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ORIGINAL ARTICLE

Sarcopenic obesity and dyslipidemia response to selective exercise program after liver transplantation

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KEYWORDS

Liver transplantation;
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Abstract *Background:* As long-term survival improves after liver transplantation, metabolic syndrome, including dyslipidemia, hypertension, diabetes, obesity and sarcopenia is emerging as a major cause of late morbidity and mortality.

Aim: The aim of this work was to evaluate the efficacy of exercise training program as a type of physical therapy approach in treatment of sarcopenic obesity and dyslipidemia after liver transplantation.

Subjects and methods: Thirty patients with liver transplantation since six months had participated in this study. The patients were randomly divided into two groups of equal numbers. The exercise group received aerobic and resisted exercise in addition to receive the traditional medical intervention. The control group received only the traditional medical intervention. Measurements of fat mass, muscle mass, cholesterol level and triglycerides level (by bioelectrical impedance and lipid profile) were collected before treatment and after three months of treatment.

Results: Comparison between exercise and control groups post treatment revealed a significant decrease in fat mass, cholesterol and triglyceride levels in the exercise group compared to the control group ($p < 0.001$), while there was a significant increase in muscle mass in the exercise group compared to control group ($p = 0.0001$).

Conclusion: Aerobic and resisted exercise has a positive effect in treatment of sarcopenic obesity and dyslipidemia (reducing fat mass, cholesterol and triglycerides levels while increasing muscle mass) post liver transplantation.

1. Introduction

Malnutrition and impaired body composition with loss of total body protein are characteristic findings in patients with end-stage chronic liver disease [1]. Liver transplantation LT is the only therapy that halts the progression of the disease [2].

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Although the survival after transplantation has improved greatly in the last decade, the combination of transplantation with immunosuppressant medication is still associated with several comorbidities, including dyslipidemia, hypertension, diabetes, obesity, osteoporosis, sarcopenia, muscle pain, and metabolic syndrome [2]. Physical function is also limited in patients who underwent a liver transplantation [3,4]and associations between poor prognosis and reduced physical function have been reported [3,5].

Obesity [body mass index (BMI) > 30 kg/m^2] develops in 21–43% of patients post-LT. The prevalence of dyslipidemia post-LT ranges from 66% to 85%. An increase in the prevalence of dyslipidemia from 8% before LT to 66% after LT. Elevated cholesterol and hypertriglyceridemia developed in 19% and 59%, respectively [6]. Another study reported an increase in the prevalence of both elevated total cholesterol (2.9% pre-LT versus post-LT 15.3%) and triglycerides (18.2% pre-LT versus post-LT 70%) at 6 months post-transplant [7].

Long-term survivors of liver transplant are not only overweight but exhibit an abnormal body composition characterized by an excess of body fat and obesity and a deficit in skeletal muscle mass, i.e., sarcopenia. This pattern closely resembles that of sarcopenic obesity in cancer or elderly patients [8].

The etiology of dyslipidemia involves many factors, though the immunosuppressive agents are the main triggering factor. Steroids are associated with hyperlipidemia as they stimulate the activity of acetyl-CoA carboxylase and the synthesis of fatty acids, thus raising concentrations of total cholesterol and triglycerides [9]. M-TOR inhibitors increase lipoprotein-lipase activity, increasing the hepatic synthesis of triglycerides [10]. Calcineurin inhibitors reduce the excretion of cholesterol to the bile and the peripheral LDL-cholesterol receptors, thereby raising circulating levels of cholesterol [11].

The link between exercise and improved physical condition has been well established in patients after different types of transplantation [12]. Exercise training can improve exercise capacity, body composition, and muscle strength following different types of transplantation [13–15]. Aerobic exercise promotes beneficial changes in whole-body metabolism and reduces fat mass, while resistance exercise preserves lean (muscle) mass [16]. While resistance training such as weight lifting increases myofibrillar muscle protein synthesis [17], muscle mass and strength [18].

