

A counterintuitive perspective for the role of fat-free mass in metabolic health

Jean-Christophe Lagacé^{1,2} , Martin Brochu^{1,2} & Isabelle J. Dionne^{1,2*}

¹Metabolic Unit, Research Centre on Aging, CIUSSS de l'Estrie-CHUS, Québec, Canada, ²Faculty of Physical Activity Sciences, University of Sherbrooke, Québec, Canada

Abstract

Fat-free mass (FFM) has long been recognized to play a role in metabolic homeostasis. Over the years, it has become widely accepted by the scientific and general community alike that having a greater FFM can be protective for metabolic health. Hence, in the context of an aging population concurrently facing sarcopenia and an elevated incidence of metabolic diseases, substantial efforts are being made to study and develop interventions aiming to maintain or increase FFM. However, accumulating evidence now suggests that a large FFM may be deleterious to metabolic health, at least in some populations. The objective of this article is thus to raise awareness surrounding these results and to explore possible explanations and mechanisms underlying this counterintuitive association.

Keywords Fat-free mass; Sarcopenia; Muscle mass; Metabolic syndrome; Insulin resistance

*Correspondence to: Isabelle J. Dionne, Research Centre on Aging, CIUSSS de l'Estrie-CHUS, 1036, Belvédère Sud, Sherbrooke, Québec J1H 4C4, Canada. Phone: 1-819-780-2220 #45671. Email: isabelle.dionne@usherbrooke.ca

This article stems from contradictory published results in the literature concerning the beneficial role of greater fat-free mass (FFM) on metabolic health.^{1–6} The widely accepted principle that greater FFM contributes to a better metabolic health overshadows available data supporting the opposite view. The objective of this article is thus to raise awareness and to urge the scientific community to take a fresh look at the association between FFM and cardiometabolic health.

The current state-of-the-art: where does it come from?

The role of FFM in metabolic health has been studied for decades. Work from Samuel Soskin dating as far back as the 1930's recognizes the role of muscle in the uptake and oxidation of glucose in diabetic individuals.⁷ Fast-forward to the 1980's, Miller *et al.* in 1984⁸ and Szczypaczewska *et al.* in 1989⁹ already reported a decreased insulin concentration following an oral glucose tolerance test in individuals who

gained muscle mass following a strength training programme⁸ or those with greater muscle mass.⁹ Both groups had similar conclusions: 'better glucose tolerance in body builders was associated with lower insulin concentrations supports the view that enlargement of muscle mass by training increases body insulin sensitivity'.⁹

Two main mechanisms are generally reported to explain observations like those of Miller *et al.*⁸ or Szczypaczewska *et al.*⁹ First, the relation between FFM and resting metabolic rate (RMR)¹⁰ has led to the logical assumption that a greater FFM, and therefore, a greater RMR, would protect against obesity and associated co-morbidities. Secondly, a classical study of DeFronzo *et al.*¹¹ showed that muscle tissue contributes to the majority of glucose uptake in insulin-stimulated conditions. These results contributed to the notion that a greater FFM, possibly through increased energy expenditure and glucose uptake, will help maintain glucose homeostasis or insulin sensitivity. Accordingly, sarcopenia—the loss of muscle mass observed with aging—is thus deemed deleterious to metabolic health. In this context, interventions in favour of FFM gains are eagerly being studied and

recommended, especially to older adults in whom sarcopenia is paralleled with an increase in cardiometabolic diseases prevalence. These recommendations are however provided broadly, irrespective of context and baseline FFM. A growing body of evidence suggests this could be suboptimal, if not harmful, in many instances.

‘Unexpected’ results

The purported idea that a larger FFM should hold a protective effect against altered metabolism is strongly rooted and could make authors hesitant to put their ‘unexpected’ observations forward or discuss them at all. As an example, we did not discuss the phenomenon when we first observed that insulin-resistant obese women had significantly greater FFM than metabolically healthy counterparts (+5 kg on average) with similar BMI.¹² However, obtaining this recurring result over the years led us to review the literature for other articles with similar observations.¹³ This review led to three key conclusions.

