The therapeutic role of physical activity in metabolic syndrome (MetS): A narrative review

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Abstract
Several studies have shown a significant correlation between physical activity (PA) and metabolic syndrome (MetS). Material: Regardless if PA is in the form of regular exercise or everyday life activity, its absence is considered one of the most important growth factors of MetS. Results: This review showed that sedentary behavior (SED), obesity and harmful dietary patterns contribute decisively to the creation of the dominant causes of MetS. High blood pressure, central obesity, elevated triglyceride levels, high fasting plasma glucose concentrations and low high-density lipoprotein appeared to trigger MetS. While PA is not associated with less SED, it is inversely related to obesity and in the long-term seems to direct the person to better eating habits and to maintain a befitting body weight. In addition, PA results in a behavioral pattern that is suitable for fighting all the MetS creation causes, because PA holds the role of a preventive and therapeutic regulator of good physical health. Conclusion: Therefore, PA is necessary and is the most important way of fighting against MetS.

Keywords: Metabolic syndrome, physical activity, obesity, sedentary behavior

1. Introduction
The notion of MetS is a conception of the last century. This formation of metabolic disorders and risk factors for developing cardiovascular disease, first described in 1920 by the Swedish doctor Kylin, was an attempt to cluster hypertension, hyperglycemia and arthritis. Later, in 1947, Vague focused on the deposition of fat in the upper body (male type obesity), as the phenotype obesity which was associated with metabolic abnormalities, was also associated with type 2 diabetes and cardiovascular disease [1, 2, 3, 4]. The term of metabolic syndrome (MetS) is defined by the International Diabetes Federation (IDF) as the clustering of metabolic risk factors. According to the IDF [1] for a person to qualify as suffering from MetS, they should have central (abdominal) obesity (determined by measuring the circumference of the abdomen which differs for each nationality or if the BMI index is > 30kg/m², in which case there is no need for abdominal and waist measurements). MetS is also known as Syndrome X or insulin resistance syndrome, as well as lethal quartet. The formation of metabolic abnormalities includes glucose intolerance (type 2 diabetes, impaired glucose tolerance, elevated fasting glycemia), insulin resistance, central obesity, dyslipidemia and hypertension. It should be emphasized that all these are well documented as risk factors for cardiovascular disease [1, 4, 5, 6, 7, 9]. When the aforementioned factors are all combined, they are associated with increased risk of cardiovascular disease. Lemieux and colleagues [2] suggested the importance of abdominal obesity and the called hypertriglyceridemia phenotype of waist as central elements. Although some valid points have been made, the causes of the syndrome have not yet been firmly determined [2]. The occurrence of MetS is growing worldwide and is referred to as a set of topics which include visceral obesity, increased blood glucose levels, dyslipidemia (increase in fasting triglyceride levels and lower high-density lipoprotein and cholesterol levels) and hypertension. This leads to an increased risk for developing cardiovascular disease, type 2 diabetes and cancer. For this reason, it could be a pre-disease state. Effective metabolic syndrome prevention strategies require reduction of disease impact and promote healthy age growth [5, 6, 7, 9]. In addition, lifestyle has been shown to correlate very closely with the development of MetS, with diet and PA identified as the most important factors in adults [10, 11] and children [6, 12].
In a recent study of Scuteri and co-workers [13] MetS was found in about 24% of the middle-aged European population. Also, this percentage varies between European countries and it is partly dependent on the fact that there are different definitions [14]. In another more recent study [15], it was shown that MetS is a worldwide epidemic with many factors which expand rapidly. In the USA MetS occurs in about 25% of the adult population and is spreading like an epidemic alongside obesity, which is estimated to affect about 312 million people worldwide. With at least 1.1 billion people being overweight, the prevalence of MetS is expected to continue rising, justifying the need for a treatment plan in a socio-economic scale [16].

