Mechanisms of weight regain after weight loss — the role of adipose tissue

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Abstract | One of the biggest challenges in the management of obesity is the prevention of weight regain after successful weight loss. Weight regain after weight loss has large interindividual variation. Although many factors probably contribute to this variation, we hypothesize that variability in biological responses associated with weight loss-induced shrinking of subcutaneous adipocytes has an important role. In this Review, we show that weight loss-induced variations in cellular stress, extracellular matrix remodelling, inflammatory responses, adipokine secretion and lipolysis seem to be associated with the amount of weight that is regained after successful weight loss. Weight regain could therefore, at least in part, depend on a combination of these factors. Further research on the causality of these associations could aid the development of effective strategies to prevent weight regain after successful weight loss.

Energy balance
The balance between energy intake and energy expenditure.

The worldwide prevalence of obesity is rising[1]. According to one estimate, every year, 42% of the world population tries to lose weight[2]. Even if the initial weight loss is successful, most individuals will regain weight over time, and only a small proportion of dieters will be able to maintain the reduced weight over the next years. For example, a meta-analysis of weight loss studies in the USA, which included 29 studies that applied hypocaloric diets with or without exercise with long-term (≥2 years) follow-up, showed that on average more than half of the weight lost is regained after 2 years and more than three-quarters is regained after 5 years[3]. In the Look Ahead study, which included patients with type 2 diabetes mellitus (T2DM) who are overweight, an intensive lifestyle intervention, with regular group sessions, structured meal plans and free provision of meal replacements during the first year, resulted in improved long-term weight loss outcomes compared with diabetes support and education alone[4]. However, the average weight regain in the intensive lifestyle intervention group was still 50% of initial weight loss after 4 years, which was maintained until 8 years. Even after bariatric surgery, weight regain can occur[5–7]. Identifying the factors that make long-term weight loss maintenance so difficult would be an important step forward for researchers and health-care professionals in the obesity field. This advance would enable investigators to explain the interindividual differences in weight regain and aid the development of better strategies for long-term weight loss outcomes.

Obesity is the consequence of small, cumulative imbalances between energy intake and energy expenditure that result in a positive energy balance and weight gain[8]. Many biological factors, including genetics, environmental and developmental factors, epigenetics and gastrointestinal factors but also socio-economic, behavioural and lifestyle factors and their interactions with one another have been implicated in weight gain[8–10]. In most cases, no single factor is solely responsible for the development of obesity. Rather, obesity results from a combination of factors, and these combinations can vary among individuals and over time[8–10].

Both in the normal weight state and following the development of obesity, fat depots are homeostatically protected, be it at different levels[8]. Presently, it is unclear (in most cases of obesity) what factors are responsible for the defence of the elevated fat stores and whether they differ from the factors that influence energy homeostasis in the normal weight range. Some factors might overlap, but additional factors could specifically be involved in protecting the increased white adipose tissue (WAT) mass in the obese state[10–15].

Factors unrelated to adipose tissue, such as eating behaviour or genetics, might have a role in weight regain after weight loss, and these factors are summarized in TABLE 1. Although changes in signals from the gastrointestinal system after diet-induced or surgery-induced weight loss are thought to be important for weight regain[16–18], their role is not included in TABLE 1, as studies on direct associations with weight regain are lacking. As this

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Key points

- Weight regain after successful weight loss is a major problem for many individuals, and many factors are probably involved in driving weight regain.
- Loss of fat mass induces shrinkage of adipocytes, which is accompanied by cell stress, inflammation, altered adipokine secretion and reduced lipolysis.
- In the absence of extracellular matrix remodelling during adipocyte shrinkage, mechanical stress builds up between the cell and the oversized extracellular matrix, which inhibits lipolysis and the release of fatty acids from adipocytes.
- Weight loss induces an inflammatory response in adipose tissue.
- Evidence for the involvement of epigenetic modifications, in particular microRNAs, in weight regain is sparse.
- Knowledge of weight regain after weight loss is mainly based on associations, and so research into the causality of such associated factors is needed.

Review focuses on adipose tissue-related factors, we do not elaborate further on non-WAT-related factors.

One of the main events that occurs during a weight loss intervention is the shrinking of WAT mass[19]. This loss of tissue mass results predominantly from a reduction in size of adipocytes within WAT. In this Review, we explain how the shrinking of adipocytes influences their function. In addition, we discuss whether this reduction in the size of adipocytes might have a role in triggering the regain of WAT mass in people who try to maintain the weight loss they have achieved. In FIG. 1, we present an overview of the potential adipose tissue-related mechanisms that we discuss.

Excess white adipose tissue

WAT expands in size when an individual's overall energy balance is positive (that is, when the intake of energy is greater than the amount of energy expended). The expansion of WAT can occur via two mechanisms, hyperplasia and hypertrophy[20].

Preadipocytes, which are present in the stromal vascular fraction of WAT, can develop into mature adipocytes[21]. The maturation of preadipocytes is accompanied by uptake and storage of lipid, which leads to an increase in cell size[22]. The increase in the number of adipocytes by preadipocyte recruitment is referred to as hyperplasia. In humans, hyperplasia can occur before adulthood, but above 20 years of age, the number of adipocytes is stable, and only ~8% are renewed each year[23].

Therefore, a positive energy balance in adults will typically lead to the expansion of WAT via hypertrophy of mature adipocytes. Interestingly, a study reported that following overfeeding, different fat depots might behave differently with regards to their expansion[24]: abdominal subcutaneous adipose tissue responded by hypertrophy, but femoral subcutaneous adipose tissue responded by hyperplasia. These differences in response are the result of a complex regulatory mechanism that includes signals from hormones and growth factors[20,25,26].

Inefficient subcutaneous fat cell lipolysis (that is, increased in vitro basal lipolysis and reduced stimulated lipolysis) has been identified as a process that promotes weight gain and increases fat cell volume[27]. With regards to hypertrophy, there seems to be a limit to the extent to which adipocytes can enlarge, which is controlled by the extracellular matrix (ECM). In mice, knocking out collagen VI — the main component of the adipocyte ECM — abolishes this limitation and allows further expansion of the adipocytes, which is accompanied by improvements to the status of metabolic parameters, such as insulin sensitivity[28].

A study that used transcriptomics to analyse WAT from individuals with obesity showed an increased amount of interstitial fibrosis, which was associated with infiltration of inflammatory cells[29]. In several human studies, a negative correlation was found between fibrosis and hypertrophy, supporting the concept that the ECM is indeed restricting hypertrophy[30,31]. Furthermore, on the basis of animal studies, WAT expansion has been proposed to lead to a state of hypoxia owing to either the blood flow to the WAT not keeping up with the tissue expansion or the adipocytes expanding beyond the diffusion range of the available oxygen[32]. In both scenarios of adipose tissue expansion, hypoxia will change the metabolic properties of WAT and promote fibrosis and inflammation[33,34]. This response to hypoxia might be mediated by the upregulation of HIF1α and/or HIF2α, which are oxygen-sensitive transcription factors[32,35]. In humans, however, measurements of oxygen pressure in subcutaneous WAT have resulted in contradictory findings, showing either a decreased or an increased oxygen pressure when comparing WAT from lean individuals with WAT from obese individuals[36,37] and a reduction in oxygen tension with weight loss[38]. These discrepant findings might be partly due to the technological complexity of the measurement.

