

## **Changes of leptin, resistin, adiponectin and free fatty acid in the impaired glucose tolerance patients with exercise intervention.**

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### **Abstract**

**Our previous studies have investigated the effects of exercise intervention on vascular endothelium functions and the endocrinological change of endothelium-dependent vasodilation in the middle-aged patients with Impaired Glucose Tolerance (IGT). The present study was aimed to explore the endocrine mechanism of the endothelium-dependent vasodilation by examining the changes of leptin, resistin, adiponectin and Free Fatty Acid (FFA) in the IGT patients after exercise intervention. Exercise intervention decreased leptin, resistin and FFA significantly, but increased adiponectin. Furthermore, correlations were identified between vascular endothelium function items and leptin, adiponectin and FFA. Exercise intervention may improve vascular endothelium-dependent dysfunction through decreasing leptin and FFA, and increasing adiponectin in middle-aged patients with IGT. This present study provided the direct clinical data supporting the implementation of exercise intervention to prevent diabetes mellitus during the early stages.**

**Keywords:** Adiponectin, Exercise intervention, Impaired glucose tolerance, Prediabetes mellitus.

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### **Introduction**

Impaired Glucose Tolerance (IGT), a particular metabolic state between the diabetic and normal states, is characterized by the elevation in postprandial glucose-one of the early characteristics of prediabetes mellitus [1,2]. IGT is a pre-diabetic state of hyperglycemia that is associated with insulin resistance (IR) and increased risks of Cardiovascular Disease (CVD) [1-4]. Without intervention, IGT can progress to diabetes and Cardiovascular Disease (CVD) [5,6]. However, IGT condition may also be improved through exercise or drug intervention. IR is a pathological condition in which insulin is excessively secreted for compensation to maintain normal physiological functions, leading to hyperinsulinaemia [7]. Associated risk factors for IR include overweight/obesity, less physical exercise, and genetic factors [3,4]. IR often leads to the increased glycogen production/output, decreased insulin-stimulated glucose uptake, loss of dystrophin-glycoprotein generation/storage, postprandial hyperglycemia, and attenuated

insulin suppression on lipolysis [4,8,9]. Endothelial Dysfunction (ED) is a significant predictor of CVD [10]. Strongly correlated with obesity and IR, ED may result in vascular complications of Diabetes Mellitus (DM) and play an important role in the CVD pathogenesis [5-7]. Therefore, IGT is an important stage to prevent the development and cardiovascular complications of DM.

At present, IGT and DM with IR have become increasingly common due to the modern sedentary lifestyle [11-13]. Currently, exercise has been deemed as the best treatment for metabolic syndrome, remarkable for preventing DM and CVD with IGT [1,2]. Exercise can increase energy consumption and muscle mass, decrease body fat and produce a profound effect on the endocrine functions [11-14]. It has several advantages over other IGT controlling methods, such as cost-effective, easy to implement, simple and safe [11-14]. Several diabetes prevention studies observed that lifestyle intervention during IGT significantly reduced the incidence of DM [1,2].

The diabetic population gradually became younger and younger [4,9,13,15], and the working population at their golden ages are increasingly affected. Given the exercise therapy is a low cost, simple, properly implemented and safe intervention without side-effects, it has attracted much attention in recent years [1,2,11-14]. Together, it is necessary to further investigate the effects of exercise on middle-aged IGT patients and its related regulatory mechanism in order to provide clinical evidence for the exercise prevention of DM.

Walking is one of the most simple and commonly used fitness exercises. Resistance exercises can increase the basal metabolic rate, facilitate energy consumption, and thereby increase insulin sensitivity [12-14]. In this study, two different exercise interventions (moderate intensity walking exercise and walking plus resistance exercise) were taken for 24 w to investigate the effects of exercise on physiological and biochemical indices as well as vascular endothelial functions in middle-aged IGT patients.

## Materials and Methods

### Study subjects and groups

In this study, 61 patients with IGT (mean age  $49.8 \pm 4.8$ ) were selected from 129 DM high-risk individuals in two residential communities (Districts of Cangshan and Gushan, Fuzhou, the capital city of Fujian province in China). IGT were diagnosed with a 2 h 75 g Oral Glucose Tolerance Test (OGTT) according to the guidelines of 2004 China Diabetes Prevention and Control. The diagnosis criteria for IGT required plasma glucose with a range of 7.8 to 11.10 mmol/l (2 h).

