

The effect of physical exercise and caloric restriction on the components of metabolic syndrome

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Recent studies of the effects of physical exercise and caloric restriction have found several benefits on the metabolic and cardiovascular risk factors related to metabolic syndrome (MS). This review examines the current state of knowledge of the effects of physical exercise on the main pathologies associated with MS: obesity, insulin resistance, type 2 diabetes mellitus (DM2), dyslipidemias and hypertension. Although there are only a few randomized and controlled studies that evaluated the prevention and treatment of MS, strong evidence from controlled studies indicates that lifestyle changes that include regular physical exercise and caloric restriction are effective in preventing and treating DM2 in overweight individuals with reduced glucose tolerance. Likewise, epidemiologic studies suggest that regular physical exercise prevents the development of DM2 and cardiovascular disease. Based on current recommendations, it is important to increase the level of physical exercise at a moderate intensity to achieve good cardiorespiratory and muscular conditions and to promote fat mass reduction, with consequent reductions of risk of developing metabolic syndrome.

Uniterms: Physical activity. Metabolic syndrome. Insulin/resistance. Type 2 diabetes mellitus. Obesity. Nutrition.

Recentes estudos, relativos aos efeitos do exercício físico e da restrição energética, têm relatado diversos benefícios sobre fatores metabólicos e de risco cardiovascular relacionados à síndrome metabólica (SM). Esta revisão aborda os aspectos mais recentes dos efeitos do exercício físico sobre as principais patologias associadas à SM: obesidade, resistência à insulina, diabetes mellitus tipo 2 (DM2), dislipidemia e hipertensão. Embora estudos randomizados e controlados que avaliam a prevenção e o tratamento da SM sejam escassos, pesquisas controladas indicam fortes evidências de que mudanças no estilo de vida, incluindo a prática de exercício físico regular e restrição energética, sejam eficazes na prevenção e tratamento de DM2 em indivíduos com sobrepeso e com tolerância à glicose diminuída. No mesmo sentido, estudos epidemiológicos sugerem que a prática regular de exercício físico previne DM2 e doenças cardiovasculares. Com base nas atuais recomendações, preconiza-se o aumento do volume total de exercício físico com intensidade moderada, na busca da boa condição cardiorrespiratória e muscular e da diminuição da massa gorda, com consequente aumento da proteção contra fatores associados ao desenvolvimento da síndrome metabólica.

Unitermos: Exercício físico. Síndrome metabólica. Insulina/resistência. Diabetes mellitus tipo 2. Obesidade. Nutrição.

INTRODUCTION

Metabolic syndrome (MS), also known as X syndrome or insulin resistance syndrome, has been considered as

a risk factor in the development of cardiovascular disease, type 2 diabetes mellitus (DM2) and other complications (Eckel, Grundy, Zimmet, 2005; Maranhão, Maniero, 2007). This has led to a growing scientific interest in studying its component conditions. According to Reaven (1988), this metabolic disorder is associated with a pathophysiological condition of insulin resistance and metabolic abnormalities seen in non-obese individuals with glucose

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tolerance. Also, some researchers have emphasized that this metabolic disorder is related to obesity (especially abdominal obesity or androgenic type), which increases the risk of various other cardiovascular risk factors (Lapidus, Bengtsson, Bjorntorp, 1994; Bjorntorp, 1996). Therefore, MS is characterized by five main pathologic conditions: obesity, hypertension, insulin resistance, glucose intolerance (reduced glucose tolerance or non-insulin dependent diabetes) and dyslipidemias. In this context, clinical diagnosis is essential to minimize the deleterious effects related to this syndrome as well as to reduce several atherosclerotic risk factors that may affect this same individual (Alexander *et al.*, 2003; Solymoss *et al.*, 2003; Girman *et al.*, 2004; Malik *et al.*, 2004; Ninomiya *et al.*, 2004; Olijhoek *et al.*, 2004; McNeill *et al.*, 2005; Donato *et al.*, 2006; Maranhão, Maniero, 2007).

Although hyperinsulinemia and insulin resistance are the main features of MS, the etiology of MS is still not clear, with some researchers suggesting the involvement of genetic and environmental factors (ATPIII, 2001; Martin *et al.*, 2003; Poulsen *et al.*, 2005). However, it is evident that the prevalence of MS depends on the criteria employed and on the features of the studied population, as the prevalence varies from 12.4 to 28.5% in men and 10.7 to 40.5% in women (Ford, Giles, 2003; Aguilar-Salinas *et al.*, 2004; Hu *et al.*, 2004; Oh *et al.*, 2004).

Considering that the health benefits of physical activity can only be seen with regular practice, a positive relationship between regular physical activity and the reduction of the risk and improvement in MS-related risk factors is expected (Braith, Stewart, 2006; Li, Liu, Lin, 2006; Wannamethee, Shaper, Whincup, 2006; Lakka, Laaksonen, 2007; Wijndaele *et al.*, 2007). On the other hand, it is well-known that sedentarism is a risk factor for the development of several degenerative diseases (ATPIII, 2001). In fact, a reduction of regular physical exercise is negatively related to most of the MS components; therefore, increasing physical exercise could prevent and/or treat the metabolic syndrome. (Eriksson, Taimela, Koivisto, 1997). Indeed, several studies have shown that regular physical exercise exerts positive effects on the control or prevention of MS (Carroll, Cooke, Butterly, 2000; Lakka *et al.*, 2003).

The aim of this paper is to discuss the recent findings related to the effect of physical exercise and caloric restriction on the MS components.

METHODS

The bibliographic review was performed based on articles found in the *Pubmed* and *Scielo* databases and on

books published from 1977 to 2008. We used the following inclusion criteria for selecting references: studies investigating the effects promoted by physical exercise and caloric restriction on obesity, insulin resistance, DM2, dyslipidemias and arterial pressure, as well as the metabolic and physiological aspects involved.

Furthermore, the papers were selected based on their originality and relevance, the quality of the experimental design, the sample size and the types of physiological and performance parameters adopted. Preference was given to classic and new studies.

CRITERIA FOR THE DIAGNOSIS OF METABOLIC SYNDROME

Some organizations, including the *World Health Organization* (WHO), *International Diabetes Federation* (IDF), *National Cholesterol Education Program Adult Treatment Panel III* (NCEP ATPIII), *European Group for Study of Insulin Resistance* (EGIR) and *American Association of Clinical Endocrinologists* (AACE), have adopted their own definitions for the MS components. In this review, we adopted three of them (NCEP ATPIII, IDF and WHO) due to the practical application of these classifications (Table 1). Furthermore, these organizations have adopted the same components described and discussed in this paper.