Approximately 34% of adults meet the criteria for MetS. Men and women aged 40-59 are three times more likely than those aged 20-39 to meet the criteria for MetS. Men and women 60 years and older are 5 to 6 times more likely to meet the criteria for MetS in comparison to younger people. Both men and women of black race (with the exception of Hispanics) were 1.5 times more likely to meet those criteria in comparison to white men and women (excluding Hispanics). Overweight men are about six times more likely and obese men 32 times more likely to meet the criteria. Similarly, women who are overweight are about 5 times more and obese women are 17 times more likely to meet the criteria than those who have normal weight [6, 15, 17].

The aim of this review was to investigate the therapeutic role of physical activity (PA) and its consequences on the metabolic syndrome (MetS). Additionally, we examined the impact and the role of sedentary behavior (SED) in MetS, the contribution of obesity to MetS and the effect of PA in both metabolic markers and risk factors. Finally, we investigated the preventive character of PA in MetS.

2. Methods
An exhaustive search on databases of Pub-Med, Sport Discuss and Medline was used to collect the necessary literature. Keywords used included "metabolic syndrome", "obesity", "physical activity", "sedentary behavior", "effect of physical activity on metabolic syndrome". Moreover, many other articles were also used to identify additional research for better enlightenment of this review.

3. Results
The effects of SED and its role in MetS. In recent years there has been a growing interest in SED and its negative effects in human health. Several recent studies have highlighted that health risks are associated with high sitting time. For example, SED has been shown to be associated with increased risk diabetes type 2 [18, 19], cancer [5, 7, 20] and all causes that lead to cardiovascular disease and mortality [7, 11, 18, 19].

In a meta-analysis study of Edwardson and his co-workers [21], the results showed that the greater amount of time spent in sedentary functions increases the chances of metabolic syndrome by 73% and thereby encourages people to limit their time spent in sedentary living reducing the risk of MetS.

Moreover, according to the same research the relationship between SED and MetS can be independent of the PA as demonstrated by the sensitivity analysis. This is important because it shows that sedentary time could be independent of the metabolic dysfunction factor, distinct from the lack of physical exercise. This finding is consistent with those reported in other studies of health [18, 22]. Similarly, SED, if measured objectively or subjectively, has been shown to be weakly linked to the amount of time spent in moderate to vigorous physical activity [23, 24], confirming that one is not simply in direct contrast of the other [21].

Sedentary behavior (SED) refers to activities related to energy expenditure at the level of 1.0-1.5 metabolic equivalent units (METs) [22]. Functionally, SED may be referred to as "time spent in sedentary functions or activities" and not just a low level of physical activity. SED includes activities such as when a person is lying down, sitting watching television or using the computer, including other forms of entertainment that the person involved was sitting. Studies have shown that people may spend more than half of their time each day in sedentary activities [25, 26]. SED and very low levels of physical activity (PA) is known to induce the development of the metabolic syndrome (MetS), type 2 diabetes and cardiovascular diseases [18]. In a study Örjan Ekblom and his co-workers [27] indicated that a person’s pattern of PA can be described as a time (or a percentage of the total time when the person is awake) spent on carrying out activities of different intensities, ranging from SED, defined as PA intensities below 1.5 METs, to light intensity PA between 1.5 and 3 METs and to PA of moderate and vigorous intensity above 3 METs.

The energy consumption depends on the intensity and quantity of PA; therefore, SED tends to result in an individual with a positive balance and body fat accumulates when PA is absent. The adipose tissue secretes bioactive factors, adipokytarokines, such as tumor necrosis factor alpha-alpha (TNF-a), the plasminogen activator inhibitor and resistin in circulation. It is considered that there is a close relationship between adipokytarokinon and health problems such as obesity, metabolic and cardiovascular disorders, which cause insulin resistance, endothelial injury and inflammation [11, 28, 29, 30]. In addition, SED causes a decrease in resting metabolic energy capacity. This decrease may be due to atrophy of skeletal muscle, having a significant amount of energy consumed by body tissues [31, 32].

