1. Research Project Version of 03.02.2025

Title: Calf circumference adjusted for body composition to assess muscle mass

Research Site: Tartu University Hospital Department of Internal Medicine

2. Researchers and Research Centre

2.1.Lead researcher

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2.3. Head of the Research Institute giving approval to the intended research project:

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2.4 Trials registration

Application in progress

3. Research Financing

Total cost including any reimbursement of researchers:

The only direct cost of the study is the working time of the researchers, which is included in the calculation of direct working time. The University of Tartu funds Prof. Forbes as a visiting professor. Grete Kurik is paid as a junior scientist by the University of Tartu. Master's and Bachelor's students are not funded. The patient's measurements (body weight, height, and simple muscle mass measurements) are not associated with any cost. The full-body DEXA scans are paid for from Prof. Alastair Forbes' personal research grant: these funds are held at the University of Tartu. Small unexpected expenses can also be covered by Professor Forbes' personal research grant. Patients in the study will not receive any benefits in kind / financial compensation.

4. Brief overview of previous research on the same topic

Muscle mass is a common criterion for the assessment of malnutrition and sarcopenia (1). However, evaluation of muscle mass with gold-standard methods is often challenging in healthcare settings due to their high cost, lack of portability, and impracticality (2). Anthropometric measurements such as calf circumference (CC) are cost-effective, simple

alternative techniques that can be performed to estimate muscle mass in clinical settings (3,4).

Earlier Asian validation studies affirmed the good diagnostic performance of CC for detecting low appendicular lean mass and sarcopenia (5,6). The Asian Working Group for Sarcopenia (AWGS) 2019 consensus recommended the addition of calf circumference in order to improve the sensitivity of sarcopenia screening (SARC-F)(7). Compared with SARC-F, Calf circumference (CC) had better diagnostic performance but its performance decreased in those with sarcopenic obesity (especially in women)(8).

The Global Leadership Initiative on Malnutrition (GLIM) also supports the use of calf circumference or mid-upper arm circumference for assessment of skeletal muscle mass when DEXA, BIA or CT are not available (3). A cohort study validated the use of GLIM criteria for malnutrition diagnosis by comparing CC and MUAC measurements against the Subjective Global Assessment (SGA) in hospitalized patients. Both measures showed strong accuracy for detecting malnutrition (9). However, CC's diagnostic performance decreases in patients with a BMI ≥ 30 kg/m², particularly women. In patients with obesity, study showed weaker correlations between CC and fat-free mass index (FFMI) as a measure of muscle mass (10).

This highlights the need for future research to define new strategies and threshold corrections for accurate muscle mass assessment in clinical practice for patients with obesity.

1. Deutz NEP, Ashurst I, Ballesteros MD, Bear DE, Cruz-Jentoft AJ, Genton L, et al. The underappreciated role of low muscle mass in the management of malnutrition. Clin Nutr. 2019;20(1):22–27.

2. Fayh APT, de Sousa IM, Gonzalez MC. New insights on how and where to measure muscle mass. *Curr Opin Support Palliat Care.* 2020;14(4):316–23.

3. Compher C, Cederholm T, Correia MITD, Gonzalez MC, Higashiguchi T, Shi HP, et al. Guidance for assessment of the muscle mass phenotypic criterion for the Global Leadership Initiative on Malnutrition diagnosis of malnutrition. *J Parenter Enteral Nutr.* 2022;46(1):1232–42.

4. Wu SE, Chen WL. Calf circumference refines sarcopenia in correlating with mortality risk. *Age Ageing.* 2022;51(2):afab239. https://doi.org/10.1093/ageing/afab239.

5. Kawakami R, Murakami H, Sanada K, et al. Calf circumference as a surrogate marker of muscle mass for diagnosing sarcopenia in Japanese men and women. *GeriatrGerontol Int.*2015;15:969–76.

6. Kim S, Kim M, Lee Y, et al. Calf circumference as a simple screening marker for diagnosing sarcopenia in older Korean adults: The Korean Frailty and Aging Cohort Study (KFACS). *J Korean Med Sci.* 2018;33:e151.

