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Research Article

A Narrative review of exercise and metabolic disease of the heart

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Abstract

According to the WHO's report, the number of people with diabetes worldwide is increasing, and the prevalence of type 2 diabetes in adults who is over 18 years old has risen from 4.7% in the 1980s to 8.5% in 2014. Among them, the prevalence of diabetes in low- and middle-income countries has even reached as high as 9.3% over the decades. Metabolic-Associated Fatty Liver Disease (MAFLD) is not only affecting the liver but is also considered a problem for the heart, as there is about 25% of the patients suffer from the cardiovascular syndrome. Around the world, the elderly population is growing rapidly. The elderly population is growing faster than expected, with Taiwan becoming an aged society in 2018. One of the health issues associated with aging is the population with cardiovascular disease increases. Patient care may result in huge expenditures on the national economy, society, family care, medical resources, and drugs. This article adopts perspectives from literature reviews using databases such as Cochrane Library, PubMed (Medline), Up-to-date and Google scholar using three main methods: search for keywords cardiovascular disease, physical fitness, exercise prescription intervention, quality of life, cardio metabolic disease, etc.; search for related articles on physical activity and cardiovascular disease, neuroendocrine, molecular biology, etc.; combined with case-control studies, systematic review and meta-analysis, analytical research, and randomized control studies to explore the effects of physical activity intervention and the fitness level of the elderly on the epidemiology of the cardiovascular disease, prevention of cardio metabolic disease, improvement of quality of life. Understanding which types of exercise intervention help improve the quality of life of patients with cardiovascular disease. This article aims to propose exercise prescriptions for physical fitness to prevent cardiovascular disease; be used as a reference for health promotion in the world, provide guidance on cardiovascular disease prevention and cardiovascular disease care for the elderly, and construct guidelines on physical fitness and exercise prescriptions in Taiwan.

Introduction

Metabolic fatty liver disease is one of the common clinical diseases, with its incidence on the rise on an annual basis, especially observing a dramatic increase since the 1980s when Ludwig and his colleagues first reported an unknown non-alcoholic fatty liver disease to be a risk factor for cardiovascular problems [1]. The disease affects as many as 25% of the adult population in the world. It is often associated with obesity, type 2 diabetes mellitus, atherosclerotic dyslipidemia, and metabolic syndrome. Metabolic fatty liver often develops into metabolic steatohepatitis (NASH), cirrhosis, or even cancer, making it a primary root of many other liver diseases; for example, a patient in the end-stage of the disease needs liver transplantation or may die from cancer development [2]. The hypothesis is that metabolic fatty liver disease shares common risk factors with some cardiovascular problems, such as atherosclerotic dyslipidemia, hypertension, type 2 diabetes and metabolic syndrome, all of which can be attributed to insulin resistance, since it is closely related to the accumulation of fats outside the liver in a body. The fat accumulation, such as at the epicardial adipose tissues, is known to exacerbate the development of cardiovascular diseases, supporting the notion that patients with metabolic fatty liver are at an increased risk

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of cardiovascular diseases. The disease will therefore require interventive treatment at a medical institution. To diagnose the disease, a biopsy of liver tissues is needed, which makes the process a bit more difficult to proceed, even though laboratory tests and abdominal ultrasound are available to "observe" the condition, especially since the invasive procedure is likely to aggravate the liver condition and increase the risk of the cardiovascular event at the same time. But nevertheless, to diagnose liver disease and determine its severity, biological indicators via ultrasound and histopathological examination to identify fibrosis in the liver will help to evaluate the risk of atherosclerosis and the likelihood to develop into cardiovascular disease, as well as help to identify the presence of metabolic fatty liver or steatohepatitis in patients [3].

Clinical features of metabolic disease of the heart

The common causes of metabolic fatty liver include obesity, hypertriglyceridemia, abnormal blood sugar metabolism (diabetes), overnutrition, etc. The disease has no specific clinical symptom and there is no subjective complaint that anyone can put into words to describe, but it is mostly discovered during annual general medical examinations [4]. Metabolic fatty liver can only be defined as a condition where various hepatic indices are elevated but without the presence of hepatitis B, hepatitis C, viral infection, drug use, alcohol consumption, or other known causes of chronic liver diseases. Also, metabolic fatty liver can be identified as lean when BMI is less than 23kg/m^2. This will contrast with the healthy population and the overweight population in terms of metabolic profile, as the patients of metabolic fatty liver disease will show different body composition than others [5].

