Available online freely at www.isisn.org

Bioscience Research

Print ISSN: 1811-9506 Online ISSN: 2218-3973

Journal by Innovative Scientific Information & Services Network

RESEARCH ARTICLE BIOSCIENCE RESEARCH, 2019 16(1):629-638. **OPEN ACCESS**

Efficacy of high intensity interval training on endothelial function in diabetics with peripheral arterial insufficiency

Hend Salem Ahmed [1] ,Zeinab Mohamed Helmy [2] , Heba Ahmed Abdeen [2] , Manal Ahmed Mohamed [3] and Ahmed Abdallah Emam [4]

[1] Physiotherapist at National Heart Institute **Egypt**
[2] Faculty of physical Therapy Cairo University **Egypt**
[3]Department of biochemistry. National Heart Institute **Egypt**
[4]Department of Cardiology. National Heart Institute **Egypt**

***Correspondence:** Hendsalem766@gmail.com **Accepted:** 26 Sep. 2018**Published online:** 11 Mar. 2019

The present study aimed to investigate the effect of the High Intensity Interval Training on endothelial function in diabetics with peripheral arterial insufficiency. Forty eligible male patients with Peripheral Arterial Insufficiency secondary to Type 2 Diabetes Mellitus (DM) for a duration more than five years, their Body Mass Index ranged from (30 to 35) kg/m2, their Ankle Brachial Index ranged between (0.6) and (0.9). They had been selected from National Heart Institute, Peripheral Vascular outpatient Clinic. They were randomly assigned into two equal groups Group (A) received high intensity interval training for 5-30 min at 85-90% of the maximal heart rate, three times per week for twelve weeks. Group (B) who did not train served as controls. Nitric Oxide (NO) and pain free walking time, the maximum walking time were evaluated pre-treatment and after 12 weeks of training. Statistical analysis revealed a significant improvement in NO by 30.19%, pain free walking time by 129.63% and the maximum walking time by 101.21%in-group (A) while group (B) showed no statistical significant effect. The results indicate that regular participation in High intensity interval training can enhance endothelial function in diabetics with peripheral arterial insufficiency.

Keywords: High Intensity Interval Training, Peripheral Arterial Insufficiency, Intermittent Claudication, Ankle Brachial Index, Nitric Oxide.

INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disease characterized by hyperglycemia resulting from defects in hormone secretion, hormone action, or both. It's a chronic medical condition, which means that though it is controlled, it lasts a lifespan (American Diabetes Association, 2012).

Type two (DM) is powerfully related to associate elevated risk of Peripheral Arterial Disease (PAD) (Criqui and Aboyans, 2015) ends up in pathology inflicting epithelial tissue, cell injury and dysfunction, the maximum amount of the impact of chronic disease falls on the microcirculation. With long period of diabetes, there is progressive narrowing of vascular lumina, causing impaired perfusion, ischemia and dysfunction of the affected tissues (Alberto et al., 2016).

The pathophysiology of macro vascular disease in diabetes involves, on a cellular level, abnormalities in endothelial, vascular smooth muscle cell and platelet function. Metabolic dysfunction related to diabetes, including hyper glycaemia, insulin resistance, dyslipidaemia and elevated levels of free fatty acids, underpins the cellular events leading to vascular dysfunction.

Population studies suggest there is a graded and independent association between glucose control and incident/prevalent PAD among patients with diabetes (Brownrigg et al., 2015).

Peripheral Arterial Disease could be a public ill health across the world with a major impact on care and a high economic burden (Marrett et al., 2013)It is associated with an increased risk of cardiovascular disorder , and is especially common in patients with Type2 DM(Shah et al., 2015). Previous studies have shown poor survival and cardiovascular outcomes in patients with each Type2 DM and PAD (Abbott et al., 2012).

Peripheral Arterial Disease could be a common and severe clinical manifestation of hardening of the arteries and is particularly frequent in patients with type 2 DM,with associate degree some threefold exaggerated risk compared with a population have not diabetes (Emdin et al., 2015).

