European Geriatric Medicine (2019) 10:677–680
https://doi.org/10.1007/s41999-019-00230-z

EDITORIAL

Sarcopenia and diabetes mellitus: evidence for a bi-directional relationship

Jakub Mesinovic[1] · **David Scott**[1,2]

Received: 31 July 2019 / Accepted: 7 August 2019 / Published online: 19 August 2019

Sarcopenia refers to the age-related decline in skeletal muscle mass, strength, quality and performance [1], whilst diabetes mellitus (DM) is characterised by hyperglycaemia resulting from defects in insulin secretion and/or action [2]. Type 1 DM accounts for only around 10% of DM cases and does not appear to be associated with lifestyle [2], whereas the more prevalent type 2 DM, like sarcopenia, is strongly associated with modifiable lifestyle factors, including low physical activity and poor diet [1, 2]. Both sarcopenia and DM are important risk factors for physical disability in ageing populations [1, 3] and evidence for a bi-directional relationship between these conditions is mounting. In the current issue of European Geriatric Medicine, Veronese et al. present the findings of a systematic review and meta-analysis exploring this relationship in 20 studies including over 50,000 participants. Their findings demonstrate that individuals with sarcopenia have increased likelihood for having DM, and individuals with DM have greater likelihood of having sarcopenia [4].

The odds for sarcopenia in patients with DM were around 1.6-fold higher than for those without DM [4]. While the authors were unable to compare associations for the different subtypes of DM, type 1 and type 2 DM share several similar characteristics and complications that can increase risk for sarcopenia. Hyperglycaemia in DM leads to increased oxidative stress, advanced glycation end-product accumulation and chronic low-grade systemic inflammation, which contribute to micro- and macrovascular complications. These characteristics and complications can directly and indirectly affect all components of sarcopenia through impaired protein metabolism, mitochondrial dysfunction, neuropathy, nephropathy and myopathy [5]. However, a fundamental difference between type 1 and type 2 DM is skeletal muscle insulin resistance, which appears to be the initial metabolic defect in type 2 DM [6]. Skeletal muscle insulin resistance negatively affects protein metabolism in type 2 DM [7] and individuals with type 1 DM may initially be spared from this defect. Despite having better insulin sensitivity than type 2 DM counterparts, some forms of type 1 DM result in permanent insulinopaenia, which can potentially contribute to muscle wasting, as insulin is thought to have anabolic and anti-catabolic effects on skeletal muscle [2, 8]. Interestingly, the number of individuals with type 1 DM that display clinical characteristics associated with type 2 DM (e.g. obesity and insulin resistance) is increasing [9], which is blurring the distinction between these subtypes of DM. This is often referred to as "double diabetes", and these individuals are at even greater risk of developing vascular complications [9], which appears to further increase risk for sarcopenia [4].

Indeed, Veronese et al. reported that the odds of developing sarcopenia are 2.4-fold greater in individuals with DM and an associated vascular complication compared to individuals with DM but without vascular complications [4]. Most individuals with DM will develop vascular complications, which are a leading cause of diabetes-related deaths [10]. Although vascular complications are more likely to exist in those with longer DM duration, or in individuals with poorly controlled DM, a large proportion of individuals in the earlier stages of DM are also affected [11]. Many pathologies associated with vascular complications accelerate declines in muscle health. DM is the leading cause of chronic kidney disease (CKD) [12], which leads to increased protein excretion, metabolic acidosis, mitochondrial dysfunction, and reduced vitamin D synthesis, which are all risk factors for sarcopenia [13]. Neuropathy is another common microvascular complication that contributes to muscle strength [14] and mass declines [15].

✉ David Scott
david.scott@monash.edu

[1] Department of Medicine, Faculty of Medicine, Nursing and Health Sciences, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC 3168, Australia

[2] Department of Medicine, Western Health, Melbourne Medical School, Australian Institute for Musculoskeletal Science (AIMSS), The University of Melbourne, St Albans, Australia

Macrovascular complications also contribute to sarcopenia. Peripheral artery disease (PAD) affects approximately one-quarter of individuals with DM [16] and reduced blood flow in PAD can result in ischaemia, which reduces nutrient transfer and contributes to muscle strength, mass and performance declines [17]. PAD often causes pain, which can lead to reduced physical activity in these individuals, further increasing risk for sarcopenia. Alone, vascular complications often fail to fully explain muscle deterioration in DM [18], however, in combination with other diabetes-related pathologies, they clearly confer greater risk for sarcopenia than DM without vascular complications.

