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Cardiac Rehabilitation in Metabolic Syndrome: An Update Review

ABSTRACT

Mortality due to cardiovascular disease is dramatically increasing worldwide. In Europe, the rate of mortality has reached 39% and 47% in females and males, respectively. Metabolic syndrome is preventable with a healthy lifestyle including body weight management. Although exercise interventions are an important and cost-effective therapy for preventing metabolic syndrome or mitigating the adverse effects of metabolic syndrome, there are limited data on cardiac rehabilitation interventions for metabolic syndrome. This review presents the current evidence regarding cardiac rehabilitation interventions in patients with metabolic syndrome. We conducted literature research on electronic databases including PubMed and MEDLINE, Google Scholar, and EMBASE to derive evidence-based, up-to-date information. We preferred novel articles for writing this review. Metabolic syndrome can be prevented and/or delayed with lifestyle modification. Cardiac rehabilitation in metabolic syndrome includes exercise therapy, lifestyle modification, and physical activity counseling. Lifestyle modification and cardiac rehabilitation may increase the efficacy of other treatments. According to literature, cardiac rehabilitation is an effective, safe, and cost-effective strategy in metabolic syndrome. Cardiac rehabilitation can delay/prevent not only metabolic syndrome but also metabolic syndrome-related complications.

Keywords: Cardiac rehabilitation, exercise therapy, metabolic syndrome

Introduction

Metabolic syndrome (MetS), also known as syndrome X and insulin resistance syndrome, is a complex disorder that involves several cardiovascular risk factors and is an important predictor of cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and all-cause mortality. Metabolic syndrome increases the risk of atherosclerotic CVD by 2-fold and the risk of T2DM by 5-fold. The prevalence of MetS is rapidly increasing worldwide and ranges from 10% to 84% according to ethnicity, age, and sex. The Westernized lifestyle, characterized by physical inactivity, high caloric intake, and consumption of high-fat foods, is a major cause of obesity and MetS. Metabolic syndrome is preventable with a healthy lifestyle including body weight management.

Metabolic Syndrome: Definition, Components, and Pathophysiology

Metabolic syndrome has many diagnostic criteria and definitions due to its complex components. The World Health Organization (WHO) described MetS as the presence of insulin resistance with any 2 of the following conditions: hyperlipidemia, hypertension, abdominal obesity, and microalbuminuria.[1] After this definition, some organizations determined that cut-off values for MetS change with ethnicity.[2] According to the revised National Cholesterol Education Program–Third Adult Treatment Panel (NCEP ATP III criteria), MetS diagnosis requires at least 3 of the following: increased blood pressure, insulin resistance, abdominal and/or visceral obesity, and dyslipidemia (Table 1).[3] Pro-inflammatory states occur in MetS in addition to these abnormalities.[4]

Metabolic syndrome is a consequence of complex interactions between genetic and environmental factors.[5] Although the pathophysiology and exact mechanism of MetS are still unclear, positive energy balance and obesity seem to be the main causes. Positive energy balance triggers fat accumulation in the body, and excess fat tissue increases inflammation and disrupts insulin action.[5,6] Insulin is a key factor for regulating energy, glucose, fat, and protein metabolism and has an important effect on the liver, heart, muscles, and many other organs and systems.[6]

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Table 1. National Cholesterol Education Program–Third Adult Treatment Panel (NCEP ATP III) Criteria for Metabolic Syndrome[3]

Dyslipidemia	Triglycerides ≥ 150 mg/dL
	High-density lipoprotein cholesterol
	<40 mg/dL for men
	<50 mg/dL for women
Elevated blood glucose	Fasting blood glucose > 100 mg/dL
Abdominal obesity	Waist circumference
	≥90 cm for men
	≥85 cm for women
Elevated blood pressure	Systolic blood pressure ≥ 130/85 mmHg or diagnosis/treatment of hypertension

