

**Effect of supervised progressive resistance exercise training protocol on insulin sensitivity, glycemia, lipids and body composition in Asian Indians with type 2 diabetes**

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**Running Title:** Resistance exercise in Asian Indians with T2DM

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## ABSTRACT

*Objective:* To evaluate the effect of supervised progressive resistance exercise training (PRT) protocol on insulin sensitivity, glycemia [blood glucose and glycosylated hemoglobin (HbA1c) levels], lipids and body composition in Asian Indians with type 2 diabetes mellitus (T2DM).

*Research design and methods:* Thirty patients with T2DM underwent 12 w PRT of six muscle groups (2 sets, 10 repetitions). The subjects were evaluated with Short Insulin Tolerance Test (for assessment of insulin sensitivity,  $K_{ITT}$ ), fasting blood glucose, HbA1c, lipids, high-sensitivity C-reactive protein (hsCRP), detailed anthropometry, total body fat, regional fat and lean body mass by Dual energy x-ray absorptiometry, cross-sectional skeletal muscle area of upper arm and thigh by computed tomography scan.

*Results:* Insulin sensitivity improved significantly from  $K_{ITT}$   $1.22 \pm 0.73$  to  $K_{ITT}$   $2.13 \pm 0.75$  ( $p < 0.0001$ ), after the intervention. Significant decline (mean difference  $\pm$  SD) from the baseline was recorded in the levels of following parameters; HbA1c ( $0.54 \pm 0.4\%$ ,  $p < 0.001$ ), fasting blood glucose ( $2.7 \pm 2.2$  mmol/L,  $p < 0.001$ ), total cholesterol ( $0.39 \pm 0.7$  mmol/L,  $p = 0.003$ ), serum triglycerides ( $0.39 \pm 0.5$  mmol/L,  $p < 0.001$ ), truncal and peripheral subcutaneous adipose tissue compartments (SCAT) ( $p < 0.001$ ). However, no significant changes were noticed in body mass index, total body fat, truncal fat, lean body mass and cross-sectional skeletal muscle area of the extremities and hsCRP levels.

*Conclusions:* Moderate-intensity PRT for 3 m resulted in significant improvement in insulin sensitivity, glycemia, lipids and truncal and peripheral SCAT in patients with T2DM. Resistance training should be an integral part of exercise regimen in Asian Indians with T2DM.

Prospective epidemiological studies across several populations have indicated that insulin resistance is the central feature of the metabolic syndrome and the primary defect in development of T2DM. It often antedates diabetes by several years. Additionally, insulin resistance is also reported to be a risk factor for development of cardiovascular disease.

**B**oth aerobic and resistance exercises effectively improve insulin sensitivity and lead to a better glycemic control in patients with T2DM (1). While aerobic exercise has been extensively investigated and shown to be beneficial for glucose-lipid metabolism, resistance exercise has been less researched. Interestingly, resistance training could be more effective than aerobic exercise in improving the glycemic profile (2). Further, a combination of these exercise regimens may even be more beneficial in improving insulin sensitivity and glycemic control (3, 4).

Asian Indians manifest insulin resistance and the metabolic syndrome at a younger age and of a higher magnitude than many other ethnic groups (5, 6). Possible determinants of insulin resistance in Asian Indians are; excess overall adiposity, in particular abdominal adiposity, excess truncal subcutaneous adipose tissue (SCAT) and low skeletal muscle mass (5-7). It has been debated whether resistance exercise will be metabolically more beneficial in Asian Indians (8). However, the effects of resistance exercise on overall adiposity, truncal and peripheral SCAT and intra-abdominal adipose tissue (IAAT) have not been properly evaluated. Further, it is also not clear if increasing the mass and augmenting the function of major skeletal muscle groups in Asian Indians could have better effect on insulin sensitivity as compared to other ethnic groups. It is possible that resistance exercise might target both excess adiposity and low skeletal muscle mass in Asian Indians. Therefore, it appears that resistance exercise could be specifically useful in improving insulin sensitivity and metabolic parameters in Asian Indians with T2DM.

