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Original article

Creatinine synthesis rate and muscle strength and self-reported physical health in dialysis patients

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SUMMARY

Background & aims: Urinary creatinine excretion reflecting endogenous creatinine synthesis rate (CSR) is an established measure of muscle mass in the general populations and in patients with chronic kidney disease. There is increasing data to suggest that CSR not only reflects muscle mass, but also muscle function. In dialysis patients, CSR has rarely been studied since it requires dialysate collection. We aimed to study whether CSR is associated with muscle strength, and self-reported physical health in dialysis patients.

Methods: Total daily CSR (dialytic removal plus, if applicable, urinary excretion), handgrip strength, and self-reported physical health according subscales of the Checklist Individual Strength and the Short Form-36 were assessed in 50 dialysis patients. Associations of CSR, indexed to body surface area, with handgrip strength and self-reported physical health were studied using multivariable linear regression models.

Results: Median age was 69 [interquartile range 60–78] years. Mean CSR was higher in men than in women (9.5 ± 3.3 mmol/24 h versus 6.8 ± 1.9 mmol/24 h respectively, $P = 0.007$). Age, BMI, and plasma albumin were positively associated with CSR. CSR was positively associated with handgrip strength (adjusted (a-) β : 0.44 [95% CI: 0.18 to 0.71], physical functioning (a- β : 0.54 [95% CI: 0.19 to 0.88]), social functioning (a- β : 0.43 [95% CI: 0.08 to 0.76]), and inversely with physical inactivity (adjusted β : -0.69 [95% CI: -1.00 to -0.38], fatigue (adjusted β : -0.61 [95% CI: -0.93 to -0.27]), and role limitation due to physical health (a- β : 0.39 [95% CI: 0.04 to 0.74]).

Conclusions: In dialysis patients, a greater CSR is associated with higher muscle strength, better physical and social functioning, and physical activity, and with less fatigue, and role limitation due to physical health. Thus, CSR reflects muscle function, self-reported physical health and social functioning in dialysis patients.

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1. Introduction

Patients with chronic kidney disease (CKD) can be considered to be in a state of accelerated aging, which is accompanied by muscle

wasting and a gradual decline in muscle functioning [1–5]. Therefore, it is not surprising that sarcopenia, a syndrome defined by loss of muscle mass and strength, is highly prevalent in patients with end-stage CKD receiving dialysis and that it is associated with adverse outcomes, including functional decline, falls, and mortality [6–10].

A relatively simple and noninvasive method to estimate muscle mass that can be used in healthy individuals as well as in patients with CKD is urinary creatinine excretion rate (uCER) [11–14]. In a recent study, uCER was associated with self-reported frailty and

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frailty-associated variables in advanced CKD patients [15], suggesting that uCER is not only a measure of muscle mass but may also capture muscle function. In addition to this study, it has been found in haemodialysis patients that plasma creatinine concentrations measured before a dialysis session, correlated with muscle function but not with muscle mass [16]. A low uCER has been shown to be associated with increased mortality risk in the general populations and in patients with CKD and other chronic diseases [17–23]. If uCER would also reflect muscle function; this might partly explain the association with mortality, since muscle function has been reported to be a stronger predictor of death than muscle mass [24,25].

uCER, reflecting endogenous creatinine synthesis rate (CSR) and thus muscle mass, cannot be simply assessed in dialysis patients. Normally, CSR is estimated by assessment of uCER by means of 24-h urine sampling. In dialysis patients, this method does not capture the true total CSR since endogenously produced creatinine is predominantly removed by dialysis (dCER), and urinary excretion of creatinine is decreased or even absent. Consequently, the measurement of CSR in dialysis patients requires both dCER and uCER.

We aimed to study (i) determinants of CSR, and (ii) whether CSR is associated with muscle strength, and self-reported physical and mental health in dialysis patients.

2. Materials and methods

2.1. Patients and study design

The study was performed according to ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, and was approved by the Medical Ethical Committee of the University Medical Center Groningen, The Netherlands. All participating patients gave written informed consent. Inclusion criteria were a dialysis vintage of ≥ 2 months and absence of clinical signs of infection. Furthermore, haemodialysis (HD) patients received dialysis treatment twice or thrice weekly, and 3–5 h per treatment. The study was performed between October 2015 and July 2016.

