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Evaluation of Irisin Levels in Cancer Anorexia Cachexia Syndrome and the Relationship between Nutrition Education and Quality of Life

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ABSTRACT

This study examines the effects of nutritional education given to individuals diagnosed with cancer anorexia cachexia syndrome (CACS) on serum irisin levels, cachectic factors, proinflammatory cytokines, quality of life scale results, and anthropometric and routine biochemical parameters. Forty-one patients diagnosed with CACS were randomly divided into two groups, experimental and control. Nutrition education was given for 12 weeks to the patients in the experimental group (n=23), while those in the control group (n=18) were not subjected to any intervention. All participants' serum irisin, proteolysis-inducing factor, zinc-α-2 glycoprotein, interleukin-6, tumor necrosis factor-α, routine biochemical parameters, and body weight were measured at the beginning and end of the study. The patients were also evaluated in terms of 24-hour recall food intake, body mass index, and quality of life scale values. No significant differences were observed at baseline between the experimental and control groups in terms of quality of life scale values, cachectic factors, inflammatory cytokines, or irisin levels. However, at the end of the study, hemoglobin levels were higher in the experimental group than in the control group. Energy and nutrient intakes were similar between the groups initially, but were higher in the experimental group at the end of the study. Nutrition education did not significantly alter the quality of life scale, BMI, or biochemical parameters. However, education yielded the expected increase in nutrient intake in the experimental group.

Keywords: CACS, QOL, Cachectic factors, Irisin, Inflammatory cytokines.

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Introduction

Cancer is the uncontrolled proliferation of a group of cells in the body. Side-effects related to cancer and treatments thereof are among the issues that particularly challenge patients and physicians [1]. The second main cause of cancer-related deaths after sepsis (multiple organ failure due to infection), cachexia progresses with weight loss and cannot be reversed using normal nutritional support [2]. Cancer cachexia is characterized by the co-occurrence of decreased energy intake and increased energy expenditure, leading to a negative energy balance. The primary contributors to reduced energy intake are loss of appetite (anorexia), dysphagia, pain, fatigue, and depression or anxiety. Cachectic cancer patients have a low tolerance for chemo- and radiation therapies and a low quality of life [3,4]. Recent studies have shown that cancer cachexia is associated with anorexia (loss of appetite), a condition known as cancer anorexia cachexia syndrome (CACS). Patients with CACS experience loss of appetite, along with involuntary weight loss, which reduces their quality of life. CACS is frequently seen in individuals with advanced disease, the occurrence of the syndrome depending on the type of cancer. Weight loss is observed before starting treatment in 50-85% of gastrointestinal, pancreatic, lung, and colorectal cancers. CACS is implicated in 20% of cancer-related deaths. However, cachexia is often considered unimportant and is frequently left untreated [5].

The etiology of CACS is multifactorial, and the biochemical mechanisms responsible have not yet been fully elucidated. In this process, proteolysis-inducing factor (PIF) and zinc-α-2 glycoprotein (ZAG), recognized cachectic factors, are released from tumor cells and cause muscle and fat atrophy. Tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, epidermal growth factor (EGF), transforming growth factor (TGF), and platelet-derived growth factor (PDGF) are proinflammatory cytokines associated with the development of cancer cachexia, although the search for biomarkers for the early diagnosis of cachexia continues. Irisin is a newly discovered adipocytokine known to exhibit anti-inflammatory, anti-diabetic, anti-apoptotic, and anti-obesity effects that cause weight loss [6,7]. Irisin levels have been measured in various types of cancer. However, no study to date has investigated whether irisin represents a cachectic factor in patients with CACS. In addition to traditional mortality and morbidity parameters, quality of life is an important factor

that should be taken into consideration when determining individuals' health levels. The Turkish-language version of the 36-item Short Form Survey (SF-36) is a tool that can be used in cancer research in Türkiye [8]. SF-36 was used to evaluate quality of life in CACS patients in the present study before and after nutrition education. This study set out to find answers to the following questions;

a) Is there any relationship between cachectic factors, pro-inflammatory cytokines, and irisin in serum in patients diagnosed with CACS?
b) can irisin represent a novel cachectic factor for patients diagnosed with CACS? And
c) can the provision of nutritional education for these patients provide quality survival in line with data obtained from the quality-of-life assessment scale?

Within the scope of this project, irisin, cachectic factors and cytokines were measured at the protein level in serum samples taken from 41 patients diagnosed with CACS using the using the enzyme linked immunosorbent assay (ELISA) method. Body weight, the amount of food consumed in the previous 24 hours, BMI (kg/m^2), routine biochemical tests, and quality of life values were evaluated at baseline and the 12th week for all patients, with and without nutrition education.

Materials and Methods

This prospective study was planned between December 2021 and December 2022. The sample collection time was extended by one year due to the COVID-19 pandemic.

Study Population

The study protocol was approved by the Ordu University (ODU) Clinical Research Ethics Committee (Decision No: 2021/184). This investigation involved 41 patients diagnosed with CACS. The patients were recruited from the Ordu University Training and Research Hospital General Surgery and Ordu State Hospital gastroenterology clinics.

Clinical findings of CACS

•> 6% weight loss in the previous six months, skeletal muscle loss (biceps and quadriceps),

• anorexia, weakness, fatigue, decreased movements and quality of life, decreases daily performance scores,

•increased acute phase response C-reactive protein (CRP), fibrinogen, and α-1 antitrypsin)

•decreases in serum proteins (albumin and total protein)

•anemia (a decrease in hemoglobin level)s, increased resting energy use, decreased lean body mass and body mass.

CACS should be consıdered and treated prompty ın the presence of these clinical findings in cancer patients. More importantly, malnutrition should be detected long before the patient reaches this condition, and screening should even be performed to identify patients at nutritional risk. Nutritional screening can be performed using the Nutrition Risk Screening (NRS-2002) scoring system [9]. Homogeneity of the study population is important, and every effort was made in this study to ensure that there were no significant differences between the groups in terms of age, gender, or BMI. Inclusion criteria were age over 18 years, similar age groups, and clinical findings of CACS being confirmed by a clinician. Exclusion criteria were age under 18, a history of any surgical procedure in the previous weeks, receipt of radiotherapy, chemotherapy, or drug therapy capable of significantly modulating metabolism and weight, diagnoses of different cancers, and having been previously followed-up in the outpatient clinic.

