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REVIEW

Association between sarcopenia and diabetes: a systematic review and meta-analysis of observational studies

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Key summary points

Aim To summarize the prevalence of diabetes in people with sarcopenia (and vice versa) through a meta-analytic approach of available observational studies.

Findings In this work, we have presented the findings of the first full methodological systematic review and meta-analysis of observational studies exploring the relationship between diabetes and sarcopenia. Our findings overall emphasize the reciprocal relationship between diabetes and sarcopenia in terms of risk of occurrence, that is sarcopenia increases the risk of diabetes being present and vice versa.

Message This study provides support for further research into the prognosis of people with both diabetes and sarcopenia and the value of interventional strategies in sarcopenia to minimize adverse outcomes such as premature death, hospitalization, and disability.

Abstract

Purpose Sarcopenia and diabetes are two common conditions in older people. Some recent literature has proposed that these two conditions can be associated. However, to date, no attempt has been made to collate this literature. Therefore, we aimed to summarize the prevalence of sarcopenia in diabetes (and vice versa) and the prevalence of sarcopenia in people with diabetes complications, through a systematic review and meta-analysis.

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Methods Two authors searched major electronic databases from inception until March 2019 for case control/cross-sectional/longitudinal studies investigating sarcopenia and diabetes. The strength of the reciprocal associations between sarcopenia and diabetes was assessed through odds ratios (ORs) with 95% confidence intervals (CIs), adjusted for potential confounders, where possible.

Results From 953 potential eligible articles, 20 were included in the systematic review, with 17 providing data for meta-analysis. Overall, 54,676 participants were included (mean age = 65.4 years). Diabetic participants had an increased prevalence of sarcopenia compared to controls ($n = 10$; OR = 1.635; 95% CI 1.204–2.220; $p = 0.002$; $I^2 = 67\%$), whilst, after adjusting for potential confounders, sarcopenia was associated with an increased odds of having diabetes (OR = 2.067; 95% CI 1.396–3.624; $p < 0.0001$; $I^2 = 0\%$). In 1868 diabetic participants with a complication, there was an increased prevalence of sarcopenia (OR = 2.446; 95% CI 1.839–3.254; $p < 0.0001$; $I^2 = 0\%$), as compared with those with no complication. Very limited data existed regarding studies with a longitudinal design.

Conclusions Our study suggests a bidirectional association between diabetes and sarcopenia, particularly when diabetic complications are present.

Keywords Diabetes · Sarcopenia · Physical performance · Meta-analysis

Introduction

The prevalence of diabetes mellitus (DM) is increasing worldwide, particularly in older age. This is due in part to increased survival owing to advances in the management of DM and of DM comorbidity [1, 2] and in part due to increasing population age and urbanisation of lifestyle [3]. During the last decade there has been increasing recognition of other diabetes-related complications such as frailty and sarcopenia which have become areas of new research interest [4].

Sarcopenia is the pathological loss of skeletal muscle mass associated with the loss of power and function [5, 6]. It is reported that sarcopenia affects approximately 10% of older people [7] and this condition, similarly to diabetes, is associated with several negative outcomes in older people, including premature mortality, re-hospitalization and disability [8, 9]. As skeletal muscle plays a major role in glucose metabolism and if altered can lead to insulin resistance [10], it has been postulated that sarcopenia and diabetes may be associated [4]. Epidemiological studies suggest that diabetes is related to an accelerated decrease in physical performance and muscle strength parameters [11–13] and consequently may lead to sarcopenia, whilst conversely, sarcopenic patients can be at an increased risk of diabetes, e.g., for higher sedentary behaviour prevalence [14].

Studies of sarcopenia in older people with diabetes are few and there is a lack of an in depth analysis of observational studies in this area [15]. Given this background, we aimed to summarize the prevalence of sarcopenia in diabetes (and vice versa) and the prevalence of sarcopenia in people with diabetes and macro- or micro-angiopathy complications versus those without, through a systematic review and meta-analysis of observational studies regarding this topic.

