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Effects of Exercise Treatment on Obesity: What Community Nutritionists Need to Know

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ABSTRACT

By improving body composition, such as fat, lean body mass and total body weight, an exercise program can be an effective treatment of obesity. The effects of exercise on obesity have been confirmed via various approaches such as type, intensity, duration, frequency, and combination with diet. Combined exercise and diet is the most efficient strategy for weight loss, and exercise alone could improve metabolism irrespective of weight loss. In addition, physical activity, including exercise, is emphasized to avoid a "yo-yo" phenomenon. Exercise increases lipolysis stimulated by such factors as catecholamine, growth hormone (GH), and hormone sensitive lipase (HSL). Moreover, changes in insulin and cortisol through exercise affect adipose tissue, which is known as not only an energy storage locale, but also as an endocrine organ. Adipocytokines secreted by adipose tissue respond to signals that modulate metabolism and inflammation. Exercise has generally shown positive effects on adipocytokines, and these effects increase in conjunction with a hypocaloric diet. However, a long duration and a high intensity of exercise could induce an inflammatory response. This review summarizes the effects of exercise on obesity treatment, which contributes to the exercise and nutritional fields, particularly of community nutritionists. (*J Community Nutrition* 8(2): 76~89, 2006)

KEY WORDS: exercise · diet · weight loss · metabolism · inflammation.

Introduction

The prevalence of obesity has increased throughout the world; this phenomenon causes serious problems in public health. Obesity is an important metabolic risk factor which is associated with disorders such as type 2 diabetes mellitus, hypertension, insulin resistance, dyslipidemia and atherosclerosis (Groop, Ortho-Melander 2001). In addition, recent reports which suggest that obesity induces a pro-inflammatory state characterized by the local production of pro-inflammation cytokines have focused on the problem of obesity and obesity related diseases (Fantuzzi 2005; Koerner et al. 2005). Obesity is caused by many genetic, physiologic, environmental, behavioral and evolutionary factors. Among these, excess dietary intake with reduced physical activity could be the main cause in the rapid increase of obese individuals. The treatment of obesity has generally included exercise, diet, behavioral modification, medicine and surgery.

Exercise is a particularly essential role for obesity treatment. Exercise improves energy balance, the main cause of obesity (Weber 2003). This has been confirmed via various approaches including type (Glowacki et al. 2004), intensity (Romijn et al. 1993), duration (Willmore, Costill 2001) and combination with diet (Tsai et al. 2003), which is most efficient strategy for weight loss (Bensimhon et al. 2006). In addition to exercise, physical activity is also recommended for maintaining weight loss (Wing, Hill 2001).

Hormonal regulation via exercise can improve lipid and carbohydrate metabolism, which modulates catecholamine, insulin, growth hormone and cortisol by activating enzymes related to free fatty acids (FFA) (Girod, Brotman 2003; Horowitz 2003). In addition to hormonal regulation, exercise also improves metabolism in skeletal muscle by the induction of FFA transport functions, β-oxidative capacity and glucose transport functions (Bonen et al. 2000; Dohm 2002; Horowitz 2003).

Recent studies have elucidated that exercise could improve adipocytokines, such as leptin, adiponectin, tumor necrosis

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factor α (TNF-α) and interleukin(IL)-6, by modulating inflammation beyond metabolism(Giannopoulou et al. 2005; Monzillo et al. 2003). Although controversial results such as the change in resistin levels during exercise have been reported(Monzillo et al. 2003), exercise could improve the inflammation response via regulating adipocytokines.

This review aims to provide a summary of the established effects of exercise on obesity treatment and an update on the latest findings of exercise effects in obesity research. This review also provides information in the treatment of obesity, which contributes not only to the exercise field but also to community nutritionists in various nutritional fields such as community health center, school and hospital where exercise is a necessary application for obesity treatment.

Exercise Strategies for Obesity Treatment

Numerous studies have suggested that exercise is an efficient means of weight loss and lipid profiles, which are markers related to obesity(ACSM 2006; Macardle et al. 2001; Willmore, Costill 2001). An optimal exercise program for obesity treatment includes exercise type, intensity, duration and frequency.

1. Exercise type

Aerobic exercise is particularly essential in obesity treatment. Previous studies have investigated the effects of the aerobic exercises, such as walking, jogging, aerobic dance and cycling, in the management of obesity(ACSM 2006; Martin et al. 1993). Moreover, aerobic exercise has been proven to affect blood pressure, insulin resistance, and lipid profiles by improving the activation of lipid metabolism (Martin et al. 1993; Hurley et al. 1986).

In addition to aerobic exercise, resistance exercise has also been shown to play a beneficial role in lean body mass, rest metabolic rate(RMR), and the resultant induction of energy expenditure(Bosselaers et al. 1994). Several studies report that resistance training could improve coronary risk factors without weight loss(Hurley et al. 1988). Furthermore, Treuth and colleagues(1995) demonstrated that a nearly twofold increase in lipid oxidation appeared after 16-week resistance training programs in older women(60 − 77yr). The American College of Sports Medicine(ACSM) recommended resistance exercise for the management of obesity; these recommendations call for one set of three to twenty repetitions (e.g., 3 − 5, 8 − 10, 12 − 15) in eight to ten different exercises including all major muscle groups(e.g., hip, thigh, arm, shoulder), twice or three times per week(ACSM 2006). However, resistance training alone is typically not considered an effective means of weight loss owing to its resultant increase of lean body mass. To increase the synergic effect of exercise in obesity treatment, combined(aerobic plus resistance) exercise is recommended. A few studies have reported that concurrent exercise could provide an interference phenomenon which results in difficulty obtaining the maximum development of strength and endurance capacity (Christensen et al. 2004). However, most studies have demonstrated that concurrent exercise improves body weight, lean body mass, body fat(%), and blood profiles without an occurrence of this interference phenomenon(Glowacki et al. 2004; Terbizan et al. 2004). If the interference phenomenon is considered, performing aerobic and resistance exercise at different days might be recommended.

Recent studies have emphasized flexibility exercise, which is generally known as stretching like yoga(ACSM 2006). Although flexibility exercise could not affect directly on obesity treatment(McCue 1963), flexibility exercise improves and maintains the range of motion in a joint or series of joints(Klein et al. 2002). Among flexibility exercises includeing static, dynamic and proprioceptive neuromuscular facilation(PNF), static exercise is recommended for obese individuals. Static flexibility exercise involves slowly stretching a muscle to the end of the range of motion and then holding that position for an extended period time such as 15 to 30 seconds. Compared with static exercise, dynamic and PNF exercise are difficult in performing to obese individuals.

2. Exercise intensity

Numerous studies have investigated the optimal intensity of exercise in obesity treatment. Fig. 1 shows a performing cycle ergometer exercise at different intensities for trained men(Romijn et al. 1993). As the intensity of the exercise increases, absolute use of glucose and muscle glycogen increases, while muscle triglyceride and plasma FFA use decrease. This confirms evidence that high intensity in exercise derived mainly from not plasma FFA but muscle glycogen. Willmore and Costill(2001) demonstrate that low intensity (50% of maximal oxygen consumption: $\dot{V}O_2max$) in exercise training is more effective than high intensity(75% of $\dot{V}O_2max$). Because this intensity induces the percentage of

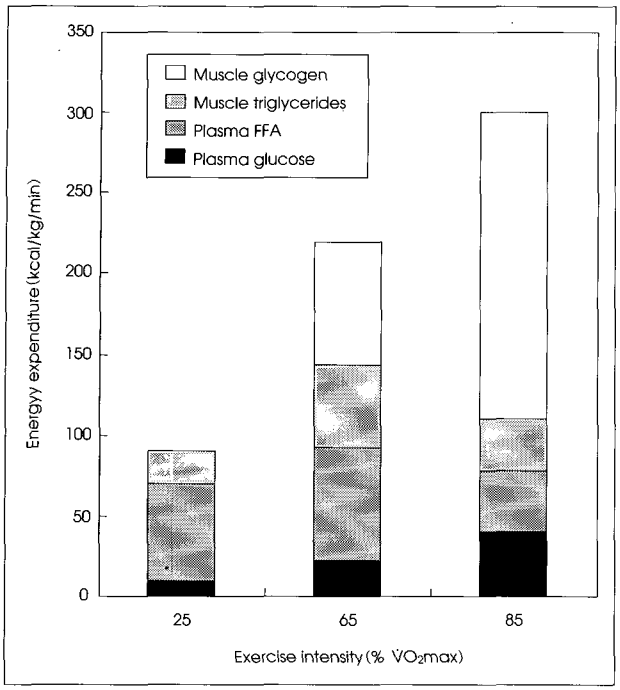

Fig. 1. Energy expenditure and exercise intensity. Source: Romijn et al. (1993), FFA: free fatty acid.

energy de-rived from fat, the energy derives from both 50% fat and 50% carbohydrate during low intensity exercise, while high intensity exercise expends only 38% of its energy from fat. Although exercise at high intensity decreases the percentage of energy derived from fat, it could induce an absolute expenditure of energy. Exercise at high intensity for a period of 30 minutes could expend 332kcal; meanwhile, 220 kcal is expended by low intensity exercise (Willmore, Costill 2001).

