[Frontiers in Bioscience E2, 98-104, January 1, 2010]

Influence of obesity, physical inactivity, and weight cycling on chronic inflammation

Strohacker, K[1], McFarlin BK[1,2]

[1]Laboratory of Integrated Physiology; Department of Health and Human Performance; University of Houston, [2]Texas Obesity Research Center; University of Houston

TABLE OF CONTENTS

1. ABSTRACT

Obesity prevalence continues to rise due to excessive caloric intake and sedentary behavior. Weight loss can be achieved through diet and/or exercise, but maintenance of a reduced weight is rare and relapse is prevalent. Repeated periods of weight loss and regain have been termed "weight cycling." It has been speculated that weight cycling may further increase the elevated disease risk common with weight gain, obesity, and physical inactivity. Alterations in adipose tissue with weight cycling may create a more hypoxic environment; hypoxic adipose tissue secretes leptin, a stimulus for macrophage activation and accumulation within adipose tissue. Hypoxic adipocytes and macrophages release pro-inflammatory cytokines into circulation. Elevated body weight and adiposity are linked to cardiovascular disease and type 2 diabetes via an inflammatory mechanism. Thus, it is reasonable to speculate that weight cycling causes a more profound change in chronic inflammation than sustained weight gain. The purpose of this review is to explore inflammatory consequences associated with weight cycling as they are related to sustained weight gain, obesity, physical inactivity as well as relative disease risk.

2. INTRODUCTION

An elevation of plasma interleukin-6 (IL-6), Tumor Necrosis Factor –alpha (TNF-a), and C-Reactive Protein (CRP) have been shown to aid in the progression of insulin resistance in obese populations and cardiovascular disease in both healthy and at-risk populations (1-6). While the exact source of IL-6 is still debated, in obese individuals, the prime source appears to be adipose tissue (7) and adipose tissue macrophages (8). IL-6 can stimulate hepatic release of CRP (5). A period of energy restriction and/or exercise, which results in a decrease in body fat, is associated with a decrease in systemic inflammation and a subsequent reduction in disease risk (9, 10).

Despite the known effectiveness of weight loss as a countermeasure against inflammation, weight stability following loss is not common (11, 12), and subsequent attempts at weight loss followed by regain results in weight cycling. It has been speculated that weight cycling is an independent risk factor for cardiovascular disease (13); however, current research lacks a definitive conclusion concerning the impact of weight cycling on ones health and this is possibly due to the variability in experimental design. Some factors that have varied in experimental

design include: quantity of weight lost and regained, duration of weight stability, and number of weight cycles. One major gap in the scientific literature is that it is not known how weight cycling impacts obesity and physical inactivity-associated inflammation.

3. OBESITY AND PHYSICAL INACTIVITY: CONTRIBUTORS TO CHRONIC INFLAMMATION?

In the U.S., obesity is the most common nutritional disorder (14). Incidence of overweight (BMI $\geq$25 kg/m^2), obesity (BMI $\geq$ 30) and severe obesity (BMI $\geq$ 40) has increased in men and women of all ages, races, smoking status, and economic and educational backgrounds (15, 16). It has been reported that 25-48% of men and women participate in no, or an insufficient amount of physical activity (17). A sedentary existence completes the common triad associated with Metabolic Syndrome, also characterized by obesity and excessive calorie consumption (18). Excess adiposity is strongly linked with a multitude of chronic diseases. A well documented relationship between obesity and a multitude of cardiovascular events is accepted by most of the population; a host of problems such as coronary disease, stroke, congestive failure are more prevalent in obese populations and the risk of coronary or cardiovascular disease death increases (19, 20). Cardiovascular disease risk factors, such as hypertension, lipid abnormalities are also exacerbated by obesity (21, 22). Obese individuals are also more likely to be glucose intolerant, predicting future development of type II diabetes (22). In recent years, chronic inflammation has been examined as the key link between obesity and concurrent disease. Physical inactivity is a major contributor to excessive weight gain and is also associated with low-level inflammation (23-26).

