Urinary creatinine excretion is an indicator of physical performance and function

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Published in:
Journal of cachexia sarcopenia and muscle

DOI:
10.1002/jcsm.12965

Publication date:
2022

Journal of Cachexia, Sarcopenia and Muscle 2022; **13**: 1431–1433
Published online 27 February 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.12965

Urinary creatinine excretion is an indicator of physical performance and function

Muscle mass is essential for performing physical activity, and low muscle mass (sarcopenia) has been found to have a strong association with all-cause mortality in patients with type 2 diabetes (T2D).[1] However, muscle mass is not routinely assessed in clinical practice and low muscle mass can easily go unnoticed in obese patients (sarcopenic obesity), which was emphasized in previous DIALECT findings.[2] The current definition of sarcopenia requires presence of either low muscle mass, low muscle strength or poor physical performance rather than low muscle mass alone.[3] Two methods for estimating muscle mass independent of kidney function in clinical practice are the 24 h urinary creatinine excretion rate (CER) and bioelectric impedance analysis (BIA), but their association with physical performance and function is unclear.[4] In this study we investigate whether CER or BIA-derived predicted muscle mass also indicate physical performance and function in patients with T2D, in order to indirectly screen patients on sarcopenia.

We performed cross-sectional analyses of n = 63 patients included in the DIAbetes and LifEstyle Cohort Twente (DIALECT) study between March 2018 and January 2020 and who had therefore baseline data available regarding muscle mass and physical performance and function. The study population consists of patients with T2D aged >18 years, treated in the outpatient clinic of the ZGT hospital as part of routine secondary care. Patients depending on renal replacement therapy or patients with insufficient knowledge of the Dutch language were excluded from participation.

Muscle mass was estimated by 24 h urinary creatinine excretion rate (CER, mmol/24 h). Patients were asked to collect their 24 h urine to obtain the urinary CER, by multiplying these concentrations with the volume of the 24 h urine collection. For proper collection of the 24 h urine samples, patients were instructed to discard the first morning urine and then collect all urine in the provided canister until the first morning urine of the following day. The canisters were stored in a dark and cool place in between, and patients returned the canister on the next day during the baseline visit. Absolute muscle mass in kilogram was calculated with the formula: [18.9 * (CER (mmol/24 h) /8.84)] + 4.1.[5] In addition, we used a bioelectric impedance analysis device (TANITA, type BC-418MA, Tokyo, Japan) which calculates segmental body composition including predicted muscle mass.

Physical performance and function was objectively assessed by the number of steps per day and the 5 m walk test, and subjectively by assessing self-reported functional status. Daily movement was measured by a triaxial Fitbit accelerometer worn around the wrist. The maximum number of steps per day was assessed during an observational period of 10 consecutive days. In addition, we asked the patients to walk three times a predefined distance of 5 m. The mean walk time was used to assess walk speed in meters per second (m/s). The RAND 36-item Health Survey (RAND-36) Physical Component Summary (PCS) score was used for assessing self-reported functional status.[6]

All statistical analyses were performed using IBM SPSS for Windows (version 27.0. Armonk, NY: IBM Corp.). Normally distributed data are presented as mean ± standard deviation (SD), and dichotomous variables are presented in number (percentage). Standardized linear regression coefficients, adjusted for age and sex, were estimated to assess the associations between physical performance and function parameters and either CER or BIA-derived predicted muscle mass. A two-tailed P value less than 0.05 was considered statistically significant.

The study population consisted of 54% male participants, mean age was 65 ± 10 years, and mean BMI was 31.8 ± 4.7 kg/m^2, reflecting a predominantly obese T2D population (Table 1). Mean HbA1c was 62 ± 13 mmol/mol and 76% of the patients used insulin, 71% had microvascular and 38% macrovascular complications. Mean CER-derived predicted muscle mass was 30.5 ± 7.9 kg, with a significantly difference between men and women (33.3 ± 8.6 kg vs. 27.2 ± 5.4 kg, P = 0.002). Mean walk speed was 1.11 ± 0.22 m/s, mean step count per day was 10 745 ± 4854 and mean self-reported functional status was valued with 277 ± 86 units. After adjustment for age and sex, patients with higher CER levels had a significantly higher walk speed (Std. B = 0.277, P = 0.043), reported a higher self-reported functional status (Std. B = 0.368, P = 0.009),

Table 1 Standardized linear regression coefficients, adjusted for age and sex, to assess the associations between either CER or BIA-derived predicted muscle mass and physical performance and function parameters

