Published in "Obesity Reviews 15(8): 640–656, 2014"
which should be cited to refer to this work.

Functional body composition and related aspects in research on obesity and cachexia: report on the 12th Stock Conference held on 6 and 7 September 2013 in Hamburg, Germany

M. J. Müller[1], V. Baracos[2], A. Bosy-Westphal[3], A. G. Dulloo[4], J. Eckel[5], K. C. H. Fearon[6], K. D. Hall[7], A. Pietrobelli[8], T. I. A. Sørensen[9], J. Speakman[10], P. Trayhurn[11], M. Visser[12] and S. B. Heymsfield[13]

[1]Institute of Human Nutrition and Food Sciences, Christian-Albrechts-University, Kiel, Germany; [2]Department of Oncology, Cross Cancer Institute, University of Alberta, Alberta, Canada; [3]Institute of Nutrition and Dietetics, University of Hohenheim, Hohenheim, Germany; [4]Department of Medicine/Physiology, University of Fribourg, Fribourg, Switzerland; [5]German Diabetes Centre, Duesseldorf, Germany; [6]Colorectal Unit, Western General Hospital, Edinburgh, Scotland; [7]National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK), Bethesda, MD, USA; [8]Verona University Medical School, Verona, Italy; [9]The Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen and Institute of Preventive Medicine, Bispebjerg and Frederiksberg Hospitals, Copenhagen, The Capital Region, Denmark; [10]Institute of Genetics and Developmental Biology, Chinese Academy of Science, Beijing, China, and Institute of Biological and Environmental Sciences, University of Aberdeen, Scotland, UK; [11]Obesity Biology Unit, University of Liverpool and University of Buckingham, Buckingham, UK; [12]VU University of Amsterdam & VU University Medical Center, Amsterdam, The Netherlands; [13]Pennington Biomedical Research Center, Baton Rouge, LA, USA

Received 12 March 2014; accepted 4 Apr 2014

Address for correspondence: Professor MJ Müller, Institut für Humanernährung und Lebensmittelkunde, Christian-Albrechts-Universität zu Kiel, Düsternbrooker Weg 17, D 24105 Kiel, Germany.
E-mail: mmueller@nutrfoodsc.uni-kiel.de

Summary

The 12th Stock Conference addressed body composition and related functions in two extreme situations, obesity and cancer cachexia. The concept of 'functional body composition' integrates body components into regulatory systems relating the mass of organs and tissues to corresponding *in vivo* functions and metabolic processes. This concept adds to an understanding of organ/tissue mass and function in the context of metabolic adaptations to weight change and disease. During weight gain and loss, there are associated changes in individual body components while the relationships between organ and tissue mass are fixed. Thus an understanding of body weight regulation involves an examination of the relationships between organs and tissues rather than individual organ and tissue masses only. The between organ/tissue mass relationships are associated with and explained by crosstalks between organs and tissues mediated by cytokines, hormones and metabolites that are coupled with changes in body weight, composition and function as observed in obesity and cancer cachexia. In addition to established roles in intermediary metabolism, cell function and inflammation, organ-tissue crosstalk mediators are determinants of body composition and its change with weight gain and loss. The 12th Stock Conference supported Michael Stocks' concept of gaining new insights by integrating research ideas from obesity and cancer cachexia. The conference presentations provide an in-depth understanding of body composition and metabolism.

Keywords: Adipose tissue, body composition, metabolism, muscle mass.

Funding: MJM: German Ministry of Education and Research, BMBF Competence Network Obesity (CNO), Reference Centre of Body Composition, (Körperzusammensetzung; FKZ 01GI1125). VB: Canadian Institutes of Health Research, Alberta Cancer Foundation. AB-W: German Ministry of Education and Research (BMBF 0315681), German Research Foundation (DFG Bo 3296/1-1 and DFG Mu¨ 714/ 8-3). JE: Ministerium für Wissenschaft und Forschung des Landes Nordrhein-Westfalen (Ministry of Science and Research of the State of North Rhine-Westphalia), Bundesministerium für Gesundheit (Federal Ministry of Health). KDH, Intramural Research Program of the National Institutes of Health, National Institute of Diabetes & Digestive & Kidney Diseases.

Introduction

From organ and tissue masses to functional relationships between organs and tissues

Manfred J. Müller

Although anatomy is central in medicine, it is only recently that the relationships between body composition and metabolic and functional characteristics came into the focus of research. During the last 20 years, there were fascinating methodological and technical achievements in *in vivo* assessment of body composition and major whole-body components have been characterized at different levels, i.e. the whole body (body mass) to tissues and organs (adipose tissue, brain, liver, skeletal muscle, bone), cells (fat and non-fat cell mass, extracellular mass, extracellular solids), molecular (fat, protein, minerals, water) and elements (e.g. whole-body nitrogen and carbon content; (1)). The descriptive concepts have been extended to the concept of functional body composition that integrates body components into regulatory systems by relating body components to their corresponding *in vivo* functions and metabolic processes (2). Suitable applications of body composition analysis are (i) interpretation of body functions (e.g. fat-free mass [FFM] as the major determinant of energy expenditure) and their disturbances in the context of body components (e.g. insulin resistance related to ectopic fat accumulation in liver, skeletal muscle and pancreas) and *vice versa*; and (ii) interpretation of the meaning of individual body components in the context of their functional consequences (e.g. adaptation of energy expenditure to weight loss is related to fat mass [FM] and body water).

Accurate tools can now be used to assess body composition for risk prediction, 'phenotyping' the obese as well as the malnourished patients and their related comorbidities (3). Individual body components such as FM are under hormonal and genetic control; they are also affected by environmental factors, lifestyle and diseases. Regulation of body weight is a multiple (and at least in part) integrated control of individual body components. Because body components are interrelated and the relationships between individual body components are stable with weight changes, control of body weight seems to be on relationships between tissues and organs rather than on individual components or masses themselves.

Evidence for the idea comes from Benedict's early starvation experiments as well as Keys' seminal semi-starvation study, which both have been re-analysed more recently (4–6). In these studies, the ratio between losses in FM and losses in FFM remained constant throughout a longitudinal weight loss protocol. There was some inter-individual variance in the so-called *P*-ratios (i.e. the ratio of protein energy mobilized to total energy mobilized) and baseline body composition was shown to be its major determinant (7,8). These coordinated changes in organ and tissue masses in response to caloric restriction go in parallel with mass- and tissue-independent changes in their specific metabolic rates (9).

Faced with the stable relations between individual organs, inter-organ and inter-tissue crosstalks are challenging area of research. The present discussion is mainly about crosstalks of adipose tissue with other organs such as skeletal muscle, liver and brain brought about by a still increasing number of secretory products derived from the adipocyte. In addition, liver, skeletal muscle, kidney, bone, immune cells and the gastrointestinal tract have also been characterized as endocrine organs with a huge number of secretory products contributing to various between-organ and tissue crosstalks and feedback control signals.

As for concepts, crosstalks may have different functional characteristics. In electronics, a crosstalk is characterized by an interaction of signals (10). Then, a crosstalk may happen at the near end such as between different fat depots and skeletal muscle. Alternatively, a sum near end crosstalk brings together multiple adjacent pairs such as the sum of signals generated in adipose tissue, muscle or immune cells acting on endothelial cells. In addition, a far end crosstalk interferes between a peripheral organ and tissue and a central control unit, e.g. between adipose tissue and the hypothalamus. Crosstalks may also be attenuated or compensated as might occur with the generation of brown fat cells within white adipose tissue (WAT) as related to and affects the adipose tissue–skeletal muscle crosstalk. Finally, there may be interferences between different crosstalks as in the case when muscle-adipose tissue crosstalk interferes with the muscle-bone crosstalk.

