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Long term effects of aerobic exercise on hemodynamic and functional capacity variables in diabetic patients on Maintenance Renal Hemodialysis, Randomized Controlled Trial

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Patients with diabetes who are on maintenance renal hemodialysis (MRH) are generally inactive and can benefit from the aerobic exercise training (AET). To evaluate the effects of the twelve weeks AET program on functional capacity (FC) and hemodynamic parameters in those patients. 47-patients were randomly assigned into AET group (n=22) and control group (CG; n=25). Resting heart rate (RHR), systolic blood pressure (SBP), diastolic blood pressure (DBP), the 6-minutes' walk test (6MWT) were all evaluated pre-study (evaluation-1), after 3-months (evaluation-2) and 2-months post-study cessation (evaluation-3). At evaluation-2; RHR, SBP, DBP, 6MWT mean values and percentages of changes were [75.41±2.77(-7.66%; P<0.05), 79.92±3.7(-0.14%; P=0.17)], [(138.42±1.65(-4.92%, P<0.05), 145.84±2.04(+0.15%; P=0.21)], [86.96±1.5(-6.64%; P<0.05), 92.76±1.3(-0.16%; P=0.86)], [443.73±21.04(+31.74; P<0.05), 337±12.23(-0.33%; P=0.3)] for the AET and the CG respectively. At evaluation-3; RHR, SBP, DBP, 6MWT mean values and percentages of changes were [78.5±3.08(+3.89%;P<0.05),80.24±3.26(-0.29%;P=0.16)],[(141±1.72(-3.14%<0.05), 145.8±1.87(+0.13%; P=0.45)], [89±1.31(-4.44%;P<0.05), 92.68±1.25(-0.25%; P=0.87)], [406.05±67.15 (+20.79; P<0.05), 337.24±11.31 (-0.25%; P=0.32)] for AET and CG respectively.AET has extended favorable effects on RHR, SBP, DBP, and 6MWT in diabetic patients on MRH. Long-term application of a well-designed AET is advisable to prevent deterioration of the hemodynamic and functional capacity parameters.

Keywords: Aerobic Exercise, Heart Rate, Blood Pressure, Functional Capacity, Diabetes, Maintenance Renal Hemodialysis.

INTRODUCTION

Renal disorders are the most feared diabetes-related complication because of its associated co-morbidities and increased mortality rate in patients with diabetes and renal failure (U.S. Renal Data System, 2008).

Impaired functional capacity (FC) and deteriorated physical activity (PA) level are prominent features of the diabetic patients on maintaianance renal hemodialysis (MRH). Low fitness level, reduced muscle strength, as well as increased comorbidities are strong contributing factors for the deterioration of the PA level in patients on MRH (Johansen et al., 2005) that are in-turn; negatively impact the daily living activities (ADL) and quality of life (QOL) in these populations (Hiraki et al., 2013).

Patients on MRH usually have significant reduction in FC and exercise tolerance (McIntyre et al., 2006), furthermore; diabetes mellitus (DM) adversely affects the functional status in patient on MRH (Martínez et al., 2015). Low FC and PA levels are associated with increased hospitalization risk and mortality rate among patients on MRH (Tamura et al., 2009). Also; renal failure is associated with numerous hemodynamic abnormalities that tend to be more sever in presence of DM (Symeonidis et al., 2006).

The importance of the exercise training for patient on MRH is not a new concept. Previous studies confirmed that practice of the regular exercise training in patients on MRH can significantly reduce the mortality and morbidity rates in those patients (Roseler et al., 1980; Cheema et al., 2005). Unfortunately, the regular practice of the exercise training is uncommon in patients with MRH (Himmelfarb, 2005). Individualized regular exercise training program, with a well-established follow-up should be considered as an essential component of the treatment regimen in patients on MRH (Fitts et al., 1999), since adding of just ten minutes PA per day can reduce the death risk by 22% in those patients (Tentori et al., 2010).

Previous studies documented the positive contribution of the exercise training programs in the improvement of many functional and psychological aspects in patient on MRH (Ouzouni et al., 2009; Konstantinidou et al., 2002), with the outpatient exercise training is more effective than the intra-dialytic training type (Kouidi et al., 2004). The exercise training for patients on MRH is an important treatment option as it can effectively control the abnormally increased blood pressure (BP) (Anderson et al., 2004), improve the lipid profile and so reduce the cardiovascular risk (Goldberg et al., 1986), as well as improving the efficacy of the renal dialysis (Kirkman et al., 2013).

Although the therapeutic exercises were described as an adjunctive treatment option many decades ago for patients with chronic kidney diseases (CKD) (Roseler et al., 1980); its incorporation in the treatment program for those patients is still limited, first because of existence of co-morbidities that require personalization of each training parameters and second because the majority of the existing protocols are research-based that may not be suitable for generalization in clinical practice (Kosmadakis et al., 2010). Additionally; majority of previous studies prescribing exercise training programs for patients on MRH were performed intra-dialysis and were conducted on a short-term basis (Anding et al., 2015), the matter that limit the ability to generalize its results.

Although proved efficacy of the aerobic exercise training (AET) in diabetic patient on MRH; but there is still a knowledge gap about the long-term effects of the AET on the blood pressure (BP), heart rate (HR) and the FC in diabetic patients on MRH. More researches are warranted in order to support the evidence level of the effects of exercise training programs for patients on MRH. Therefore; investigating the short as well as the long-term effects of a well-structured exercise training program become mandatory to effectively implement this approach in the routine clinical practice during management of patients on MRH (Williams et al., 2014). Therefore; the objective of this study was to investigate the short as well as the long-term effects of the AET program on the FC, HR, systolic blood pressure (SBP) and diastolic blood pressure (DBP) in diabetic patients on MRH.

