Effect of Resistive Training on Serum Adiponectin and Liver Fat in Prediabetic Patients with Fatty Liver

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ABSTRACT

**Purpose:** Lifestyle interventions concentrating on weight reduction remain the cornerstone of non-alcoholic fatty liver disease (NAFLD) treatment. Aerobic exercise is not well sustained and the effectiveness of the better tolerated resistance exercise upon liver lipid and mediators of liver lipid has not been assessed. The purpose of the present study was to investigate the effects of resistance training on serum adiponectin and intrahepatic fat in prediabetic fatty liver patients.

**Methods:** Sixty obese women (age, 30–40 years) participated in the study. They were randomly assigned into two groups equal in number: resistive training group (A) and control group (B). For all subjects, body mass index, waist circumference, fasting blood glucose and serum adiponectin were measured. Ultrasound examination was used to detect severity of fatty liver. The experimental group performed moderate intensity resistive training (consisted of 50–74% of 1-repetition maximum (RM) for 50–60 min of weight training per day, 3 days a week, for 12 weeks).

**Results:** There were significant decline in waist circumference, body mass index, fasting blood glucose, and severity of intrahepatic fat on ultrasound by 5.93%, 2.66%, 4.91%, 41.61% respectively and significant increase of serum adiponectin by 43.38% in response to resistive training in comparison with the control group.

**Conclusion:** Resistive training caused an improvement in serum adiponectin and intrahepatic fat score on ultrasound in prediabetic fatty liver patients so it could be used as an alternative to aerobic exercise for fatty liver patients.

**Key words:** Resistive exercise, Non-alcoholic fatty liver disease, adiponectin, intrahepatic fat prediabetic.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) represents a wide range from asymptomatic steatosis to possible life-threatening non-alcoholic steatohepatitis, with an overall incidence of NAFLD in western countries of 20-30%. Simple steatosis prognoses to a relatively benign ‘liver’ with risk of developing liver cirrhosis over 15-20 years by 1-2%. Patients with non-alcoholic steatohepatitis and fibrosis can advance to cirrhosis at a rate of nearly 12% over 8 years.

In the present century, obesity and insulin resistance related health complication (metabolic syndrome) has become main health burden. Around 30% of population is obese and three fourth of them have fatty liver disease in the United State \(^3\). With new clinical and incidence evidence, NAFLD is thought to be the hepatic part of metabolic syndrome \(^4\).

Visceral fat and liver fat are accompanied with type 2 diabetes, metabolic syndrome, and metabolic disorders\(^5\). Recent study recognize that adipose cells not only stores energy but also is an active endocrinal organ that secretes peptide hormones called adipokines \(^6,7\). Increasing of adiposity change many physiological processes, including inflammation, energy metabolism and insulin sensitivity \(^8,9\). Many studies investigating the functions and roles of more than 50 adipokines, including leptin and adiponectin in obesity and related comorbidities \(^10\).

Adiponectin , the most productive adipokine exclusively secreted by adipocytes, and exerts insulin-sensitizing effects in humans \(^11\). Adiponectin is a protein produced from adipose tissues that may couple regulation of insulin activity with energy metabolism and serve to the relation between obesity and insulin resistance \(^12\). Insulin resistance and increased lipolysis because of adipose tissue is the key to NAFLD pathogenesis \(^13,14\), and is accompanied with a change in the release of adipokines, and in particular adiponectin, a molecule which have an effect of insulin-sensitization, anti-inflammation, and anti-
fibrosis, whose decreased levels have been shown to correlate with hepatic fat accumulation\textsuperscript{15}. This observation of decreasing adiponectin levels then raises the likelihood of therapeutic options to raise circulating adiponectin levels \textsuperscript{16}.

To date, weight reduction is the main affirmed treatment for NAFLD, and lifestyle change remains the cornerstone of management\textsuperscript{17,18}. Although, the aerobic exercise may not be ideal because of increasing the cardiorespiratory demand which is accompanied with discomfort and fatigue, and long-term compliance is low. Resistance exercise with lower cardiorespiratory demand, is associated with comparable metabolic benefits\textsuperscript{19}. Up to date, resistance training or weight training has become a very common form of exercise to increase physical fitness, improve performance, increase muscle size and prevent injuries\textsuperscript{20}.

