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# An Investigation of Insulin Resistance and Cachexia Relation in Patients with Metastatic Gastrointestinal Malignancies

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ABSTRACT

***Background:*** Insulin resistance has been suggested as one of the known metabolic disorders during cachexia. This study hypothesized that cachexia in cancer patients might be related to insulin resistance as early as cachexia development.

***Methods:*** This study was performed on 46 patients with metastatic gastrointestinal cancer. Anthropometric characteristics and biochemical markers were assessed at baseline, second and third month. Insulin resistance was assessed using the homeostasis model assessment-estimated insulin resistance (HOMA IR) method. SFQ-36 questions were used to assess the patients' quality of life at baseline, second and third months.

***Results:*** Anthropometric characteristic was significantly associated between pre-cachectic and non-pre-cachectic patients in third month. Cholesterol (P-value = 0.93), albumin (P-value: 0.82), and serum creatinine (P-value = 0.88) in pre-cachectic patients decreased over three months. There was an increasing trend of insulin resistance between pre-cachectic and non-pre-cachectic patients in third month. Cholesterol had an upward trend with a significant relation in cachectic patients [(P-value = 0.00), (P-value = 0.03), (P-value = 0.01)]. We detected a decreasing trend of insulin resistance between cachectic and non-cachectic patients from second to third month (P-value = 0.04). SFQ evaluation had no significant relation with cachectic status.

***Conclusion:*** Previous studies showed that the use of NSAIDs, progesterone's, corticosteroids, COX-2 inhibitors, anabolic agents and drugs targeting inflammatory cytokines may be beneficial for improving of symptoms of cachexia. Significant relation between anthropometric variables with pre-cachexia and cachectic conditions was concluded. Patients' outcome and its relation with insulin resistance demonstrated a significant relation between the cachectic and non-cachectic patients in the third month. We also detected the increased serum cholesterol level in cachectic patients, moreover, higher cholesterol levels in expired cachectic patients than in the living.

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## Introduction

Cachexia is a common complication of patients with cancer that is defined by loss of muscle mass with or without a reduction in fat mass (1). It is considered a life-threatening condition associated with several pathologies (2). Patients with cachexia may not tolerate chemotherapy treatment and may also affect the patient's quality of life, life expectancy, and response to treatment (3, 4). About 60%

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of the 1.4 million patients with cancer in the United States suffer from cachexia each year (5, 6). Contrary to patients intending to lose diet, patients with cachexia have decreased appetite, reduced food intake, and insulin sensitivity (7). These conditions are associated with several metabolic abnormalities, including changes in carbohydrate, protein, lipid metabolism, and insulin resistance (8). Cancer cachexia can also be associated with insulin resistance, which has been shown to increase hepatic glycogenolysis (2) and increase lipid mobilization in white adipose tissue (9).

It has been shown that many factors may be involved in the development of cachexia. One of the leading causes of cachexia is systemic inflammation, which causes the production of pro-inflammatory cytokines such as Interleukin-6 and Interleukin-1 and tumor necrosis factor-alpha. All three of these cytokines cause anorexia, lipolysis, and muscle devasting (10-12).

Clinical manifestation of cachexia includes weight loss, anorexia, asthenia, and laboratory findings such as anemia and hypoalbuminemia (13).

Unlike sarcopenia (decline in muscle mass with aging), cachexia is recognized by muscle decomposition due to protein degeneration, increased basal metabolic rate, and total energy expenditure without any alterations in fat mass (14).

Insulin is an anabolic hormone with broad-spectrum actions, including coordinating glucose oxidation and glycogenesis by increasing glucose uptake in adipose and muscle tissues. It stimulates lipogenesis and inhibits protein degeneration leading to the growth of cells. Insulin is the principal hormone that controls muscle proteolysis (15).

Insulin resistance has been suggested as one of the known metabolic disorders during cachexia (4, 16). Causes of insulin resistance are categorized as acquired, hereditary, and both. Muscles, liver, and adipose tissue are three primary insulin resistance sites. It is thought that alterations in immune-mediated inflammation and free fatty acid levels lead to insulin resistance in muscle tissues and ectopic deposits of free fatty acids (17, 18). Chronic inflammation is one of the leading causes of pancreatic β-cell dysfunction and impaired insulin secretion that leads to muscle decompositions in cancer patients with cachexia (19). In addition to activating cytokines as TNF-α (20), cancer causes changes in muscle cell metabolism, especially the ubiquitin-proteasome pathway, which is involved in protein breakdown and cachexia (21).

