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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 Arthritis 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 to 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 contribu-

tion 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 compiled 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

of arms and legs and the strength of the same limb was designated as “muscle quality”, and was expressed as HQ [hand-grip strength/arm FFM (kg/kg)] and QQ [quadriceps strength/leg FFM (kg/kg)].

An ophthalmological examination including fundus was performed by specialists from the Los Andes Ophthalmological Foundation, in DM2 patients. Diagnoses were graded from stage 1 (no retinopathy) to stage 4 (proliferative diabetic retinopathy). The same patients were subject to the measurement of nerve conduction of lower limbs with a Synergy 2000 device, using normal values by Kimura [27]; neuropathy was established whenever three parameters (speed, latency and amplitude) involving at least two different nerves were altered. Creatinine clearance was calculated with MDRD 4 and all diabetic patients were excluded with creatinine clearance <45 ml/min.

Data obtained regarding ApFFM and ApFFMI were compared with international standards [28] as well as Chilean data (laboratory unpublished values), considering a decrease of fat-free mass if values were lower than these cutoff points. Handgrip strength data were compared with reference values obtained in healthy Chilean individuals, according to age and sex [29], considering significantly altered if values were below 1 standard deviation (–1 SD) of those anticipated for age and sex, according to these standards. Reference values for quadriceps strength are not available.

Statistical analyses were performed in Stata 12.0. For group comparisons, T-test or Mann Whitney tests were used depending on distribution. The Chi2 test was used for comparing frequencies. Associations were analyzed by Pearson or Spearman correlation respectively. Multiple linear regres-

sion analysis was also performed to identify variables associated with arm muscle quality and leg muscle quality, as well as logistic regression to assess the effect of intervening variables: >10 years of disease, HbA1c, retinopathy, neuropathy, nephropathy (index microalbuminuria/creatininuria  $\geq$  than 30), diagnosis of sarcopenia and ApFFM on altered HS .

### 3. Results

Table 1 shows the distribution of the measured variables, highlighting significantly higher BMI and triglycerides and lower HDL cholesterol and vitamin D among DM2. 26% of men and 65% of women were obese according to BMI.

Although DM2 women had higher ApFFM and ApFFMI, results were reversed when correcting for BMI, revealing lower ApFFM/BMI ( $p = 0.02$ ) among DM2 patients. DM2 men had significantly less ApFFM compared with ND subjects ( $p = <0.001$ ), and statistical significance is lost when correcting for BMI (Table 2).

A significant correlation between HS and ApFFM among DM2 ( $\rho = 0.4$  in women and  $0.5$  in men,  $p < 0.001$ ) and QS with ApFFM ( $\rho = 0.4$  in women and  $0.5$  in men,  $p < 0.001$ ) was observed. No significant correlation between TUG and 12MW with ApFFM was observed. When expressed as index (correcting for squared height), significant correlations between ApFFMI and QS in DM2 women ( $\rho = 0.31$ ,  $p = 0.01$ ) and ApFFMI with both HS and QS among DM2 men ( $\rho = 0.49$ ,  $p = 0.002$ ,  $\rho = 0.4$ ,  $p = 0.015$ ) were detected.

According to international cut-off points that define sarcopenia using DEXA (<7.2 kg/m<sup>2</sup> for men and <5.5 kg/m<sup>2</sup> for women), values of 2 women and 7 men with DM2 were below

