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Review

# Impact of calorie restriction on energy metabolism in humans

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ABSTRACT

Calorie restriction (CR) is the most potent, non-pharmacological intervention to support metabolic health. The effects of calorie restriction exceed weight loss. Consistent throughout many studies, calorie restriction induces a reduction in energy expenditure that is larger than the loss of metabolic mass, i.e. fat-free mass and fat mass, can explain. Per prevailing theories of mammalian aging, this disproportionate reduction in metabolic rate, defined as metabolic adaptation, reduces oxidative damage and thereby delays age-associated declines in physiological function. The aim of this narrative review is to investigate the origins of CR-induced metabolic adaptation. From a physiological standpoint this likely relates to the composition of body weight loss, reductions in insulin secretion, thyroid and leptin concentrations, and increased mitochondrial energy efficiency. Behavioral factors including physical activity and eating behaviors likely also play a role, specifically to prevent weight regain. Future studies are required to understand the interindividual differences in the response to CR, e.g. by sex, physical activity, or mitochondrial capacity, and to assess the long-term implications of CR for weight regain.

## 1. Introduction

Calorie restriction (CR) is the most potent non-pharmacological intervention to attenuate aging and prevent chronic metabolic diseases (Heilbronn and Ravussin, 2003). CR is defined as a sustained reduction in energy intake from pre-intervention energy requirements while maintaining sufficient nutrient supply to achieve weight stability. Initially CR induces weight loss and over time energy expenditure (EE) declines until it eventually matches energy intake and the new lower body weight plateaus.

The rationale to undertake CR extends beyond the goal of weight loss. The primary rationale for performing CR is to reduce metabolic rate. Metabolic rate is the energy expended by an organism at rest in order to maintain body functions including metabolic homeostasis, breathing, heart rate, blood pressure, cellular regeneration, maintenance of ion gradients, and activity of the nervous system. Per the 'rate of living' theory (Sacher and Duffy, 1979), the metabolic rate per lifespan is a species-specific characteristic and therefore individuals with higher metabolic rates have shorter lifespans (Sohal and Allen, 1985). This theory was developed upon observations of negative associations between mammalian metabolic rate (per body weight per day) and lifespan ($R^2$ = 0.26) (Hulbert et al., 2007). It should be noted that this theory may only apply within species but not between species (Speakman, 2005).

Of the oxygen consumed by mitochondria, the vast majority is utilized for ATP production, but 1–3% generate reactive oxygen species (Murphy, 2009). The accumulation of reactive oxygen species disrupts molecular and cellular structures and may therefore explain the age-associated impairments in metabolic homeostasis and function (Harman, 1956; Lopez-Otin et al., 2013). Thus, a CR-induced slowing of the metabolic rate is hypothesized to improve metabolic health and extend lifespan via a reduction in oxidative damage to cells and tissues.

The aim of this narrative review is to describe the theoretical framework for the effect of CR on energy metabolism including resting EE, physical activity-related EE and total daily EE in non-obese populations, and to discuss the evidence for and against the hypothesis that CR reduces metabolic rate. First, changes in composition of body weight loss, metabolic mediators of CR, and energy efficiency in mitochondria are reviewed. Second, the interaction between CR and physical activity and finally the implications of a reduced metabolic rate for weight regain are discussed.

## 2. Measurement of calorie restriction and energy metabolism

Due to the limitations with self-reporting methods to estimate energy intake, energy intake requirements for community-dwelling

*Abbreviations:* CR, Calorie restriction; EE, Energy expenditure; FFM, Fat-free mass; FM, Fat mass

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individuals are best assessed using the energy intake-balance method. Per First Law of Thermodynamics, energy intake during an observation period equals the sum of total daily EE and the changes in body energy stores. Total daily EE is most objectively measured using the doubly labeled water technique (Speakman et al., 2019). Changes in body energy stores are approximated as change in tissue masses usually in two compartments (i.e. fat-free mass and fat mass) between two points in time (i.e. the start and conclusion of an intervention) multiplied by their respective energy densities (e.g. 1100 kcal/kg for fat-free mass and 9300 kcal/kg for fat mass) (Racette et al., 2012). Pre-intervention energy requirements are defined as energy intake during weight maintenance, and therefore energy requirements equal total daily EE. CR is measured as the difference between baseline energy requirements and energy intake during a prescribed time period. Alternative methods to estimate energy requirements and hence calorie restriction are based predictions for total daily EE based on body weight or body composition of the individual (TDEE (kcal/d) = 2189 + 19.6 * weight (kg) - 17.6 * age (yr) - 555 (for females), $r^2$ = 0.75; or TDEE (kcal/d) = 1630 + 33.4 * FFM (kg) + 1.9 * FM (kg) - 16.9 * age (yr) - 173 (for females), $r^2$ = 0.78) (Racette et al., 2012; Redman et al., 2009).

Assessing the effects of CR on energy metabolism requires distinction between individual components of total daily EE. Total daily EE is partitioned into the energy expended at rest (resting EE), in response to meals (diet-induced thermogenesis), and to support physical activity (activity-related EE). Resting EE is measured by indirect calorimetry either with a bedside ventilated hood system, or in a whole-room metabolic chamber (Lam and Ravussin, 2016). Diet-induced thermogenesis can be measured with the same methodologies performed before and after consumption of a meal, yet is routinely assumed to equate to 10% of total daily EE (Tataranni et al., 1995). Activity-related EE then is calculated as the difference between total daily EE and resting EE plus diet-induced thermogenesis.

## 3. Calorie restriction and weight loss

The most important consideration for the study of CR is the requirement for adequate nutrition including sufficient intake of macronutrients and micronutrients. This necessity is best demonstrated by the 'Minnesota Starvation Study' a landmark study of severe CR by Keys et al. (1950). In this study, ~40% CR was induced by dietary restriction and increased exercise. The young men lost ~25% of body weight of which 70% was fat mass (FM) and 30% fat-free mass (FFM). The diet was designed to mimic conditions of warfare and therefore was deficient in many nutrients. The malnourished CR diet led to chronic weakness, reduced aerobic capacity, and severe painful lower limb edema (Keys et al., 1950). Furthermore, various abnormal psychological behaviors were observed included severe emotional distress, confusion, apathy, depression, hysteria, hypochondriasis, suicidal thoughts, and loss of sex drive.

