

Original Article



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Correspondence to









Farzad Shidfar

Department of Nutrition, School of Public Health, Iran University of Medical Sciences, P.O Box: 14665-354, Shahid Hemmat Highway, Tehran 1449614535, Iran.
Email: shidfar.f@iums.ac.ir

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ORCID iDs

Soudabeh Zare 
<https://orcid.org/0000-0001-8963-7697>
Motahareh Hasani 
<https://orcid.org/0000-0002-9002-1192>
M. Dulce Estêvão 
<https://orcid.org/0000-0002-7151-8363>
Rahim Tahmasebi 
<https://orcid.org/0000-0003-2629-5233>
Leila Azadbakht 
<https://orcid.org/0000-0002-5955-6818>
Farzad Shidfar 
<https://orcid.org/0000-0002-6531-9253>
Javad Heshmati 
<https://orcid.org/0000-0002-2676-0185>
Somayeh Ziaei 
<https://orcid.org/0009-0002-6614-3672>

Muscle Strength and Biochemical Markers as Predictors of Depression in Hemodialysis Patients: A Cross-Sectional Study

Soudabeh Zare ¹, Motahareh Hasani ², M. Dulce Estêvão ³, Rahim Tahmasebi ⁴,
Leila Azadbakht ⁵, Farzad Shidfar ¹, Javad Heshmati ⁶, Somayeh Ziaei ⁶

¹Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Tehran 1449614535, Iran

²Department of Nutritional Sciences, School of Health, Golestan University of Medical Sciences, Gorgan 49341-74515, Iran

³Universidade do Algarve, Escola Superior de Saúde, Campus de Gambelas, Faro 8005-139, Portugal

⁴Department of Epidemiology & Biostatistics, School of Health, Bushehr University of Medical Sciences, Bushehr 7514633341, Iran

⁵Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran 141556117, Iran

⁶ICU Department, Imam Reza Hospital, Kermanshah University of Medical Sciences, Kermanshah 6714415333, Iran

ABSTRACT

Patients with chronic renal failure, many of which treated with hemodialysis, present a high prevalence of impaired muscle strength which suggest that muscle mass parameters may be used as markers for changes in muscle in these patients. Measurement of handgrip strength (HGS) is a common, simple, and quick measure of muscle function an indicator of overall muscle strength which has been associated with physical activity and several anthropometric traits. Intercellular adhesion molecule-1 (ICAM-1) and insulin-like growth factor-1 (IGF-1) are biochemical markers associated with inflammatory processes which are a common consequence of dialysis. Additionally, hemodialysis patients frequently present signs of malnutrition and depression. This cross-sectional study aimed to evaluate if muscle and biochemical markers could be used to predict the risk of depression in hemodialysis patients. Several anthropometric parameters, nutrient intake, depression state and the serum levels of ICAM-1 and IGF-1 were determined and Pearson's correlation coefficient and/or Spearman's correlation coefficient were used to test the correlation between them. Our results do not show a correlation between HGF, IGF-1 and ICAM-1 with the depression status of the patients, but mid-arm muscle circumference (MAMC) was statistically and positively correlated with depression. Additionally, ICAM-1 levels were negatively correlated with HGS, MAMC, and IGF-1. Overall, the results of the present study suggest that HGS may be used as an indicator of cardiovascular diseases and MAMC may be a good predictor of the level of depression in hemodialysis patients, although further studies are required.

Keywords: Muscle strength; Intercellular adhesion molecule-1; Insulin-like growth factor I; Hemodialysis

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Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

Conceptualization: Shidfar F; Data curation: Zare S; Formal analysis: Tahmasebi R; Funding acquisition: Zare S; Investigation: Heshmati J; Methodology: Ziaei S; Project administration: Shidfar F; Resources: Hasani M; Software: Esteveo M; Supervision: Azadbakht L; Validation: Heshmati J; Visualization: Hasani M; Writing - original draft: name; Ziaei S - review & editing: Heshmati J, Shidfar F, Zare S.

INTRODUCTION

Impaired muscle strength is a well-known phenomenon occurring in disease-related chronic renal failure (CRF) and a prevalence of impaired muscle strength ranges between 18 and 75 percent of patients with CRF. Therefore, markers that may indicate the state of the muscle mass are important predictors of dialysis outcomes in these patients [1]. The most common treatment in the end stages of renal disease (ESRD) is hemodialysis or kidney transplantation [2]. ESRD can cause a negative clinical situation, which in turn results in both structural and systemic alterations in the musculoskeletal function. It has been shown that in nearly 95% of dialysis patients, will face comorbidities of kidney complications such as fatigue and frailty, related to uremia [3,4].

