What Happens to Adipokines and Cytokine in Overweight and Obese Girls with Central Precocious Puberty When They Exercise and Stop Exercising? A randomized Controlled Trial

Elnaz Shokri
Bu-Ali Sina University: Bu Ali Sina University
Ali Heidarian pour (Heidarian317@gmail.com)
Bu-Ali Sina University: Bu Ali Sina University https://orcid.org/0000-0001-8152-1489
Zahra Razavi
Bu-Ali Sina University: Bu Ali Sina University

Research

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Abstract

Background

we investigate the levels of adiponectin, resistin, tumor necrosis factor-alpha (TNF-α) and signs of puberty progression after 12-weeks of combined exercise and 4-weeks of detraining.

Methods

Thirty overweight and obese girls (age7-9) with precocious puberty who injected Differlin were randomly divided into two groups (exercise and control). At the beginning, blood samples were obtained from all subjects and serum levels of adiponectin, resistin and TNF-α were measured. Exercise group performed 60minutes of combined (aerobic and resistance) exercises 3 times a week for 12-weeks.Control group did not receive any exercise. 48 hours after the last training session and after four weeks of detraining, blood samples were collected in the second and third stage, respectively. Blood samples were collected from the control group in both steps. BMI, cholesterol, triglyceride, signs of puberty progression (bone age, uterine lengths, ovarian volumes), luteinising hormone (LH) and follicle-stimulating hormone (FSH) were measured on all three occasions.

Results

In the exercise group, adiponectin significantly increased and resistin significantly decreased after 12-weeks. After 4-weeks of detraining, adiponectin significantly decreased and resistin significantly increased. TNF-α levels did not change significantly during the study. There was no significant difference in all of the factors in the control group. Throughout the 16-week study period, the rate of puberty and LH significantly decreased in both exercise and control groups but FSH and LH/FSH significantly decreased in exercise group, alone.

Conclusion

Combined exercise increased adiponectin and decreased resistin and rate of puberty. After 4-weeks of detraining, these effects diminished but did not disappear.

Trial registration:

Trial registration: ISRCTN, ISRCTN39938. Registered 24 may 2021 - Retrospectively registered, https://www.isrctn.com/trialist

Introduction

Puberty is characterized by the growth of reproductive organs, enlargement of secondary sexual feature, accelerate growth rate, and incidence of menarche in females [1]. Gonadotropin-releasing hormone (GnRH) is produced in the hypothalamus. It releases luteinising hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland, which impact on the gonads to secretion of sex hormones [2]. This is how puberty begins. If this process of puberty occurs in girls before the age of 8 and in boys before the age of 9, central precocious puberty (CPP) has occurred which is associated with increased growth rate and accelerated bone age [3]. The incidence of CPP in girls increased from 89.4 to 415.3 per 100000 from 2008 to 2014 [4]. The treatment of precocious puberty is Gonadotropin-releasing hormone analogue (GnRHa) [5]. The diagnosis of CPP is done with clinical, biochemical, and radiographic features. 1- Clinical Features: On primary checkup of the child with CPP, both breast growth and pubic hair will be apparent in girls. Another clinical sign of precocious puberty is an increase in bone age [6]. 2- Biochemical Features: LH is one of the biochemical features used to assessment CPP [7]. GnRH stimulation test is the gold standard to identify CPP [8]. Although this test is very valuable, it has other defects such as low sensitivity, the need for an intravenous line and time-consuming [9]. Hence, ultrasound can be used instead of this test, which is non-invasive and relatively easy to carry out. 3- Radiographic features: Pelvic ultrasound (Uterine and ovarian dimensions) has been shown to be a helpful additional to verify CPP [10].

Obesity affects the timing of puberty and probably one of the reasons for earlier trends of pubertal age published in several countries [11]. Brix et al (2020) found that higher childhood body mass index (BMI) was related with earlier pubertal timing in both sibling-matched analysis and cohort analysis in both sexes [12]. Also, overweight or obese children grow sexually sooner than lean children [13]. In the obese state, the addition growth in adipose tissue has been exhibited to change the adipokine profile, thereby initiating a detrimental cascade of metabolic disturbances [14]. Two of the most important adipokines are adiponectin and resistin. Adiponectin concentration decreases with obesity [15] and resistin secretion increases in obesity [16].