**Table 1 – Characteristics and laboratory tests in type 2 diabetic patients (DM2) and non diabetic (ND) subjects.**

	ND (n = 39)	DM2 (n = 100)	p=
Age (years)	52 (41–60)	55 (41–60)	0.08
Weight (kg)	68 (48–105)	77 (48–131)	<0.001
Height (mt)	1.64 (1.5–1.8)	1.59 (1.5–1.8)	<b>0.04</b>
BMI (kg/m <sup>2</sup> )	26 (20.4–36)	30 (20.3–52)	<0.001
Diastolic BP (mm Hg)	75 (56–100)	81 (53–108)	<0.001
Systolic BP (mm Hg)	120 (90–150)	134 (86–195)	<0.001
Sex (M/F)	13/26	38/62	
Years of DM2		8 (5–27)	
Glucose (mg/dL)	80 (75–115)	141.5 (61–339)	<0.001
Creatinine (g/dL)	0.8 (0.6–1.1)	0.7 (0.4–1.6)	<b>0.05</b>
Total cholesterol (mg/dL)	203 (114–272)	196 (92–345)	0.48
LDL cholesterol (mg/dL)	120 (49–199)	107 (24–171)	0.24
HDL cholesterol (mg/dL)	58 ± 17	43 ± 11.8	<0.001
Triglycerides (mg/dL)	133 ± 73	226 ± 134	<0.001
Hemoglobin (g/dL)	14 (11.4–17.3)	14 (11.7–18)	0.47
Vitamin D (ng/ml)	29 (7.4–63.8)	18 (6–42.7)	<0.001
PTH (pg/dL)	40 (8–95)	26 (9–88)	<0.001
HbA1c (%)		7.2 (5.8–16)	
HbA1c (mmol/mol)		55 (40–151)	
Retinopathy (n)		28	
Micro or Macroalbuminuria (n)		34	
Neuropathy (n)		54	
3 simultaneous microvascular complications		14	

Values expressed as mean (standard deviation (±) or median (range). Comparisons between groups analyzed by T-test or Mann Whitney. BMI: body mass index, BP: blood pressure, LDL: low-density lipoproteins, HDL: high density lipoprotein PTH parathyroid hormone, HbA1c: glycosylated hemoglobin.

Significant differences in bold.

**Table 2 – Body composition in type 2 diabetic patients (DM2) and non-diabetic (ND) subjects.**

	Women		p=	Men		p=
	ND (N = 26)	Diabetic (N = 62)		ND (N = 13)	Diabetic (N = 38)	
TFFM (kg)	37 (30–44)	42 (33–71)	<b>&lt;0.001</b>	57 (47–64)	54 (39–71)	0.53
ApFFM (kg)	15.5 ± 1.7	17.2 ± 2.8	<b>&lt;0.001</b>	26 (DS 2.6)	23 ± 3.3	<b>&lt;0.001</b>
ApFFMI (kg/m <sup>2</sup> )	6.2 (5–7)	7.2 (5–11)	<b>&lt;0.001</b>	8.5 (7.2–9.2)	8 (6.6–10)	0.12
ApFFM/BMI	5.9 (4.2–8)	5.3 (4.4–8)	<b>0.02</b>	8.6 (7.5–10)	8.3 (5.8–10)	0.34

Values expressed as mean ± standard deviation or median (range). Comparisons between groups analyzed by T-test or Mann Whitney. TFFM: total fat-free mass, ApFFM: appendicular fat-free mass, FFMI: appendicular fat free mass index, BMI: body mass index. Significant differences in bold.

these limits, versus 1 woman and 2 men in the ND group ( $p = 0.55$ ). When comparing with cutoffs of the research group (<25th percentile of the expected for a certain height, weight and age = <1.33 and <1.06 for men and women respectively, unpublished data), 9 men and 8 women in the DM2 group, versus 2 men and 8 women of the ND group were considered sarcopenic ( $p = 0.24$ ).

Regarding muscle function, a better performance in the ND group was evident, as observed in Table 3 (12MW, TUG and muscle strength). Differences in 12MW and TUG prevailed after excluding DM2 patients with retinopathy and neuropathy (28 women and 15 men), poor metabolic control (HbA1c > 9% (75 mmol/mol)) and over 10 years of disease (25 women and 19 disease men). Unlike the differences observed in QS, HS differences remained after excluding these same patients. When confronting HS of DM patients with national standards, a decline was evident among the former, i.e. <–1 DS than expected (23 women and 13 men), while among the ND group only one woman fell under this value. Logistic regression models for estimating risk of low HS in diabetics showed that ApFFM was the only predictor in women and years of DM2 and neuropathy in men. HbA1c, retinopathy, nephropathy and sarcopenia (according to international standards), were not significant.

Muscle quality in the upper and lower limbs was significantly lower in DM2 women (Table 3), even after excluding patients with the above mentioned complications, longer time of disease and poor metabolic control. DM2 men exhibited lower muscle quality in the upper extremities. According to the regression model for predicting muscle quality among diabetic female patients, we observed that the remaining significant predictors were presence of diabetes, ApFFM and sarcopenia according to international cutoff points.