Finally, the authors observed that individuals with sarcopenia had over two-fold increased likelihood of having diabetes compared with non-sarcopenic counterparts [4]. Characteristics of sarcopenia can potentially affect metabolic health; a core component is low muscle mass, which may result in reduced glucose uptake as skeletal muscle accounts for ~ 80% of glucose clearance during euglycaemic hyperinsulinaemic conditions [19]. Another component of sarcopenia that could influence metabolic health is muscle quality. Inter- and intramuscular adipose tissue (IMAT) is a component of muscle quality that appears to modulate insulin sensitivity in human skeletal muscle [20, 21]. This is thought to occur through increased local fatty acid storage and inflammation and impaired insulin diffusion capacity and muscle blood flow [20, 22]. Furthermore, increased localised inflammation attributed to high IMAT levels [23] may worsen diabetes-related vascular complications, such as peripheral neuropathy [24]. Loss of mobility associated with sarcopenia could also contribute to reduced physical activity and subsequent increases in fat mass, further increasing risk for type 2 DM [2].

This important meta-analysis highlights the potential synergistic relationships between sarcopenia and DM, but it should be noted that the conclusions that can be drawn are limited to some extent by the quality of existing data. In particular, as noted above, it is difficult to determine the effects of the different subtypes of DM, and specific complications, on risk for sarcopenia given that these are often grouped together. Similarly, numerous definitions of sarcopenia were used in the included studies, ranging from definitions based on low muscle mass or strength alone, to multicomponent definitions that are more consistent with current recommendations for sarcopenia case-finding; notably, there are no studies available investigating the associations of sarcopenia and DM that apply the European Working Group on Sarcopenia in Older People's recently revised definition of sarcopenia [1]. Importantly, only two studies were identified that were longitudinal in nature and so causation in the relationship between sarcopenia and DM is poorly understood. High-quality longitudinal studies are required which include appropriate diagnosis of DM (specifying the subtype), measurement of diabetic complications, and assessment of muscle outcomes consistent with multicomponent definitions of sarcopenia.

Nonetheless, the data presented by Veronese et al. highlight that there is a substantial population of adults with co-morbid DM and sarcopenia, indicating that increased screening for sarcopenia is warranted in those with DM, and vice versa. There is currently a lack of evidence from interventional studies assessing appropriate treatments for individuals with co-morbid DM and sarcopenia, but conventional lifestyle therapies, including dietary modification and increased physical activity, are recommended to treat both conditions. Given the complexity of both conditions, lifestyle interventions need to be highly personalised. An effective intervention for obese individuals with DM is caloric restriction [25], which can potentially be combined with increased protein intake to ensure maintenance of muscle mass during weight loss [26]. However, it should be noted that increased protein intake may be contraindicated in individuals with diabetic CKD [27]. Regarding physical activity, combined aerobic and resistance exercise is effective for treating DM and sarcopenia, as both exercise modalities provide distinct cardiovascular and musculoskeletal benefits [28, 29]. Recently, Villareal et al. demonstrated that combined aerobic and resistance exercise during weight loss is the most effective exercise modality for improving physical function scores (increased 21%) in obese older adults with mild-to-moderate frailty [compared to aerobic exercise plus weight loss (increased 14%), resistance training plus weight loss (increased 14%) and no exercise or weight loss (increased 4%)] [30]. The combined aerobic and resistance exercise group also increased total one-repetition maximum strength scores by 18%, despite losing 3% total body lean mass [30]. Thus, maintenance of muscle quantity is potentially not necessary to maintain muscle strength and function, but it should remain a key target for individuals with DM due to its beneficial effects for metabolic health. The most effective lifestyle intervention in individuals with co-morbid DM and sarcopenia may therefore be combined aerobic and resistance training without caloric restriction, but randomised controlled trials are required to compare the effects of exercise and weight loss, both alone and in combination, in this population.

Although there are various pharmacological treatments for DM, there are currently no approved pharmacological treatments for sarcopenia. Promising interventions for sarcopenia include selective androgen receptor modulators [31] and activin type IIB receptor antagonists [32]. These drugs have demonstrated efficacy for improving muscle mass, but their ability to improve muscle strength and performance, particularly in sarcopenic populations, remains unclear [33]. Exercise may be necessary to augment the effects of these drugs on muscle strength and performance, but interestingly,

they may have positive effects on metabolic health. A recent exploratory study by Garito et al. demonstrated that a single infusion of an activin type II receptor antagonist (Bimagrumab) improved insulin sensitivity in insulin-resistant adults, independent of exercise and dietary modification [32]. This improved insulin sensitivity was not necessarily solely attributable to the increases in muscle mass that occurred in the treatment group; the authors suspected that improvements in muscle quality, losses in fat mass and favourable energy balance also contributed to this outcome [32]. The safety, pharmacokinetics and efficacy of Bimagrumab for overweight and obese patients with type 2 DM are currently being further investigated (NCT03005288).