Resistance exercise has been related to improvements in muscle strength, muscle reserves, and better life expectancy in ESRD patients [5]. In clinical evaluations, handgrip strength (HGS), the incremental shuttle walk test and the “5 times sit to stand” test are generally used for the evaluation of muscle health and strength [6]. Measurement of HGS is a common, simple, and quick measure of muscle strength in practical studies or sports medicine field as a critical factor of overall muscle function [7]. HGS can show the gross ability of the hand and has been demonstrated to be strictly related to physical activity as well as body composition and demographic factors, including hand length and shape, age, sex, body mass index (BMI) and handedness [8]. Strength physiologically declines with age and typically men have a stronger average HGS than women [9]. In both genders, hand asymmetry in grip strength was detected, with the dominant hand (represent as the hand which mostly used for object manipulation) being roughly 10% more functional than the non-dominant one, however this difference is more been observed in right-handed subjects than left-handed [10]. Moreover, the size of the hand has been demonstrated to be positively associated with grip strength for both genders. It was also revealed that shape of the hand affects grip strength and, for both males and females, individuals with big size hands (i.e., large hand length and width) tend to be remarkably stronger than individuals with smaller hands [11].

Intercellular adhesion molecule-1 (ICAM-1) is a cell surface glycoprotein and an adhesion receptor primarily known for its role in regulating the recruitment of leukocytes from circulation to sites of inflammation [12,13]. The upregulation of ICAM-1 expression in response to inflammatory signals is well-documented [14]. In vascular endothelial cells, increased expression of ICAM-1 can also strongly contribute to the response to an inflammatory state [15]. Adhesion molecules have critical role in the endothelial cells-leukocytes adherence and in the subsequent movement of white blood cells into perivascular tissues [16]. Changes of ICAM-1 expression may cause the clinical manifestations of a different type of complications, mostly by altering in normal immune activity [12]. Among these complications, atherosclerosis, many inflammatory disorders (e.g., asthma and autoimmune disorders), malignancies (e.g., melanoma and lymphomas), ischemia, and allogeneic organ transplantation could be found [17,18]. Elevated ICAM-1 levels, a marker of inflammation, have been associated with increased pro-inflammatory cytokines in the body, disrupting the delicate balance of proteins crucial for neurological function [19]. This dysregulation in protein homeostasis may contribute to altered signaling pathways in the brain, potentially fostering conditions conducive to depression. Understanding the intricate interplay between ICAM-1 levels and protein status offers insights into the complex molecular mechanisms underlying the link between inflammation and depressive disorders [20].

It has been reported that insulin-like growth factor (IGF-1) have a critical role in cellular development and maintenance in cardiovascular tissue, especially in pathological situations [21]. IGF-1 is a polypeptide growth factor that binds to the type I IGF-1 receptor, a tyrosine kinase receptor with a 70% homology to the insulin receptor [22]. Type I IGF-1 receptor is found in several cell types, such as endothelial cells and vascular smooth muscle cells. The IGF-1R is the main receptor in transformation, mutagenesis, and decreasing the process of apoptosis. Serum and tissue levels of IGF-1 are strictly regulated by various IGF-1-binding proteins [23]. Elevated IGF-1 levels in the body, a hormone crucial for growth and development, have been correlated with improved protein status, indicating a potential connection between enhanced protein metabolism and mood regulation that may contribute to lower the risk of depression [24]. Conversely, decreased IGF-1 levels and compromised protein status may be implicated in the pathophysiology of depression, suggesting a complex interplay between hormonal balance, protein homeostasis, and mental health [25]. Furthermore, in spite of the importance of the interplay between depression, muscle strength, and biochemical markers like ICAM-1 and IGF-1 in hemodialysis patients, it is essential to acknowledge that nutrition intake plays a pivotal role in modulating these factors; particularly intake of energy nutrients, can significantly impact on muscle health and immune responses, which in turn may influence depression outcomes in hemodialysis patients.

