

# Blood Levels of Resistin, Glycemic Indices and Lipid Profile in Women with Type 2 Diabetes

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## Abstract

We aimed to compare the changes in PRL with glycemic indices and lipid profile and also to investigate the relationship of insulin resistance (IR) with PRL in obese postmenopausal women with diabetes mellitus type 2 (DMT2) following 12-week aerobic, resistance and combined exercises, while our inclusion and exclusion criteria and also design exercise protocol differ from other studies in this field. In a quasi-experimental study for 12 weeks, 40 women with DMT2 were randomly selected by availability and purposive sampling and divided into four equal groups of aerobic training, resistance, combined and control group. Aerobic group accomplished aerobic exercise (AEX), 3x/week, for 20-50 minutes at 50-70% of maximum heart rate. Resistance group received resistance exercise (REX), 3x/week in three sets of 10 repetitions with 40-60% of one repetition maximum. The program in combined group consisted of a combination of AEX and REX with the same intensity and duration (included 2 sessions of AEX and 1 session of REX per week. But fortnightly, the numbers of these sessions were changed with each other). The control group was without exercise program. Blood samples for determination of PRL, lipid profile and glycemic indices in pre-and post-tests were collected. HOMA-IR equation was used to calculate insulin resistance. Statistical analysis was performed using SPSS software version 21. According to our finding; the effect of AEX and combined exercises was more than control group on the increasing PRL. The result of AEX in weight loss was more than REX however, the outcome of REX in insulin and IR reducing; also TC declining was more than the AEX. While the effect of combined group in decreasing body fat percent was more than AEX group, but the consequence of AEX was more than the combined group for reducing waist-to-hip ratio (WHR). The effect of the combined group in reducing low density lipoprotein (LDL) was more than the REX group. Also, weight, fasting blood glucose, insulin, triglycerides, LDL, glycosylated hemoglobin A1c and WHR were the predictors of IR. It seems that, during the study period, all three types of exercises through different mechanisms had valuable effects on glycemic indices and lipid profile in DMT2 patients. Also due to the increase in PRL and non-significant correlation with IR; it is doubtful that resistin be as a factor in the incidence of DMT2.

**Keywords:** Exercise; Resistin; Lipid profile; Glycemic indices; Women; Diabetes mellitus type 2

## Introduction

Currently, one of health problem is diabetes mellitus type 2 (DMT2) that characterized by hyperglycemia. It can be a result from impaired insulin secretion, insulin resistance or combination of them [1]. Waistline adipose tissue (central obesity) is one of risk factors for DMT2, especially in postmenopausal women [2,3]. Since adipose tissue secretes adipocytokines which affect metabolic status [4,5], there are several discussion about relationship between central obesity and DMT2 as metabolic disorders of carbohydrate metabolism [4,6-9].

Resistin is one of adipocytokines with a molecular weight of 12.5 KD [10]. In addition to adipose tissue, high levels of resistin exist in monocytes, macrophages, and spleen and bone marrow cells [11]. Several studies have been shown that, resistin plays a role in the development of insulin resistance (IR) [10,12,13]. Zhou et al. showed; resistin impairs glucose tolerance by lowering mRNA levels of IRS-2 (insulin receptor substrate 2) and stimulating SOCS-3 (inhibitor of cytokine signaling 3) expression [14]. On the other hand, Utzschneider et al. studied on the relationship between resistin and insulin sensitivity, body fat distribution and the metabolic syndrome in humans. They reported that association of resistin with body fat is inadequate, and its intermediary role is questionable for IR or metabolic disorder in individuals [15]. While resistin was first described as a factor contributing to the development of IR and DMT2 [13], argument continues about its exact role in obesity, insulin sensitivity and the development of DMT2 [16].

Exercise is a non-pharmacologic treatment for DMT2 [17]. Studies have shown that aerobic and resistance exercises can induce metabolic adaptations that improve insulin sensitivity [18-20]. Consequently it seems that, the combined exercises (combination of endurance and resistance training) can have multiple effects of both types of exercises [21]. However, there are controversial studies about the effect of different types of exercises on plasma resistin level (PRL), IR factors and their relationship. According to study from Giannopoulou et al. no change were observed in PRL and reduction in IR after 14 weeks of aerobic exercises (AEX) [22]. In contrast, Jones et al. showed a significant reduction in PRL but without significant change in IR in obese children, followed by 8 months of AEX [23]. Also in another study, PRL reduction was observed after 16 weeks of resistance training (REX) [24]. Unlike this study, one research revealed; no change was observed in PRL and IR after 12 weeks of REX [25].

