ISSN 1948-5204 (online)

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2022 July 15; 14(7): 1218-1374

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Oncology

Contents

Monthly Volume 14 Number 7 July 15, 2022

FRONTIER

1218 Gut microbiome and pancreatic cancer cachexia: An evolving relationship

Hendifar A, Akinsola R, Muranaka H, Osipov A, Thomassian S, Moshayedi N, Yang J, Jacobs J, Devkota S, Bhowmick N, Gong J

MINIREVIEWS

1227 Prospects and applications of enucleation in solid pseudopapillary neoplasms of the pancreas

Wang R, Li J, Tan CL, Liu XB, Chen YH

ORIGINAL ARTICLE

Basic Study

1239 KIFC3 promotes proliferation, migration and invasion of esophageal squamous cell carcinoma cells by activating EMT and β-catenin signaling

Hao WW, Xu F

1252 Claudin 18.2 is a potential therapeutic target for zolbetuximab in pancreatic ductal adenocarcinoma

Wang X, Zhang CS, Dong XY, Hu Y, Duan BJ, Bai J, Wu YY, Fan L, Liao XH, Kang Y, Zhang P, Li MY, Xu J, Mao ZJ, Liu HT, Zhang XL, Tian LF, Li EX

Clinical and Translational Research

1265 Differences of core genes in liver fibrosis and hepatocellular carcinoma: Evidence from integrated bioinformatics and immunohistochemical analysis

Li Y, Yuan SL, Yin JY, Yang K, Zhou XG, Xie W, Wang Q

Case Control Study

1281 Efficacy of neoadjuvant chemotherapy for initially resectable colorectal liver metastases: A retrospective cohort study

Takeda K, Sawada Y, Yabushita Y, Honma Y, Kumamoto T, Watanabe J, Matsuyama R, Kunisaki C, Misumi T, Endo I

Retrospective Cohort Study

1295 Increased 5-hydroxymethylcytosine is a favorable prognostic factor of *Helicobacter pylori*-negative gastric cancer patients

Fu YL, Wu YH, Cao DH, Jia ZF, Shen A, Jiang J, Cao XY

Retrospective Study

1307 Neutrophile-to-lymphocyte, lymphocyte-to-monocyte, and platelet-to-lymphocyte ratios as prognostic and response biomarkers for resectable locally advanced gastric cancer

Tomás TC, Eiriz I, Vitorino M, Vicente R, Gramaça J, Oliveira AG, Luz P, Baleiras M, Spencer AS, Costa LL, Liu P, Mendonça J, Dinis M, Padrão T, Correia M, Atalaia G, Silva M, Fiúza T

1324 Effect of obesity on post-operative outcomes following colorectal cancer surgery

Mao D, Flynn DE, Yerkovich S, Tran K, Gurunathan U, Chandrasegaram MD

1337 Predictors for malignant potential and deep submucosal invasion in colorectal laterally spreading tumors

Hao XW, Li P, Wang YJ, Ji M, Zhang ST, Shi HY

CASE REPORT

1348 Pediatric case of colonic perivascular epithelioid cell tumor complicated with intussusception and anal incarceration: A case report

Kou L, Zheng WW, Jia L, Wang XL, Zhou JH, Hao JR, Liu Z, Gao FY

1356 Primary signet-ring cell carcinoma of the extrahepatic bile duct: A case report

Xie CB, Wu Y, Li F, Zhao KF, Shi RS, Huang Q, Ao J, Ke D

1363 Da Vinci robot-assisted pancreato-duodenectomy in a patient with situs inversus totalis: A case report and review of literature

Li BB, Lu SL, He X, Lei B, Yao JN, Feng SC, Yu SP

CORRECTION

1372 Correction to "Novel long non-coding RNA LINC02532 promotes gastric cancer cell proliferation, migration, and invasion *in vitro*"