Nitric Oxide (NO) is a useful regulator within the circulatory system with roles extending on the far side its known action as a vasodilator: it controls vascular smooth muscle cell proliferation and migration, disintegration, the adhesion of platelets and white blood cells and angiogenesis (Cocks et al., 2016).

Vascular endothelium operate is crucial for maintenance of physical property of the vessel wall and for dilatation management in each passage and resistance vessels. This is often accomplished by maintaining a lively balance between dilatation and constriction. NO secreted by the endothelial NO synthase (e NOS) (Yukihito H, 2015).

The most common symptom of PAD is claudication (IC), it's outlined as pain, cramping or aching within the calves, thighs, or buttocks that seem reproducibly with walking and symptoms depart quickly with rest, sometimes inside couple of minutes. At first, symptoms could solely at the start develop once walking uphill, walking quicker, or walking longer distance and leg pain happens in one leg in four-hundredth of patients and in each legs in six- hundredth of patients (Conte et al., 2015).

Reduced walking capability was known as a consequence of IC, the hall mark symptom of PAD. Though a minority of patients expertise classic claudication, up to five hundredth describe atypical leg symptoms that interfere with mobility, the distance walked is termed claudication distance and the cluster of muscles that full of this pain depends on the positioning of blood vessel occlusion (Hamburg and Creager, 2017).

Ankle limb Index (ABI) is that the screening check of alternative for the diagnosing of patients with PAD because of its simplicity, duplicability and price effectiveness, conjointly it offers an efficient technique of objectively documenting the useful standing of the circulation within the lower limb and for the diagnosing of the lower extremity (Alahdab et al., 2015).

High Intensity Interval Training (HIIT) is broadly outlined as repetitions of high-speed/intensity work followed by periods (the periods that area unit the particular intervals) of rest or low activity. Interval training works each the aerobic and therefore the anaerobic system. This repetitive style of training ends up in the variation response. These changes lead to improved performance notably inside the circulatory system (Francois and tiny, 2015).

Exercise training not solely improves each pain – free and maximum walking ability, however conjointly improves different cardiovascular measures of perform as well as peak gas consumption, oxidative metabolism, endothelium function, and therefore the arterial sclerosis risk issue profile. Additionally, measures of health – connected quality of life are improved in persons with claudication participate in supervised exercise (Parmenter et al., 2015).

The aim of this study was to determine the effect of high intensity interval Training on endothelial function in diabetics with peripheral arterial insufficiency.

MATERIALS AND METHODS

Forty eligible male patients type2 DM with peripheral arterial insufficiency (aged 50-60 years), were screened and randomly assigned to either control or intervention group to participate in this 12- week randomized- controlled trail. They were recruited from National Heart Institute, Peripheral Vascular outpatient Clinic, to participate in this study.

Patients were selected to be enrolled into this study after they had fulfilled the inclusion criteria of the study; male patients' type 2DM with peripheral arterial insufficiency, their BMI ranged from 30 to 35, their ABI ranged from 0.6 to 0.9 and had intermittent claudication. Patients had provided informed consent for participation in the study and for publication of the results. This study was approved by University Ethics Committee for scientific research [No: P.T.REC/012/00984].

Exclusion criteria were BMI more than 35, age older than 60 or younger than 50 years, patients who had UN controlled DM, had Logistic problems to attend regular exercise training sessions, had exercise limited by angina or peripheral arterial occlusive disease, had Poorly controlled or exercise-induced cardiac arrhythmias and had a history of serious Cerebrovascular diseases or musculoskeletal problems restricting physical activity.

Study protocol and the objectives of the study were altogether explained to all participants, who were asked to maintain their pharmacologic treatment, general eating routine and typical daily activities and lifestyle all through the study.

Design of the study

Patients who fulfilled the inclusion criteria of the study were randomly assigned to either group A the study group, who received high intensity interval training for 5-30 min at 85-90% of the maximum heart rate, 3 times/ week for 12 weeks in addition to usual daily living activities and medications or group B, the control group, who performed the usual daily living activities and in addition to administration of their medications.

Randomization was done by opening an opaque envelop prepared by an independent individual using random number generation.