This is supported by the theory of excess post oxygen consumption (EPOC). Recovery from strenuous exercise requires more oxygen than from light exercise; therefore, depending on the intensity and duration of the previous exercise, oxygen requirement increases (Gillette et al. 1994; Smith, McNaughton 1993). To increase the effect of EPOC, stretching or light aerobic exercise such as brisk walking during five minutes is recommended. However, high intensity exercise acts negatively upon stress hormones (Buono et al. 1986) and the inflammation response (Kirwan, del Aguila 2003). Obese individuals also have difficulty performing high intensity exercise owing to their weight. Taken in conjunction, exercise scientists have suggested that moderate intensity (40~75% of $\dot{V}O_2max$) exercise is optimal for obesity treatment.

3. Exercise duration

The original duration of exercise is important in the treatment of obesity. A classic study (Edwards et al. 1934) shows the effects over long-durations for submaximal exercise, which displays a relationship between the respiratory quotient (RQ) and substrate use. Increased fat metabolism during prolonged exercise causes the reduction of glucose metabolism, which is related to inhibition of lipolysis. As the duration of exercise grows, FFA uptake by active muscle increases and intramuscular glycogen depletes. However, long durations like two to four hours are not realistic for obese individuals owing to the restriction of time and physical conditions such as fatigue. Moreover, long durations of exercise have been reported to produce negative effects on inflammation (Kirwan, del Aguila 2003). This phenomenon will be described in the present study. The ACSM position recommends a minimum of 20 minutes of aerobic exercise for improving aerobic capacity such as $\dot{V}O_2max$ (Pollock et al. 1998). Obese individuals are required for over 30 minutes of exercise with regards to aerobic capacity and energy expenditure. Several studies have suggested that exercise programs for obese individuals should include several shorter bouts of exercise throughout the day. 148 sedentary obese subjects either walked for 40 minutes continuously five days/week, or broke their sessions up into four ten-minute walks throughout the day over five weeks. A similar pattern of weight loss appeared in each group after 18 months (Jakicic et al. 1999). Taken together, 20 to 60 minutes of continuous or intermittent exercise (minimum of 10-minute bouts) is recommended in obesity treatment.

4. Exercise frequency

Exercise scientists recommend an aerobic exercise frequency of three to five days/week. Although aerobic exercise of three days per week is sufficient to improve or maintain $\dot{V}O_2max$, aerobic exercise of five days/week is efficient to treat obesity with regards to energy expenditure and rapid adaptation. However, aerobic exercise of over six days per week has shown minimum additional benefits, and this frequency could induce the risk of musculoskeletal injury (ACSM 2006). Compared with frequency of aerobic exercise, resistance training is recommended less frequency, two to three nonconsecutive days per week (ACSM 2006). This considers muscle fatigue and dropout rates while participating resistance training. If resistance exercise could be per-

formed daily, a different exercise for the muscle group every two to three sessions is recommended (ACSM 2006). Daily flexibility exercise is efficient to obese individuals while exercise program, particularly, resistance exercise. Two to four repetition is required in static stretching exercise involves the major muscle tendon units which focus on muscle group is recommended (ACSM 2006).

5. Physical activity

To lose weight and maintain weight loss, more exercise may be required. In the National Weight Control Registry in the U.S., 52% of those successful in maintaining weight loss expended an average of 10,500kcal/wk for women and an average of 13,860kcal/wk for men, which is equivalent to 60 to 80 minutes of moderate intensity activity on a daily basis (Wing, Hill 2001). Subsequent research also confirmed that an increased volume of exercise is required for weight maintenance in obese individuals (Fogelholm, Kukkonen-Harjula 2000; Schoeller et al. 1997).

Recent studies have demonstrated that physical inactivity is related to chronic disease such as obesity (ACSM 2006; Jeffery et al. 2003; Lee, Skerrett 2001). These studies suggested moderate-intensity activity such as brisk walking, household chores, gardening and recreational activitiy, could be an alternative to vigorous exercise, if total energy expenditure is similar amount. Recent studies elucidated effects of physical activity that life intervention through increasing physical activity is similar effects on aerobic fitness, body composition, and coronary risk factors as compared with traditional exercise program (Dunn et al. 1997; Andersen et al. 1999).

Moreover, subsequent research confirms effects of physical activity. Knowler et al. (2002) demonstrated that lifestyle modification via at least 150 minutes of physical activity per week was more effective than pharmacological treatment in reducing the incidence of type 2 diabetes. Increasing physical activity is feasible to obese individuals compared with traditional exercise with regards to activity intensity, adaptation with time and space. Therefore, in addition to exercise, increasing physical activity should be considered in obesity treatment. As shown in Fig. 2, the physical activity pyramid, which shows similar pattern to the USDA's food guide pyramid, has been suggested as model to enhance active life style and the resultant facilitating health benefits (ACSM 2006).

Based on previous studies, the following exercise prescriptions are proposed for obese individuals: 30 to 60 minutes of continuous or intermittent exercise (minimum of 10-minute bouts) five days/week at a moderate intensity of 40 − 75% of $\dot{V}O_2$max. In addition, to maintain weight loss in obese individuals, over 60 minutes of exercise, except physical activity, is recom-mended. More active life is also needed to increase energy expenditure.

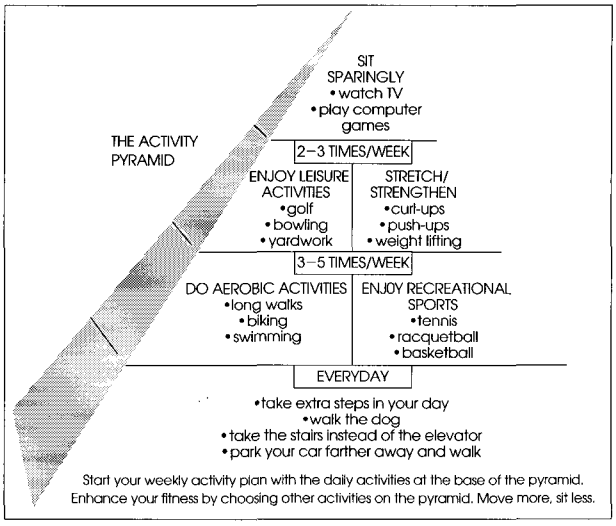

Fig. 2. Physical activity pyramid. Source: ACSM (2006).

Synergic Effects of Exercise and Diet on Obesity Treatment

Although exercise is the most integral part in obesity treatment, numerous studies have investigated that exercise alone provides an inefficient means of weight loss (Ballor et al. 1988; Lemons et al. 1989). Obese individuals particularly could be left unsatisfied with an exercise alone treatment program due to their desire for dramatic weight loss. It takes about 124 kilometers of running to burn one kilogram of fat. Therefore, combined exercise and diet in any weight loss program is recommended. Fig. 3 shows body composition changes for 40 obese women divided into four groups: control diet only and no exercise, diet plus resistance exercise, resistance exercise only and no diet (Ballor et al. 1988). In this study, diet is more effective in the reduction of weight whereas exercise increases total body weight due to an increase in lean body mass. However, diet alone in a weight loss program decreases lean body mass, which could influence the rest metabolic rate and lipid metabolism. In addition to this study, numerous researches have confirmed that diet is more

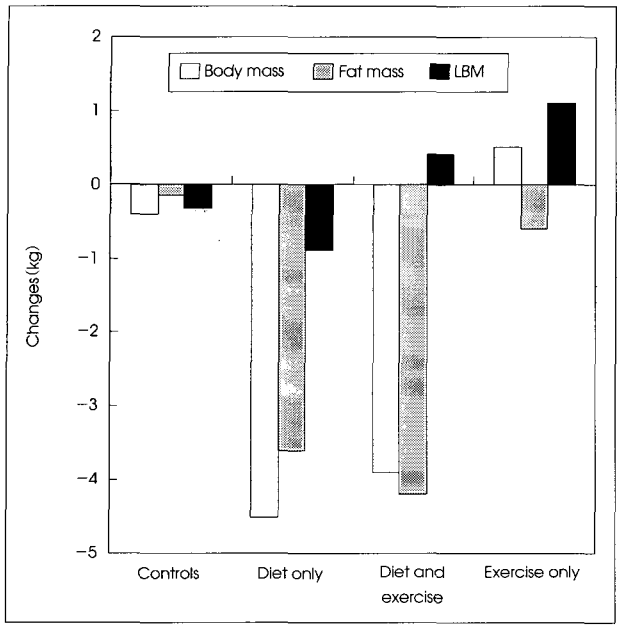

Fig. 3. Changes in body composition with combination of exercise and diet. Source: Ballor et al. (1988), LBM: lean body mass.

