Post-dieting weight gain: the role of persistent microbiome changes

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\textbf{The weight cycling paradox}

The prevalence of obesity is globally increasing and is associated with a reduction in life expectancy and quality of life worldwide \cite{1}. Obesity confers a major risk factor for the development of metabolic syndrome, consisting of co-occurring pathologies such as Type 2 diabetes, cardiovascular diseases and nonalcoholic fatty liver. Dieting is one of the major approaches to target obesity. Even a modest reduction in weight can ameliorate Type 2 diabetes, hypertension and the risk for development of cardiovascular diseases \cite{2}. Nonetheless, many dietary approaches fail due to difficulties in long-term post-dieting weight maintenance, caused by rapid weight regain that initiates repeated cycles of weight loss and regain (typically referred to as ‘yo-yo’ dieting). Weight cycling has been suggested to have detrimental effects on energy homeostasis and other metabolic pathologies \cite{3}, but the mechanisms initially driving this phenomenon remain to be fully elucidated \cite{4}. Weight gain after intentional weight loss was found to be independent of genetic background \cite{5}, suggesting that behavioral and environmental factors are critical in mediating the frequent failure to maintain a reduced weight over time.

Typically, during weight loss, a proportion of the reduced weight stems from the loss of fat-free mass. Fat-free mass, in turn, is the best determinant of 24-h energy expenditures and explains the large interindividual variability in energy expenditure observed in the population \cite{6}. A direct corollary from this association is that weight loss is frequently accompanied by a reduction in the basal metabolic rate, pointing toward a potential explanation for why the organism is more vulnerable to weight gain after weight loss compared with a stably maintained weight and energy expenditure. It has been suggested that exercise might be an efficient way out if this dilemma, since it counteracts the loss in fat-free mass and restores the basal metabolic rate. However, the mechanistic details and the full scope of this effect remain

\begin{itemize}
\item cycling obesity
\item flavonoids
\item microbiome
\item persistence
\item yo-yo effect
\end{itemize}

“…many dietary approaches fail due to difficulties in long-term post-dieting weight maintenance, caused by rapid weight regain that initiates repeated cycles of weight loss and regain…”

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Microbiome persistence in recurrent obesity
Studies in mice have recently highlighted an additional player in the pathophysiology of obesity and associated metabolic complications: the community of commensal microorganisms residing in the GI tract. The gut microbiome of obese mice was found to feature a shift toward a higher capacity of energy harvest [10]. Studies in rodents and humans have shown reduced compositional diversity of the gut microbiome in obesity and its associated morbidities [11,12]. Interestingly, this altered microbiome was not only accompanying an obese state of the host but itself contained obesogenic properties that were transmissible to germ-free mice by fecal transplantation, leading to weight gain and increased body mass compared with germ-free mice transplanted with microbiome from lean donors [10,13–14].

We have recently discovered that although many of the structural alterations of the microbiome are reversible upon weight normalization after obesity, certain elements of the obesity-associated composition and function persist after dieting, even when the majority of metabolic parameters have already normalized to preobesity levels [15]. One such persistent characteristic of the microbiome that is enhanced during obesity and persists during the post-dieting phase is the enzymatic conversion of flavonoids, resulting in reduced levels of these plant-derived dietary metabolites in the intestine. Flavonoids, however, are potent stimuli of host energy expenditure [16], suggesting that diminished post-dieting levels of intestinal flavonoids might contribute to the reduced basal metabolic rate after weight loss. Indeed, we found that the flavonoids apigenin and naringenin stimulate the expression of UCP-1 in brown adipose tissue and enhance energy expenditure in mice [15]. Consequently, treatments that elevate the levels of intestinal flavonoids, including antibiotics-mediated depletion of flavonoid-metabolizing commensals, replenishment of a preobesity community by fecal microbiome transplantation and dietary supplementation of flavonoids promoted energy expenditure and ameliorated secondary weight gain after dieting. Notably, the post-dieting microbiome composition was sufficiently informative for the accurate prediction of individual weight regain based solely on microbiome data, suggesting that microbiome features might serve as powerful biomarkers for the diagnosis and individual risk assessment for recurrent obesity.

A similar persistence phenomenon has recently been described with regard to adipose tissue inflammation, another hallmark of the obese state. Increased adiposity is associated with adipose tissue remodeling that is characterized by elevated numbers and altered activation profile of immune cells residing between adipocytes. Of note, this immune cell infiltration and expression of proinflammatory cytokines is not fully reversible upon weight reduction and persists despite metabolic normalization [17,18]. Whether persistence in adipose tissue inflammation is functionally coupled to postobesity microbiome persistence remains to be determined, but recent studies have suggested a link between intestinal microbial colonization, Toll-like receptor (TLR) signaling and the aggravation of adipose tissue inflammation [19], indicating a potential role for the microbiome in maintaining inflammatory processes in adipose tissue after successful reversal of obesity.