According to the WOMAC scale, DM2 had more pain, stiffness and altered performance compared with ND (data not shown). A negative association between pain in the WOMAC scale and 12MW in both ND and DM2 women ( $\rho = -0.4$ ,  $p = 0.002$  and  $\rho = -0.66$ ,  $p < 0.001$ ) and in DM2 men ( $\rho = -0.417$ ,  $p = 0.01$ ) was also detected. A significant association between TUG and pain was observed among both ND and DM2 women ( $\rho = 0.4$ ,  $p = 0.02$  and  $\rho = 0.7$ ,  $p < 0.001$ ) and also among ND men ( $\rho = 0.56$ ,  $p = 0.04$ ). When analyzing the functionality section of the WOMAC scale, a negative association was observed with 12MW in ND and DM2 women ( $\rho = -0.49$ ,  $p < 0.001$  and  $\rho = -0.61$ ,  $p < 0.001$ ) and also in DM2 men ( $\rho = -0.36$ ,  $p = 0.03$ ). As to TUG, associations were significant in both DM2 and ND women ( $\rho = 0.4$ ,  $p = 0.03$  and  $\rho = 0.6$ ,  $p = 0.001$ ). No associations were found between pain, stiffness and functionality in the WOMAC scale with ApFFM, ApFFMI and, muscle quality.

#### 4. Discussion

The main finding of this study was the identification of an early loss of muscle mass and function among adult DM2 patients, under the age of 60 years of age, regardless of duration of disease, metabolic control and characteristic microvascular complications of this condition. The loss of muscle mass was difficult to detect due to patients', specifically women, higher rates of obesity, so the decrease of lean mass among diabetics was evidenced only when correcting ApFFM by BMI, unlike ND where results do not change so dramatically after correcting for BMI.

According to our analysis, DM2 patients exhibited a lower fat-free mass in relation to BMI (especially in females), associated with impaired muscle function, which was premature

**Table 3 – Strength, functionality and muscle quality in type 2 diabetic patients (DM2) and non-diabetic (ND) subjects.**

	Women		p=	Men		p=
	ND (N = 26)	DM2 (N = 62)		ND (N = 13)	DM2 (N = 38)	
12MW (mt)	1153 ± 119	939 ± 168	<b>&lt;0.001</b>	1359 ± 146	1041 ± 150	<b>&lt;0.001</b>
TUG (s)	7.2 (4.3–10)	9.7 (7.5–16)	<b>&lt;0.001</b>	5.5 (4–9)	9.1 (7.4–16)	<b>&lt;0.001</b>
Handgrip strength (kg)	28.1 ± 4.2	24.1 ± 4.5	<b>&lt;0.001</b>	45.3 ± 3.9	39.1 ± 6.3	<b>&lt;0.001</b>
Quadriceps strength (kg)	35.3 ± 5.4	32.5 ± 7.6	<b>0.048</b>	52.8 ± 13	46.9 ± 11	0.06
Arm quality (kg/kg)	13.7 (11–19)	10.6 (5.4–16)	<b>&lt;0.001</b>	13 (10–15)	12 (10–16)	<b>0.03</b>
Leg quality (kg/kg)	6 (3.4–9)	4.7 (1.8–7.7)	<b>&lt;0.001</b>	5.3 (4.2–8.4)	5.5 (3.2–7.1)	0.85

