Influence of a 12-week physical activity program on leptin resistance in metabolic syndrome: a preliminary study

Parameshwar Anche¹ · G. Arun Maiya¹ · Shobha Ullas Kamath² · B. Ananthakrishna Shastry³

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Abstract

Purpose Metabolic syndrome is a condition with clustering of risk factors like insulin resistance, obesity, dyslipidemia, and hypertension. Leptin is a protein of obese gene produced by white adipose tissue. Leptin resistance is the insensitivity of leptin in hypothalamus despite high amounts in blood causing obesity and metabolic syndrome. The study focused on the influence of a 12-week physical activity promotion program on leptin resistance in people with metabolic syndrome

Methods After approval from institutional ethics committee (IEC 343-2018), 18 participants (males $N=4$, females $N=14$) of age group 45.0 ± 7.6 years with metabolic syndrome according to (NCEP ATP-III) criteria were included in the study. The participants underwent a 12-week physical activity program consisting of 150 min of moderate to vigorous activity per week as per GPAQ domains—work, transport, and recreation. The outcomes were measured at baseline and after 12 weeks.

Results Out of 18 participants, 10 participants who completed the study were analysed. Twelve-week physical activity showed significant changes in waist circumference ($p=0.047$), post prandial blood glucose ($p=0.0396$), triglycerides ($p=0.0323$), body mass index ($p=0.0056$), subcutaneous fat ($p=0.0354$), and basal metabolic rate ($p=0.0035$). Fasting blood glucose ($p=0.254$), lipid profiles (total cholesterol ($p=0.062$)), high-density lipoprotein ($p=0.367$), low-density lipoprotein ($p=0.641$), and leptin showed insignificant change ($p=0.328$). Global physical activity questionnaire showed significant change ($p=0.0254$) suggesting changes in physical activity behaviors.

Conclusion From present study, it is concluded that a 12-week physical activity promotion program brought marginal changes in leptin levels and has potential to modify metabolic syndrome parameters and improve physical activity.

Keywords Metabolic syndrome · Leptin resistance · Physical activity · Body composition

Introduction

Metabolic syndrome (MetS) is a condition characterized by clustering of several known risk factors like insulin resistance (IR), obesity, atherogenic dyslipidemia, and hypertension (HTN) [1]. It was named as syndrome X by Gerald Raven in 1988 with aggregation of several important cardiovascular risk factors. Visceral fat is considered as a major risk factor for coronary heart disease and type 2 diabetes mellitus [2]. In addition to this, elevated serum levels of fibrinogen and tissue plasminogen activator inhibitor (PAI) are related to metabolic factors of CHD. Low-density lipoprotein (LDL) is associated with insulin resistance, obesity, and type 2 diabetes. Dyslipidemia is also considered as one of the risk factors of MetS with increased serum triglycerides, decreased high-density lipoprotein (HDL), and increased LDL. Other contributing conditions of MetS include endothelial dysfunction [3], inflammation, and oxidative stress [4].

✉ G. Arun Maiya
arun.maiya@manipal.edu; ajmaiya@gmail.com

Parameshwar Anche
param.anche@gmail.com

Shobha Ullas Kamath
shobha.kamath@manipal.edu

B. Ananthakrishna Shastry
shastryba@yahoo.com

¹ Department of Physiotherapy, Centre for Diabetic Foot Care & Research, Manipal College of Health Professions, Manipal Academy of Higher Education, Manipal, Karnataka 576104, India

² Department of Biochemistry, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, India

³ Department of Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, India

Leptin is a 167-amino acid protein, a product of obese gene produced by white adipose tissue. It functions as endocrine organ with numerous functions apart from fat storage [5]. It works on hypothalamus and acts to decrease food intake and increase metabolism. It helps in decreasing appetite, increasing energy expenditure, and regulating glucose homeostasis [6]. Congenital leptin deficiency has shown to cause severe obesity, glucose intolerance, and insulin resistance in humans. Increased serum leptin can be due to increased FFA, insulin stimulation, oestrogen, TNF α , and impaired renal clearance. Increased leptin levels are associated with metabolic syndrome [7]. High levels of leptin are seen in obese individuals due to defect in leptin receptor, inhibition in leptin signalling, and alterations in leptin transport in blood brain barrier [8]. Leptin resistance occurs in β cells which may lead to hyperinsulinemia which in turn causes less energy expenditure and leads to metabolic syndrome. There are no specific criteria to diagnose leptin resistance. Studies showed that hyperleptinemia is an important marker for leptin resistance [9, 10]. Leptin resistance could be due to reduction in expression of short and long isoforms of leptin receptors (OBRa & OBRb) in hypothalamus, hepatocytes, adipose tissue, and muscles [11, 12].

