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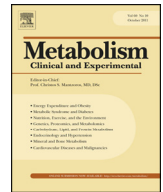
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Body mass cycling and predictors of body mass regain and its impact on cardiometabolic health

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ABSTRACT

Caloric restriction (CR) is the first line intervention to reduce adiposity and total body mass (BM) to improve insulin resistance and ameliorate metabolic derangements. However, the lost adipose mass is difficult to maintain reduced in the long term due to several factors including compensatory changes in orexigenic hormones, adipokine release, pro-inflammatory state, adipose tissue morphology, and resting metabolic rate as a consequence of the caloric deficit. Hence, most patients undergoing a BM reduction intervention ultimately regain the lost mass and too often additional adipose mass overtime, which is hypothesized to have increased deleterious effects chronically. In this mini-review we describe the effects of BM cycling (loss and regain) on insulin resistance and cardiometabolic health and factors that may predict BM regain in clinical studies. We also describe the factors that contribute to the chronic deleterious effects of BM cycling in rodent models of diet-induced obesity (DIO) and other metabolic defects. We conclude that most of the improvements in insulin resistance are observed after a profound loss in BM regardless of the diet and that BM cycling abrogates these beneficial effects. We also suggest that more BM cycling studies are needed in rodent models resembling the development of type 2 diabetes mellitus (T2DM) in humans.

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1. Introduction

Caloric restriction (CR) is a first line intervention to reduce adiposity and total body mass (BM) during obesity, which is especially important for improving the factors of metabolic syndrome (MetS). Even a modest reduction in daily caloric intake (500–1000 kcal/day) can decrease fat mass (FM) and improve insulin sensitivity to a greater extent than 5 days/week of moderate exercise [1]. Moreover, remission of T2DM with sustained normalization of basal blood glucose and liver and pancreas triglycerides (TG) was observed in patients that lost 15 kg of BM via CR [2]. Additionally, a previous systematic review categorized the decrease in total caloric intake (specifically sugar-sweetened beverages) as a primary determinant of maintaining the lost BM, surpassing meal replacement and socioeconomic factors [3]. Moreover, the CR-induced decrease in visceral adipose improved cardiometabolic risk factors (increased serum high-density lipoproteins HDL and decreased TG and very low-density lipoproteins (VLDL) concentrations) and decreased systemic inflammatory markers (high sensitivity C-reactive protein [hsCRP] and α 1-acid glycoprotein) [4]. In addition to the aforementioned benefits, CR may increase survival as observed in a DIO mouse model where 30% CR and BM cycling decreased mortality compared to ever-obese mice [5].

However, several factors make further loss of BM and maintenance a challenge, in particular energetic deficit, making CR a less effective BM loss strategy compared to other interventions (e.g. bariatric surgery) for chronic BM reduction and maintenance [6]. This is further explained by a disparity between decreased energy expenditure (EE) and increased appetite proportional to the lost BM, causing an average BM regain of 80% within 5 years after the intervention in patients undergoing long-term BM loss [7]. Additionally, total daily EE decreased in obese subjects, and more so when BM loss exceeded 10% of total mass, thus accentuating net-positive caloric intake [8], although the change in resting metabolic rate (RMR) correlated better with free-fat mass (FFM) than fat-mass (FM), which was shed in higher proportion [9]. For high BM loss (>5%), the amount and rate of BM loss had a strong, positive association ($P < 0.001$ and $P = 0.049$, respectively) with the amount of BM regain, whereas this relationship was not observed when the lost mass was lower [10]. This is particularly important to consider when a high amount of FM loss is desirable. Nonetheless, the potential detrimental effects of BM cycling on obesity (i.e. fat mass accumulation) and metabolic risk factors remain controversial and inconclusive as indicated by roughly half the studies previously reviewed from 1994 to 2015 [11].