7. Chen LK, Woo J, Assantachai P, et al. Asian Working Group for Sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. *J Am Med Dir Assoc.* 2020;21(3):300–7.

8. Kiss CM, Bertschi D, Beerli N, Berres M, Kressig RW, Fischer AM. Calf circumference as a case-finding tool for sarcopenia: Influence of obesity on diagnostic performance. *Aging Clin Exp Res.* 2024;36(1):25.

9. Maffini LF, Viegas GM, Steemburgo T, Souza GC. Global Leadership Initiative on Malnutrition criteria using calf and upper arm circumference as phenotypic criteria for assessing muscle mass demonstrate satisfactory validity for diagnosing malnutrition in hospitalized patients: A prospective cohort study. *Nutr Clin Pract.* 2024;39(1).

10. Kurik G, et al. Poor correlation between calf circumference and muscle mass in patients with obesity. Clin Nutr ESPEN. 2024;63:1121.

5. Purpose, summary and justification of the proposed research

The issue of obesity for calf circumference (CC) has been addressed in various studies. Calf skinfold thickness has been suggested for adjusting CC in patients with obesity, but the method has limitations, can lead to errors and it is time-consuming. The NHANES study in the U.S. showed that adjusting calf circumference for BMI helps to detect age- associated, and sex-specific lower values of calf circumference (1). However, few studies have validated BMI-adjusted CC in hospitalized patients (2).

The aim of the study is to find out whether calf circumference (CC), corrected with mid-upper arm circumference (MUAC), will provide more accurate estimate of muscle mass in patients w ith obesity. Mid-upper arm circumference (MUAC) is more representative of body fat mass than of muscle mass in patients with obesity, especially in women (3). Therefore, there is a reason to believe that MUAC will improve the accuracy of calf circumference as a muscle mass measure by adjusting for the influence of fat.

The research hypothesizes that calf circumference corrected with mid-upper arm circumference is more accurate than just calf circumference at detecting reduced muscle mass in patients with obesity. In case the hypothesis proves true, corrected calf circumference measurement will have the potential to be an easy and simple approach for estimating muscle mass in patients with obesity in clinical or limited settings.

1. Gonzalez MC, Mehrnezhad A, Razaviarab N, Barbosa-Silva TG, Heymsfield SB. Calf circumference: cutoff values from the NHANES 1999-2006. Am J Clin Nutr. 2021;113(6):1679-1687.

2. Sousa IM, Fayh APT, Lima J, Gonzalez MC, Prado CM, Silva FM. Low calf circumference adjusted for body mass index is associated with prolonged hospital stay. Am J Clin Nutr. 2023 Feb;117(2):402-407. doi: 10.1016/j.ajcnut.2022.11.003. Epub 2022 Dec 15. PMID: 36863830.

3. Kurik G, et al. Poor correlation between calf circumference and muscle mass in patients with obesity. Clin Nutr ESPEN. 2024;63:1121.

6. Timescale of research

It is planned that the study will run from January 2025 until June 2026. The initial data collection will end on the 31st March 2025.

7. Detailed description of the research participants and their recruitment

All patients of the internal clinic of the University of Tartu Hospital who are to have a DEXA scan can be included in the study. The goal is to recruit a maximum of 150 eligible adult (older than 18 years old) patients until 31.03.2025.

Patients isolating because of an infectious disease, with pregnancy, lactation, acute sepsis, severe dehydration or volume overload and inability to follow study procedures are excluded.

The patient is contacted in person and given an information sheet (in Estonian or Russian as appropriate). The patient will be informed about the structure of the study. If the patient agrees to participate, they will sign the consent form. Participation in the study is voluntary. The patient will not be included in the study until they have read the patient consent form, understood the content of the study, received answers to any questions they may have, and voluntarily signed two copies of the written consent form (one for the patient and one for retention at the University of Tartu.)

8. Detailed description of the research methodology

The patient's demographic data including age, sex, primary diagnosis, and diagnoses of co-morbidities are found by the investigator in the medical history (eHL). The researcher codes the current main diagnosis and its severity: we use the World Health Organization's ICD-11 classification (icd.who.int/browse11/l-m/en) and a three-point scale where 1 is mild and 3 is severe.

