

Body mass index mortality paradox in chronic kidney disease patients with suspected cardiac chest pain

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Abstract

Background Chronic kidney disease (CKD) is a silent clinical condition associated with adverse comorbidity and high cardiovascular disease (CVD) risk. An inverse relationship with body mass index (BMI) and mortality has been demonstrated in hemodialysis patients. However, it is unclear if this risk-factor paradox is evident in non-dialysis CKD patients. The aims of this study were to explore the relationship between, nutritional status, markers of inflammation, autonomic and cardiac function with BMI. Longitudinal follow-up explored the relationship between BMI and all-cause mortality.

Methods 211-consecutive CKD patients referred for dobutamine stress echocardiography to detect or exclude myocardial ischemia were recruited. BMI, albumin, C-reactive protein (CRP) and haemoglobin (Hb) were recorded as markers of nutritional and inflammatory status. Left ventricular ejection fraction (LVEF) and heart rate variability (HRV) as an indicator of cardiac function was recorded. All subjects were followed prospectively until November 2014 and study end-point was all-cause mortality.

Results BMI was inversely associated with CKD status. After covariate adjustment, this association remained. During a mean follow-up period of 3.3 ± 0.9 years there were 35 deaths (17%). BMI was inversely associated with all-cause mortality (HR 0.81, 95% CI 0.71-0.9). Other important independent predictors of mortality were heart rate variability (HR 0.98, 95% CI 0.97-0.99), myocardial ischemia (HR 1.37, 95% CI 1.17-1.81), and albumin (HR 0.86, 95% CI 0.81-0.92).

Conclusions The presence of a BMI paradox exists in non-dialysis CKD patients. This risk-factor paradox was an independent predictor of all-cause mortality and may have significant clinical implications relevant to screening, assessment and treatment and requires further study.

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Introduction

Several epidemiological studies have identified obesity as an established risk factor for cardiovascular disease and all-cause mortality. As such, the World Health Organisation (WHO) has produced guidelines on body mass index (BMI, in kg/m^2) and its relationship with health risks from obesity-related conditions such as type-2 diabetes (T2DM), CVD, and death [1]. Normal weight is deemed $18.5\text{--}24.9 \text{ kg/m}^2$, overweight, $25\text{--}29.9 \text{ kg/m}^2$ and obese $\geq 30 \text{ kg/m}^2$ [1]. However, the use of BMI screening

alone is problematic based upon current research, as there is evidence of a 'BMI paradox'. Recent research demonstrated that compared to normal weight ($18.5\text{--}24.9 \text{ kg/m}^2$), grade 1 obesity ($30\text{--}34.9 \text{ kg/m}^2$) was not associated with higher mortality and overweight ($25\text{--}29.9 \text{ kg/m}^2$) was associated with significantly lower all-cause mortality in the general population [2]. Furthermore, in clinical populations the BMI paradox is a well-known phenomenon, especially in end-stage CKD and chronic heart failure (CHF) patients, whereby high BMI has a protective effect on mortality risk [3]. The reasons for this

risk-factor paradox are not completely understood.

Chronic kidney disease (CKD) is a serious medical condition, frequently unrecognised and associated with increased risks of morbidity and mortality, in particular cardiovascular disease (CVD) [4-8]. Its development and pathology is believed to be due to many different factors including exposure to obesity and metabolic syndrome (MetS) [6, 9-11]. Worsening kidney function is associated with insulin resistance, inflammation, anaemia, acidosis, anorexia, hypermetabolism, increased protein degradation and muscle wasting [6, 12-16]. In severe CKD a relationship was identified between malnutrition, inflammation and atherosclerosis (termed the 'MIA syndrome'), which was associated with poor outcome and a BMI/obesity paradox [15-17].