Aerobic exercise increases insulin sensitivity independent of weight loss, inhibits hepatic lipid synthesis and stimulates fatty acid oxidation [19]. Also exercise increases fatty acid oxidation from adipose, intramyocellular, and possibly hepatic sources. Specifically, there is a significant increase during and after exercise in both very low density lipoprotein (VLDL) secretion and VLDL clearance by skeletal muscle, which may accelerate the removal of hepatic triglyceride concentration derived fatty acids. The capacity for VLDL clearance is also known to improve with regular exercise training [20].

2. Subjects and methods

Thirty volunteer patients from the El Sahel Teaching Hospital who had liver transplantation since six months were included in the study from February 2013 to September 2014. Their ages ranged from 45 to 55 years. They were examined carefully by the physician before the study procedures. The patients were excluded if they had cancer or were currently being treated for cancer of any origin, neurological or neuromuscular disorders, osteoarthritis or other orthopedic injury, multiorgan transplant recipients, patients used a wheelchair as their primary mode of mobility and any other cardiovascular contraindication to exercise testing and training [21].

2.1. Patients

The patients were randomly assigned into two main groups (A and B). Group A: (exercise group) included 15 patients who received the aerobic and resisted exercises in addition to traditional medical intervention. Group B: (Control group) included 15 patients who had not received any form of physical therapy intervention at any time during the study but this group was instructed and encouraged to remain active and received the traditional medical intervention.

2.2. Ethical consideration

The study protocol was explained in detail for each patient before the initial assessment and signed informed consent was obtained from each patient before enrollment in the study as well as acceptance of the Ethics committee of the University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

2.3. Assessment

Before initiating the treatment program, primary clinical and laboratory investigations were done (liver function tests, renal function tests and blood levels of the antirejection medication) to draw a complete picture of health for all patients and to decide if the patient is able to participate in the study. Each patient was examined medically in order to exclude any abnormal medical problem which was previously mentioned. The patient's name, age, weight and height, were written in the evaluation sheet of every patient. The assessment procedures were conducted before treatment application and at the end of the study after 3 months.

2.3.1. Assessment of BMI for each patient

Measuring weight and height of each patient by weight and height scale, BMI was calculated according to the following equation: BMI = weight (kg)/height (m^2). BMI was calculated before the study only to select the patients who had BMI > 30 kg/m^2 according to classification of obesity to participate in the study [22].

2.3.2. Body composition analyses

Different methods have been developed to measure body composition parameters. We used Bioelectrical Impedance Analysis (BIA), which is an easy, quick, cost-effective and painless test to determine body composition and fluid status and has been widely used in body composition analysis [23,24].

Fat mass and muscle mass were measured by using Bioelectrical Impedance Analysis (beurer BF 100_Body Complete, made in Germany).

All participants underwent body composition analysis in the morning following an overnight fast and wearing light indoor clothes. Patients were not allowed to drink during fasting and were asked to empty their bladders before measurements. The patients were asked to first wipe the sole of the feet by a wet tissue and then stand over the electrodes of the machine and data were recorded in 3–5 min.

2.3.3. Laboratory assessment

Venous blood samples were collected in polystyrene tubes after a 12 h fasting by venipuncture of the antecubital vein while patients rested in a supine position for estimation of serum triglycerides and cholesterol level.

2.3.4. Muscle strength testing (one-repetition maximum (1-RM) testing)

Only the patients in the exercise group were tested to determine the amount of weight or load to use as baseline loads in the first week of the 12-week program. They were tested in the following order of exercises: bench press, leg press, shoulder press, leg extension, biceps curl, leg curl, and triceps curl. The (1-RM) load was determined as follows. After a 30-min rest, the participants lifted increasingly heavy weights, and the maximal amount of weight that they could lift was recorded as the 1-RM for each exercise [25]. Participants were initially given instructions and shown how to perform the exercises and then practiced during a trial session before the baseline measurements. All exercise testing sessions were medically supervised.