All included individuals were free from cardiopulmonary and systematic diseases that would interfere with fitness exercise. Patients from non-sport oriented population undertook 24 w long fitness exercises. All subjects were randomly assigned into three groups: the control group without exercise ( $n=21$ ), walking exercise group ( $n=20$ ) and walking plus resistance exercise group ( $n=20$ ). The protocol was approved by the Institutional Research Ethics Boards of Fujian Normal University and Fujian Medical University. All participants understood the study protocol and provided the written informed consents.

### Exercise models and methods

The controls did not participate in exercises. In the walking exercise group, subjects were requested to walk on a running machine: to look straight ahead and keep stomach in, chest out, head out, shoulder back, relax and swing their arms rhythmically while walking. Subjects exercised four times a week for 60 min each time, including 5 min of warm-ups, 50 min of walking exercise, and 5 min of cool-downs. The exercise intensity was equivalent to 60~70% of maximal Heart Rate (HR) max, starting from 50~60HR<sub>max</sub> and gradually increasing to 60~70%HR<sub>max</sub>. In the walking plus resistance exercise group, the exercise included 30 min of resistance exercise following 20 min of walking exercise. The resistance

exercise focused on weight reduction, and included the upper arm, chest and waist exercises (15 pull-ups on the pull-up device with 2~3 repeats and 15 straight-arm forwards using the arms out machine with 3~4 repeats), abdominal exercises (15~20 sit-ups on the sit-up machine with 2~3 repeats and 15~20 supine straight-ups with 2~3 repeats), and leg exercises (15 kicks on the leg press machine with 2~3 repeats and 15 extension on the leg extension machine with 2~3 repeats). The exercise lasted for 24 w.

### Implementing and monitoring of exercise

Adaptive training was implemented for one week prior to the formal exercises. The number of heart beats within 10 s (HR 10 s) at different stages was recorded during the exercise process. The HR was calculated as six times of HR 10 s. The exercise intensity was adjusted and controlled based on self-reporting and the body reactions of the participants. Physiological and biochemical indices were examined before and after the whole exercise intervention [1,2].

### Anthropometric parameters

Anthropometric parameters were measured using a body composition resistance measurement instrument Biospace InBody 3.0 (Biospace Co. Ltd. Seoul, South-Korea) according to the national physiological constitution monitoring requirements, which included Body Mass Index (BMI), body fat percentage, waist to hip ratio and other parameters [1,2].

### Laboratory or chemical indexes

A total of 5 ml peripheral blood was collected through the antecubital vein after 48 h of banning on alcohol and tobacco and 8 h of fasting. Plasma glucose was measured using full automatic biochemical analyzer (Hitachi 7020, Tokyo, Japan) immediately after blood collection. The following biochemical indices were detected with a variety of kits by Radioimmunoassay (RIA) according to the manufacturers' instructions: C-type natriuretic peptide (CNP, intra-assay coefficient of variation (cv)<10.00%, inter-assay cv<15.00%), endothelin-1 (ET-1, intra-assay cv<10.00%, inter-assay cv<15.00%), insulin (intra-assay cv<4.30%, inter-assay cv<7.10%), leptin (intra-assay cv<10.00%, inter-assay cv<15.00%), resistin (intra-assay cv<3.59%, inter-assay cv<9.25%), adiponectin (intra-assay cv<3.59%, inter-assay cv<9.25%), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ , intra-assay cv<5.00%, inter-assay cv<8.00%) and Free Fatty Acid (FFA). The RIA kits for insulin, leptin and TNF- $\alpha$  were provided by the Gaoke Co., Ltd. Institute of Atomic Isotope, China Institute of Atomic Energy, Beijing, China. The resistin and adiponectin kits were purchased from Linco Research Inc., St Louis, Mo, USA. The ET-1 and CNP kits were obtained from the Center of Science and Technology Development, PLA General Hospital. The FFA enzyme linked immunosorbent assay kit was purchased from Randox Laboratories Ltd., Co. Antrim, Northern Ireland, United Kingdom. Homeostasis model assessment (HOMA): HOMA-IR was defined as fasting

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plasma insulin concentrations (FINS, mIU/L)  $\times$  fasting blood glucose (FBG, mmol/L)/22.5 [1,2].