effective in reducing total body weight, but relative less effective in reducing body fat mass compared to a similar level of energy depletion via exercise (Stefanick et al. 1998; Tsai et al. 2003; Wood et al. 1988). The differences in the effect are associated with the fact that exercise stimulates the release of catecholamines such as epinephrine and norepinephrine, while food restriction by diet mainly stimulates the release of glucagon and glucocorticoids. Epinephrine stimulates free fatty acids from adipose tissue and blunts the glucose uptake by skeletal muscle. Norepinephrine serves both as a hormone and as a precursor of epinephrine, and also acts as a neurotransmitter when released by the sympathetic nervous system (Horrowitz 2003). On the other hand, glucagon stimulates the breakdown of glycogen in the liver, and glucocorticoids, mainly cortisol, promotes the breakdown of protein into amino acids in all cells of the body, except for the liver, which is the active tissue in gluconeogenesis (Girod, Brotman 2003). Therefore, exercise might induce the mobilization of storage fat, while energy deficits by dieting might provoke a tendency toward energy mobilization not from fat mass but from the total body weight.

There is a well-known "yo-yo" phenomenon of weight reduction and regain. Although exercise is relatively inefficient for weight loss compared to dieting, exercise itself has shown to play an essential role in the maintenance of weight loss. Meta-analysis of six randomly controlled trials compared the effects of diet alone on the maintenance of weight loss versus combining diet and exercise (Wing 1999). Subjects in the diet-plus-exercise groups in all six studies showed a better maintenance of weight loss over one year than the subjects in the diet-only groups.

Tsai et al. (2003) demonstrated that exercise is more efficient in the quality of weight loss. Thirteen female subjects displayed a 25% energy deficit, which was achieved by either diet or exercise, over nine days, and then energy repletion was performed over five days. As expected, exercise is more effective in reduction of body fat mass and improving high density lipoprotein cholesterol (HDL-C); however, diet is more effective in weight loss. Energy repletion without exercise has been reported to be less effective for maintaining fat mass and HDL-C. Therefore, it could be suggested that exercise is needed to avoid the "yo-yo" phenomenon and to improve the quality of weight loss in the treatment of obesity.

The data from the National Weight Control Registry in the U.S. shows the most convincing evidence from the studies above (Wing, Hill 2001). The Registry, which was founded in 1999, contains data on over 3000 subjects who have kept over 13.5kg off for over one year. Those successful in maintaining their weight loss performed three behavioral strategies: (1) eating a diet low in fat and high in carbohydrates; (2) frequent self-monitoring of body weight and food intake; and (3) high levels of regular physical activity. Ninety-one percent of the Registry participants are reported to have listed regular exercise, such as walking an hour a day, as a vital factor in maintaining their weight loss.

Combining regular exercise with a hypocaloric diet provides a considerably more efficient method for obtaining metabolic benefits rather than exercise or diet alone. A statement from the National Task Force on the Prevention and Treatment of Obesity in the U.S. best summarizes the difficulty of solving obesity: "Obese individuals who undertake weight loss efforts should be ready to commit to lifelong changes in their behavioral patterns, diet, and physical activities (Bensimhon et al. 2006)."

The Effects of Exercise on Metabolism in Obesity

1. The action upon hormonal regulation

Obesity is associated with metabolic disorders, alterations

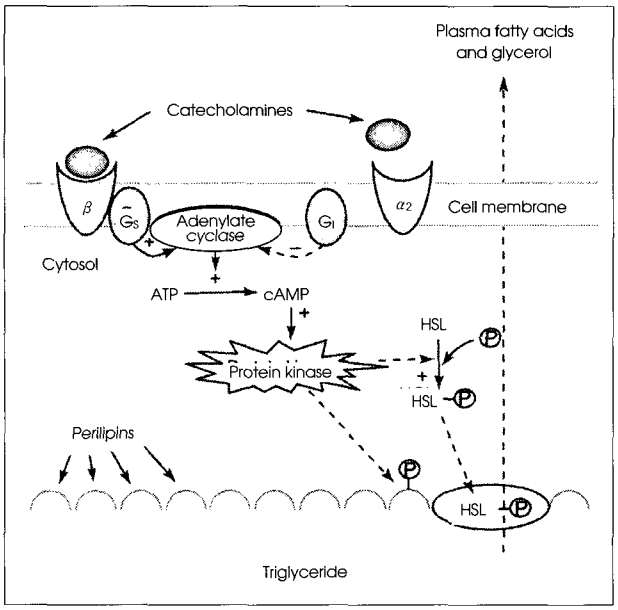

Fig. 4. The lipolytic cascade during exercise. Source: Horowitz JF (2003), $\alpha 2$: $\alpha 2$-adrenoreceptor, β: β-adrenoreceptor, G_I: inhibitory G protein, G_S: stimulatory G protein, HSL: hormone sensitive lipase, P: phosphate group.

in lipid oxidation and mobilization. Obese individuals have been shown to have difficulty regulating fatty acid metabolism. During exercise, obese individuals show higher RQs and lower capacities for fatty acid oxidation (Wade et al. 1990). This phenomenon is related to factors such as differing contents of FFA between muscle and plasma, as well as the capacity of β-oxidation in muscle and hormonal regulation (Blaak et al. 2001).

As shown in Fig. 4, the action of catecholamines upon adipocytes activates hormone sensitive lipase (HSL) via a cascade of cellular signals (Ballor et al. 1988). Catecholamies stimulate the lipolytic cascade by binding to β-adrenoreceptors (β-AR), which are coupled with a stimulatory G protein (G_S) on the plasma membrane in adipose tissue. G_S activates the conversion of ATP to cAMP, which in turn acts a secondary messenger to activate HSL and perilipin (Egan et al. 1992). On the other hand, catecholamines inhibit lipolysis via binding to $\alpha 2$- adrenoreceptors which are coupled with inhibitory G proteins (G_I). During exercise, increased catecholamines stimulate β-ARs, which can inhibit binding with $\alpha 2$-adrenoreceptors (AR), resulting in an increase in whole-body lipolysis (Londos et al. 1995; Tansey et al. 2003). Norepinephrine increases markedly at intensites exceeding 50% $\dot{V}O_2$max, meanwhile epinephrine starts increasing after 60% $\dot{V}O_2$max of exercise intensity (Macardle et al. 2001). Catecholamines have been reported to increase with increased intensity and duration of exercise (Kraemer 1988; Mora-Rodriguez, Coyle 2000).

Unlike catecholamines, Insulin inhibits lipolysis in adipose tissue. Two of the main actions of insulin upon fat storage appear in lipoprotein lipase (LPL) and HSL. LPL is the enzyme responsible for the release of FFA from circulating lipoprotein-lipid particles for uptake by tissues (Frayn et al. 1995). HSL is an enzyme which is necessary for breaking down stored intracellular lipids into circulating FFA. Insulin stimulates LPL while inhibiting HSL, inducing lipogenesis and inhibiting lipolysis (Girod, Brotman 2003). Exercise has been reported to decrease the concentration of plasma insulin resulting in an increase in the lipolytic rate (Wasserman et al. 1989; Willmore, Costill 2001). Taken together, the recommended strategy for obesity treatment is to coordinate the effects of insulin on exercise and food intake. Immediately following food intake, exercise should be avoided because increased insulin caused by food intake might interfere with the effects of exercise on lipolysis, which is involved with decreasing insulin.

Although catecholamines and insulin are the primary factors regulating adipose tissue lipolysis, other hormones could also influence the lipolytic process. Many factors, conditions and environments could diversely influence the regulation of lipolysis and fatty acid mobilization during exercise. These factors include sex (Mittendorfer et al. 2002), age (Sial et al. 1996), diet (Podolin et al. 1999), obesity (Kanaley et al. 1993), and weight loss (Kanaley et al. 1993).