Given the complex interplay between muscle strength, inflammatory processes, and the unique challenges faced by hemodialysis patients, investigating depression status of patients was justified in this study. Depression is a frequent comorbidity in hemodialysis patients, likely linked to the physical and psychological burdens of their condition. Understanding the relationship between depression and factors such as muscle strength and biochemical markers like ICAM-1 and IGF-1 could provide valuable insights into improving the overall well-being and quality of life for these individuals. Therefore, our study aims to unravel these intricate connections and potentially identify novel avenues for intervention and support in the hemodialysis patients.

MATERIALS AND METHODS

Participants and study design

This cross-sectional study was conducted in Bushehr, Iran, including 90 patients with hemodialysis who referred to the dialysis ward of Shohadaye Khalije Fars Hospital in 2019. The sample size was calculated based on Kalender et al. [26] using the coefficient from the correlation between Beck depression score and IGF-1 (0.358), considering a type 1 error (α) of 0.05 and power of 90%. The sample size of 78 patients was calculated, however, 90 patients were included, considering a 15% dropout rate.

Sociodemographic characteristics, anthropometric indices, and dietary intake

Information on sociodemographic characteristics, including age, sex, and time since the start of dialysis, was collected from each patient using a questionnaire. All the anthropometric indices were measured after dialysis. Height was measured without shoes to the nearest 0.5 cm using a tape measure, and the participants' body weight was measured using the Seca scale, without shoes and to the nearest 100 g. The mid-arm circumference (MAC) of the right arm was measured using tape measure to the nearest 1 mm. Furthermore, triceps skinfold thickness (TSF) was measured using a skinfold caliper to the nearest 1 mm. For MAC and TSF 3 measurements were taken, and the average measurement was recorded. The mid-arm

muscle circumference (MAMC) was calculated using a standard formula [27]: $MAMC \text{ (mm)} = MAC \text{ (mm)} - (3.1415 \times TSF \text{ (mm)})$. BMI was calculated using the measured height and weight, and the BMI value in 18–25 kg/m² would be considered as normal weight [28]. To evaluate the HGS, patients were asked to squeeze around a hydraulic hand dynamometer 3 times, and the highest value was recorded. Four 24-hour dietary recalls (2 days of dialysis and 2 days of non-dialysis), collected over non-consecutive days, were used to assess participants' food and nutrient intake. A modified Nutritionist IV program was used to estimate the intake of nutrients [29].

Depression assessment

The Beck Depression Inventory (BDI), including 21 items, was used to assess the depression state of each participant [30]. The total score ranges from 0 to 63. The score range between 0–9 implies the reference group (no depression), 10–19, 20–29, 30–39, and 40–63 means mild depressive symptoms, moderate depressive symptoms, severe depressive symptoms, and very severe depression, respectively. In our study, we took several measures to ensure the reliable handling of the questionnaire as follows.

Training of professionals

The professionals involved in administering the BDI underwent comprehensive training to ensure they understood the nuances of the questionnaire and how to interact with the participants during the assessment.

Standardized administration

The BDI was administered to all participants in a standardized manner. The professionals followed a set protocol to maintain consistency in the assessment process.

Privacy and confidentiality

Participants were assured of the confidentiality of their responses, which encouraged them to provide honest and accurate information.

Avoidance of leading questions

Care was taken to avoid leading questions or any form of bias during the assessment. Professionals followed a neutral and non-directive approach.

Scoring reliability

Scoring of the BDI was performed by trained professionals following a standardized scoring system to minimize subjectivity in the interpretation of responses.

Biochemical analysis

Fasting blood samples were collected from every participant before using the dialysis. A commercial kit (DiaMetra, Spello, Italy) was used to measure the serum level of IGF-1, and the commercially available enzyme-linked immunosorbent assays method (ZellBio GmbH, Berlin, Germany) was used to measure ICAM-1.

Statistical analysis

Data analysis was carried out using SPSS (version 22; IBM Corp., Armonk, NY, USA) [31]. A p value of < 0.05 was considered statistically significant. Kolmogorov-Smirnov test was used to check the normal distribution of all variables. Means and standard errors were reported for continuous variables, and the number and percentage of participants were reported for

categorical variables. Pearson's correlation coefficient and/or Spearman's correlation coefficient were used to test the correlation between depression and MAMC, HGS, ICAM-1 and IGF-1.