Immune cells are commonly found within WAT. For example, the stromal vascular fraction of adipose tissue contains immunomodulatory cells such as macrophages, of which the number is directly related to the level of adiposity and adipocyte size[39]. In healthy WAT, adipocytes and immune cells communicate and maintain a balanced situation in which anti-inflammatory cytokines counteract pro-inflammatory cytokines[40,41]. In obesity, however, hypertrophy of adipocytes leads to increased cellular stress by fibrosis and hypoxia. This increase in cellular stress results in a higher secretion of chemoattractants, which augments the invasion of immune cells, the transition of macrophages to a more aggressive immunological phenotype and the increased production of pro-inflammatory cytokines from WAT[42–44]. On the other hand, in lean men, overfeeding for 56 days resulted in increased deposition of connective tissue in the adipose tissue without a change in the number of macrophages or inflammatory cells[45].

A study in mice suggested that local insulin resistance in WAT leads to the secretion of MCP1 (also known as CCL2) and the activation of pro-inflammatory macrophages[46]. Increased cell death might also sustain a chronic condition of low-grade inflammation. The important questions that remain unanswered, however, are whether the changes observed in adipose tissue following the development of obesity are reversed by weight loss and whether the changes have a role in weight regain after weight loss.

The role of adipocytes in weight regain

Changes in adipocyte size. When people gain weight through a positive energy balance, the surplus of energy can be stored as triglycerides in adipose tissue. In adulthood, increased fat storage predominantly occurs in

Table 1 | **Predictors of weight regain after weight loss in adults with obesity**

Factor	Associations	Refs
Glucose homeostasis variables at baseline or changes during diet	• Baseline fasting insulin associated with weight regain • Baseline insulin sensitivity (M value) inversely associated with weight regain • Change in fasting insulin and insulin resistance as defined by HOMA during weight loss inversely associated with weight regain	• Kong et al. (2014)[134] • Ryan et al. (2018)[175] • Wong et al. (2012)[176] (DiOGenes study)
Total plasma cysteine level	Total plasma cysteine level 2 years after RYGB associated with weight regain between 2 and 4 years after surgery	Hanvold et al. (2017)[177]
Initial weight loss	• Increased weight loss associated with successful weight maintenance (≥10% weight loss maintained) • Increased weight loss associated with better weight maintenance • Increased weight loss achieved at 6 months associated with more successful 2-year weight loss (>5%) • Weight loss inversely correlated with weight regain • Increased weight loss at week 3 predicts success at 1 year (≥5% weight loss) • Reduced BMI inversely associated with weight regain	• Sawamoto et al. (2017)[178] • Calugi et al. (2017)[179] • Greenberg et al. (2009)[180] (DIRECT trial) • Vogels et al. (2005)[181] • Fabricatore et al. (2009)[182] • Wong et al. (2012)[176] (DiOGenes study)
Eating behaviour variables	• Reduced disinhibition and reduced food addiction at end of weight loss associated with successful weight maintenance (≥10% weight loss maintained) • Internal disinhibition associated with weight regain • Reduction in disinhibition during weight loss associated with less weight regain	• Sawamoto et al. (2017)[178] • Lillis et al. (2015)[183] • Butryn et al. (2009)[184]
Bariatric surgery aspects	A dilated gastrojejunal stoma diameter is a risk factor for weight regain	Abu Dayyeh et al. (2017)[185]
Exercise perception	Perceived exertion during submaximal exercise associated with weight regain	Brock et al. (2010)[186]
Depressive symptoms	• Antidepressant use associated with return to baseline weight • Reduced baseline depressive symptoms predict weight loss success at 1 year (≥5% weight loss)	• Price et al. (2013)[187] (DPP study) • Fabricatore et al. (2009)[182]
Satisfaction with weight loss	Increased satisfaction with weight loss associated with better weight maintenance	Calugi et al. (2017)[179]
Genetics	• SNPs in multiple genes associated with waist circumference regain • *PPARG2* genotype predicts weight regain • *FTO* genotype predicts weight regain • SNPs in multiple genes predict weight regain • SNP in the *ADRB2* gene predicts rebound weight	• Larsen et al. (2012)[188] (DiOGenes study) • Nicklas et al. (2001)[189] • McCaffery et al. (2013)[190] (Look Ahead study) • Delahanty et al. (2013)[191] (DPP study) • Masuo et al. (2005)[192]
Epigenetics	Levels of methylation in *NPY* and *POMC* promoters associated with success of weight maintenance (≥10% or <10% weight regain)	Crujeiras et al. (2013)[193]

Only factors not directly related to adipose tissue function are included in this table. M value, a measure of insulin sensitivity; RYGB, Roux-en-Y gastric bypass; SNP, single nucleotide polymorphism.

existing adipocytes and leads to the formation of large hypertrophic adipocytes[23,25]. A study in rats[47] showed that, under calorie restriction, adipocytes lose fat, and the average volume of the adipocytes declines. The authors of this study found, however, that upon refeeding the average adipocyte volume returned to the original value. They also noticed an increase in the number of very small cells (<20 μm) during calorie restriction, which were thought to be newly formed adipocytes. Following refeeding, new adipocytes joined the distribution of mature adipocytes, leading to a slight increase in the total number of cells. Therefore, in rats, weight regain seems to predominantly result from the refilling of mature adipocytes with triglycerides and is only partly due to the differentiation of new adipocytes.

In participants of the YoYo study[48] (a clinical trial comparing the effects of two rates of weight loss — a 12-week low-calorie diet (LCD) or a 5-week very-low-calorie diet (VLCD) — on weight regain), adipocytes in WAT also reduced in size during weight loss. Furthermore, and in line with the animal study, investigators reported an increase in the percentage of small adipocytes and a reduction in the percentage of large adipocytes, as well as a gradual return of adipocytes to their original size distribution after cessation of the weight loss strategy[49] (FIG. 2). The technique used in this study, however, did not allow for an estimation of changes in total cell number.

Data suggest that the adipogenic capacity of the stromal vascular fraction of WAT is impaired in individuals who are obese[50]. In a study of patients with obesity undergoing weight loss[51], the authors found that the adipogenic capacity of stromal cells in biopsy samples of subcutaneous WAT improved following weight loss. In the same study, expression of the *RUNX2* gene, which encodes a transcription factor for osteogenesis, was markedly downregulated after weight loss, which

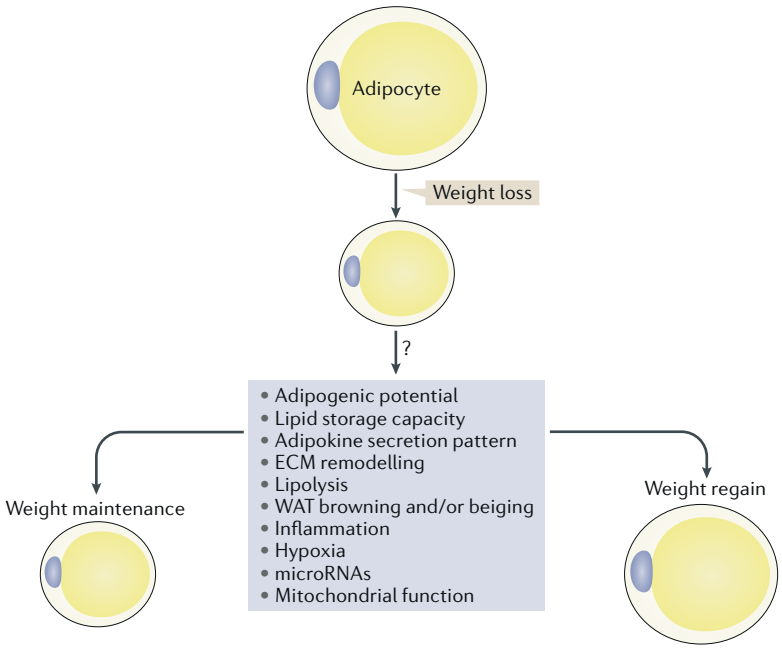

Fig. 1 | **Potential adipose tissue-related mechanisms involved in weight regain after weight loss.** Weight loss induces shrinkage of adipocytes. This shrinkage might affect several potential mechanisms, which are described in detail in this Review. Interindividual variations in response to these mechanisms might determine weight maintenance or weight regain. ECM, extracellular matrix; WAT, white adipose tissue.

