Exercise Effects of Serum Ghrelin and Insulin Resistance in First-Degree Relatives of Type 2 Diabetics

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Abstract

Objective: This study aimed to compare serum ghrelin levels and insulin resistance in first-degree relatives of type 2 diabetics before and after an exercise intervention.

Material and Methods: Participants aged 20–35, all first-degree relatives of diabetics, were recruited from PGMI and Fatima Memorial College of Medicine and Dentistry. An 8-week exercise intervention was implemented. Anthropometric and biochemical measurements, including fasting serum ghrelin, insulin, glucose, and HOMA-IR, were recorded pre- and post-intervention. SPSS version 21 was used for data analysis. The Shapiro-Wilk test assessed normality. Quantitative data were expressed as Mean ± SD, and paired t-tests or Wilcoxon signed-rank tests determined pre- and post-exercise differences, with $p < 0.05$ as the significance threshold.

Results: Exercise led to significant reductions in weight and BMI ($p < 0.001$). Biochemically, glycemic markers decreased, and ghrelin levels rose significantly post-exercise ($p < 0.001$).

Conclusion: Elevated ghrelin and reduced insulin resistance post-exercise may decrease diabetes risk in genetically predisposed individuals.

Keywords: Diabetes Mellitus; ghrelin; serum insulin; fasting glucose; insulin resistance

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Introduction

Current lifestyle modifications including obesity, lack of movement and dietary habits has increased both the incidence and risk of diabetes[1]. Diabetes can be best defined by increased serum glucose levels, which can be due to defective production of insulin from the pancreas owing to defects in pancreatic beta cells. Function of insulin can also be defected in terms of decreased ability of insulin to remove glucose from the blood and transport it to the cells of the body, this occurs due to decreased sensitivity of cells of the body to insulin.[2] Diabetes has been reported as one of the most common cause of multiple organ dysfunction, worldwide, leading to diabetic neuropathy, nephropathy, gastroparesis, dermopathy etc. along with increased risk of cardiovascular dysfunction and metabolic syndrome.[3]

Insulin resistance is defined by decreased sensitivity of the body to insulin. This occurs due to decreased transport of glucose into the cells which has been attributed to decreased physical activity, increased screen time, increased carbohydrates laden dietary habits. Insulin resistance has also been nominated as the leading cause of hyperinsulinemia and hyperglycemia that forms the basis of diabetes mellitus type.[24] Insulin resistance, not only effects the people suffering from metabolic syndrome but is also known to have significant genetic transmission, hence increasing the risk of metabolic syndrome especially diabetes mellitus in future generations.[5]

Ghrelin, a peptide hormone, increases appetite. It is primarily secreted by the oxyntic mucosa of stomach along with numerous sites in central nervous system, pancreas, liver and adipose tissue. It is a regulatory

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hormone for body energy equilibrium[6]. Ghrelin has multiple receptors of which Growth Hormone Receptor –Ghrelin (GHR-G) is of primary importance as it is present in pituitary and pancreas. This is responsible for increased growth hormone and decreased insulin secretion respectively[7]. Increased serum glucose levels owing to increased insulin resistance can lead to decreased production of ghrelin by the pancreas, the probable reason is increased levels of insulin (hyperinsulinemia), owing to the resistance developed in the body, which leads to downregulation of pancreatic ghrelin receptors,[8] hence predicating the presence of low Ghrelin levels in type 2 diabetics as well people suffering from metabolic syndrome.[9] Pre-diabetics and first degree relatives especially healthy offspring of type 2 diabetics, have been reported to have decreased ghrelin levels, hence placing them at increased risk of developing diabetes.[10]

In recent years, there has been a global surge in obesity, with alarming increases in prevalence being observed across both industrialized and developing nations.[11] Life style modifications, that involve weight reduction either by restricting calorie intake or by undergoing regular strenuous physical activity, lead to lipolysis hence decreasing body organ fat. The decrease in visceral fat is directly responsible for increasing insulin sensitivity of the body, transporting large amounts of glucose from the blood to the cells, and hence decreasing serum insulin levels. The decrease in serum insulin can free pancreatic ghrelin receptors from downregulating effect of hyperinsulinemia.[12] The present study aims at evaluating the effect of planned physical activity, as weight reduction intervention, on the serum Ghrelin levels and insulin resistance of first degree relatives of type 2 diabetics.

Material and Methods

This quasi experimental study was conducted on medical students and faculty members of PGMI and Fatima Memorial College of Medicine and Dentistry after obtaining approval from ethical committee of Post Graduate Medical Institute, Lahore. Acceptance letter of this study was taken from UHS No UHS/Education/126-14/3067 dated 20-11-2014. The sample size was estimated using WHO formula, with a confidence interval of 95%. A total of 42 normoglycemic, first degree relatives of type 2 diabetics were selected through non probability purposive sampling.