Statement

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the Iran University of Medical Sciences ethics committee (approval No. IR.IUMS.REC.1398,250). Written informed consent was obtained from all patients.

RESULTS

A total of 82 patients were diagnosed with depression based on the BDI and were included in the analysis. The characteristics of participants are presented in **Table 1**. Most participants were mid and older-aged (44%), males (62%), with a medium dialysis duration (57%), had normal weight (BMI = 18–25 kg/m²) (62%) with mild depressive symptoms (40%).

While the correlations between depression status and ICAM-1, HGS, and IGF-1 were statistically non-significant, the correlation between depression status and MAMC was statistically and positively significant ($r = 0.26$, p value = 0.016, **Table 2**). Furthermore, ICAM-1 was negatively correlated with HGS, MAMC, and IGF-1 (p value < 0.05, **Table 3**).

The association between participants' characteristics, including age, BMI and nutrient intake, including intake of energy, protein, fat, calcium, potassium, and phosphorus, over the categories of depressive symptoms are presented in **Table 4**. All correlations were statistically non-significant.

Table 1. Characteristics of participants

Characteristics	Overall (n = 82)
Age*	
Young age group	10 (12.2)
Middle-age group	36 (43.9)
Older age group	36 (43.9)
Sex	
Males	51 (62.2)
Females	31 (37.8)
Dialysis duration†	
Short	23 (28.0)
Medium	47 (57.3)
Long	12 (14.7)
BMI categories‡	
Underweight	11 (13.4)
Normal weight	51 (62.2)
Overweight	18 (22.0)
Obese	2 (2.4)
Depressive symptoms§	
Mild	33 (40.2)
Moderate	25 (30.5)
Severe and very severe	24 (29.3)

Values are presented as number (%).

BMI, body mass index.

*Young aged (18–40 years old); Middle aged (> 40–60 years old); Older aged (> 60 years old).

†Short (< 1 year); Medium (≥ 1–5 years); Long (> 5 years).

‡Underweight: BMI < 18.5 kg/m²; Normal weight: BMI 18.5 to BMI < 25 kg/m²; Overweight: BMI ≥ 25 kg/m² to BMI < 30 kg/m²; Obese: BMI ≥ 30 kg/m².

§Depressive symptoms [28].

Table 2. Correlation between depression status and anthropometric indices and biomedical parameters

Depression status	ICAM-1	HGS	MAMC	IGF-1
Coefficient, r	-0.090	0.079	0.260	0.800
p value*	0.390	0.480	0.016	0.450

HGS, handgrip strength; ICAM-1, intercellular adhesion molecule-1; IGF-1, insulin-like growth factor-1; MAMC, mid-arm muscle circumference.

*Spearman's correlation coefficient was used to determine the correlation between SICAM-1, HGS, MAMC, IGF-1 and depression status.

Table 3. Correlation between ICAM-1 and HGS, MAMC, and IGF-1

Variables, ICAM-1 (ng/mL)	HGS	MAMC	IGF-1
Coefficient, r	-0.338	-0.240	-0.252
p value*	0.002	0.029	0.021

HGS, handgrip strength; ICAM-1, intercellular adhesion molecule-1; IGF-1, insulin-like growth factor; MAMC, mid-arm muscle circumference.

*Pearson correlation coefficient was used to determine the correlation between HGS, MAMC, IGF-1, and ICAM-1.

Table 4. Participants' characteristics and nutrient intake according to the level of depressive symptoms

Characteristics (unit)	Depressive symptoms			p value*
	Mild	Moderate	Severe and very severe	
Age (yr)	53.67 ± 10.21	56.12 ± 9.67	54.5 ± 10.11	0.65
BMI (kg/m ²)	22.73 ± 3.58	21.32 ± 3.54	23.08 ± 3.17	0.16
Energy (kcal/kg bw/d)	18.35 ± 3.48	20.98 ± 5.20	17.66 ± 4.90	0.44
Protein (g/kg bw/d)	0.85 ± 0.29	0.73 ± 0.20	0.70 ± 0.18	0.66
Fat (g/d)	30.93 ± 9.50	28.47 ± 6.22	27.82 ± 4.31	0.23
Calcium (mg/d)	390.29 ± 88.67	389.94 ± 78.28	367.99 ± 75.78	0.56
Potassium (mg/kg bw/d)	22.73 ± 3.58	21.32 ± 3.54	23.08 ± 3.17	0.29
Phosphorus (mg/kg bw/d)	22.73 ± 3.58	21.32 ± 3.54	23.08 ± 3.17	0.50

Values are presented as mean ± standard deviation.