2. BM cycling and insulin resistance in rodents

Several studies on BM cycling have been performed in rodent models to elucidate the mechanisms contributing to metabolic derangements

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after BM regain. We have shown that partial BM regain following 50% CR abolished the acute improvements in insulin resistance independent of a regain in FM with further derangement in gluconeogenesis in OLETF rats [12]. These results are consistent with others in Wistar rats, which were subjected to 4 BM loss-regain cycles via 50% CR and had lower FM compared to control; however, the expected increases in ghrelin, leptin, or insulin after BM regain were not observed [13]. Furthermore, 4 bouts of diet-induced (high fat-low fat) BM cycling decreased basal EE and glucose tolerance compared to obese controls in C57BL/6J mice [14].

The effects of BM regain associated with high fat diet (HFD) in C57BL/6J mice on mediators of insulin resistance depend on diet duration. The BM regain following a 4-wk HFD intervention increased the accumulation of TG and of lysophosphatidic acid (LPC), an important lipid effector of fatty acid-induced insulin resistance, in the gastrocnemius and soleus muscles, respectively [15]. The improvements in fasting glucose and insulin induced by approximately 25% loss in BM with a control diet were abolished by 6 weeks of HFD with visceral adipose mass increasing above that of high fat-only fed mice [16]. Additionally, mice regaining BM had similar hepatic TG and higher basal insulin compared to mice that did not experience BM cycling [17]. After 8 weeks of BM cycling, relative mRNA and protein expressions of C1q/tumor necrosis factor (TNF)-related protein-3 (CTRP3), an anti-inflammatory and hypoglycemic adipokine, decreased and adipocyte volume increased [18]. Alternating low-high fat diet cycles for 9 weeks increased adipose CD4+ and CD8+ T-cells despite similar BM to the obese, non-cycling mice suggesting that BM cycling may be more detrimental than BM maintenance even if in an obese condition. Furthermore, BM cycling decreased adipose pAKT, a measure of insulin sensitivity, and increased both fasting glucose and glucose area under the curve (AUC) after glucose tolerance test (GTT) [19]. However, BM cycling induced by 20% CR reduced adipocyte size after two cycles without changing food efficiency or fasting glucose, leptin, and adiponectin [20]. Intermittent fasting (IF) cycles with a 2:1 ratio (2 days of ad libitum feeding and 1 day of fasting) decreased FM in both obese and lean mice, without any change in FFM unlike previous studies with 1:1 IF cycles. Moreover, IF reduced glucose AUC after intraperitoneal GTT in both DIO mice (C57BL/6J) and leptin deficient *ob/ob* mice [21]. These results are important to consider, as BM cycling reduces EE and insulin sensitivity regardless of the duration of CR. Moreover, BM cycling promotes accumulation of TG in the muscle and liver, and activated T-cell accumulation in adipose tissue, which further promotes insulin resistance.

3. BM cycling, blood pressure, and renin-angiotensin-aldosterone system (RAAS) in rodents

BM loss, especially in the form of FM, is suggested to improve cardiovascular health. A 9% reduction in BM in obese subjects improved the recovery of heart rate after a maximal aerobic capacity test compared to baseline [22]. The changes in systolic blood pressure (SBP) paralleled the BM loss and regain achieved by alternating an obesogenic diet with 50% CR every 2 wks in normotensive Sprague-Dawley rats; however, the BM cycling per se did not elicit a net change in SBP at the end of the study [23]. The BM regain following severe CR increased the sensitivity of the RAAS. In female Fischer rats, 60% CR for 2 weeks, reduced mean arterial pressure (MAP) by 20 mmHg after BM decreased 15%. However, 3 months after refeeding and complete BM regain, MAP reverted to basal levels. Furthermore, angiotensin converting enzyme (ACE) activity and angiotensin II (Ang II) were increased, and MAP was more sensitive to exogenous Ang II in the regain group [24].

