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Liver repair of NAFLD patients following effortless exercise and the possible involvement of endogenous stem cells

Abstract

Adipose tissue derived stem cells differentiate into mesenchymal stem cells (MSCs) and hepatocytes which are involved in anti-inflammatory, reparatory, and detoxification processes reinstating liver function. Aerobic, resistance and effortless workouts have been proven to be beneficial for patients with NAFLD, possibly due to stem cells released into the bloodstream from metabolized fat during exercise induced natural lipolysis. We analysed the serum levels of a number of variables such as ALT, AST, ALP, albumin, creatinine, bilirubin, triglycerides and CRP to determine if effortless exercise would demonstrate an improvement of the NAFLD condition that is substantially equivalent to liver repair documented after administering exogenous MSCs injections. We examined 10 prediabetic individuals with NAFLD, 5 males and 5 females 54-64 years of age, who received 15 treatments with an effortless exercise technology, originally invented at London University for obese individuals who have difficulty performing strenuous workouts, as well as those with limited mobility due to age or disease. The hypothesis was that the reduction of triglycerides and visceral adipose tissue (VAT) is accompanied by a natural release of adipose tissue contents into the bloodstream, supplying endogenous MSCs that differentiate into hepatocytes necessary for healthy liver functioning. Results demonstrated a statistically significant improvement of the NAFLD condition in ultrasonography reports along with optimal levels of ALT, AST, ALP, albumin, creatinine, bilirubin and CRP. Additional findings included a notable decrease in triglycerides, VLDL, BMI, VAT, and cortisol, accompanied by an increase in testosterone, BMR, and muscle mass. Our results replicated previous studies which documented a significant repair of hepatic steatosis in ultrasonography reports after using this effortless exercise regimen. The current clinical study strongly suggested the involvement of endogenous MSCs that are vital in organ repair. Reducing VLDL, VAT and triglycerides optimizes health, setting the conditions for the reparative process to commence. The possibility of endogenously released MSCs as a result of an exercise method is a new perspective with very little past research, therefore, more clinical studies focusing on this hypothesis are warranted. Demonstrating the production of endogenous MSCs via an exercise modality will introduce novel treatments for metabolic disorders without the adverse effects often observed after stem cells injections or invasive and trauma based procedures.

Keywords: visceral adiposity, effortless exercise, inflammation, creatinine, bilirubin, cortisol, testosterone, metabolic disorders, diabetes

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Abbreviations: NAFLD, Non-alcoholic fatty liver disease; MSCs, mesenchymal stem cells; ALP, Alkaline phosphatase; HDL, high-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, VLDL, very low-density lipoprotein; BMI, body mass index; BMR, basal metabolic rate

Introduction

The reparative function of adipose tissue-derived stromal, Mesenchymal Stem Cells (MSCs) and hepatocytes

Research has revealed that human adipose tissue can provide a fibroblast-like population of cells that manifest low levels of senescence and primarily contain mesodermal and mesenchymal cells with some endothelial cells, smooth muscle cells and hepatocytes that play a critical role in the detoxification, metabolism, and protein synthesis in the liver.[1] Another type of cell derived from adipose tissue is stromal cells can differentiate into connective tissue cells of any vital organ.[2] The term "stomal" comes from the Greek word "στρῶμα", which means mattress. Stromal cells are instrumental in binding clusters of cells together, a process that ultimately repairs tissue damage. Stromal cells can also develop into blood vessels and lymphatic tissue.[3] Despite the negative connotations associated with adipose tissue stemming from reports of compromised health as a result of obesity, in fact, the natural release of fat into the bloodstream can be utilized both for energy production, as well as provide an array of cells that can facilitate important reparative processes. The substantial benefits of naturally released fat contents, via centrally controlled processes as it happens during different exercise modalities, are not taken into consideration by popular weight loss procedures like lasers, and RF that specialize in the forceful ablation of subcutaneous adipose tissue and the traumatic rupture of fat cells membrane. This is why, after all these remarkable technological developments, exercise and an active lifestyle are still recommended as the best solutions for health maintenance and longevity.

The embryonic origin of adipose tissue appears to be intricately connected to the mesoderm. A study by Lua et al.[3] reported that the mesoderm produces mesodermal and mesothelial cells that are differentiated into hepatic stellate cells, the primary source of myofibroblasts. Myofibroblasts are involved in the formation of new

connective tissue, or granulation tissue which is an important aspect of wound healing. Hepatic stellate cells, however, are not multipotent enough to produce hepatocytes.[4]

The adipose tissue produces an abundance of mesenchymal stem cells (MSCs). MSCs are at a rate of 1 in 100 in adipose tissue in contrast to 1 in 100,000 in the bone marrow. They have been shown to be immune regulators, and proinflammatory inhibitors.[5,6] MSCs are multipotent stem cells that can divide and develop into multiple specialized cell types.

