Bulletin of the National Research Centre

REVIEW

Open Access

Is microbiota a part of obesogenic memory? Insights about the role of oral and gut microbiota in re-obesity

Antoine AbdelMassih[1,2*], Maryam Eid[3], Mahenar Gadalla[3], Nour AbouShadi[3,4], Steven Youssef[5], Batoul Ali[3], Janna AbdelDayem[6], Emmy AbdelFatah[6], Abdulrahman Mahmoud[6], Ahmed ElLithey[6], Beshoy Ghabreal[6], Doha ElSaid[7], Haya Mohamed[8], Hoda Labib[6], Mennatullah ShamselDin[6], Nada Daniel[8], Omnia Youssef[6], Rajan KC[6], Rana Ahmed[6], Rawan Sayed[6], Rodaina Ali[3], Yomna Eid[9], Rafeef Hozaien[6] and Maryam ElAhmady[3,4]

Abstract

Background Weight re-gain (which is also known as re-obesity) is an overwhelming challenge many dieters face in their pursuit to maintain consistent results following successful weight loss. This frustrating pattern of weight cycling can have various mental and physical implications, which further puts another roadblock in any weight reduction program.

Main body of the abstract A comprehensive analysis of the causes behind the phenomenon of re-obesity has been widely conducted in literature, exploring the importance of creating the right mindset for weight loss maintenance and identifying the hormonal role, specifically of insulin–leptin resistance and ghrelin enhanced affinity, on appetite and food intake regulation. Insulin–Leptin resistance, due to circulating prostaglandins and prostaglandin metabolites, along with a decline in leptin-producing adipocytes following body mass reduction, cuts off leptin's satiety signals to the brain. The persistence of this hormonal dysregulation after weight loss is collectively called obesogenic memory, and it seems to be largely mediated by dysbiosis.

Short conclusion In conclusion, understanding of the influence of hormonal dysbiosis on re-obesity is fundamental in targeting the culprits behind ineffective attempts at weight loss sustenance, optimization of diet duration, use of synbiotics. Fecal and oral microbial transplantation hold high potential in improving long-term management interventions in obesity patients.

Keywords Re-obesity, Insulin resistance, Oral and gut microbiota, Leptin resistance, Ghrelin, Obesogenic memory

*Correspondence:
Antoine AbdelMassih
antoine.abdelmassih@kasralainy.edu.eg
Full list of author information is available at the end of the article

Background

Obesity has undoubtedly evolved into an alarmingly critical modern epidemic, with over 1.9 billion overweight adults across the globe, 650 million of which are classified as obese. Concomitantly, more people are attempting to lose weight, with a little over 40% globally seeking weight reduction strategies that range from diet moderation and exercise to more invasive procedures (Santos et al. 2016).

Long-term sustenance, however, is an obstacle that many face. Coupled with a healthy balanced diet and regular physical activity, intrinsic motivation and discipline are integral principles in long-term weight loss maintenance. Nonetheless, weight regain subsequent to loss is a multifactorial phenomenon, with multiple genetic, biological, developmental, environmental, and psychosocial influences intertwining together, making its management not only complex but also time-consuming (Hall and Kahan 2018).

Several studies have documented the numerous obstacles that obese individuals face throughout their weight-loss journey, but the burden of sustaining lost weight and avoiding relapse is a particularly challenging aspect (Hall and Kahan 2018).

Even patients undergoing bariatric surgeries struggle with keeping lost weight off, as evidenced in a study by Tolvanen et al. In this study weight regain following gastric bypass was observed in 36% of study participants. Surgical failure and weight regain were among the significant findings that were found to be higher among the super-obese group of patients (El Ansari and Elhag 2021; Tolvanen et al. 2022a).

Futile attempts to keep the weight off can have great implications on an individual's mental health. After putting in tremendous effort in creating dietary and lifestyle modification, it is unsurprising that many patients struggle when their weight loss is followed by a plateau, or even worse, some gain. Unmet expectations after taking minor or major measures to control weight can leave individuals hopeless and unmotivated, eventually drawing them back to their previous habits. (Freire et al. 2021; Hall and Kahan 2018; Tolvanen et al. 2022b).

Physiologically, it has been evidenced that the obesity-induced chronic state of low-grade inflammation causes mild up-regulation of cytokines, chemokines, and acute phase reactants, although it is yet to be known whether these changes are reversed following weight loss or not (Baak and Mariman 2019; Chait and Hartigh 2020). These inflammatory changes lead to adipose tissue dysfunction and are largely orchestrated by oral and intestinal dysbiosis. The persistence of this low-grade inflammation and adipose tissue dysfunction even after weight loss is termed obesogenic memory. The aim of this review is to explore the persistence of dysbiosis and its role in mediating obesogenic memory at the hormonal level (Anastasiou et al. 2015).

Main text

Overview on hormonal theories for re-obesity: is weight regain only an issue of mindset?

Weight re-gain is without a doubt credited to the need of inspiration and self -control of the patients. On the other hand, it is well known that body weight and fat mass are controlled by various physiological instruments, distant past intentional nourishment admission and physical work out (Rubino et al. 2020).

Multiple theories and hypotheses were suggested surrounding the idea of the mechanism of re-obesity in hopes of restricting the relapse percentage of patients who had lost weight. The most accepted theory for weight re-gain is the "mindset". Behavioral and psychological factors like increased physical activity, dietary intake monitoring, and body weight are essential behavioral strategy, and the more the patient is consistent in adhering to self-monitoring the greater the initial weight loss is, as well as its maintenance (Burke et al. 2011).

Unfortunately, by time this consistency regresses, resulting in weight re-gain. Dietary lapses can be due to multiple psychological and environmental factors of which it is more likely to occur at home, on weekends, or at gatherings. In addition, emotional status including sadness, loneliness, boredom, or irritation are important factors (Forman et al. 2017).

Other characteristics dictating weight re-gain may include binge eating, emotional eating during sad or stressful times, and more advanced cases of depressive symptoms (Martins et al. 2020).

