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Dynamic changes in energy expenditure in response to underfeeding: a review

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The observation that 64 % of English adults are overweight or obese despite a rising prevalence in weight-loss attempts suggests our understanding of energy balance is fundamentally flawed. Weight-loss is induced through a negative energy balance; however, we typically view weight change as a static function, in that energy intake and energy expenditure are independent variables, resulting in a fixed rate of weight-loss assuming a constant energy deficit. Such static modelling provides the basis for the clinical assumption that a 14644 kJ (3500 kcal) deficit translates to a 1 lb weight-loss. However, this '3500 kcal (14644 kJ) rule' is consistently shown to significantly overestimate weight-loss. Static modelling disregards obligatory changes in energy expenditure associated with the loss of metabolically active tissue, i.e. skeletal muscle. Additionally, it disregards the presence of adaptive thermogenesis, the underfeeding-associated fall in resting energy expenditure beyond that caused by loss of fat-free mass. This metabolic manipulation of energy expenditure is observed from the onset of energy restriction to maintain weight at a genetically pre-determined set point. As a result, the observed magnitude of weight-loss is disproportionally less, followed by earlier weight plateau, despite strict compliance to a dietary intervention. By simulating dynamic changes in energy expenditure associated with underfeeding, mathematical modelling may provide a more accurate method of weight-loss prediction. However, accuracy at an individual level is limited due to difficulty estimating energy requirements, physical activity and dietary intake in free-living individuals. In the present paper, we aim to outline the contribution of dynamic changes in energy expenditure to weight-loss resistance and weight plateau.

Weight loss: Body composition: Energy expenditure: Adaptive thermogenesis

Overweight and obesity can be understood as 'a disorder of energy balance, arising from consuming calories in excess to the energy expended to maintain life and perform physical work'[1]. Findings from the Health Survey for England revealed that 64 % of adults were classified as overweight or obese, respectively, an increase of 11 % in less than three decades[2].

Paradoxically, this increasing prevalence of obesity coincides with a rise in weight-loss attempts[3]. Findings from the 2003–2008 National Health and Nutrition

Abbreviations: AT, adaptive thermogenesis; DIT, diet-induced thermogenesis; EAT, exercise activity thermogenesis; EI, energy intake; EE, energy expenditure; FFM, fat-free mass; FM, fat mass; NEAT, non-exercise activity thermogenesis; PAEE, physical activity energy expenditure; REE, resting energy expenditure; TEE, total energy expenditure.
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Examination Survey (NHANES) revealed that 57 and 40 % of US women and men, respectively, were actively dieting, 10–15 % higher than the 1990s[4]. A systematic review, including over one million adults worldwide, estimated the prevalence of personal weight control attempts and revealed that 42 % of the general adult population attempted to lose weight in the preceding 5 years[5]. As anticipated, the highest prevalence was observed in overweight and obese populations, particularly in women, with improved wellbeing, enhanced self-esteem, improved appearance and social pressures identified as common motives. While weight-loss was predominantly achieved through energy restriction or physical activity, others sought to improve diet quality or restrict dietary intake. A small proportion of individuals reported the use of weight-loss aids such as laxatives and diuretics or extreme strategies such as fasting or purging[5].

Very low-energy diets and low-energy diets are clinically approved weight-loss interventions that induce weight-loss through prescribed intakes of approximately 3347·2 kJ (800 kcal) and 5020·8 kJ (1200 kcal), respectively. The larger energy deficit induced by very low-energy diets results in significantly greater weight-loss than low-energy diets[6–8], with additional benefits in the treatment of diabetes[9]. Another popular mode of energy restriction is through ‘fad diets’. The British Dietetics Association[10] defines a fad diet as a very restrictive diet involving few foods or an unusual combination of foods for a short period of time, often losing weight very quickly. Such diets often restrict energy consumption through exclusion of food types, macronutrients or feeding times, with claims of drastic weight-loss and health benefits[11]. A recent review of popular fad diets suggested that juicing diets, the paleo diet and intermittent fasting were among those most popular[12]. However, when compared to isoenergetic interventions, fad diets produce comparable results, suggesting that weight-loss is determined predominantly by energy deficit rather than diet composition or meal timings, etc.

The simultaneous rise in weight-loss attempts and obesity prevalence is indicative of the observation that dieting does not necessarily induce long-term sustainable weight-loss. With large interindividual variability in observed weight-loss outcomes, an individual’s physiological response to energy restriction must be considered in order to determine the success of a weight-loss intervention.

A basic understanding of energy balance

Energy, measured in joules (J) is defined as the capacity to do work[13]. The concept of energy balance is based on the first law of thermodynamics, stating that energy can be neither created nor destroyed, but only converted from one form to another[14]. To maintain equilibrium and optimum physiological function, the human body continually expends energy by oxidative metabolism where the chemical energy of food is converted to heat, a process referred to as thermogenesis[15,16]. The body is in a state of energy balance when energy intake (EI) is equal to energy expenditure (EE). Moreover, at energy balance, the total amount of energy contained in the body as glycogen, fat and protein remains unaltered[15] and an individual maintains a stable weight[13]. In a state of negative energy balance, where EE exceeds EI, the body utilises its energy stores (fat, glycogen and protein) resulting in weight-loss. Conversely, in a state of positive energy balance, where EI exceeds EE, the body increases its energy stores (glycogen acutely, but primarily as fat) resulting in weight-gain[15]. Originally viewed as a static concept, it was assumed that one side of the energy balance equation does not change or influence the other side of the equation, i.e. no coupling of EI and EE.

