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Abdominal obesity in normal weight versus overweight and obese hemodialysis patients: Associations with nutrition, inflammation, muscle strength, and quality of life

Ilia Beberashvili M.D. [a,*], Ada Azar B.Sc. [b], Ramzia Abu Hamad M.Sc. [a], Inna Sinuani Ph.D. [c], Leonid Feldman M.D. [a], Amit Maliar M.D., Ph.D. [d], Kobi Stav M.D. [e], Shai Efrati M.D. [a]

[a] Nephrology Division, Assaf Harofeh Medical Center, Zerifin, affiliated with the Sackler Faculty of Medicine Tel Aviv University, Israel
[b] Nutrition Department, Assaf Harofeh Medical Center, Zerifin, affiliated with the Sackler Faculty of Medicine Tel Aviv University, Israel
[c] Pathology Department, Assuta Ashdod University Hospital, Ashdod, Israel
[d] The Kamila Gonczarowski Institute of Gastroenterology, Assaf Harofeh Medical Center, Zerifin, affiliated with the Sackler Faculty of Medicine Tel Aviv University, Israel
[e] Urology Department, Assaf Harofeh Medical Center, Zerifin, affiliated with the Sackler Faculty of Medicine, Tel Aviv University, Israel

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ABSTRACT

Objective: The biological basis of abdominal obesity leading to more severe outcomes in patients with normal body mass index (BMI) on maintenance hemodialysis (MHD) is unclear. The aim of this study was to compare the properties of abdominal obesity in different BMI categories of patients on MHD.
Methods: We performed a cross-sectional study of 188 MHD patients (52.7% women; mean age, 69.4 ± 11.5 y) with abdominal obesity in different BMI groups using criteria from the World Health Organization. Appetite and dietary intake, body composition, handgrip strength, malnutrition inflammation score (MIS), inflammatory biomarkers, adipokines, and health-related quality-of-life (QoL) questionnaires were studied.
Results: According to multivariable analyses, abdominally obese patients with normal BMIs consumed less protein per day ($P = 0.04$); had lower measurements of surrogates of lean ($P < 0.001$) and fat mass ($P < 0.001$); and had higher total cholesterol, tumor necrosis factor-α ($P < 0.05$), and ratios of adiponectin to leptin ($P = 0.003$) than overweight and obese patients with abdominal obesity. Multivariable analyses showed no differences in handgrip strength among the study groups.The abdominally obese study participants with normal weight had significantly lower scores in role physical ($P = 0.003$) and pain ($P = 0.04$) scales after multivariable adjustments.
Conclusions: Normal-weight MHD patients with abdominal obesity exhibited a more proatherogenic profile in terms of inflammatory markers and adipokine expression, lower body composition reserves, and lower physical ability than patients with abdominal obesity with overweight and obesity. This at least partially explains the abdominal obesity paradox in the MHD population in which worse clinical outcomes are seen in abdominally obese patients with normal BMIs, as opposed to overweight and obese patients who are also abdominally obese.

Introduction

The issue of obesity in the maintenance hemodialysis (MHD) population remains controversial and confusing. Large-scale epidemiologic studies on patients with end-stage kidney disease (ESKD) continue to report a paradoxically inverse relationship between body mass index (BMI) and cardiovascular disease (CVD) and mortality [1]. Conversely, in smaller studies, abdominal obesity has been shown to be a marker of cardiovascular and all-cause morbidity and mortality in the same population [2–10]. Among the components of the metabolic syndrome defined by American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) and the International Diabetes Federation (IDF), abdominal obesity is the only significant predictor of cardiovascular morbidity in MHD patients [2]. The higher abdominal fat accumulation in the

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* Corresponding author: Tel: +97 289 77 9383; Fax: +97 289 77 9705.
E-mail address: iliab@asaf.health.gov.il (I. Beberashvili).

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hemodialysis population is associated with insulin resistance [3], lower pentraxin-3 levels [4], inflammation [4,5], cardiovascular events [6,7], and cardiovascular and all-cause mortality [8–10]. These associations are most relevant in moderately obese patients, although abdominal obesity may also appear in BMI-categorized non-obese individuals [11]. Patients without chronic kidney disease (CKD) who have coronary artery disease and "normal-weight central obesity" have the highest long-term mortality compared with other patterns of adiposity [12,13]. In the ESKD population, the relationship between waist circumference (WC) and the incidence rate of all-cause and CVD mortality show similar results [6,8]. The incidence rate of overall and CVD death was shown to be maximal in patients with relatively lower BMIs and higher WCs and minimal in patients with higher BMIs and smaller WCs in a cohort of 537 patients with ESKD [8]. The biological basis of the "BMI paradox," where abdominal obesity by itself leads to more severe outcomes in MHD patients with normal BMIs, is currently completely unclear.