suggests inhibition of alternative lineage programmes and preferential adipogenic differentiation. The newly formed adipocytes also displayed an altered secretion profile with increased levels of leptin. However, in the YoYo intervention study, no significant change in expression of *RUNX2* was observed in WAT biopsy samples directly after weight loss or at 4 weeks after returning to energy balance (M.A.B. and E.C.M.M., unpublished observations), whereas plasma leptin levels were dramatically decreased after weight loss[52,53]. These data suggest that in humans, as in rats, weight regain after weight loss results predominantly from the refilling of mature adipocytes (FIG. 3).

Adipocyte stress model. Adipose tissue is a loose connective tissue. Therefore, it is not surprising that adipocytes secrete many different proteins and deposit a dense ECM. The adipocyte ECM is formed when preadipocytes differentiate into mature adipocytes. Adipocytes require a strong ECM to prevent mechanical disruption that could occur as the cell increases in size during lipid storage. In vitro experiments in 3T3-L1 adipocytes have shown that insulin can stimulate ECM formation, a process that probably occurs via the transcriptional upregulation of genes encoding enzymes needed to biochemically modify ECM proteins[54]. Another study in cultured mature 3T3-L1 adipocytes reported that mature adipocytes show considerable production of collagens to maintain the ECM[55]. Production and post-translational modification of collagens, and of ECM proteins in general, require a considerable amount of energy[56].

When in negative energy balance, adipocytes activate lipolysis and release fatty acids as fuel for other tissues[57,58]. Consequently, during negative energy balance, adipocytes shrink, and in parallel, the ECM is remodelled to fit the smaller cell surface. Following weight loss after bariatric surgery, subcutaneous adipose tissue displays major collagen remodelling, with increased collagen degradation and crosslinking, features that are in agreement with ECM adaptation during the loss of fat mass[59]. Under conditions of calorie restriction, however, the energy available to adipocytes might not always be sufficient for the cell to undergo ECM remodelling[56]. In the absence of ECM remodelling during adipocyte shrinkage, mechanical stress builds up between the cell and the oversized ECM. The force of the mechanical stress is highest at the focal adhesions, which are the membrane-embedded protein complexes that link the intracellular actin filaments to the ECM[60] (FIG. 4). Our hypothesis is that this mechanical stress inhibits lipolysis and the release of fatty acids from adipocytes. Moreover, we believe that adipocytes that are under stress are preconditioned for renewed fat accumulation and trigger the host to increase energy intake. Therefore, in this scenario, adipocytes would start to accumulate fat again, and the increasing cell volume would reduce the mechanical stress (FIG. 3) — which means weight regain for the host[15].

A study of female participants who underwent an 8-week LCD in the European DiOGenes intervention[61] compared the adipose tissue transcriptome between individuals who maintained weight loss (0–10% weight regain) and individuals who regained weight (10–20% weight regain) during the 6-month follow-up. The investigators found that the focal adhesion pathway was upregulated during the LCD in individuals who regained weight versus individuals who maintained weight loss. Upregulation of the focal adhesion pathway suggests that mechanical stress after the diet was higher in adipocytes of weight regainers than in those of weight maintainers.

Another group[62] studied changes in stress-related proteins in biopsy samples of WAT over an 8-week period of calorie restriction. From a cohort of 200 participants, the investigators selected 18 men and women who lost at least 10% of their body weight over the 8-week calorie restriction period. Median weight regain was 6 kg over the 12-month ad libitum follow-up period. The authors reported that, at the end of the weight loss period, the levels of heat shock protein 60 (HSP60) and HSP70 were increased significantly in people who regained >6 kg compared with people who regained <6 kg over the 12-month follow-up period. The investigators also found a trend for increased levels of β-actin and HSP27 in people who regained >6 kg. β-Actin and HSP27 are components of actin filaments, and HSP27 phosphorylation is a regulator of actin stress fibres and focal adhesion formation[63]. Furthermore, increased levels of HSP60 and β-actin were also observed in cultured adipocytes after glucose restriction[62]. The weight loss intervention did not have any effect on SOD1 and SOD2, which are markers of oxidative stress, suggesting that oxidative stress was not influencing weight regain. The findings of this study suggest that weight regain following weight loss induced by an LCD intervention results from increased mechanical stress in the adipose tissue and/or adipocytes.

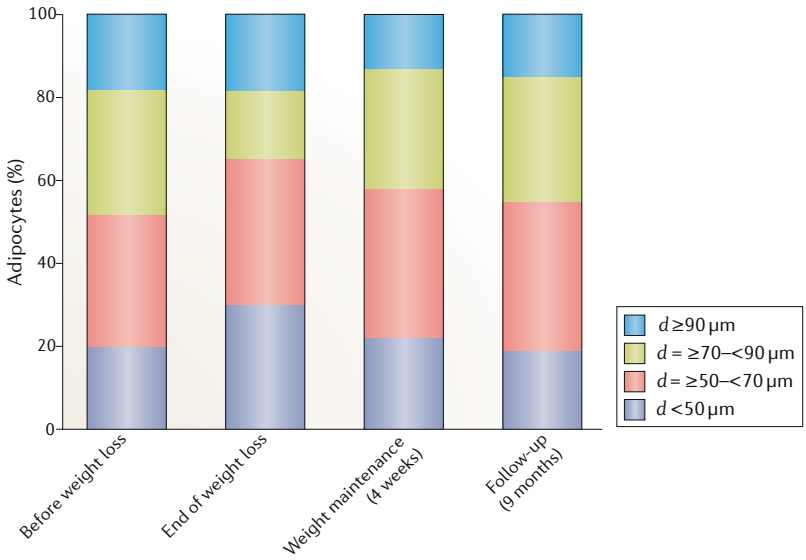

Fig. 2 | **Adipocyte diameter distribution in different phases of weight loss and weight regain.** The distribution of adipocyte diameter (*d*, in µm) in abdominal subcutaneous adipose tissue before weight loss, at the end of weight loss, after 4 weeks of weight maintenance and after 9 months of follow-up in the YoYo study[48] is shown. At the end of weight loss, the percentage of small adipocytes (with a diameter <50 µm) is increased and that of large adipocytes (70–90 µm) is reduced compared with baseline. During the subsequent 4-week strict weight maintenance period, small adipocytes refill with lipid, resulting in a decreased percentage of small adipocytes and an increase in the percentage of large adipocytes. There are no further changes in the distribution of adipocyte diameters during the follow-up period in which fat mass increases.

Another study that was focused on genes that encode stress-related proteins analysed microarray data from the YoYo intervention study. The investigators included 107 genes and found expression changes in 17 of these genes during the different phases of the weight loss intervention (weight loss phase by means of an LCD or a VLCD (12 or 5 weeks, respectively), the subsequent 4-week weight stabilization phase and the combined weight loss and weight stabilization phase) that correlated with weight regain during follow-up[64]. In the VLCD group, eight of the nine genes whose expression changes during the weight stabilization phase were correlated with weight regain during the weight stabilization phase were linked to nutrient sensing, glucose handling and actin filament dynamics of the adipose tissue[64].

