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Clinical application of protein-enhanced diet using mealworms in patients undergoing hepato-pancreato-biliary surgery

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ABSTRACT

Objective: Patients with or without cancers who undergo major gastrointestinal surgery experience malnutrition owing to their catabolic status during the postoperative period. In this study, we evaluated the effect of the clinical application of protein-enhanced diet using mealworms in patients who underwent hepato-pancreato-biliary surgeries.
Methods: This study was designed as a prospective, two-armed, and double-blinded phase III study. The target number of enrolled patients was 216, and the patients were randomized on a 1:1 basis, either to the trial group (consuming mealworms) or to the control group (consuming grain powder). The primary endpoint was to examine the changes in body composition, including phase angle. For secondary outcomes, the activities of immune cells were evaluated using the patients' blood samples.
Results: No difference in the demographic characteristics of patients was observed. The ratio of the actual protein intake to the recommended daily intake in the trial group was significantly higher than that in the control group (110.03% vs. 98.80%, $P = 0.023$). In the data on body composition measured by InBody S-10 (Biospace, Seoul, South Korea), the ratios in body cell mass, fat free mass, muscle mass, and phase angle at the study endpoint compared with those at admission showed no statistically significant difference between the two groups. Immune cell analyses suggested that cytotoxic T cells in the trial group had higher activity than in the study group (1.192 vs. 0.974, $P = 0.028$).
Conclusions: In this study, protein-enhanced diet using mealworms clinically improved the activity of immune cells. However, it did not significantly improve the patients' nutritional status after they experienced hepato-pancreato-biliary surgeries.

Introduction

Sarcopenia is well-recognized as a multifactorial syndrome characterized by ongoing losses of skeletal muscle mass and strength [1,2] that leads to progressive functional disability in patients with cancer. In previous studies, up to 50% of patients with advanced cancers had sarcopenia [3,4], which was associated with their poor survival after surgery for various diseases, including cancers [5–9].

Nutritional intervention has been expected to guarantee an improvement of sarcopenia by demonstrating a positive effect on protein anabolism. Prior researches have shown that additional dietary protein can lead to significant increase of muscle synthesis in older adults [10,11]. Recent randomized controlled trials showed a significant improvement in muscle mass and strength in

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older adults with sarcopenia through administration of combined oral supplementation of protein and vitamins [12–14]. Also from systematic reviews or meta-analyses, protein or amino acid supplementation seems to be beneficial for patients with sarcopenia [15–17]. However, a wide variety of optimal doses, duration of intervention, and characteristics of patient populations weaken the validity of additional protein intake [18].

Patients with or without cancers undergoing major gastrointestinal surgeries experience malnutrition because of their catabolic status in postoperative periods [19]. Therefore, nutritional supplementation has been regarded as a step for enhanced recovery protocols after surgery. Nitrogen balance is associated with both energy and protein consumption, and avoidance of catabolic losses after surgery may benefit patient outcomes [20]. Evidence from certain previous studies supported the use of oral nutritional protein supplements in the immediate postoperative stage [19,21–23]; however, whether this is beneficial has not been fully elucidated.

To meet the rapidly growing world population's increasing demands for foods, edible insects have emerged as an alternative, sustainable source of protein [24]. Approximately 2000 edible insect species have so far been recorded worldwide [25]. It is worth noting that mealworms—the Larva from of the mealworm beetles (*Tenebrio molitor* L.)—are most commonly used as human food because they are widely distributed and can be sustainably cultivated in various environments worldwide [26]. Mealworms have high protein and lipid contents and high levels of unsaturated fatty acids; however, their role as a nutritional supplement remains unclear.

In this context, we evaluated the effect of the clinical application of protein-enhanced diet using mealworms on the body composition and immune cell in patients who underwent hepato-pancreato-biliary surgeries.

Materials and methods

This is a single-center, prospective, randomized, and double-blinded phase III trial. The trial was approved by the institutional review board at Gangnam Severance Hospital, Yonsei University College of Medicine, South Korea (3–2017-0077). All participants provided written informed consent. The trial design has been reported previously [27] and registered at www.clinicaltrial.gov (NCT03201926).