The International Society for Renal Nutrition and Metabolism (ISRNM) developed a nomenclature and diagnostic criteria for 'protein-energy wasting' (PEW) in CKD [13]. Other definitions have been developed for related conditions including 'cachexia' [18] and 'sarcopenia' [19], and it is quite feasible that many patients with CKD may suffer from significant weight loss, reduced muscle mass/sarcopenia, inflammation and meet criteria for PEW, cachexia and sarcopenia, which may increase mortality risk. Of the differing definitions, unintentional weight loss, BMI (e.g., <23 kg/m² ISRNM [13] and <20-22 kg/m² [18]), plasma albumin (e.g., <38 mg/L ISRNM [13] and <32 mg/L [18]) and inflammation (e.g., CRP >5.0 mg/L [18]) have high importance in diagnosis. Albumin and CRP in particular, have been shown to be powerful predictors of CVD and mortality, and specifically within CKD populations (even in earlier CKD stages, II-IV) [20, 21].

Cardiac dysfunction (e.g., myocardial ischemia and reduced left ventricular ejection fraction (LVEF)) is common in CKD. Further, heart rate variability (HRV), a non-invasive marker of cardiac autonomic function, has proven to be a novel predictor of mortality in CKD patients [22]. HRV measures have been found to inversely correlate with inflammation [23] and positively correlate with neurohormonal activation (epinephrine and norepinephrine) and cachexia/wasting in CHF patients [24, 25].

The importance of BMI and these different factors in earlier stages of CKD is unknown as is their relationship with long-term mortality risk. This study aimed to explore the relationship between BMI and measures of nutritional status, inflammation and cardiac autonomic function in non-dialysis CKD patients referred for dobutamine stress echocardiography (DSE) and their relative abilities to predict long-term all-cause mortality.

Methods

Participants

This was a prospective observational study of consecutive non-dialysis CKD patients clinically referred for an outpatient DSE between December 2010 and June

2011. Two hundred and eleven CKD patients volunteered to participate in the study. Exclusion criteria were age <18 years, unstable angina, dialysis patients, patients with preserved kidney function, non-fasted patients, patients with acute illness at the time of recruiting, congenital heart disease, pregnant women, and inability to provide consent. All patients provided informed consent and the study had approval from the local ethics committee.

Study entry was at the time of the patient's DSE. At this stage a structured history and medical record review was performed to document symptoms, medical history, cardiac risk factors, and previous cardiac events and procedures. The patient's height and weight were recorded in order to calculate BMI.

Laboratory Measurements

Fasting whole blood samples were drawn from all patients via vena puncture. This was performed according to the local NHS trust hospital guidelines. All samples were immediately sent to the laboratory for processing. In total 50 ml of blood per patient was required. Blood sample concentrations of albumin, C-reactive protein (CRP), total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, creatinine, hemoglobin, potassium, sodium, and urea were measured.

Estimated glomerular filtration rate (eGFR) was calculated using the four-variable modification of diet in renal disease (MDRD) formula [26] as follows: $GFR = 186.3 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times 1.212$ (if black) $\times 0.742$ (if female). Serum creatinine is measured in mg·dL⁻¹, age is in years, and GFR is in ml/min $\times 1.73\text{m}^2$. The patients were then divided according to their eGFR where 60-89 is mild CKD (stage II), 30-59 moderate CKD (stage III), 15-29 severe CKD (stage IV) and <15 ml/min $\times 1.73\text{m}^2$ is end stage kidney failure (stage V).

Autonomic Assessment

The Task Force[®] Monitor (TFM) (CNSystems, Graz, Austria) was used for the continuous non-invasive beat-to-beat monitoring and real time calculation of cardiac autonomic function. The TFM uses an integrated two-channel ECG for R-R interval determination, which was instantaneously calculated as the difference between successive R-R peaks. Real-time beat-to-beat HRV was calculated using power spectral analysis and applying an autoregressive model [27]. Specific frequencies within the power spectrum of HRV have been previously used to quantify autonomic nervous control of the cardiovascular system. Low frequency (0.04 – 0.15 Hz) HRV is considered a marker of sympathetic activity on the heart [28] and high frequency (0.15 – 0.4 Hz) HRV is considered a marker of parasympathetic cardiac modulation [28]. Parameters of HRV were automatically calculated by the TFM and expressed in absolute (ms²) and normalised units (nu). The normalisation of the frequency components of HRV has proven crucial to the interpretation of data [29] and

the TFM automatically calculates this by dividing the absolute power of each oscillatory component by total power minus the very low frequency and multiplying by 100. The ratio of LF-to-HF for HRV is an accepted index of cardiac sympathovagal balance [30].