Adiponectin has many impacts within the hypothalamic gonadal axis and puberty. Adiponectin activates the AMP kinase pathway, which inhibits GnRH activity and thereby reduces LH [17]. The results of the study by Sitticharoon et al. showed that adiponectin concentration were lower in girls with CPP than the girls with normal puberty, and were negatively associate with BMI [18]. Also resistin found in the hypothalamus and pituitary glands of rodents [19]. However, it is worth noting that adiponectin has shown an ability to modify the inflammatory response of endothelial cells by hampering the tumor necrosis factor-alpha (TNF-α) mediated activation of nuclear factor-kappaB (NF-κB), a key protein complex played in the regulation of the immune system [14]. Research shows that precocious puberty subjects had significantly higher levels of TNF-α compared with matched controls [20].

Regular exercise promotes positive adaptation in the body and involved in the prevention and treatment of obesity, obesity-related position and chronic inflammation [21]. The results of a meta-analysis showed that exercise significantly increased adiponectin in obese children [22]. The results related to resistin are contradictory; data from several studies demonstrated a significant reduction in resistin concentration [23, 24] while the results of a meta-analysis study indicated that exercise did not decrease resistin levels

in pediatric obesity [22]. Physical activity might reduce systemic inflammation, through the decreased production of macrophage or adipocyte pro-inflammatory cytokines [25]. Interestingly, the results of Nimmo et al. (2013) indicate that combination of aerobic and resistance training probably led to the most betterment in the inflammatory profile [26]. While the effects of either aerobic training or resistance training on adipokines and inflammation are almost well reviewed [27, 28], data about the effects of combined aerobic and resistance training on adipokines and inflammation is sparse. Therefore, the purpose of this study was to investigate the effect of combination exercises on adiponectin, resistin and TNF-α levels in girls with CPP. An attempt was also made was to investigate the effect of detraining on the levels of these factors. Detraining means that training-induced psychological, anatomical, and physiological adaptations are partially or completely eliminated, as a result of training diminution or training discontinue [29]. The further aim of the present study, was to estimate changes in bone age, uterine lengths, ovarian volumes, LH, FSH at the beginning and the end of treatment period.

Method

Study design and subjects

The inclusion criteria for the study included: 1. Girls with precocious puberty; 2. Having a BMI higher than 19; 3.The age range of 7 to 9 years; 4. taking about one year before a diagnosis had been made; 5. Being on medication for one year; 6. Being treated with Differlin drug ; 7. Taking medication 1 ml every 28 days.

The exclusion criteria in the study included: 1. having another illness; 2. taking another medicine; 3. having a special diet; 4. being active in another sport; 5. being connected to drugs.

Finally, out of the 46 overweight and obese girls with precocious puberty, 36 were selected and randomly divided into two groups: The exercise group (EX) performed 12 weeks of combined training (n=18), and the control group (CON) did not receive any exercise (n=18). But some left the program during the investigation and finally 30 people were analyzed. (Fig 1). All the patients completed the written consent form of participation in the study. The research was approved by the Medical Ethics Committee of Hamedan University of Medical Sciences on 14th of Nov, 2015 with proprietary ID IR.UMSHA.REC.1394.366.

Measuring the basic indicators

Height and weight of the children were measured by the children's stadiometer of the German SSA 216 and Beurer GS20, respectively. Their age was recorded by asking from their parents. Heart rate was measured by POLAR beacon meter. BMI was calculated by dividing weight by height squared (kg/m^2) and was analyzed based on the CDC (Centers for Disease Control reference) [33]. Systolic blood pressure (SBP) and Diastolic blood pressure (DBP) were measured with a Buerer Barometer. Peak oxygen uptake (Vo_2peak) was measured by a 6-minute walk test (6MWT) that measures the maximal distance in which a person can walk in 6 minutes [34]. This test has already been performed and has been validated on children [35]. BMI, systolic and diastolic blood pressure, vo_2peak, bone age, uterine lengths, ovarian

volumes were measured before and after exercise and also after the detraining period in exercise group. All of the above were measured in the control group in all three occasions.