Eligibility assessment and randomization

All patients who are older than 18 y of age and scheduled for surgery with pancreatobiliary or liver disease were assessed for eligibility. Among eligible patients, we excluded those who had had palliative surgery or a previous history of conditions affecting their nutritional status (e.g., short bowel syndrome, post-gastrectomy syndrome).

A total of 216 patients were enrolled in this study and were randomly assigned to the trial group or to the control group on a 1:1 basis (Fig. 1). The stratification factors were sex, age, body mass index at admission, and intended surgical procedures including pancreaticoduodenectomy (PD), pancreatectomy, or liver resection.

Intervention

The surgical team was composed of three surgeons with experience of more than 300 hepato-pancreato-biliary surgeries, respectively. All patients underwent open or laparoscopy-assisted operations under general anesthesia.

The dietary intervention was conducted during the patients' hospital stay and for an additional period of 2 mo after the operation. Patients in the trial group were provided with a mealworm-based diet; 10 g of mealworm powder was provided in every meal; therefore, a total of 30 g of mealworm powder per day was offered. The mealworm powder comprised 3 g of carbohydrates, 14.4 g of protein, and 11 g of fat; each 30 g of mealworm powder provided 163 kcal of energy. Meanwhile, those in the control group were supplemented with 30 g of grain powder per day comprising 23 g of carbohydrates, 2.9 g of protein, and 0.5 g of fat. Every 30 g of grain powder provided 106 kcal of energy.

The patients who underwent PD received enteral feeding (Newcare 300 RTH, Daesang, Korea) at postoperative day 2 after surgery via nasojejunal tube placement during operation. On postoperative day 5, abdominal and pelvic computed tomography was performed, and if there were no complications including postoperative leakage of PD site, then the patients were permitted to start an oral diet. Other patients who underwent pancreatectomy only or liver resection started oral diet on postoperative day 2. The diet was gradually built up over time in both groups, as described in the previous protocol [27]. After discharge, the patients visited outpatient clinic every 2 wk until 2 mo after the operation. Nutritional intervention was provided orally after discharge from the hospital.

Figure 1.

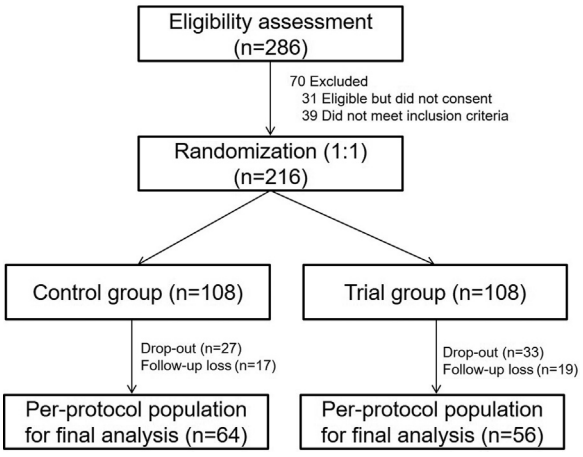

Fig. 1. Flowchart of the trial.

Outcome measurements

The patient data including sex, age, body weight, body mass index, and patient-generated subjective global assessment were collected. During postdischarge intervention, daily intake of total calories and protein was assessed by a diary entry. Recommended daily intake of total calories and protein was estimated by established guideline [28]. The primary endpoint was to evaluate the changes in body composition, including phase angle, measured by Inbody S-10 (Biospace, Seoul, South Korea). Secondary endpoints included changes in immune cell activity, confirmed by fluorescence-activated cell sorting (FACS) of the patients' blood samples.

Sample size calculation and statistical analysis

The target sample size was 216 patients, providing a power of 80% at the 5% (2-sided) level of significance to detect an increase in body cell mass from 6% in the trial group compared with the control group. In this study, the target sample size was based on the increase in body cell mass reported in previous studies [29].