Cardiac Stress Test

DSE was the test selected for the non-invasive evaluation of ischemic heart disease and assessment of global cardiac structure and function. Left ventricular ejection fraction (LVEF) was determined by the modified biplane Simpson's rule, with measurements averaged over three cardiac cycles. Patients underwent a standard DSE protocol [31] with stepwise infusion of dobutamine in 3-minute stages of 10, 20, 30, 40 $\mu\text{g}/\text{kg} \times \text{min}$. β -blocker therapy was stopped 72-hours before DSE and patients were fasted as per protocol. Based on the myocardial response during DSE, patients were categorised as non-ischaemic (normal) or ischaemic. In the normal response, a segment is normokinetic or hypokinetic at rest with an overall increase in wall motion during stress. In the ischaemic response, a segment worsens its function during stress from normokinesis to hypokinesis, akinesis, or dyskinesis.

End Point Definition

The principle end-point of interest for this analysis was all-cause mortality, with patients censored at the time of the last follow-up. Follow-up data was collated by contacting patients or a family member, general practitioners, and reviewing hospital records. The date of the last review or consultation was used to calculate the duration of follow-up through to November 2014.

Data Analysis

Continuous variables were expressed as mean \pm standard deviation and categorical variables as n (%). Group comparisons were based on 2-sample *t* test for continuous variables and χ^2 test was used for group comparisons among categorical variables.

Logistic regression was used to assess CKD status as a categorical variable (mild, moderate and severe) and its association with BMI (dichotomised into BMI <25 kg/m^2 and $\geq 25 \text{ kg}/\text{m}^2$). A multivariate model was then constructed to ascertain variables associated with BMI. For model building, demographic, clinical history, laboratory measures, cardiac autonomic, and echocardiographic parameters were considered. Stepwise forward selection logistic regression was performed with factors added at the 0.15 level of significance.

Multivariable adjusted Cox proportional hazard models were constructed to ascertain predictors of all-cause mortality. BMI was used as a continuous variable in the Cox model. For model building, demographic, clinical history, laboratory measures, cardiac autonomic and echocardiographic parameters were evaluated for their

association with mortality. Forward stepwise selection procedures were used to compare models for goodness-of-fit and a *P*-value <0.15 was used for retention in the final model. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) are reported. Survival was further analyzed by Kaplan-Meier methods, with cumulative event curves constructed and compared using the log-rank test with a *P* value <0.05 considered statistically significant. BMI was stratified according <25 and $\geq 25 \text{ kg}/\text{m}^2$.

All analysis was conducted using the statistical package for social sciences (SPSS 21, release version of SPSS for Windows; SPSS Inc., Chicago IL, USA).

Results

The descriptive characteristics of the study population according to BMI <25 kg/m^2 and $\geq 25 \text{ kg}/\text{m}^2$ are shown in Table 1. Of the clinical history parameters, the prevalence of prior percutaneous coronary intervention ($p=0.002$) significantly differed between groups. Of the cardiac autonomic parameters, HRV ($p=0.03$), LFnu ($p=0.02$), HFnu ($p=0.02$) and LF/HF ratio ($p=0.01$) significantly differed between groups. Of the laboratory parameters, Albumin ($p=0.02$), CRP/albumin ratio ($p=0.04$), cholesterol ($p=0.03$), creatinine ($p=0.003$), eGFR ($p=0.04$), haemoglobin ($p=0.01$), low-density lipoprotein ($p=0.03$), sodium ($p=0.001$), and urea ($p=0.04$) significantly differed between groups. There were no significant differences in echocardiographic parameters.