MATERIALS AND METHODS

Study Design

This was twelve-week randomized controlled study. After baseline screening; diabetic subjects on MRH were randomly allocated to the aerobic exercise group (AEG; n=22) or control group (CG; n=25). All participants received standard medical treatment for the CKD and all were on MRH. This study was carried out according to the principles of the Declaration of Helsinki 1975, revised Hong Kong 1989 and was approved by the ethics committee of the Faculty of Physical Therapy, Cairo University (ethical committee approval number: P.T.REC/012/002436).

Subjects

Fifty-Three patients were recruited from National Institute of Urology and Nephrology to be included in this study. Initially; six patients were excluded at the initial screening because they showed positive results during the exercise stress test. The remaining Forty-Seven patients of both sexes (21 male, 26 female) were eligible, fulfilled the inclusion criteria, had no exclusion criteria, and were randomly allocated to AEG or CG and completed the study.

Inclusion Criteria

Patients with type 2 diabetes (T2DM) for more than four years duration, with CKD, on regular MRH for at least 24-months or more, age ranged between 35-50 years, and able to walk with or without additional support, accepted the informed consent for inclusion in the study, have not been participated in any formal exercise program within the previous 6 months.

Exclusion Criteria

Body mass index (BMI) more than 35 kg/m^2, 35 > age > 50 years, current smoking, hospitalization or acute diseases/active infection in the last 4-weeks, active malignancy, heart failure stage 3 or 4 according to the New York Heart Association, symptomatic angina pectoris/positive treadmill exercise stress test, cognitive impairment, chronic obstructive pulmonary disease stage 3 or 4, peripheral arterial obstructive disease, decompensated liver cirrhosis, history of serious cerebrovascular or musculoskeletal problems restricting physical activity.

Study Procedures

All patients underwent the same testing battery including a full history; physical examination and an exercise stress test. All patients were informed they are free to withdraw from the study at any time during the study. Written informed consent was obtained from each participant giving agreement for participation and publication of the results of the study. The study was conducted between April 2017 to October 2018.

Forty-Seven patients were eligible and randomly assigned to one of two groups; the AEG (n=22) who received trice weekly AET program on non-dialysis days in addition to the regular medical treatment or to the CG (n=25) who received only the regular medical treatment throughout the twelve-week study duration. Patients' random assignment into either AEG or CG groups was performed through random number generation using an online random permutation generator from http://www.randomization.com. A preliminary power analysis was conducted using the G-Power "GPowerWin_3.1.9.4 for windows" program (http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3/who-we-are) to determine the suitable sample size for this study (power (1-β error probability)) =0.95, α =0.05, effect size =0.45, number of groups=2); determining a sample size of 46**.**

Outcome Measures

The primary outcome variables were the resting heart rate (RHR), SBP, DBP, and FC (evaluated by the six minutes' walk test "6MWT"). Each variable was evaluated trice throughout the study: pre-study (evaluation-1), after three months (evaluation-2) and two months post-study cessation (evaluation-3). All variables were evaluated under resting conditions, preceded by two non-exercising days to avoid the acute post-exercise effects.

Demographic Characrtistics

Data collection procedures ran according the standard protocols. Weight in kg (measured to the nearest 0.1 kg) and height (measured to the nearest 0.1 cm) were evaluated from standing against a vertical scale of portable stadiometer (Detecto's ProMed® 6129 medical scale, USA). BMI (kg/m^2) was calculated=weight / height^2.

Maximum Heart Rate (HRmax) Evaluation

The HRmax was evaluated through the maximal exercise test. The testing protocol followed the previously published guidelines (Anding et al., 2015**),** using the Ergo bike fitness 2002 pc ergometer; Daum electronic gmbh, Germany), cycling rate ≥50 rpm. All patients were closely monitored and encouraged to achieve their maximal capacity. The electrocardiogram (ECG) and the BP were closely monitored; the exercise testing was discontinued at the point of appearance of pathological ECG criteria, other serious signs, or reaching the muscular fatigue.

Resting HR, SBP and DBP Evaluation

Resting HR, SBP and DBP were evaluated in accordance with the previously published guidelines **(**Williams et al., 2018). After 10 minutes rest; three RHR, SBP, DBP evaluations from the non-fistula arm were conducted via the auscultatory method using a standard digital sphygmomanometer (BTL Cardio Point ABPM apparatus) at two-minute intervals, then the overall means of the SBP or DBP were calculated for each patient. The mean RHR was evaluated in the same manner using wireless fingertip pulse oximeter (Amydi-med, Guangdong China "Mainland").

Functional Capacity Evaluation

Evaluation of FC was performed via the 6MWT, according to previously established guideline **(**Bučar et al., 2016)**.** Each patient walked through a 30 meter straight corridor on his/her maximal pace for six-minutes, and was informed verbally every two minutes about the remaining time. Only two encouragement phrases were used during the 6MWT; “You are doing well” and “Keep up the good work”. At the end of the sixth minute; covered distance was recorded in meters. For patient safety; Oxygen saturation and heart rate were monitored during the 6MWT by pulse oximeter (Amydi-med, Guangdong China "Mainland"). No adverse events were recorded.

2.5. Interventions

Aerobic Exercise Training (AET) Program

Initially; a preliminary session was performed to familiarize the patients with the bicycle ergometer (Ergo bike fitness 2002 pc ergometer; Daum electronic gmbh, Germany) and safety measures during the AET. The program was conducted on a frequency of three times weekly, day after day, on the non-dialysis days. Patients were exercised two hours after the breakfast to prevent exercise-induced hypoglycemia.