It is reported that both the loss of fat mass without PA and age are behind the reduction in resting metabolic rate (RMR). Muscle atrophy may be due to both the atrophy of the muscle fibers and the lack of complete muscle fiber, which is due to several factors including the apoptosis of muscle cells, decreased differentiation of cells satellites and reduced protein levels, as a result of the reduction in protein synthesis and increased protein degradation. The activity of the enzymes contained in the aerobic metabolism and glucose uptake by the muscle is reduced by inactivity and age. Laboratory investigations showed that the significance of the degradation of the protein is observed within 2 days of immobilization of muscles, that leads to loss of muscle mass with 1 week. The stimulation of insulin glucose uptake in muscles is also limited by reducing the signal transmission within two days of immobilization. At the same time, the activity of lipoprotein lipase, a protein important for the control of plasma triglycerides and HDL-cholesterol catabolism and other metabolic risk factors, is lost. According to reduced function of lipoprotein lipase, the clearance of plasma triglycerides from skeletal muscle was significantly reduced, as well as the concentration of HDL plasma cholesterol was decreased [5, 9, 33, 34].

Recently, it was found that low-grade inflammation and continuous oxidative stress are associated with metabolic disorders and cardiovascular diseases. Low levels of PA lead to chronic inflammation and oxidative stress in skeletal muscles, circulatory system and other tissues. Furthermore, they lead to a decrease in circulation of adiponectin, a
cytokine with anti-inflammatory properties, which is produced exclusively by adipocytes, is present in obese people and leads to skeletal muscle and liver in insulin resistance. An increased level of oxidation of the lipids, DNA, and protein is also observed in the muscles of SED subjects, as compared to those who are physically active. Oxidative stress is also significantly related to the development of insulin resistance in skeletal muscle [5, 9, 34].

The contribution of Obesity to MetS. The excessive accumulation of visceral fat may be causally related to the characteristics of insulin resistance, but can also be a malfunction indicator of adipose tissue, which is unable to properly store the excess energy. According to this model theory, the ability of the body to cope with the excess of calories (result of excessive calorie consumption, sedentary lifestyle or as often happens a combination of both these factors) may eventually determine the sensitivity of the organization to develop MetS. There is evidence to suggest that if the excess energy is supplied to the insulin sensitive subcutaneous adipose tissue, the subject, although in a positive energy balance, would be protected from MetS. Certainly, in the case in which adipose tissue is absent or incomplete or is insulin resistant with limited ability to store the excess energy, the surplus of triacylglycerols are delivered to unwanted vital organs such as the liver, heart, or even in skeletal muscle and visceral adipose tissue - a phenomenon described as ectopic fat deposition. The factors associated with the distal accumulation of visceral fat and the resistance characteristics of insulin, include smoking, a well-documented tendency to visceral obesity and a neuro-endocrine profile associated with maladaptive stress responses. The results of the metabolic consequences of this defect in the energy separation include visceral obesity, insulin resistance, dyslipidemia, atherosclerosis and a pro-thrombotic inflammatory profile. These characteristics define the MetS. The formation of defects can be detected by clinical criteria for metabolic syndrome, the two most simple are the simultaneous presence of increased waist circumference and levels of fasting triacylglycerol, a condition which has been described as average hypertriglyceridemia [4, 11, 28, 35, 36].

A recent study confirmed that the higher the body mass index (BMI) is, the greater the risk of developing MetS [37]. Abdominal obesity is the parameter of body fat which is more related to MetS. As already noted, the definitions of abdominal obesity vary according to the population. The clinical management of obesity should adhere to established principles. The efficacy of weight reduction improves all risk factors associated with MetS and this will reduce the further risk of Type 2 diabetes [4, 6, 30].

Weight reduction best achieved by changing behavior to reduce energy intake and increase energy loss through PA. The caloric intake should be reduced by 500-1000 calories per day to promote weight loss of 0.5 to 1.0 kg per week. The ultimate goal is to reduce the body weight by 10.7% in 12.6 months, following a long-term behavioral change and maintenance of the already increased PA [34]. So far, weight reduction using medication was not particularly effective in reducing energy intake in overweight and obese men and women. Larger quantities of PA appear to reduce abdominal, visceral and subcutaneous fat, regardless of changes in energy intake or body weight. Based on survey data, about 30% of new cases of obesity could be prevented by converting to an active lifestyle, that includes more than 30 minutes of brisk walking every day and less than 10 hours a week of TV watching. Epidemiological studies indicate that 45-60 minutes of moderate intensity PA each day may be necessary to prevent the gain of unhealthy weight and obesity. Controlled efforts with a typical duration of 3-12 months, comprising of 3 to 5 exercises for 30-60 minutes per week, showed that training significantly reduces the body mass and fat mass without limiting caloric intake in obese men and women. Some of these efforts have shown that the amount of PA is more important than the volume in decreasing fat body mass, and that the exercise decreases fat body mass in doses dependent on manner, thus resulting in greater total energy expense and a stronger effect [9, 11, 36, 39, 41].