Methods

This systematic review adhered to the PRISMA [16] and MOOSE [17] statements and followed a structured, but unpublished protocol.

Data sources and literature search strategy

Two investigators (NV and DP) independently conducted a literature search using PubMed, EMBASE, SCOPUS, Cochrane Central Register of Controlled Trials and Clinicaltrials.gov without language restriction, from database inception until 01st March 2019 for observational studies investigating the prevalence of sarcopenia in participants with diabetes (vs. those without) and vice versa. Moreover, we included studies assessing the prevalence of sarcopenia in participants with diabetes and its usual macro- or micro-angiopathy complications vs. people with diabetes but without complications. Any inconsistencies were resolved by consensus with a third author (SM).

In PubMed, the following search strategy was used: "diabetes [tiab] AND sarcopenia [tiab]". Conference abstracts and reference lists of included articles were hand-searched to identify any potential additional relevant articles.

Study selection

Inclusion criteria for this meta-analysis were: (1) diagnosis of diabetes (e.g., self-reported, according to the American Diabetes Association criteria [18]) not limited only to type 2; (2) diagnosis of sarcopenia: in this case we included standardized methods of determining sarcopenia (e.g., Asia Working Group for Sarcopenia, AWGS [19] or European Working Group on Sarcopenia in Older People, EWGSOP [5] criteria) or diagnosis through body composition or muscle mass/physical performance parameters, according

to validated criteria. Studies were excluded if: (1) did not include humans; (2) did not report any meta-analysable data.

Data extraction

Two independent investigators (NV and DP) extracted key data from the included articles in a standardized Excel sheet. A third independent investigator (SM) checked the extracted data. For each article, we extracted data on authors, year of publication, country, setting, condition, number of participants, demographics (mean age, mean body mass index, BMI), diagnostic criteria for diabetes and sarcopenia, main findings for each paper, number and type of covariates used in multivariable analysis.

Outcomes

The primary outcomes considered were the prevalence of sarcopenia in diabetes and vice versa and the prevalence of sarcopenia in people with diabetes and macro- or micro-angiopathy complications (vs. those without). The data should be reported as number of events or as adjusted odds ratios (ORs).

Assessment of study quality

The Newcastle–Ottawa Scale (NOS) [20, 21] was used to assess study quality. The NOS assigns a maximum of nine points based on three quality parameters: selection, comparability, and outcome, with a cut-off of ≤ 5 being indicative of high risk of bias. NOS scores were assessed by two investigators (DP, NV) and a consensus was reached in case of discrepancy [20, 21].

Data synthesis and statistical analysis

All analyses were performed using Comprehensive Meta-Analysis (CMA) three. Only outcomes having at least three studies were meta-analysed; the other outcomes were summarized descriptively.

The primary analysis compared the prevalence of sarcopenia in diabetes and vice versa and the prevalence of sarcopenia in people with diabetes and macro- or micro-angiopathy complications (vs. those without), applying a random-effect model [22]. The data were reported as ORs with their 95% confidence intervals (CIs).

Heterogeneity across studies was assessed by the I^2 metric. Given significant heterogeneity ($I^2 \geq 50\%$ and/or $p < 0.05$) [23] and having at least 10 studies for each outcome, meta-regression analyses were carried out, taking as moderators the following factors: mean age and the difference in mean age between diabetic and controls, NOS score, the diagnostic criteria of diabetes or sarcopenia.

Publication bias was assessed by a visual inspection of funnel plots and calculating the Egger bias test [24]. We also reported the fail-safe number (i.e., the number of studies bringing alpha over the p value) and trim and fill analyses were performed [25].

For all analyses, a p value less than 0.05 was considered statistically significant.