Instrumentation

For evaluation

-Doppler Ultrasound Ankle Brachial Pressure Index: A hand-held Doppler probe (Nicolet Vascular Pocket Dop II; Nicolet Biomedical Inc, Golden, Colo) used to obtain systolic pressure in the right and left brachial, dorsalispedis and posterior tibial arteries.

-Determination of nitrite levels in serum:

Centrifuge was used for separating serum.

Spectrophotometer (UV-2300) was used for estimation of nitric oxide.

-Standard weight and height scale: (floor type, Health Scale, made in China). It was used to measure the weight and height of each participant and then calculate the BMI [weight (kg)/height (m2)].

-BORG 6-20 Rate of Perceived Exertion Scale: It used to assess the rate of perceived exertion during and after each training session.

-Electronic Treadmill: original designed by Tunturi professional line, Modular J 880 (made in Finland). It is electronic controllable and provided by display screen with adjustable elevation and speed. It was used to measure pain free walking time and the maximal time of walking.

For training

-Electronic Bicycle Ergometer:

Biodex LBC, made in New York equipped with electronic break, display screen, adjustable seat, handle bar and foot straps.

-ECG telemetry:

(Telemetry, Hewlett Packard (HP) M2604A): (made in U.S.A). It is wireless and allows monitoring of heart rate and rhythm for patients at same time during training.

Outcome measures

Both groups underwent an identical battery of tests: baseline (before training) and after 12-week exercise training program (after training).The evaluated parameters included NO and pain free walking time and maximal walking time measurements.

Firstly, data on the subject characteristics were collected in the first session including resting heart rate (HR) (beats/min), maximal heart rate and target heart rate. Weight (kg) was measured to the closest 0.1 kg a standard weight scale.

Height was measured to the closest 0.1 cm with the subject standing in an erect position against a vertical scale of a portable stadio meter. BMI (kg/m2) was estimated as weight in kilograms divided by squared height in meters to exclude BMI more than 35.

Ankle Brachial Index (ABI) was measured with the subject in supine position; the highest value from readings of the left ankle arteries used and divided it by the value of the brachial artery to exclude ABI more than 0.9 and less than 0.6.

Training procedures

After warm- ups, participants of this group performed pedaling on anelectronic bicycle three times per week (on nonconsecutive days).

High intensity interval training intensity was determined by (Karvonen's method); training heart rate (THR=HR rest + (HR max – HR res) 90-95%, (THR=HR rest + (HR max – HR res) 50-70%.

Parameters of exercise program

Mode:

Cycling on a stationary bicycle for lower limb

Duration:

15-40 min

Intensity:

They were trained using heart rate range or reserve method (Karvonen's method); training heart rate (THR=HR rest + (HR max – HR res) 90-95%, (THR=HR rest + (HR max – HR res) 50-70%.

Frequency:
Three times/ week

Treatment duration:
12 weeks each exercise session consisted of
Warming up:
Light pedaling for 5 min

Active phase:
Pedaling at 90-95% of for HIT MHR and then 50-70% of MHR for interval training

Cooling down:
Light pedaling for 5 min

Data collection

For each group, both demographic data and clinical characteristics [NO, pain free walking time and maximal walking time] of patients were collected pre and post training.

Statistical analysis

Descriptive statistics for all parameters in the form of Mean and standard deviation of [Demographic and clinical characteristics; NO, pain free walking time and maximal walking time] and percentage of change in NO, pain free walking time and maximal time post training were evaluated.

Inferential statistics in the form of Paired t-test to examine the changes in NO, pain free walking time and maximal walking time pre and post training in each group and Independent t-test to compare between the two groups regarding NO, pain free walking time and maximal walking time pre and post training. The level of significance was at $P \leq 0.05$.

RESULTS

Demographic and clinical characteristics of patients in both groups

In the base line (pre-training) evaluation, results revealed that there were non-significant differences between the two groups with regard to Demographic characteristics and clinical parameters where P ≤ 0.05, are shown table1 and figure 1.

Demographic and clinical characteristics of patients in both groups

In the base line (pre-training) evaluation, results revealed that there were non-significant differences between the two groups with regard to Demographic characteristics and clinical parameters where P ≤ 0.05, are shown table1 and figure 1.