2.4. Therapeutic exercise program

All exercise sessions and exercise prescriptions were supervised by a physical therapist and were conducted according to the guidelines set by the American College of Sports Medicine (ACSM) [26,27]. No strength training activities were permitted outside the supervised training session; however, both groups were allowed to pursue their normal daily activities. All patients were sedentary before starting the exercise program. The exercise-training sessions consisted of three 90-min sessions per week. Each session preceded by a 10 min warm-up on the treadmill at intensity of less than 50% of HR max and stretching exercises for: quadriceps, hamstring and calf muscles, 30 min of aerobic exercise, 30 min of progressive resistance training (PRT), and end with cooling down on the treadmill as intensity decreased gradually to resting heart rate.

The PRT program consisted of 8 basic resistive exercises: bench press, leg press, shoulder press, leg extension, biceps curl, leg curl, triceps curl, and toe raises. Initially, the weight-lifting sessions consisted of two sets of each exercise using a weight that allowed completion of six to eight repetitions of each exercise at ~65% of 1-RM with 60 s of rest between each set. After ~4 weeks, they progressed to three sets of 8–12 repetitions performed at 85% of initial 1-RM [25,28]. Participants tracked the amount of PRT by using a training log to document the weight and the number of repetitions performed. Measurements of 1-RM were repeated monthly so that workloads could be progressed for each participant.

The aerobic training on a treadmill either walking or running was based on heart rate, until the target heart rate was reached, according to American College of Sport Medicine guidelines. The program was conducted using the maximal heart rate index (HRmax) estimated by: 220-age. First 2 weeks = 60–70% of HRmax, 3rd to 12th weeks = 70–80% of HRmax [29].

2.5. Data analysis

Descriptive statistics and *t*-test were conducted for comparison of the mean age, weight, height, and BMI between both groups. Mixed ANOVA was conducted to compare between the pre and post treatment mean values of fat mass, muscle mass, cholesterol, and triglyceride levels in each group and between both groups. The level of significance for all statistical tests was set at $p < 0.05$. All statistical analyses were conducted through SPSS (statistical package for social sciences, version 19).

3. Results

3.1. Subject characteristics

There was no significant difference between both groups in the mean age, weight, height, and BMI ($p > 0.05$).Table 1.

3.2. Comparison between groups

There was no significant difference between exercise and control groups in fat mass, muscle mass, cholesterol, and triglycerides on pre-treatment levels ($p > 0.05$). Comparison between exercise and control groups post treatment revealed a significant decrease in fat mass, cholesterol, and triglycerides levels in the exercise group compared to control ($p < 0.001$), while there was a significant increase in muscle mass in the exercise group compared to control ($p = 0.0001$). Table 2, Figs. 1 and 2.

3.3. Comparison within the same group

3.3.1. Results of exercise group

There was a significant decrease in fat mass, cholesterol, and triglycerides levels and a significant increase in muscle mass post treatment in exercise group compared with pre treatment ($p = 0.0001$). Table 3, Figs. 1 and 2.

3.3.2. Results of control group

There was no significant difference in fat mass, muscle mass, and cholesterol level between pre and post treatment in control group ($p > 0.05$), while there was a significant increase in triglyceride level post treatment compared with pre treatment ($p = 0.02$) Table 3, Figs. 1 and 2.

4. Discussion

It can be assured that exercise training program (aerobic and resisted exercise) as a type of physical therapy approach was significantly more effective in the treatment of sarcopenic obesity and dyslipidemia (reducing fat mass, cholesterol and triglycerides levels while increasing muscle mass) post liver transplantation. Our results agree with Van et al. [30], who

Table 1 *t* Test for comparison between control and study groups in mean age, weight, height, and BMI.

	$\bar{x} \pm$ SD		MD	*t*- Value	*p*-Value
	Exercise group	Control group			
Age (years)	50.33 ± 2.87	51.2 ± 2.88	−0.87	−0.82	0.41*
Weight (kg)	93.46 ± 9.32	94.13 ± 11.39	−0.67	−0.17	0.86*
Height (cm)	166.06 ± 9.14	167.6 ± 9.91	−1.54	−0.44	0.66*
BMI (kg/cm^2)	33.86 ± 1.75	51.2 ± 2.88	0.44	0.71	0.48*

$\bar{x}$: Mean, SD: Standard deviation, MD: Mean difference, *t*-value: unpaired *t* value, *p*-value: Probability value.
* Non significant.