In contrast, the largest and best controlled clinical studies of CR in non-obese individuals prescribed CR of 25% (12–18% CR achieved) and intentionally ensured adequate intake of micronutrients by provision of a vitamin, mineral and calcium supplement to subjects (Rickman et al., 2011; Rochon et al., 2011). With this moderate level of CR and nutritional adequacy, there was no increased frequency of adverse events compared to individuals continuing their usual diet (Ravussin et al., 2015; Romashkan et al., 2016). Interventions using very low calorie-diets or bariatric surgery achieve larger degrees of CR (up to 70%) and without observing adverse effects as described in the Minnesota Starvation Study. These approaches are prescribed to patients with obesity and the intent to induce severe energy deficit and weight loss and are complemented with multivitamin supplements. Nutritional adequacy is thereby ensured despite low energy intake. While these CR approaches may be perceived to help to understand metabolic effects of CR-induced weight loss, it should be considered that the metabolic effects of such extreme energy deficits may differ from those observed during more modest and sustainable degrees of CR.

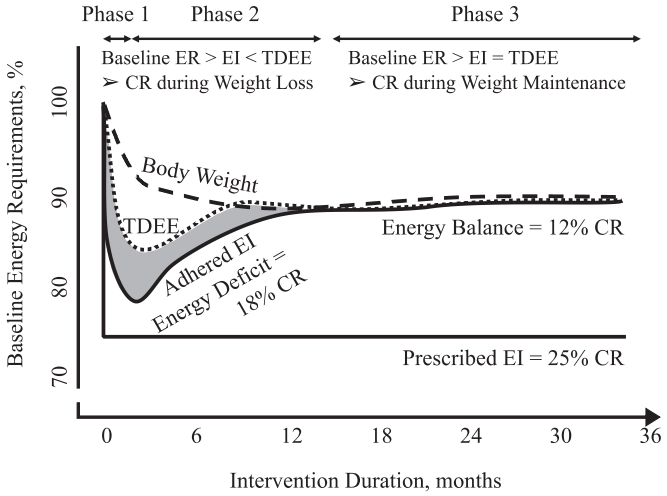


**Fig. 1.** Simplified model of energy balance components during calorie restriction interventions. Calorie restriction (CR) is initiated at month 0 by prescribing 75% energy intake (EI) as compared to the baseline energy intake requirements (100%). Adherence to the CR regimen ('Adhered EI') is highest during the first 3 months (~21%), and declines to ~10% after 12 months. The compensatory decrease in total daily EE (TDEE) is smaller than the decrease in energy intake (EI), which induces an energy deficit (in grey) and weight loss (Phase 1 and 2). After 12 months, the CR daily energy intake approximates the total daily EE and weight is maintained on a 12% reduced level of energy balance, which defines CR during weight maintenance (Phase 3).

Models describing the impact of reduced energy intake on the consequential changes in EE, and impact of the energy deficit on FM and FFM have been generated by Guo et al. (2018). These models have been largely derived from data of the CALERIE studies (Heilbronn et al., 2006; Racette et al., 2012; Ravussin et al., 2015; Redman et al., 2009; Redman et al., 2018) where all subjects followed diets with the same relative energy deficit (25% reduction in intake from the energy requirement for weight maintenance) and were forced to achieve a new energy balance (or weight maintenance) after 12 months of CR initiation. A simplified model of this data is presented in Fig. 1.

The simple model of CR-induced changes in energy balance and hence weight and EE shows that at the onset of a CR diet (Phase 1), the reduction in energy intake occurs more rapidly than the reduction in EE and hence an acute energy deficit occurs inducing weight loss. EE is proportional to body mass (Leibel et al., 1995), and thus with weight loss, EE decreases, too (Phase 2). Consequently, over time, energy intake and EE approximate each other until they reach energy balance (Phase 3), notably at a reduced level from baseline energy intake and at reduced body weight. The observed reductions in EE may exceed the extent that would be explained by the reduction in body mass. This suggests that observed reductions in EE during CR are independent of a change in FFM and may be attributed to a decline in the metabolic rate per unit of mass or to a reduction in physical activity. These physiological or behavioral adaptations to CR ,respectively, are believed to explain the intra-individual variation in weight loss and weight loss maintenance.

To study metabolic and behavioral adaptations that occur with CR, changes in EE should be evaluated independent of the changes in body composition. The common practice for assessing the metabolic effects of CR independent of body composition is to measure the change in EE induced by the intervention and to compare it to the change in EE which would be expected on the basis of the change in body composition observed (Redman et al., 2009). To derive the expected change in EE, a linear regression model of the respective study cohort is developed using the baseline (prior to CR) data. In the baseline model, EE (dependent variable, y) is explained by independent variables (x), or

**Table 1**
Metabolic adaptation in response to different weight loss interventions.

| | Duration | Intervention | Change in body weight | Metabolic adaptation |
|---|---|---|---|---|
| Normal weight and overweight | | | | |
| CALERIE Phase 1 | 3 months | 25% CR | −7% | 8% |
| | 3 months | 25% CR, (diet + exercise) | −5% | 5% |
| | 3 months | Low calorie diet | −14% | 3%[#] |
| | 6 months | 25% CR | −10% | 7% |
| | 6 months | 25% CR, (diet + exercise) | −10% | 7% |
| | 6 months | Low calorie diet | −14% | 4%[#] |
| CALERIE Phase 2 | 12 months | 25% CR | −13% | 6% |
| | 24 months | 25% CR | −12% | 5% |
| Biosphere-2 | 24 months | Low calorie diet | −9 kg | 6%[#] |
| Overweight and obesity | | | | |
| Revisited MSS, men | 3 weeks | 50% CR | −4 kg | 4% |
| Revisited MSS, women | 13 weeks | Low calorie diet | −10 kg | 4% |
| Obesity | | | | |
| Biggest Loser | 30 days | Diet & exercise | −59 kg | 11% |
| | 6 months | Diet & exercise | −49 kg | 17% |
| | 7 months | Gastric bypass | −36 kg | 9% |
| BARIA | 12 months | Gastric bypass | −36% | 8% |
| | 12 months | Sleeve gastrectomy | −33% | 11% |
| | 12 months | Gastric band | −16% | 12% |
| | 12 months | Low calorie diet | −4% | 4%[#] |
| | 24 months | Gastric bypass | −42 kg | 15% |
| | 24 months | Gastric band | −19 kg | 12%[#] |
| | 24 months | Sleeve gastrectomy | −37 kg | 20% |
| LABS | 6 months | Surgery (88% gastric bypass) | −31 kg | 8% |

