Muscle strength as a predictor of bone fragility in patients with type 2 diabetes mellitus

Hayón-Ponce M[1], García-Fontana B[1,2,3], Avilés-Pérez MD[1,2], González-Salvatierrra S[2,4], Moratalla-Aranda E[2,5], Muñoz-Torres M[1,2,3,6]
1 Unit of Bone Metabolism, Endocrinology and Nutrition. San Cecilio Clinical University Hospital. Granada (Spain)
2 Biosanitary Research Institute of Granada (IBS.GRANADA) (Spain)
3 CIBERFES, Carlos III Health Institute. Madrid Spain)
4 Foundation for Biosanitary Research of Eastern Andalusia (FIBAO). Granada (Spain)
5 Nuclear Medicine. San Cecilio Clinical University Hospital. Granada (Spain)
6 Department of Medicine. University of Granada (Spain)

Summary

Introduction: Most studies have shown a decrease in muscle function and strength in patients with type 2 diabetes mellitus (DM2). However, the relationship between muscle function and bone health in patients with DM2 is not well defined.
Objective: The objective of this study was to analyze the relationship between muscle strength and bone fragility in patients with DM2.
Material and methods: This observational cross-sectional study included 60 patients with DM2 (60% men and 40% postmenopausal women) ranging in age from 49 to 85 years. Demographic, anthropometric, clinical and biochemical variables were studied. Bone mineral density (BMD) in the lumbar spine (LS), femoral neck and total hip was determined using DXA (Hologic QDR 4500), and TBS values (TBS iNsight Software, version 3.0.2.0, Medimaps, Merignac, France). Hand grip (kg/cm^2) was measured with a Jamar® manual hydraulic dynamometer (5030j1; Jackson, MI). To assess the level of mobility and the risk of falls, the Time Up and Go test was carried out. Statistical analysis was performed using the SPSS program (SPSS, inc, v 25.0).
Results: The mean age of the patients was 66.3±8.3 years. The mean HbA1c was 7.7±1.1%, with inadequate glycemic control (HbA1c >7.5%) observed in 73.3% of the patients. 91.7% of the women and 77.8% of the men had low muscle strength. 41.7% of women and 25% of men presented a high risk of falls. Subjects with low hand grip strength and those with high risk of falls had significantly lower TBS values than those with greater hand grip strength (0.99±0.17 vs 1.12±0.15; p=0.03) and low risk of falls (0.94±0.13 vs 1.04±0.19; p=0.02). Patients with normal and partially degraded TBS had greater hand grip strength than subjects with degraded TBS (p=0.031). Hand grip strength was positively associated with TBS (p<0.05) regardless of age, waist circumference, 25OH vitamin D levels, and BMD in LS. There were no significant differences in hand grip strength as a function of BMD values.
Conclusion: Our study shows that the reduction in muscle strength may be related to bone microarchitecture deterioration determined by TBS in patients with DM2.

Key words: type 2 diabetes mellitus, hand strength, bone fragility, Trabecular bone score, bone densitometry.

INTRODUCTION

Type 2 diabetes mellitus (DM2) and osteoporosis are highly prevalent diseases due to the aging of the population that are associated with an increased risk of fragility fractures that substantially increase the morbidity and mortality of the population[1]. Recently, sarcopenia, defined as muscle weakness related to aging, has been recognized as a complication of DM2 that often increases these patients' frailty[2,3].

The musculoskeletal system is closely related, both by its physical connection and by its regulation through multiple common elements. Although muscle has been found to exert an influence on bone through the neuroendocrine system and mechanical forces, their relationship is complex and not entirely well known[4]. Many studies have shown a link between sarcopenia and osteoporosis, but the results are inconsistent due to variable diagnostic criteria and divergent assessment methods for sarcopenia and osteoporosis.

▶▶▶ **Correspondence:** Beatriz García Fontana (bgfontana@fibao.es)

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Most studies have focused on evaluating the relationship between muscle mass and bone mineral density (BMD), while only a few have assessed the effect of sarcopenia on bone quality[5,6]. However, around two thirds of patients with fractures do not present osteoporosis as defined by BMD values[7]. Patients with DM2 have an increased risk of fracture despite having preserved or even increased BMD[1]. These results suggested that BMD alone is insufficient to assess bone strength and estimate fracture risk.

Trabecular bone score (TBS) is a method for assessing the microarchitecture of the trabecular bone using TBS iNsight Software (Medimaps, Merignac, France). It is a simple application technique that permits microstructural analysis of the trabecular bone on DXA scan images of the lumbar spine with a new technological approach on the variation of image texture[8]. Studies carried out to date have shown that the determination of TBS can predict the risk of fracture independently and in addition to BMD both in the general population[9] and in patients with DM2[10].

