RESEARCH ARTICLE

Editorial Process: Submission:09/13/2023 Acceptance:02/22/2024

Dynamic Changes in Body Composition and Protein Intake in Epithelial Ovarian Cancer Patients Undergoing Chemotherapy: A Preliminary Study

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Abstract

Background: Ovarian cancer patients often face poor nutritional status, with body composition (BC) serving as a significant prognostic indicator. Skeletal muscle mass (SMM) and fat-free mass (FFM) are crucial predictors of both survival and hospitalization duration. Increasing protein intake has been linked to improvements in SMM and FFM. **Objective:** This study aimed to document the alterations in BC parameters among ovarian cancer patients undergoing chemotherapy and correlate these changes with their nutrient intake. **Methods:** Twelve female patients with stage III ovarian cancer who received first-line chemotherapy were categorized based on their body mass indices (BMI). BC parameters were assessed using an 8-point bioelectrical impedance analysis with a frequency of 50 Hz-60 Hz and measurement impedance range of 10 Ω-1000 Ω. Nutrient intake (energy, protein, fat, and carbohydrate) was assessed before (T0), during the 3rd (T3), and 6th cycle of chemotherapy (T6) through 24-hour food recall. **Results:** Significant increases in body weight (BW)were observed in the underweight group (from 40.9 to 46.8 kg, p=0.001), concomitant with enhancements in all BC parameters. While changes were noted in SMM, they were not statistically significant (p=0.105). Among the underweight group, a protein intake above 1.2 g/kg BW led to an uptrend trend in SMM. Conversely, FFM in overweight/obese patients decreased significantly (from 37.6 to 36.4 kg, p=0.005) due to a a reduction in body water. Throughout chemotherapy, fat mass (FM), visceral fat (VAT), and phase angle (PhA) increased in all patient groups, reflecting heightened fat and carbohydrate intake. **Conclusion:** Among stage III ovarian cancer patients, BC undergoes dynamic changes dynamically during the course of chemotherapy, with more pronounced enhancements observed in FFM among underweight patients. Notably, improvements in PhA, SMM or FFM were particularly evident among underweight patients with a protein intake above 1.2 g/kg BW.

Keywords: Ovarian cancer- body compositional- nutritional intake

Asian Pac J Cancer Prev, **25 (2)**, 555-562

Introduction

Cancer is responsible for being the second highest contributor of death worldwide, with ovarian cancer as ranking among the most common cancers among women. In 2020, there were approximately 207,252 reported cases of ovarian cancer globally, making it the third most common gynecologic cancer [1, 2]. Specifically, in Indonesia, according to data from Globocan 2018, there are an estimated 13.310 new cases of ovarian cancer each year, with a high mortality rate [3, 4].

There are different types of ovarian cancer, with epithelial cancer being the most frequent, accounting for 90% of all ovarian cancer cases. The risk of developing epithelial cancer is influenced by factors such as age, lifestyle, family history, and reproductive history [5]. In cancer patients, including those with ovarian cancer, poor nutritional status plays a significant role and can impact prognosis. Body compositional parameters have been extensively studied as predictors of nutritional status in cancer patients [6]. Among the methods used to assess body composition, bioelectrical impedance analysis (BIA) is the most practical method. BIA allows for the evaluation of various body compartments, including fat mass (FM), fat-free mass (FFM), skeletal muscle mass (SMM), visceral adipose tissue (VAT), and body water (extracellular water/ECW, intracellular water/ICW, ECW/ICW ratio) [7]. It has been well documented that phase

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angle (PhA) is a good predictor of sarcopenia [8, 9], frailty [10, 11], and mortality [12, 13]. Skeletal muscle depletion, often described in sarcopenic patients, is a poor prognostic factor in cancer cachexia [14]. Low levels of FM and high FFM are better predictors of hospital stay than body weight alone [15].

