The effect of nutritional support on nutritional status and quality of life as well as on inflammatory markers and cardiac functions in patients with cardiac cachexia due to chronic heart failure

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ABSTRACT

Objective: Cardiac cachexia (CC) is defined as a loss of at least 6% of total body weight in 6 months due to chronic heart failure (CHF). The prevalence of CC in patients with NYHA class II-IV is estimated to be approximately 12%-15%. There are only a few studies that demonstrate the effects of malnutrition treatment on nutrition, physical activity, quality of life (QoL), and clinical course of the disease. This study aimed to evaluate the effect of nutrition treatment on anthropometric measurements, fat free mass (FFM), muscle strength, physical performance, and QoL together with cardiac functions and immunity in patients with CC.

Method: This was a prospective clinical intervention study. Patients with NYHA stage II-IV CHF (n=725) followed-up in Internal Medicine and Cardiology Departments were screened for CC. Eighteen patients with CC were enrolled in the study. The control group included 18 healthy adults. Nutritional status assessment, anthropometric measurements, gait speed, muscle strength, bioelectrical impedance analysis (BIA Tanita, Japan), biochemical analyses, and cytokine measurements were performed. Cardiac functions were assessed by echocardiography. Nutrition support treatment was given to patients with CC, and they were followed-up for next 3 months. QoL was measured with "Ferrans and Powers" Quality of Life Index (cardiac version). Similar studies were repeated after follow-up.

Results: After excluding all other reasons for cachexia, the prevalence of CC was 2.5% in our patients with CHF. The patients with CC had higher serum C-Reactive Protein (CRP) and IL-6 levels than the healthy controls. After nutrition support treatment, the QoL scores and visceral fat level significantly increased in patients with CC. Although mid-upper arm circumference (MUAC), handgrip strength, FFM, fat mass, and serum albumin levels increased, they were not statistically significant.

Conclusion: When compared to previous studies, our CC prevalence rate was lower. Nutrition support therapy can reverse weight loss in patients with CC, which can also improve QoL. An important limitation to the study is the low number of patients that is related with the exclusion criteria regarding every type of inflammatory disease, acute medical problems, and cancer. Therefore, further studies with more patients are needed.

Keywords: Cardiac cachexia, chronic cardiac failure, nutrition support treatment

Introduction

Cardiac cachexia (CC) is defined as secondary to chronic heart failure (HF) and non-edema weight loss of 6% or more in 6 months, regardless of any other underlying disease. Common muscle and fat loss occurs in the extremities (1). While muscle protein synthesis decreases, synthesis of acute phase proteins increases (2). In addition to loss of muscle tissue, decrease in fat and bone mass is also observed (3). It is considered that 12%-15% of patients with NYHA class II-IV have CC; and 29% of patients with CC are lost within 6 months (4).

Studies show that survival rates of patients with cachexia with body mass index (BMI) above 29 kg/m² are 1-3 years more (5). In another study, the increase in BMI was found

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to be protective in patients with HF followed for a year; and the lowest risk of death was found in patients with BMI of 30.0-34.9 kg/m². This condition is known as the paradox of obesity; and patients with BMI below 20 kg/m² have a high risk of mortality (6).

Immunological cytokine activation is considered to play an important role in the pathophysiology of CC. In 1990, Levine et al. (7) demonstrated the association between tumor necrosis factor-alpha (TNF-α) and HF. Increased levels of plasma TNF-α are the most important predictors of weight loss. Apart from TNF-α, intercaline-1 (IL-1) and interleukin-6 (IL-6) also play a role in catabolism (8, 9).

In 50% of patients with HF, poor nutrition was detected. The daily energy needs of the patients with CC were increased, and the protein requirement was 1.5-2 g/kg/day (10). The imbalance associated with the use of energizing nutrients increases daily energy, protein, and fat requirements. However, it should be kept in mind that excess fat and carbohydrate intake may also increase oxygen consumption and therefore impair the clinical picture (11). It is recommended that patients with critical illnesses should be given 25 kcal/kg diet daily, 1.2-1.5 g/kg protein should be given, carbohydrates do not exceed 6 g/kg/day, and fats do not exceed 2.5 g/kg/day (12).