However, attributing re-obesity to the sole concept of "mindset", is not correct. Re-obesity is mediated by multiple neuro-hormonal mechanisms, of which we will mainly discuss the role of Insulin, Leptin and Ghrelin. The persistence of the characteristic signatures of these hormones after weight loss is termed obesogenic memory.

The regulation of body weight is a complex system that involves numerous biochemical and physiological processes, including the regulation of appetite, energy expenditure, and metabolism. This system is influenced by a variety of factors, such as genetics, environment, and lifestyle, making it challenging to control and maintain a healthy weight. Three main hormones seem to regulate food intake and body weight; Ghrelin which is produced in the stomach that stimulates appetite and plays a role in regulating body weight; leptin is a hormone produced by fat cells that helps to regulate energy balance and decrease appetite; and insulin, a hormone produced by

the pancreas that regulates blood sugar levels and plays a key role in metabolism (MacLean et al. 2011).

Leptin functions as a mediator of long-term regulation of energy balance, as well as suppressing food intake; the result of which is the induction weight loss. However, Ghrelin supports meal initiation, and is a fast acting hormone (Martins et al. 2020).

Insulin and leptin resistance persistence after weight loss, a key to re-obesity

The hormonal changes that occur after weight reduction have a tendency to be oversimplified in literature. For instance, it had been claimed that following weight loss, insulin resistance would almost completely resolve, but this does not account for why obesity recurs.

Residual insulin resistance after weight loss After achieving successful weight loss, Blaszczak and colleagues looked into whether or not insulin resistance and adipose tissue inflammation persisted. They discovered that losing weight caused an alteration in the expression of inflammatory markers, Leptin, Tumor Necrosis factor (TNF), and Interleukin 1-beta (IL-1b). These markers rose with weight reduction, while adiponectin dropped. These critical adipokines did not return to normal, and it is probable that this is what causes any remaining inflammation. Expression of fatty acid metabolism genes revealed decreased lipid synthesis and storage of Acetyl- CoA carboxylase 2 (Acc2) and increased fatty acid utilization of Carnitine Palmitoyltransferase 1B (Cpt1B), Adenosine triphosphate synthase subunit alpha (Atp5a1), Cyclooxygenase 5a (Cox5a), which may be a trial to suppress the increased dietary intake of fatty acids. These processes might result in higher circulating lipids, a recognized factor in insulin resistance, and were only partially reduced by weight loss (Blaszczak et al. 2020).

Persistence of leptin resistance after weight loss After losing weight, leptin levels noticeably decrease and leptin-sensitive states return, according to the literature. It is correct that the loss of adipose tissue mediates loss of leptin with a consequent rise in hunger however, there is research suggesting that re-obesity is a combined action of low leptin levels and chronic leptin resistance, and not only the effect of leptin loss.

The long-lasting alterations in prostaglandin in adipose tissue are related to the persistent leptin resistance Prostaglandin signaling was linked to obesity in human research, with many studies demonstrating a very significant correlation between the levels of orexigenic neuropeptides, as well as the expression of the prostaglandin D synthesizing enzyme (PTGDS) found in cerebrospinal fluid (CSF). Additionally, it was found that both the visceral adipose tissue and subcutaneous adipose tissue mass had positive and negative correlations with PTGDS levels in CSF, respectively. In a study by Hernandez-Carretero et al., adipose tissue samples from humans were obtained from lean and obese patients and was analyzed using expression databases. They discovered that the levels of Hematopoietic Prostaglandin D synthase (HPGDS) were higher in obese individuals, and these levels did not fall following weight reduction. Furthermore, weight reduction induced by gastric bypass procedure gastric did not lower circulating prostaglandin D2 (PGD2) levels, which were actually increased relative to the lean reference range (Hernandez-Carretero et al. 2018).

Another paper by Hosoi et al. demonstrated the important role of 15 deoxy delta 12–14 prostaglandin J2 (15d-PGJ2), a metabolite of PGD2 which controls important immunity-related functions, in the development of leptin resistance. They showed that leptin-induced Signal Transducer and Activator of Transcription 3 (STAT3) activation and leptin-induced anorexia were both suppressed by 15d-PGJ2 (Hosoi et al. 2015).

The CSF contains 15d-PGJ2, and it has been demonstrated that brain inflammation brought on by bacterial endotoxins increases the expression of 15d-PGJ2. Leptin resistance may be facilitated by persistent inflammation. Consequently, a rise in 15d-PGJ2 levels in the brain might be a factor for the development of leptin resistance. Microglia cells have been shown to produce more 15d-PGJ2 under inflammatory circumstances. Since the hypothalamus of obese people exhibits chronic inflammation, microglia may stimulate the synthesis of 15d-PGJ2, which might therefore play a role in the progression to leptin resistance (Hosoi et al. 2015; Li et al. 2019).

Ghrelin enhanced hypothalamic response by obesogenic memory

There is conflicting evidence in the literature regarding ghrelin's contribution to re-obesity. Almost no research has indicated or concluded that higher ghrelin levels at any time point during weight loss could be a predictor for more difficulties with the feat of weight loss maintenance. This is despite the fact that it is well known that surplus energy suppresses ghrelin and would therefore decreases the appetite (Strohacker et al. 2014).

It appears that reduced calorie intake has no effect on the obesogenic memory mediated by Cluster of differentiation 4 (CD4) cells. Instead of higher ghrelin levels following weight loss, this can be explained by ghrelin's enhanced tissue actions. Mammalian target of rapamycin (mTOR), a hypothalamic receptor that mediates the orexigenic (appetite-stimulating) impact of ghrelin, was

found to be increased by persistent low-grade inflammation during weight loss (Martins 2012).

Role of microbiota in residual hormonal changes after weight loss, indirect evidence from prebiotic and probiotic therapy

Harmful microbiota persist after weight loss and is part of the obesogenic memory

It is presently widely known that obesity has a significant impact on the intestinal and oral microbiota. The most frequent discovery of the gut microbiota is a decrease in butyrate-producing microorganisms, and families such as Rikenellaceae Christensenellaceae Bifidobacterium, Oscillospira, and Akkermansia. On the other hand, obesity has also been linked to an increase in other gut microbiota groups, including the Prevotellaceae, Coriobacteraceae, Erysipelotrichaceae, and Alcaligenaceae. Moreover, individuals with greater BMI have consistently been linked to increased abundance of the Roseburia genus. This species is able to hydrolyze and ferment polysaccharides into Short Chain Fatty Acids (SCFA), which increases the amount of energy obtained from the food. Another species, Eubacterium dolichum, has been positively linked to visceral fat mass as an indicator of obesity (Asma et al. 2021).

