Consequences of Weight Cycling: An Increase in Disease Risk?

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ABSTRACT

Int J Exerc Sci 2(3) :191 -201, 2009. Research indicates that weight cycling, or "yo-yo dieting" is a common occurrence in overweight and obese populations. The long term negative health consequences of weight cycling are debated and it is unclear whether or not this weight change pattern poses a greater disease risk compared to obesity maintenance. This review discusses the prevalence of weight cycling and physiological alterations occurring during weight loss that promotes weight regain. We also discuss the effect weight regain has upon adipose tissue in terms of rate and type of accumulation. Also within this review are discussions surrounding the previously published literature based upon human and rodent research. We focus on previous limitations and difference in experimental design that have perhaps resulted in mixed findings concerning independent effects of weight cycling on health parameters. The final purpose of this review is to discuss future directions in evaluating the pro-inflammatory response to weight cycling in order to compare the disease risk compared to obesity maintenance.

KEY WORDS: Weight cycling, inflammation, review

Overview of the Problem

As obesity is becoming increasingly more prevalent in the United States, weight loss to reduce adipose tissue mass is strongly promoted as a means to decrease the disease risk associated with excess adiposity (5, 57). Unfortunately, the majority of individuals who lose weight are unlikely to maintain the reduced weight for an extended period of time (15, 51, 59). Repeated periods of weight loss and regain form a pattern known as weight cycling. Hill (2004) indicates that popular and lay literature have asserted that weight cycling (i.e. "yo-yo dieting") may increase the risk of developing cardiovascular disease or type II diabetes to a greater extent than remaining weight stable at an obese Body Mass Index (BMI; ≥30 kg/m^2)(27). The scientific literature is inconsistent regarding the long-term consequences of weight cycling. Because there is no universally-accepted definition of weight cycling, differences in experimental design may have contributed to discrepancies in scientific outcomes.

Weight gain has significant implications concerning disease risk, which is believed

to be mediated by an elevated level of systemic inflammation. Low-grade systemic inflammation is associated with obesity and it may serve as a link between adiposity and the development of cardiovascular disease and type 2 diabetes (66). To our knowledge, the pro-inflammatory effects of weight cycling have not been examined. Discerning a difference in disease risk between maintenance of obesity and weight cycling is important and may provide insight concerning individual differences in disease progression. If weight cycling is associated with an increased disease risk, continually recommending weight loss to those unable to maintain reduced weights may be a major public health issue. This review has two aims: 1) to compare studies that both support or refute the theory that weight cycling is independently associated with increases in disease risk2) to discuss the possibility that weight cycling impacts pro-inflammatory biomarkers.

Weight Cycling: A Disruption of Body Weight Maintenance?

It has been estimated 24% of American men and 38% of women are currently attempting to lose weight (35, 53, 64). When individuals with an obese BMI are considered, 65% of men and 68% of women are trying to lose weight, which is a five-fold increase compared to those within the normal BMI (18-24.9 kg/m^2) range that are trying to lose weight (64). While successful weight loss is achieved, researchers have indicated that long-term maintenance of a reduced weight appears to be rare.

The probability of weight regain increases in the time following initial weight loss (43). Researchers believe this is due to the energy gap created during caloric restriction where decreased energy expenditure is paired with an increased drive to eat (43). Rodent studies have demonstrated that this gap persists regardless of the duration of weight reduction, which increases the probability of weight regain.(41). This drive to eat causes a hyperphagic response when free access to food is allowed and when paired with suppressed lipid utilization, weight regain is often rapid and efficient (41, 43). While this finding was elucidated through use of a rodent model, human weight regain data supports this concept. One year after a modest weight loss (14.5% of body weight), Votruba *et al.* (2002) reported that within a year of weight loss, 16 out of 28 women regained weight and had a 19% increase in body weight and a 26% increase in percent fat mass (59). Weiss reported that by one year after a modest weight loss (10% of body weight), 33% of adult subjects regained all lost weight. Furthermore, they concluded that the odds of regaining were positively associated with the percentage of initial weight lost (63). Field *et al.* reported that approximately 55% of overweight and obese women who lost 10% of their body weight regained all lost weight within 4 years (15). In support of this finding, within 9 years of the initial weight loss (5% of body weight), 95% of women and 93% of men were unable to maintain the reduced body weight(51). Collectively, these studies suggest that while initial weight loss is possible, long-term maintenance is problematic, especially when large amounts of weight are lost or an individual is overweight or obese.