In order to indicate the most effective treatment to improve symptoms, it is essential to have a thorough knowledge of the pathophysiology of cachexia in cancer patients. There are different options for treatment of cachexia (22, 23). Initial studies indicated that Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) can be regulate the pro-inflammatory cytokines, C-Reactive Protein (C-RP) and Interleukin-6 (IL-6) (24, 25). However, the efficacy of NSAIDs for cancer cachexia needs systematic further investigation. Owing to the multifactorial pathogenesis and complex clinical presentation of cachexia, particularly in end stage disease, multi-modal therapy and multitargeted approaches should be considered for reversing or improving of symptoms of cachexia.

This study hypothesized that cachexia in cancer patients might be due to insulin resistance as early as cachexia development.

## Methods

This study was performed on 46 patients with metastatic gastrointestinal cancer admitted to the Hematology and Oncology unit in Shahid Ghazi Hospital from June 2019 to April 2020. This project was an observational study, and approval was granted by the ethics committee of Tabriz University of Medical Sciences (code: IR.TBZMED.REC.1397.509). All participants have signed a written consent form and have consented to be included in the study and the publication.

Demographic information, including gender, age, weight, height, were collected. Patients with glomerular filtration rate (GFR) <30 ml/min, Body mass index (BMI) <20 kg / m2 at the time of diagnosis, diabetes, thyroid disease, severe hepatic impairment, and patients under eighteen years of age were excluded from the study. Anthropometric characteristics such as BMI, skinfold thickness, arm, and abdominal circumference, and fat percent were also assessed using calipers and tape measurements at baseline, second month, and the third month. The blood samples were obtained from patients at baseline, second month, and the third month of allocation to measure biochemical markers, including serum creatinine, cholesterol, and albumin.

The Collaborative European Palliative Care Research (EPCRC) identifies cachexia as a syndrome (1, 26, 27). It considers three stages: pre-cachexia (symptoms such as anorexia, metabolic changes, and weight loss <5%), cachexia (BMI <20, weight loss> 5%, systemic inflammation, and decreased food intake), and resistant cachexia. Insulin resistance was assessed by the homeostasis model assessment-estimated insulin resistance (HOMA IR) method, and its level was calculated using the formula: fasting plasma glucose (mmol/l) × fasting serum insulin (mU/l) divided by 22.5 (28). For this purpose, patients' fasting blood sugar (FBS) and insulin concentration were assessed at the baseline, second and third months. 36-item Short Form questionnaire (SFQ-36) was used to assess the patients' quality of Life at Baseline, second and third months (29). The growing use of measures of health which provide data on the subjective experience of respondents has brought with it a need for guidelines for interpretation.

One of the most widely used measures is the SF-36, 1 a generic measure of self-reported health status which contains 36 items and which was initially designed to tap eight dimensions of functioning and well-being. The increasing use of measures of health that make available data on the subjective experience of respondents has led to the need for guiding principle for explanation. One of the most widely used measures is the SF-36, a general measure of self-reported health status that includes 36 items.

**Statistical analysis**

After collecting information from all research units, the data were analyzed using SPSS software. Mean and standard deviation was used to describe quantitatively symmetric data, and median and amplitude for quadratic data were used. Qualitative data were also reported with frequency and percentage. We used Chi-square, Kruskal-Wallis, and Spearman correlation tests to compare clinical and demographic variables with the primary outcomes. Moreover, the relation between clinical and demographic variables with the insulin resistance variable was studied. The chi-square test determined the association between grouped insulin resistance (> 30 and above ≤ 30) and the intended outcomes. The relation between insulin resistance, recorded three times, and death outcome was determined by survival analysis using a random-effects model with Weibull regression distribution. Regression models were used to show the relation between cachexia and death. A P-value less than 0.05 was considered significant.