We hypothesized that increasing the mass and enhancing the function of major skeletal muscle groups by use of supervised progressive resistance exercise training (PRT)

protocol for 3 m will improve insulin sensitivity in Asian Indian patients with T2DM. Secondly, we also hypothesized that PRT protocol would improve the levels of fasting blood glucose, glycosylated haemoglobin (HbA1c), lipids, high sensitivity C-reactive proteins (hsCRP), and anthropometric parameters, and specifically decrease truncal SCAT and increase extremity skeletal muscle mass.

## **RESEARCH DESIGN AND METHODS**

**Subject characteristics.** This prospective study was undertaken in the Department of Medicine, All India Institute of Medical Sciences, New Delhi from April 2004 to March 2006. Thirty patients with T2DM were selected from Medicine Out-patient department and Diabetes Clinic. After ethical clearance, a written informed consent was obtained. The following subjects were excluded from the study: patients on insulin or thiazolidinedione therapy, those with coronary artery disease, significant respiratory disease, orthopedics problems which would interfere with resistance exercise training, advanced diabetes-induced end-organ damage and pregnancy. Patients were on stable doses of oral hypoglycemic drugs (sulfonylureas, biguanides and meglitinides) for the previous 3 m. Most of the patients were already following aerobic exercise regimen as prescribed by their physicians, which was further reinforced. Compliance was observed at 85% through a self maintained diary. During the 12 w intervention, patients did not change the dose of oral hypoglycemic medications, dietary pattern and the intensity of baseline activities including aerobic exercises.

**Short insulin tolerance test (SITT).** Short insulin tolerance test was performed in this study which has been validated against hyperinsulinemic euglycemic clamp technique as a simple, valid, reproducible and shorter

method for the measurement of insulin sensitivity (9, 10). A number of investigators have used this method in clinical studies to measure the whole-body insulin sensitivity (11). Venous blood samples were taken at -3 and 0 min after inserting scalp vein set in the antecubital vein. Subsequently rapid acting insulin (Huminsulin R, Eli Lilly), at an intravenous bolus dose of 0.05 U/kg body weight was given at 0 min. Venous blood was collected at 3, 6, 9, 12 and 15 min intervals for blood glucose estimation and the measured values were log transformed. The rate of decline of blood glucose levels was calculated by plotting the disappearance of glucose per unit time (K value). Patients were monitored for signs of hypoglycemia. The initial SITT was done in the beginning before the start of PRT protocol and the final SITT was done 72-96 hours after the last exercise bout, at the end of 12 w.

**Biochemical measurements.** Fasting venous blood samples were drawn for estimation of fasting blood glucose (FBG) and serum lipids [total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), very-low density lipoprotein cholesterol (VLDL-c), high-density lipoprotein cholesterol (HDL-c) and serum triglycerides (TG)]. Assay for hsCRP was carried out using ELISA kit (Biocheck Inc., CA, USA).

**Anthropometric measurements.** BMI was calculated using the formula; weight (kg)/height (m)<sup>2</sup>. Circumferences at waist (WC), hip (HC), mid-arm, mid-thigh and calf were recorded to the nearest 0.1 cm. Biceps, triceps, thigh, calf, sub-scapular, anterior axillary, lateral thoracic and supra-iliac skinfolds were measured using Lange skinfold calipers as described previously (12).

**Dual energy x-ray absorptiometry (DEXA) and Computerized Tomography (CT) scans.** Regional and global measurements of whole body fat and lean body mass were estimated by using whole body DEXA scan (Hologic QDR 4500A with fan beam).

For studying the cross-sectional area of muscle mass, two axial sections using helical CT scan (Somatom Plus 4, Siemens, Erlangen, Germany) were taken, one at the midpoint of right thigh (midpoint of line joining superior rim of femoral head and inferior surface of femoral condyle) and other at the midpoint of right arm (midpoint of line joining superior rim of humeral head and inferior surface of the humerus condyle). The muscle bulk was mapped using a user selectable region of interest, taking care to exclude adipose tissue and all other extraneous soft tissue. The skeletal muscle area (using CT images) was analyzed by a single observer, using in-built software.

