

Obesity and CV Mortality in ESRD

Abdominal Obesity and All-Cause and Cardiovascular Mortality in End-Stage Renal Disease

Maurizio Postorino, MD, Carmen Marino, TECH, Giovanni Tripepi, DRSTAT, Carmine Zoccali, PROF, on behalf of the CREDIT (Calabria Registry of Dialysis and Transplantation) Working Group

Reggio Calabria, Italy

- Objective** The aim of this study was to investigate the predictive value for all-cause and cardiovascular (CV) death of anthropometric measurements of abdominal obesity in patients with end-stage renal disease (ESRD).
- Background** Surrogate measures of abdominal obesity and segmental fat distribution (waist circumference and waist/hip ratio [WHR]) are stronger predictors of all-cause and CV death than body mass index (BMI) in the general population, but the issue has never been investigated in patients with ESRD.
- Methods** We performed a prospective cohort study in 537 patients with ESRD (age 63 ± 15 years).
- Results** In BMI-adjusted Cox models, waist circumference was a direct predictor of all-cause and CV mortality ($p < 0.001$), whereas BMI showed an inverse relationship ($p < 0.001$) with these outcomes. The incidence rates of overall and CV death were maximal in patients with relatively lower BMI scores (below the median) and higher waist circumferences (at least the median) and minimal in patients with higher BMI scores (at least the median) and small waist circumferences (below the median). The prognostic power of waist circumference for all-cause (hazard ratio [HR] [10-cm increase]: 1.23; 95% confidence interval [CI]: 1.02 to 1.47; $p = 0.03$) and CV mortality (HR: 1.37; 95% CI: 1.09 to 1.73; $p = 0.006$) remained significant after adjustment for CV comorbidities and traditional and emerging risk factors. WHR was found to be related to all-cause ($p = 0.009$) and CV mortality ($p = 0.07$).
- Conclusions** Abdominal obesity underlies a high risk of all-cause and CV mortality in patients with ESRD. Redefinition of nutritional status by combining the metrics of abdominal obesity and BMI may refine prognosis in the ESRD population. (J Am Coll Cardiol 2009;53:1265–72) © 2009 by the American College of Cardiology Foundation

Obesity has reached epidemic proportions worldwide. Temporal trends in increasing obesity in the dialysis population are of the same magnitude as those in the general population, and the prevalence of this disease in the U.S. Renal Data System was more than 25% in 2002 (1). Body mass index (BMI) (i.e., body weight scaled to height) is the most widely used anthropometric measure of overall body size in epidemiology research, and this metric has been formally recommended for nutritional status assessment and monitoring in end-stage renal disease (ESRD) (2,3). Studies in dialysis registries (4,5) and large medical databases (6–8) and worldwide extended observational studies (9) have coherently shown that BMI is inversely associated with mortality. This phenomenon is not specific to ESRD because it is also common in other chronic diseases such as

heart failure (10) and coronary heart disease (11), and recent observations indicate that the association of this metric with survival in ESRD does not deviate from that observed in the background general population (12). However, a high BMI should not be seen as a protective factor because “obese sarcopenia” (i.e., high body mass accompanying low urinary creatinine [13]), or protein energy malnutrition (14), underlies a high death risk in patients with ESRD. BMI apart, anthropometric measures of abdominal obesity and body fat distribution like waist circumference and waist/hip ratio (WHR) appear directly, rather than inversely, associated with all-cause and cardiovascular (CV) mortality in the general population. In this respect, WHR emerged as the strongest body size measure associated with myocardial infarction in a worldwide extended case-control study (INTERHEART) (15). Importantly, in the INTERHEART study, BMI had no predictive power for myocardial infarction in an analysis adjusting for WHR and other risk factors, whereas the predictive power of WHR became stronger after extensive statistical adjustment, suggesting that visceral fat is a body component that contributes

From the Nephrology, Dialysis and Transplantation Unit and CNR-IBIM Clinical Epidemiology and Pathophysiology of Renal Diseases and Hypertension, Reggio Calabria, Italy. This study was supported by grants from the Consiglio Nazionale delle Ricerche and Regione Calabria, Italy.