Whole body, sub-clinical inflammation is a common occurrence with obesity. Cytokines, markers of inflammation, are protein molecules that mediate cellular injury (27). IL-6, TNF-a, and CRP are the most commonly measured biomarkers of inflammation. Plasma IL-6 concentration is increased in obese individuals compared to lean controls (3, 7, 27). Obesity, particularly in the abdominal region is correlated to elevated CRP levels in asymptomatic and at risk men (4, 28). Age, gender, smoking history, and physical inactivity are all related to CRP and IL-6, independent of obesity status (29). Thus, it can be surmised that sedentary obese populations are at the highest risk for developing chronic inflammation and subsequent cardiovascular disease or type II diabetes in the future. Understanding the origins, actions and contribution to disease of these cytokines furthers understanding of the inflamed state in obesity.

4. CHRONIC INFLAMMATION

4.1. IL-6 and CRP: role in chronic disease

In obese individuals, IL-6 is secreted by adipocytes (2, 7, 30, 31) as well as by resident adipose tissue macrophages (8, 32). One of the main actions of IL-6 is to promote the release of other acute-phase proteins (33), thereby further increasing inflammatory status. Also, IL-6 may act as an adipostat, acting on other tissues to help mediate fat accumulation (7). Plasma IL-6 can have negative effects, possibly increasing the risk for myocardial infarction by targeting and damaging the endothelial lining and smooth muscle in the blood vessel walls (5). In the case of developing type II diabetes, IL-6 can act on skeletal muscle to impair insulin action (1) as well as increasing free fatty acids, promoting fat oxidation and inhibiting lipoprotein lipase; all of these actions act in direct opposition to the physiological actions of insulin (3).

CRP originates from the liver, its release stimulated by an increase in plasma IL-6 concentration (1). CRP is one of the most widely measured acute-phase proteins when assessing and predicting cardiovascular events (33). CRP-mediated complement plays a role in the development of atherosclerotic lesions (5) and is generally present in arterial plaques (34). Also, CRP is positively correlated with components of Insulin Resistance Syndrome (35).

4.2. Macrophage accumulation in adipose tissue

Macrophages are present in all tissues where they help maintain homeostasis and participate in tissue remodeling. Accumulation of adiposity may signal resident macrophages to act in their immune capacity, resulting in IL-6 and TNF-a (8). Adipose tissue macrophage accumulation is positively correlated to adipocyte size and BMI (36). Circulating blood monocytes are capable of migrating into adipose tissue where they mature into macrophages (37). Considering approximately 90% of macrophages crown around dead or dying adipocytes, it is possible that signals from adipocyte necrosis have potent chemoattractant effects on macrophages (38). It has been speculated that when in direct contact with macrophages, preadipocytes (adipocyte stem cell) can be rapidly converted into functioning macrophages (39). Coenen *et al.* reported that macrophage accumulation during the progression to moderate obesity is mainly driven by adipose tissue, whereas further progression to severe obesity is driven by macrophages present in the tissue (40).

The physiologic events surrounding the influx and subsequent activation of macrophages are as follows: survival of adipocytes is dependent on tissue vascularization (41); adipocyte hypertrophy preceding angiogenesis results in hypoxia (28) which may cause macrophage chemoattraction and retention (42). Along with other hypertrophy-induced stressors, such as reactive oxygen species and free fatty acids, hypoxia signals inflammatory signaling cascades that regulate necrosis (38). Unlike apoptosis, which is not inflammatory, the features of dead adipocytes suggest that obesity-associated cell death is due to necrosis (38). In addition to necrosis, hypertrophied adipose tissue releases large quantities of leptin and exhibited a suppression of adiponectin release (43). Leptin is a known chemoattractant signal for blood monocytes recruitment to adipose tissue (37).

4.3. Countermeasures to decrease inflammation

Weight loss reduces the macrophages concentration in adipose tissue, which may partially explain

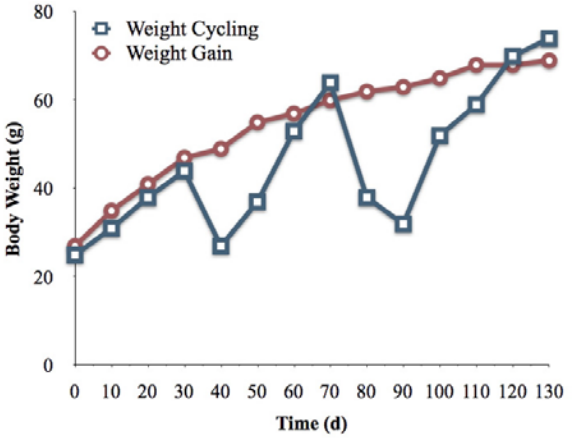

Figure 1. Demonstrates the typical change in body weight of wild type mice undergoing a period of sustained weight gain (leading to obesity) or weight cycling. It is important to note that over a similar period of time, weight cycling will result in a higher final body weight than sustained weight gain due to difference in adipose hypertrophy and hyperplasia.