Repeated bouts of weight loss followed by regain forms a pattern known as weight cycling. Survey data collected by Williamson and colleagues (64) indicated that 25% of men and 27% of women trying to lose weight have made long-term attempts (classified as trying for over 1 year or "always trying to lose weight"). It has also been shown that 7% of men and 10% of women can be classified as severe weight cyclers (intentionally lost at least 5 kg and regained at least three different times), while 11% of men and 19% of women are mild weight cyclers (lost and regained at least 5 kg on one or two occasions) (36). While these results were generated from a group of adults in Finland, the conclusion that 18% of men and 27% of women weight cycle is comparable to the prevalence described by Williamson *et al.* (64). These numbers are likely a conservative estimate of the prevalence of weight cycling, which may be even greater in the United States.

Does Weight Regain Disrupt Normal Physiology?

The physiological changes associated with weight cycling, such as energy expenditure, metabolism and fuel utilization, have been documented using a rat model. MacLean and colleagues (2004) have documented the physiological alterations occurring in obesity-prone rats that contribute to the rapid, efficient regain during relapse following weight loss and maintenance. Their focus has been on the energy gap created during a period of caloric restriction that is characterized by decreased energy expenditure and an increased drive to eat (42). They found that in addition to changes in energy intake, alterations in metabolic efficiency and fuel utilization (favoring carbohydrate oxidation) may significantly affect the propensity to regain weight (43). For instance, in the 16 weeks following moderate weight loss (14%), food efficiency was increased 10-fold upon the first day of a 56-day re-feeding in weight cycle rats compared to rats with established obesity. While this dramatic rise was reduced within several days, food efficiency remained elevated above levels in obese mice for the first 4 weeks of relapse (41). The most dramatic changes occurred during the first week of relapse, a time when nearly 40% of lost weight, which was primarily fat mass, was regained (41, 42). Researchers also noted that as the length of maintenance increased, the amount of weight regained upon relapse also increased. Furthermore, regain was accompanied by a 30% increase in adipocyte concentration per fat pad.

Based on the above literature, it is clear that weight gain during relapse appears to induce more rapid adipose tissue growth and hyperplasia due to metabolic shifts favoring lipid storage. Because adipose tissue is a metabolically active tissue, responsible for production of leptin, cytokines and adiponectin as well as responding to traditional hormone systems(32), it is possible that the consequences of weight gain during relapse may also differ from that of initial weight gain. In recent years, lay literature has asserted that weight cycling may be more detrimental to health than simply remaining overweight or obese (27, 30). Researchers have found associations between weight cycling and an overshoot of lipogenic enzyme, triglyceride and cholesterol levels in animals and increased risk of heart attack and stroke in humans (4,

16, 34, 52). However, other researchers noted no long term adverse effects on body composition, blood pressure, lipid profile or risk of developing type II diabetes (13, 22, 37, 49, 56). Due to limited research in the area of weight cycling all of the negative consequences may not be known. Existing studies differ considerably in their research design, subject population used, duration of treatment, incorporation of exercise, magnitude and frequency of weight cycles. The lack of a universal definition of weight cycling is perhaps a great contributor to the variability within experimental design. This variability is discussed in greater detail in the following sections.

According to published research, weight cycling has been evaluated in one of two main ways: using a cross-sectional survey model in humans or a longitudinal endpoint model in rodents. The next two sections highlight research that either support or refute the theory that weight cycling contributes to detriments in health, demonstrating the no definite conclusions can be reached at this time.

Longitudinal Endpoint Analysis of Weight Cycling: Rodent Models

Utilization of animal experimental models allows for more control of subject treatment than a human experimental model. Such designs are useful for examining mechanisms underlying weight cycling; however, care should be taken when translating these findings to humans. An increase in internal validity, resulting from more control of subject treatments may explain why reported conclusions regarding weight cycling in animals is a bit more consistent than humans. The most likely explanation for inconsistent findings is due to the manner in which the weight cycling response is elicited.

In agreement with the series of studies completed by MacLean *et al.*, rapid regain occurs during relapse in rats that have been on caloric restriction diets (6, 17, 26, 28). Weight cycling was associated with increased food efficiency (6, 50) and increased caloric consumption (26, 52). Reed *et al.* found that despite being at lower weights than control rats, weight cycled rats were significantly fatter(50). Ilagan *et al.* reported that weight cycled rats had a lower percentage of fat free mass than their free fed (high fat diet) counterparts and that amount of weight lost during period of restriction decreased with each successive cycle (28). During re-feeding periods in weight cycled rats, researchers have consistently reported overshoots in lipoprotein lipase, serum triglycerides, and serum cholesterol above what has been observed in rats that are free-fed a high fat diet (17, 34, 52). It has been speculated that body weight overshoot may create a state of hyperlipogenesis that may persist for several days after re-feeding. Kim *et al.* demonstrated that fasting serum leptin was significantly increased in weight cycled rats compared to lean and pair-fed controls despite similar quantities of fat mass(33). Since leptin concentration is highly correlated to the degree of adiposity (11, 39), further interpretation of this finding suggests that weight cycling may induce a physiological change in adipocyte release of leptin.