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Abbreviations and Acronyms

BMI	= body mass index
CKD	= chronic kidney disease
CRP	= C-reactive protein
CV	= cardiovascular
ESRD	= end-stage renal disease
WHR	= waist/hip ratio

to the risk for myocardial infarction in the general population. However, it was emphasized that it remains largely unknown whether metrics of waist circumference hold prognostic value for death and CV complications in patients with chronic diseases (16). Recent analyses of the sub-cohort of individuals with mild to moderate chronic kidney disease (CKD) in 2 community-based studies in the elderly indicated that WHR holds predictive power for CV events also in the early stages of CKD (17). Notwithstanding that ESRD is a chronic condition in which nutritional disorders are exceedingly common (18), to date there is no study testing the value of these indicators in this population. Also in light of the rise of overweight and obesity in the ESRD population (19,20) and the controversial interpretation of the effect of obesity on clinical outcomes in ESRD (2,3), the issue of simultaneously testing the prognostic value of metrics of overall body size (BMI) and segmental fat accumulation (waist circumference and WHR) in patients with ESRD appears of particular relevance. With this background in mind, we performed a cohort study aimed at testing the predictive power for all-cause and CV death of waist circumference and WHR.

Methods

The protocol conformed with the ethical guidelines of our institution; because we used standard, anonymous registry data, no written informed consent was required from participants.

Study population. This study was based on the dialysis registry of a southern Italian region (CREDIT [Calabria Registry of Dialysis and Transplantation]) affiliated with the Italian and the European Renal Association-European Dialysis and Transplant Association Registries. The CREDIT registry includes anonymous data of all patients with ESRD treated in 36 dialysis units of the same region. Collected data are those requested by national and European registries and additional data on comorbidities and other data driven by specific research projects of the regional registry. Twenty-four centers (67%) participated in this study, and 537 patients were enrolled in this study.

Study design and baseline data collection. Demographic, clinical, and anthropometric data of all patients treated with extracorporeal dialysis in participating centers were obtained between June and December 2003. For the purpose of this study, anthropometric data (height, weight, and waist and hip measurements) were collected in participating centers. Waist and hip circumferences were measured with a nonstretchable standard tape measure. Waist circumference was measured over the unclothed

abdomen at the midpoint of the lower thoracic cage and iliac crest in the midaxillary line, and hip circumference was measured at the level of the widest diameter around the buttocks, as recommended by the World Health Organization (21). Both weight and height were measured with standardized protocols. BMI was calculated as weight in kg divided by height in m². Serum C-reactive protein (CRP) was measured by a high-sensitivity immunoturbidimetric method (Dade Behring, Marburg, Germany) in a central laboratory. Serum lipids, glucose, calcium, and phosphate were measured by standard methods in hospital laboratories of participant centers. Pre-dialysis arterial pressures and heart rates were measured 3 times after 10-min resting periods while the patients were seated, and the average value of these measurements was considered in the statistical analysis. All measurements were obtained midweek before dialysis.

Follow-up. All patients were followed until December 2006 or censoring (study end, kidney transplantation, or lost to observation). Primary kidney disease and causes of death were classified according to the coding system of the European Renal Association-European Dialysis and Transplantation Association (22).

Statistical analysis. Data are reported as mean \pm SD, median (interquartile range), or percent frequency, as appropriate. The association between paired variables was tested by Pearson product moment correlation coefficient (*r*) and *p* value.

The prognostic value for all-cause and CV mortality of indicators of body size was investigated by unadjusted and multiple Cox regression analyses. In a first step, the predictive value of waist and hip circumferences and their ratio was tested in bivariate Cox models adjusted for BMI. In multiple Cox regression analyses, we considered traditional risk factors (age, sex, smoking, diabetes, systolic pressure, cholesterol, and triglycerides), factors specific to ESRD (dialysis vintage, hemoglobin, and calcium \times phosphate product), CV comorbidities, and serum CRP level. Starting with these variables, significant, independent predictors of all-cause and CV mortality were identified by a reverse stepwise approach (*p* < 0.10). In these analyses, we also tested the multiplicative interaction (23) between waist circumference, BMI, and WHR and sex and all independent predictors of all-cause and CV death. The 95% confidence intervals (CIs) of the crude incidence rate of all-cause and CV mortality were calculated as suggested by Haenszel et al. (24). Data are expressed as hazard ratios (HRs) and their 95% CIs that were calculated with the use of estimated regression coefficients and their standard errors in the Cox regression analysis.