Sarcopenia was first defined by Rosenberg IH in 1988 as an aging-related loss of muscle mass and function[11]. The state prior to sarcopenia is "dynapenia", defined by Clark BC and Manini TM as a decrease in muscle strength related to aging before the reduction of muscle mass[12], determined through the evaluation of the knee extension strength and hand grip strength.

Our objective was to investigate the relationship between the components of dynapenia determined by hand strength, and bone fragility determined by BMD and bone microarchitecture measured by DXA and TBS in subjects with DM2.

MATERIAL AND METHODS

Study population
A cross-sectional observational study was carried out in which 60 patients with DM2 (60% men and 40% postmenopausal women) between 49 and 85 years old, recruited consecutively from 2016 to 2018 in the reference area of the San Cecilio of Granada Clinical University Hospital.

The exclusion criteria included the presence of other conditions that alter bone metabolism such as the diagnosis of non-osteoporotic metabolic bone disease, chronic diseases, such as rheumatoid arthritis, chronic liver and kidney diseases and active neoplastic diseases, as well as hormone replacement therapy and glucocorticoid or antiosteoporotic treatment.

The study was carried out with the approval of the Ethics Committee of the San Cecilio Clinical University Hospital in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from all study subjects.

Clinical evaluation
Height, weight, and waist circumference (WC) were measured in all patients. Body mass index (BMI) was calculated as weight (kg)/height (m²).

The percentage of total body fat was estimated using a linear anthropometric equation called relative fat mass (RFM) applying the following equation: 64 - (20 x height/ waist circumference) + (12 x sex); sex = 0 for men and 1 for women[13].

The manual hand grip force (kg/cm²) was measured with a Jamar® hydraulic manual dynamometer (5030j1;

Jackson, MI) three times for each hand with the patient seated and the arm resting on a table holding the dynamometer in a vertical position[14], using the average value of these measurements to represent the strength of the hand. Hand grip strength values <27 kg (men) and <16 kg (women) were defined as low muscle strength[15].

To assess the level of mobility and the risk of falls, the Time Up and Go (TUG) test was carried out, which determines the time needed to get up from a chair, walk to a mark located at 3 meters, turn around and sit down again in the chair. A score of less than 12 seconds was defined as low risk of falling and greater than 12 seconds as high risk of falling[16].

Participants completed specific health questionnaires, which included their medical history, drug treatment, tobacco and alcohol use and level of physical activity.

Biochemical determinations
Blood samples were collected from all patients in the morning after an 8 hour overnight fast.

Serum levels of albumin, calcium, phosphorus, creatinine, alkaline phosphatase, insulin, fasting plasma glucose, albumin, and lipid profile (triglyceride and cholesterol levels (high- and low-density lipoproteins)) were measured by standard biochemical methods.

Glycated hemoglobin (HbA1c) was determined by high performance liquid chromatography (ADAMS A1c, HA-8160; Menarini, Florence, Italy) and was expressed as a percentage.

Bone densitometry and TBS
BMD (grams/cm²) in the lumbar spine (LS), femoral neck (FN) and total hip (TH) was determined using a Hologic QDR 4500 densitometer (Whatman, MA) with a coefficient of variation of 1.70%, 1.80% and 1.50% for LS, FN and TH, respectively. The diagnosis of osteoporosis was made based on World Health Organization criteria[17].

TBS was measured in LS using TBS iNsight software version 3.0.2.0 (Medimaps, Merignac, France) with a coefficient of variation of 1.82%. The bone microarchitecture classification was based on the following TBS ranges: TBS greater than or equal to 1.31 corresponded to normal microarchitecture, TBS between 1.23 and 1.31 was defined as partially degraded microarchitecture and TBS equal to or less than 1.23 as degraded microarchitecture[18].

Statistic analysis
Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were expressed as absolute (n) and relative (%) frequencies. The normality of the variables was analyzed using the Kolmogorov-Smirnov test. The difference between continuous variables was determined by Student's t test. The Chi-square test was used to compare the categorical variables. Pearson's correlation coefficient was used to evaluate linear relationships. Values of p<0.05 were considered significant. Multiple linear regression analysis was used to test the association between TBS and variables that influence bone quality, adjusted for other possible confounding factors. P values <0.10 were considered significant.

Statistical analysis was performed using the SPSS statistical program (version 25.0; SPSS, Chicago, IL, USA).