Cardiac Rehabilitation Interventions in Metabolic Syndrome

Cardiac rehabilitation (CR) is a comprehensive program that includes medical evaluation, exercise training, physical activity (PA) and exercise prescription, patient education and counseling (e.g., psychosocial approaches, diet regulation, pharmacologic management), behavioral intervention, and modification of CVD risk factors.[7,8] Lifestyle changes, primarily weight loss, diet, and exercise, are both prevention strategies and aspects of treatment. As there is no method for treating all components of MetS simultaneously in clinical practice, lifestyle management is essential as well as feasible.[5] Cardiac rehabilitation generally consists of 3 phases: inpatient, outpatient, and maintenance. Some CR programs contain an additional phase involving light monitored activity before beginning the outpatient phase.[7,8] Although the proven benefits of CR are considerable, these programs are still underutilized. The most frequently reported barriers to CR are insufficient doctor referral, female sex of patients, lack of adequate CR programs, problems related to health insurance and socioeconomic status, and lack of time.[7] Therefore, appealing CR programs should be offered to motivate patients with MetS, and any barriers to participation such as transportation or work-related problems should be discussed. Different options for setting (home, center, community, or telerehabilitation based) and times should also be offered to increase participation.[9]

Patient Education

Comprehensive and long-term CR programs include medical evaluation, exercise prescription, cardiac risk factor modification, and also patient education and counseling.[10] The British Association of Cardiovascular Prevention and Rehabilitation recommends that CR comprise following 7 key components[10]:

1. health behavior change and education;
2. lifestyle risk factor modification including
    - PA and exercise,
    - diet,
    - smoking cessation;
3. psychosocial health;
4. medical risk factor management;
5. cardioprotective treatments;
6. long-term management;
7. control and evaluation.

Exercise Therapy in Metabolic Syndrome

Aerobic Exercise Training: Aerobic exercise training is a cornerstone of treatment in MetS and has been referred to as medicine in the literature.[11] There is increasing evidence that personalized, regular exercise decreases abdominal fat content, which is closely related to the pro-inflammatory process. In addition, aerobic exercise reduces total, abdominal, and skeletal muscle fat stores, even without weight loss.[11] Glucose consumption increases with muscle contraction during exercise, and glucose is taken into muscle by translocation of GLUT-4, an important glucose transporter, to the sarcolemma. GLUT-4 expression and cellular GLUT-4 protein content increase with regular aerobic exercise. This increase in GLUT-4 results in improved glucose use, glycogen storage, and insulin action.[12] Ostman et al[13] in their meta-analysis, reported that aerobic exercise training significantly reduces body mass index (BMI), body weight, waist circumference, total fat mass, triglyceride level, systolic blood pressure (SBP), diastolic blood pressure (DBP), and fasting blood glucose and increases peak oxygen consumption (VO_{2peak}) level in individuals with MetS. In another meta-analysis, Wewege et al[14] reported a 4% increase in high-density lipoprotein cholesterol (HDL-C) level and a subsequent 12% reduction in the risk of coronary artery disease after aerobic exercise training in individuals with MetS. In addition, there was an 18% increase in cardiorespiratory fitness associated with a 15% reduction in all-cause and cardiovascular mortality. It has also been reported that increases in VO_{2peak} (≥2.5 mL/kg/min) were independently associated with improvements in survival, HDL-C level, weight loss, and body fat.[8]

Regular and structured aerobic exercise is recommended in guidelines for its metabolic benefits.[12] The American College of Sports Medicine (ACSM) recommends moderate exercise for 150 minutes per week or 30 minutes on most days of the week for individuals with MetS.[15] Individuals should be screened for atherosclerotic cardiovascular disease (ASCVD) before exercise consultation, and high-risk individuals should participate in supervised exercise programs.