To describe the unique characteristics of normal-weight centrally obese patients, we aimed to study and compare the nutritional status, muscle function, inflammation, and health-related quality of life (HRQoL) in MHD patients with abdominal obesity in different BMI categories. This may help in understanding the behavior of abdominal obesity in terms of clinical outcomes among the different BMI groups of patients on hemodialysis.

Materials and methods

Patients

We performed a post hoc cross-sectional analysis from two observational cohorts of MHD patients. Patient recruitment in the first cohort (N = 261) occurred between October 2010 and April 2012. This population was described in more detail in a recent publication [14]. The second cohort was composed of 78 patients who were recruited between August 2015 and February 2016. Inclusion criteria were outpatients who underwent MHD for ≥8 wk, were ≥18 y of age, had sex-specific WCs compatible with abdominal obesity by World Health Organization criteria [15,16], and signed a local institutional review board–approved consent form. Of the 339 patients in both cohorts, 303 had the whole set of anthropometric measurements needed for the study. Among them, 188 (62.05% of the total population) met the criteria for abdominal obesity. Twenty-three (7.59% of the total population) of 114 with normal weight had abdominal obesity; 81 (26.73% of the total population) of the 105 overweight patients fulfilled the abdominal obesity criteria, whereas all 84 obese patients were additionally abdominally obese (Fig. 1). In all, 188 MHD patients, all with abdominal obesity, were included in the analysis.

Information on the patients' diseases were obtained from their detailed medical history charts. A single clinician reviewed each patient's medical chart and extracted all relevant clinical data.

The local ethics committee approved the study protocol, and informed consent was obtained from each individual.

Appetite assessment and dietary intake

Continuous 3-d dietary histories (including a dialysis day, a weekend day, and a non-dialysis day) were self-completed in a food diary. The dietary energy and protein intake were calculated and normalized for ideal body weight according to the European Best Practice Guidelines [17].

Dietary protein intake was also estimated by calculating normalized protein nitrogen appearance (nPNA) from the patient's urea generation rate by using urea kinetics modeling [18]. A single-pool urea kinetics model was used to estimate the nPNA.

All study participants were asked to rate their appetite over the previous week in a self-reporting appetite assessment questionnaire using a 5-point Likert scale: 1: *very good*, 2: *good*, 3: *fair*, 4: *poor*, and 5: *very poor*. These assessments were performed on the same day that blood was drawn for testing. The scores from the questionnaires were arranged into two main groups for further analysis: diminished (combined appetite scores of 3, 4, and 5) and non-diminished (combined appetite scores of 1 and 2).

Anthropometric measurements and handgrip strength

BMI, triceps skinfold thickness (TSF), mid-arm circumference (MAC), calculated mid-arm muscle circumference (MAMC), WC, waist-to-hip ratio (WHR), and conicity index were measured as anthropometric variables. MAMC was estimated as follows:

$$\mathrm{MAMC(cm)} = \mathrm{MAC(cm)} - 0.314 \times \mathrm{TSF(mm)}.$$

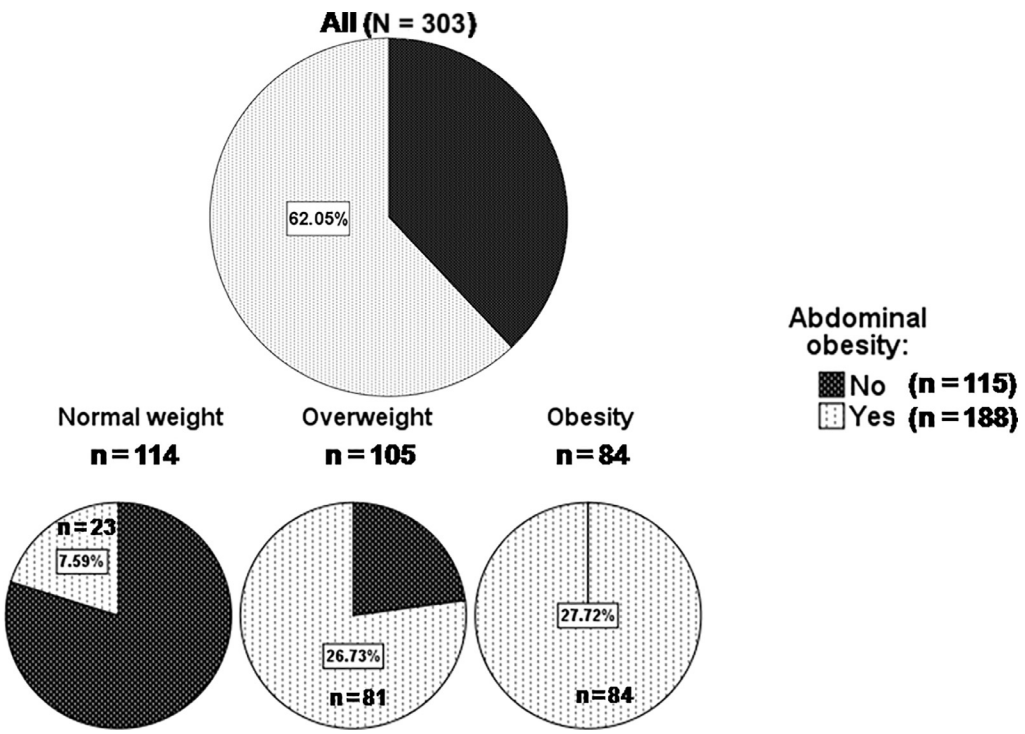

Fig. 1. Prevalence of abdominal obesity using the World Health Organization criteria (waist circumference >88 cm in women and >102 cm in men) in different body mass index groups of the study population (for a detailed description, see Methods section).

WHR was calculated by dividing WC by hip circumference. The conicity index was calculated according to the equation defined by Valdez [19], which takes into consideration WC and weight and height measurements.

All measurements were made after dialysis when the patient was at dry weight (the right upper arm was used whenever possible, with exceptions made for patients in whom dialysis access placement, injury, or stroke precluded measurement). The same trained dietitian performed all anthropometric measurements.

Handgrip strength (HGS) measurements were performed in both the dominant and non-dominant arms using the Harpenden Handgrip Dynamometer (Yamar, Jackson, MI, USA). HGS was repeated three times and the highest value was noted.

Short-Form 36 QoL scoring system, EQ-5 D, and ESAS

The Short-Form 36 (SF-36) is a short form of the HRQoL scoring system with only 36 items and includes eight independent scales. It is a well-documented, self-administered questionnaire and has been widely used and validated in MHD patients [20]. The eight scales of the SF-36 are categorized into two dimensions: physical health and mental health.

EQ-5 D is a brief, generic, preference-based measure that consists of two components: a 100-point visual analog scale and a descriptive system. EQ-5 D has been validated as a predictor of mortality in hemodialysis population [21].

The modified Edmonton symptom assessment system (ESAS) was used as a validity tool for the physical and psychological symptom burden assessment in MHD patients [22].

QoL, EQ-5 D, and ESAS data were available for 150 of the 188 (80%) patients.

Body composition analysis

Body composition was determined by body impedance analysis (BIA; Nutriguard-M, Data-Input, Frankfurt, Germany). Following the recommendations for clinical applications of BIA [23], we performed the analysis within 30 min after dialysis. The multifrequency technique (using three frequencies: 5, 50, and 100 kHz) has been used to estimate total body water and extracellular water. These estimates were obtained using the NutriPlus software, version 5.1 (Data Input GmbH, Germany).

Malnutrition inflammation score and comorbidity index

Overall nutritional assessment was achieved using the malnutrition inflammation score (MIS). The MIS is well described elsewhere [24] and has been shown to be a valid tool for longitudinal observations of the nutritional status of MHD patients [25]. This scoring system incorporates subjective global assessment and consists of 10 components. The sum of all 10 components results in an overall score ranging from 0 (*normal*) to 30 (*severely malnourished*).

The comorbidity index was calculated using a recently developed index by Liu et al. as a measure of comorbid conditions and was specifically validated for the dialysis patient population [26].

Laboratory evaluation

Blood samples for all biochemical markers were obtained from non-fasting patients on a midweek day before dialysis, with the exception of postdialysis serum urea nitrogen to calculate urea kinetics. The biochemical measurements were done by an automatic analyzer. A turbidimetric immunoassay was used to measure serum high-sensitivity C-reactive protein (CRP). Interleukin (IL)-6, tumor necrosis factor (TNF)-α, adiponectin, and leptin levels were measured in the serum samples by commercially available enzyme-linked immunosorbent assay kits (R&D System, Minneapolis, MN, USA). The mean minimal detectable level for IL-6 was 0.7 pg/mL. It was −0.6 pg/mL for TNF-α, −0.246 ng/mL for adiponection, and 7.8 pg/mL for leptin. Intra- and interassay coefficients of variation for IL-6 were 4.2% and 6.4%, for TNF-α 5.2% and 7.4%, for adiponection 3.4% and 5.8%, and for leptin −3.3% and 5.4%, respectively. The assays were done according to the manufacturer's protocol.