All calculations were done using a standard statistical package (SPSS for Windows, version 9.0.1, SPSS Inc., Chicago, Illinois).

Results

The study cohort (n = 537) was similar to the contemporary dialysis population (n = 1,143) for age (63 years vs. 62 years), male sex (58% vs. 57%), diabetes (16% vs. 19%), blood pressure (137 ± 22/75 ± 12 mm Hg vs. 139 ± 20/78 ± 11 mm Hg), causes of renal disease, and background comorbidities.

Anthropometric measurements. Clinical, biochemical, hemodynamic, and somatometric data are summarized in Table 1. Waist circumference was higher than the sex-specific reference value (men >102 cm; women >88 cm) in 212 of 537 patients (39%). Hip circumference was on average 99.7 ± 11.4 cm. WHR (average 0.93 ± 0.09) exceeded the upper limit of normal (men >0.97; women >0.85) in the majority of patients (301 of 537 [56%]), and the proportions of patients with wider waist circumferences and WHR were higher in women than in men (p < 0.001). Waist and hip circumferences were directly and significantly related to BMI (Fig. 1). BMI was normal (22.6 to 25.0 kg/m²) in 139 patients. Twenty-one patients were frankly malnourished (BMI <18.5 kg/m²), and 127 were underweight (BMI 18.5 to 22.5 kg/m²). One hundred and eighty-six were overweight (BMI 25.1 to 30.0 kg/m²) and 64 were obese (BMI >30 kg/m²).

Prognostic value of waist circumference, WHR, and BMI. During the follow-up period (average 29 months; range 1 to 47 months), 182 patients died, 113 of CV causes. In unadjusted Cox regression analyses, waist (Table 2) and hip circumferences were unrelated to all-cause and CV mortality. WHR was a direct predictor of all-cause mortality, and a 0.1 increase in this ratio was associated with a 25% increase in the risk of all-cause death (HR: 1.25; 95% CI: 1.08 to 1.46; p = 0.003). In contrast, in unadjusted analyses, BMI was an inverse predictor of both all-cause and CV mortality (Table 2).

In Cox models adjusting for BMI, hip circumference remained unrelated to death. However, this adjustment substantially improved the prediction power of waist circumference for all-cause (HR [10-cm increase]: 1.49; 95% CI: 1.26 to 1.77; p < 0.001) and CV mortality (HR [10-cm increase]: 1.55; 95% CI: 1.25 to 1.93; p < 0.001). Indeed, the relationship between waist circumference and the incidence rate of all-cause and CV mortality was closely dependent on BMI categories (above and below the median value), the incidence rate of overall and CV death being maximal in patients with relatively lower BMI (less than median) and higher waist circumferences (at least median) and minimal in patients with higher BMI (at least median) and small waist circumferences (less than median) (Fig. 2).

Table 1 Main Clinical, Hemodynamic, and Biochemical Characteristics of the Study Population