All analyses were conducted on the per-protocol population. The patients who withdrew consent or took powder less than 50% of expected doses in both groups were regarded as "drop-out" patients. The patients who were lost to follow-up or had missing data at the study endpoint were considered "follow-up loss" patients. A total of 120 patients were finally included for statistical analyses.

All statistical analyses were performed using SPSS software, version 21.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed by χ^2 tests or Fisher's exact tests, while continuous variables were analyzed by Student's *t* tests. $P < 0.05$ was considered statistically significant.

Results

Two groups showed no significant differences in baseline characteristics, including body cell mass index, body weight, patient-generated subjective global assessment scoring, and the ratio of surgical procedures (Table 1).

Nutritional outcomes and changes in body composition

The actual total calorie intakes in both groups were below the recommended daily intake. However, the ratio of the actual protein intake to the recommended daily intake in the trial group was

Table 1
Baseline characteristics and surgical procedures

Variables	Control(n = 64)	Trial(n = 56)	*P* value
Sex			
Men	42 (65.6%)	32 (57.1%)	0.354
Women	22 (34.4%)	24 (42.9%)	
Age (y)	61.8 ± 10.7	63.8 ± 9.3	0.294
ASA score			
<3	53 (82.8%)	45 (80.4%)	0.455
≥3	11 (17.2%)	11 (19.6%)	
Body mass index	Mean ± SD	Mean ± SD	
At admission	23.7 ± 2.9	23.8 ± 2.8	0.705
At study endpoint	23.0 ± 2.8	22.9 ± 2.8	0.812
Body weight (kg)	Mean ± SD	Mean ± SD	
At admission	63.2 ± 10.9	62.8 ± 11.0	0.853
At study endpoint	61.6 ± 10.8	60.4 ± 11.1	0.565
PG-SGA	Mean ± SD	Mean ± SD	
At admission	5.4 ± 4.0	6.2 ± 4.2	0.314
At study endpoint	3.2 ± 2.9	2.7 ± 2.2	0.277
Surgical procedures			0.355
Pancreaticoduodenectomy	24 (37.5%)	27 (48.2%)	
Pancreatectomy(total/distal)	14 (21.9%)	13 (23.2%)	
Liver resection	26 (40.6%)	16 (28.6%)	

ASA, American Society of Anaesthesiologists; PG-SGA, patient-generated subjective global assessment; SD, standard deviation

significantly higher than that in the control group (110.03% vs. 98.80%, $P = 0.023$).

The body composition analysis revealed no significant difference in body cell mass, fat free mass, skeletal muscle mass, and phase angle between two points of time, namely at the study endpoint and at the admission (Table 2).

Activities of immune cells

Observing immune cells at the study endpoints and at postoperative day 1, we found that the activity of cytotoxic T cells increased in the trial group (control vs. trial = 0.974 vs. 1.192, $P = 0.028$). The activity of natural killer cells also demonstrated an increase in the trial group, but it was not statistically or significantly different from the control group (control vs. trial = 1.583 vs. 1.903; $P = 0.052$). Regarding other immune cells, namely T cells, B cells, and helper T cells, no significant differences were seen between the two groups (Table 3).

In FACS analysis, both CD 56+ natural killer cells and CD8+ T cells demonstrated enhancement in cell activities at the study endpoint in the trial group (Fig. 2). In the control group, no increase in their activities was observed by the end of intervention.

Table 2
Comparison in nutritional outcomes between the two groups

Variables	Control(n = 64)	Trial(n = 56)	*P* value
Total calorie intake/recommended daily intake at study endpoint (%)	(n = 40) 90.68 ± 15.80	(n = 39) 91.65 ± 17.84	0.784
Total protein intake/recommended daily intake at study endpoint (%)	(n = 40) 98.80 ± 20.65	(n = 39) 110.03 ± 25.60	0.023
Changes in body composition (at study endpoint/at admission)*			
Body cell mass	0.975 ± 0.059	0.969 ± 0.049	0.506
Fat free mass	0.983 ± 0.057	0.975 ± 0.048	0.423
Skeletal muscle mass	0.983 ± 0.057	0.975 ± 0.048	0.416
Phase angle	0.914 ± 0.103	0.924 ± 0.101	0.585

