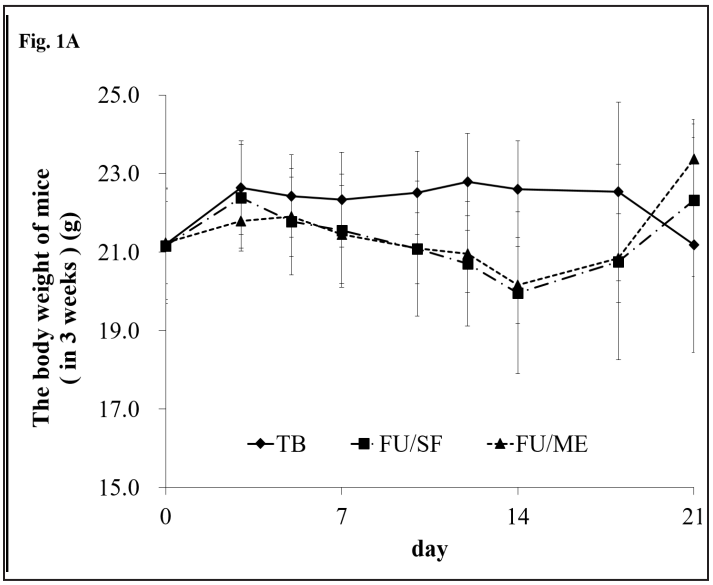
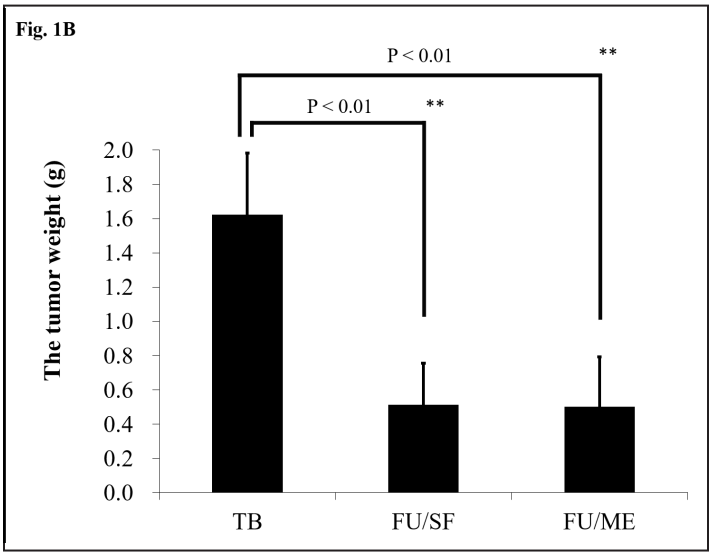
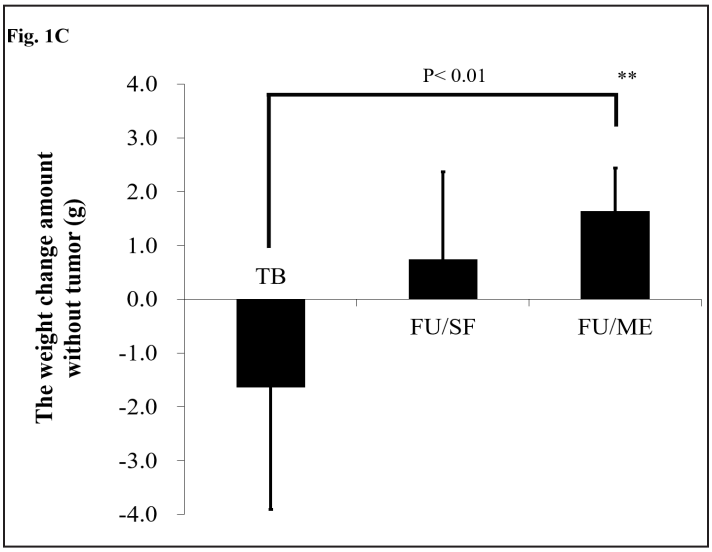
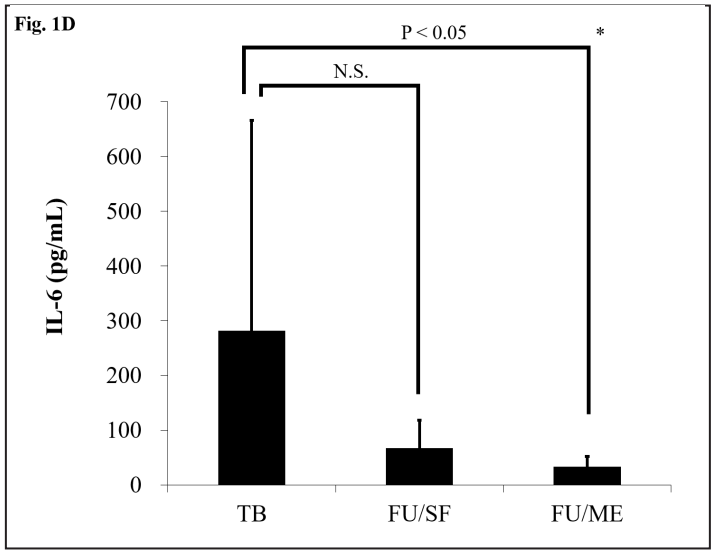