Each AET session started and ended with a 5-10 minutes warm up/cool down in form of cycling at intensity of 50% HRmax achieved during the exercise stress test. The intensity of the AET was controlled through monitoring the HR (picked via the cardio chest band and the pulse sensors on the ergometer handle) and by the rate of perceived exertion (Borge’s score scale). The participants of the AEG were closely monitored during the training and continuously directed to maintain their rate of perceived exertion between 11 and 13 on Borge’s score scale during the exercise training **(**Henrique et al., 2010) because it is the most suitable exercise training intensity for these patients **(**Van Vilsteren et al., 2005).

Both the AET session intensity (determined according to the HRmax) and duration followed stepwise gradually increasing pattern throughout the study. The exercise duration ranged between 30 to 45 minutes, the AET intensity ranged between 55% to 70% HRmax throughout the study (Figure 1).

Control Group (CG)

Twenty-Five patients underwent the same testing procedures, received regular medical treatment but did not participate any exercise training throughout the study.

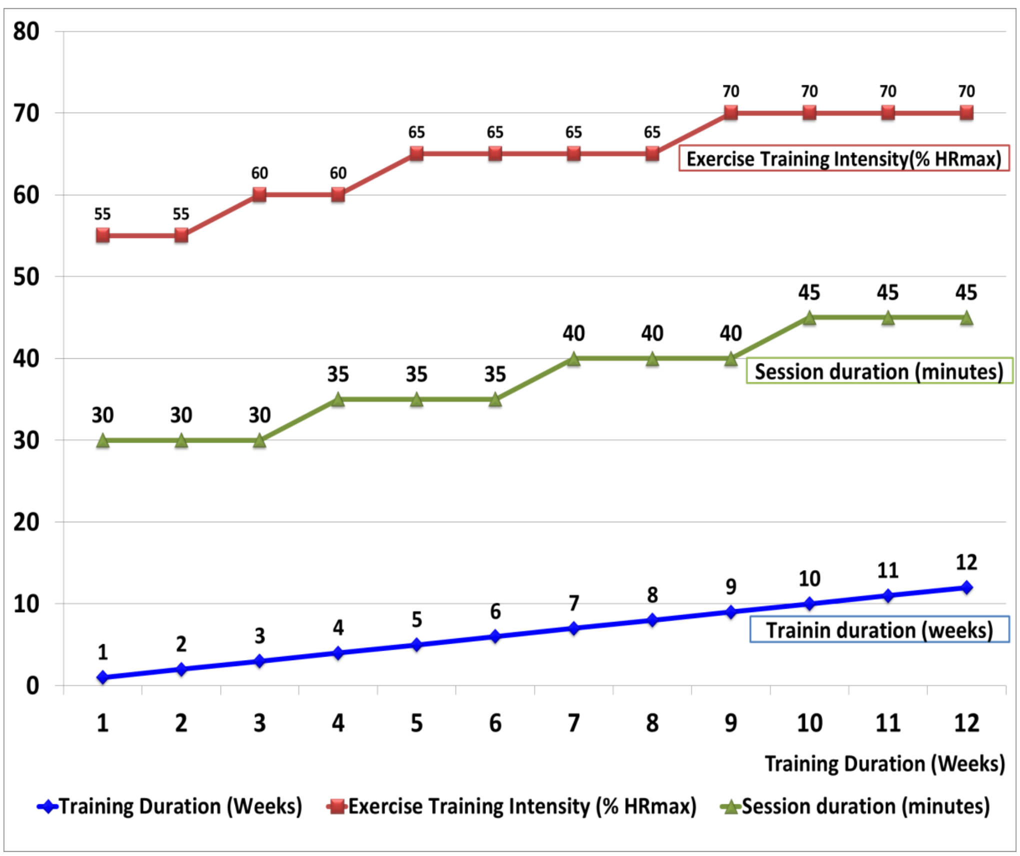

Figure 1: Aerobic Exercise Training Duration and Intensity throughout the study.

Statistical Analysis

All data were examined using BMI SPSS version 20 (SPSS Inc, Chicago, IL). Normality of the data distribution was tested via the Kolmogorov–Smirnov test. Results were reported as means and standard deviations. Mean changes in RHR, SBP, DBP, FC values within and between groups at the three evaluation points were analyzed with repeated measures ANOVA, with two within-subjects factors; treatment (AET, control) and time (pre, post-1, post-2) to test hypothesis within and between groups. The level of significance was set at $p < 0.05$.

RESULTS

Fifty-Three patients were recruited; six subjects did not qualify due to a positive stress test. Forty-Seven patients were enrolled, signed the consent form and randomly allocated to either AEG (n=22) or CG (n=25) and completed the study (Figure 2).

Patients Characteristics

Table I shows the general characteristics of the participants of the AEG and the CG at the beginning of the study. Results revealed that there were non-significant differences in age, weight, height, BMI, glycated hemoglobin (HbA1c), diabetes duration (years), average length of hemodialysis vintage (months), hours of dialysis per week between the two groups ($P > 0.05$) (Table I).

Within Group's Comparison

At evaluation-2 (after twelve weeks): results revealed that there were significant decreases in RHR, SBP, DBP mean values, and significant increase in the 6MWT mean value in the AEG ($P < 0.05$). Results revealed that there were non-significant changes in RHR, SBP, DBP, 6MWT mean values, in the CG ($P>0.05$). At evaluation-3: in spite of the re-increase in the RHR, SBP, DBP and the reduction in the 6MWT mean values; results revealed that there were still significant decreases in the RHR, SBP, DBP as well as significant increase in the 6MWT mean values in the AEG ($P< 0.05$). Results revealed that there were non-significant changes in the RHR, SBP, DBP, 6MWT mean values in the CG ($P> 0.05$) (Table II).