Table 2 Comparison of fat mass, muscle mass, cholesterol level, and triglycerides level between exercise and control groups pre and post treatment.

		Exercise group $\bar{x} \pm$ SD	Control group $\bar{x} \pm$ SD	MD	*p*-Value
Pre treatment	Fat mass (%)	35.18 ± 3.45	36.02 ± 3	0.84	0.48*
	Muscle mass (%)	29.24 ± 3.48	28.64 ± 3.3	0.6	0.62*
	Cholesterol (mg/dl)	289.06 ± 15.79	285.86 ± 16.42	3.2	0.59*
	Triglycerides (mg/dl)	289.8 ± 10.37	285.93 ± 12.17	3.87	0.35*
Post treatment	Fat mass (%)	31.83 ± 3.36	36.41 ± 3.3	−4.58	0.001**
	Muscle mass (%)	32.22 ± 2.9	28.3 ± 2.92	3.9	0.001**
	Cholesterol (mg/dl)	262.2 ± 12.57	289.86 ± 17.84	−27.66	0.0001**
	Triglycerides (mg/dl)	261.66 ± 15.77	291 ± 11.38	−29.34	0.0001**

$\bar{x}$: Mean, SD: Standard deviation, MD: Mean difference, *p*-value: Probability value.
* Non significant.
** Significant.

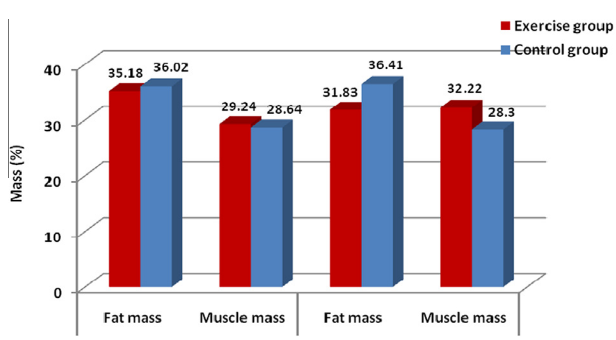

Figure 1 Pre and post treatment mean values of fat and muscle mass (%) of exercise and control groups.

found that eighteen recipients of a liver transplant participated in a 12-week rehabilitation program. After the program, participants were significantly less fatigued, and body fat was significantly lower.

Similarly, Roi et al. [31], who performed exercises consisting of 3 sessions per week of aerobic and strengthening exercises for 1 year on 5 patients with liver transplantations. Patients show a significant decrease in body mass index ($t = 1.966$; $p < .05$) and a maximum strength of knee extensors ($t = 2.933$; $p < .05$) and elbow flexors ($t = 2.450$; $p < .05$). These results confirm the positive effects of supervised physical exercise. Also, in a systemic review by Didsbury et al. [32] he found that, there was a consistent reduction in percentage body fat associated with exercise training compared with standard care in liver transplant recipients.

Tomás et al. [33] found that exercise improved body composition (lean mass and total body skeletal muscle mass), weight, and walking capacity in patients with LT. The improvements were more pronounced within the patients with supervised exercise training compared with the patients on the home-based program. In general, the benefits of the exercise training persist even after a 24-week detraining period.

According to, Donges et al. [34], who reported that the effect of 10 weeks of resistance or aerobic exercise training on alterations of total body fat mass (TB-FM), intra-abdominal fat mass (IA-FM), and total body lean mass (TB-LM). The results showed that the aerobic group exhibited significant

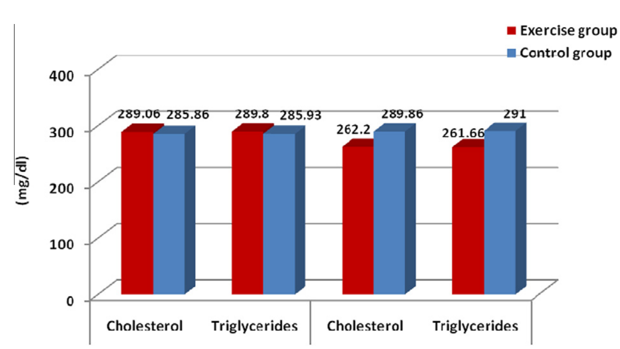

Figure 2 Pre and post treatment mean values of cholesterol and triglycerides (mg/dl) of exercise and control groups.