The consensus in CR guidelines is that the duration of aerobic exercise training is determined based on the patient's initial functional capacity. It can start at 10 min/session and gradually progress to 60 min/session with a 10%-20% increase in duration per week. Training sessions of 3-5 times per week are advised, with each session including warm-up, training, and cool-down periods. Preferred modes of exercise include walking, jogging, cycling, and rowing. Although walking is generally the preferred exercise, non-weight-bearing aerobic exercise modes are recommended for MetS patients with musculoskeletal pain or limitations.[8,9] Exercise intensity adjustment is crucial, and the amount of improvement and the risk of adverse events during exercise should be considered for safety. Optimum exercise intensity ranges between 40% and 70% of the heart rate (HR) reserve or between 50% and 80% of the HR_{peak}/VO_{2peak} ratio reached during an exercise test.[8] The talk test and Borg Rate of Perceived Exertion (RPE) scale should be evaluated as adjuncts to an objective aerobic exercise intensity assessment method in patients with MetS.[16]

There is no consensus in the literature regarding vigorous and moderate-intensity exercise in individuals with MetS.[12] It has been reported that home-based moderate-intensity exercise monitored by a pedometer and supervised high-intensity and moderate-intensity exercise have a similar effect on metabolic parameters.[17] High-intensity interval training (HIIT), which alternates high-intensity activities with lower-intensity activity (or passive recovery intervals), has been shown in recent years to have several beneficial effects on all CVD risk factors.[8] Interval training with long exercise periods can improve insulin signaling and increase the expression of GLUT-4 in skeletal muscle, whereas interval training with short exercise periods seems less effective in improving insulin signaling in the skeletal muscle in MetS.[18] High-intensity interval training was found to be more effective in improving endothelial function in individuals with hypertensive-MetS compared to8 weeks of moderate-intensity continuous training.[19] Significantly greater improvement was also observed in epicardial fat thickness, nitric oxide level, and amount of endothelial progenitor cells in the HIIT group. A decrease in fasting glucose level after HIIT is uncommon; some studies investigating the effects of high-intensity interval training (consisting of 2 or more weeks) reported a decrease in fasting glucose level, while others reported no change.[20] High-intensity interval training has been shown to improve peripheral insulin sensitivity in individuals with impaired glucose control. All of these adaptations, including increased GLUT-4 content, increased aerobic enzyme capacity and mitochondrial content are associated with improved insulin sensitivity. Studies evaluating the metabolic effect of HIIT in those with common metabolic diseases did not find a change in homeostatic model assessment for insulin resistance (HOMA-IR), while others showed an improvement of about 20% in this value compared to the control group. Compared to moderate-intensity continuous training, HIIT appears to have a small but significant favorable effect on insulin resistance in MetS.[18,20] The key physiological benefits of HIIT are summarized in Table 2.[21] The workload in HIIT is usually set to at least 80% of maximal HR (HR_{max}) and training intensity is adjusted according to VO_{2max}, RPE, and maximum workload. HIIT can be applied in cycling, walking, or running exercise modes. Current evidence supports the use of short-interval protocols (15-60/15-120 seconds) for patients with low exercise capacity (<5 metabolic equivalents, [METs]) or during the beginning stage of CR (0-4 weeks), and the use of medium- (1-2/1-4 minutes) or long-interval (3-4/3-4 minutes) protocols for patients with intermediate or high exercise capacity (≥5 METs) as well as for those in the improvement (4-12 weeks) and maintenance stages (>12 weeks) of CR.[22] Intensity is adjusted to 85%-95% of HR_{peak} or VO_{2peak}.[21]

Resistance Exercise Training: Resistance exercise training is known to improve biomarkers of cardiometabolic health. According to the ACSM, combined resistance and aerobic exercise training provides greater decrease in MetS prevalence compared to aerobic exercise training alone. It has been shown that resistance exercises performed 2 days a week improve MetS subparameters including impaired fasting glucose level, dyslipidemia, prehypertension, and increased waist circumference.[22,23] There are fewer studies examining the effects of resistance exercise in MetS than those evaluating aerobic exercise. There is also conflicting information regarding the effectiveness of resistance exercise training in reducing risk factors associated with MetS. Some studies support that resistance exercise training can be an effective strategy to improve all MetS risk factors, while others report no changes in MetS risk factors with this type of training. Ribeiro et al[24] showed that resistance exercise training improves the metabolic profile in older women, and exercise training with longer duration mainly leads to more significant reductions in C-reactive protein (CRP). On the other hand, resistance exercises significantly improved SBP compared to controls but had no effect on other MetS risk factors according to a meta-analysis published by Lemes et al.[23] a subanalysis revealed that longer interventions (>6 months) are more effective in improving SBP. A 2018 review examined different exercise modes (aerobic, resistance, and combined) to determine which is most effective in improving CVD risk factors in individuals with non-T2DM MetS. Of the studies on resistance exercise, only 1 study showed a 11% increase in cardiorespiratory fitness ($P < .05$). Resistance exercise training did not affect any MetS risk factors, possibly due to the limited number of studies included in the analysis ($n = 4$).[14] Other studies in the literature have shown that resistance exercise has significant benefits for patients with poor glycemic control[25] and reduces the risk of developing T2DM and CVD.[26]