In summary, Veronese et al. have provided further evidence of a bi-directional relationship between sarcopenia and DM, and that vascular complications in DM further increase the odds of developing sarcopenia. There are a multitude of pathologies associated with sarcopenia and DM that can accelerate declines in metabolic and muscle health, respectively, and prevention and early intervention are crucial to maintain health and independence in patients with either, or both conditions.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent None.

References

1. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T et al (2018) Sarcopenia: revised European consensus on definition and diagnosis. Age and Ageing 5:1–6. https://doi.org/10.1093/ageing/afy169
2. Association AD (2015) Classification and diagnosis of diabetes. 2015 Contract No.: Supplement 1
3. Gregg EW, Mangione CM, Cauley JA, Thompson TJ, Schwartz AV, Ensrud KE et al (2002) Diabetes and incidence of functional disability in older women. Diabetes Care 25(1):61–67. https://doi.org/10.2337/diacare.25.1.61
4. Veronese N, Pizzol D, Demurtas J, Soysal P, Smith L, Sieber C et al (2019) Association between sarcopenia and diabetes: a systematic review and meta-analysis of observational studies. Eur Geriatr Med 15:8. https://doi.org/10.1007/s41999-019-00216-x
5. Mesinovic J, Zengin A, De Courten B, Ebeling PR, Scott D (2019) Sarcopenia and type 2 diabetes mellitus: a bidirectional relationship. Diabetes Metab Syndr Obes Targets Ther 12:1057–1072. https://doi.org/10.2147/DMSO.S186600
6. DeFronzo RA, Tripathy D (2009) Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. Diabetes Care 32(Suppl 2):S157–S163. https://doi.org/10.2337/dc09-S302
7. Pereira S, Marliss EB, Morais JA, Chevalier S, Gougeon R (2008) Insulin resistance of protein metabolism in type 2 diabetes. Diabetes 57(1):56. https://doi.org/10.2337/db07-0887
8. Dimitriadis G, Mitrou P, Lambadiari V, Maratou E, Raptis SA (2011) Insulin effects in muscle and adipose tissue. Diabetes Res Clin Pract 93:S52–S59. https://doi.org/10.1016/S0168-8227(11)70014-6
9. Merger SR, Kerner W, Stadler M, Zeyfang A, Jehle P, Muller-Korbsch M et al (2016) Prevalence and comorbidities of double diabetes. Diabetes Res Clin Pract 119:48–56. https://doi.org/10.1016/j.diabres.2016.06.003
10. Einarson TR, Acs A, Ludwig C, Panton UH (2018) Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol 17(1):83. https://doi.org/10.1186/s12933-018-0728-6
11. Kosiborod M, Gomes MB, Nicolucci A, Pocock S, Rathmann W, Shestakova MV et al (2018) Vascular complications in patients with type 2 diabetes: prevalence and associated factors in 38 countries (the DISCOVER study program). Cardiovasc Diabetol 17(1):150. https://doi.org/10.1186/s12933-018-0787-8
12. Xie Y, Bowe B, Mokdad AH, Xian H, Yan Y, Li T et al (2018) Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016. Kidney Int 94(3):567–581. https://doi.org/10.1016/j.kint.2018.04.011
13. Wang XH, Mitch WE (2014) Mechanisms of muscle wasting in chronic kidney disease. Nat Rev Nephrol 10(9):504–516. https://doi.org/10.1038/nrneph.2014.112
14. Nomura T, Ishiguro T, Ohira M, Ikeda Y (2018) Diabetic polyneuropathy is a risk factor for decline of lower extremity strength in patients with type 2 diabetes. J Diabetes Investig 9(1):186–192. https://doi.org/10.1111/jdi.12658
15. Andersen H, Gjerstad MD, Jakobsen J (2004) Atrophy of foot muscles. Diabetes Care 27(10):2382. https://doi.org/10.2337/diacare.27.10.2382
16. Lange S, Diehm C, Darius H, Haberl R, Allenberg JR, Pittrow D et al (2004) High prevalence of peripheral arterial disease and low treatment rates in elderly primary care patients with diabetes. Exp Clin Endocrinol Diabetes 112(10):566–573. https://doi.org/10.1055/s-2004-830408
17. McDermott Mary M (2015) Lower extremity manifestations of peripheral artery disease. Circ Res 116(9):1540–1550. https://doi.org/10.1161/CIRCRESAHA.114.303517
18. Strotmeyer ES, de Rekeneire N, Schwartz AV, Faulkner KA, Resnick HE, Goodpaster BH et al (2008) The relationship of reduced peripheral nerve function and diabetes with physical performance in older white and black adults. Diabetes Care 31(9):1767. https://doi.org/10.2337/dc08-0433
19. Thiebaud D, Jacot E, DeFronzo RA, Maeder E, Jequier E, Felber JP (1982) The effect of graded doses of insulin on total glucose uptake, glucose oxidation, and glucose storage in man. Diabetes 31(11):957–963
20. Sachs S, Zarini S, Kahn DE, Harrison KA, Perreault L, Phang T et al (2019) Intermuscular adipose tissue (IMAT) directly modulates skeletal muscle insulin sensitivity in humans. Am J Physiol Endocrinol Metab. https://doi.org/10.1152/ajpendo.00243.2018
21. Boettcher M, Machann J, Stefan N, Thamer C, Häring H-U, Claussen CD et al (2009) Intermuscular adipose tissue (IMAT): association with other adipose tissue compartments and insulin sensitivity. J Magn Reson Imaging 29(6):1340–1345. https://doi.org/10.1002/jmri.21754

