Obesity: The allostatic load of weight loss dieting

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A R T I C L E   I N F O

Article history:
Received 30 March 2011
Received in revised form 11 May 2011
Accepted 16 May 2011

Keywords:
Energy balance
Homeostasis
Pollutant
Sleep duration
Mental work

A B S T R A C T

The obesity epidemic that is prevailing in most countries of the world is generally attributed to the increased amount of opportunities to be in positive energy balance in a context of modernity. This obviously refers not only to sedentariness and unhealthy eating that may dominate life habits of many individuals but also to unsuspected non-caloric factors which produce discrete allostatic changes in the body. In this paper, the focus is put on the impact of some of these factors with the preoccupation to document the allostatic burden of weight loss. Thus, beyond the fact that modernity favors opportunities to eat much and not to be active, the proposed conceptual integration leads to the conclusion that a modern lifestyle makes weight loss more difficult for obese individuals. In addition to the natural effects of weight loss favoring resistance to lose fat, a lifestyle promoting shorter sleep duration and more cognitive demand produces allostatic changes that may interfere with weight loss. The case of persistent organic pollutants (POPs) is also discussed as an example of the potential detrimental effects of a contaminated environment on metabolic processes involved in the control of energy expenditure. Taken together, these observations suggest that weight loss is more than ever a search for compromise between its metabolic benefits and its allostatic effects promoting body weight regain.

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1. The RQ–FQ balance

Variations in fat mass have been shown to influence fat mobilization and oxidation. Many years ago, Bjorntorp et al. [4] documented the existence of a relationship between the expansion of fat mass and free-fatty acid levels and turnover. In a subsequent study by Schutz et al. [5], it was shown that a significant relationship exists between variations in fat mass and those in resting lipid oxidation. Specifically, these authors deduced from their cross-sectional observations that a change of 10 kg in fat mass was positively related to a change of 20 g per day in resting lipid oxidation. These findings thus imply that fluctuations in body fat are associated with changes in fat oxidation that should normally result in a new fat balance, i.e. a threshold of equilibrium between fat intake and oxidation at a reduced level, following a weight loss program.

The demonstration by Flatt et al. [6] that fat oxidation is not responsive to an acute increase in fat intake represented the cornerstone of the justification integrating the above referenced observations into an allostatic mechanism that was called the RQ–FQ balance [7]. In brief, this notion stipulates that energy balance occurs in both animals and humans when macronutrient balance is achieved. This balance represents the equilibrium between respiratory quotient (RQ), a marker of the composition of the fuel mix oxidized, and food quotient (FQ) which is an indicator of the macronutrient composition of the diet. This concept also considers each macronutrient component of the substrate balance, i.e. protein, carbohydrate and fat balances. As described by Flatt [8], amino acid and glucose oxidation...
rates are acutely adjusted to the amounts of protein and carbohydrate consumed. Since this mechanism does not seem to exist for fat metabolism [6], fat oxidation is primarily determined by the gap between daily energy expenditure and the amount of energy ingested as carbohydrates and proteins [8]. Taken together, these observations emphasize the relative vulnerability of fat balance to substantial fluctuations in energy/fat intake due to its inaccurate regulation. In fact, as indicated above, this regulation is performed on a more long term basis compared to proteins and carbohydrates and it seems to partly operate in proportion to changes in body fat mass.