*The ratio of the values at the study endpoint to those at the admission

Table 3
Comparison in activities of immune cells between the two groups

Variables (at study endpoint/at POD 1)*	Control(n = 56)	Trial(n = 45)	*P* value
T cells	1.091 ± 0.177	1.148 ± 0.391	0.333
Cytotoxic T cells	0.974 ± 0.322	1.192 ± 0.639	**0.028**
Regulatory T cells	1.121 ± 1.068	0.991 ± 0.352	0.436
T_h1 cells	1.916 ± 1.738	1.773 ± 1.442	0.651
T_h2 cell	0.975 ± 0.202	1.166 ± 0.990	0.165
B cells	0.896 ± 0.588	0.733 ± 0.331	0.099
Natural killer cells	1.583 ± 0.665	1.903 ± 0.962	**0.052**

POD, postoperative day
*The ratio of the values at the study endpoint to those at POD 1

Discussion

This study aimed to evaluate whether mealworm protein used as a dietary supplement for patients who underwent hepato-pancreato-biliary surgeries could help improve their nutritional status and immune functions. Our study findings showed no significant improvement in their nutritional status; nevertheless, the activities of immune cells increased in the trial group compared with those in the control group.

Most patients with major gastrointestinal surgeries experience malnutrition in postoperative periods [19]; hence, nutritional support is regarded as one of the routine postoperative procedures. It is noted that clinicians mainly focus on losses of skeletal muscle mass because ongoing sarcopenia leads to progressive functional muscle impairment and delays the recovery [3]. For this reason, certain previous studies suggested the optimal protein supplementation regimen for patients after major gastrointestinal surgeries. According to a systematic review of seven clinical trials on humans, the oral postoperative protein supplementation had no effect on mortality, but reduced weight loss and improved nutritional status [19].

Nevertheless, no recommendation on the optimal amount of dietary protein supplementation is currently available. A previous study demonstrated that muscle protein synthesis increased when patients took a medical food containing 40 g of casein protein and some other substances. However, no increase in muscle protein synthesis was recorded among patients consuming 24 g of casein protein alone [30]. In this study, we provided an additional 14.4 g of protein per day using mealworms. However, we did not observe any clinically significant improvement in the patients' nutritional status based on their body composition. In this current study, the lack of direct improvement in the body composition, including skeletal muscle mass, may result from insufficient additional protein supply. Another possible explanation for these findings is that, as we could not control the patients' diet after discharge from the hospital, patients in the control group might have consumed a protein-enhanced diet by themselves after receiving an intensive education from dietitians during their hospital stays.

This study has several limitations that need to be addressed. The most important point to be considered is the high drop-out rates of >25% in both groups. According to the recent systematic review by Hubbard et al. [31], overall compliance to oral nutritional supplements is more than 70% even if the trials were performed in a wide variety of patient groups in hospital and community settings. One of the reasons for having a high compliance rate is that the oral nutritional supplements used in most trials were ready made and easy to use. In this study, we used a powder for nutritional intervention in both groups and instructed patients to mix the powder with liquids such as water or milk. Therefore, the additional step of mixing the powder with liquids may have caused discomfort to ill patients with an average age of 60 y or older.

