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# The Effect of Aerobic Exercise on Plasma Visfatin and Glycemic Control in Type 2 Diabetic Men Treated with Metformin

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## Abstract

**Introduction:** Visfatin is a newly discovered adipokine. Previous studies showed a direct relationship between plasma visfatin levels and type 2 diabetes mellitus (T2DM). The current study was conducted to investigate the effect of aerobic exercise on plasma visfatin in type 2 diabetic men treated with metformin.

**Material and Methods:** Thirty-six men with type 2 diabetes who consumed metformin (age 46/08 ± 3/08 years, BMI 30/1± 2/32 kg/m$^2$, mean ± SD) volunteered to participate in this study. Subjects were randomly assigned in 2 groups. 18 subjects were in the aerobic exercise group (3 days per week, 35 to 50 minutes per day, 40-55% heart rate reserve) and 18 subjects in the control group. Fasting Plasma visfatin, insulin and glucose concentrations were measured before and after 8 weeks exercise in patients with T2DM and data was analyzed using Repeated Measures (ANOVA) at a Significance level of ($P<0.05$).

**Results:** The results showed that plasma visfatin levels, insulin, glucose, BMI, WHR and body fat percentage significantly decreased in aerobic exercise group compared with control group ($p<0.05$). The peak rate of oxygen consumption (vo2peak) significantly increased in aerobic exercise group compared to control group ($p<0.05$).

**Discussion and Conclusion:** The present study showed decrease of plasma visfatin induced by aerobic exercise is most likely the result of improving glycemic control in patients with T2DM treated with metformin.

**Key words**: Aerobic exercise, Visfatin, metformin, Type 2 diabetes

## Introduction

Diabetes mellitus is a chronic disease that affects almost 6% of the world's population. The prevalence of diabetes is increasing [1]. Studies have shown that increased risk of type 2 diabetes mellitus (T2DM) and insulin resistance are correlated with body fat content and exacerbated with increased Body Fat Mass. It is shown that the percentage of body fat influences the insulin sensitivity [2]. Indeed, adipose tissue, in addition to the storage and release of triglyceride, secrete variety of enzymes and proteins as adipokine that have a role in cholesterol metabolism, immune system, regulating energy expenditure, and insulin action [3]. Visfatin, also known as pre-B cell colony-enhancing factor or nicotinamide phosphoribosyltransferase, is a cytokine that is highly expressed in visceral fat and plays important roles in energy and glucose homeostasis [4]. Studies have shown that visfatin levels are increased in patients with T2DM and visfatin may be involved in the pathogenesis of T2DM [5]. It is accepted that prolonged aerobic exercise is an appropriate treatment strategy and can through increasing the Glucose Transporter Type 4 (GLUT4) and insulin receptor substrates (IRS) in muscle cells and also increasing in muscle mass improve the body response to insulin and insulin sensitivity [6]. Previous studies have shown that visfatin has insulin mimetic effect and stimulate glucose uptake in adipose tissue cells. Also visfatin binds to insulin receptor sites (α- subunit extracellular) in another place except where insulin is connected [4]. However, few studies have reported the effect of exercise on plasma visfatin levels in different individuals. For example, it has been reported that 12 weeks endurance exercise, at 80% HRmax for 60 min/session and 5 days a week, causes significant reduction of plasma visfatin

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levels in obese subjects [7]. Studies also have shown that 8 weeks aerobic exercise, at 65-80% HRmax for 20-34 min/session and 3 days a week, causes significant decrease of plasma visfatin in Middle-aged men [8]. But the effects of aerobic exercise on visfatin levels in patients with T2DM have shown conflicting results. Brema et al reported that 3 months of aerobic exercise, 4 sessions per week with 75% $VO_2$peak, causes significant decrease in the levels of plasma visfatin in obese 30-15 year old patients with newly diagnoses T2DM [9]. While, Jorge et al reported 12 weeks aerobic exercise (3 times a week, 60 minutes per session) causes significant increase in plasma visfatin of patients with T2DM [10]. Since visfatin is secreted from visceral adipose tissue, so consuming some drugs are effective in altering gene expression and plasma visfatin levels due to altered in visceral adipose tissue. Studies demonstrated that pioglitazone consumption reduces the visfatin gene expression [11], but metformin consumption has no effect on plasma visfatin levels in patients with T2DM [12,13]. According to Pharmacological interventions and conflicting results about the effects of exercise on plasma visfatin in patients with T2DM, this study is conducted to find the effects of aerobic exercise on plasma visfatin levels in type 2 diabetic men treated with Metformin.

## Material and Methods

### *Subjects*

Thirty-six men diabetic who consumed metformin (age 46/08 ± 3/08 years) volunteered to Participate in this study. Written informed consent was signed by all participants. The Physiology Research Center of Kerman Ethics Committee approved the protocols, which were fully explained to all subjects. The subjects were randomly assigned in control group (n=18) and training group (n=18).