Banas et al.[7] have reported that MSCs derived from adipose tissue can differentiate into hepatocytes, the primary cell types of the liver after they have been incubated with certain growth factors that include hepatocyte and fibroblast growth factors.[7] The hepatocyte cells derived from MSCs are involved in producing albumin, a protein made by the liver. Abnormal levels of albumin may indicate liver disease, kidney problems or an inflammatory illness. Hepatocyte cells are also involved in the detoxification and clearance of LDL (low-density lipoprotein) and VLDL (very low-density lipoprotein). High LDL and VLDL have been consistently associated with atherosclerosis and coronary heart disease.[8]

Adipose tissue derived MSCs contribute to the repair of vital organs such as the liver, heart, kidney, lung, and brain, via the delivery of signalling agents such as cytokines and growth factors.[9]

According to Li et al.[10] MSCs were more instrumental in modulating inflammation and fibrosis in the injured liver than hematopoietic stem cells.[10] Chronic liver disease results in liver fibrosis which eventually becomes liver cirrhosis, a major health problem worldwide.

In conclusion, MSCs have been widely implemented in liver regeneration and repair of liver dysfunction, injury, or disease. Kharaziha et al.[11] noted improvements in eight patients suffering from liver cirrhosis based on a variety of aetiologies that included hepatitis B, C and alcoholism. Patients were injected with around 30 to 50 million MSCs. Significant improvements in liver function were reported: Serum creatinine decreased from 114+/-35 to 80+/-18μmol/l (P<0.05), in the absence of any side effects or adverse reactions. Serum albumin and bilirubin decreased, however, these results were statistically non-significant.[11]

Overall, MSCs therapies are preferable due to being more accessible and safer than liver transplantation. MSCs can enhance liver tissue regeneration without usually invoking an undesirable immune response while increasing albumin, and reducing alanine aminotransferase (ALT) which is generally associated with jaundice, a condition identified by a yellowish hue on the skin and eyes, and interleukin- 1β (IL-1β), a pro-inflammatory cytokine produced by macrophages, a type of white blood cells, activated during inflammatory infections.[12] Despite its remarkable benefits, cell transplantation involves some negative effects like cell rejection by the body and adverse reactions such as abnormal cell division leading to the formation of tumours and carcinogenesis that is irreversible.[13] In light of such adverse reactions, it becomes obvious that centrally produced endogenous MSCs, following the natural adipose tissue release into the bloodstream via different exercise modalities is the optimal solution.

The problem with fatty liver

Non-alcoholic fatty liver disease (NAFLD) begins with what is commonly known as fatty liver and progresses to non-alcoholic steatohepatitis and which can eventually result in liver cirrhosis and hepatic cancers. Liver integrity is central to overall health.

Caldwell et al.[14] reported that 74% of patients with cryptogenic cirrhosis had a history of diabetes and/or obesity. Cryptogenic cirrhosis is an irreversible condition of liver scarring that may be due to a viral infection, genetics or alcoholism.[14] Angulo[15] also postulated that risk factors for non-alcoholic steatosis included obesity, non-insulin-dependent diabetes and hyperlipidaemia.

Adams et al.[16] analysed the morbidity rate of 420 patients with fatty liver and found that survival was lower and that liver disease was the third leading cause of death. Additionally, these investigators postulated a correlation between NAFLD and impaired fasting glucose.[16]. Ekstedt et al.[17] confirmed that NAFLD results in higher mortality rates among people with non-alcoholic hepatic steatosis and reported a close association between liver disease, obesity, impaired glucose tolerance and insulin resistance. Marchesini et al.[18] connected the presence of metabolic disorders with non-alcoholic liver disease and postulated a high correlation between liver disease and obesity, diabetes, dyslipidaemia, hypertension, and metabolic syndrome.

The relationship between creatinine, fatty liver and kidney disease

Niu et al.[19] examined the serum creatinine levels of 8862 individuals between 40-73 years old and found that elevated creatinine levels were associated with the risk of developing non-alcoholic hepatic steatosis, which results from visceral fat deposits surrounding and invading the liver, a condition commonly known as fatty liver. According to these investigators, high serum creatinine levels were also correlated with alanine aminotransferase or ALT ($p<0.001$), aspartate aminotransferase or AST which also indicates hepatitis, cirrhosis or other liver disease ($p<0.001$), as well as insulin resistance which is prognostic of prediabetes ($p<0.014$).[19]

Sookoian and Pirola[20] analysed serum creatinine levels and uric acid levels in 3359 subjects and concluded that a high ratio of creatinine /uric acid was highly correlated with non-alcoholic hepatic steatosis suggesting the involvement of a connection between fatty liver and kidney disease.[20] Other investigators who used computed tomography have confirmed the validity of these results of a high uric acid/creatinine index being predictive of NAFLD.[21] Sinn et al.[22] followed 41,430 adult men and women with non-alcoholic steatosis diagnosed on the basis of ultrasonography and concluded that NAFLD adversely affects kidney function, increasing the risk of chronic kidney disease.

Alanine aminotransferase (ALT) as a predictor for fatty liver

Excess of Alanine Aminotransferase (ALT) or otherwise known as serum glutamic-pyruvic transaminase (SGPT), an enzyme primarily found in the liver, often produces jaundice (yellow skin or eyes), nausea, fatigue, light-coloured stool and dark-coloured urine.

