The prevalence of muscle wasting (sarcopenia) in peritoneal dialysis patients varies with ethnicity due to differences in muscle mass measured by bioimpedance

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Abstract

Background/objectives

Sarcopenia is associated with increased mortality. European and North American recommended screening for low muscle mass uses gender specific cut points, with no adjustment for ethnicity. We wished to determine whether the prevalence of sarcopenia was altered by ethnicity in peritoneal dialysis (PD) patients.

Subjects/Methods

We measured appendicular lean mass indexed to height (ALMI) in PD patients by segmental bioimpedance and determined sarcopenia using different cut off points for reduced muscle mass.

Results

We measured ALMI in 434 PD patients, 55.1% males, mean age 55.3±16.2 years, 32.3% diabetic, 54.1% white, 23.7% Asian. 19.1% black. ALMI was lower in Asian women, compared to white and black women (6.4±1.1 vs 6.6±1.0 and 6.9±1.4 kg/m^2), and lower in Asian men (7.5±1.3 vs 8.5±1.2 and 8.7±1.3 kg/m^2), p<0.001. Depending on the ALM/ALMI cut point; the prevalence of sarcopenia was greater in Asian patients (25.6-41.2% using North American or European cut points) compared to white (12.3-18.7%) and black patients (3.8-15.7%), p<0.001, but <11% when using Asian specific cut points. The prevalence of sarcopenia obesity (BMI ≥30 kg/m^2) was < 3%, for all groups. There was no association with duration of PD, dialysis prescription, residual renal function or small solute clearances.

Conclusion

There is no universally agreed consensus definition for loss of muscle mass (sarcopenia) and current European and North American recommended cut points for screening are adjusted only for gender. As body composition differs also with age and ethnicity, then ideally cut points should be based on age, gender and ethnicity normative values.

Introduction

Muscle mass initially increases throughout childhood, and peaks in adulthood, before starting to naturally decline after the 6th decade. Sarcopenia, a word derived from the Greek for muscle wasting, is used to describe loss of muscle mass. Although sarcopenia is associated with increased mortality risk [1], in addition to sarcopenia associated with aging, the prevalence of sarcopenia is increased in patients with malignancy, chronic heart failure, respiratory failure, cirrhosis, chronic kidney disease and other chronic inflammatory states. Despite its clinical importance, sarcopenia generally remains under-recognized, which may due to a lack of a universally agreed definition [2]. As patients often have other medical conditions, clinical management is typically focused at these conditions, with little attention directed to trying to prevent or reverse further muscle loss.

More recently there has been a move to introduce a functional component into the definition of sarcopenia, especially for the older aged patient. Even so, these definitions still include cut points defining sarcopenia in terms of reduced

muscle mass. Two of the more commonly used cut points come from a European consensus group (European Society on Clinician Nutrition and Metabolism (ESPEN) Special Interest Groups (SIG)) [3], and the North American Foundation for the National Institutes of Health (FNIH) Sarcopenia Project [4]. The cut points chosen differ between guideline groups, with some choosing cut points derived from older patients [4], and others opting for muscle mass more than 2 standard deviations below mean muscle mass measured in young adults (aged 18–39 years from the 3rd National Health and Nutrition Examination Survey (NHANES) population), adjusted for gender and ethnicity [5]. To allow for comparison between patients, muscle mass has been measured in the limbs (appendicular) and then adjusted for height [6]. Most studies have relied on dual energy X ray absorption (DXA) measurements of appendicular lean mass (ALM) [7], although with advances in bioimpedance devices, more recent studies have reported similar results [8,9].

The earlier NHANES study of healthy subject demonstrated differences in muscle mass between ethnic groups [5,7]. However, neither the European nor the North American FNIH guidelines take into account ethnicity [3]. The current cut offs advocated for detecting sarcopenia are adjusted for gender but not for ethnicity. As such we wished to determine whether the prevalence of sarcopenia differed between ethnic groups in a multi-ethnic group of patients with chronic kidney disease treated by dialysis.