According to the *National Cholesterol Education Program (Adult Treatment Panel III)*, a diagnosis of MS is established when the individual presents three or more of the five components adopted by this organization (Table 1). In the IDF consensus (2005), visceral obesity is considered a mandatory component for MS diagnosis, along with two additional components. On the other hand, the WHO criteria for MS require the presence of glucose intolerance or DM2 and two other risk factors.

PHYSICAL EXERCISE AND OBESITY

The global epidemic of obesity has been rapidly turning into a priority in the public health system. In 2005, the *World Health Organization* (WHO) indicated that over 1.6 billion adults were classified as overweight, of whom 400 million were obese. Currently, it is estimated that by 2015, over 2.3 billion people living in the developed and underdeveloped countries will suffer from problems related to being overweight and obese (WHO, 2006).

Obesity is considered a risk factor for several cardiovascular events and metabolic diseases. Obesity can be measured using a number of methods, and Body Mass Index (BMI) is the most common measurement method

TABLE I - Criteria for the diagnosis of metabolic syndrome

CRITERIA	NCEPATP III	WHO	IDF
Abdominal obesity (waist circumference or waist-hip ratio)	> 102 cm (men) > 88 cm (women)	Waist-hip ratio: > 0.9 (men) > 0.85 (women) and/or IMC > 30 kg/m ²	≥ 94 cm (men) ≥ 80 cm (women)
Fasting glucose concentration (mmol/L)	> 5.6 (> 110 mg/dL)	≥ 6.1 mmol/l (≥ 120 mg/dL) or ≥ 7.8 mmol/l (2-hour post challenge plasma glucose or DM2 diagnosis)	≥ 5.6 or DM2 diagnosis
Blood Pressure (mm Hg)	> 130/85	≥ 140/90	≥ 130/85
Fasting triglycerides (mmol/L)	≥ 1.7 (150 mg/dL)	≥ 1.7	≥ 1.7
HDL-cholesterol concentration (mmol/l)	< 1.0 (men) (< 45 mg/dL) < 1.3 (women) (< 50 mg/dL)	≤ 0.9 (men) (35 mg/dL) ≤ 1.0 (women) (39 mg/dL)	< 1.03 (men) < 1.29 (women)

NCEPATP III: National Cholesterol Education Program, Third Adult Treatment Panel (2004); WHO: World Health Organization (1999); IDF: International Diabetes Federation (2005).

that provides information about general adiposity. However, a few studies have highlighted the importance of body fat distribution; for example, visceral fat presents distinct properties from subcutaneous fat. Thus, body fat distribution is also a major parameter to evaluate the risk of diseases (Han *et al.*, 1995; Pouliot *et al.*, 1994; Despres *et al.*, 2001).

Abdominal fat can be divided into three different types: visceral, subcutaneous and retroperitoneal. The differences among them are important, as visceral fat, the type of fat that surrounds and weighs upon falls onto the abdominal organs such as the liver, is strongly linked with a high risk of cardiovascular disease and DM2. Visceral fat is also easily measured by the waist circumference (Despres *et al.*, 2001). Furthermore, a recent study demonstrated a positive correlation between waist circumference and insulin resistance – one of the crucial factors in the development of DM2. This effect is specifically attributed to the visceral adipose tissue (Barnett, 2008).

Based on this evidence, studies have suggested that sedentarism, characterized by low energy expenditure and increased intake of high-energy-density food, is the major etiological factor in the development and rapid increase of obesity in most parts of the population (Kuczmarski *et al.*, 1994; Prentice, Jebb, 1995; Westerterp-Plantenga *et al.*, 1998; Hill, Melanson, 1999).

In general, treatments aiming to reduce excess body weight are based on promoting negative energy balance, i.e., a daily energy intake lower than the energy expenditure. Typically, caloric restriction is utilized as the only strategy (Bjorntorp, 1996). However, changes in lifestyle, to include regular physical exercise and food reeducation,

are still considered the best strategies for MS treatment (Jakicic *et al.*, 2001; Wannamethee, Shaper, Whincup, 2006).

The main factors that contribute to daily energy expenditure are resting metabolic rate (RMR), thermic effect of exercise (TEE) and thermic effect of food (Sunami *et al.* 1999). Tataranni *et al.* (2002) suggested that the distribution of daily energy expenditure in sedentary adults is relatively constant, representing 60 to 70% of TMR and 10% of TEE. On the other hand, TEE can vary among individuals, and it may be considered the leading factor in increasing the energy expenditure, and consequently, in assisting body weight control. This important effect of TEE on the energy expenditure might significantly impact weight loss, and thereby promote negative energy balance.

The effect of physical activity in increasing energy requirement assists in weight loss (or loss of body fat mass) by contributing to a higher daily energy expenditure. Additionally, the findings obtained from short-term interventions, i.e., up to six month durations, showed that physical exercise, diet or a combination of both factors promoted similar effects on weight loss in both sexes. For example, the classic study developed by Hagan *et al.* (1986) demonstrated weight loss of 11.4%, 8.4% and 0.3 % in men enrolled in a 12-week intervention (exercise + diet, diet only and exercise only, respectively). Similarly, the weight reductions in women submitted to the same strategies were 7.5%, 5.5% and 0.6%, respectively.

Conversely, some studies have demonstrated that weight loss promoted by a very low calorie intake is associated with increased muscle catabolism, which compromises the protein nutritional status (Oster *et al.*, 1995;

Pedrosa *et al.*, 2004a; Pedrosa *et al.*, 2004b). A reduction in energy availability can provoke a number of metabolic adaptations in the system, which aim to preserve body mass (Pedrosa *et al.*, 2007). These adaptations include altered utilization of the metabolic substrates, changes in body composition and appetite and the reduction of the basal metabolic rate (Prentice *et al.*, 1991). Besides the presence of negative energy balance, which is required in the reduction of body weight, there are still other physiological factors that can affect body mass composition during the weight loss process. Among them, it is worth highlighting the following factors: genes, obesity level at the beginning of the treatment, duration and intensity of body weight reduction, physical exercise and the use of pharmacological agents (Prentice *et al.*, 1991).

To reverse this picture, it is necessary to adopt methods that promote the maintenance of lean mass, with consequent mobilization of lipids, especially from the adipose tissue, liver, heart, skeletal muscle and plasma lipoproteins (Pedrosa *et al.*, 2004a; Pedrosa *et al.*, 2004b). The weight loss strategy of encouraging physical exercise has been considered suitable due to the beneficial effects seen among physically active people (ACSM, 1998). The adaptive responses promoted by physical exercise are represented by a post-exercise increase in TEE, an increase in the substrate oxidation and body temperature and also stimulation of protein synthesis (Bielinski, Schutz, Jequier, 1985; Horton, 1986). The increase in the post-exercise TEE promoted by physical exercise is capable of lasting from three hours to three days depending on the type, intensity and duration of the exercise (Tremblay *et al.*, 1988; Mcardle, Katch, Katch, 1998). Furthermore, it has been demonstrated that physical exercise significantly prevents weight gain and promotes the weight maintenance after body weight loss.