Heart failure is associated with immobilization, fatigue, gastrointestinal symptoms and early satiety. (13). This can lead to severe malnutrition. To increase muscle mass and improve exercise capacity, energy reserves need to be replaced; thus nutritional status should be improved. Despite the decrease in physical activity in patients with CC, the daily energy demand increases as a result of increased inflammation and catabolic process (14).

Only a few studies show the results of prevention of weight loss with nutritional support therapy. This prospective longitudinal study aimed to investigate the effects of nutritional therapy on anthropometric measurements, fat free mass (FFM), and muscle strength as well as physical performance and quality of life in patients with CC. Possible changes in cardiac functions and immune system that may occur during nutritional follow-up of patients were also examined.

Methods

Operation type and population
In this prospective longitudinal study, 725 patients who were followed-up at an outpatient clinic between August 2014 and May 2015 in Istanbul Medical Faculty Internal Medicine and Cardiology Departments or who were treated inpatient during the study were screened. Eighteen patients with stage II-IV HF and CC were included in the study. Eighteen healthy adults were included in the control group. The criteria for inclusion and exclusion are given in Table 1.

Nutritional status assessment
Two same nutritional nurses in the Clinical Nutrition Unit of Istanbul Faculty of Medicine performed nutritional status assessment and anthropometric measurements of the patients. Subjective global assessment test was used for nutritional status assessment (15). BMI, mid-upper arm circumference (MUAC), and calf circumference were measured during anthropometric analyses. MUAC is measured from the midpoint of the distance between the acromion of the scapula and the ulna olecranon projection in the upper arm. The calf circumference is measured at the widest point of the calf.

Nutrition support plan (NDP)
The daily energy requirement of patients diagnosed with CC was calculated by formula (Harris Benedict Formula, stress factor and activity factor) (16). Daily protein requirements were planned to be 1.2-1.5 g/kg/day. The European Journal of Clinical Nutrition and Metabolism (ESPEN) was used to determine the daily energy and protein requirements (17). The diet lists were prepared based on these accounts. The dietary list compliance was done by taking daily food consumption lists during polyclinic con-

Table 1. Inclusion and exclusion criteria	
Inclusion criteria	**Exclusion criteria**
Having consent	Those with chronic inflammatory disease
Being 18 years and older	GFR <30 mL/min/1.73 m²
Identifying NYHA Grade II-IV HF and CC by clinical and laboratory methods	Chronic liver disease
Involuntary loss of 6% or more weight without edema in the last 6 months	Organ transplantation
	Any acute medical problem except HF
	Cancer
	Immunosuppressive therapy
	ICU requirement1
	(1If occurs during the follow-ups, they will be excluded from the study)
GFR: glomerular filtration rate; CC: cardiac cachexia; HF: heart failure; ICU: intensive care unit	

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trols. The patients who could not adapt were provided with supplemented meals with energy- and protein-enriched meals or their needs during the follow-up period. After 3 months of nutritional support plan, the patients were re-evaluated.

Determination of cytokines

Five milliliters of venous blood samples were taken from the patients included in the study and the healthy individuals in the control group. IL-1beta, IL-6, IL-10, and TNF-alpha levels in the serum samples were determined by ELISA kit with sandwich enzyme immunoassay method. Blood samples taken from the patients were incubated for 20-30 min at room temperature; and they were then centrifuged at 2000-3000 RPM for 10 min. The supernatant was taken to the microcentrifuge tube and stored at −80°C until the day of the test. The standard mix in the lyophilized state was diluted with diluent. Three hundred microliters of mix diluent was added to seven microcentrifuge tubes: 300 μL of the standard solution was added to the first tube and mixed, and 300 μL was transferred to the second tube, and the same procedure was done until the sixth tube. The mix diluent in the last tube was used as the zero standard. Fifty microliters of standards were added to the eight predefined standard wells, respectively. Fifty microliters of the samples were added to the sample wells. The plate was closed and incubated for 2 h at room temperature. After the incubation, the wells were washed six times with wash buffer. Fifty microliters of prepared Biotin conjugate was added to all wells. The plate was again closed and incubated for 2 h at room temperature. After incubation, the wells were again washed six times. Fifty microliters of prepared streptavidin horseradish peroxidase was added to all wells. The plate was closed and incubated for 30 min at room temperature. The wells were washed six times with the wash buffer. Fifty microliters of TMB substrate solution was added to all wells. The plate was closed and incubated for 10 min at IL1-β, 25 min at IL-6 and TNF-alpha, 15 min at IL-10 at room temperature in the dark. Fifty microliters of the stop solution was added, and the plate was read in an ELISA reader at 450 nm in 10 min. The logarithmic regression equation of the standard curve was calculated according to the OD values corresponding to the concentration of the standards. According to the OD values of the samples, the corresponding sample concentrations were calculated according to this equation. Cytokine measurements were performed before and after NDP.