In spontaneously hypertensive rats (SHRs), 50% CR increased cardiac atrophy and sarcoplasmic remodeling of myofibrils and mitochondria, and decreased the inotropic effect when stimulated with Ca^{2+} and isoproterenol compared to ad libitum fed rats. However, these differences were absent in the cycling group (weekly between 50% CR and ad libitum refeeding) compared to non-cycling group [25]. These results support the notion that the improvements in blood pressure are related

to BM reduction. However, they also demonstrate the loss of these improvements with BM cycling. Moreover, the cardiac remodeling after severe CR may potentiate adverse effects on cardiovascular health.

4. Potential regulators of BM regain in rodents

In the agouti-related peptide (AgRP)-carnitine acyltransferase (Crat) KO mouse, 9 days of 60% CR decreased RQ, FM, and plasma leptin without changing basal glucose; however, FM regain was greater after 11 days of ad libitum refeeding [26]. In C57BL/6 mice, 9 weeks of HFD-induced obesity was not reverted by a subsequent low-fat diet (LFD) for 9 weeks. However, glucose tolerance was improved with LFD but adipose and prostaglandin signaling were maintained, while most of the liver metabolome was reverted to basal levels [27]. Conversely, BM regain induced by 4 weeks of HFD decreased several liver amino acids and lactate, a gluconeogenic intermediate, and increased the gluconeogenic enzymes, glucose-6-phosphatase (G6Pase) and pyruvate carboxylase (PC), which translated into higher fasting glucose [28]. In mice, 40% CR with LFD after 8 weeks of HFD, increased respiratory exchange ratio (RER) compared to the LFD controls suggesting that the transition from glucose to fatty acid oxidation was delayed, a sign of obesity-induced metabolic dysregulation. Furthermore, when re-challenged with HFD, adipose hormone-sensitive lipase (HSL) phosphorylation was lower translating into reduced lipolysis compared to lean mice [29].

The BM loss achieved by LFD following an obesity-inducing diet increased feeding motivation compared to non-cycling mice without changing physical activity. Additionally, the rate of BM loss was positively correlated with rate of regain [30]. Suppressed thermogenesis may also increase BM regain especially when disproportionate FM recovery is associated. In Sprague-Dawley (SD) rats, BM cycling (50% CR for 2 weeks followed by 16 days of ad libitum refeeding) reduced mean core body temperature during CR and BM regain, and increased the rate of FM regain, compared to age- and mass-matched controls [31].

5. Effects of gut microbiota and adipose inflammation on BM cycling in rodents

Gut microbiota has been shown to affect the rate of BM gain after a HF diet in rodents. For instance, in obesity-prone SD rats, a higher relative abundance of Clostridiales and Enterobacteriales was found in cecal samples, compared to obesity-resistant rats after 8 weeks of HF diet [32], and a HFD for 16 weeks in the same model decreased the relative abundance of Firmicutes and increased Bacteroidetes in fecal samples, along with a global decrease of butyrate-producing species, compared to control fed rats. This may explain the low-grade intestinal inflammation and endotoxemia associated with obesity [33]. Moreover, DIO altered the bacterial abundance in HFD-induced obesity in mice, which is only reversed 21 weeks after achieving body mass normalization with 4 weeks of normal chow diet. This dysbiosis decreased isoflavonoid and steroid biosynthesis in lieu of an increased biosynthesis of unsaturated fatty acids. This translated to a decrease in glucose tolerance and RMR, and an increased rate of gain in BM compared to normal chow fed mice, which was exacerbated with multiple, continuous BM cycling [34].