It is challenging to discuss these new concepts in two opposite situations, obesity and cachexia. The feature common to both is perturbation in energy balance. As Stock and others have already noted, both areas may provide possibilities for an integrated approach (11). Integration of research ideas and joint discussion of similarities and extremes will benefit future understanding and research in obesity and cachexia (11,12). If present, a malignant tumour adds an additional dimension both in terms of the specific metabolic rate of the tumour mass as well as its secretory products which may override normal physiological controls (see Cachexia section).

Concepts

A model of functional body composition in humans

Kevin D. Hall

Dynamic changes in functional body composition result from an imbalance between the metabolizable energy content of the diet and the body's energy demands. More specifically, body composition changes at the chemical level result from imbalances between the macronutrients absorbed from the diet and the metabolic fuels oxidized to

meet energy requirements. Because energy expenditure and metabolic fuel utilization are both strongly influenced by body composition, there results a complex dynamic interplay between these variables.

Mathematical modelling provides a useful approach to dealing with this complexity (8). These models can be envisioned by analogy to a 'flex-fuel automobile' that can run on an arbitrary mixture of different fuels (as it occurs in humans with carbohydrate, protein and fat). Such a 'flex-fuel vehicle' would allow the driver to fill the tank with whatever fuel that was cheaper or more readily available, regardless of what mixture is already in the tank. Designing such a vehicle would be a significant engineering challenge, but imagine how much more difficult it would be if the vehicle was not allowed to have a fuel tank. Rather, the vehicle itself must be composed of its fuel and would be continually breaking down and reconstructing its components. Despite the daily turnover of its components and fluctuations of fuel delivery, the composition of the vehicle must remain relatively stable and maintain similar performance characteristics. The human body accomplishes this remarkable engineering feat by the use of three dietary macronutrients (carbohydrate, protein and fat) to both fuel metabolism and provide substrates for body constituents.

While the physiological mechanisms underlying the regulation of human macronutrient metabolism and body composition dynamics are exceedingly complex, the whole-body system obeys thermodynamic laws that make the overall system amenable to mathematical modelling. These conservation constraints form the basis of mathematical models that relate macronutrient imbalances between dietary intake and metabolic utilization with changes in stored glycogen, protein and fat. The changes in these chemical constituents and the fluid shifts associated with these changes allow for mathematical models of functional body composition dynamics at multiple levels of organization ranging from the chemical to tissue and organ levels.

Model predictions have been validated against the data from independent-controlled feeding studies in humans (4,5,13,14) and were found to match the model predictions (8,15,16). This was not only true for prediction of weight and body composition changes, but also resting energy expenditure (REE), carbohydrate and fat oxidation, nitrogen balance, and individual substrate fluxes, e.g. *de novo* lipogenesis, protein degradation, and synthesis, as well as gluconeogenesis (13–17). This can be extended by taking into account metabolic adaptations, i.e. the thermic effect of feeding, adaptive thermogenesis in response to underfeeding, and the effects of physical activity and exercise on energy expenditure and substrate oxidation rates. Applying models to available experimental data allows for exploration of unaccounted for variance and the potential to infer unmeasured quantities and reveal new metabolic findings (18).

Simplification of complex macronutrient balance models can be achieved by quantifying how energy imbalances are partitioned between either FM or FFM (or body protein) during weight loss and weight gain, and most models of human body composition dynamics have used such simplifications (8). It is also possible to derive energy partitioning relationships between different body fat compartments. For example, visceral adipose tissue (VAT) changes as fraction of the change in whole-body FM is strongly correlated with the initial VAT/FM ratio (19). Data suggest that there is a preferential loss in VAT with a higher initial VAT/FM ratio and that the same allometric relationship describes the VAT response to exercise, diet, diet + exercise, and weight loss after bariatric surgery in both men and women.

Dynamic mathematical models provide an integrative framework to help design, predict and interpret the results of human experiments and in clinical practice. For example, modelling weight loss in response to diet and exercise provides a sound basis in treating obese patients (17). Furthermore, mathematical modelling is beginning to help better understand the metabolic and body composition derangements that occur in diseases such as cancer cachexia (20).

Regulation of body composition: body components–brain feedback in weight control

Abdul Dulloo

The regulation of body composition in response to energy deficit and energy surplus can be conceptualized as being brought about through control systems that operate via the control of body energy partitioning between lean and fat tissues, via compensatory changes in energy intake and via adaptive changes in thermogenesis. Despite considerable advances made over the past decades towards establishing the existence and operational modes of these control systems, a mechanistic explanation of body composition regulation in humans remains largely fragmentary. Fundamental questions have been raised and addressed from the analysis of data from longitudinal studies of experimentally induced weight loss/recovery or weight gain/recovery. These findings have been integrated into conceptual models of body composition autoregulation and they pinpoint some of the important issues and gaps in knowledge about various components of feedback loops between changes in body composition and compensatory changes in energy intake and energy expenditure (6,21,22).

For example, the adipocyte-releasing hormone leptin – which acts on brain areas to induce satiety and enhance sympathetic control of thermogenesis – is often integrated in the lipostatic theory of weight regulation. Yet, the role of leptin as a circulating 'adipostatic' signal controlling body fat is questionable in view of the poor correlation between the kinetics of circulating leptin and dynamic changes in body fat in response to energy deprivation and refeeding.

Furthermore, a feedback loop between body fat depletion and the brain circuitries controlling food intake cannot alone explain why human subjects recovering weight after starvation continue to overeat well after body fat has been restored to pre-starvation values, thereby resulting in 'fat overshooting'. Indeed, a detailed re-analysis of the classic Minnesota Experiment of semi-starvation and refeeding suggests that the autoregulatory component of the hyperphagic response to energy deprivation goes beyond an explanation based solely on the lipostatic theory because, in addition to the depletion of FM, the reduction in FFM also contributes to the compensatory hyperphagia (23).

The integrated outcome of this re-analysis suggests that the critical event that eventually leads to the prolongation of hyperphagia beyond the complete recovery of FM resides in the suppression of thermogenesis which drives fat recovery at a rate that is greater than that determined by the partitioning characteristic of the individual (24). As this enhanced metabolic efficiency that drives fat acceleration is a function of fat depletion, and the prolongation of hyperphagia (after complete recovery of FM) is a function of depleted FFM still to be recovered, the extent of fat overshooting would therefore depend upon the extent to which both FM and FFM are depleted. This, in turn, would depend upon the partitioning characteristic of the individual which is known to be dictated primarily by the initial (pre-starvation) adiposity. Indeed, the extent of fat overshooting can be shown to increase exponentially with decreasing initial %body fat (22). From a perspective of autoregulation of body composition therefore, lean dieters are at greater risk for fat overshooting than the obese dieters. Given the increasing prevalence of dieting among those in the normal weight range (due to pressure for a slim image, body dissatisfaction or athletic performance), together with accumulating evidence suggesting increased cardiometabolic risks associated with weight fluctuations in the non-obese population groups (25), the notion that large fluctuations in body weight may predispose to increased fatness and the metabolic syndrome warrants greater experimental scrutiny and deserves greater public health concern than so far acknowledged.