Methods

We measured ALM in 434 peritoneal dialysis patients when attending for peritoneal membrane function assessment using an 8 electrode multi-frequency segmental bioelectrical impedance device (InBody 720, Seoul, South Korea). Patients with amputations, limb disability such as that due to stroke or polio myelitis, and those with implantable cardiac devices were excluded. Patients who had peritonitis or other infections, or hospital admissions within the previous 3 months were excluded. Bioimepedance measurements were made in a standardised manner; after patients had emptied the bladder and then drained out peritoneal dialysate [10,11]. Muscle loss was defined by cut off points taken from the European Working Group on Sarcopenia in Older People (ESWGOP) soft lean mass index (SLMI) kg/m^2 <8.87 for men and < 6.42 women (ESWGOP) [3], and appendicular lean mass index (ALMI) kg/m^2 more than 2 standard deviations (SD) below normal aged matched adult values for white and black patients [7], and also the cut points of ALM <19.75 kg for men and <15.02 for women (FHIN Sarcopenia project) [4], and ALMI <7.26 and < 5.5 kg/m^2 (ESWGOP) [3], and also ALM adjusted for body mass index (BMI) [4], <0.789 for men and <0.512 for women. We also used recognised cut points of ALM for patients of Asian ethnicity; 7.0 kg/m^2 for men and 5.7 kg/m^2 [12]. We used the World Health Organisation BMI cut offs (23·0, 27·5, 32·5, and 37·5 kg/m^2) to categorise patients [13], and a BMI cut off of 30 to determine sarcopenic obesity [14].

Peritoneal dialysis adequacy (Kt/Vurea) was determined using standard methods to determine weekly residual renal function, peritoneal and total weekly

urea clearance from 24-hour urine and peritoneal dialysate effluent collections [15,16]. Peritoneal and urinary urea losses were used to estimated daily dietary protein intake normalised for body weight, as the protein nitrogen appearance rate (nPNA) [17].

Patient demographics and ethnicity were obtained from hospital computerised records, and Davies-Stoke co-morbidity score used to determine co-morbidity [18].

This retrospective audit complied with the UK National Health Service (NHS) guidelines for clinical audit and service development, (UK NHS guidelines for clinical audit and service development, available at http://www.hra.nhs.uk/documents/2013/09/defining-research.pdf, and http://www.gov.uk/government/publications/guidance-on-getting-permission-for-research-involving-nhs-patients

Statistical analysis

Data is presented as mean ± standard deviation, median (interquartile range), or percentage. Standard statistical tests were used to analyse data, (t test, Mann Whitney U test, ANOVA , Kruskal Wallis, or Chi square test) with appropriate post hoc corrections made for multiple testing. Prism 6.0 (Graph

Pad, San Diego, USA) and SPSS 24 (University Chicago, Chicago, USA). Statistical significance was taken as $p<0.05$.

Results

ALM was measured in 434 patients out a possible total cohort of 490 patients. Patients with amputations, limb deformities and those, clinically volume over loaded were excluded. The mean age of the patients studied was 55.3 ±16.2 years, 239 (55.1%) were male and 195 females, and 32.3% diabetic. Patient demographics are set out in table 1. As expected male patients were heavier with greater muscle mass and less fat. Depending on the cut off used, the prevalence of sarcopenia varied between 6.5 and 26.3% (Figure 1). Taking a BMI of ≥30, then between 0.25 – 9% of patients were classified as sarcopenic obesity (Figure 2).

When we compared the prevalence of sarcopenia by loss of muscle mass according to the different criteria, then more male patients had greater loss of muscle mass using the cut offs advised by the EWG and FNIH guidelines, whereas female Asian patients had a much higher prevalence of muscle wasting using the AWGS criteria (figure 3).