Further to the aforementioned studies, genetic and genomic evidence supports the adipocyte stress model for weight regain and a role for the ECM. On the basis of genome-wide association study data from the European DiOGenes intervention study, researchers found that variation in genes encoding proteins of the ECM is associated with the risk of weight regain in a sex-specific manner[65]. In males, weight regain-associated variations were reported in the genes that encode periostin (*POSTN*), laminin subunit-β1 (*LAMB1*), collagen type XXIII α1 (*COL23A1*) and fibulin 5 (*FBLN5*), whereas in females, a weight regain-associated variation was reported for the gene that encodes fibronectin 1 (*FN1*). In addition, these data suggest a link with focal adhesions (FIG. 4), as collagen XXIII and the LAMB1-containing laminin 111 interact with α2β1 integrin[66] and, in mice, FBLN5 competes with FN1 for binding to β1 integrin[67].

In the YoYo intervention study, the expression change of 16 out of 277 genes encoding ECM proteins over different phases of the VLCD intervention correlated with weight regain[68]. For 11 of these genes, the correlated change in expression occurred over the 4-week weight stabilization phase. Using these genes to build a correlation co-expression network, the genes that could be clustered in the network seemed to suggest changes in adipose tissue inflammation, insulin sensitivity and ECM remodelling during the weight-stable phase. Moreover, stress-related genes and genes that encode ECM proteins seemed to interact in relation to the risk of weight regain[69]. Gene–gene interaction analysis suggested that epidermal growth factor receptor-mediated phosphorylation of α-actinin, a β-actin crosslinking protein and target of focal adhesion kinase, is involved in the risk of weight regain[69] (FIG. 4).

Fatty acid metabolism and weight regain. The pull model[8], which is proposed as a mechanism to explain why some individuals on an isocaloric diet might develop more fat mass than others, predicts that adipocyte-autonomous processes can pull substrates preferentially into adipocytes. One group has suggested that weight loss can trigger an increased pull of substrates into the adipocytes, which in turn leads to weight regain[70]. In support of this model, data show that ≥1 year after bariatric surgery, high maximal capacity for long-chain fatty acid uptake persists in isolated adipocytes despite a reduction in adipocyte size[71]. In vivo research suggests that an increase in the storage capacity of fatty acids per volume of adipose tissue after bariatric surgery exactly compensates for the decrease in fat mass during weight loss[72].

Proteomics experiments on human adipose tissue biopsy samples taken before and 3 weeks after a 5-week VLCD intervention revealed that shortly after weight loss glucose transporter type 4 (GLUT4) is translocated to the cell membrane, and perilipin 1 isoform B, which is proposed to be involved in fatty acid uptake and positively correlated with LPL, is strongly upregulated[73]. These data suggest that adipocytes, apart from developing stress during the weight loss phase, prepare for renewed energy uptake immediately after host energy balance is restored (such as upon termination of an LCD)[74]. Adipocyte stress and an increased capacity for glucose and fatty acid uptake might be linked; however, cause and effect in this respect have not yet been studied.

In the YoYo study, we measured in vivo meal-derived fatty acid uptake by subcutaneous adipose tissue before and at the end of the intervention (which consisted of a diet-induced weight loss phase followed by a 4-week weight stabilization phase). We applied the arteriovenous balance technique across abdominal subcutaneous adipose tissue, where blood is sampled from catheters inserted in a superficial epigastric vein draining subcutaneous WAT and in an artery or heated hand vein, thus retrieving arterialized venous blood. This method enables measurement of plasma concentration differences across subcutaneous WAT and, in combination

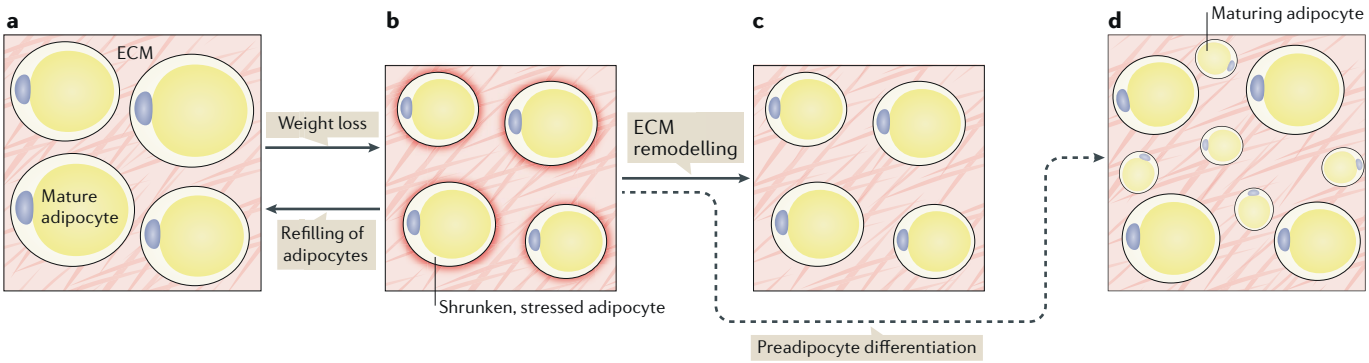

Fig. 3 | **Model of resolution of weight loss-induced adipocyte stress.** Mature adipocytes are surrounded by an extracellular matrix (ECM) (part **a**). In the absence of ECM remodelling during adipocyte shrinkage, mechanical stress builds up between the cell and the oversized ECM (part **b**). In principle, this stress can be resolved in three ways: by refilling of the adipocytes, which will be accompanied by weight regain (parts **b**–**a**), by ECM adjustment with maintenance of weight loss (part **c**) or by preadipocyte differentiation (part **d**). The latter does not seem to be a major contributor to weight regain.

Fasting fatty acid rate of appearance
The rate of release of fattyacids into the plasma in thefasting state, which can bedetermined by measuring thedilution of an infused fatty acidtracer in plasma.

with the measurement of WAT blood flow by the xenon wash-out technique, can be used to calculate net fluxes of metabolites. We combined this methodology with a ^{13}C-palmitate tracer added to a high-fat mixed meal, which allowed us to also measure meal-derived fatty acid uptake in subcutaneous WAT[75]. We found that meal-derived fatty acid uptake per volume of WAT was unchanged after weight loss, which is consistent with data from elsewhere[76] that were obtained using a different stable isotope tracer technique. Moreover, in our study, weight loss-induced changes in meal-derived fatty uptake were not associated with weight regain[75]. These data do not support the pull model, at least not for meal-derived fatty acids in the postprandial state. Nevertheless, the average diameter of the adipocytes increased during the 4-week energy balance period compared with immediately at the end of the energy-restricted diet, suggesting a change in adipose tissue fatty acid metabolism after weight loss. One possibility is that de novo lipogenesis increases in the adipocytes following weight loss, which is supported by studies that have reported an upregulation of fatty acid synthase[73,77].

The effect of weight loss on adipose tissue lipolysis has been the topic of a number of studies. A review of the literature[57] concluded that a negative energy balance stimulates fasting adipose tissue lipolysis and its responsiveness to neural and hormonal stimulation. The degree of stimulation of fasting lipolysis seems to depend on the size and duration of the negative energy balance[57]. With prolonged weight loss maintenance, that is, without a concomitant negative energy balance, fasting lipolysis and its responsiveness to stimulation are reduced compared with baseline[57].

