



### Keywords

NAFLD,  
NASH,  
Fatty Liver,  
Electrostimulation,  
Systematic Review

Received: April 26, 2017

Accepted: May 31, 2017

Published: August 25, 2017

# Electrostimulation of Muscles Mimics the Effect of Physical Exercise on Non-alcoholic Fatty Liver Disease: A Systematic Review

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### Citation

Iain Swan, Zi Yi Tew, John F Dillon, Rami J Abboud. Electrostimulation of Muscles Mimics the Effect of Physical Exercise on Non-alcoholic Fatty Liver Disease: A Systematic Review. *AASCIT Journal of Medicine*. Vol. 3, No. 1, 2017, pp. 1-9.

### Abstract

Non-alcoholic fatty liver disease (NAFLD) is closely linked to the metabolic syndrome, and affects up to 30% of the population of the western world, and this is expected to increase even further in the near future. Pharmacological therapy has proved ineffective while lifestyle interventions improve outcomes. Unfortunately many patients struggle to exercise, and therefore have poor outcomes. New techniques such as externally stimulating the muscle electronically using cheap and existing technology, are hoped to mimic resistance exercise and produce the same benefits. Pubmed, the Cochrane Library, MEDLINE, and clinicaltrials.gov were searched throughout December 2015 by 2 reviewers independently. English articles with adult participants undergoing muscular electrical stimulation were included. Whereas studies with participants <18 years old, non-human studies, cell based studies, studies without controls, observational studies, sample size <5, and case studies or expert opinions were excluded. Changes in metabolic markers, physique, impact on NAFLD, and resemblance to exercise were recorded. 5994 articles were identified, and 10 met the inclusion criteria. These were split into multiple session resistance exercise, single session resistance exercise, and stimulated cycling groups. Multiple session resistance lead to improved fasting serum insulin, HOMO-IR, HOMO-%B, HDL levels, and quadriceps size; it had no effect and plasma glucose or OGTT. Single session resistance decreased plasma glucose; increased VO<sub>2</sub> max, heart rate, and respiratory quotient; had no impact on serum resistance. The stimulated cycling results were inconclusive. There are encouraging signs that muscle electrostimulation can mimic the effects of exercise both acutely and chronically.

## 1. Background

Non-alcoholic fatty liver disease (NAFLD) is now regarded as the most common liver condition in the western world, affecting up 30% of the general population [1]. It is

closely linked with the metabolic syndrome and its component parts including obesity, type 2 diabetes mellitus and dyslipidaemia, the pathogenic mechanisms involve insulin resistance and excess oxidative stress [1].

NAFLD encompasses a spectrum of phenotypes ranging from simple steatosis (fatty infiltration), through non-alcoholic steatohepatitis (NASH) to cirrhosis along with its associated complications of portal hypertension and hepatocellular carcinoma. About 30% of adults in the general population have NAFLD, and 10% to 20% of these have NASH [1]. Amongst patients with NASH, 20-30% are at risk of developing cirrhosis and subsequently dying from end-stage liver disease within 20 years [2]. As many as 60% of obese individuals may have NAFLD and 30% of these will have NASH [3]. In view of the tens of thousands of individuals who are likely to develop NASH in the next decade, it is clear that this disease will represent a major burden to healthcare globally.

Compounding this issue is the relative paucity of treatment options. Evidence of the benefits of pharmacological therapy appears unconvincing, with thiazolidinediones being the only drug shown to improve steatosis, but raising concerns over their long term safety and efficacy [4].

However non-pharmaceutical interventions based on lifestyle modifications, such as dietary weight loss and increasing exercise levels, have been shown to improve outcomes when they are adhered to. Aerobic exercise has been proven to enhance whole body lipid oxidation, and improves steatosis and cardio-metabolic risk profile, independent of weight loss [5-7]. However the high cardiorespiratory demand is associated with fatigue and discomfort, as well as a fear of cardiovascular incident in some patients, subsequently the long term adherence of such regimes is poor. Alternatively resistance exercise has a much lower cardiovascular demand, and therefore potentially a better long term compliance. It has also been demonstrated that resistance exercise provides similar metabolic benefits to aerobic exercise [8-10].