Zhang C, Ma MH, Liang Y, Wu KZ, Dai DQ

World Journal of Gastrointestinal Oncology

Monthly Volume 14 Number 7 July 15, 2022

Contents

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INDEXING/ABSTRACTING

The *WJGO* is now abstracted and indexed in PubMed, PubMed Central, Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJGO* as 3.404; IF without journal self cites: 3.357; 5-year IF: 3.250; Journal Citation Indicator: 0.53; Ranking: 162 among 245 journals in oncology; Quartile category: Q3; Ranking: 59 among 93 journals in gastroenterology and hepatology; and Quartile category: Q3. The *WJGO*'s CiteScore for 2021 is 3.6 and Scopus CiteScore rank 2021: Gastroenterology is 72/149; Oncology is 203/360.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jia-Ru Fan*.

NAME OF JOURNAL
World Journal of Gastrointestinal Oncology

ISSN
ISSN 1948-5204 (online)

LAUNCH DATE
February 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Monjur Ahmed, Florin Burada

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5204/editorialboard.htm

PUBLICATION DATE
July 15, 2022

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INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

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ONLINE SUBMISSION
https://www.f6publishing.com

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E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Gastrointestinal Oncology

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World J Gastrointest Oncol 2022 July 15; 14(7): 1218-1226

DOI: 10.4251/wjgo.v14.i7.1218

ISSN 1948-5204 (online)

FRONTIER

Gut microbiome and pancreatic cancer cachexia: An evolving relationship

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Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Manojlovic N, Serbia; Yu L, Singapore

Received: March 3, 2022
Peer-review started: March 3, 2022
First decision: April 17, 2022
Revised: May 10, 2022
Accepted: June 20, 2022
Article in press: June 20, 2022
Published online: July 15, 2022

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Abstract

Nearly 80% of patients with pancreatic ductal adenocarcinoma (PDAC) develop cachexia along their disease course. Cachexia is characterized by progressive weight loss, muscle wasting, and systemic inflammation and has been linked to poorer outcomes and impairments in quality of life. Management of PDAC cachexia has historically involved a multidisciplinary effort comprised of nutritional support, pancreatic enzyme replacement therapy, and/or pharmacologic interventions. Despite current interventions to mitigate PDAC cachexia, a significant proportion of patients continue to die from complications associated with cachexia underscoring the need for novel insights and treatments for this syndrome. We highlight the feasibility and effectiveness of a recent enteral feeding prospective trial at our institution to improve cachexia outcomes in patients with advanced PDAC. Additionally, we were among the first to characterize the stool microbiome composition in patients with advanced PDAC receiving enteral feeding for the treatment of cachexia. Novel insights into the relationship between enteral nutritional support, cachexia, and the gut microbiome are presented. These promising results are discussed in the context of a potential ability to modulate the stool microbiome as a new interventional strategy to mitigate PDAC cachexia.

Key Words: Gut microbiome; Pancreatic cancer; Stool; Cachexia; Inflammation; Weight

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Core Tip: Cachexia is a hallmark of pancreatic cancer and is characterized by muscle wasting, weight loss, and systemic inflammation. Despite advancements in nutritional support, pancreatic enzyme replacement therapy, and pharmacologic interventions for treating pancreatic cancer cachexia, it continues to have a significant negative impact on patient outcomes. We detail the results of a recent prospective clinical trial wherein cachectic patients with advanced pancreatic cancer achieved weight stability with 12 wk of enteral feeding. Notably, gut microbiome changes and an increased abundance of a specific microbe associated with enteral feeding highlight a potentially novel approach to mitigate cachexia through microbial modulation.