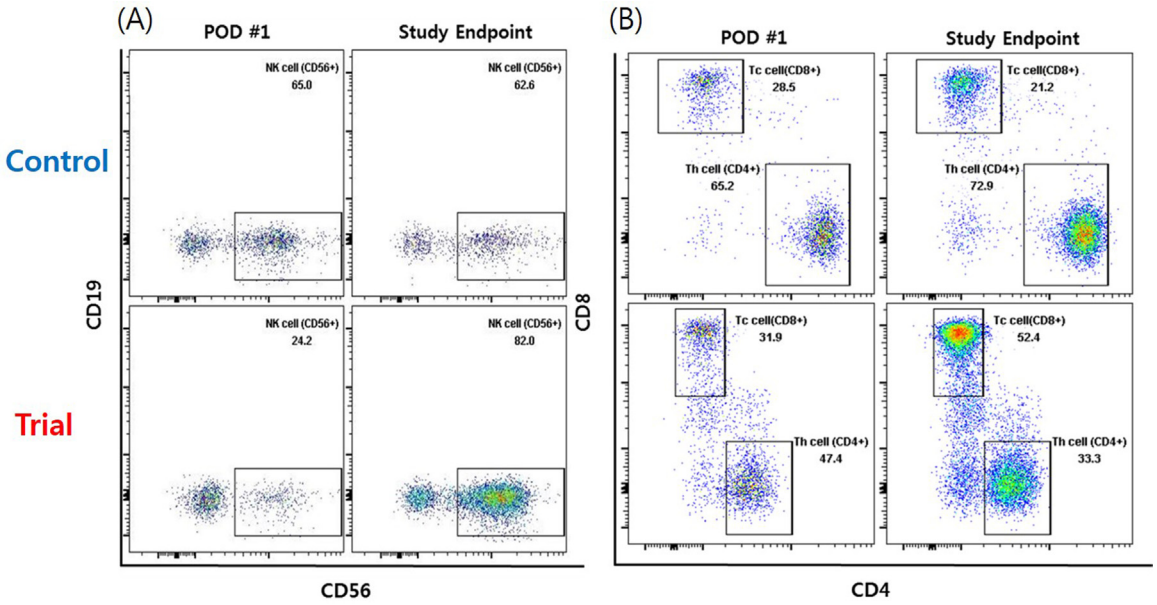

Fig. 2. Comparison of cell activities (A) CD 56+ natural killer cells, (B) CD8+ T cells) by using FACS analysis. FACS, fluorescence-activated cell sorting.

Moreover, especially in patients with gastrointestinal cancer, previous studies demonstrated the poor adherence of oral nutritional supplements [32,33]. Qin et al. [32] reported the median adherence of 50.0%, and 51.35% of participants consumed no more than 50% of the recommended amount. The participants with poor adherence to oral nutritional supplements mentioned that they were confused about their daily target intake, or the taste did not meet their personal preference. In this study, we instructed the patients to take 10 g of powder in every meal with 100 to 150 cc liquids, and this may have caused poor compliance owing to the bulk of fluid and the patients' low appetite.

Another shortcoming of this study is that the composition of powder is not isocaloric between the two groups. For adjusting total volume of powder, the caloric difference between the two groups were developed (trial group vs. control group = 163 kcal vs. 106 kcal per 30 g). However, as described in published protocol, the difference of total calories provided in the two groups was less than 150 kcal, which cannot be regarded to affect clinical outcomes.

Patients with PD have been known to have a higher risk of malnutrition than those with other gastrointestinal surgeries. To avoid bias from surgical procedures, we performed subgroup analyses with the patients divided into three groups (PD, pancreatectomy, liver resection). However, in the subgroup analyses, no significant differences in body composition were seen between the trial and control groups (data described in the supplementary file).

The strength of the current study is that the trial group showed an enhancement in activities of cytotoxic T cells, which represent the acquired immune system. According to a recent review, the immune status of individuals affected by malnutrition and infectious diseases improves after using specific amino acids as dietary supplements; hence, their morbidity and mortality significantly declined [34]. In contrast, short-term protein supplementation could hardly promote immune functions. Strasser et al. [35] conducted a randomized controlled trial to investigate the effect of the protein-enhanced diet on immune activation and muscle function in older patients during hip fracture recovery. They showed that a higher protein intake had no impacts on immune biomarkers and tryptophan metabolism. In our present study, we only suggested increased activities of cytotoxic T cells, while other immune cell activities experienced no improvement in both groups. To clarify the roles of dietary protein in immune responses, integrative interpretation should be considered, including patients' protein metabolism and altered immune system.