Chemotherapy patients are at an increased risk developing malnutrition due to the potential weight loss associated with gastrointestinal symptoms [16, 17]. This weight loss during chemotherapy is primarily attributed to SMM loss, which is caused by an imbalance between protein synthesis and degradation, decreased protein intake, and increased pro-inflammatory activity [18]. An adequate protein intake is crucial for maintaining muscle mass and compensating for reduced muscle protein synthesis. Increasing protein intake is not only associated with an increase in muscle quantity, FFM and SMM [19, 20], but also with improvements in muscle quality, ECW/ICW ratio [21], and PhA [22].

While numerous studies have focused on the relationship between ovarian cancer and body composition, few have taken into account nutrient intake. Therefore, the current study aimed to investigate the dynamic changes in body composition among ovarian cancer patients undergoing chemotherapy, while also examining the influence of nutrient intake. Addressing this research gap is essential, given that nutritional intake plays a significant role in modulating body compositional turnover in various clinical conditions [23].

Materials and Methods

Participants

Twelve patients diagnosed with stage III epithelial ovarian cancer who underwent chemotherapy were recruited from January 2021 to April 2023 at Dharmais National Cancer Hospital and dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia. These patients underwent structured interviews using questionnaires and body compositional assessments at three time points: before chemotherapy (T0), after the 3rd chemotherapy (T3), and after the 6th chemotherapy (T6). Inclusion criteria for participants included being adult women between the ages of 30-65 years, scheduled for (neo)adjuvant first-line chemotherapy treatment for newly diagnosed ovarian cancer based on histopathology indicating pre-cachexia or cachexia, and possessing the ability and willingness to participate in the study while understanding the study's procedures. Written informed consent was obtained individually and participants with autoimmune disease, chronic liver disease, chronic renal disease, hypercalcemia, and refractory cachexia were excluded from this study.

This study is a part of the clinical trial titled 'Vitamin D and Pre-Cachexia and Cancer Cachexia in Epithelial Ovarian Cancer' (registered at ClinicalTrials.gov NCT04864431), and the ethical clearance was obtained from the institutional ethical committee prior to the commencement of the study (Dharmais National Cancer Hospital 011/KEPK/I/2020 and Faculty of Medicine University of Indonesia KET-1375/UN2.F1/ETIKPPM.00.02/2020).

Body Composition AnalysisBody composition parameters, including SMM, FFM, FM, VAT, ECW, ICW, ECW/IBW ratio, and PhA were measured using an 8-point bioelectrical impedance analysis (Seca mBCA-514, Germany). The analysis was performed at a power frequency of 50 Hz-60 Hz, with impedance readings taken from the right arm, left arm, right leg, left leg, right half and left half of the body, and the torso. The instrument used validated predictive equations for FM, FFM and ECW developed by Bosy-Westpal [24].

Nutrient Analysis

Data on energy, protein, carbohydrate, and fat intake data were collected at three-time points: one month before chemotherapy (T0), after the 3rd cycle of chemotherapy (T3), and after the 6^{th} cycle of chemotherapy (T6). Nutritional analysis was obtained from 24-hour food recalls and analyzed using Nutrisurvey 2007, which is a professional German nutrition software translated into English (EBISpro). Average protein and nutrient intake were calculated based on the average values from the three data points collected during chemotherapy.

Classification of Nutritional Status

BMI was calculated as weight in kilograms divided by the square of height in meters (weight/Ht2). For classification purposes, the World Health Organization Asia Pacific regions guidelines were used. BMI values below 18.5 kg/m² were classified as underweight, values between 18.5 and 22.9 kg/m² were considered normo-weight, and values equal to or greater than 23 kg/m² were classified as overweight/obese [25].

Sample size

The sample size calculation was based on a primary study with two-sided Z values ($Z\beta$=0.842 and $Z\alpha$=1.96), aiming for a power of 80% and significance level of 5%. In order to account for potential dropouts, we aimed for a final total sample size of 54 patients, including 10% dropouts rate. For this manuscript, we have reported the results from the first 12 patients who had completed all six cycles of chemotherapy.

