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REVIEW

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Diagnosis of obesity based on body composition-associated health risks—Time for a change in paradigm

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Summary

Traditional diagnosis and understanding of the pathophysiology of obesity are based on excessive fat storage due to a chronically positive energy balance characterized by body mass index (BMI). Quantitative and qualitative analysis of lean and adipose tissue compartments by body composition analysis reveals that characterization of obesity as "overfat" does not facilitate a comprehensive understanding of obesity-associated health risk. Instead of being related to fat mass, body composition characteristics underlying BMI-associated prognosis may depend (i) on accelerated growth by a gain in lean mass or fat-free mass (FFM) in children with early BMI rebound or adolescents with early puberty; (ii) on a low muscle mass in aging, associated chronic disease, or severe illness; and (iii) on impaired adipose tissue expandability with respect to cardiometabolic risk. It is therefore time to call the adipocentric paradigm of obesity into question and to avoid the use of BMI and body fat percentage. By contrast, obesity should be seen in face of a limited FFM/muscle mass together with a limited capacity of fat storage.

KEYWORDS
cardiometabolic risk, fat mass, lean mass, obesity paradox, sarcopenic obesity

1 | INTRODUCTION

It was Ancel Keys[1] who coined the term "body mass index" (BMI) for Quetelet's normalization of body weight (kg) by height squared (m^2) that is based on the observation that the transverse growth of the human body is less than the vertical. BMI is still widely used today for the quantitative study of body mass in health and disease. When the American Medical Association in 2013 recognized obesity as a disease rather than a "condition" or "disorder," the decision was, however, controversial because of considerable doubts that the diagnosis of obesity by BMI can improve health outcomes in patients. In fact, studies on the prevalence of "metabolically healthy" individuals with obesity phenotype and "metabolically overfat" individuals with lean phenotype reveal the apparent limitations of the BMI.[2–4]

Traditional understanding of the pathophysiology of obesity is based on excessive fat storage due to a chronically positive energy balance. BMI is a good indicator of percentage fat mass (%FM) at the population level and therefore met the expectations as a diagnostic criterion with internationally accepted and mortality-based cutoffs.[5] More recently, the evolution and implementation of body composition analysis began to question the adipocentric paradigm of obesity. Quantitative and qualitative analysis of lean and adipose tissue compartments reveals that characterization of obesity as overfat based on the widespread use of BMI did not facilitate a comprehensive understanding of obesity-associated health risk. The present paper reviews

the evidence that identifies lean mass, the relationship between fat and lean mass, and limited fat storage capacity rather than %FM or BMI as important predictors for obesity-associated morbidity and mortality.

2 | THE IMPORTANCE OF LEAN MASS FOR DIAGNOSIS OF OBESITY-ASSOCIATED RISK ACROSS THE LIFE CYCLE AND IN HEALTH AND DISEASE

2.1 | Children: BMI does not always reflect an increase in fat mass at the BMI rebound

During the first year of life BMI increases followed by a decline thereafter and then a second increase between 5 and 7 years of age that is designated as "adiposity rebound." An earlier rebound predicts a higher prevalence of obesity in adolescence and adulthood and future cardiometabolic risk (reviewed by Kang et al.[6]). Two studies have shown that the rebound in BMI is, however, not due to adiposity but is explained by a steady increase in lean mass, whereas an increase in fat mass index (FM in kg/m^2) lagged 2–3 years behind, particularly for boys.[7,8] The discovery that the early rebound in BMI is due to faster growth and accelerated increase in lean mass rather than an increase in fat mass is supported by the finding that earlier rebound occurred in children who were tall at age 3 years but not in children with a higher BMI at that age.[9] Small for gestational age birth weight and high protein intake are among the risk factors for "catch-up growth" that may be triggered by endocrine signals as insulin-like growth factor 1 (reviewed by Kang et al.[6]). By contrast, the longitudinal FLAME study suggests that in girls, early BMI rebound was entirely due to differences in the rate of weight gain, rather than in height velocity, and that this weight differential is predominantly due to increased deposition of FM.[8]

2.2 | Adolescents: Increase in BMI does not reflect an increase in fat mass with early puberty