Measuring blood samples

After measuring anthropometric indices and other primary specifications, all the patients attended the laboratory for blood sampling. To measure biochemical variables 24 hours before the training program, blood sampling was carried out by a laboratory specialist in the morning; 6cc of blood samples were taken from the participants. The ESTBIOPHARM company kit of China with 0.023 ng/ml degree of sensitivity and ELISA method were used to measure adiponectin serum levels. To measure resistin serum levels, we used ESTBIOPHARM company kit of China with a 10.23 ng/ml degree of sensitivity and the ELISA method. To measure TNF-α serum levels, we used BOSTER company kit of Canada with a 1 pg/ml degree of sensitivity and ELISA method. Plasma levels of total cholesterol (TC) and triglycerides (TG) were measured by enzymatic procedures [36,37]. The estimation of High-density lipoprotein (HDL) was performed using the method described by Burstein et al. [38] while the method used by Assman et al. was adopted in determining low-density lipoprotein (LDL) [39]. LH and FSH were measured by electrochemiluminescence immunoassay (DxI800 automated chemiluminescence assay and commercial kit; Beckman Coulter, Inc., CA, USA) with sensitivity of 0.2 IU/L. To remove the effect of the last training session, forty-eight hours after the last exercise session, blood samples were measured in patients in the exercise group to evaluate the effect of the exercise program on the mentioned biochemical indices. 4 weeks after the end of the exercise, the third blood sampling was performed. The reason for choosing 4 weeks of detraining was that the results indicated that although 2 weeks of detraining is not long enough to completely eliminate the beneficial effects of regular exercise, continued detraining may lead to damaging effects [40]. All of the above were measured in the control group in all three occasions.

Intervention

The 3-month intervention in exercise group involved a physical activity program with 3 60-min sessions/week without any dietary intervention. Exercise sessions were controlled by 2 experienced physical education teachers and consisted of 30 min of aerobic exercise (fast walking, running, ball games) at a heart rate corresponding to 55% to 65% of individual maximal cardio-respiratory fitness (based on baseline maximal oxygen consumption [VO2max] measures by 6MWT), followed by 20 min of strengthening exercises and 10 min of stretching and cool-down. Children wore a heart rate monitor (Polar S610, Kempele, Finland) during each training session, and watch alarms warned them if the heart rate was too low (55% VO2max) or too high (65%VO2max). The aerobic period was followed by strengthening exercises of the arms, legs, and trunk (2 to 3 series of 10 to 15 repetitions), with the resistance being provided by the child's body weight and elastic bands [41]. The control group did not receive any interventions and was asked to protect the current level of physical activity during the first 3 months. After the 3-month intervention, we asked participants not to participate in any exercise programs for 4 weeks.

Statistical analysis

The Kolmogorov Smirnov test was used to specify the normal distribution of the data. The Analysis of Variance (ANOVA) with repeated measures and Bonferroni post hoc test was used to compare the difference between groups and within groups. The Pearson correlation coefficient was analyzed to examine the relationship between some parameters. The collected data were analyzed using the SPSS 20 software. The results are expressed as mean ± the standard deviation (SD). Differences were judged to be statistically different at $P< 0.05$.

Results

The individual physiological and anthropometric characteristics of the participants in 3 stages (Baseline, 12 weeks, and 16 weeks) are in Table 1 that shows there is no significant difference in any of the parameters between the control group and exercise in the baseline stage. Additionally, Table 1 shows that in exercise group; weight, BMI, BMI Standard Deviation Score (SDS), TC, LDL, TG, SBP significantly decreased after 12 weeks of combined exercise but HDL, 6MWT and Vo2peak significantly increased after 12 weeks of combined exercise ($p < 0.05$). After 4 weeks of detraining Weight, BMI, TC, LDL and TG significantly increased compared to 12 weeks of training, but the levels of these cases are still significantly higher than the baseline stage ($p < 0.05$). Also, Table 1 shows that HDL, SBP, 6MWT, and Vo2peak significantly decreased after 4 weeks of detraining ($p < 0.05$). Table 1 shows that in control group; none of the cases were significantly changed.

In exercise group bone age before treatment was 10.49 ± 2.11 years, which was 2.07 ± 0.83years more than chronological age. At 12 weeks after exercise, the difference between bone age and chronological age was 1.64 ± 0.63 years, and after 4 week of detraining was 1.66 ± 0.57 which was lower than the difference before exercise. In control group the difference between bone age and chronological age in baseline was 2.03 ± 1.24years. At the end of 16 weeks of treatment was 1.67 ± 0.55 years (Table 1). This difference in the exercise group is lower than the control group.

Statistical analysis showed that uterine and ovarian size, LH, FSH and LH/FSH ratio decreased significantly after 12 weeks of combined exercise and 4 weeks of detraining in exercise group (Table 1). While in control group, the above cases decreased significantly after 16 weeks of treatment. Ironically, FSH levels, LH/FSH ratio and ovarian volumes have not decreased even after 16 weeks in control group (Table 1).