Statistical analysis

Data analysis was performed using SPSS version 20 (SPSS software, IBM, USA). The Shapiro-Wilk test was utilized to assess data normality. If the data followed a normal distribution, they were presented as the mean and standard deviation (mean ± SD). If the data had an abnormal distribution, they were presented as the median with the minimum and maximum values.. To analyze trend changes in the body composition and nutrients intake variables at three-time points (T0, T3, T6), we used the Repeated Measures test or the Friedman test as appropriate. Additionally, we analyzed changes in BW before and after chemotherapy within the group using paired T-test.

Results

This study was conducted from January 2021 to April 2023, with follow-up extending through all 6th cycles of chemotherapy. Patients' characteristics are summarized in Table 1. The mean age of the patients was 49.5 years, ranging from 30 to 65 years. The majority of patients used birth control (8 out of 12 women), while the rest had never used birth control (4 out of 12 women). High-grade serous epithelial ovarian cancer was the most prevalent type among the patients (7 out of 12 women). According to the International Federation of Gynecology and Obstetrics (FIGO) staging, all patients were diagnosed with stage III ovarian cancer. BW showed a significant increase (p= 0.004) from 51.7 ± 10.3 kg at T0 to 54.5 ± 9.3 kg at T6.

Body composition

Throughout the course of chemotherapy, body compositional parameters (BW, FM, FFM, SMM, VAT, ICW, ECW, ECW/ICW ratio, and PhA) exhibited linear increases among underweight patients. Meanwhile, only VAT and FM displayed increments among normoweight and overweight/obese patients (Figure 1). This study also observed a continued improvement in PhA during chemotherapy, with values rising from 4.08° to 4.5° in underweight, 3.75° to 3.85° in normoweight group, and from 4.93° to 5.03° in overweight/obese group, with the most significant increase noted in the underweight category..

Nutritional Intake

Macronutrient intake pre-chemotherapy and during treatment are illustrated in Figure 2. Energy intake peaked at T3 across all patient categories, with a notable contribution from fat and carbohydrate, especially reaching a maximum among underweight patients. On the contrary, protein and fat intake decreased at T6 in all patient categories.

Table 1. Characteristics of Patients

Variable (n=12)	Result
Age (year)	49.8 (8.7)
Birth control method	
Contraceptive injection	4 (33.3%)
Combination (pill, injection, IUD)	2 (16.7%)
Oral contraceptive pill	1 (8.3%)
Intrauterine device	1 (8.3%)
Never been used birth control	4 (33.3%)
Type of epithelial ovarian cancer	
Serous high grade	7 (58.3%)
Clear cell	2 (16.7%)
Endometrioid	2 (16.7%)
Mucinosum	1 (8.3%)
Cancer stage	
3A	2 (16.7%)
3B	2 (16.7%)
3C	8 (66.7%)
Body weight T0 (kg)	51.7 (10.3)
Body weight T3 (kg)	53.4 ±10 kg
Body weight T6 (kg)	54.5 (9.3)
Body mass index T0 (kg/m^2)	21.7 ± 4.4
Body mass index T6 (kg/m^2)	22.9 ± 4.5

Discussion

Many medical and nutrition literature have shown that BW and lean body mass are important determinants of survival in ovarian cancer patients. Maintaining these factors during hospitalization has been shown to reduce both morbidity and mortality rates [15]. Ovarian cancer patients, due to various pathophysiological and therapeutic regimens, are posed to high risk of malnutrition and protein deficiency, which can significantly affect their chances of survival. This current study captures the opportunity to monitor the sequential changes in body composition and nutrient intake alongside standard cancer care practices during chemotherapy for stage III ovarian cancer patients.