**Results**

Our data showed that among 46 patients, we observed 13 patients in the second month and 33 patients in the third month who developed pre-cachexia. As shown in Table 1, the result showed that weight (P=0.00), arm circumference (P= 0.00), skinfold (P= 0.03), and abdominal circumstance (P=0.00) were significantly related between pre-cachectic and non-pre-cachectic patients in the third month. No prominent relation was detected between fat percent changes in these patients during three months. Cholesterol (P= 0.93), albumin (P= 0.82), and serum creatinine (P= 0.88) in pre-cachectic patients decreased over three months. However, these markers were insignificant between non-pre-cachectic and pre-cachectic patients (Table 1). In pre-cachectic individuals, FBS had a decreasing trend from 119.92 ± 30.81 to 111.68 ± 35.12 in the second to third months, while in non-pre-cachectic individuals, it had an increasing trend from 103.06 ± 30.36 to 112.71 ± 32.42 in the second to the third months (Table 1). We detected an increasing trend of Insulin resistance in pre-cachectic patients from the second to the third month. There was no significant relation with FBS changes, insulin concentration, insulin resistance, and SFQ in pre-cachectic and non-pre-cachectic individuals (Table 1).

**Table 1.** Relationship between biochemical and anthropometric variables with Pre Cachexia.

| | Pre Cachexia$_1$ | Pre Cachexia$_2$ | | **P value** | Pre Cachexia$_3$ | | **P value** |
|---|---|---|---|---|---|---|---|
| | **NO(N=46)** | **NO(N=33)** | **Yes(N=13)** | | **NO(N=14)** | **Yes(N=32)** | |
| **Age(year)** | 56.43±12.95 | 57.27±14.22 | 54.30±9.08 | 0.43 | 55.14±15.73 | 57.00±11.77 | 0.68 |
| **Height(cm)** | 165.73±9.00 | 165.39±9.39 | 166.61±8.24 | 0.70 | 163.35±9.73 | 166.78±8.62 | 0.19 |
| **Weight** | 66.30±12.09 | 65.48±13.32 | 68.61±8.86 | 0.58 | 56.96±15.96 | 68.39±9.10 | 0.00 |
| **Fatpercent (%)** | 32.46±6.14 | 32.08±6.93 | 33.30±3.74 | 0.46 | 29.17±8.14 | 33.37±4.59 | 0.07 |
| **Skinfold** | 27.01±12. 73 | 26.94±13.55 | 26.66±9.97 | 0.87 | 22.52±15.83 | 28.41±11.08 | 0.03 |
| **Arm (cm)** | 26.16±3.29 | 25.39±3.64 | 26.23±2.71 | 0.55 | 22.64±4.32 | 26.18±2.75 | 0.00 |
| **Abdomen (cm)** | 91.95±12.50 | 90.87±14.67 | 91.15±8.15 | 0.99 | 84.64±16.81 | 93.46±10.67 | 0.00 |
| **FBS (mg/dl)** | 122.80±49.72 | 103.06±30.36 | 119.92±30.81 | 0.01 | 112.71±32.4 | 111.68±35.1 | 0.90 |
| **Cholestrol (mg/dl)** | 177.13±59.99 | 187.00±50.34 | 206.46±49.16 | 0.10 | 199.00±66 | 191.59±47.4 | 0.93 |
| **Albumin (mg/dl)** | 3.78±0.50 | 3.88±0.50 | 4.01±0.59 | 0.75 | 3.89±0.48 | 3.94±0.52 | 0.82 |
| **Cratinine (mg/dl)** | 0.99±0.19 | 0.97±0.20 | 1.08±0.24 | 0.16 | 1.01±0.22 | 1.02±0.21 | 0.88 |
| **Insulin Concentration** | 20.58±20.60 | 17.75±12.30 | 13.78±9.58 | 0.38 | 11.75±8.72 | 17.93±14.93 | 0.18 |
| **Insulin Resistance** | 123.15±140.1 | 80.89±63.65 | 75.22±56.63 | 0.91 | 62.18±54.19 | 83.09±66.24 | 0.22 |
| **SFQ-36** | 89.04±4.15 | 87.27±4.20 | 87.15±4.50 | 0.93 | 82.92±3.49 | 85.00±3.69 | 0.07 |