Results

Search results

As shown in eFig. 1, altogether, the searches gave 953 non-duplicated articles. After excluding 920 articles based on title/abstract review, 33 articles were retrieved for full text review. Among these, 20 studies were included in the systematic review [26–45] and 17 of them in the meta-analysis: two studies, in fact, were longitudinal [41, 42] and another one adjusted estimates for the association between diabetic complications and sarcopenia, without reporting the prevalence of sarcopenia in those having diabetes complications [26].

Study and patient characteristics

Table 1 summarizes the data regarding the included studies. Overall, 54,676 participants were included having a mean age of 65.4 years (SD = 11.2), with a mean BMI of 25 (SD = 3.7). Of the 20 studies included, the majority ($n = 14$) were carried out in Asia. Seven studies investigated participants having type two diabetes and six studies used the criteria suggested by the AWGS that defined sarcopenia as low skeletal muscle mass plus low muscle strength and/or low physical performance according to predefined criteria [19]. All the studies used diagnosis of diabetes validated by a physician or using medical data.

Looking to the main findings of the included articles, we observed a significant association between diabetes and sarcopenia and vice versa.

The median NOS was 6 (range 3–8), indicating a sufficient quality of the studies included.

Prevalence of sarcopenia in diabetes

Figure 1 reports the prevalence of sarcopenia in participants with diabetes versus controls. In patients with diabetes, the prevalence of sarcopenia was 28.4% (95%CI 18.9–40.2), whilst in the control group was 18.7% (95%CI 11.9–28.1). Ten studies were included, overall showing that diabetic participants had an increased prevalence of sarcopenia compared to controls ($n = 10$; OR = 1.635; 95% CI 1.204–2.220; $p = 0.002$; $I^2 = 67\%$). The meta-regression analysis (using as moderators mean age and the difference in mean age between diabetic and controls, NOS score, the diagnostic

Table 1 Descriptive characteristics of the studies included

Author, year	Country	Type of diabetes (or complication)	Diabetes diagnosis	Diagnosis of sarcopenia	Sample size	Mean age (SD)	Mean BMI (SD)	Covariates	NOS	Main findings
Bouchi, 2017	Japan	LADA	PD	AWGS	61	65 (10)	24 (4.4)	Age, gender, BMI, HDL	7	Patients with LADA are at a high risk for sarcopenia compared to control subjects
Bouchi, 2017	Japan	Type 2	PD	AWGS	249	65 (10)	25.4 (4.1)	Age, gender, BMI, HDL	7	Patients with T2DM are at a high risk for sarcopenia compared to control subjects
Bouchi, 2017*	Japan	Albuminuria	PD	AWGS	238	64 (12)	25.4 (4.1)	Age, gender, BMI, visceral fat area, insulin resistance	5	Sarcopenia is a significant determinant of albuminuria in patients with T2DM
Çeliker, 2018	Turkey	Nephropathy	PD	EWGSOP	159	60.9 (6.9)	31.4 (5.1)	Gender	6	The prevalence of sarcopenia was higher in patients with diabetic nephropathy compared to controls
Cheng, 2017	China	Diabetic foot	PD	Low SMI (< 7 kg men; 5.2 women)	1105	66.6 (10.5)	24.03 (3.55)	Gender, age, diabetes duration, diabetic foot duration, BMI, smoking, hypertension, creatinine, White Blood Cell, HbA1c, kidney disease, retinopathy, neuropathy, peripheral arterial disease, medications (metformin, insulin secretagogues, insulin, ACEI/ARB and diuretics)	5	Sarcopenia is independently associated with diabetic foot

Table 1 (continued)