Energy intake

The macronutrients, i.e. carbohydrate, protein and fat in addition to alcohol, yield energy. The energy content of food was traditionally measured using a bomb calorimeter by calculating total heat liberated under combustion. The result of which is referred to as gross energy value, a value that varies among the macronutrients[15]. However, not all ingested food is completely absorbed, with approximately 5–10 % of gross energy lost as faecal matter and through urinary excretion. The remaining ‘metabolisable energy’ (ME), expressed per gram of dietary substrate, is available for use by the body[15]. The metabolisable energy of carbohydrate, protein, fat and alcohol is 17 kJ/g (4 kcal/g), 17 kJ/g (4 kcal/g), 37 kJ/g (9 kcal/g) and 29 kJ/g (7 kcal/g), respectively[17], with an additional energy factor of 8·0 kJ/g (2 kcal/g) for dietary fibre[18].

Energy expenditure

Total energy expenditure (TEE) can be split into three conventional components;

1. Resting energy expenditure (REE)
2. Diet-induced thermogenesis (DIT)
3. Physical activity energy expenditure (PAEE) – of which there are two subcategories
   a) Exercise activity thermogenesis (EAT)
   b) Non-exercise activity thermogenesis (NEAT)

REE refers to the energy required by the body in a resting condition[19], i.e. the ‘metabolic cost of processes such as the maintenance of transmembrane ion gradients and resting cardiopulmonary activity’ [20]. It is measured under standardised conditions, when the individual is awake, at rest, lying in a supine position and in a thermoneutral environment[15]. While REE and BMR are often used interchangeably, REE is more routinely used in research and practice. It is measured exclusively in a post-absorptive state, typically 10–12 h after the last meal and at normal room temperature[15]. REE represents the largest component of TEE, contributing approximately 60–70 % of TEE[16,20].

DIT refers to the energy required by the body in the post-prandial period, representing the energy cost of digestion, absorption, transport and storage of dietary nutrients[16,21]. It is calculated by dividing the increase in EE above basal fasting level by the energy content

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of the food ingested[21]. Although DIT is a product of EI, it belongs as a component of TEE, equivalent to approximately 5–15 % of total energy consumption, assuming an individual is at or near energy balance[16,21].

Finally, PAEE refers to the additional energy required by the body for movements produced by the skeletal muscle[22]. It is subdivided into EAT and NEAT, with EAT representing energy expended through intentional moderate-vigorous exercise, and NEAT representing energy expended as a consequence of daily living and vocation, including low-intensity daily activities above rest (e.g. sitting, standing and walking) and more subtle spontaneous physical activities such as fidgeting[23]. There is no gold standard for measuring PAEE, with estimates often derived from TEE and REE, or expressed as a factor of BMR or REE, e.g. using physical activity level index[24]. Nevertheless, PAEE is by far the most variable component of TEE, both within and between individuals[23] typically contributing between 15 and 40 % of TEE[15,25,26].

Refining our understanding of energy balance

Factors determining obligatory energy expenditure

Body composition is the primary determinant of REE, explaining 60–90 % of the inter-individual variability[1,27,28]. Elia[29] measured the specific REE of different body tissues, referred to as Ki values (expressed as kcal/kg daily). Fat-free mass (FFM) has a significantly higher metabolic rate than fat mass (FM). While metabolic organs and skeletal muscle have Ki values of 200–400 and 13, respectively, adipose tissue has a Ki value of 4·5[30]. Therefore, an individual with a greater proportion of FFM (comprising muscle and organs) will have a higher REE than height- and weight-matched individuals with a greater proportion of FM. Accordingly, REE is also determined by body size, with a larger body size indicating more metabolically active tissue and higher energy requirements than a smaller body size, despite the same proportional body composition[24].

Sex differences in REE are mainly attributed to differences in body composition. Females generally have approximately 10–15 % higher body fat[29,31–33] and 5–10 % lower REE than BMI-matched males[24]. Such differences in body composition are suggested to be influenced by sex hormones with oestrogen reducing lipid oxidation and promoting fat deposition in females[34–36] and testosterone promoting muscle protein synthesis in males[37,38].

Nevertheless, in both males and females REE has been reported to decrease by 1–2 % per decade[39,40], due to age-related decreases in FFM[41] and increases in overall adiposity[42,43]. Short *et al.*[44] reported that skeletal muscle contributes only 25 % of total weight in 75–80-year-old adults as opposed to 50 % in young adults. This decline in FFM, however, is determined by changes in sex hormones. Males reach peak FFM at 31–40 years, followed by a rapid decrease due to significant declines in testosterone[45]. In contrast, females start losing FFM 10 years later than males, and to a lesser degree, possibly due to protective anti-inflammatory effects of oestrogen that do not attenuate until the onset of menopause[24].

While body composition accounts for the most observed variation in REE, research suggests that residual variability may be explained by differences in the amount and distribution of organ tissue, which range in metabolic activity (836·8 kJ/kg (200 kcal/kg) daily for liver, 1004·16 kJ/kg (240 kcal/kg) daily for brain and 1840·96 kJ/kg (440 kcal/kg) daily for heart and kidneys)[29,46,47]. Despite accounting for <6 % of total weight[29], metabolic organs contribute 60–80 % of REE[48,49], meaning even small variations among individuals may influence REE.

Whilst energy content of food is the primary determinant of the obligatory energy cost of DIT, values are specific to each macronutrient due to differing ATP requirements for the initial steps of metabolism and storage[21]. As a consequence, macronutrient composition also determines DIT. Fat has the lowest DIT value estimated between 0 and 3 % of ingested intake, followed by carbohydrate with a value of 5–10 %. Protein has the highest DIT value estimated between 20 and 30 %, in addition to alcohol with a value of 10–30 %[21]. In healthy-weight individuals, in energy balance and consuming a mixed diet, DIT accounts for approximately 10 % of energy ingested over 24 h[21].