P values are calculated by Kruskal-Wallis statistical tests. FBS: Fasting Blood Sugar, SFQ-36: 36-item Short Form Quesstionare

Among 46 patients, five patients in the second month and 11 patients in the third month developed cachexia. The weight (P= 0.02, P= 0.00), arm circumference (P= 0.00, P= 0.00), fat percent (P= 0.00, P= 0.00) between cachectic and non-cachectic patients in the second month. Moreover, skinfold (P= 0.00) and abdominal circumstance (P= 0.00) evaluation detected significant correlations between cachectic and non-cachectic patients in the third month (Table 2). In cachectic patients, the cholesterol trend was elevated from 152.80 ± 34.96 to 196.90 ± 73.44 during three months; however, the considerable relation between cachectic and non-cachectic patients was observed only in the second month (Table 2). We also observed decreased cholesterol levels in cachectic patients at month two while increasing in month three. The albumin and creatinine trend in cachectic patients were insignificant clinically. FBS had an increasing trend in cachectic and non-cachectic individuals in the second and third months, while it also had a decreasing trend in non-cachectic individuals (Table 2). No significant relation was detected with FBS changes in cachectic and non-cachectic individuals. There was meaningful relation of insulin concentration between cachectic and non-cachectic patients in the third month (P= 0.03) (Table 2). We detected a decreasing trend of insulin resistance between cachectic and non-cachectic patients from the second to the third month (P= 0.04). (Table 2). SFQ evaluation had no significant relation with cachectic status (Table 2). Examination of biochemical and anthropometric changes with patients' fate showed only cholesterol had an upward trend with a significant relation in cachectic patients [(P = 0.00), (P= 0.03), (P= 0.01), (Table 3)].

**Table 2.** Relationship between biochemical and anthropometric variables with Cachexia.

| | Cachexia $_1$ | Cachexia $_2$ | | P value | Cachexia $_3$ | | P value |
|---|---|---|---|---|---|---|---|
| | NO(N=46) | NO(N=41) | Yes(N=5) | | NO(N=35) | Yes(N=11) | |
| Age(year) | 56.43±12.95 | 57.14±12.11 | 50.60±19.29 | 0.31 | 57.48±11.87 | 53.09±16.11 | 0.34 |
| Height(cm) | 165.73±9.00 | 165.68±8.85 | 166.20±11.32 | 0.89 | 166.45±8.33 | 163.45±11.03 | 0.36 |
| Weight1(kg) | 66.30±12.09 | 68.02±11.40 | 52.80±10.89 | 0.02 | 69.18±10.55 | 51.31±7.96 | 0.00 |
| Fatpercent (%) | 32.46±6.14 | 33.24±5.78 | 25.80±5.75 | 0.01 | 33.92±4.88 | 26.26±6.22 | 0.00 |
| Skinfold | 27.01±12.73 | 27.85±12.69 | 18.74±7.90 | 0.12 | 29.19±12.70 | 18.43±9.73 | 0.00 |
| Arm (cm) | 26.16±3.29 | 26.17±3.08 | 21.20±2.77 | 0.00 | 26.51±2.88 | 20.63±1.70 | 0.00 |
| Abdomen (cm) | 91.95±12.50 | 92.02±12.91 | 82.20±12.09 | 0.10 | 94.62±12.29 | 78.54±8.14 | 0.00 |
| FBS (mg/dl) | 122.80±49.72 | 109.41±32.1 | 94.80±18.57 | 0.25 | 112.25±34.8 | 111.18±32.75 | 0.76 |
| Cholestrol (mg/dl) | 177.13±59.99 | 197.34±49.9 | 152.80±34.96 | 0.04 | 192.88±46.7 | 196.90±73.44 | 0.93 |
| Albumin (mg/dl) | 3.78±0.50 | 3.97±0.50 | 3.50±0.56 | 0.07 | 3.97±0.53 | 3.76±0.39 | 0.23 |
| Creatinine (mg/dl) | 0.99±0.19 | 1.00±0.21 | 0.99±0.26 | 0.88 | 1.00±0.21 | 1.05±0.23 | 0.57 |
| Insulin Concentration | 20.58±20.60 | 16.14±10.41 | 20.62±20.44 | 0.98 | 18.26±14.35 | 9.01±6.06 | 0.03 |
| Insulin Resistance | 123.15±140.1 | 77.27±53.49 | 95.78±114.51 | 0.73 | 86.61±67.24 | 45.25±32.2 | 0.04 |
| SFQ-36 | 89.04±4.15 | 87.56±4.33 | 84.60±2.30 | 0.10 | 85.20±3.70 | 81.72±2.37 | 0.00 |