Cortisol has been reported to act both as a lipolytic stimulator (Samra et al. 1996) and an inhibitor (Ottosson et al. 2000). Although previous studies are inconsistent and unclear, cortisol might contribute lipogenesis in obese individuals with metabolic syndromes. Cortisol, known as a fat sparer, is involved with insulin in stimulating lipogenesis and inducing LPL. Increasing fat storage through cortsiol induces the Cushing syndrome, which shows a nearly similar pattern to the metabolic syndrome (Ramsey 1996). The 'fat sparing' role in cortisol could increase metabolic efficiency (Eden et al. 1999). This increase in metabolic efficiency could frustrate weight loss although it provides some benefit in cases of starvation. Exercise training has been reported to regulate the cortisol level. A moderate intensity of exercise could particularly decrease cortisol in obese individuals, but acute exercise or high intensity of exercise could frustrate the

decrease of cortisol concentrations (Buono et al. 1986).

Obese people have been shown to be relative deficient in the production of growth hormone (GH), which is related to the metabolic syndrome (Nam, Marcus 2002). It is no surprise that GH acts on muscle tissue through increased muscle mass by exercise. GH also diminishes adipose tissue by suppressing LPL activity and stimulating HSL activity (Ho et al. 2001). A decrease of GH in the metabolic syndrome has been reported to indirectly stimulate cortisol (Girod, Brotman 2003). With increased age, insensitivity to the circadian cortisol pattern, which shows a high concentration in the morning (9 AM) and a low concentration in the evening (9 PM) (Bradbury et al. 1994; Samra et al. 1996), and reduction in circulating GH cause central obesity and a greater prevalence of the metabolic syndrome. Decreased sex hormones, such as testosterone, in the elderly could also influence not only the loss of muscle mass but also the development of central obesity.

Numerous studies have reported that exercise, particularly resistance exercise, could increase GH concentration, which affects muscle mass (McMilan et al. 1989; Vanhelder et al. 1984). GH concentration depends on the intensity of exercise, therefore low-intensity exercise has shown no changes of GH secretion (Stokes 2003). These studies demonstrate the effects of exercise on the quality of obesity treatment irrespective of the resulting weight loss, although increased muscle mass by resistance training could increase total body weight.

It is unlikely that a single hormone might directly influence obesity or obesity-related disorders such as the metabolic syndrome. However, once the state of dysregulation in any single hormone occurs, an entire state of dysregulation could arise because obesity can be triggered through any factor which is related to the metabolic syndrome. Furthermore, by controlling factors such as hormones and enzymes which are involved in lipolysis or lipogenesis, exercise can be a key weapon for solving the obesity problem.

2. Action on skeletal muscle

During exercise, FA released from TG in adipose tissue uses fat as a fuel. This FA must be transported into the skeletal muscle and then on to the mitochondria, the main site of fat oxidation. Exercising for several hours could exhaust the contents of intramyocelluar lipids (IMCL) in human muscle. Endurance training could increase the capacity of extramyocellular FA oxidation and increase the use of lipids as a substrate with regard to both relative and absolute exercise intensity (Horrowitz, Kleins 2000). This is demonstrated by an increase in mitochondrial volume, density and content of IMCL during bicycle training and long-distance running (Howald et al. 1985). Fig. 5 shows the metabolization of FA, which aligns transport, storage, and conversion steps in skeletal muscle (Schmitt et al. 2003). LDL and several proteins are related to transporting FA, which might be stored as IMCL or transferred to the mitochondria for immediate oxidation (Glatz, Storch 2001; McArthur et al. 1999). Therefore, the muscle fatty acid binding protein (FABPc) has been reported to play a key role in the intramyocellular transport of FFA (Glatz, Storch 2001). Diacylglycerol O-acyltransferase 1 (ARGP1) also acts upon the storage of FA as IMCL by joining FA to diacyclglycerol (Oelker et al. 1998). HSL stimulates the release of FFA from IMCL for mitochondrial oxidation. Carnitine palmitoyltranferase 1 (CPT 1) is an essential enzyme for the uptake of FA into the mitochondrial matrix, and long chain acyl-coenzyme A de-

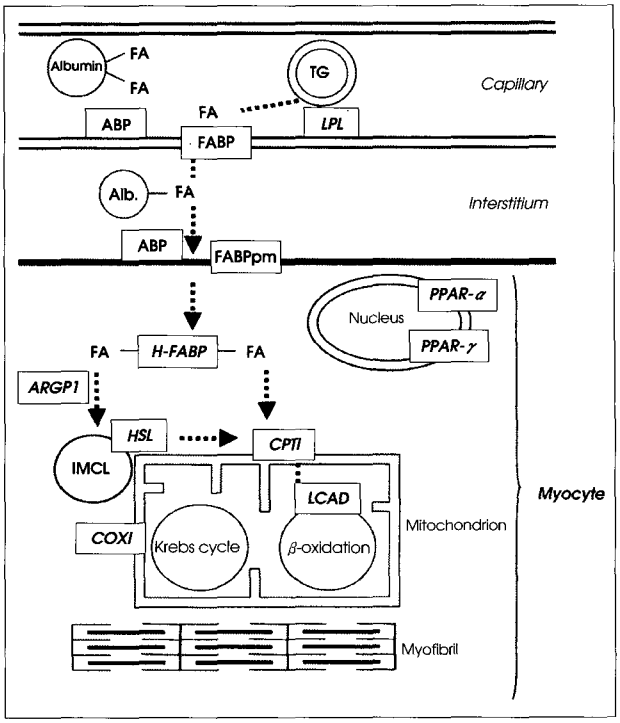

Fig. 5. Scheme of fatty acid transport and metabolism. Source: Schmitt et al. (2003), ARGP1: Diacylglycerol O-acyltransferase 1, Cox1: Cytochrome c oxidase 1, CPT 1: Carnitine palmitoyltranferase 1, FABP: fatty acid binding protein, HSL: hormone sensitive lipase, IMCL: intramycellular lipids, LCAD: long chain acyl-coenzyme A dehydrogenase, LPL: lipoprotein lipase, PPARs: peroxisome proliferator-activated receptors.

hydrogenase (LCAD) is involved in mitochondrial oxidation (Jeukendrup 2002). Cytochrome c oxidase 1 (COX 1) is a major enzyme in mitochondria, which encode oxidative phosphorylation and the final electron transfer to O_2 (Schmitt et al. 2003). The integral enzymes in lipid metabolism like the peroxisome proliferator-activated receptors (PPAR- α, PPAR-r) in muscle are stimulated by exercise training (Desvergne, Wahli 1999).

In addition to lipid metabolism, recent studies have reported that glucose metabolism in skeletal muscle is involved with exercise (Brozinick et al. 1993; Dohm 2002; Friedman et al. 1990; Goodyear et al. 1992). The action of insulin on glucose metablism is to recruit the glucose transporter (GLUT) from an intracellular pool to the cell's surface. Fat and muscle cells have been reported to require the presence of insulin for the production of significant glucose transporters such as GLUT-4 (Ezaki 1997). Because skeletal muscle is an important tissue in glucose homeostasis, an increase in GLUT-4 through exercise could reduce the risk of diabetes, which is related to obesity. Exercise could rapidly change GLUT-4 expression, which has a short half life (Dohm 2002). Terada et al. (2001) demonstrate the change of GLUT-4 expression in high intensity, intermittent training (fourteen 20-second exercise bouts/day for eight days) and low intensity, prolonged exercise (total exercise time of 360 min/day for eight days). Meanwhile, eccentric exercise, such as prolonged downhill running and marathon running, could decrease muscle GLUT-4 in men (Asp et al. 1995). These excessive eccentric contractions cause muscle damage and disruption of the integrity in the cell, including insulin signaling (Kirwan, del Aguila 2003). Blakemore et al. (1996) showed that physical inactivity, such as casting, for one week could decrease muscle GLUT-4 by 50%, and this level remained after six weeks of casting. In addition to exercise, GLUT-4 expression can be induced by increased levels of insulin (Jones, Dohm 1997), thyroid hormone (Torrance et al. 1997) and decreased levels of cAMP (Jones, Dohm 1997; Vinals et al. 1997). However, exercise directly regulates muscle GLUT-4 irrespective of insulin action. Kawanaka et al. (1996) provided evidence that treadmill training increases muscle GLUT-4 protein and mRNA in streptozotocin diabetic rats which have abnormal insulin actions.