Throughout the chemotherapy process, BW tended to increase, correlating with an increase in body fat. A study conducted by Backes et al., revealed that BW initially decreased before surgery but began to increase post-chemotherapy [26]. These fluctuations in body weight were found to be closely associated with overall survival and progression-free survival rates in ovarian cancer patients [27]. Despite the observed weight gain in this study, the BMI of the patients remained within the normal range following chemotherapy. The weight gain was due to increased energy and macronutrient intake, particularly from T0 to T3, with the increased intake possibly stemming from reduced edema and ascites during chemotherapy, which could potentially enhance the subjects' appetite.

This study documented an increase in FM and VAT levels throughout the chemotherapy period. A study from Tayyem et al., found that higher levels of VAT were associated with increased energy consumption from fats and carbohydrates [28]. Similarly, in line with this research, all subjects in the study saw an increase in VAT over the course of chemotherapy, with overweight and obese individuals experiencing the most significant rise due to their higher fat intake, which increased from 24.5% to 38.25% of their total daily energy intake. Even though most of the patients adhered to the recommended dietary guidelines in terms of fat consumption, the predominant source of fats for the majority of Indonesians surveyed was saturated derived from fried protein sources like fish, egg, chicken, meat, tofu, tempeh, and peanut. A study by Sartika RA revealed that a high intake of trans and saturated fats from fried foods among both rural and urban populations in Indonesia heightened the risk of chronic degenerative diseases [29].

The dietary landscape in the Indonesian population has undergone a notable shift, as reported by Lipoeto et al. in 2004, with a decrease in carbohydrate consumption and a corresponding in protein and fat intake [30]. This transition was observed to have implications for health outcomes. In their meta-analysis, Qiu W et al., reported