Consequently there is recognition that altering metabolic signalling pathways has a greater role in preventing disease than simple weight loss, suggesting that muscle activity is more important than consumption of energy and burning of calories [8-10]. Unfortunately co-morbid disease or body mass renders many patients incapable or fearful of even resistance exercise, preventing them from increasing their muscle activity. There is however an alternative approach, as existing technology can generate muscle activity via electrical muscle stimulation, and it has already been used extensively within rehabilitation programs without any adverse effects [11-12]. Despite this there is some debate as to whether electrical stimulation, also known as electro-myographic stimulation, directly mimics voluntary exercise; as it enlists motor units in relation to their proximity to the stimulator, instead of progressively recruiting larger motor units. Furthermore it does not affect the antagonistic muscle [13]. An observation from these rehabilitation programs was

an improvement in features of metabolic control, which has been subsequently more formally documented, and led to investigations of the metabolic effects of electro-myographic stimulation.

The objective of this review was to determine the efficacy of electro-myographic stimulation in mimicking the metabolic effects of exercise on adults. The controls will include individuals who did not receive the treatment, and the baseline values of those that did. Secondary subgroups investigated include different sexes, age, length of intervention, site of intervention and the diagnosis of NAFLD. The primary outcomes measured were changes in metabolic markers e.g. oral glucose tolerance test, HOMO-IR, HbA1c, fasting glucose, and LFTs. Changes in physique such as BMI and hip-waist circumference were also scrutinized.

## 2. Methods

### *Protocol and Registration (PICO)*

This systematic review investigated adults receiving electro-myographic stimulation of their muscles, with individuals who do not receive the intervention or the baseline values prior to stimulation acting as controls, where there was measurement of metabolic parameters and markers, irrespective of underlying diagnosis. Studies were included if there were any measurements of changes in metabolic markers including: fasting serum insulin, oral glucose tolerance test (OGTT), steady state glucose infusion, plasma glucose, post prandial glucose, fasting glucose, muscle glucose uptake, arterial glucose, HbA1c, HOMA-IR, HOMA-% $\beta$ , low density lipoproteins (LDL), high density lipoproteins (HDL) total cholesterol, non-esterified fatty acids, plasma free fatty acids, and triglyceride levels. Additionally any differences in physique such as BMI, abdominal circumference, hip to waist ratio, and quadriceps size were recorded. Furthermore secondary outcomes including the impact on NAFLD (measured via ALT and hepatic steatosis) and resemblance to exercise ( $VO_2$  max, heart rate, and respiratory quotient) were investigated.

### *Eligibility Criteria*

Inclusion criteria: English articles with adult participants of any sex or ethnic origin undergoing electro-myographic stimulation.

Exclusion criteria: participants <18 years old, non-human studies, cell based studies, studies without controls (baseline pre intervention counted as an acceptable control), observational studies, sample size <5, and case studies or expert opinions.

### *Information Sources and Search Strategy*

Pubmed, the Cochrane Library, MEDLINE, and clinicaltrials.gov were searched throughout and up to December 2015 using the terms: electrical muscle stimulation, myostimulation, exercise, non alcoholic fatty liver disease, NASH, NAFLD, fatty liver, steatohepatitis, insulin resistance, insulin sensitivity, metabolic syndrome, syndrome X, dysmetabolic, liver function tests. Abstracts from the American Association for the Study of Liver

Disease, American Gastroenterological Association, European Association for the Study of Liver, American Diabetes Association, and European for the Study of Diabetes, were also reviewed. These were subject to the same assessment as regular articles.