BMI does not reflect changes in energy partitioning as fat and lean mass during puberty. During adolescence, the steady increase in BMI in boys is explained by an increase in fat-free mass (normalized by height squared FFMI) at a concomitant decrease in fat mass (normalized by height squared FMI), whereas in girls, the increase in BMI is explained by a higher increase in FMI compared to FFMI.[10] Similar to early BMI rebound, precocious puberty leads to accelerated growth and is considered a risk factor for obesity in adulthood.[11] A longitudinal study with serial anthropometric measurements (4 years before to 4 years after onset of pubertal growth spurt) allowed to compare sex-specific trajectories of FMI and FFMI among those with an early or late pubertal growth spurt.[12] This study found that children who experience an early pubertal growth spurt accrue progressively more FFM and not FM during the first years of puberty when compared with late-maturing peers of the same age. The authors concluded that higher adiposity commonly observed in adults with early puberty onset likely develops subsequently in later adolescence. In line with these findings, girls who experience an earlier menarche age were taller in early adolescence.[13]

2.3 | Novel insights from accelerated growth and gain in lean mass during BMI rebound and early puberty

These results impact our understanding of the etiology of future excessive weight gain predicted by early BMI rebound or early onset of puberty. Lean body mass and resting metabolic rate (and other aspects of energy expenditure) were proposed to constitute a biological drive to eat, whereas fat mass was negatively associated with food intake, especially in leaner subjects.[14] Instead of an adipocentric view on the regulation of energy balance where a proliferation of fat cells and their secretome determine the drive for energy intake,[15,16] energy requirement (i.e., a higher energy requirement due to accelerated growth or the increase in lean mass) may therefore be the major determinant of increased appetite and energy intake. It was already proposed in 1993 that "the impetus for lean tissue growth, or protein accretion" "regulates nutrient supply".[17]

2.4 | Elderly: BMI does not reflect the same mortality risk in young and older adults

The fact that the BMI associated with the lowest mortality rate shifts toward heavier BMIs with increasing age is known as the obesity paradox in older adults.[18–20] This paradox suggests that fat mass becomes less harmful or even protective with increasing age. However, the decrease in bone mineral content with age leads to a decrease in height that is associated with an overestimation of BMI with increasing age. By age 70 years, BMI values are reported to be inflated by 0.7 for men and 1.6 for women.[21] In addition, it was shown that the U-shaped relationship between BMI and mortality was determined by the relationship between two body components, lean body mass and fat mass and mortality. Higher mortality at low BMI is therefore not explained by a low fat mass but by a low lean mass.[22,23] Since older adults need a higher BMI to have the same lean mass than younger people[24,25] the obesity paradox in older adults may be largely explained by low lean body mass, rather than low fat mass with lower BMI. In line with this hypothesis, older people (>65 years) with the lowest quartile of skeletal muscle mass index had the highest total mortality rate.[26] The same study also shows that the BMI with the lowest mortality in this age group is in the slightly overweight range (24–26.9 kg/m^2), and a higher mortality at lower BMI was only observed in subjects below the lowest quartile of skeletal muscle index. In addition, the Korean Longitudinal Study on Health and Aging has shown that in subjects ≥65 years, baseline BMI, waist circumference, and % fat mass were not correlated with mortality

after 3.5 years follow-up, but a higher lean mass index was a predictor of lower mortality (relative risk reduction of 69% between the highest and lowest lean mass index quartile, $P = 0.03$).[27] An age-related redistribution of subcutaneous adipose tissue from the extremities to the trunk and especially the visceral and ectopic fat depots[24,28] also argues against a protective role of a high adiposity with age. In summary, the survival advantage of a higher BMI in older adults is not explained by a protective effect of fat mass but is due to a higher lean mass with a higher BMI.

2.5 | Disease: BMI does not reflect the same mortality risk in healthy subjects and patients with chronic disease or severe illness

In patients with chronic kidney disease, obesity defined by BMI was found to be associated with a lower risk of death, whereas obesity defined by percentage of fat mass (>25% in men and >35% in women) was associated with a higher risk of death.[29] At first sight, this result suggests that fat mass impairs the prognosis of patients with chronic renal failure. The opposite is, however, true. A high percentage of fat mass is tantamount with a low percentage of lean mass. In order to be interpreted correctly, both fat and lean mass (kg) need to be normalized by height squared (m^2) as FMI and FFMI. The limited value of % fat mass to understand body composition-associated health risk in patients with kidney disease was demonstrated in the same study by stratification of patients according to fat mass % and BMI. This stratification revealed that in two groups of patients with a similar and high fat mass % only those with a low BMI had an increased risk of mortality.[29] Because patients with a high fat mass % and a low BMI have a low absolute amount of muscle mass, a low lean mass at a high fat mass (sarcopenic obesity) was a major determinant of body composition-associated mortality in patients with chronic kidney disease. Similar results were obtained in patients with heart failure.[30] In these patients, the "obesity paradox" was observed only when defined using BMI, with waist-to-height ratio showing the opposite association with mortality or hospitalization due to heart failure. The authors also observed that "lean-fat patients," with high waist-to-height ratio and low BMI, had the worst outcomes.