Citation: Hendifar A, Akinsola R, Muranaka H, Osipov A, Thomassian S, Moshayedi N, Yang J, Jacobs J, Devkota S, Bhowmick N, Gong J. Gut microbiome and pancreatic cancer cachexia: An evolving relationship. *World J Gastrointest Oncol* 2022; 14(7): 1218-1226
URL: https://www.wjgnet.com/1948-5204/full/v14/i7/1218.htm
DOI: https://dx.doi.org/10.4251/wjgo.v14.i7.1218

INTRODUCTION

Pancreatic cancer is an aggressive malignancy characterized by progressive therapeutic resistance and a multifactorial syndrome of weight loss, muscle wasting, and systemic inflammation known as cachexia [1,2]. Cachexia is pervasive and an unfortunate hallmark of pancreatic cancer as nearly 85% of patients with pancreatic ductal adenocarcinoma (PDAC) will meet the definition of cancer cachexia along their disease course[3,4]. Cancer cachexia is generally defined as a multifactorial syndrome characterized by progressive loss of skeletal muscle mass (with or without loss of fat mass) that is not fully reversible through conventional means of nutritional support and leads to ongoing impairment in patient function [5]. Diagnostic criteria for cancer cachexia have been defined by international consensus guidelines as well (Table 1).

The management of PDAC cachexia is multidisciplinary and has historically been comprised of the following: Nutritional support with oral nutrition supplements and involvement of a registered dietitian, pancreatic enzyme replacement therapy, exercise, pharmacologic interventions, and in select cases, specialized nutrition support through the use of enteral or parenteral nutrition[4,6]. The importance of systemic therapy for the underlying PDAC cannot be underscored as well given that the negative impact of cancer cachexia on patient outcomes can be offset, to a degree, with systemic chemotherapy[7]. Despite the mechanisms of PDAC cachexia having been increasingly described, the cachexia syndrome in pancreatic cancer patients remains difficult to treat with a profoundly negative impact on outcomes including overall survival (OS), response to chemotherapy, and quality-of-life[6,7]. As such, novel interventions for PDAC cachexia are of high unmet need.

PANCAX-1

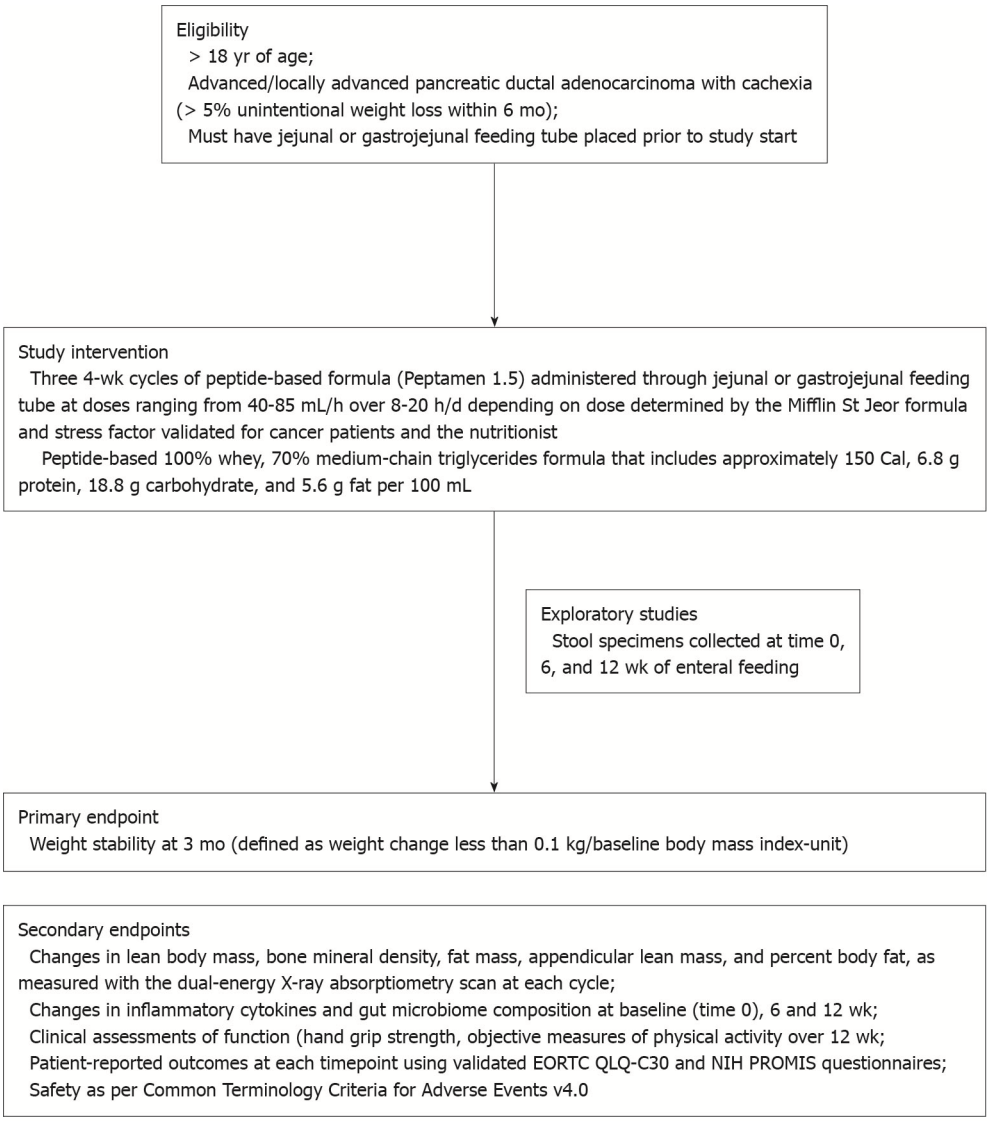
Our group has historically focused on the development of biomarkers and therapeutic strategies for PDAC cachexia across interventional and observational trials[1,8]. We conducted PANCAX-1 (NCT02400398), which was a single-institution, single-arm prospective clinical trial, to evaluate the feasibility and efficacy of enteral feeding on weight stability in cachectic patients with advanced pancreatic cancer[9,10]. Eligible patients included those aged > 18 years having been diagnosed with advanced or locally advanced pancreatic cancer and cachexia. Candidates were required to have a jejunal or gastrojejunal feeding tube placed prior to study intervention. Cachexia was defined using consensus criteria (Table 1). Anticancer therapy or previous surgical resection for pancreatic cancer was permitted. Patients were enrolled to receive the study intervention of a peptide-based formula (Peptamen 1.5) over three 4-week cycles (total of 12 wk) of enteral feeding as per protocol (Figure 1).