Intestinal microbiomes in obese mice were compared both before and after weight loss in a study by Thaiss and colleagues. Gut microbiota's composition had developed a dysbiotic condition throughout the early stages of obesity (Thaiss et al. 2016).

Instead of clearly demonstrating particular changes in distinct species, this study largely indicated persistent reduction of alpha diversity and sustained reduction in apigenin synthesis by gut microbiota. These findings signified long-lasting alterations of dysbiosis following weight loss (Thaiss et al. 2016).

As a result, the nature of the intestinal microbiota, which had developed a dysbiotic state during the main obesity phase, did not shift back to previous composition, even after post-diet weight and metabolic normalization (Mervish et al. 2019; Palleja et al. 2016; Thaiss et al. 2016).

Oral and gut microbiota and low-grade inflammation

The presence of a low-grade type of inflammation is a known indicator of weight problems and Type 2 diabetes. Production of pro-inflammatory cytokines are coordinated via the Toll-like receptors (TLRs) and the regulator of inflammatory cascades the nuclear factor kappa B (NF-kB). These pathways were proven to be activated through the manufacturing of lipopolysaccharides (LPS) which are the main element of the outer membrane of Gram-negative bacteria which is produced inside the gut. Higher LPS ranges were related to elevated fat intake seen in overweight mice models. It has been proposed that nutritional fats mediated the absorption of LPS linking them to weight problems. In fact, it has been tested that including LPS to normal-food plan prompted insulin-resistance and result in weight gain. It has been additionally proven that LPS binds to Toll-like receptor (TLR4) on macrophages and lead to the release of inflammatory markers thus impairing the β-cells of the pancreas by suppressing insulin secretion and reducing gene expression of Pancreatic and Duodenal Homeobox 1 (PDX1) (Baothman et al. 2016).

Insulin resistance mediated by oral and gut microbiota

Dietary fats have been found to be correlated to the increased absorption of LPS, which has been associated with changes in gut microbiota, such as a reduction in Bifidobacteria, Eubacterium rectale as well as Clostridium coccoides groups (Caricilli and Saad 2013).

It is possible that other bacterial factors may be contributing to the emergence of insulin resistance. Like TLRs, the peptidoglycan (PGN) moieties of the bacterial cell wall that are known to trigger stress and inflammatory pathways are sensed by the nucleotide oligomerization domain (NOD)-1 and -2 proteins, which are intracellularly located pattern recognition receptors. Gram-negative bacteria have PGN structures that are detected by NOD1, whereas gram-positive bacteria often have PGN segments that are detected by NOD2. Recent research has linked bacterial patterns that activate NOD1 and NOD2 to insulin resistance. Inflammatory processes are activated when adipocytes are given PGN-based NOD1 activator, which decreases insulin-stimulated uptake of glucose and impairs insulin signaling. Similar to this, PGN motifs that affect NOD2 cause insulin resistance in muscle cells on their own. Mice can develop acute systemic insulin resistance as a result of NOD1-activating bacterial PGN motifs (Caricilli and Saad 2013).

This NOD1 activation reduced insulin-mediated glucose absorption in adipocytes and deactivated insulin within the liver and isolated hepatocytes. Therefore, it appears that cells from mostly from adipose and hepatic tissue, communicate with one another to cause insulin resistance that indirectly affects skeletal muscle (Caricilli and Saad 2013).

Given that NOD1 transcript levels were found elevated in epididymal adipose tissue of the mice that were given a HFD, it is plausible that several levels of regulation for NOD1-mediated sensing of PGN happen in a state of obesity. The extent to which these NOD1 ligands, which may be produced from the gut microbiota, contribute to the onset of insulin resistance and whether or not they are altered during obesity, has yet to be determined (Caricilli and Saad 2013).

Amar and colleagues have demonstrated that bacterial translocation happens within the adipose tissue and circulation where inflammation is generated after just a week following the ingestion of a HFD. It was shown that mice with a deficiency of recognition receptors NOD1 or CD14 are unable to undergo this translocation. This indicates that these receptors play significant roles in the emergence of the low-grade inflammatory state that underlies the state of insulin resistance (Klopp et al. 2011).

A study was done using antibiotics to modify the gut microbiota to observe its effect on insulin signaling in HFD fed mice. The treatment decreased the number of Bacteroidetes and Firmicutes. Also reduced was the overall bacterial count and circulating levels of LPS. This in turn was shown to reduce fasting insulin, TNF-α and IL-6. This further emphasizes the role of inflammation in diabetes, and thus the role of microbiota in modulating glucose levels (Carvalho et al. 2012; Sharma and Tripathi 2019; Blasco-Baque et al. 2016).

A study done on the effects of intermittent fasting on weight loss and metabolic disease has shown that there is an association between intermittent fasting and a decrease in serum glucose and insulin. The same study has shown that intermittent fasting has a major effect on the gut microbiome by increasing the Firmicutes: Bacteroides ratio. This was linked to an improvement in metabolic syndrome. This was not the case, however, in microbiota depleted mice, where intermittent fasting was not shown to improve obesity or liver steatosis in them. This further strengthens the connection between gut microbiota and insulin sensitivity (Stockman et al. 2018).

Last but not least, one study has shown that insulin clearance during diet-induced obesity is controlled by gut microorganisms. One of the ways of preventing defects in insulin clearance and hyperinsulinemia as obesity and type 2 diabetes advance is by targeting a small cluster of microbiota or their metabolites (Foley et al. 2020).