How metabolic fatty liver affects cardiovascular health

Hormones secreted by fat cells, primarily by White Adipose Tissues (WAT) and Brown Adipose Tissues (BAT), are known to exert different effects on organs and tissues. Adiponectin, which is an essential compound for maintaining glucose homeostasis, insulin sensitivity, and organ function during chronic inflammation, is downregulated in obesity [6,7]. The hormonal axes that are in charge of suppressing appetite, improving peripheral insulin resistance, increasing body temperature, and circulating levels of leptin will regulate the total adipose tissue mass. Adipsin is an important protein of adipose cells and functions in an alternative complement pathway to stimulate insulin secretion through C3a receptors on β-cells. Elevated plasma level of the lipid chaperone Fatty Acid-Binding Protein 4 (FABP4), as a result of obesity, will increase hepatic gluconeogenesis, peripheral insulin resistance, and arterial plaque formation. On the other hand, the level of anti-inflammatory palmitoleate is reduced in obesity [8].

Diagnosis of metabolic fatty liver disease

Patients of metabolic fatty liver disease and coronary heart disease may also suffer from chronic inflammation. The high sensitivity C-Reactive Protein (hs-CRP) can be used clinically to predict the risk of cardiovascular disease or serves as an index of severity for metabolic fatty liver disease. Several clinical studies have already proven that hs-CRP is an independent risk predictor of myocardial infarction, ischemic cerebral infarction, or peripheral arterial disease. However, when screening for cardiovascular diseases in the healthy population using hs-CRP, the result was the opposite, showing no correlation between the two, as the later studies eventually proved that the correlation between hs-CRP and cardiovascular diseases would vary among the categories of population, specifically indicating the protein to be used only for people with a high risk of cardiovascular conditions, such as myocardial infarction, arrhythmia, diabetes, hypertension and installment of a pacemaker, rather than being used as a general screening tool [9,10]. The process of atherosclerosis involves a low-grade systemic inflammatory response; thus, it is speculated that inflammatory compounds may well play a role in predicting the risk of cardiovascular diseases. The American Heart Association and the US Center for Disease Control and Prevention (AHA/CDC) jointly published a report, recommending three categories of hs-CRP as low, medium, and high (respectively, with the value of < 1, 1-3 and > 3 mg/L) in terms of risk of cardiovascular diseases [10].

Non-drug treatment of metabolic fatty liver

Losing weight and increasing physical exercise is currently the only effective treatment for the fatty liver because it turns out to be a reversible condition. Regular physical exercise not only burns calories but will also increase the sensitivity of body tissues to insulin and reduce insulin resistance [11]. Moreover, empirically, there is just no specific drug for targeting the metabolic fatty liver.

The mechanism of Physical activity for older adults to prevent cardiometabolic disease

Metabolic Equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. MET is used to indicate the relative energy metabolism level of various activities, and another way to express exercise intensity and the number of heartbeats and conscious exercise intensity, which can reduce the incidence of cardiovascular disease [12]. Importantly, exercise training attenuates the inflammatory response in visceral adipose tissue, as evidenced by a decrease in macrophage recruitment and the production of inflammatory markers in this fat depot. Not all of them are bad; for example, adiponectin is a hormone produced by fat. It has anti-inflammatory effects. It contains a large amount of adiponectin in the plasma of healthy and thin people. Unfortunately, high blood pressure and ischemic heart disease reduce the amount of adiponectin. Recently, myokines have noticeably improved that health problem. There is much evidence that skeletal muscle can secrete many biologically active proteins to the extracellular fluids. These proteins are affected by exercise and are regulated through autocrine and paracrine pathways, such as metabolic and anti-inflammatory pathways, that impact other organs.