P values are calculated by Kruskal-Wallis statistical tests. FBS: Fasting Blood Sugar, SFQ-36: 36-item Short Form Quesstionare

**Table 3.** Relationship between biochemical and anthropometric variables with Fate.

| | Fate | | P-value |
|---|---|---|---|
| | Death(N=12) | Alive(N=34) | |
| **Height(cm)** | 162.00±10.08 | 167.05±8.36 | 0.06 |
| **Age(year)** | 53.16±16.28 | 57.58±11.62 | 0.26 |
| **Weight1(kg)** | 61.33±15.04 | 68.05±10.58 | 0.24 |
| **Weight2(kg)** | 61.08±15.01 | 68.23±10.70 | 0.20 |
| **Weight3(kg)** | 59.95±14.53 | 66.66±11.51 | 0.23 |
| **Fatpercent1(%)** | 31.82±7.40 | 32.69±5.74 | 0.89 |
| **Fatpercent2(%)** | 31.62±7.26 | 32.72±5.84 | 0.81 |
| **Fatpercent3(%)** | 31.43±7.11 | 32.32±5.83 | 0.87 |
| **Skinfold 1** | 26.38±13.15 | 27.24±12.78 | 0.99 |
| **Skinfold2** | 25.90±12.39 | 27.20±12.75 | 0.99 |
| **Skinfold3** | 25.72±12.33 | 26.93±13.16 | 0.98 |
| **Arm1(cm)** | 25.33±3.82 | 26.45±3.10 | 0.41 |
| **Arm2(cm)** | 24.66±4.03 | 25.97±3.14 | 0.36 |
| **Arm3(cm)** | 24.04±3.95 | 25.48±3.52 | 0.19 |
| **Abdomen 1(cm)** | 87.50±14.17 | 93.52±11.67 | 0.10 |
| **Abdomen2(cm)** | 86.83±13.83 | 92.41±12.68 | 0.21 |
| **Abdomen3(cm)** | 86.58±14.10 | 92.26±12.90 | 0.18 |
| **FBS1(mg/dl)** | 138.58±60.76 | 117.23±44.93 | 0.48 |
| **FBS2(mg/dl)** | 113.16±35.85 | 105.94±29.61 | 0.78 |
| **FBS3(mg/dl)** | 113.00±32.33 | 111.64±34.99 | 1.00 |
| **Cholestrol1(mg/dl)** | 213.58±5.76 | 164.26±57.97 | 0.00 |
| **Cholestrol2(mg/dl)** | 221.33±48.56 | 182.32±47.42 | 0.03 |
| **Cholestrol3(mg/dl)** | 226.16±53.26 | 182.44±49.30 | 0.01 |
| **Albumin 1(mg/dl)** | 3.91±0.54 | 3.73±0.49 | 0.19 |
| **Albumin 2(mg/dl)** | 4.09±0.48 | 3.86±0.53 | 0.42 |
| **Albumin 3(mg/dl)** | 4.05±0.43 | 3.87±0.53 | 0.35 |
| **Creatinine 1(mg/dl)** | 0.92±0.15 | 1.02±0.20 | 0.17 |
| **Creatinine 2(mg/dl)** | 0.92±0.15 | 1.03±0.23 | 0.14 |
| **Creatinine 3(mg/dl)** | 0.98±0.25 | 1.03±0.20 | 0.31 |
| **Insulin Concentration 1** | 23.50±21.48 | 19.55±20.51 | 0.57 |
| **Insulin Concentration 2** | 16.85±10.45 | 16.55±12.17 | 0.65 |
| **Insulin Concentration 3** | 10.79±7.90 | 17.91±14.51 | 0.15 |
| **Insulin Resistance 1** | 140.58±118.48 | 117.00±148.14 | 0.36 |
| **Insulin Resistance 2** | 76.70±39.97 | 80.20±67.58 | 0.51 |
| **Insulin Resistance 3** | 51.32±34.79 | 85.69±68.46 | 0.14 |
| **SFQ-36 1** | 89.41±3.89 | 88.91±4.29 | 0.49 |
| **SFQ-36 2** | 86.08±4.10 | 87.64±4.27 | 0.31 |
| **SFQ-36 3** | 83.50±3.28 | 84.67±3.86 | 0.31 |