- i. There is a publication bias favouring the generally accepted view

There is an abundance of articles in the literature reporting body composition and metabolic variables, be it insulin sensitivity, blood pressure, various cardiometabolic risk factors or plasma concentrations of glucose, cholesterol, inflammatory cytokines, and so on. The articles showing the ‘anticipated’ effect of FFM on cardiometabolic profiles generally disclosed their results.¹³ In contrast, those who found a negative association of FFM, and there were many, either merely discussed their results or disregarded them. This leads to a publication imbalance between the two opposite perspectives in favour of the protective effect of FFM. This publication bias contributes to maintain the idea that FFM holds a protective effect on metabolic health. Interestingly, some authors have raised the two viewpoints in their respective article,^{1–3} that is, a protective and a deleterious association between FFM and cardiometabolic health. The divergences are due to the way of expressing FFM. This led to our second conclusion.

- ii. There is an overwhelming proclivity in the literature to favour the FFM expression that fits the narrative

A recent publication by Hirasawa *et al.*¹ showed that the way FFM is expressed leads to contrasting conclusions regarding the protective effect of FFM in individuals with type 2 diabetes (T2D). Park and Yoon² and Scott *et al.*³ showed similar results for the metabolic syndrome (MetS).

There are three common ways to express FFM: in absolute terms (absolute FFM; kg), relative to body weight [FFM%;

FFM (kg)/total body weight (kg) * 100], and relative to height (FFM index; kg/m²).

Results from Hirasawa *et al.*¹ showed that appendicular FFM index (kg/m²) was positively associated with Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) in younger men and women and in older women, while FFM% was negatively associated with it in younger and older men and women. In the articles of Park and Yoon² and Scott *et al.*³, individuals with lower FFM index (kg/m²) had lower odds ratios of having the MetS, and, in contrast, participants with lower FFM% had higher odds ratios of having it. Despite their opposite results, the conclusion of Hirasawa *et al.*¹ strikingly depicts the inclination towards *status quo*:

In conclusion, the two major indices of skeletal muscle mass showed different associations with IR. Although ASMI [appendicular skeletal muscle index—kg/m²] was positively associated with IR, RTSM [relative total skeletal muscle mass—FFM%] was negatively associated with IR independent of gender and age, suggesting that RTSM is a better indicator of IR than ASMI in patients with type 2 diabetes.

In other words, they favoured the expression suitable to the assumed protective effect of FFM in health. Many studies used FFM% in large cohorts and also concluded that greater FFM was protective against insulin resistance (IR) and T2D,⁵ MetS,⁶ or cardiovascular disease risks.¹⁴ However, the use of FFM% *per se* is problematic because it inherently represents FM and FFM as well. Consequently, its use limits the capacity to draw clear conclusions and can lead to flawed inferences regarding the real contribution of FFM. For instance, Lee *et al.*⁴ recently concluded that ‘skeletal muscle mass may play a protective role against future metabolic deterioration’. Yet while baseline FFM% was indeed greater in those who remained healthy after the 4 year follow-up, there were no differences in absolute appendicular FFM (kg), leaving the main disparity between the groups to be FM. Overall, as shown above, the way to express FFM largely influences the direction of the association with the metabolic health. Considering that the current literature predominantly uses FFM% to quantify FFM, we can question the purported contribution of the FFM to metabolic health.

- iii. Associative and cross-sectional conclusions of a protective effect of FFM on metabolic health are not supported by interventional studies

Considering the purported idea that low FFM is associated with deteriorated metabolic health, many interventional studies have focused on increasing FFM, notably through a resistance exercise programme. Results from these studies are however inconsistent. For instance, we observed that the loss of FFM was the only independent predictor of improvements in IS assessed with HOMA-IR after a 6 month

intervention in a sample of 48 post-menopausal women.¹⁵ In contrast, Baldi *et al.*¹⁶ found that improvements in HbA1c were inversely associated with changes in FFM in a sample of nine individuals with T2D who exercised for 10 weeks, which suggests a protective effect of FFM. Their results could have been confounded by medication, as Lee *et al.*¹⁷ have reported that insulin-sensitizing medication therapy could attenuate FFM loss observed in individuals with T2D. Last but not least, a recent meta-analysis of studies investigating the effect of resistance training in older individuals showed that, altogether, improvements in glycaemic control assessed with HbA1c were independent of variations in FFM,¹⁸ suggesting that the other mechanisms could be at play. In sum, it remains to be determined what the true role is of a large FFM in the development of cardiometabolic diseases, and, as such, if it is only an artefact or if this phenotype, and if its inherent characteristics are actually deleterious to metabolic health. Mechanistic studies are thus required to settle this ambiguity.