	Whole Cohort	Women (n = 227)	Men (n = 310)	p Value (Women vs. Men)
Age, yrs	63 ± 15	64 ± 15	62 ± 14	0.06
Dialysis vintage, months (range)	48 (19-97)	47 (20-106)	48 (19-92)	0.67
Smokers	62 (11)	3 (0.1)	59 (19)	<0.001
Patients with diabetes	86 (16)	33 (15)	53 (17)	0.45
Patients with cardiovascular comorbidities	145 (27)	58 (26)	87 (28)	0.57
Body mass index, kg/m ²	25.1 ± 4.5	25.6 ± 5.4	24.8 ± 3.6	0.09
Waist/hip ratio	0.93 ± 0.10	0.90 ± 0.10	0.96 ± 0.09	<0.001
Waist circumference, cm	93.0 ± 13.3	91.5 ± 14.1	94.2 ± 12.6	0.02
Hip circumference, cm	99.7 ± 11.4	101.4 ± 12.6	98.5 ± 10.4	0.005
Systolic pressure, mm Hg	137 ± 22	135 ± 24	138 ± 21	0.21
Diastolic pressure, mm Hg	75 ± 12	74 ± 13	76 ± 11	0.02
Pulse pressure, mm Hg	62 ± 17	61 ± 18	62 ± 16	0.81
Heart rate, beats/min	75 ± 15	75 ± 14	75 ± 15	0.67
Cholesterol, mg/dl	158 ± 44	169 ± 49	150 ± 39	<0.001
Triglycerides, mg/dl	140 (91-215)	156 (99-231)	134 (87-200)	0.01
Calcium × phosphate, mg ² /dl ²	45 ± 20	46 ± 18	44 ± 22	0.20
Hemoglobin, g/dl	11 ± 2	11 ± 2	11 ± 2	0.23
Glucose, mmol/l	5.8 ± 2.7	5.7 ± 2.7	5.9 ± 2.8	0.48
C-reactive protein, mg/l	4.7 (2.0-11.7)	4.2 (1.8-11.7)	5.2 (2.3-11.6)	0.11
Abnormal waist circumference	212 (39)	137 (60)	75 (24)	<0.001
Abnormal waist/hip ratio	301 (56)	171 (75)	130 (42)	<0.001
Body mass index distribution, kg/m ²				
<18.5	21 (4)	12 (5)	9 (3)	
18.6-22.5	127 (24)	56 (25)	71 (23)	0.89
22.6-25.0	139 (26)	54 (24)	85 (27)	
25.1-30.0	186 (35)	67 (30)	119 (38)	
>30	64 (12)	38 (17)	26 (8)	

Data are n (%), mean ± SD, median (interquartile range), or percent frequency, as appropriate.

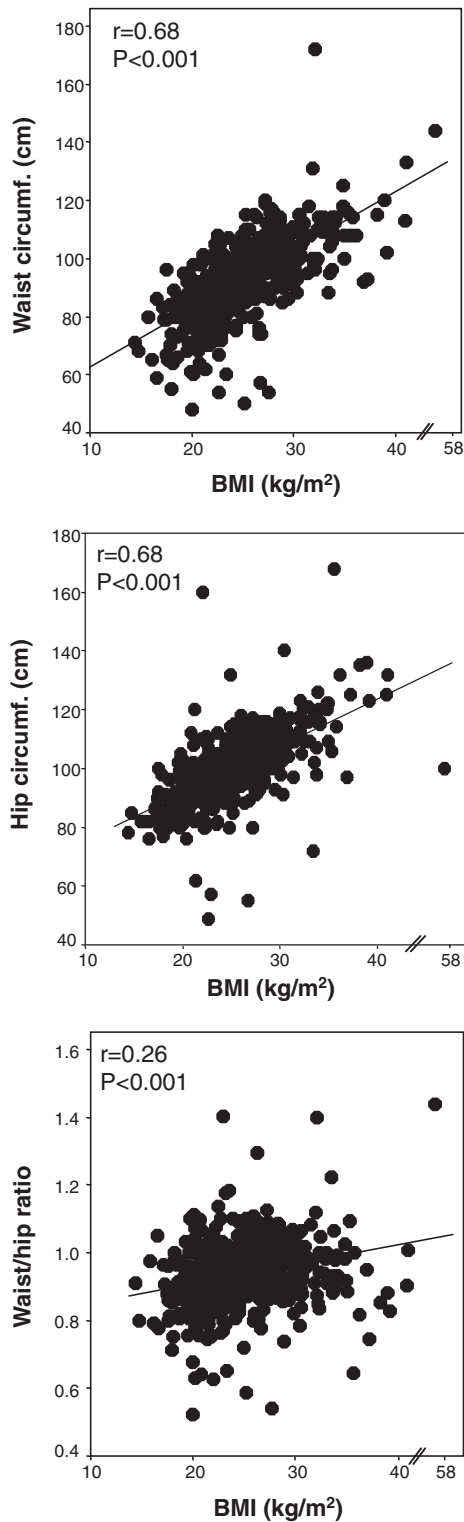


Figure 1 Mutual Relationships Among BMI, Waist and Hip Circumferences, and Waist/Hip Ratio

Data are Pearson correlation coefficients and p values. BMI = body mass index; circumf = circumference.