The primary endpoint was weight stability at 3 mo, defined as weight loss < 0.1 kg/baseline body mass index (BMI)-unit. Secondary endpoints included changes in body composition measurements, clinical metrics of function and activity, safety, and patient-reported outcomes (PROs).

Table 1 Consensus definitions of cancer cachexia[5]

Definition of cancer cachexia is met with one of the following
Weight loss > 5% over past 6 mo (in absence of simple starvation)
Body mass index < 20 and weight loss > 2%
Evidence of sarcopenia with weight loss > 2%[1]

[1]Generally accepted measures of sarcopenia include: mid upper-arm muscle area by anthropometry (men < 32 cm^2, women < 18 cm^2); appendicular skeletal muscle index determined by dual energy x-ray absorptiometry (men < 7.26 kg/m^2; women < 5.45 kg/m^2); lumbar skeletal muscle index determined by computed tomography imaging (men < 55 cm^2/m^2; women < 39 cm^2/m^2); whole body fat-free mass index without bone determined by bioelectrical impedance (men < 14.6 kg/m^2; women < 11.4 kg/m^2).



DOI: 10.4251/wjgo.v14.i7.1218 **Copyright** ©The Author(s) 2022.

Figure 1 Study design of the single-institution, single-arm prospective PANCAX-1 trial evaluating the feasibility and efficacy of enteral feeding on weight stability in cachectic patients with advanced pancreatic cancer.

From April 2015-March 2019, a total of 31 patients were consented onto the study. From this, 16 patients were able to complete all 12 wk of enteral tube feeding and were deemed evaluable for the primary endpoint. The study achieved its primary endpoint whereby weight stability was achieved in 10/16 patients (62.5%). Additionally, enteral feeding was associated with improvement in key secondary outcomes including decreases in body fat mass and inflammatory markers (CRP) but increases in lean body mass (Table 2). Improvements were seen in PROs using both NIH PROMIS and EORTC QLQ-C30 scores from baseline to 12 wk of enteral feeding in this cohort[9].