Kim et al.[23] stressed the significance of persistently elevated ALT in the diagnosis of liver disease.[23] Wedemeyer et al.[24] reported that elevated ALT levels are correlated with liver disease. However, these investigators revealed that increased ALT values are also associated with Diabetes Mellitus (type 2), metabolic syndrome, cardiovascular diseases and cancer. These investigators also reported that ALT levels are generally elevated in the majority, but not all individuals with liver disease, suggesting the possibility that liver disease may be also present in patients with normal ALT levels.

The relationship between ALT, Insulin resistance and metabolic syndrome

Fraganzani et al.[25] has reported that older individuals with NAFLD who manifest relatively lower levels of triglycerides, BMI (body mass index) and insulin resistance may present normal levels of ALT. In other words, insulin resistance and metabolic syndrome that are associated in most patients should also be taken into consideration in addition to ALT levels in diagnosing liver disease.

Verma et al.[26] examined 222 patients with non-alcoholic liver disease and reported that 23% of these patients had normal ALT. These investigators concluded that other variables associated with metabolic syndrome should be taken into consideration in evaluating liver disease which may be present despite normal ALT levels.

Aspartate aminotransferase (AST) as a predictor of NAFLD

Patients with elevated levels of AST present similar symptoms as those presented with increased ALT values, which include jaundice, nausea, fatigue, swollen belly, swelling of the ankles, bruises, etc.

Abangah et al.[27] indicated that high BMI and AST are reliable predictors of non-alcoholic fatty liver disease (NAFLD). They also suggest that high levels of triglycerides should be also taken into consideration in evaluating NAFLD, because laboratory tests may not be sensitive in the diagnosis of early stages of NAFLD.[2] Hossain et al.[28] examined 432 patients with NAFLD that was histologically documented. They found that these patients have both elevated AST ($p<0.0001$) and ALT ($p<0.0001$). Additionally, these patients had increased levels of triglycerides ($p<0.0154$). They also found that NAFLD was highly correlated with males ($p<0.0189$), Caucasians ($p<0.0375$), Diabetes Mellitus ($p<0.0238$) and hypertension ($p<0.0375$).

Elevated AST and ALT combined as a more accurate predictor of NAFLD

Research studies concur that elevated AST and ALT analyzed together are reliable predictors of NAFLD.[29-32] Tomei et al.[33] investigated the effects of hepatotoxic substances (e.g., glues) in the liver in 61 shoe repair craftsmen, based on the laboratory results of AST, ALT, bilirubin, and ALP. All these variables were elevated indicating liver damage even in those workers who presented no symptoms of liver disease. The ratio of ALT to AST was greater than 1, with a mean of 1.5.

Papadia et al.[34] investigated 1000 obese patients with hepatic steatosis and bridging fibrosis based on liver biopsies. They found a significant correlation between steatosis/bridging fibrosis and AST, ALT, AST/ALT ratio, BMI, glucose, triglycerides levels and bilirubin. These investigators reported that bridging fibrosis was associated with diabetes, hypertension and significantly higher values of AST, glucose, and cholesterol. Inflammation was more pronounced in older patients. As expected since inflammation increases with ageing and is considered one of the most significant contributors to the ageing process.

Alkaline phosphatase, ALP as predictor of NAFLD

ALP is a liver enzyme primarily found in the liver. It is also available in the bones, kidneys, intestines, placenta, and generally throughout the body. High levels of ALP may indicate liver disease or a certain bone disorder.

Razavizade et al.[35] compared the ultrasonography of 245 NAFLD patients with their serum results on ALT, ALP, triglycerides, high and low-density lipoproteins (HDL and LDL) and cholesterol. Patients were divided into mild, moderate, and severe NAFLD based on the ultrasonography reports. These investigators reported a correlation between the level of severity as diagnosed by ultrasonography and serum concentrations of ALT, triglycerides, and high-density lipoprotein (HDL). Alkaline phosphatase (ALP) did not make the threshold for diagnosing severity level of NAFLD.

Other investigators analyzed the serum variables of 132,377 individuals (64,875 men and 67,502 women aged 35-79). They found correlations between NAFLD, ALT, AST, and ALP and an increased risk for diabetes. Hazard ratio (HR) as calculated by Cox regression produced significant results for diabetes risk as follows for men: ALT: HR 1.27 AST: HK 1.23 ALP: HR 1.37. And for women ALT: HR 1.56 AST: HK 1.18 ALP: HR 1.44. This research indicated that ALT and ALP are slightly better predictors in women rather than men in evaluating risk for Diabetic disease.[36]

Ali et al.[37] examined 210 patients with at least stage 2 fibrosis and used logistic regression to determine the independent predictors of fibrosis. They concluded that ALP and ALT were both reliable predictors of liver fibrosis.

Elevated cortisol as a predictor of NAFLD

Targher et al.[38] examined 50 patients with NAFLD whom he compared to 40 controls. They reported that patients identified with NAFLD presented a "subclinical hypercortisolism," indicating elevated cortisol levels.

Ahmed et al.[39] found that cortisol metabolites were elevated in patients with steatosis as expected by the involvement of glucocorticoids in NAFLD who usually have high glucocorticoids. About 20% of Cushing syndrome patients, a condition that develops as a result of hypercortisolism or excess cortisol, manifest abdominal adiposity, insulin resistance and NAFLD. On the other hand, a study on 1326 NAFLD patients, 662 women and 664 men did not find a direct association between high cortisol levels and liver disease.[40]

Elevated cortisol values have been widely associated with stress-eating behaviours and weight gain. Cortisol levels are beyond the direct control of lasers and RF methodologies that promise effective lipolysis. Hence, results after laser and RF lipolysis will rebound.