Table 2. Key Physiologic Benefits of High-Intensity Interval Training[21]

- Respiratory muscle function ↑
- Respiratory impulse ↑
- Parasympathetic activity ↑
- Peak cardiac output ↑
- Peak stroke volume ↑
- Blood volume ↑
- Capillary density ↑
- Mitochondrial content and density ↑
- Ability to utilize oxygen ↑
- Ability to utilize fat and glucose ↑
- Vascular function ↑
- Endothelial function ↑
- Arterial compliance ↑

Conceição et al[27] reported a significant decrease in MetS z-scores and fasting blood glucose level and significant improvements in body fat percentage, lean body mass, and muscle strength after 16 weeks of resistance training (3 days/week, 8-10 repetition maximum [RM], 3 sets) in postmenopausal women. Tomeleri et al[28] also showed that a 12-week resistance training program (3 sessions/week, 3 sets of 10-15 RM, 1-2 minutes rest interval between sets, and 2-3 minutes rest between each exercise) provided improvements in body composition, MetS risk factors, and selected inflammatory biomarkers in postmenopausal women. According to the results of this study, resistance exercise training was found to be effective in decreasing the levels of pro-inflammatory biomarkers such as tumor necrosis factor-alpha and CRP, increasing skeletal muscle mass and strength, decreasing total body fat, and decreasing fasting plasma glucose level, HOMA-IR index, SBP, and MetS z-scores.[28]

A recent European Association of Preventive Cardiology statement report stated that initial training loads should be light, individuals completing 12-15 repetitions at 30% of 1RM for upper body and 40% of 1RM for lower body, and exercises should be performed at a slower pace. The exercise recovery period should be at least twice the working period. The intensity of resistance exercises should be gradually increased up to 70% of 1 RM and 80% of 1 RM for the upper and lower body, respectively. These recommendations are similar for individuals with MetS.[16] Supporting evidence for the safety of 1 RM testing during CR is scarce, so prediction equations can be used to safely estimate 1 RM from multiple RM tests: $1\ RM = \text{applied weight}/(1.0278 - 0.0278 \times \text{repetitions})$.[18] It is also suggested that a ≤10 RM test can be used to set the initial loads and the OMNI Resistance Exercise Scale (OMNI-RES) (Table 3) can be used to determine perceived intensity during the exercise sessions.[16]

Table 3. The OMNI Resistance Exercise Scale (OMNI-RES)[16]

0	1	2	3	4	5	6	7	8	9	10
Extremely easy		Easy		Somewhat easy		Somewhat hard		Hard		Extremely hard

Although it is unclear how resistance exercise training affects the cardiometabolic profile and MetS parameters, it appears to be associated with decreased inflammation and improved body composition and muscular fitness.[22] Lean body mass, GLUT-4 protein expression, and insulin sensitivity in skeletal muscles increase with resistance exercise training.[29] Myokines are released from the muscle with increasing muscle mass and produce an anti-inflammatory response. Therefore, inflammation level decreases and cardiometabolic risk factors decrease in individuals with MetS. Resistance exercise training may play an important role in improving MetS parameters when considering the inverse relationship between muscular fitness and the incidence of MetS.[29,30]

Other Exercise Modalities: New exercise modalities are being investigated to develop CR programs suitable for patient's needs, experience, risk profile, and preferences.[8] Yoga, tai chi, and virtual reality/exercise-based videogames (exergames) are alternative exercise modalities for which there is a growing body of evidence.[8]