Oral microbiota also has a clear effect on insulin sensitivity and glucose levels. This was evidenced by a trial involving a specific animal model with induced periodontitis. The periodontitis in turn caused an oral microbiota dysbiosis without involving the gut microbiota. This was found to impair glucose metabolism and induced a systemic immune response, with the end result of enhancing insulin resistance in these animal models when compared to the healthy controls (Schertzer and Lam 2020). This was also evidenced by a trial involving a specific animal model with induced periodontitis by the organisms Porphyromonas gingivalis (Pg), Fusobacterium nucleatum (*F. nucleatum*) as well as Prevotella intermedia (*P. intermedia*). This in turn resulted in an oral microbiota dysbiosis without involving the gut microbiota. This was found to impair glucose metabolism and induce a systemic immune response, therefore enhancing the insulin resistance in these animal models compared to healthy controls (Blasco-Baque et al. 2016).

Oral and gut microbiota and leptin signaling

Serum leptin levels, as well as the composition of gut microbiota, were evaluated in rat groups under different diets and exercise programs. A positive correlation was established between the quantity of gut microbiota species including Bifidobacterium and Lactobacillus species, and the levels of serum leptin among all groups. A negative correlation was found however, between the quantity of Prevotella, Clostridium, and Bacteroides, as well as and serum leptin levels in all rat groups (Amabebe et al. 2020; Queipo-ortun et al. 2013).

Regarding Leptin, evidence tested the effect of using probiotic bacteria in restoring the responsiveness of leptin, for example Lactobacillus rhamnosus GG (LGG), Bifidobacterium longum PI10 (*B. longum* PI10), and mixtures composed of a strain of *B. animalis* subsp. lactis and a strain of *L. gasseri* (Cheng and Liu 2020).

Leptin resistance prohibits the administration of exogenous leptin from stimulating weight reduction. The effect of LGG administration on leptin resistance was assessed utilizing an acute method in a study by Cheng and Liu. After receiving leptin intraperitoneally for three days, the mice's body weight changes were assessed. The mice's food intake did not vary across the groups during the course of the 3 days of exogenous leptin treatment (Cheng and Liu 2020).

Another in vitro screening method was helpful in identifying at least one high-potential strain, Bifidobacterium longum PI10. *B. longum* PI10 is a single strain with the capacity to significantly affect obesity, and a high-potential combination made up of a single strain, as well as a high-potential mixture composed of a strain of *L. gasseri* and *B. animalis* subsp. lactis. These possible probiotic therapies might work via improving leptin resistance and fasting glycemia (Alard et al. 2021).

Another study looked at how the expression of leptin in the body, as well as body weight were affected by gut microbiota among different types of nutritional diets (Yao et al. 2020).

Differences between CV and GF mice fed normal or high fat diet were documented regarding expression of leptin, leptin receptor (Lep-R) and body weight change. They showed an increased messenger Ribonucleic acid (mRNA) expression of leptin gene in the adipose tissue of GF feeding on a NFD and subsequently increased plasma leptin levels in comparison to CV mice (Yao et al. 2020).

A study observed the effect of prebiotics on gut microbiota and leptin sensitivity modulation in genetic obese

(ob/ob) and diet induced leptin resistant mice that were being feed a high fat (HF) diet. Quantitative PCR analysis revealed a significant shift in the gut microbiota profile in prebiotic treated obese mice. An observed increase was seen with the Bifidobacterium spp. And the Eubacterium rectale (*E. rectale*)/Clostridium Coccoides (*C. coccoides*) group, decrease in Firmicutes and Roseburia spp. No effect was observed on the Bacteroidetes, Lactobacillus spp., and the Bacteroides-Prevotella groups. These changes were associated with improved glucose tolerance and leptin sensitivity, reduced fat mass and body weight. An increase in muscle mass was also observed. Leptin was then administered to mice fed with HF diet and prebiotics (HF-pre) and the control group fed only HF diet. This caused a greater decrease in body weight and food intake in HF-pre in comparison to mice feeding a HF diet. To conclude, gut microbiota changes by prebiotic intake affects energy homeostasis in genetic obese mice and diet-induced leptin-resistant mice, and this the result of improving leptin sensitivity. (Everard et al. 2011; Zhang et al. 2018).

According to literature, individuals with severe periodontitis had significantly higher levels of C-reactive protein (CRP) and IgG against *P. gingivalis*. Lower plasma adiponectin levels were found in them, however, without any relation to their weight status. Additionally, without the influence of severe periodontitis, people with overweight or obese BMIs had greater plasma levels of intercellular adhesion molecule-1 [ICAM-1], CRP, and leptin, but lower levels of adiponectin, than those with normal weight (Thanakun and Izumi 2016).

Role of microbiota in modulation of ghrelin

The hormone ghrelin is composed of 28 amino acids and is produced peripherally in gastric X/A-like cells. It plays an important and primary role in the gut brain axis by stimulating food intake centrally; this occurs within the via hypothalamic nuclei. This results in the establishment of an orexigenic communication between these central food intake-regulating centers and the gut. Additionally, the gut microbiome is a further element of the gut-brain axis that has attracted attention of much research in recent years due to its capacity to affect central signaling via metabolites (Schalla and Stengel 2020; Schalla and Stengel 2020).

Evidence ascertains the detrimental impact of certain bacteria on gut hormones. Vila et al. suggested the role of gram-negative bacteria in implementing biphasic changes in ghrelin levels by administering Lipopolysaccharides (LPS). This situates ghrelin centrally in the chronic inflammation cultivated by gut colonization by gram-negative bacteria by providing adequate nutrients to alter the quantity and efficiency of cytokines (Vila et al. 2007). Similarly, Esteve et al. (2011) described the comparable effect of a high-lipid diet to LPS by increasing enteric permeability thereby initiating similar endotoxemia.

After the excessive intake of sugars and starches, these sugars and starches are then transformed into short chain fatty acids (SCFAs). These SCFAs work as secretagogues for Peptide YY (PYY) and Glucagon-like peptide 1 (GLP-I) release (Heiman and Greenway 2016).

This speculates the exhaustive potential of SCFAs as an energy source on ghrelin producing cells. This leads us to suspect the role bariatric procedures associated with the accumulation of preexposure SCFAs vis a vis accruing complex indigestible carbohydrates as a contributor of re-obesity (Queipo-ortun et al. 2013).