Strong evidence exists that both children and adults benefit from being physically active. Benefits of physical activity include lower risk of chronic diseases such as obesity, heart disease, diabetes, cancer, and depression [13–19]. It is widely accepted that physical activity is a low-cost alternative to disease treatment and prevention [20]. Phillip Tusso discussed the five strategies to be physically active which are to (1) measure physical activity as a vital sign; (2) encourage patients to be physically active at least 150 min per week; (3) create healthy environments by making it easier for patients to be physically active where they live, learn, work, play, and pray; (4) monitor disease incidence of patients who are physically active vs those who are not physically active; and (5) spread best practices [20]. MetS affects people whose excess body weight, and sedentary lifestyle determine the phenotype expression of genetic trait [21]. Maintaining normal weight and practising physical activity remain the most effective prevention strategy of MetS [22]. Management of MetS should be based on effective weight loss program and exercise program which needs specific strategies for the maintenance of the program. Weight loss is associated with significant improvements in clinical components of MetS, and there is association between moderate weight loss and improvements in metabolic profile [23]. Physical activity (PA) has a major role in the treatment of MetS. Cardiopulmonary fitness has shown to modify cardiovascular events, thus providing a strong and protective effect on cardiovascular health. Several studies have shown that increased levels of physical activity are associated with less prevalence and incidence of MetS [24].

However, the effect of PA promotion on leptin resistance among people with metabolic syndrome is not known. The purpose of this study is to determine the influence of a 12-week PA promotion program on leptin resistance in people with metabolic syndrome (Fig. 1).

Methods

After approval from institutional ethics committee (IEC 343-2018), 18 participants (males $N=4$, females $N=14$) with age group 45.0 ± 7.6 with 3 out of 5 criteria of metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Protocol III (NCEP ATP-III) criteria were included in the study (Fig. 2). In the present study, the screened participants have been advised to continue the medication as per the physician advice. Standard diet prescription was given by the hospital dietician. Participants were excluded if they have a history of smoking past 6 months, cardiovascular disease, stroke, transient ischemic attack (TIA), any cognitive impairment, any systemic illness, and if they are having any other contraindications for PA as mentioned in PARQ+ physical activity readiness questionnaire.

Study design

The study is preliminary pre-post non-randomized interventional with a single group of participants with metabolic syndrome. The sample size for this study was estimated as general rule of thumb as suggested by Julious [25]. The participants were selected using convenience sampling from the Kasturba Hospital after a thorough medical evaluation and clearance for physical activity from the physician.

Procedure

The participants were enrolled into the study after physician clearance and low risk as per AHA/ACSM pre-participation questionnaire and PARQ+ physical activity readiness questionnaire. If the participants were found to be under moderate or severe risk category, they were advised to consult a physician before the start of any physical activity. Participants who were included in the study were assessed for fasting blood sugar (FBS), waist circumference (WC), blood pressure (BP), body composition, physical activity, leptin, lipid profile, and basal metabolic rate (BMR). BP is taken with digital sphygmomanometer *Omron* HEM-7113 (*Omron* Health Care Inc, Illinois) (Accuracy: Pressure: ± 3 mmHg Pulse: $\pm 5\%$ of display reading) after making the participant rest for 3 min in a quiet room.

Fig. 1 Flow chart of the participant recruitment and analysis

Fig. 2 Diagnostic criteria of metabolic syndrome according to NCEP-ATP III

Body composition and anthropometry

Body composition (BC) was analysed using Omron Karada Scan HBF 362 bio impedance analyser (BIA) (Omron Health Care, Inc, Illinois). Body composition included total body fat (TBF), subcutaneous fat (SCF), visceral fat (VF), musculo-skeletal mass (MSM), and basal metabolic rate (BMR). For assessing BC using BIA, the participant was instructed to wear light clothing, 8-h fasting, avoiding of caffeine intake, alcohol intake and exercise 2 h prior to test, and no fluid intake 2 h prior to the test. The participant age, gender, and height are entered into the analyser, and the participant is made to stand on the BIA platform. TBF, SCF, VF, MSM, and BMR readings are recorded. WC is taken in centimetres with a non-

stretching tape at the level above iliac crest. Basal metabolic rate was calculated using Mifflin-St Jeor equation

$$\text{BMR (kcal/day)} = 10 * \text{weight (kg)} + 6.25 * \text{height (cm)} - 5 * \text{age (y)} + s \text{ (kcal/day)},$$

where s is +5 for males and −161 for females.