Figure 1: IMD affects body weight and inflammatory cytokine levels in tumor transplanted mice. (A) Body weight after colorectal cancer cell transplantation. A significant difference was not observed between the TB group, FU/SF group and FU/ME group. (B) Tumor weights on day 21. A significant increase in tumor weight was observed in the TB group (** P<0.01, Dunnett's test). A difference was not observed between the FU/SF group and FU/ME group.(C) Body weight without tumor mass. Only the FU/ME group showed a significantly greater gain in body weight without tumor mass than the TB group (** p<0.01, Steel's test). (D) Plasma IL-6 levels on day 21. Significant reductions were observed in only the FU/ME group compared to the TB group, but not in the FU/SF group (*p<0.05, Steel's test). IMD, immune-modulating diet; TB, tumor bearing control; FU/ME, IMD fed with 5-FU administration; FU/SF, SF fed with 5-FU

abbreviation; IL-6, interleukin 6; SF, control enteral diet; 5-FU, 5-Fluorouracil; ME, IMD supplementation.

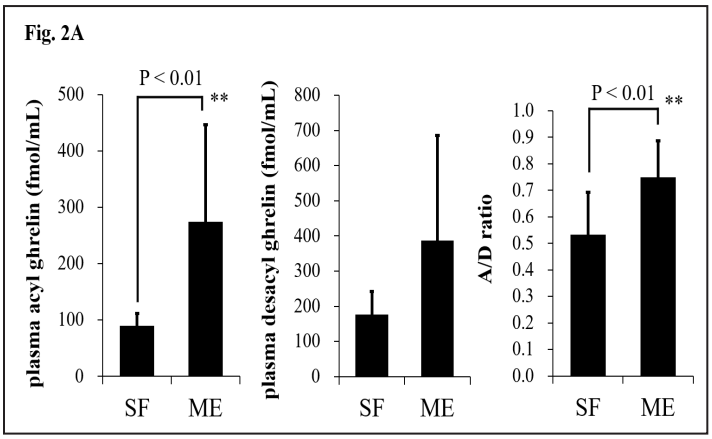






IMD promotes serum Ghrelin levels in normal mice

The ME group showed higher level of acyl ghrelin in the blood than the SF group, but a significant difference was not observed in the desacyl ghrelin levels (Fig. 2A). The ME group had also significant higher acyl/desacyl ghrelin ratio ($p<0.01$) (Figure 2A). Since medium-chain fatty acid (MCT) which is a component of the IMD is reported to promote ghrelin secretion, we also investigated the effect of MCT contained in the IMD on the plasma ghrelin level [12]. No significant difference was observed between these two groups neither in the acyl ghrelin levels nor desacyl ghrelin levels (Figure 2B). However, the AIN-93G+MCT group showed significant higher acyl/desacyl ghrelin ratio than the AIN-93G group (Figure 2B).



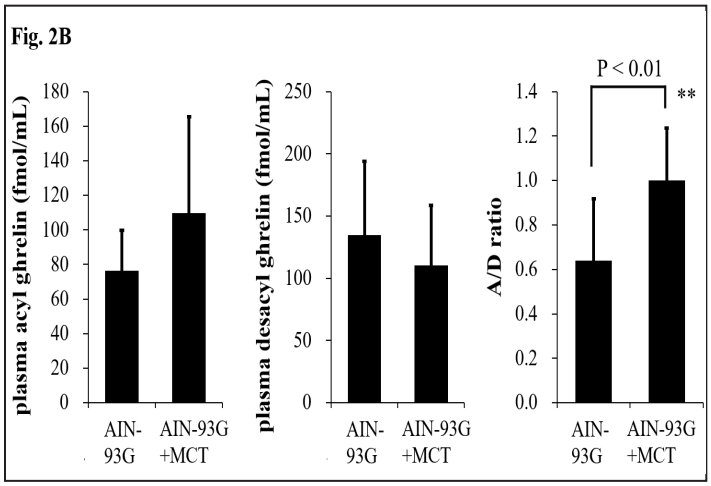
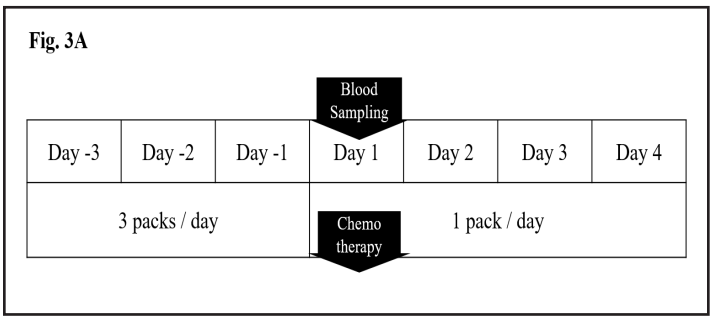