There is currently limited evidence suggesting an association between obesity and DIT. Early research by Wang *et al.*[50] identified lower DIT in obese subjects compared to lean subjects. This is consistent with findings from a critical review by De Jonge and Bray[51] where 22/29 studies reported a significantly reduced DIT in obese subjects, associated with insulin resistance and reduced postprandial sympathetic response[51,52].

Some studies report that DIT normalises in weight-reduced subjects[53,54], suggesting reduced postprandial response is a consequence rather than a cause of obesity. However, others report that DIT remained suppressed in weight-reduced subjects, suggesting that reduced postprandial response contributes to the development of obesity[55–57]. However, several studies report no association between obesity and DIT[58]. Such association is further confounded by variation in methodology, energy and macronutrient content of test foods, duration of the postprandial periods and inaccuracy calculating DIT from REE and PAEE[21,58]. Currently, while reduced postprandial response in obesity seems plausible, further standardisation and validation of experimental protocol is needed to reach a consensus.

For PAEE, both EAT and NEAT are determined by the metabolic cost and the frequency of body movement, both of which are largely influenced by bodyweight. In turn, larger individuals have a higher energy cost of movement compared to smaller individuals, however they can also be behaviourally less active[22,59,60]. Other suggested determinants of PAEE include age, exercise training, genetics, EI and disease[22].

Assumption of current weight-loss strategies

Clinical weight-loss prescriptions assume that 14644 kJ (3500 kcal) is equivalent to 1 pound of fat (or about

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32·5 MJ is equivalent to 1 kg)[61] translating into advice that a 2092 kJ (500 kcal) deficit daily will result in 1 pound (lb) weight-loss per week. The '3500 kcal (14644 kJ) rule' is based on the findings of researcher Max Wishnofsky who reported that 1 lb of fat stores approximately 3500 kcal (14·6 MJ) of energy[62]. This observation rests on the assumption that weight-loss is composed of 25 % FFM and 75 % FM[63], a concept based on observations from the Minnesota starvation experiment[64]. Further simplified assumptions assume FFM consists of about 75 % water (0 kJ/g (0 kcal/g)) and about 25 % protein (16·74 kJ/g (4 kcal/g)), meaning 1 g of FFM stores 4·184 kJ (1 kcal) of energy, while FM consists of 100 % fat (37·66 kJ/g (9 kcal/g)), meaning 1 g of FM stores 37·66 kJ (9 kcal) of energy[65]. Based on this assumption, 1 g of total weight-loss is equivalent to 29·29 kJ (7 kcal), hence 1 kg is equivalent to 29288 kJ (7000 kcal) and 0·5 kg is equivalent to 14644 kJ (3500 kcal).

However, this approach assumes the composition of weight lost as FM and FFM is fixed and remains constant throughout the period of dynamic weight loss. Additionally, it disregards dynamic changes in EE observed when the body is in a negative energy balance, resulting in the significant overprediction of weight-loss[61]. Despite recognised as over-simplistic, the 3500 kcal (14644 kJ) rule continues to appear in scientific literature and has been cited in over 35 000 educational weight-loss websites[66]. It is observed in recommendations by the National Health Services[67], British Dietetics Association[68], National Institutes of Health[69] and American Dietetic Association[70]. By way of illustration, Lin *et al.*[71] demonstrated the bias of the 3500 kcal (14644 kJ) rule in the development of population obesity intervention strategies, where static modelling overestimated weight-loss associated with the sugar-sweetened beverages tax by 63, 346 and 764 % at year one, five and ten, respectively.

Popular models of weight-loss

Influence of behaviour. Traditionally, weight-loss is viewed simply as a product of energy deficit, i.e. the discrepancy between energy in and energy out, where EI and EE are independent variables driven purely by behaviour. This model considers EE to be a fixed value, where a sustained energy deficit (through simply 'eating less' and/or 'moving more') will produce weight-loss at a constant rate resulting in infinite weight-loss, which we know to be physiologically impossible. This view has been referred to as *a static model of weight-loss*[1], which disregards changes in EE observed in response to underfeeding. Such a model provides an overly simplistic view of energy balance and a significant over-estimation of weight-loss[66,72].

Influence of body composition. While weight-loss is a product of energy deficit, there is some recognition that EE is not constant, but rather a product of body composition. This model considers the loss of metabolically active tissue as a consequence of weight-loss, resulting in an obligatory decrease in EE, albeit EI remaining an independent variable. This view has been referred to as a *settling point model of weight-loss*[1,73], where an individual in energy deficit will reach a natural equilibrium at a lower weight despite a sustained energy deficit, at a point where a new energy balance is determined by the reduced EE.

Influence of biology. In more recent years, the influence of homeostatic control has been recognised, where the body employs physiological mechanisms that manipulate energy balance to maintain weight at a genetically and environmentally determined set-point. This model considers weight-loss to be regulated by adaptive changes in both EI and EE, which are functionally interdependent.

This view has been referred to as a *set point model of weight-loss*, based on the principle of the set-point theory, which assumes that the human body has a genetically pre-determined body fat content for optimal function that is protected by biological mechanisms within the brain stem and hypothalamus[74]. Accordingly, weight will decrease exponentially and reach an equilibrium despite a sustained energy deficit. First suggested by Kennedy in 1953[75], the model has been widely adopted, and strengthened particularly after the discovery of leptin in the 1990s[1,73,76].

Response to weight-loss and drivers of weight maintenance

Weight-loss is induced by an imbalance between EI and EE. However, the components of energy balance do not function independently, but rather dynamically interact with each other to preserve energy homeostasis. Hence, several obligatory changes and metabolic adaptations are observed during periods of energy imbalance, resisting weight change (Table 1). This supports the notion that unsuccessful weight-loss or regain can be caused by more than behaviourally driven sloth or gluttony.