Other studies found that independent from lean mass, fat mass is associated with higher mortality in more severe obesity only. Among patients with nonmetastatic breast cancer, those with sarcopenia or those in the highest tertile of total adipose tissue showed higher overall mortality.[31] However, etiology and severity of cancer disease may play a role for the impact of fat mass on survival. Higher energy stores could improve prognosis in patients with wasting disease. In line with this supposition, in patients with advanced colorectal cancer the protective role of a higher BMI was explained by both a higher adipose tissue index and skeletal muscle index (adipose tissue and muscle mass normalized by height squared).[32] Other authors investigated patients with stage I to III colorectal cancer and found that both sarcopenia and a high absolute amount of adipose tissue (not normalized for height squared)[33] or only sarcopenia[34] were independently predictive of cancer-specific survival.

In patients with coronary artery disease, low lean mass index (LMI) but not FM% was found to predict all-cause mortality.[35] Others found that in addition to a protective effect of lean body mass, FM% was associated with a higher risk of major adverse cardiovascular events.[36] By contrast, a protective effect of FM% in patients with stable coronary heart disease was suggested by the finding that both low LMI and a low FM% predicted a higher mortality, with mortality particularly high in the group with low LMI/low FM% and lowest in those with high LMI/high FM%.[37]

Critically ill patients are at higher risk for sarcopenia, and BMI is only poorly associated with muscle mass in these patients.[38] Sarcopenia assessed by computed tomography (CT) images was found to be a prognostic marker in critically ill patients.[38] Because a low respiratory musculature can impair weaning from mechanical ventilation, low muscle mass (assessed by psoas muscle area at L3) was found to be an independent risk factor for difficult-to-wean and mortality among critically ill surgical patients.[39] Likewise, sarcopenia and not total adipose tissue was found to be a significant predictor for mortality, and intensive care unit (ICU)- and ventilator-free days in older patients.[40] Similarly, larger admission pectoralis muscle area but not subcutaneous fat area was associated with better outcome and survival in ICU patients.[41] In critically ill patients with intra-abdominal sepsis, sarcopenic obesity but not sarcopenia or visceral obesity alone was a risk factor for mortality.[42] These results argue against a protective role of fat mass as the underlying cause of the obesity paradox in sepsis.

In summary, the obesity paradox in ICU patients may be mainly explained by a protective effect of lean mass and not fat mass with a higher BMI. However, there is also a hypothesis about several potential protective mechanisms of a high fat mass like higher metabolic reserve in catabolic disease or higher lipoprotein levels associated with improved endotoxin clearance.[43,44] These ideas warrant further studies on the impact of fat and lean mass on morbidity and mortality in ICU patients.

2.6 | Summary: Impact of lean body mass on the obesity paradox

Body composition analysis revealed a high lean body mass as an important goal for prevention and preservation of lean body mass as a therapeutic goal in patients. The etiology of the relationship between lean mass and health outcome may be manifold and related to immune function, pulmonary function, frailty, organ function like ejection fraction or glomerular filtration rate, and thermoregulation.[45] Regarding the consistent impact of lean body mass to BMI-associated health risk, the remaining task is to unravel the yet contradictory independent or interacting function of fat mass on morbidity and mortality in different diseases. Appropriate normalization of FM and FFM for height squared or the combined use of FFMI and FM% or FFMI and BMI facilitate to investigate the proportional contribution of fat and lean compartments to health risk as well as their presumable interaction.