Biochemical measurements

Blood sample was taken after 8 h of fasting state to measure FBS, total cholesterol (TC), triglycerides (TG), high-density lipoproteins (HDL), low-density lipoprotein (LDL), and leptin. FBS was analysed using hexokinase method, TC was analysed using CE-CHOD-POD method (Atlas Medicals, Cambridge), triglycerides were analysed using GPO trinder method (BQ kits Inc, San Francisco, CA), HDL was assessed using direct-homogenous assay, and LDL was calculated using the Friedewald formula. Leptin was analysed by enzyme-linked immunosorbent assay (ELISA) sandwich technique using commercially available kits DBC ELISA (Diagnostic Biochem Canada Inc) with specificity of 0.50 ng/ml, intra assay CV 3.7%, and interassay CV of 5.9 %.

Physical activity measurement

PA was measured using the World Health Organization global physical activity questionnaire (WHO-GPAQ). It contains 4 domains: work, transport, recreational, and sedentary time. GPAQ demonstrated good-to-very good test-retest reliability with time intervals that ranged from 3 days to 2 weeks [21]. GPAQ is used to assess the PA for a week and is expressed in met.min/week. The individual is said to be sedentary if the GPAQ score is less than 600 met.min/week.

PA promotion program

After assessing the PA using GPAQ, the participants were given a 12-week PA program which consisted of 150 min/week moderate to vigorous PA. Before giving the PA, the participants were asked about the daily routine and explained how they can modify their work routine into PA by monitoring themselves using commercially available fitness trackers which measure the step count. The participants using these fitness trackers were instructed to maintain 10,000 steps/day. People who did not have access to fitness trackers were given PA program according to the WHO compendium of physical activities which contain list of activities with specific MET values. To maintain adherence, the participants were advised to do PA in their convenient time without disturbing their daily routine but were instructed to maintain 150 min moderate to vigorous PA per week. The PA included various activities like brisk walking, gardening, house chores,

workplace physical activity, and leisure time physical activities like group activities in a park which included yoga, general drills, and light jogging. To monitor PA, the participants were called by telephone every week to enquire about the activities they are doing. The progression of PA was measured every third week using GPAQ. The target was to achieve 150 min of physical activity per week. All the participants had less than 60 min/week of physical activity at the start of the study. The target was to increase the physical activity in a steady phase until they reach the required 150 min/week target. After 12 weeks, the participants are re-assessed for the outcomes like leptin, GPAQ, BP, TC, TG, HDL, LDL, BMR, SCF, VF, MSM, and WC.

Statistical analysis

Descriptive statistics were presented as mean and standard deviation. Shapiro-Wilk test was performed for normal distribution. Paired t test was performed to analyse the difference pre- and post-intervention. p value was set at $p < 0.05$ at 95% CI.

Results

Participants ($N=18$) aged 30–50 years of either gender who were diagnosed with metabolic syndrome under NCEP ATP

Table 1 Baseline characteristics of the participants

Baseline characteristics of the participants $N = 18$	
Variable	Mean $\pm$ SD
Age (years)	47.2 $\pm$ 4.86
GPAQ (met.min/wk)	231.7 $\pm$ 138.18
LEPTIN (ng/ml)	25.9 $\pm$ 10.69
Metabolic syndrome parameters	Mean $\pm$ SD
WC (cm)	101.8 $\pm$ 8.5
SBP (mmhg)	134.2 $\pm$ 3.96
DBP (mmhg)	88.2 $\pm$ 4.62
FBS (mg/dl)	152.5 $\pm$ 42.44
HDL (mg/dl)	43.3 $\pm$ 10.14
LDL (mg/dl)	129.1 $\pm$ 32.7
TG (mg/dl)	177.1 $\pm$ 34.81
BMI (kg/m ²)	28.3 $\pm$ 4.57
PPBS (mg/dl)	188.8 $\pm$ 44.39
Body composition	Mean $\pm$ SD
TC (mg/dl)	214.1 $\pm$ 29.24
SCF (%)	28.9 $\pm$ 3.7
VF(%)	11.2 $\pm$ 1.6
MSM(%)	23.4 $\pm$ 5.8
BMR (Kcal)	2025.54 $\pm$ 138.6
TF (%)	31.3 $\pm$ 8.5