On another note, Schalla & Stengel demonstrated the role of Lactobacillus in body weight reduction by extrapolating the negative action Lactogen has on ghrelin mRNA. The liability of Lactobacillus alteration can thus be insinuated as a factor in re-obesity after bariatric procedures. (Queipo-ortun et al. 2013; Leeuwendaal et al. 2021).

Prebiotics are non-digestible dietary components, that are mostly polysaccharides which have the ability to selectively stimulate the development and/or activity of microbiota. This particularly includes lactobacilli and bifidobacterial, and results in beneficial effects on the host's energy balance. They alter the microbiota to restore and/or sustain eubiosis or normobiosis, which in turn reduces the risk of dysbiosis and related gut and systemic illnesses. The majority of fermentable dietary fibers, especially the non-digestible oligosaccharides such as resistant starch, galacto-oligosaccharides, and fructo-oligosaccharides (e.g., inulin), which are present in many foods, have demonstrated the ability to cause changes within the gut flora. They also boost GLP-1 and PYY levels and lower ghrelin release, which leads to increased satiety and decreased appetite. In the large intestine, prebiotics are processed by bacteria into metabolically active SCFA. The SCFA, which includes acetate, propionate, and butyrate, is thought to mediate, at least in part, the anti-obesogenic actions of prebiotics (Amabebe et al. 2020; Nogueira et al. 2022).

While the relationship of microbiota to ghrelin and other orexigenic hormones is definite, the mediators of this relationship remain elusive. Ghrelin affinity in the hypothallus is increased, as mentioned earlier by the mammalian target of rapamycin (mTOR). Interestingly, there is increasing evidence that mTOR signaling is modified by dysbiosis which can explain the putative effects of dysbiosis on orexigenic stimuli.

Therapeutic implications and promising therapies to prevent re-obesity

Duration of dieting to abolish obesogenic memory

Leeming et al. discusses the present understanding of the length of time needed for a dietary intervention to affect the gut microbiome. A beneficial effect on gut bacteria can be determined as significant if it results in a new state of balance or homeostasis within the gut flora (Leeming et al. 2019).

Short versus long term dietary exposure

Short term dietary exposure and the gut microbiome A longitudinal study, conducted by David et al., involved the daily investigation of the gut microbiota among two human individuals across the duration of one year. They noticed that the changes in fiber intake were positively correlated with an abundance change in 15% of the microbial community; this change was observed the following day. However, regarding the duration needed of any intervention to results in complete and total change in the core microbial profile is still not determined. Among humans, the response to dietary intervention can result in rapid transitory changes among the gut microbiota in as early as the first 24 h period (David et al. 2014).

Long-term dietary exposure and the gut microbiome (Long-term studies that are predominantly epidemiological and over a longer period (36 months).

Long-term diet–microbiome relationships is assessed through epidemiological studies that rely on capturing a persons' typical diet using questionnaires like food frequency questionnaires (FFQs).

Evidence suggests the effect of habitual diet in the formation of the microbial community. Studies suggest that gut microbiota is altered by certain diets, especially the types of diets that contain substrates that provide a competitive environment for the gut microbiota (Leeming et al. 2019).

For example, after a 2-year study, it was found that consumption of either a Mediterranean diet or a low-fat diet helped to partially restore the loss of key bacterial groups in all 33 participants with obesity and different levels of metabolic dysfunction (Haro et al. 2017).

Based on the current evidence available, although we have a general understanding of how diet affects the gut microbiome, more research is still needed to learn about the specific duration of the effects of different dietary components. There is a lack of long-term studies in humans and follow-up studies of short-term dietary interventions (Yang et al. 2019).

Use of prebiotics and synbiotics for weight loss in a low-carbohydrate high-protein diet

Despite the associated weight loss, the altered gut microbiota caused a rise in the bacterial fermentation of undigested proteins. As a result of this, harmful health effects including genotoxicity and cancer-associated metabolites were more evident. Synbiotics supplements were useful in combatting those undesirable consequences, and resulted in a less proteolytic environment as they contain prebiotics and assist with the growth of the beneficial intestinal bacteria (Sergeev et al. 2020)

Synbiotics were administered for a period of 3 months in a study by Sergeev et al. They contained Galactooligosaccharides, Bifidobacterium, as well as Lactobacillus acidophilus. These exact strains were developed in abundance, as a result, among the gut microbiota. Prebiotics improve insulin sensitivity and lipid metabolism, as proved by lowered total plasma cholesterol and triglycerides in a previously conducted meta-analysis. Strains linked to chronic inflammation and obesity, such as Prevotella and Gardnerella, were reduced. These findings signaled that the host's metabolism and microbiota balance could be improved using synbiotics, but they are equally dependent on the host's long-term diet, fiber intake and microbiota composition. (Sergeev et al. 2020).

Autologous fecal microbiota transplant (aFMT) effect on microbiota and weight loss/regain following isocaloric Mediterranean/green-Mediterranean diet

A trial conducted by Rinott et al. that included 90 participants that were either abdominally obese or had dyslipidemia, which were categorized randomly into groups that consumed healthy diets in the form of isocaloric Mediterranean diet and Green-Mediterranean diets, found that, the Green-Mediterranean that induced a significant change in microbiome composition, as well as in the preservation of weight-loss-associated specific bacteria and microbial metabolic pathways (mainly microbial sugar transport). In mice, however, during the weight-loss phase, it was found that Mankai-modulated aFMT compared to control diet aFMT, resulted in the prevention of weight regain with evidence of enhanced glucose tolerance during a HFD-induced regain phase (all, $P < 0.05$). Ultimately, in order to maintain glycemic control and achieve weight-loss, autologous fecal microbiota transplantation (aFMT) can be used to collect specific microbiome signatures during the weight-loss phase for administration during the regain phase (Rinott et al. 2021).