Author, year	Country	Type of diabetes (or complication)	Diabetes diagnosis	Diagnosis of sarcopenia	Sample size	Mean age (SD)	Mean BMI (SD)	Covariates	NOS	Main findings
Cuthbertson, 2016*	Ireland	Type 2	PD	Lowest tertile of handgrip strength	5953	65 (10)	29.5 (4.8)	Age, gender, BMI, smoking, alcohol, physical activity, depressive symptoms and prevalent cardiovascular disease	8	Sarcopenia is associated with increased risk of incident T2DM in older people
de Freitas, 2018	Brasil	Not specified	PD	EWGSOP	76	> 60	NA	Sex, diabetes, beta-blockers use, cardiovascular disease, BMI, physical activity level, smoking habit	3	Similar prevalence of diabetes in sarcopenia and controls
Fukuda, 2017	Japan	Retinopathy	PD	AWGS	316	65 (12)	24.3 (3.3)	Age, gender, BMI, body fat and the use of angiotensin receptor blockers	5	Diabetic retinopathy was associated with sarcopenia and muscle quality in patients with T2DM
Han, 2015	China	Not specified	PD	AWGS	769	67.3 (6)	25.5 (3.5)	Age, BMI, widowed, living alone, illiteracy, farming, drinking, diabetes, peptic ulcer, pulmonary disease	7	Sarcopenia prevalence is significantly higher in males, but not in females
Handajani, 2018	Indonesia	Not specified	PD	ASMMI < 7.26 in men or 5.45 in women	118	71.8 (7.9)	NA	Gender, diabetes mellitus, ADL-disability, carbohydrate and energy intake	6	Diabetes is a significant risk factor for severe sarcopenia
Kim 2014	Korea	Type 2	PD	ASMMI < 7.40 in men or 5.14 in women	810	71 (5)	24.5 (3.5)	Age, BMI, current smoking, blood pressure, lipid levels	6	The risk of sarcopenia was approximately two- to fourfold higher in older adults with T2DM
Koo, 2016	Korea	Not specified	PD	Janssen criteria	12,792	> 45	24.2 (3.5)	Age	8	Sarcopenia was significantly associated with recent-onset diabetes only in patients aged ≥ 75 years

Table 1 (continued)

Author, year	Country	Type of diabetes (or complication)	Diabetes diagnosis	Diagnosis of sarcopenia	Sample size	Mean age (SD)	Mean BMI (SD)	Covariates	NOS	Main findings
Kreidieh, 2018	Lebanon	Type 2	PD	FNIH criteria	184	NA	30.01 (5.57)	Lifestyle factors (i.e., sedentary lifestyle, fast-food consumption, and smoking) and central adiposity	8	Sarcopenic obesity increases the odds of having T2DM by 550%
Lim, 2018	Korea	Not specified	PD	ASMMI < -1 SD of a reference population	3492	68.8 (8.2)	NA	Age, gender, appendicular skeletal muscle, moderate physical activity, smoking, drinking, and nutrient intake	3	The sarcopenic-obesity group had the highest ratio of diabetes compared to the other groups
Ma, 2016	USA	Type 2	PD	24 h urine creatinine excretion	769	69.7	NA	Age, sex, ethnicity	6	Older adults with sarcopenic obesity had more adverse midlife cardiometabolic risks, particularly diabetes 10 years earlier
Moon, 2013	Korea	Not specified	PD	Janssen criteria	10,432	48.3 (15.5)	23.5 (3.2)	Age, sex, region, smoking, alcohol consumption, regular exercise, and family income	6	Sarcopenia was found to be a risk factor for diabetes in the non-obese group
Murata, 2017	Japan	Macroangiopathy	PD	AWGS	288	73.3 (6.1)	24.5 (3.5)	Age and BMI	5	No difference of macroangiopathy in sarcopenia vs. controls
Murata, 2017	Japan	Retinopathy	PD	AWGS	288	73.3 (6.1)	24.5 (3.5)	Age and BMI	5	No difference of retinopathy in sarcopenia vs. controls
Srikanthan, 2010	USA	Not specified	PD	FNIH criteria	14,528	45	26.3 (NA)	Age, sex, race, education.	8	Sarcopenia is associated with diabetes and the association is strongest in individuals under 60 years of age

Table 1 (continued)