Patients who met the inclusion and exclusion criteria were followed-up in the general and gastroenterological surgery outpatient clinic. The research was explained, and those individuals willing to take part signed informed consent forms and received nutrition education from a nutrition and dietetics specialist for 12 weeks (three months). No intervention was performed on the patients in the control group during the study period.

Data Collection Tools Used in Assessing Nutritional Status

National risk screening (NRS-2002)

The NRS screening isntrument was used to assess the risk of malnutrition in the cancer patients enrolled in the trial. This evaluates the likelihood of developing undernutrition as well as the presence of undernutrition. The main screening, which inquires into nutritional status disorders (BMI and previous unplanned weight loss), and grades the severity of disease with its metabolic effects, is carried out if any of the four prescreening questions are answered affirmatively. A further point is added for patients aged 70 or older. A total score of 3 or higher indicates that the patient is at nutritional risk.

24-Hour food consumption record

The 24-hour dietary recall approach was used to determine food intake. A qualified dietitian interviewed the patients by telephone, asking them to recall their entire food and fluid intake on the previous day. The investigator investigated each patient's eating habits in detail. The number of units consumed was determined by describing quantities in household measures (such as pieces, slices, tea- or tablespoonfuls, cups, glasses, or portions), each of which corresponded to a specific weight. Dietary and nutrient intakes were than calculated using nutritional analysis software (BeBIS, Nutrition Information System, Version 8). The nutritional values included any additional oral nutritional supplements used, but did not include additional parenteral feeding.

Anthropometric Measurements

Body weight was measured at the beginning and end of the study, and BMI values were calculated in both groups using the formula "weight (kg)/height^2 (m^2)."

Nutrition Education

Nutrition education was given to 21 patients by a specialist dietician once a week for approximately 45 minutes over three months. Since it was difficult for patients to visit the hospital or other site where education could be given every week, and because the study coincided with the COVID-19 pandemic, interviews with patients and nutrition education were both carried out by phone. The aim of the education was to provide adequate and balanced nutrition, as well as to offer solutions to nutritional problems caused by the disease and the treatments applied. In the first week of nutrition education, patients and their relatives were informed about providing adequate and balanced nutrition, daily energy and nutrient requirements, the nutrients and quantities thereof they should consume daily, common nutritional problems specific to their diseases (loss of appetite, nausea, vomiting, mouth sores, dry mouth, tooth and gum problems, changes in the senses of taste and smell, early satiety, difficulty in chewing and swallowing, diarrhea, and constipation), and suggested solutions. The importance of adequate and balanced nutrition was explained and reiterated at weekly meetings, and individual nutritional problems experienced by the patients were discussed separately, with suggested solutions being given.

Assessment of quality of life

All patients, whether or not they received nutrition education, were evaluated using SF-36 at the beginning of the study and the end of the 12th week.

Collection of Patient and Control Serum Samples

Detailed histories were taken from all patients, and all underwent physical examinations and routine biochemistry tests. Briefly, 5 ml of 13 x 100 mM blood samples was taken from the peripheral vessels of all participants on the day of diagnosis of CACS and at the end of the 12th week, when the nutrition education had been completed. These samples were kept in Vacutainer® tubes for approximately 30 minutes before being stored at 4° C. Serum samples were obtained by centrifugation at 3000 rpm for 10 minutes and then stored at -80° C until biochemical analysis.

Biochemical Measurements

Routine biochemical test results and cancer markers were determined in all patients from both groups (with and without nutrition training) at the beginning and the end of the third month at the Ordu University Training and Research Hospital medical biochemistry laboratory.

Human irisin, TNF-α, IL-6, PIF, and ZAG (AZGP1) serum levels were determined using ELISA kits (reference nos. DZE201125328, DZE201120083, DZE201120091, DZE201125751, and DZE201123131, Sunred Biological Technology, Shanghai, China)) in line with the manufacturer's instructions using the ELISA)method at the Ordu University medical biochemistry research laboratory. Absorbance was measured at 450 nm using a BioTek Instrument EL800 microplate reader (Winooski, VT, USA). The results were expressed as ng/mL, ng/L, ng/L, µg/mL, and ng/mL respectively.

Statistical Analysis

The test results were analyzed on SPSS 13.0.1 statistical software (license n. 9069727) (Statistical Package for the Social Sciences; SPSS Inc. Chicago, IL, USA). Data were presented as mean±standard deviation (SD) for normally distributed variables and as median (25%-75%) in case of non-normal distribution. The distributions of biochemical parameters, irisin, TNF-α, IL-6, PIF, and ZAG (AZGP1) levels in both groups were calculated using the Shapiro-Wilk test. Group comparisons were performed using Student's t-test in case of normal distribution and the Mann-Whitney U test in case of non-normal distribution. Comparisons of the experimental and control groups before and after the nutrition education were evaluated with the paired-sample t-test in the parametric groups and with the Wilcoxon test in the non-parametric groups. Statistical significance was determined as $p<0.05$.

Results

The CACS patients' quality of life scale subdimensions, summary scores, and serum parameters (routine biochemical and ELISA tests) are shown in tables 1-4. There was no statistically significant difference between the experimental and control groups in terms of quality of life scale results. The groups were also evaluated within themselves in the form of pre- and post-tests conducted initially and at the end of the 12th week, and no statistically significant difference was again observed (Table 1). There was also no statistically significant difference between two groups regarding cachectic factors, inflammatory cytokines, and irisin levels (Table 2). In the experimental group, PIF and IL-6 levels increased and BMI levels decreased significantly after nutrition education (post-test) compared to the beginning(pre-test) ($p=0.027$, $p=0.010$, $p=0.014$). At the end of the training, Hgb levels increased significantly in the experimental group compared to the control group ($p=0.041$). There was no significant difference between the experimental and control groups in terms of BUN, creatinine, ALT, AST, or amylase levels. Creatinine levels decreased significantly in the experimental group after training ($p=0.015$), while LDH level increased significantly after training ($p=0.027$). Iron levels increased after training in both groups. Albumin levels increased significantly after training in the experimental group ($p=0.020$). CA 15.3 level increased significantly after training in the experimental and control groups ($p=0.011$, $p=0.008$). There was no significant change in α-1 antitrypsin, fibrinogen, hepatitis markers, or thyroid hormones (TSH, T3, T4) in the experimental or control groups before and after training (Table 3). While energy and nutrient intakes were similar between the groups at the beginning of the study, they were higher in the experimental group at the conclusion ($p<0.05$). When the groups were evaluated within themselves, an increase in energy, protein, fat, vitamin B12, sulfur, manganese, and fluoride was observed in the experimental group after the study ($p<0.05$), while no change was detected in the control group ($p>0.05$) (Table 4).

