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Effect of Progressive Resistance Exercise Training on Hepatic Fat in Asian Indians with Non-Alcoholic Fatty Liver Disease

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Authors' contributions

This work was carried out in collaboration between all authors. Author KD examined the subjects and collected the data. Author KM designed and supervised the resistance exercise protocol. Author ASB performed the ultrasonography and interpreted the MRI data. Author RMP was involved in data interpretation and statistical analysis. Author KL was involved in supervision of all the biochemical investigations carried out. Authors RS and RG were involved in the designing the study, supervision of author KD and editing first and final drafts of the manuscript. Author NKV directed the study, created the tables and figures and wrote and edited the first and final drafts of the manuscript. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Introduction: Nonalcoholic fatty liver disease (NAFLD) is closely associated with obesity and insulin resistance and lifestyle measures form the cornerstone of therapy.
Objective: To study the effect of progressive resistance training (PRT) on hepatic fat

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content, body composition and insulin sensitivity in patients with NAFLD.
Methods: This study included 24 adult patients with NAFLD diagnosed on ultrasonography. Subjects with alcohol intake >140 gm/week and any secondary cause of fatty liver were excluded. Patients underwent thrice weekly sessions (40 minutes each) of resistance exercises including flexion at biceps, triceps, and hip flexion, knee extension and heel rise for 12 weeks. Pre- and post-intervention evaluation included anthropometry, BIA analysis, short insulin tolerance test (SITT), lipid profile and hepatic fat quantification by MRI.
Results: Twenty four patients (17 males, 7 females, mean age 39.8±10.5 yrs) completed the study protocol with 78.7% compliance to PRT protocol. There was significant decrease in waist, hip and mid-thigh circumferences and skinfold thicknesses at biceps, triceps, subscapular and suprailiac regions ($p<0.05$), with no significant change in BMI and WHR. Insulin sensitivity improved significantly at 12 weeks as indicated by increase in k-value (rate of change of glucose) on SITT (0.84 vs 1.3, $p=0.002$). A decrease in total cholesterol and LDL-c with increase in HDL-c was noted after 12 weeks ($p<0.05$). Hepatic fat content also decreased at 12 weeks (22.3±3.9 vs 21.4±4.0 %, $p=0.01$).
Conclusion: Moderate intensity PRT is associated with significant improvement in hepatic fat, truncal subcutaneous fat and insulin sensitivity in patients with NAFLD.

Keywords: NAFLD; resistance exercise; insulin resistance; Asian Indians.

1. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a wide spectrum of clinicopathological conditions which are present in individuals who either do not consume alcohol, or consume it in quantities not considered harmful to liver [1]. It ranges from relatively benign simple steatosis at one end to steatohepatitis and cirrhosis at the other end. The prevalence of NAFLD ranges from about 20-35% in the Western population and about 19-32% in Indian population [2], with the prevalence being higher (70-90%) in obese and diabetic individuals [3,4]. Insulin resistance is closely related with, and appears to be the primary underlying abnormality in NAFLD [5,6]. It has been shown that both insulin resistance and NAFLD are more common in Asian Indians as compared to other ethnic groups [7]. Several comparative studies have shown that Asian Indians have excess body fat (particularly in truncal and abdominal region) than Caucasians at a comparable BMI. This may be attributed to genetic influences. This predisposes them to develop insulin resistance at a lower BMI. This copupled with factors such as poor dietary habbits (excessive saturated fat intake) and lack of physical activity predisposes Asian Indians to develop NAFLD more frequently. Accumulating evidence from several observational and longitudinal studies suggests that NAFLD may be associated with increased risk of atherosclerosis and cardiovascular disease [8]. We have recently demonstrated that NAFLD is significantly associated with sub-clinical atherosclerosis, independent of obesity in Asian Indians [2].