Table 2 Key outcome measures in cachectic patients with advanced pancreatic cancer over 12 wk of enteral feeding

Outcome (*n* = 16)	Change (SD)
Average weight (kg)	+1.29 (5.8)
Body mass index (kg/m^2)	+0.6 (1.7)
% Body fat	-1.6 (5)
Bone mineral density (T-score)	-0.01 (0.02)
Body fat mass (g)	-602 (2794)
Lean body mass (g)	+1273.1 (4078)
Appendicular lean mass (kg/m^2)	+0.45 (0.62)
C-reactive protein (mg/mL)	-9.77 (SE 11.6)
Patient-reported outcomes	
NIH PROMIS (mean difference in score)	
Pain interference	-7.5 (P = 0.05)
Fatigue	-7.1 (P = 0.06)
Depression	-10.4 (P = 0.006)
EORTC QLQ-C30 (mean difference in score)	
Global health	+13.3 (P = 0.05)

THE GUT MICROBIOME AND CACHEXIA

The PANCAX-1 trial successfully demonstrated the feasibility and efficacy of enteral feeding alongside systemic chemotherapy for the treatment of cachexia in patients with advanced PDAC. Despite a drop in consented subjects who were unable to complete 12-wk of enteral feeding due to advanced disease, deteriorating performance status, and/or rapid changes in symptom burden as expected from a high-risk population, enteral feeding resulted in weight stability and improved PROs in cachectic patients with advanced pancreatic cancer. We next sought to identify predictive biomarkers associated with weight stability in this prospective cohort for insight into the possible mechanisms by which enteral feeding served an effective intervention for cachexia. In preplanned exploratory studies of the PANCAX-1 prospective cohort, blood and stool samples were collected longitudinally for profiling of inflammatory cytokines and the gut microbiome.

Our group characterized for the first time the gut microbiome composition in patients with advanced pancreatic cancer treated with enteral feeding for cachexia[11]. DNA extraction and sequencing of the 16S ribosomal RNA gene was performed on fecal samples, as previously described[12], with several unique findings (Table 3). Firstly, in stool samples collected over 12 wk of enteral feeding, differential abundance testing identified an increased relative abundance of the Gram-negative genus *Veillonella* (P = 0.0150) and the Gram-positive genus *Actinomyces* (P = 0.0390). As *Veillonella* represented a bacterial genus that increased in abundance over time with enteral feeding for PDAC cachexia, it was interesting to discover that a significantly increased abundance of *Veillonella* was also identified in baseline stool samples of cachectic patients who achieved weight stability with enteral feeding.

Veillonella are Gram-negative, anaerobic bacteria known for its lactate fermenting abilities and are nonpathogenic colonizers of the intestines and oral mucosa in humans whereby *Veillonella atypica* and its active metabolite propionate has been shown to enhance physical performance in mouse models[13]. Interestingly, in a separate cohort of cachectic patients comprised predominantly of subjects with pancreatic cancer, *Veillonella* was among the most abundant bacterial genera among cachectic cancer patients[14]. In a comparison of the oral microbiome collected from PDAC patients and healthy controls, *Veillonella* were among the genera in significantly greater abundance in salivary samples from healthy controls than those with PDAC[15]. Furthermore, when comparing subjects with resectable *vs* unresectable PDAC, *Veillonella* was found to be the most abundant bacterial genera in those with less advanced, resectable disease when compared to more advanced, unresectable disease. When compared to healthy controls, *Veillonella* had the lowest odds ratio (OR) for risk of PDAC development across all sampled oral bacteria (OR 0.187, 95% confidence interval 0.055-0.631, P = 0.007). The relative abundance of *Veillonella* in saliva samples was observed to show a gradual decline from healthy controls to those with resectable PDAC and unresectable PDAC. The lowest abundance of *Veillonella* was observed in saliva samples from subjects with unresectable PDAC, whereas the highest abundance of *Veillonella* was observed in the saliva from healthy subjects.