Between Groups' Comparison

At evaluation-1: Results revealed that there were non-significant differences in the RHR, SBP, DBP and the 6MWT mean values ($P> 0.05$). At evaluation-2: Results revealed that were significant differences in the RHR, SBP, DBP and 6MWT mean values; but in favor of AEG group ($P< 0.05$). At evaluation-3: Results revealed that there were significant differences in the RHR, SBP, DBP and 6MWT mean values; in favor of AEG group ($P < 0.05$) (Table III, Fig. 3-6).

Resting Heart Rate (RHR)

The mean value of the RHR is reported in Table II. At the evaluation-2; there was statistically significant decrease in RHR mean values by 7.66% in the AEG ($P<0.05$), compared with non-significant decrease in the RHR mean value by 0.14% ($P=0.17$) in the CG. In spite of the re-increase of the RHR in the AEG at evaluation-3; there is still significant decrease in the RHR mean values by about 3.89% ($P<0.05$) in the AEG, compared with non-significant increase in the RHR mean value by 0.29% ($P=0.16$) in the CG (Figure 3).

Systolic (SBP) and diastolic blood pressure (DBP)

The mean value of the SBP is reported in Table II. At the evaluation-2; there was statistically significant decrease in the SBP (-4.92%, $P<0.05$) and the DBP (-6.64%, $P<0.05$) mean values in the AEG, compared with non-significant changes in the SBP ($P=0.21$) and DBP ($P=0.86$) mean values by +0.15%, -0.16% respectively in the CG. In spite of the re-increase of the SBP and DBP in the AEG at evaluation-3; there is still significant decrease by about -3.14% and -4.44% for the SBP and the DBP mean values respectively ($p<0.05$), compared with non-significant changes in the CG by 0.13 % ($P=0.45$) and 0.25% ($P=0.87$) for the SBP and DBP mean value respectively (Figure 4).

Functional Capacity (6MWT)

The mean value of the 6MWT is reported in Table II. At the evaluation-2; there was statistically significant increase in the 6MWT mean values by +31.74 % in the AEG ($P<0.05$), compared with non-significant decrease in the 6MWT mean value by -0.33% ($P=0.3$) in the CG. In spite of the reduction of the 6MWT in the AEG at evaluation-3; there is still significant increase in the 6MWT mean values by about +20.79% ($P<0.05$) in the AEG, compared with non-significant decrease in the 6MWT mean value by -0.25% ($P=0.32$) in the CG (Figure 5).

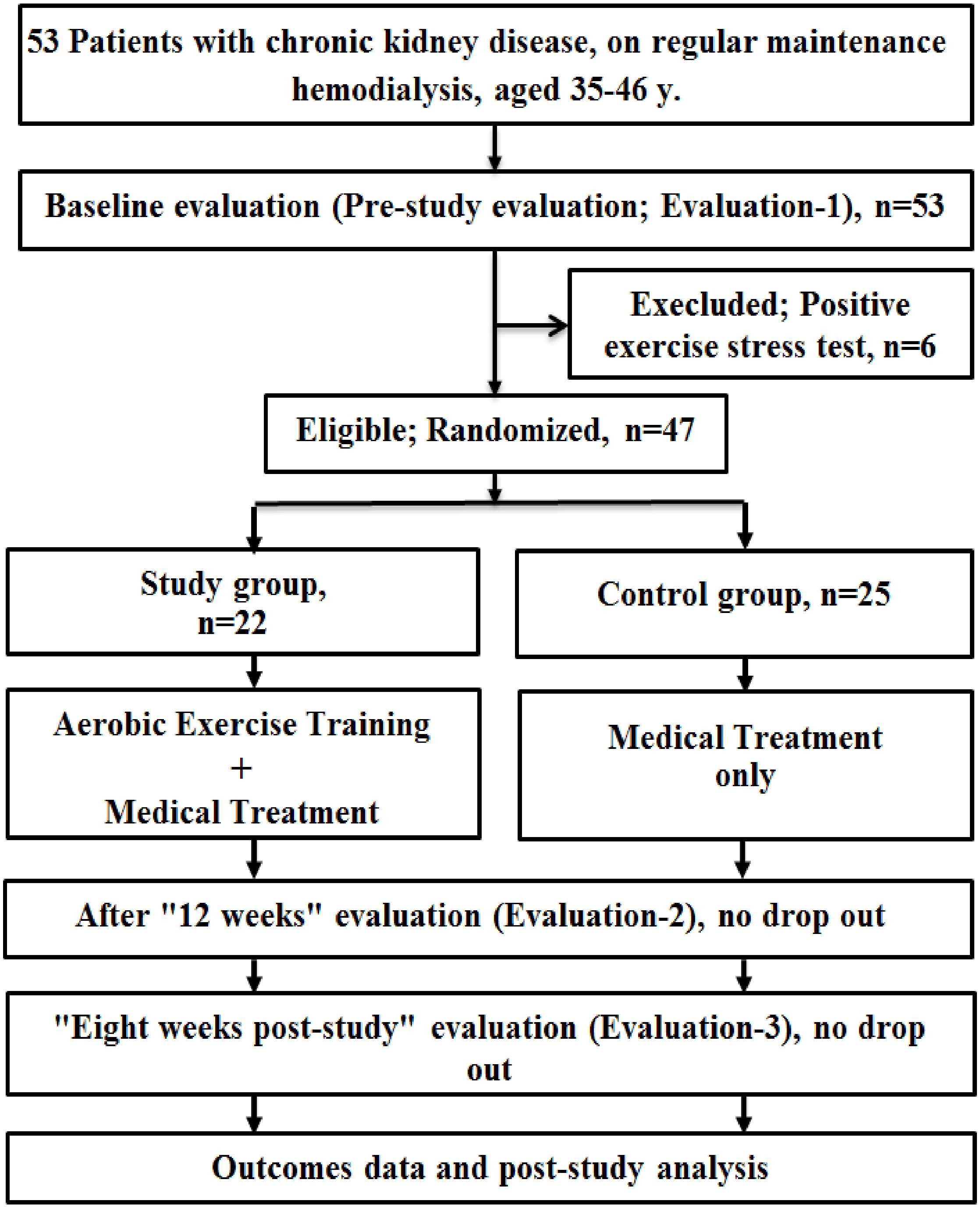

Figure 2: Patient's flow chart.