the reduction in inflammatory status following a period of weight loss (42). This is supported by findings indicating that weight loss is associated with a decrease in plasma IL-6 concentration and an improvement in insulin sensitivity (9). Holdstock *et al.* reported that CRP concentration was decreased following a 12 month period of weight loss in subjects who were insulin sensitive and obese at baseline (33). Kopp *et al.* reported that CRP and IL-6 were significantly decreased in obese patients and this was associated with the improvement in their manifestations of Insulin Resistance Syndrome (10). A decrease in plasma cytokine concentration is consistent with an anti-inflammatory effect, which may reduce cardiovascular disease risk (10).

Similar to weight loss, long-term exercise training has also been demonstrated to have anti-inflammatory properties (23-26, 44). Physical activity status is negatively associated with plasma CRP (44). Interestingly, IL-6 is found in greater concentrations after exercise; however, it has been previously mentioned that IL-6 is unique is its capacity to act as both pro-and anti-inflammatory (45). Unlike in obesity, the increased level of IL-6 during exercise is not originating from monocytes (46) but from contracting skeletal muscle. Muscle-derived IL-6 promotes the release of IL-1ra and IL-10, which inhibits pro-inflammatory cytokine release (47).

5. WEIGHT CYCLING

5.1. Characteristics

While many people successfully lose weight, long-term maintenance is rare and relapse to pre-intervention body weight is common (11, 48). One underlying factor is an "energy gap" created by caloric restriction, characterized by an increased drive to eat paired with a decrease in energy expenditure (49). Long term maintenance of a reduced weight does not resolve the energy gap; with increasing time, it has been found that the difference between an increased hunger drive and decreased energy expenditure becomes larger and more profound, making the individual more likely to relapse (49). The relapse period is accompanied by a rapid, efficient regain of lost weight, possibly due to the energy gap, suppressed fat utilization, and/or adipocyte hyperplasia (50, 51). Using rats, Maclean *et al.* and Harris *et al.* found that within the first week of relapse, rats regained 40% and 86% of the previously lost weight (50, 51). Subsequent bouts of weight loss and regain begin the pattern known as weight cycling, or "yo-yo dieting" (Figure 1).

5.2. Prevalence

Lahti-Koski *et al* reported that 18% of men and 29% of women were defined as "weight cyclers" (52). This study was cited as one of the first to describe weight cycling prevalence in a general population and few investigations have taken place looking at correlates for long term weight loss and maintenance (11). It is estimated that 25% to 40% of American men and women are trying to lose weight (53). The NIH task force found that of successful US dieters, less than 5% sustained their weight loss after one year (54). Using these findings, if 95% of American dieters relapse, it can be concluded that approximately 23% of men and 38% of women complete at least one weight cycle in their lifetime. Obesity is a documented risk factor for development of chronic disease; however, it is not clear if weight cycling is more deleterious than sustained weight gain.

5.3. Inconclusive research concerning risk

Current research is split concerning the risk of weight cycling over a lifetime. Investigators using rat models promote weight cycling as a risk factor for disease based on the fluctuation and overshoot of lipogenic enzyme activity and lipid profiles (55, 56). Increased risk of myocardial infarction and stroke has been found in some studies using humans (57, 58). Lahti-Koski *et al.* found that women who weight cycle visit the doctor more frequently and report poor self-perceived health (52). In contrast, much research has been done to show that weight cycling is not associated with adverse changes in body composition or cardiovascular risk factors, such as hypertension and lipid profile (12, 59-63). Weight variability has not been shown to be independently predictive of type II diabetes (64). It has also been reported that weight cycled women had a decrease in HDL, but this did not translate to increased prevalence of coronary artery disease (54).