### ***Ultrasonic of color Doppler evaluation***

The determination of carotid artery structure and function was conducted by Celermajor method [1,2]. Brachial artery endothelium dependent vasodilation was measured with color Doppler supersonic diagnostic equipment (IU-22, Phillips-Medisize Corporation, Hudson, WI, USA) with a L17-5 transducer of 17 to 5 MHZ extended frequency range. Endothelium-independent vasodilation:  $\text{Dia-N} = (\text{artery diameter with } 0.4 \text{ mg sublingual nitroglycerin for } 1 \text{ min} - \text{basic diameter}) / \text{basic diameter} \times 100\%$ . Brachial artery endothelium-dependent vasodilation:  $\text{Dia-P} = (\text{maximum diameter inside brachial artery with } 1 \text{ min decompression} - \text{basic diameter}) / \text{basic diameter} \times 100\%$ .

### ***Statistical analysis***

All experimental data are presented as mean  $\pm$  standard deviation. A Paired Student's t-test was used to evaluate statistical differences. SPSS 11.5 software (IBM Corp. Chicago, IL, USA) was used to perform Pearson correlation analysis and multivariate regression analysis.  $P < 0.05$  was considered to be statistically significant.

## **Results**

### ***Equilibrium analysis of leptin, resistin, adiponectin and FFA prior to exercise intervention among the three groups***

Fifty patients with IGT out of 61 initial participants completed the whole experiment. Four from the control group, three from the walking exercise group and four from the walking plus resistance exercise group did not complete the experiment. The dropout rate was 18.03%. No significant differences were noted in the serum levels of leptin, resistin, adiponectin and FFA ( $P > 0.05$ ) among the three groups prior to the exercise intervention (Table 1).

### ***Comparison of leptin, resistin, adiponectin and FFA before and after exercise intervention in the three groups***

Serum leptin, resistin, adiponectin and FFA levels were tested after the exercise intervention to determine the effect of exercise. After the exercise intervention, significant reductions were noted in the leptin, resistin and FFA levels ( $P < 0.01$  for all) while a significant increase was found in the adiponectin level ( $P < 0.01$ ) in the walking exercise group (Table 2). Similar

results were obtained in the walking plus resistance exercise group. Leptin, resistin and FFA levels decreased while adiponectin level increased with significant difference after exercise intervention ( $P < 0.01$  for all, Table 3). In the control group, leptin, resistin and adiponectin levels did not differ significantly ( $P > 0.05$ , Table 4). These results indicate that serum leptin, resistin, adiponectin and FFA levels may play an important role in the regulation of vascular endothelium-dependent functions during exercise intervention.

### ***Variance analysis of leptin, resistin, adiponectin and FFA after exercise intervention among the three groups***

Variance analysis was performed to compare the changes of leptin, resistin, adiponectin and FFA after the exercise intervention among the three groups. Compared with the control group, significant differences were observed in leptin, resistin, adiponectin and FFA in the walking exercise group ( $P < 0.01$ , Table 5). In the walking plus resistance exercise group, leptin, resistin, adiponectin and FFA differed significantly from the control group, while adiponectin and FFA showed significant difference from the walking exercise group ( $P < 0.01$ , Table 5). These results further indicate that these factors may regulate vascular functions during exercise intervention.

### ***Pearson regression analysis of vascular endothelium functions***

Pearson regression analysis was conducted to determine the correlations of vascular endothelium functions with laboratory or chemical indices. In the walking exercise group, CNP was found to be correlated with leptin and adiponectin, with the regression equation as:  $\text{YCNP} = 0.945 \times \text{Xleptin} + 0.678 \times \text{Xadiponectin} - 2.363$  (Table 6). In addition, a correlation of ET-1 with OGTT2h was verified and ET-1 regression equation was:  $\text{YET-1} = -10.146 \times \text{XOGTT2h} + 0.775$  (Table 6). Moreover, carotid artery Intima-Media Thickness (IMT) was correlated with adiponectin with the regression equation as:  $\text{YIMT} = 0.007 \times \text{Xadiponectin} + 0.011$  (Table 6).