The RQ–FQ concept is important for health professionals relying on weight loss dieting to modify body composition in obese individuals. Indeed, this concept implies that fat oxidation decreases over time proportionally with fat loss and that a threshold will occur beyond which it will not be possible to maintain fat balance even if the patient strictly adheres to a fat-reduced diet. In other words, “fat burning” in the weight-reduced obese individuals might become sufficiently low not to permit an equilibrium between fat intake and fat oxidation. In such a context, the spontaneous question to be addressed pertains to the possibility to compensate for the decreased ability of a reduced fat mass to support lipid oxidation. As described by Flatt [7], exercise then becomes the primary lifestyle modality to stimulate lipid metabolism. Indeed, physical activity can acutely increase fat oxidation [9] and can contribute to maintain a reduced body weight up to certain limits which are fixed by the balance between the enhancing effect of exercise and the reducing effect of fat loss on lipid mobilization/oxidation. For instance, ex-obese long distance runners were able to maintain a mean weight loss of 39 kg by mostly relying on an exercise program including 90 km of running per week [10]. At that time, their demanding training program was at best allowing the maintenance of their lean sedentary controls. This demanding training program was at best allowing the maintenance of their low energy intake. However, our estimates of daily intake data revealed that at resistance to lose fat, they were mainly justifying the need to improve the metabolic profile of the obese, including the decrease of hyperglycemia towards a normal glycemic state. However, precise regulation of plasma glucose levels also imposes the prevention of hypoglycemia. In this regard, Mayer [18] proposed a glucostatic theory of food intake control that is based on the idea that reduced glucose utilization in the brain represents a stimulus that is detected by glucosensitive brain sites and that can influence appetite sensations. In addition, Mayer [19] argued that this theory could account for short term variations in hunger and food intake whereas he proposed that a lipostatic mechanism, such as that described above, could explain long term variations in energy balance. In a recent paper [20], we have reviewed evidence pertaining to the clinical implications of this theory, with a particular focus on body weight variations. Although Mayer’s hypothesis has some limitations, it at least provided us a conceptual basis for further investigations by our research group.

The follow-up of subjects tested in phases 2 and 3 of the Quebec Family Study allowed a prospective analysis of the relationship between glucose concentrations at the end of an oral glucose tolerance test (OGTT) and changes in body weight over a 6-year follow-up period [21]. In this study, we observed that glucose concentrations at 120 min of the OGTT were negatively correlated with weight gain over time, indicating that the proneness to reactive hypoglycemia was predictive of a more pronounced weight gain in the long run. We also tested obese individuals subjected to a 15-week weight-reducing program. Again, the focus of this study was the association between glycemic stability and weight gain which was recorded over a mean follow-up of 81 weeks after the weight loss dieting treatment. The results showed that the glucose area below fasting values (a standardized index of reactive hypoglycemia during an OGTT) increased significantly after weight loss and was significantly correlated with weight regain [21]. To summarize, our clinical experience revealed that reduced glucose concentrations at the end of an OGTT were correlated with weight gain over time and with the amount of weight regained after weight loss. Although these results tend to support Mayer’s hypothesis, it might also be attributed to endocrine changes in response to food/glucose intake that induced mild hypoglycemia and promoted weight gain. Because insulin generally promotes fat storage, postprandial hyperinsulinemia might also explain weight gain in individuals experiencing mild hypoglycemia.

We have also performed several studies to evaluate the impact of weight loss up to a resistance threshold to fat loss on glucose homeostasis. In the first study of this series, obese women were subjected to an intervention based on the RQ–FQ concept, i.e. a low fat diet and an exercise program, up to the occurrence of fat loss plateau [12]. At that time, their health-related metabolic profile was normalized even if they still displayed a BMI typical of an obese state. Furthermore, the examination of their glucose curve during the OGTT revealed a proneness to mild hypoglycemia at the end of the intervention. The repetition of this treatment approach in both obese men and women who were also tested up to resistance to lose fat
confirmed the manifestation of reactive hypoglycemia following a substantial fat loss [22].

To further validate the hypothesis of an increased risk of reactive hypoglycemia promoted by weight loss dieting, we designed a sequential therapeutic approach requiring the testing of male obese subjects at every 5 kg of weight loss and at resistance to fat loss. According to our previous experience, the treatment was based on low fat diet and exercise. This protocol induced weight loss in the participants who became resistant to lose fat after an 11 kg weight loss [23]. As expected, reactive hypoglycemia at the end of the OGTT was accentuated following the program. In addition, we used this protocol to evaluate some clinical implications of the allostatic changes found in this study. As illustrated in Fig. 1, changes in the area of plasma glucose below basal levels were related to those of the Beck Depression Inventory score. Apart from an increase in depression symptoms as a result of weight loss dieting [23], recent results have shown that dieting increases psychological stress and cortisol production in women [24], suggesting that we may have to rethink recommending dieting as a means of improving health.

