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FRAILTY AND BRAIN-MUSCLE CORRELATES IN OLDER PEOPLE WITH TYPE 2 DIABETES: A STRUCTURAL-MRI EXPLORATIVE STUDY

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Abstract: *Objectives:* Muscle alterations, mainly functional alterations are frequently observed in older people with type 2 diabetes (T2DM). Sarcopenia may be one mechanism of transition to frailty in these people. Thus, we aim to explore the characteristics of muscle and its association with cerebral grey matter volumes within this group. *Methods:* Single center study nested within the international MID-Frail (a randomized clinical trial to evaluate the effectiveness of a multi-modal intervention in older people with T2DM on frailty and quality of life) trial participants underwent both brain and muscle T1 MRI, nutritional and functional assessments. Muscle areas were measured in rectus femoris (RF). Relationships between MRI grey matter volumes and muscle areas or function tests were described using positive and negative regressions. *Results:* Twenty-six subjects (7 female, mean age 78.2 y, SD 5.0), 6 frail and 20 pre-frail were explored in this sub-study. Frail subjects had lower Mini Nutritional Assessment (MNA), Short Physical Performance Battery (SPPB), hip flexor strength than pre-frail ones but similar BMI and balance. Total SPPB was positively related with hip flexor strength and maximal RF area. Balance SPPB sub-score was unrelated to strength or RF area. MNA score was correlated with hip flexor strength and to global grey matter but not to SPPB. Hip flexor strength was correlated with grey matter areas involved in motor control. Walking time was negatively and rising chair sub-score was positively associated with grey matter volumes of motor areas. *Conclusions:* Sarcopenia features were more frequent in frail than prefrail subjects and were associated with decrease in grey matter volumes involved in motor control.

Key words: Frailty, sarcopenia, NMR imaging, muscle, grey matter volumes, SPPB, MID-FRAIL.

Introduction

Older people with type 2 diabetes (T2DM) have an important risk of frailty through physical, mental and social pathways (1-3). T2DM mainly affects physical health related quality of life (2). Sarcopenia may be one of the conditions increasing the risk of frailty associated with T2DM (3) but its pathogenesis in this population is likely multifactorial.

Brain microangiopathy related to T2DM (4) is one main candidate as a frailty inducing factor. Brain white matter hyperintensities (WMHs) were shown to be associated with frailty in general older population (5). Indeed, vascular factors are probably important in the occurrence of physical and cognitive decline. It was also shown that WMHs and arterial stiffness were associated with higher rate of both muscle mass and cognitive decline in the general population (6). Possible changes in grey matter volumes in relation to sarcopenia were very sparsely considered. In a sample of healthy older men brain volumes were positively correlated with neck muscle area (7). But this study only focused on relationships between muscle and brain volumes.

Another pathway common to sarcopenia and frailty may be cachexia syndrome through chronic low grade inflammation (8). Overweight and obesity are main features of T2DM but when older they are frequently considered as at risk for malnutrition according to the MNA (9). The proportion at risk was estimated in this population-based study 26 % as compared with 0.1% in other subjects. Assuming "at risk for malnutrition" belongs to risk factors for sarcopenia (10) relationships between both need to be studied in older people with diabetes.

MID-Frail is a 24 months international randomized control trial (RCT) in frail and pre-frail subjects older than 70 years with T2DM, investigating the effect of a multidimensional intervention aiming at improving their physical performance measured using the Short Physical Performance Battery (SPPB) (11) and their quality of life with medico-economic efficiency as compared with usual care group (12). We took advantage of the MID-Frail study to investigate muscle function with combined clinical testing, nutritional assessment and brain and muscle T1 MRI at baseline in a sample of included subjects (SARTRAIN-MRI: evaluation of morphological and bioenergetic alteration of muscle and brain tissues in older patients with T2DM). MID-Frail study included both prefrail and frail subjects. Giving that prefrail subjects were reported to have more than twice the risk of becoming frail over 3 years (13) we also aim to compare prefrail and frail subjects for these parameters.

Patients and Methods

SARTRAIN-MRI sub-study is a descriptive cross sectional study. It took place in Bordeaux Metropole recruiting centers

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Table 1
Characteristics of the study population

Mean (SD)	Total (n=26)	Frail (n=6)	Pre-frail (n=20)	P frail/pre-frail
Age	78.2 (5.0)	79.0 (4.2)	77.9 (5.2)	NS
F/M	7/19	4/2	3/17	
BMI kg/m²	30.8 (6.7)	34.9 (7.4)	29.5 (5.8)	NS
MNA (0-30)	25.0 (3.0)	23.8 (1.3)	25.4 (3.3)	0.014
SPPB total (0-12)	9.7 (2.4)	6.3 (1.4)	10.7 (1.6)	0.0005
Balance (0-4)	3.5 (0.8)	3.5 (0.5)	3.5 (0.9)	NS
Gait (0-4)	3.5 (0.9)	2.0 (0.6)	4.0 (0.2)	<0.0001
Chair-rise test (0-4)	2.7 (1.4)	0.8 (0.9)	3.3 (1.1)	0.0007
4-meter walking time (s)	4.7 (2.5)	7.9 (3.0)	3.6 (0.7)	
Hip flexor strength (Newton)				0.003
Male	196.0 (77.7)	105.5 (61.5)	206.7 (74.5)	
Female	121.6 (49.4)	100.0 (7.8)	150.3 (79.1)	
Rectus femoris maximal area (mm²)	953.8 (245.5)	815.0 (127.4)	1013.3 (260.5)	NS

Comparisons between frail and prefrail subjects were done with Wilcoxon rank sum test; NS: non-significant; MNA, mini nutritional assessment; SPPB short physical performance battery.