Table 2 shows the Odds Ratios for the association with a BMI <25 kg/m^2 . The unadjusted model (model 1) showed a significant inverse relationship between the odds of being a BMI <25 kg/m^2 and moderate (OR 1.67; 95% CI 1.56-5; $p=0.02$) and severe (OR 2.4; 95% CI 1.16-9.9; $p=0.03$) CKD status. Model 2 shows the Odds Ratios for the significant determinants in which BMI was adjusted using stepwise forward selection logistic regression. Albumin and LF/HF ratio emerged as significant predictors of a BMI <25 kg/m^2 . CKD status remained significantly and inversely associated with a BMI <25 kg/m^2 .

Survival Analysis

The primary end-point of all-cause mortality was observed in 35 (16.6%) patients over a 4-year follow-up period. Mean whole group eGFR was $61.5 \pm 19.6 \text{ ml}/\text{min} \times 1.73 \text{ m}^2$. There was a significant difference ($p<0.001$) in eGFR between those that died ($46.8 \pm 15.9 \text{ ml}/\text{min} \times 1.73 \text{ m}^2$) and survived ($64.4 \pm 19.0 \text{ ml}/\text{min} \times 1.73 \text{ m}^2$). BMI was $23.8 \pm 2.3 \text{ kg}/\text{m}^2$ (normal weight) in the patients who died compared to $28.7 \pm 4.7 \text{ kg}/\text{m}^2$ (overweight), in those that survived ($p<0.001$) (Supplementary Table 1). Of the patients alive ($n=176$), 2.8% ($n=5$) were stage V and 1.1% ($n=2$) stage IV; of the deceased group 2.9% ($n=1$) were stage V and 14.3% ($n=5$) stage IV.

Table 1 Descriptive characteristics of the study population. PCI = Percutaneous coronary intervention; CABGS = Coronary artery bypass graft surgery; HRV = Heart rate variability; LFnu RRI = Low frequency normalized units RR interval; HFnu RRI = High frequency normalized units RR interval; VLFnu RRI = Very low frequency normalized units RR interval; LF RRI = Low frequency RR interval; HF RRI = High frequency RR interval; LF/HF Ratio = Low frequency/high frequency ratio; eGFR = Estimated glomerular filtration rate; HDL = High density lipoprotein; LDL = Low density lipoprotein

Characteristics	<25 kg/m ² (n = 63)	≥25 kg/m ² (n = 148)	P Value
Demographics			
Age, y	63.9 ± 16.4	64.7 ± 14.3	0.2
Men	39 (61.9)	80 (54.1)	0.29
Ethnicity			0.78
Black	6 (9.5)	16 (10.8)	
Caucasian	25 (39.7)	53 (35.8)	
Indian Asian	32 (50.8)	79 (53.4)	
Clinical History			
Hypertension	17 (27)	56 (37.8)	0.13
Diabetes mellitus	16 (25.4)	29 (19.6)	0.64
Hypercholesterolemia	19 (30.2)	51 (34.5)	0.54
Family history of cardiovascular disease	7 (11.1)	12 (8.1)	0.49
Prior myocardial infarction	4 (6.3)	12 (8.1)	0.7
Prior PCI	9 (14.3)	53 (35.8)	0.002
Prior CABGS	10 (15.9)	27 (18.2)	0.68
Cardiac Autonomic Function			
HRV total power spectrum (ms ²)	1243 ± 1834	1932 ± 2185	0.03
LFnu RRI (%)	41.4 ± 21.3	28.6 ± 23.5	0.02
HFnu RRI (%)	58.6 ± 21.3	71.4 ± 23.5	0.02
VLF RRI (ms ²)	175 ± 299	203 ± 262	0.73
LF RRI (ms ²)	435 ± 712	554 ± 651	0.49
HF RRI (ms ²)	626 ± 833	1234 ± 1354	0.84
LF/HF Ratio	0.91 ± 0.9	0.41 ± 0.5	0.01
BRS (ms/mmHg)	9.2 ± 10.7	10.1 ± 8.1	0.54
Cardiac Stress Test			
Left ventricular ejection fraction (%)	54.5 ± 9.8	55.9 ± 7.8	0.28
Myocardial ischemia	18 (28.6)	30 (20.3)	0.21
Laboratory Values			
Albumin (mg/L)	40.2 ± 5.4	42.1 ± 4.7	0.02
C-reactive protein (mg/L)	8.6 ± 3.8	8 ± 2.9	0.07
C-reactive protein /Albumin ratio	0.23 ± 0.12	0.19 ± 0.09	0.04
Cholesterol (mmol/L)	3.82 ± 1	4.23 ± 1.1	0.03
Creatinine (mmol/L)	133 ± 89	105 ± 45	0.003
eGFR (ml/min × 1.73m ²)	57 ± 19.8	63 ± 19	0.04
Hemoglobin (g/dL)	12 ± 2	12.8 ± 1.8	0.01
HDL (mmol/L)	1.29 ± 0.4	1.39 ± 0.5	0.31
LDL (mmol/L)	1.8 ± 0.8	2.1 ± 0.9	0.03
Potassium (mmol/L)	4.6 ± 0.5	4.6 ± 0.5	0.88
Sodium (mmol/L)	136 ± 4.4	139 ± 4.7	0.001
Triglyceride (mmol/L)	1.4 ± 0.7	1.5 ± 0.9	0.67
Urea (mmol/L)	9.2 ± 5.6	7.7 ± 4.2	0.04