#### Data Collection Process

Data was collected by 2 authors independently and in duplicate, any disagreements were resolved via discussion

#### Risk of Bias in Individual Studies

Studies were assessed for bias, and rejected if any bias was found

#### Synthesis of Results

If  $\geq 2$  studies RCTs assessed the same outcome via the same methods they would be meta-analyzed. If this was not possible, then a narrative approach was used.

#### Additional Analyses

Further analysis of NAFLD vs. non-NAFLD patients was planned

### 3. Results

As shown in figure 1, the search produced a total of 5994 papers, of which 12 were accepted based on review of abstracts. There was disagreement between reviewers regarding a further 3 studies, all 3 of which were rejected following discussion. Following a full review of the articles, 2 more studies were rejected due to methodological issues, leaving 10 papers.

A variety of methods of electrostimulation were used within these studies, so it was decided to sub-divide them into separate categories for a more appropriate comparison. These categories were chronic resistance training (5 studies) acute resistance (3 studies) and stimulated cycling, which attempted to imitate aerobic exercise (2 studies).

#### Chronic Resistance training

The category of chronic resistance training encompassed studies that used electrostimulation to produce muscle movement against significant resistance i.e. similar to weight training. To be counted as chronic resistance, the stimulation took place over the course of several sessions, at least 6 weeks in the case of the studies selected.

Analysis of this group of studies revealed that this significantly decreased the fasting serum insulin, but had no significant effect on plasma glucose or OGTTs. Similarly there was no impact on LDL levels, however HDL levels were significantly increased. Furthermore there were conflicting outcomes for cholesterol and triglyceride levels. In addition the effect on BMI was also uncertain although 2 of the 3 studies investigating found a significant decrease in BMI. On top of this HOMA-IR and HOMA-% $\beta$  and was significantly improved in one study, and displayed a tendency to improve in another following chronic resistance training. Finally quadriceps size was significantly increased. Other variables were only investigated by a single study so were not considered.

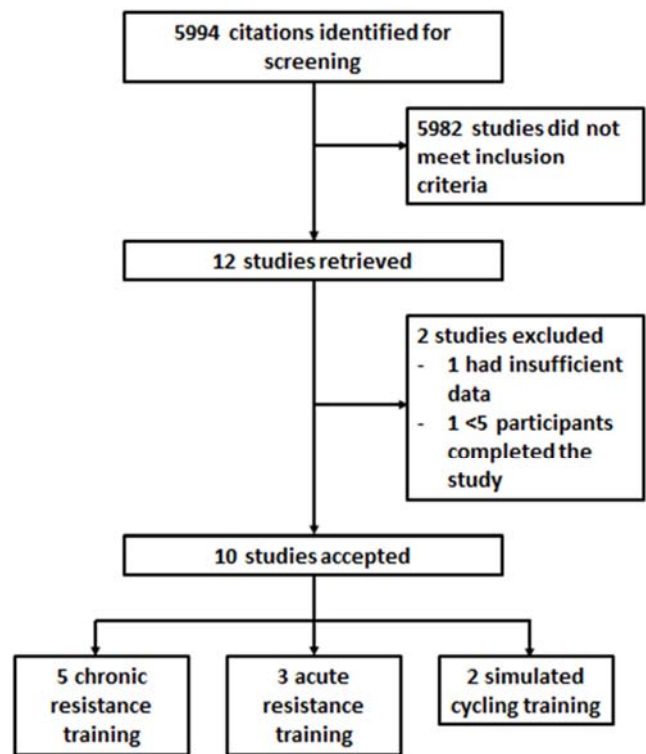


Figure 1. Flow chart for selection of studies.

Table 1. Effects of chronic resistance training.