**Progressive resistance exercise training protocol.** The subjects were familiarized with the correct method of performing the following exercises: biceps flexion, shoulder flexion, finger grip, hip flexion, knee extension and heel rise. They underwent on-site supervised PRT protocol for 12 w (three days per w) in the physiotherapy clinic supervised by the same physiotherapist (KM). The first, second and third training sessions were performed every alternate day in a week and were within/around 48 hours of the last exercise bout. The gap between the third and fourth training (performed at the start of next week) session was more than 48 hours because of the weekend. Similar training schedules were implemented for each week till 12 w. Each subject underwent warming up for 10 min by doing gentle stretching exercises of upper and lower limb. For each subject, the repetition maximum (RM) was calculated for a particular group of muscle. First, a 3RM for that particular set of muscle was identified. Then, the patient was started on one weight lesser than that for 3RM. The subject performed 10 such repetitions using that weight and 2 sets (moderate intensity) in each group of muscle. If the patient was able to perform such exercise at the end of the week, then 0.5 kg weight was added in the

next week. Compliance was analyzed to be 100% at each visit.

**Statistical analysis.** For quantitative variables, arithmetic mean and standard deviation were computed as measures of descriptive statistics. Student's *t*-test was applied to compare the mean values before and after the protocol. Mean difference of the values at end (3 m) and start (0 m) of the protocol were calculated for all the variables. P value of < 0.05 was considered statistically significant. STATA 9.0 intercooled version statistical software (College Station Road, Houston, Texas, USA) was used for data analysis.

## RESULTS

**Sample description.** The subjects were middle-aged ( $40.8 \pm 8.1$  y; range 24–50 y), with a wide range of BMI ( $24.1 \pm 3.9$  kg/m<sup>2</sup>; range 17.5–30.0 kg/m<sup>2</sup>). Of the 30 subjects (22 males, 8 females), 10 were hypertensive and 11 had diabetic retinopathy.

**Insulin sensitivity (Figure 1) and metabolic parameters (Table 1).** Insulin sensitivity improved as the K value increased [from  $K_{ITT} 1.22 \pm 0.732$  to  $K_{ITT} 2.13 \pm 0.751$  ( $p < 0.0001$ )] significantly after the protocol. HbA1c (%) showed a significant decline from  $7.72 \pm 0.47$  at baseline to  $7.18 \pm 0.33$  ( $p < 0.001$ ). Also, FBG (mmol/L) decreased significantly from  $10.07 \pm 2.0$  to  $7.4 \pm 1.2$  ( $p < 0.001$ ). Significant decrease (mean difference  $\pm$  SD) in the levels of lipids (mmol/L) were recorded from the baseline; TC ( $0.39 \pm 0.7$ ,  $p = 0.003$ ), TG ( $0.39 \pm 0.5$ ,  $p < 0.001$ ) and VLDL-c ( $0.34 \pm 0.6$ ,  $p = 0.003$ ).

**Anthropometric measurements (Table 2).** There was no significant change in BMI, however, a significant decrease ( $p < 0.001$ ) in the body circumferences and skinfold thicknesses at truncal and peripheral sites was observed, after the protocol.

**Adiposity, lean mass and circumferential extremity skeletal muscle area (Table 3).** No significant differences were noted in the

following parameters; total body fat, ratio of truncal/total body fat, regional fat in right upper arm and thigh, total body lean mass, lean mass of right arm and leg, mid-arm and mid-thigh skeletal muscle cross-sectional area.

## DISCUSSION

For the first time, we report a significant improvement in insulin sensitivity and HbA1c, decrease in truncal and peripheral SCAT and a decline in lipid values after 3 m of supervised PRT in Asian Indians with T2DM. The study is significant as it is likely that PRT may be more effective in Asian Indians as compared to white Caucasians because of excess overall adiposity, higher truncal SCAT and lower skeletal muscle mass. Among the risk factors for the metabolic syndrome, WC, TG and FBG levels decreased significantly.

