MSIG Grant 2017: Report of Research results

a. Title:

MUSCLE-DM study - MUscle Strength in Community Living Elderly with Diabetes Mellitus

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c. Summary

Background: Sarcopenia is the age-related loss of muscle mass and function, which increases fall risks in older persons. Hyperglycemia relating to Type-2 Diabetes Mellitus (T2DM) is postulated to aggravate sarcopenia. This study aimed to determine the prevalence of sarcopenia among ambulatory community-dwelling older patients, aged 60-89 years, with T2DM in a primary care setting and to identify factors which mitigate sarcopenia.

Methods: A total of 387 patients were recruited from a public primary care clinic in Singapore. Data on their socio-demography, clinical and functional status, levels of physical activity (International Physical Activity Questionnaire) and frailty status was collected. The Asian Working Group for Sarcopenia (AWGS) criteria were used to define sarcopenia based on muscle mass, grip strength and gait speed.

Results: The study population comprised men (53%), Chinese (69%), mean age=68.3±SD5.66 years, lived in public housing (90%), had hypertension (88%) and dyslipidemia (96%). Their mean muscle mass was 6.3±SD1.2kg/m^2; mean gait speed was 1.0±SD0.2m/s and mean grip strength was 25.5±SD8.1kg. Overall, 30% had pre-sarcopenia, 24% with sarcopenia and 4% with severe sarcopenia. Age (OR=1.14; 95%CI=1.09-1.20; p<0.001), multi-morbidity (OR=1.25;95%CI=1.05-1.49; p=0.011) diabetic nephropathy (OR=2.50;95%CI=1.35-5.13; p=0.004), hip circumference (OR=0.86;95%CI=0.82-0.90;p<0.001) and number of clinic visits in past one year (OR=0.74; 95%CI=0.59-0.92;p=0.008) were associated with sarcopenia.

Conclusions: Using AWGS criteria, 58% of older patients with T2DM had pre-sarcopenia and sarcopenia. Age, diabetic nephropathy, hip circumference, multi-morbidity and fewer clinic visits, but not a recent single HBA1c reading, were significantly associated with sarcopenia among patients with T2DM. A longitudinal relationship between clinic visits and sarcopenia should be further evaluated.

d. Aim of Research

This study primarily aimed to determine the prevalence of sarcopenia in ambulatory, older Asian patients with T2DM in a primary care setting in Singapore using the AWGS criteria. The secondary aim was to identify factors which may potentially mitigate sarcopenia risks in patients with T2DM. Understanding the magnitude of sarcopenia and associated mitigating factors in a

vulnerable older population due to concurrent T2DM will influence the allocation of healthcare resources to scale up sarcopenia screening and facilitate the design of interventions to prevent further deterioration of muscle strength and function.

e. Method of Research and Progression

This baseline study was conducted from October 2017 to March 2018 at a public primary care clinic (polyclinic) located within Pasir Ris estate in the north-eastern region of Singapore. The polyclinic serves 140,000 multi-ethnic Asian residents and manages about 570 patient attendances daily during office hours, of which 30% are aged 65 years and above. This study is part of a longitudinal study in which the study population will be reviewed one year later to re-assess for the development or progression of sarcopenia, to develop a predictive risk model of sarcopenia. In order to better quantify any progression one year later, we classified the participants into the different stages of sarcopenia according to the EWGSOP criteria, on top of using the AWGS diagnostic criteria, which did not include the different stages of sarcopenia.

Study participants

The study population comprised multi-ethic Asian patients aged 60-89 years old, with a diagnosis of T2DM for at least one year from the data of their electronic medical records, regardless of their mode of therapeutic treatment. They were on regular medical reviews with two or more visits at the study site in the past one year. The participants can be treated with any therapeutic options compatible with their glycaemic control, ranging from diet control alone, oral hypoglycaemic agents alone, or a combination of oral hypoglycaemic agents with insulin injections.

Those with known risks which hindered or compounded sarcopenia assessment, such as history of stroke, carpal tunnel syndrome, severe hip or knee osteoarthritis, dysarthria or dysphasia, hearing difficulties, use of walking aid, physical disabilities that affect hand-grip and/or walking, use of electronic implants such as pacemaker, and living in residential care facilities were excluded. Patients with any form of other disabilities, such as cognitive impairment, which rendered them incapable of providing informed written consent were also excluded.

Sample size estimation

The primary aim was to determine the prevalence of the sarcopenia in community-living, unassisted ambulatory T2DM primary care patients aged 60-89 years old. Utilizing the prevalence estimate (59.8%) for sarcopenia among older persons regardless of diabetes status from a recent Malaysian study,[12] the sample size was computed to be 370, at 5% precision and 95% confidence level, using the following sample size formula: $n = \frac{Z^2 P(1-P)}{d^2}$ where Z is Z statistic for a level of confidence, P is the expected prevalence and d is precision level. To account for 5% incomplete or missing data, the sample size was increased to 388. This was projected as a conservative estimate, as the prevalence was anticipated to be higher in the presence of T2DM.