	Sample	Age (years)	% Male	Stimulation
Mahoney et. al. (2005) [14]	5 subjects with complete spinal cord injury	35.6 +/- 4.9	100	2 electrodes on distal vastus medialis and the proximal vastus lateralis muscle – 4 sets of 10 weighted knee extensions 2 sessions/week 12 week duration
Ryan et. al. (2013) [15]	14 subjects with complete spinal cord injury	26.7+/-4.7	78.6	2 electrodes proximally over the vastus lateralis and distally over the vastus medialis 4 sets of 10 weighted knee extensions 2 sessions/week 16 weeks duration
Zhiyuan (2015) [16]	90 type 2 diabetics	Control 63.23±10.41 Aerobic exercise 63.53±9.36 Acu-TENS 63.87±9.19	Control 40.0 Aerobic exercise 40.0 Acu-TENS 36.7	Four pairs of electrodes were separately fixed bilaterally at the following acupuncture points: Quchi (LI 11), Hegu (LI 4), Zusanli (ST 36), and Sanyinjiao (SP 6) 5 x 30min/week 8 week duration
Kawaguchi et. al. (2011) [10]	35 NAFLD patients	Control 52.0 ± 3.5 Intervention 55.2 ± 3.7	Control 60.9 Intervention 41.7	Electrodes on motor points of the bilateral vastus medialis and lateralis of the anterior thigh; for the

Sample	Age (years)	% Male	Stimulation
Vivodtzev et. al. (2013) [17]	14 cystic fibrosis patients	Control + ERGO 21+/-11 NMES + ERGO 28+/-6	Control + ERGO 85.7 NMES + ERGO 42.9
			posterior thigh, electrodes were placed on the motor points of the medial and lateral hamstrings 10 sets of 10 knee extensions 2 sessions/week 12 weeks  Quadricep contractions 30 min, 4x/week, 6 weeks

Table 1. Continued.

	Fasting glucose	Blood glucose OGTT	Plasma glucose	HbA1c	Fasting Serum Insulin	HOMA-IR	HOMA-%β	BMI
Mahoney et. al. (2005) [14]	-	1hr - 46.3mg/dL 2hr -8.5mg/dL	Trend for reduction (exact values unavailable)	-	-	-	-	-
Ryan et. al. (2013) [15]	+4.0mg/dL	2hr +15.4mg/dL	-	+0.2	-	-0.1	-14.0	-0.2
Zhiyuan (2015) [16]	-	-	-	Significant decrease* (exact values unavailable)	Significant decrease* (exact values unavailable)	-	-	Significant decrease* (exact values unavailable)
Kawaguchi et. al. (2011) [10]	-	-	-	+0.4	-20.6μU/ml*	-6.6*	+101.6*	-2.95*
Vivodtzev et. al. (2013) [17]	-5.4mg/dL	-	-	-	-	-	-	-

Table 1. Continued.

	Abdominal circumference	Hip: waist ratio	Total Cholesterol	Triglyceride	LDL	HDL	Quadriceps Cross Sectional Size	ALT	Hepatic Steatosis
Mahoney et. al. (2005) [14]	-	-	-	-	-	-	+37%*	-	-
Ryan et. al. (2013) [15]	-	-	-6.9mg/dL	-11.9mg/dL	-8.0mg/dL	+3.6mg/dL*	-	-	-
Zhiyuan (2015) [16]	-	-	Significant decrease*	No effect	-	-	-	-	-
Kawaguchi et. al. (2011) [10]	-5.6*	-0.033*	+0.85mg/dL	+19.0mg/dL	+6.6mg/dL	+5.5 mg/dL*	-	-17.6 U/L*	-0.86*
Vivodtzev et. al. (2013) [17]	-	-	-	-	-	-	3.0cm*	-	-

Key: \*=significant change

### Acute Resistance

The studies within the acute resistance group measured the effect of electrostimulation causing the muscles to work against resistance for a single session, the maximum time spent by those analysed was 30 minutes.

This form of stimulation resulted in significantly decreased

plasma glucose levels, although it did not appear to affect serum insulin. Additionally VO<sub>2</sub> max, heart rate and respiratory quotient were found to significantly increase during and following acute stimulation. There was a mixed outcome for non-esterified fatty acid, and only 1 study measured glucose muscle uptake so it was not considered.