High BMI is associated with a significant increase in triglycerides which is one of the landmarks of NAFLD that is generally identified by a liver triglyceride content of >5% by weight.[41] Therefore, cortisol appears to be indirectly linked to the development of NAFLD.

Visceral adipose tissue triglycerides as a predictor of NAFLD

Excess triglycerides in the hepatocytes (the main liver parenchymal cells) increase the number of fatty acids stored in the liver leading to NAFLD which is considered an independent predictor of cardiovascular disease, diabetes, hepatic steatosis, and metabolic syndrome. The primary source of liver triglycerides comes from fatty acids in the visceral adipose tissue. Excess triglycerides overload the liver with reactive oxygen species (ROS) that increase inflammation via cytokine production and chemoattraction of inflammatory cells. According to Vanni et al.,[42] NAFLD is untreatable.

Kawano et al.[43] postulate that excess triglycerides in the liver are the result of insulin resistance. Insulin is like a key to a lock of

the glucose channel, signalling the cells to release glucose into the blood which is ultimately burned in the mitochondria for energy production. An insulin-regulated feedback loop triggers the storage of excess glucose in the blood back into the cells, via additional insulin action. This process is interrupted both by insulin resistance and hyperinsulinemia which are characterized by defective insulin signalling. According to Kawano et al, hyperinsulinemia "promotes the transcriptional upregulations of genes" involved in increased "lipogenesis in the liver".

The results of exercise on NAFLD

Hashida et al.[44] have reported that 12 weeks of aerobic and resistance exercises improved hepatic steatosis in NAFLD patients. However, exercise did not completely repair the NAFLD condition.

Aamann et al.[45] examined 173 individuals with stage A or B cirrhosis whom they divided into the exercise and the control group. The experimental group underwent eight o thirteen weeks of aerobics, resistance, and aerobics plus resistance exercises. The overall exercise program was neither beneficial nor detrimental to the 84 patients in the exercise group and did not seem to make a difference in these individuals' health or quality of life. Thirteen patients from the control group and eight patients from the exercise group had serious adverse effects indicating that there were no significant differences between the exercise and no exercise groups in terms of harmful side effects.

Romero-Gomez et al.[46] discuss the importance of lifestyle in the regulation of NAFLD. They report that a combination of diet, physical activity and exercise can improve NAFLD by at least one stage.

Effortless exercise solutions

Several research studies have used an effortless exercise technology, originally invented at London University. They have reported optimal levels of creatinine, bilirubin, C-reactive protein (CRP), cortisol, VLDL (very low-density lipoprotein), HDL (high-density lipoprotein), glucose, insulin, and triglycerides. They have also documented a significant decrease in visceral fat, and weight loss, juxtaposed with an optimal increase of testosterone, Free Triiodothyronine (T3), the active thyroid hormone involved in the regulation and control of metabolism, growth hormones, muscle mass, and a balanced profile of leptin and ghrelin that is necessary to stabilize appetite and eliminate cravings to avoid rebound.[47-50]

How effortless exercise works

The treatment sends a motor nerve blueprint signal developed over a period of 20 years at London University. This resonates with the nervous system, exciting the sensory nerves which carry the signal to the brain, triggering the secretion of hormones that naturally release the fat contents into the bloodstream reinstating hormonal balance. Simultaneously, the motor nerves synchronize the muscles into a full body coordinated contraction that is induced centrally as seen during a strenuous workout.

This is a different process than electrostimulation which directly depolarizes small clusters of muscle cells, without involving the central nervous system and without causing a coordinated full-body muscle contraction as is observed during regular exercise.

After fifteen treatments with this technology, patients with nonalcoholic hepatic steatosis prior to the procedure exhibited a healthy liver in sonography reports after a period of 5 weeks.[47]

Pilot clinical study

The hypothesis of this clinical trial was based on the reasoning that reducing visceral fat alone cannot account for the substantial liver repair observed in previous studies.[47-50] Regular exercise research has revealed that twelve weeks of aerobics and resistance exercises improve hepatic steatosis but without completely repairing the condition. Overall, exercise helps reduce visceral fat and fatty liver triglycerides but without any significant changes in BMI.

Other studies that implement regular exercise with liver cirrhosis patients report no improvement. If 15 effortless exercise treatments result in no fatty liver in sonography reports, visceral fat and triglycerides decrease can only be part of the story. An additional mechanism must be involved in the liver reparative process that involves adipose tissue stem cells, naturally released into the bloodstream. We evaluated the serum levels of the most common predictors of liver damage, ALT, AST, ALP, Albumin, CRP, Triglycerides, Creatinine and Bilirubin along with ultrasonography results before and two weeks after 15 effortless exercise procedures.