The meta-analysis performed by Ross and Janssen (2001) was based on studies that evaluated individuals featuring body mass index (BMI) > 25 kg/m² and adopting a regular physical exercise regimen. The authors studied the isolated effect of physical exercise on obesity in nine controlled studies and in twenty-two non-controlled studies. Based on the results obtained from short-term experiments (< 16 weeks) (n=20) involving exercises that promoted an energy expenditure of 2.200 kcal/week, the authors concluded that the weight loss promoted by exercise was related to a loss of total fat. The same effect could not be seen in visceral and abdominal fat as the available evidence was not sufficient to demonstrate this dose-response relationship.

In the study performed by Slentz *et al.* (2004), 120 individuals from both genders who had sedentarism,

overweight and dyslipidemias (age between 40 – 65 years old) were evaluated and assigned to four groups: (1) control group (or 8-month physical exercise or other activity); (2) moderate-intensity and low-volume training exercise; (3) high-intensity and low-volume training exercise; (4) high-intensity and high-volume training exercise. The three exercise programs saw benefits with regard to the reduction of fat mass and central obesity. These benefits were more accentuated in the group that performed high-intensity and high-volume training exercises (Slentz *et al.*, 2004). Ross *et al.* (Ross *et al.*, 2000) performed a study in which 52 obese men were randomly distributed into the following groups: weight loss diet, weight loss exercise, no-weight loss exercise and control. The authors observed that after three months of the experimental study only the individuals from the weight loss groups showed a body weight reduction of 7.5 kg.

With regard to the effects promoted by high-intensity and endurance exercises in different periods of the weight loss intervention, Jeffery *et al.* (2003) evaluated the effect of physical exercise above the recommended levels on weight loss at 6, 12 and 18 months of intervention. Individuals were divided into two different categories of energy expenditures from physical exercise: 1.000 kcal/week and 2.500 kcal/week. The authors tested the hypothesis that individuals spending 2.500 kcal/week would achieve better physical conditioning, and consequently, higher weight loss compared with the 1.000 kcal/week group. The results of this study suggest that the highest level of physical exercise (2.500 kcal/week) promotes greater weight loss in the long term compared with the conventional recommendations. However, a small weight gain in this group was also observed, which suggests a long term deterioration of the weight-loss effect, despite the maintenance of the levels of physical conditioning. Therefore, even physical exercise with high energy expenditure might not work as an absolute protection against the weight gain. Thus, further studies are necessary with longer periods of intervention to clarify whether the effects of the highest levels of physical activity are sustainable for longer periods.

In another study, Jakicik *et al.* (2003) compared the effect of duration and intensity of physical exercise on weight loss in sedentary individuals who were distributed into 4 groups based on the level of energy expenditure (1.000 kcal/week vs. 2.000 kcal/week) over a 12-month period. The participants performed high intensity exercises with distinct characteristics (moderate vs. intense), (1) high intensity/long duration, (2) moderate intensity/long duration, (3) moderate intensity/medium duration and (4) high intensity/medium duration. Furthermore, all parti-

Participants were instructed to reduce energy intake between 1,200 and 1,500 kcal/d and dietary fat between 20 and 30% of the total energy intake. The authors verified that both intensities of exercise, when combined with reduction of energy intake, promoted between 8 to 10% of body weight loss, over the 12-month intervention. Furthermore, the groups that performed high intensity exercises did not present the highest body weight reductions, when compared with the groups assigned to moderate intensity exercises. However, the authors concluded that there is a strong relationship between exercise intensity and the magnitude of body weight reduction after 12 months of intervention. Therefore, the interventions could initially start with an average of 150 min/week of moderate intensity exercises, aiming to encourage the individual to the exercise program and if necessary, to follow the 60 min/day recommendations of the *Institute of Medicine* (2002).

In another study, Williams (2007) studied whether the maintenance of physical exercise for 7 years could prevent weight gain. The author concluded that the maintenance of a vigorously active lifestyle reduces the natural tendency of gaining weight with age. Furthermore, he suggested that physical exercise attenuates rapid weight gain, which might represent a beneficial effect, due to the existing relationship between body weight, morbidity and mortality. In the study of Williams & Thompson (2006), the authors investigated whether physical exercise could reduce body weight and examined the dose-response relationship between physical exercise changes and total and regional adiposity. The authors found that intense exercise promotes weight loss, the interruption of its practice increases the intra-abdominal fat and these changes are proportional to the intensity of the exercise. Furthermore, they suggested that intense physical exercise can be considered as an activity capable of reducing body fat percentage regardless of dietary interventions.

In the meta-analysis performed by Anderson *et al.* (2001), six non-randomized studies ($n = 492$) were included to evaluate the effect of physical exercise in maintaining body-weight loss. The authors verified that after 2.7 years, the group that performed physical exercise reduced 15 kg while the sedentary group lost only 7 kg. These studies demonstrated a positive correlation between volume of exercise and maintenance of weight loss after a diet (Haapanen *et al.*, 1997; Barefoot *et al.*, 1998). The individuals who increased the volume of exercise after following a weight-loss diet were more prone to maintaining the weight loss (Haapanen *et al.*, 1997; Fogelholm, Kukkonen-Harjula, 2000) — and few studies showed results disagreeing with this observation (Bild *et al.*, 1996; Crawford, Jeffery, French, 1999). In fact, some

non-randomized studies concluded that the reduction of body weight in individuals in good physical condition was lower compared with sedentary individuals (Crawford, Jeffery, French, 1999; McGuire *et al.*, 1999).

It is established that reduction in energy expenditure in relation to age favors a higher accumulation of adipose tissue (Roberts, 1996). However, it is unknown whether the increase in body adiposity is a cause or a consequence of the reduction in energy expenditure with age (Roberts, Leibel, 1998). Thus, daily physical exercise is recommended to promote an increase in energy expenditure between 160 and 180% of the basal energy expenditure, which can be achieved in most adults with 60 minutes of physical activity (Institute of Medicine, 2002; Erlichman, Kerbey, James, 2002). The studies evaluating the effect of physical exercise on body weight composition demonstrated an improvement in the metabolic state regardless of the presence of weight loss, with reduction in abdominal visceral fat mass and improvements in the cardiometabolic risk factors, including triglyceride, HDL-cholesterol levels and insulin resistance.