Overall, the available evidence suggests that feedback signals from both fat and lean tissues operate in the regulation of body composition through their central effects on food intake and thermogenesis, although the various key components of these adipostatic and proteinostatic feedback mechanisms remain undefined. However, the discovery that a multiplicity of factors are secreted by adipocytes and myocytes opens new avenues in the search for adipostatic and proteinostatic feedback signals to the brain in the regulation of body composition, with major implications for the pathogenesis and management of obesity and cachexia. Furthermore, there is emerging evidence of a role for brain–muscle interactions in the mechanisms by which inflammatory signals mediate the loss of skeletal muscle mass during cachexia. In addition to the direct effects of inflammatory cytokines in inducing skeletal muscle atrophy, the integration of inflammatory cytokines signalling pathways within the central nervous system has been shown to play a critical role in muscle wasting via activation of the hypothalamic–pituitary–adrenal axis (26). Future investigations along such brain–muscle interactions are bound to provide powerful insights into the mechanisms of muscle wasting during cachexia and in the pathogenesis of sarcopenic obesity.

What is an appropriate energy expenditure for body composition?

Steven B. Heymsfield

Determining if a subject's REE is low or high for its body size is a pervasive question in clinical nutrition research (27,28). High or low REE values can signal variance in the composition of FFM (i.e. the relative proportion of high, metabolic rate organs such as brain, heart, liver and kidneys), underlying metabolic disease, predisposition to weight gain or loss, or metabolic processes that are unrelated to body size. Early investigators applied body mass and height as size measures, all that they had available at the time, and formulated the surface law ($REE \propto Mass^{0.66}$) and Kleiber's law ($REE \propto Mass^{0.75}$), although each has limitations when adjusting REE (29).

Body composition methods first developed and then introduced during the mid-20th century provided the first opportunity to identify 'homogeneous' metabolically active compartments (29). REE is highly correlated with the body size composition measures and the adjusted value of REE should be independent of body size. Consider the simple regression model,

$$REE = m\text{FFM} + b, \quad (1)$$

with m being the slope and b (REE) the y-axis intercept. For the ratio REE/FFM to be independent of FFM, the y-axis intercept must be zero so that

$$REE = m\text{FFM}, \text{ and thus} \quad (2)$$

$$REE/FFM \quad (3)$$

is a stable value (i.e. m) across all healthy adults. In fact, when REE is regressed against FFM, the b intercept term is positive and differs significantly in magnitude from zero. REE for men and women plotted against FFM results in a regression line with a significant intercept term of 410.4 kcal d^{-1} (27,29).

FFM has remained the main compartment used by investigators over the past several decades to adjust REE for body size (27,28), although the need to remove low

metabolic rate compartments other than fat from body mass as a means of estimating 'metabolically active' body mass was recognized.

At the tissue-organ level, the present availability of estimates of organ and tissue masses provided a new opportunity to develop physiological REE prediction formulas based upon established heat production rates of major body tissues (9,30,31). Tissue and organ mass can be estimated with great accuracy using computed tomography (CT) or magnetic resonance imaging (MRI); the energy expended by each tissue and organ can be calculated as the product of mass and mass-specific metabolic rate based on compiled from *in vivo* and *in vitro* observations. REE can be calculated as the sum of all tissue and organ metabolic rates. Viewing REE from the tissue–organ perspective, the large contributions of four FFM components (brain, liver, heart and kidneys) to whole-body REE become obvious. While <6% of representative body mass, these organs contribute to 60–70% of REE. REE is then calculated from

$$\begin{aligned}\text{REE (kcal d}^{-1}) = {} & (240 \times \text{brain mass}) + (200 \times \text{liver mass}) \\ & + (440 \times \text{heart mass}) + (440 \times \text{masses} \\ & \text{of kidneys}) + (13 \times \text{mass of skeletal} \\ & \text{muscle}) + (2.3 \times \text{bone mass}) \\ & + (4.5 \times \text{adipose tissue mass}) \\ & + (12 \times \text{residual mass}).\end{aligned} \quad (4)$$

Residual mass is the difference between the sum of measured body components and body weight. Today, physiological REE model terms for brown fat and the microbiome are not yet available.

Tissue–organ proportions vary with body size (i.e. among normal-weight, overweight and obese subjects), in adolescents and adult age, across men and women, between race groups, and with stature (29,30,32). All tissues and organs scale to FFM with powers approaching 1.0, except brain, which has powers <0.2 for both men and women (29). Multiple regression analysis was used to establish how skeletal muscle, heart, liver, kidney, brain and residual mass (weight minus the sum of other tissues, including adipose tissue and organs) scale to FFM. Tissue–organ mass was set as the dependent variable and FFM, age and adipose tissue mass as potential predictor variables in multiple regression models. The explained variance of traditional REE model with FFM alone as the predictor was 0.78 and SEE = 129.4 kcal d^{-1}. Adding age and adipose tissue mass increased R^2 to 0.84 (SEE, 112.2 kcal d^{-1}).

All these models had statistically significant intercepts and they resemble the general form of traditional FFM-based REE prediction models (29). However, brain, liver, skeletal muscle, bone, adipose tissue, residual mass and age added as significant covariates and the final R^2 reached 0.86 with lowest SEE (105.9 kcal d^{-1}) of the developed series of REE prediction models with a non-significant intercept of 40.6 kcal d^{-1}. Because REE links to tissue-organ level, the traditional REE-FFM model given in formula (1) is converted into

$$\begin{aligned}\text{REE (kcal d}^{-1}) = {} & 40.6 + 5.1\ \text{AT} + 294.2\ \text{Br} + 141.5\ \text{Li} \\ & + 20.3\ \text{SM} + 13.7\ \text{RM} - 1.6\ \text{Age}.\end{aligned} \quad (5)$$

The newly defined compartments have improved correlations with REE estimates over body weight-height approaches, but all share a common limitation: REE-body composition ratios are not 'constant' but vary across men and women and with race, age and body size (27,28). The currently accepted alternative to ratio-based norms is to statistically adjust for predictors by applying regression models to calculate 'residuals' that determine if a measured REE is relatively high or low (27,28).

The distinguishing feature of statistical REE-body composition models is a 'non-zero' intercept, the cause of which is unknown. FFM is not a metabolically homogeneous compartment, but instead FFM varies systematically in tissue–organ proportions as a function of body size. The non-zero intercept observed with traditional REE models largely becomes non-significant when organ volumes (e.g. brain and/or liver mass) are included as model covariates (29). These new findings provide a context for future research aimed at establishing between subject differences in energy metabolism. To go beyond the whole body or tissue/organ mass is to directly measure specific energy expenditure of individual tissues and organs as well as their changes in response to changes in weight and body composition (9,31). These advances will likely improve our understanding of energy expenditure effects of disease, including cancer and other chronic conditions associated with cachexia.

Functional aspects of adipose tissue and muscle

Effects of over- and under-nutrition on body composition and metabolism of the mouse – what goes up does not necessarily come down

John Speakman

When animals consume excess calories they gain weight, and when they consume insufficient calories relative to expenditure they lose weight. However, these gross changes in body weight mask the details of the changes in body composition that accompany the responses to over- and under-nutrition. These relations were studies in adult mice (5 months old) with stable body weights who were fed two graded levels of over-nutrition (high-fat diets with differing % fat up to 60%) and five graded levels of caloric restriction (from 0 to 40% less calories than their individual baseline intakes). As anticipated, greater over-nutrition led to greater total body weight gain and greater levels of under-nutrition led to greater levels of body weight loss.

The changes in 23 tissues assessed, however, were radically different. When animals gained weight they did so primarily by increasing the sizes of their fat stores in different body regions (i.e. subcutaneous, epididymal, retroperitoneal, omental, mesenteric and brown adipose tissue). The sizes of the vital organs (i.e. brain, liver, kidneys, heart, lungs, pancreas and spleen) were unaffected but structural organs (bone and skeletal muscle, pelage and tail) also increased in size.