In contrast, Brownell *et al.* did not observe alterations in body composition, but this could be contributed to an experimental

design that only allowed weight cycled rats to regain weight until they matched their obese controls, even though weight gain was still persisting at that time (6). Also, Cleary *et al.* indicated that weight loss and weight regain were linear in nature, opposing the "energy gap" theory proposed by MacLean *et al.* that contributes to rapid and efficient regain (9, 10). However, rats in the Cleary model were fed a purified diet rather than a high fat diet; the purified diet contained 20.5% high nitrogen casein, 50% cornstarch, 5% sucrose and 5% corn oil with 9% celufil as a filler (9). Sea *et al.* demonstrated that re-feeding rats a moderate fat (22%) diet yielded blunted responses compared to those fed a high fat (45%) diet (52). Furthermore, given a choice, weight cycled rats have been shown to self-select diets with high fat content during re-feeding(50), so perhaps a purified diet was not an appropriate variable for re-creating the weight cycling experience. Gray *et al.* stated that the rate of each weight loss was not hindered by weight cycling(23); however, in this study, the first restriction was marked by a 50% reduction of intake and the second restriction was a 75% reduction, so perhaps weight loss would not have been similar between weight cycles had the second restriction not have been so severe. Kim *et al.*(33) were not able to demonstrate a hyperphagic response, but their use of a 24hr fast plus 24hr relapse for 21 cycles may not have been a design that could show effects of weight cycling seen in previously mentioned studies; every-other-day restriction has lead to other positive adaptations (less weight gain, increased insulin sensitivity) elsewhere (1). This may indicate that larger weight cycles (increased weight loss frequency / magnitude per cycle) have differing effects as suggested by weight cycling studies in humans.

Cross-sectional Evaluation of Weight Cycling: Human Models

Some existing scientific literature supports the theory that weight cycling increases disease risk (directly or indirectly) in humans. Wallner and colleagues found that a history of weight cycling was associated with a more pronounced android fat distribution in women compared to those who were normal-weight or overweight without a history of weight cycling (60). It is possible that women who are prone to the accumulation of abdominal adiposity may be more likely to weight cycle for a more aesthetically desirable figure (48). Regardless of whether weight cycling causes the accumulation of android adiposity or vice versa, other researchers have found that a history of weight cycling was independently associated with an increased risk of developing hypertension (24) and clinically significant decreases in HDL-cholesterol in women (47). French et al(16) and Vergnaud *et al.*(58) demonstrated associations between weight cycling and risk for heart attack and stroke, as well as the development of metabolic syndrome(16, 58). Blair *et al.* studied men enrolled in the Multiple Risk Factor Intervention Trial who were at elevated risk for coronary heart disease due to smoking, hypertension and hypercholesterolemia, finding that greater weight variability over 4 years of follow up was associated to increase all-cause mortality(4).

In contrast to the preceding reports, several other researchers reported that weight

cycling has no independent impact on health status. Prentice *et al.* found that weight cycling did not significantly alter body composition (49). However, unlike Wallner *et al.*(60), who asked for 4 years worth of weight history, this study was completed in only 18 weeks. It may be possible that any deleterious effects of weight cycling do not manifest immediately or that the magnitude of the weight loss was not sufficient to induce long-term change. Li *et al.* studied obese patients, in a multi-disciplinary weight loss program, who had relapsed and re-entered. Multiple attempts at weight loss over 12 years showed no effect on the rate at which weight could be lost each time or on blood pressure or lipid profile; in fact, these measurements at baseline were significantly lower at the time of re-entry compared to the initial start for men and women (37). Initial blood pressure in men (134/88 mmHg) and women (126/82 mmHg) was recorded at the restart baseline at 129/85 mmHg and 121/78 mmHg, respectively. While no subjects were hypertensive, all values remained within the pre-hypertensive range. Furthermore, BP has been documented to fluctuate throughout the day (29). Triglyceride levels in men and women were reduced by 0.1 and 0.2 mmol/L between initial and restart baselines and cholesterol was reduced by 0.1 and 0.5 mmol/L, respectively. Women's values were all within the normal/low risk range and men's values remained in the borderline high range. Cholesterol values for both genders were all in the borderline high risk range. While deemed statistically significant, the differences between baselines may not be physiologically relevant as disease risk did not appear to change. Even though this study was longitudinal in nature, perhaps the use of regular exercise as part of the program acted as a confounding factor, as aerobic exercise is independently and positively correlated with decreases in blood pressure and cholesterol (19, 25).