In conclusion, protein-enhanced diet using mealworms clinically improved the activity of immune cells. However, it did not significantly improve the patients' nutritional status undergoing hepato-pancreato-biliary surgeries.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.nut.2021.111538.

References

[1] Rosenberg I. Epidemiologic and methodologic problems in determining nutritional status of older persons (summary comments). Am J Cli Nutr 1989;50:1231–3.
[2] Rosenberg IH. Sarcopenia: origins and clinical relevance. J Nutr 1997;127:990S–1S.
[3] Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12:489–95.
[4] Fearon KCH. Cancer cachexia and fat–muscle physiology. N Engl J Med 2011;365:565–7.
[5] Englesbe MJ, Patel SP, He K, Lynch RJ, Schaubel DE, Harbaugh C, et al. Sarcopenia and mortality after liver transplantation. J Am Coll Surg 2010;211:271–8.
[6] Itoh S, Shirabe K, Matsumoto Y, Yoshiya S, Muto J, Harimoto N, et al. Effect of body composition on outcomes after hepatic resection for hepatocellular carcinoma. Ann Surg Oncol 2014;21:3063–8.
[7] Reisinger KW, van Vugt JLA, Tegels JJW, Snijders C, Hulsewé KWE, Hoofwijk AGM, et al. Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. Ann Surg 2015;261:345–52.
[8] Peng YC, Wu CH, Tien YW, Lu TP, Wang YH, Chen BB. Preoperative sarcopenia is associated with poor overall survival in pancreatic cancer patients following pancreaticoduodenectomy. Eur Radiol 2021;31:2472–81.
[9] Trejo-Avila M, Bozada-Gutiérrez K, Valenzuela-Salazar C, Herrera-Esquivel J, Moreno-Portillo M. Sarcopenia predicts worse postoperative outcomes and decreased survival rates in patients with colorectal cancer: a systematic review and meta-analysis. Int J Colorectal Dis 2021;36:1077–96.
[10] Houston DK, Nicklas BJ, Ding J, Harris TB, Tylavsky FA, Newman AB, et al. Dietary protein intake is associated with lean mass change in older, community-dwelling adults: the Health, Aging, and Body Composition (Health ABC) study. Am J Clin Nutr 2008;87:150–5.