PA reduces abdominal, visceral and subcutaneous fat, regardless of changes in energy intake in overweight and obese men and women. Larger quantities of PA appear to result in more significant reductions in abdominal obesity. Some randomly tested PA efforts with substantial data revealed that PA decreases the total fat mass of the body and does not specifically target visceral or abdominal subcutaneous fat. Certainly, the results of current research...
suggest that PA reduces visceral fat more efficiently than the overall or abdominal subcutaneous fat. The data shows that exercise reduces total, visceral and abdominal subcutaneous fat without losing weight for people with normal body mass, obese individuals with abdominal obesity and people with type 2 of diabetes [8, 34, 42].

Physical activity and insulin sensitivity. PA improves insulin sensitivity, both acute and chronic. Acute exercise causes improved insulin sensitivity and glucose uptake by skeletal muscle and appears to be related to changes in the signaling response of muscle contraction, such as the increased displacement of insulin, regardless of the transport of glucose GLUT4 to the surface of cells. The effect is short-lasting for 48-72 hours. Thus, to obtain the maximum benefits of exercise in insulin sensitivity, exercise should be done on a daily basis [39, 43, 44].

The main exercise programs have a duration of 3 months or more and have an effective volume and size, while improving insulin sensitivity, regardless of the direct effect of exercise. The results of the frequency of exercise in regards to the size of weight variation and the effect of exercise on insulin sensitivity are strongest when related to the weight reduction. It can be difficult to separate the independent effects of exercise and weight loss on insulin sensitivity. Similarly the absence of changes in body weight from various programs of PA of moderate and vigorous intensity or strengthening programs, may alter body composition and fat distribution in the long term, which may in turn affect the sensitivity of insulin [54, 44].

Even though the effects of body composition are an important mechanism through which the exercise improves the sensitivity of the term insulin, exercise also increases the carrier concentration of glucose GLUT4, the glucose synthesis activity, the enzyme activity of mitochondria and the density of capillaries and the mitochondria of the skeletal muscles; thus, improving endothelial function and equally altering the type of muscle fibers. These effects may contribute to the variability of body weight by the time effect of exercise and thus contribute to insulin sensitivity [45, 46].

Physical activity and dyslipidemia. A single stimulus of PA lowers plasma triglyceride concentrations and increases HDL cholesterol concentrations in plasma in relation to the magnitude of the total energy consumed. Endurance training has shown better results in increasing HDL cholesterol. Based in future epidemiological studies, this is a mechanism that reduces the risk of cardiovascular diseases. Aerobic exercise showed a decrease in the concentration of LDL cholesterol in plasma and of apolipoprotein-B, higher levels of apolipoprotein-A plasma and reduced concentration of plasma triglyceride [5, 7].

The effect of LDL and HDL cholesterol in the plasma triglyceride concentration is small, in most studies around 3.5%. Nevertheless, because the favorable changes occur generally in lipids, lipoproteins, and in the operation of off-lipoproteins and in addition to the advantages of other cardiovascular and metabolic risk factors, the effect of aerobic exercise on dyslipidemia should not be underestimated. Also, exercise can reduce the decline of HDL cholesterol, when this happens with a reduction in saturated fat intake during weight reduction programs. The effects of exercise on plasma lipids and lipoproteins are stronger if they coincide with the loss of body weight [42, 47, 48].