### *Aerobic Exercise Protocol*

The subjects in the training group underwent an 8-weeks aerobic exercise by cycling the Technogym exercise bike, with a frequency of 3 days a week at intensity 40-55% Heart Rate Reserve for 35 minutes in the first session and increasing gradually to 50 minutes by the end of the eighth week. Heart Rate was constantly checked by the polar device (POX 1000 Japan) during exercise.

### *Measurements of Anthropometric and Biochemical characteristics*

Height and body weight were measured, and body mass index (BMI; kg/m2) was calculated from height and weight of each subject. 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). Subcutaneous body fat was measured at 3 sites (chest, abdominal, and thigh) with a Lafayette caliper. Body fat percent was calculated from the formula developed by Jackson and Pollock [14]. All subjects fasted at least for 12 hours and a fasting blood sample was obtained from the Brachial Vein. The plasma visfatin level was measured by using an enzyme-linked immunosorbent assay (ELISA) kits (Cat: EIA-VIS-1, Ray Biotech, Inc) (intra-Assay: CV<10%, inter-Assay: CV<15%). Serum insulin was measured by a commercial chemiluminescence assay kit (Cobas®, USA) (intra-Assay CV: 1.9%, inter-Assay CV: 2.6%) and Serum glucose was measured by a glucose oxidase method kit (Pars Azmoon, IRAN).

### *Aerobic capacity measurements*

Age-adjusted physical fitness was determined by bicycle ergometry during a submaximal exercise test. The patients performed six minutes of cycling at a resistance (50–150 W) that resulted in a steady-state heart rate. Heart rate, sex and age were used in the Astrand nomogram to calculate the predicted maximal oxygen consumption (VO2 peak) [15].

## Statistical analysis

All Statistical analyses were performed with SPSS program (version 16, SPSS, Inc., Chicago, IL). Values were expressed as mean ± standard deviation (SD). The Kolmogorov-Smirnov test was used to determine the normality of distribution, and variables were found to be normally distributed. Independent sample t-test was used to evaluate Homogeneous groups at baseline. Repeated Measures ANOVA was used to evaluate differences within groups and between groups. P-values less than 0.05 were considered statistically significant.

## Results

Anthropometric and biochemical characteristics of subjects are shown in Table1. Results showed that prior to intervention, all variables were homogeneous (Table 1). Comparing the within groups differences showed that body weight, Body Mass Index, body fat percent and WHR were significantly decreased (P<0.05). While Maximal oxygen consumption, significantly increased (P<0.05) in exercise group compared with control group (Table 2). Plasma visfatin, Insulin and glucose significantly decreased (P<0.05) after 8 weeks aerobic training (Table 2). Also, comparing the between groups differences showed that all variables in two groups have significant differences (Table 2).

**Table 1:** Anthropometric and Biochemical characteristics of subjects at Baseline

| Group/characteristics | Control | Training | P value |
|---|---|---|---|
| **Age (years)** | 45/50 ± 3/20 | 46/67 ± 2/93 | 0/262 |
| **Duration of diabetes (years)** | 3/5 ± 2/1 | 3/3 ± 2/5 | 0/862 |
| **Daily dose of Metformin (mg)** | 972 ± 362 | 946 ± 379 | 0/824 |
| **BMI ($kg/m^2$)** | 30/21 ± 2/16 | 29/99 ± 2/53 | 0/778 |
| **WHR (cm)** | 0/93 ± 0/02 | 0/93 ± 0/01 | 0/857 |
| **Percentage Body Fat** | 28/32 ± 2/40 | 28/45 ± 2/46 | 0/872 |
| **$Vo2_{peak}$ ($ml.kg^{-1}.min^{-1}$)** | 22/04 ± 1/2 | 22/15 ± 1/5 | 0/814 |
| **Plasma Visfatin (ng/ml)** | 31/01 ± 3/0 | 30/39 ± 2/7 | 0/533 |
| **Plasma Insulin (µU/ml)** | 12/3 ± 2/3 | 12/5 ± 2/9 | 0/841 |
| **Blood glucose (mg/dL)** | 169/1 ± 33 | 168/9 ± 43 | 0/990 |

Data are mean ± SD. No significant differences were observed between groups (P> 0.05).