In the present study, except one, all other patients had improved insulin sensitivity after 3 m as determined by SITT. Similar to our findings, other researchers studying disparate populations have shown an improvement in insulin sensitivity in sedentary non-obese (13), and older (14) men with T2DM with resistance exercise regimens alone. While the former study used moderate intensity PRT, high-intensity PRT was used in the latter. However, Dunstan *et al.* (15) reported a minimal change in insulin sensitivity in older men and women (60–80 y) after a regimen of combined resistance training and weight loss. Discrepancies in the findings of different investigators could be due to variable and often inadequate duration of intervention and use of different methods to measure insulin sensitivity.

Exercise training, whether aerobic or resistance leads to an increase in skeletal muscle glucose transporter-4 (GLUT4) content. Resistance training produces an increase in fat-free mass (FFM) contributing to increased glucose disposal, whereas

aerobic training enhances glucose disposal independent of changes in FFM, fat mass, or maximum aerobic capacity, bringing about functional changes in the muscle. It is likely that due to different mechanisms of action, the addition of resistance exercise to aerobic training can help achieve the targets in shorter time than that by isolated aerobic exercise.

We reported a decline in values of HbA1C and FBG (0.54% and 2.7 mmol/L, respectively) from the baseline, indicating a significant improvement in glycemic control. Several investigators have shown a decline of HbA1c ranging from 0.5 to 1.2% after resistance exercise alone (16) or combined with weight loss regimen (15), spanning over a period of 3-6 m, whereas others (13, 14) failed to show any improvement after 8-16 w of training. Balducci *et al.* (17) reported an improvement of 1.2% in HbA1C value after combined aerobic and resistance exercise for 1 y. It is possible that a longer course of exercise may lead to more improvement in glycemia. The fact that glycemic control improved significantly in our study within 3 m could also mean that Asian Indians may respond better to PRT than other ethnic groups. We demonstrated a significant decline in lipid levels; however, better effect has been seen on long-term resistance exercise protocol (17). Finally, we were not able to demonstrate significant decrease in hsCRP levels as has been reported after a 12 m study (18).

Our hypothesis was that PRT would improve insulin sensitivity by increasing the lean body mass in Asian Indians with T2DM. As skeletal muscle is the principle area of glucose disposal, increasing the muscle bulk would increase insulin sensitivity assuming that this may occur due to improved muscle physiology and vascularity. However, we did not observe any change in lean body mass and cross sectional area of skeletal muscles of upper arm and thigh. Contradictory results have been reported regarding the effect of resistance exercise on skeletal muscle

area/mass (4, 19). It is possible that more number of resistance exercises using more muscle groups than used in our protocol may increase the muscle mass significantly. While varying duration of study and different protocols may be offered as explanations, there is a possibility that resistance exercise may decrease intra-myocellular triglycerides (IMCL) content, which may mask the increase in the muscle mass and both effects could lead to an improvement in insulin sensitivity. Specifically, we have previously reported high IMCL content of soleus muscle in Asian Indians with or without T2DM (20).

There was a significant decrease in all the central as well as peripheral skinfolds, signifying a loss of both truncal and peripheral SCAT. In contrast to white Caucasians in whom IAAT is believed to be more important determinant of insulin resistance, we believe that truncal SCAT is quantitatively more and a better correlate of insulin sensitivity in Asian Indians (21). While most studies have demonstrated a decrease in both IAAT and SCAT with PRT alone (14, 19) or combined (3) with aerobic training, Sigal *et al.* (4) reported a significant decrease in abdominal SCAT without any alteration in IAAT in a case-control study, both after aerobic and resistance exercise alone. A significant decrease in SCAT in our patients with T2DM after short-term PRT protocol is interesting, and we speculate that decrease in SCAT may have had significant contribution in improved insulin sensitivity in Asian Indians, as seen in our study.

Regardless of how it is achieved, whether through calorie restriction, aerobic exercise, resistance training, or any combination of lifestyle factors, a reduction in truncal obesity appears to improve insulin sensitivity (19). While calorie restriction and/or aerobic exercise are effective at inducing weight loss and reducing truncal obesity, lean body mass (skeletal muscle tissue) may be sacrificed in the process. When resistance training is

included as part of the weight loss regimen, lean body mass can be simultaneously maintained or even gained (22). This may prove advantageous in the long-term management of T2DM and the metabolic syndrome.