These analyses indicate that adjustment for BMI is relevant to capture the risk of all-cause and CV death portended by waist circumference and suggest that BMI is a suppressor variable for the relationship between waist circumference and death risk in patients with ESRD. The prognostic power of waist circumference for all-cause and CV mortality was modestly influenced by the inclusion of CV comorbidities and a series of traditional and emerging risk factors (Table 2), and the predictive value of this indicator did not materially change forcing into the models the remaining risk factors listed in Table 1 (data not shown). In multiple Cox regression models, WHR was related to all-cause mortality (HR [0.1 increase in WHR]: 1.24; 95% CI: 1.06 to 1.46; $p = 0.009$) and related ($p = 0.07$) to CV mortality (HR [0.1 increase in WHR]: 1.21; 95% CI: 0.98 to 1.50). No interaction was found between waist circumference and BMI with sex and the remaining risk factors listed in Table 2.

Discussion

In this cohort study in patients with ESRD, a large waist circumference was directly associated with an increased risk of all-cause and CV mortality, whereas BMI was once again confirmed as an inverse predictor of these outcomes. After statistical adjustment, a 10-cm larger waist circumference remained associated with a 26% risk excess for death and 38% risk excess for CV death. Because of the opposing associations of waist circumference and BMI with death, patients with ESRD with large waist circumferences and low BMI were at the highest risk of overall and CV mortality, whereas the probability of death appeared to be minimal in patients with high BMI but small waist circumferences.

In 2002, the prevalence of obesity in the U.S. Renal Data System was 29%, and the forecasted prevalence for 2007 was 35% (1). Like other European countries, in our cohort, the proportion of obese patients on dialysis (12%) was less than in the U.S., which mirrors differences in the general population (1,25). BMI is strongly related to body fat in the general population (26), and it is applied worldwide to define the whole range of alterations in nutritional status, from malnutrition to extreme obesity (21). Studies in ESRD associating high BMI with reduced death risk and vice versa abound (27). Even though there are biologic reasons why a high BMI may be a protective factor in patients with ESRD (28), the importance of associating measures of lean body mass or protein-energy nutrition with refining the prognostic implication of a high BMI is well recognized. In overweight patients, a relatively higher urinary creatinine (denoting a higher muscle mass) predicts a lower risk of death (13). Overweight patients with evidence of protein energy wasting (as assessed by the subjective global index of nutrition) manifest increased death risk in comparison with those with the same BMI without protein energy wasting (obese sarcopenia) (14). It should be noted that the relationship between global fat mass as measured by dual energy X-ray absorptiometry or bioelectrical impedance and mor-

Table 2 Multivariate Cox Models of All-Cause and Cardiovascular Mortality

Variables (Units of Increase)	Unadjusted	Adjusted for Cardiovascular Comorbidities	Fully Adjusted (Reverse Stepwise Analysis)
All-Cause Mortality			
Waist circumference (10 cm)	1.08 (0.96–1.21)	1.48 (1.25–1.76)	1.23 (1.02–1.47)
p value	0.20	<0.001	0.03
Body mass index (1 kg/m ²)	0.95 (0.92–0.99)	0.87 (0.83–0.92)	0.89 (0.84–0.94)
p value	0.006	<0.001	<0.001
Cardiovascular comorbidities (yes/no)		1.58 (1.17–2.14)	1.31 (0.97–1.78)
p value		0.003	0.08
Age (1 yr)			1.06 (1.04–1.08)
p value			<0.001
Diabetes (yes/no)			2.73 (1.91–3.91)
p value			<0.001
Dialysis vintage (10 months)			1.03 (1.01–1.05)
p value			0.02
Hemoglobin (1 g/dl)			0.90 (0.81–0.99)
p value			0.03
C-reactive protein (5 mg/l)			1.07 (1.03–1.11)
p value			<0.001
Cardiovascular Mortality			
Waist circumference (10 cm)	1.09 (0.94–1.27)	1.53 (1.23–1.91)	1.37 (1.09–1.73)
p value	0.24	0.001	0.006
Body mass index (1 kg/m ²)	0.95 (0.91–0.99)	0.87 (0.81–0.93)	0.86 (0.80–0.92)
p value	0.03	<0.001	<0.001
Cardiovascular comorbidities (yes/no)		2.08 (1.43–3.02)	1.71 (1.17–2.49)
p value		<0.001	0.005
Age (1 yr)			1.07 (1.05–1.09)
p value			<0.001
Diabetes (yes/no)			2.88 (1.87–4.41)
p value			<0.001
Calcium × phosphate (1 mg ² /dl ²)			1.01 (1.00–1.03)
p value			0.007

