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Effect of Weight Reduction Program on Adropin Hormone among Obese Premenopausal Women with and without Metabolic Syndrome

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Abstract: The aim of this study is to evaluate the weight loss program efficacy on adropin hormone in obese premenopausal women with and without metabolic syndrome. This study was conducted on 60 obese premenopausal women (BMI; between 30 and 38 kg/m^2), with an age ranged from 40 to 47 years. The patients were randomly divided into 2 groups; group 1(G1) obese women with metabolic syndrome (n=30) and (G2) obese women without metabolic syndrome "metabolically healthy obese" (n=30). Both groups enrolled in weight reduction program for 12 weeks. The weight reduction program in the form of aerobic exercise training program on treadmill and diet- induced weight loss (1200-1400 k.cal/day. Women were sedentary (< 1 hr/week of physical activity), with no evidence of participation in weight reduction program within the last 6 months and completed a personal health and medical history questionnaire. Weight, height, body mass index (BMI), waist circumference (WC), fasting blood sugar (FBS), fasting insulin, HOMA-IR, lipid profile and serum adropin. Statistical analysis using pre and post treatment design indicated that there was a significant decrease in anthropometric measurements (weight, BMI and WC), ($p<0.05$), a significant improvement of lipid profile, glycemic control and insulin sensitivity ($p<0.05$) and a significant increase in serum adropin level ($p<0.05$) at post treatment compared to pretreatment for both groups. Weight loss program including aerobic exercise and low-caloricdiet improved all modifiable risk factors of metabolic syndrome and increased anti-inflammatory and vascular endothelial function properties of adropin hormone in preventing obesity in premenopausal women with and without metabolic syndrome.

Key words: Weight reduction · Pre-menopausal women · Metabolic syndrome · Adropin

INTRODUCTION

Obesity is considered as a universal public health problem [1]. Obesity is a low grade of inflammation that is a high risk factor for insulin resistance, diabetes, hypertension, angina pectoris, metabolic syndrome and other disorders [2]. Ischemic heart disease risk of death is also greater in individuals with high BMI [3]. Obesity is considered as the main component of the metabolic syndrome and often the main cause of insulin resistance [4].

Metabolic syndrome [MetS] or insulin resistance syndrome is a cluster of diseases and is characterized by the presence of multiple risk factors including visceral obesity, hyperlipidemia, insulin resistance, impaired glucose tolerance and hypertension [5]. These multiple

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risk factors progressively raise the risk of insulin resistance; type II DM and ischemic heart disease [6]. The prevalence of is rising dramatically worldwide. Globally, approximately 20% to 25% of adults already have metabolic syndrome [7].

A number of obese patients do not develop metabolic syndrome. Such individuals are known as "healthy obese." [8]. Central obesity and excessive visceral fat are often associated with insulin resistance syndrome, type II DM, ischemic heart disease, hypertension and cerebrovascular infarction [4]. There was a positive correlation between the abdominal obesity and the waist circumference and the higher the risk for occurrence of insulin resistance syndrome and other chronic disorders [9]. Weight reduction protocols can promote metabolic parameters and prevent or even delay cardiometabolic disorders.

Adropin hormone was discovered by [11]. Current research demonstrated that the energy metabolism, the carbohydrate metabolism control and fatty acid metabolism may be attributed to this protein hormone [12]. Adropin is also involved in modulation and regulation of insulin level and the balance of energy homeostasis. Recent data suggested that hypoadropinemia is a risk factor of angina and myocardial infarction. There was an inverse correlation between the levels of adropin and the severity of ischemic heart diseases [13].

[14] used mouse endothelial cells found that adropin plays an important role in protection of vascular system as adropin activates the pathway of endothelial nitric oxide synthase [eNOS], which controls vascular endothelial function. The aerobic exercise protocol significantly increased levels of adropin in old age people and the changes in serum adropin concentration may be a reasonable mechanism of exercise therapy to prevent arteriosclerosis [15].