The study subjects were briefed in detail regarding research methodology and an informed consent was obtained on a proforma. Height was measured in meters while subjects were standing straight and barefoot. Weight was measured in kilograms with minimal clothing and BMI of the subjects was calculated by the following formula

$$\text{Body mass index} = \frac{(\text{Weight in (Kg)}}{(\text{Height in m}^2)} \quad \text{(WHO, 2004)}$$

Demographic information, anthropometric data, medical history, and findings from the general physical examination were documented on a data collection form. Fasting blood samples were taken from anti-cubital vein to measure baseline of biochemical markers.

A regime of aerobic exercise was designed, comprising of a 5 minute warm up exercise followed by a 30 minutes running on treadmill or cycling and ending with a 10 minutes cool off. The exercise intervention was carried out in 4 sessions a week, and was extended over a period of 8 weeks. During the first four weeks, each session's strength and duration were gradually increased. After that, the strength for 60–75% of maximum heart rate was attained, and each session lasted the same 45 minutes. Blood samples were collected after exercise intervention, following an overnight fast of 10 hours to measure biochemical markers after intervention. Blood samples were centrifuged at 3000rpm for 15 minutes and separated serum was stored at -80°C within 24 hours of collection. Serum levels of ghrelin were estimated by using Human Active Ghrelin ELISA kit, Glory Science Co., Ltd, China, serum levels of insulin were measured via using enzyme-linked immunosorbent (ELISA) assay test kit from Pointe Scientific, Inc. USA,. Fasting blood glucose was measured by glucose oxidase method using photoelectric colorimeter, AE-11, Tokyo Erma Optical works, LTD. Japan. Fasting insulin and glucose levels were used for the calculation of HOMA-IR by the following formula. Fasting insulin levels (μU/mL) × Fasting glucose levels (mmol/L)/22.5.[12] The data was entered and analyzed by using IBM- SPSS version 21. Normality of the data was assessed using Shapiro-Wilk test. Quantitative variables were presented as mean ± SD and median (IQR). Paired t-test was applied for normally distributed data and Wilcoxon signed-rank test was applied to non-normal data. P-value of ≤ 0.05 was considered statistically significant.

Results

Before the commencement of physical intervention the average weight and BMI of the subjects were 63.98 ±

10.38 kg and 23.81(20.69-25.73) respectively. After an 8 week of regular exercise, statistically highly significant difference (<0.001) was reported with decrease in both weight and BMI. (Table no. 1) The frequency distribution of the subjects in the above BMI bar chart indicates the effective response to exercise by both normal weight and overweight subjects. After exercise the total number of subjects in normal weight group has increased and that in over weight group has decreased respectively. On comparing the biochemical markers, using Wilcoxin signed-Rank test, between pre and post exercise groups, significant decrease in serum fasting glucose levels (from 87 to 80.5mg/dl;p<0.001), serum insulin levels (from 12.11 to 6.27 µIU/ml; p<0.001) and inuslin resistance (from 2.68 to 1.29;p<0.001) were recorded in the post exercise group of study subjects. However, serum ghrelin levels showed a significant (p<0.001) increase after 8 weeks of exercise (370.58pg/ml) when compared to their per-intervention levels (160.98pg/ml) as shown in Table no. 2.

Table 1: *Comparison of anthropometric variable before and after exercise.*

Anthropometric variables	Before exercise	After exercise	*p*-value
Weight (Kg)**	63.98 ± 10.38	61.97 ± 9.79	<0.001*
BMI (Kg/m^2) ***	23.81 (20.69-25.73)	23.24 (20.10-25.03)	<0.001*

**p- value of <0.05 is considered statistically significant,*
***Comparison was done using paired t- test.*
****Comparison was done using Wilcoxon signed-rank test.*

Table 2: *Comparison of Biochemical variables before and after exercise using Wilcoxon signed-rank test.*

Biochemical variables	Before exercise Median(IQR)	After exercise Median(IQR)	*p*-value
Glycemic variables			
Serum fasting glucose levels (mg/dl)	87.00(79.75-93.25)	80.5 (75.75-90.00)	<0.001 *
Serum insulin levels (µIU/ml)	12.11(11.00-14.89)	6.27 (3.88-7.84)	<0.001 *
HOMA-IR	2.68(2.24-3.23)	1.29 (0.79-1.74)	<0.001 *
Hormone levels			
Serum ghrelin levels (pg/ml)	160.98(142.75-236.32)	370.58 (349.04-400.79)	<0.001 *