PHYSICAL EXERCISE AND INSULIN RESISTANCE

Insulin resistance is defined as a clinical condition in which a normal or elevated insulin concentration produces a reduced biological response that consequently cause impaired glucose tolerance (IGT). Currently, it has been reported that 40% of the population with diminished glucose tolerance develops DM2 in 5 to 10 years. IGT patients are susceptible to developing other risk factors, such as overweight, hypertension and dyslipidemia. Furthermore, IGT is associated with a high prevalence of coronary heart disease (Pedersen, Saltin, 2006).

The insulin-mediated glucose uptake in the skeletal muscle is directly related to the amount of muscle mass and inversely associated with the amount of body fat (Yki-Jarvinen, Koivisto, 1983). A few studies (Devlin *et al.*, 1987; Caro *et al.*, 1989; Burstein *et al.*, 1990) demonstrated that physical activity increases the peripheral insulin sensitivity in obese diabetic individuals. This improved sensitivity effect is sustained after 12 to 24 hours after exercise (Andersen, Hostmark, 2007); however, the insulin dose-response curve does not completely return back to normal levels with just one exercise bout (Burstein *et al.*, 1990). The effect of acute exercise on insulin sensitivity is lost one day after the exercise bout with the effect considered to be discrete in the DM2 individuals. Therefore, regular practice of low-to-medium intensity exercise is recommended to reduce the insulin resistance found in

DM2 individuals. The results of this study also suggest that the effects of high intensity exercises on insulin sensitivity are yet to be clarified. In fact, this study showed discrepancy in the insulin-sensitizing effects promoted by the practice of high-intensity exercise, which can be justified by the following factors: 1) different methods to evaluate insulin sensitivity; 2) the lack of standardization of the exercise intensities that were adopted in this study; and/or 3) heterogeneity of the individuals with DM2 and their distinct responses to acute exercise.

Few studies have evaluated the isolated effect of physical exercise in preventing diabetes in IGT patients; however, there is evidence in the literature indicating a beneficial effect of this strategy when combined with diet modifications. Pan *et al.* (1997) performed a study with IGT individuals who were enrolled into four groups: 1) diet only (25 to 30 kcal/kg), 2) physical exercise only, 3) physical exercise + diet (25 to 30 kcal/kg) and 4) control, with a 6-year follow-up. This study demonstrated that diabetes risk was reduced by 31% in the diet group (25 to 30 kcal/kg), 46% in the physical exercise group, and 42% in the physical exercise + diet group. Likewise, Knowler *et al.* (2002) investigated the effects of lifestyle changes (diet and physical exercise - 150 minutes per week) in IGT individuals over a period of 2.8 years. The authors verified that changes in lifestyle were capable of reducing the DM risk by 58%.

A study evaluating the exercise effect on different states of pre-exercise glucose concentrations (fasted and post-prandial) demonstrated that exercise in the fasting state was safe in male DM2 individuals. Furthermore, it was shown that glucose concentrations during aerobic exercise depend on the pre-exercise glucose levels (Gaudet-Savard *et al.*, 2007).

Although there are other studies demonstrating favorable responses to strategies involving physical exercise and/or diet, the same was not seen in some individuals (Tuomilehto *et al.*, 2001; Knowler *et al.*, 2002). A possible explanation for this observation could be the intensity of the weight-loss strategy that may affect the lifestyle of these individuals (Lindstrom, Eriksson *et al.*, 2003; Lindstrom, Louheranta *et al.*, 2003).

Although long-term aerobic and medium-to-high intensity exercise is the central point of most studies of the exercise in treating insulin resistance, strength exercises with many repetitions may also improve insulin sensitivity (Holten *et al.*, 2004). Furthermore, this type of exercise improves the cardiorespiratory ability and muscle strength, which in turn, are independently inversely associated with MS (Jurca *et al.*, 2004).

The mechanisms triggered by exercised muscles

during and after the exercise bout favor glucose uptake, improve the signaling of the inner portion of the insulin receptor (Dela *et al.*, 1993), increase messenger ribonucleic acid (mRNA) expression of the glucose transporter (GLUT-4) (Dela *et al.*, 1994), increase the enzymatic activity of glycogen synthase (Ebeling *et al.*, 1993) and hexokinase (Coggan *et al.*, 1993), reduce the release and increase the clearance of free fatty acids (Ivy, Zderic, Fogt, 1999) and promote a higher glucose influx in muscles due to an increase in angiogenesis and blood flow (Saltin *et al.*, 1977; Mandroukas *et al.*, 1984).

The benefits of physical exercise on insulin sensitivity have been demonstrated with both predominantly aerobic exercises and predominantly strength exercises (Perseghin *et al.*, 1996; Ivy, 1997; Hurley, Hagberg, 1998; Pollock *et al.*, 2000). However, the mechanism by which these modalities of exercise promote an improvement on the insulin sensitivity seems to be different (Pollock *et al.*, 2000), indicating that the combination of two exercise modalities may potentiate this effect (Kim *et al.*, 2007).

PHYSICAL EXERCISE AND TYPE 2 DIABETES MELLITUS

According to the *American Diabetes Association* (2008), diabetes is defined as a group of metabolic disorders characterized by the presence of hyperglycemia. Among the factors contributing to the high blood glucose levels, the most important are the reduction in insulin secretion and impaired action of this hormone, which negatively affect hepatic and peripheral glucose uptake. Currently, DM2 is considered a disorder associated with obesity (Gregg *et al.*, 2004; Flegal *et al.*, 2005), and as a consequence of the growing number of obese people with sedentary lifestyle, the DM prevalence has been rising in many countries.

Several studies have demonstrated that physically active individuals are less prone to develop insulin resistance, IGT and DM2 (Ruderman, Ganda, Johansen, 1979; Saltin *et al.*, 1979; Hughes *et al.*, 1993; Dela *et al.*, 1995; Holten *et al.*, 2004). Also, DM2 individuals are recommended to adopt a planned physical exercise program aimed at controlling their glucose levels. Aside from exercise, other therapy approaches include diet control, insulin infusions and oral antidiabetic drugs (CDA, 2003).

The effects of exercise on glycemic control and other related physiological parameters have been extensively studied in DM2 patients. In systematic reviews (Boule *et al.*, 2001; Eves, Plotnikoff, 2006; Snowling, Hopkins, 2006; Thomas, Elliott, Naughton, 2006), it has been shown that aerobic and strength exercises reduce the

absolute values of glycosylated hemoglobin by 0.6%. The glycosylated hemoglobin concentrations reflect the mean plasma glucose levels from the last 2 to 3 months. A 1% reduction in glycosylated hemoglobin is associated with a 15 to 20% reduction in the risk of cardiovascular events (Selvin *et al.*, 2004) and a 37% reduction in the risk of microvascular complications (Stratton *et al.*, 2000).