No single pharmacotherapeutic agent has been confirmed to be useful in treatment of NAFLD. Lifestyle interventions in the form of calorie restriction and physical activity with an aim to reduce weight remain the cornerstone of treatment. At least 5% weight loss may be required for improvement in steatosis, but a greater weight loss (up to 10%) may be necessary for improvement in necrosis and inflammation [9]. Thiazolidinedione therapy has been shown to be effective in reducing steatosis and inflammation [10] but weight gain and other adverse effects limit its long term use. Higher levels of physical activity may reduce hepatic steatosis [11,12].

Both aerobic and resistance exercises effectively improve insulin sensitivity and may be beneficial for glucose-lipid metabolism. Regular exercise may be therapeutic in reducing liver fat deposition by increasing energy expenditure, improvement in skeletal lipid oxidation, reduction in total and abdominal adiposity and free fatty acid flux to liver [13-15]. Regular exercise may improve liver enzymes in patients with NAFLD independent of obesity [16]. Resistance exercise on the other hand has been less investigated. Progressive resistance training (PRT) is defined as exercise in which the resistance against which a muscle generates force is progressively increased over time. Resistance exercise may be less demanding in terms of cardiorespiratory fitness and is associated with better compliance. We have earlier shown that short term PRT is associated with significant improvement in insulin sensitivity, glycemic control, lipids and truncal adiposity in Asian Indians with type 2 diabetes [17]. Overall, there is very limited data on the effectiveness of resistance exercise on hepatic function in NAFLD. In a recent study, Hallsworth et al. reported 13% relative reduction in liver fat and improvement in insulin resistance without significant weight loss after 8 weeks of resistance exercise in patients with NAFLD [18]. There is no data on the effect of resistance exercise on hepatic fat and insulin sensitivity in Asian Indians to the best of our knowledge, therefore this study was undertaken.

2. MATERIALS AND METHODS

This study was a pre-post intervention study conducted in the Department of Medicine at the All India Institute of Medical Sciences (AIIMS), New Delhi from January 2009 to December 2011. The study was approved by the Institutional Ethics Committee and written informed consent was obtained from subjects before participation. Adult subjects diagnosed to have NAFLD on ultrasonography were included in the study. Exclusion criteria included alcohol consumption >140 gm/week, intake of any drugs causing fatty liver, known seropositivity for HIV, HBV and HCV, any severe acute or chronic illness, concomitant participation in any exercise or weight loss program, pregnancy and lactation. Individuals with contraindications to PRT such as unstable CAD, valvular heart disease, pulmonary thromboembolism, cerebrovascular accident, inflammatory joint disease or fracture within past six months, abdominal or inguinal hernias or hemorrhoids etc. were also excluded.

2.1 Measurements

Baseline evaluation included a detailed clinical examination, anthropometric measurements and bioelectrical impedance analysis as described earlier [2]. Trans-abdominal ultrasonogram was performed using a 3.5 MHz convex transducer (Voluson 730 Pro, GE Healthcare) by subcostal and intercostal approach to confirm fatty liver. Venous blood samples were obtained after an overnight fast of at least 10 hours for biochemical measurements including liver function tests, fasting plasma glucose (FPG) and lipid profile (total cholesterol [TC], triglycerides [TG] and high-density lipoprotein cholesterol [HDL-c]) using reagent kits as mentioned earlier [2]. The value of low-density lipoprotein cholesterol (LDL-c) was calculated using Friedewald's equation [19].

Subjects also underwent a short insulin tolerance test on another day to assess insulin sensitivity as per the methods mentioned earlier [2]. After an overnight fast of at least 10 hours, a scalp vein set was introduced into a peripheral vein and venous blood samples were taken at -3 and 0 minutes. Subsequently, rapid acting insulin (Huminsulin R; Eli Lilly) at an intravenous bolus dose of 0.1 U/kg body weight was given. Venous blood was collected at 3-, 6-, 9-, 12-, and 15-minute 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.

2.2 Hepatic Fat Quantification by MRI

Hepatic fat quantification was done by Magnetic Resonance Imaging (MRI) using chemical shift imaging. Patient was positioned supine for imaging using the body coil. Spoiled gradient echo (GRE) images ware acquired for in-phase and out-of-phase. Three individual image slice pairs were obtained through liver, with each image obtained separately and during single breath hold. Fat fraction was calculated from the mean pixel signal intensity (SI) data by (SI in-phase - SI out-of-phase)/2*SI in-phase. Hepatic fat fraction was considered to be normal at a value < 9% [20].