Changes in body weight and metabolic adaptation, measured in rest, in calorie restriction (CR) studies, and weight loss studies, induced by low calorie diet and bariatric surgery. [#]indicates that metabolic adaptation as compared to the control group did not reach statistical significance. BARIA, Bariatric Surgery and Weight Loss on Energy Metabolism and Insulin Sensitivity; CALERIE, Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy; LABS, Longitudinal Assessment of Bariatric Surgery; MSS, Minnesota Starvation Study.

factors with well-known effects on EE. Independent variables typically included are body mass or body composition (FFM and FM), sex, age and sometimes race. For resting EE, coefficients for FFM are 17–27 kcal/kg and 2–5 kcal/kg for FM (Hall, 2010; Martin et al., 2007; Ravussin et al., 2015; Redman et al., 2018). Imputing data values of the independent variables included in the model from individual subjects provides an estimate for EE that is expected based on the body mass composition, and while also considering age, sex and race. Therefore, if the relationship between EE and body mass/composition remains constant, the linear regression model approach allows one to determine how EE would change for a given individual as a function of weight change over time.

## 4. Metabolic adaptation

A decline in EE which is beyond what would be expected relative to the changes body mass (or composition) is termed metabolic adaptation. In Table 1, we summarize metabolic adaptation observed in response to different CR and weight loss intervention studies. Metabolic adaptation was the primary outcome of the CALERIE studies and was investigated after 3 and 6 months of 25% prescribed CR in CALERIE Phase 1, and after 12 and 24 months in CALERIE Phase 2. As hypothesized, after 6–24 months of CR, metabolic adaptation was observed during sleep (Heilbronn et al., 2006; Redman et al., 2018), at rest (Martin et al., 2007; Ravussin et al., 2015), over 24 h in the confined environment of the room calorimeter (Heilbronn et al., 2006; Redman et al., 2018), and over 14-days in free-living conditions (Ravussin et al., 2015; Redman et al., 2009; Redman et al., 2018). The metabolic adaptation observed during sleep, which is arguably the most reproducible measure of metabolic rate, was 8% at 3 months, 7% at 6 months, 6% at 12 months, and 5% at 24 months. In contrast the metabolic adaptation in free-living conditions was almost double at each time point across the 24-month period (13% at 3 months, 7% at 6 months, 8% at 12 months and 9% at 24 months, respectively). The larger metabolic adaptation in free-living conditions suggests that the culprit of such adaptations is not only changes in metabolic processes but also compensations in behaviors likely occurring in an effort to conserve energy. Importantly, body weight loss occurred only during the first 6–12 months, after which time it was maintained. This implies that metabolic adaptation is not exclusive to periods of chronic energy deficiency, but that it persists in energy balance. The CALERIE data also suggests that metabolic adaptation is related to the degree of CR (21% CR achieved during the first 3 months, 18% during the first 6 months, 11% from month 6 to 24).

The cause of metabolic adaptation appears to be specific to calorie restriction because studies that demonstrated exercise-induced weight loss did not observe metabolic adaptation (Hopkins et al., 2014; Jennings et al., 2009; Karstoft et al., 2017; Lee et al., 2009; Mourier et al., 1997). The energy deficits induced in these studies were small (~250 kcal/d), so an alternative hypothesis might be that larger energy deficits are needed to induce a metabolic adaptation. Indeed these studies observed marked inter-subject variability in metabolic adaptation, and one reported that metabolic adaptation was related to changes in energy intake (Hopkins et al., 2014). This later study supports the argument that reduced energy intake, i.e. calorie restriction, rather than an energy deficit induces metabolic adaptation.

In a pilot study (Catenacci et al., 2016) comparing the effects of CR vs alternate day fasting (ADF), mass-adjusted RMR was reduced more by CR as compared to ADF, despite a smaller energy deficit (28% vs 47%) and comparable reductions in fat and lean masses. This data also implies that a continuity of CR is needed to promote metabolic adaptation, whereas intermittent periods of CR and ad libitum eating may ameliorate the decline in RMR. Furthermore, a recent study showed that ADF for 4 weeks did not affect RMR, although the intervention led to reductions in energy intake (−37%) and body weight (−5%) (Stekovic et al., 2019). Similar findings have been made for the comparison between continuous CR and CR implemented every other week (Byrne et al., 2018). While the intermittent fasting approach achieved more pronounced weight loss, RMR declined less, after adjustment for changes in body mass and the mechanism for this difference is unexplored.

To our knowledge, CALERIE is the only study in which metabolic

adaptation was prospectively assessed in a randomized, controlled intervention of CR in individuals without obesity. Our findings of a CR-induced metabolic adaptation is supported by comparable observations of CR induced by diet-induced weight loss including the revisited Minnesota Starvation study in men (Muller et al., 2015), and women (Bosy-Westphal et al., 2013), the 'Biggest Loser' competition (Fothergill et al., 2016; Knuth et al., 2014) as well as the BARIA (Tam et al., 2016a; Tam et al., 2016b), and LABS (Wolfe et al., 2018) bariatric surgery trials.

## 5. Mechanisms of metabolic adaptations

Collectively, these studies indicate that reductions in EE induced by CR are larger than changes in FFM and FM explain. Likely mechanisms of metabolic adaptations include changes in the composition of FFM, slowing of energy costly, metabolic processes, or an increased efficiency converting consumed oxygen and energy rich-substrates into cellular available energy (ATP).