Since in the lower range BMI is a less sensitive parameter for fat mass and a better indicator of lean mass,[10] only 18% of overweight women (BMI 25 to <30) and 73% of women with class 1 obesity (BMI 30 to <35) fell into the highest tertile of adiposity[31] the protective effect of lean mass may be especially evident among those in the BMI range of overweight or slight obesity.[31]

3 | THE IMPORTANCE OF THE FAT TO LEAN MASS RELATIONSHIP FOR DIAGNOSIS OF OBESITY-ASSOCIATED RISK

Research on sarcopenic obesity revealed a higher morbidity and mortality in patients with a low muscle mass and a high fat mass when compared to patients with a high fat mass only (reviewed by Baracos and Arribas[46]). It remains, however, under debate whether the risk of a low lean mass and a high fat mass is additive or if the risk of a high fat mass is disproportionally or exclusively high at a concomitantly low skeletal muscle mass. Future studies that aim to investigate this issue need to improve the assessment of a normal lean mass by taking into account the relationship between fat and lean mass. Current definitions of sarcopenic obesity rely on BMI cutoffs for overweight and obesity in combination with fixed cutoffs for a low muscle mass that are derived from normal weight subjects[47] or normal and overweight subjects.[48] Definitions based on static cutoffs disregard the quantitative relationship between fat and lean mass; that is, a normal muscle mass may depend on the amount of fat mass. Fat-free mass index therefore needs to be adjusted for BMI[49] or FMI. In addition, the relationship between FFMI and FMI decreases with age, with a progressive increase in FMI with age allowing to maintain a stable FFMI.[50]

Two prevailing concepts allow to investigate deviations from the normal relationship between fat and lean mass. One concept is called the Forbes rule and is based on the observation that energy partitioning (the fraction of energy lost or gained as protein) is a nonlinear function of body fat mass[51] (Figure 1A). The second concept is based on the two-dimensional plot of FMI versus FFMI in the Hattori chart[52] (Figure 1B). Application of the Hattori chart reveals that the relationship between lean and fat mass depends on age and sex,[53–55] adiposity,[55] and race.[54,56]

4 | THE IMPORTANCE OF LIMITED FAT STORAGE CAPACITY FOR DIAGNOSIS OF OBESITY-ASSOCIATED RISK

Remarkably, the obesity paradox is also demonstrable in type 2 diabetes,[57,58] a disease that is thought to represent the metabolic consequences of increased lipid storage. Muscle is the major organ for insulin-dependent glucose uptake, and muscle mass may be impaired by insulin resistance and a lower insulin-stimulated protein synthesis in type 2 diabetes.[59,60] Muscle mass was indeed shown to be lower in patients with type 2 diabetes compared to healthy subjects controlled for age, sex, height, weight, and race.[61] Concomitantly, sarcopenia was more pronounced in individuals with type 2 diabetes than in normoglycemic controls.[62–66]

In addition to lean mass, fat mass may be a prognostic parameter for metabolic risk. Compared to BMI, fat mass % was not, however, a better predictor of metabolic risk factors.[67,68] Body fat distribution may solve this issue since abdominal obesity has been identified as a characteristic of metabolic risk and diabetes already in 1953 by Jean Vague.[69] As a proposed underlying mechanism, lipolysis of visceral adipose tissue leads to increased portal free fatty acid (FFA) that stimulate hepatic very low density lipoprotein (VLDL) secretion, activate gluconeogenesis, and inhibit hepatic uptake of insulin.[70] This portal hypothesis was therefore thought to generate risk factors for cardiovascular disease and diabetes. In line with this idea, a large waist circumference was shown to increase the future risk of cardiovascular disease (CVD) and diabetes twofold to threefold for a given BMI.[71] Despite the association of abdominal obesity with cardiometabolic risk, subsequent work raised considerable doubts about the importance of visceral adipose tissue and the portal hypothesis. No differences in insulin sensitivity or VLDL-triglyceride secretion were observed between subjects with different VAT volumes matched on intrahepatic fat content, whereas hepatic, adipose tissue,