Obligatory changes in energy expenditure

Foremost, the weight-loss-induced decline in REE is primarily due to loss of metabolically active tissue, i.e. skeletal muscle[77], which expends approximately 54·4 kJ/kg (13 kcal/kg) daily[30]. This obligatory decrease in EE represents that considered in a settling point model of weight-loss, by which energy deficit decreases as weight decreases, resulting in a new energy balance at a lower bodyweight.

The widely cited quarter FFM rule[78] states that FFM, i.e. glycogen, protein and water accounts for 25 % of total weight-loss while FM accounts for the remaining 75 %. Despite having 'limited mechanistic basis'[78], the quarter FFM rule is considered the best approximation of body composition changes in response to underfeeding. However, this rule still incorrectly assumes that the proportion of weight lost as FM and FFM is constant between individuals and during weight-loss.

Early findings from Grande and Henschel[79] revealed that the composition of weight-loss differs in the early

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Table 1. Summary of obligatory and adaptive changes in energy expenditure

	Obligatory	Adaptive
REE	↓ Metabolically active tissue (skeletal muscle and organ mass)	↑ Adaptive thermogenesis by reduced substrate cycling in skeletal muscle
EAT	↓ Energy cost of movement proportional to reduced bodyweight	↑ Skeletal muscle work efficiency
NEAT	↓ Energy cost of movement proportional to reduced bodyweight	↓ Spontaneous physical activity, e.g. pacing and fidgeting
DIT	↓ Postprandial response due to reduced energy intake	Adaptive postprandial response associated with overfeeding only

DIT, diet-induced thermogenesis; EAT, exercise activity thermogenesis; NEAT, non-exercise activity thermogenesis; REE, resting energy expenditure.

and late stages of energy restriction, with early weight-loss composed of predominantly water (70 %), some fat (25 %) and little protein (5 %), and later weight-loss composed of predominantly fat (85 %), some protein (15 %) and no water (0 %). The Minnesota starvation experiment[64] reported similar findings, where weight-loss was composed of about 40 % FM in weeks 1–12, increasing to about 70 % in weeks 12–24.

The rapid rate of early weight-loss is largely attributed to water and glycogen[80]. Liver and skeletal muscle glycogen stores are mobilised into circulation by glycogenolysis to provide short-term energy when external energy sources, i.e. food, cannot meet demands[80–83]. Glycogen is stored in a hydrated form, with each gram stored with 3–4 g of water[84]. Once mobilised, the associated water is excreted in urine[85]. However, glycogen stores are largely depleted within a week of even moderate energy restriction[80].

Before complete depletion of body glycogen stores, there is a shift from glucose oxidation to fatty acid oxidation. Ketone bodies are used as a glucose substitute through conversion from a surplus of fatty acid-derived acetyl CoA in the liver via ketogenesis[83]. Amino acids are also used as a glucose source for the brain and peripheral tissues through hydrolysis of skeletal muscle and conversion to glucose in the liver, via gluconeogenesis[80,83,86,87]. However, increasing availability of ketone bodies during prolonged and significant underfeeding lessens the demand for amino acids, therefore the proportion of weight lost as metabolically active tissue often assumes this lower stable level for the duration of dieting period[78,88]. The composition of weight lost as FM and FFM can be influenced further by the degree of energy restriction, protein intake, magnitude of weight-loss, baseline adiposity and physical activity level[80].

Alongside obligatory changes in REE due to loss of FFM, obligatory decreases in DIT are observed in response to underfeeding due to reduced EI, as less energy is required in the ingestion, digestion, absorption, metabolism, transport and storage of food and nutrients[89]. Assuming a healthy mixed diet, a 2092 kJ (500 kcal) energy deficit would reduce TEE by about 104·6–313·8 kJ/d (25–75 kcal/d).

Finally, an obligatory decrease in PAEE is also observed in response to underfeeding, in both EAT and NEAT compartments, which is proportional to overall weight-loss[89]. This is due to a reduced metabolic cost of movement (i.e. a reduction in 'ballast'), where 5 % weight-loss has been associated with a 393·3 kJ (94 kcal) daily reduction in PAEE[90].

Adaptive changes in energy expenditure

Energy restriction has been associated with a decline in REE, exceeding that explained by changes in body composition alone[91]. Weight-loss studies have shown that the magnitude of fat stores in the body is protected by mechanisms mediated by the central nervous system, which adjust EI and EE through signals from adipose tissue, the gastrointestinal tract and endocrine tissue to maintain homeostasis and resist weight change[92]. The body's protective metabolic mechanism that attempts to preserve energy stores whilst in energy crisis is known as adaptive thermogenesis (AT). AT is defined as the underfeeding-associated fall in REE independent of changes in FFM and FM[90,93]. This definition is based on findings from the Minnesota starvation experiment[64], where a 50 % energy restriction was associated with a 39 % or about 2510·4 kJ/d (600 kcal/d) decline in REE, 35 % (or about 836·8 kJ/d (200 kcal)) of which was independent of obligatory FFM loss[90]. AT can be estimated by calculating the decrease in mass-adjusted REE in response to underfeeding, i.e. the difference between measured REE and predicted REE post-intervention[94]. However, some studies have extended this definition to include DIT in response to both underfeeding[95,96] and overfeeding[96,97] and cold-induced thermogenesis in response to changes in environmental temperature[96,97]. The inconsistent definition of AT makes the quantification of metabolic adaptation challenging.

Research to date suggests that AT can explain half of the unsatisfactory weight-loss cases, where weight-loss was significantly less than that predicted by loss of FFM alone[98,99]. For example, a 10 % weight reduction has been associated with a 20–25 % reduction in TEE, 10–15 % beyond that predicted by changes in body composition[92].