Adropin level changes in various physiological and pathophysiological conditions. Low concentration of adropin associated with many diseases such as insulin resistance associated with obesity, gestational diabetes mellitus acute myocardial infarction and endothelial dysfunction and non-alcoholic fatty liver disease [16]. Also, the hypoadropinemia can lead to impaired glucose tolerance and other components of the metabolic syndrome, such as dyslipidemia [17]. There was an inverse correlation between the levels of adropin and BMI and age.. Also, males have higher levels of adropin compared to females [18].

As there is a lack of studies conducted on the efficacy of weight loss program on adropin in premenopausal women without metabolic syndrome. The previous studies which were conducted on adropin hormone were on obese with metabolic syndrome. Therefore, the aim of this randomized clinical trial was to evaluate the efficacy of low caloric diet and aerobic exercise program on serum adropin in obese premenopausal women with and without metabolic syndrome.

MATERIALS AND METHODS

Design: The study was designed as a randomized, Pre-post- test-controlled trial. It was conducted on 60 obese premenopausal women (BMI; between 30 and 38 kg/m^2), with an age ranged from 40 to 47 years. The women were selected from obesity unit at October 6 University hospitals. The study was conducted from April 2018 to February 2019 and the guidelines for the reporting of randomized controlled studies have been followed by consolidated reporting standards.

Ethical Approval: All relevant national laws and institutional policies have been followed up in human use research, followed the principles of the Helsinki Declaration and approved by the Research Ethics Committee of the Faculty of Physical Therapy, University of Cairo.

Patients: A sample of 60 obese premenopausal women. The participants were excluded if they were postmenopausal, had a history of thyroid dysfunction, acute or chronic renal failure, acute infection within the previous 7 days, acute or chronic hepatic failure, hematological disorders, presence of any chronic inflammatory and autoimmune disease, moderate or severe osteoarthritis, osteoporosis or other orthopedic problems causing inability to undertake the training protocol, evidence of any other systemic or malignant diseases and any medication interfere with the study. Other no pathological exclusion criteria included pregnancy, breastfeeding and use of medications for dyslipidemia also excluded.

Randomization: Informed consent was obtained from all patients after the detailed explanation of the study. The privacy of all the received data and the right to refuse or leave at any moment were also provided to all

participants. The patients were randomly assigned to Two groups; obese with metabolic syndrome group (A) (*n = 30*) and obese without metabolic syndrome group (B) (*n = 30*).

Metabolic Syndrome: Was defined using the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) criteria. The NCEP-ATP III definition requires the presence of three or more of the following: (a) abdominal obesity ;(WC) more than or equal to 88 cm for women and more than or equal to 102 cm for men, (b) HDL-c less than 40 mg/dL for males and less than 50 mg/dL for females (c) TG level more than or equal to 150 mg/dl, (d) SBP higher than or equal to 130 and/or DBP, 85 mmHg and (e) FBS higher than or equal to 100 mg/dl**. (7)** Randomization was performed by a blinded and an independent research assistant using a computer-generated randomization cards saved in sealed envelopes.

Interventions: The weight reduction program in the form of aerobic exercise training program on treadmill and diet- induced weight loss. Patients were sedentary (< 1 hr/week of physical activity), they did not participate in any weight loss program within the last 6 months and completed a personal health and medical history questionnaire.

Procedures: All patients of both groups underwent the following:

- Detailed medical history including: demographic (age and sex) and family history of diabetes and through physical examinations including vital signs.

Anthropometric Measurements: Weight, height, BMI and waist circumference.

Weight, height and waist circumference were obtained using standardized methods BMI was calculated as weight (kg) divided by height (m) squared [19].

Laboratory Investigations:

- Fasting Blood Sugar (FBS).
- Fasting insulin.
- HOMA-IR.
- Lipid Profile:
  - Total cholesterol.
  - Triglyc erides.
  - HDLc.
  - LDLc
  - Serum Adropin.