P values are determined by random-effect Weibull regression distribution.
FBS: Fasting Blood Sugar, SFQ-36: 36-item Short Form Questionnaire

In addition, as shown in Table 3, there are higher cholesterol levels in expired cachectic patients than in the living.

Patients' outcome and its relation with insulin resistance (age of > 30, and above) demonstrated a significant relation between the cachectic and non-cachectic patients in the third month (P= 0.02) (Table 4).

**Table 4.** Relationship between insulin resistance and intended outcomes.

| | | Insulin Resistance 1 | | Insulin Resistance 2 | | Insulin Resistance 3 | |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| **Pre cachexia$_1$** | **Yes** | - | - | - | - | - | - |
| | **No** | 12(100) | 34(100) | 7(100) | 39(100) | 12(100) | 34(100) |
| | **P-value** | - | | - | | - | |
| **Pre cachexia$_2$** | **Yes** | 3(25) | 10(29) | 3(42.9) | 10(25.6) | 4(33.3) | 9(26.5) |
| | **No** | 9(75) | 24(70.6) | 4(57.1) | 29(74.4) | 8(66.7) | 25(73.5) |
| | **P-value** | 1.00 | | 0.3 | | 0.45 | |
| **Pre cachexia$_3$** | **Yes** | 9(75) | 23(67.6) | 5(71.4) | 27(69.2) | 6(50) | 26(76.5) |
| | **No** | 3(25) | 11(32.4) | 2(28.6) | 12(30.8) | 6(50) | 8(23.5) |
| | **P-value** | 0.72 | | 1.00 | | 0.09 | |
| **Cachexia$_1$** | **Yes** | - | - | - | - | - | - |
| | **No** | 12(100) | 34(100) | 7(100) | 39(100) | 12(100) | 34(34) |
| | **P-value** | - | | - | | - | |
| **Cachexia$_2$** | **Yes** | 1(8.3) | 4(11.8) | 2(28.6) | 3(7.7) | 2(16.7) | 3(8.8) |
| | **No** | 11(91.7) | 30(88.2) | 5(71.4) | 36(92.3) | 10(83.3) | 31(91.2) |
| | **P-value** | 1.00 | | 0.16 | | 0.39 | |
| **Cachexia$_3$** | **Yes** | 2(16.7) | 9(26.5) | 2(28.6) | 9(23.1) | 6(50.) | 5(14.7) |
| | **No** | 10(83.3) | 25(73.5) | 5(71.4) | 30(76.9) | 6(50) | 29(85.3) |
| | **P-value** | 0.7 | | 1.00 | | 0.02 | |
| **Fate** | **alive** | 9(75) | 25(73.5) | 5(71.4) | 29(74.4) | 8(66.7) | 26(76.5) |
| | **death** | 3(25) | 9(26.5) | 2(28.6) | 10(25.6) | 4(33.3) | 8(23.5) |
| | **P-value** | 1.00 | | 1.00 | | 0.37 | |

P values are calculated by Chi-square statistical tests.

## Discussion

Cancer is the second prominent cause of morbidity and mortality worldwide and the leading cause of death, accounting for nearly 10 million deaths in 2020 (30). About 30% to 90% of patients with cancer are suffering from cachexia (16). Consequently, mortality rates have been reported to be more than 20% (31). Evidence suggests that the prevalence of cachexia is 60% in lung cancer and about 80% in GI cancers (32).