Tai chi is a type of low-/moderate-intensity aerobic exercise. In addition to increased cardiorespiratory fitness, it has beneficial effects such as improved psychosocial status.[8] After a 12-week, 2 sessions/week tai chi intervention for adults with MetS diagnosed according to NCEP ATP III criteria, the participants stated that this type of exercise was acceptable and feasible. Tai chi exercises also decreased SBP and DBP, and participants exhibited better mental health at 12 weeks.[31] Another study in which older adults with MetS performed 50 minutes of tai chi exercises for 5 days/week over 6 months showed that supervised tai chi exercises decreased glycated hemoglobin (HbA1c) level and significantly improved antioxidant capacity.[32] However, tai chi studies have mostly been conducted in the Chinese population, and further research on individuals with MetS is needed.

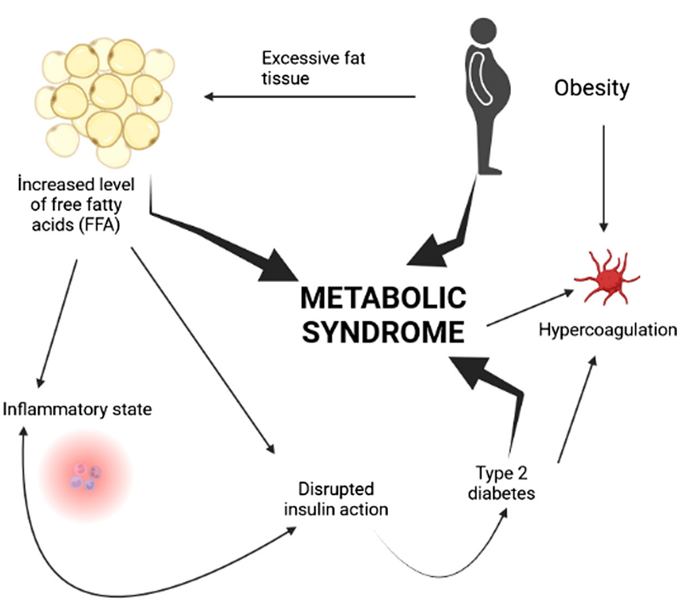

Figure 1. Pathophysiology of metabolic syndrome.[6]

Yoga is a type of mind and body exercise that combines specific body postures (*asana*), breathing exercises (*pranayama*), and meditation (*dhyana*).[33] Although evidence shows that yoga has positive effects on systemic inflammation, mental status, autonomous nervous system function, and CVD risk factors, large and high-quality randomized controlled studies are still needed.[8,33] Guddeti et al[33] reported in their meta-analysis that yoga was not associated with significant differences in MetS components except for decreases in SBP and waist circumference.

The use of virtual reality and active video games is a new approach that increases the motivation to exercise during CR.[8,34] Virtual reality provides a computer-based simulation of a real or imaginary environment, while exergames enable patients to exercise in an entertaining way and at an individually adjusted intensity level.[34] Recent evidence indicates that exergames using virtual reality can increase HR and walking ability and reduce perceptions of fatigue and pain in patients with CVD. Moreover, these exercise tools improve motivation and adherence.[34] At present, however, the quality of trials is not adequate and there remains the need for studies with different target populations, technological systems, and durations.[8,34]

Physical Activity Counseling in Metabolic Syndrome

Evidence shows that there is a consistent curvilinear and inverse dose–response relationship between PA and all-cause mortality, CVD mortality, T2DM, and cancer.[35] Although PA counseling is now seen as vital by many health systems, it seems that activity counseling is rarely used as a part of clinical studies. Considering the importance of exercise interventions for health outcomes among individuals with metabolic disorders, the lack of attention paid to PA is an unfavorable situation.[36] Conducting an intense lifestyle modification during a CR program is thought to be a cost-effective alternative to reduce CVD risks, fatigue, and functional capacity loss associated with MetS in the short and long term.[37]

Chen et al[38] reported that after a home-based CR program including activities such as walking or jogging 3 days a week, MetS z-scores showed progressive improvement in the intervention group at 3 and 12 months. In another randomized controlled study, Blackford et al[39] conducted a home-based motivational interview program with MetS participants and demonstrated significant improvements in dietary behaviors and mean walking, moderate-intensity activity, total activity, and sitting times compared to baseline. Morita-Suzuki et al[40] provided MetS patients with individual and group exercise counseling and reported improvements in the patients' physical and metabolic profiles after counseling.