Physical activity and blood pressure. The systolic blood pressure is increased during aerobic exercise, in relation to the intensity of the effort, but the blood pressure levels fall below resting levels in 2-4 hours or more, following an exercise period of at least 20 minutes. In individuals without hypertension, systolic blood pressure decreases after a training session at 8-10 mmHg and diastolic blood pressure is reduced to 3-5 mmHg, but this reduction may be 2 times more in patients with hypertension [9, 49, 50].

Physical activity and inflammation. A single period of intense PA causes an immediate inflammation, as a typical reaction to the increased freedom of pro-inflammatory cytokines, while leukocytosis occurs as well as an increase in plasma concentrations of reactive protein C. The pro-inflammatory reaction in the direct effect of exercise is accompanied by an immediate increase of oxidative stress. The immediate increase in oxidative stress and inflammation may cause adjustment of the reactions for cell protection that reduces inflammation [51, 52].

Many longitudinal studies have found small plasma concentration of inflammation signs in active people or people who are in a good physical condition, compared to individuals who are inactive or are not in a good physical condition. The survey data is incomplete. In some surveys regular exercise reduces the reactive protein C concentrations in subjects with moderate to high risk for cardiovascular disease. In other studies, exercise reduces the pro-inflammatory activity of mononuclear blood cells, but the C reactive protein concentrations are not reduced [52]. Some studies reported on the effect of exercise in plasma markers of inflammation. In a 6-month program that included diet and exercise decreased plasma levels of interleukin-6 and alpha factor-alpha tumor necrosis were reported in obese postmenopausal women. In a 6-year period, low to moderate exercise does not significantly reduce the concentrations of reactive protein C. On the other hand, neither the moderate or intense exercise affects the C reactive protein or the levels of adiponectin. The views are conflicting, but regular exercise and maintenance of cardiorespirator fitness may slightly reduce the degree of inflammation, despite the direct pro-inflammatory reaction from a single exercise stimulus [42, 53].

Physical activity and endothelial function. In healthy individuals, the effect of exercise on endothelial function appears to be contradictory. PA improves endothelial function, most often measured as an expansion in proxy flow brachial artery, in people with obesity, hypertension, diabetes, hypercholesterolemia, cardiovascular disease and heart failure, and all that is characterized by endothelial dysfunction. Many of these conditions and diseases are part of or related to the MetS, which is also associated with endothelial dysfunction. Therefore, it seems likely that PA can improve endothelial function in subjects with METS, but this remains to be demonstrated [16, 42, 54].

Physical activity in the prevention of metabolic syndrome. Current guidelines recommend regular, moderate-intensity PA (30 minutes daily of moderate intensity exercise). Regular and prolonged PA will reduce all risk factors for the MetS. Sedentary activities during leisure time should be replaced with more active behaviors such as fast walking, leisure jogging, swimming, golf, cycling and team sports. The combination of weight loss and PA reduces the incidence of type 2 diabetes in patients with glucose intolerance and therefore should not be rejected [34, 35, 44].

Regular PA has a mild or moderate to large positive effect on a large number of metabolic and cardio-respiratory risk factors that are related to MetS. To a large extent, when it concerns these risk factors, regular PA appears to prevent type 2 diabetes and early mortality. The favorable results of PA in
the main metabolic and cardio-respiratory risk factors such as insulin resistance, glucose intolerance, type 2 diabetes, dyslipidemia and high blood pressure are strongest when combined with weight loss. There are also large individual differences in the magnitude of the effect of regular exercise on metabolic and cardio-respiratory risk factors. This variability is due to PA affected by age, sex, health status, body size and genetic factors [34, 48].

The evidence for the effect of PA in the prevention of MetS is the basis of longitudinal studies. In a population, the basic sample of 1069 middle-aged Finnish men free of diabetes, cardiovascular diseases or cancer, who were associated with moderate or high PA intensity in their free time, for less than 1 hour per week were 60% more likely to have MetS than those who spent at least three hours per week for the same amount of PA. Men with a maximum oxygen consumption (VO2max) of less than <29.1mL / kg / min, were seven times more likely to have MetS than those who had VO2max ≥ 35.5 mL / kg / min. The analysis results suggest that low cardio-respiratory capacity may be regarded as a characteristic of the MetS. Other studies with men and women from the USA, the United Kingdom and Canada have provided more information about the high levels of PA or cardio-respiratory endurance, which is associated with reduced extension of MetS. In a study by Lee and co-workers [12] in Canada involving healthy men, they found that high levels of cardio-respiratory capacity are associated with a reduced risk for MetS, regardless of the amount of visceral or subcutaneous fat [34, 39, 42, 44].