Oral microbial transplantation, the future through dentistry

Despite its beneficial effects, FMT has some drawbacks including the way it is delivered into patients, which is done via nasojejunal tube and colonoscopy, and this has been associated with high fevers and elevated C-reactive protein (CRP) when nasojejunal tube was used. On the other hand, perforation, bleeding, and anesthesia-associated symptoms have been observed while using colonoscopy (AbdelMassih et al. 2021). So, the future is with the oral microbial transplantation (OMT) as it exhibited impediments and side effects, which occurred with FMT. It was also found that OMT exhibit characteristics that can make it be considered as a vital tool of probiotic therapies essential for the treatment of the array diseases associated with microbial dysbiosis (Pozhitkov et al. 2015). Pozhitkov was the first to propose OMT technique steps, which include the following: (Pozhitkov et al. 2015).

(I) Obtaining supra-gingival plaque from a caries-free donor (it is preferred that the donor be related to the recipient of OMT).
(II) Collected plaque preserved in saline, and then.
(III) Transplanted using a nylon swab on to the teeth of the recipient.

Studies have noted that OMT has very promising results that may be more superior to that of using FMT. So clinical trials are still needed to prove its feasibility and success (AbdelMassih et al. 2021).

Conclusions

With obesity rates increasing every year and with many failed attempts of long-term weight loss ending into re-obesity, multiple hypotheses were brought to the table regarding the different mechanisms of re-obesity which is led by not only the behavioral and psychological factors but also other significantly important factors including the role of persistent insulin, Leptin resistance and continued affinity of the CNS to ghrelin. The latter hormonal mechanisms are collectively termed obesogenic memory and we proved in our article that they are largely mediated by persistence of dysbiotic strains in the gut and oral cavity. Duration of diet, use of synbiotics and prebiotics as well as fecal microbial and the newest oral microbial transplantation can play a pivotal role in reducing the rates of re-obesity and in erasing obesogenic memory (Fig. 1 summarizes the main hormonal mechanisms underlying obesogenic memory).

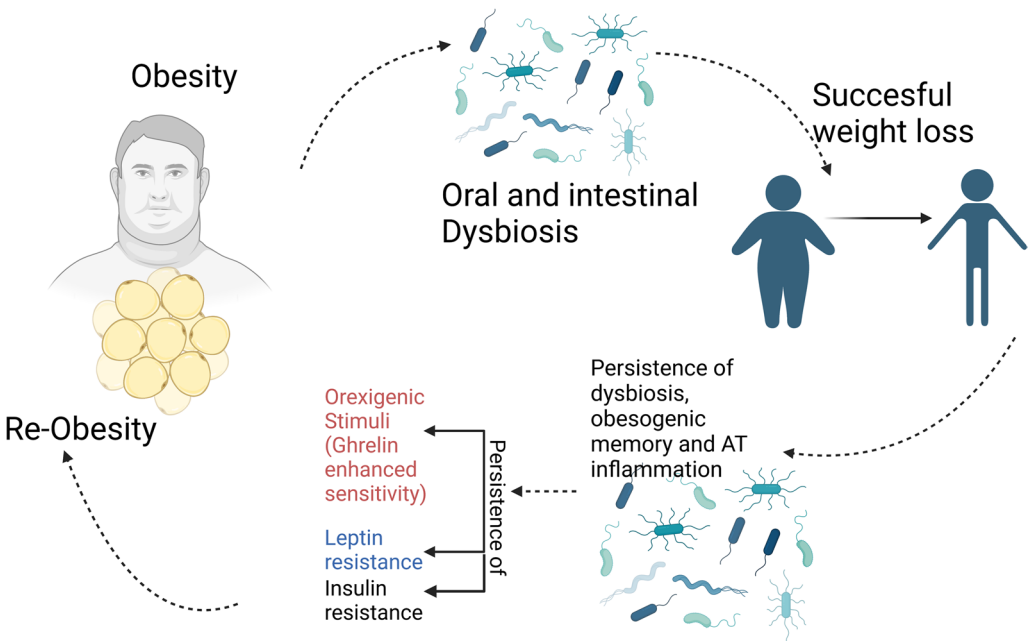

Fig. 1 The role of microbiota in mediating Re-obesity. *Abbreviations* AT: Adipose tissue. Created with BioRender.com

Abbreviations

ACC2	Acetyl co-A carboxylase 2
aFMT	Autologous fecal microbiota transplant
AT macrophages	Adipose tissue macrophages
Atp5a1	Adenosine triphosphate synthase subunit alpha
B. animalis	Bifidobacterium animalis
B. dentium	Bifidobacterium dentium
B. longum	Bifidobacterium longum
BMI	Body mass index
BsS-RS06550	Genetically modified Bacillus subtilis SCK6 strain
C. coccoides	Clostridium coccoides
CD 14	Cluster of differentiation14
CD4	Cluster of differentiation 4 a co receptor for t helper receptor
CDI	Clostridium difficile infection
Cox 5a	Cytochrome c oxidase subunit 5a
Cpt1B	Carnitine palmitoyltransferase 1B
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CV	Conventional
E. rectale	Eubacterium rectale
F. nucleatum	Fusobacterium nucleatum
F. prausnitzii	Faecalibacterium prausnitzii
FFQs	Food frequency questionnaires
FMT	Fecal microbial transplantation
GF	Germ-free
GHSR1a	Growth hormone secretagogue receptor 1a
GI	Gastro-intestinal
GIT	Gastrointestinal tract
GLP-1	Glucagon-like peptide 1
GLUT-4	Glucose transporter type 4
GLUTs	Glucose transporter
HBA1B	Hemoglobin A1-B
HF	High fat
HFD	High-fat diet
HGF	Hepatocyte growth factor
HPGDs	Hematopoietic prostaglandin D synthase
IBD	Inflammatory bowel disease
ICAM1	Intercellular-adhesion molecule 1
IgG	Immunoglobulin G
IL-10	Interleukin 10
IL-1b	Interleukin-1 beta
IL-2	Interleukin 2
IL-6	Interleukin 6
L. gasseri	Lactobacillus gasseri
LEP-R	Leptin receptor
LGG	Lactobacillus rhamnosus GG
LPs	Lipopolysaccharides
MCFA	Medium chain fatty acids
mRNA	Messenger ribonucleic acid
mTOR	Mammalian target of rapamycin
NFD	Normal-fat diet
NF-KB	Nuclear factor kappa B
NOD 1&2	Nucleotide oligomerization domain 1&2
OMT	Oral microbial transplantation
P. intermedia	Prevotella intermedia
PCR	Polymerase chain reaction
PDX1	Pancreatic and duodenal homeobox 1
PG or *P. gingivalis*	Porphyromonas gingivalis
PGD2	Prostaglandin D2
PGN	Peptidoglycan
PPAR-γ	Peroxisome proliferator activated receptor gamma
PREDIM	Predicted M insulin sensitivity index
PTGDs	Prostaglandin D2 synthase
PYY	Peptide YY
rCDI	Recurrent clostridium difficile infection
RYGB	Roux-en-y gastric bypass
SCFAs	Short chain fatty acids
SCK6-BsS-RS06550	Bacillus strains
SGLTs	Sodium-glucose co-transporter protein
STAT3	Signal transducer and activator of transcription 3
Streptococcus spp.	Streptococcus species
TLRs	Toll-like receptors
TNF	Tumor necrosis factor
Veillonella spp.	Veillonella species