Subjects and methodology

Ten prediabetic subjects with NAFLD were included in this study with an average BMI of 31.99, 5 males and 5 females aged 54 to 64 years of age. All subjects had been diagnosed with prediabetes and hepatic steatosis on sonography reports and other independent tests, the results of which are shown below. Each subject financed his/her own ultrasonography reports and blood tests that were obtained pre and two weeks post the 15 treatments. The subjects were approached by their doctors, two to three months after treatment completion. Very few subjects, a total of ten agreed to release their results for research purposes. This eliminated the selection threat to validity since neither the author nor the subjects' doctor chose any of the subjects. Subjects' participation was determined by their consent to publicize their results which was based purely on personal reasons. The subjects were never privy to the purpose or the study's hypotheses.

This entire research was based on a post-hoc data analysis after the subjects had completed all the treatments and had received their test results which were done in independent laboratories. Neither the subjects, the laboratory technicians, nor the doctors were aware of the purpose and hypotheses of this clinical study or its hypothesis before, during or after completing the 15 procedures which were offered three times weekly over a period of 5 weeks. This clinical trial took around two years to complete, mainly because most individuals did not agree to release their results. Finding subjects who were willing to share their results proved to be a laborious expedition.

Inclusion and exclusion criteria

Subjects that were included in the study had a BMI>29. They were all diagnosed with Prediabetes and NAFLD. Only subjects who had received 15 treatments in a period of 5 weeks with the effortless exercise technology were included in the clinical data. Subjects who had received less or more treatments at a different length of time were not included.

All subjects agreed to share the results of their ultrasonography reports. All subjects agreed to share their blood test results on ALT, AST, ALP, Albumin, Creatinine, Bilirubin, Triglycerides, VLDL, and CRP. Only subjects who had documented before and after treatment measurements on their BMI, BMR, visceral adipose tissue, cortisol, testosterone, and overall muscle mass were included. None of the subjects had a surgical procedure or any other invasive or minimally

invasive procedure in the past year. Subjects with a history of Diabetes, Alcoholism, Drug Addiction, Cancer, Liver Cirrhosis or COVID-19 infection were excluded.

Instruments and variables measured

The data collected included Ultrasonography repots, blood tests that tested before and after serum levels of ALT, AST, ALP, Albumin, Creatinine, Bilirubin, Triglycerides, VLDL, CRP, testosterone, and cortisol. Other measurements were based on the subjects' before and after results on the athletic setting of Tanita Conductance scale that calculate, Visceral Fat. Body Mass Index (BMI), Basal Metabolic Rate (BMR) and Muscle Mass (MM)

Ethical consideration

Every precaution was taken to protect the subjects' privacy and the confidentiality of their personal information. Subjects were informed that they had the right to discontinue treatment at any time. The data collected was approved by the Ethical Boards of the participating clinics.

Results

Subjects previously diagnosed with NAFLD prior to the 15 treatments showed no fatty liver on their follow-up ultrasonography reports.

Hernaez et al.[51] reviewed 49 studies with 4720 participants that compared ultrasonography results with those of histology or other imaging techniques. They concluded that ultrasonography is a reliable method of diagnosis of moderate to severe cases of hepatic steatosis.

Subjects' individual results on ALT, AST and ALP and albumin are given on Table 1. T-test for repeated subjects design yielded statistically significant results.

Table 1 Blood Test Results on ALT (SGPT), AST (SGOT), ALP and Albumin

Gender Age	ALT IU/L Pre	ALT IU/L Post	AST IU/L Pre	AST IU/L Post	ALP IU/L Pre	ALP IU/L Post	Albumin g/dL Pre	Albumin g/dL Post
F/64	28	24	38	31	109	89	3.0	3.9
F/58	34	25	39	28	117	92	3.4	4.3
F/59	33	26	41	30	114	87	3.1	4.1
F/54	36	23	39	29	120	105	3.6	4.2
F/62	29	22	41	26	122	112	3.2	4.0
M/54	27	19	40	22	119	106	3.3	4.3
M/57	32	21	36	24	112	98	3.5	4.0
M/59	31	26	38	31	118	102	3.1	3.9
M/60	27	22	39	18	121	104	3.7	3.9
M/55	33	25	42	29.	118	105	3.3	4.0
Mean Total	31	23.3	39.3	26.8	117	100	3.32	4.06
	ALT Average Decrease: -24.83%		AST Average Decrease: -30.407%		ALP Average Decrease: -14.529%		Albumin Average Increase: +%22.289	
	Value of t= -8.724 The value is p=0.00001 Significance: p<0.0001		Value of t= -8.83 The value is p=0.00001. Significance: p<0.0001		Value of t= -10.8912 The value is p=0.00001. Significance: p<0.0001		Value of t=+9347886 The value is p<0.00001. Significance: p<0.00001	

ALT Normal Range: 0-32 IU/L

AST Normal Range: 0-40 IU/L

ALP Normal Range: 44-121 IU/L

Albumin Normal Range: 3.8-4.8

Subjects' individual results on Bilirubin, Creatinine and Ultrasonography reports are given on Table 2. T-test for repeated subjects design yielded statistically significant results. In terms of the ultrasonography reports 7 out of 10 subjects evidenced normal liver (70%).