Table (1): Comparison of physical characteristics mean values between study and control groups.

Items	Age (year)	Weight (kg)	Height (cm)	BMI (kg/m^2)	Chronicity (year)	ABI ratio
Study group	57.00 ±1.35	76.77 ±1.30	165.31 ±2.72	32.94 ±1.03	5.54 ±0.66	0.72 ±0.04
Control group	56.54 ±1.76	75.00 ±3.89	164.00 ±3.65	32.72 ±1.24	5.38 ±0.65	0.71 ±0.04
t-value	0.749	1.554	1.036	0.479	0.599	0.089
P-value	0.461	0.133	0.311	0.636	0.555	0.930
Significance	NS	NS	NS	NS	NS	NS

SD: standard deviation P-value: probability value NS: non-significant.

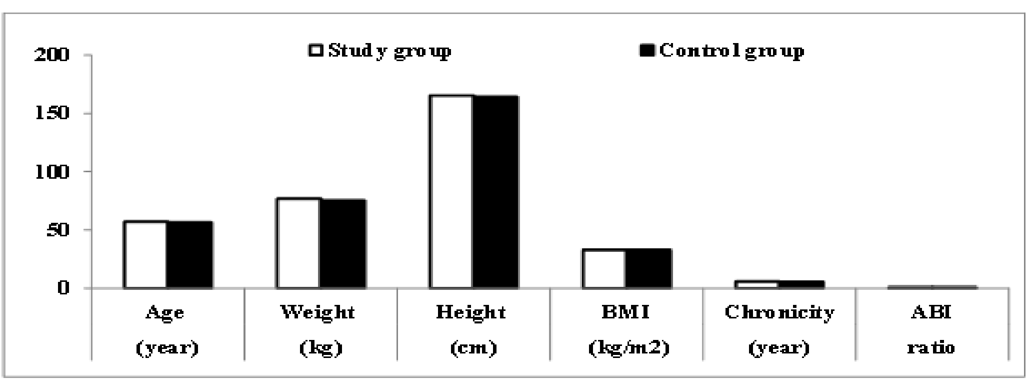

Figure (1): Show mean values of demographic data in study and control groups.

Table (2): Comparison between mean values of pre- and post-NO in study and control groups.

Items		NO					
		Study group	Control group	Mean difference	Independent t-test		
		Mean ±SD	Mean ±SD		t-value	P-value	Significant
Pre-treatment		25.57 ±1.98	26.52 ±1.49	0.95	1.384	0.179	NS
Post-treatment		33.29 ±2.63	25.42 ±1.67	7.87	9.093	0.0001	S
Mean difference		7.72	1.10				
Improvement %		30.19%	4.15%				
Paired t-test	t-value	9.874	2.270				
	P-value	0.0001	0.092				
	Significant	S	NS				

SD: standard deviation %: percentage S: significant NS: no significant P-value: probability value