Effects of Exercise on Inflammation

Obesity has originally been considered a metabolic disease rather than an inflammatory disease. With the rising prevalence of obesity, many scientists have focused on adipose tissue, which is the main site for energy storage. However, with the discovery of leptin in 1994, our understanding of adipose tissue, which secretes signaling molecules, the so-called "adipocytokines," has undergone a revolutionary change. In addition to leptin, several adipocytokines have been discovered over the last ten years. Recent research efforts have

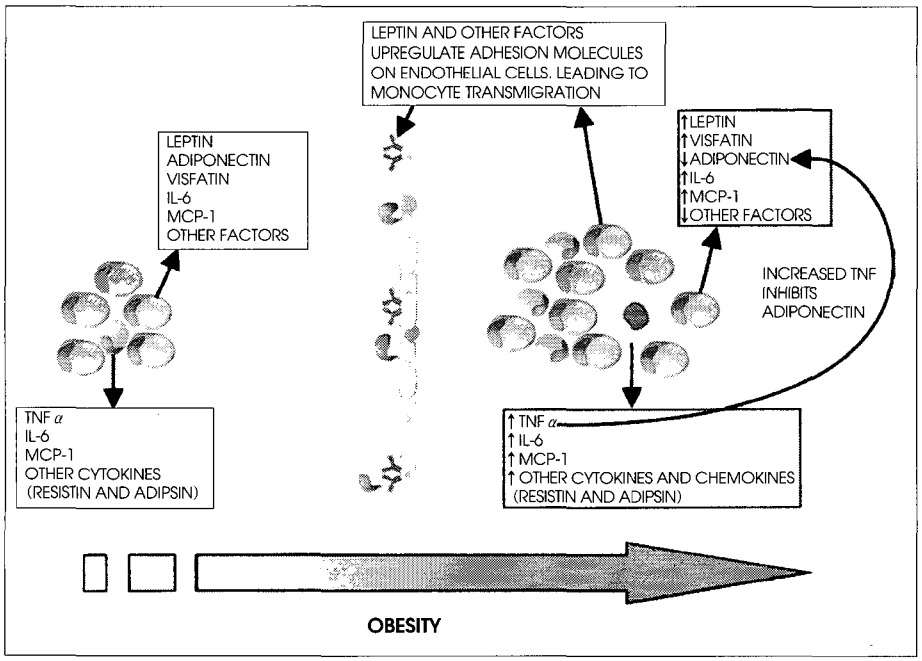

Fig. 6. Adipocytokines released by adipose tissue. Source: Fantuzzi (2005), MCP-1: Monocyte chemoattractant protein 1, TNF-α: tumor necrosis factor α, IL-6: interleukin-6.

revealed other functions of adipocytokines extending far beyond metabolism, such as inflammatory response (Fantuzzi 2005; Koerner et al. 2005). Obesity provokes inflammatory conditions via production of inflammatory cytokines, which stimulate signal pathways. Adipocytokines and inflammatory signal molecules from adipose tissue have been implicated in the development of obesity-related diseases, such as type 2 diabetes, cardiovascular disease (CVD) and atherosclerosis (Fantuzzi 2005; Koerner et al. 2005; Koh et al. 2005). Fig. 6 shows adipocytokines released by adipose tissue. Adipocytokines include adipokines leptin, adiponectin, resistin, and visfatin, as well as chemokines and cytokines such as tumor necrosis factor α (TNF-α) and interleukin (IL)-6 (Fantuzzi 2005; Koh et al. 2005)

Leptin, the most well known of the adipocytokines, is regulated via hormone, nutrient, and energy balance (Frayn et al. 2003). The circulating leptin is positively related to fat mass, as shown in human and rodent studies (Considine 1997; Ahren et al. 1997). Leptin has been reported to regulate appetite and resultant control energy homeostasis (Elmquist 2001). In addition to metabolism, leptin is also associated with inflammation, which was confirmed by evidence that leptin deficiency induces susceptibility to the toxicity of the pro-inflammatory response, such as TNF-α (Takahashi et al. 1999; Faggioni et al. 1999). And several hormones associated with the regulation of leptin which are altered by exercise include cortisol, growth hormone, and catechlamines (Ahima, Flier 2000; Kreamer et al. 1999; Berneis et al. 1996). Growth hormone and cortisol have been reported to stimulate leptin production (Berneis et al. 1996; Wabitsh et al. 1997), meanwhile catecholamines inhibit leptin production (Gettys et al. 1996; Carulli et al. 1999). Numerous studies report that leptin levels can be improved through various exercise programs (Monzillo et al. 2003). Although short-term (< 60 min) acute exercise has no effect on the changes of leptin levels, long-term acute exercise such as a 25km sea swimming could reduce the circulating leptin levels (Landt et al. 1997) owing to the change in energy balance. Exercise scientists recommend combined exercise training and diet to improving leptin levels (Halle et al. 1999; Ishii et al. 2001; Kraemer et al. 2002) because the reduction in leptin concentration is caused by changes in energy balance (Hickey et al. 1997).

Circulating resistin, which is reported to induce insulin resistance, increases with high fat diets and in obese models (Frayn et al. 2003). Based on studies published to date, the physiological role of resistin in obesity-related insulin resistance in humans is unclear. However, Lehrke and colleagues (2004) demonstrate that stimulated macrophages with pro-inflammatory cytokines show a marked increase in resistin production. From the limited number of previous studies, we can observe that exercise does not affect resistin levels in obese individuals (Giannopoulou et al. 2005; Monzillo et al. 2003).

Visfatin, a newly discovered adipocytokine, is secreted mainly from visceral fat (Fukuhara et al. 2005). Visfatin binds to the insulin receptor, and resultantly acts as an insulin mimic (Fukuhara et al. 2005). Moreover, Jia et al. (2004) report that visfatin is secreted by endotoxin-stimulated neutrophils and inhibits neutrophil apoptosis. Based upon the limited studies on visfatin, this adipocytokine could reflect the relationship between adipose tissue and inflammation. Because visfatin was only recently discovered, there are few studies about whether exercise might improve visfatin. Further studies are expected to demonstrate the effects of exercise on visfatin.

Adiponectin is also secreted by adipocyte, which regulates insulin sensitivity to energy metabolism and is associated with obesity and insulin resistance (Koh et al. 2005). Plasma levels of adiponectin are negatively correlated with adipose tissue, and decreased levels of adiponectin have been shown in obese and type 2 diabetic individuals (Yu et al. 2002). The anti-inflammatory activities of adiponectin are related to a reduction of TNF-α and IL-6 (Fantuzzi 2005). Bluher et al. (2006) report that exercise causes increases not only in plasma adiponectin, but also in muscular adiponectin receptors' (AdipoR1 and R2) expression, which is relatively high in order to compensate for the low levels of adiponectin in obese individuals. However, acute and intensive exercise for over three hours has no effect on circulating adiponectin although it does increase AdipoR1 and R2 expression. Increased adiponectin levels were reported in a weight loss program with life modification, which involved a low energy Mediterranean-style diet and increased physical activity (Esposito et al. 2003). On the other hand, some reports have revealed that exercise training could not improve adiponectin levels in obese subjects (Marcell et al. 2005). Therefore, further studies on adiponectin changes caused by exercise are needed, including exercise type, intensity and volume.

TNF-α and IL-6 are well-known cytokines related to obesity and show increased levels in serum and adipose

tissue (Cottam et al. 2004). TNF-α and IL-6 regulate C-reactive protein (CRP) release from the liver and increased plasma CRP production. In addition, increased levels of TNF-α and IL-6 are related to increased insulin resistance, deterioration of glycemic control, and contribute to the dysfunctional metabolic status in obese and type 2 diabetic individuals (Kanemaki et al. 1998). The reduction in total body fat mass could play a role in decreased IL-6 levels (Fried et al. 1998). Monzillo et al. (2003) demonstrate that decreased IL-6 levels and a tendency toward decreased TNF-α levels, via life modification programs consisting of a hypocaloric diet combined with moderate physical activity, cause weight reduction in obese individuals. Giannopoulou et al. (2005) report no change of IL-6 and TNF-α levels by either exercise or combined exercise and diet, irrespective of fat mass in obese postmenopausal women with type 2 diabetes. Exercise, particularly aerobic exercise, has been reported to improve cytokine levels independent of the individual's body mass index (BMI) (Kohut et al. 2006). However, exercise, such as running in marathons, induces production of TNF-α, which is stimulated through muscle-damage, impaired glucose homeostasis, and the acute-phase response (APR) (Kirwan, del Aguila 2003). This could provide a warning to obese individuals currently in a weight loss program who exercise over a long duration or perform excessively high intensity exercises. Elderly obese individuals, particularly, should choose deliberately when exercising because aging invokes a pro-inflammatory state. From these results, we suggest that a proper exercise program can improve the quality of obesity treatment with regards to not only weight loss but also the regulation of the inflammation response.