Hypertension was defined as predialysis systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg or use of antihypertensive drugs. A history of diabetes, chronic obstructive pulmonary disease (COPD), and cardiovascular disease was obtained from the patients' medical records. Cardiovascular disease was defined as a history of ischemic heart disease, congestive heart failure, coronary artery bypass grafting, percutaneous coronary intervention, stroke, or peripheral vascular disease. The validated Patient Health Questionnaire (PHQ-9) was used as a screening tool for depression, with a score > 9 indicating a major depression [26,27]. In HD patients, blood pressure and weight were measured before and after HD. In peritoneal dialysis (PD) patients, blood pressure and weight were measured during an outpatient visit. Protein intake was assessed according to total daily urea excretion using the Maroni formula and was expressed as g/kg body weight/day [28]. In this formula the protein intake is calculated as $6.25 * ((0.0276 * 24 \text{ h urine and dialysate urea nitrogen}) + (\text{post-dialysis weight in kg} * 0.031)) + 24 \text{ h urine and dialysate protein}$. Post-dialysis body weight was measured immediately after the dialysis session.

2.2. Dialysis settings

HD patients were dialyzed using a Fresenius 5008 dialysis apparatus with a low-flux polysulphon dialyzer (Polyflux L17 or L21, Baxter, Deerfield, USA). Blood flow and dialysate flow rates were 200–300 ml/min and 500–700 ml/min, respectively. Dialysate temperature was 36.0 or 36.5 °C. For information on dialysate

composition, see [Supplementary Methods](#). PD patients followed their usual continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (ADP) scheme (Fresenius Medical Care, Nieuwkuijk, Netherlands).

2.3. Dialysate and urine collection for CSR measurement

In HD patients, during a regular HD session the total dialysate was collected in a 200 L tank. The total dialysate volume was measured by calculating the weight difference of the tank before and after the HD session. At the end of treatment, a dialysate sample was taken and the creatinine concentration was measured immediately after HD. dCER was normalized to dCER/24-h ($\text{dCER} \times \text{number of dialysis sessions per week} / 7$). Patients were studied during a mid-week dialysis.

PD patients collected the spent dialysate during 48 h preceding a regular outpatient visit, at which the dialysate volume of each bag was measured and samples were taken for creatinine measurement. 24-hour dCER was then averaged from the two dialysate collections. Daily ultrafiltration (UF) volume was calculated as the difference between total dialysate volume instilled and removed from the peritoneal cavity of PD patients per 24 h.

Patients with significant residual diuresis (> 200 mL/24 h) performed two 24-h urine collections before the HD session during which dialysate was collected, or before the outpatient visit during which dialysate was collected. 24-hour uCER was then averaged from the two urinary collections. CSR was calculated as the sum of 24-h dCER and uCER. Similar to CSR, total urea and protein excretion were calculated.

2.4. Muscle strength and gait speed

Handgrip strength was measured using the JAMAR hydraulic hand dynamometer (Lafayette instrument company, Indiana, USA), and in HD patients before the HD session during which dialysate was collected. Measurements were performed at the non-fistula arm, which was the dominant arm in most patients. In patients without an arteriovenous fistula, handgrip strength was measured at the dominant hand. Low grip strength was defined as handgrip strength < 27.0 kg in men and < 16.0 kg in women, according to the second guideline of the European Working Group on Sarcopenia in Older People [29]. Gait speed was measured in a subgroup of 23 patients. The gait speed measurement was repeated twice with the mean of the two trials used for the analyses. Patients were instructed to walk from a standing start at a pace that was normal and comfortable for them until they had passed the sign at 4 m distance. A trained tester walked behind the participant and stopped timing when the participant's foot at first contacted the floor behind the 4-m sign. Low gait speed was defined as < 0.8 m/s according to the second guideline of the European Working Group on Sarcopenia in Older People [29].

2.5. Self-reported physical and mental health

We assessed self-reported physical health and mental health with subscales of the Checklist Individual Strength (CIS), and the Short Form of Health Survey 36 (SF-36).

The CIS is a self-reported multidimensional instrument to assess four qualitatively different aspects of fatigue (fatigue severity, concentration problems, reduced motivation, and reduced activity level) [30–32]. For the analyses of self-reported physical health, the fatigue severity (range 8–56 points) and the activity level subscale (range 3–21 points) were used as a measure of fatigue burden or physical inactivity, respectively. For the analyses of mental health, the subscales concentration problems (range 5–35 points) and

reduced motivation (range 4–28 points) were used. Higher CIS scores indicate higher fatigue burden, and less physical activity, concentration, or motivation, respectively.