Because most obese dieters will face relapse, determining the health consequences of weight cycling is imperative. Although there is nearly universal agreement that never becoming obese is the healthiest, the reality is that with the rise in the obesity epidemic, most people will have to lose weight at some point in their adult lives. With weight loss comes the risk of relapse associated with weight regain. The physiological changes associated with weight cycling are not well understood and it is not known if this process increases disease risk. Given the role of inflammation in the pathophysiology of various disease

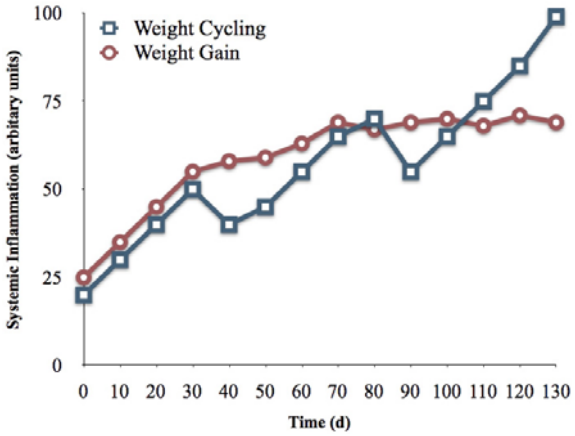

Figure 2. Demonstrates the speculated change in systemic, low-grade inflammation following a period of sustained weight gain or three weight cycles over the same amount of time. At the conclusion of this period, weight cycled mice would weigh significantly more than mice in the sustained weight group. Under the scenario shown in this figure, one would expect the weight-cycled mice to have a greater disease prevalence than the sustained weight gain mice.

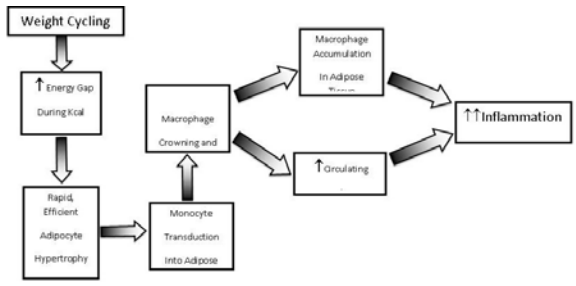

Figure 3. Demonstrates the pathways associated with further increases in systemic inflammation due to weight cycling in comparison to sustained obesity. The energy gap created with caloric restriction leads to rapid hypertrophy and hyperplasia in the adipose tissue during weight cycling which leads to increased macrophage infiltration and cytokine production.

states, it seems reasonable to examine weight cycling in the context of chronic inflammation.

5.4. Weight cycling and inflammation

Considering that whole body inflammation can be dictated by body fat mass, it is reasonable to speculate that a period of weight cycling may have profound inflammatory consequences on the body (Figure 2). During the progression to obesity, adipose tissue hypertrophy leads to hypoxia, macrophage accumulation and pro-inflammatory cytokine production. Weight regain during relapse seems to be unique in that the gain is very rapid and adipocyte hyperplasia is evident. We have therefore hypothesized that a period of weight cycling will result in greater levels of inflammation compared to a similar period of sustained weight gain in mice. Our hypothesis is based upon the following three reasons: 1) The increased rate of weight gain will cause a greater amount of cell stress due to hypertrophy leading to excessive cytokine release (65); 2) Neels *et al.* found that functional vasculature is present 5 days after cell implantation that was morphologically and synthetically similar to control adipose tissue vasculature by day 21 (66). However, during relapse, a large amount is regained within one week and this may lead to the conclusion that during relapse, angiogenesis may not be able to keep up with the rapidly expanding fat mass, leading to hypoxia and necrosis, which has been shown to be pro-inflammatory while signaling macrophage accumulation, in a more pronounced fashion; and 3) While regain is characterized by hyperplasia, weight loss only reduces cell size (67). Thus, the hyperplasia associated with weight cycling may increase the propensity for weight regain as well as enhance the inflammatory capacity of the adipose tissue mass.

6. SUMMARY

Obesity and physical inactivity contribute to the accumulation of systemic, low-grade inflammation, which is involved in the pathophysiology of cardiovascular disease and type II diabetes (6, 8, 9, 24, 57). Weight loss achieved via an energy-restricted diet and/or exercise attenuates inflammation, reducing the risk of developing the aforementioned diseases (23-26, 68). While weight loss is an effective countermeasure against systemic inflammation, maintenance of reduced body weight is difficult especially in adults where relapse occurs in 95% of those that lose weight (54). Inability to maintain body weight following weight loss is associated with pattern of weight cycling, which may increase disease risk compared to sustained weight gain (52, 54-56). These diseases have a known inflammatory origin, and thus it is likely that weight cycling influences one's level of systemic, low-grade inflammation. Research currently being completed in our laboratory will examine the relationship between weight cycling and systemic, low-grade inflammation.