RESULTS

Table 1 shows the characteristics of the study subjects according to sex. The consumption of tobacco and alcohol, as well as cardiovascular disease and the time of evolution of DM2 was greater in men than in women, while women presented higher levels of total cholesterol and LDL cholesterol. Men presented lower RFM values and higher hand grip strength and BMD values in LS and TBS than women.

91.7% of the women and 77.8% of the men had low muscle strength. The prevalence of low muscle strength was analyzed by age group, quartiles of BMI and WC (figure 1). When the prevalence of dynapenia was evaluated by age group, we observed a progressive increase with age (figure 1a). The prevalence of low hand grip strength was higher in the first and fourth quartiles of BMI. The prevalence of low muscle strength by quartiles of WC is shown in figure 1c, the group of the fourth quartile was the one that showed the highest prevalence of low hand grip strength.

According to the results obtained in the TUG test, 25% of men and 41.7% of women had a high risk of falls. Patients with high risk of falls showed significantly lower hand grip strength values than those with low risk of falls (13.8±7.4 vs 18.7±8.1; p=0.027).

81.7% of the patients with DM2 had a degraded microarchitecture (TBS ≤1.23), 13.3% had partially degraded microarchitecture (TBS between 1.23 and 1.31) and 5% had normal values of TBS (TBS ≥1.31). According to the BMD values in LS, 3.7% of the patients were classified in the range of osteoporosis (T-score ≤2.5), 37% in that of osteopenia and 59.3% had a BMD in LS normal. Subjects with normal and partially degraded TBS presented greater hand grip strength than subjects with degraded TBS (p=0.031). However, there were no significant differences in hand grip strength between subjects with osteopenia/osteoporosis compared to those with normal BMD.

Mean DM2 evolution was 14.9±8.7 years with inadequate glycemic control in 73.3% of the patients. Patients with a high risk of falls had longer term DM2 evolution than those with a low risk of falls (18.1±8.9 vs 13.1±8.1 p=0.037). Patients with adequate metabolic control (HbA1c <7.5%) showed greater hand strength, although no significant differences were observed with respect to the group with worse metabolic control. No significant association was observed between insulin treatment (66.7%) and the risk of falls or the presence of fractures.

Simple correlation analysis showed a significant positive association of weight with BMD in LS (r=0.372; p<0.01), FN (r=0.430; p<0.01) and TH (r=0.547; p<0.01) and negative with TBS (r=-0.369; p<0.01). Both WC and BMI were significantly associated with BMD in TH (positive) (r=0.464; p<0.01) and (r=0.418; p<0.01), respectively, and with TBS (negative) (r=-0.402; p<0.01) and (r=-0.624; p<0.001). RFM was negatively correlated with TBS in both men (r=-0.620; p<0.001) and women (r=-0.410; p<0.05) while hand strength was positively associated with TBS (r=0.326; p<0.05). Although we did not observe a significant correlation between BMI, WC and RFM with the manual grip strength, we did find a significant progressive decrease in the grip strength of the hand with the increase in the quartiles of RFM (p<0.001) (figure 2).

Given the significant relationship between bone quality measured by TBS and hand grip strength, a subgroup analysis of hand grip strength was carried out.

Subjects with low hand grip strength had significantly lower TBS values than those with greater hand strength (0.99±0.17 vs 1.12±0.15; p=0.03). Although there was no significant correlation between the TUG test and TBS, lower TBS values were also observed in subjects with high risk of falls versus those with low risk of falls (0.94±0.13 vs 1.04±0.19; p=0.02) (figure 3). There were no significant differences in BMD values in both groups. As shown in figure 4a, mean values of hand grip strength showed a progressive decrease according to the TBS categories. Furthermore, the percentage of patients presenting degraded TBS (TBS <1.23) showed a decreasing trend with increasing quartiles of hand grip strength (figure 4b).

To determine the variables that influence the TBS (dependent variable), a multiple linear regression analysis was performed adjusting for the effect of age, WC, manual grip strength, levels of 25 (OH) vitamin D and BMD in LS. Our results showed that WC (B=-0.491, [-0.013-/-0.004], p=0.001) negatively affect TBS values while hand grip strength (B=0.284, [0.000-0.013], p=0.038) exerts a positive effect on the bone microarchitecture determined by TBS.