The SF-36 is a questionnaire that measures quality of life across eight domains [33]. All SF-36 subscales range from 0 to 100 points, with a higher score indicating less disability. For the analyses of self-reported physical health, the SF-36 subscales physical functioning, vitality (assessing energy levels and fatigue), bodily pain (assessing pain frequency and pain interference with usual roles), and role physical (assessing role limitations due to physical health) were used. For the analyses of mental health, the SF-36 subscales emotional wellbeing (assessing psychological distress), social functioning (measuring the extent to which ill health interferes with social activities), general health (measuring individual perceptions of general health), and role emotional (assesses role limitations due to emotional problems) were used.

2.6. Laboratory procedures

Blood samples were drawn at the start and end of the HD session, or once at the outpatient visit in PD patients. Creatinine was measured in dialysate and urine using an enzymatic creatinine assay. Hemoglobin was routinely measured on Sysmex XN-analyzers (Sysmex, Kobe, Japan). Urea, albumin, and C-reactive protein (CRP) were measured on Roche routine chemistry analyzers (Modular P/Cobas C, Roche Diagnostics, Mannheim, Germany). To estimate the residual renal function, the glomerular filtration rate (GFR) was calculated as the mean of urinary urea and creatinine clearance, using the mean of pre- and postdialysis plasma creatinine and urea concentration in HD, and a single plasma creatinine and urea measurement in PD patients.

2.7. Statistical analysis

Data were analysed with SPSS version 24 (IBM, Armonk, USA). Normally distributed variables are expressed as mean $\pm$ standard deviation (SD), and non-parametric variables as median [interquartile range]. Categorical variables are expressed as number (%). Differences between the sex-adjusted CSR tertiles were tested for statistical significance with one-way analyses of variance for variables with a normal distribution, Kruskal–Wallis tests for variables with a skewed distribution, and Chi-square tests for categorical variables. A two-sided $P < 0.05$ indicated statistical significance.

To study determinants of CSR, associations of patient characteristics with CSR were evaluated using univariable linear regression. Subsequently, the significantly associated characteristics were added in a multivariable linear regression model using a stepwise elimination algorithm with the criterion probability of F to enter: ≤ 0.50 , and probability of F to remove: ≥ 0.10 . For this analysis of potential determinants of CSR, we did not index CSR for body size, since we also wanted to evaluate the associations of different body size measures with CSR.

For the cross-sectional analyses of associations between CSR and physical and mental health, CSR was indexed to body surface area (BSA-CSR) according DuBois and DuBois [34], to acquire a relative muscle mass index, which is widely used for diagnosis of sarcopenia [6,35]. The linear regression models were performed crude (Model 1), and adjusted for sex, age and race (Model 2). Since cardiovascular disease may affect physical health, whereas depression may affect mental health, we performed additional analysis with adjustment for cardiovascular disease in the analyses of the association between BSA-CSR and physical health, and adjustment for depression in the analyses of the association between BSA-CSR and mental/general health (Model 3). The correlation of BSA-CSR with handgrip strength was also visualized in a

sex-specific correlation plot. Furthermore, we tested for a potential interaction of dialysis modality with CSR. All but 9 patients had a 100% score on the role emotional score thus skewing the scale outcome to the right. Therefore, we additionally dichotomized role emotional in normal (100%) versus low ($<100\%$), and tested whether a low score was associated with CSR using logistic regression. In an additional subgroup analysis, we tested the association between BSA-CSR and gait speed, both crude, and adjusted for sex, age, race and cardiovascular disease.

Several sensitivity analyses were performed. First, because comorbidities can affect physical health, we added a multivariable linear regression model adjusting for diabetes and COPD as well (in addition to cardiovascular disease). Of note, the sample size of the study limited the number of covariates that could be included in the main analysis of the multivariable linear regression model. Second, because inflammatory status is a determinant of sarcopenia, CRP was added to the multivariable linear regression model (in addition to cardiovascular disease). Third, as the most appropriate method of indexing muscle mass remains unknown [8], we also studied CSR indexed to height² (height²-CSR), and to body mass index (BMI-CSR). Fourth, because plasma creatinine can be measured more easily than CSR, we also evaluated whether BSA-indexed plasma creatinine was associated with muscle strength and self-reported physical health. Finally, since gender is an important indicator of muscle mass and strength, analyses of BSA-CSR and handgrip strength were also performed separately for men and women.

3. Results

3.1. Patient enrolment and characteristics

A total of 50 patients were enrolled in this study, 40 were treated with HD and 10 with PD therapy (4 APD, 6 CAPD). Patients within the highest sex-stratified CSR tertile were younger and had higher BMI and urea concentrations (Table 1). Plasma albumin concentrations were significantly lower in the lowest sex-stratified CSR tertile. No significant differences between HD and PD patients were found. UF volume was mean 1929 ± 856 mL/dialysis session in HD patients, and median 925 [581–1388] mL/day in PD patients, respectively.