Statistical analysis

Data are expressed as mean ± SD, as median (interquartile range) for variables that did not follow a normal distribution, or as frequencies for categorical data.

Differences in means of groups were compared using one-way analysis of variance. Analysis of covariance using a general linear model was performed to compare differences in nutritional and inflammatory parameters between normal-weight, overweight, and obese groups of hemodialysis patients with abdominal obesity adjusted for age, sex, dialysis vintage, diabetes status, comorbidity index, Kt/V, smoking, and residual renal function. All non-normally distributed variables (dialysis vintage, comorbidity score, MIS, triacylglycerols, CRP, IL-6, TNF-α, adiponectin, leptin, and the ratio of adiponectin to leptin) were log-transformed before insertion to analysis of covariance multivariable models. $P < 0.05$ were accepted as significant, and all statistical tests were two-sided.

Multivariate logistic regression was used to determine whether a significant association between appetite and BMI existed in hemodialysis patients with abdominal obesity after adjustments for all aforementioned potential confounders. Further exploration of the association between BMI and appetite was done by modeling BMI using a restricted cubic spline with three internal knots. This method allowed for the examination of nonlinear effects of continuous predictors of appetite as an alternative to inappropriate linearity assumptions. All statistical analyses were performed using SPSS software, version 18 (SPSS Inc, Chicago, IL, USA).

Results

Patients with abdominal obesity in the normal BMI group ("normal-weight abdominal obesity") were older, mostly female, and had a lower incidence of diabetes and higher Kt/V than overweight or obese patients with abdominal obesity (Table 1). No differences were observed in dialysis vintage, comorbidities, residual renal function, smoking, or appetite among the groups. To rule out the effect of each aforementioned factor as a confounder, all of these factors (with the exception of appetite, which was one of the variables of interest) were included in the multivariate models for further statistical analyses.

Diminished appetite appeared at the same frequency in all three BMI groups in the study population, according to a univariate analysis (Table 1). In multivariate logistic regression analyses, no differences were observed between these groups in predicting diminished appetite (odds ratio [OR], 0.70; 95 confidence interval [CI], 0.38–1.29 in overweight and OR, 0.59; 95% CI, 0.31–1.16 in obese versus normal-weight group). Interestingly, the trend of appetite improvement across higher levels of BMI continued up to a BMI of 30 kg/m^2, whereas for BMI >30 kg/m^2, appetite did not change practically with an increase in BMI (Fig. 2). This might explain another observation in the study population: MHD patients with abdominal obesity in the obese BMI group consume more protein per day than normal-weight MHD patients with abdominal obesity (Table 1). After multivariate adjustments, total cholesterol (TC) was the only biochemical marker that was significantly different between the groups. It was higher in the "normal-weight abdominally obese" group. Of the anthropometric measurements, TSF as a surrogate of peripheral fat mass and MAMC as surrogate of lean mass were expectedly higher in MHD patients with abdominal obesity in BMI-determined overweight and obese groups. However, these differences did not translate into muscle function as measured by HGS and in the overall nutritional status as measured by MIS. The differences between the groups observed in a univariate analysis did not survive multivariate adjustments.

Higher levels of TNF-α after multivariable adjustments were seen in MHD patients with abdominal obesity and normal weight compared with overweight or obese patients with abdominal obesity as defined by BMI. CRP and IL-6 levels did not differ between the study groups. The distribution between the study groups of the two major adipokines, leptin and adiponectin, were interesting as well (Table 1). Leptin levels were lower and the ratio between adiponectin and leptin was higher in MHD patients with normal-weight abdominal obesity compared with overweight and obese MHD patients with abdominal obesity.

Table 2 shows crude SF-36 HRQoL scores, overall EQ-5 D index, and the ESAS in the study groups of 150 MHD patients who answered these questionnaires. The normal-weight abdominal obesity group demonstrated significantly lower total SF36 score, lower dimensions of physical health, and lower scores in most scales of the SF36 by univariate analysis in comparison with overweight and obese MHD patients with abdominal obesity. Crude EQ-5 D and ESAS scores were significantly lower in the MHD

Table 1
Comparison of the demographic and clinical characteristics of study participants (N = 188) with abdominal obesity* stratified according to BMI groups