In male C57BL/6J mice fed an alternating HFD-normal diet (ND)-HFD (re-challenged), a greater accumulation of epididymal adipose tissue macrophages (ATM) was observed despite a reduction in adiposity compared to mice fed only a HFD over the 6 weeks before the end of study [17] suggesting that the inflammatory response to BM cycling in adipose is independent of adipose mass. Moreover, in mice undergoing BM regain with a similar diet regiment (HFD-ND-HFD) presented with a greater density of dying adipocytes surrounded by macrophages, or crown-like structures (CLS), in epididymal adipose, in addition to increased hepatocyte size and hepatic lipid droplet accumulation compared to mice undergoing a single period of HFD [35]. Activated CD4+ cells have also been suggested to determine BM regain because of their contributions to chronic inflammation and accumulation in

adipose. Activation of CD4+ cells were increased in DIO C57BL/6J mice experiencing 1 month of HFD followed by BM normalization. In these mice, the rate of BM regain and adipose T-cell abundance increased compared to non-cycling mice, whereas these differences were abrogated with administration of dexamethasone, a T-cell and pro-inflammatory cytokine inhibitor. Moreover, mice experiencing BM cycling had a lower RER even after normalization of BM suggesting that “memory” adaptation to acquire most of the lost energy via fatty acid oxidation may exist [36]. While there is a general consensus of the metabolic shift from lipid oxidation to gluconeogenesis and FA mobilization to the liver and muscle after substantial BM loss, it is of interest that suppressed thermogenesis and maintained inflammation in adipose, even after BM loss, are factors that may facilitate BM regain. It may be of interest to further investigate the extent to which altered diets influence adipose and systemic inflammation as these relate to the successful maintenance of BM following loss. Nonetheless, these studies demonstrate the potential consequences of BM cycling compared to maintenance even in an obesity phenotype emphasizing the importance of maintenance over loss if the lost BM cannot be maintained.

6. Predictive biochemical markers of regain in clinical BM loss interventions

Changes in basal fasting insulin and insulin sensitivity after BM loss have been suggested to be predictors of future BM regain. However, two independent studies, one with obese, non-diabetic patients and another with T2DM patients failed to find a correlation between decreased basal insulin (non-diabetic patients) or increased insulin sensitivity (diabetic patients) and BM regain after 30 and 24 months, respectively [37]. In contrast, fasting plasma glucose (FPG) has been suggested to predict BM regain. In a randomized diet (high monounsaturated fatty acids (MUFA) vs low-fat, high fiber diet) study in obese, non-hyperglycemic adults (FPG > 105 mg/dL), after losing >8% of BM on average, patients with FPG below 90 mg/dL and/or insulin below 50 pM regained BM to a lesser extent than the cohort with higher basal glucose and insulin, when undergoing a MUFA diet [38]. However, the proportion of dietary fat was not found to have a significant impact on the rate of regain [39].

Fasting levels of appetite modulating hormones such as leptin and ghrelin may discriminate between future BM regainers from non-regainers. In overweight or obese patients enrolled in a 2-month nutritional BM loss program, the leptin:ghrelin ratio was greater at baseline in patients that regained >10% of BM lost over the next 6 months [40], while in T2DM patients with obesity, the reduction in plasma leptin after 6 months of BM loss, but not basal plasma leptin, strongly predicted the regain of BM in the following 18 months [41]. In addition, obesity and parameters of MetS were inversely correlated with adiponectin, sex hormone-binding globulin (SHBG), and testosterone, and positively correlated with leptin, luteinizing hormone (LH), prolactin, and retinol-binding protein 4 (RBP4) in males with obesity [42]. These observations are important to consider as they highlight the increased risk of BM regain when low levels of FPG and leptin are not maintained prior to BM reduction. Furthermore, this risk is not corrected with short-term leptin reduction following BM loss whatsoever. Therefore, monitoring FPG and hormonal profile well before the onset of obesity in at-risk individuals for successfully managing the potential BM gain and loss may be critical to properly managing BM in those susceptible individuals. Biomarkers that are found to be correlated with BM regain are listed in Table 1.

7. Long-term re-examination of biomarkers after BM loss and their correlation with regain

Recent follow-up studies have tried to identify associations between basal levels of adipokines and other biomarkers before BM loss intervention with the rate of BM regain, with a focus on circulating leptin due to its effects on increasing EE and insulin sensitivity [43]. This is of

Table 1
Potential regulators of BM regain by correlation.