The unadjusted Kaplan-Meier survival curve for the cumulative freedom from all-cause mortality, dichotomized according to BMI (<25 and ≥25 kg/m²) is presented in Figure 1.

The differences amongst the curves are significant

($p < 0.001$). Following adjusted multivariate Cox regression; BMI used as a continuous variable (HR 0.81; 95% CI 0.71-0.9; $p < 0.001$), HRV (HR 0.98; 95% CI 0.97-0.99; $p = 0.02$), albumin (HR 0.86; 95% CI 0.81-0.92; $p < 0.001$), CRP (HR 1.14; 95% CI 1.11-1.34; $p = 0.04$) and presence of

myocardial ischemia (HR 1.37; 95% CI 1.17-1.81; $p=0.01$) (Table 3).

were independently associated with all-cause mortality

Figure 1 Kaplan-Meier hazard curves dichotomized according to body mass index (<25 and ≥ 25 kg/m²).

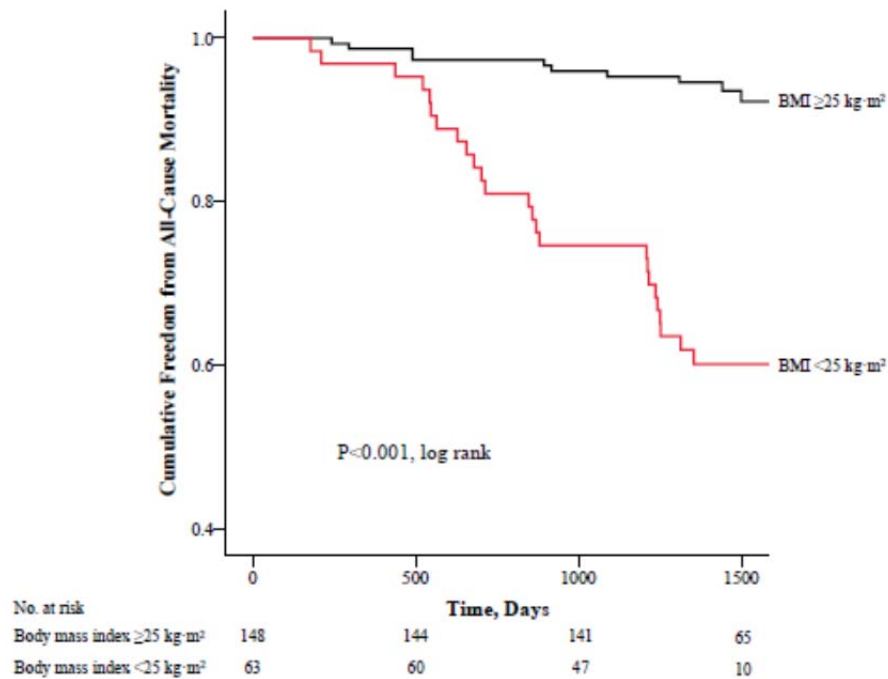


Table 2 Odds ratios for the association with a BMI <25 kg/m². CKD = Chronic Kidney Disease; OR = Odds Ratio; CI = Confidence Interval

Independent variable	Model 1		Model 2	
	OR (95% CI)	P	OR (95% CI)	P
CKD				
Mild	1 (reference)		1 (reference)	
Moderate	1.67 (1.56-5)	0.02	1.12 (1.02-1.38)	0.02
Severe	2.4 (1.16-9.9)	0.03	1.15 (1.12-1.78)	0.02
Albumin (mg/L)			0.95 (0.91-0.98)	0.04
Creatinine (mmol/L)			1.01 (0.91-1.19)	0.16
LF/HF ratio			1.28 (1.19-1.67)	0.02
Sodium (mmol/L)			0.92 (0.9-1.07)	0.08

Table 3 Multivariate predictors of all-cause mortality. HRV = Heart rate variability; eGFR = Estimated glomerular filtration rate

Characteristics	HR (95% CI)	P Value
Demographics		
Body mass index (kg/m ²)	0.81 (0.71-0.9)	<0.001
Cardiac Autonomic Function		
HRV total power spectrum (ms ²)	0.98 (0.97-0.99)	0.02
Cardiac Stress Test		
Myocardial ischaemia	1.37 (1.17-1.81)	0.01
Laboratory values		
Albumin (mg/L)	0.86 (0.81-0.92)	<0.001
eGFR (ml/min \times 1.73m ²)	1.01 (0.97-1.04)	0.39
Sodium (mmol/L)	0.92 (0.84-1.01)	0.07

Discussion