3.2. Potential determinants of CSR

Mean CSR was 9.5 ± 3.3 mmol/24 h in men, and 6.8 ± 1.9 mmol/24 h in women (difference $P = 0.007$). Age was inversely associated with CSR whereas BMI, BSA, systolic blood pressure, plasma albumin, and daily protein intake were positively associated with CSR (Table 2, left column). The stepwise multivariate linear regression model that characterized the covariates that were most strongly associated with CSR included age, gender, BMI, protein intake, and plasma albumin (Table 2, right column). Together, these covariates explained 76% of the variance in CSR.

3.3. Associations of CSR with muscle strength and gait speed

Mean handgrip strength was 29.6 ± 10.3 kg in men, and 19.2 ± 5.8 kg in women. Low grip strength was present in 46% and 31% of the male and female participants, respectively. The sex-specific correlation between BSA-CSR and handgrip strength is visualized in Fig. 1. BSA-CSR was significantly associated with handgrip strength, independent of adjustment for potential confounders (Table 3). Dialysis modality did not interact with BSA-CSR in the analysis of handgrip strength. Using logistic regression analysis, every 1 mmol/24 h/m² increase in BSA-CSR was associated with a 45% lower risk of having low grip strength (OR 0.55; 95% CI

0.33–0.91; $P = 0.02$). Adjusting for age and gender attenuated this association (OR 0.67; 95% CI 0.36; 1.24; $P = 0.7$).

Additionally, gait speed was measured in a subgroup of 23 patients. Patients in whom gait speed was available had less often diabetes (4% vs. 37%, $P = 0.006$) as compared to patients in whom gait speed had not been measured. Mean gait speed was 0.87 ± 0.34 m/s. Low gait speed (<0.8 m/s [29]) was present in 11 of the 23 patients (48%) in whom gait speed was measured. Using linear regression analysis, higher BSA-CSR was associated with faster gait speed both crude (β : 0.47 [95% CI 0.07; 0.96], $P = 0.03$), and after adjustment for gender, sex and cardiovascular disease (β : 0.58 [95% CI 0.03; 1.26], $P = 0.04$). Mean BSA-CSR was not significantly different in those with normal versus low gait speed (4.95 vs. 4.03 mmol/24 h/m², $P = 0.09$).

3.4. Associations of CSR with self-reported physical health

The mean CIS-subjective fatigue and physical activity score were 27.6 ± 12.9 and 11.1 ± 5.6 points, respectively. A higher BSA-CSR was significantly associated with less fatigue, and with more physical activity (Table 3).

The SF-36 subscale scores were median 65 [40–90] points for physical function, 37.5 [0–100] points for role physical, and mean 66.3 ± 19.8 points for vitality, and 76.5 ± 27.9 points for bodily pain. Higher BSA-CSR was significantly associated with better self-reported physical functioning, and with less role limitation due to

Table 2

Associations of patient and clinical characteristics with Creatinine Synthesis Rate; Data are presented unadjusted for each individual characteristic (left column), and adjusted in a stepwise multivariable linear regression model (right column).

	β	P	β	P
Age (year)	–0.38	0.007	–0.34	<0.001
Female gender	–0.38	0.007	–0.39	<0.001
Body mass index (kg/m ²)	0.50	<0.001	0.20	0.03
Body surface area (m ²) [#]	0.50	<0.001		
Height squared (m ²)	0.26	0.07		
Non-Caucasian race	–0.19	0.2		
PD vs. HD treatment	0.04	0.8		
Systolic BP (mmHg) †	0.33	0.02		
Diastolic BP (mmHg) †	0.23	0.1		
Dialysis vintage (months)	–0.06	0.7		
Diabetes	0.09	0.5		
Cardiovascular disease	–0.04	0.8		
Statin use	0.17	0.2		
Urea (mmol/L) †	0.24	0.1		
CRP (mg/L) †	–0.22	0.1		
Albumin (g/L) †	0.39	0.005	0.21	0.02
Protein intake (g/kg/day)	0.76	<0.001	0.40	<0.001

First (left column), associations with CSR were tested in a univariable model for each individual characteristic. The significantly associated characteristics were added in a stepwise multivariable linear regression model (right column. Model $R^2 = 0.76$. Covariates considered in the model but removed via stepwise regression: body surface area, systolic blood pressure. [#]Body surface area was calculated according DuBois and DuBois [34]. †Measured before haemodialysis, if applicable. Abbreviations: β , standardized coefficient; PD, peritoneal dialysis; HD, haemodialysis; BP, blood pressure; CRP, C-reactive protein.