In the YoYo study, we found a positive association between the decrease in fasting plasma concentrations of free fatty acid (FFA) from baseline to the end of the intervention phase and subsequent weight regain[52]. Low FFA concentrations might signal a shortage of energy stores, which has been suggested to promote energy intake[70]. Therefore, one of the factors that could explain variations in weight regain after weight loss between individuals is the extent to which fasting lipolysis is suppressed after weight reduction. Whether the observed differences in the suppression of fasting lipolysis are due to variations in the extent to which adipocytes decrease in size is unclear. Whereas the average reduction in adipocyte size was not reported to be associated with weight regain[52], a role for differences in the change in size distribution cannot be excluded[70].

A low fasting fatty acid rate of appearance phenotype has been described in obesity, which was beneficial for insulin sensitivity[78]. The authors compared adipose tissue factors (plasma metabolites, mRNA and protein expression in subcutaneous WAT) in adults with obesity who had a low or high fasting fatty acid rate of appearance. Individuals with a low fasting fatty acid rate of appearance were characterized by reduced *HSL* gene expression, increased expression of genes involved in fatty acid re-esterification, reduced ECM deposition and reduced fibrosis, suggesting an increased capacity for adipocyte expansion. Other mechanisms that might be involved are interindividual differences in the response of adipose tissue blood flow and genetics.

Following weight loss, there is an associated reduction in resting energy expenditure, which provides another line of evidence supporting a role for reduced fasting lipolysis in weight regain. Weight loss lowers resting energy expenditure ~15% more than would be expected on the basis of the change in body composition (this process is referred to as adaptive thermogenesis)[79,80]. This extra reduction results in a risk of weight regain if it is not compensated for by increased activity-induced energy expenditure or a lower energy intake[81]. To date, the molecular basis for this phenomenon has not been defined.

After an 8-week VLCD, we observed that the decrease in resting energy expenditure correlated with the change in abundance of hydroxyacyl-CoA-dehydrogenase (HADH) in subcutaneous adipose tissue[82]. HADH is a crucial enzyme for mitochondrial β-oxidation, suggesting that reduced activation of the β-oxidation underlies the extra weight loss-associated decrease in resting energy expenditure. However, a reduction in the activation of lipolysis could be the reason for the observed extra decrease in resting energy expenditure, as it was shown

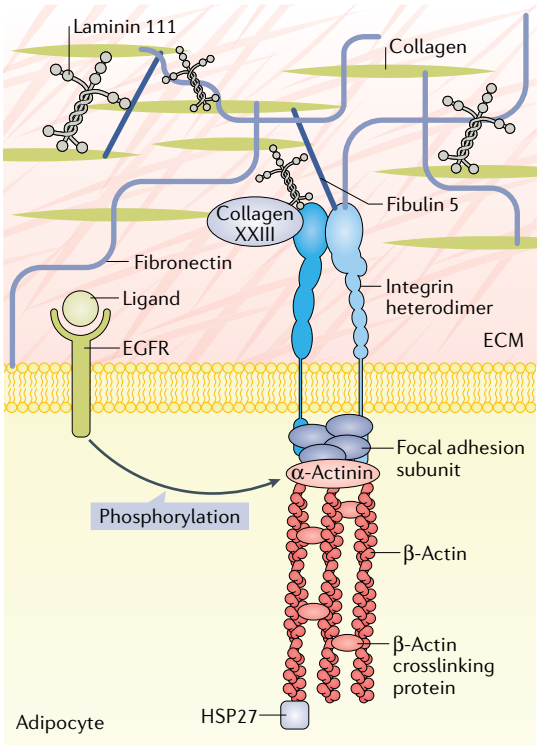

Fig. 4 | **Structure of the focal adhesion as the centre for mechanical stress.** The structure of the integrin-containing focal adhesions in the adipocyte membrane connecting the cytoskeleton (intracellular actin filaments) to the extracellular matrix (ECM) enabling the passage of mechanical signals from the ECM to the cell is shown. Increased levels of β-actin and heat shock protein 27 (HSP27) after weight loss are compatible with increased mechanical stress and are associated with higher weight regain[63]. Variations in *COL23A1*, encoding collagen XXIII; *FBLN5*, encoding fibulin 5; *LAMB1*, encoding laminin subunit-β1 (which is a component of laminin 111); and *FN1*, encoding fibronectin were found to be associated with weight regain[65]. Epidermal growth factor receptor (EGFR)-mediated phosphorylation of α-actinin, a β-actin crosslinking protein and target of focal adhesion kinase, might be involved in the risk of weight regain[69].

that changes in the activity of HADH and other enzymes of β-oxidation in adipose tissue correlate positively with changes in the plasma levels of FFA[83]. A study investigated mitochondrial capacity in WAT by measuring the expression of genes involved in nuclear-encoded mitochondrial pathways, mitochondrial DNA gene expression, subunits of the oxidative phosphorylation machinery and the number of mitochondria in a weight loss intervention. The investigators found that baseline mitochondrial capacity was negatively associated with weight regain[84]. In another study, transcriptomics analysis showed that, in individuals with continued weight loss, mitochondrial gene expression was upregulated, whereas it was downregulated in individuals with weight regain on an ad libitum diet after a period of energy restriction[85].

These observations suggest that, when a deficit in energy from the diet during calorie restriction cannot be compensated for by lipolysis and/or β-oxidation, energy expenditure will adjust to a reduced level, which persists after weight loss and increases the risk of weight regain. Thus, changes in the concentration of plasma FFA and HADH in adipose tissue during weight loss are possible markers for the risk of weight regain.

One further factor that might have a role in an individual's susceptibility to weight regain after weight loss is the degree to which brown adipose tissue (BAT) activity changes or browning of WAT occurs. Studies have shown that BAT volume increases after bariatric surgery in mice[86] as well as in humans[87,88]. By contrast, no effect of caloric restriction on browning of subcutaneous abdominal WAT was found in individuals with obesity[89], although this effect of weight loss has been demonstrated in mice[90,91]. At this moment, no studies have investigated the potential association between the weight loss-induced increase in BAT activity or browning of WAT and weight regain in animals or humans and, therefore, the importance of these factors is currently unclear.

Adipose tissue as an endocrine organ

Adipose tissue has been considered an important endocrine organ since the discovery of leptin almost 25 years ago[92], although the role of adipose tissue as a source of hormones was first described in 1987 in the context of adipose tissue-derived oestrogens and breast cancer in women with obesity[93]. Currently, we know that the adipose tissue secretome is very diverse and that it has an important role not only in the crosstalk between adipose tissue and other organs but also in a paracrine or autocrine manner[94]. Apart from the classical adipokines such as leptin and adiponectin, various other factors are secreted by adipose tissue, such as enzymes, lipokines and extracellular vesicles that transport bioactive molecules, such as lipids, proteins and microRNAs[95]. Furthermore, adipocytes secrete metabolites such as FFA and glycerol (the potential role of FFA in weight regain is discussed earlier in the manuscript). Factors secreted by cells other than adipocytes (such as macrophages) in adipose tissue also contribute to the secretome of adipose tissue[96]. Several studies[52,97–99] have investigated the relationship between weight loss-induced changes to the secretome of adipose tissue and weight regain, which we describe in detail in the following section.

Changes to the adipose tissue secretome. Leptin is an obvious candidate in the regulation of the replenishment of fat depots after weight loss. Several studies have investigated the association between plasma leptin levels and weight regain[97]. Although some studies suggest that either a large decrease in leptin during weight loss or the baseline leptin level predicts weight regain, most studies did not detect such associations[97]. Studies that investigated the association between the weight loss-induced change in leptin concentration and weight regain are complicated by the fact that energy restriction has a very prominent effect on lowering plasma leptin concentrations on top of the effect of fat mass loss[100]. Measuring changes in plasma leptin concentrations at the end of a weight loss intervention, when participants are still in a negative energy balance, might therefore give different

results than when leptin is measured after weight loss in the absence of a negative energy balance.