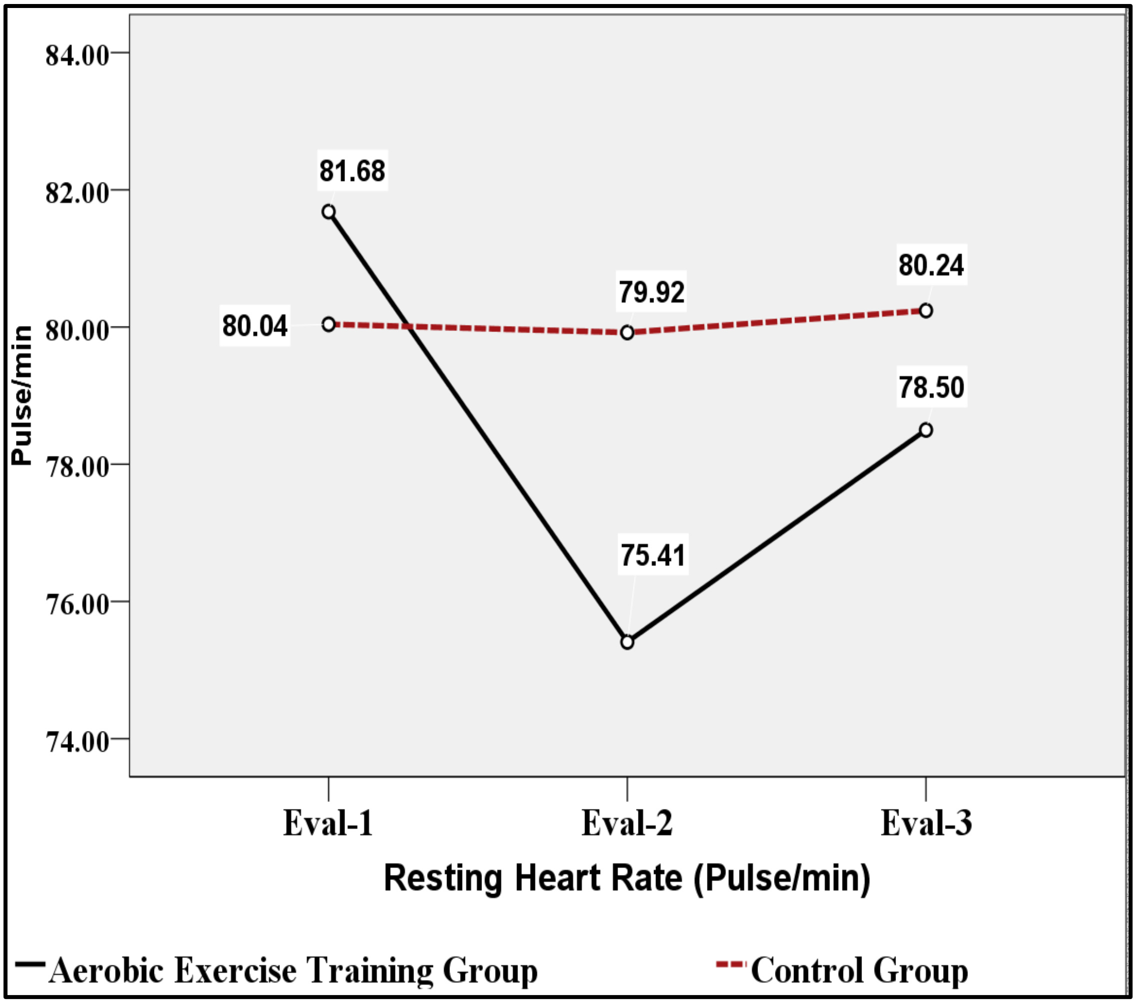

Figure 3: Mean values of resting heart rate (Pulse/min) for both groups.

Table I: The demographic characteristics of participants in both groups

Variables	Aerobic Exercise group (n=22)	Control group (n= 25)	T value	P value
Age (year)	39.73± 3.67	40.88 ± 3.64	1.16	0.29 **
Height (meter)	1.68 ± 0.09	1.68± 0.08	0.0001	0.99 **
Weight (kg)	75.77 ± 7.97	75.88± 7.06	0.002	0.96 **
BMI (Kg/m^2)	27.03 ± 2.51	27.17± 3.28	0.03	0.87 **
Glycated Hemoglobin(HbA1c)	8.28 ± 0.63	8.28 ±0.72	0.00004	0.99 **
Diabetes Duration (years)	5.64 ± 1.002	5.7±0.74	0.063	0.8 **
Average Length of Hemodialysis Vintage (months)	38.27 ± 7.75	38.16 ± 7.26	0.003	0.96 **
Hours of dialysis per week	14.5 ± 3.01	15.04± 2.32	0.482	0.49 **
Hypertension (%)	18(81.82%)	20(80%)		
Gender (Female/Male)	12/10	13/12		

BMI: Body mass index, Level of significance at P<0.05. * = significant, ** = non-significant.

Table 2: Within group's comparison of RHR, SBP, DBP and 6MWT mean values.