A WHO guideline published in 2020 strongly recommends adults do at least 150-300 minutes of moderate-intensity aerobic PA, at least 75-150 minutes of vigorous aerobic PA, or a combination of moderate- and vigorous-intensity activity per week for significant health benefits. Moderate or higher intensity muscle strengthening exercises involving all major muscle groups for 2 or more days a week are also recommended. The WHO guideline also advises all adults to decrease the amount of sedentary time and replace it with any intensity of PA.[35] Mobile technologies such as smartphones, smartwatches, and fitness trackers may help individuals reach these goals and are increasingly used for PA counseling, but evidence is still insufficient. A review of mobile technologies published in 2021 showed that home-based exercises supported with mobile technologies significantly improved exercise capacity. Cardiac rehabilitation staff should ensure patient compliance with these devices to achieve these improvements.[41] Physical activity interventions as a part of CR have a favorable impact on MetS and incorporating PA counseling as an integral part of CR for patients with MetS.[40]

Lifestyle Modification

Individuals with MetS or T2DM should receive self-management training and receive the necessary support to facilitate mastery of knowledge, decision-making, and skills.[42] Patient education and support should be patient-centered and can be delivered in group or individual settings and/or using technology.[42] Patient education should focus on 2 main objectives, improving knowledge and understanding risk factor reduction, and use evidence-based health behavior change theory in its presentation. Including both aspects of education ensures that successful change is sustained over the long term.[10] Patient education and support help people maintain effective self-management as they face new challenges and treatment advances throughout their lives.[42] Lifestyle modification plays a key role in patient education for individuals with MetS, and this patient education and lifestyle behavior changes require a multidisciplinary approach.[43]

Brandao et al[37] demonstrated that small lifestyle changes that focus on PA can lead to clinical improvement in MetS. Intensive lifestyle intervention also resulted in greater reductions in HbA1c and greater improvements in fitness and all CVD risk factors except low-density lipoprotein cholesterol.[36] A recent meta-analysis showed that physical and mental health-related quality of life improved with lifestyle change interventions.[44]

The transtheoretical model describes the patient's process of adopting behavioral changes and is widely applied in chronic diseases to improve health-related behaviors, including exercise.[45] This model consists of 5 basic stages: *precontemplation* (not exercising and not thinking about starting in the next 6 months), *contemplation* (being aware of the existence of the problem and planning to start exercise in the next 6 months), *preparation* (currently exercising but not regularly), *action* (successfully exercising regularly for less than 6 months), and *maintenance* (more than 6 months of regular exercise).[45,46] Johnson et al[47] showed that a multiple behavioral intervention based on the transtheoretical model improved healthy eating, exercise, emotional distress management, and weight on a population basis, and the authors emphasized the potential synergistic effects of multiple behavioral interventions. Transtheoretical model-based exercise interventions were also reported to have significant positive effects on exercise behavior in sedentary chronic heart patients.[46] A meta-analysis of technology-based interventions including 18 studies (median duration of intervention: 4 months with 1.5-30 months of follow-up) demonstrated improved components of MetS such as decreased excess body fat, fasting glucose, and BMI.[48]

Conclusion

Lifestyle modification is an important treatment strategy for the prevention of adverse cardiovascular outcomes in patients with MetS. Although attendance in a CR program is associated with several health benefits, the level of CR utilization is inadequate. Metabolic syndrome can be prevented and managed with increased PA level, structured exercise programs, and decreased sedentary behaviors. Therefore, barriers to participating in CR programs for patients with MetS should be identified, and CR programs with different options and settings should be offered to these patient groups to increase participation and decrease the CVD burden associated with MetS.

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