With the possible measurement differences in mind, in the YoYo study, we measured leptin after a 4-week period in which participants were weight stable after a weight loss intervention. Neither the change in leptin from baseline to the 4-week weight-stable measurement time point nor the leptin level at this measurement time point was associated with weight regain[52]. These data add to the evidence that there is no association between weight loss-induced changes in leptin plasma concentration and weight regain. Concomitant changes in leptin sensitivity, however, cannot be excluded. A 2017 study[101] reported that leptin receptor expression in human adipose tissue was increased after bariatric surgery, although this might not reflect receptor expression in the hypothalamus.

Leptin links adipose tissue dynamics directly to brain responses. Adiponectin, along with several other cytokines from adipose tissue, is also known or suggested to cross the blood–brain barrier and act centrally[102]. Intracerebroventricular administration of adiponectin has been shown to result in the loss of fat mass in mice and rats by increasing energy expenditure independent of leptin[103,104]. In the YoYo study[52], we looked at a number of adipokines with known or suspected functions in the regulation of energy metabolism and body weight, such as IL-6, retinol-binding protein 4 (RBP4), apelin, adiponectin, vaspin, nesfatin 1 and angiotensin-converting enzyme (ACE) activity. We found that weight loss-induced changes in RBP4 and ACE activity were associated with weight regain, but no association was found for the other factors.

RBP4, a pro-inflammatory adipokine that is associated with insulin resistance[105–107], is predominantly secreted by the liver but is also secreted by adipose tissue[106,107]. Secretion of RBP4 is elevated in obese WAT owing to the presence of hypertrophic adipocytes[107]. Presently, whether weight regain and plasma concentration of RBP4 are causally related remains unclear, but the pro-inflammatory action of RBP4 could be involved.

ACE is a carboxypeptidase that is expressed in many tissues including adipose tissue but predominantly in the vascular endothelium and the lung. The enzyme is anchored to cell membranes and is shed into the plasma by enzymatic cleavage[108]. The weight loss-induced change in plasma ACE concentration was reported to predict continued weight loss on an ad libitum diet after a period of energy restriction in women in the European multicentre DiOGenes study[98]. Furthermore, a positive association between the weight loss-induced change in serum ACE concentration and weight regain during the ad libitum phase was found in men in the same study[99]. By contrast, in the YoYo study, the change in plasma ACE activity over the weight loss intervention (consisting of a weight loss phase followed by a 4-week weight stabilization phase) was negatively associated with weight regain[52]. The discrepancy between the two studies could be related to the different time points at which ACE was measured: at the end of the weight loss intervention in the DiOGenes study[99] or after a subsequent weight stabilization phase in the YoYo study[52]. Whether a causal relation exists between ACE and weight regain remains to be determined, and the underlying mechanism is also unclear. We know that ACE might have a role in many processes other than the regulation of blood pressure, such as inflammation, fibrosis and the regulation of food intake by the hypothalamus[108], but whether plasma concentrations of ACE or ACE activity reflect inflammation, fibrosis and regulation of food intake is unclear.

MicroRNAs in weight regain

Research has shown that microRNAs influence adipose tissue development and function, and as such, they might also be involved in regulating weight regain after weight loss[109,110]. Specific microRNAs can either promote or inhibit adipogenesis, for instance, via the regulation of adipose stem cell development and by lineage determination[111]. RNAs of the miR-30 family are able to target RUNX2 and therefore influence the decision of stem cells to become committed to the adipogenic or osteogenic lineage[112]. Another microRNA that can influence adipocyte morphology and lineage commitment is miR-181d. This microRNA determines the enzymatic activity of ADAMTS1, which is involved in ECM remodelling and in determining adipose tissue mass, insulin sensitivity and lipid homeostasis[113]. Lipid handling by adipocytes, including lipolysis, is influenced by microRNA targeting of peroxisome proliferator-activated receptor-γ (PPARγ)[114].

In humans, miR-26 is upregulated during early adipogenesis and seems to have a role in the browning of adipocytes, regulating lipid accumulation, mitochondrial morphology and uncoupled respiration[115]. The shift between white and beige adipogenesis is mediated by the miR-26 target ADAM17.

The microRNA profile of adipose tissue is changed in individuals who are obese[116]. A role for microRNAs, in particular, miR-365 and miR-574, is proposed in adipose tissue hypertrophy via the regulation of transcription factor EBF1 (REF.[117]). As such, microRNAs are thought to contribute to the development of obesity-related comorbidities such as insulin resistance and cardiovascular disorders. Indeed, research has identified several microRNAs that can influence insulin sensitivity. Interestingly, as is the case with adipokines, microRNAs contained in exosomes can be excreted from the adipose tissue[118]. In this way, they can travel to other tissues and organs to modify whole-body metabolism.

Obesity-induced changes in the concentration of microRNA within adipocytes might promote the chemotaxis of macrophages and other immune cells towards the adipocyte[119,120]. As such, microRNAs could contribute to a state of chronic low-grade inflammation within adipose tissues, as observed in obesity. In addition, adipocytes alter their microRNA profile when exposed to TNF or other cytokines[121]. Thus, under the influence of inflammation, the secretion of microRNAs from adipose tissues changes, and this might contribute to the development of insulin resistance. Of note, one study reported that 2 years after laparoscopic Roux-en-Y gastric bypass surgery in 16 women with morbid obesity, the obesity-related and inflammation-related

Weight cycling
The repeated loss and regain of body weight.

Bayesian analysis
A statistical paradigm that answers research questions about unknown parameters using probability statements.

impairment of microRNA target gene expression had improved[122].

Altogether, the effect that microRNAs seem to have on adipogenesis, adipose tissue functioning and whole-body metabolism makes it highly probable that they are involved in the risk of weight regain after weight loss. Notably, the consequences of weight cycling can be modified by microRNAs. In mice, high levels of hypothalamic miR-219 after weight cycling are associated with increased risk of metabolic syndrome[123]. More knowledge of possible similar influences of adipose tissue-derived microRNAs on weight regain would be welcome, as microRNAs could be a promising therapeutic target for preventing weight regain after weight loss and the consequences of weight cycling[118].

Regulation of gene expression by microRNAs is usually categorized as epigenetic modification. In this respect it is noteworthy that changes in DNA methylation, which is another type of epigenetic modification, were observed in human subcutaneous adipose tissue during weight regain or continued weight loss in the course of a 1-year weight loss intervention[124]. Similarly, chromatin modifications might influence weight loss and regain[125]. However, these studies are only descriptive and require functional follow-up studies.