Table 3 Comparison of fat mass, muscle mass, cholesterol level, and triglycerides level between pre and post treatment in exercise and control groups.

		Pre treatment $\bar{x} \pm$ SD	Post treatment $\bar{x} \pm$ SD	MD	% of change	p-Value
Exercise group	Fat mass (%)	35.18 ± 3.45	31.83 ± 3.36	3.35	9.58	0.0001**
	Muscle mass (%)	29.24 ± 3.48	32.22 ± 2.9	−2.98	11	0.0001**
	Cholesterol (mg/dl)	289.06 ± 15.79	262.2 ± 12.57	26.86	9.23	0.0001**
	Triglycerides (mg/dl)	289.8 ± 10.37	261.66 ± 15.77	28.14	9.75	0.0001**
Control group	Fat mass (%)	36.02 ± 3	36.41 ± 3.3	−0.39	1.06	0.12*
	Muscle mass (%)	28.64 ± 3.3	28.3 ± 2.92	0.34	1.01	0.15*
	Cholesterol (mg/dl)	285.86 ± 16.42	289.86 ± 17.84	−4	1.42	0.08*
	Triglycerides (mg/dl)	285.93 ± 12.17	291 ± 11.38	−5.07	1.81	0.02**

$\bar{x}$: Mean, SD: Standard deviation, MD: Mean difference, p-value: Probability value.
** Significant.
* Non significant.

($p < 0.05$) improvements in all aerobic fitness measures and significant reductions in IA-FM (7.4%) and body mass (1.1%). Compared with the aerobic and the control groups, the resistance group significantly ($p < 0.05$) improved TB-FM (3.7%) and upper (46.3%) and lower (56.6%) body strength.

Garcia et al. [35], who concluded that the exercise program promoted significant improvements in functional capacity. These findings have positive implications for the control of metabolic diseases, which are common in patients after liver transplantation. Also, Kallwitz et al. [36] observed that, the exercise intensity is inversely related to metabolic syndrome after transplantation.

Ben Ounis et al. [37], they found that training intervention increased lipid oxidation during exercise, improved the plasma triglycerides and increased HDL-C. According to Johnson et al. [20], who assessed the effect of aerobic exercise training on blood lipids. Four weeks of aerobic cycling exercise, in addition to the current physical activity guidelines, the results was a significantly reduced visceral adipose tissue volume by 12% ($p < 0.01$) and hepatic triglycerides concentration by 21% ($p < 0.05$) and a significant (14%) reduction in plasma free fatty acids ($p < 0.05$).

The impact of exercise training on the lipid profile is variable. The possible mechanisms that explain the improvement in the lipid profile include increased muscle and adipose tissue PPARγ and PGC-1α messenger RNA expression after physical training, as demonstrated by Ruschke et al. [38]. Some studies [39,40] have reported low-density lipoprotein cholesterol reductions after aerobic and resistance training. Another study demonstrated a trend towards triglyceride level reductions after resistance training only [41], whereas others did not find any change after aerobic, resistance, and combined training [42].

Exercise exerts an effect on HDL-C maturation and composition, cholesterol efflux, and cholesterol delivery to receptors (reverse cholesterol transport). Positive effects of exercise are also seen with blood triglycerides (TG), but little specific effect is seen on low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) [43].

In conclusion, we found that, a combination of aerobic exercise and resisted exercise had a significant effect on sarcopenic obesity (reduce fat mass and increase muscle mass) and dyslipidemia (reduce cholesterol and triglyceride levels). For this, a program of aerobic and resisted exercise training should form a core for most patients after liver transplantation aiming to improve post transplantation health and survival, helping to ensure that physical activity becomes a safe routine medical treatment plan of patient management.

Conflict of interest

The authors declare no conflict of interests.

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