Acknowledgements
To anyone who goes the extra mile to make another one happy, or fulfilled, that's what life is lived for.

Author contributions
AA, ME, MG, MA participated in conception of the idea of the manuscript. AA, ME, MG, NA, SY, BA, JA, EA, AM, AE, BG, DS, HM, HL, MS, ND, OY, RJ, RAA, RS, ROA, YE, RH, MA Participated in collection of data. AA, ME, MG, NA, SY, BA, JA, EA, AM, AE, BG, DS, HM, HL, MS, ND, OY, RJ, RAA, RS, ROA, YE, RH, MA Participated in drafting of the manuscript. AA, ME, MG proofread and revised the final manuscript. All authors have read and approved the final manuscript

Funding
This research received no specific grant from any external or internal funding agency, commercial or not-for-profit sectors.

Availability of data and materials
Not applicable for this study.

Declarations

Ethics approval and consent to participate
Not applicable for this study.

Consent for publication
Not applicable for this study.

Competing interests
The authors declare that they have no competing interests, financial or otherwise.

Author details
[1]Pediatric Cardiology Unit, Department of Pediatrics, Faculty of Medicine, Cairo University, P.O. BOX 12411, Cairo, Egypt. [2]Cardiac Sciences' Department, Pediatric Cardiology Division, Sheikh Khalifa Medical City, Abu Dhabi, UAE. [3]Faculty of Dentistry, New Giza University, Giza, Egypt. [4]Faculty of Dentistry, Galala University, Suez, Egypt. [5]Faculty of Medicine, New Giza University, Giza, Egypt. [6]Faculty of Medicine, Cairo University, Cairo, Egypt. [7]Faculty of Medicine, Mansoura University, Mansoura, Egypt. [8]Faculty of Medicine, Ain Shams University, Cairo, Egypt. [9]Faculty of Medicine, Alexandria University, Alexandria, Egypt.

Received: 7 July 2023 Accepted: 1 August 2023
Published online: 15 August 2023

References

AbdelMassih A et al (2021) The forgotten oral microbial transplantation for improving the outcomes of COVID-19. N Microbes N Infect 43:100923
Alard J et al (2021) Multiple selection criteria for probiotic strains with high potential for obesity management. Nutrients 13(3):713
Amabebe E, Robert FO, Agbalalah T, Orubu ESF (2020) Microbial dysbiosis-induced obesity: role of gut microbiota in homoeostasis of energy metabolism. Br J Nutrit 123(10):1127–1137
Anastasiou CA, Karfopoulou E, Yannakoulia M (2015) Weight regaining: from statistics and behaviors to physiology and metabolism. Metabolism 64(11):1395–1407
Asma GB et al (2021) Association between the gut and oral microbiome with obesity. Anaerobe 70:102248
Baothman OA et al (2016) The role of gut microbiota in the development of obesity and diabetes. Lipids Health Dis 15:1–8
Blasco-Baque V et al (2016) Periodontitis Induced by porphyromonas gingivalis drives periodontal microbiota dysbiosis and insulin resistance via an impaired adaptive immune response. Gut 66(5):872–885