The results of ANOVA with repeated measures and Bonferroni post hoc test showed that adiponectin levels increased significantly after 12 weeks of combined training and decreased significantly after 4 weeks of detraining. However, adiponectin levels are still significantly higher than baseline levels (Fig. 2).

The results of statistical analysis also showed that resistin levels decreased significantly after 12 weeks of combined training and increased significantly after 4 weeks of detraining. However, resistin levels are still significantly lower than baseline levels (Fig. 3).

The results indicated that TNF-a levels did not change significantly after 12 weeks of combined training and 4 weeks of detraining (Fig. 4).

Table 1
Subject's physiological and anthropometric characteristics in 3 stage (Baseline, 12 weeks,16 weeks) and 2 groups (Exercise and Control)

Parameters	Group	baseline		12 weeks		16 weeks		Observed power
		Mean	SD	Mean	SD	Mean	SD	
Age (year)	Ex	8.42	0.75	8.67	0.83	8.9	0.85	—
	Con	8.28	0.64	8.53	0.66	8.61	0.71	—
Height (cm)	Ex	134.5	9.2	134.9	6.71	135	5.36	0.89
	Con	134.2	8.31	134.5	9.56	135.1	7.88	0.89
Weight (kg)	Ex	40.51	1.98	38.25[a]	2.51	38.94[a b]	2.33	1
	Con	39.93	1.97	40.05	1.9	40.09	1.91	0.87
BMI (kg/m^2)	Ex	21.76	1.53	20.47[a]	1.56	20.78 [a b]	1.61	1
	Con	21.75	1.71	21.76	1.72	21.76 [a b]	1.72	0.55
BMI SDS	Ex	1.71	0.14	1.18 [a]	0.1	1.43 [a b]	0.13	0.97
	Con	1.82	0.23	1.85	0.24	1.67	0.18	0.94
TC (mg/dl)	Ex	195.8	5.23	168.1[a]	4.71	171.58 [a b]	5.39	1
	Con	196.3	6.34	193	6.41	194.8	7.38	0.88
LDL (mg/dl)	Ex	124	5.71	98.57[a]	3.5	100 [a b]	4.25	0.93
	Con	124.7	6.01	123.4	5.55	125.03	6.1	0.91
HDL (mg/dl)	Ex	39	2.21	48.5[a]	2.1	47.29 [a b]	3.51	0.85
	Con	39	2.54	40.2	3.59	40.55	3.92	0.77
TG (mg/dl)	Ex	83.5	3.33	72[a]	4.2	77.33 [a b]	5.07	1

Data presented are the mean and standard deviation (SD). a: significantly different from baseline, b: significantly different from 12-weeks. (BMI: Body Mass Index, SDS: Standard Deviation Score,TC: Total Cholesterol, LDL:Low-Density Lipoprotein, HDL: High-Density Lipoprotein, TG: Triglycerides, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, RHR: Resting Heart Rate, 6MWT: 6-Minute Walk Test,Vo2 peak: Peak oxygen uptake, LH:Luteinising Hormone, FSH: Follicle-Stimulating Hormone)

	Con	84	4.58	84.6	5.78	85.11	6.23	1
SBP (mmHg)	Ex	114.5	7.28	102.19[a]	5.9	107 [b]	9.14	1
	Con	114.8	10.59	112.5	10.28	116.2	10.73	0.58
DBP (mmHg)	Ex	71.7	0.93	69.5	0.91	70.66	1.01	0.64
	Con	75.9	1.27	74	1.9	75	1.25	0.68
RHR	Ex	84.35	8.79	82.28	8.49	83.27	7.93	0.94
	Con	85.96	7.22	84.39	7.57	84.2	6.71	0.92
6MWT (m)	Ex	570	43	696[a]	49	605[b]	48.58	1
	Con	581	45	599	48.1	575	47.99	0.84
Vo2peak (ml/kg/min)	Ex	37.7	4.36	40.21[a]	5.11	38.68[b]	6.27	1
	Con	37	5.99	38.06	6.01	38.05	6.81	0.93
Bone age (year)	Ex	10.49	2.11	10.31	2.07	10.56	2.3	—
	Con	10.31	2.05	10.28	2.01	10.28	1.79	—
Uterine lengths (cm)	Ex	4.15	1.7	3.07 [a]	0.66	2.96 [a]	0.5	1
	Con	4.27	1.9	3.64	0.73	3.12 [a]	0.69	1
Ovarian volumes (ml)	Ex	2.47	0.98	2.03 [a]	1.21	2 [a]	0.83	1
	Con	2.58	1.17	2.36	1.19	2.29	1.06	1
LH (IU/L)	Ex	1.34	0.32	0.76 [a]	0.15	0.68 [a]	0.19	0.98
	Con	1.59	0.76	1.02 [a]	0.39	1 [a]	0.24	0.94
FSH (IU/L)	Ex	3.78	1.11	2.85 [a]	1	2.73 [a]	0.99	1
	Con	3.94	1.38	3.61	1.2	3.44	1.1	0.89
LH/FSH	Ex	0.68	0.2	0.49 [a]	0.2	0.38 [a]	0.15	1
	Con	0.75	0.3	0.61	0.2	0.55	0.1	0.88