8. REFERENCES

1. Bastard, J. P., M. Maachi, J. T. Van Nhieu, C. Jardel, E. Bruckert, A. Grimaldi, J. J. Robert, J. Capeau & B. Hainque: Adipose tissue IL-6 content correlates with resistance to insulin activation of glucose uptake both *in vivo* and *in vitro*. *J Clin Endocrinol Metab*, 87, 2084-9 (2002)

2. Kern, P. A., S. Ranganathan, C. Li, L. Wood & G. Ranganathan: Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. *Am J Physiol Endocrinol Metab*, 280, E745-51 (2001)

3. Bastard, J. P., C. Jardel, E. Bruckert, P. Blondy, J. Capeau, M. Laville, H. Vidal & B. Hainque: Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. *J Clin Endocrinol Metab*, 85, 3338-42 (2000)

4. Lemieux, I., A. Pascot, D. Prud'homme, N. Almeras, P. Bogaty, A. Nadeau, J. Bergeron & J. P. Despres: Elevated

C-reactive protein: another component of the atherothrombotic profile of abdominal obesity. *Arterioscler Thromb Vasc Biol*, 21, 961-7 (2001)

5. Wisse, B. E.: The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. *J Am Soc Nephrol*, 15, 2792-800 (2004)

6. Chambers, J. C., S. Eda, P. Bassett, Y. Karim, S. G. Thompson, J. R. Gallimore, M. B. Pepys & J. S. Kooner: C-reactive protein, insulin resistance, central obesity, and coronary heart disease risk in Indian Asians from the United Kingdom compared with European whites. *Circulation*, 104, 145-50 (2001)

7. Mohamed-Ali, V., S. Goodrick, A. Rawesh, D. R. Katz, J. M. Miles, J. S. Yudkin, S. Klein & S. W. Coppack: Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, *in vivo*. *J Clin Endocrinol Metab*, 82, 4196-200 (1997)

8. Lumeng, C. N., S. M. Deyoung, J. L. Bodzin & A. R. Saltiel: Increased inflammatory properties of adipose tissue macrophages recruited during diet-induced obesity. *Diabetes*, 56, 16-23 (2007)

9. Bruun, J. M., C. Verdich, S. Toubro, A. Astrup & B. Richelsen: Association between measures of insulin sensitivity and circulating levels of interleukin-8, interleukin-6 and tumor necrosis factor-alpha. Effect of weight loss in obese men. *Eur J Endocrinol*, 148, 535-42 (2003)

10. Kopp, H. P., C. W. Kopp, A. Festa, K. Krzyzanowska, S. Kriwanek, E. Minar, R. Roka & G. Schernthaner: Impact of weight loss on inflammatory proteins and their association with the insulin resistance syndrome in morbidly obese patients. *Arterioscler Thromb Vasc Biol*, 23, 1042-7 (2003)

11. Sarlio-Lahteenkorva, S., A. Rissanen & J. Kaprio: A descriptive study of weight loss maintenance: 6 and 15 year follow-up of initially overweight adults. *Int J Obes Relat Metab Disord*, 24, 116-25 (2000)

12. Field, A. E., T. Byers, D. J. Hunter, N. M. Laird, J. E. Manson, D. F. Williamson, W. C. Willett & G. A. Colditz: Weight cycling, weight gain, and risk of hypertension in women. *Am J Epidemiol*, 150, 573-9 (1999)

13. Kannel, W. B.: Effect of weight on cardiovascular disease. *Nutrition*, 13, 157-8 (1997)

14. Khan, L. K. & B. A. Bowman: Obesity: a major global public health problem. *Annu Rev Nutr*, 19, xiii-xvii (1999)

15. Flegal, K. M., M. D. Carroll, C. L. Ogden & C. L. Johnson: Prevalence and trends in obesity among US adults, 1999-2000. *Jama*, 288, 1723-7 (2002)

16. Mokdad, A. H., E. S. Ford, B. A. Bowman, W. H. Dietz, F. Vinicor, V. S. Bales & J. S. Marks: Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *Jama*, 289, 76-9 (2003)