Author, year	Country	Type of diabetes (or complication)	Diabetes diagnosis	Diagnosis of sarcopenia	Sample size	Mean age (SD)	Mean BMI (SD)	Covariates	NOS	Main findings
Trierweiler, 2018	Brazil	Type 2	PD	FNIH and low handgrip strength	166	65.9 (8.8)	27.0 (3.6)	BMI, dyslipidemia, healthy nutrition, osteoporosis, and past history of fractures	6	Diabetes was associated with a higher prevalence of sarcopenia compared to control group
Wang 2015	China	Type 2	PD	AWGS	1090	69.9 (8.1)	24.0 (3.6)	Age, gender, anti-diabetic medication, energy intake, protein intake, physical activity, and visceral fat area	8	T2DM was significantly associated with increased risks of sarcopenia and pre-sarcopenia
Yang, 2016	China	Nephropathy	PD	ASMMI < 7.26 in men or 5.45 in women	793	51.53 (9)	24.2 (3.8)	Age, BMI, systolic and diastolic pressure, Hba1c, FPG, diabetes duration, smoking, drinking, drugs, physical activity	5	Sarcopenia is associated with a significant decline renal function
Total	Asia: 14 studies; Europe: 2 studies; North America: 2 studies; South America: 2 studies.	7 studies: type 2 diabetes; 7 studies: not specified; 1 study: LADA; 6 studies: diabetes complications		6 studies: AWGS criteria; 5 studies: body composition criteria; 2 studies: EWGSOP; 2 studies: FNIH criteria; 1 study: low handgrip strength; 1 study: 24 h creatinine excretion	54,676	65.4 (11.2)	25.0 (3.7)		Median = 6 (range 3–8)	

LADA latent autoimmune diabetes of adults, *AWGS* Asian Working Group for Sarcopenia, *EWGSOP* European Working Group on Sarcopenia in Older People, *SMI* skeletal mass index, *ASMMI* appendicular skeletal muscle mass index, *FNIH* Foundation for the National Institutes of Health, *PD* physician diagnosed, *SD* standard deviation, *BMI* body mass index