BMI categorization	≤24.9 kg/m^2 (n = 23)	25–29.9 kg/m^2 (n = 81)	≥30 kg/m^2 (n = 84)	*P*-value	P_{ANCOVA}
Demographic and clinical variables					
Age (y)	74.5 ± 12.2	70 ± 11.4	67.3 ± 10.9	0.02	–
Sex (women, %)†	95.7	37	56	<0.001	–
Dialysis vintage (mo)‡	27 (10–62)	12.5 (8–56)	22 (9.3–48)	0.49	–
DM (%)†	52.2	64.2	82.1	0.005	–
Comorbidity score‡	3 (2–6)	5 (2–7)	4 (2–7)	0.40	–
RRF (yes, %)†	43.5	61.4	53.8	0.30	–
Kt/V	1.50 ± 0.31	1.29 ± 0.26	1.26 ± 0.31	0.003	–
Smoking (yes)	8.7	15	7.1	0.25	–
Appetite (diminished)†	47.8	49.4	36.1	0.21	–
MIS[2]	8.5 (6–10)	5 (3–8)	5 (3–8)	<0.001	0.22
Handgrip strength (kg)‡	10.7 (8.7–14.6)	18.9 (11.7–29.7)	15.3 (11–24)	0.002	0.28
Dietary intake					
Energy intake (kcal·kg·d^{-1})	19.8 ± 5.9	21.9 ± 5.6	22.7 ± 7	0.19	0.34
Protein intake (g·kg·d^{-1})	0.81 ± 0.3	1.02 ± 0.3	1.06 ± 0.3	0.005	0.04
nPNA (g·kg·d^{-1})	1.01 ± 0.2	1.05 ± 0.3	1.02 ± 0.2	0.75	0.46
Biochemical markers					
Creatinine (mg/dL)	6.11 ± 1.3	7.61 ± 2.1	7.31 ± 2.3	0.01	0.14
Albumin (g/dL)	3.70 ± 0.3	3.82 ± 0.3	3.81 ± 0.3	0.32	0.73
Uric acid (mg/dL)	5.28 ± 1	5.88 ± 1.3	5.99 ± 1.2	0.05	0.36
Cholesterol (mg/dL)	175 ± 34.6	141.5 ± 35.8	155.3 ± 40	0.001	0.046
Triacylglycerols (mg/dL)‡	146 (103–170)	133 (103–183)	176.5 (113.3–237.5)	0.03	0.57
CRP (mg/L)‡	5.7 (4.6–10.6)	7.4 (4.5–15)	10.8 (4.9–19.1)	0.06	0.22
IL-6 (pg/mL)‡	6.4 (3.5–11.8)	9.2 (5.6–18.9)	10 (6.4–15.7)	0.22	0.41
TNF-α (pg/mL)‡	25.5 (21–34.2)	21.4 (16.2–29.7)	24.4 (18.4–30.2)	0.09	0.048
Adiponectin (μg/mL)‡	8.3 (4.9–25.7)	6.8 (3.6–37.6)	7.2 (3–29.5)	0.37	0.16
Leptin (ng/mL)‡	5.6 (2.5–16.9)	8.2 (3.6–18.5)	18.3 (10.4–26)	<0.001	0.006
Adiponectin/Leptin‡	2.2 (0.4–7.2)	1.2 (0.4–5.2)	0.3 (0.2–1.1)	<0.001	0.003
Anthropometric measurements					
WC (cm)	97.3 ± 5.4	108 ± 7	120 ± 11.2	<0.001	<0.001
WHR	1.00 ± 0.08	1.05 ± 0.08	1.06 ± 0.08	0.02	0.05
Conicity index	1.45 ± 0.08	1.47 ± 0.08	1.47 ± 0.10	0.75	0.32
BMI (kg/m^2)	23.8 ± 0.7	27.6 ± 1.4	34.7 ± 4.6	<0.001	<0.001
MAMC (cm)	21.2 ± 2.3	23.3 ± 2.4	25.3 ± 3.9	<0.001	<0.001
TSF (mm)	15.9 ± 5	15.6 ± 4.9	20.6 ± 6.5	<0.001	<0.001