Cross-sectional studies have investigated AT by comparing formerly-obese subjects who had lost weight, with BMI-matched subjects who were never obese. A meta-analysis by Astrup *et al.*[100] reported a 3–5 % lower REE in formerly-obese subjects compared to never-obese controls. However, several cross-sectional studies failed to detect AT[101,102], likely due to large inter-subject variability in body composition and REE[103].

Longitudinal weight-loss studies have provided a more accurate method of investigating metabolic adaptation, where AT of clinical significance has been detected in both lean[64,90,104] and overweight/obese subjects[20,105,106]. In most cases, 10–20 % weight-loss is associated with AT

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equivalent to 418·4–1255·2 kJ/d (100–300 kcal/d)[20,64,107,108]. Based on such evidence, a formerly-obese individual will theoretically require 418·4–1255·2 kJ (100–300 kcal) fewer daily for weight maintenance compared to never-obese individual of the same weight and body composition.

However, reductions as much as 2092 kJ/d (500 kcal/d) have been detected, suggesting large inter-individual variability. Such a case was observed in a weight-loss study at Laval University[109] where a woman adhering to a 2092 kJ/d (500 kcal/d) energy deficit for 15 weeks had a resultant weight gain of 2·1 kg, despite strict compliance and close nutritional support. This clinical paradox can be largely explained by indirect calorimetry measurements, which revealed a 552 kcal daily decrease in REE at the end of the weight-loss phase.

Nevertheless, there is inconsistent evidence regarding the onset of metabolic adaptation. Heinitz *et al.*[110] detected AT within a week of energy restriction, associated with the rapid declines in insulin secretion, depletion of glycogen stores and loss of intra- and extracellular fluid. This aligns to resultant alterations in glycolytic and oxidative activity reported to induce metabolic slowing, with the primary aim of ensuring the brain's energy needs are met[77]. Muller *et al.*[90] reported similar findings with metabolic adaptation detected after 3 d of energy restriction. The magnitude of the observed AT closely correlated with reductions in insulin secretion, changes in glucose oxidation, fluid balance and free water clearance rate[90].

In contrast, substantial evidence suggests that underfeeding-associated AT takes weeks to develop[111,112] and is associated with lower sympathetic nervous system activity, triiodothyronine and leptin[92,107,113]. This delayed onset of metabolic adaptation is reported to be triggered by signals from depleted adipocytes with the primary aim of preserving TAG stores and preventing loss of basic biological function, e.g. reproduction[77]. Such findings support the possible existence of two components of AT, an immediate metabolic adaptation associated with decreased insulin and carbohydrate availability, and a delayed adaptation associated with decreased leptin secretion from depleted adipose tissue stores.

There is, however, conflicting evidence regarding the persistence of metabolic adaptation. While some research suggests that underfeeding-associated AT can be reversed within 2 weeks of refeeding or 4 weeks of weight stability at energy balance[20,103], others report that the effects of AT are long-term, being still detectable 6 months to 1-year post-surgical[114–116] and diet-induced weight-loss[64,117] and even up to 6 years post weight-loss[118].

Mechanisms of adaptive thermogenesis. Skeletal muscle and brown adipose tissue have been identified as important sites of thermogenesis regulation[119] using uncoupling proteins, proton leakage and substrate cycling[120] to alter EE in response to changes in the external environment.

Such mechanisms increase the body's capacity to dissipate energy, with an established role of brown adipose tissue and skeletal muscle in non-shivering[121,122] and shivering thermogenesis[122,123] under conditions of chronic cold exposure.

Animal studies have also supported a role of brown adipose tissue thermoregulation as a means of energy dissipation in response to chronic overfeeding[124–126]. However, these animal observations are not consistent with findings from short-term[127–129] or long-term human studies[130], where no change in brown adipose tissue activity was observed after overfeeding, despite a greater-than-predicted increase in REE.

In human subjects, it has been proposed that underfeeding-associated AT is predominantly mediated by thrifty mechanisms specific to skeletal muscle which downregulate thermogenesis, particularly in response to signals from adipose tissue (Fig. 1)[131].

The skeletal muscle is the primary site of a thermogenic effector system[131]. This system is orchestrated by substrate cycling between lipid oxidation and lipogenesis, and regulated by hormones including insulin, leptin, triiodothyronine and norepinephrine[131].

Leptin is secreted by adipocytes in adipose tissue in proportion to existing FM[132]. During periods of energy restriction, depleted TAG stores result in reduced leptin production, which directly downregulates substrate cycling in the skeletal muscle. Additionally, leptin indirectly downregulates skeletal muscle thermogenesis through suppression of the sympathetic-thyroid axis, with reduced norepinephrine and triiodothyronine production having similar regulatory effects on substrate cycling[131].

Insulin is secreted by the pancreas in response to elevated blood glucose concentrations, hence during periods of energy restriction, lower dietary carbohydrate intake results in reduced insulin production, which is reported to have similar direct and indirect effects on substrate cycling and thermogenesis in the skeletal muscle[131]. This suggests that early alterations in glycolytic activity are one explanation for the proposed immediate onset of AT.

However, the skeletal muscle is a major glucose consumer and a primary site for glucose metabolism, meaning suppressed thermogenesis will result in reduced glucose utilisation during periods of refeeding. The resulting hyperinsulinemia will cause spared glucose to be redistributed for lipogenesis (tri-acylglyceride storage) in adipose tissue. This phenomenon, referred to as 'catch-up fat', is characterised by a disproportionate rate of FM recovery relative to FFM[131]. This preferential restoration of FM has been observed in several influential weight-loss studies[104,133] including the Minnesota starvation experiment[64], where FM exceeded prestarvation values by over 75 % after refeeding[134].