Conclusion

Exercise training contributes to decreasing weight loss, including fat mass, and improves lipid and glucose metabolism through the regulation of hormone, muscle, and adipose tissue. Exercise can also modulate the inflammation response in obese individuals irrespective of weight loss. Various approaches toward exercise have been reported to improve metabolism and inflammation in obesity treatment. Moderate, but not long, durations of exercise are recommended, although high intensity and long durations (> 2h) of exercise induce positive effects on the balance of energy. Even if a single exercise stimulates the lipolytic process, this will not cure obesity if exercise is discontinued. The following recommendation for exercise treatment of obesity is proposed. This includes 20 to 60 minutes of continuous or intermittent exercise (a minimum of 10-minute bouts), three to five days/week at a moderate level of intensity. Lifestyle modification, such as increased physical activity and a hypocaloric diet, is also needed for maximum synergic effects in losing and maintaining weight loss.

In conclusion, although diet is more efficient in the quantity of obesity treatment with regards to weight loss, exercise including physical activity improves the quality of obesity treatment with regards to body composition, metabolism and inflammation. This review verifies the crucial role of exercise in obesity treatment. However, previous studies on exercise and adipocytokines produced controversial and unclear results. Further studies are required in order to gain a more complete understanding of the relation between exercise and obesity-related factors, such as nutrition, genes, hormones and lifestyle.

References

Ahima RS, Flier JS (2000): Leptin. *Annu Rev Physiol* 62: 413-437

Ahren B, Mansson S, Gingerich RL, Havel PJ (1997): Regulation of plasma leptin in mice: influence of age, high-fat diet, and fasting. *Am J Physiol* 273 (1pt2): R113-R120

American College of Sports Medicine (ACSM) (2006): ACSM's guidelines for exercise testing and prescription. Lippincott Williams & Wilkins, USA

Anderson RE, Wadden TA, Bartlett SJ, Zemel B, Verde TJ, Franckowiak SC (1999): Effect of lifestyle activity vs structured aerobic exercise in obese women: a randomized trial. *JAMA* 281: 335-340

Asp S, Daugaard JR, Rishter EA (1995): Eccentric exercise decreases GLUT4 protein in human skeletal muscle. *J Physiol* 482 (pt3): 705-712

Ballor DL, Katch VL, Beque MD, Marks CR (1988): Resistance weight training during caloric restriction enhances lean body weight maintenance. *Am J Clin Nutr* 47 (1): 19-25

Bensimhon DR, Kraus WE, Donahue MP (2006): Obesity and physical activity. *Am Heart J* 151 (3): 598-603

Berneis K, Vosmeer S, Keller U (1996): Effects of glucocorticoids and of growth hormone on serum concentrations in man. *Eur J Endocrinol* 135 (6): 663-665

Blaak EE, Glatz JF, Saris WH (2001): Increase in skeletal muscle fatty acid binding protein (FABPC) content is directly related to weight loss and to changes in fat oxidation following a very low calorie diet. *Diabetologia* 44 (11): 2013-2017

Blakemore SJ, Rickhuss PK, Watt PW, Rennie MJ, Hundal HS

(1996): Effects of limb immobilization on cytochrome c oxidase activity and GLUT5 protein expression in human skeletal muscle. *Clin Sci (Lond)* 91(5): 591-599

Bluher M, Bullen JW Jr, Lee JH, Kralisch S, Fasshauer M, Kloting N, Niebauer J, Schon MR, Williams CJ, Mantzoros CS(2006): Circulating adiponectin and expression of adiponectin receptors in human skeletal muscle: Associations with metabolic parameters and insulin resistance and regulation by physical training. *J Clin Endocrinol* March 21

Bonen A, Luiken JJ, Arumugam Y, Glatz JF, Tandon NN(2000): Acute regulation of fatty acid uptake involves the cellular redistribution of fatty acid translocase. *J Biol Chem* 275(19): 14501-14508

Bosselaers I, Buemann B, Victor OJ Astrup A(1994): Twenty-four-hour energy expenditure and substrate utilization in body builders. *Am J Clin Nutr* 59(1): 10-12

Bradbury MJ, Akana SF, Dallman MF(1994): Roles of type I and II corticosteroid receptors in regulation of basal activity in the hypothalamo-pituitary-adrenal axis during the diurnal trough and the peak: evidence for a nonadditive effect of combined receptor occupation. *Endocrinolgy* 134(3): 1286-1296

Brozinick JT Jr, Etgen GJ Jr, Yaspelkis BB 3rd, Kang HY, Ivy JL (1993): Effects of exercise training on muscle GLUT-4 protein content and translocation in obese Zucker rats. *Am J Physiol Endocrinol Metab* 265: E419-E427

Buono MJ, Yeager JE, Hodgdon JA(1986): Plasma adrenocorticotropin and cortisol responses to brief high-intensity exercise in humans. *J Appl Physiol* 61(4): 1337-1339

Carulli L, Ferrari S, Bertilini M, Tagliafico E, Del Rio G(1999): Regulation of ob gene expression: evidence for epinephrine-induced suppression in human obesity. *J Clin Endocrinol Metad* 84: 3309-3312

Christensen BK, Terbizan DJ, Deblauw C(2004): No changes in commitment to exercise in adults during a 14 week concurrent exercise training program. *Med Sci Sports Exerc* 36(5): 64.

Considine RV(1997): Leptin and obesity in humans. *Eat Weight Disord* 2(2): 61-66.

Cottam DR, Mattar SG, Barinas-Mitchell E, Eid G, Kuller L, Kelley DE, Schauer PR(2004): The chronic inflammatory hypothesis for the morbidity associated with morbid obesity: implications and effects of the weight loss. *Obes Surg* 14: 589-600

Desvergne B, Wahli W(1999): Peroxisome proliferator-activated receptors: nuclear control of metabolism. *Endocr Rev* 20(5): 649-688

Dohm GL(2002): Invited review: Regulation of skeletal muscle GLUT-4 expression by exercise. *J Appl Physiol* 93: 782-787

Dunn AL, Marcus BH, Kampert JB, Garcia ME, Kohl HW 3rd, Blair SN(1999): Comparison of lifestyle and structured interventions to increase physical activity and cardiorespiratory fitness: a randomized trial. *JAMA* 281: 327-334

Eden NK, Moshirfar A, Potter GM, Castonguay TW(1999): Adrenalectomy reduces adiposity by decreasing food efficiency, not direct effects on white adipose tissue. *Obesity Res* 7(4): 395-401

Edwards HT, et al(1934): Metabolic rate, blood sugar and utilization of carbohydrate. *Am J Physiol* 108: 203

Egan JJ, Greenberg AS, Chang MK, Wek SA, Moos MC Jr, Londos C(1992): Mechanism of hormone-stimulated lipolysis in adipocytes: translocation of hormone-sensitive lipase to the lipid storage droplet. *Proc Natl Acad Sci U.S.A.* 89(18): 8537-8541

Elmquist JK(2001): Hypothalamic pathways underlying the endocrine, autonomic, and behavioral effects of leptin. *Physiol Behav* 74: 703-708

Esposito K, Pontillo A, Di Palo C, Giugliano G, Masella M, Marfella B, Giugliano D(2003): Effects of weight loss and life style changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA* 289: 1799-804

Ezaki O(1997): Regulatory elements in the insulin-responsive glucose transporter(GLUT4) gene. *Biophys Commun* 241: 1-6

Faggioni R, Fantuzzi, G, Fuller J, Dinarello CA, Feingold KR, Grunfeld C(1999): Leptin deficiency enhances sensitivity to endotoxin-induced lethality. *Am J Physiol* 276: R136-142

Fantuzzi G(2005): Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol* 115: 911-919

Fogelholm M, Kukkonen-Harjula K(2000): Does physical activity prevent weight gain-a systematic review. *Obes Rev* 1: 95-111

Frayn KN, Coppack SW, Fielding BA, Humphreys SM(1995): Coordinated regulation of hormone-sensitive lipase and lipoprotein lipase in human adipose tissue in vivo: implications for the control of fat storage and fat mobilization. *Adv Enzyme Regul* 35: 163-178

Frayn KN, Karpe F, Fielding BA, Macdonald IA, Coppack SW (2003): Integrative physiology of human adipose tissue. *Int J Obes Relat Metab Disord* 27: 875-888

Fried SK, Bunkin DA, Greenberg AS(1998): Omental and subcutaneous adipose tissue of obese subjects release interleukin-6. *J Clin Endocrinol Metab* 83: 847-50

Friedman JE, Sherman WM, Reed MJ, Elton CW, Dohm GL(1990): Exercise training increases glucose transporter protein GLUT-4 in skeletal muscle of obese Zucker(fa/fa) rats. *FEBS Lett* 268: 13-16

