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Effects of lifestyle activity modification on insulin resistance and pancreatic-cells function in obese men with insulin resistance

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Abstract

Introduction: Pancreatic β-cells function and insulin sensitivity resistance were impaired in type 2 diabetes. The effect of lifestyle activity modification (LAM) on these parameters is unclear. The aim of present study was to examine the effect of 8 weeks LAM on pancreatic β-cells function and insulin resistance in middle aged men with insulin resistance.

Material & Methods: Sixteen obese and overweight middle aged men (age, 35-50 years) with insulin resistance participated in this study. The subjects were randomly assigned to LAM group (n=8) or control group (n=8). The subjects in LAM group walked 2 miles in 30 minutes on a treadmill on 4 days per week for 12 weeks according to the guidelines of the Centers for Disease Control and Prevention and American College of Sports Medicine.

Results: The results indicated that fasting blood sugar, fasting insulin and insulin resistance index decreased and pancreatic β-cells function increased significantly after the intervention.

Conclusion: In summary, it seems that LAM improves insulin resistance and pancreatic β-cells function in obese men with insulin resistance.

Keywords: Obesity, Lifestyle activity modification, Pancreatic β-cells function, Insulin resistance

1. Introduction

Obesity, as one of the most prominent noncommunicable diseases, has come into focus of health science researchers. The increased risk of obesity and its consequences, along with the industrialization of societies and lifestyle changes, foregrounds the prevention and treatment of obesity as a major challenge for the health system. Studies have demonstrated a strong association between inflammatory markers, metabolic disorders, obesity and its related diseases such as Atherosclerosis, metabolic syndrome and diabetes (1). The increasing prevalence of obesity, especially in developed countries is linked to certain diseases such as diabetes type 2, hypertension, metabolic syndrome, Atherosclerosis, asthma and cardiovascular disease (2). The prevalence of diabetes mellitus is striking. It is estimated that more than 360 million will develop diabetes mellitus by 2030 (3). According to the Center for Disease Control and Prevention (CDC), 7.8% of the United States population had diabetes mellitus in 2007. The total estimated cost of diabetes mellitus in 2007 was $174 billion dollars (4).

Apart from genetic factors and overeating, inactivity and lack of exercise are the main causes of obesity and the related disorders. Besides, along with genetic and physical inactivity, obesity is the most important environmental factor underlying the syndrome of insulin resistance in a way that the loss of weight or reduction of body fat levels leads to both insulin balance and reduction of insulin resistance (5,6). However, factors that promote beta cell failure and diabetes in obese persons have not yet

fully understood. The presence of Hyperglysymy and Hyperphagia in obese individuals, despite the presence of high insulin levels, indicates their resistance to this hormone (7). Type 2 diabetes is sustained by insulin resistance and impaired insulin secretion. Impaired insulin secretion due to either β-cell dysfunction and/or β-cell loss is now recognized in the pathogenesis and progression of diabetes. The loss of β-cell mass and the progressive decline in β-cell function is an early feature of the natural history of diabetes and it is detectable prior to diagnosis (8). The United Kingdom Prospective Diabetes Study (UKPDS) showed that β-cell function, as evaluated by the homeostatic model assessment (HOMA-B) index, was already decreased by 50% by the time of the diagnosis and that it continued to decline over the 6-year observation period, even with on-going hypoglycemic therapy (9). The relative increase of α-cells mass, another typical defect on Langerhans islets of diabetic subjects, may even precede β-cells loss, being already observed in normoglycaemic baboons with different degrees of obesity (10).

β-cell mass is influenced by a balance between proliferative and pro-apoptotic signals, which may be modulated by various growth factors, cytokines, and hormones, whose specific role in the rate of β-cell decline remains unclear. High levels of glucose and free fatty acids (gluco-and lipotoxicity), islet amyloid polypeptide deposition, and circulating inflammatory cytokines have been all implicated in β-cell apoptosis (10,11). At any rate, whenever it appears, impaired β-cell function leads to the progressive failure of islet cells to secrete sufficient amounts of insulin to overcome peripheral insulin resistance, ultimately resulting in failure to maintain normal glucose homeostasis over time. However, the rate of β-cell failure is unpredictable and not all persons with Type 2 diabetes will need insulin therapy to maintain their blood glucose levels (12).