**p- value of <0.05 is considered statistically significant*

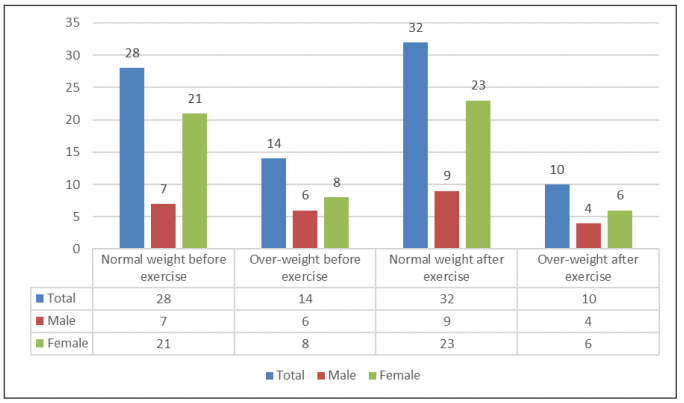

Fig-1: *BMI categories in both groups*

Discussion

The current study was carried out to evaluate the effect of exercise on weight loss, serum ghrelin levels and insulin resistance in first degree relatives of type 2 diabetic patients. Eight weeks of planned exercise intervention resulted in significant decrease in weight and insulin resistance while an increase in serum ghrelin levels of the study subjects were reported. Obesity is a known cause of increased glucose and insulin levels which leads to the development of insulin resistance, type 2 diabetes and metabolic syndrome. In our study overall the subjects were overweight and after the intervention a significant decrease in weight and BMI were reported. Many studies have shown similar result of weight loss with exercise but with greater than the general exercise recommendations for health (150 minutes /week) while in our study with a physical activity of only 120 minutes/week, led to a significant weight loss, the possible reason could be predominant young adult population in our sample with mean age of 23.1±1.4 years when compared to the middle aged adults in these studies.[13]

Reflecting the results of a case control study conducted on basketball players[14] in 2019 similar findings have been reported in our study that is increase in ghrelin levels after physical activity intervention. Partially similar results were presented by another study,[15] when they observed the effect of 12 months long high intensity exercise regime on serum ghrelin levels. First three months were structured showing significant improvement in ghrelin levels followed by a decline in the levels on completion of study. The reason of decline might be non-adherence to the structured exercise. An Iranian study[16] carried out on obese women undergoing combined (aerobic and resistance) exercise regime, did not report a significant increase in serum ghrelin levels in post exercise group. The reason behind this difference

from the present study might be the type of exercise intervention undertaken by that study, as the present study only focused on the effects of aerobic exercise.

Increased insulin levels downregulate the secretion of ghrelin from pancreas, hence obesity leads to decreased serum ghrelin levels.[17] All weight reduction interventions result in increased serum ghrelin levels, probably due to improved insulin resistance and glucose levels.[18] The present study indicated significant improvement not only in serum ghrelin but also decreased insulin and glucose levels ($p \leq 0.001$) and significant decrease in insulin resistance in the study subjects after exercise ($p \leq 0.001$). Similar changes in HOMA-IR have been reported by another study, after conducting six months long randomized control trial on obese subjects undergoing weight reduction interventions.[19] A Turkish study has also reported significant improvements in fasting glucose, insulin levels and HOMA-IR after conducting six months long exercise intervention in obese subjects[20] indicating a positive effect of strenuous physical activity on insulin resistance.

Insulin resistance is primarily influenced by increased adiposity, hence a decrease in the adipocytes have a better chance to improve insulin sensitivity.[21] After weight loss in our subject a decrease in insulin resistance was noted. In a study conducted in USA on 6,561 participants found a significant decrease in insulin resistance among adult males with low to moderate strength training without the influence of waist circumference and total body fat.[22] Exercise is said to increase the insulin mediated glucose uptake in both healthy and IR subjects by increasing TBC1D4 signaling which promotes GLUT4 translocation on both adipocytes as well as skeletal muscle cells.[23] Our study did not have equal distribution of subjects within the two genders and the study lacked calorie restriction and measuring body fat percentage apart from weight and BMI which are not true representative of adipocyte loss. Hence a better understanding of the underlying cause of improvement in insulin resistance and its relation with ghrelin production can be elucidated. Nevertheless, goal of study has been achieved indicating a positive effect of exercise on serum ghrelin and insulin resistance of the subjects more predisposed to the development of diabetes mellitus.[2]

Conclusion

This study demonstrates that structured, strenuous physical activity positively impacts weight, BMI, and biochemical markers in first-degree relatives of type 2 diabetics. By raising ghrelin levels and reducing insulin resistance, exercise interventions may lower the risk of metabolic syndrome in those genetically predisposed to type 2 diabetes.

Conflict of Interest *None*

Funding Source *None*

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Authors Contribution

HS: Conceptualization of Project

QAN: Data Collection

HS: Literature Search

SAF: Statistical Analysis

MQ, BH: Drafting, Revision

MA: Writing of Manuscript