DISCUSSION

Loss of muscle mass and strength, called sarcopenia and dynapenia respectively, has recently been recognized as a complication associated with diabetes mellitus[3]. Mori, et al. observed that the prevalence rate of dynapenia was higher than sarcopenia in patients with DM2[19]. The European Working Group on Sarcopenia in the Elderly (EWGSOP)[15] and the Asian Working Group on Sarcopenia (AWGS)[20] consider hand grip strength as a simple method that reliably predicts deterioration in muscular function. The prevalence of sarcopenia in DM2 varies between 5% and 50% in the different studies carried out to date[21]. In a recently published meta-analysis, it were patients with DM2 reportedly had lower muscle strength than non-diabetic patients, despite no difference in muscle mass[22]. In our study, the prevalence of low muscle strength was 83.3 %.

When analyzing the prevalence of low hand grip strength, we observed a progressive decrease with increasing age. Not surprisingly, increasing age represents a risk factor for low muscle strength in DM2, as well as in the general population, due to age-related decline in muscle mass and strength. However, it would be interesting to know if the age factor could be more decisive for the development of dynapenia and sarcopenia in individuals with DM2 compared to non-diabetic patients.

In this regard, Tamura, et al. did not show differences in the risk of sarcopenia according to age categories between individuals with and without DM2[23]. Similarly, Çeliker, et al. and Trierweiler, et al. observed a higher prevalence of sarcopenia in individuals with DM2 compared to those without DM2, while no significant differences were observed in terms of age[24,25].

In previous studies, too low or too high a BMI and a high percentage of body fat have been associated with higher mortality[26]. According to the results of the body composition analysis, the prevalence of low muscle strength was higher in the first and fourth quartiles of BMI. However, the evaluation of the relative fat mass showed a significant progressive decrease in the manual grip strength with the increase of the quartiles of RFM. This finding suggests that diabetic patients with a high

Table 1. Demographic characteristics and clinical variables

	Total (n=60)	Man (n=36)	Woman (n=24)	p
Age (years)	66.35±8.09	66.19±7.62	66.58±8.92	0.857
Weight (Kg)	83.89±13.06	86.37±10.68	80.18±15.50	0.072
Size (cm)	165.09±8.25	169.54±6.32	158.42±6.03	<0.001*
BMI (kg/m^2)	30.80±4.60	30.11±3.95	31.86±5.36	0.152
WC (cm)	103.83±11.44	104.60±9.42	102.95±13.58	0.635
RFM (%)	69.28±6.06	63.67±0.03	75.69±0.04	<0.001*
Smoker (%)	56.7	75.0	29.2	<0.001*
Alcohol (%)	23.3	33.3	8.3	0.025*
Sedentary lifestyle (%)	11.8	13.9	4.5	0.163
Hypertension (%)	83.3	86.1	79.2	0.480
Dyslipidemia (%)	88.3	88.9	87.5	0.870
Overweight/Obesity (%)	86.7	88.9	83.4	0.535
Cardiovascular disease (%)	45.0	63.9	16.7	<0.001*
Microvascular complications (%)	33.3	41.7	20.8	0.094
Falls (%)	30.0	25.0	37.5	0.301
Fractures (%)	13.3	11.1	16.7	0.535
Basal glucose (mg/dl)	147.97±52.27	144.08±51.03	153.79±54.66	0.486
HbA1c (%)	7.70±1.13	7.64±1.24	7.79±0.96	0.612
Time evolution of DM2 (years)	14.93±8.68	16.81±9.21	12.13±7.10	0.031*
Total cholesterol (mg/dl)	162.65±44.06	150.33±39.06	181.13±45.44	0.007*
HDLc (mg/dl)	45.35±12.19	42.14±10.36	50.17±13.33	0.054
LDLc (mg/dl)	87.83±36.84	80.36±32.66	99.04±40.48	0.01*
Triglycerides (mg / dl)	155.02±74.55	146.61±71.84	167.63±78.26	0.289
Hand grip (Kg)	17.29±8.12	22.50±5.62	9.47±3.82	<0.001*
TUG (s)	11.74±4.35	10.39±2.75	13.70±5.45	0.01*
BMD_LS (gr/cm^2)	1.07±0.22	1.12±0.23	0.99±0.16	0.032*
BMD_FN (gr/cm^2)	0.82±0.15	0.84±0.14	0.78±0.17	0.157
BMD_TH (gr/cm^2)	1.04±0.17	1.07±0.17	0.99±0.18	0.082
TBS	1.01±0.18	1.06±0.17	0.94±0.17	0.012*