Table 3 Gut microbiome compositional changes in patients with advanced pancreatic cancer receiving 12 wk of enteral feeding for cachexia

Stool microbiome assessment[1]	Outcome
Relative abundance from baseline (time 0) to 12 wk (n = 6)	Increased abundance: *Veillonella* genera (P = 0.015); *Actinomyces* genera (P = 0.039). Decreased abundance: *Bacteroides* genera (P = 0.015); *Butyricicoccus* genera (P = 0.039)
Relative abundance in baseline stool samples from subjects achieving weight stability (n = 8)	Increased abundance: *Veillonella* genera (P = 0.0006). Decreased abundance: *Bifidobacterium* genera ($P = 2.35 \times 10^{-5}$)[2]
Diversity indices (n = 8)	Weight stability associated with reduced diversity by Chao1 index of richness (P = 0.0208) but not reduced species richness and evenness by Shannon index (P = 0.187)

[1]Performed through 16S ribosomal RNA gene sequencing.
[2]Taxa summary plot suggested that this finding was driven by a high percentage of this bacterium in one patient who had a much higher overall survival than the mean.

MICROBIAL INTERVENTIONS AS A POTENTIAL NEW THERAPEUTIC STRATEGY FOR CACHEXIA

The relationship between the gut microbiome and cachexia has long been implicated in earlier investigations wherein alterations in gut microbiome composition were associated with anorexia nervosa and low BMI states, body weight loss, low muscle mass, low appetite, and systemic inflammation[16]. However, the role that the gut microbiome plays in the cachexia process has been better established with studies on its impact with systemic inflammation and muscle wasting, which are hallmarks of cachexia[16-18].

Inflammation has classically served in host defense against pathogens but has increasingly been shown to be equally important in tissue repair, regeneration, and remodeling with programmed cell death including apoptosis, necroptosis, and pyroptosis representing means to clear dying cells and promote tissue homeostasis[19,20]. In this sense, localized transient inflammation is generally protective, helping the host to remove harmful stimuli including physical, chemical, carcinogenic, and infectious and facilitate degradation of dying cells as a nutritional source to facilitate tissue regeneration. However, the inflammatory response underlying cachexia often is characterized by impairment in the correct utilization of nutrients such that meeting energy and protein requirements in patients with cachexia without addressing inflammation can result in improper restoration of body composition as most proteins and energy are diverted to production of acute-phase proteins and adipose tissue, which in turn, can sustain and promote systemic inflammation[21]. In critically ill patients, for example, concepts of restrictive eating during acute phases of critical illness have been explored to potentially minimize the negative effects of overfeeding and systemic inflammation[22]. Evidence is emerging to suggest that specific bacteria within the gut microbiome may possess pro- and anti-inflammatory effects, providing another relationship between the microbiome and cachexia that could be exploited to counteract the systemic inflammation underlying cachexia[23].

Animal studies have illustrated several key findings of the gut microbiome-cachexia relationship: (1) Gut microbes can lead to muscle wasting through decreasing amino acid availability for the host or synthesis of noxious bacterial metabolites (*e.g.*, indoxyl sulfate and lipopolysaccharide or LPS) that activate PI3K/AKT, NF-κB, and MAPK (p38, JNK, ERK) signaling to upregulate Atrogin-1/MAFbx and MuRF1 genes encoding E3 ubiquitin ligases; (2) Pathogen-associated molecular patterns (PAMPs) from microbes (*e.g.*, circulating peptidoglycans, LPS, bacterial nucleic acids, short-chain fatty acids or SCFA, branched-chain amino acids or BCAAs, or flagellin) can induce muscle atrophy by stimulating the Toll-like receptor/NF-kB pathway; (3) Increased gut permeability in cachectic disorders and subsequent translocation of PAMPs from the gut lumen can stimulate pro-inflammatory cytokine cascades; and (4) Depletion of certain bacterial conditions can induce muscle wasting by activating the AMPK-FoxO3-Atrogin-1/MuRF1 cascade and BCAA catabolism, reducing expression of growth factors and muscle growth-related genes (IGF-1, myogenin, SIK1, and MyoD), increasing myostatin, and impairing neuromuscular junction function and mitochondrial function[16-18].