During weight loss with caloric restriction, there was also a loss in body fat, but the largest weight losses were actually among structural organs – such as the skeletal muscle, skin and tail. The vital organs were also generally decreased but to a lesser extent than structural organs or fat. Testes mass decreased at the highest level of caloric restriction only, whereas the mass of accessory organs such as seminal vesicles linearly decreased with the degree of starvation. Some vital organs related to the alimentary tract (i.e. stomach, small intestine, caecum, large intestine) actually increased or remained unchanged in size under restriction.

Calculations reveal that tissue loss contributes to about 20% of the energy shortfall explaining 52–81% of the reduction in whole-body energy expenditure. This is associated with decreases in circulating IGF-1 and resistin levels.

Two hypotheses emerge about the implications of organ and tissue mass loss during caloric restriction. First, animals oxidize the energy derived from those tissues. Second, reducing organ-tissue mass lowers energy expenditure and thus contributes to metabolic adaptation. These changes reflect the functional responses of the animals that attempt to minimize expenditure while preserving vital functions and sustaining food intake.

With overfeeding, weight gain is mostly explained by expansion of WAT. In addition, there were small changes in structural body components. By contrast, masses of vital organs and brown adipose tissue remained unchanged.

Functional correlates of fat mass and fat-free mass relationships during underfeeding and refeeding in humans

Anja Bosy-Westphal

Short-term voluntary perturbations in energy balance lead to metabolic and neuroendocrine adaptations that counteract weight changes. For example, regain of weight and FM may exceed prior weight loss, the so-called 'catch-up fat phenomenon' (5,23). Fat regain at an intense rate can also occur in patients with cancer cachexia during short-term remission of their disease, suggesting that the impetus for catch-up is also present in disease (33). Adaptive thermogenesis and reduced energetic efficiency of physical activity add to compensate body weight whereas insulin sensitivity and a low metabolic flexibility contribute to the partitioning of weight regain (i.e. as gain of either FM or FFM (34,35)). Beyond energy and macronutrient balances, diet composition (e.g. glycaemic load; glycaemic index (GI); protein content) contributes to these adaptations.

When compared with high GI diets with a lower protein content, a low GI diet with a higher protein content resulted in improved weight loss maintenance in weight-reduced obese patients (36). These findings point to insulin secretion and/or insulin sensitivity as determinants of weight gain. However, insulin sensitivity had no effect on weight gain (37), but in Pima Indians insulin resistance was associated with reduced risk of weight gain (38). By contrast, improved insulin sensitivity with energy restriction was associated with lower weight regain after previous weight loss (39).

Using a controlled dietary intervention study protocol to investigate whether diets differing in carbohydrate content and GI affect regain in fat and FFM under conditions of fixed energy intake and physical activity, 32 healthy, normal-weight, young men followed 1 week of overfeeding protocol (mean weight gain of 1.8 kg), 3 weeks of caloric restriction (mean weight loss of about 6.0 kg) and 2 weeks of hypercaloric refeeding at ±50% energy requirement (mean weight regain of 3.4 kg; for details, see 40–43). During refeeding, four study groups differing in carbohydrate intake (50%CHO, 65%CHO) and GI (low GI, high GI) were formed. Changes in FM were measured by quantitative magnetic resonance (EchoMRI; Houston, TX, USA; 43) and adjusted for predicted values using mathematical modelling of energy balance (15).

Both GI and carbohydrate content affected insulin sensitivity, metabolic flexibility (i.e. the increase in respiratory ratio [RQ] with refeeding, and thus the capacity to utilize lipid and carbohydrate fuels and to transition between them; 44), and the partitioning of weight regain. Refeeding was associated with impaired fasting fat oxidation and thus augmented fat regain. Energetic efficiency at low work intensities was reduced in response to caloric restriction. The higher the fall in energetic efficiency during low-level exercise, the greater the regain of body weight.

As to the determinants of weight regain, (i) decreases in plasma leptin levels, (ii) reduced energetic efficiency at low work intensities during preceding caloric restriction, as well as (iii) a limited activation of the sympathetic nervous system (SNS) with refeeding were significantly associated with regain in body mass. Weight regain as either FM or FFM was associated with a reduced insulin sensitivity and low metabolic flexibility during refeeding (40,41).

Taken together, during caloric restriction, the decrease in plasma leptin levels, the increase in energetic efficiency at low-grade physical activity, and a relatively low SNS activity are associated with regain in body weight during subsequent refeeding. During refeeding, insulin resistance and a low-fat oxidation add to regain of FM.

Skeletal muscle crosstalk in response to exercise and nutrition

Jürgen Eckel

Regular physical activity has beneficial effects on whole-body metabolism, while a sedentary lifestyle is a major risk factor for developing metabolic diseases such as type 2 diabetes mellitus. Besides their established roles in work performance, energy and protein stores, skeletal muscle and adipose tissue are endocrine organs. Skeletal muscle cells and adipocytes both secrete a broad range of proteins and cytokines, generally termed adipokines in the case of adipocytes, and myokines for muscle cells. Myokines have been shown to affect muscle physiology and additionally exert systemic effects on other tissues and organs.

Several myokines are regulated by contraction, such as angiopoietin-related protein 4, fibroblast growth factor 21, interleukin (IL)-6, IL-7, IL-15, leukaemia-inhibitory factor, myonectin, myostatin and vascular endothelial growth factor (VEGF) (45). The beneficial effects of physical activity are often considered due to an improved energy metabolism; however, myokines are also thought to be involved because skeletal muscle secretes higher levels of myokines in response to contraction (45).

With contraction, muscle glucose uptake and fat oxidation rates increase, and these effects are associated with the release of myokines such as IL-6, IL-7 and BDNF (brain-derived neurotrophic factor). Until now, there are more than 540 myokines, and IL-6 is the most prominent muscle-derived protein, which was demonstrated to be up-regulated in plasma after exercise (46). By contrast, contraction blocks TNFα release and signalling in muscle. As IL-6 and BDNF result in increased lipid oxidation, IL-7 regulates muscle cell development. Novel contraction-regulated myokines are YKL-40, irisin and MCP-1.

Many of the contraction-regulated myokines described in the literature are additionally known to be secreted by adipocytes. These proteins were termed adipo-myokines. The current literature mainly describes a negative crosstalk between excess body fat and skeletal muscle, while the data of IL-6 and irisin indicate an additional crosstalk from the muscle to the adipose tissue (47,48).

Adipokines and myokines appear to have autocrine effects within skeletal muscle and adipose tissue. Additionally, they are involved in an endocrine crosstalk with other tissues such as liver. Depending on the serum level and the incubation time, adipo-myokines appear to have a beneficial or an adverse effect on the target tissue (49). Adipokines and myokines may also have inconsistent effects. It is presently unclear why pro-inflammatory adipokines are up-regulated in the obese state, and thus may be associated with negative sequelae even though they also have beneficial effects after exercise.

Myokines have been proposed to increase energy expenditure, an effect explained by the development of brown-fat-like cells of white adipocytes (47). At the cellular level, the transcriptional co-activator, PGC1alpha, activated by FGF21 (fibroblast growth factor) generated in brown adipocytes, stimulates glucose uptake, lipolysis and metabolic rate. PGC1alpha expression in muscle increases the expression of FNDC5, a membrane protein that is cleaved to the myokine irisin. Irisin is induced in mice but its existence in humans is questionable (48). In contrast to mice, FNDC5 is not up-regulated by contractile activity in humans and irisin was not found in supernatants of human myotubes (48). Genome analysis revealed that irisin is a pseudogene in humans, the protein is not translated due to a mutation in the start codon. In addition, irisin had no effect on the white-to-brown transition of human pre-adipocytes.