RFM: relative fat mass; BMI: body mass index; WC: waist circumference; HbA1c: glycated hemoglobin; HOMA2-IR: insulin resistance index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TUG: test Time Up and Go; TBS: Trabecular bone score; BMD: bone mineral density; LS: lumbar spine; FN: femoral neck; TH: total hip; SD: standard deviation. Continuous variables are expressed as mean ± SD. Categorical variables are expressed as percentages. P values were determined using Student's t test for continuous variables and the Chi-square test for categorical variables. * Significance level <0.05.

percentage of body fat and a low or too high BMI present an increased risk of developing dynapenia. Furthermore, our results showed an inverse association between WC and TBS, suggesting a predictive role for WC regardless of age, hand grip strength, 25(OH) vitamin D levels and BMD in LS. These results support the role of central fat mass in bone microarchitecture determined by TBS[27,28]. Therefore, the assessment of obesity in diabetic patients should not focus solely on BMI. Rather, it should be considered in combination with body fat mass.

Although the link between sarcopenia, risk of falls, and risk of fractures has been studied in the general population, there are few studies that have examined the clinical impact of sarcopenia and bone fragility in patients with DM2. Our study analyzed the relationship between hand strength and bone fragility measured by BMD determined by DXA and the bone microarchitecture estimated by TBS in patients with DM2.
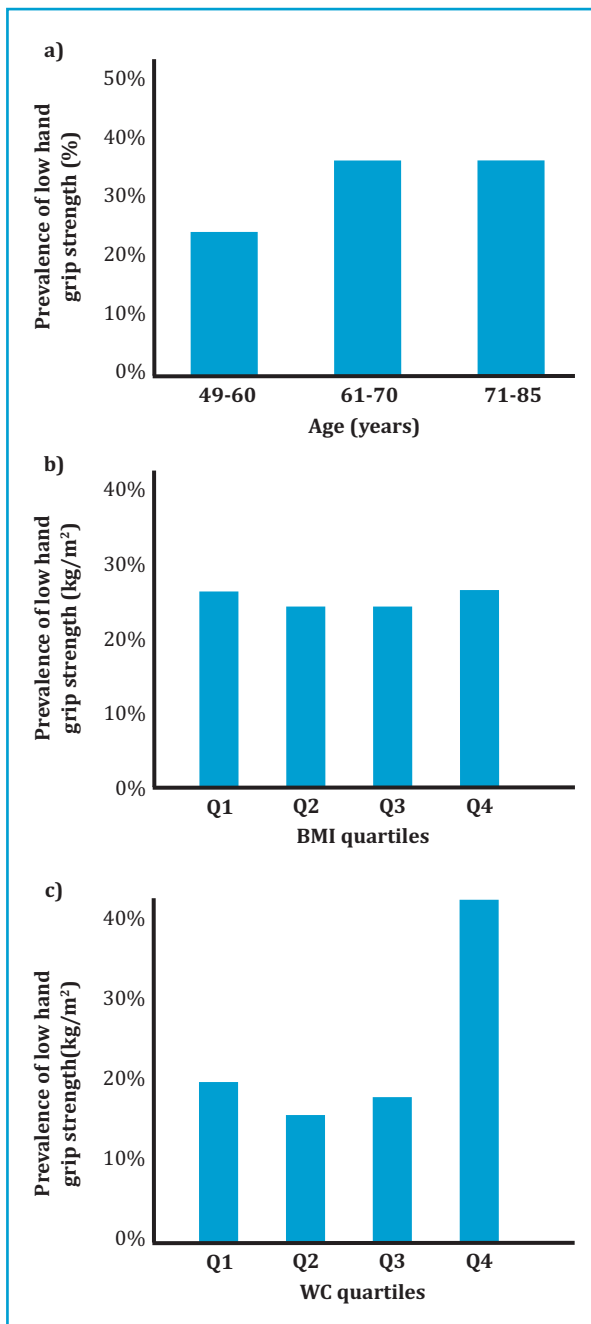
There are inconsistent results regarding the relationship between hand grip strength and BMD. Aydin's group concluded that hand grip strength was not a good predictor of BMD in men[29] while Pereira's group did observe a significant correlation between hand grip strength and BMD[30]. In our study, we did not observe an association between hand grip strength and BMD.

Most of the studies that have evaluated the relationship between sarcopenia and bone quality have used data derived from invasive techniques such as quantitative computed tomography (QCT), presenting a limitation in routine clinical practice due to its low availability[31,32]. TBS is a non-invasive technique for evaluating bone quality that can predict the risk of fracture independently and in addition to BMD in patients with DM2[10]. In our study, we observed a positive relationship between hand grip strength and TBS values. Subjects with lower hand grip strength had lower TBS values and a decreasing trend was observed in the prevalence of degraded TBS (TBS <1.23) with increasing hand grip strength quartiles. In agreement, our results showed a positive association between TBS and manual grip strength independent of the effect of age, WC, levels of 25 (OH) vitamin D and BMD in LS in the multivariate analysis. These findings suggest that the measurement of manual grip strength could be an easily implemented strategy to estimate the state of bone microarchitecture in clinical practice.