2.3 Exercise Training

After baseline evaluation, patients were enrolled for progressive resistance exercise training (PRT) in the physiotherapy clinic supervised by the same physiotherapist (K.M.). Total duration of the program was 12 weeks with thrice weekly sessions of exercise of 40 minutes duration each (including a 10 minute warm-up). In the first week, sessions were completely supervised in the clinic. In second to fourth week, one session was supervised in the clinic with other sessions being done at home unsupervised. In the remaining duration, one supervised session was done at the clinic every fortnight. Exercises were performed twice daily. Patients were asked to maintain a log recording the date, time, duration and the type of exercise performed to ensure compliance. The study subjects were instructed not to make any changes to their usual diet pattern and normal level of physical activity during the study period.

2.4 PRT Protocol

Specially designed weight belts of 0.5, 1.0, 2.0, 3.0 and 4.0 kg were used for PRT. These weight belts were applied to the respective limb before exercise. The subjects were familiarized with the correct method of performing the following exercises: elbow flexion, shoulder flexion, hip flexion, knee extension, and heel rise. Each subject underwent warming up for 10 minutes by doing gentle stretching exercises of upper and lower limbs. For each subject, the repetition maximum (RM) was calculated for a particular muscle group. First, a three RM for that particular set of muscles was identified. The 3 RM load is the amount of weight that can be lifted through the available range of motion three times before needing a rest. Then, the patient was started on one kg weight less than three RM. The subject had to perform 10 such repetitions using that weight and two sets (moderate intensity) in each group of muscles. If the patient was able to perform such exercise at the end of the week, 0.5 kg weight was added in the next week. The exercise protocol was to be terminated in case of an unusual chest pain or shortness of breath.

2.5 Outcome Assessment

At the end of three months of intervention, anthropometric measurements, body fat analysis using bioelectrical impedance, biochemical measurements, SITT and hepatic fat quantification by MRI were repeated.

2.6 Statistical Analysis

For quantitative variables, arithmetic mean and standard deviation (SD) were computed as measures of descriptive statistics. Paired 't' test was applied to compare the difference in mean values of parameters before and after PRT. A p value of <0.05 was considered statistically significant. SPSS 17.0.0 (SPSS Inc., Chicago, IL) was used for data analysis.

3. RESULTS AND DISCUSSION

3.1 Study Population

Out of 97 patients diagnosed to have NAFLD on ultrasonography, a total of thirty two patients started PRT sessions (Fig. 1). Eight patients were lost to follow up and twenty four completed the study protocol and were included in the final analysis. Overall compliance was observed at 79% through a self-maintained diary. However, it was noted that compliance decreased steadily from 84% during the first month to 74% during the third month.

