STUDY PROTOCOL

official title:

Improving Sarcopenia During Cancer Chemotherapy

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Research Purpose:

In recent years, sarcopenia has become an important issue. According to statistical data from the literature, the prevalence of sarcopenia ranges from 3.9% to 7.3%, and it increases annually due to population aging. Elderly patients and cancer patients often suffer from multiple comorbidities, physical and cognitive impairments, and malnutrition. Elderly patients with cancer are more prone to significant muscle loss leading to sarcopenia during chemotherapy, which results in poor treatment tolerance, lower quality of life, increased mortality rates, decreased disease-free survival rates, and prolonged hospital stays (Pamoukdjian et al., 2017; Marhold et al., 2020; G. Colloca et al., 2018; NIPP et al., 2017; Ryan et al., 2016).By collaborating with a multidisciplinary professional team, providing high-protein nutritional interventions to cancer patients in the early stages of sarcopenia can help reduce muscle loss. This approach can mitigate the disability, cancer-related fatigue, and mortality caused by sarcopenia in cancer patients, and improve their quality of life.

Project Summary:

Background:With the rapid aging of the global population and the increasing number of cancer cases, the health issues of the elderly are gaining attention. According to the Ministry of the Interior, as of 2020, individuals aged 65 and above constitute 16.1% of the total population, indicating a move towards a "super-aged society." Cancer is the leading cause of death in Taiwan, with the 2018 Cancer Registry Annual Report recording 116,131 new cancer cases. The physiological and functional decline associated with aging reduces daily activities, leading to malnutrition and disease-induced frailty, which in turn causes muscle atrophy, decreased muscle strength, slower walking speed, and balance problems, ultimately resulting in disability. This age-related disability imposes significant economic, medical, and caregiving burdens on society. Literature indicates that 5-13% of elderly cancer patients aged 60-70 and above suffer from sarcopenia. Exercise and nutrition are effective and highly autonomous interventions for improving sarcopenia.

Objective:

To evaluate the benefits of implementing a high-protein nutrition program during cancer chemotherapy and to explore the effectiveness of nutritional interventions in improving sarcopenia in cancer patients.
Methods:
Cancer patients aged 40 and above who meet the criteria for early-stage sarcopenia will receive an 8-week high-protein nutritional intervention with the ETHANWELL BALANCED nutritional formula. Muscle strength and quality of life will be assessed. Paired sample tests will be used for statistical data analysis to investigate whether there are differences in the degree of sarcopenia among participants following the ETHANWELL BALANCED nutritional formula intervention。

Inclusion and Exclusion Criteria:

Inclusion Criteria:

1. Age 40 and above.
2. Patients receiving chemotherapy or expected to undergo thoracic surgery (stage I~IV)
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and SARC-F score ≥ 4
4. Grip strength: <28kg for males and <18kg for females.
5. Conscious and able to communicate.

Exclusion Criteria:

1. Central nervous system disorders and chronic kidney failure.

2. Mental illness or inability to cooperate.
3. Expected survival period less than 3 months.
4. Gastrointestinal dysfunction—patients who have undergone gastric resection surgery or have intestinal obstruction.
5. Heart failure—NYHA class IV.
6. Uncontrollable infection diagnosed by a physician.
7. Poorly controlled diabetes diagnosed by a physician.
8. End-stage renal disease—requiring hemodialysis or peritoneal dialysis.
9. Liver cirrhosis with severe ascites.

Research Method:

A pre-post-test research design will be employed to investigate the effects of high-protein nutritional intervention on improving muscle strength, balance, nutrition, and quality of life in cancer patients with sarcopenia. Recruitment will be conducted in the thoracic ward or outpatient department of our hospital, with participants being allocated to either the experimental group or the control group.

Recruitment will involve posting posters in the ward or outpatient department and researchers visiting these areas to recruit participants. Participants will be orally briefed about the trial and will provide informed consent by signing a consent form. Research assistants will then conduct grip strength tests using an electronic dynamometer, and only those with grip strength below 28kg for males and below 18kg for females will be included in the trial.

Participants will be randomly assigned to either the experimental group or the control group in a 2:1 ratio, with 34 participants in the experimental group and 17 participants in the control group. The control group will receive 12 cans of ETHANWELL BALANCED nutritional formula free of charge upon completion of the study. Researchers will conduct pre-intervention assessments (grip strength test) and fill out the Fatigue Improvement and Quality of Life Scale, explaining the filling method and timing.