No previous study has investigated the effects of resistance training on adiponectin concentration and intrahepatic fat on ultrasound. Therefore, the present study was designed to determine the effects of resistance training on adiponectin concentration and intrahepatic fat in prediabetic fatty liver.

\section*{MATERIALS AND METHODS}

\subsection*{Subjects}
Sixty women with ages ranged from 30 to 40 yrs were recruited from out clinic departments of Faculty of Physical therapy. Patients who had the following features were included in the study: (1) central obesity—an abdominal circumference (AC) $\geq$ 80 cm and body mass index (BMI) from 35-39.9 kg/m2; (2) fasting plasma glucose (FPG) levels $\geq$100 mg/dl (5.6 mmol/l) but $<$126 mg/dl (7.0 mmol/l); (3) fatty liver according to liver ultrasound examination. Patients were excluded if they had hepatitis B or C, hypothyroidism, anemia and subjects who could not participate in a resistive exercise program due to high risk of adverse events were also excluded.

Subjects were randomly assigned into two equal groups: resistance training group (A) or control group (B). Subjects in the resistance training group received moderate resisted exercise program at a frequency of three times a week for 12 weeks. Subjects in the control group received the traditional medical treatment only. All subjects performed the exercise under a professional instructor. An ultrasound examination of the liver, blood samples, anthropometric indices was performed at baseline and after 12 weeks.

All subjects were completed a medical history and personal health questionnaire, which served as an assessment tool. The Faculty’s ethics committee approved the experimental procedures and study protocols were fully explained to all patients. A written consent form was signed by each subject after understanding and reading and the details of the experiment.

\subsection*{Experimental design}
Two sessions for familiarization were designed to habituate subjects with the testing and treatment procedures. The aim of these sessions was to familiarize subjects with performing the 1-RM test and also to familiarize them with different resistance exercises using free weights. During this sessions, it was ensured that the correct techniques for all exercises was used prior to the main test sessions. After familiarization, a test session designed to determine one-repetition maximum (1-RM) for 10 exercises involving the upper and lower body. Maximal strength was identified using a concentric, 1-RM. The warm-up included light stretching exercises for 5 min, after the warm-up, subjects done the 1-RM test, and the heaviest weight that could be lifted once correctly was considered as 1-RM for all the exercises and used to calculate the percentage of resistance.

\subsection*{Resistance training}
Resistance training consisted of 50–60 min of weight training per day, 3 days a week, for 12 weeks. This training was performed at 50–60\% of 1-RM in each set. Each exercise and set was separated by 30 s rest. Warm-up were performed before each training session and test
the 1-RM determination, also each training session was terminated by cool-down.

The resistance program included a series of 10 whole-body exercises three times per week for about 60 min/session. Each training session included knee extensors, knee flexors, hip flexors, hip abductors, hip extensors, elbow flexors, elbow extensors, shoulder flexors, abdominal muscles and back muscles exercises. Subjects performed 2-3 sets, 8-12 repetitions per session for each group of muscles.

Blood sampling and analysis
Blood samples were obtained after an overnight fasting period of at least 8 hours before and after the training program. Levels of fasting glucose were measured using commercial kits on an automated analyzer (SynchroN CX9; Beckman Coulter Co., Fullerton, CA, USA). Serum Adiponectin level was determined using ELISA technique (EZRADP-62k, 96-Well Strip Plate, Linco Research).

Liver ultrasound
Liver ultrasound was done by specialized gastroenterologist and graded on a scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe) at baseline and at end of study. Mild was recognized by slight increase in liver echogenicity and relative preservation of echoes from the walls of the portal vein. Moderate was recognized by moderate loss of echoes from the walls of the portal vein, particularly from the peripheral branches, and moderate diffuse abnormally bright echoes. Severe was recognized by a greater reduction in beam penetration, loss of echoes from most of the portal vein wall, and extensive abnormally bright echoes.