Cuff *et al.* (2003) compared the combined effect of aerobic and strength exercises with the effect of aerobic exercise alone. The authors did not find any in the glycosylated hemoglobin levels; however, they observed reduced values in the mean glycosylated hemoglobin by 6.7%. The authors also emphasized that the small sample sizes of the groups (9 to 10 people per group) might have limited the detection of statistically significant differences. This also called attention to the inter-individual differences, in which individuals may present distinct responses to the same exercise.

In a recent study by Sigal *et al.* (2007), the authors compared the effect of aerobic vs. strength exercises with sedentarism. Furthermore, the authors investigated the combined effect of the two modalities on glycemic control and other cardiovascular risk factors. The results indicated that both aerobic and strength exercises promote improvements in the glycemic control, and when combined, these effects were increased when compared with isolated exercises, especially in individuals with higher glycemic concentrations. Therefore, DM2 individuals who intend to improve their metabolic control via physical exercise must be encouraged to perform aerobic as well as strength exercises.

The molecular mechanisms that increase glucose transport during physical exercise are considered a clinically relevant pathway to increase the glucose availability in skeletal muscle in insulin-resistant individuals. Currently, evidence suggests the existence of distinct pathways responsible for regulating glucose uptake in skeletal muscle, and the most important are the following: (1) glucose transport into the skeletal muscle cells; (2) membrane permeability to glucose (ex: glucose transport) and (3) glucose influx via intracellular metabolism (Rose, Richter, 2005).

Glucose utilization during physical exercise is predominantly triggered by muscle contraction, either concentric or eccentric (Zinker *et al.*, 1993). Although this effect is independent from insulin action, it does not mean that insulin is marginal to the glucose transport process. Additionally, the benefits of exercise on insulin sensitivity and on the GLUT4 protein are relevant to the glucose uptake in skeletal muscle (Hayashi, Wojtaszewski, Goodyear, 1997; Goodyear, Kahn, 1998). It has been ob-

served that exercise potentiates the insulin response via phosphorylation of insulin receptor substrate-2 (IRS-2), resulting in an increase in the activity of phosphoinositide 3-kinase (PI3K) (Howlett *et al.*, 2002). Also, exercise promotes a higher phosphorylation of serine in protein kinase B (AKT), which is essential for stimulating GLUT4 translocation to the cellular membrane (Wojtaszewski *et al.*, 1999).

The skeletal muscle presents numerous isoforms of the glucose transporter (Ploug, Ralston, 1998), of which GLUT4 is the most abundant. GLUT4 translocation from the intracellular compartment to the plasma membrane and T-tubules constitutes the main mechanism by which insulin and physical exercise promote glucose transport in this tissue (Hayashi, Wojtaszewski, Goodyear, 1997; Goodyear, Kahn, 1998). Additionally, studies have already demonstrated that even in the absence of insulin, GLUT4 translocation is stimulated by the contractile action in the skeletal muscle (Hayashi, Wojtaszewski, Goodyear, 1997; Goodyear, Kahn, 1998).

The signaling mechanisms involved in the insulin-stimulated glucose uptake are yet to be completely elucidated (Watson, Pessin, 2001); therefore, little is known with respect to the molecular mechanisms responsible for the increase in glucose uptake and GLUT4 translocation during muscle contraction. However, it is accepted that the signaling is triggered by local factors during the skeletal muscle contraction regardless of the release of circulating hormones (Richter, 1996).

A few findings from the literature suggest the existence of different GLUT4 intracellular pools and indicate that the molecular activation of this protein via insulin and muscle contraction is triggered by different pathways (Lund *et al.*, 1995; Wright *et al.*, 2004). The authors highlighted that exercise can exert additive effects, through insulin and muscle contraction, by activating glucose transporters from different pathways in DM2 individuals. They also suggested that the acute and chronic effects seem to trigger specific pathways in insulin-independent glucose uptake as well as insulin-dependent glucose uptake via exercise.

Recent studies have approached the traditional theories concerning the role of intracellular calcium (released by the sarcoplasmic reticulum to induce the contraction process) on glucose transport, suggesting that AMP activated protein kinase (AMPK) or nitric oxide (NO) can act as mediators of the exercise effect (Figure 1) (Hayashi, Wojtaszewski, Goodyear, 1997; Zierath, 2002).

The contractile activity of skeletal muscle stimulates the recruitment of specific GLUT4 intracellular *pools* to the plasma membrane, which increases the glucose up-

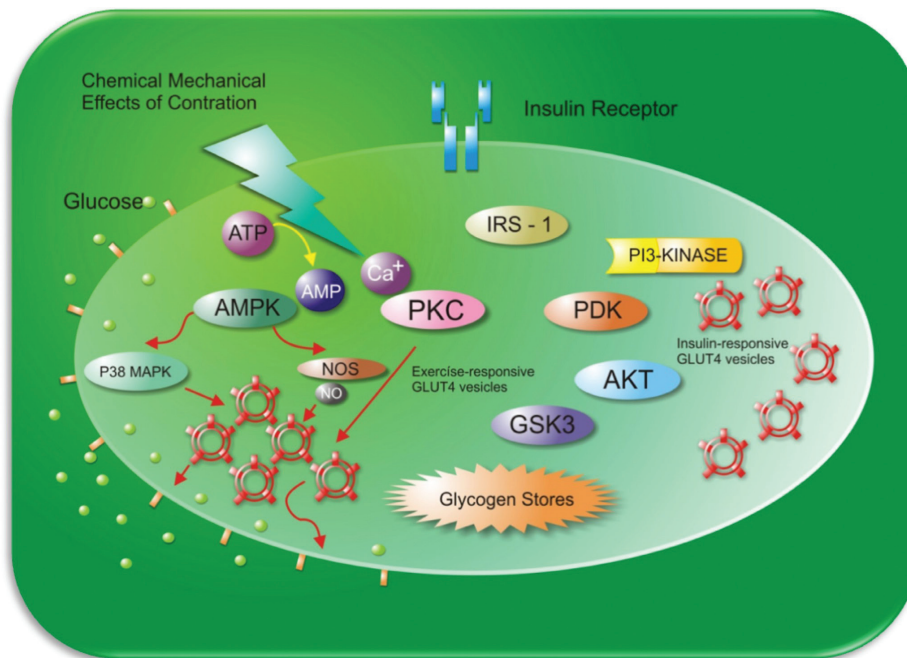


FIGURE 1 - Mechanisms evolved in the acute exercise-induced glucose transport. (Hayashi, Wojtaszewski, Goodyear, 1997; Zierath, 2002).

take. This effect is independent from the insulin signaling pathway components. Muscle contraction is initiated with the calcium release that favors the cross-bridge formation. The intracellular calcium activates a serine protein kinase C (PKC), which has been associated with the activation of GLUT4 recruitment by unknown mechanisms.