[11] Børsheim E, Bui QUT, Tissier S, Kobayashi H, Ferrando AA, Wolfe RR. Effect of amino acid supplementation on muscle mass, strength and physical function in elderly. Clin Nutr 2008;27:189–95.
[12] Bo Y, Liu C, Ji Z, Yang R, An Q, Zhang X, et al. A high whey protein, vitamin D and E supplement preserves muscle mass, strength, and quality of life in sarcopenic older adults: A double-blind randomized controlled trial. Clin Nutr 2019;38:159–64.
[13] Bauer JM, Verlaan S, Bautmans I, Brandt K, Donini LM, Maggio M, et al. Effects of a vitamin D and leucine-enriched whey protein nutritional supplement on measures of sarcopenia in older adults, the PROVIDE study: a randomized, double-blind, placebo-controlled trial. J Am Med Dir Assoc 2015;16:740–7.
[14] Verlaan S, Maier AB, Bauer JM, Bautmans I, Brandt K, Donini LM, et al. Sufficient levels of 25-hydroxyvitamin D and protein intake required to increase muscle mass in sarcopenic older adults–the PROVIDE study. Clin Nutr 2018;37:551–7.
[15] Luo D, Lin Z, Li S, Liu SJ. Effect of nutritional supplement combined with exercise intervention on sarcopenia in the elderly: a meta-analysis. Int J Nurs Sci 2017;4:389–401.
[16] Artaza-Artabe I, Sáez-López P, Sánchez-Hernández N, Fernández-Gutierrez N, Malafarina V. The relationship between nutrition and frailty: effects of protein intake, nutritional supplementation, vitamin D and exercise on muscle metabolism in the elderly. A systematic review. Maturitas 2016;93:89–99.
[17] Martínez-Arnau FM, Fonfría-Vivas R, Cauli O. Beneficial effects of leucine supplementation on criteria for sarcopenia: a systematic review. Nutrients 2019;11:2504.
[18] Gkekas NK, Anagnostis P, Paraschou V, Stamiris D, Dellis S, Kenanidis E, et al. The effect of vitamin D plus protein supplementation on sarcopenia: a systematic review and meta-analysis of randomized controlled trials. Maturitas 2021;145:56–63.
[19] Crickmer M, Dunne CP, O'Regan A, Coffey JC, Dunne SS. Benefits of post-operative oral protein supplementation in gastrointestinal surgery patients: A systematic review of clinical trials. World J Gastrointest Surg 2016;8:521–32.
[20] Jensen MB, Hessov I. Dietary supplementation at home improves the regain of lean body mass after surgery. Nutrition 1997;13:422–30.
[21] Bastow M, Rawlings J, Allison S. Undernutrition, hypothermia, and injury in elderly women with fractured femur: an injury response to altered metabolism? Lancet 1983;321:143–6.
[22] Lassen K, Soop M, Nygren J, Cox PBW, Hendry PO, Spies C, et al. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. Arch Surg 2009;144:961–9.
[23] Lassen K, Coolsen MM, Slim K, Carli F, de Aguilar-Nascimento JE, Schäfer M, et al. Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS®) Society recommendations. Clin Nutr 2012;31:817–30.
[24] Belluco S, Losasso C, Maggioletti M, Alonzi CC, Paoletti MG, Ricci A. Edible insects in a food safety and nutritional perspective: a critical review. Comp Rev Food Sci Food Safety 2013;12:296–313.
[25] Ramos-Elorduy J. Anthropo-entomophagy: cultures, evolution and sustainability. Entomol Res 2009;39:271–88.
[26] Megido RC, Poelaert C, Ernens M, Liotta M, Blecker C, Danthine S, et al. Effect of household cooking techniques on the microbiological load and the nutritional quality of mealworms (Tenebrio molitor L. 1758). Food Res Int 2018;106:503–8.
[27] Kim HS, Lee YS, Jang SY, Jun SY, Lim JH, Kim IK, et al. Clinical application of invalid foods using mealworms and evaluation of nutrition status and immune function: a study protocol for a randomized, double blind, placebo-controlled trial. BMC Nutr 2019;5:44.
[28] Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr 2017;36:11–48.
[29] Kraft M, Kraft K, Gärtner S, Mayerle J, Simon P, Weber E, et al. L-Carnitine-supplementation in advanced pancreatic cancer (CARPAN)-a randomized multicentre trial. Nutr J 2012;11:52.
[30] Deutz NEP, Safar A, Schutzler S, Memelink R, Ferrando A, Spencer H, et al. Muscle protein synthesis in cancer patients can be stimulated with a specially formulated medical food. Clin Nutr 2011;30:759–68.
[31] Hubbard GP, Elia M, Holdoway A, Stratton RJ. A systematic review of compliance to oral nutritional supplements. Clin Nutr 2012;31:293–312.
[32] Qin L, Xu D, Tian Q, Wu B. Adherence to oral nutritional supplements in patients with gastrointestinal cancer: a mixed-method study. Cancer Nurs 2021. https://doi.org/10.1097/NCC.0000000000001022. accessed November 28.
[33] Kobayashi D, Ishigure K, Mochizuki Y, Nakayama H, Sakai M, Ito S, et al. Multi-institutional prospective feasibility study to explore tolerability and efficacy of oral nutritional supplements for patients with gastric cancer undergoing gastrectomy (CCOG1301). Gastric Cancer 2017;20:718–27.
[34] Li P, Yin YL, Li D, Kim SW, Wu G. Amino acids and immune function. Br J Nutr 2007;98:237–52.
[35] Strasser B, Kohlboeck G, Hermanky M, Leitzmann M. Role of dietary protein and exercise on biomarkers of immune activation in older patients during hospitalization. Aging Clin Exp Res 2020;32:2419–23.