Table 1. Quality of Life Scale Subdimension and Summary Scores

Quality of Life Scale Subdimension and Summary Scores		Experimental group (n=23)	Control group (n=18)	Test value	p-value
Sub Dimensions					
General Health Perception	Pre-test	36.74±19.45	35.88±17.99	0.143	0.887[a]
	Post-test	31.44±15.97	33.35±15.24	-0.383	0.704[a]
		t= 1.958 p=0.063[c]	t= 1.457 p= 0.165[c]		
Pain	Pre-test	49.61±25.49	45.22±22.61	0.574	0.569[a]
	Post-test	52.00±23.39	40.88±22.85	1.500	0.142[a]
		t=-0.710 p=0.485[c]	t=1.557 p=0.139[c]		
Physical Function	Pre-test	72.39±25.17 75.00 (60.00-95.00)	65.00±30.91 72.50 (40.00-91.25)	-0.712	0.476[b]
	Post-test	66.74±27.20 75.00 (45.00-90.00)	61.17±31.74 75.00 (25.00-87.5)	-0.577	0.564[b]
		Z=-1.984 p=0.047*[d]	Z=-1.373 p=0.170[d]		
Physical Role	Pre-test	45.65±46.25 25.00 (0.00-100.00)	31.94±45.21 0.00 (0.00-100.00)	-0.964	0.335[b]
	Post-test	39.13±40.47 25.00 (0.00-75.00)	36.76±42.49 25.00 (0.00-87.50)	-0.273	0.785[b]
		Z=-0.907 p=0.364[d]	Z=-0.816 p=0.414[d]		
Mental Role	Pre-test	52.17±19.66 66.67 (33.33-66.67)	48.14±17.04 33.33 (33.33-66.67)	-0.873	0.383[b]
	Post-test	53.63±21.88 66.67 (33.33-66.67)	47.05±23.74 33.33 (33.33-66.67)	-1.045	0.296[b]
		Z=-0.173 p=0.862[d]	Z=-0.447 p=0.655[d]		
Social Function	Pre-test	77.71±21.96 87.50 (62.50-100.00)	63.88±29.97 68.75 (46.87-87.50)	-1.469	0.142[b]
	Post-test	67.39±16.74 62.50 (62.50-75.00)	61.02±29.93 62.50 (37.50-87.50)	-0.307	0.759[b]
		Z=-2.549 p=0.011*[d]	Z=-1.179 p=0.238[d]		
Vitality	Pre-test	48.04±20.87 45.00 (25.00-70.00)	46.38±19.83 45.00 (32.50-65.00)	-0.330	0.741[b]
	Post-test	51.30±14.94 50.00 (40.00-65.00)	42.94±16.96 45.00 (27.50-57.00)	-1.564	0.118[b]
		Z=-1.577 p=0.115[d]	Z=-1.968 p=0.049*[d]		
Mental Function	Pre-test	56.17±17.66 64.00 (36.00-72.00)	59.55±14.76 62.00 (52.00-69.00)	-0.370	0.711[b]
	Post-test	58.26±14.21 60.00 (52.00-72.00)	57.64±13.42 60.00 (52.00-68.00)	-0.442	0.658[b]
		Z=-1.000 p=0.317[d]	Z=-1.264 p=0.206[d]		
SUMMARY SCORES					
Physical Health Score	Pre-test	39.80±11.61	35.62±13.32	1.070	0.291[a]
	Post-test	37.08±11.74	34.67±13.18	0.609	0.546[a]
		t=1.825 p=0.082[c]	t=1.009 p=0.328[c]		
Mental Health Score	Pre -test	37.54±11.61	36.12±10.07	0.410	0.684[a]
	Post-test	37.81±8.75	35.09±9.59	0.932	0.357[a]
		t=-0.205 p=0.839[c]	t=1.598 p=0.130[c]		

[a] Independent Sample T Test, [b] Mann Whitney U, [c] Paired- Sample T Test,[d] Wilcoxon
*p<0,05

Table 2. CACS Patients' Serum Parameters and BMI Values

Serum Parameters		Experimental group (n=23)	Control group (n=18)	Test value	p-value
PIF (µg/mL)	Pre-test	0.999±0.83 0.66 (0.34-1.70)	1.94±2.52 1.22 (0.34-2.85)	-0.827	0.409[b]
	Post-test	2.00±1.43 1.80 (0.46-3.35) Z=-2.215 p=0.027*[d]	1.83±1.25 1.52 (0.52-3.28) Z=-0.267 p=0.790	-0.358	0.720[b]
ZAG (ng/mL)	Pre-test	29.47±11.82	26.21±12.00	0.793	0.991[a]
	Post-test	25.76±8.31 25.83 (19.38-32.62) Z=-1.198 p=0.231[d]	30.93±6.24 31.55 (27.2-36.0) Z=-1.412 p=0.158	-1.859	0.063[b]
Irisin (ng/mL)	Pre-test	5.98±1.191 5.33 (4.65-6.85)	6.72±3.18 6.29 (4.35-8.12)	-0.303	0.762[b]
	Post-test	5.88±2.31 Z=-0.469 p=0.639[d]	6.76±1.89 Z=-0.220 p=0.826	-1.208	0.236[a]
IL-6 (ng/L)	Pre-test	48.94±14.29	71.03±22.1	-3.20	0.089[a]
	Post-test	74.07±29.72 t=-2.935 p= 0.010*[c]	65.32±18.9 t=0.140 p=0.892	0.897	0.341[a]
TNF-α (ng/L)	Pre-test	0.72±0.34	0.61±0.41	0.797	0.557[a]
	Post-test	0.73±0.49 t=-0.132 p=0.896[c]	0.85±0.51 t=-1.342 p=0.204	-0.703	0.946[a]
BMI(kg/m^2)	Pre-test	26.72±6.49 24.45 (21.22-32.04)	26.90±6.57 24.33 (22.91-28.22)	-0.223	0.823[b]
	Post-test	25.43±5.59 24.33 (21.30-28.60) Z=-2.451 p=0.014*[d]	26.19±6.66 25.15 (21.91- 27.70) Z=-2.385 p=0.017	-0.424	0.671[b]