4. Discussion

As demonstrated in a recent study all forms of PA and the use of fitness associated independently with the MetS. According to this study fitness status remains the strongest predictor of MetS. The results of this study also support the clinical use of PA to be established, not only in patients at risk of MetS [27]. Other studies suggest the same and recommend that PA is effective for the treatment of MetS. The study of Katzmarzyk and his co-workers [32] showed that 32 of the 105 people with SED had MetS, but after 20 weeks of aerobic exercise they no longer had the syndrome. Research on the use of PA as a treatment model for people with MetS has not yet been published. Certainly, the focus on type 2 diabetes in people who are overweight and have impaired glucose tolerance, may possibly be the way to treatment and prevention of MetS, because both the increased body weight and decreased glucose tolerance are common in individuals with MetS [42, 52, 55, 56, 57].

In a Swedish study of 260 middle-aged men with impaired glucose tolerance, of whom 181 participated voluntarily in a diet and an exercise program and 79 formed the control group, the results for type 2 diabetes were a 50% reduction in the proxy group after 5 years. Improved VO2max was associated with a low risk of diabetes during follow-ups, suggesting that an increase in PA was protective against diabetes [42].

The combination of mediation and control groups for persons with increased PA during leisure time, tested for an extended period of 4.1 years, was associated with lower levels of risk for type 2 diabetes. The increase in total PA during leisure time was associated with lower risk for developing diabetes. The risk of type 2 diabetes in men and women who increased their total PA by 30%, was 70% lower than those who reduced their overall PA by 30%, in whom the levels of PA actually decreased regardless of the basic standard of PA, age, the research group, body mass index (BMI) and nutrition. The increase in moderate to vigorous PA, such as intense configuration of PA and walking as exercise appears to substantially reduce the risk of diabetes [42, 55, 57].

Those who reported walking an average of at least 2.5 hours per week during monitoring, had half the chance of developing diabetes than those who walked less than 60 minutes per week. Also, those who are commuting daily to work (walking or cycling at least 30 minutes a week) had a lower risk of diabetes. The correlation of low intensity PA as a lifestyle in people with type 2 diabetes has been considered to be small [9, 42, 55, 58].

Lack of PA is a major cause in the development of obesity. Both PA and obesity are common standards related to clinical risk markers such as fasting plasma glucose, blood pressure and inflammatory markers, while they are regarded as the main health effects [59]. Therefore, lack of PA increases obesity and obesity creates a lack of PA. There are several studies who have explained the importance of PA using questionnaires on the morbidity and mortality from cardiovascular diseases, however, Blair and his colleagues have clarified that the cardio-respiratory status, as determined by checking the maximal exercise is stronger in the case where the level of PA self-identified as a predictive indicator for prognosis [55].

Whilst in general overweight and obese people have lower levels of fitness compared to lean individuals, Wei and colleagues reported that obese people with at least moderate cardio-respiratory condition, have a lower level of risk of cardiovascular diseases and about 1.5 times likelihood of death from all causes compared to individuals who have normal weight but are equally untrained. In addition, Blair and colleagues showed that only 150 minutes of moderate intensity PA per week, such as brisk walking, swimming, housework and gardening is effective, while the meta-analysis of 24 studies showed the relationship between PA, overall physical fitness, obesity and the main results of health. Also, a large number of studies indicate that the effects of increasing regular PA are indicators of increased exercise capacity and an important element in weight loss programs, especially for long-term weight maintenance [9, 33, 34, 59]. Finally, PA protect against situations that are a part of a varied composition of MetS [59].

5. Conclusions

From the results of this review, it could be derived that PA is necessary and is the most important way of fighting against MetS. Further research is needed for the investigation of the different kinds of physical activity and their effect on individuals with MetS.

References