Fukuhara A, Matsuda M, Nishizawa M, Segawa K, Tanaka M, Kishimoto K, Matsuki Y, Murakami M, Ichisaka T, Murakami H, Watanabe E, Takagi T, Akiyoshi M, Ohtsubo T, Kihara S, Yamashita S, Makishima M, Funahashi T, Yamanaka S, Hiramatsu R, Matsuzawa Y, Shimomura I(2005): Visfatin: A protein secreted by visceral fat that mimics the effects of insulin. *Science* 307: 426-430

Gettys TW, Harkness PJ, Watson PM(1996): The β3-adrenergenic receptor inhibits insulin-stimulated leptin secretion from isolated rat adipocytes. *Endocrinology* 137: 4054-4057

Giannopoulou I, Fernhall B, Carhart R, Weinstock RS, Baynard T, Figueroa A, Kanaley JA(2005): Effect of diet and/or exercise on the adipocytokine and inflammatory cytokine levels of postmenopausal women with type 2 diabetes. *Metabolism* 54(7): 866-875

Gillette CA, Bullough RC, Melby CL(1994): Posterxercise energy expenditure in reponse to acute aerobic or resistive exercise. *Int J Sport Nutrition* 4(4): 347-360

Girod JP, Brotman DJ(2003): The metabolic syndrome as a vicious cycle: does obesity beget obesity? *Medical Hypotheses* 60(4): 584-589

Glatz JF, Storch J(2001): Unravelling the significance of cellular fatty acid-binding proteins. *Curr Opin Lipidol* 12: 267-274

Glowacki SP, Martin SE, Maurer A, Baek W, Green JS, Crouse SF (2004): Effects of resistance, endurance, and concurrent exercise on training outcomes in men. *Med Sci Sports Exerc* 36(12): 2119-2127

Goodyear LJ, Hirshman MF, Valyou PM, Horton ES(1992): Glucose transporter number, function and subcellular distribution in rat skeletal muscle after exercise training. *Diabetes* 41: 1091-1099

Groop L, Ortho-Melander M(2001): The dysmetabolic syndrome. *J Intern Med* 250: 105-120

Halle M, Berg A, Garwers U, Grathwohi D, Knisel W, Kuel J (1999): Concurrent reductions of serum leptin and lipids during weight loss in obese males with type II diabetes. *Am J Physiol Endocrinol Metab* 277: E277-E282

Hickey MS, Houmard JA, Considine RV, Tyndall GL, Midgette JB, Gavigan KE, Weidner ML, McCammon MR, Israel RG, Caro JF(1997): Gender-dependent effects of exercise training on serum leptin levers in humans. *Am J Physiol Endocrinol Metab* 272: E562-566

Ho SC, Chen YM, Leung SS(2001): Association between simple anthropometricindices and cardiovascular rick factors. *Int J Obes Relat Metab Disord* 25: 1689-1697

Horowitz JF(2003): Fatty acid mobilization from adipose tissue during exercise. *Trends Endocirol Metab* 14(8): 386-392

Horowitz JF, Klein S(2000): Lipid metabolism during endurance exercise. *Am J Clin Nutr* 72: 558S-563S

Howald H, Hoppeler H, Claassen H, Mathieu O, Straub R(1985): influences of endurance training on the ultrastructural composition of the different muscle fiber types in humans. *Pfliigers Arch* 403: 369-376

Hurley BF, Hagberg JM, Goldberg AP, Seals DR, Ehsani AA, Brennan RE, Holloszy JO(1988): Resistance training can reduce coronary risk factors without altering O_2max or percent body fat. *Med Sci Sport Exerc* 20: 150-154

Hurley BF, Nemeth PM, Martin WH, Hagberg JM, Dalsky GP, Holloszy JO(1986): Muscle triglyceride utilization during exercise: effect of training. *J Appl Physiol* 60(2): 562-567

Ishii T, Yamakita T, Yamagami K, Yamamoto T, Miyamoto M, Kawasaki K, Hosoi M, Yoshioka K, sata T, Tanaka S, Fujii S (2001): Effect of exercise training on serum letin levers in type 2 diabetic patients. *Metabolism* 50: 1136-1140

Jakicic JM, Winters C, Lang W, Wing RR(1999): Effects of intermittent exercise and use of home exercise equipment on adherence, weight loss, and fitness in overweight women. *JAMA* 282: 1554-1560.

Jeffery RW, Wing RR, Sherwood NE, Tate DF(2003): Physical activity and weight loss: does prescribing higher physical activity goals improve outcome? *Am J Clin nutr* 78: 684-689

JeuKendrup A(2002): Regulation of fat metabolism in sKeletal muscle. *Ann NY Acad Sci* 967: 1-19

Jia SH, Li Y, Parodo J, Kapus A, Fan L, Rotstein OD, Marshall JC (2004): Pre-B cell colony-enhancing factor inhibits neutrophil apoptosis in experimental inflammation and clinical sepsis. *J Clin Invest* 113(9): 1318-1327

Jones JP, Dohm GL(1997): Regulation of glucose transporter GLUT-4 and hexokinase II gene transcription by insulin and epinephrine. *Am J physiol Endocrinol Metab* 273: E682-687

Kanaley JA, Cryer PE, Jensen MD(1993): Fatty acid kinetic responses to exercise. Effects of obesity, body fat distribution, and energy-restricted diet. *J Clin Invest* 92(1): 255-261

Kanemaki T, Kitade H, Kairobi M(1998): Interleukin I beta and interleukin 6, but not tumor necrosis factor alpha inhibit insulin stimulated glycogen synthesis in rat hepatocytes. *Hepatology* 27: 1296-303.

Kawanaka K, Higuchi M, Ohmori H, Shimegi S, E zaki O, Katsuta S(1996): Muscle contractile activity modulates GLUT4 protein content in the absence of insulin. *Horm Metab Res* 28: 75-80

Kirwan JP, del Aguila LF(2003): Insulin signaling, exercise and celluar integrity. *Biochem Soc Trans* 31: 1281-1285

Klein DA, William JS, Wayne TP(2002): PNF training and physical function in assisted-living older adults. *J Aging Phys Activity* 41: 476-488

Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, Diabetes Prevention Program Research Group(2002): Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346(6): 393-403

Koerner A, Kratzsch J, Kiess W(2005): Adipocytokines: leptin-the classical, resistin-the controversial, adiponectin-the promising, and more to come. *Best Pract Res Clin Endocrino Meatab* 19 (4): 525-546

Koh KK, Han SH, Quon MJ(2005): Inflammatory markers and the metabolic syndrome. *J Am Coll Cardiol* 46(11): 1978-85

Kohut ML, McCann DA, Russel DW, Konopka DN, Cunnick JE, Franke WD, Castillo MC, Reighard AE, Vanderah E(2006): Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of β-blocker, BMI, and pscychosocial factors in older adults. *Brain, Behav, and Immun* 20(3): 201-209

Kraemer RR, Chu H, Castracane VD(2002): Leptin and exercise. *Exp Biol Med* 227: 701-708

Kraemer RR, Jhonson LG, Haltom RW, Hebret EP, Gimpel T, Castracane VD(1999): Serum leptin concentrations in response to acute exercise in postmenopausal females with and without hormone replacement therapy. *Proc Soc Exp Biol Med* 221: 171-177

Kramer WJ(1988): Endocrine response to resistence exercise. *Med Sci Sport Exerc* 29: S152

Landt M, Lawson GM, Helgeson JM, Davila-Roman VG, Ladenson JH, Jaffe AS, Hickner RC(1997): Prolonged exercise decreases serum leptin concentrations. *Metabolism* 46: 1109-1112

Lee IM, Skerrett PJ(2001): Physical activity and all-cause mortality: what is the dose- response relation? *Med Sci Sports Exerc* 33: S459-71

Lehrke M, Reilly MP, Millington SC, Iqbal N, Rader DJ, Lazar MA(2004): An inflammatory cascade leading to hyperresistinemia in humans. *PloS Med* 1(2): 45

Lemon AD, Kreitzman SN, Coxon A, Howard A(1989): Selection of appropriate exercise regimes for weight reduction during VLCD and maintenance. *Int J Obes Metab Disord* 12(Suppl