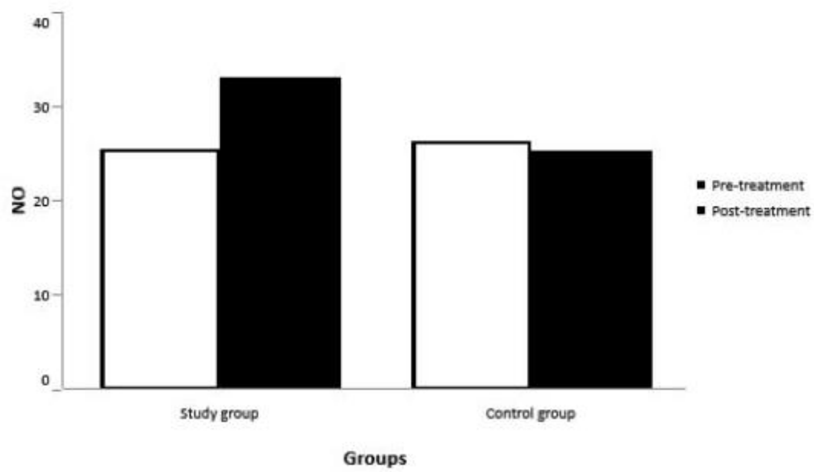

Figure (2): Show mean values of pre- and post-NO in study and control groups

Table (3) and Figure (3) represented the comparative mean values of pre- and post-maximal walking time between study and control groups. The mean values of pre-treatment maximal walking time were 72.14 ±3.26 second in study group and 70.18 ±3.19 second in control group. Whereas, the mean values of post-treatment maximal walking time were 145.15 ±5.94 second in study group and 68.35 ±3.44 second in control group. The statistical analysis by independent t-test revealed that there were no significant difference in pre-maximal walking time (P=0.130; P>0.05) while, a significant difference in post-maximal walking test (P=0.0001; P<0.05) between study group and control group.

Table (4) and Figure (4) represented the comparative mean values of pre- and post-pain-free walking time between study and control groups. The mean values of pre-treatment pain-free walking time were 89.40 ±3.29 second in study group and 88.29 ±3.99 second in control group. Whereas, the mean values of post-treatment pain-free walking time were 205.29 ±7.16 second in study group and 88.29 ±3.99 second in control group. The statistical analysis by independent t-test revealed that there were no significant difference in pre-pain-free walking time (P=0.448; P>0.05) while, a significant difference in post-pain-free walking time (P=0.0001; P<0.05) between study group and control group.

Table (3): Comparison between mean values of pre- and post-maximal walking time in study and control groups.

Items		Maximal walking time (second)					
		Study group	Control group	Mean difference	Independent t-test		
		Mean ±SD	Mean ±SD		t-value	P-value	Significant
Pre-treatment		72.14 ±3.26	70.18 ±3.19	1.96	1.567	0.13	NS
Post-treatment		145.15 ±5.94	68.35 ±3.44	76.8	40.324	0.0001	S
Mean difference		73.01	1.83				
Improvement %		101.21%	2.61%				
Paired t-test	t-value	77.689	2.832				
	P-value	0.0001	0.186				
	Significant	S	NS				

SD: standard deviation %: percentage S: significant NS: no significant P-value: probability value

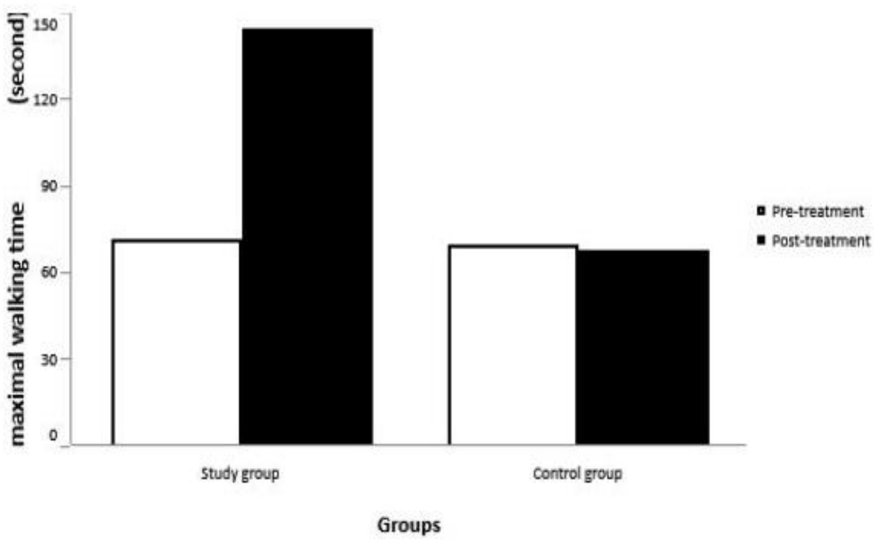

Figure (3): Show mean values of pre- and post-maximal walking time in study and control groups

Table (4): Comparison between mean values of pre- and post- pain-free walking time in study and control groups

Items		Pain-free walking time					
		Study group	Control group	Mean difference	Independent t-test		
		Mean ±SD	Mean ±SD		t-value	P-value	Significant
Pre-treatment		89.40 ±3.29	88.29 ±3.99	1.1	0.771	0.448	NS
Post-treatment		205.29 ±7.16	88.29 ±3.99	117	51.444	0.0001	S
Mean difference		115.89	0.000				
Improvement %		129.63%	0.00%				
Paired t-test	t-value	99.685	0.000				
	P-value	0.0001	1.000				
	Significant	S	NS				