Table 1

Baseline characteristics according the sex-stratified tertiles of the Creatinine Synthesis Rate.

	All patients (N=50)	Sex-stratified tertiles of the creatinine synthesis rate			P
		1st N=16	2nd N=17	3rd N=17	
Age (years)	68.8 [59.7–78.3]	72.6 [69.0–79.4]	76.2 [61.0–80.3]	60.5 [53.3–67.5]	0.001 ^{a,b}
Female sex (%)	14 (28)	4 (25)	5 (29)	5 (29)	1.0
Non-Caucasian race	4 (8)	1 (6)	1 (6)	2 (12)	0.8
Body mass index (kg/m ²)	25.4 $\pm$ 4.2	23.7 $\pm$ 3.8	25.0 $\pm$ 3.3	27.5 $\pm$ 4.6	0.03 ^a
Height (m)	1.76 $\pm$ 0.1	1.75 $\pm$ 0.1	1.77 $\pm$ 0.1	1.75 $\pm$ 0.1	0.9
Body surface area (m ²) †	1.94 $\pm$ 0.22	1.88 $\pm$ 0.22	1.95 $\pm$ 0.18	2.00 $\pm$ 0.26	0.3
Dialysis vintage (months)	15 [9–41]	15 [12–40]	12 [6–26]	15 [10–49]	0.5
Residual diuresis (%)	38 (76)	10 (63)	15 (88)	13 (77)	0.2
Diabetes (%)	11 (22)	4 (25)	2 (12)	5 (29)	0.4
Hypertension (%)	32 (64)	8 (50)	10 (59)	14 (82)	0.1
Cardiovascular disease (%)	15 (30)	7 (44)	4 (24)	4 (24)	0.4
COPD (%)	2 (4)	1 (6)	0	1 (6)	0.4
Depression (%)	3 (6)	0	0	3 (18)	0.03 ^{a,b}
Primary renal disease (%)					0.9
Glomerulonephritis	6 (12)	2 (13)	3 (18)	1 (6)	
Diabetes	8 (16)	2 (13)	3 (18)	3 (18)	
Renovascular disease	19 (38)	6 (38)	7 (41)	6 (35)	
Other	17 (34)	6 (38)	4 (24)	7 (41)	
Medication (%)					
Aspirin	21 (42)	10 (63)	6 (35)	5 (29)	0.1
CCB	19 (38)	2 (13)	8 (44)	9 (53)	0.03
β -blocker	26 (52)	9 (56)	10 (59)	7 (41)	0.5
ACE-inhibitor	7 (14)	2 (13)	2 (12)	3 (18)	0.9
ARB	5 (10)	1 (6)	2 (12)	2 (12)	0.8
Statin	16 (32)	4 (25)	5 (29)	7 (41)	0.6
Hemoglobin (mmol/L) ‡	6.9 [6.6–7.4]	6.9 [6.5–6.7]	6.9 [6.5–7.4]	6.9 [6.7–7.7]	0.8
CRP (mg/L) ‡	5 [2–13]	7 [3–27]	4 [2–11]	6 [1–10]	0.4
Albumin (g/L) ‡	39 [17–25]	36 [32–39]	40 [38–42]	40 [38–42]	0.003 ^{a,c}
GFR (mL/min/1.73)	2.5 [0–4.7]	0.7 [0–3.5]	3.7 [1.3–5.9]	3.3 [0.4–4.6]	0.1

Normally distributed variables are expressed as mean with the SD as measure of variance, whereas variables with a skewed distribution are given as median with the [interquartile range] as measure of variance. Values for categorical variables are given as number (percentage). † Body surface area was calculated according DuBois and DuBois [34]. ‡ Measured before dialysis, if applicable. ^a indicates a significant difference between the 1st and 3rd tertile, ^b indicates a significant difference between the 2nd and 3rd tertile, ^c indicates a significant difference between the 1st and 2nd tertile. Abbreviations: COPD, chronic obstructive pulmonary disease; CCB, calcium channel blocker; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CRP, C-reactive protein; GFR, glomerular filtration rate, as a reflection of the residual renal function.

physical health (Table 3). Dialysis modality did not interact with BSA-CSR in the analyses of self-reported physical health.