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Excess body fat due to sedentary lifestyles more commonly seen in postmenopausal women, this issue led to an increase in the incidence of diabetes in these women [26]. Since regular exercise is recognized to decrease risk for metabolic disorder via several mechanisms [27] this question arises that; whether implementation of exercise as a therapeutic strategy, can lead to changes in IR by changing the PRL among patients with DMT2?

Therefore, this study aimed to compare changes in PRL, lipid profile and glycemic indices in obese postmenopausal women with DMT2 followed by 12 weeks of aerobic, resistance and combined exercises. Also we intended to provide regression models for insulin resistance in both pre-and post-test conditions.

## Materials and Methods

### Study design and sampling method

This quasi-experimental study with pre- and post-test design was achieved by purposive sampling method based on availability among the study population.

### Study population and setting

The study population included 40 obese postmenopausal women with DMT2 who referred to the endocrinology and metabolism clinic of Imam Khomeini Hospital, Urmia city- the capital of West Azarbaijan province, located in north-western of Iran. Participants were randomly divided into four equal groups of aerobic training, resistance, combined and control group. Inclusion criteria included; having fasting blood glucose (FBG) more than 126 mg/dl - according to World Health Organization (WHO) criteria- [28] for at least six months, lack of a history of physical activity, weight fluctuations amounting to 10% of own weight. It should be noted that, all subjects were taking metformin (500 mg), 2 glibenclamide (5 mg) and 1 atorvastatin (20 mg) daily three times a day during the last 6 months and during the study. Exclusion criteria included insulin therapy, acute or chronic disease (high blood pressure, nephropathy, retinopathy, cardio-vascular, kidney, liver, thyroid and orthopedic disease) and any intervention that affecting the experimental results.

### Experimental procedures

For all participants were explained that our aim is not weight loss due to a regimen. So they should not alter their diet as directed by their physician. It was emphasized that we attempt about the effects of exercises. The study continued with the following phases:

**Screening sessions:** At the start, informed consent was obtained. Then all subjects complete Physical Activity Readiness Questionnaire (PAR-Q) which is a safe preliminary screening of candidates for exercise testing and prescription [29]. Afterward, blood glucose, blood pressure, resting heart rate and medical history were assessed and recorded. For each participant, the systolic and diastolic blood pressure was taken using OMRON M3 Intellisense upper arm blood pressure monitor (HEM-70 51-E) made in China, after at least 10-15 minutes of rest. If the pre-exercise blood pressure was less than 140/90 mm hg, subject could participate in training exercise. If the pre-exercise blood pressure was greater than or equal to 140/90 mm hg, she was asked for 10 minute break and re-evaluate their blood pressure. With an uncontrolled hypertension, intervention had not been done on that day. If the subjects had low blood glucose levels (less than 100 mg/dl), they had to consume the syrup contains about 15 grams of carbohydrates. If they had high blood glucose levels (greater than 300 mg/dl), they had to control their blood glucose level by exercise

within 20 to 30 minutes. Pointed out that, all variables relevant to the parameters were measured 2 days before, and 2 days after the study.

**Measurement of anthropometric indices:** Initially the anthropometric indices included weight, height, and body fat percent (BF %), body mass index (BMI), waist-hip ratio (WHR) was measured with minimal clothing and no shoes. Body weight and stand height was measured using weight machine Seca type, made in Germany (Seca 714, seca Vogel and Halk GmbH) with precision  $\pm 0/1$  kg and height machine Seca type, made in Germany (Seca 714, seca Vogel and Halk GmbH) with precision  $\pm 0/1$  centimeters, respectively. BMI was calculated by dividing body weight (kg) by height square (square meters). Moreover, calipers RH.15.9LB model made in Germany [30] was used for measuring the thickness of skinfold with its underlying fat layer by three-point method (assessing skinfolds in triceps, abdomen and suprailiac). Then the sum of skinfolds was implanted in the general equation of Jackson and Pollock for determining BF% in study population [31]. Participants' WHR was also calculated by taking the waist circumference (cm) dividing by the hip circumference (cm).