Treatment of cachexia is a challenge for clinicians in practice field (33). It's suggested that single therapy may be not suitable approach for treating of cachexia in cancer patients. Although there are studies that indicated use of NSAIDs, progesterone's, corticosteroids, COX-2 inhibitors and anabolic agents may be beneficial (34). In addition, studies demonstrated optimistic results of ghrelin and ghrelin mimetics, and drugs targeting inflammatory cytokines (34). Appropriate treatment of

cachexia should include medications aimed at ameliorating the inflammatory state, nutritional disorders, metabolic disorders, immunodeficiency, poor quality of life, and especially fatigue (34).

Our study showed that weight, arm circumference, abdomen circumference, and skin folding were significantly associated with pre-cachexia and cachexia patients. Moreover, we observed a fat percent relation with cachexia. Weight loss in cancer patients occurs due to an imbalance between energy intake and metabolic needs. It also can play a fundamental role as an independent factor for responding to anti-cancer therapies and reducing survival time (35-37). Adipose tissue is a valuable source of energy in cachectic patients, and the reduction of fat mass is a prominent feature of cachectic cancer patients. Most cancer patients suffer from tissue and muscle wasting because they cannot attain a positive energy balance and, in many cases, cannot preserve their initial body weight (38).

Martin et al.'s study (2013) on patients with cancer (lung or GI; N = 1,473) showed that in cachectic patients, high weight loss, low muscle mass index, and muscle weakness are considered as prognostic factors for patients survival (39). A case-control study was conducted on 262 patients in a multicenter clinical investigation from 2013 to 2020 using the Fearon criteria for patients with cachexia. Based on clinical experience and previous studies, variables including BMI, mid-arm circumference, mid-arm muscle circumference, calf circumference, and triceps skinfold (TSF) were carefully chosen for inclusion in the multivariable model. Results showed That TSF ($P = 0{\cdot}014$) was a significant independent protective factor (40).

Low serum albumin levels are the strongest predictors of mortality and poor disease outcomes in cancer patients (41). Our study demonstrated a reduction in albumin serum levels over three months in pre-cachectic patients. Nevertheless, these markers were insignificant between non-pre-cachectic and pre-cachectic patients.

Cachexia induced by cancer is associated with widespread metabolic disorders (2). Reduced serum cholesterol has been detected in newly diagnosed solid tumors and lung cancer with different histological types (42, 43). Nevertheless, in some other studies, elevated serum triacylglycerol and cholesterol levels have been detected in patients suffering from cancer-associated cachexia (44-47). A significant relation of cholesterol alteration with cachectic and non-cachectic patients was observed in our study in the second month. We detected decreasing cholesterol trend in pre-cachectic patients over three months. We also observed decreased cholesterol levels in cachectic patients at month two while increasing in month three. Over the three months in alive patients, serum cholesterol levels were meaningfully lower than those who had expired. Furthermore, there was a significant relation between cholesterol levels with patients' fate during three months. It may be due to differences in cancer type, diet, and lifestyle of studied patients.

Rosa-Caldwell et al., (2020), evaluated the markers of fatty acid and cholesterol metabolism for the development and progression of cancer cachexia in mice. The results demonstrated altered lipid and cholesterol metabolism mRNA content. Srebp1, mRNA as an essential transcription factor for lipid and cholesterol synthesis, showed a linearly reduced content with cancer progression ($R2 = 0.33$, $P = 00.004$). In contrast, consistent with the results of our study, as an essential mediator for cholesterol synthesis and mRNA content, HMG-CoA reductase demonstrated a quadratic correlation with cancer progression, with a trough at one week of cancer development gradually increasing in 2, 3, and 4wk animals ($R2 = 0.16$, $p = 0.032$) (48).

Pihlajamäki et al., performed a study in 2004 on 72 healthy normoglycemic men about the connection between serum cholesterol precursors, reflecting cholesterol synthesis, and serum plant sterols and cholestanol, reflecting cholesterol absorption efficiency, with insulin sensitivity measured with the hyper insulinemic-euglycemic clamp (49). Their result showed that insulin resistance is related to high cholesterol precursors ratios ($P < 0.05$), while no significant difference was observed in serum absorption sterols. The authors concluded that insulin resistance is associated with high cholesterol synthesis and decreased cholesterol uptake. In order to fasting insulin is associated with cholesterol synthesis independent of BMI and whole-body glucose uptake (WBGU), it should be assumed that hyperinsulinemia's regulation of cholesterol synthesis may be related between insulin resistance and cholesterol metabolism.