[a] Independent Sample T Test, [b] Mann Whitney U , [c] Paired- Sample T Test, [d] Wilcoxon
*p<0.05

Table 3. Routine Biochemical Parameters

Serum Parameters		Experimental group (n=23)	Control group (n=18)	Test value	p-value
Hgb (g/dL)	Pre-test	12.65±2.32 13.5 (7.9 - 16)	11.74±1.77 11.7 (8.1 - 14.4)	1.328	0.193[a]
	Post-test	12.4±1.41 12.6 (10.4 - 16.3) t= -1.443 p= 0.149[d]	11.3±1.47 11.5 (8.1 - 13.6) t= 0.576 p= 0.573[c]	109.000	0.041*[b]
BUN (mg/dL)	Pre-test	26.75±9.93 24.15 (13.9 - 57.4)	30.73±13.66 30.7 (9.4 - 66.09)	163.000	0.341[b]
	Post-test	28.26±11.07 25.55 (8.9 - 59.2) t= -0.608 p= 0.543[d]	31.39±12.94 32 (6.7 - 56.2) t= -0.177 p= 0.862	157.000	0.395[b]
Creatinine (mg/dL)	Pre-test	0.86±0.13 0.86 (0.62 - 1.11)	0.88±0.23 0.84 (0.6 - 1.56)	-0.468	0.642[a]
	Post-test	0.79±0.13 0.78 (0.59 - 1.1) t= 2.654 p= 0.015[c]	0.85±0.24 0.78 (0.56 - 1.5) t= 0.847 p= 0.409[c]	-0.912	0.372[a]
ALT(U/L)	Pre-test	16.92±8.76 13 (7.6 - 36)	14.16±8.87 10.1 (6 - 31.2)	0.945	0.351[a]
	Post-test	18.39±9.57 16.5 (6.3 - 46.2) t= -1.062 p= 0.302[c]	15.85±8.62 12.9 (7.8 - 42.5) t= 0.398 p= 0.691[d]	140.500	0.265[b]
AST(U/L)	Pre-test	18.65±7.27 16.2 (9.6 - 39.2)	16.64±8.3 12.7 (10 - 42.2)	129.500	0.150[b]

	Post-test	23.08±8.71 22.2 (11.1 - 42.3) t= -1.654 p= 0.115 [c]	19.81±10.54 15.25 (9.2 - 43.9) t= -0.568 p= 0.570	124.500	0.128 [b]
Amilase(U/L)	Pre-test	64.8±18.22 62 (26 - 96)	61.93±24.49 56 (29 - 109)	91.000	0.541 [b]
	Post-test	78.17±27.58 72.5 (44 - 152) t= -1.719 p= 0.111 [c]	70.33±27.82 64 (43 - 150) t= -1.119 p= 0.263 [d]	107.000	0.311 [b]
LDH(U/L)	Pre-test	178.56±46.44 169.5 (128 - 289)	183.57±39.68 167 (140 - 280)	95.500	0.492 [b]
	Post-test	205.6±41.6 199.5 (140 - 318) t= -2.215 p= 0.027 [d]	200.47±39.74 189 (141 - 288) t= -1.630 p= 0.134 [c]	0.368	0.715 [a]
Iron(µg/dL)	Pre-test	57.14±30.89 48 (10.3 - 129.2)	34.28±24.88 28.75 (11.1 - 115.8)	2.419	0.021* [a]
	Post-test	60.8±34.12 59.7 (16.2 - 127.2) t= -1.028 p= 0.318 [c]	52.48±26.63 57.15 (18.6 - 102.9) t= -2.649 p= 0.019 [c]	0.806	0.426 [a]
Total Protein (g/dL)	Pre-test	43.82±32.59 63.45 (6.5 - 75.9)	48.16±28.81 63.1 (6.4 - 73)	-0.328	0.746 [a]
	Post-test	68.26±6.38 69 (59.2 - 79) t= -1.433 p= 0.225 [c]	65.97±5.57 66.15 (53.2 - 74.4) t= -1.243 p= 0.269 [c]	0.877	0.392 [a]
Albumine(g/dL)	Pre-test	33.17±17.47 40.4 (3.8 - 48.9)	34.89±16.34 42.8 (3.4 - 47)	143.000	0.815 [b]
	Post-test	43.12±3.68 42.5 (36 - 50.7) t= -2.543 p= 0.020 [c]	41.85±4.58 42.5 (29.4 - 49.1) t= -1.083 p= 0.279 [d]	0.935	0.356 [a]
CRP (mg/dL)	Pre-test	5.58±6.74 2.67 (0.13 - 23.69)	4.76±4.33 3.4 (0.51 - 16.41)	163.000	0.831 [b]
	Post-test	5.08±4.75 3.69 (0.62 - 17.23) t= 0.113 p= 0.911 [c]	3.32±4.33 1.7 (0.6 - 16.28) t= -1.193 p= 0.233 [d]	112.000	0.058 [b]
Anti-HCV (IU/mL)	Pre-test	0.05±0.04 0.04 (0.02 - 0.23)	0.03±0.01 0.03 (0.02 - 0.05)	141.500	0.277 [b]
	Post-test	0.05±0.05 0.04 (0.03 - 0.26) t= -0.922 p= 0.357 [d]	0.04±0.01 0.04 (0.02 - 0.06) t= -1.100 p= 0.271 [d]	0.805	0.426 [a]
HBsAg (mIU/mL)	Pre-test	0.59±0.13 0.61 (0.27 - 0.79)	0.51±0.18 0.53 (0.2 - 0.84)	110.500	0.066 [b]
	Post-test	0.61±0.12 0.62 (0.33 - 0.85) t= -0.735 p= 0.472 [c]	0.57±0.15 0.61 (0.22 - 0.77) t= 0.738 p= 0.460 [d]	1.031	0.310 [a]
Anti-HBs (mIU/mL)	Pre-test	31.83±67.27 1.7 (1.3 - 240.6)	13.6±27.28 2.06 (1.4 - 106.6)	138.000	0.482 [b]
	Post-test	42.96±92.83 1.7 (1 - 342.2) t= -0.831 p= 0.406 [d]	43.62±110.81 1.75 (1.4 - 389) t= -1.482 p= 0.138 [d]	105.500	0.442 [b]
Anti-HIV	Pre-test	0.2±0.03 0.21 (0.14 - 0.25)	0.19±0.03 0.18 (0.15 - 0.25)	0.594	0.556 [a]
	Post-test	0.2±0.04 0.19 (0.11 - 0.3) t= 0.454 p= 0.655	0.19±0.04 0.18 (0.14 - 0.27) t= 0.526 p= 0.607 [c]	0.634	0.530 [a]
CA-125(U/mL)	Pre-test	13.11±7.43 11.2 (4.89 - 30.2)	12.18±4.42 11.9 (6.69 - 24.1)	123.000	0.865 [b]