The majority of patients were of white ethnicity (235), followed by 83 African or Afro-Caribbean, who were classified as black, 80 from the South Asian continent and 33 East-Asian, who we grouped together as Asian, and 13 patients of other ethnicities. Black males and females were younger than white males and females (table 2). Asian females had lower total body muscle and ALM

adjusted for BMI compared to black females, whereas Asian male patients had lower total and appendicular muscle mass compared to both white and black males (table 2). There were no differences in the duration of dialysis treatment, or total dialysis urea clearance, daily fluid removal, or peritoneal dialysis transport. Residual renal urea clearance was lower for Asian males. Serum albumin and C reactive protein concentrations were similar. However, both serum urea and creatinine concentrations were lower for Asian patients, and normalised protein accumulation rate was lower for Asian males. The prevalence of sarcopenia was greater for Asians compared to whites and blacks using all guideline criteria apart from the EWG soft lean body mass index and the AWGS appendicular mass index cut off criteria (Figure 1), with > 35% of Asian patients meeting either of the FNIH criteria for muscle wasting, and > 40% with the EWG appendicular muscle mass index criteria compared to only 10.5% using the AWGS criteria. As the total number of patients with sarcopenic obesity was so few, there was no difference between the three main ethnic groups.

Discussion

In patients with chronic kidney disease, sarcopenia is associated with an increased risk of mortality [19]. However, the definition of sarcopenia varies between specialist interest groups, with different groups advocating different cut points for their definition of muscle loss. As such the prevalence of sarcopenic muscle loss in our cohort of peritoneal dialysis patients varied between 6.5 and 26.3%. This is much lower than previous studies reporting

prevalence rates for sarcopenia between 45% - 63% [20]. In part, this may be due to studies reporting using cut points to define sarcopenia based on data obtained from young healthy, predominantly Northern European, adults. We found the lowest prevalence of sarcopenia when comparing measurements of appendicular muscle with corresponding age and sex and ethnicity normative values [7,12].

Dialysis patients, particularly haemodialysis patients change weight during a dialysis session, and changes in hydration lead to differences in the estimation of muscle mass by magnetic resonance imaging, DXA and bioimpedance [21,22,23]. To exclude such confounding, we excluded patients with clinical signs of hypervolaemia. In addition, for peritoneal dialysis patients, an abdomen filled with peritoneal dialysate, or ascites can also lead to changes in bioimpedance derived estimates of muscle mass [24,25]. As such, bioimpedance measurements were made after the bladder had been emptied, and dialysate drained out. In addition, treatment with peritoneal dialysis has been suggested to increase abdominal girth and fat mass [26]. To exclude any confounding by changes in abdominal girth we used a segmental bioimpedance machine to measure ALM, and then to allow for comparison between patients indexed this to height.

The FNIH group also suggested adjusting ALM for BMI [4]. Although there were no differences in BMI between genders, we found that there was a significant different in prevalence of sarcopenia when adjusting ALM for BMI, and when we measured total body muscle, including the trunk. Whereas, the

EWGSOP and FNIH noted a higher prevalence for sarcopenia in women compared to men. when using their ALMI and ALM/BMI cut points [3,4]. This highlights the difference in screening for sarcopenia in a relatively healthy, but elderly population, compared to a cohort of patients with a chronic disease, who are at increased risk of muscle loss [27]. Patients with chronic disease are more likely to lose muscle mass but retain fat weight, and this concept has led to the introduction of the term sarcopenic obesity [14], which has been used to describe the coexistence of increased fat mass and low muscle mass. As with the differences in cut points for defining sarcopenia, there are differences in defining sarcopenic obesity [28]. We chose a BMI of ≥30 [14], and found a much lower prevalence of < 3% for all categories of sarcopenia, part from ALM adjusted for BMI, compared to previous reports, with estimates ranging from 12-62% for men and 2-78% for women [29].

We did not find an association between the prevalence of sarcopenia and residual renal function, or serum albumin or C reactive protein of co-morbidity score. The NHANES study provided normative data for age and gender, but also for white, black and Mexican ethnicity [7]. As such, we were able to calculate the prevalence of sarcopenic muscle loss for patients of white and black ethnicity. Our study population did not have any Mexicans, but did have patients from Asia, particularly originating from the South Asian continent. Previous studies have shown that Asians have more body fat than Northern Europeans for the same body mass index (BMI). However, as the amount of body fat varies between different Asian countries, a World Health Organisation expert group

advised using similar cut off points for determining obesity in both European and Asian patients [13].