Asian Indians are interesting ethnic groups to study the effects of resistance exercise because of distinctive body composition and high tendency to develop insulin resistance and T2DM. To further validate these interesting results obtained by us, additional studies are required which should include the following; larger sample size, longer duration of study, more intensive PRT protocol involving more number of muscle groups, more accurate documentation of SCAT and IAAT and total abdominal fat measured by CT/MRI scan as has been done in our previous study (23).

## **CONCLUSION**

Supervised PRT for 3 m leads to significant improvement in insulin sensitivity, values of Hb1Ac, TC, TG, VLDL-c and truncal and peripheral SCAT in Asian Indians with T2DM. We suggest moderate intensity PRT for Asian Indians with T2DM to improve insulin sensitivity, glycemia, lipid levels and decrease SCAT.

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**TABLE 1. Changes in metabolic parameters with PRT protocol**

Variables	PRT ( 0 m)	PRT (1 m)	PRT (2 m)	PRT (3 m)	Mean diff	P value*
FBG	10.07 ± 2.0	8.7 ± 1.3	8.2 ± 1.1	7.4 ± 1.2	2.7 ± 2.2	p<0.001
TC	4.58 ± 0.7	4.35 ± 0.5	4.29 ± 0.6	4.19 ± 0.5	0.39 ± 0.7	0.003
TG	1.99 ± 0.6	1.81 ± 0.5	1.63 ± 0.5	1.59 ± 0.4	0.39 ± 0.5	p<0.001
HDL-c	1.19 ± 0.08	1.19 ± 0.06	1.19 ± 0.09	1.21 ± 0.09	-0.02 ± 0.1	0.331
LDL-c	1.46 ± 0.6	1.35 ± 0.4	1.34 ± 0.4	1.35 ± 0.4	0.09 ± 0.4	0.210
VLDL-c	1.06 ± 0.6	0.82 ± 0.3	0.75 ± 0.2	0.71 ± 0.2	0.34 ± 0.6	0.003
HbA1c	7.7 ± 0.5	7.5 ± 0.5	7.3 ± 0.5	7.2 ± 0.3	0.54 ± 0.4	p<0.001

*n* = 30. Data are means ± SD, \*p value < 0.05; PRT, Progressive Resistance Training; m, month; Mean diff, Mean difference (PRT at 3m – PRT at 0m); FBG, Fasting blood glucose; TC, Total cholesterol; TG; Serum triglycerides; HDL-c, High-density lipoprotein cholesterol; LDL-c, Low-density lipoprotein cholesterol; VLDL-c; Very low-density lipoprotein cholesterol; HbA1c; Glycosylated hemoglobin.