SD: standard deviation %: percentage S: significant NS: no significant P-value: probability value

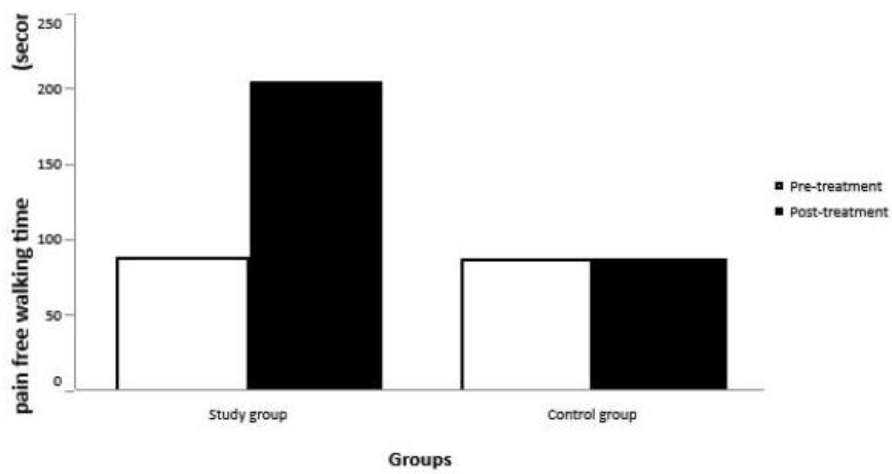

Figure (4): Show mean values of pre - and post-pain free walking time in study and control groups

DISCUSSION

In (group A), there is increase of e NO from 25.57 ±1.98 to 33.29 ±2.63mmol/L, with improvement percentage 30.19%, there is increase in pain free walking time from 72.14 ±3.26 to 145.15 ±5.94 second, with improvement percentage 101.21%, there is increase in the maximum walking time from 89.40 ±3.29 to 205.29 ±7.16 second and with improvement percentage 129.63%, respectively, with improvement percentage 87.50%.

In (group B), there is no significant improvement in e NO, pain free walking time, the maximum walking time.

Regular physical activity has been suggested as an efficient treatment alongside medications and dietary management to enhance endothelial function (EF).muscle contraction throughout physical activity will increase local blood flow and cardiac output, which ends in accrued shear stress on vascular endothelium and accrued NO production (Ando and admiral, 2011).

In patients with PAD, HIIT was shown to be superior to continuous, moderate aerobic exercise (CME) in improving endothelial function and in one study, similar changes were seen over 6 week of training in both HIIT and CME subjects, although HIIT subjects performed only 20% of the exercise duration performed by the CME group, making it an extremely efficient intervention (Barcely, 2012).

Exercise training stimulates endothelial – dependent vasodilatation, by periodic exposure to recurrent episodes of exercise – induced hyperemia, raised the blood flow augments vascular expression of nitric oxide and prostacyclin resulting in vasodilatation. Exercise training improves hemorheology, facilitating gas delivery to ischemic muscle, inflicting improvement in blood consistence and tissue gas extraction following exercise training, these advantages could also be even additional applicable and desirable for patients with PAD (Milani and Lavie, 2007).

The finding of this study is according to many alternative previous studies that examined the results of HIIT on endothelial tissue function and IC. In a study of Mitranun et al., (2013) to see the results of continuous aerobic exercise (CON) versus HIIT on endothelium-dependent vasodilatation, forty three participants with Type 2 DM were every which way allotted to, CON, and HIIT groups. The CON and INT exercise training programs were designed to yield a similar energy expenditure/exercise session and enclosed walking on treadmill for thirty and forty min/day, three times/week for twelve weeks. Only within the HIIT group, highest aerobic capability and flow-mediated dilation, accrued significantly in each exercise groups; but, the magnitude of enhancements was larger within the HIIT group. Solely in the HIIT group there is increase in plasma peroxidase and nitric oxide (all $P < 0.05$).That each continuous and interval training were effective in up aerobic fitness, and endothelium-dependent dilatation, however the interval training program seems to confer larger enhancements than the continuous training program.