In the walking plus resistance exercise group, different results were presented. Carotid artery IMT had correlations with waist to hip ratio, FFA and fasting insulin, and the IMT regression equation was:  $\text{YIMT} = -0.794 \times \text{Xwaist to hip ratio} - 0.101 \times \text{Xfree fatty acid} + 0.005 \times \text{Xfasting insulin} + 0.020$  (Table 7). And Dia-P was correlated with waist to hip ratio, as Dia-P regression equation- $\text{YDia-P} = 114.153 \times \text{Xwaist to hip ratio} + 2.734$  (Table 7). Collectively, these results indicate that exercise intervention may regulate vascular endothelium functions through endocrinological changes.

**Table 1.** Comparison of leptin, resistin, adiponectin and FFA prior to exercise intervention in patients with IGT.

Group	n	Leptin (ng/ml)	Resistin (ng/ml)	Adiponectin (ng/l)	FFA (mmol/l)
Control	21	17.434 $\pm$ 2.330	23.710 $\pm$ 2.926	8.731 $\pm$ 3.510	0.766 $\pm$ 0.142

Walking exercise	20	17.373 ± 2.372	23.840 ± 2.854	8.722 ± 3.521	0.762 ± 0.135
Walking plus resistance exercise	20	17.192 ± 2.615	24.195 ± 2.094	8.756 ± 3.473	0.761 ± 0.091
F		0.054	0.181	0.025	0.009
P-value		P<0.05	P<0.05	P<0.05	P<0.05

Note: IGT: Impaired Glucose Tolerance; FFA: Free Fatty Acid.

**Table 2.** Comparison of leptin, resistin, adiponectin and FFA before and after exercise intervention in the walking exercise group.

Index	Before intervention	After intervention	t	P-value
Leptin (ng/ml)	17.373 ± 3.372	15.508 ± 3.287	17.519	P<0.05
Resistin (ng/ml)	23.840 ± 4.854	22.348 ± 4.409	10.067	P<0.05
Adiponectin (ng/L)	8.722 ± 3.521	9.974 ± 3.701	10.499	P<0.05
FFA (mmol/L)	0.762 ± 0.239	0.706 ± 0.210	5.35	P<0.05

Note: P<0.05 vs. before intervention. FFA: Free Fatty Acid.

**Table 3.** Comparison of leptin, resistin, adiponectin and FFA before and after exercise intervention in the walking plus resistance exercise group.

Index	Before intervention	After intervention	t-value	P-value
Leptin (ng/ml)	17.192 ± 3.615	15.443 ± 3.379	12.158	P<0.05

**Table 5.** Analysis of leptin, resistin, adiponectin and FFA after exercise intervention in patients with IGT.

Group	n	Leptin (ng/mL)	Resistin (ng/ml)	Adiponectin (ng/L)	FFA (mmol/L)
Control	17	-0.121 ± 1.232	-0.218 ± 0.674	-0.003 ± 0.209	-0.003 ± 0.018
Walking exercise	17	1.865 ± 0.4760*	1.493 ± 0.663*	-1.253 ± 0.534*	0.056 ± 0.046*
Walking plus resistance exercise	16	1.749 ± 0.643*	1.515 ± 0.996*	-1.336 ± 0.572* <sup>b</sup>	0.112 ± 0.067* <sup>#</sup>
F		34.984	32.626	53.412	29.34
P-value		P<0.05	P<0.05	P<0.05	P<0.05

Note: \*P<0.05 vs. control group; <sup>#</sup>P<0.05 vs. walking exercise group. IGT: Impaired Glucose Tolerance; FFA: Free Fatty Acid.