	Post-test	16.64±9.9 14.3 (6.17 - 41.8) t= -2.685 p= 0.017 [c]	13.18±7.66 10.7 (7.46 - 34.2) t= -0.157 p= 0.875 [d]	1.130	0.266 [a]
CA15-3 (U/mL)	Pre-test	16.17±8.16 14.85 (4.85 - 40.5)	17.57±7.19 16 (5.81 - 35)	160.000	0.444 [b]
	Post-test	20.98±9.77 18.9 (7.42 - 44.6) t= -2.555 p= 0.011 [d]	23.19±9.94 23.75 (7.88 - 42.9) t= -3.189 p= 0.008 [c]	-0.656	0.516 [a]
CA 19-9 (U/mL)	Pre-test	11.39±10.5 7.13 (2 - 43.5)	13.88±14.22 10.3 (2 - 56.86)	131.500	0.536 [b]
	Post-test	10.03±7.43 7.14 (2 - 29) t= 0.555 p= 0.586 [c]	14.87±9.91 13.15 (2 - 33.7) t= -0.711 p= 0.477 [d]	-1.721	0.094 [a]
CEA (U/mL)	Pre-test	3.91±4.51 2.17 (0.83 - 16.4)	6.26±5.12 5.52 (0.59 - 18.3)	124.000	0.110 [b]
	Post-test	2.99±2.22 2.39 (0.91 - 8.79) t= -0.713 p= 0.476 [d]	2.71±2.08 2.26 (1.36 - 9.58) t= -2.417 p= 0.016 [d]	169.000	0.917 [b]
Folate (ng/mL)	Pre-test	9.06±3.72 8.4 (4.08 - 18.5)	7.16±3.98 6.47 (3.13 - 19.7)	63.500	0.044* [b]
	Post-test	9.57±5.43 6.73 (3.48 - 20) t= -0.284 p= 0.776 [d]	9.71±5.94 7.97 (3.53 - 20) t= -1.020 p= 0.308 [d]	162.000	0.854 [b]
Ferritin (ng/mL)	Pre-test	79.77±48.45 66.95 (24.3 - 169)	31.6±22.86 25.8 (10.3 - 71.8)	18.000	0.006 * [b]
	Post-test	129.58±129.75 73.9 (10.3 - 472) t= -1.423 p= 0.155 [d]	96.47±125.7 40.4 (8.45 - 437) t= -0.700 p= 0.484 [d]	116.000	0.183 [b]
TSH(mIU/L)	Pre-test	1.46±1.09 1.13 (0.16 - 4.67)	2.49±2.08 1.57 (0.3 - 7.57)	-1.868	0.075 [a]
	Post-test	1.7±1.22 1.45 (0.09 - 4.86) t= -2.183 p= 0.041 [c]	1.33±0.98 1.18 (0.08 - 3.21) t= 1.510 p= 0.157 [c]	0.968	0.340 [a]
Free T4 (ng/dL)	Pre-test	1.24±0.21 1.19 (0.86 - 1.72)	1.22±0.16 1.21 (0.99 - 1.58)	185.000	0.955 [b]
	Post-test	1.24±0.25 1.26 (0.79 - 1.77) t= -0.260 p= 0.795 [d]	1.19±0.17 1.14 (0.96 - 1.51) t= -0.408 p= 0.683 [d]	0.709	0.483 [a]
Free T3(ng/dL)	Pre-test	2.83±0.47 2.92 (2.04 - 3.74)	2.66±0.48 2.58 (1.98 - 3.36)	93.000	0.337 [b]
	Post-test	2.68±0.68 2.65 (1.45 - 3.49) t= -0.051 p= 0.959 [d]	2.53±0.34 2.45 (2.19 - 2.98) t= -0.716 p= 0.506 [c]	20.000	0.191 [b]
Alpha-1 Antitrypsin (mg/dL)	Pre-test	174.27±36.3 165 (122 - 238)	175.85±46.04 173 (118 - 279)	70.000	0.931 [b]
	Post-test	164.15±33.4 158 (91.1 - 253) t= -0.357 p= 0.721 [d]	170.27±41.08 171 (107 - 264) t= -0.663 p= 0.508 [d]	-0.492	0.626 [b]
Fibrinogen (mg/dL)	Pre-test	380.09±64.81 379.5 (280 - 479)	405.4±50.77 418 (328 - 512)	121.500	0.178 [b]
	Post-test	386.35±71.46 380.5 (246 - 523) t= -0.411 p= 0.681 [d]	380.6±99.52 350 (244 - 622) t= -1.503 p= 0.133 [d]	0.199	0.843 [b]