Factors determining adaptive thermogenesis

Shifts in energy balance. There is compelling evidence to suggest that metabolic adaptation is determined by shifts in energy balance, with values of AT halved under conditions of weight stability (representing energy balance), when compared to

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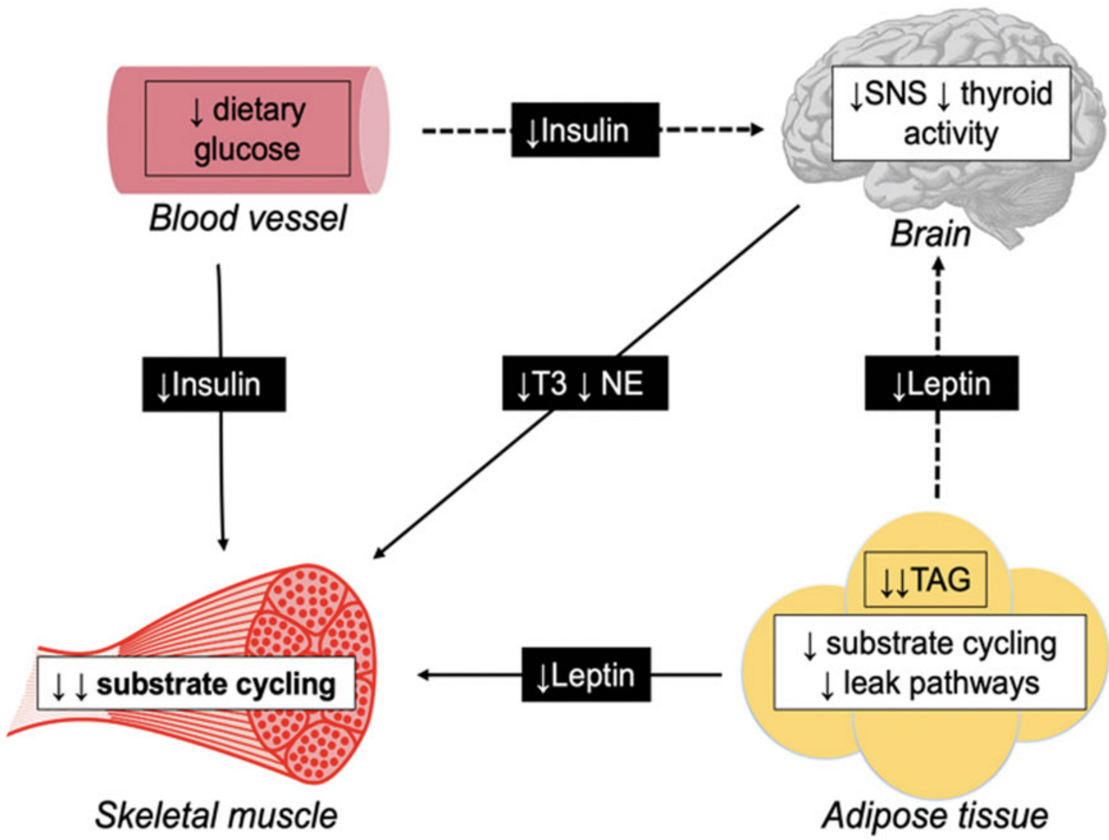

Fig. 1. Schematic diagram illustrating direct (—) and indirect (– –) pathways for adaptive thermogenesis, triggering thrifty mechanisms specific to the skeletal muscle. During periods of energy restriction, leptin secretion in the adipose tissue decreases due to reduced TAG stores. Also, a reduction in plasma insulin is observed secondary to restricted dietary intake. Such hormones directly downregulate substrate cycling in the skeletal muscle. Additionally, both leptin and insulin indirectly reduces skeletal muscle thermogenesis through suppression of the sympathetic nervous system (SNS) and thyroid gland, and subsequent triiodothyronine (T3), and norepinephrine (NE) production.

conditions of dynamic weight-loss (representing energy imbalance)[103].

Early research by Leibel *et al.*[20] reported REE was 10–15 % lower immediately after the weight-loss phase, compared to after 14 d of weight stability. As it was assumed that body composition was constant during the weight stability period, the increase in REE was attributed to the lessening effects of AT. The idea that metabolic adaptation is determined by energy balance is supported in recent research by Martins *et al.*[135] who reported AT equivalent to 226 kJ/d (54 kcal/d) immediately after a 5-month 3347·2 kJ (800 kcal) daily diet, yet no AT was present at 1- and 2-year follow-up. An additional study by the same group[103] reported a 50 % reduction in AT from the end of an 8-week weight-loss programme to the end of a 4-week weight stability period (385 kJ (92 kcal) decreasing to 159 kJ (38 kcal)), with no AT present at 1-year follow-up. Moreover, of those who gained weight during the weight stability period, i.e. were in a positive energy balance, no AT was detected.

The concept that energy balance shifts drive AT would explain the long-term metabolic adaptation reported in studies with longer dynamic weight-loss phases, where subjects were still in negative energy balance at the time AT was measured.

The Biosphere 2 experiment[104] reported metabolic adaptation after 2 years of moderate energy restriction and about 15 % weight-loss. While AT was significant immediately after the weight-loss phase, i.e. at the end of year two, no AT was detected 6 months later, at which point participants had returned to an *ad libitum* diet and bodyweight had completely recovered. Similarly, the CALERIE study reported metabolic adaptation after 1 year[136] of 25 % energy restriction and about 12 % weight-loss. While AT was significant immediately after the weight-loss phase, i.e. at the end of year one, no AT was detected a year later (year two), when participants had regained a proportion of lost weight. In contrast, Butte *et al.*[114] reported metabolic adaptation was still present 6 and 12 months after bariatric surgery. However, due to the long-term effects of gastric bypass on EI, patients continued to lose weight throughout the 12 months. Hence, measurements of AT were taken while the subjects were most likely still in negative energy balance.