This is supported by Da Silva et al., (2012) compared HIIT (HI 75-85% of HRMAX) to low-intensity training (LW 50-60% HRMAX) in thirty one diabetic patients. Once the randomized method and 6 weeks of intervention, the authors ascertained that people within the HI group were active for an extended time on the maximal exercise test than LW group. Regarding endothelium tissue function, there was associate degree communicatory improvement in endothelium-dependent dilation within the HI group compared to LW. Supported these knowledge, authors ended that the HIIT is effective in enhancement the functional capacity and therefore the endothelium-dependent dilator response in obese patients with T2DM and being a crucial preventive strategy.

Studies administrated in T2DM patients showed reduced blood glucose, multiplied mitochondrial capacity and EF when solely a pair of weeks of 3 twenty minutes sessions of HIIT per week (Little et al., 2011).

Exercise-induced enhancements in walking ability enhance routine daily activities, quality of life and community-based practical capability. A meta-analysis of twenty one irregular and non-randomized trials of exercise training discovered that painless walking time improved a mean of one hundred and eightieth and peak walking time accrued by one hundred twenty (Richard et al., 2007).

For individuals with diabetes and PAD, physical activity is suggested as a result of success in treatment of PAD could also be measured in distance walked while not pain. During a systematic review of ten irregular clinical trials of exercise programs in patients with symptomatic disability of walking, supervised exercise therapy was effective in increasing walking time compared to straightforward care (Steffen et al., 2008).

Januszek et al., (2014) investigated the effect of 12 weeks of supervised intermittent treadmill walking on endothelial function and maximal walking time, exercise sessions were conducted three times a week at speed of 3.2 km/h and grade individually determined for each patient that would induce claudication within 3-5 minutes. This cycle of intermittent walking exercise was applied for 35 min at the start of the program with progressive increase of session time by 5 min / 2weeks. The results showed that there was significant improvement in the maximal walking time by 90% and FMD values increased by 43% after the training program.

Classic meta-analysis of the potential elements of an exercise program for IC determined the best effects were achieved with a > six month walking program that had a minimum of three sessions per week of durations >thirty minutes per session that used nearly maximal claudication pain because the claudication pain finish purpose. Claudication pain finish purpose, mode of exercise (walking), and length of the exercise program were all freelance predictors of enhanced walking distance with an exercise program. Exercise programs for patients with IC are found to extend the distance to onset of disability of walking and increase the distance to most disability of walking pain. A meta-analysis of 1200 patients determined exercise therapy, compared with placebo or usual care, provides associate overall improvement in walking ability of fifty to 2 hundredth, with enhancements maintained for up to a pair of years (Michael et al., 2015).

CONCLUSION

High intensity interval training has valuable effect on endothelial function in diabetics with peripheral arterial insufficiency as evidenced by the significant increase in mean values of NO and pain free walking time and maximal walking time in the study group compared with the control group.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

ACKNOWLEGEMENT

The author would thank all participants.

AUTHOR CONTRIBUTIONS

All authors contributed equally in all parts of this study.

Copyrights: © 2019 @ author (s).
This is an open access article distributed under the terms of the **Creative Commons Attribution License (CC BY 4.0)**, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author(s) and source are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

REFERENCES

Abbott J D, Lombardero M S, Barsness G W, Pena-Sing I, Buitron LV, Singh P, Woodhead G, Tardif J C& Kelsey S F.2012; Ankle-brachial index and cardiovascular outcomes in the bypass angioplasty revascularization investigation 2 diabetes trialm; Am Heart,164(4):585–90.

Alahdab F, Wang A T, Elraiyah T A, Malgor R D, Rizvi A Z, Lane M A, Prokop L J, Victor M. Montori V M, Conte M S, &Mohammad Hassan Murad M H.2015; A systematic review for the screening for peripheral arterial disease in asymptomatic patients; J VascSurg, 61:42S-53S

Alberto da Silva, C, Sérgio F , Filho V, Serafim M , Botura E , Cristina da Rocha R, Pacheco C, Marques O F A, Melo L S I.2016; Effect of high intensity exercise on endothelial function in patients with T2DM;Rev Bras Med Esporte ,22 (2): 126-130.