Blood Samples: Were collected in the morning, after 8 to 12 hours of overnight fasting and 20 minutes of supine rest. Venous blood was drawn into ethylene diamine tetra acetic acid (EDTA) tubes and promptly centrifuged at 4°C. Plasma was frozen at -80°C until analyses of adropin was performed. The plasma insulin and adropin levels were measured using a commercial ELISA kit (Cusabio Biotech Co, Wuhan, CN) according to the manufacturer's instructions. FBS was measured by an automated glucose oxidase method (Automatic Analyzer 2700, Olympus, Japan. Serum lipid profiles were measured by glycerol phosphate oxidase and phosphotungstic acid.

All anthropometric measurements and laboratory investigations were repeated at the end of the study.

Treatment Protocol: Both groups received low caloric diet provides 1200 to 1400 k.cal/day. A diet with low glycemic index, such as fruits, vegetables, whole grains, on-refined complex carbohydrates and high fiber diets was emphasized.

Women in Both Groups: Received an aerobic exercise program performed on Electric Treadmill: Kistler Instrument Corporation, Amherst, NY, Type 2813M01 was used for aerobic training in both groups for 50 minutes, three times weekly for 12 weeks and included three phases:

- Five minutes as *warming up* with low intensity (50-60% of maximal heat rate).
- Forty minutes as a *stimulus phase* with speed of 60-75% of maximal s heart rate with zero inclination.
- Five minutes as *cool down* with low intensity (50-60% of maximal heat rate).

Data Analysis: Results were expressed as mean±standard deviation (SD) for normally distributed data. Comparison of different variables between groups was performed using unpaired t test in normal distributed data. Pair-wise comparison (pre- versus post-assessment) within the same group for different variables was performed using paired t test in normal distributed data Statistical Package for Social Sciences (SPSS) computer program (version 23 windows) was used for data analysis. P value $\leq$ 0.05 was considered significant.

RESULTS

Results of Anthropometric Measurements: Before the study, there was no statistically difference between both groups G1 and G2 regarding mean values of age and

Table 1: Comparison between mean values of age and anthropometric measurements before and after treatment in both groups

Variables	*G1 Before*	*G1 After*	*P value*	*G2 Before*	*G2After*	*P value*
Age (years)	43.1±2.9		*NS >0.05*	43.4±2.1		*NS >0.05)*
Weight (Kg)	92.23±6.8	84.7±5.8	*0.001*	92.1±5.1	84.5±4.9	*0.01*
BMI (Kg/m2)	34.78±3.6	32.06±3.2	*0.001*	34.8±3.83	32.1±3.24	*0.01*
WC (cm)	106.1±8.5	94.03±7.3	*0.001*	104.1±9.2	93.06±7.4	*0.001*

Abbreviations: SD= Slandered deviations NS =Non-significant BMI= Body Mass Index. WC= Waist Circumference.. Significance at < 0.05

Table 2: Comparison between mean values of fasting blood glucose, fasting insulin and HOMA-IR before and after treatment in both groups

Variables	*G1 Before*	*G1 After*	*P value*	*G2 Before*	*G2After*	*P value*
FBS (mg/dl)	134.5±10.6	106.2±8.7	0. 01	105.9±10.23	94.7±7.34	0. 02
Insulin (µL/Ml)	23.5±6.74	11.3±4.53	0.001	14.2±4.27	8.5±2.95	0.001
HOMA-IR	7.8±2.4	2.96±1.6	0.001	3.71±1.9	1.98±1.22	0.001

Abbreviations: FBS=Fasting blood sugar. HO MA-IR = Homeostasis Model Assessment for Insulin Resistance.

Table 3: Comparison between mean values of Lipid profile (Total cholesterol, Triglycerides, Low-density lipoprotein cholesterol and High density lipoprotein cholesterol) before and after treatment in both groups.

Variables	*G1 Before*	*G1 After*	*P value*	*G2 Before*	*G2After*	*P value*
TC (mg/dl)	211.5±	146.2±8.7	0. 01	185.9±12.7	139.7±11. 4	0. 01
TG (mg/dl)	175.7±11.74	126±7.53	0.001	144.7±8.93	119.5±2.95	0. 01
LDL-c (mg/dl)	184.36±11.3	132.6±8.2	0.012	137.2±.9.66	108±7.42	0.001
HDL-c (mg/dl)	49.9±7.5.	51.6±8.2	0.25	51.4±7.5.	52.2±6.2	0.34

Abbreviations: TC= total cholesterol, TG = triglycerides, LDLc= low density lipoprotein cholesterol, HDL c= high density lipoprotein cholesterol

Table 4: Comparison between mean values serum Adropin before and after treatment in both groups.