Exercise has been introduced as a non-pharmacologic approach to reduce the prevalence of obesity and its complications. It is known that exercise alone will lead to an improvement in insulin sensitivity (13,14). As in some other studies, 6 to 9 months of aerobic exercise improved insulin action and insulin resistance in healthy older adults (15,16). But the effect of exercise on beta-cell function in adults or elderly people has been less studied. Recently, Omidi and Moghadasi (2017) reported that 8

weeks aerobic training with 60-75% of maximum heart rate improves insulin resistance but it had not effective on pancreatic β-cells function in female patients with type 2 diabetes (17). However, Farbod et al. (2014) noted that β-cell function improved and fasting glucose decreased after 6 weeks aerobic exercise (18).

CDC and American College of Sports Medicine (ACSM) suggest that the accumulation of 30 minutes of moderate intensity physical activity on most days of the week (lifestyle activity modification or LAM) will produce significant health benefits (19). It is important to investigate whether or not these activity guidelines improve insulin resistance and β-cell function in obese men. Thus we examined the effects of short term LAM on insulin resistance and pancreatic β-cell function in obese men with insulin resistance.

2. Material & Methods

Subjects

Fifty sedentary obese and overweight middle-aged men enroll and volunteered to participate in this study. All the people were asked to complete a personal health and medical history questionnaire, which served as a screening tool. Sixteen obese men with insulin resistance (BMI: 31.2 ± 4.1 kg/m^2) selected as the subject after screening by inclusion criteria. All the subjects had insulin resistance and all of them were complete inactive at least 6 month before the study and they were nonsmokers and free from unstable chronic condition including dementia, retinal hemorrhage and detachment; and they have no history of myocardial infarction, stroke, cancer, dialysis, restraining orthopedic or neuromuscular diseases. Thereafter, the subjects were randomly assigned to a control group (n=8) or LAM group (n=8). The subjects were given both verbal and written instructions outlining the experimental procedure, and written informed consent was obtained.

Exercise training

The subjects in the LAM group walked 2 miles at 30 minutes (40-59% maximal oxygen consumption [VO_{2max}]) on a treadmill without incline on 4 days/week for 12 weeks according to the CDC and ACSM guidelines.

Anthropometric and body composition measurements

Height and body mass were measured, and body mass index (BMI) was calculated by dividing body mass (kg) by height (m^2). Waist circumference was determined by obtaining the minimum circumference (narrowest part of the torso, above the umbilicus) and the maximum hip circumference while standing with their heels together. The waist to hip ratio (WHR) was calculated by dividing waist by hip circumference (cm) (20). Fat mass and lean body mass were assessed by bioelectrical impedance analysis using a Body Composition Analyzer (Biospace, Inbody 3.0, Jawn, Korea).

Measurement of VO_{2max}

VO_{2max} was determined during graded exercise testing using modified Bruce protocol (21). Each subject performed a graded treadmill exercise test to estimate VO_{2max} by indirect calorimetry. A pulmonary gas exchange system (Cosmed, Quark b2, Italy) was used to evaluate the participants' VO_{2max}. Oxygen uptake (VO_2) was measured continuously via breath by breath analysis with the use of a computerized system. To ascertain that VO_{2max} had been attained, standard criteria had to be met. The criteria for reaching VO_{2max} test were: RER $>$ 1.00, HR $>$ 85% percentile of age predicted maximum and plateau of VO_2 maximum (22).

Biochemical analyses

Fasting blood samples were collected at rest (before training) and after last session of training. All the subjects fasted at least for 12 hours and a fasting blood sample was obtained by venipuncture. Blood samples were kept in the temperature of –20°c. Glucose was determined by the oxidase method. Insulin was also determined by ELISA kit (Mercodia, Sweden). The intra and inter-assay coefficients of variation for glucose were $<$1.3% and a sensitivity of 1 mg/dl. Pancreatic β-cell function was assessed with the HOMA-B model and insulin resistance was calculated using the HOMA-IR model (23,24).