Table 2. Effects of acute resistance training.

Sample	Age (years)	% Male	Stimulation	Plasma glucose	Serum Insulin	
Miyamoto et. al. (2012) [18]	11 type 2 diabetics	57 +/-2	100	1x 30min stimulation Electrodes over quadriceps, biceps femoris, and gluteus maximus	Significant decrease* (exact values unavailable)	Not significant (exact values unavailable)
Miyamoto et. al. (2014) [19]	18 type 2 diabetics	56.3 ± 9.2 63.9 ± 11.9	44.4	1x 30min stimulation Electrodes over quadriceps, biceps femoris, and gluteus maximus	+4.47mmol/L* +3.25mmol/L*	+128.93pmol/L +86.93pmol/l
Hamada et. al. (2003) [20]	14 healthy patients	Not available	100	1x 20 min stimulation of quadriceps	-	-

Table 2. Continued.

	Non-esterified fatty acids	VO <sub>2</sub>	Heart Rate	Respiratory Quotient	Glucose Muscle Uptake
Miyamoto et. al. (2012) [18]	Significant decrease* (exact values unavailable)	Significant increase* (exact values unavailable)	Significant increase* (exact values unavailable)	Significant increase* (exact values unavailable)	-
Miyamoto et. al. (2014) [19]	-0.12mmol/L -0.31mmol/L	+6.2 ± 1.3 ml/kg/min* +5.9 ± 1.3 ml/kg/min*	73.1 ± 10.1 bpm* 73.8 ± 8.6 bpm*	0.9* 0.5*	-
Hamada et. al. (2003) [20]	-	Significant increase*	Not measured	Significant increase*	+ 4.2 mg/kg/min*

Key: \*=significant change

### Simulated Cycling

Finally the stimulated cycling category was created to cover electrostimulation that resulted in participants pedalling exercise bicycles, this form of exercise was deemed to be more akin to aerobic exercise than resistance exercise and therefore deserved its own category. Only 2 studies of this kind were identified, 1 measuring its findings over a year and another recording results after 1 session.

Between these 2 studies only plasma insulin and plasma

free fatty acids were comparable. Plasma insulin was significantly reduced in one study and in the controls of the second, but not found to be significant in the spinal cord injured group. The plasma free fatty acids were found to be significantly decreased in one study, while another found no impact. Steady state glucose infusion, OGTT, and arterial glucose were only measured in 1 study but all found to be significantly decreased.

Table 3. Effects of stimulated cycling training.

	Sample	Age (years)	% Male	Stimulation	Plasma Insulin (Mean difference 95% confidence)
Mohr et. al. (2001) [21]	10 subjects with traumatic spinal cord injury	35+/- 10	80%	Stimulated cycling for 30min, 3x week, 1 year	-5μU/ml*
Kjaer et. al. (2001) [22]	10 subjects with spinal cord injury 6 healthy controls	35+/- 10 25+/-7	-	30 min stimulated cycling	0mU/l -3mU/l*

Table 3. Continued.

	Steady State glucose infusion (Mean difference 95% confidence)	Plasma free fatty acids (Mean difference 95% confidence)	Plasma glucose OGTT (Mean difference 95% confidence)	Arterial glucose (Mean difference 95% confidence)
Mohr et. al. (2001) [21]	+6.2 mg.min <sup>-1</sup> .kg <sup>-1</sup> *	+30mmol.L <sup>-1</sup>	No significant effect (exact values unavailable)	-
Kjaer et. al. (2001) [22]	-	-369μmol/L* +60 μmol/L	-	-0.57*mmol/L -0.2mmol/L

Key: \*=significant change

## 4. Discussion

Reviewing these results, most suggest that electrostimulation may have a positive impact on NAFLD; as demonstrated by a decreased BMI plus the changes in HOMA-IR. Other markers, for example OGTT, did not show improvements that would be associated with traditional physical activity. Examining the different categories of studies in more detail could potentially explain these discrepancies.