ANCOVA, analysis of covariance; BMI, body mass index; CI, conicity index; CRP, C-reactive protein; DM, diabetes mellitus; IL, interleukin; MAMC, mid-arm muscle circumference calculated; MHD, maintenance hemodialysis; MIS, malnutrition -inflammation score; PNA, normalized protein nitrogen appearance; RRF, residual renal function; TNF, tumor necrosis factor; TSF, triceps skinfold thickness; WC, waist circumference; WHR, waist-to-hip ratio.
Continuous variables are expressed as mean ± SD or as median with the 25th to 75th percentile shown in parentheses in cases of skewed distributed data. Categorical variables are expressed as a percentage.
Not-normally distributed variables (dialysis vintage, comorbidity score, MIS, triacylglycerols, CRP, IL-6, TNF-α, adiponectin, leptin, and adiponectin-to-leptin ratio) were log-transformed (data not shown) before insertion to ANCOVA multivariable models.
Multivariable models were adjusted for age, sex, dialysis vintage, diabetes status, comorbidity index, Kt/V, smoking, and residual renal function.
*Increased abdominal adiposity was defined as recommended by the World Health Organization (WC >88 cm in women and >102 cm in men).
†Assessed by χ^2 test.
‡Compared by the Kruskal–Wallis test.

patients with normal-weight abdominal obesity as well. After multivariable adjustments, however, these associations were attenuated, and the study participants with normal-weight abdominal obesity reported significantly lower scores only in role-physical and pain scales.

Discussion

In the present study, we reported on the differences in different BMI groups in the nutritional, inflammatory, and functional profiles of MHD patients with abdominal obesity. Although the rate of abdominal obesity in our population was relatively high compared with MHD patients from a southern Italy study [8], the distribution of abdominal obesity according to the WC in the normal-weight, overweight, and obese patients was quite similar compared with the 130 473 UK Biobank participants ages 60 to 69 y [27] and the participants of the Framingham offspring study [28]. Studying differences among the aforementioned groups, we found that the normal-weight abdominal obesity group, previously reported as the most dangerous pattern of obesity in terms of clinical outcomes in the general population and MHD [6,8,12,13], was characterized by many negative factors compared with overweight and obese MHD patients with abdominal obesity. These include higher serum levels of TC, lower measurements of surrogates of lean (MAMC) and fat mass (TSF), higher levels of TNF-α, higher ratio of adiponectin to leptin, and lower scores on the physical and pain scales of the HRQoL.

We found that daily protein intake and body composition indices, as expected, were higher in the overweight and obese groups than in those with abdominal obesity and normal -weight MHD patients. The trend for appetite improvement across the elevating BMI observed in the present study is a good explanation for higher daily protein intake in MHD patients with higher BMI and abdominal obesity. Lean BMI has been previously found to be a positive correlate of appetite in a Brazilian hemodialysis population [29]. Additionally, higher protein consumption was associated with good appetite in the study by Kalantar-Zadeh et al. [30]. Furthermore, higher TSF as a surrogate of fat mass and higher MAMC as a surrogate of lean mass [31] has been found to denote better