These observations demonstrate that weight loss up to the point of apparent resistance to further lose fat disrupts glucose homeostasis in a way that promotes weight regain in previously obese individuals. This increased predisposition to hypoglycemia might explain the state of hyperglucagonemia that was found to persist in weight-reduced obese individuals [25]. Moreover, recent data of the Quebec Family Study showed that an increase in the area of plasma glucose below basal levels is an independent predictor of the risk to develop glucose intolerance/diabetes over a 6-year follow-up period [26].

In summary, it seems that weight loss dieting should be perceived as a matter of compromise between the benefits of a small to moderate weight loss and the physiological vulnerability that is conferred by a moderate to large weight loss. As discussed in the next section, this perception is maybe even more relevant in a context of modernity where the lifestyle clearly promotes undesirable effects on the regulation of energy metabolism.

3. Metabolic allostasis and body weight stability in a modern environment

The modern way of living appears to impose a tremendous challenge to anybody who wants to remain lean — it encourages the consumption of energy and discourages the expenditure of energy. The high prevalence of obesity appears fundamentally linked to our so-called “obesogenic environment” — high stress levels, lack of sleep, abundant supplies of cheap, highly palatable, energy-dense foods, automation and elimination of physical activity from our homes and workplaces, dependence on powered transportation instead of our feet, etc. Unfortunately, these conditions are unlikely to be reversed in the short term. It is important to realize that the excess weight gain observed in prone individuals should be perceived as a normal physiological adaptation to a changed environment, rather than a malfunction of the regulatory system [27,28]. Accordingly, prevention and treatment strategies for obesity should ideally focus on modifying the root causes of weight gain. Furthermore, it is important to better understand the implications of this new reality of living on metabolic allostasis, appetite control and ultimately body weight. This better understanding is crucial if we want to increase our chances of success in any dietary intervention aimed at losing weight.

Technological advances that occurred over the past 30 years, particularly with respect to electronic engineering and computer sciences, have increased the demand for mental activities (as opposed to physical activities). As recently reported [29], we are only starting to document the implications of mental work on energy metabolism and it seems that these implications far exceed those associated with a lack of physical activity. Indeed, a careful examination of computer-related activities reveals that they represent a particular type of sedentary activities — they are stressful and biologically demanding for the body [30]. Recent experimental studies have shown that computer-based activities increase ad libitum food intake without increased sensations of hunger [31,32]. These results agree with a study involving scientists from the University of Washington who increased their energy and fat intake at the time of the preparation of NIH grant applications [33]. These results are also concordant with recent studies showing that television viewing and video game playing stimulate food intake despite their low “calorie-burning” nature [34]. Moreover, cognitive work acutely induced increased fluctuations in plasma glucose and insulin levels compared with a control, resting condition [32]. In accordance with the glucostatic theory of appetite control, the increased variability of glycemia was related to a compensatory increase in energy intake [20]. Interestingly, we also observed that mental work produced an increase in cortisol levels which was related to a compensatory increase in food intake [35]. Future studies will be necessary to better clarify the underlying mechanisms and to determine the relative contribution of homeostatic (hormonal signals that trigger food intake) vs. non-homeostatic (eating in the absence of hunger) feeding behaviors.