Correlation	Potential Regulators of BM regain
Found	<ul style="list-style-type: none"> ▲ <i>Abundance of Clostridiales and Enterobacteriales</i> [32] ▲ <i>Rate of BM regain</i> [30] ▲ FPG [38] ▲ Leptin: Ghrelin ratio [40,42] ▼ Adiponectin [42] ▼ SHBG [42] ▼ Testosterone [42] ▲ LH [42] ▲ Prolactin [42] ▲ RBP4 [42] ▲ Leucocyte integrin genes [58]
Not found	<ul style="list-style-type: none"> Insulin sensitivity [37,46] Proportion of dietary fat [39] Basal leptin [41] Rate of excess mass loss [45] Presence of diabetes [45] Serum leptin [46] RMR [46]

BM: Body mass; FPG: Fasting plasma glucose; LH: Luteinizing hormone; RBP4: Retinol binding protein 4; RMR: Resting metabolic rate; SHBG: Sex hormone-binding globulin; []: Reference; ▲: Positive correlation; ▼: Inverse correlation; *Italics*: Studies in rodents.

particular interest to identify potential pharmaceutical targets to prevent regain [44]. In a study of patients with morbid obesity participating in a 2 month BM loss intervention with a daily intake of 20–25 kcal/kg of ideal BM, a re-examination 3 months after the intervention showed that BM was maintained, while after 12 months excess BM was only partially recovered (17.7% of the 35.5% lost on average) and did not correlate to the rate of excess mass loss or the presence of diabetes [45]. In non-diabetic women who were overweight with an 800 kcal/day diet intended to reduce BMI below 25 kg/m², re-examination after 2 years revealed that 80% of BM was recovered, which had no correlation to basal insulin sensitivity, serum leptin concentrations, or RMR [46].

Fasting active ghrelin was increased and RMR decreased in non-diabetic subjects who were overweight, undergoing an 8-week, 550–660 kcal/day diet followed by 4 weeks of BM maintenance [47] and in diabetic subjects undergoing 10% BM loss without reversal after a 1-year follow-up [48]. Additionally, a >10% loss in BM decreased circulating cholecystokinin (CCK), insulin, leptin, and peptide YY [49]. This is important to consider because these hormones regulate appetite and are key to helping to regulate BM maintenance.

In addition to the associations between adipokines and appetite regulation with BM regain, higher circulating levels of long-chain acyl carnitines (AC) (particularly C18:1, C20:1 and C20:2), higher free fatty acids (FFA), and lower respiratory quotient (RQ) predicted the maintenance of BM after >8% diet-induced BM loss [50]. Moreover, greater subcutaneous adipose mitochondrial capacity was associated with BM loss without regain. Basal expression of important mitochondrial pathway genes (tricarboxylic acid (TCA) cycle, oxidative phosphorylation, β -oxidation, and branched-chained amino acid (BCCA) catabolism) was lower in the group that partially regained BM (11% to 5% BM loss) compared to the non-regain group 12 months after the start of BM loss [51]. Collectively, these studies demonstrate that profound reductions in BM elicit adaptations on appetite regulating hormones, both orexigenic and anorexigenic, in response to a proportionally lower FM, which may help explain why it is difficult to maintain BM loss chronically. Conversely, efficient mitochondrial activity and a successful shift toward greater lipid metabolism after BM loss are influential factors that may prevent regain. A list of long-term follow up biomarkers for both BM loss and regain can be found in Table 2.

8. BM loss and regain in insulin resistance

The CR-induced reduction in BM may improve markers of MetS, especially insulin resistance and systolic blood pressure (SBP). This was

Table 2
Long-term Follow up biomarkers for BM loss and BM regain.