Anthropometric measurements
BMI was calculated as weight (kilograms) divided by height (meters) squared. The subject’s waist circumference was measured midway between the lowest rib and the iliac crest.

Statistical Analysis
Data were analyzed using SPSS version 16. Results were expressed in terms of mean ± standard deviation. Two-tailed, paired t-tests were used to determine if the post training-pre training difference within each group was significant. P < 0.05 was considered significant.

RESULT
A total of 60 subjects with prediabetic fatty liver were recruited, including 30 in the A group (study group) and 30 in the B group (control group). There was no subject who dropped out. Subjects in the A group adhered to the 12-week resisted exercise program very well. Table 1 lists the basic characteristics of the subjects at the start of the study. Before the intervention, there were no significant differences in age, BMI, body weight and waist circumference among the two groups. Baseline Fasting blood glucose, serum adiponectin and Severity of fatty liver on ultrasound were also similar in the two groups.

Table (1): Baseline characteristics of the study subjects.

<table>
<thead>
<tr>
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<th>Resistive Training</th>
<th>Control</th>
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<tr>
<td>Age(yr)</td>
<td>34.53±2.74</td>
<td>34.66±2.25</td>
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<tr>
<td>Anthropometric indices</td>
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<td></td>
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<tr>
<td>Weight(kg)</td>
<td>98.25±9.008</td>
<td>99.3±8.05</td>
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<tr>
<td>BMI(kg/m²)</td>
<td>37.7±1.31</td>
<td>37.39±2.11</td>
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<tr>
<td>waist circumference(cm)</td>
<td>120.90±3.08</td>
<td>121.27±3.06</td>
</tr>
<tr>
<td>Biochemical profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>113.4±7.33</td>
<td>117.33±5.006</td>
</tr>
<tr>
<td>Adiponectin (mg/mL)</td>
<td>4.58±0.53</td>
<td>4.59±0.50</td>
</tr>
<tr>
<td>Severity of fatty liver on ultrasound</td>
<td>2.06±0.69</td>
<td>2.066±0.74</td>
</tr>
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</table>
Table 2 shows that Resistive training caused significant changes in body weight, waist circumference and BMI when pre- and post-training values were compared. Serum adiponectin concentration increased significantly by 1.99±0.67ug/ml after resistive training while no significant change in the control group was found. Fasting serum glucose declined significantly (P<0.05) from 113.4±7.33 to 107.83±8.18 mg/dl in response to resistive training while the changes in the control group after 12 weeks were not statistically significant. Significant improvement in severity of intrahepatic fat accumulation on ultrasound was observed in resistive training group compared to the control group.

**Table 2**: Physiological characteristics of the subjects before and after 12 weeks.

<table>
<thead>
<tr>
<th></th>
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<tr>
<td><strong>Anthropometric indices</strong></td>
<td></td>
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<tr>
<td>Weight (kg)</td>
<td>98.25±9.008</td>
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<td></td>
<td>99.3±8.05</td>
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<td>BMI (kg/m²)</td>
<td>37.7±1.31</td>
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<td>37.391±2.11</td>
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<tr>
<td>Waist circumference (cm)</td>
<td>120.9±3.08</td>
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<td>121.27±3.06</td>
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<td><strong>Biochemical profile</strong></td>
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<td>Fasting blood glucose (mg/dl)</td>
<td>113.4±7.33</td>
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<td></td>
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<td>6.58±0.74*</td>
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<td>4.59±0.50</td>
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<tr>
<td>Severity of fatty liver on ultrasound</td>
<td>2.06±0.69</td>
<td>1.2±0.92*</td>
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<td>2.0667±0.74</td>
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Data presented as mean± standard deviation ; *P < 0.05

The ultrasound score for the severity of fatty liver for both groups at baseline and at study end are shown in Table 3. There were no significant differences among both groups at the baseline ultrasound examination. However, a statistically significant difference was seen after 12 weeks.