III criteria were recruited for the study. Ten participants who completed the study were included in the analysis. The main parameters of the MetS are presented in Table 1 which included all 18 participants. All the participants had increased waist circumference, dyslipidemia, hyperglycemia, and elevated blood pressure according to NCEP ATP III for metabolic syndrome (Fig. 3). Table 2 describes the changes in all outcomes with a 12-week physical activity of the 10 participants who completed the study. Two participants who were enrolled into the study were not available for the post-intervention analysis. One participant was available but followed intervention less than 6 weeks so could not be analysed; 3 participants had adherence issues due to their work-related stress and stopped intervention abruptly. Two participants who did not find time for the intervention described of unable to balance time due to change of their job. The results showed that the mean physical activity levels of the participants were 330.4±85.6 met.min/week which is less than the recommended levels of >600met.min/week according to GPAQ. This clearly had shown the elevation of MetS parameters showing the importance of physical activity. All the participants were diagnosed as leptin resistant with elevated leptin levels (25.5±9.3 ng/ml) which correlated with the elevation of BMI (27.5±2.36 kg/m²). We also observed that all the participants had elevated BMR levels (1954.35±142.5 kcal) suggesting decreased lean mass and increased total fat mass (30.7±6.8). The 12-week physical activity program brought changes in some parameters of MetS. The participants were motivated and explained the benefits of physical activity which brought a significant change in physical activity levels ($p = 0.0254$). As the physical activity levels increased, WC changed significantly ($p=0.047$). PPBS has shown significant change ($p=0.0396$), whereas FBS did not show significant change ($p=0.254$). No significant changes were seen in lipid profiles (TC ($p=0.062$), HDL ($p=0.367$), LDL ($p=0.641$)). But triglycerides have shown significant change in 12 weeks ($p=0.0323$). Body composition assessment has shown significant changes in BMI ($p=0.0056$), SCF ($p=0.0354$), and BMR ($p=0.0035$). Leptin levels did not show significant change ($p=0.328$) despite changes in BMI and SF. Out of 10 participants who were analysed, 1 participant had improvement in three

Fig. 3 Changes in individual parameters of metabolic syndrome according to NCEP-ATP III

Table 2 Mean change in leptin, body composition, and metabolic syndrome parameters of the participants who completed the study

Variable	Baseline (N=10)	12 weeks (N=10)	p value
Leptin (ng/ml)	25.5±9.3	23.7±11.5	0.328
GPAQ (met.min/wk)	330.4±85.6	420.5±122.4	0.0254*
Metabolic syndrome parameters			
WC (cm)	98.6±5.4	96.4±2.8	0.047*
SBP (mmhg)	132.5±4.25	131.5±3.68	0.549
DBP (mmhg)	86.2±5.83	86.8±2.95	0.269
FBS (mg/dl)	148.5±39.65	147.7±38.63	0.254
PPBS (mg/dl)	185±41.36	183.54±36.52	0.0396*
Lipid profile			
TC (mg/dl)	213.4±29.24	212.2±25.63	0.062
HDL (mg/dl)	45.3±9.6	43.9±3.8	0.367
LDL (mg/dl)	132.4±27.5	130.7±26.8	0.641
TG (mg/dl)	180.6±26.3	176.3±26.7	0.0323*
Body composition			
BMI (kg/m ²)	27.5±2.36	25.3±2.89	0.0056*
SCF (%)	29.3±5.6	26.5±2.92	0.0354*
VF (%)	10.8±0.8	9.7±1.6	0.296
MSM (%)	23.5±4.6	22.8±4.9	0.074
BMR (Kcal)	1954.35±142.5	2026.4±142.9	0.0035*
TF (%)	30.7±6.8	28.9±5.6	0.086

* p value < 0.05

criteria of metabolic syndrome (WC, FBS, and TG), 2 participants had improvements in 2 criteria of MetS (FBS and WC), 1 participant showed improvement in parameters (WC, TG), 2 participants showed improvement in SBP and DBP, and 4 participants showed changes in BMI (Fig. 2).