Long-term Follow-up Biomarkers for BM loss	Long-term Follow-up Biomarkers for BM regain
↑RER [29]	↑Gluconeogenic enzymes [28]
↑Active ghrelin [47,48]	↓Thermogenesis [30]
↓RMR [47,48]	↓Glucose tolerance [34]
↓CCK [49]	↓RMR [34]
↓Insulin [49,53]	↓Long-chain AC [50]
↓Leptin [49]	↓FFA [50]
↓Peptide YY [49]	↑Respiratory quotient [50]
↓FPG [53]	↑Mitochondrial gene expression [51]
↓HOMA-IR [53]	↑FPG [28,53]
↓HbA1c [55]	↑Insulin [53]
↓SBP [55]	↑HOMA-IR [53]
	↑HbA1c [55]
	↑SBP [55]
	↑TG [55]

AC: Acylcarnitines; CCK: Cholecystokinin; FFA: Free-fatty acids; FPG: Fasting plasma glucose; HbA1c: Glycated hemoglobin; HOMA-IR: Homeostatic model assessment of insulin resistance; RER: Respiratory exchange rate; RMR: Resting Metabolic Rate; SBP: Systolic blood pressure; TG: Triglycerides; []: Reference; ↑: Increase; ↓: Decrease; *Italics*: Studies in rodents.

observed in a cohort of pre-diabetic patients with obesity, which had an average reduction in BM of 8.7–10.2% after 6 months of a lifestyle intervention associated with reduced FPG, insulin, and homeostatic model assessment of insulin resistance (HOMA-IR) [52]. However, 18 months after BM reduction, these parameters increased in the loss-regain group compared to the loss-maintain group, to the point where FPG was higher in the loss-regain group compared to the group that did not experience an initial loss in BM [53] further demonstrating the potential detriment of BM cycling compared to maintenance alone especially during impaired glucose metabolism such as during insulin resistance. Additionally, a short-term intervention with healthy, non-overweight participants subjected to variable caloric intake (1 wk. of overfeeding at 50% above daily caloric requirements followed by 3 wks of 50% CR then 2 wks of refeeding) increased fasting insulin and HOMA-IR after overfeeding that were corrected after CR and increased again after refeeding. Moreover, the transient improvement in insulin sensitivity was correlated with increased ghrelin and decreased leptin, thyroid stimulating hormone (TSH), and free tri-iodothyronine (fT3) [54]. An analysis of the Look AHEAD (Action for Health in Diabetes) trial, comprised of diabetic patients with $\geq 3\%$ BM loss after a 1-year intervention demonstrated that patients with $\geq 10\%$ BM loss had lower basal glycosylated hemoglobin (HbA1c) and diastolic blood pressure, and more favorable cardiovascular risk factors suggesting that greater and sustained mass loss in T2DM individuals promotes improved health outcomes. However, patients who regained $>75\%$ of their lost BM during the 1-year intervention had higher HbA1c, SBP, and TG concentrations 3 years after the intervention [55]. Nonetheless, the improvement in HbA1c after 4 years was more profound in patients with higher BM loss compared to those with small or no BM loss, even with full regain [56].

Different degrees of CR (500 kcal/d [very low carbohydrate diet (VLCD)] and 1250 kcal/d [low carbohydrate diet (LCD)]) with equivalent BM loss did not induce differential effects between groups (including regain) except for a greater decrease in angiotensin-converting enzyme (ACE) activity. However, at 9 months re-examination, the post-oGTT glucose was lower in VLCD group, while glucose returned to basal levels in LCD [44] suggesting that the degree of CR and not absolute BM loss had a greater effect on improving insulin resistance. Nonetheless, a high-saturated-fat meal test in a pooled sample did not alter fatty acid uptake in subcutaneous adipose before or after BM loss [57]. Additionally, expression of several leucocyte integrin genes following BM loss correlated positively with the percentage of BM regain suggesting that residual inflammation is present following BM loss, increasing the risk of BM regain and the metabolic risks associated

with BM cycling [58]. CR-induced BM loss may reverse β -cell functionality in early onset T2DM. Several patients undergoing a CR for 16 weeks and achieving an average loss of 16.4 kg of BM achieved non-diabetic HbA1c and FPG without needing antidiabetic drugs, and half of these patients maintained normoglycemia after re-examination at 2 years [59]. In short, a higher degree of CR confers more profound benefits to improving insulin sensitivity and has the potential to delay the onset of T2DM in healthy subjects, while a profound reduction of BM via CR reduces cardio metabolic risk factors in diabetic patients. However, the degree of CR may not be sustainable chronically due to the metabolic adaptations summarized previously, and even partial BM recovery ($>70\%$) [44,53] is enough to abolish these benefits ultimately.