[a] Independent Sample T Test, [b] Mann Whitney U , [c] Paired- Sample T Test, [d] Wilcoxon
*p<0.05

Table 4. Energy and Nutrients

Energy and Nutrients		Experimental group (n=23)	Control group (n=18)	Test value	p-value
Energy ((kcal)	Pre-test	1211.37±550.23 1216.71 (375.08 - 2440.34)	1314.28±522.21 1305.8 (595.94 - 2512.07)	-0.608	0.547[a]
	Post-test	1526.93±422.11 1446.83 (701.85 - 2316.6) t= -2.466 p= 0.022*[c]	1071.07±477.35 1038.24 (539.35 - 2257.09) t= 1.918 p= 0.072[c]	3.240	0.002*[a]
Protein (g)	Pre-test	48.83±25.65 50.21 (13.84 - 98.11)	52.39±20.66 49.69 (21.89 - 85.02)	-0.478	0.635[a]
	Post-test	67.11±26.76 67.53 (24.53 - 135.7) t= -2.396 p= 0.026*[c]	47.44±24.94 44.58 (18.55 - 104.86) t= 0.773 p= 0.450[c]	2.406	0.021*[a]
Fat (g)	Pre-test	47.89±27.22 44.99 (11.9 - 110.62)	57.3±32.93 47.45 (17.27 - 155.71)	-1.003	0.322[a]
	Post-test	64.03±24.69 60.6 (26 - 128.83) t= -2.414 p= 0.025*[c]	44.82±23.79 38.6 (17.38 - 99.39) t= 1.651 p= 0.117[c]	2.512	0.016*[a]
Carbohydrate (g)	Pre-test	141.15±63.71 126.68 (37.61 - 263.38)	143.34±51.15 157.87 (50.03 - 213.33)	-0.119	0.906[a]
	Post-test	165.68±53.54 157.24 (83.32 - 323.34) t= -1.517 p= 0.144[c]	116.32±51.52 103 (51.17 - 246.74) t= 1.867 p= 0.079[c]	2.978	0.005*[a]
Vitamin A(µg)	Pre-test	898.89±1118.2 575.88 (216.16 - 5602.51)	859.13±475.4 960.24 (151.6 - 1814.12)	-0.972	0.331[b]
	Post-test	1186.21±1232.71 645.6 (293.68 - 4949.65) t= -0.152 p= 0.879[d]	650.83±901.7 372.32 (201.85 - 4147.52) t= -1.851 p= 0.248[d]	-2.338	0.019*[b]
Vitamin E (mg)	Pre-test	7.42±7.2 6.45 (1.02 - 30.3)	9.85±8.05 8.53 (2.04 - 33.26)	-1.314	0.189[b]
	Post-test	10.21±7.04 6.95 (2.35 - 26.21) Z= -0.821 p= 0.411[d]	6.07±5.61 4.12 (1.91 - 24.78) Z= -1.764 p= 0.078[d]	-2.509	0.012*[b]
Thiamine (mg)	Pre-test	0.62±0.32 0.65 (0.17 - 1.34)	0.64±0.28 0.66 (0.2 - 1.11)	-0.221	0.826[a]
	Post-test	0.8±0.33 0.84 (0.26 - 1.49) t= -1.901 p= 0.070[c]	0.52±0.26 0.5 (0.21 - 1.01) t= 1.681 p= 0.111[c]	2.951	0.005*[a]
Riboflavin (mg)	Pre-test	1.04±0.62 1.07 (0.21 - 2.14)	1.18±0.49 1.16 (0.47 - 1.89)	-0.786	0.436[a]
	Post-test	1.29±0.44 1.21 (0.44 - 2.12) t= -1.589 p= 0.126[c]	0.98±0.46 0.98 (0.39 - 1.94) t= 1.500 p= 0.152[c]	2.174	0.036*[a]
Niacin (mg)	Pre-test	8.41±8.09 4.83 (1.84 - 38.56)	7.83±4.15 7.03 (1.61 - 20.16)	-0.709	0.478[b]
	Post-test	11.66±6.06 10.95 (1.71 - 25.76) Z= -1.734 p= 0.083[d]	7.62±5.88 6.54 (1.31 - 25.7) Z= -0.936 p= 0.349[d]	-2.391	0.017*[b]
Biotin (µg)	Pre-test	35.37±21.86 35.14 (4.96 - 81.52)	41.54±18.31 39.97 (17.04 - 78.78)	-0.961	0.343[a]
	Post-test	43.22±13.07 42.51 (23.99 - 68.6) t= -1.279 p= 0.214[c]	30.99±12.2 26.78 (16.26 - 56.89) t= 2.081 p= 0.053[c]	3.061	0.004*[a]
Vitamine B12 (µg)	Pre-test	3.04±2.09 2.59 (0 - 6.67)	4.25±2.3 3.65 (1.42 - 8.82)	-1.759	0.086[a]
	Post-test	5.05±3.96	2.94±2.07	2.200	0.035*[a]