The relative ability to identify individuals with mild-moderate CKD at greater risk of morbidity and mortality has high clinical importance. This study demonstrated an inverse relationship between the prevalence of CKD and BMI. Furthermore, in contrast to observations from the general population, overweight and obese CKD patients had a lower adjusted risk of all-cause mortality compared to normal weight CKD patients. This is the first study to identify a BMI risk paradox in predominantly mild-moderate CKD patients (mean group eGFR: 61.5 ± 19.6 ml/min \times 1.73m^2) referred for a cardiac investigation. The obesity paradox has been observed previously in the elderly [32], and in end stage kidney disease [17] and CHF patients [3]. The mechanisms responsible for this observation are not completely clear, but may in part be due to inflammation, malnutrition, cardiac dysfunction, heightened sympathetic activity, oedema, and drug interactions. In this patient group, the acute phase proteins, albumin and CRP were measured and analysed to act as principle markers of inflammation, although it is understood that albumin is also a marker of nutritional status. Albumin was 33.7 ± 5.5 g/L for those who died, which indicates hypoalbuminemia. The mean albumin levels were below the cut-point suggested by ISRNM to indicate PEW (38 g/L) and above Evans et al. (2008) for cachexia (32 g/L) [13, 18]. CRP was clinically significant for both dead and alive patients (i.e., >5 g/L). Multivariate Cox regression analysis showed that albumin and CRP were significant predictors of mortality. However, Albumin was the only marker significantly associated with a BMI <25 kg/m². Inspection of other blood markers further indicates inflammation and metabolic dysfunction e.g., significantly lower Hb and higher urea in patients who died (Supplementary Table 1). Patients who died had an average Hb of 11.3 ± 2.3 g/dL indicating anemia risk (<12 g/dL), which is a hallmark of the 'cardio-renal syndrome' and is also utilised in the cachexia diagnosis algorithm [18, 33]. It is understood that inflammation itself promotes anemia, through causing erythropoietin resistance and would only worsen a systemic physiological situation of reduced kidney and cardiac function, e.g. through potential tissue hypoxia (36).