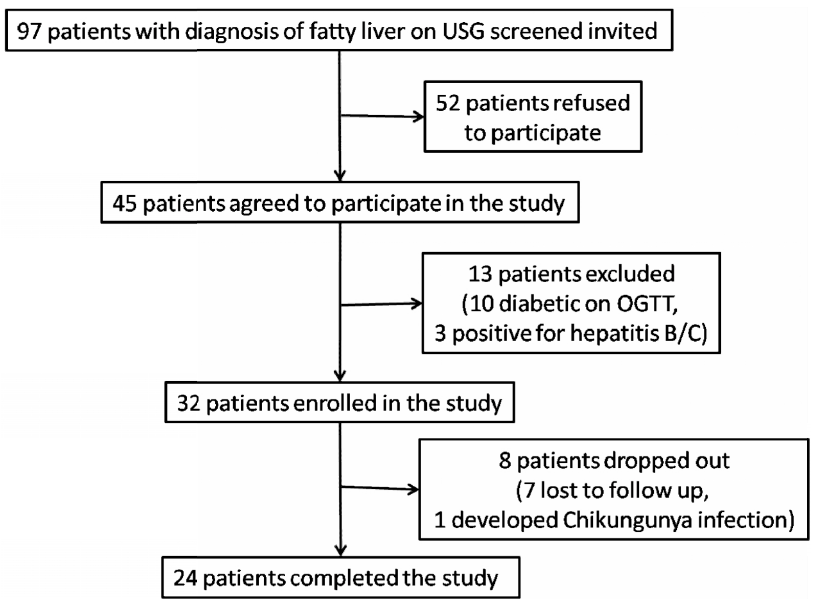

Fig. 1. Screening, enrollment and follow-up of study subjects

3.2 Baseline Characteristics (Table 1)

The baseline characteristics of the study sample are shown in Table 1. The characteristics of subjects who did not complete the study were similar to those who completed the study (data not shown). Males constituted 71% (n=17) of the study population. The mean±SD age of the subjects was 39.8±10.5 years. Overall, 79% of subjects were overweight (males 70.6%, females 100%) and 54% of subjects had abdominal obesity (males 47%, females 71.4%). Among the dyslipidemias, hypercholesterolemia was present in 20.8% (males 17.6%, females 28.6%), hypertriglyceridemia in 33.3% (males 29.4%, females 42.9%) and low HDL-c in 79.2% (males 82.3%, females 71.4%) of subjects.

Table 1. Baseline and post-PRT characteristics of the study population

Parameter	Pre-PRT (Baseline, n=24	Post-PRT (3 months, n=24)	Mean difference (95% CI)	% Change from baseline	P-value*
Weight (kg)	70.6 ± 8.7	70.3 ± 8.8	0.26 (-0.10, 0.62)	0.36	.20
BMI (kg/m^2)	26.7 ± 3.7	26.5 ± 3.6	0.10 (-0.03, 0.24)	0.37	.10
SBP (mm hg)	128.1 ± 9.4	126.8 ± 7.0	1.33 (-1.26, 3.93)	1.03	.30
DBP (mm hg)	80.7 ± 7.0	80.1 ± 7.1	0.58 (-1.27, 2.44)	0.72	.50
Circumferences (cm)					
Waist	87.0 ± 8.7	86.3 ± 8.7	0.76 (0.42, 1.10)	0.87	<0.001
Hip	96.4 ± 7.7	95.5 ± 7.6	0.93 (0.55, 1.30)	0.96	<0.001
Mid-arm	29.6 ± 3.7	28.9 ± 3.5	0.70 (0.42, 0.98)	2.36	<0.001
Mid-thigh	53.4 ± 4.4	52.6 ± 4.8	0.83 (0.48, 1.19)	1.55	<0.001
Waist-to-hip ratio	0.90 ± 0.06	0.90 ± 0.06	0.004(-0.002, 0.003)	0.44	.60
Skinfold thickness (mm)					
Biceps	12.8 ± 3.1	12.4 ± 2.8	0.45 (0.23, 0.67)	3.51	<0.001
Triceps	17.5 ± 5.4	16.6 ± 5.4	0.84 (0.65, 1.03)	4.80	<0.001
Subscapular	31.3 ± 3.1	30.3 ± 3.2	0.97 (0.70, 1.24)	3.10	<0.001
Suprailiac	29.6 ± 3.4	28.5 ± 3.5	1.05 (0.77, 1.33)	3.55	<0.001
KITT	-0.84 ± 0.80	-1.30 ± 0.63	0.45 (0.20, 0.70)	53.57	.002
FBG (mg/dl)	99.8 ± 16.1	99.3 ± 14.0	0.52 (-4.4, 5.43)	0.52	.33
TC (mg/dl)	174.5 ± 27.4	168.8 ± 24.1	5.72 (0.54, 10.9)	3.28	.03
LDL-c (mg/dl)	112.0 ± 23.2	104.3 ± 19.1	7.68 (2.39, 13.0)	6.86	.006
HDL-c (mg/dl)	36.4 ± 7.9	37.4 ± 6.7	-0.98 (-1.7, -0.26)	2.70	.009
TG (mg/dl)	130.7 ± 45.1	135.6 ± 43.8	-4.9 (-12.3, 2.5)	3.75	.18
Total bilirubin (mg/dl)	0.58±0.19	0.50±0.08	0.07(-0.003, 0.15)	-12.07	.06
AST (IU)	37.0±12.3	37.3±6.8	-0.33(-4.17, 3.50)	0.89	.85
ALT (IU)	43.6±25.1	38.1±9.2	5.46 (-1.89, 12.8)	-12.52	.14
SAP (IU)	247.5±86.5	258.8±68.7	-11.3 (-28.6, 5.9)	4.56	.19
Body fat by bioimpedance (%)	27.7 ± 8.8	27.0± 8.4	0.72 (0.11, 1.32)	2.60	.02
Hepatic fat by MRI (%)	22.2 ± 3.9	21.3 ± 4.0	0.89 (0.18, 1.6)	4.00	.01