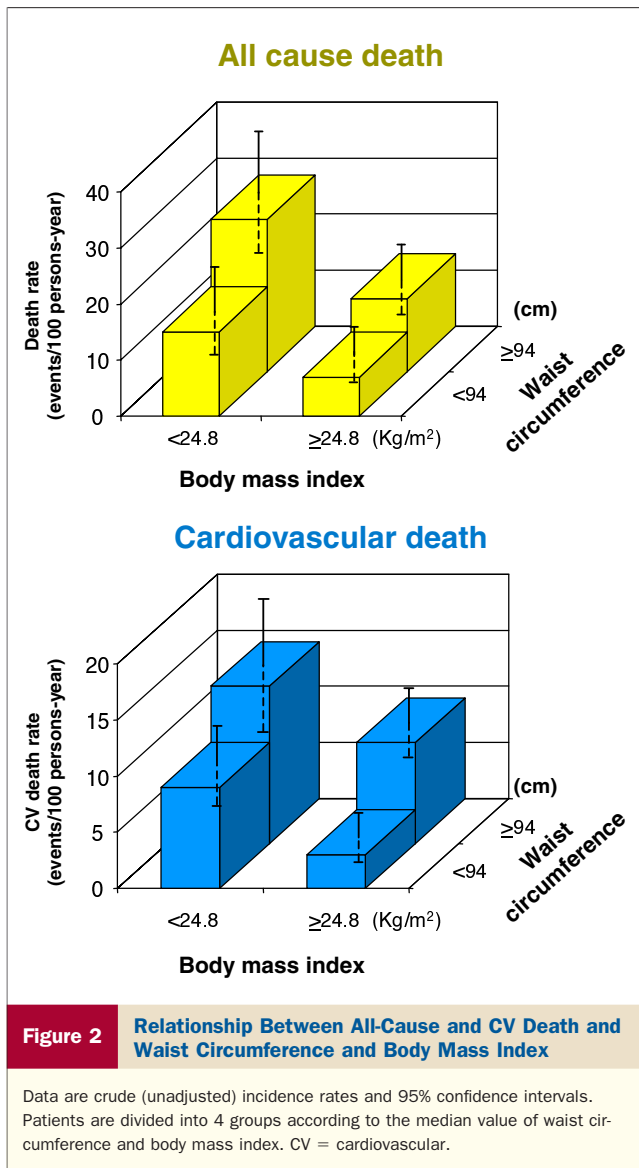
Data are expressed as hazard ratios (95% confidence intervals) and p values.

tality is very similar to that between BMI and the same clinical outcome. In fact, global fat mass was inversely associated with mortality in both American (29) and Japanese (30) patients on dialysis. Furthermore, in female Japanese patients on dialysis, a decrease in global fat mass was associated with a worse prognosis (31). These findings echo observations in the general population showing a J-shaped association between global fat mass and mortality in a middle-aged Danish population (32) and an inverse one in elderly women in another community-based study in Sweden (33).