Recruitment and Sarcopenia Assessment

Case-encounter approach was used to recruit the potential participants. They were screened based on eligibility criteria at service points at the study site. They were provided the approved patient information sheet, clarified on their queries and recruited after the investigator obtained their informed written consent. Next, the subjects administered the study questionnaire, either by themselves or assisted by the investigator, to collect their demographic, lifestyle habits (alcohol intake, smoking status, and physical activity), socio-economic status and clinical information. Next, anthropometric assessments were performed to measure their weight,

height, body mass index (BMI), waist circumference (WC), hip circumference (HC), systolic and diastolic blood pressures.
The participants stood erect on the calibrated AVAMECH Model B100U device, which measured their weight and height, automatically computed the BMI and printed out the parameters. The blood pressures were measured twice using the automatic blood pressure monitor (OMRON HEM-7280T). WC was measured at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest while HC was measured around the widest portion of the pelvis.[13] Both WC and HC were determined using the same measuring tape.

Next, the sarcopenia assessment was performed:
(1) body muscle mass was measured using a bio-electrical impedance analysis machine (OMRON Body composition monitor, Model HBF-375) according to the study protocol. The skeletal muscle index was then calculated as body muscle mass divided by squared body height.

(2) handgrip strength was measured twice on each hand, using a dynamometer (JAMAR Plus Digital Hand Dynamometer #563213) with the subject seated with elbow flexed at ninety degrees, forearm in neutral position and wrist between 0-30 degrees of dorsiflexion and supported on a table, according to the American Society of Hand Therapists' guidelines.[14] The average handgrip strength of the dominant hand was used for analysis;

(3) six-meter gait speed was computed based on measurement of the average time taken for the subject to walk along a straight distance of six meters at usual walking speed. In this gait speed assessment, there were run-in and run-out phases of approximately one meter, before and after the six-meter distance respectively. Two time measurements were taken for each subject using a digital stopwatch (CASIO Model 611Q24R).

Sarcopenia was diagnosed according to the AWGS criteria[5] and further staged according to European Work Group for Sarcopenia (EWGSOP) guidelines.[1] Sarcopenia was diagnosed when there was low muscle mass (defined as skeletal muscle index <7kg/m^2 in males and < 5.7kg/m^2 in females), together with either low muscle strength (defined as handgrip strength <26kg in males and <18kg in females) or low physical performance (defined as six-meter gait speed $\leqslant$0.8m/s) or both.

The participants' electronic medical records (EMR) were accessed to retrieve information on the latest glycemic control index (HbA1C) and fasting lipid profile (total cholesterol, high-density lipoprotein cholesterol [HDL], low-density lipoprotein cholesterol [LDL], triglycerides [TG]) from the laboratory test results. The duration of diabetes, presence of diabetic complications (any documented retinopathy, nephropathy, neuropathy, vasculopathy), co-morbidities (diagnosis list) and medications (electronic prescription) were also obtained. All data were audited and de-identified before being analyzed.

Statistical analyses:
Data were analyzed using the Statistical Package for Social science (SPSS) software (IBM, Version 21). Prevalence of sarcopenia (in stages) and categorical demographic and clinical variables were reported in frequencies and percentages. Muscle mass, handgrip strength, gait speed and continuous parameters were reported as mean ± standard deviation (SD). In the univariate and multivariate analyses, the outcome "Sarcopenia" is defined as those having sarcopenia and severe sarcopenia. No sarcopenia and pre sarcopenia were grouped as "No sarcopenia". Univariate logistic regression analysis was performed to explore the factors associated with the presence of sarcopenia. Significant variables via backward selection approach were entered into the multivariable logistic regression to determine the factors associated with sarcopenia.

Statistical significance was set at $P \leq 0.05$.

Ethics approval and funding

This study was reviewed and approved by the SingHealth Centralized Institutional Review Board (CIRB reference 2017/2393). This study was funded by a grant from Mitsui Sumitomo Insurance Welfare Foundation. The SingHealth-Duke NUS Academic Medicine Ethos Award supported the medical student (FFY) in the team and Omron Healthcare Singapore sponsored the Bio-impedance Assessment (BIA) device.

f. Results

In total, 2056 patients were screened, of which 1483 failed the eligibility criteria, 183 declined study participation, 2 withdrew from the study, 1 disqualified after review of EMR due to exclusion criteria, and 387 patients with complete data were analyzed. The response rate was 67.7. Their mean age was 68.3±5.7years. The duration of T2DM in the participants ranged from one year to fifty years. The therapeutic interventions received by the participants included diet control alone, oral hypoglycemic agents alone, or a combination of oral hypoglycemic agents with insulin injections.