Data are mean ± standard deviation (unless specified); *: comparison of mean difference against zero; BMI: Body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; KITT: rate of decline of blood glucose during the short insulin tolerance test; FBG: fasting blood glucose; TC: total cholesterol; TG: triglycerides; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; SAP: Serum alkaline phosphatase; MRI: magnetic resonance imaging

Abnormally low (<1.5%) KITT values indicating insulin resistance were present in 79% of subjects. About 17% had abnormal serum ALT levels (> 50 IU) whereas AST levels were normal in all subjects.

3.3 Post PRT Intervention Observations (Table 1)

Subjects were re-evaluated after completion of PRT. There was no significant change in the weight or BMI but, there was a significant decrease in the waist, hip, mid-arm and mid-thigh circumferences and skinfold thickness measured at various central and peripheral sites indicating a decrease in subcutaneous fat. A decrease in systolic and diastolic blood pressures and FBG with PRT was noted but the difference was not statistically significant. Insulin sensitivity as indicated by SITT showed a significant improvement with PRT (Fig. 2). Serum levels of TC and LDL-c decreased significantly ($p<0.05$) along with a significant increase in HDL-c cholesterol ($p<0.05$). None of the liver function tests (total bilirubin, AST, ALT and ALP) showed a significant change with PRT. Significant reduction in both % body fat measured by bioelectrical impedance analysis and hepatic fat measured by MRI was observed after completion of PRT. Since some of the parameters (KITT, serum triglycerides, serum total bilirubin, ALT, ALP) had a non-Gaussian distribution, they were re-analyzed using the Wilcoxon signed rank test. However, this did not produce any change in the results. There was a significant improvement in KITT at the end of 3 months without any statistically significant change in the other parameters.

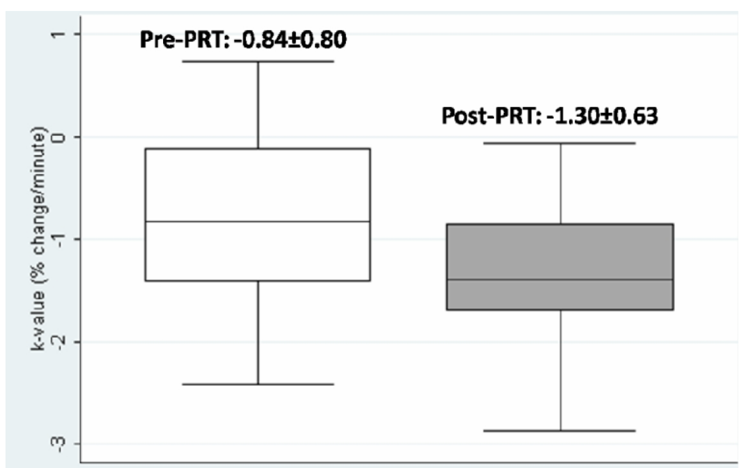

Fig. 2. K-values of SITT before and after PRT

This is the first study in Asian Indians with NAFLD showing beneficial effects of short term PRT in terms of improving insulin sensitivity and hepatic fat content without significant change in adiposity.