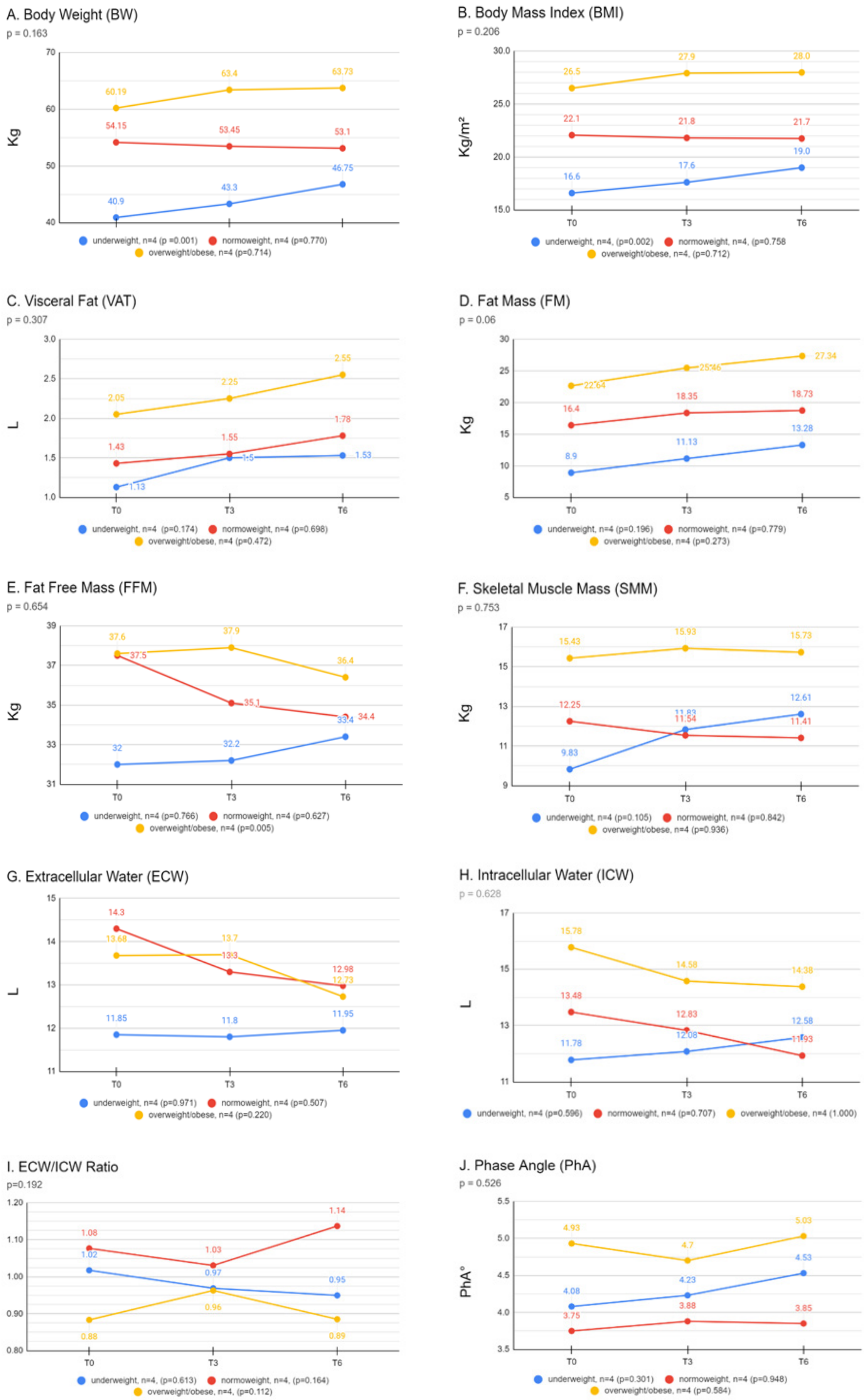

Figure 1. Body Compositional Parameters ((A) BW, (B) BMI, (C) VAT, (D) FM, (E) FFM, (F) SMM, (G) ICW, (H) ECW, (I) ECW/ICW, (J) PhA)changes before chemotherapy (T0), after 3rd chemotherapy (T3) and last chemotherapy (T6).