**Table 6.** Pearson regression analysis of vascular endothelium functions in the walking exercise group.

Pearson analysis	regression B	SE	β	t	P-value
CNP					
Constant	-2.363	0.363		-6.51	P<0.05
Leptin	0.945	0.218	0.815	4.343	P<0.05
Adiponectin	0.678	0.194	0.655	3.492	P<0.05
ET-1					
Constant	-0.775	2.323		-0.334	P<0.05
OGTT2h	-10.146	3.824	-0.53	-2.653	P<0.05

Resistin (ng/ml)	24.195 ± 5.194	22.680 ± 5.203	6.805	P<0.05
Adiponectin (ng/L)	8.756 ± 3.47291	10.092 ± 3.641	10.448	P<0.05
FFA (mmol/L)	0.761 ± 0.191	0.649 ± 0.1953	7.44	P<0.05

Note: P<0.05 vs. before intervention. FFA: Free Fatty Acid.

**Table 4.** Comparison of leptin, resistin, adiponectin and FFA before and after exercise intervention in the control group.

Index	Before intervention	After intervention	t-value	P-value
Leptin (ng/ml)	17.434 ± 3.330	17.555 ± 3.442	0.45	P>0.05
Resistin (ng/ml)	23.710 ± 4.926	23.928 ± 4.810	1.479	P>0.05
Adiponectin (ng/L)	8.731 ± 3.510	8.734 ± 3.485	0.073	P>0.05
FFA (mmol/L)	0.766 ± 0.242	0.769 ± 0.235	0.719	P>0.05

Note: P>0.05 vs. before intervention. FFA: Free Fatty Acid.

#### Carotid artery IMT

Constant	0.011	0.005		2.498	P<0.05
Adiponectin	0.007	0.003	0.446	2.112	P<0.05

Note: CNP: C-Type Natriuretic Peptide; OGTT: Oral Glucose Tolerance Test; ET-1: Endothelin-1; IMT: Intima-Media Thickness; B: Regression Coefficient; SE: Standard Error; β: Standardized Coefficient.

**Table 7.** Pearson regression analysis of vascular endothelium functions in the walking plus resistance exercise group.

Pearson analysis	regression B	SE	β	t value	P-value
Carotid artery IMT					

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Constant	0.02	0.005		4.237	P<0.05
Waist to hip ratio	-0.794	0.221	-0.618	-3.595	P<0.05
FFA	-0.101	0.03	-0.626	-3.347	P<0.05
Fasting insulin	0.005	0.002	0.484	2.519	P<0.05
Dia-P					
Constant	-2.734	0.87		-3.145	P<0.05
Waist to hip ratio	114.153	52.784	0.454	2.163	P<0.05

Note: IMT: Intima-Media Thickness; FFA: Free Fatty Acid; ΔDia-P: The Percentage Changes in Artery Diameter after a 5 min Compression; B: Regression Coefficient; SE: Standard Error; β: Standardized Coefficient.

## Discussion

IGT is a critical stage to prevent DM, and the lifestyle intervention can significantly decrease the occurrence of DM in the IGT population [5,6,16]. In our previous studies, it was found that endothelium-dependent dysfunction was an important early pathophysiological change in IGT patients [1,2]. In addition, the exercise intervention significantly improved endothelium-dependent vascular functions through enhancing the physiological constitution and insulin sensitivity, thus preventing further vascular deterioration during prediabetes mellitus [1,2]. However, the regulatory mechanism of this process is still unclear, therefore, the present study investigated the effects of exercise intervention on vascular endothelium function through detecting the quality (fatty cell factors of leptin, resistin and adiponectin, and fatty metabolism product FFA) and the quantity (BMI, body fat, waist circumference and waist to hip ratio) of fatty. There were significant reductions in leptin, resistin and FFA and remarkable increase in adiponectin after exercise intervention. Furthermore, vascular endothelium functions were correlated with leptin, adiponectin and FFA in the two exercise groups. Results from this study suggest that endocrinological changes are also involved in the regulation of endothelium-dependent vascular functions. In addition, exercise intervention can improve the vascular endothelium-dependent function through decreasing leptin and FFA, and increasing adiponectin in middle-aged patients with IGT.