	Total population	Std. B	*P* value
N	63		
Age, years	65 ± 10		
Sex, male	34 (54)		
Length, cm	171 ± 9		
Body weight, kg	94 ± 16		
BMI, kg/m^2	31.8 ± 4.7		
Waist circumference, cm	112 ± 13		
BSA, m^2	2.05 ± 0.21		
CER			
CER, mmol/24 h	12.4 ± 3.7		
CER-derived predicted muscle mass, kg	30.5 ± 7.9		
Walk speed, m/s	1.11 ± 0.22	0.277	0.043
Self-reported functional status	277 ± 86	0.368	0.009
Max. steps per day	10 745 ± 4854	0.275	0.042
BIA-derived predicted muscle mass			
BIA-derived predicted muscle mass, kg	57.1 ± 10.6		
Walk speed, m/s	1.11 ± 0.22	−0.031	0.88
Self-reported functional status	277 ± 86	0.065	0.76
Max. steps per day	10 745 ± 4854	−0.195	0.34

and walked a higher number of steps per day (Std. B = 0.275, *P* = 0.042). BIA-derived predicted muscle mass showed neither significant associations with walk speed (*P* = 0.88), self-reported functional status (*P* = 0.76), nor the number of steps per day (*P* = 0.34). Sensitivity analyses were performed, addressing the potential impact of height on the association between either CER or BIA-derived predicted muscle mass and physical performance and function parameters, wherein conclusions did not materially change from those from the primary analyses. Additional adjustments for body weight also did not materially change the association between CER and physical performance and function. Due to collinearity between PMM and body weight, it was not possible to adjust the association between PMM and physical performance and function for body weight.

The major finding of this study in patients with T2D is that CER is an indicator of physical performance and function, while BIA-derived predicted muscle mass showed no associations with physical performance and function. Of note, the positive association between CER and physical performance and function was tested for several domains of physical performance and function, which was also found when using D3-creatine dilution method.[7] CER showed consistent associations between objective assessment of the number of steps per day (muscle endurance) and the 5 m walk test (gait speed). In addition, we found a significant association between CER and subjective physical performance and function, suggesting that a reduced muscle mass is associated with increased risk of functional impairment and disability.[8,9]

CER is a well-accepted method which directly reflects functional metabolic muscle mass, independent of kidney function.[4] BIA was originally developed to estimate extracellular volume, and estimation of fat free mass (FFM) by BIA is one of the secondary parameters.[10] However, FFM does not solely reflect muscle mass and may lead to inaccuracies in estimating muscle mass.[11] In our study, BIA-derived predicted muscle mass was defined as bone-free lean tissue mass, and was almost twice as high as the muscle mass estimated by the CER. Therefore, BIA-derived predicted muscle mass was not reliable for assessment of functional metabolic muscle mass.

To the best of our knowledge, this is the first study to show associations between CER and physical performance and function in patients with T2D. The main strength of this study is the availability of multiple objective assessments of physical performance and function, since it has previously been demonstrated that self-reported physical activity provides an overestimation.[12] In addition, evaluation of muscle mass based on 24 h creatinine excretion rate has been validated as a measure of muscle mass.[4] Obviously, we do not represent healthy controls in our cohort, which limits the generalizability, and our observational design limits us in determining causations. In addition, we cannot completely rule out that patients suffer from incontinence or voiding issues. Also, day-to-day variation in diet can explain some of the variation in creatinine excretion, but substantial effects on creatinine excretion can only be observed if after prolonged low-protein creatine-free (meat-free) diets endogenous creatine pools start to decrease, resulting in decrease of endogenous creatinine generation.[13]

Because CER not only reflects muscle mass but also muscle functional status, it is an interesting tool to indirectly screen for sarcopenia, especially in obese populations such as T2D where the presence of sarcopenia could easily go unnoticed. Until now, there is no gold standard for estimating muscle mass, but our study suggests that it is useful to include assessment of CER in the guidelines for indirect assessment of sarcopenia over BIA assessment.

DOI: 10.1002/jcsm.12965

Ethical guideline statement

The study was performed according to the guidelines of good clinical practice and the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to participation. The study was been approved by the local institutional review boards (METC-registration numbers NL57219.044.16 and 1009.68020) and is registered in the Netherlands Trial Register (NTR trial code 5855). The authors of this manuscript certify that they comply with the Ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.[14]

Conflict of interest

GDL reports grants and personal fees from Sanofi, personal fees from Jansen, grants and personal fees from AstraZeneca, grants and personal fees from Astellas, grants and personal fees from Novo Nordisk, outside the submitted work. SJLB, NB and MMO has nothing to disclose.

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DOI: 10.1002/jcsm.12965