Data presented are the mean and standard deviation (SD). a: significantly different from baseline, b: significantly different from 12-weeks. (BMI: Body Mass Index, SDS: Standard Deviation Score,TC: Total Cholesterol, LDL:Low-Density Lipoprotein, HDL: High-Density Lipoprotein, TG: Triglycerides, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, RHR: Resting Heart Rate, 6MWT: 6-Minute Walk Test,Vo2 peak: Peak oxygen uptake, LH:Luteinising Hormone, FSH: Follicle-Stimulating Hormone)

Discussion

The present study showed that combined exercise for 12 weeks increased adiponectin in overweight and obese girls with CPP. As previously mentioned, adiponectin is directly related to weight [15]. In the present study, the weight of girls in the exercise group decreased by 5.57%, which could be a possible mechanism for increasing adiponectin. Also, the findings of previous studies confirm the fact that if BMI SDS is reduced by 0.5, it with improvements in important measures of body composition and significant reductions in TG and LDL [42]. On the other hand it has been proven that circulating adiponectin levels were inversely correlated with TG and LDL cholesterol [43]. In this study, BMI SDS reduced by 0.53 unit in the exercise group after 12 weeks of combined exercise; this can lead to a decrease in TG and LDL and thus an increase in adiponectin. Aside from these, Miyatake et al. (2014) showed that peak oxygen uptake was associated with circulating adiponectin levels [44] and we know certainly that after regular exercise, VO2peak increases. So another factor that can increase adiponectin after exercise is increased VO2peak.

Besides, this study showed that after 4 weeks of detraining, the positive effects of exercise remain. There may be several reasons for this: 1. After 4 weeks of cessation of exercise, the weight and BMI increased, but it is still less than the initial amount before exercise, and since adiponectin is directly related to weight and BMI [15], so this could be a possible mechanism for adiponectin levels to remain high; 2. An interesting finding of Jeonetetal. (2013) was that adiponectin was extremely increase subsequent 6 weeks of detraining not subsequent the 12 weeks of exercise training [45]. In fact, there is a potential effect even after 6 weeks of training; 3. In our study, 4 weeks of detraining is did not thoroughly eliminate the effects of regular combined exercise. As Agarwal et al. (2012) pointed out that 2 weeks of detraining cannot completely eliminate the beneficial effects of regular exercise and further stop of exercise may result to complete reversal of the beneficial effects [40].

Another finding of the present study was a decrease in resistin levels after 12 weeks of combined exercise in girls with precocious puberty. In line with our findings, Marcelinoet et al. (2017) confirmed the inverse association between resistin and physical activity in the general adult population and stated that resistin is lower people who do more than 20 minutes a day of physical activity than people with sedentary lifestyles [23].

Furthermore, the results of the current study showed that 4 weeks of detraining increases resistin levels, but resistin levels are still significantly lower than basic levels before exercise. This finding demonstrates that12 weeks of combined exercise was so effective that the positive effects remained after 4 weeks of detraining. Research in this area is limited, however.

We knew that endurance exercise affects the secretion of pro-inflammatory cytokines [46]. Therefore, we hypothesized that combined exercise would also reduce TNF-α. But our study yielded a different result: after 12 weeks of combined exercise and 4 weeks of detraining, TNF-α levels did not change significantly in obese girls with precocious puberty. However, the results on the effects of exercise on TNF-α are very different. In line with our results, Conraads reported that a combination of endurance and resistance

exercises did not affect the plasma levels of TNF-α [47]. But Park (2015) examined the effect of combined exercise on postmenopausal women with abdominal obesity and concluded that after 12 weeks of combined exercise, visceral fat and TNF-α were reduced [25]. The difference in results may be due to differences in the age and physical condition of the participants. Collectively, more research is needed to resolve the ambiguities.