(N=7) close to the Philips 3-Tesla ACHIEVA MRI device. The Main RCT MID-Frail study (ClinicalTrials.gov Identifier: NCT01654341) and the present sub-study protocols were approved in France by the Comité de Protection des Personnes (CPP) "SUD-Ouest et Outre Mer III".

Patients were recruited in MID-Frail study if aged 70 years or older, with a diagnosis T2DM for at least 2 years, frail or pre-fail according to Fried's criteria (13) and willing to participate after signature of a written informed consent. Exclusion criteria were: dependent living with Barthel index (14) lower than 60/100, significant cognitive troubles with MMSE (15) lower than 20/30, history of myocardial infarction in the last 6 month, unstable coronary heart disease, stage NYHA III or IV heart failure or illness at terminal stage. SARTRAIN-MRI sub-study additional exclusion criteria were the presence of ferromagnetic material in body. The sub-study was aimed to recruit up to 60 volunteers and 26 agreed to participate after signature of a separate inform consent.

Clinical variables

The lower limbs performance was assessed with Short Physical Performance Battery (SPPB). SPPB explores balance (tandem test: max score 4), gait speed (4-meter: max score 4) and strength (chair rise test: max score 4); higher scores corresponds to better performance. The 4-meter walking time was also considered. Nutrition was assessed with BMI (weight kg / height m²) and Full Mini Nutritional Assessment (MNA) (16) and analyzed as continuous variables. The best of three attempts was chosen for determination hip flexion maximal isometric strength of the dominant limb (in Newton, Microfet 6®). For this measure, the patient was in sitting position, hip and knee joints of the test limb at 90 degree, non-tested leg in relaxed position and the dynamometer applied at the distal femur extremity.

Magnetic resonance imaging (MRI)

MRI scans were obtained using an ACHIEVA 3 Tesla machine (Phillips® Medical System, Netherlands) with a SENSE 8-channel head coil and a SENSE body coil.

Muscles T1 MRI scans were manually contoured to measured maximal muscle thigh area and maximal rectus femoris (RF) area using the free software of National Institutes of Health MIPAV® (Medical Image Processing, Analysis, and Visualization). Because we have assessed in this sample that maximal muscle area was correlated with volume (intra-class correlation coefficient single rater 0.97 [IC 95% 0.92-0.99] we only considered maximal muscle area in the present study.

The Voxel Based Morphometry (VBM) analyze was performed using statistical parametric software (SPM12, Wellcome Trust center for Neuroimaging, Institute of Neurology, London, UK, http://www.fil.ion.ucl.a-c.uk./spm/) in conjunction with MATLAB version 7.0.1 (The Mathworks, MA). We used an optimized VBM procedure to analyze grey matter volumes (17) conducted in a two-steps-processing using VBM2 toolbox (v1.06; C. Gaser; http://dbm.neuro.uni-jena.de/vbm: 1/creation of study-specific priors and template 2/ segmentation and normalization of the native 3D-MRI scans of each subject using study-specific priors and template.

Analyses

Frail and pre-frail subjects were compared with Wilcoxon rank sum test and correlations between clinical variables

were analyzed with Spearman's correlation rank test. Grey matter volumes and muscle assessments relationships were described using positive and negative regressions corrected for confounding variables (Total Volume Intracranial, age and sex) with a threshold peak of p<0.001 and extended voxels of 50).

Results

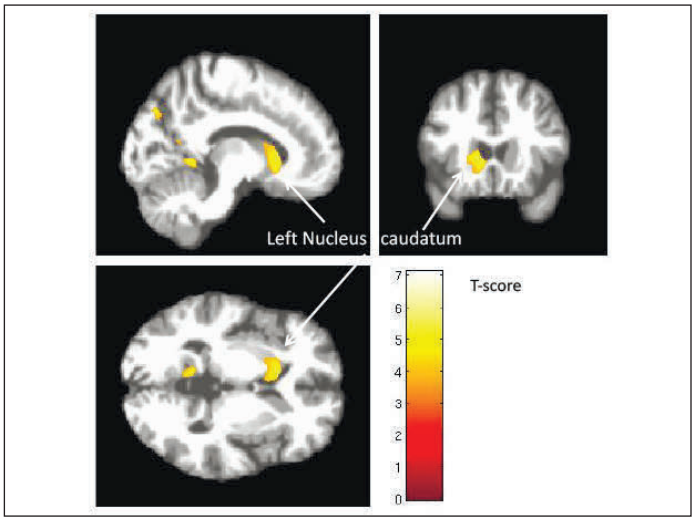
Twenty-six subjects (7 female, mean age 78.2 y, SD 5.0), were explored in this sub-study. Among them 6 were frail and the others were pre-frail. Characteristics of these subjects are presented in Table 1. Frail subjects had lower MNA scores (23.8 vs 25.4), SPPB scores (6.3 vs 10.7) and lower hip flexor strength (male 105.5 vs 206.7 and female: 100.0 vs 150.3) than pre-frail subjects. They were similar on BMI, SPPB balance and age. The BMI mean's in both group was high; 1 frail and 3 pre-frail subjects had BMI<25kg/m^2.