Based on this preclinical rationale, it is not surprising that early efforts for gut microbiota-targeted nutritional interventions of cachexia have already begun exploration. For example, administration of a mixture of *Lactobacillus reuteri* and *Lactobacillus gasseri* to cachectic mice with leukemia restored the levels of these bacteria in the gut while reducing inflammation and partially counteracting the induction of muscle atrophy markers[24]. Administration of bacterial metabolites have also shown applicability in the treatment of cachexia where pectic oligosaccharides given to leukemic mice with cachexia was able to delay the cachectic phenotype and spare fat mass while increasing abundance of *Bacteroides dorei*[25].

There is growing evidence to suggest that *Veillonella* represents a genus of gut bacteria that is protective against PDAC and performance enhancing in human subjects[13,15]. In our preplanned analyses of the gut microbiome in stool samples serially collected from a prospective cohort of enteral

fed patients with PDAC cachexia, we identified compositional changes in the gut microbiome and an increase in abundance of the bacterial genus *Veillonella* over time with enteral feeding associated with weight stability. We are therefore the first to posit another beneficial role of *Veillonella* as a microbe associated with weight stability in the treatment of cachexia. However, before positioning *Veillonella* as a potential future and novel intervention to mitigate cachexia, there are several lessons that can be learned from microbial manipulation strategies thus far.

FUTURE CONSIDERATIONS FOR CLINICAL TRANSLATION

Interventions to target the gut microbiome in cancer cachexia can largely be classified into: (1) Prebiotics, which are nondigestible substrates that can induce growth or activity of microorganisms in the host; (2) Probiotics that contain live microorganisms to be introduced to the host; and (3) Synbiotics, which are mixtures of live microorganisms and substrates utilized by the host (combination of prebiotics and probiotics)[17].

Recently, the double-blind, randomized phase II TRANSIT trial enrolled patients with unresectable or metastatic gastroesophageal junction adenocarcinoma who were planned to receive standard first-line chemotherapy and met criteria for cachexia to receive allogenic fecal microbiota transplantation (FMT) from obese donors or autologous FMT (control)[26]. Donor and recipients delivered fresh fecal samples within 6 h before use on day of fecal infusions wherein the feces were mixed until fully homogenized and the fecal solution filtered to remove food derived debris. The filtrate was then transferred to a 1000-mL sterile bottle and stored at room temperature. Enrolled subjects underwent bowel lavage with polyethylene glycol solution through a nasoduodenal tube to remove endogenous fecal contamination. This was followed by infusion of the gut microbiota solution over 30 minutes approximately. The primary outcome of this study was effect of allogenic FMT on satiety after 4 wk with secondary outcomes on cachexia domains including nutritional and appetite assessments and conventional cancer efficacy outcomes.

Between August 2016 to January 2019, 24 patients were randomized to receive allogenic FMT (n = 12) and autologous FMT (n = 12). Donors for allogenic FMT were all healthy overweight or obese subjects by BMI criteria. There was no significant difference in satiety levels, caloric intake, or change in any other measure related to cachexia between allogenic and autologous FMT groups. There was no difference in completion rates or adverse events associated with chemotherapy across groups either. However, those receiving allogenic FMT had higher disease-control rates at 12 wk, longer median OS (365 d *vs* 227 d), hazard ratio 0.38 (95% confidence interval: 0.14-1.05, P = 0.057) and longer progression-free survival (204 d *vs* 93 d) than those receiving autologous FMT. The microbiome composition from the allogenic recipients resembled the donor microbiome more closely after the FMT compared to baseline, suggestive of proper engraftment of donor microbiota.