Adipose tissue inflammation

As mentioned before, obesity is often accompanied by chronic low-grade inflammation of the adipose tissue with an increase in pro-inflammatory markers in the circulation[126]. Although one might expect that the inflammatory status would be lowered upon weight loss, gene expression measurements during weight intervention studies show that the adipose tissue inflammatory pathways are in fact upregulated during calorie restriction and are gradually downregulated during the 3–9-month follow-up periods after the weight loss intervention[127–129]. Following weight loss after bariatric surgery, adipose tissue retains its level of inflammation as if it memorizes the obese state despite continued weight reduction[130]. Furthermore, during the active weight loss phase following bariatric surgery, plasma markers of low-grade inflammation are unchanged or increased and decline only during the weight maintenance phase[52,131,132]. In the YoYo study, co-expression analysis of ECM genes in the 4-week weight-stable period following a VLCD intervention showed that genes encoding various leukocyte-specific integrins correlated with the risk of weight regain[68]. These gene expression data suggest that individuals in whom adipose tissue retains a high level of leukocyte activity in the first weeks after weight loss — which might be a marker for ongoing tissue stress — are at an increased risk of weight regain. On the other hand, individuals who have a resistance to adipose tissue inflammation would be expected to be at a reduced risk of weight regain after weight loss. These findings seem to comply with the existence of an obesogenic memory[130], which in mice might be mediated by $CD4^+$ T cells[133].

As described earlier, a weight loss-induced increase in levels of plasma RBP4 was associated with weight regain in the YoYo study[52]. Data from the DiOGenes study also suggested that inflammation is involved in weight regain[134]. A continued inflammatory state would be expected to increase adipose tissue lipolysis and energy expenditure[135,136], which could be considered beneficial for the prevention of fat mass regain. However, how these two opposing mechanisms might interact in the process of weight regain following weight loss remains to be seen.

Models to predict weight regain

Although many factors, such as weight loss-induced effects on adipose tissue but also behavioural and environmental factors, have been shown to correlate with weight regain after diet-induced weight loss, the correlation of each factor alone with weight regain is usually low, and the independent contribution of each factor is unknown. Few studies have tested whether a combination of these factors can be used to predict successful weight loss maintenance.

One study[137] used data from the DiOGenes trial, which studied weight regain after weight loss by caloric restriction in 191 individuals without T2DM who were overweight or obese. In this study, the authors analysed the adipose tissue transcriptome at baseline and investigated how it changed in response to a LCD. They combined this analysis with clinical variables, including BMI, Matsuda index (a measure of insulin sensitivity), age and sex, at baseline and how BMI and Matsuda index changed during the LCD with the aim of developing a model to identify individuals who are susceptible to weight regain after weight loss.

The authors found that 18 of the 1,173 differentially expressed genes during the LCD were associated with both BMI changes and Matsuda index changes during the calorie restriction phase. At the end of the 6-month follow-up, the model that was the most accurate at classifying individuals who had BMI changes above or below the median from baseline included weight loss-induced changes in clinical variables and baseline adipose tissue gene expression of the 18 identified genes[137]. Compared with a model that included only the clinical variables, this model was significantly more accurate at predicting whether an individual would regain weight or maintain the reduced weight following the LCD intervention ($P = 0.012$; area under the receiver operating characteristic curve 0.73 and 0.87, respectively).

In a study of 100 individuals[138], the investigators combined various psychosocial variables with simple clinical baseline variables with the aim of predicting successful long-term (60 months) weight reduction (≥10% from baseline) after an 8-week VLCD intervention. Including the psychosocial variables did not improve the prediction model compared with a model based on baseline clinical variables alone (sex, BMI, waist-to-hip ratio and insulin sensitivity) (88% versus 86% of participants classified correctly).

A further study[134] analysed predictors of body weight change using a Bayesian analysis in a study that included a 6-week energy restriction phase followed by a 6-week weight maintenance diet prescription phase. A large number of potential predictors were studied, including metabolic and inflammatory variables and

Box 1 | **Strategies to prevent weight regain that target adipose tissue function**

Increased physical activity

- Negative association between physical activity score and weight regain[48,154,157]
- Individuals who maintained on average 25% of their weight loss increased physical activity more than individuals who on average did not maintain their weight loss[155]
- Successful weight loss maintainers spent 2–4% more awake time in moderate-to-vigorous physical activity than weight-matched control individuals[156]

Increased protein content of diet

- Improved weight loss maintenance after 1 year in individuals who were advised a diet consisting of 25% of energy intake from protein compared with individuals who were advised a diet consisting of 15% of energy intake from protein (DiOGenes study)[165]
- Analysis of six studies that compared high-protein diets (range 18–30% energy intake) versus average-protein diets (15% energy intake) showed better weight loss maintenance with high-protein than with normal-protein diets[166]

Drug treatment

- Improved weight loss maintenance in groups taking sibutramine, orlistat or liraglutide[167–169]

Meal replacements

- Improved weight loss maintenance in groups using one meal replacement per day compared with groups without meal replacement use[166,170]

Dietary supplements

- Improved weight loss maintenance with caffeine–green tea supplementation compared with placebo in low habitual caffeine consumers[171]

Extended care after a period of weight loss

- Improved weight loss maintenance in groups receiving more care (such as telephone contact and group meetings) after a weight loss intervention compared with groups receiving no or less care[172,173]

Daily weight monitoring

- Daily self-weighing mediated 24-month weight loss maintenance[174]

gut microbiota composition. A combination of baseline fasting plasma insulin and IL-6 concentrations, plasma leukocyte number and the number of HAM56$^+$ cells (macrophages) in subcutaneous WAT was able to predict resistance to weight loss and proneness to weight regain with a prediction accuracy of 75%[134].

These models are far from being able to accurately predict individual weight loss success, and research in this area needs to be further expanded before this goal will become a reality. Large data sets that include a variety of potential predictors of different types (biological, behavioural and environmental) will be necessary for this type of analysis.

Strategies to prevent weight regain

Several strategies unrelated to adipose tissue to limit weight regain after successful weight loss have been investigated in adults with obesity, some of which have been effective (BOX 1). In this section, we discuss strategies based on adipose tissue-related factors that show promise in predicting weight regain (FIG. 5).

One strategy could be to try to reduce the cellular stress response that is associated with weight loss-induced reduction in adipocyte size by increasing the fluidity of the adipocyte membrane. Omega-3 polyunsaturated fatty acids have been shown to increase membrane fluidity[139], but whether using them as a treatment will reduce the weight loss-induced stress response is unknown.

Another strategy could be to stimulate lipolysis, which would reduce the nutrient shortage signalling to the brain[70] and increase energy expenditure in individuals who have low plasma FFA levels after weight loss. Strategies that increase browning of WAT, such as cold exposure[140] or nutraceuticals (including conjugated linoleic acid)[141], are options that could be tested in individuals with low plasma FFA levels after weight loss. Regular exercise can also stimulate lipolysis and has been shown to be beneficial for the prevention of weight regain after weight loss (BOX 1). Whether regular exercise induces browning of WAT in humans is still a matter of debate, but most human studies have reported no increases in browning following exercise training[142–145]. Animal studies suggest that regular exercise can diminish the drive for weight regain by shifting energy metabolism to decrease de novo lipogenesis and increase plasma FFA concentration[146,147]. The effect of pharmaceutical agents that increase lipolysis also deserves study in the context of weight regain, although lipolysis-stimulating agents such as β-adrenergic agonists will be of limited practical use because they are associated with adverse effects, including muscle tremor, elevated blood pressure, tachycardia and insomnia[148].

Although the mechanisms underlying weight regain are far from clear, a potential strategy to limit weight regain is to try to reduce inflammation in individuals who maintain high levels of inflammation after weight loss. Several approaches to achieve a reduction in inflammation can be considered: anti-inflammatory drug treatment and exercise and dietary strategies (including alterations to diet composition or dietary supplements). Several anti-inflammatory drugs have been tested in individuals with metabolic disturbances associated with obesity, but their effects on body weight have not been reported[107,149,150]. Furthermore, none of these drugs have been tested in the context of weight maintenance after weight loss.