22. Goodpaster BH, Thaete FL, Kelley DE (2000) Thigh adipose tissue distribution is associated with insulin resistance in obesity and in type 2 diabetes mellitus. Am J Clin Nutr 71(4):885–892
23. Addison O, Drummond MJ, LaStayo PC, Dibble LE, Wende AR, McClain DA et al (2014) Intramuscular fat and inflammation differ in older adults: the impact of frailty and inactivity. J Nutr Health Aging 18(5):532–538. https://doi.org/10.1007/s12603-014-0019-1
24. Bittel DC, Bittel AJ, Tuttle LJ, Hastings MK, Commean PK, Mueller MJ et al (2015) Adipose tissue content, muscle performance and physical function in obese adults with type 2 diabetes mellitus and peripheral neuropathy. J Diabetes Compl 29(2):250–257. https://doi.org/10.1016/j.jdiacomp.2014.11.003
25. Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L et al (2018) Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. The Lancet 391(10120):541–551. https://doi.org/10.1016/S0140-6736(17)33102-1
26. Deutz NEP, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A et al (2014) Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. Clin Nutr (Edinburgh, Scotland) 33(6):929–936. https://doi.org/10.1016/j.clnu.2014.04.007
27. Levin A, Stevens PE, Bilous RW, Coresh J, De Francisco AL, De Jong PE, Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group et al (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 3(1):1–150
28. Pan B, Ge L, Xun Y-Q, Chen Y-J, Gao C-Y, Han X et al (2018) Exercise training modalities in patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. Int J Behav Nutr Phys Act 15(1):72. https://doi.org/10.1186/s12966-018-0703-3
29. Yoo S-Z, No M-H, Heo J-W, Park D-H, Kang J-H, Kim SH et al (2018) Role of exercise in age-related sarcopenia. J Exerc Rehabil 14(4):551–558. https://doi.org/10.12965/jer.1836268.134
30. Villareal DT, Aguirre L, Gurney AB, Waters DL, Sinacore DR, Colombo E et al (2017) Aerobic or resistance exercise, or both, in dieting obese older adults. N Engl J Med 376(20):1943–1955. https://doi.org/10.1056/NEJMoa1616338
31. Dalton JT, Barnette KG, Bohl CE, Hancock ML, Rodriguez D, Dodson ST et al (2011) The selective androgen receptor modulator GTx-024 (enobosarm) improves lean body mass and physical function in healthy elderly men and postmenopausal women: results of a double-blind, placebo-controlled phase II trial. J Cachexia Sarcopenia Muscle 2(3):153–161. https://doi.org/10.1007/s13539-011-0034-6
32. Garito T, Roubenoff R, Hompesch M, Morrow L, Gomez K, Rooks D et al (2018) Bimagrumab improves body composition and insulin sensitivity in insulin-resistant individuals. Diabetes Obes Metab 20(1):94–102. https://doi.org/10.1111/dom.13042
33. Hardee JP, Lynch GS (2019) Current pharmacotherapies for sarcopenia. Expert Opin Pharmacoth. https://doi.org/10.1080/14656566.2019.1622093