		4.46 (1.03 - 18.03)	2.44 (0.85 - 8.84)		
		t= -2.140	t= 1.760		
		p= 0.044*[c]	p= 0.096 [c]		
Potassium (mg)	Pre-test	2033.7±1047.77	2127.57±882.97	-0.604	0.546 [b]
		1966.25 (779.38 - 4402.53)	2194.88 (543.74 - 3472.35)		
	Post-test	2526.22±909.75	1686.91±872.92	2.838	0.005*[b]
		2672.79 (971.96 - 4394.8)	1516.26 (653.43 - 4128.85)		
		Z= -1.369	Z= -1.459		
		p= 0.171 [d]	p= 0.145 [d]		
Magnesium (mg)	Pre-test	193.42±94.45	206.04±93.46	-0.426	0.672 [a]
		203.69 (59.32 - 408.7)	216.58 (70.44 - 334.82)		
	Post-test	243.8±84.51	167.84±80.6	2.914	0.006*[a]
		236.7 (95.54 - 398.35)	158.85 (72.89 - 342.7)		
		t= -2.038	t= 1.608		
		p= 0.054 [c]	p= 0.126 [c]		
Sulfur	Pre-test	279.59±167.32	226.11±178.66	0.986	0.330 [a]
		270.79 (40.8 - 722.54)	168.55 (34.06 - 677.9)		
	Post-test	758.77±294.45	564.5±300.23	2.079	0.044*[a]
		740.35 (287.81 - 1571.76)	515.29 (241.51 - 1288.61)		
		t= -2.103	t= 0.531		
		p= 0.047*[c]	p= 0.602 [c]		
Iron (mg)	Pre-test	6.88±3.58	7.08±3.42	-0.173	0.863 [a]
		5.89 (1.99 - 14.65)	5.62 (2.99 - 11.57)		
	Post-test	8.81±3.8	5.72±3.2	2.761	0.009*[a]
		8.08 (2.38 - 16.34)	5.52 (2.39 - 14.5)		
		t= -1.927	t= 1.563		
		p= 0.067 [c]	p= 0.136 [c]		
Copper (mg)	Pre-test	1.05±0.62	1.06±0.6	-0.171	0.864[b]
		0.96 (0.31 - 2.41)	0.87 (0.29 - 2.24)		
	Post-test	1.55±0.98	1.07±0.87	-2.286	0.022*[b]
		1.22 (0.36 - 4.2)	0.72 (0.28 - 3.15)		
		Z=-1.867	t= -0.008		
		p= 0.062 [d]	p= 0.994 [c]		
Manganese (mg)	Pre-test	2.32±1.45	2.61±1.78	-0.079	0.937 [b]
		2.08 (0.57 - 6.31)	2.18 (0.74 - 6.45)		
	Post-test	3.55±1.85	2.06±1.6	-2.786	0.005*[b]
		3.45 (1.05 - 6.92)	1.53 (0.72 - 5.85)		
		Z=-2.768	t= 1.217		
		p= 0.006*[d]	p= 0.240 [c]		
Fluorine (µg)	Pre-test	424.11±270.7	416.32±227.35	-0.079	0.937 [b]
		354.7 (130.48 - 1255.17)	344.14 (119.56 - 865.67)		
	Post-test	556.5±207.44	430.76±258.78	-2.102	0.036*[b]
		569 (244.64 - 935.33)	318.26 (160.7 - 1018.45)		
		Z=-2.190	t= -0.199		
		p= 0.029*[d]	p= 0.845 [c]		
Omega-3(g)	Pre-test	1.13±0.67	1.23±0.71	-0.486	0.630 [a]
		0.88 (0.42 - 2.88)	0.92 (0.41 - 3.1)		
	Post-test	1.26±0.44	0.94±0.35	2.541	0.015*[a]
		1.22 (0.46 - 2.42)	0.85 (0.54 - 1.69)		
		t= -0.815	t= 1.691		
		p= 0.424 [c]	p= 0.109 [c]		
Omega-6(g)	Pre-test	4.92±4.19	6.69±5.38	-1.196	0.232 [b]
		3.83 (1.12 - 18.37)	4.91 (1.13 - 19.81)		
	Post-test	6.23±3.79	4.44±4.07	-2.233	0.026*[b]
		4.81 (2.02 - 15.12)	2.5 (1.38 - 16.05)		
		Z=-1.247	Z=-1.851		
		p= 0.212 [d]	p=0.064 [d]		

[a] Independent Sample T Test, [b] Mann Whitney U , [c] Paired- Sample T Test, [d] Wilcoxon
*p<0.05

Discussion

Cachexia is the second most important cause, after sepsis, of cancer-related deaths. The condition progresses with weight loss in cancer patients and cannot be reversed using normal nutritional support. Research in recent years has shown that cancer cachexia is associated with anorexia, a condition known as CACS [10]. The etiology of CACS involves numerous factors. Its most important feature is the deterioration of fat tissue along with muscle loss. Cancer patients experience loss of appetite in addition to involuntary weight loss, and this reduces their

quality of life. In its advanced stages, CACS cannot be completely treated by eating more or using nutritional supplements. Increasing weight loss over time causes patients with this syndrome to experience difficulties in meeting their daily needs. The occurrence of the syndrome depends on the type of cancer involved. Weight loss is observed before starting treatment in 50-85% of patients with gastrointestinal, pancreatic, lung, and colorectal cancers. Cancer anorexia-cachexia is responsible for 20% of all cancer-related deaths, and is most commonly seen in gastrointestinal and lung malignancies [11]. When a tumor is present, numerous metabolic factors are produced by the host and the tumor, and these play a critical role in tissue (fat and skeletal muscle) wastage in cancer cachexia. Although the mechanism has not been fully elucidated, lipid mobilizing factor (LMF)/Zinc-α-2-glycoprotein (ZAG), TNF-α, IL-1, and IL-6, which are excessively synthesized by the body, are released from tumor cells in cancer cachexia, while factors that cause cancer cachexia continue to be investigated [12]. PIF is secreted by the tumor and causes a severe decrease in muscle mass by increasing protein catabolism, primarily by activating the ATP-dependent proteolytic system. PIF has particularly been detected in the urine of patients experiencing body weight loss. LMF increases lipolysis in adipose tissue, and both are secreted by the tumor [13,14]. A previous study reported elevated serum TNF-α levels in 36.5% of 63 patients with pancreatic cancer, in patients with metastatic pancreatic tumors, and others [15]. TNF-α, IL-1, IL-6, and IFN-γ levels were not found to be associated with weight loss in advanced and terminal cancer patients in another study [16]. Pro-inflammatory mediators are released by the tumor microenvironment and systemically. This leads to reduced muscle protein synthesis by downregulating the mammalian target of rapamycin (mTOR) and increased muscle degradation by upregulating atrogin-1 and muscle RING-finger protein-1 (MuRF-1) [17]. The connection between irisin, known as weight loss myokine, and "cancer and weight loss" (irisin and cancer, irisin and weight loss) has to date been reported in immunological and biochemical studies. Strong irisin immunoreactivity was observed in cancerous tissues of the gastrointestinal system (the pancreas, liver, spleen, and stomach) in one study [18]. Other research examined the tumor tissues of mice with gastric cancer, and no expression of irisin precursor FNDC5 was found in stomach tumor tissue However, it was suggested that some factors released from the tumor tissue activate numerous unknown signaling pathways, first stimulating the expression of FNDC5 in white and brown adipose tissue, thus increasing the level of irisin in the circulation. Irisin then causes weight loss by increasing the degradation of triacylglycerol in white adipose tissue [19]. An in vitro study conducted with lung, breast, prostate, osteosarcoma, and pancreatic cancer cell lines showed that irisin applied at a specific dose and duration exhibited an inhibitory effect. However, the application of irisin did not affect endometrial, colon, thyroid, or esophageal cell lines [20]. Another in vivo study suggested that serum irisin may represent a potential diagnostic marker for breast, renal, colon, and rectal cancers [21].