In cancer patients, insulin resistance is presented by dwindled insulin sensitivity or impaired glucose tolerance (50) and is assumed to increase during cachexia progression (8). In addition, plasma glucose levels may be increased in patients with cancer cachexia by increasing glucagon levels and increasing hepatic gluconeogenesis (51). However, some studies demonstrated no altered plasma glucose levels in cancer cachexia (16, 52). Our finding showed that fasting plasma glucose levels had a decreasing trend in pre-cachectic individuals in the second month. In comparison, it had an increasing trend in both non-cachectic and cachectic individuals in the second and third months. FBS also had a decreasing trend in cachectic patients rather than non-

cachectic individuals. High levels of FBS in non-cachectic patients may be due to the good nutritional status of these patients than cachectic people. Furthermore, we did not detect a significant relation with FBS changes in cachectic and non-cachectic individuals. It may be the feasibility of reflecting a complex metabolic dynamic in cancer cachexia (53).

Honors and Kimberly conducted review examining evidence supporting insulin resistance in developing muscle wasting during cancer cachexia. Their study demonstrated that patients suffering from cancer cachexia tend to exhibit insulin resistance, and improvements in insulin resistance can improve cachexia symptoms. In addition, evidence suggests that insulin resistance may occur prior to the onset of cachexia symptoms (4).

The method used in our study to assess insulin resistance is HOMA IR. In this method, fasting blood sugar and insulin concentration are expected to increase due to the development of insulin resistance. In contrast, we detected low levels of FBS and insulin concentration in cachectic patients. Patients may have poor nutritional status depending on the location of the gastrointestinal tumor, which often prevents them from an adequate diet and contributes to the early manifestations of malnutrition. The results may also be due to the fact that in the cachectic stage of cancer patients, the body's metabolism increases, and on the other hand, fasting blood sugar decreases due to a decrease in energy intake.

According to the HOMA IR, we also expected an increased level of insulin concentration in cachectic patients, which was decreased. Since the HOMA IR method is based on FBS and is prone to confounding factors, independent FBS methods are suggested to assess insulin resistance. Some studies have shown the association of some serum proteins and lipids with insulin resistance. Protein factors include some adipokines such as leptin and adiponectin. The ratio of leptin to adiponectin is one of the indicators of insulin resistance (54).

The present study concluded that there was an inverse relation between insulin resistance and cachexia. In addition, lower resistance was observed in cachectic patients. In patients with pre-cachexia, there was an increasing trend of insulin resistance in the second and third months. It may be because of an adequate number of cases and the quarterly follow-up of pre-cachectic patients. Therefore, the follow-up to assess insulin resistance should continue for more than three months. Over time, patients with pre-cachexia develop cachexia and may develop insulin resistance. In patients with pre-cachexia, an increase in insulin resistance was observed in the second and third months. It may be due to the sufficient number and the quarterly follow-up of pre-cachectic patients. Therefore, the follow-up to assess insulin resistance should continue for a more extended time. Over time, patients with pre-cachexia develop cachexia and may develop insulin resistance.

This study was performed on a small group of patients with gastrointestinal cancer over a short period. Therefore, it is suggested that a large study population with various cancers be conducted for an extended time. In addition, we propose methods for measuring FBS-independent insulin resistance to remove the confounder.

This study hypothesized that insulin resistance might be a factor in cachexia development in cancer patients. We find a decreasing trend of insulin resistance in pre-cachectic patients in the third month. While a decreasing trend of insulin resistance we detected. Moreover, a significant relation between anthropometric variables with pre-cachexia and cachectic conditions was concluded. We also detected the increased serum cholesterol level in cachectic patients, moreover, higher cholesterol levels in expired cachectic patients than in the living ones. It may be due to differences in cancer type, diet, and lifestyle of studied patients.

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