**Measurement of blood indices:** Fasting blood samples were collected in two stages; pre-test and post-test (two days before and two days after completion of 12 weeks of exercise). The sample consisted of 7 ml of antecubital venous blood that was taken between the hours of 7 to 10 am following an overnight fast. The subjects were asked to avoid performing any hard exercise during the 48 hours before both stages of blood sampling. Blood samples were maintained to measure resistin after centrifugation and separation of serum at a temperature of  $-80^{\circ}\text{C}$  to analyze with post-test blood samples. Serum resistin level was measured with sandwich immunoassay enzyme method, using an ELISA kit Mediagnost, E 50, made in Germany with a sensitivity 0.012 ng/ml and the inter rater coefficient variation 6.8% and 5% respectively. Values of FBG, low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride (TG) and total cholesterol (TC) was performed by enzymatic method on a Roche Cobas Integra 400 analyzer. Glycosylated hemoglobin A1c (HbA1c) was measured by electrochemiluminescence method using Elecsys 2010 equipment (Roche Kit). Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated to assess the insulin resistance according to the formula given below [32].

$$\text{HOMA-IR} = \text{fasting glucose (mmol/l)} \times \text{fasting insulin } (\mu\text{U/ml}) / 22.5$$

**Exercise intervention:** Participants in the AEX group performed impulse PT300 treadmill walking/running exercise; 3x/week for 12 weeks. Their program included 10 minutes warm-up, exercises with intensity of 40-50% of HR max for 20 minutes and then cool down periods. Exercises intensity gradually increased with the progress of the training program to 70-80% of HR max for 45-50 min. In order to determine percentage of target heart rate for each [33] session; HR max of every subject was calculated using the formula; "HR max=220-age", then following equation was calculated [34];

$$\text{Target heart rate} = (50-70)\% (\text{HR max}-\text{resting heart rate}) + \text{resting heart rate}$$

Exercises intensity was controlled using stethoscope Polar (Polar, S810, Kempele, Finland) to ensure compliance activity. To learn the correct exercises; program for resistance exercise participants was begun one day earlier. In their first training session; for each of the exercises one repetition maximum (RM 1) was estimated according to the following formula [35];

$$\text{Weight} \times \{1 + (30/\text{number of reps})\} = \text{RM 1}$$

Participants in REX group performed 9 power moves as 3 sets with 10 repetitions, rest periods between sets was considered 60-90 seconds. Each resistance session was 1 hour consists of 10 minutes of warming up, 40-45 minutes of main training and 5 minutes of cooling-down. Every two weeks work load (RM 1) was recalculated to observe the principle of over load and increase the intensity, thus the first four weeks, with 40-45% of RM 1, the second four weeks with 50-55% of RM 1 and the last four weeks, with 60-65% of one RM 1 [36]. Resistance training included 4-motion for upper body muscles: bench press, shoulder press, standing cable curl with rope and rope press down and 3 motion for lower body muscles: leg press, leg extension and leg flexion and the two movements for anterior muscles, abdominal and back extension.

Combined training program included all programs of AEX and REX with the same intensity, duration and time. Their program composed two sessions of AEX and one REX session during the first two weeks and within the second two weeks; two sessions of REX training and one AEX training session. The program was repeated intermittently for 12 weeks.

All exercise sessions were performed under the supervision of a physical therapist.

During the study period, the control group was advised to continue their normal daily routines and activities.

**Ethical considerations:** Our research approved by the ethics committee of Urmia University of Medical Sciences. All of the participants were briefed on the study objectives and related sports activities. Subjects were informed that their participation was voluntary. Consent was obtained from all subjects and emphasized that they could refuse participation or leave the study at any, and thus would not adversely affect treatment or care provided by their endocrinology clinic.

**Statistical analyses:** All the descriptive data were expressed in terms of mean  $\pm$  standard error of the mean (SEM). Kolmogorov-Smirnov test (KS test) and Levene's test were used for the detection of normal distribution of data and homogeneity of variance, respectively. One-way ANOVA test was used to examine group differences in the various parameters in the base line and two-way ANOVA and Tukey test was used to compare parameter changes between intervention groups. To determine the independent predictor variables of insulin resistance linear regression method was used. All data was analyzed using an SPSS version 21 with statistical significance set at an alpha level of  $\leq 0.05$ .