In the present study, the signs of puberty (bone age, uterine lengths, ovarian volumes, LH, FSH and LH/FSH ratio) decreased in both exercise and control group after 16 weeks of the beginning of the study but there are two important points:1- The rate of reduction of the mentioned factors in the exercise group has been more and faster. 2- The levels FSH, LH/FSH ratio and ovarian volume in the control group did not change significantly even after 16 weeks. These show that when exercise is combined with medication, it has a better effect on preventing precocious puberty in overweight and obese girls. In this way Pellerinet al. (1987) suggested that the onset of puberty in rats is dependent on a critical weight and that exercise and stress can delay the onset of puberty [48].

Conclusion

Finally, it can be concluded, based on the findings, that the regular combined exercise that lasts for 12 weeks is likely to increase adiponectin and decrease resistin in overweight and obese girls with precocious puberty, and combined exercise can play a role in preventing puberty. Furthermore, since the positive effects of exercise reduce during the detraining period, we recommend that these children exercise regularly.

List Of Abbreviations

GnRH: Gonadotropin-releasing hormone

LH: Luteinising hormone

FSH: Follicle-stimulating hormone

GnRHa: Gonadotropin-releasing hormone analogues

CPP: Central precocious puberty

BMI: Body mass index

TNF-α: Tumor necrosis factor-alpha

NF-Kb: Nuclear factor-kappa beta

CDC: Centers for disease control reference

SBP: Systolic blood pressure

DBP: Diastolic blood pressure

Vo_2peak: Peak oxygen uptake

6MWT: 6-minute walk test

TC: Total cholesterol

TG: Triglycerides

HDL: High-density lipoprotein

LDL: Low-density lipoprotein

SDS: Standard deviation score

Declarations

Ethics approval

The research was approved by the Medical Ethics Committee of Hamedan University of Medical Sciences on 14th of Nov, 2015 with proprietary ID IR.UMSHA.REC.1394.366.

Consent for publication

Not applicable

Availability of data and material

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

E.SH conduct research,monitoring the implementation of the exercise protocol, acquiring data, analyzing data, writing the manuscript; A.H idea, designing research studies, supervision, guidance,writing the manuscript; Z.R diagnosis and introduction of children with precocious puberty.

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Consent to participate

Informed consent was obtained from all individual participants included in the study.