**Table 2:** compares difference between and within groups after 8 weeks of training

| Group/characteristics | Post Test | | P value within groups | | P value between groups |
|---|---|---|---|---|---|
| | Control | Training | Control | Training | |
| **BMI ($kg/m^2$)** | 30/10 ± 2/12 | 28/49 ± 2/36 | 0/113 | 0/001 † | 0/001* |
| **WHR (cm)** | 0/93 ± 0/01 | 0/90 ± 0/02 | 0/754 | 0/001 † | 0/001* |
| **Percentage Body Fat** | 28/10 ± 1/78 | 26/43 ± 1/88 | 0/254 | 0/001 † | 0/001* |
| **$Vo2_{peak}$ ($ml.kg^{-1}.min^{-1}$)** | 22/3 ± 1/2 | 26/18 ± 2/3 | 0/106 | 0/001 † | 0/001* |
| **Plasma Visfatin (ng/ml)** | 31/17 ± 3/2 | 27/64 ± 3/3 | 0/597 | 0/001 † | 0/001* |
| **Plasma Insulin (µU/ml)** | 12/2 ± 2 | 10/8 ± 1/9 | 0/714 | 0/001 † | 0/001* |
| **Blood glucose (mg/dL)** | 165/6 ± 17 | 135/5 ± 18 | 0/579 | 0/001 † | 0/001* |

Data are mean ± SD.
† P< 0.05 significant difference in each group before and after 8 weeks of aerobic exercise.
* P< 0.05 significant difference between groups.

## Discussion and Conclusion

The results showed that Plasma visfatin levels decreased (P<0.05) in response to 8 weeks aerobic training compared to the control group. The biological role of visfatin in the pathogenesis of type 2 diabetes is not well understood. But it is demonstrated that visfatin has insulin mimetic effect and concentration increase with hyperglycemia [4]. Control mechanisms of regulating visfatin are not still clearly known. But studies show that gene expression and plasma levels of visfatin may be influenced by factors such

as obesity and weight gain [16], caloric restriction [17], diabetes [18], plasma levels of TNF-α [19], glucose and insulin [20], weight loss [21], blood lipids levels and overfeeding [22]. In this regard, it has been reported that 12 week exercise training including aerobic exercise (45 min/session, 300 Kcal/day) and muscle strength training (20 min/session, 100 Kcal/day) five times per week, causes significant reduction of fasting plasma visfatin levels associated with reduced fasting glucose and insulin levels, weight, WHR and percentage of body fat in 48 non-diabetic women aged 50 to 55 who were overweight or obese [23]. Also it has been reported that 12 week aerobic exercise, at 300-400 cal energy expenditure for 45-50 min/session and 4 days a week, causes significant decrease in plasma visfatin concentration associated with weight loss in adolescents and obese women [24]. In the present study, 8 week aerobic exercise lead to the decrease of plasma visfatin levels in patients with T2DM. That seems the decrease of visfatin is most likely the result of decrease glucose and insulin levels induced by aerobic exercise in patients with T2DM. In addition, studies showed that visfatin levels have a positive correlation with the percentage of body fat [25]. Also it has been reported that each 1 cm increase in waist circumference of subjects associated with 4/2 ng/mL increase in plasma visfatin level [26]. In this regard, Haider et al it has been reported that aerobic exercise decreased the plasma visfatin levels associated with the decrease of WHR after 2 and 4 months in patients with type 1 diabetes [27]. In this study, it seems that another of the reasons for decreased plasma visfatin is the reduction of the body fat percentage and WHR induced by aerobic exercise in patients with T2DM. Have been reported conflicting results about the effects of aerobic exercise on visfatin levels in patients with T2DM, some increase [10] and some decrease [9] in plasma visfatin levels induced by aerobic exercise has been reported. One of the possible reasons for these conflicting results can be the effects of hypoglycemic drugs on plasma visfatin level in T2DM patients. Metformin is one of the hypoglycemic agents and it is known that metformin consumption has no effect on plasma visfatin levels in patients with T2DM [12,13]. In present study in order to prevent the intervention effects of hypoglycemic agents on plasma visfatin levels, all subjects consumed metformin at least in past 6 months. This study showed that 8 week aerobic exercise had a significant effect on glycemic control in patients with T2DM who consumed metformin and improved cardiorespiratory function in these individuals. Also, the results of this study confirmed the decrease of plasma visfatin levels induced by aerobic exercise and emphasized that patients with T2DM who consumed metformin should be encouraged to do aerobic exercise in order to control their glycemic.

The present study seems to have some limitations. Since type 2 diabetic patients have special diets, all participants in this study were asked to follow their previous diet but their diet could not be controlled completely. Due to the effects of diet on glycemic control and visfatin levels, it is recommended in future studies to have a complete control of patients diet.

In conclustion, this study shows the decrease of plasma visfatin levels induced by aerobic exercise associated with the decrease in fasting glucose and insulin levels, percentage body fat and WHR. The findings suggest that changes in visfatin levels may be related to the beneficial effect of aerobic exercise on glycemic control in T2DM patients treated with metformin. Finally, more studies are needed to elucidate the role of visfatin in the pathogenesis of T2DM.

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