Potential mechanisms

To the best of our knowledge, no studies have directly investigated the mechanisms underlying the association between FFM index and IR or the MetS. Here, we propose hypotheses regarding potential mechanisms that could explain these counterintuitive observations.

i. Fibre typology

Because type II fibres hold the greatest capacity for hypertrophy, a larger FFM is generally associated with greater percentage of type II and type IIX muscle fibres. It is interesting to note, however, that fibre typology has been associated with health status.^{19,20} Fisher *et al.*¹⁹ have reported an inverse association between a high percentage of type II fibres, especially type IIX fibres, and IS measured with a clamp. This association extended to mean arterial blood pressure and low-density lipoprotein cholesterol concentrations.¹⁹ Furthermore, Gueugneau *et al.*²⁰ reported larger type II muscle fibres in older individuals with MetS compared with healthy counterparts. These two studies suggest that having larger and a high relative quantity of type II fibres, particularly type IIX, may hold a role in cardiometabolic disease risk.

This inverse association between type II fibre distribution and size with health status could be attributable to the vascular and oxidative characteristics of muscle fibre types.^{20,21} Indeed, type II fibres have a reduced capillary-to-fibre ratio and capillary density compared with type I fibres, thus limiting glucose transport to muscles.²¹ Also, while it is known that type II fibres are less oxidative than type I fibres, it has been recently reported that older adults with MetS have a reduced

oxidative capacity compared with their healthy counterparts.²⁰ These results support the idea that a diminished systemic oxidation capacity, potentially due to a high number of low-oxidative muscle fibres, could be associated with adverse metabolic outcomes. Overall, characteristics associated with type II fibres—a low capillary density and low-oxidative capacity—seem to contribute to an adverse metabolic profile. This association could also be mediated by an increase in fat storage, as reported by Gueugneau *et al.*²⁰

ii. Intramuscular fat accumulation

Aside from endurance athletes, in whom the athlete's paradox has been previously described, greater accumulations of intramuscular triglyceride has been associated with adverse metabolic outcomes such as IR, MetS, and T2D.^{20,22} For instance, Gueugneau *et al.*²⁰ showed that individuals with MetS had a larger proportion of muscle fibres area occupied by lipid droplets. Interestingly, while intramuscular triglycerides are generally stored in type I fibres to be used as an energy substrate, it was shown that older men with MetS had greater lipid accumulation in type IIX fibres than had healthy counterparts.²⁰ This relation between fat infiltration and an altered metabolic health could be mediated by secreted factors, namely, ceramides, that are known to alter insulin signalling pathways.²²

Altogether, having a larger FFM and larger type II muscle fibres could act as a greater reservoir, thus leading to an increased capacity for ectopic fat accumulation. In addition, having a large amount of lipid infiltration was inversely associated to muscle quality,²³ which could further contribute to metabolic deteriorations.

iii. Muscle quality

Muscle quality, typically evaluated with relative strength, is a major contributor to overall health.^{23–26} Indeed, results from a large cohort study in the US showed a significant association between higher relative strength and a more favourable cardiometabolic profile.²⁵ It is interesting to note that while absolute strength increased significantly with weight status (from normal weight to obese) in all groups but women aged 40 to 59, relative strength significantly decreased with weight status.²⁵ Similarly, Mesinovic *et al.*²⁴ recently showed that individuals with MetS had lower muscle quality despite a larger FFM. They concluded that greater FFM does not grant a functional advantage, whereas muscle quality may be useful for identifying individuals with MetS who are at risk of functional declines.²⁴ Supporting this notion are the results of Barbat-Artigas *et al.*²⁶ who reported a negative association between muscle quality and FFM, and greater functional impairments with low relative strength.

To counter for a potential confounding effect of body composition on the relation between metabolic health and

relative strength, Poggiogalle *et al.*²³ studied metabolically healthy and unhealthy adult women matched for body composition. They reported greater relative strength in metabolically healthy women compared with unhealthy counterparts and a negative association between relative strength and HOMA-IR.²³ Interestingly, the two major differences between groups were greater visceral adipose tissue and intramuscular fat accumulation in metabolically unhealthy women,²² supporting our previous assumption that a large FFM is not protective of the deleterious impact of intramuscular fat accumulation to muscle quality and health.

Taken as a whole, muscle quality, assessed as relative strength, seems to be a great predictor of metabolic health, while, in contrast, having a larger FFM does not seem to confer a protective effect.

Taking a step back

We first urge research groups to discuss their counterintuitive results in an effort to balance the current publication bias. Care must however be taken when reporting FFM, as different expressions may lead to contrasting conclusions. Studies using state-of-the-art methods for the quantification of body composition (e.g. dual-energy X-ray absorptiometry) should pay special attention not to use the percentage of FFM. Furthermore, sound results establishing the causal role of low FFM in metabolic diseases are insufficient, and several

interventional studies show that improvements in metabolic health are independent of changes in FFM.¹⁸ Nevertheless, a great deal of research is still built on the premise that low FFM can lead to cardiometabolic diseases.

Considering the counterintuitive nature of the subject, studies investigating the mechanisms underlying the association between a large FFM index and deteriorated metabolic health would contribute to determine the exact role of FFM in metabolic health. Current data hint towards a potential role of microvasculature, muscle fibre-type distribution and size, fat infiltration, and FFM function, but elegantly designed studies are required to confirm our observations.

In conclusion, the wide recommendations to maintain or increase FFM in an effort to improve cardiometabolic health, regardless of baseline FFM, are based on unsubstantiated premises and could lead to suboptimal if not deleterious outcomes in some populations.

Acknowledgements

The authors have no conflicts of interest to disclose. I.J.D. holds the Canada Research Chair on Exercise Recommendations for a Healthy Aging. J.C.L. is financially supported by the University of Sherbrooke. M.B. declares no conflict of interest. The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.²⁷

References

- Hirasawa Y, Matsuki R, Ebisu T, Kurose T, Hamamoto Y, Seino Y. Evaluation of skeletal muscle mass indices, assessed by bio-electrical impedance, as indicators of insulin resistance in patients with type 2 diabetes. *J Phys Ther Sci* 2019;**31**:190–194.
- Park BS, Yoon JS. Relative skeletal muscle mass is associated with development of metabolic syndrome. *Diabetes Metab J* 2013;**37**:458–464.
- Scott D, Park MS, Kim TN, Ryu JY, Hong HC, Yoo HJ, et al. Associations of low muscle mass and the metabolic syndrome in Caucasian and Asian middle-aged and older adults. *J Nutr Health Aging* 2016;**20**:248–255.
- Lee MJ, Kim EH, Bae SJ, Choe J, Jung CH, Lee WJ, et al. Protective role of skeletal muscle mass against progression from metabolically healthy to unhealthy phenotype. *Clin Endocrinol (Oxf)* 2018.
- Son JW, Lee SS, Kim SR, Yoo SJ, Cha BY, Son HY, et al. Low muscle mass and risk of type 2 diabetes in middle-aged and older adults: findings from the KoGES. *Diabetologia* 2017;**60**:865–872.
- Zhang H, Lin S, Gao T, Zhong F, Cai J, Sun Y, et al. Association between sarcopenia and metabolic syndrome in middle-aged and older non-obese adults: a systematic review and meta-analysis. *Nutrients* 2018;**10**.
- Soskin S, Levine R. A relationship between the blood sugar level and the rate of sugar utilization, affecting the theories of diabetes. *Am J Physiol* 1937;**120**:761–770.
- Miller WJ, Sherman WM, Ivy JL. Effect of strength training on glucose tolerance and post-glucose insulin response. *Med Sci Sports Exerc* 1984;**16**:539–543.
- Szczypaczewska M, Nazar K, Kaciuba-Uscilko H. Glucose tolerance and insulin response to glucose load in body builders. *Int J Sports Med* 1989;**10**:34–37.
- Wang Z, Heshka S, Gallagher D, Boozer CN, Kotler DP, Heymsfield SB. Resting energy expenditure-fat-free mass relationship: new insights provided by body composition modeling. *Am J Physiol Endocrinol Metab* 2000;**279**:E539–E545.
- DeFronzo RA, Gunnarsson R, Björkman O, Olsson M, Wahren J. Effects of insulin on peripheral and splanchnic glucose metabolism in noninsulin-dependent (type II) diabetes mellitus. *J Clin Invest* 1985;**76**:149–155.
- Brochu M, Tchernof A, Dionne IJ, Sites CK, Eltabbakh GH, Sims EA, et al. What are the physical characteristics associated with a normal metabolic profile despite a high level of obesity in postmenopausal women? *J Clin Endocrinol Metab* 2001;**86**:1020–1025.
- Perreault K, Lagacé JC, Brochu M, Dionne IJ. Association between fat free mass and glucose homeostasis: common knowledge revisited. *Ageing Res Rev* 2016;**28**:46–61.
- Byeon CH, Kang KY, Kang SH, Bae EJ. Sarcopenia is associated with Framingham risk score in the Korean population: Korean National Health and Nutrition Examination Survey (KNHANES) 2010-2011. *J Geriatr Cardiol* 2015;**12**:366–372.
- Glouzon BK, Barsalani R, Lagacé JC, Dionne IJ. Muscle mass and insulin sensitivity in postmenopausal women after 6-month exercise training. *Climacteric* 2015;**18**:846–851.
- Baldi JC, & Snowling N. Resistance training improves glycaemic control in obese type 2 diabetic men. *Int J Sports Med* 2003;**24**(6):419–423. <https://doi.org/10.1055/s-10002/jcsm.12520>

- 2003-41173: <https://europepmc.org/article/med/12905089>
17. Lee CG, Boyko EJ, Barrett-Connor E, Miljkovic I, Hoffman AR, Everson-Rose SA, et al. Insulin sensitizers may attenuate lean mass loss in older men with diabetes. *Diabetes Care* 2011;**34**:2381–2386.
 18. Lee J, Kim D, Kim C. Resistance training for glycemic control, muscular strength, and lean body mass in old type 2 diabetic patients: a meta-analysis. *Diabetes Ther* 2017;**8**:459–473.
 19. Fisher G, Windham ST, Griffin P, Warren JL, Gower BA, Hunter GR. Associations of human skeletal muscle fiber type and insulin sensitivity, blood lipids, and vascular hemodynamics in a cohort of premenopausal women. *Eur J Appl Physiol* 2017;**117**:1413–1422.
 20. Gueugneau M, Coudy-Gandilhon C, Théron L, Meunier B, Barboiron C, Combaret L, et al. Skeletal muscle lipid content and oxidative activity in relation to muscle fiber type in aging and metabolic syndrome. *J Gerontol A Biol Sci Med Sci* 2015;**70**:566–576.
 21. Prior SJ, McKenzie MJ, Joseph LJ, Ivey FM, Macko RF, Hafer-Macko CE, et al. Reduced skeletal muscle capillarization and glucose intolerance. *Microcirculation* 2009;**16**:203–212.
 22. Amati F, Dubé JJ, Alvarez-Carnero E, Edreira MM, Chomentowski P, Coen PM, et al. Skeletal muscle triglycerides, diacylglycerols, and ceramides in insulin resistance: another paradox in endurance-trained athletes? *Diabetes* 2011;**60**:2588–2597.
 23. Poggiogalle E, Lubrano C, Gnessi L, Mariani S, Di Martino M, Catalano C, et al. The decline in muscle strength and muscle quality in relation to metabolic derangements in adult women with obesity. *Clin Nutr* 2019.
 24. Mesinovic J, McMillan LB, Shore-Lorenti C, De Courten B, Ebeling PR, Scott D. Metabolic syndrome and its associations with components of sarcopenia in overweight and obese older adults. *J Clin Med* 2019;**8**.
 25. Lawman HG, Troiano RP, Perna FM, Wang CY, Fryar CD, Ogden CL. Associations of relative handgrip strength and cardiovascular disease biomarkers in U.S. adults, 2011–2012. *Am J Prev Med* 2016;**50**:677–683.
 26. Barbat-Artigas S, Rolland Y, Vellas B, Aubertin-Leheudre M. Muscle quantity is not synonymous with muscle quality. *J Am Med Dir Assoc* 2013;**14**:852 e1-7.
 27. von Haehling S, Morley JE, Coats AJ, Anker SD. Ethical guidelines for publishing in the journal of cachexia, sarcopenia and muscle: update 2017. *J Cachexia Sarcopenia Muscle* 2017;**8**:1081–1083.