### 5.1. Fat-free mass composition

The simplest, reliable and cost-effective approaches for ascertainment of body composition result in the distinction of mass in two compartments; FFM and FM. In contrast, a more detailed assessment of FFM such as measurement of organ mass including skeletal muscle, liver, kidney, heart, spleen, and brain is complex and requires costly, intensive magnetic resonance imaging protocols and sophisticated data analysis pipelines. A limitation to the simple distinction of mass in two compartments is the assumption that the entire FFM compartment changes proportionally during weight loss, e.g. muscle mass decreases and to the same extent as the liver. Changes in the contribution of different organ masses to the overall FFM may explain inter-individual differences in metabolic rate with CR because, as Pits (1962) and later Forbes (1993) proposed, different organs have different metabolic rates (Heymsfield, 2018; Heymsfield et al., 2019; Muller et al., 2018; Wang et al., 2011a). Indeed, when including mass of the liver, kidney, heart, spleen, brain, skeletal muscle and adipose tissue mass obtained from whole-body MRI to predict EE, more variation in metabolic rate attributed to age (Geisler et al., 2016; He et al., 2009; Heymsfield et al., 2012), sex (Wang et al., 2011b) or race (Gallagher et al., 2006; Javed et al., 2010) is explained compared to FFM alone. Thus, a disproportionate decline in the mass of organs, especially the high metabolic rate organs such as liver, kidney and skeletal muscle would explain a steeper decline in metabolic rate, and hence metabolic adaptation.

In the 24-month CALERIE Phase 2 ancillary study at Pennington Biomedical Research Center, LA (clinicaltrials.gov: NCT02695511), such data has been acquired, but changes in organ size are not yet published. Shorter-term studies of diet-induced weight loss in patients with overweight and obesity support the hypothesis that differential change in organ mass explains proportion of observed metabolic adaptation. In a replication of the Minnesota Starvation Study, Muller et al. (2015) found that after three weeks of 50% CR, metabolic adaptation adjusted for changes FFM and FM, was 108 kcal/d or 48% of the decrease in resting EE. Within FFM they observed that mass of skeletal muscle (−5%), liver (−13%), and kidneys (−8%) decreased differently. Accounting for specific changes in FFM composition further explained 36 kcal of the metabolic adaptation, leaving 72 kcal/d as the true, mass-adjusted metabolic adaptation. Comparable findings were reported in a study of overweight and obese women after 13 weeks on a low calorie diet (Bosy-Westphal et al., 2009). Reductions in skeletal muscle (−3.1%), heart (−5.2%), liver (−4.4%), and kidney (−6.1%) were noted alongside a small yet significant increase in bone mass (+1.3%). No change in brain mass (+0.4%) was observed. Notably, the relative loss of mass in high metabolic rate organs was significantly higher than the loss of mass in low metabolic rate-organs, e.g. muscle and bones. Accounting for changes in FFM composition as compared to FFM as such explained 30% of the decline in resting EE. After adjustment for the CR-induced changes in organ mass, metabolic adaptation was ~55 kcal/d (Bosy-Westphal et al., 2009). Of the FFM compartment, the most significant predictors for the changes in resting EE were changes in skeletal muscle mass and kidney mass explaining 34.9% and 4.5%, respectively (Pourhassan et al., 2014).

Changes in organ mass may depend on the intervention modality and metabolic health of subjects at baseline. In LookAhead, 82 patients with overweight or obesity and type 2 diabetes achieved ~6 kg body weight loss through dietary restriction and aerobic exercise (Gallagher et al., 2017). The lifestyle intervention group did not have a disproportionate change in high metabolic rate organs (change in liver −5.9%, spleen −4.3%, and kidney −1.5%) as compared to low metabolic rate organs (skeletal muscle, −6.4%). Unfortunately, EE was not reported in this study and thus, this hypothesis remains to be tested. Importantly, the intervention modality, i.e. the inclusion of exercise to induce CR, did not affect the degree of metabolic adaptation in the 6-month CALERIE-study, but in this study, changes in organ masses were not reported (Heilbronn et al., 2006) (Table 1).

### 5.2. Metabolic mediators of CR

The CR-induced reduction in metabolic rate may be related to changes in metabolic activity of the heart, i.e. heart rate and blood pressure, and of the sympathetic nervous system (Muller et al., 2015). These effects may be mediated by CR-induced responses in circulating hormones such as leptin, thyroid hormones and insulin.

#### 5.2.1. Leptin

Leptin is an adipose tissue-derived hormone and its concentration is proportional to fat mass. Evolutionarily, leptin is interpreted as anti-obesity signal because it signals satiety and stimulates energy expenditure (Rosenbaum et al., 2010). A marked reduction in leptin is consistently reported with CR and likely occurs as a result of the decreased adipose tissue mass. This reduction in leptin occurs regardless of the duration of the CR intervention; 6-month CALERIE 1, −44% (Lecoultre et al., 2011), 24-month CALERIE 2 ancillary, −6% (Redman et al., 2018), 3-week revisited Minnesota Starvation men, −44% (Muller et al., 2015), 13-week revisited Minnesota Starvation women, −42% (Bosy-Westphal et al., 2009).

In CALERIE, the decline in circulating leptin was related to metabolic adaptation measured during weight loss after six months ($r$ = 0.22) and 12 months ($r$ = 0.35) (Redman et al., 2018). This association disappeared during weight loss maintenance (Redman et al., 2018). A similar finding was observed in patients with obesity. Following a very low calorie-diet for 8 weeks and achieving 11% weight loss, the decline in leptin (−48%) was weakly associated ($r$ = 0.24) with metabolic adaptation (4%) (Camps et al., 2015). Interestingly, weight loss-induced changes in leptin were not associated with metabolic adaptation calculated considering changes in organ size (Bosy-Westphal et al., 2009; Muller et al., 2015).

Metabolically, a reduction in leptin may influence metabolic adaptation through its interaction with skeletal muscle proteins. Skeletal muscle chemomechanical work efficiency is increased and the ratio of glycolytic/oxidative enzyme activities decreased in subjects with a decline in leptin following diet-induced weight loss (Baldwin et al., 2011). This role of leptin is further supported by the observation that leptin repletion stimulates less energy-efficient myosin heavy chain IIx isoform and thus reverses the weight-loss induced effects (Baldwin et al., 2011).

#### 5.2.2. Thyroid hormones

Thyroid axis hormones, e.g. thyroid stimulating hormone, triiodothyronine (T3) and thyroxin (T4), affect EE and thereby are potential mediators of CR-induced reductions in metabolic rate. Specifically, thyroid hormones regulate metabolic cycles, e.g. lipolysis/lipogenesis,

glucogenolysis/gluconeogenesis and protein synthesis/catabolism, accelerate heat generation in the mitochondria, and accelerate heart rate (Yavuz et al., 2019).