Variable		Aerobic Exercise group (n=22)			Control group (n=25)		
		Eval-1	Eval-2	Eval-3	Eval-1	Eval-2	Eval-3
RHR (pulse/min	F, p value	989.91, <0.05 *			0.42, 0.52 **		
			564.56, <0.05 *			2.62, 0.12**	
		728.068, <0.05 *			1.31, 0.28 **		
SBP (mmHg)	F, p value	316.57, <0.05*			0.67, 0.42**		
			160.54, <0.05*			0.04, 0.84**	
		258.39, <0.05*			0.26, 0.77**		
DBP (mmHg)	F, p value	916.08, <0.05*			0.41, 0.53**		
			277.94, <0.05*			0.19, 0.66**	
		587.23, <0.05*			0.64, 0.53**		
6MWT (m)	F, p value	403.95, <0.05*			1.97, 0.17**		
			8.82, 0.01*			0.14, 0.72**	
		40.63, <0.05*			1.42, 0.25**		

RHR: resting heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, 6MWT: 6 minutes' walk test * Significant. ** Non significant, $^{\Psi}$ Degree of freedom (DF)= 1, 44.

Table 3: Between groups' comparison of RHR, SPB, DBP, and 6MWT.

Variable		Pre-study (evaluation-1)		After twelve weeks (evaluation-2)		Eight weeks post-study (evaluation-3)	
		AET (n=22)	**CG** (n=25)	**AET** (n=22)	**CG** (n=25)	**AET** (n=22)	**CG** (n=25)
RHR (pulse/min)	Mean± SD	81.68± 3.34	80.04± 3.81	75.41± 2.77	79.92± 3.7	78.5± 3.08	80.24± 3.26
	F, P value	2.43, 0.13**		21.91, 0.00003*		3.51, 0.04*	
		250.97, <0.05$^{\Psi}$*					
SPB (mmHg)	Mean ±SD	145.59± 2.63	145.64± 2.78	138.42± 1.65	145.84± 2.04	141±1.718	145.8± 1.87
	F, P value	0.01, 0.95**		185.59, P< 0.05*		83.101, P< 0.05*	
		157.66, <0.05$^{\Psi}$*					
DBP (mmHg)	Mean ±SD	93.14± 1.08	92.92± 1.71	86.96± 1.5	92.76± 1.3	89± 1.31	92.68± 1.25
	F, P value	0.26, 0.61**		202.8, P< 0.05*		97.11, P< 0.05*	
		165.32, <0.05 $^{\Psi}$*					
6MWT (m)	Mean ±SD	337.5±17.43	338.08±10.69	443.73± 21.04	337±12.23	406.05±67.15	337.24±11.31
	F, P value	0.02, 0.89**		465.33, P< 0.05*		25.51, P< 0.05*	
		291.13, <0.05$^{\Psi}$*					

AET: Aerobic Exercise group, CG: Control group, RHR: resting heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, 6MWT: 6 minutes' walk test, * Significant, ** Non-significant, $^{\Psi}$ Degree of freedom (DF)= 1, 44

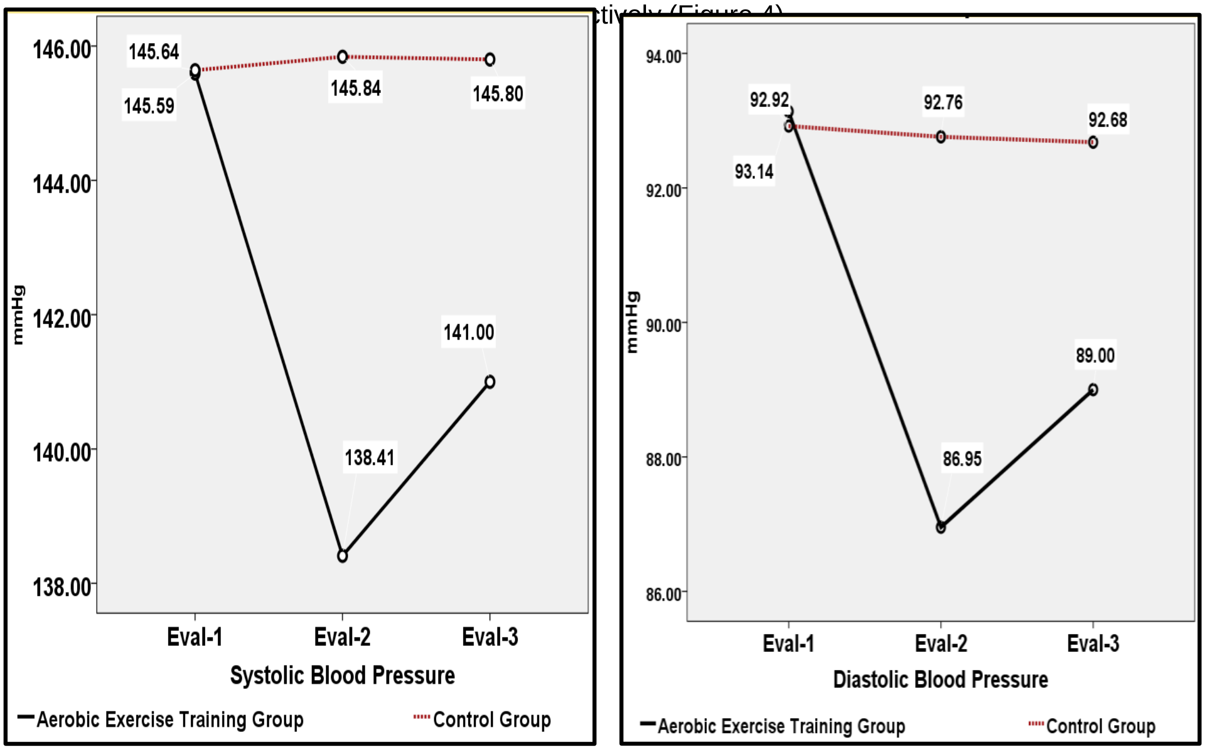

Figure 4: Mean values of systolic and diastolic blood pressure (mmHg) for both groups.