Echocardiography

The echocardiography (ECO) measurements were made according to the recommendations of the American Society of Echocardiography with the General Electronic VIVID 7 device and 3.5 MHz probe (18). EF, PAP, left ven-

tricular end diastolic diameter, left ventricular end-systolic diameter, interventricular septum diameter, and posterior wall diameters were recorded. The same cardiologist performed the ECO before and after the NDP.

Scoring of the quality of life

The "Ferrans and Powers" Quality of Life Index, which was developed to measure general health, was applied to all patients (n=18) by face-to-face interviews (19). The scale consists of two parts, and it includes questions on satisfaction and importance. The scale has four subsections: health and function, socioeconomic, psychological/spiritual, and family. The scores for each subsection and the total scale score ranged from 0 to 30. Higher scores indicate better quality of life. Two researchers performed life quality scoring before and after the NDP.

Bioelectrical impedance analysis (BIA)

Bioelectrical impedance analysis (TANITA, BC-532) was used to evaluate the body composition. FFM, fat mass, and visceral fat level were evaluated during the measurement. The same two nurses performed the BIA examinations before and after the NDP. Before the BIA, the patients were asked to refrain from activities requiring physical force and not to eat until 2 h. All patients were evaluated before noon and after urine/defecation so that the measurements did not show an unbalanced distribution.

Hand strength measurement and walking speed

Muscle strength assessment was obtained by the standard hand dynamometer (Janmar, USA) three times from the dominant hand. Existing hand measurement was performed in patients with an upper extremity. Measurement of handgrip strength was made in the sitting position, shoulder adduction and neutral rotation, elbow at 90° flexion, forearm midrotation and support, and wrist neutral. Muscle strength measurement results were evaluated according to the standards determined in EWGSOP II data (20). Existing hand measurement was performed in patients with an upper extremity. The walking speed was assessed by conducting the 4-m distance at normal speed. The walking speed was obtained by dividing 4 m by the time (s) through which this distance was exceeded (m/s). The same expert made the measurements before and after NDP.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) version 17 program was used for statistical analysis. The average, standard deviation, lowest, highest, median, 25th and 75th percentile, ratio and frequency values were used in descriptive statistics of the data. The categorical variables were compared with the

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chi-square test. The results of the variables were compared with Mann-Whitney U, Student T, and Wilcoxon tests. The p value <0.05 was considered significant.

Consent

The consent was obtained from each patient according to the Helsinki Declaration. The Istanbul University Istanbul Medical Faculty Ethics Committee approved the study (File No: 2014/925). Istanbul University Scientific Research Projects Unit with project no: 52928 supported the recruitment of the cytokine ELISA kits used in the study.

Results

The study included 18 patients with CC (CC prevalence: 2.5%, 13 male, 5 female) and 18 healthy controls (13 male, 5 female). The mean age was 63.2±17.5 years (range 24-83 years) in the patients with CC, and 59.7±16.2 years in the control group (range 24-85 years). The mean weight and BMI of the patients before the treatment was 63.3±14.1 kg and 22.4±4.5 kg/m², and the control group was 78.6±12.1 kg and 27.8±3.7 kg/m², respectively. The results of the initial ECO examination are given in Table 2.