**TABLE 2. Changes in anthropometric variables with PRT protocol**

<b>Variables</b>	<b>PRT (0 m<sup>†</sup>)</b>	<b>PRT (3 m)</b>	<b>Mean diff</b>	<b>P value*</b>
BMI (kg/m <sup>2</sup> )	24.1 ± 3.9	24.1 ± 3.7	0.1 ± 1.1	0.614
<b>Circumferences(cm) and ratios:</b>				
Waist	87.9 ± 13.1	86.3 ± 12.7	-1.6 ± 1.9	p<0.001
Hip	94.3 ± 10.5	92.5 ± 10.5	1.8 ± 1.2	p<0.001
Mid-thigh	46.5 ± 5.9	44.9 ± 5.6	1.7 ± 1.1	p<0.001
Mid-arm	29.3 ± 5.2	28.1 ± 4.6	-1.2 ± 1.0	p<0.001
W-HR	1.0 ± 0.2	1.0 ± 0.1	-0.0 ± 0.1	0.091
<b>Skinfolds (mm):</b>				
Biceps	7.2 ± 2.1	6.3 ± 1.9	-0.9 ± 0.6	p<0.001
Triceps	15.4 ± 8.6	14.1 ± 8.1	-1.3 ± 1.3	p<0.001
Subscapular (SS)	25.9 ± 10.3	24.3 ± 9.8	-1.6 ± 1.3	p<0.001
Anterior axillary	18.4 ± 11.8	17.4 ± 11.2	-0.9 ± 1.2	p<0.001
Supra-iliac	27.2 ± 13.4	25.8 ± 13.1	-1.4 ± 1.3	p<0.001
Thigh	23.8 ± 11.6	22.4 ± 11.3	-1.5 ± 1.1	p<0.001
Calf	7.9 ± 3.9	7.1 ± 3.4	-0.9 ± 0.9	p<0.001
Lateral thoracic	26.6 ± 11.0	25.6 ± 10.7	-1.3 ± 0.9	p<0.001
SS- triceps skinfold ratio	1.8 ± 0.7	1.90 ± 0.8	0.08 ± 0.2	0.075
Central skinfolds	98.1 ± 40.5	92.9 ± 38.7	5.2 ± 3.5	p<0.001
Peripheral skinfolds	54.4 ± 21.6	49.8 ± 20.4	4.5 ± 3.1	0.001

*n* = 30. Data are means ± SD, \*p value < 0.05; PRT, Progressive Resistance Training; m, month; Mean diff, Mean difference (PRT 3 m --PRT 0 m); W-HR, Waist-to-hip circumference ratio; Central skinfolds: Sum of values of subscapular and supra-iliac skinfolds; Peripheral skinfolds: Sum of values of biceps and triceps skinfolds.

**TABLE 3. Changes in % BF<sup>¶</sup>, regional fat<sup>¶</sup>, lean body mass<sup>¶</sup> and cross-sectional skeletal muscle area<sup>#</sup> of upper and lower extremities with PRT protocol**

Variable (n=30)	PRT (0 m)	PRT ( 3 m)	Mean diff	P value*
Body fat (%)	27.7 ± 10.6	27.3 ± 10.3	0.3 ± 1.5	0.239
Truncal/Total body fat (ratio)	0.6 ± 0.1	0.6 ± 0.1	0.0 ± 0.0	0.96
Lean body mass (Kg)	42.3 ± 6.0	42.6 ± 6.2	0.2 ± 1.5	0.384
R arm fat	25.1 ± 12.5	23.9 ± 12.6	1.2 ± 6.2	0.311
R arm regional fat	23.9 ± 12.1	22.8 ± 12.5	1.2 ± 6.3	0.328
R arm lean mass (kg)	2.8 ± 0.8	2.9 ± 0.6	0.1 ± 0.5	0.166
R mid-arm muscle area (cm <sup>2</sup> )	34.1 ± 6.7	33.6 ± 8.3	- 0.5 ± 3.8	0.487
R leg fat	25.0 ± 11.8	24.7 ± 11.3	0.3 ± 1.5	0.218
R leg regional fat	23.9 ± 11.4	23.7 ± 10.9	0.2 ± 1.4	0.386
R leg lean mass (kg)	6.8 ± 1.2	6.9 ± 1.2	0.1 ± 0.4	0.294
R mid-thigh muscle area (cm <sup>2</sup> )	111.4 ± 17.8	111.6 ± 19.0	- 0.1 ± 6.7	0.092

n = 30. Data are means ± SD, \*p value < 0.05; ¶% BF, percentage of total body fat; PRT, Progressive Resistance Training; m, month; ¶ Measurements done by Dual-energy x-ray absorptiometry (DEXA); # Measurements done by CT scan; Mean diff, Mean difference (PRT 3 m - PRT 0 m); R arm/leg fat, % of fat present in the right arm/right leg as compared the whole body fat; R arm/leg regional fat, % fat present in the right arm/leg as compared to the right arm/leg tissue.

## **FIGURE LEGEND**

**FIGURE 1.** Insulin sensitivity as assessed by Short Insulin Tolerance Test and depicted as K Value (see text for details) before and after intervention. Increasing value denotes improved insulin sensitivity, PRT, Progressive Resistance Training.

Figure 1