More recently, a novel cytokine, YKL-40 (also known as Chitinase-3-like protein1, CHI3L1), has been identified in the secretome of primary human skeletal muscle cells by mass spectroscopic analysis. This protein is expressed by many other cells (e.g. macrophages and hepatocytes). It lacks enzymatic activity and binds to PAR2 (protease-activated receptor2). YKL-40 secretion goes down during differentiation and is up-regulated by inflammatory cytokines. YKL-40 reduces (i) TNFα but not IL-1beta-induced NF-kB activation, and (ii) the TNFα-mediated secretion of MCP1, IL-8 and IL-6 secretion. In addition, YKL-40 protects from TNFα-mediated insulin resistance. Taken together YKL-40 reflects the versatility of an individual myokine.

Adipokines, myokines and tissue crosstalk

Paul Trayhurn

WAT, which was traditionally considered to have little or no function beyond that of a fuel storage organ, is now recognized to have multiple roles. These include thermal insulation (particularly in marine mammals), mechanical protection, and as a key signalling and endocrine organ. Our current perspective on the physiological roles of white fat follows from the discovery that white adipocytes are major secretory cells, releasing a multiplicity of metabolic and signalling factors (50–54). Adipocyte secretions, the quantitatively most important of which are fatty acids, comprise both lipids and proteins. Most attention has been focused on the protein factors secreted from fat cells – the adipokines. Nevertheless, there is a range of lipid moieties released from white adipocytes, and these include prostaglandins, endocannabinoids, α-tocopherol, cholesterol and the active form of vitamin D_3 (51,52).

More than 100 different adipokines have been clearly identified based on gene expression, and the demonstration that the encoded protein is secreted from adipocytes. However, proteomic studies indicate that there are several hundred adipokines in total (55). Many adipokines are linked to immunity and the inflammatory response (including both classical cytokines and chemokines), to insulin sensitivity, and to the architecture of the extracellular matrix of adipose tissue

(53–56). Others are involved in lipid metabolism, vascular haemostasis, the regulation of blood pressure or energy balance. Much attention has been focused on inflammation-related adipokines and the state of inflammation that develops in adipose tissue as tissue mass expands in obesity (53). This inflammatory state, which involves the recruitment of macrophages and other immune cells, as well as the increased synthesis and release of inflammation-related adipokines, is widely considered to underpin the development of obesity-associated disorders – particularly insulin resistance and the other components of the metabolic syndrome (53–56).

Two particular adipokines – leptin and adiponectin – are major hormones that were first discovered in adipose tissue and which have multiple actions, both locally and distally. Indeed, it was the discovery of leptin in 1994 as the product of the 'ob' (now LEP) gene, a mutation that leads to the profound obesity of the *ob/ob* mouse, that has led to the unambiguous recognition of WAT as an endocrine organ (57). Some adipokines may function locally, through autocrine or paracrine actions, rather than being endocrine factors. By definition, endocrine factors secreted from adipocytes are involved in communicating with other tissues and organs. One of the most potent examples of the endocrine action of an adipokine comes from the central effects of adipocyte-derived leptin on the neuroendocrine regulation of appetite in the hypothalamus. This demonstrates a direct communication from fat cells to the brain.

While the synthesis and secretion of many key adipokines, including leptin and inflammation-related factors such as IL-1β and IL-6, rise with increasing adipose mass in obesity, the production and release of the other major adipocyte hormone, adiponectin, falls (58,59). Importantly, this has implications for inflammation and insulin sensitivity because the hormone has both anti-inflammatory and insulin-sensitizing actions (60–62). One of the conundrums in adipose tissue biology is why the production of many adipokines changes with tissue expansion in the obese. One proposed mechanism is that it is a response to hypoxia, mouse data demonstrating clearly that the O_2 tension is markedly lower in adipose tissue depots of obese than lean animals (51,63). Hypoxia may underpin the inflammatory response and other functional changes in adipocytes that occur with obesity. Indeed, in adipocytes in culture, reduced O_2 tension leads to the stimulation of the expression and release of adipokines such as leptin, VEGF, IL-6 and angiopoietin-like protein 4/fasting-induced adipose factor (ANGPTL4), while inhibiting the production of adiponectin (63).

The identification of the rapidly growing family of adipokines has revolutionized our understanding of the biology of WAT and the extent to which it is integrated into metabolic regulation and whole-body homeostasis. It has also increasingly served as a model for other tissues and organs which had not been previously considered to exhibit a significant secretory function. Perhaps the most potent example is skeletal muscle. While myostatin (also known as growth differentiation factor 8) had been recognized as a secretion from myocytes, inhibiting muscle differentiation and growth, the possibility that there is a range of protein secretory products from muscle cells appeared unlikely. However, the perspective began to change following the discovery that skeletal muscle releases large quantities of IL-6 into the circulation following exercise (64–67). Muscle contraction leads to the stimulation of the expression of the IL-6 gene in muscle cell cultures and the encoded protein is released. This has led to the development of the concept of myokines as secreted proteins from muscles, paralleling the adipokine paradigm.

Subsequent studies, taking in effect a candidate gene/protein approach, have identified several other myokines, including IL-7, Il-8, IL-15, chemokine CXC motif ligand-1 (CXCL-1) and leukemia inhibitory factor (LIF) (65,67–69). This has recently also been followed by proteomic approaches in which the muscle protein secretome has been investigated. Proteomics suggests that the number of myokines may be in the low hundreds (70–72), although caution has to be exercised in that there is the risk that cell damage leads to the leakage of proteins into the culture medium which would not otherwise be released – similar caution needs to be considered in the case of proteomic studies on adipocytes. Nevertheless, it is increasingly evident that the myokines as a group are not restricted to a small number of proteins. A recently identified myokine of particular interest is irisin. This is encoded by the skeletal muscle fibronectin domain containing protein 5 (FNDC-5) gene, the immediate product of which is a membrane protein that is subsequently cleaved and secreted as irisin (73). Irisin has the intriguing action of 'browning' of white adipose depots – i.e. of driving the tissue towards a thermogenic, energy-dissipating profile (73,74). However, while this is the case in rodents, as with resistin, the situation appears different in humans, as noted above in the previous part of this manuscript.

Irisin provides a strong example of crosstalk between tissues, and between skeletal muscle and adipose tissue in particular. A further example is leptin, which has actions on muscles as well as other organs, including the brain as noted earlier. There has been some emphasis on the role of muscle-derived IL-6 as a lipolytic factor, but this is increasingly viewed as an action within muscle itself rather than distally on adipose tissue (66).

Cachexia

Body composition and clinical course in patients with cancer cachexia

Vickie Baracos

The cardinal diagnostic criterion of cachexia is the appearance of involuntary weight loss, signalling alteration of the

normally precise controls that serve to maintain body weight and body composition throughout adulthood. Skeletal muscle wasting is considered the central feature of cancer cachexia, and a 2011 international consensus of experts (75) underscored that this muscle loss may occur with or without concurrent loss of FM. Clinical and basic research on cancer cachexia has a strong focus on the aetiology and clinical implications of this muscle loss. Severe depletion of skeletal muscle, termed sarcopenia (Greek 'sarx' of flesh), is defined as a low level of muscle associated with statistically significant increases in health risks and an impaired health state (e.g. mortality, pharmaceutical drug toxicity, loss of strength and reduced physical disability (75)). Cut-offs defining sarcopenia and its relation to risk of mortality which were solved using statistical approaches have been published for cancer patients (76,77). Sarcopenia is prevalent in older populations and is frequently seen in cancer patients. Cancer patients presenting with a loss of muscle mass may be underweight, normal weight, overweight or even obese (76,77).