### Chronic Resistance Training

Considering the link between insulin resistance and NAFLD, it was one of the most commonly investigated metabolic parameters. Chronic electrostimulation resulted in significantly decreased serum insulin concentrations across the studies included in the review, appearing to mimic the lower levels of insulin seen after prolonged exercise training, possibly suggesting decreased insulin resistance [10, 16].

Furthermore HOMA-IR significantly improved following intervention, whereas HOMA-%β was slightly reduced in one study [10] and showed a significant increase in another<sup>15</sup>. As HOMA-%β indicates β-cell function, and the increase was seen in the study with the biggest reduction in HOMA-IR it could represent a recovery of β-cells once they have been subjected to less stress [23]. This change was seen in the “hybrid training” method, aiming to accurately imitate natural exercise by alternatively stimulating antagonistic muscles [10]. In addition that intervention involved more knee extensions than others [10]. This may mean that the difference in results is due to a more intense stimulation, and that a greater level of intervention can reduce insulin resistance more dramatically.

In theory increased insulin sensitivity would lead to an increased glucose uptake into the cells, although there are multiple counter-regulatory systems to maintain normoglycaemia and these would fall in response to any increased insulin sensitivity. However there was no

significant change in the glucose concentrations, despite the increase in quadriceps size [14, 17]. This is not surprising as most of the studies were on patient groups who had insulin resistance rather than overt diabetes. Only 1 study measuring HbA1c saw a reduction [16], with the other 2 showing a trend to increase following intervention [10, 15]. Additionally there was a universal lack of response in plasma glucose or OGTT [14, 15].

While this may simply represent little impact of the intervention, it could be highlighting the fact that there are differences between NAFLD and the metabolic syndrome, as a substantial number (40% in one study) do not have both conditions [24]. New evidence points towards lipid dysregulation as the main cause of NAFLD, with alterations in transcription factors responsible for fatty acid oxidation such as sterol regulatory element-binding protein-1c (SREBP-1c), leading to lipid accumulation within the liver. Hyperglycaemia is certainly a risk factor for these issues, but it is not a simple progression [25, 26].

Despite this evidence that lipids are supposedly the main molecules involved in the pathogenesis, there was no uniform effect of electrostimulation on different forms of lipid measurements, which may be partially explained by the difference in length and intensity of stimulation. The longest intervention showed a decrease in total cholesterol, triglycerides, and LDL levels [15]; whereas the shorter study saw an increase in these parameters [10]. One explanation for this is that they are showing a progressive response, as the cholesterol and triglycerides are being mobilised from the liver into the circulation, in order to be metabolised rather than simply stored. While with a longer intervention there is reversion to a more physiological state, and normalisation of fat metabolism [26, 27].

NAFLD patients have also been noted to have decreased HDL levels and the mechanism and reasoning for this is not yet completely understood. But as HDL is responsible for transporting lipid back to the liver, it has been suggested that this accumulation of lipid within the hepatocytes gives rise to oxidative stress and consequently cellular damage. Therefore a rise in HDL levels would indicate a reduction in hepatic damage and ultimately fibrosis [26, 28].

Finally every study that measured BMI noted a decrease [10, 15, 16], and while there is plenty of evidence to suggest that a decrease in intrahepatic fat is not necessarily linked to losing peripheral fat [5, 7, 28]; patients observing any kind of physical difference in themselves may be more likely to feel as though the intervention is beneficial, and are consequently more likely to continue with it.

Overall it appears as though the longest interventions and those with the most intense training produced the most beneficial outcomes, based on the parameters measured. However a recent systematic review indicates that any form of exercise decreased intra-hepatic fat on biopsy, irrespective of circulatory biomarkers [29]. If this is true and the body responds to electrostimulation in the same way as traditional exercise, then it should decrease intrahepatic steatosis.