17. Hootman, J. M., C. A. Macera, S. A. Ham, C. G. Helmick & J. E. Sniezek: Physical activity levels among the general US adult population and in adults with and without arthritis. *Arthritis Rheum*, 49, 129-35 (2003)

18. Liu, S. & J. E. Manson: Dietary carbohydrates, physical inactivity, obesity, and the 'metabolic syndrome' as predictors of coronary heart disease. *Curr Opin Lipidol*, 12, 395-404 (2001)

19. Paul, O., M. H. Lepper, W. H. Phelan, G. W. Dupertuis, A. Macmillan, K. H. Mc & H. Park: A longitudinal study of coronary heart disease. *Circulation*, 28, 20-31 (1963)

20. Hubert, H. B., M. Feinleib, P. M. McNamara & W. P. Castelli: Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation*, 67, 968-77 (1983)

21. Chiang, B. N., L. V. Perlman & F. H. Epstein: Overweight and hypertension. A review. *Circulation*, 39, 403-21 (1969)

22. Kannel, W. B., T. Gordon & W. P. Castelli: Obesity, lipids, and glucose intolerance. The Framingham Study. *Am J Clin Nutr*, 32, 1238-45 (1979)

23. Flynn, M. G., B. K. McFarlin, M. D. Phillips, L. K. Stewart & K. L. Timmerman: Toll-like receptor 4 and CD14 mRNA expression are lower in resistive exercise-trained elderly women. *J Appl Physiol*, 95, 1833-42 (2003)

24. McFarlin, B. K., M. G. Flynn, W. W. Campbell, B. A. Craig, J. P. Robinson, L. K. Stewart, K. L. Timmerman & P. M. Coen: Physical activity status, but not age, influences inflammatory biomarkers and toll-like receptor 4. *J Gerontol A Biol Sci Med Sci*, 61, 388-93 (2006)

25. McFarlin, B. K., M. G. Flynn, W. W. Campbell, L. K. Stewart & K. L. Timmerman: TLR4 is lower in resistance-trained older women and related to inflammatory cytokines. *Med Sci Sports Exerc*, 36, 1876-83 (2004)

26. Smith, J. K., R. Dykes, J. E. Douglas, G. Krishnaswamy & S. Berk: Long-term exercise and atherogenic activity of blood mononuclear cells in persons at risk of developing ischemic heart disease. *Jama*, 281, 1722-7 (1999)

27. Roytblat, L., M. Rachinsky, A. Fisher, L. Greemberg, Y. Shapira, A. Douvdevani & S. Gelman: Raised interleukin-6 levels in obese patients. *Obes Res*, 8, 673-5 (2000)

28. Trayhurn, P. & I. S. Wood: Adipokines: inflammation and the pleiotropic role of white adipose tissue. *Br J Nutr*, 92, 347-55 (2004)

29. Fischer, C. P., A. Berntsen, L. B. Perstrup, P. Eskildsen & B. K. Pedersen: Plasma levels of interleukin-6 and C-reactive protein are associated with physical inactivity independent of obesity. *Scand J Med Sci Sports* (2006)

30. Mohamed-Ali, V., J. H. Pinkney & S. W. Coppack: Adipose tissue as an endocrine and paracrine organ. *Int J Obes Relat Metab Disord*, 22, 1145-58 (1998)

31. Lehrke, M. & M. A. Lazar: Inflamed about obesity. *Nat Med*, 10, 126-7 (2004)

32. Xu, H., G. T. Barnes, Q. Yang, G. Tan, D. Yang, C. J. Chou, J. Sole, A. Nichols, J. S. Ross, L. A. Tartaglia & H. Chen: Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest*, 112, 1821-30 (2003)

33. Holdstock, C., L. Lind, B. E. Engstrom, M. Ohrvall, M. Sundbom, A. Larsson & F. A. Karlsson: CRP reduction following gastric bypass surgery is most pronounced in insulin-sensitive subjects. *Int J Obes (Lond)*, 29, 1275-80 (2005)

34. Nesto, R.: C-reactive protein, its role in inflammation, Type 2 diabetes and cardiovascular disease, and the effects of insulin-sensitizing treatment with thiazolidinediones. *Diabet Med*, 21, 810-7 (2004)

35. Festa, A., R. D'Agostino, Jr., G. Howard, L. Mykkanen, R. P. Tracy & S. M. Haffner: Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation*, 102, 42-7 (2000)

