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COMMENTARY

Physical exercise improves low cardiorespiratory fitness associated with intramyocellular lipids in patients with metabolic syndrome

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In recent years, factors such as the westernization of dietary habits and an increasingly sedentary life style have led to a striking increase in the number of people with metabolic syndrome (MetS). Obesity is situated at the origin of the MetS and causes insulin resistance.[1] Insulin resistance itself is a characteristic feature of type 2 diabetes and obesity. The etiology of insulin resistance is multifactorial and involves both genetic and environmental factors.[2] Several lines of evidence have been provided in support of the hypothesis that intramyocellular lipids (IMCLs) and intrahepatic lipids (IHLs), as assessed non-invasively by localized ^{1}H-magnetic resonance spectroscopy, are associated with reduced-insulin action in both obese and non-obese subjects.[2,3]

In addition, high IMCL levels are associated with the impairment of early insulin signal transduction in specimens obtained from muscle biopsies, because IMCLs and related intracellular substances, such as diacylglycerol or protein kinase C, are important regulators of insulin resistance in skeletal muscle.[4]Insulin-resistant individuals have a reduced rate of fat oxidation, compared with normal, insulin-sensitive individuals, and thus, the decreased mitochondrial fat oxidative capacity could lead to an increase in the intracellular fat content.[5] It has also been reported that IHL accumulation is associated with impaired hepatic glucose metabolism. The suppressive effect of insulin on hepatic glucose production was shown to be negatively correlated with the IHL content in both healthy subjects and patients with type 2 diabetes.[4] DeFronzo[5] stated that the accumulation of toxic lipid metabolites (fatty acyl CoA, diacylglycerol, ceramide) in muscle, liver, adipocytes, β-cells and arterial tissues contributes to insulin resistance, β-cell dysfunction and accelerated atherosclerosis, respectively, in individuals with type 2 diabetes. Given the close relationship between IHLs and insulin sensitivity, Haufe *et al.*[2] investigated the relationship between IHLs and both fitness and insulin sensitivity, and concluded that the positive effect of increased cardiorespiratory fitness (CRF) on insulin sensitivity in overweight and obese subjects seems to be indirectly mediated by IHL content rather than the amount of total, visceral and subcutaneous fat. Potential mechanisms linking CRF and IHLs may include factors that regulate hepatic lipid oxidation. Substrate oxidation is tightly coupled to mitochondrial oxidation capacity. Mitochondria occupy nearly 18% of the hepatocyte volume, and their function, a strong determinant of fitness, could conceivably affect hepatic lipid oxidation.[2]

Low CRF is a predictor of all-cause mortality in patients with type 2 diabetes and in healthy people.[6]

Sawada *et al.*[7] investigated the relationship between long-term trends in CRF and the incidence of type 2 diabetes in a cohort of 41 787 non-diabetic Japanese men who completed annual health checkups and fitness tests for the estimation of maximal oxygen uptake over 7 years. Their study revealed a strong inverse relationship between long-term trends in CRF and the development of type 2 diabetes. In addition, a meta-analysis conducted by Kodama *et al.*[6] indicated that better CRF was associated with a lower risk of all-cause mortality and coronary heart disease/cardiovascular disease.

In this issue of *Hypertension Research*, Yokota *et al.*[8] investigated the relationship between muscle dysfunction and lower aerobic capacity in patients with MetS. To assess high-energy phosphate metabolism in skeletal muscle during aerobic exercise and to measure IMCL content, ^{31}phosphorus-magnetic resonance spectroscopy (^{31}P-MRS) and proton (^{1}H)-magnetic resonance spectroscopy, respectively, were performed.

In this study, the peak oxygen uptake (peak VO_2) and the anaerobic threshold were lower in MetS patients than in control subjects. Phosphocreatine loss during exercise was 1.5-fold greater in MetS patients. Phosphocreatine loss was inversely correlated with peak VO_2 and anaerobic threshold. IMCL content was threefold higher in MetS patients and was inversely correlated with peak VO_2 and anaerobic threshold. These results suggest that CRF in MetS patients was lower than in healthy subjects, and this difference might be due to the reduced oxidative metabolism of intramuscular fatty acids.

The results of various follow-up epidemiological studies have revealed that proper diet, combined with physical exercise, is not only useful in type 2 diabetes mellitus, but is also effective for the prevention and treatment of all other insulin resistance-related diseases (lifestyle-related diseases/MetS) by improving CRF and sensitivity to insulin.[9] It is now well established that participation in regular physical exercise improves blood glucose control and positively affects lipid levels, blood

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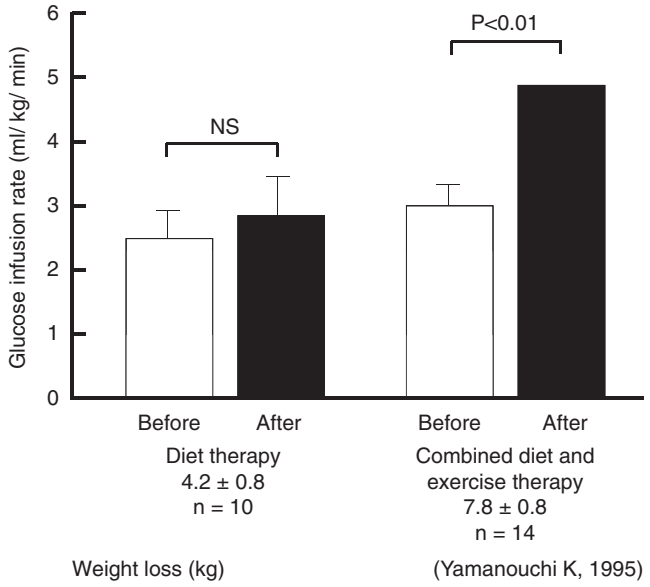

Figure 1 Changes in insulin sensitivity (glucose infusion rate) in patients on diet therapy alone and on combined diet and exercise therapy.