*Longitudinal cohort study

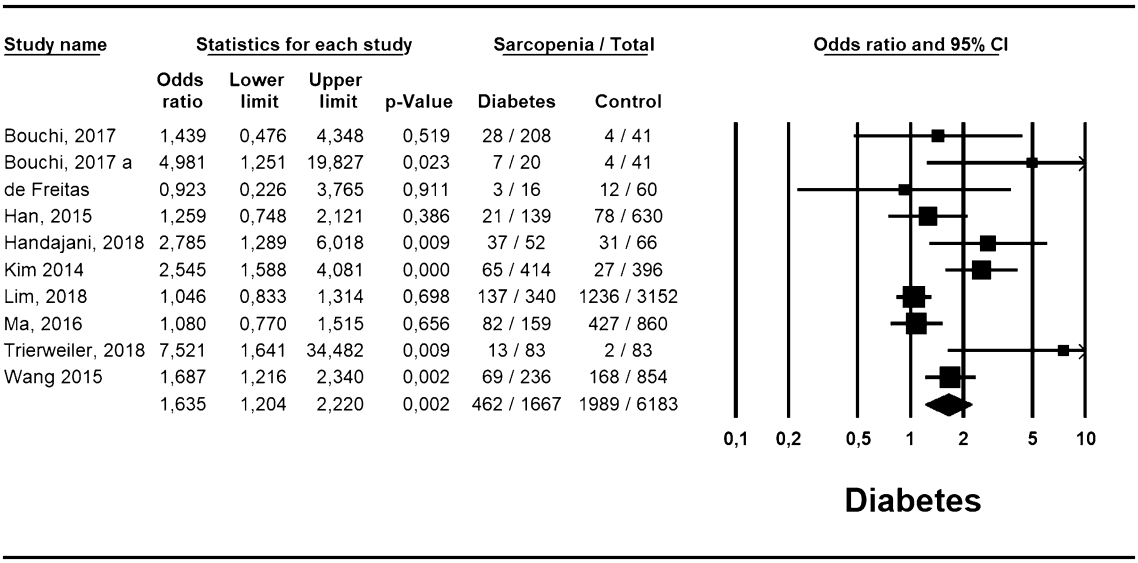

Fig. 1 Odds ratio of sarcopenia in diabetic participants vs. healthy controls

criteria of diabetes or sarcopenia) did not explain any of the heterogeneity found (details available upon request).

The Egger's test suggested that there was a potential publication bias ($=1.88 \pm 0.85$; $p=0.05$). The trim and fill analysis suggested that, after trimming two studies at the left of the mean, the recalculated OR was 1.478 (95% CI 1.080–2.026). The fail-safe number for this outcome was 63. Only one study reported data adjusted for potential confounders, substantially confirming these findings [45].

Association between sarcopenia and diabetes

Figure 2 reports the association between sarcopenia and diabetes, adjusted for potential confounders. This analysis involved 37,396 participants. After adjusting for a median of three potential covariates (range 0–7), sarcopenia was associated with an increased odds of having diabetes (OR = 2.067; 95% CI 1.396–3.624; $p<0.0001$; $I^2=0\%$). This outcome did not suffer on publication bias as revealed by the visual inspection of the funnel plots and/or using the Egger's test (p value > 0.05). The fail-safe number was nine.

One study reported the association between sarcopenia at baseline (reported as the lowest tertile of handgrip strength at the baseline) and incident diabetes in the English Longitudinal Study of Ageing [41]. After adjusting for seven potential confounders, in more than 5000 participants, the authors failed to find any significant association between these two conditions.