Obesity and lack of exercise are high-risk factors for metabolic syndrome and type 2 diabetes, causing mild inflammation of the body. It has been found that in obesity, fat tissue alters endocrine function, resulting in increased

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release of pro-inflammatory hormones such as TNF-α, chemerin, monocyte chemoattractant protein-1, and dipeptidyl peptidase-4. Among all the myokines, IL-6, irisin, and myoglobin can affect lipid metabolism. IL-6 is an early explored cytokine. It has been shown that skeletal muscle cells secrete IL-6 during exercise to improve systemic insulin sensitivity and protect against inflammation33. IL-6 is also considered an indicator of inflammation, which is often confused with the anti-inflammatory role of IL-6 secreted by muscle. The main difference is that when IL-6 is regarded as an indicator of inflammation, IL-6 maintains a high concentration in the blood for a long time. When muscle contraction during exercise causes a large increase in IL-6 in a short period of time (hours), it returns to its normal level, at the same time IL-6 is considered an anti-inflammatory role. In addition, adiponectin has protective effects against cardiomyocyte hypertrophy, avoiding ischemia-reperfusion injury and avoiding the role of angiotensin II in causing myocardial fibrosis. Studies have shown that adipose tissue is an endocrine organ that secretes a variety of cytokines, such as adipokines. Adipokines increase the inflammatory response of the entire body, especially the circulation system. Cytokines secretion within fat tissue may lead to chronic inflammation. However, physical activity and exercise are the best non-pharmaceutical way to treat obese patients. Physical activity and exercise can reduce whole-body inflammation and reconstruct lipid distribution4. In addition, studies have shown that three hormones, interleukin-6(IL-6), myostatin (CTRP15) and irisin are related to fat metabolism5. Interestingly, one of the most important adipokines, leptin, regulates the expression and activity of irisin in skeletal muscle and adipose tissue, confirming the crosstalk between adipokines and myokines. Dysregulation of the expression, function, or both adipokines and myokines due to a sedentary lifestyle might contribute to the onset of obesity and its associated comorbidities. In addition, increasing the amount of exercise helps the secretion of myokines. For example, the concentration of irisin in the blood is increased after exercise. However, in the absence of exercise effects, irisin in the blood is related to body composition. A patient with anorexia nervosa, whose Body Mass Index (BMI) is only 12.6 kg/m^2, has a low level of irisin in the blood, that is, 14% lower than that of normal-weight people, obese people (BMI 30-40 kg/m^2) whose blood is similar to normal-weight people, and severe obesity (BMI 40-50 kg/m^2 - BMI > 50 kg/m^2) people whose blood concentration of irisin is significantly higher than that of anorexia patients, probably because it improves the glucose tolerance of obesity. This result indicates that the amount of physical activity is positively correlated with the concentration of irisin. In addition, irisin can promote oxygen intake, and energy supply and is considered to be used as a strategy for the treatment of obesity and diabetes. Improve fat metabolism and the release of adipokines, which reduces the secretion of pro-inflammatory hormones, avoiding cardiac dysfunction. This mechanism is subject to further research in the future. Obesity is an important public health problem worldwide and a major cause of many chronic diseases, such as type 2 diabetes and cardiovascular diseases. Some methods for assessing the amount of physical activity include the maximum or minimum amount of physical activity, the number of exercises per week, the number of calories burned by physical activity, and the amount of walking as comparative indicators. Researchers studied the effects of doing physical activities ≥ 4 times/week compared to only 0-1 time/week, the reduction in the likelihood of cardiovascular disease was 49%; analysis of the research as mentioned above reports found that all exercise types were aerobic exercises. A study of 400,000 people in Taiwan found that 100 minutes of moderate-intensity exercise per day has the highest health benefits. Another study has recommended that reaching 700 minutes of physical exercise a week can provide significant health benefits. It is concluded that recreational physical activities of more than 4 hours per week or at least twice a week should reduce the risk of cardiovascular disease [13]. Completing 100 minutes of moderate-intensity aerobic exercise every day may be the best-recommended amount of exercise to prevent cardiovascular disease. A systematic retrospective study analyzed 32 kinds of physical activity intervention studies. Most of the studies lasted 6 months, and a few were followed up for 1-2 years. The results of a short-term single-item exercise intervention (aerobic exercise, resistance exercise, or Tai Chi) for the elderly in preventing cardiovascular disease or the occurrence of cardiovascular disease have shown insufficient evidence. Aerobic exercises, resistance exercises, Tai Chi exercises, and multiple combinations of exercises are beneficial to adults' cardiovascular function over 50 years old. To have the best effect, each exercise session should last at least 45-60 minutes with medium to high intensity, alternate between aerobic and resistance exercises, and be divided into multiple sessions spread throughout the week. Increasing the amount of physical activity in the elderly does have the effect of preventing cardiovascular diseases. Suggestions for exercise are as follows:

1. **Balance exercise:** 10 minutes to help maintain the stability of the body in daily life or exercise. An example of a balance exercise is standing on one foot, but the elderly may require something to hold onto to avoid falling.

2. **Flexibility or stretching activity:** Use muscle stretching activities to increase the range of motion (ROM), including dynamic and static types. It is recommended to warm up or stretch before any exercise to avoid injuries.

3. **Aerobic activity:** 150 minutes/week divided into 7 days, 20-30 minutes per day.

4. **Muscle strengthening activity:** Also known as resistance activities or weight training. 60-100 minutes a week is recommended, done 2-3 times a week every other day after aerobic exercises. Past research reports provide favorable evidence that increasing physical activity can prevent cardiovascular diseases in the elderly from the level of nerve cell physiology and molecular biology. Based on this evidence, it can be concluded that exercising more than 150 minutes a week or at least 3 times a week in addition to usual leisure and physical activities can reduce the risk of cardiovascular diseases. If 100 minutes of moderate-intensity aerobic exercise every week can be achieved, the prevention

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effect for dementia. It is recommended that at least 2-3 times a week, more than 4 hours of moderate to high-intensity physical activity is completed, or that five days a week, moderate-intensity aerobic exercise for 100 minutes is completed. The exercise time, frequency, and intensity of these two exercise models may be an effective way to reduce dementia. It is recommended for individuals to begin once they have reached middle age to prevent the onset of cardiovascular diseases in the elderly, strategies such as increasing the amount of physical exercise. The conclusion of this review is that in older individuals, excess adipose tissues trigger the dysregulation of adipokines. This dysregulation leads to myocardial inflammation, resulting in left ventricular dysfunction. Physical activity induces an increase in energy expenditure and triggers the release of myokines into the circulation by skeletal muscles, accelerating lipid metabolism, and improving the altered secretion profiles of adipokines. This process helps to alleviate myocardial inflammation and prevents the impairment of ventricular function. The conclusion suggests that future studies can investigate the effects of myokines on lipid metabolism, including how to reduce fat deposition and alleviate inflammation efficiently. In effect, muscle-derived cytokines (myokines) can be considered anti-inflammatory mediators.

The prognosis of metabolic disease of the heart

Cardiovascular disease is the leading cause of death in Europe and the United States, not to mention other parts of the world, too. Potentially modifiable risk factors for cardiovascular diseases include smoking, a sedentary lifestyle, high blood pressure, elevated LDL/cholesterol, and other metabolic risk factors [14]. By realizing the relationship of metabolism with cardiovascular events, the focus on eliminating metabolic disorders has significantly reduced the mortality rate. However, the majority of the world population has yet to control the related risk factors, despite that they have been well recognized by the public, especially the increasing prevalence of obesity and type 2 diabetes have actually undermined the effort to promote health around the world. In fact, in the United States alone, approximately two-thirds of adults are overweight or obese when we already know that even moderately overweight is associated with a significantly increased risk of cardiovascular disease-related death. Intervention by changing their lifestyle to lose weight can truly reduce the risk of cardiovascular diseases, but it is often quite difficult for people to maintain the habit in the long term. The increased prevalence of obesity has also led to a marked increase in the prevalence of other important cardiovascular risk factors, including hypertension, dyslipidemia, insulin resistance, and type 2 diabetes. Pharmacotherapies are currently available to address each risk factor, such as endocannabinoid receptor antagonists, inhibitors of peroxisome proliferator-activated receptor subtypes alpha and gamma, and several other drugs that modulate the activities of glucagon-like peptide-1. These new drugs have the potential to significantly improve several cardiovascular risk factors [15,16].