Collectively, current research indicates that metabolic adaption is present only during the dynamic phase of

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weight-loss, with minimal impact on weight stability and no persistence during periods of weight regain.

Body mass. A follow-up study of 14 *Biggest Loser* competitors reported significant persistence of metabolic adaptation equivalent to 2092 kJ/d (500 kcal/d)[118]. The magnitude of AT was highest in those with greater weight-loss after the competition and in those most successful at maintaining weight-loss at follow-up[118]. Contrary to most weight-loss research, metabolic adaptation was detected 6 years post-intervention despite subjects regaining two-thirds of lost weight. One explanation for this could be the higher body mass of participants, with a mean baseline bodyweight of 150 kg. Larger body mass indicates a greater proportion of FFM, a significant predictor of REE[27]. Recent research reports that higher TEE at baseline is associated with greater metabolic adaptation during periods of acute fasting[137].

Another possible explanation for the observed AT is the overprediction of REE used for comparison, with predictor equations shown to inaccurately estimate REE in morbidity obese populations[138], due to variances in hydration status and fat distribution that are not recognised by bio-impedance[139]. The use of linear regression in such equations assumes a proportional increase in REE with bodyweight, which is unlikely in morbidly obese subjects where excess FFM is predominately low-metabolic skeletal muscle, rather than high-metabolic organs[140]. This will elude to a much larger metabolic adaption when calculating the difference between measured and predicted REE.

Degree of weight-loss. Several studies suggest that the magnitude of AT is determined by the degree of weight-loss[76,90,118]. Based on these observations, Rosenbaum and Leibel proposed three different models for AT following different degrees of weight-loss[141]. They reported that 10 % weight-loss was associated with declines in REE and PAEE beyond that predicted by changes in body composition, suggesting the existence of metabolic adaptation in both compartments. However, with an additional 10 % weight-loss (20 % in total), REE did not decline any further, suggesting a threshold model, where maximum AT is reached once an individual's threshold for FM is crossed, a point considered to be determined by biological and environmental factors[141]. This supports early observations by Leibel *et al.*[20] where AT persisted up to 10 % weight-loss, at which point maximum adaptation was reached and sustained.

However, an additional 10 % weight-loss was associated with a further decline in PAEE beyond that predicted by changes in body composition, suggesting an adaptive response in PAEE that is proportional to the degree of weight-loss[141]. Butte *et al.*[114] reported a similar finding, where most metabolic adaptation occurred in the first 4–6 weeks, at which point subjects had lost about 10 % bodyweight, despite the bariatric surgery leading to continued weight-loss for up to 1 year. However, PAEE continued to decline for the remainder of the intervention.

Several studies support the existence of AT in non-resting compartments[94], persisting where no further AT in REE is observed. This was explained by increases in skeletal muscle efficiency[20], resulting in reduced metabolic cost of movement and decreases in spontaneous physical activity[104], resulting in reduced frequency of movement.

Genetic phenotypes. The large interindividual variability in AT may be explained by a genetic influence. Recent research suggests AT is an individualised trait under biological control[77], with metabolic phenotype determining the ability to efficiently alter fuel utilisation and manipulate energy balance. A cross-sectional study by Weyer *et al.*[142] was among the first to suggest phenotypic differences in EE response, after observing a correlation between increasing EE with overfeeding, and decreasing EE with fasting in 14 male subjects. This observed variation in EE response is reported to be independent of changes in macronutrient composition[143], but rather associated with leptin, insulin, sympathetic nervous system activity and thyroid hormones[114].

A proposed *thrifty phenotype* is characterised by low AT in response to overfeeding, driving weight-gain and high AT in response to energy restriction, limiting weight-loss[77,144]. In contrast, a proposed *spendthrift phenotype* is characterised by a high AT in response to overfeeding, limiting weight-gain and a low AT in response to energy restriction favouring weight-loss[77,144].

Metabolic phenotype has been shown to be a significant predictor of weight-loss, independent of age, sex and race. A 6-week weight-loss study[144] revealed that spendthrift phenotypes had a 1 % smaller decrease in TEE and a 518.8 kJ/d (124 kcal/d) larger energy deficit, equating to a 20920 kJ (5000 kcal) greater cumulative energy loss over the 6-week study period.

The existence of metabolic phenotype would also explain the large variability in AT observed among participants on comparable dietary interventions. Muller and Bosy-Westphal[107] reported significant metabolic adaptation in <50 % of subjects across multiple different weight-loss strategies. Similarly, Martins *et al.*[103,135] reported that one in three weight-reduced subjects exhibited greater-than-predicted declines in EE, only half of which experienced metabolic adaptation beyond 167.4 kJ/d (40 kcal/d)[145].

Mathematical modelling in weight-loss prediction

In recent years, the use of mathematical modelling has greatly advanced our understanding of underfeeding-induced changes in EE. The first simple equation was proposed by Forbes over 30 years ago[146] describing the proportion of weight lost as FFM as a function of initial body fat. This idea has since been replicated and updated, resulting in the development of several web-based models including *The NIH Body Weight Planner*[147] and *The Pennington Biomedical Research Centre Weight Loss Predictor*[148]. These models are developed based on the energy balance principle, i.e.