MNA was related to hip flexor strength (r=0.61, p= 0.001) and 4-meter walking time (r=-0.55, p=0.007) but not to total SPBB (r=0.28), or RF maximal area (r=035).

Hip flexor strength was related to total SPPB (r=0.53, p= 0.005), rising test sub-score (r= 0.52, p= 0.006) and to walking time (r= -0.56; p=0.005). Maximal RF area was also related to strength (r=0.45, p= 0.045), total SPPB (r= 0.68, p< 0.0001), rising chair subscore (r= 0.60, p= 0.005) and walking time (r= -0.51, p= 0.23). Balance sub-score was unrelated to strength or RF area.

Figure 1

Grey matter volumes associated with SPPB rising chair subscore: Positive regressions adjusted on age, sex and total intracranial volumes. Clusters presenting statistically significant associations with rising chair score are overlaid on a spatially normalized TI image of one subject of the sample



MNA score was positively associated to grey matter volumes. Hip flexor strength was positively associated with structure volumes involved in motor control (occipital mid and sup, left and right, right calcarine fissure, left cerebellum, temporal, cingulum, thalamus, frontal).

Walking time was negatively associated with thalamus, left and right calcarine fissure, right occipital and left cerebellum volumes.

Higher scores in chair rising SPPB subscore were positively associated with several structures volumes among them caudate nucleus, frontal and temporal lobe and calcarine fissure (Figure 1).

Higher score in balance SPPB subscore were positively associated with left caudate nucleus and left olfactory bulb areas. On the other side they were negatively associated with right lingual gyrus, hippocampus, occipital superior and cuneus areas and left cerebellum and occipital areas.

Discussion

This exploratory study in frail and prefrail older patients with T2DM showed that MNA but not BMI was associated with physical performance as assessed with SPPB, particularly chair rise and gait. Only five subjects were not overweight or obese and body composition was not the main factor explaining the lower performance scores. The relationships between RF area and function were significant but lower than those of RF strength and function. We also show that lower MNA were associated with widespread lower grey matter volumes; strength was associated with all structures involved in motor control (occipital mid and sup, left and right, right calcarine fissure, left cerebellum, temporal, cingulum, thalamus, frontal); in contrast lower limb performance was associated with specific motor area (mainly caudate nucleus for ring chair and thalamus for walking time). Balance impairment, another feature of frailty was not associated with nutritional status or strength. We observed that the best scores corresponded to the highest volume of caudate nucleus. On the other side several structures involved in balance and spatial cognition (hippocampus, cerebellum, olfactory bulb, visual areas) were greater when the balance is impaired. This may suggest compensatory adaptation to peripheral afferents impairment, such as sensitive neuropathy.

This study confirmed that muscle functioning more than muscle wasting was altered in frail subjects with diabetes. This suggests an impairment in muscle quality. Indeed, muscle metabolism is impaired with diabetes due to several reasons (18). The relationships between MNA and SPPB in diabetes was already shown (19). MNA has been considered as a marker of cachexia syndrome, particularly in cancer (20), and cachexia syndrome in T2DM cannot be rule out. The fact that RF strength was associated with large grey matter area may be in favor of this hypothesis.

T2DM, known or unknown was shown associated with decreased grey matter volumes as compared with those without hyperglycemia (21). Here we showed association of decreased grey matter volumes and muscle function. This is however

not possible to state if reduced grey matter volumes are consequence or cause of alterations in function muscle.

This study has several limitations; among them the number of subjects was low but sufficient to provide comprehensive description of muscle function in frail/pre-frail subjects with T2DM. The lack of assessment of total skeletal muscle mass prevented classification of subjects according to sarcopenia categories. However, we were able to describe a proxy with the RF muscle area and we found that muscle mass was lower in frail than in pre-frail and that decreased muscle mass was associated with lower strength and lower limb performance. This follows the revised consensus for sarcopenia case-finding and diagnosis (22).

In conclusion this study of muscle function in frail or prefrail older people with diabetes showed an important role of muscle function in performance. Furthermore, sarcopenia features were more frequent in frail than prefrail subjects and were associated with decrease in grey matter volumes involved in motor control. This emphasizes the potential role of exercise for muscle reinforcement in older people with T2DM in addition to endurance training as recommended.

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Ethical standard: This article complies with the current laws. The study received approval from «Comité de protection des personnes Sud Ouest et Outre-mer III. Participants gave their written informed consent.

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