The mechanism of Physical activity for older adults to prevent cardiometabolic disease

The evidence shows that regular physical activity is safe for health and for frail older people and the risks of developing major cardiovascular and metabolic diseases, obesity, falls, cognitive impairments, osteoporosis, and muscular weakness are decreased by regularly completing activities ranging from the low intensity. Previous research has shown that participation in physical activity declines with age and is associated with obesity and cardiovascular diseases [8]. This contributes to decreased functional ability and an increased need for assistance with activities of daily living. Walking, jogging, swimming, dancing, or riding a bike. By improving your cardiovascular fitness, you'll be able to perform more activity without shortness of breath. Walking and other forms of moderate-intensity physical activity can provide protective effects, and emerging evidence now suggests the importance of efforts to reduce time spent in prolonged sedentary behaviors for optimal health outcomes. Physical activity can help reduce blood pressure in some people with hypertension. Helps people with chronic, disabling conditions improve their stamina and muscle strength. Reduces symptoms of anxiety and depression and fosters improvements in mood and feelings of well-being. It also helps maintain healthy bones, muscles, and joints. It helps improve both stability and mobility. Done at a higher level, it can help athletes improve how they play sports, but we fitness trainers for older adults also find it useful for increasing one's capacity to perform activities of daily living or ADLs.

Conclusion

Adipocyte-secreted hormones have multiple effects on other organs. Although most adipose tissue hormones are produced by both White Adipose Tissue (WAT) and Brown Adipose Tissue (BAT), only major sites of origin are shown. Adiponectin is downregulated in obesity and is important for maintaining glucose homeostasis, insulin sensitivity, and organ function in chronic inflammatory states. The circulating levels of leptin, which suppresses appetite, improves peripheral insulin resistance, raises body temperature, and regulates hormonal axes, correlate with total adipose tissue mass. The protease adipsin is an essential component of the alternative complement pathway and stimulates insulin secretion via C3a receptors on β-cells. In obesity, increased plasma levels of the lipid chaperone fatty acid-binding protein 4 increase hepatic gluconeogenesis, peripheral insulin resistance, and plaque formation in the arteries. By contrast, levels of the anti-inflammatory fatty acid palmitoleate are decreased in obesity.

Because non-alcoholic fatty liver disease, by definition, must exclude other possibilities that are attributable to alcohol consumption and liver conditions, this type of disease is not easy to diagnose. Recently, some experts proposed a new concept of diagnostic standard, placing an emphasis on the presence of a "fatty" liver with any one of the following conditions, including overweight/long waistline, type 2 diabetes, or evidence of metabolic abnormalities, such as high blood pressure, high triglycerides, low high-density cholesterol, pre-diabetic condition, insulin resistance and

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increased high sensitivity C-reactive protein (hs-CRP). Since most patients with fatty liver are asymptomatic, which makes it difficult to detect the condition, the physician can only observe through abnormal liver function, blood routines, and abdominal ultrasound. Plus, liver fibrosis scans, abdominal magnetic resonance imaging, and other examinations can also assist in the diagnosis. Currently, the gold standard for diagnosis is still liver biopsy. Based on the above, the conclusion of this review is that lack of exercise, and excessive diet can cause obesity. Due to the accumulation of excessive adipose tissue in individuals, the secretion of adipokines is imbalanced, increasing inflammation and myocardial fibrosis and finally causing ventricular dysfunction. For decreasing calorie consumption and reducing fat tissue, exercise may also promote muscle secretion of myokines, increase adipose metabolism, reduce inflammation, and prevent damage to heart function. Therefore, it is recommended that future research can better understand the effects of muscle hormones released from skeletal muscle on the function of adipose metabolism, including how to effectively reduce the accumulation of fat, reduce the inflammatory response, and myokines secreted by skeletal muscle during exercise. It is considered an inflammatory inhibitor; therefore, regular exercise is recommended to improve the health of patients with cardiovascular disease and to reduce cardiac function damage in older adults and patients with cardiovascular disease.

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