The contractile activity alters the AMP/ATP ratio, promoting AMPK activation. Its activation stimulates an increase of the glucose transport, possibly through several different mechanisms. This protein phosphorylates and activates the endothelial nitric oxide synthase (eNOS) and increases the nitric oxide (NO) production, contributing to the exercise-stimulated glucose transport. Additionally, AMPK favors the p38 MAPK phosphorylation that seems to be involved in the GLUT4 translocation (Hayashi, Wojtaszewski, Goodyear, 1997; Zierath, 2002).

Over the last few decades, studies have investigated the effect of acute exercise on insulin action during the post-exercise period, since the cellular mechanisms involved in this process are not well understood. In the post-exercise period, insulin phosphorylates and activates its receptor, which is found in a state similar to that of the non-exercised period. Paradoxically, it has been reported that insulin-stimulated PI3K activity and insulin receptor substrate-1 (IRS-1) phosphorylation are reduced when the action of hormone is increased by exercise (Klip, Paquet, 1990). During the post-exercise period, insulin action is increased, and this effect is similar in insulin-resistant and insulin-sensitive individuals. Furthermore, there are other insulin-independent

mechanisms (Kelley, Goodpaster, 1999).

Another factor that might contribute to insulin sensitivity during the post-exercise period is glycogen storage. However, the mechanisms underlying the association between glycogen concentrations and insulin action are still unknown. It has been suggested that the possible mechanism is through the action of AMPK, which possesses a mediating effect on this response. Studies evaluating AMPK activation in isolated muscles showed that the increase in AICAR production favors a higher insulin-stimulated glucose uptake (within 3.5 hours), and this effect is similar to the effects of muscle contractile activity (Fisher *et al.*, 2002). Also, there is a direct relationship between the increase in insulin sensitivity and AMPK activation.

After an acute bout of exercise, insulin-stimulated glucose uptake increases significantly. This fact does not result from the increase in the activation of the insulin-signaling components. The increase in the GLUT4 translocation to the plasma membrane in response to insulin seems to be related to reduced post-exercise glycogen storages. However, the mechanisms are still unknown. It is possible that the increased AMPK activity might be related to this effect after the exercise bout (Figure 2) (Hayashi, Wojtaszewski, Goodyear, 1997; Zierath, 2002; Wojtaszewski *et al.*, 2003).

The long-term adaptations due to exercise generate positive responses by increasing insulin sensitivity; however, these effects are induced by different mediators, i.e.,

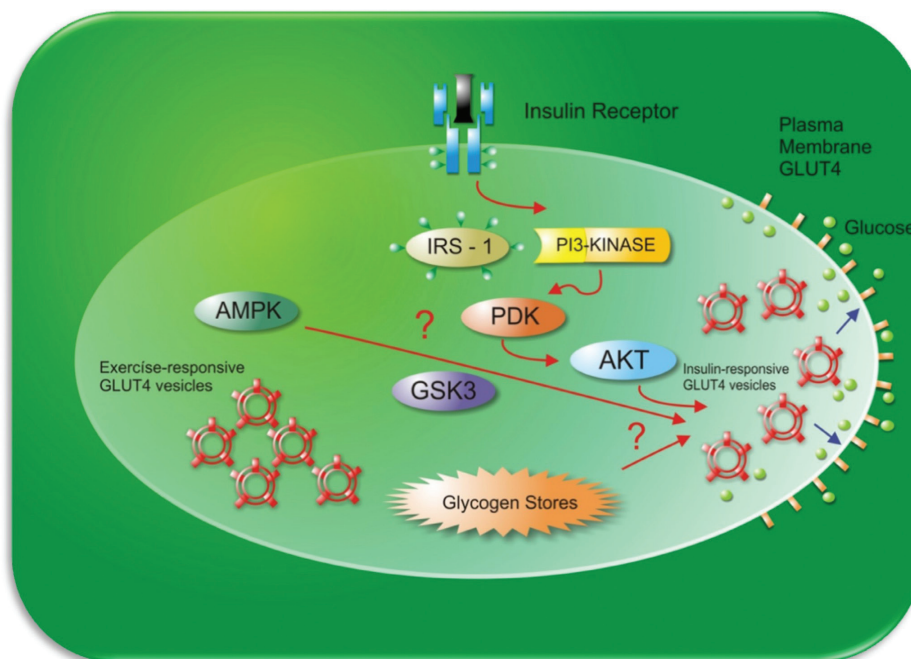


FIGURE 2 - Post-exercise mechanisms evolving insulin sensitivity (Hayashi, Wojtaszewski, Goodyear, 1997; Zierath, 2002; Wojtaszewski *et al.*, 2003).

the acute and chronic exercise effects arise from distinct pathways. At first, the increase in insulin sensitivity after a bout of chronic exercise is lost rapidly. Furthermore, no hormonal activity has been observed 24 hours after the exercise bout. These effects are related to glucose uptake, which derive from a higher activation of the insulin signaling pathways (Wojtaszewski *et al.*, 2000).

Although the clinical benefits promoted by exercise are well-known, the long-term benefits are more sustained than the benefits promoted by acute exercise. Also, the benefits are yet to be completely understood with regard to the efficiency of insulin action on the skeletal muscle. In diabetic individuals, the improvement in the glycemic control can be seen during exercise; however, these effects are associated with reductions of glucose levels that are promoted during exercise and with an increase in post-exercise insulin sensitivity, as these hormonal effects are related to the training adaptation.

Additionally, the improvement of insulin action and of glucose tolerance in physically active individuals can be considered beneficial effects that are promoted by exercise, along with weight loss, reduction of free fatty acids levels and others. Therefore, it is unlikely that the benefits of the long-term exercise are exclusively due to the insulin signaling pathways in muscle during the many exercise bouts.

Chronic exercise increases significantly insulin-stimulated glucose uptake in the skeletal muscle. The metabolic adaptations in muscle involve an increase in

insulin signaling through the second messenger pathway of insulin. The insulin receptor autophosphorylation and the tyrosine kinase activity are increased in the trained skeletal muscle, which consequently activates PI3K and AKT. This response represents an increase in the signal transduction and in the GLUT4 cellular content, which has been demonstrated to be the result of long-term exercise and is responsible for increasing the insulin action and promoting the translocation of this protein to the cell membrane in trained individuals (Figure 3) (Wojtaszewski *et al.*, 2003).