9. BM cycling and intermittent fasting in clinical studies

BM cycling (a.k.a. yo-yo dieting) is driven by an absence of compensatory changes in hunger and satiety in response to overfeeding and impairs the ability of subjects to sustain BM loss chronically [60]. Studies have suggested that BM cycling may be more deleterious than simply maintaining BM and may increase the risk of T2DM and cardiovascular disease (CVD). For example, in non-diabetic patients with MetS including obesity, BM regain after 60 months increased pulse wave velocity (PWV), a measure of arterial stiffness [61]. Additionally, follow-up studies after 4 [62], 10 [63] and 16 years [64] showed that higher BM fluctuations increased HOMA-IR and mortality [64], with the added detriments of increased SBP, total cholesterol, and TG [63] or higher risk for T2DM [62]. Conversely, the incidence of T2DM decreased with higher fluctuations in BM (protective effect) in overweight subjects [64] demonstrating the inconsistency in BM cycling effects. Nonetheless, patients with an average loss of 16.7 kg after a 21-day intervention regained 15.1 kg (90.4% regain) after discharge but did not report differences in resting EE (REE), SBP, glucose, or insulin before CR and after BM regain [65] suggesting that acute alterations in BM cycling may be less detrimental and indicative of a more gradual acclimatization to metabolic shifts in T2DM patients.

Despite the potential deleterious effects of BM cycling, intermittent cycles of energy restriction (ER) of 2 weeks, due to the bi-phasic nature of adaptation to BM loss, has been recommended to trigger the acute alterations in cellular metabolism without reaching the later phase of REE reduction. BM loss and attenuation of REE was greater with intermittent ER compared to 33% CR after 16 weeks [66]. A similar trend in BM loss and REE attenuation was observed in healthy, lean subjects, albeit to a lower magnitude [67], potentially due to higher proportion of FFM in these subjects. A short-term intervention consisting of 5 days ad libitum intake followed by 2 days of absolute restriction in a healthy adult male ($n = 1$; case-study) achieved short-term improvements in BM, FM, and hs-CRP but not lipid profiles [68]. In general, these studies suggest that multiple BM cycling events may increase the risk factors for metabolic syndrome, and that intermittent fasting (IF) without cycling could be a viable alternative to avoid BM cycling by preventing the undesired metabolic adaptations caused by sustained CR. The benefits of chronic intermittent fasting on body composition and markers of cardio-metabolic health have been reviewed and the data would substantiate an approach of IF as opposed to CR for sustaining reduced BM, as the associated benefits of short term (3–12 months) reduction of waist circumference, fat mass and basal insulin [69] improved lean mass retention (when 25% caloric requirement is met on fasting days) and increased TG and fat oxidation [70] are found across several studies when comparing different IF regimens vs continuous energy restriction.

10. Limitations and future directions

The focus of this review was the evaluation of studies that perform intentional, controlled interventions to reduce BM and achieve BM cycling. We recognize that a significant body of literature exists from clinical data for T2DM patients in which collateral BM regain was due to