The phase II TRANSIT trial, although negative, should be praised for testing the feasibility of such an approach in human subjects with cancer cachexia. There are multiple take-away points from this important study that need to be considered in future applications of microbial interventions in human subjects with cachexia. Firstly, although microbiome analyses revealed a significant shift in microbiome composition following allogenic FMT, a specific microbe or group of microbes mediating the beneficial oncological outcomes in the allogenic group were not identified. Is a healthy obese subject the ideal donor for FMT to treat cancer cachexia? An alternative mechanism could entail the administration of microbes isolated from stool of successfully treated patients for cachexia. This could arguably reflect the compositional changes in the gut microbiome indicative of a responding host to anti-cachexia therapy. The microbiome in an obese individual could also differ significantly from those of non-obese individuals and can induce weight gain or weight loss dependent on a variety of environmental and host biologic factors[26]. The uniqueness of the PANCAX-1 cohort lies in the fact that all subjects received enteral feeding as their primary source of nutrition thereby representing a homogeneous and internally controlled population for microbiome and metabolomics analyses. The finding that *Veillonella* was a microbe of interest with increased abundance over time with enteral feeding and was associated with weight stability in cachectic patients with advanced PDAC receiving enteral feeding provides an innovative opportunity to explore microbial interventional strategies for cachexia with this organism.

However, individual microbes may not be sufficient to elect pro- or anti-cachexia effects alone. Animal models have demonstrated that a series of functional and structural changes occur in the gut bacterial population during the development of cachexia[27]. Microbial dysbiosis has shown to play a role in shaping the gut microbiome and pancreatic tumorigenesis as well[28]. We showed that weight stabilizing, cachexia therapy through enteral feeding was associated with multiple taxonomic shifts including increased abundance of the *Veillonella* genus (P = 0.015) and *Actinomyces* genus (P = 0.039) and decreased abundance of the *Bacteroides* genus (P = 0.015) and *Butyricicoccus* genus (P = 0.039) (Table 3). In this sense, it would be prudent for future studies to evaluate the impact of microbial dysbiosis on cachexia, with emphasis on community microbes that altogether contribute to anti- or pro-cachexia effects in microbial interventional strategies for cachexia.

Lastly, it would be important to consider that microorganisms themselves may not be the key constituent for developing therapies against cachexia. Instead, the active metabolites of the gut microbiota may be just as (if not more) important in contributing to anti- or pro-cachexia effects. Here, studies have shown that branched-chain amino acids, LPS, polyamines, and metabolites of other biosynthetic pathways have correlated with altered microbial flora, tumorigenesis, and development of cachexia across animal models[28,29]. Therefore, the logical next step in addition to exploring the potential of *Veillonella* as a microbial intervention in the treatment of cachexia would be for metabolomics to profile the active metabolite(s) of this microorganism and microbial communities associated with weight stabilization on cachexia therapy. The impact of these metabolites as a mechanism to address the cachexia syndrome could then be formally evaluated in preclinical models [30].

CONCLUSION

Cachexia represents a multifactorial syndrome of weight loss, muscle wasting, and systemic inflammation that is pervasive across multiple advanced disease states. Using PDAC as a model, we identified a unique relationship between the gut microbiome and treatment of cachexia in a prospective cohort of advanced PDAC subjects treated with enteral feeding. Specifically, an increased abundance in the bacterial genus *Veillonella* was observed over time in stool samples of cachectic subjects effectively treated with weight-stabilizing intervention through 12 wk of enteral feeding. Our findings are hypothesis-generating and add to an exciting body of evidence suggesting a potential role for microbial-based interventions for cachexia. Future clinical translation of microbial modulation to mitigate cachexia will need to consider the role of microbial dysbiosis and microbial-derived metabolites in cachexia as well.

FOOTNOTES

Author contributions: Hendifar A and Gong J conceptualized the manuscript; Akinsola R, Muranaka H, Thomassian S, Moshayedi N, Yang J and Jacobs J analyzed the data; all authors have read and approve the final manuscript.

Supported by UCLA Clinical and Translational Science Institute UL1TR001881 Award.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Gao CC
L-Editor: A
P-Editor: Gao CC

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