The physiological role of microbiome persistence
The stable obesogenic property conferred by the microbiome of obese donors upon transplantation to a lean recipient [10,14] seems to be in contradiction with the rapid adaptation of the composition and function of the intestinal microbiome to abrupt changes in diet [20–22]. The finding of microbiome persistence after a dietary challenge might provide a potential explanation for this discrepancy, since it suggests that the intestinal microbial
community is shaped by the past history of dietary encounters and does not fully return to a ‘naïve’ state. Indeed, a subset of gut bacteria exhibit hysteretic patterns when exposed to bouts of rapidly changing diets [22]. Microbial hysteresis has also been observed over longer time frames. This has been exemplified by experiments in germ-free mice colonized with human microbiota and exposed to defined experimental diets, which revealed that the dietary history of the respective donor influences the extent to which the microbiome responds to a new dietary challenge in the murine recipient [23]. The refractory properties of the microbiome after prolonged dietary exposure can even persist across generations, as has been found in mice harboring a human microbiome and fed a diet deficient in plant polysaccharides [24]. Similarly, the maternal diet might shape the infant long-term microbiome in humans [25].

It thus seems that the microbiome at any given time point can be interpreted as a ‘memory-like’ function of its past dietary influences, and that these past influences determine its responsiveness to future exposures. What is the physiological relevance of this phenomenon? In the case of microbial alterations induced by a high-fat diet, post-dieting microbiome persistence renders the host more susceptible to exacerbated weight regain, but only upon re-exposure to the obesogenic diet. Thus, while the initial property of the obesity-associated microbiome to confer weight gain is lost upon weight normalization, the memory-like properties generate a ‘window of susceptibility’ for weight regain that lasts for the duration of microbiome persistence [15]. Although the length of this time window remains to be determined and is likely dependent on the dietary context and duration of past dietary exposure, it might offer a microbiome-based mechanistic explanation to the enhanced tendency in humans to regain weight promptly after successful dieting.

From an evolutionary perspective, such memory-like microbiome characteristics might have potentially be purposed to contribute to the stability and persistence of host metabolism over prolonged periods of time. Beneficial effects of such memory characteristics might include the buffering of environmental noise, thereby maintaining homeostatic physiological functions of the host while avoiding overly fluctuating responses to incidental nutritional or environmental signals. However, in contexts in which the host induces erratic changes in its physiology, exemplified by cycling weight gain and dieting, this may result in the refractory state of the microbiome preventing the return of the host toward baseline metabolic homeostasis and thus predispose to exaggerated metabolic responses in ensuing weight gain cycles. A plausible, but currently speculative explanation might be that coevolution of the host and its microbiome favored long-term stabilization of metabolic responses in face of a generally stable environment, withstanding short-term alterations in dietary conditions, while not anticipating the rapid behavioral changes that characterize human weight management in the past century.

**Outlook: microbiome-targeted strategies counteracting post-dieting weight regain**

The findings described here point toward a critical role of the post-dieting phase in preventing exacerbated and accelerated weight regain. Strategies aimed at increasing the basal metabolic rate, such as prolonged exercise, might be complemented with potential microbiome-based interventions to further impact host energy expenditure. The recent realization that the microbiome is involved in regulating brown adipose tissue biology, and that intestinal flavonoid levels might be centrally involved in this regulatory pathway [15, 26], provides a rationale for modulating post-dieting energy expenditure through alterations of the composition and function of the intestinal microbiome. More importantly, flavonoids might serve in this case as ‘post-biotics’, microbiota-modulated metabolites with a beneficial effect on the host [27], which might help to bypass the large interindividual variability in microbiome compositions found in the human population.

Several important insights need to be established in human trials before such microbiome-targeted strategies can be therapeutically implemented: the role of persistent postobesity microbiome alterations in humans, the importance of such persistent microbiome effects in post-dieting weight regain, the duration and pervasiveness of postobesity signature in the human microbiome and the role of flavonoids in human weight management. Future research is warranted to address these open questions, which are critically important on the path toward a rational approach to preventing post-dieting weight regain. First results from large human cohort studies including more than 100,000 individuals monitored over up to...
24 years support a potential beneficial role for flavonoids in weight management [28], raising the hope that the first piece of the recurrent obesity puzzle might be in place.

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