BMI, body mass index; bw, body weight.

*Pearson correlation coefficient was used to determine the association between the mean of age, BMI and nutrient intake of patients over the categories of depressive symptoms.

Table 5. Associations between participants' characteristics and nutrient intake over HGS, MAMC, IGF-1, ICAM-1

Characteristics	HGS		MAMC		IGF-1		ICAM-1	
	r*	p value	r	p value	r	p value	r	p value
Age (yr)	0.14	0.20	0.31	0.004	0.017	0.87	0.05	0.61
BMI (kg/m ²)	0.15	0.16	0.37	0.001	0.09	0.39	0.027	0.80
Energy (kcal/kg bw/d)	0.21	0.05	0.05	0.63	0.20	0.81	0.04	0.70
Protein (g/kg bw/d)	0.13	0.23	0.02	0.83	0.15	0.17	1.33	0.23
Fat (g/d)	0.14	0.19	0.21	0.05	0.01	0.89	0.007	0.95
Calcium (mg/d)	0.14	0.18	0.07	0.48	0.17	0.12	0.12	0.27
Potassium (mg/kg bw/d)	0.08	0.43	0.06	0.54	0.20	0.82	0.40	0.70
Phosphorus (mg/kg bw/d)	0.04	0.66	0.12	0.25	0.20	0.60	0.70	0.51

BMI, body mass index; bw, body weight; HGS, handgrip strength; ICAM-1, intercellular adhesion molecule-1; IGF-1, insulin-like growth factor; MAMC, mid-arm muscle circumference.

*Pearson correlation coefficient was used to examine the mean of age, BMI and nutrient intake of patients over HGS, MAMC, IGF-1 and ICAM-1.

Table 5 presents the association between participants' characteristics, over HGS, MAMC, IGF-1, and ICAM-1. A positive correlation between age, BMI and MAMC was determined (p value < 0.05). Furthermore, a positive correlation was found between energy intake and HGS, and between fat intake and MAMC (p value = 0.05).

DISCUSSION

This cross-sectional study was carried out to investigate a possibility if anthropometric indices, including body protein status, and biochemical biomarkers (ICAM-1 and IGF-1)

might be used to predict severity depression, in 90 hemodialysis patients referred to the dialysis department of Shohadaye khalijfars Hospital, Bushehr, Iran, in 2019. According to our results, the amount of energy and protein intake was less than recommended amounts in 95.1% and 96.3% of patients, respectively. Also, in 92% of the patients, the intake of high-quality proteins was less than the recommended amounts. Lack of energy and protein intake is a common nutritional problem in these patients. Other studies carried out in Iran [32] and other countries [33,34] have shown similar results. It is important to consider that inadequate energy and protein intake in hemodialysis patients worsens malnutrition and increases the risk of mortality [34,35]. The most important reason for lack of energy and protein intake in these patients is anorexia, which is the result of different factors, such as inflammation, the accumulation of toxic products, changes in hormones levels (ghrelin and leptin), neural mediators affecting appetite and underlying diseases like infection, and mental disorders. All these factors can not only affect the appetite of patients but can also affect the nutritional status, quality of life, and vitality [33,34,36].

It has been proposed that IGF-1 can have an effect on depression by regulating the immune system and its anti-inflammatory effects [25]. Individuals with major depressive disorder, who reported sadness, inner tension and concentration difficulties, presented a depression status that was positively and significantly associated with serum IGF-1 concentrations [37]. On the other hand, serum levels of IGF-1 have been shown to have a negative statistically significant correlation with the risk of depression in ischemic heart disease patients [38]. Although the present study did not show any relationship between serum levels of IGF-1 and depression, Chigogora et al. [39], revealed a 'U'-shaped pattern of association, meaning that lower and higher levels of IGF-1 were associated with a slightly elevated risk of depression. The limited number of participants in the current study may hinder our ability to identify any significant relationship in this regard. Large-scale studies are still needed to elucidate the correlation between IGF-1 levels and depression.

Depression is commonly associated with insufficient intake of food, leading to malnutrition which is particularly relevant for hemodialysis patients. In addition, depression is also associated with the activation of pro-inflammatory cytokines, which are usually elevated during the dialysis process, leading to increase in protein catabolism [26,40]. In a study by Koo et al. [41], a significant negative correlation between MAMC and depression, measured by Beck questionnaire, was observed, which is in line with our results. In the present study, the correlation between depression status and MAMC was positively significant and confirmed by logistic regression. Several reasons may explain why no relationship between HGS and IGF-1 with depression was observed in this study, which include the small sample size, the use of different methods for evaluating and categorizing depression, and the study design (cross-sectional) that includes only one assessment point.

ICAM-1 is a transmembrane glycoprotein that is overexpressed in various pathological states. Although, like many other immune-related molecules, ICAM-1 appears to play a limited role in the complex immune response, its effects may be more important than it appears. In the central nervous system, ICAM-1 is expressed in microglial cells, astrocytes, and in endothelial cells in the white and gray matter of the human forebrain. It is of particular interest in psychiatric disorders for 2 reasons: 1) it has a key function in the blood–brain barrier, which plays a critical role in the biology of psychiatric disorders, and 2) it is a marker for inflammation, which is particularly relevant considering that depression is associated with inflammation [17]. Our results do not establish any relationship between depression

and ICAM-1. Studies with larger sample sizes are probably a better option to evaluate the relationship between serum biomarkers and emotional status.

In this study, an examination of the relationship between nutrient intake and depressive symptoms reveals several important findings. The majority of patients had insufficient energy and protein intake, highlighting a prevalent nutritional issue among this population, which is known to worsen malnutrition and increase mortality risk. This inadequacy in nutrient intake is often attributed to factors like anorexia, inflammation, hormonal imbalances, neural mediators, and underlying health conditions.

Cardiovascular diseases (CVDs) are one of the most common complications and the leading cause of death in dialysis patients affecting more than 52% of patients and causing a mortality rate 82 times higher than in the normal population. Dyslipidemia, diabetes, obesity and inactivity are the traditional causes of CVDs while hyperhomocysteinemia, chronic inflammation, anemia, malnutrition and electrolyte imbalance are causes less associated with CVDs [42,43]. During hemodialysis, circulating leukocytes are activated and cause the release of pro-inflammatory cytokines, which can induce the synthesis of vascular inflammatory factors such as ICAM-1. Elevation of vascular inflammatory factors is associated with inflammation, dyslipidemia and cardiovascular complications [44]. On the other hand, decreased muscular strength (MusS), which is common in these patients, has been showed to be related to inflammation [45]. The role of MusS has been investigated over the years, as it relates to the risk to develop CVD and CVD risk factors. Reduced MusS, also known as dynapenia, has been associated with increased risk for CVD, CVD-related mortality and all-cause mortality. In addition, reduced MusS is associated with increased cardiometabolic risk [46]. HGS can be controlled by multiple physiological systems and there is specific indication that patients with heart failure or multiple chronic diseases suffer from skeletal muscle atrophy, altered muscle metabolism, and decreased levels of mitochondrial enzyme that can lead to reduced muscle strength [47]. Low HGS is also associated with subclinical inflammation, increased interleukin-6, defects in insulin resistance and glucose metabolism, and reduced IGF-1 [48]. Also, increased serum ICAM-1 level in dialysis patients has been related to inflammation [44]. These observations may explain why ICAM-1 is negatively correlated with HGS, MAMC, and IGF-1 in the hemodialysis patients evaluated in the present study. To the best of our knowledge, this is the first study which evaluated the relationship between IGF-1 and ICAM-1, which was negative and statistically significant. No study investigated the relation between MAMC and ICAM-1, but Atkins et al. [49], found a negative and significant relationship between MAMC and other heart disease inflammatory risk factors. This study has some limitations. Firstly, the limited number of participants may decrease our ability to find significant results. Secondly, the analysis was confined to a subset of nutrients, and other important nutrients, such as vitamin D, sodium, and carbohydrate intake, were not evaluated.

The results of the present study suggest that HGS can be considered as a cheap, simple, and non-invasive method in the initial evaluation of CVDs risk in hemodialysis patients and that MAMC was the only predictor of the level of depression, although further research in this area is needed. The observed results also suggest that the improvement of nutritional indicators may lead to a better control of depression.

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