Figure 2: IMD and MCT promotes serum acyl ghrelin production in normal mice. (A) plasma active ghrelin and desacyl ghrelin levels after the ingestion of the SF or IMD. It was shown that the ME group had a significantly higher acyl/desacyl ghrelin ratio (A/D ratio) (** $p<0.01$, Student's t-test). (B) Plasma acyl ghrelin and desacyl ghrelin levels after MCT ingestion. The AIN-93G+MCT group had a significantly higher acyl/desacyl ghrelin ratio (A/D ratio) than the AIN-93G group (** $p<0.01$, Student's t-test). MCT, medium-chain fatty acid; IMD, immune-modulating diet; SF, control enteral diet; ME, IMD supplementation

IMD supplementation increases food intake and the acyl/desacyl ghrelin ratio during chemotherapy in a patient with malignant lymphoma

We studied the effect of IMD on a Japanese woman of standard proportion (BMI: 18.7) suffering from malignant lymphoma during relatively stable period of the chemotherapy from 5th to 8th

course in R-CHOP treatment. After supplementation of the IMD with meal for seven days during chemotherapy (Figure 3A), total calorie intake and total protein intake was increased compared with the period when she didn't ingest the IMD (Figure 3B). This increase was observed all through the period, both before and after the treatment. The acyl/desacyl ghrelin ratio in the blood was also higher when the IMD was fed in accordance with the total calorie intake (Figure 3B). However, no distinctive tendency was observed in the concentration of inflammatory cytokine IL-6 or nutrition index Prealbumin (PreAlb) (Figure 3B). Besides, when the IMD was ingested, her persistent numbness of fingers was improved, which is a side effect of R-CHOP treatment (data not shown).



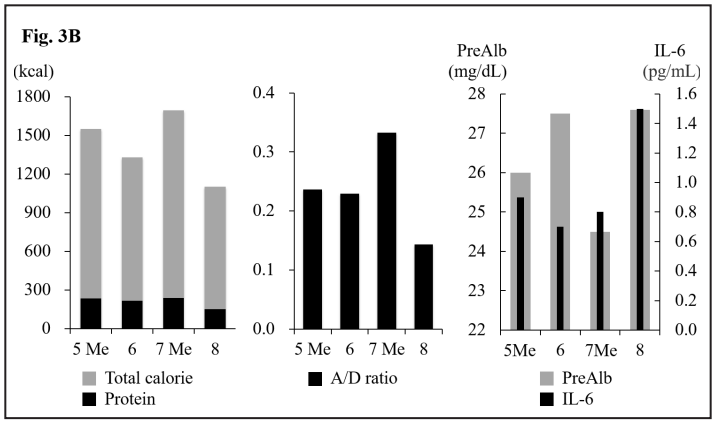


Figure 3: IMD supplementation increases food intake and the acyl/desacyl ghrelin ratio during chemotherapy in the patient with malignant lymphoma. (A) IMD supplementation protocol. Three bottles of the IMD a day were orally ingested from 3 days before chemotherapy, and 1 bottle a day from the day of chemotherapy treatment to the fourth day from treatment. This protocol was applied on the 5th and 7th course of R-CHOP (Me). (B) Total calorie and total protein intake, and plasma acyl/desacyl ghrelin ratio, PreAlb and IL-6 levels during chemotherapy. The acyl/desacyl ghrelin ratio in the blood was high when the IMD was ingested (Me) and the tendency was correlated to total calorie intake. IMD, immune-modulating diet; PreAlb, prealbumin; IL-6, interleukin 6.

Discussion

It is reported that many of patients with advanced cancer get into cachexia, and suggested that cancer cachexia is related to about one fourth of total cancer deaths [13]. Paraneoplastic syndrome such as loss of appetite, weight loss, weakness and pain threaten patients' livelihood and lives. Anorexia and weight loss are also caused as side effects of chemotherapy.

Various knowledge and treatment strategies have been developed with the progress of recent studies about cancer and nutrition. It has been known as the Warburg Effect that cancer cells increase glucose uptake and enhances glycolysis [1]. Not only glycolysis but also *de novo* fatty-acid synthesis is enhanced in cancer cells, and several lipid metabolic enzymes including fatty acid synthase (FASN) promotes the development and the malignant transformation of cancer. The lipid metabolic pathway might become a new target of anti-cancer treatment, and cancer prevention by statin is expected [14, 15].