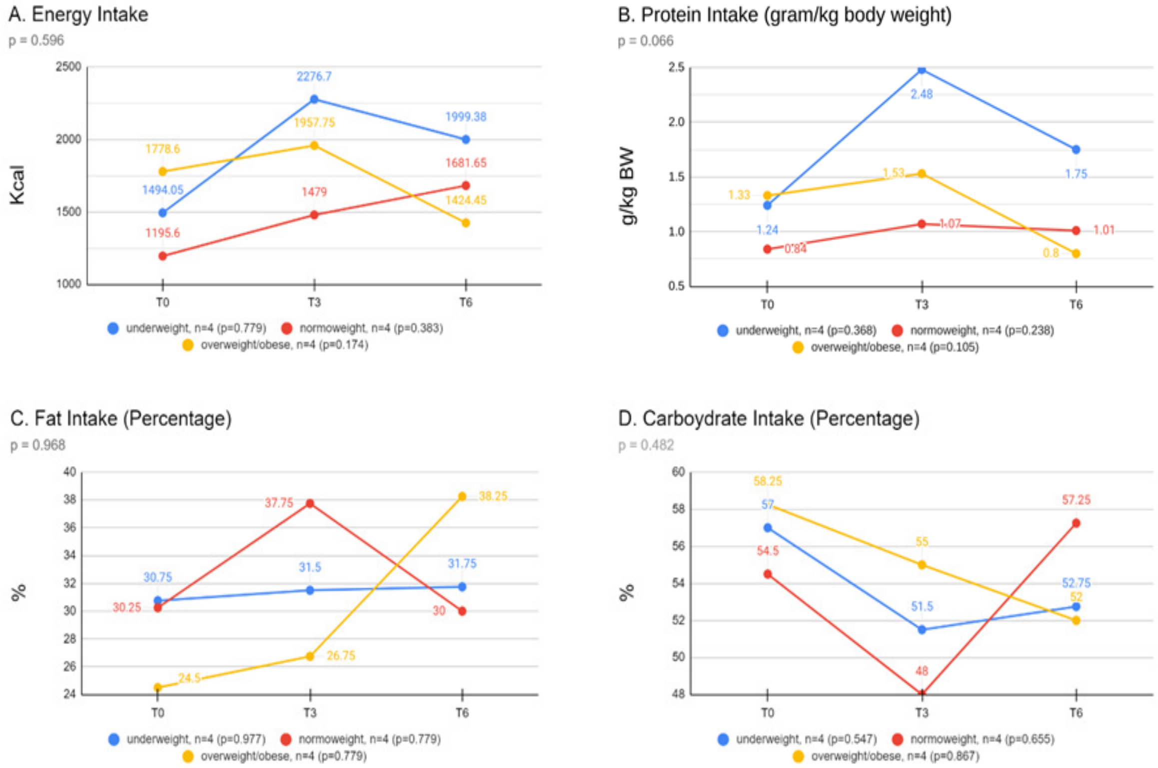

Figure 2. Nutritional Intake ((A) Energy, (B) Protein, (C) Fat, (D) Carbohydrate) changes before chemotherapy (T0) and during chemotherapy (T3,T6).

that a high intake of total, saturated, and trans-fat increased ovarian cancer risk, with saturated fats specifically linked to higher risks of serous and endometrioid ovarian cancer [31]. In our study, we also found that besides fats, a high carbohydrate intake may contribute to an increase in VAT, particularly evident in normoweight subjects. This elevated carbohydrate intake predominantly stemmed from sources such as rice, fruits, vegetables, processed flour, and sugar-sweetened beverages.

Body compositional parameters have garnered significant attention in many medical nutrition literatures. Metrics like ICW, ICW/ECW ratio and PhA are recognized for their role in maintaining cell wall integrity and cellular health. Studies like those by Yoon et al. [32] and Marques et al. [33] have demonstrated how these parameters can help differentiate between normal and cancerous cells during various stages of oncogenic transformation [32, 33]. The current study showed that fluctuations in ICW levels among different patient groups. Overweight and normoweight patients showed a tendency towards decreased ICW, while underweight patients exhibited an increase. Chemotherapy, while crucial for treating cancer, can lead to dehydration and systemic strain on the body, which can impact parameters like ICW . Lower ICW levels, particularly in females, may be attributed to stress and inflammation, leading to compromised cellular integrity and muscle loss [32]. The ECW/ICW ratio plays a role in maintaining cellular functions such as osmotic pressure and ion concentration gradients. This ratio is inversely related to PhA, which itself is a significant determinant of cellular health. Gonzalez et al. [34] highlighted the importance of this ratio in understanding cellular dynamics [34]. PhA, reflecting cell membrane integrity and function, serves as a vital prognostic tool in various medical conditions. It tends to increases with higher BMI, corresponding to increased muscle and fat cell numbers. The enhancement of nutritional status is often accompanied by an increase in PhA levels, as observed in studies like the one by Norman et al. in 2012 [35].