Some investigators have suggested TNF inhibition in combination with recombinant IL-33 administration as a potential strategy to maintain healthy adipose tissue immune function[107]. Regular exercise is known to reduce inflammation in humans, and several mechanisms for this effect have been proposed, such as a reduction in adipose tissue mass, increased production of anti-inflammatory cytokines by active skeletal muscle and a reduction in the release of circulating pro-inflammatory cytokines by macrophages and monocytes[151]. Reduced macrophage infiltration in adipose tissue and beneficial phenotypic switching of adipose tissue macrophages by exercise have been reported in rats[151]. However, the effect of exercise on adipose tissue inflammation in humans remains unclear[152]. One study[153] reported an increase in CD163$^+$ cells after exercise training in the adipose tissue of individuals who were overweight or had obesity. CD163$^+$ cells are supposed to be anti-inflammatory. Several studies have shown that individuals who are active after a weight loss intervention regain less weight than individuals who are inactive[48,154–157] (BOX 1), but whether a reduction in inflammation is involved remains unclear.

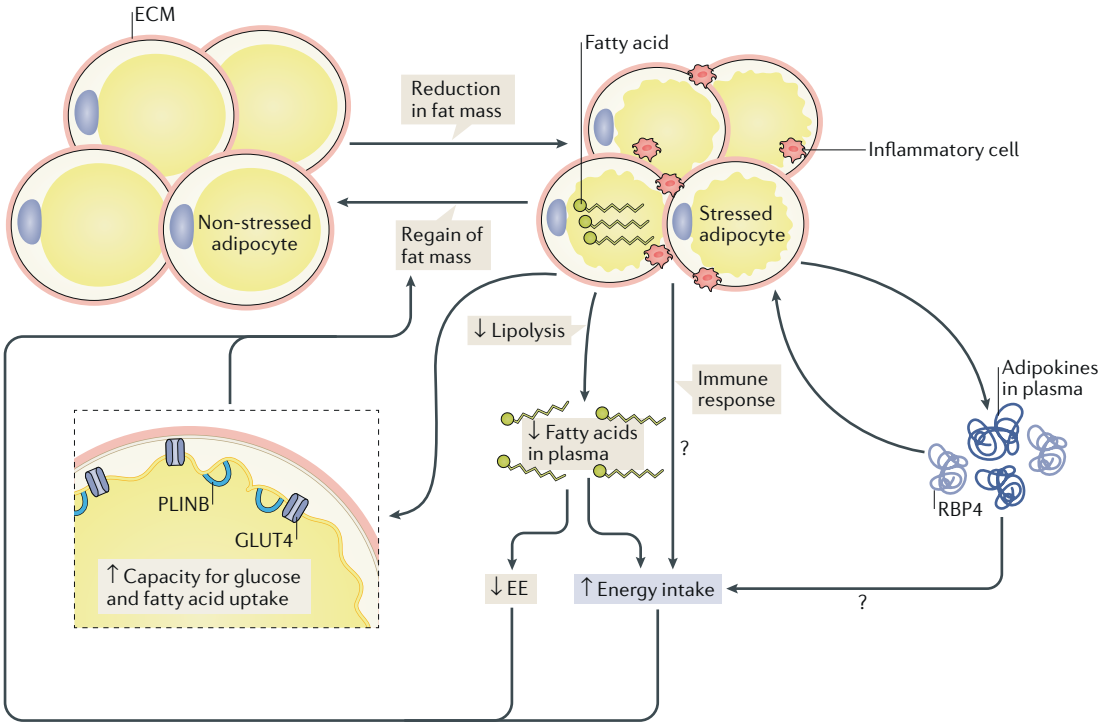

Fig. 5 | **Working model for the role of weight loss-induced changes in adipose tissue in weight regain.** Loss of fat mass induces shrinkage of adipocytes, which is accompanied by cell stress, inflammation, altered adipokine secretion (for example, retinol-binding protein 4 (RBP4)) and reduced lipolysis. These changes may affect energy balance by reducing energy expenditure (EE) and increasing energy intake, thus promoting regain of fat mass and body weight and relieving stress. In addition, the cells express an increased capacity for glucose uptake (glucose transporter type 4 (GLUT4)) and fatty acid uptake (perilipin 1 isoform B (PLINB)), which facilitates renewed fat storage[73]. ECM, extracellular matrix.

Inflammation can also be influenced by diet. One of the potentially anti-inflammatory nutraceuticals is resveratrol. The anti-inflammatory properties of resveratrol have been clearly demonstrated in animal studies[150]. The suggested mechanisms are primarily decreased activation of NF-κB and reduced adipose tissue macrophage infiltration[150]. Nevertheless, the studies on the anti-inflammatory action of resveratrol in humans have been equivocal[150]. A 2015 clinical trial in individuals with obesity and metabolic syndrome found no effect of low-dose or high-dose resveratrol treatment on adipose tissue inflammation, circulating inflammatory markers or body composition[158]. Another strategy to reduce inflammation might be supplementation with omega-3 polyunsaturated fatty acids, which reduce inflammation via a variety of mechanisms[159]. To date, however, neither resveratrol nor omega-3 polyunsaturated fatty acids have been tested in the context of weight loss maintenance.

Diet composition has been shown to influence the level of inflammatory markers in the circulation, and an index (called the Dietary Inflammatory Index) has been developed to reflect the inflammatory properties of the diet[160,161]. In a non-overweight adult cohort of Spanish individuals, the Dietary Inflammatory Index score was not associated with BMI at baseline, but a high score was associated with increased body weight and an increased risk of developing overweight or obesity after 8 years of follow-up[162]. In the YoYo study, we found that a high Dietary Inflammatory Index score was associated with increased weight regain over the follow-up period[163]. The circulating concentrations of individual inflammatory markers, such as IL-6 and RBP4, showed mixed results, with weight loss-induced changes in RBP4 being found to be associated with weight regain, whereas changes in IL-6 were not[52]. Clinical trials that compare diets with a low or high Dietary Inflammatory Index score after a weight loss intervention are needed to answer the question of whether the inflammatory properties of diet have a role in weight regain and whether the underlying mechanism is related to adipose tissue function.

Mouse studies have suggested that local insulin resistance in adipose tissue leads to secretion of MCP1 and activation of pro-inflammatory macrophages[46]. Therefore, another strategy to prevent weight regain after weight loss could be targeting adipose tissue insulin resistance. In addition, as we described earlier, targeting adipose tissue microRNAs for the prevention of weight regain might be a promising strategy, but this approach awaits further exploration. The same can be said for epigenetic marks like DNA methylation and chromatin modification.

Finally, altering adipokine production and/or secretion or mimicking their effect by drugs is another strategy that might prove successful at preventing weight regain, although the role of adipokines in weight regain is still far from clear. A study[164] investigated the effect of metreleptin (a synthetic leptin analogue for the treatment of

lipodystrophy) in combination with pramlintide treatment on body weight after an initial weight loss period by dietary energy restriction in individuals with obesity. The addition of metreleptin to the treatment regimen was associated with a further decrease in body weight compared with pramlintide alone, but the duration of the study was too short to provide information on weight regain[164].

Conclusions

In this Review, we have summarized the evidence that shows that the interindividual differences in weight loss-induced changes in subcutaneous adipose tissue have a role in the interindividual differences in weight regain. As most of the evidence comes from associations, further research on the causality of these associations might eventually lead to the development of targeted strategies to effectively prevent weight regain after successful weight loss. Promising research areas are weight loss-induced variations in cellular stress, ECM remodelling, inflammatory responses, adipokine secretion, lipolysis and epigenetic modifications, including regulation by microRNAs.

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