Table 2 Subjects results on creatinine and bilirubin & ultrasonography results

Gender/ Age	Medical History	Creatinine Serum PRE mg/dL	Creatinine Serum POST mg/dL	Bilirubin PRE mg/dL	Bilirubin POST mg/dL	Ultrasonography Results
F/64	Pre diabetes Fatty Liver	1.35	0.94	1.13	1.09	Normal Liver
F/58	Prediabetes Fatty Liver	1.23	0.87	1.29	1.18	Normal Liver
F/59	Pre diabetes Fatty Liver	1.26	1.05	1.23	1.14	Normal Liver

Table Continued...

Gender/ Age	Medical History	Creatinine Serum PRE mg/dL	Creatinine Serum POST mg/dL	Bilirubin PRE mg/dL	Bilirubin POST mg/dL	Ultrasonography Results
F/54	Pre diabetes Fatty Liver	1.33	0.96	1.75	1.19	Normal Liver
F/62	Pre diabetes Fatty Liver	1.25	1.02	1.21	1.15	Normal Liver
M/54	Pre diabetes Fatty Liver	1.13	1.01	1.27	1.19	Normal Liver
M/57	Pre diabetes Fatty Liver	1.16	0.82	1.23	1.12	Normal Liver
M/59	Pre diabetes Fatty Liver	1.18	0.98	1.41	1.15	Normal Liver
M/60	Pre diabetes Fatty Liver	1.11	0.87	1.22	1.17	Normal Liver
M/55	Pre diabetes Fatty Liver	1.96	1.23	1.47	1.20	Normal Liver
MEAN TOTAL		1.22 mg/dL	0.98 mg/dL	1.321 mg/dL	1.158 mg/dL	
Mean Average Creatinine % Decrease -19.67% mg/dL Value of t=-59420 The value is p=0.00011. Significance: p<0.001				Mean Average Bilirubin % Increase -12. 33% mg/dL Value of t=-3.1911 The value is p=0.00549. Significance: p<0.01		

Creatinine Normal Range: 0.5-1.10 mg/dL

Bilirubin Normal Range: 0.3-1.2 mg/dL

Subjects' individual results on Triglycerides, VLDL and CRP are given on Table 3. T-test for repeated subjects design yielded statistically significant results.

Table 3 Blood Test Results on TG, VLDL and CRP

Gender Age	Medical History	TG mg/dL Pre	TG mg/dL Post	VLDL mg/dL Pre	VLDL mg/dL Post	CRP mg/L Pre	CRP mg/LPost
F/64	Fatty Liver Prediabetes	195	146	45	32	14	9
F/58	Fatty Liver Prediabetes	193	147	43	35	12	7
F/59	Fatty Liver Prediabetes	167	123	41	34	11	8
F/54	Fatty Liver Prediabetes	156	129	38	31	12	9
F/62	Fatty Liver Prediabetes	178	134	48	36	15	10
M/54	Fatty Liver Prediabetes	188	139	40	29	13	8

Table Continued...

Gender Age	Medical History	TG mg/dL Pre	TG mg/dL Post	VLDL mg/dL Pre	VLDL mg/dL Post	CRP mg/L Pre	CRP mg/LPost
M/57	Fatty Liver Prediabetes	183	141	42	32	15	9
M/59	Fatty Liver Prediabetes	191	146	37	28	10	7
M/60	Fatty Liver Prediabetes	172	132	39	29	11	8
M/55	Fatty Liver Prediabetes	159	115	43	32	13	9
Mean Average		178.2	135.2	41.6	31.8	12.6	8.4
		TG % decrease: -24.130%		VLDL % decrease: -23.55%		CRP % decrease: -33.333%	
		Value of t=-7.431		Value of t=-9.175		Value of t=-11.698	
		The value is p=0.00002. Significance: p<0.0001		The value is p<0.00001. Significance: p<0.00001		The value is p<0.00001. Significance: p<0.00001	

TG Normal Range: 0-149 mg/dL

VLDL Normal Range: 5-40 mg/dL

CRP Normal Range: 0-10 mg/L

Subjects' individual results on BMI, BMR and visceral adipose tissue (VAT) are given on Table 4. T-test for repeated subjects design yielded statistically significant results.

Table 4 BMI, BMR and VAT

Gender Age	Medical History	BMI Pre	BMI Post	BMR Pre	BMR Post	VAT Pre	VAT Post
F/64	Fatty Liver Prediabetes	34.2	26.5	920	1490	39	27
F/58	Fatty Liver Prediabetes	33.5	25.9	1005	1510	33	21
F/59	Fatty Liver Prediabetes	30.4	24.7	1156	1499	51	32
F/54	Fatty Liver Prediabetes	32.3	26.6	1098	1620	39	23
F/62	Fatty Liver Prediabetes	30.8	24.9	953	1457	42	29
M/54	Fatty Liver Prediabetes	31.6	25.7	1167	1663	48	31
M/57	Fatty Liver Prediabetes	31.1	24.8	1249	1833	35	26
M/59	Fatty Liver Prediabetes	32.4	27.4	1055	1692	39	28
M/60	Fatty Liver Prediabetes	31.2	26.3	1012	1757	41	27

Table Continued...