SMM improvement was more prominent among underweight patients during the course of chemotherapy, which might be due to an increase in protein intake compared to the normoweight and overweight patients. This observation was supported by the progressive increase in of PhA values. Capitao et al. [36] highlighted the significance of protein intake, suggesting that levels above 1.4 g/kg BW are necessary for muscle maintenance, while levels below 1.2 g/kgBW are associated with muscle wasting [36]. Moreover, studies revealed that a protein intake more than 1.2 g/kgBW led to notable improvements in muscle strength and an increased in FFM [37, 38], with a daily intake of 1.3 g/kgBW being linked to a reduction in VAT in functionally limited adults [39]. The enhancement of SMM was predominantly observed in underweight patients whose protein intake fell within the recommended range of 1.2-2.5 g/kg BW. However, this study did not measure nitrogen balance as an indicator of protein adequacy; instead, it only relied on patients' dietary intake. In addition, the phenomenon of increased nutrient intake post-chemotherapy, also known as food hedonism, may have played a role in the significant rise in nutrient consumption. . In a study on breast cancer patients undergoing chemotherapy, an overall increase in appetite from the beginning to the end of the chemotherapy cycle was reported [40]. Although this phenomenon seemed to be aligned with this study, especially from T0 to T3, variations in chemotherapy regimens between ovarian and breast cancer treatments should be noted. Ascites per se contributes to the reduction in food intake, with procedures like ascites tapping or paracentesis linked to changes in fasting gastric volumes [41], concentrations of hormones like ghrelin and leptin [42], and patient discomfort symptoms such as dyspnea, abdominal tenderness and pain, nausea, and anorexia [41]. Ascites is a common occurrence in ovarian cancer patients, and tapping or draining it has been associated with an immediate improvement in caloric intake [41]. The increase in SMM was not only due to protein intake, but also due to increased physical activity. Skeletal muscle depletion during cancer treatment can occur due to various reasons, such as anorexia, low nutritional intake, hormonal changes, and an increased in inflammatory cytokines levels, potentially leading to sarcopenia and cachexia [43, 44]. Post-chemotherapy, many patients often complained of fatigue, contributing to a slight decline in SMM among normoweight groups. Chemotherapy exerts a negative impact on physical function by directly impairing muscle function through muscle wasting, triggering the release of pro-inflammatory cytokines, and inducing oxidative stress and tissue injury [45]. The cytotoxic agents present in chemotherapy can also stimulate the production of endogenous glucocorticoids, which detrimentally affect skeletal muscle by breaking down contractile proteins, mobilizing amino acids, locally affecting the expression of insulin-like growth factor-I and myostatin, and limiting muscle protein synthesis [46, 47]. The administration of chemotherapy elevates the risk of sarcopenia by inducing weight reduction, primarily caused by SMM loss and changes in water content as opposed to FM changes [48]. Nutritional intake, encompassing energy, protein, and fat, primarily increased from T0 to T3, with a trend towards a decreased intake observed at T6. In this study, all patients underwent first-line chemotherapy using carboplatin-paclitaxel. Chemotherapy, a commonly employed treatment modality, can lead to various nutritional alterations. These alterations can be associated with the toxicity of the treatment, as conventional chemotherapy lack specificity and can harm normal cells. As a result, chemotherapy can cause adverse nutritional effects, such as nausea, vomiting, diarrhea, anorexia, and weight loss [16]. According to a study by Marinho et al. [40], it was found that nausea reached its peak intensity during the intermediate and final chemotherapy cycles, with the most severe episodes occurring towards the end of the treatment regimen [40]. Patients in this study experienced nausea and anorexia in the initial two weeks after chemotherapy, while their appetite gradually recovered in the weeks that followed the completion of chemotherapy. The discrepancy between BW gain and decreased intake analysis, mainly at T6, can be attributed to the timing variance in body composition assessments.

In conclusion, throughout the course of chemotherapy in stage III ovarian cancer patients, there were dynamic changes in body composition. The improvement of FFM was more noticeable in underweight patients compared to their norm weight and overweight/obese counterparts. In present study, improvements in PhA, SMM, or FFM were particularly distinct among underweight patients who maintained a protein intake above 1.2 g/kg BW.

Author Contribution Statement

NRM, A, FN, FW contributed for conception and design. A, JS, AW were involved in provision of study materials or patients. NRM, AK, JS, AW had collected and assembled the data. NRM, A, AK performed data analysis and interpretation. All authors wrote and finalized the manuscript.

Acknowledgements

Funding Statement

Vitamin D supplementation was supported by Kalbe Pharmaceutical. This study was funded by first author.

It is a part of an approved doctoral thesis of first author (NRM).

Ethical Declaration

All procedures conducted in this study were under the ethical standards of the Institutional Review Board of the Dharmais National Cancer Hospital and Faculty of Medicine University of Indonesia. Ethical approval was performed in accordance with ICH-GCP standard procedures.

Study Registration

This study is registered in ClinicalTrials.gov NCT04864431.

Conflict of Interest

All authors declare no conflicts of interest.

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