Our results concur with the study carried out by Hanmei's group, which showed that TBS was positively correlated with hand grip strength in women[33] and with the STRAMBO study, which showed that bone size and not bone size BMD seemed to correlate mainly with muscle mass, while bone microarchitecture was mainly correlated with muscle strength[32]. Our results confirm previous data and suggest that muscle strength has a greater influence on bone quality than on BMD and may reflect a deterioration of bone microarchitecture more reliably than bone status measured by BMD. Therefore, low muscle strength could be a good predictor of bone fragility measured by TBS in patients with DM2.

Both sarcopenia and dynapenia increase the risk of falls in patients with DM2[19]. The TUG test assesses the level of mobility and the risk of falls and is an indicator of severe sarcopenia[15]. Lower TBS values and hand strength in patients with a higher risk of falls suggests that the higher risk of fragility fractures in these patients could be related to the coexistence of severe sarcopenia and deterioration of the microarchitecture trabecular

Figure 1. Prevalence of low hand grip strength: a) Evaluation of low hand grip strength by age; b) Evaluation of low hand grip strength by BMI quartiles; c) Evaluation of low manual grip strength by quartiles of WC
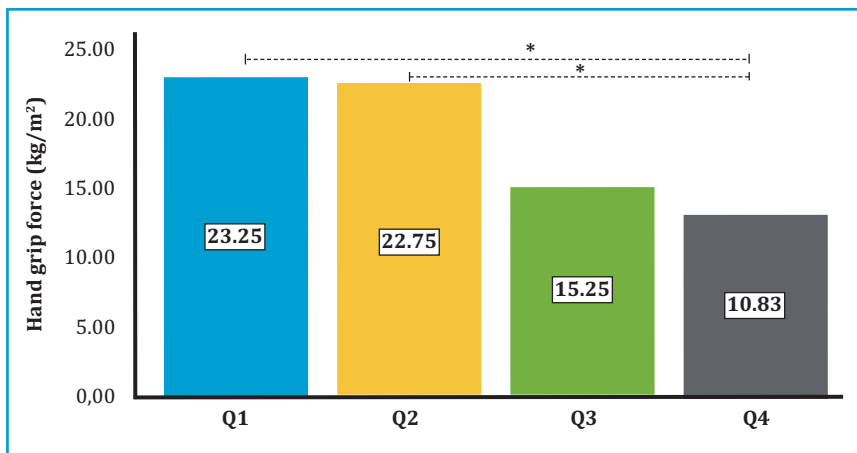