## Results

Seven women were excluded from the study subjects ; one subject from the aerobic group because of an illness unrelated to this study, four subjects from resistance and combined groups due to non-participation in training program, also two subjects from the control group because they did not participate for the blood sampling test in post-test phase. Finally the results analysis was performed with 33 subjects. The mean age of participants and their BMI were  $58.30 \pm 5.28$  and  $32.10 \pm 3.31$ , respectively. The subjects' characteristics did not significantly differ between the groups at the baseline according to one way Anova test ( $P > 0.05$ ) (Table 1). Table 2 illustrated results of Tukey test to determine differences between groups in mean changes of anthropometric and biochemical variables of four groups, before and after the intervention.

The results of two-way Anova test followed by Tukey test shown that; Among the anthropometric variables; While the mean changes of weight had significant difference between AEX and REX groups ( $p=0.04$ ), the effect of AEX group ( $-2.14 \pm 0.32$ ) in weight loss was more than REX group ( $-2.08 \pm 0.99$ ). The mean changes of BF% had significant difference between the aerobic -control groups ( $p=0.01$ ), AEX - REX ( $p < 0.001$ ) and AEX - combined groups ( $p < 0.001$ ). The effect of combined group in decreasing BF% ( $-2.5 \pm 0.42$ ) was more than AEX group ( $-2.07 \pm 0.56$ ) and the effect of AEX group was more than control group ( $0.95 \pm 0.52$ ) and REX group ( $-0.35 \pm 0.93$ ). Whereas the mean changes of WHR had significant difference between AEX - combined groups ( $p=0.01$ ), the effect of AEX group ( $-0.06 \pm 0.008$ ) was more than the combined group ( $0.01 \pm 0.03$ ) (Table 2).

Also, among the glycemic indices; the mean difference of insulin changes was significant between AEX and REX groups ( $p=0.01$ ). The effect of REX for insulin reduction ( $-0.70 \pm 0.88$ ) was more than AEX group ( $-0.04 \pm 0.81$ ). The mean difference of IR changes was significant between AEX and REX groups ( $p < 0.001$ ) and REX - combined groups ( $p=0.02$ ). The effect of the REX group ( $-4.07 \pm 1.23$ ) in IR reduction was more than the AEX group ( $-1.94 \pm 1.16$ ) and the combined group ( $-1.88 \pm 0.79$ ) (Table 2).

Among the lipid profile parameters; while the mean difference of LDL changes was significant between REX - combined groups ( $p=0.04$ ), the effect of the combined group ( $-13.28 \pm 2.48$ ) in reducing LDL was more than the REX group ( $-11.84 \pm 6.76$ ). The mean difference of TC changes was significant between AEX - REX groups ( $p=0.04$ ) and REX -combined groups ( $p = 0.04$ ) whereas the effect of the REX group ( $-42.55 \pm 10.73$ ) was more than AEX ( $-34.44 \pm 5.26$ ) and combined groups ( $-36.00 \pm 3.54$ ) in TC reduction (Table 2).

Moreover, about the mean changes of PRL; a significant difference between AEX -control groups ( $p=0.03$ ) and control-combined groups ( $p=0.03$ ) was observed. The effect of AEX group ( $9.35 \pm 0.93$ ) and combined group ( $3.50 \pm 1.43$ ) was more than control group ( $0.23 \pm 0.20$ ) for increasing PRL (Table 2).

The value of R square in multiple regressions; for insulin resistance as dependent variable in both pre-and post-test was 0.983 and 0.985 respectively. The regression model in both pre-and posttest is as follows:

**Pre-test:** IR = - 9.20+0.04 Weight+0.05 FBG+1.05 Insulin+0.009 TG+0.01 LDL

**Post-test:** IR = - 3.30+0.02 Weight+2.14 WHR+0.31 HbA1c+0.07 FBG+0.93 Insulin

So that; with 1- unit increase in the amount of body weight, FBG, insulin, TG and LDL in the pretest phase , if all other variables remain constant, a change order of 0.04, 0.05, 1.05, 0.009, 0.01 units was predict in IR. In post-test phase also one unit change of body weight, WHR HbA1c, FBG and insulin , if all other variables remain constant, predicts a change order of, 0.02, 2.14, 0.31, 0.07, 0.93 units in IR.