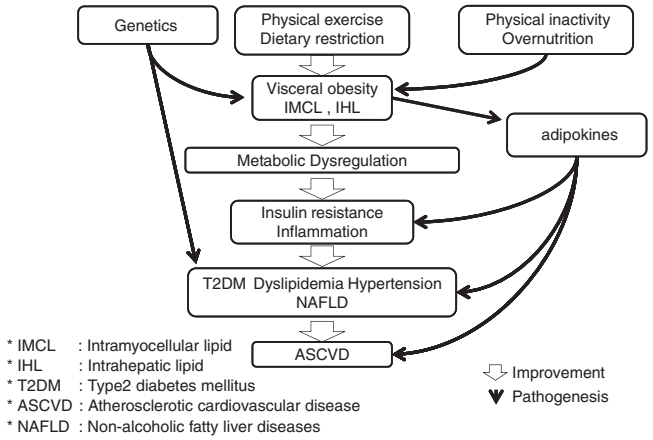

Figure 2 Physical exercise improves or prevents metabolic syndrome-associated disorders.

pressure, cardiovascular events, mortality and quality of life.[10]

We have reported that, if continued for a prolonged period of time, even mild aerobic exercise increases insulin action even if there is no influence on body mass index or VO_2 max. The implementation of dietary restrictions and physical exercise regimens for obese people and obese patients with type 2 diabetes will result in an efficient decrease in body fat, leading to weight loss, whereas causing no changes in lean body mass. Thus, dietary restriction combined with physical exercise is more useful for improving insulin sensitivity than dietary restriction alone (Figure 1). In addition, the increased glucose metabolic clearance rate (ΔMCR: an index of insulin sensitivity) is positively correlated with the number of steps per day measured by a pedometer. Aerobic exercise such as jogging is more useful than anaerobic exercise such as weight lifting for improving *in vivo* insulin sensitivity. However, mild resistance training, if performed in an aerobic manner, is also useful for elderly patients who have decreased muscular mass and strength.[9] A recent joint position statement of the American College of Sports Medicine and the American Diabetes Association indicated that both aerobic and resistance training improve insulin action, blood glucose control and fat oxidation and storage in muscle; in addition, resistance exercise enhances skeletal muscle mass.[10]

A new method of resistance training has been reported. By applying blood-flow restriction, the metabolic stress in skeletal muscle during low-intensity resistance exercise was significantly increased. Further significant dose effects on intramuscular metabolites and pH were observed. This low-intensity exercise could be safely performed by the elderly and diseased patients.[11]

The effects of interval versus continuous training on cardiorespiratory and mitochondrial function have also been investigated. The results suggested that the fluctuations of the workload and oxygen uptake during training sessions, rather than exercise duration or global energy expenditure, are key factors in improving muscle oxidative capacity.[12]

Therefore, intermittent training appears to be optimal for maximizing both peripheral muscle and central cardiorespiratory adaptations, permitting significant functional improvements.

The effects of diet and exercise on the intracellular lipid contents in muscle and liver and on insulin sensitivity in type 2 diabetic patients were investigated. Tamura *et al.*[4] reported that calorie restriction, combined with moderate-intensity physical exercise (50-60% of VO_2 max), resulted in a decrease in IMCLs and an increase in insulin-mediated glucose uptake in muscle in type 2 diabetic patients (Figure 2). They also found that changes in total physical activity negatively correlated with changes in IMCL contents.[4]

We also showed that low-intensity exercise using a horseback riding fitness equipment (JOBA, Panasonic Electric Works Co., Ltd., Osaka, Japan) is especially useful as an alternative exercise therapy for elderly patients with diabetes and obesity who are incapable of performing independent exercise or for those who suffer from knee-joint disorders.[13]

Recently, the Australian Diabetes, Obesity and Life Study reported that television-viewing time was associated with increased risk of all-cause and cardiovascular disease mortality. Although the continued emphasis of the current public health guidelines on the importance of moderate- to vigorous-intensity exercise should remain, the findings of this study suggest that reducing the time spent watching television (and possibly other prolonged sedentary behaviors) may also be of benefit in preventing cardiovascular disease and premature death.[14] Additionally, Bankoski *et al.*[1] examined sedentary life and noticed that the proportion of sedentary time was strongly related to a moderate risk of MetS, independent of physical activity. These results suggest that older people may benefit from reducing their total sedentary time and

avoiding prolonged periods of sedentary time by increasing the number of breaks during sedentary time.[1]

CONFLICT OF INTEREST

The author declares no conflict of interest.

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