American Diabetes Association: 2012"Standards of Medical Care in Diabetes." Diabetes Care; vol 35 (Supplement 1): 11- 63.

Ando J& Yamamoto K.2011; Effects of Shear Stress and Stretch on Endothelial Function; Antioxid. Redox Signal, 15:1389–1403.

Barclay G.2012; Clinical benefits of high intensity interval trining;Australian Family Physician,vol 41. No.12.

BrownriggJ R W, Schaper N C &Hinchliffe R J. 2015; Diagnosis and assessment of peripheral arterial disease in the diabetic foot; Diabet. Med. (32): 738-747.

Cocks M, Shaw C S, Shepherd S O, Fisher J P, Ranasinghe A, Barker T A &Anton J. M.2016; Sprint interval and moderate-intensity continuous training have equal benefits on aerobic capacity, insulin sensitivity, muscle capillarisation and endothelial eNOS/NAD(P)Hoxidase protein ratio in obese men; J Physiol, 594(8) : 2307–2321.

Conte M S , Pomposelli F B, Clair D G, Patrick J, McKinsey G J, Mills J L, Moneta G L, Murad M H et al., 2015; .) Management of asymptomatic disease and claudication; J VascSurg, 61:2S-41S.

Criqui M H &Aboyans V. 2015; Epidemiology of Peripheral Artery Disease; Circ Res, 116:1509-1526.

De silva C A, Riberio J P, Canto J C, de Silva R E, Silva Junior G B, et al,.2012. High intensity aerobic training improves endothelium dependent vasodilation in patients with metabolic syndromeand type diabetes mellitus; Diaetes Res ClinPract, 95(2): 237-245.

Emdin C A, Anderson S G, Callender T, et al.,2015; Usual blood pressure, peripheral arterial disease, and vascular risk: cohort study of 4.2 million adults. BMJ; 351:h4865.

Francois M E &Little J P.2015; Effectiveness and Safety of High Intensity Interval Training in Patients with Type 2 Diabetes; volume 28, number1.

Gerhard-Herman M D, Gornik H L, Barrett C, Barshes N R, Corriere M A, Drachman D E, Fleisher L A et al., 2017; Lower Extremity PAD Guideline: extremity peripheral artery disease: Executive Summary; JACC, 69 (11):1465 – 5.
Hamburg N M&Creager M A.2017; Pathophysiology of Intermittent Claudication in Peripheral Artery Disease; Circ J, 81: 281 – 289.
Higashi Yukihito .2015; Assessment of Endothelial Function History, Methodological Aspects, and Clinical Perspectives; Int Heart J, 56: 125-134.
Little J P, Percival M E, et al., 2011; Low- volume high- intensity interval training reduces hyperglycemia and increases muscle mitochondrial capacity in patients with type 2 diabetes.;JAppl Physioi,111: 1154- 60.
Marrett E, DiBonaventura M& Zhang Q.2013; Burden of peripheral arterial disease in Europe and the United States: a patient survey. Health Qual life Outcomes. (11):175.
Milani R V &Lavie C J. 2007; The role of exercise training in peripheral arterial disease; Vascular Medicine, 12: 351.
Mitranun W, Deerochanawong C, Tanaka H&Suksom D.2014; Continuous vs interval training on glycemic control and macro-and microvascular reactivity in type 2 diabetic patients; Scand J Med Sci Sports, 24: e69–e76.
Parmenter B J, Dieberg G & Smart N A.2015; Exercise Training for Management of Peripheral Arterial Disease: A Systematic Review and Meta-Analysis; Sports Medicine, (45) 2: 231–244.
Shah A D, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale C P, Deanfield J, Smeeth L, TimmisA& Hemingway H.2015; Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. Lancet Diabetes Endocrinol; 3(2):105.
Steffen L M, Duprez D A, Boucher J L, Ershow A G &Alan T. Hirsch.2008;Management of Peripheral Arterial Disease; Diabetes Spectrum, (21): 171-177.