#### *Acute Stimulation*

Following conventional exercise, plasma glucose levels decrease as glucose is taken up by the myocytes for additional fuel [31]. The results from the acute interventions appear to mirror this [18, 19], and the idea of the muscles working is supported by the muscle hypertrophy seen in the chronic stimulation trials [14, 17].

Furthermore significant increases in VO<sub>2</sub> max, heart rate and respiratory quotient, hint that the electrostimulation also appears to be having a systemic effect, increasing the activity of the entire body rather than just the muscle stimulated [18-20]. This could lead to some modest improvements to cardiovascular fitness.

This systemic activity would explain the lower levels of fatty acids seen, which would be metabolised into sugars for additional energy. Although 1 study with mixed sexes used an almost identical methodology to a male only trial and failed to replicate the significant decrease, suggesting gender differences in the response to electrostimulation [18, 19].

On top of this, there was no expected drop in insulin levels during exercise, due to the glucose uptake into the muscle during this time primarily being induced via glucose transporter type 4 (GLUT-4) [30]. This could indicate that insulin resistant patients take longer to respond to interventions, re-enforcing the idea that insulin sensitisation is a chronic process.

#### *Stimulated Cycling*

Unlike the previous studies mentioned, the stimulated cycling interventions resembled aerobic exercise more closely than resistance exercise. This form of stimulation was included in the review to observe if there was any difference between that and resistance training, despite the claims of Golabi *et al* [29]. To further complicate matters both studies investigated vastly different time frames of intervention.

The investigation into long term stimulation found a significant decrease in arterial glucose for the controls, and a trend to decrease in the individuals with a spinal cord injury (SCI) [21]. This may indicate that aerobic electrostimulation is more effective at driving glucose into the muscle cells, a statement further supported by the fact that the results were mirrored by a decrease in plasma insulin. However it has been documented that arterial and plasma samples are not interchangeable and therefore it is an unfair comparison [31].

Both acute and chronic experiments saw no impact on plasma free fatty acid concentrations unlike the resistance interventions [21, 22]. This would suggest that while aerobic electrostimulation may be more effective at improving peripheral insulin sensitivity it has less effect on NAFLD; potentially explained by the emerging theories regarding the different mechanisms for insulin resistance [24, 26].

Whereas the acute intervention demonstrated an increased hyperglycaemic-euglycaemic clamp, there was no difference in the OGTT [22]. The hyperglycaemic-euglycaemic clamp is able to provide continuous data and perceive more subtle changes, while the OGTT is more likely to be confounded by other physiological variables. It could therefore be insinuated that there was an improvement to insulin sensitivity, but only a modest one as it was not observed in the OGTT [23].

Given the different variables measured it would be unfair to compare the 2 forms of electrostimulation, but it does not appear that the aerobic form has any advantage over the stimulated resistance.

#### *Overall Impressions*

One of the common themes from all the studies was the extremely low dropout rate, with only 2 individuals in the entire review, and they were both due to unrelated deteriorations in health [17]. This suggests that electrostimulation is extremely well tolerated by individuals. Only 2 adverse reactions were recorded, both in a study that was rejected for having a sample size <5, and both were an allergic reaction to the stimulator of unknown severity [18]. Consequently, it would be worthwhile obtaining more information regarding this, but as this was not seen in the other research the initial signs appear promising.

There was also a lack of long term follow up, preventing the identification of any long term beneficial or adverse effects. Although the long term cycling study repeated the measurements 6 months after stopping interventions and found any improvements had since regressed, they were still better than the baseline values [21]. This pattern is well documented, and critics could argue that the rate of weight regain is worse than reported, as it is not recorded by all experiments, and was not reported by some of those that did measure it [32].