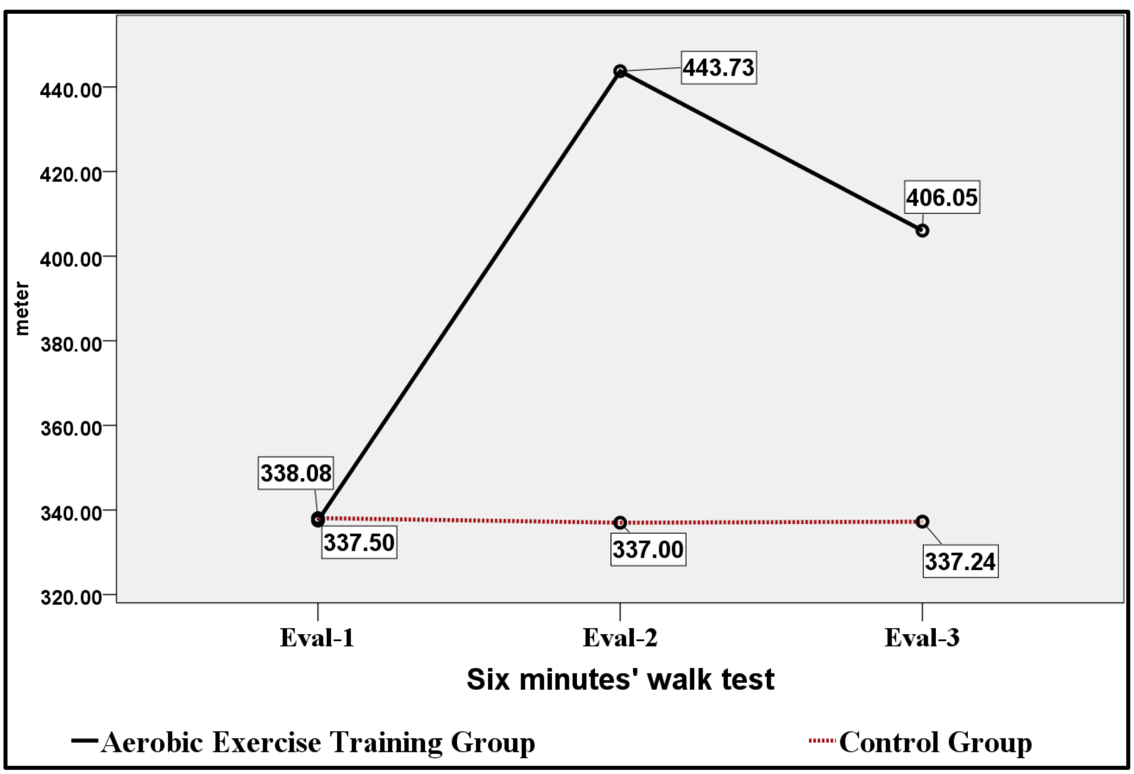

Figure 5: Mean values of six minutes' walk test (meter) for both groups.

DISCUSSION

Patients on MRH are characterized by significantly reduced FC compared with healthy sedentary controls (Painter, 2005).These disturbances are owing to exertional dyspnea, easy fatigability, frustration and psychological disturbances (Ouzouni et al., 2009). Regular exercise training is accompanied with increased physical performance and control of abnormally elevated BP, and so decrease the relative risk of death in general population (Fletcher et al., 1996).

Patients on MRH are usually associated with reduced cardiopulmonary fitness and low FC levels to the level that make them hardly fulfill the basic ADLs requirements. The FC in patients on MRH are usually limited to about 50-70% of the expected normal values (Painter, 2005; Clyne, 1996), with about one-third of patients on MRH fail to do the normal ADLs without assistance (Ifudu et al., 1994), which has direct negative impact on their QOL (Jang et al., 2004).

Although regular exercise training positively affects FC and cardiovascular risk factors in patients on MRH; however, limited percentage of them are able or willing to participate the outpatient exercise training programs (Daul et al., 2004). The supervised outpatient exercise training program is the most effective type for patients on MRH (Kouidi et al., 2004). Supervised AET offers motivational support and encourages the patients to be active and adhere to the prescribed exercise training program (Van Vilsteren et al., 2005).

Evaluation of functional aspects is more feasible than laboratory-based evaluations and easy to be accomplished by the low-capacity diabetic patients on MRH (Segura-Ortí, 2010). The 6MWT is usually used to evaluate the FC and the cardiovascular endurance in patients with chronic diseases (Solway et al., 2001), because it is considered the best submaximal stress walk test represents the ADLs (ATS, 2002). The 6MWT is the predominant practical test to evaluate the walking and the FC. Indeed; the 6MWT is a better indicator of the ability to perform the ADLs than other physiological exercise capacity tests (Depaul et al., 2002). Beside its importance in evaluating of functional ability; it is correlated with the survival rate in patients with CKD, since there is a 2.82-fold increase in the death rate when the 6MWT results is less than 350 meter in patients with CKD (Roshanravan et al., 2013). Furthermore; the mortality risk was reduced by 11% for each 20 meters increase in the 6MWT in patients on MRH (Torino et al., 2014). The changes in the functional aspects in response to moderate exercise training in patients on MRH usually follow a slow pattern and the significant improvements are commonly appear after 12-weeks of the exercise training (Konstantinidou et al., 2002).