Gender Age	Medical History	BMI Pre	BMI Post	BMR Pre	BMR Post	VAT Pre	VAT Post
M/55	Fatty Liver Prediabetes	32.4	25.3	1179	1633	43	29
		31.9	25.81	1079.4	1615.4	41	27.3
Mean Average		BMI % decrease: -19.09%		BMR% INCREASE: +49.650%		VAT % decrease: -33.41%	
		Value of t= -14.012		Value of t=+15.685		Value of t=-12.064	
		The value is p<0.00001. Significance: p<0.00001		The value is p<0.00001 Significance: p<0.00001		The value is p<0.00001 Significance: p<0.00001	

BMI Normal Range Men (depending on weight and height): 1-24

BMI Normal Range Women (depending on weight and height): 1-23

BMR Normal Range Men: 1600-1800 cal/ per day.

BMR Normal Range Women: 1550. Cal/per day

VAT (ranges from 1-59)

Normal Range: 1-12

Subjects' individual results on Cortisol, Testosterone and overall muscle mass are given on Table 5. T-test for repeated subjects design yielded statistically significant results.

Table 5 Blood Test Results on Cortisol (F), Testosterone (T) and Muscle Mass (MM)

Gender Age	Medical History	Cortisol Pre	Cortisol Post	T Pre	T Post	MM Pre	MM Post
F/64	Fatty Liver Prediabetes	481	319	0.4	1.27	24	36
F/58	Fatty Liver Prediabetes	455	247	0.6	1.26	29	38
F/59	Fatty Liver Prediabetes	462	325	0.5	1.38	26	40
F/54	Fatty Liver Prediabetes	449	354	0.8	1.44	25	39
F/62	Fatty Liver Prediabetes	396	286	0.7	1.22	23	42
M/54	Fatty Liver Prediabetes	476	368	11.99	18.54	29	49
M/57	Fatty Liver Prediabetes	451	312	12.89	19.33	30	51
M/59	Fatty Liver Prediabetes	479	347	11.92	17.62	29	46
M/60	Fatty Liver Prediabetes	478	366	12.12	17.57	26	38
M/55	Fatty Liver Prediabetes	429	325	14.7	20.33	31	52

Table Continued...

Gender Age	Medical History	Cortisol Pre	Cortisol Post	T Pre	T Post	MM Pre	MM Post
Mean Average		455.6	324.9	6.36	9.996	27.2	43.1
		Cortisol % decrease: -28.687%		Testosterone % INCREASE: +50.04%		Muscle Mass % INCREASE: +58. 45%	
		Value of t= -14.01212.190		Value of t=+3.786		Value of t=+11.746	
		The value is p<0.00001 Significance: p<0.00001		The value is p=0.00215 Significance: p<0.01		The value is p<0.00001 Significance: p<0.00001	

Cortisol Normal Range Men and Women: 80-477 nmol/l

Testosterone Normal Range Men: 10-35 nmol/l

Testosterone Normal Range Women: 0.5 – 2.4 nmol/l

Muscle Mass Male and Female ages 54-64: Average; 33-55

Low: < 33 High: >55

Subjects' detailed t-test values are given on Table 6. All variables were statistically significant.

Table 6 Statistical calculations and significance tables

	Mean	$S^2 = SS/df$	$S^2_M = S^2/N$	$S_M = \sqrt{S^2_M}$	$t = (M - \mu)/S_M$	%	P=value	P<
ALT	-7.7	7.79	0.78	0.88	-8.72	-24.83%	0.00001	P<0.0001
AST	-12.5	20.06	2.01	1.42	-8.83	-30.4%	0.00001	P<0.0001
ALP	-17	26.8	2.44	1.56	-10.89	-14.5%	0.00001	P<0.0001
Albumin	+0.74	0.06	0.01	0.08	+9.35	+22.28%	0.00001	P<0.0001
Creatinine	-0.32	0.03	0	0.05	-5.95	-19.67%	0.00011	P<0.001
Bilirubin	-0.16	0.03	0	0.05	-3.19	-12. 33%	0.00549	p<0.01
TG	-32.3	188.9	18.89	4.35	-7.43	-24.13%	0.00002	p<0.0001
VLDL	-6.9	5.66	0.57	0.75	-9.18	-23.55%	0.00001	p<0.00001
CRP	-4.2	1.29	0.13	0.36	-11.7	-33.33%	0.00001	p<0.00001
BMI	-5.33	1.45	0.14	0.38	-14.01	-19.09%	0.00001	p<0.00001
BMR	+536	11677.33	1167.73	34.17	+15.69	+49.650%	0.00001	p<0.00001
VAT	-12.9	11.43	1.14	1.0	-12.06	-33.41%	0.00001	p<0.00001
Cortisol	-130.7	1149.57	114.96	10.72	-12.19	-28.68%	0.00001	p<0.00001
TTST	+3.33	7.75	0.78	0.88	+3.79	+50.04%	0.00215	p<0.01
MM	+15.9	18.32	1.83	1.35	+11.75	+58. 45%	0.00001	p<0.00001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TG: triglycerides

VLDL: very low density lipoprotein; CRP: C-reactive protein; BMI: body mass index; BMR: basal metabolic rate VAT: visceral adipose tissue; MM: muscle mass; TTST: testosterone

Discussion

The study hypothesis was that effortless exercise naturally releases adipose tissue stem cells into the bloodstream which can be subsequently used for the repair of the liver in NAFLD. Our hypothesis was based on the reasoning that triglycerides and visceral fat reduction alone cannot account for liver repair. Another healing mechanism must be involved. This brought into play the concept of endogenous mesenchymal stem cells and hepatocytes being derived by the naturally induced lipolysis during effortless exercise.