BMI: body mass index; Q1, first quartile, <27.9 kg/m^2; Q2, second quartile, 27.9-30.7 kg/m^2; Q3, third quartile, 30.8-33.9 kg/m^2: Q4, fourth quartile >33.9 kg/m^2. WC: waist circumference; Q1, first quartile, <96 cm; Q2, second quartile, 96-104 cm; Q3, third quartile, 104.1-111.5 cm; Q4, fourth quartile >111.5 cm.
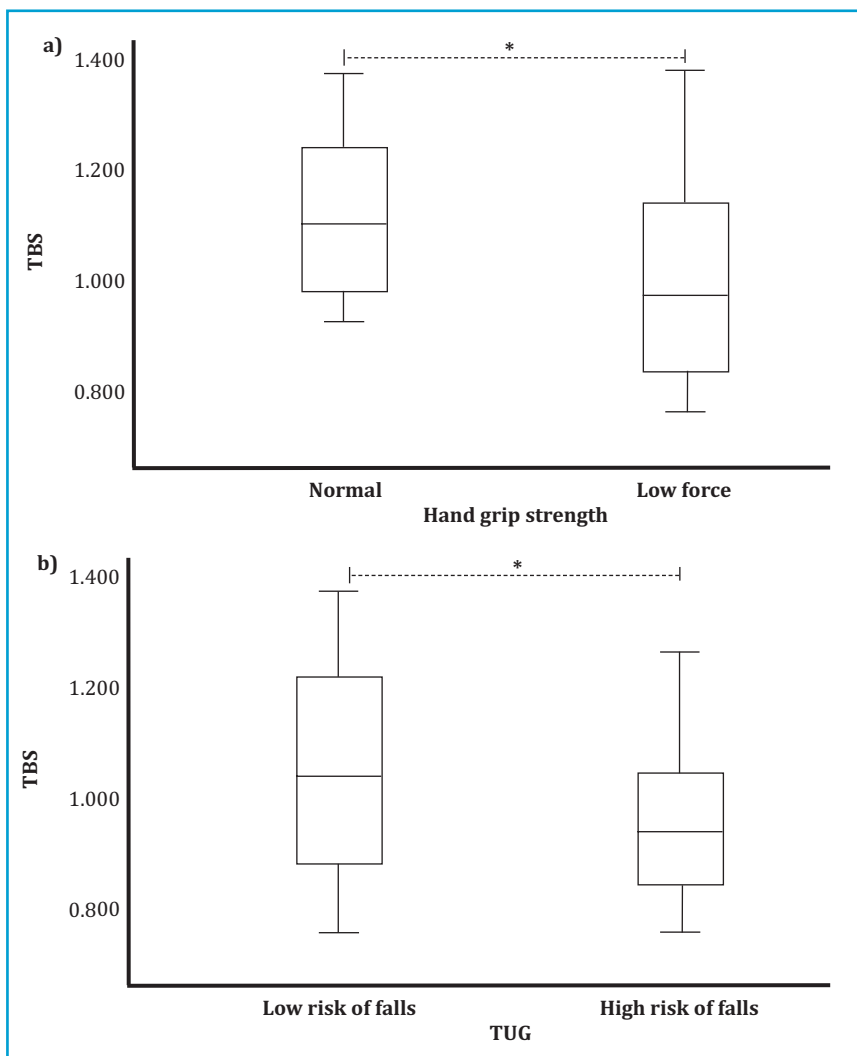
bone despite increased BMD.

The etiology of the effect of DM2 on the musculoskeletal system is multifactorial and not entirely well known[34]. Previous studies suggest that a longer duration of diabetes and sustained hyperglycemia affect muscle weakness in patients with DM2[35]. In our study, patients with a high risk of falls had a greater evolution of DM2 than those with a low risk of falls. However, we did not observe significant differences in the time of evolution of

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Figure 2. Hand strength and quartiles of RFM

Hand grip force (kg/cm²) was measured with a Jamar® RFM hydraulic hand dynamometer: relative fat mass. Q1, first quartile, <63.6; Q2, second quartile, 63.6-63.7; Q3, third quartile, 63.8-75.7: Q4, fourth quartile >75.7. * Significance level <0.01.

Figure 3. Effect of hand strength and risk of falls on TBS

Hand grip force (kg/cm²) was measured with a Jamar® hydraulic hand dynamometer. Hand grip strength values <27 kg (men) and <16 kg (women) were defined as low muscle strength. The risk of falls was assessed using the Time up and Go test. A score of less than 12 seconds was defined as low risk of falling and greater than or equal to 12 seconds, high risk of falling. TUG: test Time Up and Go; TBS: Trabecular bone score. P values were determined using Student's t test. * Significance level <0.05.
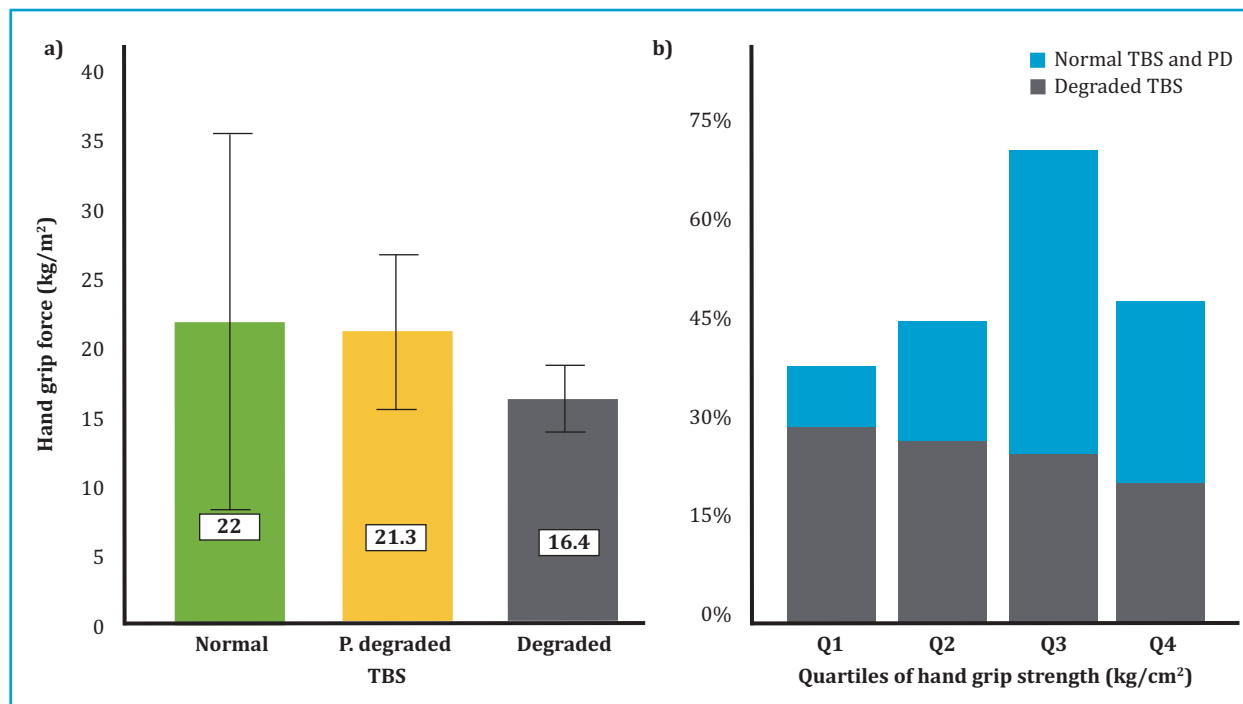
the disease between subjects with normal or decreased muscle strength. Some studies have reported a higher prevalence of sarcopenia associated with longer term diabetes[36]. However, other studies have not found a relationship between the prevalence of sarcopenia and the time of DM2 evolution[22].