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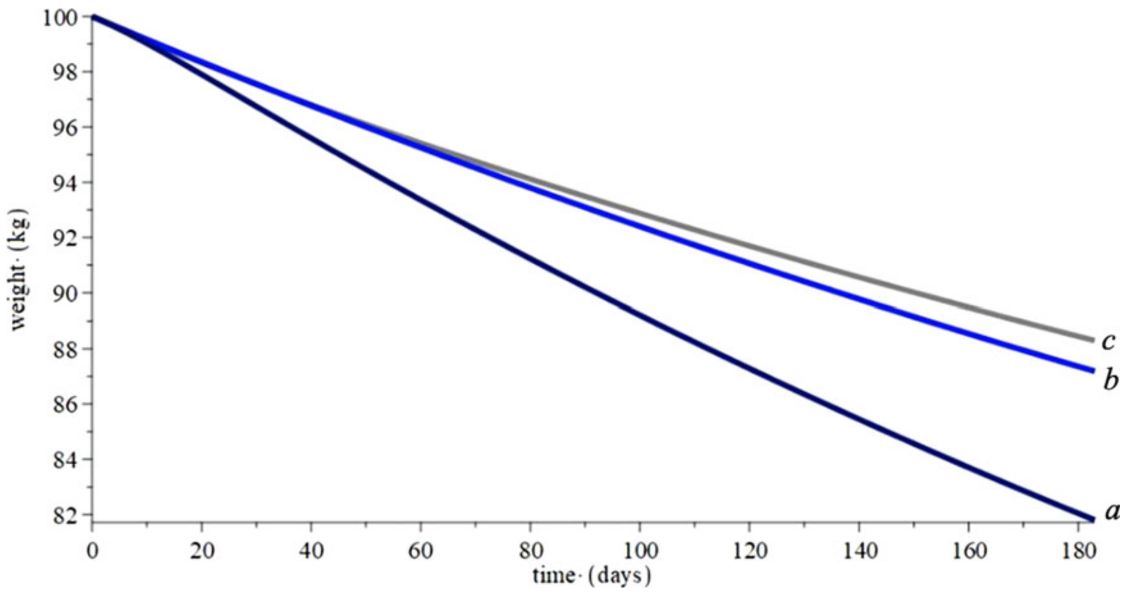

Fig. 2. Predicted weight trajectory of a 100 kg female on a low-energy diet (7531·2 kJ (1800 kcal/d)) for 6 months modelling static (a), obligatory (b) and adaptive and obligatory (c) changes in energy expenditure.

the first law of thermodynamics where weight-loss is a product of EI minus EE.

By modelling changes in EE in response to underfeeding, such models may provide a more accurate prediction of weight-loss compared to static modelling, i.e. the 3500 kcal (14644 kJ) rule, which has been reported to predict weight-loss 100 % greater than that predicted by mathematical modelling[72]. Additionally, by measuring the greater-than-expected decline in REE in response to underfeeding, i.e. the difference between observed and predicted REE, mathematical modelling can be used to quantify AT (Fig. 2).

Models vary in complexity depending on how EE is compartmentalised. While most models subdivide EE into DIT, REE, PAEE[149–151], others include an independent function for spontaneous physical activity[152]. More simple models describe changes in overall bodyweight rather than body composition, i.e. FM and FFM independently[149], whereas more complex models subdivide FFM further into glycogen and protein, describing the influence of macronutrients on body composition and weight change[150,151].

Mathematical modelling is primarily used in research, with limited accuracy at an individual level. This is largely due to inaccuracy in estimating baseline energy requirements. Calculating energy deficit requires baseline values for REE, which is associated with an uncertainty of over 5 % in free-living individuals[72]. This translates into a larger margin of error in predicted weight-loss. Additionally, accuracy is limited by difficulty ascertaining precise dietary intake in free-living individuals. Findings from Subar *et al.*[153] revealed that obese populations underreport dietary intake by up to 40 % using methods such as 24 h recall, FFQ and diet histories. Therefore, when using experimental weight-loss data to validate mathematical models, it can be difficult to identify whether deviation from an expected weight trajectory is due to an inaccurate input for dietary intake or whether an error exists within the model.

This is illustrated by Hall *et al.*[72], who compared weight-loss observed in an outpatient intervention to that predicted by mathematical modelling. While weight plateau was generally observed within 6–8 months, mathematical modelling predicted weight plateau to occur significantly later, after several years. Mathematical modelling assumed perfect adherence to the prescribed intervention, therefore relaxed compliance was most likely responsible for the discrepancy between observed and predicted weight-loss. This limitation could be minimised through the use of a tightly controlled dietary intake, e.g. an inpatient intervention group or a total-diet replacement programme.

More recently, a mathematical model of weight-loss[154] was developed using data from a commercial very low-energy total-diet replacement and behavioural change programme. The model uses simple inputs of weight and EI only to convert energy deficit to weight-loss over time. On comparison to observed weight-loss, while static modelling overestimated weight-loss by about 50 % (12·5 (SD 3·6) % *v.* 8·5 (sd 4·5)%), mathematical modelling predicted a comparable mean weight-loss of 9·3 (SD 2·2) %, with an overall mean error of −0·6 (SD 3·45) %[155]. The use of a prescribed total-diet replacement programme reduces errors associated with misreported EI, suggesting that any discrepancy between observed and predicted weight-loss is largely attributed to inaccuracies in modelling EE.

Conclusion

A magnitude of evidence exists demonstrating the obligatory and adaptive changes in EE that occur in response to an energy deficit (e.g. weight loss). It is clear that static

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modelling significantly overestimates weight-loss by disregarding the changes in EE observed when the body is in a negative energy balance. Despite this, the 3500 kcal (14644 kJ) rule continues to be used in clinical weight management, possibly due to ease of use or lack of a clinically feasible alternative. Nevertheless, by accounting for existing evidence, the present research suggests that mathematical modelling can provide a more accurate method of weight-loss prediction and may prove a valuable tool in setting weight-loss prescriptions and assessing dietary compliance in the treatment of obesity.

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Conflict of Interest

None.

Authorship

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