In the CALERIE trials, metabolic adaptation in 24-h EE after 3 months was positively associated with reductions in both T3 and T4 (Heilbronn et al., 2006). This effect was transient during weight loss since no associations between metabolic adaptation and thyroid hormones were observed during active weight loss at 6 (Heilbronn et al., 2006) or 12 months (Redman et al., 2018). Thyroid hormones may be important for EE regulation in the preservation of the metabolic adaptation in weight loss maintenance. After 12 months of weight loss maintenance in CALERIE (at month 24), reduced T4 concentrations were associated with metabolic adaptation (Redman et al., 2018). Furthermore, in a long-term observational study of 2–4 years comparing energy metabolism during weight gain and weight loss, changes in T3 explained 5.3% of the variance in changes in resting EE (Pourhassan et al., 2014). These longer trials imply that the thyroid axis might have differential roles in energy metabolism during weight loss and weight loss maintenance.

Similar to leptin, thyroid hormones may also affect skeletal muscle work efficiency. In weight-reduced humans, T3 repletion reduced relative expression of the more-efficient/less-efficient myosin heavy chain I/myosin heavy chain II isoforms and increased the ratio of the less-efficient to the more-efficient sarco(endo)plasmic reticulum Ca2+-ATPase isoforms (SERCA1/SERCA2) (Rosenbaum et al., 2018). Similar effects have been observed after short-term T4 supplementation (Johannsen et al., 2012).

The involvement of the thyroid axis in the regulation of metabolic adaptation might also be sex specific. In the short-term studies of severe CR by Muller et al. (2015) and Bosy-Westphal et al. (2009), T3 concentrations decreased by −39% in men after three weeks and −8% in women after 13 weeks. Whereas in men the decrease in T3 concentrations was not associated with metabolic adaptation (Muller et al., 2015), despite smaller changes of T3 in women an association with metabolic adaptation was observed (Bosy-Westphal et al., 2009). To summarize, there are indications that thyroid axis activity influences metabolic adaptation with CR but the variation in metabolic rate explained by thyroid hormones does not exceed 5% and may differ between men and women.

#### 5.2.3. Insulin

Insulin is the central anabolic hormone in metabolic homeostasis. In response to a meal, insulin increases and stimulates storage of glucose and lipid which is accompanied by an increase in energy expenditure (diet-induced thermogenesis). Weight loss induced metabolic adaptation was strongly associated with insulin secretion ($r = 0.92$) assessed as 24-hour C-peptide excretion (Muller et al., 2015) in overweight and obese men and with decreased fasting insulin concentrations in women (Bosy-Westphal et al., 2009). Similarly, insulin secretion, assessed as 30-min postprandial insulin concentrations and maximal insulin secretion, as well as insulin resistance (HOMA, and during oral glucose tolerance test) predicted changes in resting EE (independent of changes in body composition) in a study of 21 overweight and obese men and women during weight loss (10–15%) maintenance (Hron et al., 2015). In the CALERIE study, insulin concentrations and insulin resistance declined with CR at all time points (Heilbronn et al., 2006; Larson-Meyer et al., 2006; Ravussin et al., 2015) but no association between glucose homeostasis and metabolic adaptation was reported. Collectively, these studies show that a metabolic adaptation is attributed in part to the reduced energetic costs of insulin secretion, and likely anabolic processes induced by insulin.

#### 5.2.4. Neuroendocrine Hormones

A shift in neuroendocrine function from sympathetic to parasympathetic tone is one of the proposed mechanisms to explain the attenuation in the rate of aging and longevity in rodents undergoing CR, and thus possibly is related to the effect of low metabolic rate (Fontana, 2009). Sympathetic nervous system activity as assessed through 24-hour urinary epinephrine and norephinephrine excretion was not affected by CR after 6 (Lecoultre et al., 2011), 12 or 24 months (Redman et al., 2018). Moreover, there was no observed changes in growth hormone, growth hormone secretion or insulin-like growth factor 1 (Redman et al., 2010). But notably the participants in the CALERIE studies were normal weight or overweight but otherwise healthy to begin with. Considered alone, these studies argue the notion that a reduction in sympathetic tone mediated by catecholamines or the growth-IGF1 axis contributes to CR-induced metabolic adaptation in humans.

#### 5.2.5. Sex steroids

CR has been shown to induce transient-3 weeks (Muller et al., 2015), 12 months, but not 24 months (Martin et al., 2016) or 7 year-reductions in testosterone concentrations (Cangemi et al., 2010). While CR-induced reduction in testosterone may contribute to the decline in FFM, no associations between metabolic adaptation and testosterone concentrations have been observed after 3 weeks CR in men (Muller et al., 2015).

### 5.3. Mitochondrial energy efficiency

Energy intake requirements are the sum of energy expenditure for ATP generation and for heat production (Fig. 2). Thus, reducing resting EE can be achieved through a reduction in metabolic processes consuming ATP, i.e. reducing ATP requirements, or through a reduction of heat production. The ratio of ATP production to heat generation, or alternatively, ATP production to oxygen consumption, can be defined

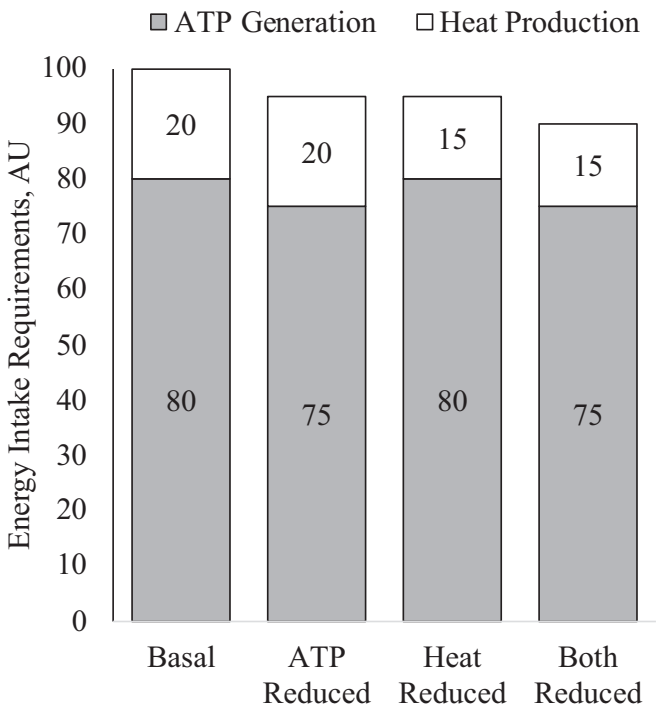


**Fig. 2.** Models for reduction of energy intake requirements.
In basal conditions, energy intake requirements are the sum of energy requirements for ATP generation and for heat production (column 1). Through CR, energy intake requirements for mass-adjusted metabolic rate, defined as metabolic adaptation, are reduced (column 2–4). Energy intake requirements can be reduced through reduction of ATP production, that is an attenuation of metabolic processes (column 2). Alternatively, or simultaneously (column 3 and 4) requirements can be reduced via reduced heat production which is achieved through improving mitochondrial coupling.

as mitochondrial energy efficiency. Increased mitochondrial energy efficiency can be achieved by reducing uncoupling proteins or by alleviating protonmotive force on oxidative phosphorylation proteins such as through less supply of protons or increased mitochondrial mass (Cadenas, 2018).