A recent study has shown that hyperglycemia itself reduces muscle mass through increased KLF15 in myocytes[37]. On the other hand, Kalyani, et al. observed that HbA1c is associated with weakness in muscle strength independent of muscle mass[35]. In agreement, our results showed that patients with adequate metabolic control (HbA1c <7.5%) presented greater muscle strength in the hand, although no significant differences were observed between both groups, probably due to the limited number of patients included in the study. However, previous studies have not found a relationship between metabolic control and muscle strength[38]. Therefore the prevention of the development of dynapenia and sarcopenia cannot be exclusively focused on metabolic control, in older patients, especially in elderly patients. Other factors must be taken into account, such as the presence of micro and macrovascular complications, body composition, nutritional status, and life expectancy, which determine morbidity and mortality.

Our study has certain limitations. First, the cross-sectional design of the study allowed investigating the association between study variables, but not causality. Second, the sample size was relatively small; however, our participants are representative of patients with DM2 in daily clinical practice. Third, we did not assess muscle mass, which is a determinant of sarcopenia, although when the components of sarcopenia have been examined individually in other studies, only low muscle strength was associated with recurrent incidence of falls, independent of muscle mass or gait speed[39].

Despite these limitations, to our knowledge, the present study is the first to investigate

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Figure 4. a) Mean values of manual pressure force according to the TBS categories. b) Prevalence of degraded bone microarchitecture (TBS ≤1.23) according to quartiles of hand grip strength

Hand grip force (kg/cm^2) was measured with a Jamar® hydraulic hand dynamometer. TBS: Trabecular bone score; PD: partially degraded. The classification of bone microarchitecture was based on the following TBS ranges: TBS ≥1.31 corresponded to normal microarchitecture, TBS between 1.23 and 1.31 was defined as partially degraded microarchitecture and TBS ≤1.23 as degraded microarchitecture. Q1, first quartile, <9.5 kg/cm^2; Q2, second quartile, 9.5-19.7 kg/cm^2; Q3, third quartile, 19.8-23.5 kg/cm^2; Q4, fourth quartile >23.5 kg/cm^2.

the association between manual grip strength and TBS in patients with DM2.

In conclusion, our study suggests that patients with DM2 present a high prevalence of age-related decrease in muscle strength. The results of the body composition analysis highlight the importance of assessing fat mass rather than assessing BMI in diabetic patients at risk of sarcopenia. A low or too high BMI and a high percentage of body fat tend to increase the risk of developing dynapenia. The TBS in patients with DM2 is usually low despite an increased BMD. Muscle strength was significantly associated with a deterioration in bone microarchitecture. The decrease in manual grip strength and the TUG test can be an easily applied tool in routine clinical practice to identify patients with DM2 at risk of falls and osteoporotic fractures.

▶▶ **Conflict of interests:** The authors declare no conflict of interest.

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