Variables	*G1 Before*	*G1 After*	*P value*	*G2 Before*	*G2After-*	*P value*
Serum Adiropin (ng/ml)	1.85±0.72	3.2±0.83	0.001	2.35±0.63	3.47±0.92	0.01

anthropometric measurements, weight, BMI and waist circumferences. After weight reduction program in metabolic syndrome (group 1) and in group 2 (without metabolic syndrome), a highly significant improvement was found in anthropometric measurements in both groups compared to before the study.

Results of Fasting Blood Glucose, Fasting Insulin and Homa-ir Before and after Treatment in Both Groups: Before the study, there was no statistically significant difference between both groups G1 and G2 regarding mean values of fasting blood sugar (FBS), fasting insulin and HOMA-IR. After 12 weeks, a highly significant improvement was found in both groups compared to before the weight reduction program.

Results of Mean Values of Lipid Profile (TC, TG, LDLc and HDLc) Before and after Treatment in Both Groups: Before the study, there was no statistically significant difference between both groups G1 and G2 regarding mean values of total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDLc) and high density lipoprotein cholesterol (HDLc). After 12 weeks, a highly significant decrease was found in total cholesterol, triglycerides and low density in both groups compared to before the weight reduction program. On the other hand, there was no statistically significant difference between both groups G1 and G2 regarding mean values high density cholesterol compared to before the weight reduction program.

Results of Serum Adropin Before and after Treatment in Both Groups: Before the study, there was statistically significant difference between both groups G1 and G2 regarding mean values of serum adropin. After weight reduction program, a highly significant increase was found in both groups compared to before the study.

DISCUSSION

In the current study there was a significant decrease of anthropometric measurements [weight, BMI and WC] [$p<0.05$] at post treatment in comparison to pretreatment for both groups.

Also, there was a significant improvement of lipid profile [TC, TG and LDLc] [$p<0.05$] at post treatment in comparison to pretreatment for both groups. In serum HDLc, there was non- significant difference [$p>0.05$] in the "post treatment" analysis compared to before the weight reduction program.

There was a significant reduction of glycemic control and insulin resistance [$p<0.05$] at post treatment compared to pretreatment for both groups. It also showed that a significant increase in the serum adropin in the "post treatment" analysis between both groups [$p<0.05$] compared to pretreatment for both groups.

To our knowledge, no previous studies have evaluated the impact of weight loss program on adropin in obese women without metabolic syndrome [metabolically healthy obese] in humans. Therefore, this research is considered the first study on this point. Accordingly, the results cannot be compared or discussed directly with other research outcomes.

In our study, women in group 2 were in healthy status the "healthy obese" phenomenon, in spite of having central obesity and an increased body composition. Wu *et al*. [20] in consistence with our study who suggested that increased basal adropin levels in healthy obese individuals compared with insulin resistance syndrome patients may be lead to improvement in insulin sensitivity and the prevention of this syndrome in healthy obese individuals [20]. Lancet reported a study on individuals with BMI more than 25 kg/m^2 in 188 countries in June 2014. This research suggested that the total number of those adult people worldwide increased from 857 million in 1980 to 2.1 billion in 2013. The primary treatment for obese with or without metabolic syndrome is weight reduction and aerobic exercise training is an important component [21].

Our results demonstrated that body weight, BMI, waist circumference, decreased significantly after 12 weeks of diet -induced weight loss and aerobic exercise. The marked improvements in all the anthropometric indices in obese patients in both groups and most of the risk factors in metabolic syndrome group indicate that the weight loss protocol was very beneficial. Our study also showed a significant decrease in weight [by 8.3 % in group 1 and 8.25% in group 2], body mass index by [7.98 % in group1 and 7.75 % in group2] and waist circumference by [11.3 % in group 1 and 10.6 % in group 2].