3.5. Associations of CSR with self-reported mental health

The median CIS-concentration and motivation scores were 9 [5–15], and 11 [5–16] points, respectively. The median SF-36 subscales scores were 80 [68–92] points for emotional wellbeing, 100 [100–100] points for role emotional, and mean 47.9 ± 19.5 , and 74.5 ± 24.1 points for general health, and social functioning, respectively. Higher BSA-CSR was associated with better social functioning according the SF-36 subscale, but not with other measures of self-reported mental health (Table 3). Using logistic regression modelling, a low score on the role emotional scale was also not associated with CSR.

3.6. Sensitivity analyses

First, additional adjustment for diabetes and COPD in the multivariable linear regression models of BSA-CSR with muscle strength and self-reported physical health yielded similar findings (Table S1). Second, additional adjustment for CRP did not essentially change the associations of BSA-CSR with muscle strength and self-reported physical health (Table S2). Third, correlations of $\text{height}^2\text{-CSR}$ ($\rho = 0.62$, $P < 0.001$) and BMI-CSR ($\rho = 0.63$, $P < 0.001$) with handgrip strength were similar to BSA-CSR ($\rho = 0.63$, $P < 0.001$). Furthermore, the multivariable analyses of $\text{height}^2\text{-CSR}$ and BMI-CSR with muscle strength and physical health yielded essentially similar results as BSA-CSR (Tables S3–S4).

Fourth, plasma creatinine indexed to BSA was associated with handgrip strength, fatigue, physical activity, physical functioning, and vitality, but the associations were less strong compared to CRS (Table S5).

Finally, the analysis of BSA-CSR for men and women separately showed similar correlation coefficients in the crude model (men: $\rho = 0.61$, $P < 0.001$; women: $\rho = 0.56$, $P < 0.001$). However, after adjusting for age and race, the correlation was attenuated in women (men: ρ

0.56 , $P < 0.001$; women: $\rho = 0.29$, $P = 0.2$). This may be explained by the small subgroup of women ($N = 13$).

4. Discussion

This study showed that CSR is associated with muscle function and self-reported physical health in dialysis patients, as well as with self-reported social functioning. Independent determinants of lower CSR were higher age, lower BMI, female sex, and lower plasma albumin.

This is the first study, by our knowledge, that evaluated the relation between CSR and physical performance in patients with CKD. Our findings add to our previous study in patients with advanced CKD, in which we found that uCER was associated with self-reported frailty according to a modified Fried frailty definition, which also included subscales of the SF-36 [15]. Other studies that evaluated associations of muscle mass with physical performance in dialysis patients, used different methods to measure muscle mass and physical performance. First, Panaye et al. reported that serum creatinine levels were positively associated with pedometer-measured physical activity in dialysis patients [36]. Likewise, a study in CKD and HD patients showed a significant association of MRI-measured quadriceps muscle area with measured physical activity, muscle strength, the 6-min walk test, and with static balance [37]. A study in HD patients comparing DEXA to Computed Tomography (CT) showed superiority of CT-measured muscle mass in the associations with physical performance measurements [38]. Third, a study in 80 HD patients showed that both performance-based and self-report-based frailty was associated with smaller quadriceps muscle area [39]. The performance-based and self-report-based frailty definitions included SF-36 subscales and self-reported physical activity. Interestingly, Itoyama et al. reported that muscle mass measured by dual-energy x-ray absorptiometry (DEXA) was not associated with self-reported physical activity in dialysis patients. The authors further noted that contrary to muscle mass as assessed by DEXA, muscle strength as assessed by handgrip strength was associated with physical activity level [24].

DEXA is an established technique for muscle mass measurement, which however in dialysis patients can be affected by hydration status [40]. DEXA can easily overestimate muscle mass, because this method lacks the capability to differentiate between muscle mass and intramuscular fat infiltration [41,42]. Accordingly, in aging individuals, DEXA was reported to be less accurate to detect age-related loss of muscle mass by underestimating the age-related loss of muscle mass and fat infiltration in muscle tissue in comparison to MRI [43], and CSR [12], which might be the effect of increasing extracellular water [44]. Therefore, it has been suggested that CSR might be more sensitive compared with DEXA to detect age-related changes in body mass [12,41]. The estimation of lean mass by bioelectric impedance analysis (BIA) does have the same drawback [45], and in healthy individuals and in PD patients a discrepancy between CSR and BIA has been shown, with the CSR method resulting in a higher prevalence of low muscle mass as compared to BIA [46–48]. The advantage of CSR is that its generation from the non-enzymatic conversion of creatine and creatine phosphate in muscle [49] makes it insensitive to intramuscular fat and edema and thereby provides a direct reflection of muscle mass. CSR might specifically reflect the metabolically active muscle mass. This hypothesis is further supported by a study in HD patients that showed that plasma creatinine levels did not predict sarcopenia as assessed by BIA, whereas it did predict muscle strength as assessed by handgrip strength [16]. Second, in the Chronic Renal Insufficiency Cohort including patients with CKD stage 1 through 5, a