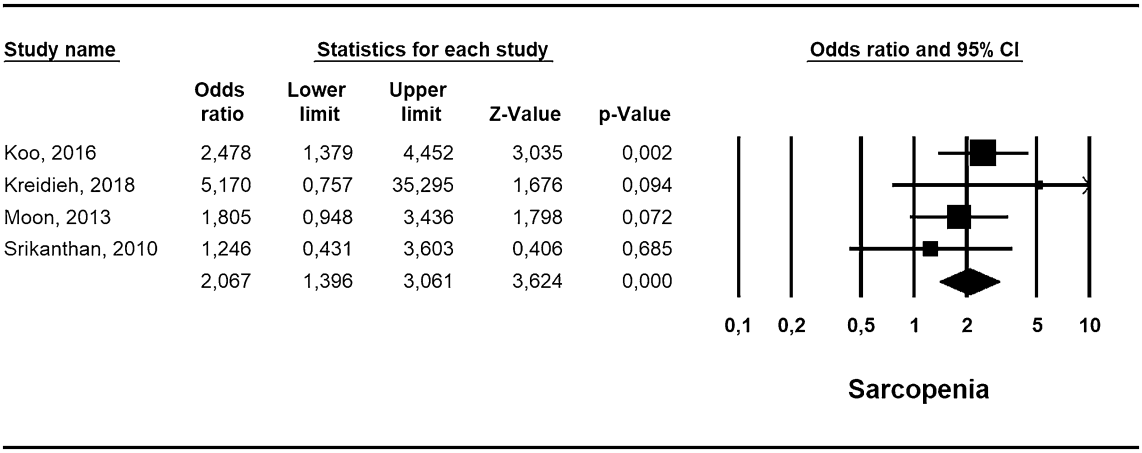

Fig. 2 Adjusted odds ratio of diabetes in sarcopenia vs. healthy controls

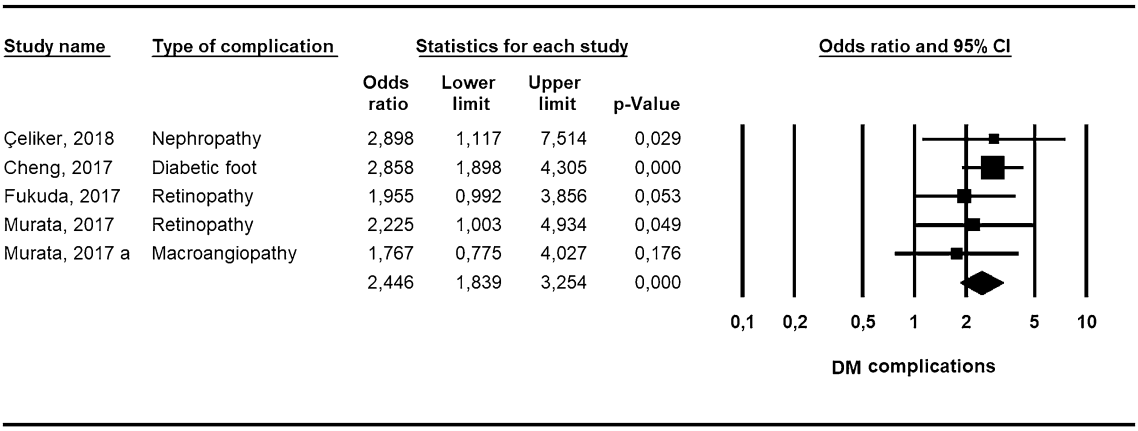

Fig. 3 Odds ratio of sarcopenia in diabetic people with micro or macro-complications vs. diabetics without complications

Association between diabetes complications and sarcopenia

As reported in Fig. 3, five studies reported the association between diabetes complications and the presence of sarcopenia. Retinopathy was the most common complication assessed. These studies included 1868 participants and reported that diabetic people with a complication had an increased prevalence of sarcopenia when compared to diabetic people without (OR = 2.446; 95%CI 1.839–3.254; $p < 0.0001$; $I^2 = 0\%$). This outcome did not suffer on publication bias as revealed by the visual inspection of the funnel plots and/or using the Egger's test (p value > 0.05). The fail-safe number was 36.

One cross-sectional study confirmed these findings, using an OR adjusted for 11 potential confounders [26]. Interestingly, one study reported the prospective association between sarcopenia at baseline and incident micro-albuminuria, again supporting the potential association between sarcopenia and poor renal function [42].

Discussion

In this systematic review and meta-analysis which included 20 studies, we found that sarcopenia was more prevalent in diabetic patients (when compared to their counterparts without diabetes) and associated with an increased odds of having diabetes in 37,396 participants. Moreover, diabetic complications were associated with a higher frequency of sarcopenia, when compared to people with diabetes, but without any complication. In that sense, one longitudinal study suggests that sarcopenia can be associated with a decline in renal function. Taken together, these findings suggest a bidirectional association between diabetes and sarcopenia and that the presence of a diabetic complication can further increase the presence of sarcopenia.

The association between insulin resistance (as observed in type 2 diabetes), abdominal obesity and sarcopenia may be explained by several pathways, such as the loss of the anabolic action to insulin, the reduced insulin-inhibition of proteolysis, and the loss of anti-inflammation actions. Inflammation (particularly when associated with obesity) is an important determinant of sarcopenia, as we recently reported in a systematic review and meta-analysis regarding this topic [46]. For example, TNF-α, which is highly expressed in adipose tissues in obese subjects may block muscle tissues differentiation leading to sarcopenia [47]. Other works have reported that a reduction in oxidative type I fibres and a concomitant increase in glycolytic type IIb fibres, combined with ageing effects on muscle, leads to an overall decrease in mitochondrial function and consequently an increase in insulin resistance and oxidative stress, finally leading to sarcopenia [4, 47]. Finally, insulin resistance may also alter the glycogen storage in type IIa muscle fibres, decreasing the efficiency of oxidative phosphorylation [48]. In this sense, a study excluded from our meta-analysis since the cohort was already included (Korean Sarcopenic Obesity Study) and no meta-analysable data were available, reported that appendicular skeletal mass values were significantly decreased in patients with diabetes compared with subjects without diabetes [49].