Table 2. Comparison of measurements of the patients and healthy individuals			
	Healthy control group (n=18)	Cardiac cachexia group (n=18)	p
Weight (kg)	78.6±12.1	63.3±14.1	0.004
BMI (kg/m²)	27.8±3.7	22.4±4.5	0.001
Right MUAC (cm)	31.3±2.8	25.6±4.0	<0.001
Right CC (cm)	37.5±3.0	34.6±3.9	0.019
EF%	66±7	31±12	<0.001
PAP (mmHg)	23.5±2.5	46.8±15.3	<0.001
LVESD (cm)	3.0±0.4	5.1±1.2	<0.001
LVEDD (cm)	4.7±0.5	6.1±1.1	<0.001
Pro-BNP (pg/mL)	69 (30-148)	2131 (928-9170)	<0.001
BIA-FFM (kg)	53.6±9.8	46.1±8.2	0.044
BIA-fat (%)	28.3±6.5	19.5±10.2	0.008
BIA- visceral fat (kg)	12±5	9±5	0.172
BIA-bone (kg)	2.8±0.5	2.5±0.4	0.05
Right hand strength (kg)	35.2±9.6	26.9±6.7	0.007
Walking speed (m/s)	1.23±0.23	0.92±0.37	0.018
Albumin (g/dL)	4.3±0.4	3.9±0.7	0.020
CRP (mg/L)	1.9 (1.2-3.9)	13.1 (10.4-12.5)	0.014
TNF-alpha (pg/mL)	2.31 (2.10-3.04)	3.18 (2.13-4.81)	0.07
IL-1 (pg/mL)	1.31 (1.18-1.57)	1.39 (1.26-1.60)	0.339
IL-6 (pg/mL)	2.39 (2.01-2.78)	6.11 (4.30-18.52)	0.001
IL-10 (pg/mL)	49.05 (45.7-57.0)	51.25 (49.1-61.6)	0.214
Health and functional score	24.4±3.4	14.9±4.7	<0.001
Psychological score	26.0 (22.1-29.6)	18.0 (17.1-21.3)	0.001
Total score	25.1±4.3	18.2±3.8	<0.001
BMI: body mass index; MUAC: mid-upper arm circumference; CC: calf circumference; EF: ejection fraction; PAP: pulmonary artery pressure; LVESD: left ventricle end-systolic diameter; LVEDD: left ventricle end diastolic diameter; Pro-BNP: brain natriuretic peptide; BIA: bioimpedance analysis; FFM: fat free mass; CRP: c-reactive protein; TNF: tumor necrosis factor; IL: interleukin			

Mid-upper arm circumference , calf circumference, FFM, BIA-fat percentage, bone mass, muscle strength, and walking velocities of patients and healthy individuals are given in Table 2. The serum IL-6 level was found to be significantly higher in patients with CC; although the serum TNF-alpha level was higher in the patients, the difference was not statistically significant (Table 2). The quality of life scores of healthy individuals were significantly higher than of patients with CC (Table 2).

One patient who underwent heart transplantation during the study, one patient diagnosed with lung cancer, and six patients hospitalized in the intensive care unit for various reasons were excluded from the study. After 3 months of NDP, weight, BMI, and visceral fat significantly increased in ten patients who completed the study (Tables 3 and 4). While MUAC, hand muscle strength, fat percentage, FFM, and serum albumin levels were increased after NDP, this increase was not statistically significant (Table 4). No sig-

Table 3. Dietary and nutritional support treatments of patients who completed the study

Patient no	Gender/age	BMI1	BMI2	DEN	DPN	Diet	ONS
1	E, 63	24.8	26.7	2000	80	100%	Absent
2	K, 24	16.3	18.5	1750	55	70%	1.5 kcal/mL product (600 kcal/day)
3	E, 67	29.7	30.6	1500	85	60%	0.9 kcal/mL diabetic product (600 kcal/day)
4	E, 54	23.9	25.9	1900	80	60%	2.0 kcal/mL product (800 kcal/day)
5	K, 83	24.6	29.1	1500	75	50%	1.5 kcal/mL product (750 kcal/day)
6	E, 71	18.4	19.6	1800	80	50%	1.5 kcal/mL product (900 kcal/day)
7	E, 80	16.3	17.4	1900	65	75%	2.0 kcal/mL product (400 kcal/day)
8	E, 58	19.3	20.1	2000	75	60%	1.0 kcal/mL diabetic product (800 kcal/day)
9	K, 76	19.6	21.0	1500	60	100%	Absent
10	E, 61	27.6	27.9	2000	80	100%	Absent