2): 119-123
Londos C, Brasaemle DL, Gruia-Gray J, Servetnick DA, Schultz CJ, Levin DM, Kimmel AR (1995): Perilinin: unique proteins associated with intracellular muetral lipid droplets in adipocytes and steroidogenic cells. *Biochem Soc Trans* 23 (3): 611-615
Macardle WD, Katch FI, Katch VL (2001): Exercise physiology. Lippincott Williams & Wilkins, USA
Marcell TJ, McAuley KA, Traustadottir T, Reaven PD (2005): Exercise training is not associated with improved levels of C-reactive protein or adiponectin. *Metabolism* 54 (4): 533-541
Martin, WH, Dalsky GP, Hurley BF, Matthews DE, Bier DM, Hagberg JM, Roger MA, King DS, Holloszy JO (1993): Effects of endurance training on plasma free fatty acid turnover and oxidation during exercise. *Am J Physiol* 265: E708-E714
McArthur MJ, Atshaees BP, Frolov A, Kier AB, Schroedur F (1999): Cellular uptake and intracellular trafficking of long chain fatty acids. *J Lipid Res* 40: 1371-1383
McCue BF (1963): Flexibility measure of college women. *Res Quart Exerc Sport* 24 (3): 316-324
McMillan J, Brown C, Keith B, Blessing D, Wilson D, Stone M (1989): The 36-hour metabolic, hormonal and pscychological response of a single bout of weight training. *J Appl Sport Sci Res* 3: 68
Mittendorfer B, Horowitz JF, Klein S (2002): Effect of gender on lipid kinetics during moderate intensity endurance exercise in untrained subjects. *Am J Physiol* 83 (1): E58-E65
Monzillo LU, Hamdy O, Horton ES, Ledbury S, Mullooly C, Jarema C, Porter S, Ovalle K, Moussa A, Mantzoros CS (2003): Effect of lifestyle modification on adipokine levels in obese subjects with insulin resistance. *Obes Res* 11 (9): 1048-1054
Mora-Rodriguez R, Colye EF (2000): Effects of plasma epinephrine on fat metabolism during exercise: interaction with exercise intensity. *Am J Physiol Endocrinol Metab* 278 (4): E669-E676
Nam SY, Marcus C (2002): Growth hormone and adipocyte function in obesity. *Horm Res* 53: S87-S97
Oelkers P, Behari A, Cromley D, Billheimer JT, Sturley SL (1998): characterization of two human genes encoding acyl coenzyme A: cholesterol acyltransferase-related enzymes. *J Biol Chem* 273: 26765-26771
Ottosson M, Lonnroth P, Bjorntorp P, Eden S (2000): Effects of cortisol and growth hormone on lipolysis in human adipose tissue. *J Clin Endocrinol Metab* 85 (2): 799-803
Podolin, DA Wei Y, Pagliassotti MJ (1999): Effects of a high-fat diet and voluntary wheel running on gluconeogenesis and lipolysis in rats. *J Appl Physiol* 86 (4): 1374-1380
Pollock ML, Gaesser GA, Butcher JD (1998): The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. *Med Sci Sports Exerc* 30: 975-991
Ramsey T (1996): Fat cells. *Endocinol Metab Clin North Am* 25: 847-868
Romijn JA, Coyle EF, Sidossis LS, Gastaldelli A, Horowitz JF, Endert E (1993): Regulation of endogeneous fat and carbohydrate metabolism in relation to exercise intensity and duration. *Am J Physiol* 265 (3 pt 1): E380-E391
Samra JS, Clark ML, Humphreys SM, Macdonald IA, Matthews DR, Frayn KN (1996): Effects of morning rise in cortisol concentration on regulation of lipolysis in subcutaneous adipose tissue. *Am J Physiol* 271 (6 pt 1): E996-E1002
Schmitt B, Fluck M, Decombaz J, Kreis R, Boesch C, Wittwer M, Graber F, Vogt M, Howald H, Hoppeler H (2003): Transcriptional adaptations of lipid metabolism in tibialis anterior muscle of endurance-trained athletes. *Physiol Genomics* 15 (2): 148-157
Schoeller DA, Shay K, Kushner RF (1997): How much physical activity is needed to minimize weight gain in previously obese women? *Am J Clin Nutr* 66 (3): 551-556
Sial S, Coggan AR, Carroll R, Goodwin J, Klein S (1996): Fat and carbohydrate metabolism during exercise in elderly and young subjects. *Am J Physiol* 271 (6 pt 1): E983-E989
Smith J, McNaughton L (1993): The effect of intensity of exercise on excess postexercise oxygen consumption and energy expenditure in moderately trained men and women. *Eur J Appl Phsiol* 67 (5): 420-425
Stefanick ML, Mackey S, Sheehan M, Ellsworth N, Haskell WL, Wood PD (1998): Effects of diet and exercise in men and postmenopausal women with low levels of HDL cholesterol and high levels of LDL cholesterol. *N Eng J Med* 339 (1): 12-20
Stokes K (2003): Growth hormone response to sub-maximal and sprint exercise. *Growth horm IGF Res* 13 (5): 225-238
Takahashi N, Waelput W, Guisez Y (1999): Leptin is an endogenous protective factor against the toxicity exerted by tumor necrosis factor. *J Exp Med* 189 (1): 207-212
Tansey JT, Huml AM, Vogt R, Davis KE, Jones JM, Fraser KA, Brasaemle DL, Kimmel AR, Londos C (2003): Functional studies on native and mutated forms of perilinins: a role in protein Kinase A-mediated lipolysis of triacylglycerols in CHO cells. *J Biol Chem* 278 (10): 8401-8406
Terada S, Yokozeki T, Kawanaka K, Ogawa K, Higuchi M, Ezaki O Tabata I (2001): Effects of high-intensity swimming training on GLUT-4 and glucose transport activity in rat skeletal muscle. *J Appl Physiol* 90 (6): 2019-2024
Terbizan DJ, Christensen B, Deblauw C (2004): Concurrent training adaptation in adults. *Medi& Sci Sports Exerc* 35 (5): 159
Torrance CJ, Devente JE, Jones JP, Dohm GL (1997): Effects of thyroid hormone on GLUT4 glucose transporter gene expression and NIDDM in rats. *Endocrinology* 138: 1204-1214
Treuth MS, Hunter GR, Weinsier RL, Kell S (1995): Energy expenditure and substrate utilization in older women after strength training: 24-h calorimeter results. *J Appl Physiol* 78 (6): 2140-2146
Tsai AC, Sandretto A, Chung YC (2003): Dieting is more effective in reducing weight but exercise is more effective in reducing fat during the early phase of a weight-reducing program in healty humans. *J Nutr Biochem* 14 (9): 541-549
Vanhelder WP, Radomski MW, Goode RC (1984): Growth hormone response during intermittent weight lifting exercise in men. *Eur J Appl Physiol* 53 (1): 31-34
Vinals F, Ferre J, Fandos C, santalucia T, Testar X, Palacin M, Zorzano A (1997): Cyclic adenosine 3',5'-monophosphate regulates GLUT4 and GLUT1 glucose transporter expression and stimulates transcriptional activity of the GLUT1 promoter in

muscle cells. *Endocrinology* 138(6): 2521-2529

Wabitsh M, Blum WF, Muche R, Braun M, Hube F, Rasher W, Eberhard H, Teller W, Hauner H(1997): Contribution of androgens to the gender difference in leptin production in obese children and adolescents. *J Clin Invest* 100(4): 808-813

Wade AJ, Marbut MM, Round JM(1990): Muscle fiber type and aetiology of obesity. *Lancert* 335(8693): 805-808

Wasserman DH, Lacy DB, Goldstein RE, Williams PE, Cherrington AD(1989): Exercise-induced fall in insulin and increase in fat metabolism during prolonged muscular work. *Diabetes* 38(4): 484-490

Weber J(2003): Energy balance in obesity. *Proc Nutr Soc* 62: 539-543

Weinsier RL, Hunter GR, Heini AF, Goran MI, Sell SM(1998): The etiology of obesity: Relative contribution of metabolic factors, diet, and physical activity. *Am J Med* 105(2): 145-150

Willmore JA, Costill DL(2001): Physiology of sports and exercise. Human Kinetics Publishers, Inc., USA

Wing RR(1999): Physical activity in the treatment of the adulthood overweight and obesity: current evidence and research issues. *Med Sci Sports Exerc* 31(11Suppl): S547-S552

Wing RR, Hill JO(2001): Successful weight loss maintenance, *Annu Rev Nutr* 21: 323-341

Wood PD, Stefanick ML, Dreon DM, Frey-Hewitt B, Garay SC, Williams PT, Superko HR, Fortmann SP, Albers JJ, Vranizan KM, et al(1988): Changes in plasma lipids and lipoproteins in overweight men during weigh loss through dieting as compared with exercise. *N Eng J Med* 319(18): 1173-1179

Yu JG, Javorschi S, Hevener AL, Kruszynska YT, Norman RA, Sinha M, Olefsky JM(2002): The effect of thiazolidinediones on plasma adiponectin levels in normal, obese, and type 2 diabetic subjects. *Diabetes* 51(10): 2968-2974