DSE was utilised as a model to examine cardiac structure, function and presence or absence of myocardial ischemia. The presence of myocardial ischemia was significantly greater in CKD patients who died and LVEF was significantly reduced indicating greater cardiac dysfunction, which has been well characterised in this population. However, echocardiographic parameters were not significantly associated with a BMI <25 kg/m², perhaps demonstrating that these are not mechanisms driving the BMI risk paradox. HRV was utilised as a marker of cardiac autonomic function and was a significant

independent predictor of mortality. In addition a greater LF/HF ratio, which is an indicator of heightened sympathetic activity was significantly associated with a BMI <25 kg/m². HRV parameters have been linked to the cardiac cachexia-wasting syndrome in CHF patients [24, 25] and may be one mechanism driving the BMI risk paradox in non-dialysis CKD patients.

A hallmark of cachexia is the association of body wasting and muscle loss with neurohormonal activation, heightened circulating stress hormones; epinephrine, norepinephrine, cortisol and proinflammatory cytokines, as part of an acute phase response to illness [6, 12-14, 18, 24]. The loss of tissue is due to a combination of a reduction in appetite/anorexia, hypermetabolism, and increased cellular protein breakdown. This is a well-known and common occurrence in CKD stage V and in dialysis patients; however, understanding the pathogenesis and trajectory within mild-moderate CKD is unknown. It could be hypothesised that patients in this study who showed clinically significant inflammation (high CRP, low albumin), anemia (low Hb), and cardiac and autonomic dysfunction may have experienced detectable cachexia (measurable significant weight loss and skeletal muscle mass depletion) during the study follow-up period, which may have affected survival. Furthermore, these commonly associated alterations in body composition in diseases such as CKD and CHF (e.g. body protein tissue wasting and simultaneous oedema) may mask changes in overall BMI and could be one explanation for a BMI paradox. Future studies would be necessary to confirm this hypothesis and would need to include full body weight and body composition assessment throughout long-term follow-up.

An important observation in this study was that the patients were predominantly of Asian ethnicity (n=118/211 56%). Within the United Kingdom (UK), the National Institute for Health and Clinical Excellence (NICE) has published numerous reports and clinical guidance on BMI, health risks and weight reduction. Recently, NICE has suggested that lower BMI thresholds (23 kg/m² and 27.5 kg/m² respectively) should be utilised to indicate greater risk of T2DM, CVD and death in black and Asian populations [34]. This could have important implications, since overweight and obese patients with mild-moderate CKD would usually be encouraged to undergo weight loss, as they would be deemed at higher risk. This study demonstrates that patients with a lower and normal BMI are at increased risk of all-cause mortality. Therefore, it is unclear whether or not a weight loss programme would be harmful without full clinical screening and understanding of the BMI paradox and any underlying metabolic and inflammatory disturbances in this patient population.

Limitations

This was a small sample size single centre study and

therefore there is potential for referral bias. In addition, the participants were a select group of non-dialysis CKD patients referred for a DSE and the findings may not be relevant to other CKD patients. Furthermore, the patient ethnicity was predominately of UK Indian Asian origin and the results may not be representative of other populations. Screening and assessments were performed once only and it is therefore unclear whether there were significant changes in variables during the follow-up period.

Conclusions

This study highlights the presence of a BMI paradox in non-dialysis CKD patients. This risk-factor paradox was an independent predictor of all-cause mortality and may

have significant clinical implications relevant to screening, assessment and treatment and requires further study.

Acknowledgments

The authors certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle - Clinical Reports* (Haehling S, Ebner N, Morley JE, Coats AJS, Anker SD) [35].

Conflicts of Interest

The authors declare that they have no conflict of interest.

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