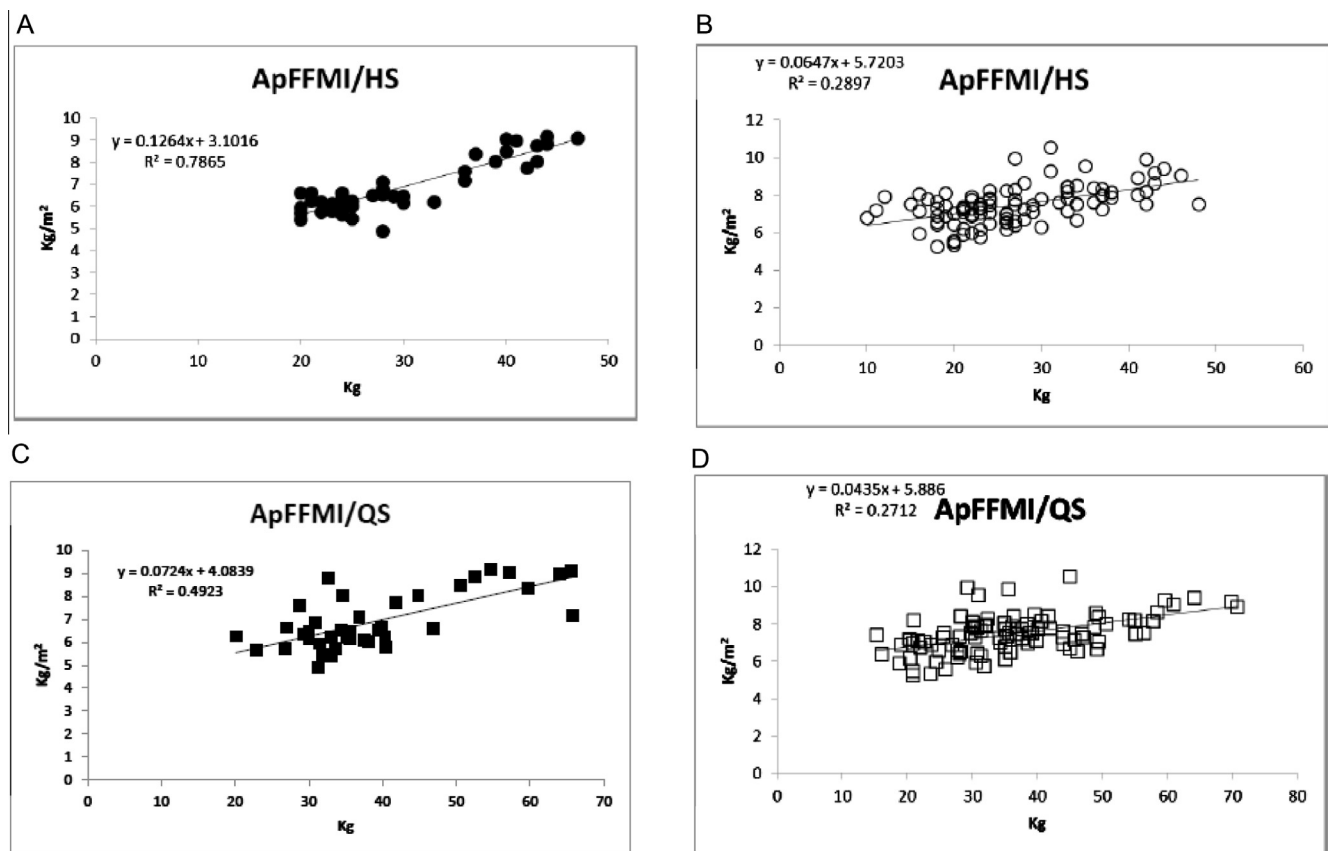
Values expressed as mean ± standard deviation or median (range). Comparisons between groups analyzed by T-test or Mann Whitney. T12 MW: 12 min walking capacity, TUG: Timed up and Go, quality: strength/fat free mass of upper or lower limbs. Significant differences in bold.



considering chronological age, and can therefore be attributable to diabetes itself, independent of the years of disease, metabolic control and microvascular complications. Advanced glycation end-products (AGEs) possibly underlie premature aging of muscle tissue among diabetic patients and animals [30] and obese humans [31]. When analyzing the presence of stiffness, pain and impaired functionality according to the WOMAC scale, we found similar correlations with 12MW and TUG, in both groups (DM2 and ND), but no association with ApFFM or ApFFMI, which suggests that the functional impairment found is connected with the presence of DM2 and not with pain or muscular, joint or skeletal disorders.