Based on the studies investigating the effect of exercise on the metabolic abnormalities seen in DM2, it is important to emphasize that the rise in the prevalence of this metabolic disorder is due, in part, to reduced exercise levels. The adoption of this strategy and exercise training reduces DM incidence. Regular exercise can also improve insulin action and glucose tolerance in IGT and DM2 individuals. These beneficial effects are attributed to four distinct factors: (1) contractile activity of the skeletal muscle, (2) acute stimulation of the glucose transporter in muscle, which is insulin independent, (3) improvement of insulin sensitivity during post-exercise period, which is independent from the hormone signaling pathway and (4) long-term adaptations of the insulin signaling pathway components in skeletal muscle as a consequence of regular physical exercise. Furthermore, these effects have distinct actions from those of exercise-induced adaptations, including weight loss and improvement in the lipid profile

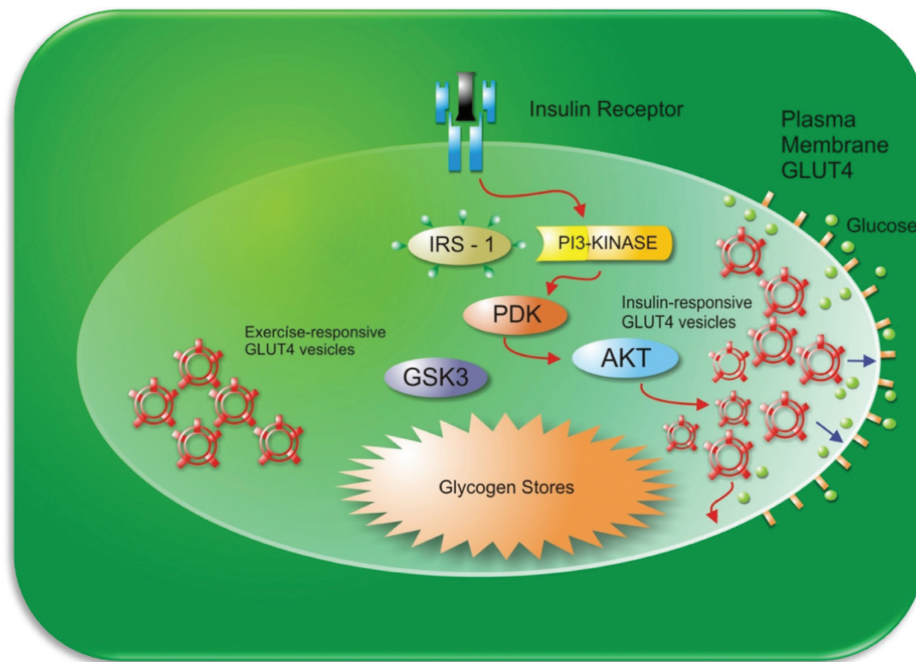


FIGURE 3 - Mechanisms responsible for the improvement in insulin action as a consequence of the skeletal muscle adaptation to the physical training.

(Gaede *et al.*, 2003; Church *et al.*, 2004; Gregg *et al.*, 2004; Bassuk, Manson, 2005; Church *et al.*, 2005).

PHYSICAL EXERCISE AND DYSLIPIDEMIA

Dyslipidemia represents a group of lipoprotein metabolism disorders, which is characterized by high blood cholesterol and triglyceride concentrations (Sposito *et al.*, 2007). Its etiology is primarily genetic factors and secondly environmental factors. The most frequent types of dyslipidemias are isolated hypercholesterolemia and combined dyslipidemia, which is caused by excessive consumption of dietary fat (Pedersen, Saltin, 2006).

Regular exercise has been accepted as a component of the strategies to normalize the lipid profile and to reduce the risk of coronary heart disease in hypercholesterolemic individuals (Superko, 1998). Exercise as a strategy can provide changes in the lipid and lipoprotein measurements in normolipidemic individuals (Mestek *et al.*, 2006). Based on these findings, a few researchers have demonstrated reductions in plasma triglyceride (TG) and increases in high density lipoprotein (HDL) levels after exercise in normolipidemic groups. (Sunami *et al.*, 1999; Grandjean, Crouse, Rohack, 2000). Furthermore, when exercise is followed by the reduction of body mass or body fat in normolipidemic individuals, there is also a reduction in the total and HDL-cholesterol levels (Katzel *et al.*, 1997). However, the effect of exercise on the lipid profile of hypercholesterolemic men is still inconsistent,

due to the general lack of studies in this area.

Regular aerobic exercise may influence the lipid profile, by modifying the activity of intravascular enzymes and lipid transporter proteins (Berg *et al.*, 1994). In fact, some reports demonstrated that exercise promoted an increase in the activity of lipoprotein lipase (Kiens, Lithell, 1989) and lecithin: cholesterol acyltransferase (LCAT) (Dufaux *et al.*, 1986).

According to the literature, physically active individuals present higher concentrations of HDL- and the subfraction HDL₂-cholesterol and lower concentrations of triglycerides, low density lipoprotein (LDL) and very low density lipoproteins (VLDL), as compared with sedentary individuals (Kraus *et al.*, 2002; Magkos *et al.*, 2006; Mestek *et al.*, 2006; Kelley, Kelley, 2007). On the other hand, there are other studies demonstrating that physical activity does not exert beneficial effects on the lipid profile (Durstine, Haskell, 1994).

Despite the lack of studies on the effect of exercise on the lipid and lipoprotein profiles in MS individuals, it is likely that exercise may offer benefits. These effects are possibly related to an increase in the ability of the skeletal muscle to oxidize fatty acids (Brouns, Van Der Vusse, 1998) and to stimulate the enzymatic activity of lipoprotein lipase (Pollare, Vessby, Lithell, 1991; Blomhoff, 1992).

Currently, changes in lifestyle to include regular exercise and healthy diets have been recommended to promote the reduction of total and LDL cholesterol levels and the increase of HDL cholesterol levels (Varady, Jones,

2005). However, the diet- and exercise-induced effects on the lipid profile and on the lipoprotein levels are still hard to distinguish from each other.

Therefore, a few studies have investigated the effects of isolated and combined (diet and exercise) strategies on weight loss, lipid levels and lipoprotein levels in overweight individuals. The authors of these studies reported significant increases in HDL and its subfractions HDL₂ and HDL₃ concentrations and reduction in triglyceride levels with both treatments (Wood *et al.*, 1988; Stefanick *et al.*, 1998). Furthermore, it was shown that aerobic exercise associated with a low fat diet can normalize the metabolic profile in even obese women, despite their higher adiposity compared with lean women (Tremblay *et al.*, 1991).

Based on the evidence previously mentioned in this review, it is likely that physical exercise alone or combined with a diet represents an effective strategy to improve the lipid profile and the serum lipoprotein levels in MS individuals. Exercise benefits include changes in blood lipid concentrations, maintenance of lean body mass, reduction in body fat, modifications in body fat distribution and the activity of enzymes that regulate the lipoprotein metabolism. However, the source of the improvement in these measurements is difficult to distinguish between the independent effect of exercise and the effect promoted from the adoption of healthy habits such as regular exercise across a variety of populations studied (sedentary, physically active or diabetic individuals).