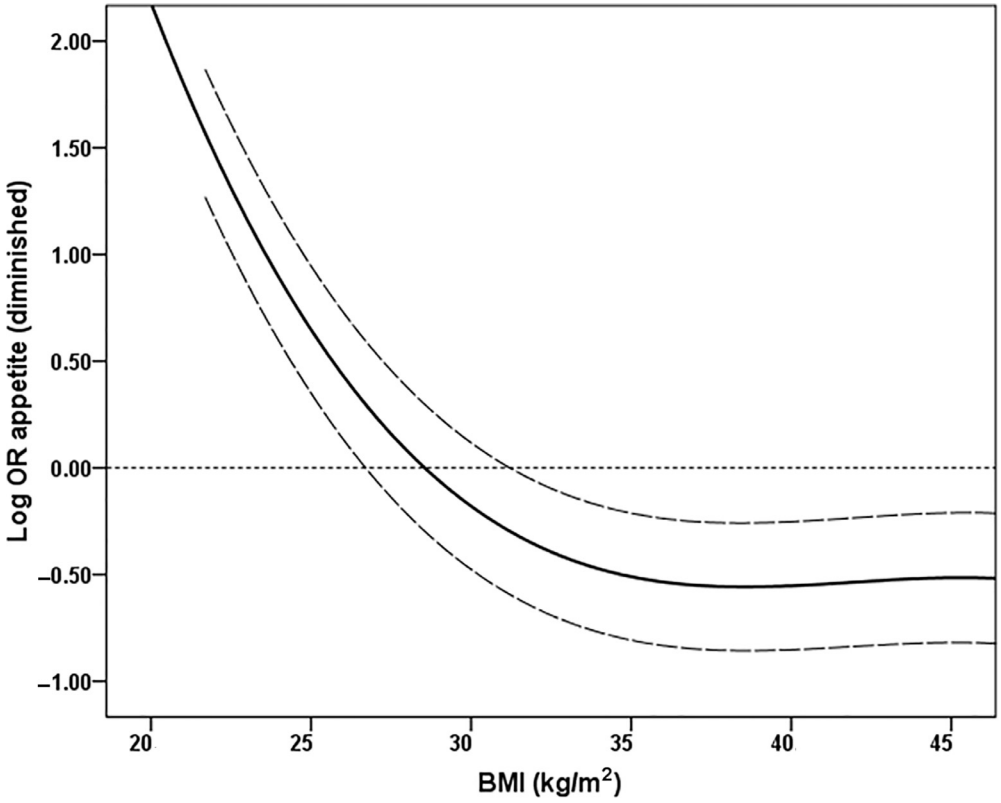

Fig. 2. Multivariable-adjusted spline curves of anorexia (diminished appetite) in the whole population (N = 188) presented as log odds ratio (OR; solid line) and 95% CI (dashed lines) of diminished appetite associated with body mass index in a multivariable logistic regression model. The model was plotted as restricted cubic splines with three internal knots. The multivariable model was adjusted for age, sex, dialysis vintage, diabetes status, comorbidity index, Kt/V, smoking, and residual renal function(for a detailed explanation, see Results section).

nutritional status in MHD patients in higher BMI groups [32]. However, the overall nutritional status measured by MIS and the muscle function measured by HGS did not differ between the groups after multivariate adjustments. In terms of nutritional assessment, MIS is a comprehensive assessment that combines subjective assessments (subjective global assessment), visceral proteins (e.g., albumin), and measurements of body composition [24]. However, the shortcoming of this nutritional assessment may be that all the MHD patients were only compared with abdominal obesity. The latter is associated with several specific health risks that are similar for MHD patients in all BMI groups, which can limit the identification of differences in the subjective assessment among these groups. The absence of a difference in albumin levels between the groups, probably due to a higher level of chronic inflammation in abdominally obese patients [4,5], is the second limiting factor in finding differences in nutritional status among the patients using MIS. The European Society for Clinical Nutrition and Metabolism (ESPEN), in a consensus group, decided that diagnosis of malnutrition should be objective and should rely only on body composition criteria [33]. Because we lacked fat-free mass index measurements by bioimpedance or dual x-ray absorptiometry for all of the participants, we were unable to use the ESPEN criteria for diagnosis of malnutrition. Therefore, the patients with abdominal obesity and normal BMI had poorer nutritional status than the patients with abdominal obesity and overweight or obese BMIs, despite the lack of differences in the MIS scores between these BMI groups.

In the context of higher levels of TC in the normal-weight abdominally obese group, this is similar to the cross-sectional association described between TC and BMI in patients with CKD [34], with an increase in TC levels up to a BMI of 30 kg/m^2 and a decrease above a BMI of 30 kg/m^2. In dialysis patients, it was found that the inverse association of cholesterol levels with clinical outcomes is a product of the confounding effects of inflammation and malnutrition [35], is mainly short term, and is the reflection of the time discrepancy of competing risks [36]. Therefore, it is difficult to assess the biological importance of this observation. However, our finding of the higher leptin-to-adiponectin ratio in the study participants in the normal-weight abdominally obese group may successfully explain the higher rate of cardiovascular morbidity and mortality in similar groups of patients reported in the literature [6,8,12,13]. The leptin-to-adiponectin ratio is a well-documented atherogenic index in obese patients with type 2 diabetes [37] and is an independent predictor of intima media thickness of the common carotid artery in the general population [38]. Additionally, TNF-α, a known link in cardiovascular and all-cause mortality in the MHD population [39], was higher in the abdominally obese patients with normal body weight and might strengthen the proatherogenic profile of the aforementioned group. Indeed, high plasma TNF-α levels have been shown to be dependent on visceral fat amounts [40], with TNF-α increasing over time, especially in lean women, but remaining unchanged in overweight and obese individuals, regardless of fat mass changes [41]. The latter explains the cross-sectional relationship between TNF-α and BMI in the study participants, especially as patients in the normal-weight abdominally obese group were predominantly women.