Although our findings are consistent with the definition of sarcopenia, there is still no agreement as to the way of establishing this diagnosis, since it involves decline of both skeletal muscle mass and function, which can be assessed through various measures; however consensus on cutoffs are still pending. Moreover, as mentioned above, sarcopenia is a condition wherein various interrelated factors may coincide in an unpredictable way. For instance there is a constantly positive but rather weak relationship between muscle mass and strength, and the influence of immobility and training are variable. In fact, a study on knee extensors including more than 1600 adults showed that the rate of decline in muscle quality is 2.5% per year, while cross-sectional area decreased only 1% per year [10]. Although the latter study included only

elderly individuals, it suggests that decrease in muscle mass is slower than functional deterioration, and it is therefore important to establish early diagnostic criteria and to study the consequences of muscle function decline, before reaching stages that may be evident from a clinical point of view, but difficult to reverse. In older adults, Cruz-Jentoft has proposed a diagnostic algorithm for sarcopenia that involves both mass and function [32], however values proposed for the walking tests are extremely low (<0.8 m/s) and cutoffs of ApFFMI are based on Baumgartner's [33], which are significantly higher than in the Chilean population (unpublished data). If we had applied these criteria among the subjects of the present study, only 3 DM2 patients (1 woman and 2 men) walked at a speed <0.8 m/s, while the ApFFM of a similar number of patients and controls (9 versus 7.7%) was below international standards [34]. Furthermore, the similar ApFFMI between diabetic patients and non-diabetic controls can be explained using an index that corrects for height and not BMI, in a predominantly obese population. ApFFM corrected by BMI can detect deterioration of muscle mass in patients with DM2, i.e. muscle mass is reduced together with a high total body mass, and thus indicative of sarcopenic obesity. Other studies in the elderly have also reported that DM2 patients have higher FFM values compared with ND subjects, attributable to a higher BMI and not to an actual increase of muscle mass [12]. Furthermore, we have gathered evidence indicating that



**Fig. 1 – Correlation plots between appendicular fat free mass index (ApFFMI) and skeletal muscle strength in non diabetic subjects (ND) and type 2 diabetic patients (DM2). (A) Handgrip strength in ND, (B) handgrip strength in DM2, (C) quadriceps strength in ND, and (D) quadriceps strength in DM2.**

lean body mass [35] and muscle strength in Chilean and Mexican population are lower than international standards [29].

The mentioned lower ApFFM/BMI observed in DM2 patients coincided with altered overall functionality (HS, muscle quality, 12MW and TUG), which configures the diagnosis of sarcopenia. Sarcopenic obesity is a matter of concern because it definitively compromises survival in several diseases such as cancer [36] and functionality in the elderly [37]. However there is no consensus on its definition. The review from Stenholm et al. highlights the fact that the mismatch between the decline of muscle mass and strength can be explained by an altered muscle quality, suggesting that functional parameters are better indicators of sarcopenia. These authors also propose that obesity and sarcopenia are somehow causally related due to several factors which have been extensively identified among the elderly [38], but not studied in diabetes mellitus (see Fig. 1).

Our results cannot be attributed to length or complications of diabetes, because they prevailed even after excluding patients who had been on treatment for over 10 years, had poor metabolic control, retinopathy or neuropathy. In agreement, HS was significantly lower in DM2 patients compared with ND, which was confirmed by confronting with the reference values for age and sex [29], where 39 DM2 and only one ND subject were below national standards. Then, as expected, a similar pattern was observed when analyzing muscle quality in upper extremities, i.e. a better performance in the ND group in both sexes. Regarding QS, although performance was also better in the ND group in both sexes, it reached significance only among women, probably due to the smaller sample size of the group of men.

The present study has several weaknesses, including the descriptive cross-sectional design, the limited sample size, the under-representation of men and obese ND subjects, to address the contribution of insulin resistance and secondary chronic low grade inflammation on muscle quality. To confirm our current findings a case control matched design or a longitudinal study to examine secular changes of muscle mass and function in DM2 compared with healthy controls would be desirable. We must clarify, however, that the over-representation of DM2 patients allowed subdividing them for multiple regression analyses, including and excluding patients with complications associated with the disease.

Despite the above, the main strength of this study consists in that it provides information regarding sarcopenia among middle-aged DM2 patients, because literature mostly reports data from older subjects. Our results confirm the premature deterioration of muscle mass and function, i.e. sarcopenia, associated with the condition of DM2, independent of length of disease, metabolic control and microvascular complications. Future studies are necessary to confirm our data and analyze for possible contributing factors.

### Conflict of interest

I declare no conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. Financing: FONIS SA06120037 and INTA, University of Chile.

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