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Premature loss of muscle mass and function in type 2 diabetes

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ABSTRACT

Introduction: Muscle mass and function are among the most relevant factors that contribute to an optimal quality of life, and are strong predictors of mortality in the elderly. Loss of lean tissues and deterioration of muscle function have been described as one of the many complications of type 2 diabetes mellitus (DM2), but most studies do not isolate age as an intervening factor.

Aim: To study whether adult DM2 patients up to 60 years of age have decreased muscle mass and function compared with healthy non-diabetic (ND) subjects of similar age.

Methodology: Appendicular fat-free mass (ApFFM) by dual X-ray absorptiometry (DEXA), handgrip strength (HS), quadriceps strength (QS), 12 min walking capacity (12MW) and the Timed Up and Go test (TUG) were measured in 100 DM2 patients and 39 ND controls. Muscle quality, or the ratio between lean mass and muscle strength of upper and lower limbs, and the functional limitations associated with pain and stiffness assessed according to the Western Ontario and McMaster Universities Arthrosis Index (WOMAC) were also recorded. Specific tests were performed to rule out microvascular diabetic complications (retinal and peripheral nerves), metabolic control, kidney function and vitamin D status and examine their association with ApFFM and function.

Results: ApFFM was significantly higher among DM2 female patients and lower among diabetic men. However opposite results were obtained when individual values were corrected for body mass index (BMI), specifically among women, who were more likely to be obese. As for muscle strength and global functionality tests, significantly better performances in TUG, 12MW, QS and HS were observed among ND subjects of both sexes. These differences prevailed even after excluding diabetic patients with microvascular complications as well as those with more than 10 years of diabetes. Muscle quality was also significantly better among ND women. Higher scores of pain and stiffness in the WOMAC scale correlated with 12MW and TUG in both groups but did not correlate with ApFFM.

Conclusions: We found a clear deterioration of lean mass and muscle functions among adult DM2 patients of up to 60 years old, independent of length of disease, metabolic control, vitamin D status and presence of microvascular complications and pain.

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1. Introduction

Type 2 diabetes mellitus (DM2) is a highly prevalent chronic metabolic disease, related with obesity and a sedentary lifestyle [1]. This impacts health costs, mostly owing microvascular complications of the disease, which are already present in 20–40% of patients at diagnosis [2]. A less known but important problem associated with DM2 is loss of muscle mass and function (sarcopenia), a condition usually attributed to aging, immobility or various chronic diseases [3–7], but typically not considered as a complication of DM2. It has been suggested that sarcopenia could derive from micro and macrovascular changes associated with this disease [8], chronic inflammation [9] and muscle lipid infiltration [10,11]. It must also be kept in mind that many DM2 patients suffer from chronic pain of bone, articular or neurogenic origins [12] which also contribute to sarcopenia, since they can alter the ability to perform physical activity, a factor that negatively affects muscle mass and function [13]. On the other hand, low levels of vitamin D and increase of parathyroid hormone (PTH) have also been associated with decreased muscle mass and strength [14,15].

Several studies have shown muscle involvement associated with DM2. A North American study confirmed a decrease in muscle quality (strength relative to mass) of legs and arms in subjects with DM2, compared with a control group [16]. Another follow-up study covering a period of three years described greater loss of mass, strength and quality of the knee extensor muscles in diabetic patients compared with ND [17]. Similarly, a Korean study found a decrease in appendicular muscle mass in older diabetic adults compared with an age-matched control group [18]. It should be noted that these reports included mostly elderly patients and control subjects.

Some authors have termed the stage prior to sarcopenia as *dynapenia*, where there is a decrease in muscle strength or other muscle functions without obvious loss of muscle mass [19]. This designation could become relevant when considering that a high proportion of the diabetic population is overweight or obese, so that the same degree of reduction in muscle mass relative to eutrophic subjects of comparable age and sex is not expected. However, in these circumstances muscle quality (function relative to mass) can be affected.

Muscle mass can be assessed by direct methodologies such as computed tomography or magnetic resonance imaging, which are accurate but restricted due to their high costs. It can also be estimated indirectly through impedance, ultrasonography or dual energy X-ray absorptiometry (DEXA). The latter is currently the gold standard for measuring body composition in clinical trials [20,21]. As indicators of muscle mass, the equipment measures total (TFFM) or appendicular fat-free mass (ApFFM) (i.e. the sum of FFM of both upper and lower extremities), to eliminate interference of viscera. These measurements can be expressed either as absolute values or as FFM Index (FFMI), when corrected for squared height.

Both sarcopenia and dynapenia are multifactorial disorders; its most relevant causal factors are aging, sedentary lifestyles and chronic diseases associated with inflammation, such as DM2. However, in most studies the contribution of the aging process cannot be isolated from the effects of disease. Therefore, the purpose of this study was to compare muscle mass and functionality of middle-aged diabetic patients with that of healthy subjects of comparable ages, excluding those over 60 years old. Among diabetic patients, the study also covered the influence of years of disease, microvascular complications, chronic pain, metabolic control, parathyroid hormone (PTH) and vitamin D serum levels on muscle variables.

2. Patients and methods

We selected DM2 patients with over 4 years on oral antidiabetic drugs or insulin ($n = 100$; 62 women and 38 men) and ND subjects as controls ($n = 39$; 26 women and 13 men), aged between 40 and 60 years old, from the city of Santiago. Healthy controls were contacted as usual by our trained research assistant and the research team, using local advertising and phone calls offering a free preventive medical assessment. All participants signed a written informed consent form, which had been previously approved by the ethics committee of INTA, University of Chile.

Exclusion criteria were the existence of other diseases such as heart, lung or liver failure, alcoholism, inflammatory conditions or cancer, treatment with steroids, advanced renal failure with creatinine clearance <30 ml/min, high intensity regular physical activity and physical disabilities that precluded performance of muscle function tests.

A complete medical history of each patient or healthy volunteer was complied in order to rule out the existence of other diseases, the length of diabetes and the use of drug treatments. The WOMAC scale, a questionnaire of perception of pain, stiffness and functionality, previously validated for musculoskeletal diseases, was registered [22,23]. Other assessments included anthropometric measurements [weight and height to calculate body mass index (BMI)], and a fasting blood sample for measuring glucose, lipoproteins, creatinine, hemoglobin, thyrotropin, 25OH-vitamin D, PTH and glycosylated hemoglobin (HbA1c) (the latter only among DM2). A morning urine sample was also obtained in diabetics for assessment of microalbuminuria. All determinations were performed at Vida Integra Laboratory, using automated methods.

Body composition was assessed by DEXA (LUNAR series computer software 200674 13.6) recording total body fat mass, bone mineral density, TFFM, ApFFM and ApFFMI.

As indicators of muscle function, we measured handgrip strength (HS), quadriceps strength (QS), 12 min walking capacity (12MW) and the Timed Up and Go test (TUG). HS was measured with a hand dynamometer (Therapeutic Instruments, Clifton, NJ, USA), considering the best of three measurements in the dominant hand. QS was evaluated by measuring the maximum voluntary contraction of this muscle, in a quadriceps table connected to a transducer, using previously published methodology [24], considering the highest value of 3 repetitions on the dominant leg. The 12MW was the distance subjects could walk at a steady pace on a flat surface for 12 min [25]. The TUG was the time recorded after standing up from a chair, walking a short distance (6 Mt) and re-sitting [26]. The relationship between fat-free mass