**Table 3**: Severity of fatty liver on ultrasound score in both groups before and after the study period.

<table>
<thead>
<tr>
<th>Time</th>
<th>Liver ultrasound score</th>
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<th>$\chi^2$ test</th>
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<tr>
<td></td>
<td></td>
<td>Value</td>
<td>Exact significant Value (2-sided)</td>
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<tr>
<td>Initial</td>
<td>1(mild)</td>
<td>6</td>
<td>7</td>
<td>13</td>
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<td></td>
<td>2(moderate)</td>
<td>16</td>
<td>14</td>
<td>30</td>
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</tr>
<tr>
<td></td>
<td>3(sever)</td>
<td>8</td>
<td>9</td>
<td>17</td>
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</tr>
<tr>
<td></td>
<td>Total</td>
<td>30</td>
<td>30</td>
<td>60</td>
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<tr>
<td>12wk</td>
<td>0(none)</td>
<td>6</td>
<td>0</td>
<td>6</td>
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<tr>
<td></td>
<td>1(mild)</td>
<td>16</td>
<td>8</td>
<td>24</td>
<td>13.200</td>
</tr>
<tr>
<td></td>
<td>2(moderate)</td>
<td>4</td>
<td>14</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3(sever)</td>
<td>4</td>
<td>8</td>
<td>12</td>
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</tr>
<tr>
<td></td>
<td>Total</td>
<td>30</td>
<td>30</td>
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**DISCUSSION**

The present study demonstrated the effects of 12-weeks resistance training program on anthropometric indices, serum fasting blood glucose, serum adiponectin and severity of fatty liver on ultrasound in patients with ultrasound-diagnosed NAFLD. With regard to anthropometric indices, our study results are in line with those of previous studies. We
observed that resisted exercise significantly decreased BMI and waist circumference. Bacchi et al.\textsuperscript{21} reported similar findings: after 4 months of both aerobic or resistance exercise in sedentary with type 2 diabetic patients with NAFLD, total body fat and BMI significantly reduced.

In the present study, 12 weeks of resistance training decreased fasting blood glucose by 43.66%. These findings confirm those of other studies\textsuperscript{22,23} that observed improvement in fasting plasma glucose in type 2 diabetes mellitus after resistance training.

Hotta et al. and Yang et al.\textsuperscript{24,25} explained that increased plasma adiponectin level is accompanied with improvement in insulin sensitivity, glucose tolerance and cardiovascular disease.

The possible mechanisms responsible for the resistance training effect on insulin sensitivity and glucose homeostasis are like to endurance training\textsuperscript{26}. Many mechanisms could be responsible for the elevation of insulin sensitivity after exercise training. These include increased glucose transporter protein and mRNA, elevated post-receptor insulin signaling, increased glycogen syntheses and hexokinase activity, increased muscle glucose delivery and changes in muscle composition, decreased release and increased clearance of free fatty acids\textsuperscript{20}.

Twelve weeks of resistance training increased serum adiponectin concentrations. There are few endurance-training studies that have demonstrated different findings\textsuperscript{27-28,29-30,31}. Yatagai et al.\textsuperscript{27} observed decreases in adiponectin concentration after 16 h of training. Moreover, Kriketos et al.\textsuperscript{28} and Oberbach et al.\textsuperscript{29} have reported that in overweight subjects and patients with impaired glucose tolerance and type 2 diabetes, increases in adiponectin level post short-term physical training. Similarly, Ring-Dimitriou et al.\textsuperscript{30} identified the changes in serum adiponectin over 24 months of exercise intervention in middle-aged adults predisposed to metabolic syndrome and increases in plasma adiponectin level with 15% increase in cardiorespiratory fitness. In addition, Saunders et al.\textsuperscript{31} demonstrated that both acute and short-term aerobic exercise have a significant increase in plasma adiponectin concentrations in sedentary, abdominally obese men whatever the intensity of exercise.