In terms of HRQoL, WC rather than BMI was associated with a low QoL physical health score in hemodialysis patients [42], whereas higher muscle mass measured as midthigh muscle area by magnetic resonance imaging [43] and higher MAMC as a surrogate of larger lean body mass [31] have been shown to be associated with better

Table 2
Comparison of the health-related quality of life scores (according to SF-36*), general health status (according to EQ-5 D) and the ESAS of study participants (n = 150)† with abdominal obesity‡ in different BMI groups

BMI categorization	≤24.9 kg/m^2 (n = 18)	25–29.9 kg/m^2 (n = 68)	≥30 kg/m^2 (n = 64)	*P*-value	P_{ANCOVA}
SF-36 Overall					
SF-36 Total score	33.5 (25.7–47.5)	49.9 (36.2–57.9)	39 (33.2–50.9)	0.003	0.12
SF-36 Dimensions					
SF-36 Mental Health	38.7 (29.6–49.6)	49.1 (38–58.8)	42.6 (34.8–51)	0.07	0.38
SF-36 Physical Health	25.1 (20.1–37.4)	42 (31–53)	34.5 (26.8–44.8)	0.001	0.07
SF-36 Scales					
Body pain	37.5 (21.9–50)	50 (37.5–75)	37.5 (25–62.5)	0.02	0.04
General health	27.5 (20–45)	30 (20–50)	25 (11.3–45)	0.46	0.33
Mental health	47.5 (40–70)	60 (50–70)	60 (50–65)	0.26	0.14
Physical function	10 (0–36.3)	32.5 (15–60)	25 (10–40)	0.006	0.24
Role–emotional	50 (25–75)	50 (41.7–75)	50 (25–56.3)	0.21	0.69
Role–physical	6.3 (0–50)	43.8 (25–56.3)	38.8 (25–50)	0.007	0.003
Social functioning	50 (12.5–62.5)	50 (37.5–75)	50 (25–50)	0.04	0.50
Vitality	21.9 (15.6–51.6)	50 (37.5–56.3)	40.6 (31.3–50)	0.006	0.12
EQ-5 D	0.43 (0.05–0.73)	0.62 (0.52–0.81)	0.59 (0.32–0.71)	0.02	0.16
ESAS	54.5 (31.5–62.5)	36 (26.3–49.8)	43 (27.3–55)	0.03	0.59

ANCOVA, analysis of covariance; BMI, body mass index; SF-36, Short-Form 36; ESAS, Edmonton symptom assessment scale; WC, waist circimference.
The variables are expressed as median with the 25th to 75th percentile shown in parentheses because of skewed distributed data.
Multivariable models were adjusted for age, sex, dialysis vintage, diabetes status, comorbidity index, Kt/V, smoking, and residual renal function.
All variables presented in the Table followed non-normal distributions. Therefore, they were log-transformed before insertion to ANCOVA multivariable models.
*Short form quality-of-life score with 36 questions.
†Of the 188 patients in the study, quality-of-life data were available for only 150.
‡Increased abdominal adiposity was defined as recommended by the World Health Organization (WC >88 cm in women and >102 cm in men).

QoL scores in the physical and mental health scales in the MHD population. Given the significantly lower MAMC in the normal-weight abdominally obese group compared with the overweight and obese MHD patients with abdominal obesity, the lower scores in the physical health scales in the HRQoL of patients with abdominal obesity and normal BMI observed in the present study is not particularly surprising. In another look, apart from the body composition, the lower scores in the physical health scales of the HRQoL can be related to chronic inflammation, which is usually associated with abdominal obesity [4,5]. In terms of inflammatory markers, the groups in the present study were no different except for elevated TNF-α levels in abdominally obese normal BMI patients. However, a recent study [44] has not shown a link between inflammatory markers including TNF-α and most of the HRQoL scales.

The present study had a number of limitations. First, this was an observational study without any manipulations of exposure factors. This did not allow for finding of causal effects for any of the risk factors analyzed. Second, due to a low rate of abdominal obesity in dialysis patients with normal BMI, a relatively small number of patients formed this group. However, the phenotype of the normal-weight abdominally obese group in the present study expressed most of the characteristics typical of this group, such as being mostly female, having advanced age, and having a high prevalence of diabetes, as seen in large epidemiologic studies in different populations [45]. Dietary intake assessed by the 3-d food records was another limitation of the study, as results can be subjective and incomplete. Despite these limitations, the availability of a wide array of applied nutritional parameters, which include biochemical markers, anthropometric estimates of body composition, adipokines, and inflammatory biomarkers, strengthen our study.

Conclusions

Normal-weight MHD patients who are abdominally obese exhibit a more proatherogenic profile in terms of inflammatory markers and adipokine expression (higher levels ofTNF-α and higher adiponectin-to-leptin ratio), lower body composition reserves (lower measurements of surrogates of lean and fat mass), and lower physical ability (lower scores in role-physical scales of SF-36 HRQoL) compared with overweight and obese abdominally obese patients. This at least partially explains the abdominal obesity paradox in MHD population, in which worse clinical outcomes are seen in abdominally obese patients with normal BMIs, as opposed to overweight and obese patients who are also abdominally obese.

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