Researchers will provide nutritional education and free high-quality protein nutritional products (ETHANWELL® BALANCED nutritional formula), provided by Ethan Nutraceutical Co.,Ltd . Each serving of the ETHANWELL® BALANCED nutritional formula provides 250 kcal of energy, 13.5 grams of protein (6.75 grams of whey protein and 2740 mg of BCAAs), and 166.953 mg of patented POLYCAN® black yeast fermentation product (β-glucan 20.03 mg). It is consumed by mixing one serving with 220 ml of water below 40°C. Participants in the experimental group will consume 3 servings of the ETHANWELL® BALANCED nutritional formula per day, while the control group will receive standard treatment. The control group and maintained conventional treatment. And you need to perform five movements of elastic band training on your own, (Action 1. Lift up and press down, Movement 2. Straight arm lift, Movement 3. Seated rowing, Movement 4. Squat, Movement 5. Sitting leg raise, each movement is a group of 10 times) three groups each time, three times a week. Both groups of patients will sign consent forms and undergo assessments before intervention (pre-test), at 1 week (mid-test), 2 weeks (mid-test), 4 weeks (mid-test), 8 weeks (mid-test), and 12 weeks (post-test) of nutritional intervention, including questionnaire completion and physiological measurements. Data collected will include mid-arm circumference, muscle strength, fatigue, quality of life, and blood test reports.

The experimental group will receive at least one nutritional consultation via telephone from researchers each week. In addition to conventional treatment and high-protein nutrition intervention, the experimental group also required subjects to perform five movements of elastic band training on their own (movement 1: push up and press down, movement 2: straight arm lift, movement 3: seated rowing, movement 4: squat, movement 5: seated leg raise, each movement is 10 times in one group) three groups each time, three times a week. Subjects can refer to the elastic band exercise teaching。https://youtu.be/ukO5bkiVXEU。

Research has demonstrated that one way to increase muscle protein synthesis is to supplement with leucine in the diet. Leucine is one of the branched-chain amino acids (BCAAs), which include leucine, isoleucine, and valine. Among them, leucine can only be obtained from the diet in animals and cannot be synthesized endogenously. Its initial metabolism occurs in skeletal muscle rather than in the liver. BCAAs constitute approximately 35% of the essential amino acids in most mammals. [3]， The functional groups R of all three BCAAs are branched, small, and hydrophobic, making them key components of most proteins.[4]，Therefore, these three branched-chain amino acids are almost always ingested and metabolized together.[5]，There is abundant clinical evidence demonstrating that regulating protein turnover in skeletal muscle can be achieved by reducing protein degradation and increasing protein synthesis.[2]，Supplementing with BCAAs can increase the rate of intramuscular protein synthesis and improve protein synthesis in muscles.[1, 2, 6]。

Beta-glucan is a dietary fiber composed of D-glucose monomers or polysaccharides, primarily linked by β-1,3/1,6-glucan connections, purified from Aureobasidium pullulans SM-2001 (EAP).[7, 8]， It also includes amino acids, monounsaturated fatty acids, or polyunsaturated fatty acids (such as linoleic acid and linolenic acid), and polysaccharides.[9]，The β-1,3/1,6-glucan is derived from the cell walls of natural bacteria, fungi, algae, and higher plants (such as grains).[7]。Beta-glucan can be enzymatically extracted from the cell walls of yeast, fungi, seaweed, or cereal seeds, and it can modulate various in vivo and in vitro activities. These specific components confer beta-glucan with anti-tumor, anti-inflammatory, anti-obesity, anti-allergic properties, and immune-regulating activities. Research has found that EAP can improve muscle loss in elderly individuals and enhance muscle function.[8]。In animal experiments, it was found that EAP effectively inhibited dexamethasone-induced sarcopenia in mice.[10]；Another study indicated that EAP exhibited efficacy in exerting anti-osteoporotic effects in rats undergoing ovariectomy. [9]

Assessment tools:

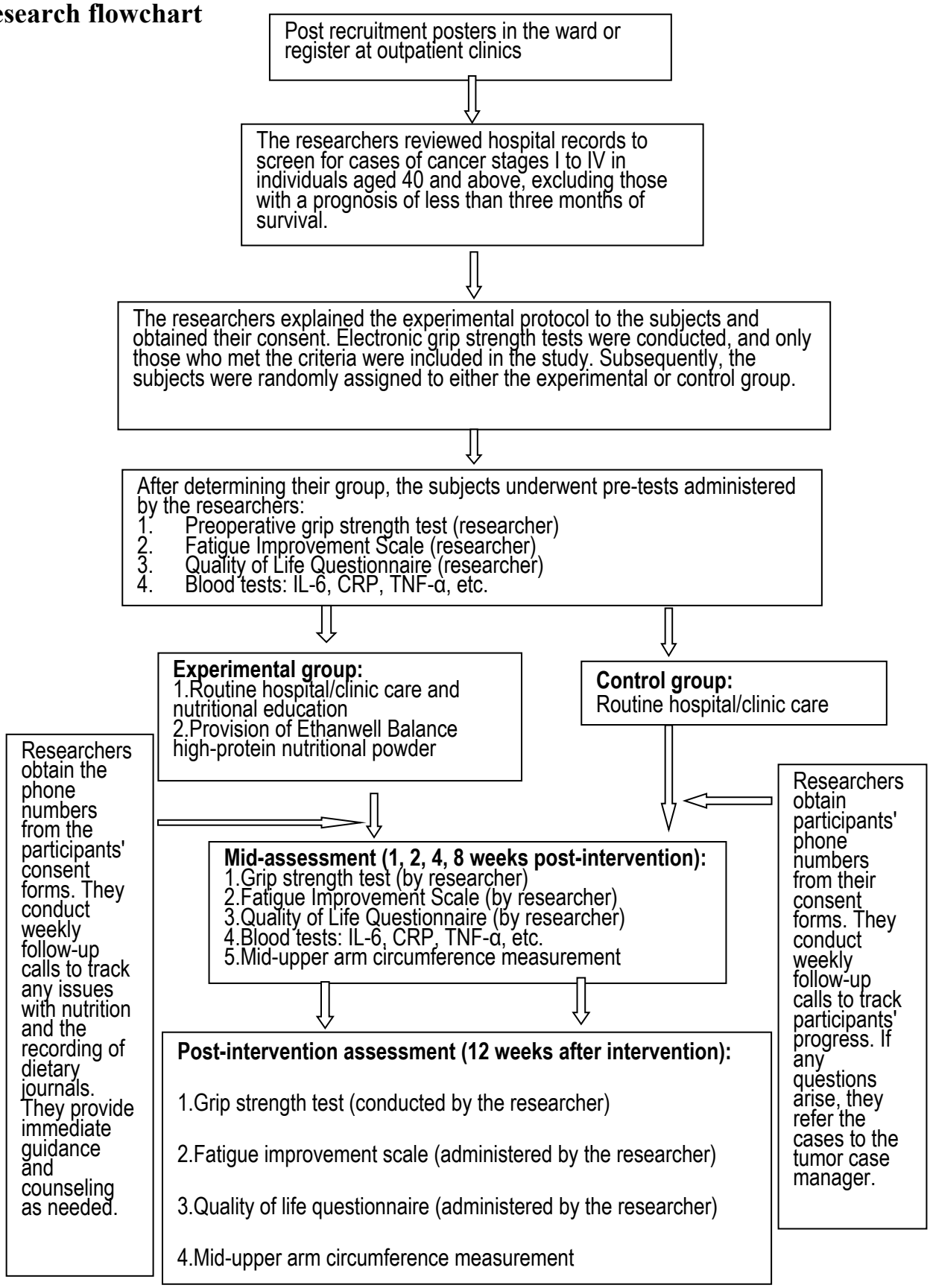
conducted before and after the intervention include:

1. Preoperative hand grip test (HGT)
2. Brief Fatigue Inventory - Taiwanese version (BFI-T)
3. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC)
4. Blood tests: IL-6, CRP, TNF-α
5. Mid-upper arm circumference measurement (MUAC)

Sample Size

The required sample size for this study was determined using statistical software Prism 6. To achieve statistical significance, Prism 6 software estimated that the experimental group would require 34 participants, and the control group would require 17 participants, totaling 51 participants. The researchers also estimated that approximately 10% of participants might withdraw from the study prematurely. Therefore, the study aims to recruit 10% more participants than the required sample size. It is estimated that there will be 38 participants in the experimental group and 19 participants in the control group, totaling 57 participants meeting the criteria.

Research flowchart



Period	**Screening**	**Treatment** Baseline				**Follow-up**
Visit	V0	V1	V2	V3	V4	V5
Days	- 14~0	0	14± 3	28± 3	56± 7	84± 7
Informed Consent Form Signed	*					
Inclusion/Exclusion criteria evaluation	*	*				
Demographics	*					
Medical/Surgical History	*					
ECOG	*					
SARC-F	*					
hand-grip test[5]	*	*	*	*	*	*
mid-upper arm circumference measurement[6]		*	*	*	*	*
Body weight[1]		*	*	*	*	*
Physical examination		*	*	*	*	*
Vital signs		*	*	*	*	*
Laboratory Tests						
Albumin		*		*	*	*
Pre-albumin		*		*	*	*
BUN		*		*	*	*
Creatinin		*		*	*	*
Aspartate aminotranferase (AST) (GOT)		*		*	*	*
Alanine aminotransferase (ALT) (GPT)		*		*	*	*
Cholesterol		*		*	*	*
Triglyceride		*		*	*	*
Fasting Glucose		*		*	*	*
Ca, P, Mg[2]		*		*	*	
Uric Acid[2]		*		*	*	
IL-6[3]		*		*	*	
CRP		*		*	*	
TNF-α[3]		*		*	*	
Randomization		*				
ETHANWELL BALANCED		*	*	*	*	
Diary Card[4]		*	*	*	*	*
BFI-T		*	*	*	*	*
EORTC		*	*	*	*	*
Concomitant Medication		*	*	*	*	*
Adverse Events		*	*	*	*	*

1. Body weight will be recorded by CRC using same platform scale.

2 If abnormal value is found, the subject will be followed on next visit.

3 IL-6/ TNF-αwill be examined for the interval of two months not otherwise the subject withdraw.

4 Including nutritional supplement record.
5 Hand-grip test will be recorded by CRC using same hand dynamometer.
6. mid-upper arm circumference measurement will be recorded by CRC using same tape.