PHYSICAL EXERCISE AND HYPERTENSION

Epidemiological studies have demonstrated that uncontrolled high blood pressure (BP) is capable of triggering a number of diseases, such as coronary heart disease, heart failure and of aggravating pre-existing renal diseases (He, Whelton, 1999). Based on these findings, clinical trials have demonstrated that blood pressure reduction promotes a decrease in mortality associated with cardiovascular diseases (He, Whelton, 1999). The trials also indicated that a 2 mmHg reduction in the systolic arterial pressure corresponds to a 6% reduction in the risk of sudden death and a 4% reduction in mortality associated with coronary heart disease. When the arterial pressure reduction is at 5 mmHg, the reduction in mortality risk is even more pronounced, at 14% for sudden death and 9% for mortality associated with coronary heart disease (Chobanian *et al.*, 2003).

Sedentarism is considered one of the main risk factors for the development of cardiovascular disease, conferring an increase of 30% to 50% in the risk of increased arterial pressure (Rosamond *et al.*, 2007). However,

studies reported that regular physical exercise reduces the arterial pressure in normotensive and hypertensive individuals, regardless of any weight loss (Arroll, Beaglehole, 1992; Fagard, 1993; Kelley, 1995; 1999). It is well known that regular physical exercise is considered an effective strategy to prevent and treat hypertension (Chobanian *et al.*, 2003; Esh-Esc, 2003; Pescatello *et al.*, 2004). Therefore, over the last year, the increase in the number of people getting regular physical exercise has been considered one of the major achievements in the public health area, which indicates that the general public is more aware of the health benefits gained by physical exercise.

Given the benefits promoted by exercise, a few meta-analyses of randomized studies were performed, and they demonstrated that aerobic exercise has definite beneficial health effects (Pescatello *et al.*, 2004). In other meta-analyses, the authors emphasized the large number of controlled experiments included in the analysis, which resulted in more precise estimates of the overall effect of exercise in several measurements, including arterial pressure (Fagard, 2001; Kelley, Kelley, Tran, 2001; Whelton *et al.*, 2002).

An important aspect that should be discussed involves the mechanisms by which exercise promotes a reduction in arterial pressure. For this, controlled studies were performed, and many of them emphasized decreases in the sympathetic activity and in insulin resistance as the most important exercise effects. Cornelissen & Fagard (2005) analyzed 75 controlled and randomized studies that aimed to evaluate the effect of aerobic exercise on arterial pressure and to investigate the regulatory mechanisms. The authors found significant reductions in resting (3.0/2.4 mmHg) and daytime (3.3/3.5 mmHg) arterial pressures in normotensive individuals. In other studies with hypertensive individuals, reductions of 6.9/4.9 mmHg for resting and 1.9/1.6 mmHg for daytime blood pressures were observed. With regard to the regulatory mechanisms, reductions in the systemic vascular resistance (7.1%), norepinephrine (29%) and in the renin activity (20%) were found.

Clinical and experimental trials evaluating the hyperactivity of the sympathetic nervous system revealed that this factor can be an important mechanism responsible for the initial increase of arterial pressure. The results of these studies have demonstrated that exercise promotes a decrease in the activity levels of the sympathetic nervous system. Thus, Cherry and Woodwell (2002) evaluated adrenergic hyperactivity in hypertensive and normotensive individuals subjected to moderate intensity exercise. The authors verified that exercise exerted a hypotensive effect with reductions of 10 to 15 mmHg in hypertensive and normotensive sedentary individuals.

Many researchers emphasized that the reductions in arterial pressure promoted by exercise are not only associated with a reduction in plasma catecholamine levels, but also with an increase in vagal tonus. Based on these findings, Cushman, Ford and Cutler (2002) studied the effect of endurance exercise on the sympathetic activity via microneurography, performing the tests before and after a ten-week exercise period. The authors concluded that the hypotensive effect in systolic and diastolic arterial pressures was a result of a reduction of the sympathetic nervous activity in the resting state. Furthermore, it was verified that the hypotensive effect promoted by exercise was rapidly lost when this strategy was interrupted, which emphasized the importance of maintaining regular physical activity.

Most the studies that evaluated the effects of physical activity on the post-exercise arterial pressure (AP) levels adopted aerobic exercise as the main strategy. Information about changes in AP after one bout of strength exercise is still relatively scarce, especially for a population of individuals with hypertension. Additionally, it is important to mention that the results from these studies demonstrated that strength exercise is able to reduce the post-exercise systolic AP in normotensive and hypertensive women (Fisher, 2001).

Most published studies have emphasized that regular exercise has an anti-hypertensive effect and is therefore recommended for the treatment of hypertension. In sedentary and hypertensive individuals, it was possible to observe clinically significant reductions in arterial pressure with a relatively modest increase in physical exercise. Finally, it is worth emphasizing that the amount of exercise required to reduce arterial pressure can be relatively low, which is achievable even by sedentary individuals.

FINAL CONSIDERATIONS

Several randomized studies have demonstrated that physical exercise has a positive effect on many metabolic and cardiovascular risk factors that are components of or are related to MS. Furthermore, other studies have provided strong evidence that a positive change in lifestyle, such as regular physical exercise, could be used as a strategy to prevent the development of DM2 in overweight and IGT individuals.

The current exercise recommendations for increasing the total amount of exercise from medium to high and for maintaining good cardiorespiratory and muscular conditioning are important in reducing the risks of developing MS, especially in individuals with a high risk profile. Although there are several activities promoting a

reduction of the metabolic and cardiovascular risk, further information is required with regard to the relative benefits of exercises recreational (not periodized). Therefore, further clarification is necessary regarding the amount and intensity of such exercise (not periodized) required to improve the comorbidities of MS and to reduce the incidence of MS in different groups at risk.

Another important aspect to be discussed is the compliance of the patient to regular physical exercise, which represents a fundamental change in lifestyle. Encouragement of physical exercise during youth can be an effective strategy in preventing the development of adult disorders. On the other hand, physical exercise alone can not correct the harmful effects caused by the high consumption of high-energy-density foods, smoking and other factors. In order to maximize the positive effects of physical exercise, re-education on healthy foods and on other healthy habits must be encouraged to promote a better quality of life. Therefore, as a consequence of these findings, other experimental trials could be performed to determine the benefits of physical exercise as a health strategy in individuals presenting disorders that are components of MS. A further understanding of the genetic basis of MS, DM2 and cardiovascular disease, as well as their interactions with physical exercise might be useful for obtaining a genetic profile that distinguishes individuals with a genetic predisposition for MS from those who may be more responsive to this type of intervention.

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