## Discussion

Physical activity improves homeostasis, energy balance and various types of regulatory responses [37]. Indeed, physiological adaptations such as hormonal and metabolic responses are under the influence of different types of exercises. These efficacies are different based on the exercise type [38]. So, we aimed to compare changes in PRL, lipid profile and glycemic indices in obese postmenopausal women with DMT2 following the implementation of 12 weeks of AEX, REX and combination exercises and also to provide regression models for IR in

Variable	Group	Aerobic (n:9)	Resistance (n:8)	Combined (n:8)	Control (n:8)	*p-value
Age (year)	pre	58.33 ± 1.88	57.12 ± 1.79	56.50 ± 1.87	61.25 ± 1.77	0.29
	post	-	-	-	-	-
Height (cm)	pre	154.61 ± 1.57	158.93 ± 1.74	158.62 ± 0.65	156.56 ± 2.69	0.30
	post	-	-	-	-	-
Time of diabetes diagnosis (year)	pre	4.88 ± 1.07	10.12 ± 1.27	8.00 ± 1.46	7.25 ± 1.34	0.06
	post	-	-	-	-	-
Weight (kg)	pre	75.66 ± 3.67	83.56 ± 3.06	79.68 ± 2.17	77.62 ± 3.00	0.321
	post	73.52 ± 3.48	81.58 ± 2.40	76.27 ± 2.27	77.95 ± 3.11	-
BMI (kg/m <sup>2</sup> )	pre	31.73 ± 1.60	33.25 ± 1.19	31.77 ± 0.89	31.71 ± 0.69	0.75
	post	30.84 ± 1.53	32.55 ± 0.98	30.40 ± 0.89	31.84 ± 0.74	-
BF (%)	pre	36.33 ± 1.79	43.08 ± 1.14	43.81 ± 0.93	39.48 ± 1.86	0.55
	post	34.25 ± 1.78	42.95 ± 1.19	41.26 ± 1.09	40.43 ± 1.42	-
WHR	pre	0.89 ± 0.02	0.87 ± 0.01	0.92 ± 0.02	0.87 ± 0.02	0.44
	post	0.82 ± 0.02	0.88 ± 0.01	0.94 ± 0.02	0.88 ± 0.01	-
HbA1c (%)	pre	7.94 ± 0.40	8.80 ± 0.63	8.07 ± 0.50	7.63 ± 0.26	0.36
	Post	7.03 ± 0.43	7.73 ± 0.48	6.70 ± 0.29	7.57 ± 0.31	-
FBG (mg/dl)	pre	144.88 ± 13.19	178.75 ± 19.13	155.87 ± 11.12	136.12 ± 9.63	0.17
	post	105.55 ± 7.73	124.12 ± 14.86	117.25 ± 6.01	146.12 ± 4.32	-
Insulin (µIU/ml)	pre	6.09 ± 0.80	9.09 ± 0.70	7.04 ± 1.18	7.86 ± 0.67	0.10
	Post	6.04 ± 0.64	8.09 ± 0.64	6.82 ± 0.95	6.88 ± 0.67	-
IR (HOMA-IR)	pre	7.00 ± 1.12	12.65 ± 1.33	8.44 ± 1.21	8.48 ± 0.95	0.12
	post	5.06 ± 0.64	8.02 ± 1.23	6.28 ± 0.77	8.00 ± 0.73	-
TG (mg/dl)	pre	166.88 ± 22.76	212.75 ± 30.66	138.12 ± 24.87	166.50 ± 24.77	0.26
	post	111.11 ± 10.87	146.00 ± 24.58	102.00 ± 16.93	168.00 ± 24.69	-
HDL (mg/dl)	pre	52.66 ± 2.81	52.87 ± 5.19	52.47 ± 2.11	50.41 ± 3.24	0.95
	post	60.43 ± 2.12	53.91 ± 3.92	59.95 ± 1.21	49.60 ± 2.61	-
LDL (mg/dl)	pre	110.78 ± 4.51	126.87 ± 12.00	101.58 ± 12.57	111.25 ± 9.79	0.37
	post	91.24 ± 3.92	114.46 ± 10.36	87.55 ± 11.22	117.71 ± 9.63	-
TC (mg/dl)	pre	180.77 ± 3.19	214.62 ± 14.17	180.75 ± 16.99	190.00 ± 12.05	0.19
	post	146.33 ± 3.05	171.12 ± 7.89	144.62 ± 13.91	189.50 ± 9.61	-
Resistin (ng/ml)	pre	11.88 ± 1.30	12.94 ± 1.04	15.06 ± 0.93	13.22 ± 0.54	0.19
	post	21.24 ± 1.64	18.70 ± 1.43	18.13 ± 0.99	13.45 ± 0.66	-