Statistical analysis:
Statistical analysis was performed using Prism 6 software for data processing and analysis. The basic demographics of the participants were presented using descriptive statistics. Considering the limited sample size, the Wilcoxon Signed-Rank Test was utilized to compare the assessment results before and after the intervention. All values were presented as mean ± standard deviation, and statistical significance was defined as $p < 0.05$.

Literature review:
According to the Population Statistics Report of 2020 in Taiwan, the population aged 65 and over accounted for 16.1% of the total population. It is projected to increase to 95.7% by 2060. The latest data from the Cancer Registry Annual Report in 2018 showed that there were 116,131 cases of cancer diagnosed in 2017, with an average age of 65 years. Cancer has been the leading cause of death in Taiwan for several years. Marzetti (2016) conducted a literature review suggesting that 30 minutes of resistance training combined with nutritional and vitamin D interventions for elderly individuals can reduce the risks of cardiovascular diseases, diabetes, stroke, depression, and falls. Loss of muscle mass due to cancer treatment leads to cancer-related sarcopenia, which makes it difficult for elderly cancer patients to tolerate treatment, resulting in poor prognosis, decreased quality of life, and reduced survival rates (Bozzetti, 2020; Davis et al., 2018).

Sarcopenia, derived from the Greek roots "sarx" (flesh) and "penia" (deficiency), refers to the loss of muscle mass with aging (Colloca et al., 2019; Bozzetti, 2020). Zheng et al. (2016) defined sarcopenia as a complex syndrome caused by multiple pathogenic factors, including chronic diseases, hormonal changes, inflammation, insulin resistance, and malnutrition. Sarcopenia in older adults leads to physical function deterioration, impaired cardiorespiratory function, metabolic slowing, falls, disability, increased healthcare costs, and reduced quality of life (Davis et al., 2019; Stewart et al., 2019; Marhold et al., 2020). The comprehensive symptoms and disability caused by sarcopenia cannot be explained by a single disease or its pathology and require interdisciplinary collaboration to provide interventions to improve sarcopenia (Marhold et al., 2020).

According to the consensus of the Asian Working Group on Sarcopenia in 2019, diagnostic criteria for sarcopenia include: dual-energy X-ray absorptiometry (DXA) measurement, with values less than 7.0 kg/m2 for men and less than 5.4 kg/m2 for women; bioelectrical impedance analysis (BIA), with values less than 7.0 kg/m2 for men and less than 5.7 kg/m2 for women; decreased grip strength, less than 28 kg for men and less than 18 kg for women; and reduced gait speed (less than 0.8 m/s). Computed tomography can detect muscle mass loss in cancer patients during the chemotherapy period (Oflazoglu et al., 2019). Sarcopenia can be classified into pre-sarcopenia, sarcopenia, and severe sarcopenia based on severity, with pre-sarcopenia indicating the presence of slow walking or reduced grip strength without muscle mass reduction.

Domestic studies have shown that the prevalence of sarcopenia in men ranges from 4.0% to 23.6%, and in women, from 0.4% to 18.6% (Han, 2016; Chen et al., 2020). Studies on chemotherapy-induced sarcopenia have indicated associations with age ≥65 years, BMI < 25, Nutritional Risk Screening (NRS) 2002 score < 3. Sarcopenia occurred in 14.5% of patients during chemotherapy, 21.4% at the third month of chemotherapy, and 23% at six months (Oflazoglu et al., 2019). Approximately 35% of cancer patients have inadequate nutritional intake, leading to malnutrition-related increased mortality rates by 20% (Ryan et al., 2016). Therefore, it is recommended that cancer patients maintain a daily intake of 25-30 Kcal/kg/day and consume at least 1-1.5 g/kg of protein per day to reduce chemotherapy-induced muscle mass loss (Ryan et al., 2016; Prado et al., 2020).

Currently, research in Taiwan on sarcopenia primarily focuses on chronic diseases, with fewer studies investigating cancer-related sarcopenia. Cancer is the leading cause of death in Taiwan, with increasing incidence rates each year, emphasizing the importance of cancer cure and survival rates. Appropriate nutritional interventions for sarcopenia can reduce disability and cancer-related fatigue, improve quality of life, and increase survival rates in cancer patients.

References:

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