In association with those disorders of metabolic/nutrition pathways, the increase of IL-6 and the decrease of ghrelin are observed characteristically in advanced cancers. It is considered that the inflammatory cytokine IL-6, which cancer cells produce, plays a crucial role to induce cancer cachexia in tumor-host interaction [16-19]. It has been shown in rodent models that blocking with anti-IL-6 receptor antibody leads to the improvement of cancer cachexia and malnutrition [17]. On the other hand, ghrelin, the peptide hormone produced in the stomach, has been reported that administering this peptide to patients with cancer cachexia improves their loss of appetite and nutritional status [20]. Selective ghrelin receptor agonist has also been reported to improve cachexia syndrome with anorexia [21].

The IMD used this study has been reported in various animal inflammatory models to inhibit the rise of the inflammatory cytokines including IL-6, to suppress liver damage, to lower blood glucose level after surgery, to improve survival rate and so on [22]. It is considered that the reduction in inflammation was due to effects of whey peptide, which is contained only in the IMD, not in control liquid diet. It has been reported in the sepsis model by administering lipopolysaccharide (LPS) that the ingestion of whey peptide for one week inhibited the rise of the inflammatory cytokines (TNF-α, IL-6) in the blood after LPS administration [23]. It has been also shown in the concanavalin A (ConA)-induced hepatitis model that whey peptide suppressed liver damage and inhibited the plasma inflammatory cytokine [24]. In this study, only the group fed with the IMD with chemotherapy (FU/ME) showed significant reduction in plasma IL-6, compared with the control group (Figure 1D). On the other hand, the clinical study of a patient with malignant lymphoma didn't reveal a correlation between the ingestion of the IMD and IL-6 concentration (Figure 3B). Further investigation is needed to use the IMD for more patients, and although it is difficult to investigate it because of ethical concerns, significant effects might be observed in case the IMD was used for cancer patients with strong inflammation.

In this study, feeding the IMD along with the anti-cancer agent showed significantly more gain of the body weight excluding tumor (Figure 1C). The normal mice fed with the IMD showed higher level of ghrelin in the blood, above all, the increase of the acyl/desacyl ghrelin ratio in the blood (Figure 2A). The mechanism causing this elevation might be the effect of MCT contained in the IMD (Figure 2B). The patient with malignant lymphoma increased their total calorie intake including total protein intake by ingesting the IMD with her meal during the chemotherapy treatment. The acyl/desacyl ghrelin ratio in the blood was well correlated with the total calorie intake (Figure 3B). Therefore, it was considered that ingesting the IMD during cancer chemotherapy enables

maintaining of acyl ghrelin-mediated food intake, and furthermore maintaining of their body weight. Although several reports suggest that ghrelin itself might drive tumor growth, the mice fed with the IMD didn't show any enlargement of the tumor size (Figure 1B) [25, 26].

It is expected that the IMD leads not only inhibiting the inflammatory cytokine production and elevating the acyl ghrelin but also many other physiological effects. The IMD has reported to enhance intestinal barrier function (to increase the number of lymphocytes in immune tissues and the amount of secretory IgA in the small intestine) *in vivo* [27]. In clinical, it has also been suggested that the IMD might avoid the development of bacteremia and hyperglycemia after surgery and shorten the length of hospital stays without increasing the rate of rejection response after liver transplantation [28]. Supplementation of the IMD treated with exercise therapy for the chronic obstructive pulmonary disease (COPD) patients has also been reported to improve body composition, physical capability, quality of life (QOL) and so on [29].

Although further clinical trials will be necessary to establish this effect in humans, the IMD during chemotherapy might not only maintain appetite and total calorie intake but also improve QOL and reduce various side effects such as neurological disorders. The findings obtained in the present study will give some insight into new nutritional therapies during cancer chemotherapy.

Acknowledgement

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Authors' contributions

All contributors met the criteria for authorship. KN and HN conceived and designed the study; KN and HT performed the animal experiments; MM, YS, AT, SO and HN performed the clinical trials; NN, KN, HT, YT, AI, IS, KK and HN analyzed the data; NN, KN and HN wrote the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All animal experiments reported herein were approved by the Animal Experiment Committee of Meiji Co., Ltd. (Tokyo, Japan). (Approval #2011_3871_0177 and #2014_3871_0158). The experiments carried out in strict accordance with the guidelines of this committee.

The clinical study received ethics approval from Ageo central general hospital Ethics Committee (Saitama, Japan), and written informed consent to participate was obtained from all of the patients.

Competing interests

KN and HT are employees of Meiji Co., Ltd. NN and HN declare that they have no competing interests.

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