Although most of the progress realized to date on the understanding of the negative influence of excess body fat on health has been achieved through studies based on BMI (26), evidence is emerging that BMI is an imperfect metric for obesity (34). Waist circumference and WHR appear to be better indicators of this disease than BMI (15,35,36). An international group of experts gathered by the World Health Organization formally recommends measurement of waist circumference and WHR as valid instruments to estimate the health burden posed by the obesity epidemic (37), and these measurements are incorporated in the Adult

Treatment Panel III guidelines (38). These considerations may extend to the CKD population because recent studies documented that waist circumference is strongly related to visceral fat in these patients (39). To our knowledge, there is no study measuring waist circumference and WHR and relating these metrics to clinical outcomes in patients with ESRD. In this study, we observed that, independent of other risk factors, waist circumference is directly rather than inversely associated with overall and CV death. These findings were robust and evident across all BMI strata. Simultaneous consideration of waist and hip circumferences is deemed important because a larger hip circumference at any given waist circumference may confer protection against coronary heart disease (17,40), a phenomenon that may underlie dissimilar metabolic effects of visceral and peripheral fat (41). Although we found no association between hip circumference and death in patients with ESRD, WHR was strongly associated with death, indicating that visceral fat in this population denotes a high-risk condition when scaled to peripheral fat.

Our results are relevant to the current debate on whether or not overweight and obesity are protective in patients with



ESRD (28,42). Visceral fat produces a variety of factors that may impinge upon erythropoiesis, the immune response to infectious agents, and the CV and nervous systems. Truncal fat mass is associated with inflammation in ESRD (43). Thus, adiponectin, a CV-protective factor with pleiotropic effects, is reduced in the obese; although the issue remains controversial (44), adiponectin levels are inversely related with CV events in patients with ESRD (45). Leptin, a peptide implicated in insulin resistance, sympathetic overactivity, and hypertension in the obese, is increased in patients with ESRD and predicts adverse CV outcomes in overweight and obese patients with ESRD (46). Furthermore, visceral fat is currently seen as an organ with multiple direct and indirect connections with endocrine, nervous, and CV systems, with a relevant role in the generation and modulation of systemic inflammation. Evidence exists that visceral fat may have a proinflammatory role in CKD (47) and ESRD (48). In this regard, it is noteworthy that the

predictive power of waist circumference and WHR was largely independent of inflammation as measured by high-sensitivity CRP. CRP is a pentraxin produced in the liver under stimulation of cytokines synthesized in fat tissue such as interleukin-1-beta, interleukin-6, and tumor necrosis factor-alpha. Circulating CRP is more dependent on insulin resistance rather than on waist circumference (49). Our finding that waist circumference predicts death independently of CRP suggests that this marker may be an imperfect indicator of the inflammation burden associated with abdominal obesity in patients with ESRD or that mechanism(s) other than inflammation contribute to the high risk of fat excess in this population.

Study limitations. Although the demographic and anthropometric characteristics of our cohort and the mortality rate were similar to the corresponding average values (50) described in the national Italian registry, the present study was based on a relatively small cohort of white patients and therefore our findings need to be confirmed in larger studies and other ethnicities. The results of our study just apply to the ESRD population and may not be valid in cohorts of patients with coronary heart disease and/or heart failure, higher BMI, and milder forms of renal insufficiency. Second, although we standardized WHR measurements according to World Health Organization recommendations, there may be substantial absolute errors in measuring waist and hip circumferences, which are greater in women than men (51) and greater than in measuring BMI. Therefore, because of the regression to the mean phenomenon, we may have underestimated the effect of waist circumference and WHR on clinical outcomes. Third, our study does not provide any information on interventions that result in weight loss or reductions in waist circumference.

Conclusions

At all BMI categories, from underweight to frank obesity, waist circumference is a strong, direct, independent predictor of all-cause and CV death. Similarly, WHR is linearly related in a direct fashion with adverse clinical outcomes. Redefinition of nutritional status by combining metrics of abdominal obesity and BMI may refine prognosis in the ESRD population. Further studies will clarify the mediators in visceral fat tissue that determine the high risk of a large waist circumference in ESRD.

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Reprint requests and correspondence: Prof. Carmine Zoccali, CNR-IBIM, CNR e Nefrologia, Ospedali Riuniti, c/o EUROLINE di Ascrizzi Vincenzo, Via Vallone Petrarà 55-57, 89124 Reggio Calabria, Italy. E-mail: carmine.zoccali@tin.it.

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Key Words: body mass index ■ cardiovascular risk ■ dialysis ■ waist circumference ■ waist/hip ratio.