The exercise training intensity and frequency were adjusted to match status of early muscle fatigue during exercise that is commonly encountered in patients on MRH (Sangkabutra et al., 2003). Because the inter-dialytic exercise training programs are superior in effects on aerobic capacity than the intra-dialytic training programs, since more gains in the FC were observed when training the patients on non-dialysis days (Konstantinidou et al., 2002), so participants in the current study received the AET on the non-dialysis days.

Inclusion of diabetic patients in regular exercise training was continuously faced with the ancient though and fear of increased risk of autonomic dysregulation in response to regular exercise training (Grubeck-Loebenstein et al., 1982), but actually; regular exercise training suppresses this increased risk (Heffernan et al., 2009). Furthermore; patients on MRH with other co-morbidities as pulmonary, cerebrovascular and coronary artery diseases can significantly benefits from regular exercise training program through controlling of these co-morbidities (Joshi, 2007).

The significant improvements seen in diabetic patients on MRH can be attributed in part to the favorable effects on controlling the blood glucose levels (Conn et al., 2007), and enhancing the insulin resistance in those patients (Goldberg et al., 1986). Additionally; the AET proved to increase the hemodialysis efficiency through increasing the phosphate and potassium ions shift from the poorly perfused tissues to the muscle interstitial fluid during exercise training, improving muscle capillarization, enhancing urea clearance, reducing fatigue and anxiety occurrence Lott et al., 2001).

Regular practice of the AET is advisable for patients on MRH; it should be incorporated as a routine and essential component of the treatment program for patients on MRH (Böhm et al., 2012). Exercise training has favorable anti-inflammatory (Afshar et al., 2011), and anti-oxidant effects (Pechter et al., 2003), increase the nitric oxide concentration (Gielen et al., 2010), reduces the lipid per-oxidation products and increases the glutathione concentration effects (Pechter et al., 2003) in patients on MRH.

The noticeable high BP in patients on MRH is in part secondary to endothelial dysfunction and progressive loss of arterial elasticity (Garcia-Cardena and Gimbrone, 2006) caused by decreased nitric oxide (NO) bioavailability (Briet and Burn, 2012). The predominant sympathetic vasomotor over-activity that is seen in patients with CKD can result in the further deterioration of the kidney function as well as increasing the blood pressure in these patients (Grassi et al., 2011).

Several studies investigated the effects of increasing PA level on the BP. Henrique et al. reported significant reduction in both SBP and DBP after the 12-weeks AET in patients on MRH (Henrique et al., 2010). The AET-related anti-hypertensive effect was also reported by Anderson et al. who observed significant reduction in the BP after 3 and 6-months AET (Anderson et al., 2004). Ouzouni et al., also studied the effect of the AET in management of patients on MRH and found that there was about 6% reduction in the resting BP mean value in patient on MRH (Ouzouni et al., 2009). Previous study conducted on non-diabetic patients with CKD found significant reduction in the SBP and DBP in response to 4-months of the AET (Boyceet al., 1997). Clyne et al., reported that 3-months of bicycle exercise training can significantly increase the maximum exercise performance and reduce the HR in patients with CKD **(**Clyne et al., 1991).

Exercise training can effectively reduce the SBP and DBP in pre-hypertensive subjects (Cornelissen et al., 2013), furthermore; the AET proved to have a suppressant effect on the abnormally elevated BP in patients with CKD stages 2-4 (Heiwe and Jacobson, 2014). The AET-related improvement in the cardiovascular parameters can be attributed to improved endothelial function of the blood vessels and the exercise-related control of the vasomotor over-activity **(**Cornelissen and Fagard, 2005). Additionally; the AET can effectively down-regulated the renin-angiotensin system in patients with CDK **(**Bergamaschi et al., 1997), as well as in healthy sedentary hypertensive subjects **(**Cornelissen and Fagard, 2005).

Regarding the BP response to exercise; results of the current study contradict that of Kosmadakis et al., who reported more fall in the BP in the control group compared to the study group, this contradiction can be simply resolved when considering the non-randomized nature and the non-controlled increases in the BP medications utilized by the control group in the Kosmadakis et al., study (Kosmadakis et al., 2011). Boyce et al., also reported that effects of the AET on the BP are completely reversed after 2-months of training cessation in pre-dialysis patients (Boyce et al., 1997). Short study duration and poor patients compliance in the previous studies can solve this contradict **(**Shalom et al., 1984).

Regarding the FC; the significant increase in the AET group is consistent with the study by Parsons et al., who reported that the 6MWT was increased by 14% after 20-weeks exercise training in patients on MRH **(**Parsons et al., 2006). The FC results are also consistent with results of Henrique et al., who found a 10 % increase in the FC in response to the 12-weeks intra-dialytic AET in patients on MRH (Henrique et al., 2010). Other studies showed a 6-19% increase in the FC after the resistance or the AET 2 days/week in patients on MRH **(**Fitts et al., 1999; Rossi et al., 2014). The generally deteriorated FC of patients on MRH magnifies their improvement potential response to the AET (Storer et al., 2005). Results of this study came in accordance with that of Heiwe and Jacobson; Smart and Steele, who reported that the AET can significantly improve the physical function in patients on MRH (Heiwe and Jacobson, 2014; Smart and Steele, 2011).

CONCLUSION

The AET has extended favorable effects on RHR, SBP, DBP, and 6MWT in diabetic patients on MRH. Long-term application of a well-designed AET is advisable to prevent deterioration of the hemodynamic and the functional parameters. This study confirmed the importance of regularly applying outpatient AET in diabetic patients on MRH since The AET proved to have favorable short and long-term effects on the RHR, SBP, DBP and FC in diabetic patients on MRH.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

Both authors have contributed substantially to all parts of this study and approved the final version.

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