Fig. 1. Scatter plot of the correlation between Creatinine Synthesis Rate, indexed to BSA, and handgrip strength. Legend Fig. 1: Scatter plot of the correlation between creatinine synthesis rate, indexed to body surface area, and handgrip strength. For the total cohort the correlation coefficient was 0.63 ($P < 0.001$); The correlation coefficient was 0.61 in men (solid circles, $P < 0.001$), and 0.56 (open circles, $P = 0.045$) in women.

Table 3

Associations of Creatinine Synthesis Rate indexed to BSA with muscle strength and self-reported physical functioning, and general and mental health, evaluated by multi-variable linear regression modelling.

Dependent variables	Model 1 Estimated effect of BSA-CSR on the dependent variable:			Model 2 Estimated effect of BSA-CSR on the dependent variable:			Model 3 Estimated effect of BSA-CSR on the dependent variable:		
	β	95% CI	P	β	95% CI	P	β	95% CI	P
Muscle strength									
Handgrip strength (kg)	0.63	0.41; 0.88	<0.001	0.43	0.18; 0.70	0.002	0.44	0.18; 0.71	0.002
Self-reported physical functioning									
CIS Activity level	−0.48	−0.75; −0.21	0.001	−0.67	−0.98; −0.37	<0.001	−0.69	−1.00; −0.38	<0.001
CIS Fatigue severity	−0.32	−0.60; −0.04	0.03	−0.59	−0.91; −0.26	0.001	−0.61	−0.93; −0.27	0.001
SF-36 Physical functioning	0.40	0.12; 0.66	0.005	0.55	0.20; 0.87	0.002	0.54	0.19; 0.88	0.003
SF-36 Role lim. due to physical health	0.13	−0.16; 0.43	0.4	0.41	0.06; 0.76	0.02	0.39	0.04; 0.74	0.03
SF-36 Vitality	0.10	−0.20; 0.39	0.5	0.32	−0.03; 0.67	0.07	0.33	−0.21; 0.68	0.06
SF-36 Bodily Pain	0.12	−0.18; 0.41	0.4	0.12	−0.26; 0.48	0.5	0.09	0.29; 0.46	0.7
Self-reported general and mental health									
CIS Concentration problems	0.26	−0.04; 0.54	0.08	0.08	−0.27; 0.43	0.7	0.02	−0.32; 0.34	0.9
CIS Reduced motivation	−0.13	−0.42; 0.17	0.4	−0.18	−0.55; 0.19	0.3	−0.22	−0.57; 0.15	0.2
SF-36 General health	0.11	−0.18; 0.40	0.5	0.28	−0.07; 0.64	0.1	0.34	−0.01; 0.68	0.06
SF-36 Emotional wellbeing	−0.09	−0.39; 0.20	0.5	0.02	−0.34; 0.38	0.9	0.11	−0.20; 0.42	0.5
SF-36 Social functioning	0.19	−0.11; 0.48	0.2	0.38	0.005; 0.73	0.047	0.43	0.08; 0.76	0.02
SF-36 Role lim. due to emotional wellbeing	0.14	−0.16; 0.44	0.4	0.22	−0.16; 0.59	0.3	0.26	−0.11; 0.62	0.2

The independent variable in the analyses is creatinine synthesis rate indexed to body surface area ($\text{mmol}/24\text{ h}/\text{m}^2$); the standardized coefficient (β) and standardized 95% confidence interval (95% CI) are reported. A higher CIS activity or fatigue severity score indicates more inactivity or more severe fatigue, respectively. A higher CIS motivation or concentration score indicates worse mental function. A higher SF-36 level indicates better physical or mental functioning. Model 1: crude, Model 2: adjusted for age and sex, Model 3: additionally adjusted for race and cardiovascular disease; and for race and depression in case of self-reported general and mental health. Abbreviations: BSA, body surface area; CSR, creatinine synthesis rate; β , standardized coefficient; CI, confidence interval; CIS, Checklist Individual Strength; SF, Short Form; lim., limitation.

lower creatinine generation rate per kilogram of muscle mass among patients with lower eGFR was reported [20]. This lower creatinine generation rate might be explained by altered muscle metabolism in higher CKD stages leading to lower CSR and poorer muscle function. Third, a murine study found a strong linear correlation in rat muscle between CSR and myofibrillar protein mass [50]. Thus, it could be hypothesized that CSR might especially capture information on functional and metabolic active muscle mass, thereby better reflecting muscle function.

