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Review

Association between fat free mass and glucose homeostasis: Common knowledge revisited

Karine Perreault[a,b], Jean-Christophe Lagacé[a,b], Martin Brochu[a,b], Isabelle J. Dionne[a,b,*]

[a] University of Sherbrooke, Faculty of physical activity sciences, Sherbrooke, Quebec, Canada
[b] Research Centre on Aging, Institute of Geriatrics of Sherbrooke, University of Sherbrooke, Sherbrooke, Quebec, Canada

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Abbreviations: DXA, dual-energy x-ray absorptiometry; FI, fasting insulin; FFM, fat-free mass; FM, fat mass; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance = [Fasting insulin concentration (μU/ml)) X Fasting glucose concentration (mg/dl)]/22.5; IR, insulin resistance; IS, insulin sensitivity; MA, Ometabolically abnormal and obese; MetS, metabolic syndrome; MHO, metabolically healthy and obese; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; QUICKI, quantitative insulin sensitivity check index = 1/([log fasting insulin (mU/ml)] + [log fasting glucose (mg/dl)]); SMM, skeletal muscle mass.

* Corresponding author at: Research Centre on Aging, 1036, Belvédère Sud, Sherbrooke, Québec J1H 4C4, Canada.
E-mail address: Isabelle.Dionne@USherbrooke.ca (I.J. Dionne).

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1. Introduction

Fat Free Mass (FFM) or Skeletal Muscle Mass (SMM) are generally associated with the notions of health and well-being (Moon, 2014; Wolfe, 2006). In most people's mind, the thought of an imposing musculature automatically brings the idea of an athletic morphology (or mesomorph phenotype). Consequently, it is generally accepted that a large FFM or SMM could be associated with healthy characteristics on a physiologic standpoint. Some studies from the 80's supported this common assumption by showing FFM to be associated with glucose uptake in body builders (Szczypaczewska et al., 1989; Yki-Jarvinen et al., 1984).

However, Szczypaczewska et al. (1989) questioned the real contribution of FFM to glucose homeostasis when they compared blood glucose and insulin responses to a 100-g oral glucose tolerance test (OGTT) in three groups of men (10 body builders, 11 untrained lean control, and 11 mildly obese), all of similar age (19–35 years). They found that body builders and obese men had the same amount of FFM in absolute terms, even though body builders had better responses to the OGTT (lowest blood glucose and insulin levels during the test, performed at least 40–48 h after their last training session) (Szczypaczewska et al., 1989). The authors concluded that fat mass (FM; as a percentage of body weight), which differed significantly between groups, could better explain the metabolic responses observed than FFM alone. This concern with regards to the link between FFM and glucose regulation was also raised by Hurley et al. (1987) when they compared middle-aged elite powerlifters (52 +/− 9 years) to distance runners of similar age. They showed that middle-aged powerlifters, in marked contrast to endurance athletes, had deteriorated glucose metabolism. The area under the curve during the OGTT for glucose and insulin in powerlifters was respectively 229% and 332% higher than for runners. Noteworthy, powerlifters had a significantly greater FFM and, surprisingly, a similar percentage of body fat (Hurley et al., 1987). Hurley et al. results brought some nuance to those of Szczypaczewska et al. (1989) by suggesting that FM is not the only factor explaining glucose metabolism alterations. Indeed, based on results from the latter study, a larger FFM may have deleterious impact on glucose metabolism.

In a different context, Kohrt and Holloszy (1995) pointed out in a literature review that glucose intolerance, which prevalence increases in the older populations, may not be attributable (at least solely) to the loss of FFM with aging. The authors mentioned in their discussion that increases in abdominal adiposity combined with physical inactivity account to an important part of the development of insulin resistance and the deterioration in glucose tolerance that has previously been attributed to the aging process (Kohrt and Holloszy, 1995). They suggested that FFM was not a significant contributor to glucose tolerance.

> "*The fact that the 60- to 72-year-old women had excellent glucose tolerance that was almost identical to that of the 25-year-old men, despite having less than half as much muscle mass, strongly suggests that, within wide limits, muscle mass plays a minor role, if any, in the determination of glucose tolerance*." (Kohrt and Holloszy, 1995)

Their conclusion was reasonably prudent. In the last 30 years, the prevalence of obesity and metabolic disorders have reached the level of an "epidemic burden" according to several health authorities (James et al., 2001; Strumpf, 2004; Wang and Beydoun, 2007). This new reality may affect the composition of FFM (or SMM) and consequently, its role with regards to glucose regulation. It has been demonstrated that obesity and aging are associated with abnormal lipid infiltration within muscle, so-called intramuscular adipose tissue. This feature is now known to contribute to the development of metabolic disorders such as metabolic syndrome and type 2 diabetes (Addison et al., 2014; Goodpaster and Brown, 2005). The growing prevalence of obesity across all ages, combined with previous findings presented above, led us to question the assumption that a large FFM is associated with healthier metabolic outcomes, more specifically glucose homeostasis.

The primary objective of this narrative review is to revisit the preconceived idea that greater FFM is associated with better glucose homeostasis. The secondary objective is to examine how different scaling methods (FFM in relation to body size or composition) can affect the relation between FFM and glucose homeostasis.

2. Search strategy

The literature search was conducted between January and November 2014. Studies selected for this review were found on PubMed using the following search terms: ("glucose metabolism" [OR] "glucose tolerance" [OR] "glucose intolerance" [OR] "glucose homeostasis" [OR] "insulin resistance" [OR] "insulin sensitivity") AND ("muscle mass" [OR] "lean mass" [OR] "lean body mass" [OR] "fat-free mass" [OR] "body composition"). Filters were applied to include only studies on humans, published in English language. Articles were selected because they reported the degree of association between fat free or skeletal muscle mass and glucose homeostasis markers, be it a main or secondary finding. Because the search strategy was conducted according to the authors' scientific judgment and imply a certain degree of subjectivity, we consider this review to be a narrative review.

3. Literature review

3.1. Measuring fat free mass & glucose homeostasis

3.1.1. Fat free mass

Several methods have been developed to measure FFM such as underwater technique, plethysmography, bioelectrical impedance, ultrasound, dual-energy x-ray absorptiometry (DXA), computed tomography scans (CT-scan), and magnetic resonance imaging (MRI) (Micklesfield et al., 2012; Segal et al., 1988; Tothill et al., 1996; Wingfield et al., 2014). Because FFM includes all lean tissues in the body, such as viscera, multiples indices and equations have also been proposed to better estimate SMM *per se* (Janssen et al., 2000; Kim et al., 2002). Most of the time, the measured FFM or estimated SMM are further divided by body weight or height to allow comparison between people of different statures. The different indices or units used to define FFM and SMM may lead to different conclusions or associations. The matter will be further discussed in section 3.6. To avoid confusion and for brevity concern, the abbreviation FFM is used to describe all measurements of lean mass (sometimes referred to as lean body mass in original articles) and the abbreviation SMM (also referred to as muscle mass or skeletal muscle) is