Data are shown as mean ± standard error of the mean (Mean ± SEM). Difference were not seen between groups at baseline levels of all variables (one way Anova test, significant level (p ≥ 0/05\*))

Table 1: Anthropometric and biochemical characteristics of subjects at different stages (pre-test and post-test).

Groups	Control			aerobic		Resistance
	aerobic	Resistance	Combined	Resistance	combined	Combined
Weight (kg)	0.70	0.40	1.00	0.04*	0.66	0.43
BMI (kg/m <sup>2</sup> )	0.97	0.77	0.93	0.49	0.99	0.41
BF (%)	0.01*	0.18	0.32	□0.001*	□0.001*	0.98
WHR	0.85	1.00	0.10	0.84	0.01*	0.10
HbA1c (%)	0.99	0.42	0.96	0.27	0.99	0.19
FBG (mg/dl)	0.51	0.81	0.98	0.11	0.75	0.59
Insulin (µIU/ml)	0.35	0.44	0.94	0.01*	0.69	0.18
IR (HOMA-IR)	0.14	0.19	0.83	□0.001*	0.56	0.02*
TG (mg/dl)	0.59	0.95	0.19	0.29	0.83	0.06
HDL (mg/dl)	0.15	0.70	0.20	0.73	1.00	0.80
LDL (mg/dl)	0.48	0.91	0.17	0.16	0.90	0.04*
TC (mg/dl)	0.08	0.99	0.07	0.04*	1.00	0.04*
Resistin (ng/ml)	0.03*	0.16	0.03*	0.91	1.00	0.91

\*The mean difference is significant at p=0.05.

Table 2: Results of Tukey test to determine differences between groups in mean changes of anthropometric and biochemical variables.

two phases of our research; pre-test and post-test. It should be noted that, our inclusion and exclusion criteria and also design exercise protocol differ from other studies in this field (Table 3).

Comparing mean changes of anthropometric indices; determined

that the result of AEX in weight loss was more than REX. While the effect of combined group in decreasing BF% was more than AEX group, but the consequence of AEX was more than the combined group for reducing WHR. Hereon, the more effect of combined exercise beside AEX as compared to REX may be display the compensatory mechanism



Studies	Duration, Intensity	Type of exercise	Sample Size	Type of Subjects	Sex	Age (years)	Diet intervention	Results
Giannopoulou et al. [22]	14 weeks(3 to 4x/week for 60 min at 65%-70% VO <sub>2</sub> peak)	aerobic	33 subjects	Human	Female	50-70	yes	No significant change of resistin
Jones et al. [23]	32 weeks(3 days/week, for 60 min, 60%-85% VO <sub>2</sub> max)	aerobic	12 subjects	Human	Female/Male	15.3 ± 0.5	No	Resistin decreased
Prestes et al. [24]	16 weeks(two weekly sessions of three sets of 6-14 repetition maximum)	resistance	35 subjects	Human	Female	mean age 63.18	No	Resistin decreased
Jorg et al. [25]	12 weeks(3 days/week 60 minutes)	Aerobic(cycling) Resistance Combined(Aerobic-Resistance)	48 subjects	Human	Female/Male	53.9 ± 9.9	No	No significant change of resistin

**Table 3:** Comparison of this study with some other published papers in this field.

of AEX in combined training. Nevertheless; the beneficial effects of all types of training on anthropometric indices were mentioned in studies [39,40]. Our results related to weight loss and BF% were in opposition to the results from Yavari et al. [41] but consistent with the results from Sigal et al. [38] About comparing the WHR changes between groups, the results of this study was different from Jorg et al. study [25] and consistent with the results from Sigal et al. that shown the high impact of AEX for WHR reduction [38].