Few resistance-training researches that have investigated changes in adiponectin, have also reported conflicting results\textsuperscript{32-20}. Klimcakova et al.\textsuperscript{32} reported no changes in adiponectin level after 3 months of resistance training performed at 60–70% of 1-RM with 12–15 repetitions for each exercise. Moreover Ahmadizad et al.\textsuperscript{20} demonstrated that Twelve weeks of endurance and circuit weight training did not change serum adiponectin concentrations, The lack of effect of training on adiponectin in his study might be due to the absence of reductions in body weight and BMI. In an interesting study, Fatouros et al.\textsuperscript{33} investigated 6 months of resistance training effect at different intensities (low, moderate and high intensities) on adiponectin level in elderly individuals. They reported significant elevation of adiponectin after moderate and high-intensity training but not after low-intensity training, which were associated with weight reductions. Recently, Brooks et al.\textsuperscript{34} demonstrated significant increases in adiponectin level in response to 14 weeks of high-intensity resistance training. These different results may be attributed to differences in timing of blood sampling, subject populations and variation of the exercise protocols.

Our finding that resistance training, is associated with significant reductions in intrahepatic fat score on ultrasound in prediabetic fatty liver patients and this decline in intrahepatic fat is strongly associated with increased adiponectin concentration.

Some resistance-training studies that have investigated changes in hepatic fat have reported similar results as Lee et al.\textsuperscript{35} reported that either aerobic exercise or resistance exercise are effective for decreasing intrahepatic lipid by MRI and abdominal fat in obese adolescent boys. Moreover, Bacchi et al.\textsuperscript{21} demonstrated a new finding in his study is that resistance training, like to aerobic
training, markedly reduced hepatic fat content by MRI in diabetic patients with NAFLD. Hallsworth et al (19) reported that resistance exercise was associated with a 13% relative reduction in hepatic fat content, without any changes in body weight, whole body fat mass or visceral adipose tissue .Zelber-Sagi et al. 36 reported that resistance exercise, at least once a week, was accompanied with a decreased proportion of subjects with NAFLD, independently of BMI, insulin resistance, nutritional factors, and some circulating adipokines, such as adiponectin and resistin. Another studies have reported conflicting results as Davidson et al. 37 observed no effect of resistance training on visceral fat. However, as their study include only 20 min of resistance training, three times per week, and so cannot rule out that a more long program might have a significant effect. Sigal et al. 38 found that resistance training didn't have a significant effect on visceral fat; although, nor did aerobic training in the study.

The possible mechanisms of exercise, especially resistance training, may reduce hepatic fat score on ultrasound are not entirely identified. They may include changes in energy balance, insulin sensitivity, circulatory lipids, fat oxidation 19 and the significant increase in adiponectin concentration. As ADPN levels correlate inversely with insulin resistance and hepatic fat in diabetic patients 39, whereas in healthy subjects, low ADPN concentration are associated with elevated liver enzymes, suggesting a possible role of ADPN in preserving liver integrity 40,41. Moreover, Louthan et al.42 reported that adiponectin appears to play a more vital role than circulating pro-inflammatory cytokines dysregulation in the mechanisms leading to NAFLD in children. Other studies have reported that ADPN has anti-inflammatory and antifibrogenic effects in rodents and humans 43,44,45,46,47. In addition, ADPN is reported to have anti-steatotic effects on the liver.48 Recently, study based on liver histology has demonstrated that serum APN concentrations were like to simple steatosis patients and controls, and hypoadiponectinemia could play a vital pathophysiological role only from the progression of steatosis to steatohepatitis 49. Interestingly, Hamano et al.50, pointed out that plasma ADPN levels were significant and negative determinants of liver dysfunction only in fatty liver subjects.

Limitation of Our study that we identified fatty liver by ultrasound. The gold standard for the diagnosis of NAFLD is liver biopsy but this is an invasive procedure so is not acceptable without clinical indication.

In summary, 12 weeks of resistive training have significant effect on serum adiponectin concentrations and decreased intrahepatic fat in prediabetic fatty liver patients. It was concluded that resistive training could be used as alternative to aerobic training to reduce intrahepatic fat.

Acknowledgements

The authors wish to thank the volunteers for their enthusiastic participation in this study.

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diabetes mellitus. Metabolism. 60(9): 1244-1252, 2011.
Таблица 1

Таблица 1

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<td>Intervention</td>
<td>Exercise</td>
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References:


