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

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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

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. However, obtaining this recurring result over the years led us to review the literature for other articles with similar observations. 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. 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, 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. 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 Yoon and Scott et al. 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. 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 older women, while FFM% was negatively associated with it in younger and older men and women. In the articles of Park and Yoon and Scott et al., 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. 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, MetS, or cardiovascular disease risks. 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. In fact, Lee et al. 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. In contrast, Baldi et al. 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. 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, 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. Fisher et al. 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. Furthermore, Gueugneau et al. 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. 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. 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. 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.

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. For instance, Gueugneau et al. 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. 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.

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, which could further contribute to metabolic deteriorations.

iii. **Muscle quality**

Muscle quality, typically evaluated with relative strength, is a major contributor to overall health. Indeed, results from a large cohort study in the US showed a significant association between higher relative strength and a more favourable cardiometabolic profile. 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. Similarly, Mesinovic et al. 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. Supporting this notion are the results of Barbat-Artigas et al. 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.28 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.

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