Statistical analysis

Results were expressed as the mean ± SD and distributions of all variables were assessed for normality using Shapiro-Wilk test. ANCOVA

was used to assess the impact of the intervention while controlling the co-variant effects of the pre-test. Assumptions of normal distribution of scores and homogeneity of variance were evaluated. The level of significance in all statistical analyses was set at $P<0.05$. Data analysis was performed using SPSS software for windows (version 17, SPSS, Inc., Chicago, IL).

3. Results

All data were not significant for normality check. Anthropometric and body composition characteristics of the subjects before and after training are presented in Table 1. Before the intervention, there were no significant differences in any of variables among the two groups. Body weight, BMI, body fat percent and WHR decreased ($P<0.05$) after 12 weeks LAM training compared to the control group. After 12 weeks intervention, maximal oxygen consumption increased ($P<0.05$) in the LAM group, while no significant change in the control group was found.

Table 1. Physical and physiological characteristics (mean ± SD) of the subjects before and after training

	Control		LAM	
	Pre	Post	Pre	Post
Body mass (kg)	90.4 ± 13.9	90.6 ± 14.1	86.1 ± 4.6	84.1 ± 4.3[a]
BMI (kg/m^2)	32 ± 5.3	32.1 ± 5.3	30.3 ± 2.1	29.5 ± 2.1[a]
Body fat (%)	31.4 ± 5.5	31.4 ± 5.5	30 ± 3.4	28.1 ± 3.2[a]
WHR	0.99 ± 0.08	0.99 ± 0.08	0.96 ± 0.03	0.95 ± 0.03[a]
VO_{2max} (ml.Kg^{-1}.min^{-1})	31.8 ± 5.6	31.9 ± 5.7	30.3 ± 3.7	34.5 ± 2.6[a]

a $P<0.05$ for between-group differences.
b $P<0.05$, pretraining *vs.* posttraining values.

Biochemical parameters of the subjects are presented in Table 2. The ANCOVA test indicated that fasting glucose, fasting insulin and insulin resistance determined by HOMA-IR decreased in the LAM group compare to the control group ($P<0.05$). The results, also demonstrated that pancreatic β-cell function determined by HOMA-B increased in the LAM group after training ($P<0.05$).

Table 2. Metabolic characteristics (mean ± SD) of the subjects before and after training

	Control		LAM	
	Pre	Post	Pre	Post
Fasting glucose (mmol.l^{-1})	5.5 ± 0.4	5.6 ± 0.4	5.4 ± 0.4	5.3 ± 0.4[a]
Fasting insulin (μU.ml^{-1})	11.6 ± 2.7	12.5 ± 2.2	11.6 ± 2.8	11.4 ± 2.7[a]
HOMA-IR	2.8 ± 0.7	3.1 ± 0.6	2.8 ± 0.8	2.7 ± 0.8[a]
HOMA-B	120.8 ± 39.3	123.3 ± 34.7	117.0 ± 18.8	126.3 ± 13.3[a]

a $P<0.05$ for between-group differences.
b $P<0.05$, pretraining *vs.* posttraining values.

4. Discussion

Type 2 diabetes is described as a combination of low amounts of insulin production from pancreatic β-cells and peripheral insulin resistance (25). Insulin resistance leads to elevated fatty acids in the plasma, causing decreased glucose transport into the muscle cells, as well as increased fat breakdown, subsequently leading to elevated hepatic glucose production. Insulin resistance and pancreatic β-cell dysfunction must occur simultaneously for type 2 diabetes to develop. Anyone who is overweight and/or obese has some kind of insulin resistance, but diabetes only develops in those individuals who lack sufficient insulin secretion to match the degree of insulin resistance. Insulin in those people may be high, yet it is not enough to normalize the level of glycemia (26). The present study evaluated the effects of LAM training, suggested exercise program by CDC and ACSM, without diet control in sedentary middle-aged men who were overweight or obese. The major finding of the present study is that 12 weeks LAM alone can improve insulin resistance in addition to the improvement in pancreatic β-cell function and decrease in body mass and body fat percent, suggesting that this intervention is effective to induce glucose homeostasis in obese men.