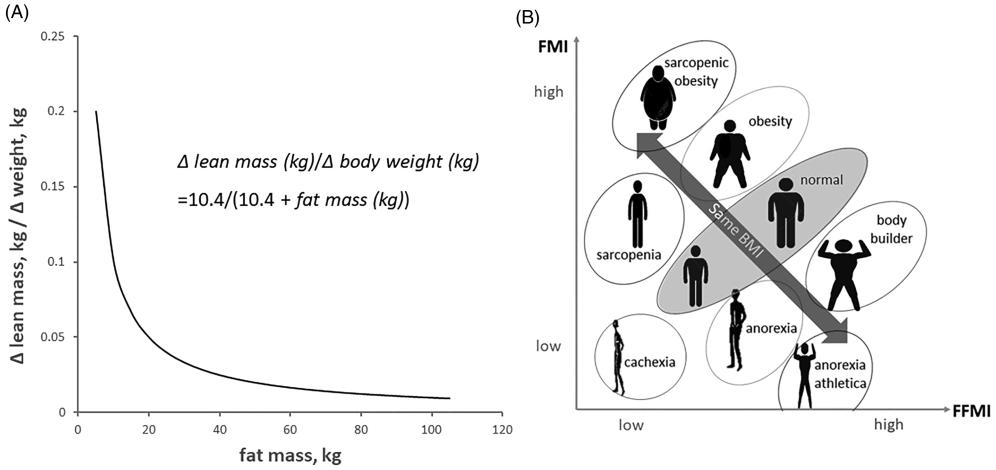

FIGURE 1 (A) Nonlinear relationship between the proportion of body weight lost or gained as lean mass and total fat mass according to Forbes et al.[51]; (B) schematic presentation of the body composition phenotypes as a function of FFMI and FMI using Hattori's body composition chart[52]

and muscle insulin sensitivity were substantially lower and VLDL-triglyceride secretion was almost double in subjects with higher than normal hepatic fat content matched on visceral adipose tissue (VAT).[72] Intrahepatic fat, not visceral fat, was therefore deduced to be linked with metabolic complications.

Because increased visceral fat is usually highly correlated with increased ectopic fat in other sites, such as the liver and the heart,[73] abdominal fat distribution can now be considered a marker of ectopic fat in many sites and may simply indicate dysfunctional subcutaneous fat leading to impaired storage of excess lipids in the subcutaneous metabolic sink (overflow hypothesis). Only ≈20% of portal vein FFA delivered to the liver and 14% of systemic FFA delivered to skeletal muscle are derived from lipolysis of visceral adipose tissue in subjects with obesity.[74,75] The majority of FFA therefore derive from lipolysis of subcutaneous adipose tissue (mainly abdominal subcutaneous adipose tissue) and reach the portal circulation.

In line with the overflow hypothesis, the adipose tissue expandability hypothesis proposes that a failure in the capacity for adipose tissue expansion, rather than obesity per se, is the key factor linking positive energy balance and type 2 diabetes.[76] Support for this hypothesis comes from genetic evidence. Variants associated with a failure of adipocyte differentiation may predispose for type 2 diabetes.[77,78] Selective loss of adipose tissue in rare genetic or acquired forms of lipodystrophies lead to insulin resistance and dyslipidemia.[79,80] In addition, stimulation of fat cell hyperplasia in subcutaneous adipose tissue by PPARγ-agonists (thiazolidinediones) leads to improvements of the metabolic profile, especially in subjects with prediabetes.[81,82] As an indicator of peripheral subcutaneous adipose tissue dysfunction, abdominal obesity was associated with impaired fat storage after meals and failure to extract fatty acids from chylomicron triglycerides.[83] Larger adipocytes were shown to have higher basal and stimulated rates of lipolysis[84] and lower insulin sensitivity and lipid uptake.[85] Overfeeding-induced weight gain led to hypertrophy of abdominal subcutaneous adipose tissue, whereas hyperplasia occurred in gluteofemoral subcutaneous adipose tissue.[86] In this study, a higher fat gain in the lower body was able to prevent the increase in abdominal subcutaneous adipocyte size. After diet-induced weight loss, a disproportionately higher regain (as a percentage of loss) in subcutaneous trunk fat in men and leg fat in women was observed,[87] which may indicate improved lipid storage with weight cycling. In rats, weight regain after sustained weight loss has indeed been shown to increase adipocyte hyperplasia.[88]

Visceral adipose tissue may, however, not be an innocent bystander but could also be responsible for many of the metabolic abnormalities associated with abdominal obesity because of a high secretion of proinflammatory cytokines into the portal circulation (endocrine hypothesis). Altered adipokine secretion and macrophage infiltration in visceral obesity may thus contribute to low-grade inflammation and impaired glucose and lipid metabolism and increased cardiometabolic risk and steatohepatitis.[89,90] Adipocyte size and adipose tissue distribution are again major determinants of inflammatory cytokine secretion.[91,92]

5 | CONCLUSIONS

In conclusion, a positive energy balance increases BMI and fat mass (%), but adverse consequences on health and survival depend on the ability to increase lean mass and subcutaneous adipose tissue. Considering the overwhelming evidence for the protective function of muscle mass and adipose tissue expandability, the definition and diagnosis of obesity based on "adiposity/overfat" and characterized by BMI does not represent a meaningful outcome. In the era of precision medicine, we should avoid using BMI and our goal should be to characterize patients and target interventions based on individual body composition phenotypes.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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