In clinical practice, sarcopenia may be camouflaged by overweight and obesity and, thus, there is a need of detailed body composition analysis. Because cancer patients are routinely followed in clinical practice by CT imaging, there is a considerable opportunity for detailed quantification of different tissues with high specificity and precision. CT imaging has enormous potential within the field of body composition analysis. In clinical practice, abdominal scans are often available and images can be evaluated at the level of the third lumbar vertebra where cross-sectional areas of muscle strongly correlate with whole-body muscle mass. Using these measures (77) in a prospective clinical study of cancer patients with body mass index (BMI >30 kg m^{-2}), survival was about 11 months in sarcopenic cancer patients compared with 21 months in a group of patients with normal muscle mass, and this was independent of cancer site, stage and performance status. This was subsequently confirmed and expanded (76) in a population cohort of patients crossing all categories of BMI. Sarcopenia also predicted poor outcomes of cancer surgery including infectious complications and use of inpatient rehabilitation (78). Cancer patients with sarcopenia appear unusually prone to chemotherapy-associated severe toxicity across a wide array of cancer sites and cancer therapies, and these studies have been summarized by (79).

An emerging set of findings relates to the presence of fatty infiltration of muscle, termed myosteatosis. This is detected as reduced skeletal muscle X-ray attenuation in quantitative analysis of CT (i.e. between –29 and +29 HU, low attenuation muscle; between +30 and +150 HU, normal attenuation muscle). Independent of classic prognostic factors in cancer such as disease stage, site and patient performance status, low attenuation values in muscle predict increased mortality (76,80); however, the underlying basis of the fatty infiltration of muscle and its relation to survival remain to be understood. Myosteatosis is discussed in further detail by Dr. Fearon in the next section.

Longitudinal studies provide an opportunity to study the body composition changes of cachexia over time (20,33). Repeated measurements suggest that tumour progression is correlated with losses in adipose tissue and muscle mass, and this would be expected given the high energy demand of tumour tissue (20,33). The progression of muscle and fat loss with tumour progression was exponential and appears similar in different cancers (lung, colorectal, pancreas cancer, and cholangiocarcinoma) (33), with the exception that patients with pancreatic cancer had higher overall incidence and rate of fat loss.

In patients with advanced cancer, the potential for positive energy balance skeletal muscle anabolism is not well characterized. In a longitudinal study (33), a mixed population of patients with advanced solid tumours was studied over a period of ~12 months, and each interval between two CT scans (~3 months) was assessed for loss, gain and stable behaviour of fat and muscle. The overall frequency of muscle gain was 15.4% whereas muscle mass was stable in 45.6% of intervals between any two scans, making maintenance or gain of muscle the predominant behaviour. Likewise, adipose tissue was stable in 27.1% of intervals and gain occurred in 24.8% of intervals. These findings suggest that cachexia is not an unmitigated trajectory of loss, but rather a period dominated by the opposing forces of the cancer (catabolic) and treatment (anabolic) in a context where controls of body energy balance are functional and may result in periods of stability and regain, as well as loss. The clinical course of skeletal muscle wasting in advanced cancer and the window of possible muscle anabolism were assessed. Multinomial logistic regression revealed that being within 90 d (vs. >90 d) from death was the principal risk factor for muscle loss (odds ratio [OR] = 2.67) and muscle gain was correspondingly less likely (OR = 0.37) at this time (33). Thus, a window of anabolic potential exists at defined early phases of the disease trajectory (>90 d survival) creating an opportunity for intervention to stop or reverse muscle wasting. A variety of nutrition therapies (macro- and micronutrients, branched chain amino acids, leucine, *n*3-fatty acids) and drugs (e.g. selective androgen receptor agonists, antagonists of myostatin, cytokines and protein degradation) are under investigation to exploit and expand anabolic potential.

Adipose tissue muscle crosstalk in cancer cachexia

Kenneth C.H. Fearon

Cancer cachexia is multifactorial characterized by an ongoing loss of skeletal muscle (with or without loss of FM) that cannot be reversed by conventional nutritional support (75). The pathophysiology is characterized by a negative protein and energy balance driven by reduced food

intake, low physical activity, systemic inflammation and abnormal metabolism. Cachexia in patients with cancer is characterized by anorexia, increased or decreased energy expenditure, increased lipolysis, insulin resistance, reduced protein turnover and reduced physical activity. The degree of weight loss and the severity of the underlying metabolic changes are mainly driven by inflammation: cancer patients with a positive acute phase response had a low energy intake at concomitantly increased REE.

Mediators of cachexia include cytokines, neuroendocrine hormones and tumour-specific factors. Presently, it is not known to what extent tissue crosstalk (via myokines or cytokines) contributes to these features in humans. Recent evidence does, however, raise the possibility that lipotoxicity from increased fatty acids may be important (81–83). In cachectic cancer patients, macro- and microscopic changes indicate skeletal muscle lipid infiltrations. Mean lipid droplet count in muscle tissue correlated positively with the severity of weight loss and increases further with loss of adipose mass in other body compartments (82).

With regard to muscle fibre type, type II fibres are targeted selectively with relative preservation of type I fibres (84). Protein synthesis and myogenic cell proliferation, and protein degradation and apoptosis determine muscle mass. Faced with the clinical features of cancer cachexia, protein degradation and, thus, the activity of the proteasome is a driver of muscle wasting. In fact, an increased proteasome activity and increased autophagy markers in skeletal muscle have been described in cancer cachexia (84,85). By contrast, divergent effects on protein synthesis have been reported with expression profiles characterized by 1,750 down-regulated genes but 150 up-regulated genes (85). However, when compared to healthy controls, muscle transcriptome was indistinguishable in cancer patients 8 months after tumour resection.

Altered adipocyte metabolism leads to a loss of FM and adipose atrophy in cancer cachexia. Metabolically, adipose tissue wasting is characterized by suppressed lipogenesis at increased lipolysis. A high rate of lipolysis appears to be a key factor underlying fat loss, while inhibition of adipocyte development and lipid deposition may also contribute to the problem (83). This metabolic pattern is partly explained by reduced substrate supply (in anorectic patients) and the increase in inflammatory markers (such as cytokines, TNFα, IL-6) as part of a tumour–adipose tissue interaction. These cytokines are also generated locally in macrophages reflecting a state of chronic inflammation. Zinc-α2-glycoprotein (ZAG), a 43-kDa protein, is overexpressed in certain human malignant tumours and acts as a lipid-mobilizing factor to stimulate lipolysis in adipocytes leading to cachexia (86,87). ZAG mRNA levels in WAT are positively correlated with weight loss and the rate of lipolysis. By contrast, leptin mRNA levels are reduced in WAT of cachectic cancer patients and showed a negative correlation with weight loss. However, plasma leptin levels were shown to be decreased or even increased in cachectic cancer patients.

Fat–muscle crosstalks might be a critical regulator in the development of cachexia. This is brought about through free fatty acids, myokines or adipokines. Data derived from a model of cachexia and lipolysis in tumour-bearing mice with wild-type adipose tissue triglyceride lipase (Atgl +/+) or Atgl–/– (i.e. the gene has been ablated) suggested that at normal plasma free fatty acid concentrations (due to the lack of triglyceride lipase and thus failing to increase lipolysis), fat tissue mass was conserved, and muscle wasting and, thus, cancer cachexia did not occur (83). The mechanism through which skeletal muscle mass is maintained in the presence of the systemic mediators is unknown but may involve muscle–adipose crosstalk through free fatty acids. Until now, there has been little effort to manipulate the integrative physiology of adipose tissue and muscle tissue for therapeutic weight gain in tumour patients.