Energy-rich substrates are oxidized in the mitochondria and provide energy to transport electrons and protons across the inner mitochondrial membrane against their concentration gradients. Majority of protons and electrons are transported back into the mitochondrial lumen via coordinated relief of this gradient through ATPase, which uses the energy to convert ADP to ATP. Alternatively, electrons or protons can leak from the mitochondrial intermembrane space into the mitochondrial lumen, avoid ATPase, and thereby produce heat instead of ATP. Leakage of electrons and protons can occur passively caused by an increased mitochondrial membrane gradient or can be facilitated through uncoupling proteins. With CR where supply of energy-rich substrates is reduced, proton motive force may be alleviated such that proton leakage declines. Alternatively, inhibition of uncoupling proteins can reduce proton leakage. Through either process, less energy dissipates as heat and consequently less energy-rich substrates and oxygen are required to convert the same amount of ADP to ATP.

In the 6-month CALERIE study, CR increased mitochondrial DNA content by 35% and increased expression of genes encoding proteins involved in mitochondrial function (Civitarese et al., 2007), supporting the hypothesis that increased mitochondrial mass and function may associate with metabolic adaptation. In the 24-month CALERIE study, mitochondrial energetics were investigated in vivo using 31P-magnetic resonance spectroscopy and optical spectroscopy (Sparks et al., 2017). Surprisingly, mitochondrial capacity, measured as maximal ATP synthesis rate, and mitochondrial efficiency which was defined as ATP flux relative to oxygen consumption (P:O-ratio), were unaffected by 12 months of CR. In line with the in vivo findings, targeted transcriptional profiling of vastus lateralis muscle showed no effects on pathways involved in mitochondrial biogenesis or function. Interestingly, a secondary analysis showed that individuals with higher P:O-ratio (mitochondrial coupling) at baseline demonstrated a greater increase in mitochondrial capacity and function, compared to those with lower coupling at baseline (Sparks et al., 2017). This implies that poorly functioning mitochondria may preclude CR-induced improvements in mitochondrial function, and possibly generation of free radicals and hence oxidative stress. The CALERIE studies did not report any associations between mitochondrial function (in vivo or in vitro) and metabolic adaptation. However, uncoupling protein 2 in skeletal muscle has been shown to associate with metabolic adaptation in 24-h EE after 6-week 50% CR (Heinitz et al., 2018). Importantly, mitochondrial function has only been assessed in skeletal muscle, but energy efficiency may be more sensitive to changes in mitochondrial function in high metabolic rate organs.

Improved mitochondrial efficiency can be achieved through stimulation of oxidative ATP production at the expense of glycolytic ATP production. Such a change may contribute to substantially lower (~15%) oxygen requirements (Welch et al., 2007). CR has been shown to decrease glycolytic (phosphofructokinase, PFK) enzyme activity and increase oxidative (cytochrome *c* oxidase, COX) enzyme activity (Goldsmith et al., 2010), but the impact on energy requirements remains to be determined. In turn, an increased efficiency in ATP production would reduce skeletal muscle PI3K/AMPK signaling and reduce the rate of substrate cycling between de novo lipogenesis and lipid oxidation, leading to lower energy intake requirements (Summermatter et al., 2008).

Mitochondrial efficiency is considered beneficial, because mitochondrial oxygen consumption is proportional to production of reactive oxygen species, i.e. oxidative damage ('Oxidative Damage Theory of Aging'). CR-induced reductions in oxygen requirements are therefore hypothesized to reduce oxidative stress and damage. The CALERIE trials support this hypothesis by reporting that the observed decline in metabolic rate was associated with reductions in measures of oxidative stress. For example in the 6-month CALERIE study, CR reduced DNA damage (Civitarese et al., 2007; Heilbronn et al., 2006), plasma protein carbonyl concentrations and increased glutathione peroxidase (reflecting antioxidant defense) (Meydani et al., 2011). In the 24-month CALERIE study, reactive oxygen species (F2-isoprostane) production was reduced (Il'yasova et al., 2018; Redman et al., 2018). Noteworthy, not all measures of oxidative stress improved, e.g. serum protein carbonyl concentrations (Heilbronn et al., 2006; Redman et al., 2018), suggesting that CR exerts differing effects on tissue specific oxidative damage or that some measures of oxidative stress are not sensitive enough.

## 6. Characteristics of metabolic adaptation

It was recently proposed by Muller et al. (2016) that there may be different phases of CR-induced metabolic adaptation (Fig. 1). They postulated that different regulatory systems are involved at three distinct phases: the initial phase which occurs during the first week, the weight loss phase which is between one week to one year, and the weight maintenance phase.

During the first phase of weight loss, metabolic adaptation is characterized by the immediate response to a negative energy balance. During this period, changes in FM are minimal, whereas declines FFM are greater in comparison due to depletion of glycogen stores and associated losses of intracellular fluid and sodium (Heymsfield et al., 2011). Therefore, declines in FFM during the first three weeks of CR are most pronounced for the liver (−40% of baseline) and a less in adipose tissue (−15%). A decline in skeletal muscle mass is not observed before ~5 weeks after initiation.

Commensurate with an acute energy deficit, insulin, leptin, and thyroid axis hormones fall, there is a decline in sympathetic nervous system activity, and aldosterone. During this initial phase, insulin secretion is decreased, gluconeogenesis enhanced, and glucose oxidation is decreased at the expense of increased fat and protein oxidation. Metabolic adaptation during this initial period is therefore likely related to an attenuation of insulin secretion due to reduced insulin requirements and may relate to a substrate switch for ATP production.