A similar exercise effect was reported by Field *et al*. where mild and severe weight cycling was strongly associated with weight gain and hypertension, controlling the statistical analysis for weight and weight gain greatly attenuated this correlation(13); however, the questionnaire data also revealed that severe weight cyclers exercised significantly more that non weight cyclers. Graci *et al.* (2004) noted that weight cycling had no effect on cardiovascular disease risk factors; weight cycling throughout adulthood was not associated with changes in body composition, fat distribution blood pressure or insulin levels(22). One major difference in this study, compared to those with competing findings, was that Graci *et al.*(22) used morbidly obese subjects (BMI up to 69 kg/m^2) and perhaps there is a less-pronounced response to weight cycling in this population because the subjects already have an elevated disease risk. Similar results by Wing *et al.* (65) and Jeffery *et al.*(31) may have been effected by the short duration of measurement period (2.5 years) or the failure to use appropriate blood pressure cuffs for obese patients(24). Field *et al.* concluded that 4 years of weight cycling, prior to diagnosis of type 2 diabetes, was not predictive of disease development while Wannamethee *et al* found that weight fluctuation does not directly increase risk of death (14, 61).

Role of Inflammation in Disease Progression: Implications for Weight Cycling

When differences in experimental design are accounted for, a significant gap in scientific knowledge exists concerning the exact role of weight cycling in the progression of chronic diseases that are normally attributed to excess adiposity. IL-6 stimulates hepatic release of acute phase proteins, including C-Reactive Protein (CRP) (3, 66). Free fatty acids and TNF- α act in concert to exacerbate systemic inflammation (54). IL-8, released from adipocytes, monocytes and macrophages, has been thought to induce chemotaxis helping to form atherosclerotic plaques(21). IL-6 and TNF-α can act in an autocrine or paracrine manner, impairing insulin receptor activity and glucose sensitivity in adipocytes and muscle tissue (2, 3, 45, 66). IL-6 and CRP in circulation target and damage arterial endothelial lining; this damage helps to initiate or progress atherosclerosis (3, 46, 66). An increase in systemic inflammation increases the risk of developing a variety of diseases.

Several mechanisms are responsible for the pro-inflammatory response in adipose tissue due to hypertrophy. Cytotoxic stressors, such as oxidative stress and hypoxia, induced by hypertrophy in adipose tissue have been reported to trigger subsequent pro-inflammatory events (18, 55). As cellular stress persists, adipocytes secrete IL-6, TNF-α and leptin (38, 55) and unless revascularization is adequate, cells may become necrotic (44). The level of necrotic adipocyte death is positively correlated with increased adiposity and concentration of resident macrophages (8). Leptin aids in the transmigration of blood monocytes into adipose tissue compartments, where they mature into macrophages (12). Also, leptin stimulates pre-adipocyte stem cells to mature into adipocytes or macrophages. Thus, an adiposity driven increase in adipose tissue macrophages concentration is a result of monocyte influx and directed pre-adipocyte transformation (7). Evidence exists that macrophages may be retained longer in adipose tissue from obese compared to lean subjects (40). In lean individuals, the actions of leptin and granulocyte macrophage – colony stimulating factor (GM-CSF) are opposed by ghrelin; however, reduced ghrelin in obese individuals causes deregulation of macrophage development in adipose tissue (20). Macrophage accumulation has significant implications for inflammatory disease risk because they are a significant source of IL-6, TNF-α, and IL-8 (62, 67).

To our knowledge, there is only one published study that examined the effect weight variability has on pro-inflammatory or related factors. Yatsuya *et al.* reported that Japanese men with a history of weight variability had an independently increased odds ratio of elevated CRP (68). One limitation of this study was that it was a cross-sectional design thus it was not possible to evaluate cause and effect, no information on intentionality of weight change and the cross-sectional design with a majority of subjects having final BMIs less than 25 kg/m^2. This lack of literature suggests that in order to fully understand the possible effects of weight cycling, we must include examination of pro-inflammatory responses to this pattern.

Summary

In recent years, lay and popular literature has claimed that weight cycling may be more detrimental that simply remaining overweight or obese. Scientific research has yielded mixed results, but this may be due to differences in population used, experimental design and method of weight cycling. A current gap in research is the pro-inflammatory effect of weight cycling. . Since obesity is so prevalent, weight loss is almost universally recommended as treatment to reduce disease risk. But because research indicated that relapse is likely, it is important to understand if weight cycling adds to the current disease risk of obesity. Because weight cycling has a distinct effect on adipose tissue and adipose tissue is a source of inflammatory cytokines, elucidating any increases in inflammation beyond that measured in sustained obesity may help us to understand the independent disease risk that can be associated with weight cycling.

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