The “selfish brain” theory [36] is another interesting concept that has recently received attention in providing a more complete understanding of the brain’s priority in energy metabolism. During acute mild stress, the energy supply of the human brain increases by 12% [37]. In an attempt to better understand this phenomenon, Hitze and colleagues [38] recently reported that the brain under mental stress demands for energy from the body by making use of cerebral insulin suppression. Additionally, cognitive demand did also increase the brain’s energy need. After psychological stress, energy intake was found markedly increased to supply the brain and the body with energy for replenishment [38]. Interestingly, changes in cerebral energy state were parallel to the changes in mood. Mental stress induced a state of both neuroglycopenia and impaired mood, which was corrected by the supplementation of exogenous energy. However, contrary to the hypothesis that “comfort food” reduces the activity of the stress system and thereby relieves bad mood [39], the subjects displayed robust sympatho-adrenal responses, which were not affected by exogenous energy (either orally or intravenously). Thus, the fact that mental-stress-induced mood changes were resolved by food ingestion cannot be attributed to changes in the stress system but it rather indicates that mood was restored by restoring cerebral energy homeostasis [38].

Lack of sleep is another feature of our modern lifestyle that has been shown to be a metabolic stressor. Indeed, sleep curtailment has become an endemic condition of modern societies, with population statistics revealing that sleep duration has decreased by more than 1 h over the last few decades [40]. The proof-of-concept for short sleep duration as a possible cause of obesity is growing. Prospective cohort
studies have shown that short sleep duration is associated with weight gain and an increased incidence of obesity in children and adults [41,42]. Intervention studies have provided a mechanistic explanation for the short-sleep-obesity connection (i.e. that sleep restriction impacts hormonal control of appetite) [43]. Indeed, lack of sleep has been reported to decrease plasma leptin levels, increase plasma ghrelin and cortisol levels, alter glucose homeostasis, and activate the orexin system, all of which impact the control of appetite [43–45]. Interestingly, we have recently shown that short sleepers present lower glucose concentrations at the end of an OGTT [46], thereby providing another potential explanation on the basis of the glucostatic theory of appetite control (Fig. 2). Besides, the increased time and opportunities for eating as well as the increased fatigue associated with lack of sleep are other explanations that have been proposed [47]. Hence, a good night’s sleep is expected to favor a good coupling between energy input and output and should be encouraged in the prevention of weight gain. Future research is needed to determine whether sleep extension in sleep-deprived obese individuals will influence appetite control and/or reduce the amount of body fat. In this regard, we recently observed that a change towards longer sleep duration promoted the interruption of excess weight gain in short sleepers [48]. We also have to keep in mind that lack of sleep can be a symptom of chronic stress or typical depression. In this context, chronic stress would lead to impaired sleep on the one hand, and the adaptation to chronic stress would lead to weight gain on the other hand.

In the context of weight loss, dietary restriction is widely used as a means of inducing a caloric deficit. However, recent evidence suggests that adequate sleep might be an important factor in successful weight loss, and perhaps sleep should be included as part of the lifestyle package that traditionally has focused on diet and exercise [49]. In this crossover study, overweight adults were randomly assigned to sleep either 5.5 h or 8.5 h each night for 14 days in conjunction with moderate caloric restriction in a closed clinical research environment. The authors found that the participants lost the same amount of weight under both conditions; however, sleep restriction decreased the proportion of weight lost of fat by 55% and increased the loss of fat-free mass by 60%. Fat oxidation was lower in the sleep-deprived state, and ghrelin and hunger levels were also found to be higher with sleep deprivation. These findings are novel and suggest that getting too little sleep might prevent dieters from losing as much body fat as they otherwise would have.

Altogether, the modern way of living has many implications on energy metabolism and we should pay particular attention to this new reality. As discussed in this section, mental stress (either in the forms of cognitive working, television viewing or video game playing) and unrestorative sleep can partly explain the inter-individual variability in response to diet-induced weight loss. Targeting the root causes of weight gain will definitively improve our chances of success.