During the second phase of weight loss termed 'settling phase', the metabolic changes observed during the first phase persist. The sustained increase in fat oxidation now leads to a pronounced decrease in FM. The longer the duration of CR, the larger the proportion of FM loss as compared to FFM loss (Heymsfield et al., 2011). Changes in EE in the settling phase are now proportional to weight change and there is no further increase in metabolic adaptation with ongoing weight loss (Muller et al., 2016). Metabolic adaptation during this period may be supported by changes in FFM composition (Muller et al., 2015).

After reaching a new energy balance a weight loss plateau is realized. This maintenance phase is characterized by reductions in sympathetic nervous system activity, thyroid hormones, and insulin. Further reductions in FM cause low leptin concentrations and increased free fatty acid concentrations. Together these physiological adaptations maintain low EE, likely as an evolutionary defense mechanism to resist against further weight loss (Miller and Parsonage, 1975) and preserve triglyceride stores in order to protect basic biological functions (e.g., reproduction) (Muller et al., 2016).

## 7. Physical activity

The interaction between CR, physical activity, EE, and aging is complex. As discussed, CR reduces body weight and EE at rest, but CR also reduced EE during activity (Redman et al., 2009). The reduction in EE can be due to the smaller metabolic mass, lower energy requirements for ATP generation or to lower requirements for ATP for a given activity through improved movement economy. According to the Rate of Living theory, lower EE is proposed to be beneficial for an organism

to achieve longer life. Paradoxically, physical activity also promotes longevity, yet acutely increases EE (Booth et al., 2011). The longevity promoting effect of activity is therefore independent of the acute increase in EE and due to unique metabolic adaptations induced by the activity itself. Physical activity induces an acute energy deficit which activates AMPK, uptake of substrates from plasma, lipolysis, mitochondrial function, and fat oxidation. Chronically, these effects lead to increased cardiorespiratory capacity, mitochondrial oxidative capacity, reduced lipid in plasma, tissues and cells, improved insulin sensitivity and improved metabolic function of merely every organ in the body. A crucial mediator of physical activity is oxidative stress. Per the Oxidative Damage theory of aging, oxidative stress is detrimental but transient increases in oxidative stress induced by physical activity are vital for inducing adaptations such as increased mitochondrial function and increasing anti-oxidative capacity ('Metabolic hormesis') (Ristow and Zarse, 2010).

In CALERIE, a reduction in total daily EE and absolute activity-related EE was observed after 6 (Martin et al., 2011; Redman et al., 2009), 12 (Martin et al., 2011) and 24 months (Racette et al., 2017; Ravussin et al., 2015). After adjustment for the change in body mass, or sleeping metabolic rate, activity-related EE was still reduced after 6 months of CR. This suggests a lower level of physical activity, or a non-intentional "behavioral adaptation" thought to conserve energy (Redman et al., 2009). Accelerometry and physical activity captured by 7-day recall did not confirm a reduction in activity-related EE suggesting that increased muscle efficiency and/or decreased fidgeting accounted for some of the variability in activity-related EE (Martin et al., 2011). As CR continues, declines in total daily EE and activity-related EE are no longer evident (Redman et al., 2018). Thus, behavioral adaptations to decrease physical activity with CR appear to resolve over time. Importantly, the behavioral adaptations to CR may vary between individuals. For example, after 24 months CR, activity-related EE declined more in females as compared with males (Racette et al., 2017).

A reduction in activity-related EE may also be a result of increased movement economy. The energy cost of walking was found to be reduced by 22% after 6 kg weight loss (Muller et al., 2015) and mechanical efficiency of skeletal muscle at low workloads (pedaling a bicycle to generate 10 or 25 W of power) was increased following 10% weight loss (Goldsmith et al., 2010). This data is further supported by studies in rhesus monkeys, demonstrating that long-term CR decreased metabolic cost of movement (Yamada et al., 2013). Increased work efficiency observed after weight loss may be mediated by leptin (Baldwin et al., 2011) and thyroid hormones (Johannsen et al., 2012; Rosenbaum et al., 2018). Unfortunately, such measurements have not been performed in participants of CALERIE.

## 8. Persistence of metabolic adaptation and weight regain

In prospective observational cohorts, low metabolic rate adjusted for body mass has been shown to predict long-term weight regain (Ravussin et al., 1988). In addition, blunted diet induced thermogenesis in response to low-protein overfeeding, i.e. thrifty phenotype, may attenuate the effects of CR on weight loss (Reinhardt et al., 2015) and may increase weight regain (Hollstein et al., 2019; Reinhardt et al., 2016). The poor physiological defenses against weight regain may in part be explained by observations that metabolic adaptations are larger after weight loss and do not fully recover when weight is regained. Muller et al. (2016) observed a −108 kcal/d metabolic adaptation after three weeks of 50% CR which was recovered by only 20 kcal/d with two weeks of refeeding. Similarly, in an observational study of 83 patients (50% with obesity), resting EE adjusted for FFM and FM decreased by ~50 kcal/d during weight loss, but increased by 25 kcal/d during subsequent weight regain (Pourhassan et al., 2014).

Long-term studies of CR on metabolic rate have demonstrated that metabolic adaptation persists long after the intervention. In a follow-up of the CALERIE participants, 54% of the weight lost during the intervention was regained after two years, while the control group remained weight stable (Marlatt et al., 2017). Differences in sleep EE observed between the groups during the intervention persisted during follow-up. These findings were extended by Rosenbaum et al. (2008), who observed that metabolic adaptation persisted long after the initial weight loss occurs (1–9 years). Prospective observational studies in patients with overweight or obesity support the hypothesis that metabolic adaptations contribute to weight regain. Among 103 subjects with overweight or obesity who completed a 13-week low-calorie diet intervention, metabolic adaptation (defined as resting EE, adjusted for changes in organ and tissue masses) was compared between those who regained weight after 6 months (≥30% of loss, $n = 27$) to those who maintained weight (within < ± 20% of weight change, $n = 20$) (Bosy-Westphal et al., 2013). As hypothesized, metabolic adaptation, i.e. lower EE was evident in individuals who regained weight compared to those who remained weight-stable (Bosy-Westphal et al., 2013). To our knowledge, weight regain has not yet been associated with metabolic adaptation in a prospective, observational study, except for during pregnancy (Berggren et al., 2017; Most and Redman, 2019).