No statistically significant differences were observed between the experimental and control groups in this study in terms of cachectic factors, inflammatory cytokines, or irisin levels (Table 2). However, in the experimental group, PIF and IL-6 levels increased and BMI levels decreased significantly following nutrition education (post-test) compared to baseline (pre-test) ($p=0.027$, $p=0.010$, and $p=0.014$, respectively). Interestingly, nutrition education given to the experimental group may have raised those patients' stress levels, resulting in a decrease in BMI and increased inflammation (IL-6 and TNF-α).

Quality of life is one of the indicators of health. In addition to traditional mortality and morbidity measures, it is also an important factor that should be taken into consideration when determining individuals' health levels. Since the creation and development of quality of life scales is a labor-intensive process, the use of scales developed by others and whose validity and reliability have already been tested is becoming increasingly widespread. SF-36 was developed and has been made available by the Rand Corporation for the evaluation of quality of life [22,23]. It was translated into Turkish and validated by Koçyiğit et al. [24]. The scale is short, easy to apply, and highly versatile [25]. The Turkish version of SF-36 can be used in cancer research in Türkiye [8]. The scale subdimensions and summary scores are shown in Table 1. There was no statistically significant difference between the experimental and control groups in terms of SF-36. The groups were also evaluated within themselves in the form of pre- and post-tests initially and at the end of the 12th week, and no statistically significant difference was again observed.Studies have reported that nutrition education increases patients' quality of life [26-32]. In a study examining the effect of education on the quality of life of breast cancer patients, a comprehensive education program, including nutrition education, was applied to an experimental group for 12 weeks. At the end of the study period, a significant increase was observed in the quality of life of the patients who received education [26]. Lee et al. observed that three-week nutrition education given to postgastrectomy patients increased their quality of life and improved their nutritional status [27]. Another study examining the effect of nutrition education on eating habits and quality of life in stomach cancer patients, significant improvements were determined in serum albumin and hematocrit levels after education, together with a significant increase in the amount of food consumed and quality of life [28]. Research involving other patients (with kidney, liver, and lung diseases) has also reported that nutrition education improves quality of life [29-32]. We attribute the fact that nutrition education in the present study did not produce significant changes in the quality of life of cancer patients to the data collection process coinciding with the Covid-19 pandemic, cancer patients losing hope as a result of the pandemic,

and physical activity being limited by the curfew. All these factors had an adverse psychological effect on cancer patients. Additionally, the nutrition education given to the experimental group may have caused an increase in patients' concerns about the disease and therefore a decrease in BMI. Studies have reported that nutrition education exhibits positive effects on biochemical parameters [28,33-38]. Studies examining the effectiveness of nutrition education in cancer patients are scarce. However, the effects of nutrition education on biochemical parameters in other diseases have been investigated. Both a desired change in dietary intake and BMI and improvements in biochemical parameters were observed in a previous study involving patients with metabolic syndrome [33]. Another study found that nutrition education given to obese and hypertensive patients resulted in a decrease in BMI and an improvement in biochemical parameters [34]. Studies conducted with other patient groups have similarly reported positive effects of nutrition education on BMI and biochemical parameters [35-38].

Chao et al. reported a significant increase in nutritional intake following nutrition education in their study of 444 oncology patients [39]. Nutrition education (information about both good management of the treatment process and nutrition) given to gastric cancer patients receiving chemotherapy has been shown to result in a significant increase in food intake [40]. Similarly to the results of other studies, nutrition education in the present study produced a desired change in nutrient intake. Nutrition education given to malnourished patients with cancer can produce the desired change in nutritional intake.

At the end of the training, Hgb levels increased significantly in the experimental group compared to the control group ($p=0.041$). However, no significant differences were observed between the two groups in terms of BUN, creatinine, ALT, AST, or amylase levels. Creatinine levels decreased significantly in the experimental group after training, while LDH levels increased significantly ($p=0.015$ and $p=0.027$, respectively). Iron levels increased after training in both groups. Albumin levels increased significantly after training in the experimental group ($p=0.020$). CA 15.3 levels increased significantly after training in the experimental and control groups ($p=0.011$ and $p=0.008$, respectivelyThere was no significant change in α-1 antitrypsin, fibrinogen, hepatitis markers, or thyroid hormones (TSH, T3, T4) in either group before and after training.

Limitations

The COVID-19 epidemic throughout the study period caused our project duration to be extended, and additional time was requested for completion (12 months). The majority of patients with CACS died due to cachexia before completing the nutrition education period. Our project commenced with CACS patients diagnosed with stomach cancer, but due to the prolonged nature of the pandemic and our inability to reach the desired number of samples, patients with colon and rectal cancers were also included. Differences in the stages and types of cancer may have affected the results. The effects of chemotherapeutic drugs taken for 12 weeks on biochemical parameters, quality of life, and nutrition should not be ignored. Patients with the same type of cancer, with similar stages, and using similar drugs for treatment should be selected when planning further studies. Once the nutrition education has been completed, in order to observe the long-term results, blood specimens should be collected at the end of the third, sixth, and ninth months

Conflict of Interest

The authors declare that they have no conflicting interests.

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Ethical Approval

This study was reviewed and approved by the Institutional Review Board at Ordu University, Turkiye, and was performed in agreement with the principles of the Declaration of Helsinki. Ethics committee approval was received from the Ordu University local ethical committee under reference no. 2021/184.

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