4. Weight loss and the allostatic burden of environmental pollutants

The weight gain observed over recent years has been shown to occur not only in humans but also in various animal species [50]. Since the usually advocated “Big Two” factors [51] to explain obesity, i.e. sedentariness and unhealthy macronutrient diet composition, cannot explain weight gain in some animals, this has raised the hypothesis that common unsuspected environmental factors may underly weight gain in humans and animals [51]. Among these factors, lipid soluble persistent organic pollutants (POPs) have frequently been pointed out as potential determinant of allostatic changes promoting obesity. POPs are endocrine-disrupting chemicals and include polychlorinated biphenyls (PCBs) and organochlorine pesticides. Despite the ban on their use in several countries including Canada and the United States, their stability, resistance to degradation, and lipophilicity has led to significant bioaccumulation in most compartments of the ecosystem and human tissues [52]. This bioaccumulation leads to an ongoing human exposure to POPs through several pathways (food intake being the main one), so the present concentration of POPs in serum reflects both a release from fat storage compartments as well as an uptake from present exposure. It has recently been shown that low levels of polychlorinated biphenyl-77 increase adipocyte differentiation, promote the expression of proinflammatory adipokines, and augment the expression of the peroxisome proliferator-activated receptor γ, a key promoter in regulating cell energy homeostasis [53,54]. Thus, these data suggest that even low-level exposure to POPs, as observed today in the human population, might have obesogenic effects.

Lim et al. [55] have recently reexamined this issue in a large population study by analyzing the relationship between serum concentrations of POPs and weight gain over 1 and 10 years. The results showed that POPs concentrations were higher in individuals with long term weight loss (due to a hyperconcentration of POPs in serum as a result of fat loss) whereas they were lower in those with a history of long term weight gain. Although both beneficial health effects after weight loss and harmful health effects after weight gain are generally expected, changes in serum concentrations of POPs in relation to weight change may act on health in directions opposite to what we expect with weight change. This then highlights another contribution of adipose tissue to body homeostasis due to its ability to store and then dilute POPs with the beneficial consequence to reduce their exposure to other tissues. In fact, as further explained in this section, this effect becomes more apparent during weight loss which can then be described as a decrease in the storage space of POPs.

To our knowledge, Backman and Kolmodin-Hedman [56] were the first investigators to demonstrate the enhancing effect of a substantial fat loss on circulating concentrations of POPs. Over the last decade, we have pursued the study of this issue with the preoccupation to identify some allostatic consequences of the weight loss-induced changes in plasma POPs concentrations. As expected, we observed a significant increase in POPs concentrations after a weight loss of about 10 kg in obese individuals [57]. This increase was highly correlated with that of POPs concentrations [58] in adipose tissue and was also associated with a greater than predicted decrease in skeletal muscle oxidative enzymes [59], plasma triiodothyronine and resting metabolic rate (RMR) [60], and sleeping metabolic rate (SMR) [61]. The use of an ANOVA in this context also showed that changes in plasma concentrations of POPs were the best predictor of changes in RMR [60] and SMR [61] in response to the weight-reducing program. Taken together, these observations provide an indication of the vulnerability of the control of energy expenditure that is promoted by body weight loss. This is concordant with the arguments of Lim et al.
5. Conclusions

This paper presents some observations pertaining to the allostatic burden of body weight loss that help in understanding the difficulties experienced by obese pigeons in their attempt to normalise their body weight. On one hand, it seems that weight loss naturally favors metabolic changes that ultimately lead to resistance to further lose fat and maybe weight regain. Second, evidence supports the idea that our modern way of living characterized by reduced sleep duration and more demanding cognitive effort can interfere with the outcome of a weight loss attempt. Finally, from an ecologic standpoint, fat loss involves a reduction of the anti-toxins protective role of adipose tissue that is related to its capacity to dilute POPs. Thus, in response to weight loss dieting, the resulting allostatic changes globally favor a decreased potential of the body’s metabolic “furnace” and of the ability to spontaneously match energy intake and expenditure.

Acknowledgments

The research reported in this paper was partly funded by the Canada Research Chair in Environment and Energy.

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