The consequence of the REX in insulin and IR reduction was more than the AEX group. This finding is inconsistent with Jorg et al. who reported no significant differences was observed about these two variables [25], while is consistent with the study from Al-Kader et al. [42] The greater impact REX on changes in insulin and IR can be justified by the effect of this exercise on muscle mass. The insulin sensitivity is present in skeletal muscle; therefore, increasing muscle mass by REX can be effective in glycemic control and reducing IR [17].

In this study, no significant differences were observed in the mean changes of HbA1c and FBG between groups. This result is inconsistent with study results by Reid et al. who reported the superiority of REX to AEX in HbA1c reduction [43] and reported from Sigal et al. who stated the greater effect of AEX on HbA1c decrease [38]. Sigal et al. and Arora et al. reported that, exercise were more effective among patients with higher baseline HbA1c compared with lower HbA1c [38,44]. Moreover, our results about FBG was inconsistent with Shenoy et al. that showed REX are more effective in improving FBG compared to AEX [45].

Among lipid profile index; significant difference were observed in the mean changes of LDL and TC. Our findings revealed that, the effect of the combined group was more than REX for LDL reducing. In addition; the effect of REX was more than AEX and combined groups in TC decreasing. These results were inconsistent with Sigal et al. study [38] and one meta-analysis study [46] that did not find any change for these variables following exercises. While reducing TC in our study was consistent with a study that shown a greater efficacy of REX in terms of improving levels of TC and LDL among Hindi population [44]. The possible mechanisms for interpretation of improving the lipid profile can be the increased Peroxisome Proliferator-activated Receptor gamma (PPAR $\gamma$ ), PPAR $\gamma$  coactivator-1alpha (PGC-1 $\alpha$ ) as a key regulator of energy metabolism and messenger ribonucleic acid (mRNA) expression in adipose and muscle tissue after exercise [47].

The main finding of this study was that; the mean changes of resistin were significant between the control- AEX groups and control-combined groups. So that AEX and combined groups have shown greater effect on the PRL increasing as compared to control group. Even though one study was reported that no significant difference were observed in the mean changes of PRL among the three exercises groups [25]. But consistent with our study, PRL increasing was reported due

to exercise in the studies by Camera et al. [48 ] and Monzillo et al. [49]. On the other hand, PRL reduction were stated in the two survey; one of them evaluated the effects of 12-months physical activity in patients with DMT2 [50] and the other assessed the effects of 16 weeks of resistance training in older postmenopausal women [24]. Notably, increased resistin levels has been reported in study on obese mice [51] and also it should be noted that; resistin levels are described higher in men than in women [52].

This issue is noteworthy that; resistin in addition to adipose tissue is produced in blood mononuclear cells and leukocytes in human body [11,49]. It is likely; these cells play a role for increasing resistin gene expression in response to exercise stimulation. In confirmed of this possibility, some studies have expressed that increased resistin levels due to exercises associated with reducing the anthropometric indices and pro-inflammatory cytokines, including IL-1, IL-6, and TNF- $\alpha$ . While these cytokines stimulate resistin gene expression in blood mononuclear cells [53]. The most important mechanism to explain increased resistin after exercise training is its role in defending the body against oxidation, as resistin acts as an antioxidant in response to inflammatory stimuli [54].

According to regression model in this study; there was no significant correlation in IR with increased resistin. This finding is in consistent with the study by Leehey et al. [26] and inconsistent with Coello et al. study [55]. Although; resistin known as a hormone that potentially links obesity to diabetes [56,57].

### Limitation of the Study

The present study was a quasi-experimental research among DMT2 patients. Control factors such as genetic factors or other factors independent to the obesity and diabetes were out of the researchers' responsibility, while these factors can affect the study results. The low number of subjects in the different study groups can be also considered as a limitation of this study that is effective in our findings.

### Conclusion

All three types of exercises- AEX, REX and combinatorial - through different mechanisms have beneficial effects in patients with DMT2 in terms of weight loss, BF % and FBG; however, combined exercise can apply multiple effects due to compensatory mechanisms of AEX and REX on some parameters. This study did not confirm the idea that adipocytokines secreted by adipose tissue like resistin has effect on insulin resistance since according to the regression results, resistin may not be the link between obesity and IR in DMT2 patients. It also seems that an increasing in PRL cannot induce IR. However, further research is recommended to determine the association between resistin and IR in humans and also the effects of exercise on the levels of this adipokines among patients with DMT2.

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