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Figures

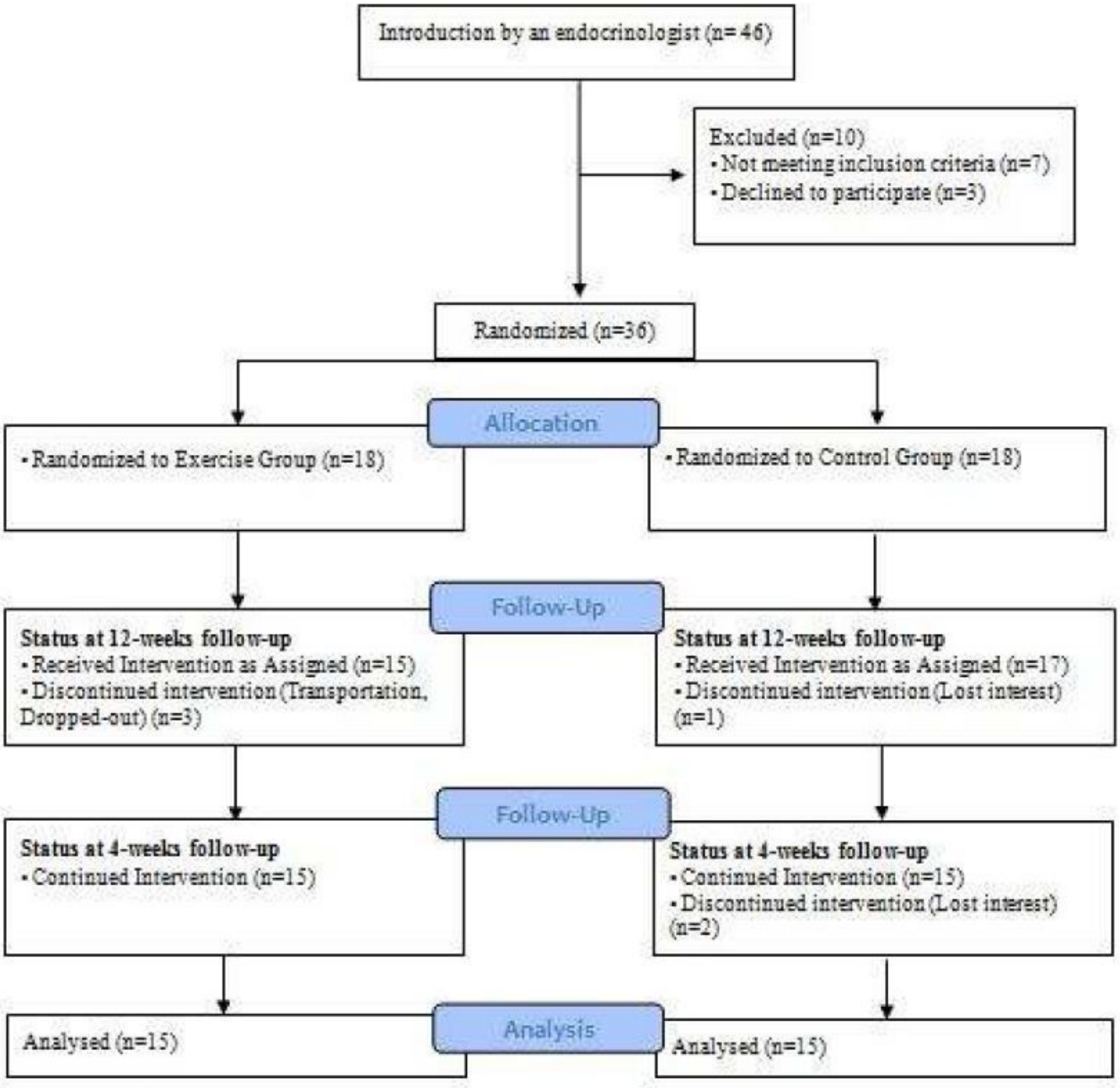

Figure 1

Flow diagram of the study

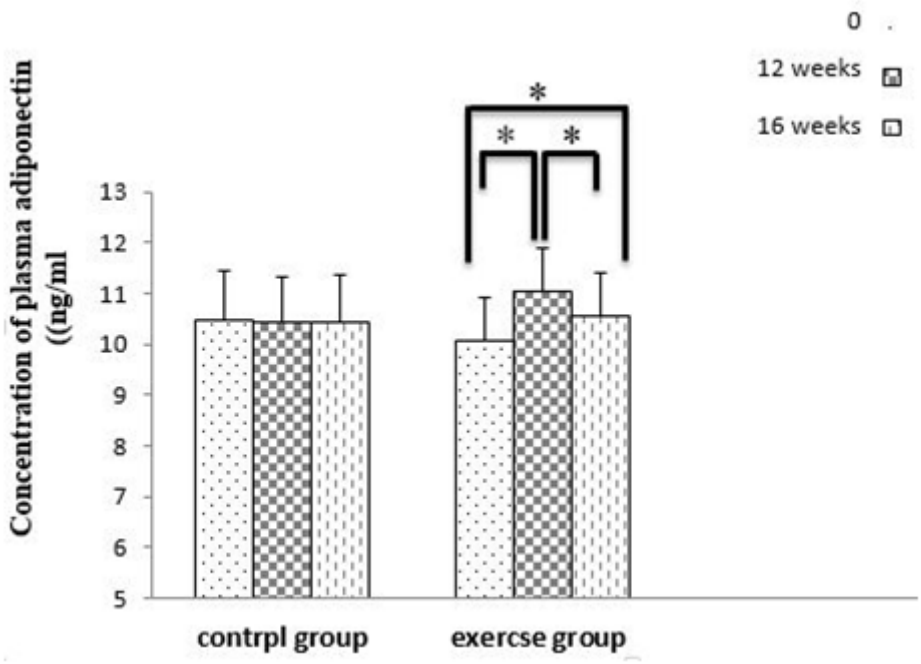

Figure 2

Comparison of serum levels of adiponectin in the two groups (control, exercise) and 3 times (0, 12 weeks, 16 weeks) (Data are reported as Mean ± SEM)*p<0/05