A twenty-four week of intensive lifestyle intervention protocol performed by a community health nurse included 60 sessions of aerobic exercise for 40 minutes and diet-induced weight loss [< 1,500 kcal/day] resulted in weight reduction of 6.5 % after twelve weeks and 8.1 percent weight reduction after twenty-four weeks [22]. An increased weight reduction resulted in marked decrease in the cytokines and inflammatory mediators and produced effective health impacts [23]. Bays *et al.* [24] reported that significant improvement in all metabolic syndrome components was markedly observed after reduction in visceral adiposity [24].

Our study is in consistence with above mentioned reports that showed a significant improvement in all metabolic syndrome components in both groups. The insulin resistance index [HOMA-IR] in both groups reduced significantly as well as fasting blood glucose decreased to its preferable range. The effective weight loss protocol results in enhancement in insulin sensitivity and metabolic sensitivity [25].

The increased percentage of weight loss also leads to higher improvement in insulin sensitivity due to the decrease in the visceral adiposity and waist circumference [26]. Our study is in consistent with the research conducted by Ward J, *et al*., who suggested that increased physical activity programs promote the lipolytic enzyme activity, increases fat uptake and decomposition and seriously inhibits lipid storage [27]. So, a programmed physical activity protocol reduces fat storage in the body and enhances metabolic flexibility and insulin sensitivity [28].

There is a significant positive correlation in insulin resistance patients and coronary artery disease. Therefore, enhancement of insulin sensitivity condition by using aerobic exercise training may be lead to dramatic reduction in future ischemic heart disease in obese pre-menopausal women with or without metabolic syndrome [29].

Adropin is a newly identified stable protein and is expressed in brain, liver and the endothelial cells of the coronary artery [11]. The overweight and obesity in adults may lead to many risk factors such as; lower adropin levels, ischemic heart disease, chronic high blood pressure and insulin resistance syndrome [30]. In our study, there was a significant decrease in adropin levels in obese women with metabolic syndrome [group 1] than in healthy obese women without metabolic syndrome [group 2].

After the weight loss program, there was a significant increase in adropin levels in both groups. The increased adropin levels was associated with improvement in glycemic control even in obese, the so-called "healthy obese phenomenon." Also, our study agrees with the work conducted by Kumar et al., who reported that hypoadropinemia is associated with obesity with or without metabolic syndrome [11].

Previous studies suggested that there was an association between vascular endothelial dysfunction and the decreased levels of adropin in diabetic type-2 diabetes mellitus and insulin resistance syndrome [28].

Physical activity program results in increased the levels of adropin and improved atherosclerosis and visceral obesity in adults [29]. After weight reduction program the increased levels of adropin promotes the production of nitric oxide, which promotes vascular endothelial function [30].

These results suggest that weight loss program and aerobic exercise can lead to improvement in all components of metabolic syndrome also leads to favorable changes in adiposity determinants and increase in the systemic levels of adropin.

In summary, our findings indicate that intensive weight loss program and aerobic exercise protocol reduced the resting levels of fasting blood glucose, serum insulin and HOMA-IR [insulin resistance] and improved the level of lipid profile, as well as serum adropin in obese premenopausal women with and without metabolic syndrome. Our present study supports the concept that aerobic exercise and weight loss program increase the level of adropin hormone and can lead to prevention of all components of metabolic syndrome [obesity, insulin resistance and dyslipidemia].

CONCLUSIONS

We recommend that diet-induced weight loss and aerobic exercise program are beneficial methods for weight reduction to reduce weight, body mass index, waist circumference, fasting blood glucose level, insulin level and insulin resistance [HOMA-IR] and increased level of serum adropin.

Limitations: Although the current study reveals objective data with statistically significant differences, there are some limitations. This study was limited to the small number of the sample, age of the patients and restricted only to women. Future studies should search on large number, in children, young age, postmenopausal and old age as well as in men.

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