DEN: daily energy need; DPN: daily protein need; ONS: oral nutrition supplement; BMI: body mass index (kg/m^2); BMI1: initial BMI; BMI2: Third month control of BMI

Table 4. Comparison of mean and median values of the measurement parameters before and after the nutritional support plan (n=10)

	Before NSP	After NSP	p
Weight (kg)	63.6±14.7	66.0±15.1	0.05
BMI (kg/m^2)	22.19±5.07	23.21±5.31	0.034
Right MUAC (cm)	26.0±4.4	26.6±3.6	0.48
Left MUAC (cm)	25.9±4.2	26.8±3.4	0.18
Right CC (cm)	34.2±3.9	33.1±4.7	0.26
Left CC (cm)	33.9±4.2	33.5±4.6	0.65
BIA-FFM (kg)	46.3±8.7	49.7±7.5	0.168
BIA-fat (% median)	26.4 (19.6-30.3)	22.4 (14.6-27.7)	0.237
BIA-visceral fat level	9±4	11±5	0.042
Right hand strength (kg, median)	30 (26-37)	30.5 (29-31)	0.228
Left hand strength (kg)	28.9±6.7	29.4±4.5	0.596
Walking speed (m/s)	1.04±0.33	1.05±0.32	0.86

NSP: nutritional support plan; BMI: body mass index; MUAC: mid-upper arm circumference; CC: calf circumference; BIA: bioimpedance analysis; FFM: fat free mass

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nificant difference was observed in the cardiac functions of the patients under medical treatment after NDP (Table 5).

There was no significant difference in the serum albumin, CRP, and cytokine levels before and after NDP (Table 6). A significant increase was observed in the total quality of life score (median: 21.1 [18.2-25.6] vs 22.3 [16.7-25.4], p=0.005).

Discussion

Heart failure is observed in approximately 1%-2% of the adult population in the developed countries. The prevalence of HF increases up to ≥10% in individuals aged 70 years and older. In these patients, the average five-year survival was reported as 50% (21). HF establishes a continuous catabolic state with neurohumoral and immuno-

Table 5. The comparison of the ECO measurements before and after the nutritional support plan (n=10)

	Before NSP	After NSP	p
EF (%)	33±12	36±12	0.136
PAP (mmHg)	46±14	45±13	0.867
LVESD (cm)	4.9±0.8	4.8±0.9	0.221
LVEDD (cm)	6.0±0.7	5.9±0.9	0.445
IVST (cm)	1.1±0.2	1.1±0.2	0.411

NSP: nutritional support plan; EF: ejection fraction; PAP: pulmonary artery pressure; LVESD: left ventricle end-systolic diameter; LVEDD: left ventricle end diastolic diameter; IVST: interventricular septum thickness

Table 6. Laboratory parameters before and after the nutritional support plan (n=10)

	Before NSP	After NSP	p
GFR (mL/min)	61±21	68±32	0.308
Albumin (g/dL)	4.1±0.6	4.4±0.4	0.101
CRP (mg/L, median)	3.8 (1.5-15.1)	3.1 (1.7-5.8)	0.285
Hgb (g/dL)	12.2±2.1	12.1±2.4	0.783
TNF-alpha (pg/mL)	3.52±1.66	3.18±1.21	0.551
IL-1 (pg/mL)	1.58±0.67	1.42±0.52	0.144
IL-6 (pg/mL, median)	3.28 (2.15-9.97)	3.43 (2.88-11.53)	0.721
IL-10 (pg/mL)	70.27±36.67	64.17±29.25	0.546

NSP: nutritional support plan; GFR: glomerular filtration rate; CRP: c-reactive protein; TNF: tumor necrosis factor; IL: interleukin

logical complex changes, and it affects nutritional status through energy and substrate metabolism and increased cytokine burden. CC is defined as 6% weight loss in the past 6 months, unrelated to diuretic treatment and unintentionally, without any other underlying disease (cancer, hyperthyroidism, liver disease, etc.). Involuntary weight loss and low BMI are associated with poor prognosis in HF and are associated with a decreased survival of KK (18% survival is 50%) (4).