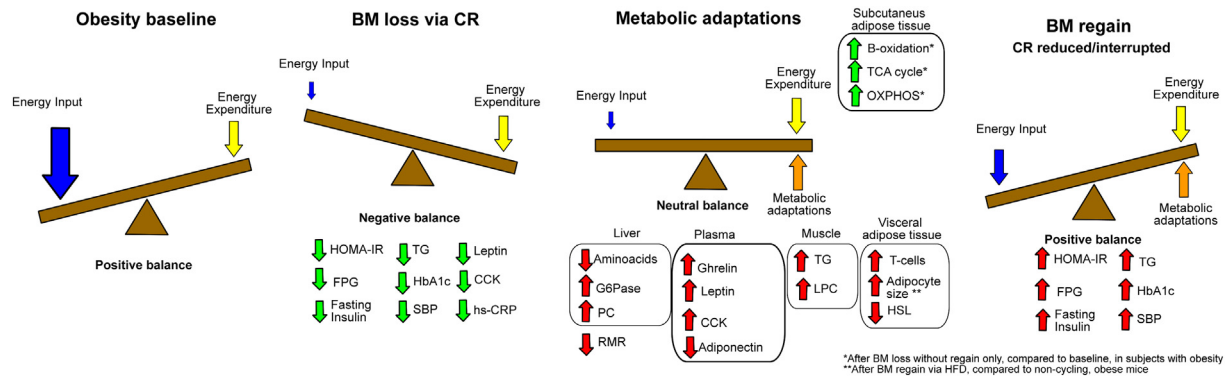


Fig. 1. Progression of changes in energy balance from obesity baseline to body mass (BM) regain, and metabolic adaptations in response to caloric restriction (CR). Green arrows: Beneficial effects, red arrows: deleterious effects. CCK, cholecystokinin; FPG, fasting plasma glucose; G6Pase, Glucose 6-phosphatase; HbA1c, glycated hemoglobin; HFD, high fat diet; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, hormone sensitive C-reactive protein; HSL, lysophosphatidic acid; LPC, lysophosphatidic acid; OXPHOS, oxidative phosphorylation; RMR, resting metabolic rate; SBP, systolic blood pressure; TCA, tricarboxylic acid; TG, triglycerides. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

unsuccessful maintenance regimens rather than an intentional BM regain. Thus, this review did not include or account for these studies. However, clinical studies of intentional BM regain are scarce and challenging especially in already compromised individuals because of ethical considerations. Therefore, retrospective studies on patients with prior, uncontrolled BM cycling were also considered to complement this review as “real-world” data. Furthermore, BM cycling studies in rodents, especially those that model metabolic defects in humans, will be of great importance for the advancement of the field.

11. Concluding remarks

While the benefits of CR-induced BM loss are established in rodents and humans, the effects of BM regain and cycling are not well defined. Furthermore, biomarkers to predict the potential severity of the BM regain on health are lacking and inconsistent. From our review, we conclude that: (1) the CR benefits are proportional to the extent of the BM loss, especially in the form of FM, but can be abrogated by partial or complete BM regain, (2) multiple (>1) cycles of BM loss-regain are associated with worse metabolic outcomes, and (3) the metabolic adaptations related to BM cycling have a strong hormonal and pro-inflammatory component, especially adipokines, orexigenic hormones, and activated T-cells. A diagram summarizing our interpretation of the metabolic adaptations that lead to BM regain can be found in Fig. 1. Collectively, the data to date suggest that oscillations in body mass may be as detrimental as maintaining an obese phenotype, placing a greater emphasis on maintaining BM fixed especially after an initial reduction in mass. The available research suggests that recommendations for maintenance of body mass should be emphasized as opposed to reduction if patients are not able to maintain a lower body mass following caloric restriction. Additionally, the unintended consequences of losing lean tissue and disproportionately regaining fat mass must be considered and accounted for in any weight loss program especially for individuals that have existing impaired substrate metabolism. Alternatively, intermittent fasting may serve as an appropriate substitute for CR. Furthermore, the current data provide interesting insights to the metabolic adaptations evolved that counter the purposeful reductions in body mass. Thus, evolutionary adaptations in metabolism to protect against the loss of body mass introduce an added layer of complexity that challenges an individual's desire to lose primarily fat mass.

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CRediT authorship contribution statement

MAC: Writing-Original draft preparation; RMO: Writing-Review and Editing.

Declaration of competing interest

None.

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