Perspectives

Rethinking why obesity develops and why it is harmful

Thorkild I.A. Sørensen

The prevailing conventional ideas about obesity are that it is a passive reflection of a positive energy balance due to an 'obesogenic' environment favouring excess food intake and physical inactivity, eventually leading to an excessive amount of stored fat that by itself threatens the health. In other words, obesity results from a passive storage of surplus energy which may give rise to inflammation and thus comorbidities. This is also reflected by the definition of obesity and its association with diabetes, cardio- and cerebrovascular diseases, and certain cancers. A more positive view of FM is that body fat is an energy reserve available for the future. Then, obesity may be seen as a healthy and active response to an expected future lack of energy (88,89). This challenges conventional ideas about obesity.

The ability to store and mobilize triglycerides in adipocytes is a very efficient and biologically inert way of securing the energy supplies in the future when needs for energy cannot be met by available food. Fat storage is without health problems unless triglyceride stores can be expanded and have not reached their limits. Excessive storage of fat (i.e. obesity) may be considered as a consequence of a spurious unopposed signal of expected future needs of energy that leads to the harmful metabolic effects when the limits of storage capacity are reached. Weight gain and overweight happen if the body senses the risk of possible future shortage of food, although today this nearly never happens to people living in Western societies. This unifying theory requires profound revision of the approach to obesity, which may lead to new modalities of prevention and treatment of obesity.

One may ask how and when this sensing occurs, how it translates into obesity and, finally, how comorbidity results. Evidence for sensing future lack of energy as a cause of overweight comes from experimental data as, for example, groups of mice develop greater fat stores with a reduced food supply (90). Sensing may be based on social conditions and, thus, social insecurity is considered as a driver. Thus, besides other consequences, any social challenge also would imply food insecurity in the future. This is independent of the present food supply. Evidence for this idea comes from the observation that when compared with middle and high socioeconomic state, obesity is highly prevalent in low socioeconomic states and social insecurity. Faced with the developments of modern societies, a considerable segment of populations, even in rich countries, live in financial and social insecurity. Sensing social insecurity will vary between different age groups and is unlikely to occur in children where obesity rates also have increased during the last decades. It is tempting to speculate that in children, the sensing of insecurity is transferred from their parents, perhaps by the way they treat them. Another possibility is that the parental sensing of insecurity is transferred to the next generation by epigenetic mechanisms either before or during pregnancy or direct effects on the fetus. Obviously, there may well be individual genetic differences in the sensing and response to the insecurity.

From a biological point of view, it is presently unclear how sensing of future food shortages is translated into deposition of triglycerides and, thus, an increase in FM. It is likely that central-peripheral psycho-neurobiological mechanisms influence this process which is finally characterized by an expansion and renewal of adipocytes (91). Both the number of fat cells and their size (i) have an upper limit and (ii) determine the upper limit of weight gain. Because adaptation of adipocytes and increased storage may reflect different and at least partly independent processes, this may explain the development of different forms of obesity resulting (i) from simple overfeeding or (ii) true obesity as a disease.

In terms of survival during food shortages, triglyceride synthesis in adipocytes is beneficial as long as limits of storage capacity have not been reached. By contrast, when storage exceeds its limits, this will result in ectopic fat deposition, insulin resistance and inflammation. Then negative effects on metabolism and health become evident. Thus, the association between storage of triglycerides and metabolic disturbances is not directly due to the triglyceride accumulation, but is explained by factors co-occurring with it (89). This idea is supported by the finding that many obese individuals do not have adverse health effects and survive until old age (92). As a consequence, the arbitrary definition of obesity simply based on BMI cut-offs as well as comparing FM between different individuals in clinical practice becomes questionable unless the capacity of fat storage is taken into account. In conclusion, there is a need of a redefinition of fat accumulation and obesity faced with its benefits and harms.

Intrauterine growth retardation, fat and fat-free mass relation, and metabolic risks in later life

Angelo Pietrobelli

Low birth weight (LBW) and rapid post-natal growth have been positively associated with obesity in adulthood (for a detailed description of that concept, see 93–95). Maternal factors affecting intrauterine development and growth include age, weight, height, nutrition, stress, smoking, drugs, infections, endocrine disorders, vascular diseases and exposure to environmental contaminants. Normal growth biology involves relationship among hormonal levels, body composition, growth patterns with gender and time-sensitive maturation programs. LBW and infants born preterm reflect a stressful intrauterine milieu and demonstrate a constellation of aberrant developmental trajectories, which are apparent by term equivalent age and persist into adult life. In fact, when the fetus is exposed to malnutrition, the organism diverts the limited nutrient supply for favouring survival of vital organs such as brain at the expense growth and other organs such as pancreas. Fetal malnutrition or, in general, a suboptimal uterine environment adds to permanent anatomical and functional changes in various tissues and organs, ultimately leading to increased risk of metabolic and cardiovascular disease. Adverse long-term effects may reflect a mismatch between early (fetal and neonatal) conditions and environmental and nutritional effects in later life (93,94).

The exposure to a different, and sometimes opposite, environment in intrauterine life affects the expression of multiple genes involved in different metabolic pathways. This is partly brought about by epigenetic changes affecting programming in multiple organs including the liver (95). Epigenetic alterations have been proposed as one mechanism to mediate the influence of early life exposures and gene-environment interactions. These changes alter the ability to coordinate fat and carbohydrate metabolism, favouring a shift to a preferential use of fatty acids as an energy source in order to adapt the organism to the *in utero*-reduced nutrient supply. Altogether, these changes induce adaptations in hypothalamic-lipid sensing mechanisms, ultimately affecting food intake and endogenous glucose production in post-natal life (94–96).

Intrauterine adverse cues have been related obesity, type 2 diabetes mellitus, and hypertension, disturbances in lipid metabolism, non-alcoholic fatty liver, asthma, food allergy, depression and neurobehavioral impairment (96,97). In high school girls, there is a significant and inverse correlation between birth weights and either blood pressure or blood levels of triglycerides and insulin (98). In addition, early post-natal nutrition may affect adult health by

altering gut microbiota with long-lasting effects on later immunity and overall health status (96). In this regard, probiotics, which have the potential to restore the intestinal microbiota balance, may add to prevent the development of chronic immune-mediated diseases (99). If so, this may be explained by epigenetic mechanisms elicited by probiotics through the production of short-chain fatty acids (95).

Analysing the effects of LBW related to childhood family, neighbourhood and socio-demographic conditions on disease onset in adulthood clearly showed that LBW increased the risk of asthma, hypertension, type 2 diabetes mellitus and cardiovascular disease stroke, and heart attack with ORs by age 50 between 1.51 and 2.16 (100). When compared to normal birth weight, LBW has long-lasting effects on chronic diseases in children; at age 14, there were no differences between ages 8 and 14, but the rate of obesity increased (99). After birth, maternal-child feeding patterns may also promote overweight and eating disorders. However, feeding strategies were associated with reduced body weight rather than child overweight (101).

In light of these findings, it is fundamental to monitor early life growth of children and the associated changes in their body composition. Fat and FFM increase rapidly during gestation and infancy, but the majority of studies have relied upon serial measurements of weight, length, and head circumference to assess growth with very little information regarding the composition and the quality of the fat and FFM compartments of the body. Because absolute weight change has limited utility in the identification of infants at risk of later adverse health outcomes that stem from elevated adiposity, and/or reduced FFM, better accurate and precise body composition assessment techniques are needed to evaluate the quality of the body mass during this key period of life (102).