36. Weisberg, S. P., D. McCann, M. Desai, M. Rosenbaum, R. L. Leibel & A. W. Ferrante, Jr.: Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest*, 112, 1796-808 (2003)

37. Curat, C. A., A. Miranville, C. Sengenes, M. Diehl, C. Tonus, R. Busse & A. Bouloumie: From blood monocytes to adipose tissue-resident macrophages: induction of diapedesis by human mature adipocytes. *Diabetes*, 53, 1285-92 (2004)

38. Cinti, S., G. Mitchell, G. Barbatelli, I. Murano, E. Ceresi, E. Faloia, S. Wang, M. Fortier, A. S. Greenberg & M. S. Obin: Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. *J Lipid Res*, 46, 2347-55 (2005)

39. Charriere, G., B. Cousin, E. Arnaud, M. Andre, F. Bacou, L. Penicaud & L. Casteilla: Preadipocyte conversion to macrophage. Evidence of plasticity. *J Biol Chem*, 278, 9850-5 (2003)

40. Coenen, K. R., M. L. Gruen, A. Chait & A. H. Hasty: Diet-induced increases in adiposity, but not plasma lipids, promote macrophage infiltration into white adipose tissue. *Diabetes*, 56, 564-73 (2007)

41. Hausman, G. J. & R. L. Richardson: Adipose tissue angiogenesis. *J Anim Sci*, 82, 925-34 (2004)

42. Cancello, R., C. Henegar, N. Viguerie, S. Taleb, C. Poitou, C. Rouault, M. Coupaye, V. Pelloux, D. Hugol, J. L. Bouillot, A. Bouloumie, G. Barbatelli, S. Cinti, P. A. Svensson, G. S. Barsh, J. D. Zucker, A. Basdevant, D. Langin & K. Clement: Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. *Diabetes*, 54, 2277-86 (2005)

43. Wiecek, A., F. Kokot, J. Chudek & M. Adamczak: The adipose tissue--a novel endocrine organ of interest to the nephrologist. *Nephrol Dial Transplant*, 17, 191-5 (2002)

44. Ford, E. S.: Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. *Epidemiology*, 13, 561-8 (2002)

45. Opal, S. M. & V. A. DePalo: Anti-inflammatory cytokines. *Chest*, 117, 1162-72 (2000)

46. Starkie, R. L., J. Rolland, D. J. Angus, M. J. Anderson & M. A. Febbraio: Circulating monocytes are not the source of elevations in plasma IL-6 and TNF-alpha levels after prolonged running. *Am J Physiol Cell Physiol*, 280, C769-74 (2001)

47. Petersen, A. M. & B. K. Pedersen: The anti-inflammatory effect of exercise. *J Appl Physiol*, 98, 1154-62 (2005)

48. Field, A. E., R. R. Wing, J. E. Manson, D. L. Spiegelman & W. C. Willett: Relationship of a large weight loss to long-term weight change among young and middle-aged US women. *Int J Obes Relat Metab Disord*, 25, 1113-21 (2001)

49. MacLean, P. S., J. A. Higgins, G. C. Johnson, B. K. Fleming-Elder, W. T. Donahoo, E. L. Melanson & J. O. Hill: Enhanced metabolic efficiency contributes to weight regain after weight loss in obesity-prone rats. *Am J Physiol Regul Integr Comp Physiol*, 287, R1306-15 (2004)

50. MacLean, P. S., J. A. Higgins, M. R. Jackman, G. C. Johnson, B. K. Fleming-Elder, H. R. Wyatt, E. L. Melanson & J. O. Hill: Peripheral metabolic responses to prolonged weight reduction that promote rapid, efficient regain in obesity-prone rats. *Am J Physiol Regul Integr Comp Physiol*, 290, R1577-88 (2006)

51. Harris, R. B. & R. J. Martin: Recovery of body weight from below "set point" in mature female rats. *J Nutr*, 114, 1143-50 (1984)

52. Lahti-Koski, M., S. Mannisto, P. Pietinen & E. Vartiainen: Prevalence of weight cycling and its relation to health indicators in Finland. *Obes Res*, 13, 333-41 (2005)

53. Williamson, D. F., M. K. Serdula, R. F. Anda, A. Levy & T. Byers: Weight loss attempts in adults: goals, duration, and rate of weight loss. *Am J Public Health*, 82, 1251-7 (1992)