Blaszczak AM et al (2020) Obesogenic memory maintains adipose tissue inflammation and insulin resistance. Immunometabolism 2(3):1–18
Burke LE, Wang J, Sevick MA (2011) Self-monitoring in weight loss: a systematic review of the literature. J Am Dietet Assoc 111(1):92–102
Caricilli AM, Saad MJA (2013) The role of gut microbiota on insulin resistance. Nutrients 5:829–851
Carvalho BM et al (2012) Modulation of gut microbiota by antibiotics improves insulin signalling in high-fat fed mice. Diabetologia 55:2823–2834
Chait A, Den Hartigh LJ (2020) Adipose tissue distribution, inflammation and its metabolic consequences, including diabetes and cardiovascular disease. Front Cardiovasc Med 7(February):1–41
Cheng Y-C, Liu J-R (2020) Effect of lactobacillus rhamnosus gg on energy metabolism, leptin resistance, and gut microbiota in mice with diet-induced. Obesity 12(9):2557
David LA et al (2014) Host lifestyle affects human microbiota on daily timescales. Genome Biol 15:1–15
El Ansari W, Elhag W (2021) Weight regain and insufficient weight loss after bariatric surgery: definitions, prevalence, mechanisms, predictors, prevention and management strategies, and knowledge gaps-a scoping review. Obes Surg 31(4):1755–1766
Esteve E, Ricart W, Ferna J (2011) Gut microbiota interactions with obesity, insulin resistance and type 2 diabetes: did gut microbiote co-evolve with insulin resistance? Curr Opin Clin Nutrit Metab Care 14(5):483–490
Everard A et al (2011) Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice. Diabetes 60(November):2775–2786
Foley KP et al (2020) Gut microbiota impairs insulin clearance in obese mice. Mol Metab 42(August):101067
Forman EM et al (2017) Ecological momentary assessment of dietary lapses across behavioral weight loss treatment: characteristics, predictors, and relationships with weight change. Physiol Behav 176(1):139–148
Freire CC et al (2021) Associations between binge eating, depressive symptoms and anxiety and weight regain after roux - en - y gastric bypass surgery. Eat Weight Disord Stud Anorexia Bulimia Obes 26:191–199
Hall KD, Kahan S (2018) Maintenance of lost weight and long-term management of obesity. Med Clin 102:183
Haro C et al (2017) Consumption of two healthy dietary patterns restored microbiota dysbiosis in obese patients with metabolic dysfunction. Mol Nutr Food Res 1700300:1–9
Heiman ML, Greenway FL (2016) A healthy gastrointestinal microbiome is dependent on dietary diversity. Mol Metab 5(5):317–320
Hernandez-Carretero A et al (2018) Obesity-induced Changes in lipid mediators persist after weight loss. Int J Obes 42(4):728–736
Hosoi T et al (2015) Possible involvement of 15-Deoxy-Δ12,14-prostaglandin J2 in the development of leptin resistance. J Neurochem 133:343–351
Klopp P et al (2011) Intestinal mucosal adherence and translocation of commensal bacteria at the early onset of type 2 diabetes: molecular mechanisms and probiotic treatment. EMBO Mol Med 3:559–572
Leeming ER, Johnson AJ, Spector TD, Le Roy CI (2019) Effect of diet on the gut microbiota: rethinking intervention duration. Nutrients 11(12):1–28
Leeuwendaal NK, Cryana JF, Schellekens H (2021) Gut peptides and the microbiome: focus on ghrelin. Curr Opin Endocrinol Diabet Obes 28:243
Li J, Guo C, Jianye W (2019) 15-Deoxy-Δ- 12,14 -Prostaglandin J2 (15d-PGJ2), an endogenous ligand of PPAR- Γ: function and mechanism. PPAR Res 2019:1–10
MacLean PS, Bergouignan A, Cornier MA, Jackman MR (2011) Biology's response to dieting: the impetus for weight regain. Am J Physiol Regul Integr Compar Physiol 301:3
Martins L et al (2012) Hypothalamic MTOR signaling mediates the orexigenic action of ghrelind. PLoS ONE 7(10):e46923
Martins C, Dutton GR, Hunter GR, Gower BA (2020) Revisiting the compensatory theory as an explanatory model for relapse in obesity management. Am J Clin Nutrit 112:1170–1179
Mervish NA et al (2019) Associations of the oral microbiota with obesity and menarche in inner city girls. J Child Obes 04(01):1–10
Nogueira AVB et al (2022) Effect of bacterial infection on ghrelin receptor regulation in periodontal cells and tissues. Int J Mol Sci 23:6
Palleja A et al (2016) Roux-En-Y gastric bypass surgery of morbidly obese patients induces swift and persistent changes of the individual gut microbiota. Genome Med 8(1):1–13
Pozhitkov AE et al (2015) Towards microbiome transplant as a therapy for periodontitis : an exploratory study of periodontitis microbial signature contrasted by oral health, caries and edentulism. BMC Oral Health 15:1–11
Queipo-ortun I, Marı L, Murri M (2013) Gut microbiota composition in male rat models under different nutritional status and physical activity and its association with serum leptin and ghrelin levels. PLoS ONE 8:e65465
Rinott E et al (2021) Effects of diet-modulated autologous fecal microbiota transplantation on weight regain. Gastroenterology 160(1):158–173
Rubino F et al (2020) Joint international consensus statement for ending stigma of obesity. Nat Med 26(April):485
Santos I et al (2016) Prevalence of personal weight control attempts in adults: a systematic review and meta-analysis. Obes Rev 18(5):32
Schalla MA, Stengel A (2020) Effects of microbiome changes on endocrine ghrelin signaling – a systematic review. Peptides 133:170388
Schertzer JD, Lam TKT (2020) Peripheral and central regulation of insulin by the intestine and microbiome. Am J Physiol Endocrinol Metab 320:1–25
Sergeev IN, Aljutaily T, Walton G, Huarte E (2020) Effect of synbiotic supplement on human gut microbiota, body composition and weight loss in obesity. Nutrients 12(1):222
Sharma S, Tripathi P (2019) Gut microbiome and type 2 diabetes: where we are and where to go? J Nutr Biochem 63:101–108
Stockman M, Thomas D, Burke J, Apovian CM (2018) Intermittent fasting: is the wait worth the weight? Curr Obes Rep 7:172–185
Strohacker K, McCaffery JM, Maclean PS, Wing RR (2014) Adaptations of leptin, ghrelin or insulin during weight loss as predictors of weight regain: a review of current literature. Int J Obes 38(3):388–396
Thaiss CA et al (2016) Persistent microbiome alterations modulate the rate of post-dieting weight regain. Nature 540(7634):544–551
Thanakun S, Izumi Y (2016) Effect of periodontitis on adiponectin, C-reactive protein, and immunoglobulin G against porphyromonas gingivalis in Thai people with overweight or obese status. J Periodontol 87(5):566–576
Tolvanen L, Christenson A, Surkan PJ, Lagerros YT (2022a) Patients' experiences of weight regain after bariatric surgery. Obes Surg 32(5):1498–1507
Tolvanen L, Christenson A, Surkan PJ, Trolle Y (2022b) Patients' experiences of weight regain after bariatric surgery. Obes Surg 32:1498–1507
Van Baak MA, Mariman ECM (2019) Mechanisms of weight regain after weight loss — the role of adipose tissue. Nat Rev Endocrinol 37(2015):2015–2017
Vila G et al (2007) Bacterial endotoxin induces biphasic changes in plasma ghrelin in healthy humans. J Clin Endocrinol Metabol 92(10):3930–3934
Yang B et al (2019) Assessing the influence of dietary history on gut microbiota. Curr Microbiol 15:237–247
Yao H et al (2020) Effects of gut microbiota on leptin expression and body weight are lessened by high-fat diet in mice. Br J Nutrit 124:396–406
Zhang Y, Wang X, Yan F (2018) Human oral microbiota and its modulation for oral health yangheng. Biomed Pharmacother 99:883–893

Publisher's Note