Lifestyle modifications which promote weight loss form the cornerstone of therapy in NAFLD [21,22]. A combination of dietary restrictions and exercise has been shown by several investigators to be associated with improvements in liver enzymes and lipid parameters in patients with NAFLD [13,23,24]. Intensive lifestyle intervention over 48 weeks was associated with significant reduction in steatosis and improvement in NASH histological activity score (NAS) as compared to structured education alone in overweight or obese individuals [11]. The data on the effectiveness of exercise alone in NAFLD is very limited, particularly in Asian Indians. Majority of the available studies performed have included aerobic exercise alone or a combination of aerobic and resistance exercises [13,14,24,25].

Limited number of studies have explored the role of resistance exercises alone on NAFLD. Hallsworth et al. compared the effectiveness of 8 weeks of resistance exercise to that of normal treatment in sedentary subjects with NAFLD. In those who underwent resistance exercise, there was 13% relative reduction in liver lipid, improvement in fat oxidation and significant reduction in insulin resistance without any significant change in adiposity [18]. In our study, resistance exercise training for 12 weeks elicited a 4% reduction in hepatic fat, 2.5% reduction in body fat, and was also accompanied by about 54% increase in the insulin sensitivity. These changes occurred in the absence of any significant change in body weight. However, resistance exercise did not produce any significant change in the liver enzymes. Our observations are consistent with a recent meta-analysis which showed a clear evidence of benefit of exercise on liver fat but not on alanine transaminase (ALT) levels, despite an absent or minimal weight loss [26]. This probably indicates that the benefit provided by exercise is over and above that of that weight loss which is a well-established intervention for NAFLD.

Insulin resistance by promoting visceral and hepatic fat accumulation plays a pivotal role in the development of metabolic syndrome and NAFLD. Persistently high insulin levels lead to upregulation of SREBP-1c and ChREBP expression in the liver, which in turn stimulates de novo lipogenesis [27]. In patients with NAFLD the contribution of de novo lipogenesis to intrahepatic lipid content is much higher than that in healthy normoglycemic individuals [28]. Exercise has two predominant effects on body metabolism namely, weight loss and improved muscular insulin sensitivity. Skeletal muscles of healthy individuals can manifest considerable plasticity of mitochondrial content adapting to match energy demands of physical activity. Such plasticity appears to be preserved in insulin resistance associated with obesity and aging. Reduction in skeletal muscle mitochondria along with decreased activity of the electron transport chain have been observed in patients with type 2 diabetes [29] and NAFLD [30].

Although this study lends further credence to the role of PRT in NAFLD, it has some limitations. Liver biopsy was not performed in this study due to ethical considerations. Although PRT produced significance decrease in the hepatic fat, it did not produce any significant change in the hepatic enzymes. It was not possible to determine the effect of PRT on the histological changes in this study. Another major limitation of the study was lack of data on the dietary habbits. It would be difficult to determine if there were any dietary changes during the study period which may have influenced the observations. Other limitations included a relatively small sample size due to high dropout rate and the lack of a comparator group. The PRT provided in this study was partly supervised. Whether similar benefits can be obtained when PRT is provided in a completely home-based manner is not clear. In a study which assessed the effects of resistance training in diabetics, the improvement in glycemic control achieved during the initial 6 months of supervised resistance training was not maintained during the subsequent 6 months of home based training [31]. This was primarily attributed to reduced adherence to exercise and a reduction in the volume and intensity of home based training.

4. CONCLUSION

In conclusion, moderate intensity resistance exercise for three months produced significant improvements in insulin sensitivity, hepatic fat, and subcutaneous fat in patients with NAFLD. Resistance exercise may be better tolerated than aerobic exercise as it is less demanding on cardio-respiratory fitness and could be an effective form of therapy in NAFLD. The long term sustainability of PRT and the effectiveness of home-based PRT program needs to be evaluated in future studies.

CONSENT

All authors declare that written informed consent was obtained from the patients before their participation in the study.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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