The patient will be interviewed for changes in body weight and food intake. Anthropometric measurements will be recorded, including height, weight, body mass index (BMI), mid upper arm circumference, calf circumference, and waist circumference.

The accurate muscle mass measurement will be done using total body DEXA scan, that was already ordered for other purposes. Bone mineral density (BMD) from DEXA scan will be recorded. This allows us to see if calf circumference can be used for estimating bone mineral density. Patients will be followed up one year after data collection. Follow up will involve calling the patients and asking them questions from SarQoL (sarcopenia quality of life questionnaire)

Calf circumference will be measured using non-elastic tape at the widest part of the dominant calf in the seated position with the weight evenly distributed on both feet (1). Mid upper arm circumference will be measured at the midpoint between the acromial surface of the scapula and the olecranon process of the elbow over the dominant arm when bent at 90 degrees. Waist circumference will be measured using measuring tape 2.5 cm above the umbilicus in standing position. Waist circumference is used to define obesity as it is a marker of abdominal obesity (2). We aim to keep the interview no longer than 10 minutes.

Demographic and anthropometric data will be analyzed using descriptive statistics. The sensitivity, specificity of muscle mass measurements will be calculated. Corrected calf circumference will be compared to DEXA (gold standard diagnostic tool) and new cutoffs will be defined by using Receiver operating characteristic curves. Statistical analyses will be performed using R.

1. Rose Berlin Piodena-Aportadera M, Lau S, Chew J, et al. Calf circumference measurement protocols for sarcopenia screening: differences in agreement, convergent validity, and diagnostic performance. Ann Geriatr Med Res. 2022;26:215–24.
2. Lim JP, Chew J, Ismail NH, Lim WS. Letter to the editor: Obesity definition for muscle outcomes in sarcopenic obesity: Utility of waist circumference revisited. J Frailty Aging. 2021;10:334–6.

9. Description of the ethical aspects of the research

The study addresses the issues of confidentiality and protection of personal data.
The consent form does not contain contact information, confidential information, date of birth or ID code. Sensitive personal data is processed in accordance with the procedure established in the University Hospital of Tartu, which is in accordance with the requirements provided for in the Personal Data Protection Act.

Personal data is collected and then coded. The coded data is further processed and analyzed. Personal data is stored in a folder on the University of Tartu OneDrive server, which is accessible to the investigators. The link between the data collected during the study and the patient's identity is known only to the researcher conducting the interview and the researchers who have access to the code key. The code key will involve the following information: the patient’s name, study ID, personal identification code, phone number, and the date of data collection. The code key will be deleted one year after the follow-up check is completed. After that, the data will become anonymous. The data will be anonymized by 04/2026. Anonymous data will be stored in a OneDrive folder protected by a password at the University of Tartu. Pseudonymized data (i.e., the study data before code key is deleted) can only be accessed by the researchers involved in the study. Copies of the consent forms

are stored in a locked office at the University of Tartu Hospital, in a locked cabinet. The locked office and cabinet are located on the sixth floor of the University of Tartu Hospital's L-building, room L6027. Informed consent forms will be kept until 06/2032. The responsible data controller is the University of Tartu.

10. Information about previous or similar projects undertaken elsewhere

The researchers have been a part of a similar project conducted at Tartu University Hospital from December 2023 to May 2024. The aim of the project was to establish whether a limb circumference, namely calf circumference (CC) or mid-upper arm circumference (MUAC), has the potential to become the preferred muscle mass assessment method of a standardised, globally accessible GLIM protocol. In both males and females there was good correlation between CC and fat-free mass index (FFMI) in patients without obesity. The correlation between CC and FFMI was weaker in patients with obesity and almost absent in females with obesity. The researchers have not encountered any problems. This experience helps to improve confidence in the feasibility of the new study given a similar time frame.

After we complete the current study, we also aim to look at this previous dataset to find out whether the new corrections work for the patients with obesity. This will validate the results of the study.

11. Supplementary papers:

11.1 CVs of the Researchers

11.2 Information and consent form(s + Russian)