54. Olson, M. B., S. F. Kelsey, V. Bittner, S. E. Reis, N. Reichek, E. M. Handberg & C. N. Merz: Weight cycling and high-density lipoprotein cholesterol in women: evidence of an adverse effect: a report from the NHLBI-sponsored WISE study. Women's Ischemia Syndrome Evaluation Study Group. *J Am Coll Cardiol*, 36, 1565-71 (2000)

55. Sea, M. M., W. P. Fong, Y. Huang & Z. Y. Chen: Weight cycling-induced alteration in fatty acid metabolism. *Am J Physiol Regul Integr Comp Physiol*, 279, R1145-55 (2000)

56. Kochan, Z., J. Karbowska & J. Swierczynski: The effects of weight cycling on serum leptin levels and lipogenic enzyme activities in adipose tissue. *J Physiol Pharmacol*, 57 Suppl 6, 115-27 (2006)

57. Blair, S. N., J. Shaten, K. Brownell, G. Collins & L. Lissner: Body weight change, all-cause mortality, and cause-specific mortality in the Multiple Risk Factor Intervention Trial. *Ann Intern Med*, 119, 749-57 (1993)

58. French, S. A., A. R. Folsom, R. W. Jeffery, W. Zheng, P. J. Mink & J. E. Baxter: Weight variability and incident disease in older women: the Iowa Women's Health Study. *Int J Obes Relat Metab Disord*, 21, 217-23 (1997)

59. van Dale, D. & W. H. Saris: Repetitive weight loss and weight regain: effects on weight reduction, resting metabolic rate, and lipolytic activity before and after exercise and/or diet treatment. *Am J Clin Nutr*, 49, 409-16 (1989)

60. Jeffery, R. W.: Does weight cycling present a health risk? *Am J Clin Nutr*, 63, 452S-455S (1996)

61. Prentice, A. M., S. A. Jebb, G. R. Goldberg, W. A. Coward, P. R. Murgatroyd, S. D. Poppitt & T. J. Cole: Effects of weight cycling on body composition. *Am J Clin Nutr*, 56, 209S-216S (1992)

62. Graci, S., G. Izzo, S. Savino, L. Cattani, G. Lezzi, M. E. Berselli, F. Balzola, A. Liuzzi & M. L. Petroni: Weight cycling and cardiovascular risk factors in obesity. *Int J Obes Relat Metab Disord*, 28, 65-71 (2004)

63. Li, Z., K. Hong, E. Wong, M. Maxwell & D. Heber: Weight cycling in a very low-calorie diet programme has no effect on weight loss velocity, blood pressure and serum lipid profile. *Diabetes Obes Metab*, 9, 379-85 (2007)

64. Field, A. E., J. E. Manson, N. Laird, D. F. Williamson, W. C. Willett & G. A. Colditz: Weight cycling and the risk of developing type 2 diabetes among adult women in the United States. *Obes Res*, 12, 267-74 (2004)

65. Rudich, A., H. Kanety & N. Bashan: Adipose stress-sensing kinases: linking obesity to malfunction. *Trends Endocrinol Metab*, 18, 291-9 (2007)

66. Neels, J. G., T. Thinnes & D. J. Loskutoff: Angiogenesis in an *in vivo* model of adipose tissue development. *Faseb J*, 18, 983-5 (2004)

67. Faust, I. M., P. R. Johnson, J. S. Stern & J. Hirsch: Diet-induced adipocyte number increase in adult rats: a new model of obesity. *Am J Physiol*, 235, E279-86 (1978)

68. Stewart, L. K., M. G. Flynn, W. W. Campbell, B. A. Craig, J. P. Robinson, B. K. McFarlin, K. L. Timmerman, P. M. Coen, J. Felker & E. Talbert: Influence of exercise training and age on CD14+ cell-surface expression of toll-like receptor 2 and 4. *Brain Behav Immun*, 19, 389-97 (2005)

Key Words: Inflammation, Weight cycling, Inactivity, Obesity, Exercise, Review

Send correspondence to: Brian K. McFarlin, University of Houston; 3855 Holman St; Houston, Texas 77204-6015, Tel: 713-743-9929, Fax 713-743-9860, E-mail: bmcfarlin@uh.edu

http://www.bioscience.org/current/vol2E.htm