The overall prevalence of sarcopenia among the community-living, unassisted ambulatory patients aged 60-89 years with T2DM was 27.4%, among which 3.9% had severe sarcopenia and 30.5% had pre-sarcopenia (Figure 1). The proportion with low muscle mass, low muscle strength and low gait speed were 57.9%, 31.3% and 9.6% respectively.

Univariate logistic regression analyses showed that demographic factors, such as age (OR=1.15, 95%CI= 1.10-1.20, p<0.001), women (OR=1.82, 95%CI=1.16-2.86, p=0.009) and Chinese ethnicity (OR=2.08, 95%CI=1.16-2.86, p=0.007) were associated with greater risk of sarcopenia. However, multivariable logistic regression analyses revealed that only age remained as a significant demographic factor.

Engaging in physical activities such as having done light house work (OR=1.75, 95%CI=1.02-3.03, p=0.043) and having worked for pay/volunteer (OR=2.00; 95%CI=1.25-3.13, p=0.004) are associated with higher risk of sarcopenia, while sitting (OR=0.998, 95%CI=0.997-0.999; p=0.005) was associated with lower risk of sarcopenia. Smoking and alcohol consumption were not associated with sarcopenia.

For dietary habits, univariate analysis found that consumption of legumes/lentils (OR=0.579, 95%CI=0.37-0.91, p=0.018) was associated with reduced risk of sarcopenia. In contrast, consumption of meat/seafood/eggs (OR=1.40, 95%CI=1.01-1.93, p=0.041) was associated with higher risk of sarcopenia. However, the physical activity and dietary factors were not significantly associated with sarcopenia after multivariable analyses.

The number of medical conditions or comorbidities (OR=1.22; 95%CI=1.06-1.39, p=0.005), history of chronic kidney disease (OR=1.76, 95%CI=1.01-3.06, p=0.013), anemia (OR=2.73; 95%CI=1.30-5.74, p=0.008) and the number of polyclinic visits for consultation over the past year (OR=0.78, 95%CI=0.64-0.95, p=0.013) were associated with sarcopenia in univariate analyses. Multivariate analyses showed that multiple morbidities and number of consultations at polyclinics in past year were significantly associated with sarcopenia.

Clinical parameter such as diastolic blood pressure (OR=0.98, 95%CI=0.95-1.99, p=0.042) and anthropometric measurements such as BMI (OR=0.76, 95%CI=0.70-0.83, p<0.001), WC (OR=0.92,

95%CI=0.90-0.95; p<0.001) and HC (OR=0.87, 95%CI=0.83-0.90; p<0.001) were associated with lower risk of sarcopenia. Only HC remained a significant factor after multivariable analyses.

The recent glycemic control index (up to 6 months ago), HbA1C (OR=0.81, 95%CI=0.63-1.04, p=0.093) and lipid profiles were not associated with sarcopenia. Duration of T2DM (OR=1.04, 95%CI=1.01-1.07, p=0.013) and the presence of diabetic nephropathy based on laboratory investigation (OR=1.99, 95%CI=1.16-3.41, p=0.013) were identified as significant risk factors but only the latter remained associated with sarcopenia after multivariate analyses (OR=2.50, 95%CI=1.30-5.00, p=0.006).

Advanced age, hip circumference, diabetic nephropathy, number of consultations at polyclinics and number of medical conditions (multiple morbidities) were associated with sarcopenia. The association between recent glycemic control index (HbA1C) and sarcopenia was not established in this study.

g. Future Areas to Take Note of, and Going Forward

Among every three community-dwelling, unassisted ambulatory older patients aged 60-89 years with T2DM in Singapore, nearly one had sarcopenia and one had pre-sarcopenia. Sarcopenia was significantly associated with advanced age, multiple morbidities, diabetic nephropathy, hip circumference and number of consultations at primary care clinics. A single recent glycaemic control index, HbA1C was not significantly associated with sarcopenia. A longitudinal relationship between clinic visits and sarcopenia should be further evaluated. Identifying the associated risk factors from this study may enable stratification of resource allocation for sarcopenia screening and intervention in this vulnerable group of older patients with T2DM.

h. Means of Official Announcement of Research Results

The results have been published in the journal BMC Geriatrics, which is in the top 20% of medical journal in the field of geriatrics and gerontology (Thomson Reuters).

Foon Yin Fung , Yi Ling Eileen Koh, Rahul Malhotra, Truls Ostbye, Ping Yein Lee, Sazlina Shariff Ghazali, Ngiap Chuan Tan. Prevalence of and factors associated with sarcopenia among multi-ethnic ambulatory older Asians with type 2 diabetes mellitus in a primary care setting. BMC Geriatrics. 2019(19):122

SHP and Duke NUS are planning to publicise the findings in the media to raise awareness of the public towards maintain their muscle health amongst the population with type 2 diabetes mellitus in the community.