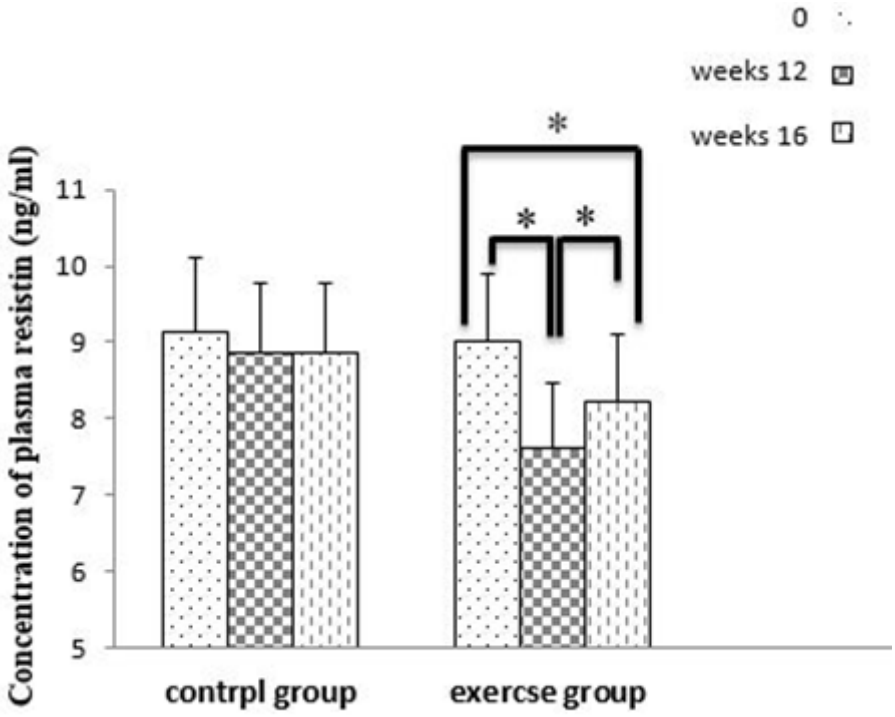

Figure 3

Comparison of serum levels of resistin in the two groups (control, exercise) and 3 times (0, 12 weeks, 16 weeks) (Data are reported as Mean ± SEM)*p<0/05

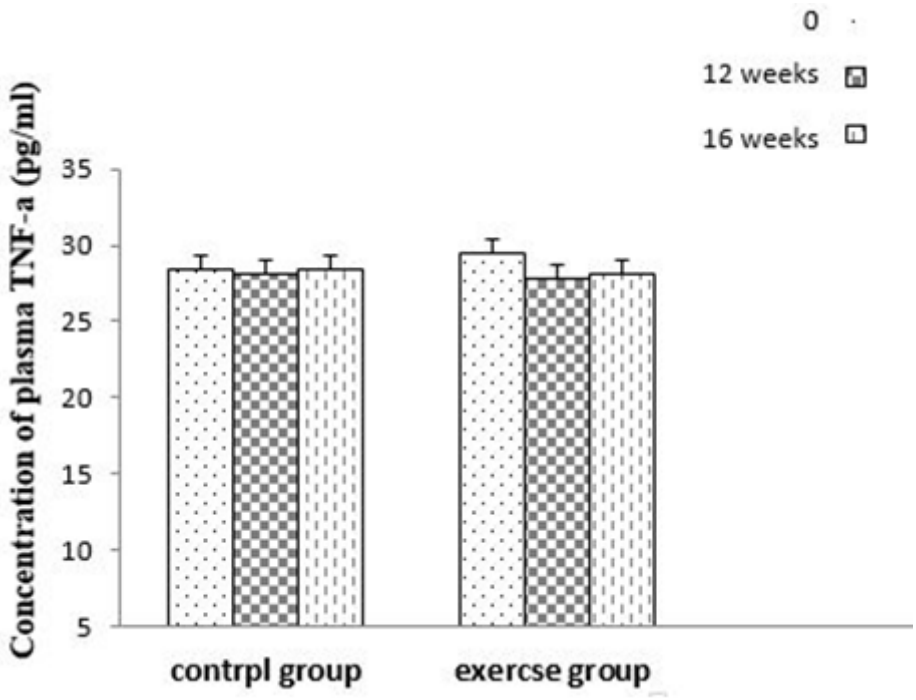

Figure 4

Comparison of serum levels of TNF-α in the two groups (control, exercise) and 3 times (0, 12 weeks, 16 weeks) (Data are reported as Mean ± SEM)