In our study, the prevalence of CC was found to be 2.5%. One of the reasons for lower prevalence rates in previous studies may be the exclusion of the individuals with all other diseases who can perform cachexia from our study. On the other hand, when talking about the current prevalence data, possible values were mentioned (22). Increased inflammation and sarcopenia (decreased muscle strength and muscle mass) can be seen in HF. CC causes significant changes in muscle, fat, and bone tissue that make up the body composition (22). Our study aimed to evaluate the possible effects of NDP on anthropometric measurements, muscle mass and muscle strength, physical performance, quality of life, cardiac functions, and immune system in patients with advanced stage II-IV cardiac arrest.

In a study conducted by Anker et al. (1, 2), when compared with CC, non-cachectic HF and healthy individuals, BMI was found to be lower in patients with HF than in those with CC. The muscle, fat, and bone tissues decrease in CC. In our study, compared to in healthy subjects, weight and BMI were found to be lower in patients with CC. Similarly, MUAC, calf circumference, and hand strength measured from both sides were lower in patients with CC than those in healthy subjects. When measured by bioelectric impedance analysis, fat percentage, FFM, and bone mass were significantly lower in patients with CC. The serum albumin levels were found to be low because of inflammation and increased catabolic rate; the serum CRP and IL-6 levels were found to be high in the CC group. This result is similar to the results of the previous studies (23).

Rozentryt et al. (23) were able to increase weight and BMI with high-calorie, protein-rich oral NDP in patients with CC. They found that this increase was found in the fat tissue when examined with DEXA. In our study, there were also significant increases in weight and BMI values of our patients when compared to before and after NDP. In BIA analysis, visceral fat percentage (p=0.042) was found to be significantly increased; total fat content, bone mass and muscle mass were also found to be increased by 2.5%, 1.25%, and 3.4%, respectively, but these increases were not statistically significant. The fact that patients with only

CC were included in the study, thus the number of patients being low, and the presence of patients who were excluded during the study were among the most important limiting factors of our study. Another limitation was that during the study, no exercise program was applied and patients' daily activity levels could not be measured.

In a study conducted by Levine et al. (7), the serum albumin levels were not different between patients with CC, patients with non-cachectic HF, and healthy individuals; and the serum IL-6 levels were found to be high in patients with CC. In our study, serum albumin levels were low and serum CRP levels were found to be high in patients with CC. The serum albumin level may be low because of malnutrition and increased catabolic process, but also because of high acute phase response (negative acute phase reactant). The serum IL-6 level was also found to be high in our patients.

In their study, Levine et al. (7) showed that the role of cytokines in patients with HF and CHD was shown by the increased serum TNF-alpha levels. In another study conducted by Anker et al. (1), the serum TNF-alpha levels were found to be significantly higher in patients with CC. However, in our study, although the serum TNF-alpha level was higher in the patient group compared to the healthy control group, this increase was not statistically significant. This may be related to the small number of patients.

The quality of life reflects the multidimensional effect of a clinical condition and treatment on the patient's daily life. Compared to healthy individuals, patients with HF have significantly impaired qualities of life. In our study, life scores of patients with CC were also lower than of the healthy controls. In the study by Rozentryt et al. (23), positive results were obtained in quality of life scales of patients with high-calorie, protein-rich oral NDP. Similarly, in our study, the total quality of life scores of the patients with CC significantly increased after NDP.

In conclusion, the weight loss can be prevented with effective nutritional support plan in patients with CC, and quality of life can be positively affected. The most important limiting factor of the study was the inability to take enough cases in the study group because of inclusion conditions. Although there was an increase in many anthropometric measurements after treatment in a limited number of patient groups, this difference was not statistically significant. Hence, new studies are needed to examine a large number of cases.

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