At birth and normal weights (i.e. about 3,500 g for boys and 3,300 g for girls), normal FM is around 480–500 g or 14–15% of body weight (103). Concomitantly, the hydration of FFM is about 80% with a protein content of 15% (103,104). The neonate's later risk of obesity is then determined by the presence of gestational diabetes in the mother, parental obesity, ethnic background, high birth weight as well as rapid early growth, which deserve a special consideration (105).

Age-related changes in fat and muscle: relationship with bone and fracture risk

Marjolein Visser

Aging is associated with metabolic, physiologic and functional impairments, in part through age-related changes in body composition. Across the lifespan, body weight generally increases until age 80 after which a decline is observed (106). Even when body weight remains stable in old age, changes in the composition of soft tissues can be detected. Changes in body composition with aging relate to body fat and individual fat depots, skeletal muscle mass, and bone mineral content. Body weight, fat and muscle mass are related to bone mineral content and fracture risk. Longitudinal data show mean weight gains in groups up to 60 years, whereas older age groups are more frequently characterized by weight losses (107). The rate of weight gain decreases from 20 to 60 years, whereas the rate of weight loss increases from about 2 kg/11 years to more than 5 kg/11 years in subjects above 80 years (107). Weight loss, but not weight gain, was associated with increased mortality among older men and women (108). People who lost weight had a higher mortality rate compared with those who were weight stable, with similar associations found for cardiovascular and non-cardiovascular mortality (108).

Measurements have been performed in large prospective cohort studies conducted in older adults that have used dual-energy X-ray absorptiometry and/or CT or MRI to assess age-related changes in FM, muscle fat infiltration and skeletal muscle mass. The total amount of body fat increases until 75–80 years, after which a decline is observed which seems to parallel the decline in body weight in very old age (109). Skeletal muscle and bone masses decreased, and detailed analyses showed a decrease in skeletal muscle mass but an increase in muscle fat infiltration (or intramuscular adipose tissue, IMAT) and VAT (110). Even though total body fat tends to decline in very old age, the infiltration of fat into the muscles seems to continue with relative changes between 15 and 30% (in women and men, respectively; 111). With age, fat also accumulates in vertebral bone marrow (112), and bone marrow fat content is related to lower bone mineral content at spine, hip, and femoral neck, and thus osteoporosis and prevalent vertebral fractures (113,114).

With regard to the lean soft tissue, appendicular skeletal muscle mass decreases with aging and this decline seems to accelerate in very old age (110,111,114). Concomitantly, IMAT increases but subcutaneous fat area in mid-thigh decreases with weight loss (115). Age-related changes in muscle mass impact muscle function and the loss of muscle mass is considered to be a major determinant of strength loss in aging. An annualized 1% decline in muscle mass with aging is paralleled by a 3% fall in muscle strength (116). Thus, the strength decline is much more rapid than the concomitant loss of muscle mass. The loss of lean mass, higher baseline strength, lower baseline leg lean mass, and older age are independently associated with strength decline in both men and women. However, maintaining or gaining muscle mass does not prevent aging-associated declines in muscle strength, suggesting body composition independent processes in age-related functional impairments (116). All these data give evidence for an age-related remodelling of body composition with reductions in skeletal muscle and corresponding increases in VAT and IMAT. These changes impact body function.

In white and black women, lean soft tissue and FM are both associated with bone mineral density (BMD), whereas in men lean tissue is the only determinant of BMD (117). Weight loss and a low body weight increase the risk of hip, spine and wrist fractures; by contrast, a high BMI decreases the risk (118–121). However, weight-related fracture risk may differ between locations with ankle fractures increasing with increasing BMI, but pelvic and rib fractures had a U-shaped association with an increased risk at low as well as at high BMIs (118,120). In addition to mass, muscle density also relates the age-related incidence of fractures: low thigh muscle attenuation increased the 7-year hip fracture incidence (122).

Sarcopenia parallels osteoporosis. With age above 45 years, the prevalence of osteopenia, osteoporosis and sarcopenia ll began to increase with prevalences of 56, 12 and 34%, respectively, at ages above 70 years (123). There are numerous connections between bone and skeletal muscle as, for example, (i) they share mesodermal origin; (ii) have overlapping signalling pathways during development; (iii) their masses peak around the same time; (iv) have a shared genetic background; and (v) both respond to similar anabolic stimuli as well as mechanical forces (123,124). At the cellular level, sarcopenia is characterized by a loss in myocyte number, a decrease in myofibrillar protein content, and mitochondrial dysfunction.

Inflammation and reduced anabolic stimuli are among other factors to explain sarcopenia. Abnormalities in growth hormone IGF1 secretion and signalling may add to both sarcopenia and osteoporosis (125). In muscle, these abnormalities result in increased myocyte apoptosis, decreased myofibre cross-sectional area and increased expression of proteolytic genes. Concomitantly, low activity of the growth hormone-IGF1-axis adds to delayed mineralization, impaired osteoblast differentiation and proliferation, as well as increased apoptosis in bone cells. Low mechanical forces due to bed rest, sedentary behaviour and low activity impact gravitational loading as well as muscle contractions (124).

There are correlations between muscle mass and either bone mass and bone quality (123,126,127). As to muscle–bone crosstalks, muscle secretes myokines, e.g. myostatin, leukaemia-inhibitory factor, IL-6 and IL-7, IGF1, fibroblast growth factor (FGF23). Besides its effects on the muscle itself, myostatin, a strong regulator of muscle mass in response exercise and muscle damage, also has an effect on bone mass (128). In humans, myostatin gene polymorphisms are associated with peak bone mass. In addition in mice, overexpression of the myostatin propeptide increases BMD. Epidemiological data also showed an increased risk of falls and fractures with decreasing muscle mass (128,129). However, when compared with muscle mass, muscle strength seems to be the more important determinant of falls and fractures (130).

Conclusions

The presentations given at the occasion of the 12th IASO Stock Conference in 2013 in Hamburg, Germany, supported Stocks' view that integration of research ideas about similarities and extremes in obesity and cachexia benefits future understanding. Body composition data are interpreted within broader contexts of intermediary metabolism and inflammation by taking into account the relationships between organs and tissues rather than their individual masses *per se* only. Communication is brought about by numerous crosstalks between organs and tissues, which are related to their masses as well as their functions. It is tempting to speculate that changes in body composition with weight changes (i.e. either weight gain resulting in overweight and obesity or voluntary weight loss in response to diet or involuntary weight loss in cancer patients leading to cachexia) go together with and partly result from altered or even disturbed crosstalks between organs and tissues. Because body composition is not fixed throughout life, a functional body composition approach including (i) the masses of organs and tissues, (ii) between-organ/tissue mass relationships, and (iii) between organ and between tissue crosstalks should become part of a lifetime approach in humans. This will provide a better understanding of trajectories of organ/tissue masses and their related functions and, thus, add to future modelling as a reference of normal integrative physiology throughout life. This will again serve as a background for understanding extremes like obesity and cancer cachexia. Then, understanding obesity and cachexia is more about their differences to models and references rather than the issue itself.

Conflict of interest statement

The authors do not have conflicts related to this manuscript.

Author contributions

MJM and SBH organized the meeting and wrote the manuscript; AD and PT wrote their specific paragraphs. All authors have critically reviewed and revised the manuscript and accepted the final version.

Acknowledgements

The authors wish to thank IASO for giving them the opportunity to organize the 2013 Stock Conference. Special thanks to David York and Natasha Joyner from IASO for their help in preparing and conducting the conference. The financial support provided by the following is acknowledged: BMBF Competence Network Obesity (CNO), Germany; Seca, Hamburg; Zensa Analytic, Frankfurt;

EchoMRI TM, Houston; and Cosmed Companies, Fridolfing.

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