Subjects with obesity frequently have basal hyperinsulinemia and an exaggerated response to stimulation by a test meal or glucose attributed to increased insulin secretion and reduced insulin clearance (27,28). Previous studies indicated that exercise training is a useful therapy for improving insulin resistance (17,29-31). The results of the current study in line with previous studies demonstrated that fasting glucose, fasting insulin and insulin resistance determined by HOMA-IR improve after 8

weeks LAM. Insulin resistance is marked by a decreased responsiveness to metabolic actions of insulin such as insulin-stimulated glucose disposal and inhibition of hepatic glucose output (32). The exercise-induced increase in insulin sensitivity is believed to reflect adaptations in muscle insulin signaling (33,34), glucose transporter type 4 (GLUT4) protein expression, content and action (35,36) and associated improvement in insulin-stimulated glucose disposal and glycogen synthesis (33,34). This is accompanied and influenced by enhanced intramyocellular oxidative enzyme capacity and possibly changes in muscle architecture from fast-type to slow-type fibers (37,38).

Exercise increases insulin-mediated GLUT4 translocation to the sarcolemma and subsequent glucose uptake, which may reflect a transient elevation as a consequence of the "last bout" (35). The underlying increase in GLUT4 transcription and expression of GLUT4 mRNA has been shown to persist for 3 to 24 hours after exercise (36,39). In this way, regular exercise translates into a steady-state increase of GLUT4 protein expression, and subsequent improvement in glucose control over time (36). Similarly, enhanced whole-body insulin sensitivity has been shown to occur in the hours immediately following exercise, and evidence from a limited number of studies using hyperinsulinaemic-euglycaemic clamp and oral glucose tolerance test (OGTT) suggests that this may persist for up to 24 to 72 hours after the last bout (40-42).

The results indicated that β-cell function determined by HOMA-B improves after 12 weeks LAM. There is still the issue of which between insulin resistance and HOMA β-cell precedes the occurrence of diabetes (43). In the case where insulin resistance is argued to be the primary cause, decline in the function of β-cell is the later response to the gradual increase in insulin secretion due to the insulin resistance. However, those who argue that the malfunction of β-cell as the primary cause of diabetes state that the reduction in the insulin secretion is the reason that normal blood sugar levels would increase (44). In addition, the HOMA-IR index seems to reflect insulin resistance, but there is still room for discussion regarding the correlation between HOMA β-cell index and the β-cell function of the pancreas.

Haffnet et al. (1996) noted that the β-cell malfunction is the primary cause of diabetes (45). Through regular exercise, less insulin can carry the same amount of glucose to muscles and the liver. Therefore, β-cells in the pancreas do not have to excessively secrete insulin, resulting in decreased HOMA-IR and HOMA β-cell indexes (45). The mechanisms behind the improved pancreatic β-cell function to increase insulin action could be multifaceted, including perhaps an improved coordinated feedback loop between liver (decreased hepatic gluconeogenesis), muscle (attenuated insulin resistance) and pancreas (slowly wakening of β islets to secrete insulin). However, given that type 2 diabetes is a disease characterized by perturbations in several organs, anti-inflammatory cytokines secreted by both adipocytes (e.g. adiponectin) and myocytes (e.g. IL-6) could be involved in the improvement of pancreatic β-cell function (46).

On the other hand, increased levels of free fatty acids, triglycerides Citozolic or hyperglysymic associated with obesity and insulin resistance, severely affects the function of β-cells (47), and their improvement in response to weight loss is a potential description for improvement of β-cell function and insulin sensitivity. However, some researchers have reported that improvement of β-cell function may possibly be affected by factors independent of weight loss (48). In this regard, some studies have reported the improvement of β-cell function in response to weight loss in those suffering from diabetes type 2 (49,50) but their response to weight loss resultant from diet or exercise in obese non-diabetes patients have less been studied. In the present study, a significant increase in β-cell function in obese female subjects was associated with a significant reduction in body weight. In other words, LAM program, in addition to a significant reduction in body weight, led to a significant reduction of BMI and body fat percent.

5. Conclusion

LAM training, suggested exercise program by CDC and ACSM, can improve insulin resistance in addition to the improvement in pancreatic β-cell function and decrease in body mass and body fat percent, suggesting that this intervention is effective to induce glucose homeostasis in obese men.

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