Discussion

The present study aimed to find the effect of a 12-week physical activity promotion on leptin resistance in people with metabolic syndrome. This preliminary study results showed changes in some parameters of metabolic syndrome, body composition, and changes in PA behavior. Out of 18 participants, 10 participants completed the study (Fig. 1). The reason could be that unlike exercise, PA is more generalized and does not follow a structured protocol, and we observed that participants were not aware of the difference between an exercise protocol and physical activity. Moreover, awareness and self-motivation play an important role in maintaining the adherence to program. Previous studies were in line with our findings about the adherence to physical activity [26]. In our study, the dropped-out participants reported that they did not have time for exercise mostly due to their work schedule and type of work. Participants who enrolled into the study were

clearly explained the importance of physical activity to maintain optimum health and bring changes in metabolic syndrome parameters and lead a healthy lifestyle. Participants were encouraged to use technology like smart wearables and smart phone apps which monitor and provide motivation to increase physical activity and continue the new active lifestyle. There is a strong evidence on benefits of technology in improving physical activity [27–31]. Overall, the 12-week PA promotion program has brought changes in most metabolic syndrome parameters. Leptin levels did not change significantly despite significant decrease in BMI levels. Previous studies done by Xenachis C et al. [32] found that a 7% decrease in body weight was associated with a 22% reduction in serum leptin; Bastard et al. [33] found that decrease in leptin with a decrease of 2.1 kg/m² in BMI was followed by a 45% reduction in leptin levels. The discrepancy in leptin levels in our study may be due to sample size being too low to determine the effect of this intervention in decreasing leptin resistance. Leptin levels remained stable despite decrease in SCF. The participants were mostly females, and they have comparatively higher fat content than male population. This could be the reason of unchanged leptin levels. The changes in BMR can be attributed to change in SF and non-significant increase in MSM. Because BMR is the marker of lean body mass, increase in MSM and decrease in SF could decrease in BMR suggesting healthy weight loss. We have observed a statistically insignificant change in VF. The reason could be the unique characteristics of VF like increased blood flow and more response to norepinephrine. Studies have shown that increase in VF could lead to increased BMR [34]. In our study, MSM and VF have shown insignificant changes supporting the statement of higher BMR values. Further assessment is needed to assess the difference in BMR per unit decrease in VF and per unit increase in MSM. SBP and DBP did not show a significant change suggesting that the intervention could not bring out much change in sympathetic system which regulates the blood pressure. The results for SBP and DBP were inconsistent with other studies [35–37] probably due to small sample size. Although there was insignificant change in TC, TG had shown a significant change post-intervention suggesting that a moderate amount of physical activity for longer duration could help in fat metabolism especially TG which is source of energy for long duration steady-state activity. E.G. Oh et al. [38] found a decrease in TG with a 3-month total lifestyle modification which supported our results concerning decrease in TG. In the present study, based on the WHO-GPAQ questionnaire, all the participants were sedentary with the MET value <600met.min/week. Our main purpose of the study was to sensitize people about the physical activity and to include physical activity in their day-to-day life. Based on our results, we observed that all participants' physical activity has been improved. However, as a part of ongoing research, we had followed them telephonically regarding the continuation physical activity promotion, but the data was not reported in the present study.

The strengths of the study were that the 12-week physical activity promotion program could bring changes in metabolic syndrome parameters, decrease sedentary time, and improve physical activity. Waist circumference showed a significant change with the intervention which suggests that healthy lifestyle with physical activity as a daily routine could bring out weight loss and help in improving optimum health.

The limitations of the study were small sample size and disparity between gender which could have interfered with the results. As this is a longitudinal study and no control group was involved, there was no comparison for the results. Another limitation of the study was high attrition rate showing poor adherence to the program which needs to be addressed in the future studies. Future studies should investigate a randomized controlled trial with appropriate control group and address the above issues for more clear results and the effect of intervention.

Future studies should also investigate association between leptin resistance and BMR, total fat, and effect of the PA intervention on these variables. However, our study was able to show a considerable change in the metabolic syndrome parameters, some components of body composition, and anthropometry.

Conclusion

From the present study, we have concluded that a 12-week physical activity promotion program brought marginal changes in the leptin levels and has a potential to modify the metabolic syndrome parameters and changes in body composition and improve physical activity behavior.

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Declarations

Conflict of interest The authors declare no competing interests.

Informed consent Informed consent has been obtained from all the participants prior to the inclusion into the study.

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