When we used cut offs for the white population to estimate sarcopenic muscle wasting for the Asians, and found that Asians had higher prevalence of muscle wasting, particularly Asian males. Asian males had lower weights compared to their male counterparts, and lower serum urea and creatinine concentrations, with a lower estimated dietary protein intake, in keeping with lower muscle mass and energy expenditure [30,31]. Previous studies from Asian countries have reported that both Asian men and women have lower skeletal muscle mass compared to Norther Europeans, and as such cut off points to determine the prevalence of muscle wasting have been set lower. Although studies in different Asian countries have suggested some different cut points for defining muscle wasting [32,33,34,35] there has been a recent consensus definition by the AWGS [12]. Using the AWGS cut points, then Asian patients did not have greater muscle wasting, and the prevalence of sarcopenic muscle wasting was less than that reported in some community based studies [33,34]. However, whereas we generally found a greater prevalence of muscle wasting with male PD patients using the European and North American recommended cut offs, when using the AWGS for the Asian patients, then there was a greater predominance for female patients. Whether this reflects patient choice as to the type of kidney dialysis treatment remains to be determined, as generally larger patients are treated by haemodialysis, which may bias a greater number of smaller white and black males opting for treatment by peritoneal dialysis.

Alternative explanations may lie in differences in body composition, and total body water between the ethnic groups [36]. As muscle mass is lower in Asian patients, different Asian countries have suggested different targets in terms of functional assessment [12].

Although sarcopenia is defined in terms of both functional assessment of muscle and measurement of muscle mass, measurement of muscle mass is less likely to be affected by confounders. For patients with chronic kidney disease, who have an increased rate of self-reported depression [37], then functional assessments may be confounded not only by physical factors including renal metabolic bone disease, with joint and bone pains, carpal tunnel syndrome, anaemia, and also due to additional co-morbidities, but also lack of motivation to voluntarily perform maximally. As such reproducible methods which can reliably measure muscle mass remain key in the definition of sarcopenic muscle wasting [6,34].

The cut point definitions of sarcopenic muscle wasting used by both the current North American FNIH and European EWGSOP recommendations, and those of many other interest groups ignore the effect of ethnicity, although earlier studies reported differences between African Americans and Hispanic Americans [5]. Increasing patterns of migration and immigration leads to increasing minority populations, and these ethnic minority groups often have a greater prevalence of chronic kidney disease and requirement for dialysis. As such it is becoming clearer that current definitions from Europe and North America of what constitutes pathological muscle wasting in patients with chronic

kidney disease are not equally applicable for all patients, and new definitions are required based on appropriately age, gender and ethnicity matched normative data. When using this approach then the prevalence of muscle wasting is much lower than that previously reported.

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Figure 1: Loss of muscle mass according to cut offs from the European Working Group on Sarcopenia in Older People (EWG), North American Foundation for the National Institutes of Health (FNIH) Sarcopenia Project, and National Health and Nutrition Examination Survey (NHANES) and the Asian Working Group for Sarcopenia (AWGS). Appendicular lean mass (ALM), Appendicular lean mass index (ALMI), soft lean mass index (SMI). EWG, FNIH and NHANES are for all Ethnicities, whereas the AWGS is only for Asian patients. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ vs FNIH ALM.

Figure 2: Sarcopenic obesity. Percentage of patients with a body mass index $\geq$ 30 and reduced muscle mass using cut offs from the European Working Group on Sarcopenia in Older People (EWG), North American Foundation for the National Institutes of Health (FNIH) Sarcopenia Project, and National Health and Nutrition Examination Survey (NHANES). Appendicular lean mass (ALM), Appendicular lean mass index (ALMI), soft lean mass index (SMI).

Figure 3. Loss of muscle mass according gender using the cut offs from the European Working Group on Sarcopenia in Older People (EWG), North American Foundation for the National Institutes of Health (FNIH) Sarcopenia Project, and National Health and Nutrition Examination Survey (NHANES) and the Asian Working Group for Sarcopenia (AWGS). Appendicular lean mass (ALM), Appendicular lean mass index (ALMI), soft lean mass index (SMI). EWG, FNIH and NHANES are the "complete" cohort (all Ethnicities), whereas the AWGS is only for Asians. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ vs female.