In this clinical trial, we found an optimal increase of the abnormally low albumin levels which are considered to be a marker of hepatic dysfunction. Increased albumin suggests higher number of hepatocytes which in turn indicates a higher availability of endogenous MSCs. Adipose tissue MSCs differentiate into hepatocytes which synthesize albumin in the liver.

Other hepatocyte cells' functions include detoxification and the clearance of VLDL (very low-density lipoprotein), a variable that showed a substantial decrease after the course of 15 effortless exercise treatments.

There was a substantial improvement in NAFLD as indicated by ultrasonography reports. There was also a statistically significant optimization in the values of several relevant variables such as ALT, AST, ALP, CRP, triglycerides, creatinine, and bilirubin. Usually, procedures that involve exogenous MSCs injections examine only a limited number of variables before concluding that the exogenous MSCs have a vital role in the repair of NAFLD.[52-54]

VAT, BMI, and cortisol significantly decreased accompanied by an optimal statistically significant increase in testosterone, BMR and skeletal muscle mass. This additional data suggested an overall health improvement and enhanced fitness.

Other procedures that do not use exercise modalities like lasers and/or RF-induced lipolysis have not demonstrated improvements in any of the variables tested in this clinical study such as NAFLD status, albumin, ALT, AST, ALP, CRP, creatinine, bilirubin, visceral fat, cortisol, testosterone, BMR and muscle mass. Some investigators have indicated that conventional laser lipolysis destroys both adipocytes and MSCs.[55,56] A thorough literature search did not reveal any radiofrequency studies that claim involvement of MSC's after RF lipolysis.

All weight loss methods involve the release of toxins, including persistent organic pollutants (POS) which are eventually eliminated through the kidneys, liver, and immune system via the cooperative function of the circulatory and lymphatic systems. The body is programmed to purge toxins, provided that (i) the circulatory system is not blocked by deposits of triglycerides, (ii) the lymphatic system is not overwhelmed, and (iii) the liver and kidneys are functioning efficiently. Laser and RF lipolysis marketing claims lymphatic drainage which they do not perform directly, taking credit for detoxification performed by the body. Moreover, lasers and RF loosely rely on the unsubstantiated assumption that all bodies, including unhealthy bodies, shall perform efficient lymphatic drainage. In fact, detoxification is compromised during NAFLD because the liver does not function sufficiently. Excess VLDL and triglycerides in the blood will result in erythrocyte aggregation, poikilocytosis, increased radical oxygen species, all of which will obstruct the detoxification process. An inefficient lymphatic system cannot possibly ensure adequate detoxification following laser or RF lipolysis.

Lymphatic drainage is naturally enhanced by all active and passive workout regiments. Exercise modalities in general increase blood flow reinforcing the detoxification process. Additionally, they may increase MSCs and subsequently hepatocytes which are pivotal in liver detox and repair.

Both effortful and effortless exercise clinical trials have repeatedly demonstrated decreased VAT while laser or RF studies primarily target subcutaneous fat. The sparse laser and RF studies that claim VAT reduction are either based on animal models, or they combine specific laser or RF technologies with exercise, presenting confounding results that may not have been obtained if the subjects underwent laser or RF procedures alone.[57-60]

This clinical trial was based on a small sample. However, it is rather unlikely that selection bias posed a threat to internal validity since neither the author, nor the doctors and technicians were involved in subject selection. Subjects' participation depended entirely on the subjects' willingness to finance their blood tests, their ultrasonography reports and consent to being included in the research. Still, it is recommended that this study is replicated with a larger number of subjects. Biopsies and other imaging methods may offer more conclusive proof of the involvement of MSCs in the repair of NAFLD. Additional variables should be examined, such as glucose and/or insulin levels, high-density lipoprotein (HDL) and low-density lipoprotein (LDL).

Conclusion

Five weeks of effortless exercise significantly improved NAFLD in ultrasonography reports, as well as serum levels of ALT, AST, ALP, albumin, CRP, triglycerides, creatinine, and bilirubin. Several research teams have tested some of these variables to evaluate liver repair after administering exogenous MSCs. The liver repair currently observed in ultrasonography reports, along with the optimization of several NAFLD associated variables suggested that effortless exercise may induce the natural release of endogenous MSCs into the bloodstream. The notable reduction of triglycerides and VAT sets the conditions for the liver healing process to begin.

An important advantage of effortless exercise is the increased testosterone, juxtaposed with reduced cortisol that was documented by this study, supporting previous studies' results.[47-50] Research has shown that the relationship between testosterone and cortisol is adversely reversed after regular exercise due to the laborious effort involved.[61-66]

Research that focuses on different forms of exercise releasing endogenous MSCs can have important implications in developing novel treatments for metabolic disorders that are safe and efficient without the adverse effects often observed after stem cells injections or invasive and trauma based procedures.

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