From an epidemiological point of view, sarcopenia and diabetes seem to be reciprocally related and could share similar pathogenetic pathways. As diabetes leads to sarcopenia, as mentioned before, it is also possible that sarcopenia can lead to lower muscle glucose uptake, hyperglycaemia/hyperinsulinemia and finally to insulin resistance, precursors of diabetes [50]. We have also reported that poor physical performance can be associated with an increased risk of diabetes [51]. Muscle fat infiltration, a component that

seems increasingly important in several aspects of geriatric medicine, might also lead to insulin resistance promoting both the development of sarcopenia and diabetes [51]. On the contrary, in the only study including people with latent autoimmune diabetes of adults, we did not observe any significant difference in sarcopenia prevalence when compared to controls; overall suggesting that particularly insulin-resistance typical of type 2 diabetes is implicated in the development of sarcopenia [38]. Chronic low-grade inflammation is another factor that can have a role in the development of both diabetes and sarcopenia [46, 52, 53].

Finally, we found that sarcopenia is more common in diabetic people with complications than in DM patients without complications. Even if this analysis is limited by the fact that all the complications were pooled together (micro and macro-vascular), these findings suggest a potential role of the vascular system in the development of sarcopenia [54]. In one exploratory study, for example, the authors found that in sarcopenic patients there was a lower skeletal muscle capillarization that may contribute to the development of sarcopenia and reduced exercise capacity by limiting the diffusion of substrates essential for the muscle, such as oxygen, hormones, or nutrients [55]. However, it is also possible that the complication profile depends on the mechanisms of diabetes itself and that the contribution of vascular factors, even if pivotal, is probably not enough to explain the link that we observed.

Our meta-analysis reports, however, some preliminary findings regarding the potential association between sarcopenia and diabetes and vice versa limited to cross-sectional and case–control studies. We can suggest that future longitudinal studies could specifically investigate, for example, the role of singular complication in predicting sarcopenia (e.g., neuropathy or renal failure) or the role of sarcopenia in predicting more rare forms of diabetes such as type 1 diabetes and LADA.

Findings from the present meta-analysis should be interpreted within its limitations. First, the results were heterogenous. Second, our findings were mainly based on case control or cross-sectional studies, whilst only two papers were longitudinal. Moreover, in case control and cross-sectional studies, the prevalence of sarcopenia in diabetes is not adjusted for potential confounders. Third, the diagnosis of sarcopenia was made through multidimensional tools only in 8 over 20 studies, whilst many others assessed sarcopenia only through muscle mass or muscle function parameters. Fourth, the majority of the studies included Asiatic people and the mean age was only 65 years, suggesting that further studies in more old people are needed. Finally, in the outcome characterized by a high heterogeneity (i.e., the prevalence of sarcopenia in diabetes), we were not able to find any significant moderator explaining this factor. In this regard, for example, it is possible that the higher presence of diabetic complications in people with diabetes than controls can contribute to explain the heterogeneity found in our analysis. For example, some authors suggest that neuropathy (a common and traditional complication of diabetes) can lead to sarcopenia [56].

In conclusion, our systematic review and meta-analysis indicated that sarcopenia and diabetes can be bi-directionally associated, even if the findings are mainly based on cross-sectional and case control studies. People with diabetic complications reported a significantly higher presence of sarcopenia compared to diabetic participants without complications. Since both diabetes and sarcopenia are two highly prevalent conditions in ageing populations, future longitudinal studies are needed to better explain this association.

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Compliance with ethical standards

Conflict of interest The authors have not conflict of interest to declare for this work.

Ethical approval Not required since it is a review of already published works.

Informed consent For this type of study, formal consent is not required.

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