Importantly, resting EE only accounts for 60–70% of total daily EE, which ultimately determines energy balance and weight gain. Thus, the contribution of metabolic adaptation to weight gain, may be masked by behavioral variations in physical activity and eating behavior (Marlatt et al., 2017). Maintaining or increasing physical activity after weight loss is likely the most promising option to buffer the persistent metabolic adaptation and resist weight regain. While maintaining energy balance, physical activity has been shown to improve protein balance (i.e. less protein oxidation relative to intake) and fat balance (increased fat oxidation relative to fat intake) (Nas et al., 2019). These findings support the 'collateral fattening hypothesis' (Dulloo et al., 2018), which posits that low FFM drives overeating. In agreement with this hypothesis, FFM (and not FM or BMI) has been shown to associate with self-determined meal size and daily energy intake in humans (Blundell et al., 2012).

In different studies, metabolic determinants of weight regain are largely investigated for the effect on EE. However, it has been argued that the observed effects on EE (< 100 kcal/d) are too small to explain the effects in weight regain (Rosenbaum et al., 2010). In contrast, it is proposed that induced changes in metabolic hormones may be more relevant to hunger and satiety (Sumithran et al., 2011). For example, decreased concentrations of leptin reduce satiety and thus may stimulate energy intake (Rosenbaum and Leibel, 2012). Weight regain appears to be driven by processes involved in EE and energy intake, but ultimately are defined by the ability for an individual to resist them. Indeed, during CR long-term reduction in food cravings, and improvements in dietary restraint and self-efficacy are observed, supporting success in weight loss maintenance (Dorling et al., 2019). Learned behaviors such as dietary restraint and avoidance of 'forbidden foods' were maintained after the intervention which may counteract the risk for weight regain due to low metabolic rate (Marlatt et al., 2017). Lastly, the reduction in FFM induced by CR may promote weight regain. For example, low FFM relative to body size has been associated with appetite (Hopkins and Blundell, 2017), weight gain and obesity (Dulloo et al., 2018), possibly due to a stimulation of food intake at meals (Blundell et al., 2012).

## 9. Future directions

Calorie restriction reduces metabolic rate, independent of changes in fat-free mass, or mass of high metabolic rate organs. Metabolic effects of CR include the reduction in hormones related to energy expenditure, but direct associations are inconclusive and may relate to the duration of CR. CR-induced improvements in mitochondrial functions are reported, but again, the effect on energy efficiency may be small. Poor mitochondrial function at baseline may prevent CR-induced improvements in mitochondrial capacity and energy efficiency. Parallel

dietary supplements that stimulate mitochondrial capacity in patients with poor mitochondrial function may overcome this limitation (Most et al., 2016; Timmers et al., 2011).

Reductions in energy expenditure (~5–10%) induced by 15–20% CR are reported consistently. Per 'Rate of Living'-theory, this reduction attenuates the primary aging process and is therefore beneficial. The extent of this improvement is debatable. Previous studies have estimated that CR may increase lifespan by 5 years, if implemented early in adulthood, but only by 2 months, if implemented at age 60 (Most and Redman, 2017). These relatively small benefits in the elderly may be outweighed by the potential adverse effects of CR, e.g. reductions in metabolic rate and fat-free mass increase the risk for weight regain and frailty. CR may therefore not be an appropriate intervention for older individuals or those with relatively low fat-free mass.

The observed reductions in metabolic rate which are attributed to hormone concentrations and physiological processes such as insulin secretion, heart rate, and blood pressure may explain 50% of this reduction, hence do not exceed 3% of total daily EE. The increased risk for weight regain, as demonstrated by different studies, may therefore relate to an insufficient adjustment of energy intake-regulating systems, which require further study. Investigating such systems including satiety and hunger sensation may also lead to strategies to facilitate long-term compliance to CR which is generally poor, and declines with the degree of CR prescription and duration of the intervention (Doucet et al., 2018).

Many factors in the interaction between CR, metabolic rate and weight management are still unknown. For example, great controversy exists about the optimal macronutrient composition. Some suggest low-carbohydrate intake to increase EE (Ebbeling et al., 2012), while other suggest that low-fat is more beneficial (Hall et al., 2016). The positive association between insulin secretion and metabolic adaptation observed by Muller et al. (2015) would support the latter, while data from Ebbeling and Ludwig suggest the contrary (Ebbeling et al., 2018). In addition, metabolic rate, or the effect of CR on metabolic rate, may be modified by the genetic background (Mulvey et al., 2014), gastrointestinal morphology (Mitchell et al., 2015) and the gut microbiota (Canfora et al., 2015; Rosenbaum et al., 2015), although clinical studies are not yet convincing (Canfora et al., 2017; Reijnders et al., 2016; van der Beek et al., 2018; Vrieze et al., 2014; Vrieze et al., 2012).

The interaction between energy intake and physical activity requires further study. For example, under controlled conditions, exercise training may prevent declines in total daily EE and FFM (Redman et al., 2009), both risk factors for weight regain. Moreover, increasing physical activity (in energy balance) also results in beneficial effects on hunger and satiety regulation (Nas et al., 2019). In an ad libitum environment however, exercise training is an ineffective means for weight loss due to compensatory increases in energy intake (Martin et al., 2019).

Factors that have been demonstrated relevant to the effects of CR in rodent studies are energy homeostatic systems and sex-specificity. For example, excitatory synapses on arcuate nucleus proopiomelanocortin neurons have been shown to defend a higher level of body fat (Ravussin et al., 2011). Interestingly, POMC-neuron activation increased physical activity and EE only in males, but not in females (Burke et al., 2016). These findings may relate to observations in CALERIE, where activity-related EE declined less in males after 24 months CR as compared with females (Racette et al., 2017).

## 10. Conclusion

CR induces weight loss and a disproportionate reduction in energy expenditure. This reduction is partly explained by changes in organ sizes (~25–50%), while energy requirements for metabolic homeostasis are also reduced. The inter-individual variability in these changes requires further investigation as does the effects of CR on energy intake-regulating mechanisms, specifically in free-living environments.

## Author statement

Jasper Most: Conception of idea, prepared original draft. Leanne Redman: Conception of idea, critical reviewing, editing and approval of final draft.

## Declaration of competing interest

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