Leptin, an important regulator of energy balancing, is involved in the body's energy intake, storage and release [17-19]. It plays a regulatory role in the expression and/or activity of glucose metabolism key enzymes including glucokinase and phosphoenolpyruvate carboxykinase, and then promotes myotube glucose transporter. Moreover, it can increase glucose oxidation, which has a role in reducing blood sugar level [17-19]. Therefore, leptin is used as an indicator of the progression of obesity, diabetes and hypertension. Okazaki et al. suggested that in sedentary women that undertook aerobic exercise, there was no decrease in the insulin level and no change in the leptin level in the group of unchanged body mass, while both insulin and leptin levels decreased in the group of decreased body mass [19]. Other studies demonstrated significantly lower serum leptin levels in athletes than in normal healthy people, which may be related to the

effect of exercise on the expression and secretion of leptin [20,21]. Hickey et al. reported a significant reduction in the leptin level in young women instead of men after 12 w of fasting aerobic exercise (4 d/w, 30~45 min/times), while the body fat did not significantly decreased [22]. Another study of the obese women after 12 w of exercise showed decrease in the total amount of leptin and content of subcutaneous adipose tissues [23]. These results suggest that energy balance change leads to the leptin change [24,25]. In the present study, we found that serum leptin levels differed significantly in both exercise groups, however, no obvious difference was observed in the leptin level between two exercise groups. It can be concluded that walking exercise can prevent and treat early vascular diseases by regulating the concentration of leptin.

Resistin is a recently discovered adipocytokine. McTernan et al. found that resistin was secreted by preadipocytes and adipocytes, and its expression was increased in abdominal tissues [26]. The findings suggest that resistin is related to the centripetal obesity. Further, serum resistin level was found to be higher in obese population [27] and positively correlated with BMI, IR and body fat [28]. These studies imply that resistin may be involved in the IR development in type 2 DM (T2DM). Exercise can also affect resistin level. For example, in the study of Valsamakis et al. on 44 obese subjects with 6 weeks of dietary control and exercise intervention, serum resistin level decreased significantly (from 9.1 ng/ml to 7.0 ng/ml, P<0.01) as weight reduced (13.50±1.00 kg dropped of average weight), indicating that body weight loss can lead to reduced resistin levels in obese subjects [29]. Azuma et al. demonstrated that resistin was positively correlated with BMI after body weight loss [30]. Thus, exercise intervention can reduce fat, change the body composition, improve the secretion function of adipose cells, reduce IR and improve the metabolism of sugar. Nevertheless, the influence of exercise on vascular endothelial function in the middle-aged IGT patients was not studied in previous literature. In the current study, significant difference was found in the serum resistin level after 24 w of exercise intervention in both exercise groups, indicating that exercise may improve endothelial functions through resistin-related mechanism.

Adiponectin, a kind of adipose tissue specific protein, can decrease blood glucose concentration and fat synthesis, and increase fatty acids oxidation, which has a similar function to leptin and activate adenosine 5'-monophosphate-activated protein kinase (AMPK) of skeletal muscle [31,32]. Serum adiponectin was found to have a positive correlation with insulin signaling in the skeletal muscle and a negative correlation with IR [32]. Through a negative feedback, weight loss can increase serum adiponectin [32]. The present study observed significant increase in adiponectin after exercise intervention in the two exercise groups. Exercise can prevent and treat early vascular lesions through regulating adiponectin.

FFA is the product of the intracellular triglyceride in fat metabolism. FFA is the second insulin signal in muscular and hepatic regulation of sugar production and utilization [33]. Abnormalities of FFA and vascular endothelial function were

found in patients with IGT, implying high FFA levels may selectively inhibit the insulin/phosphoinositide 3-kinase (PI3K) signaling pathway in vascular endothelial cells [34]. The significant decrease in FFA suggested that exercise intervention may prevent and improve early vascular lesions through adipose cell metabolism pathways.

In conclusion, the exercise intervention can decrease leptin, resistin and FFA as well as increase adiponectin to improve the endocrine function and the vascular endothelium function. The present study has provided clinical information on the vascular endothelium functions in IGT patients, suggesting that exercises can help to prevent the progression of IGT to DM and the development of CVD.

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### Disclosure of Conflict of Interest

None

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