Finally the aim of the review was to investigate the impact of electrostimulation on NAFLD, unfortunately only 1 study was found that measured hepatic changes [10], so the authors were unable to assess the impact on NAFLD directly. However there are some studies that have doubted the validity of liver function tests for assessing NAFLD, and instead advocate metabolic biomarkers. Consequently the results from other studies focusing on these metabolic parameters could be applied to NAFLD [28, 33]. Overall the effects on insulin sensitivity and metabolism seen in exercise and associated with improvements in NAFLD are seen with electro-stimulation of muscles, which is surprising given the much smaller volume of muscle in use and the reduced frequency of the simulated exercise.

#### *Limitations*

The main limiting factor for this study was not related to the study itself, but the relatively small amount of literature currently available. Only 10 papers were included in the review creating a small sample, and this was compounded by the fact that the studies included had small samples themselves. A number of variables displayed “tendencies to increase” which may in fact have produced significant results in larger samples.

The wide variety of stimulations made it even more difficult compare between studies. Research was grouped according to the type of stimulation, however even within the different subgroups there was a range of intervention e.g. electrostimulation at acupuncture points [16], or with a “hybrid technique” [10]. This was most evident within the stimulated cycling sub-group which only 2 studies: one looking at one acute intervention [22], while the other

investigated the effects of a year’s worth of training [21].

The samples also included a range of different conditions. While they are all theoretically part of the metabolic syndrome, the different manifestations of the condition may produce different physiological responses to electrostimulation; in the same way that they produce different signs in individuals [24]. Several studies included investigated individuals with an SCI, and while research into this group suggests their metabolic changes are similar albeit more dramatic than sedentary individuals, their results are unlikely to be identical to individuals with NAFLD [34, 35].

In addition to the different conditions, it is possible that the studies investigated different ethnicities. Asian populations have a higher prevalence of diabetes than western countries, despite a relatively lower obesity rate [36, 37]. This may be due to differences in metabolism [37] and therefore potentially response to exercise, although this author could not find any research investigating any ethnic differences in exercise response excluding elite athletes. There is however substantial evidence regarding various physiological differences in males and females, and the majority of trials included had samples dominated by males, which may have influenced the findings [38-40]. Moreover many of the studies investigated different parameters, further narrowing the results.

Despite these constraints, the review ensured it had a solid methodology by searching multiple databases to ensure no potential data was missed, and utilising 2 reviewers to reduce selection bias. Additionally the selection criteria was independent of outcomes, selection bias was virtually eliminated.

## **5. Conclusion**

This systematic review indicates that electrostimulation produced many of the same benefits of conventional exercise, although it did not appear to influence all the metabolic markers that exercise does. Ideally physical exercise would be preferred, but there are encouraging signs that electrostimulation could be a viable alternative for individuals who cannot exercise in the future, providing further research is conducted into the area.

## **List of Abbreviations**

ALT	-	Alanine transaminase
BMI	-	Body Mass Index
GLUT-4	-	Glucose 4 transporter
HbA1c	-	Glycated Haemoglobin
HDL	-	High Density Lipoprotein
HOMA-%β	-	Homeostatic Model Assessment of β-cell Function
HOMA-IR	-	Homeostatic Model Assessment of Insulin Resistance
LDL	-	Low Density Lipoprotein
LFTs	-	Liver Function Tests
NAFLD	-	Non-Alcoholic Fatty Liver Disease

NASH	-	Non-Alcoholic Steato-Hepatitis
OGTT	-	Oral Glucose Tolerance Test
RCT	-	Randomised Control Trial
SCI	-	Spinal Cord injury
SREBP- 1c	-	Sterol Regulatory Element-Binding Protein-1c
VO <sub>2</sub> max	-	Maximal Aerobic Capacity

## Availability of Data and Material

All data generated or analysed during this study are included in this published article

## Competing Interests

The authors declare that they have no competing interests

## Authors' Contributions

IS – helped create search criteria, reviewed articles, discussed disagreements between reviewers, drafted manuscript

ZT - helped create search criteria, reviewed articles, discussed disagreements between reviewers

JD – helped create search criteria, critically appraised manuscript

RA – critically appraised manuscript

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