SF-36 subscales have been used previously to evaluate physical performance in dialysis patients [51,52]. To our knowledge, the CIS has not been used in dialysis patients before. The CIS was originally tested in a population of chronic fatigue syndrome patients [30]. Recently, specific population norms including for the general population and nine groups with medical conditions were published, thus rendering comparison of our findings possible [32]. First, patients in our study had a higher mean CIS subjective fatigue score, indicating more fatigue severity, compared with the general population (23.0 ± 10.8) but similar scores as breast and haematological cancer survivors (28.5 ± 13.6 and 26.7 ± 13.9 , respectively). Second, the physical activity score in this study was higher, indicating more physical inactivity, as compared with the general population (8.3 ± 4.3), and several other chronic disease populations. This finding is in accordance with previous studies that reported low physical activity in dialysis patients [53,54].

The sensitivity analysis showed that plasma creatinine also associated with muscle strength and self-reported physical health, which is accordance with previous studies [16,55]. However, the associations were less strong compared with CSR, indicating that CSR better reflects muscle strength and physical performance than plasma creatinine.

The strength of this study is that we collected the total dialysate instead of taking several samples during the dialysis sessions, thereby increasing the accuracy of the dialysate excretion measurements. Furthermore, both muscle strength and self-reported physical health measures were collected. Limitations of our study should also be noted. First, the sample size of the study is relatively small, with two dialysis modalities included. Nevertheless, we

found no association with dialysis modality or an interaction effect of dialysis modality, suggesting that the associations between CSR and physical function are not modified by dialysis modality. Furthermore, the equipment for collecting the total dialysate volume may not be available in all dialysis centers. Future studies should address whether continuous partial dialysate sampling is a reliable alternative for the collection of the total dialysate volume. Third, we did not specifically measure muscle mass with e.g. MRI or CT and, therefore, we were not able to evaluate whether CSR also reflected muscle function and physical health independent of muscle mass. Furthermore, we did not measure frailty and cognitive functioning in this study, which might have affected the relation between CSR and physical health, and between CSR and mental health, respectively. Nevertheless, additional adjustment for major comorbidities that are associated with frailty, (cardiovascular disease, diabetes, COPD) even strengthened the associations of CSR with muscle strength and most measures of self-reported physical health. Finally, this study does not fully represent the group of HD patients or the group of PD patients, as HD and PD patients are not likely to have the same underlying disease or functional status.

Although collection of the total dialysate in HD patients is more accurate, total creatinine excretion in the dialysate can also be estimated by continuous partial dialysate sampling (which is more easily performed). Repetitive creatinine dialysate sampling in dialysis patients could be useful to timely detect a decline in CSR over time, thus reflecting loss of function. A decline in CSR could be used to identify those patients in whom special attention is needed (for their physical performance, and who might need a physical exercise program and dietary interventions). Although the favourable effects of physical exercise on improving muscle strength, physical fitness, and also cognitive function and quality of life in dialysis patients are now well established [56], it has to be studied whether CRS-guided interventions such as a physical exercise program with or without additional dietary intervention may help stabilize CSR and muscle function.

In conclusion, a greater CSR was associated with higher muscle strength, better physical and social functioning, and physical

activity, and with less fatigue and role limitation due to physical health. Thus, CSR reflects muscle function, self-reported physical health and social functioning in dialysis patients.

Statement of authorship

Research idea and study design: HAPB, KJRI, SJLB, CFMF, CAJMG. Data acquisition: ESJMP, MH, KJRI, SV. Data analyses/interpretation: ESJMP, HAPB, MH, KJRI, RTG, SJLB, CFMF. Statistical analyses: HAPB, ESJMP. Supervision: CFMF, CAJMG. Each author contributed important intellectual content during manuscript drafting (HAPB) or revision (other authors) and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Data statement

The dataset that was used and analyzed during the current study is available (conditional on agreement on privacy matters and appropriate usage of the data) upon request from the last author, C.F.M. Franssen of the Department of Nephrology of the Groningen University Medical Center (c.f.m.franssen@umcg.nl).

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnu.2019.07.010>.

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