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Effect of Aerobic Exercise Training on Cardiovascular Responses in Type 1 Diabetic Autonomic Neuropathy

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Abstract- Background: Diabetes Mellitus is a chronic, multifaceted disorder caused by reduction in insulin action and secretion or the both, it's characterized by hyperglycemia and disruption of the metabolism of carbohydrates, fats and proteins, over time, it results in small and large vessels complications and neuropathies. This disease is ranked as the third cause of death and leading factor of blindness. One of the most overlooked of all serious complications of diabetes is cardiovascular autonomic neuropathy (CAN), which encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics. The complications of diabetes mellitus are macro and micro vascular disorders, central, Peripheral and autonomic neuropathy. The autonomic neuropathy is the most common complication of the long standing diabetes. Autonomic neuropathy is a well recognised complication of diabetes mellitus, and its incidence has been reported to be 20 - 40%.

Subjects and Methods: Fifty diabetic patients type-1, diagnosed by concerned Doctor with autonomic neuropathy, with duration of disease more than five years, their age ranged from 45 to 65 years old, they were chosen from National Institute for Diabetes and Endocrine Glands, They were randomly assigned to two equal groups. Study group included twenty five diabetic patients with autonomic neuropathy, practiced a program of aerobic exercise with intensity from 60 to 75 % of maximal heart rate (HR_{max}) on treadmill for self limiting intensity for 3 sessions / week for three months and received their medical management (16 men and 9 women, mean age was 52.2 ± 4.9 years) that had been received aerobic moderate intensity exercise training on treadmill for 40 minutes, 3 times/week, day after day, for 3 months, while control group included twenty five diabetic patients with autonomic neuropathy they received only their medical treatment. All patients had been evaluated to measure age, Body mass index (BMI), fasting blood glucose, heart rate (HR) responses to valsalva maneuver, HR response to deep

breathing, HR response to change of position, systolic blood pressure (BP) response to valsalva maneuver, systolic BP response to sustained hand grip and systolic BP response to change of position. ECG machine and its accessories will be used to do stress test for each patient by attending physician and to monitor heart rate, rhythm, R-R interval and Q-T interval for each patient of both groups. All measurements were done before and after the study program.

Results: After completion of the study, a significant improvement was observed in (BMI), fasting blood glucose, (HR) responses to valsalva maneuver, HR response to deep breathing, HR response to change of position, systolic blood pressure (BP) response to valsalva maneuver, systolic BP response to sustained hand grip and systolic BP response to change of position ($P < 0.05$), when compared to control group.

Conclusion: Aerobic moderate intensity exercise training could improve cardio vascular responses in diabetic autonomic neuropathy. Aerobic exercise is a good method that improve cardiac autonomic neuropathy in type 1 diabetes mellitus.

Keywords: aerobic exercise, type 1 diabetes mellitus, cardiac autonomic neuropathy.

I. INTRODUCTION

Diabetes Mellitus is a chronic, multifaceted disorder caused by reduction in insulin action and secretion or the both, it's characterized by hyperglycemia and disruption of the metabolism of carbohydrates, fats and proteins, over time, it results in small and large vessels complications and neuropathies. This disease is ranked as the third cause of death and leading factor of blindness (Boulton AJ et al 2010).

The complications of diabetes mellitus are macro and microvascular disorders, central, Peripheral and autonomic neuropathy. The autonomic neuropathy is the most common complication of the long standing diabetes, It's due to the accumulation of sorbitol in nerve cell that result in abnormal fluid and electrolyte shift, which causes nerve cell dysfunction,. Balanced cardiac ANS function is based on strong impaired cardiovascular ANS function has been associated with type 1 diabetes (T1D) (Stevens et al., 2008).

Data from the 2008 Egypt Demographic and Health Survey (EDHS 2008) were used to show the Prevalence of diabetes for selected socio-demographic

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variables was calculated by gender. Prevalence of co morbid conditions, and risk factors for complications of diabetes, were estimated by gender. Health care utilization among diabetics was estimated. The crude prevalence rate of known diabetes in Egypt in 2008 was 4.07% (0.25). It increased with age, to reach 19.8% among females aged 50-59. Only 18% of males, and 7.8% of females, had a normal body mass index. 37.5% of male diabetics smoked. The prevalence of hypertension among diabetics was 75% for males, and 66.9% for females; of these, only 2% of males, and 14.3% of females, were controlled to < 130/80 mmHg. 13.3% of males had a history of myocardial infarction or stroke. 44.9% of males, and 80.4% of females, had no insurance coverage. More than half of diabetics visited a private physician at their last visit. 9.3% of males, and 3.8% of females, had been hospitalized in the past year. They concluded that Diabetes is highly prevalent among older persons in Egypt. Public health policy should educate the public on the risk factors for diabetes, and should implement guidelines for adequate control of this disease (Naglaa et al 2010).

Autonomic neuropathy is a well recognised complication of diabetes mellitus, and its incidence has been reported to be 20 - 40%. Numerous non-invasive tests have been in use for the diagnosis of cardiac autonomic neuropathy (Ewing DJ et al 1985).

CAN, manifested as changes in HRV, may be detected within 1 year of diagnosis in type 2 diabetes and within 2 years of diagnosis in type 1 diabetes (Drake-Holland AJ et al, 2006)

Resting tachycardia. Resting heart rates of 100 bpm with occasional increments up to 130 bpm usually occur later in the course of the disease and reflect a relative increase in the sympathetic tone associated with vagal impairment (Young et al., 2009).

Diabetic autonomic neuropathy (DAN) is classified as subclinical or clinical depending upon the presence or absence of symptoms. A wide spectrum of symptoms affecting many different organ systems can occur, including the cardiovascular, gastrointestinal, genitourinary, pupillary, sudomotor, and neuroendocrine systems (Teskaye S et al 2005).

One of the most overlooked of all serious complications of diabetes is cardiovascular autonomic neuropathy (CAN), which encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics (Schumer MP 1998).

Our data and those of others confirm that early in the progression of CAN complicating type 1 diabetes, there is a compensatory increase in the cardiac sympathetic tone in response to subclinical peripheral denervation, CAN may critically influence myocardial substrate utilization (Drake-Holland AJ et al, 2006) and contribute to mitochondrial uncoupling regional

ventricular motion abnormalities, functional deficits, and cardio myopathy (Pop-Busui R, 2004)

Aerobic exercise is a physical exercise that intends to improve the oxygen system. Aerobic means "with oxygen", and refers to the use of oxygen in the body's metabolic or energy-generating process. Many types of exercise are aerobic, and by definition are performed at moderate levels of intensity for extended periods of time. The two types of exercise differ by the duration and intensity of muscular contractions involved, as well as by how energy is generated within the muscle. Initially during aerobic exercise, glycogen is broken down to produce glucose, which then reacts with oxygen (Krebs cycle) to produce carbon dioxide and water and releasing energy. In the absence of these carbohydrates, fat metabolism is initiated instead (Colberg S et al., 2003).

II. PATIENTS AND METHODS

This study was consists of fifty type 1 diabetes mellitus (IDDM) patients with autonomic neuropathy (36 males and 14 females) attended to the Outpatient Clinic in National Institute for Diabetes and Endocrine Glands. Their age ranged from 45 to 65 years with a mean value of (49 ± 7.2) , height ranged from 162 to 181 cm with a mean value of (172 ± 9) , and the body weight ranged from 67 to 91 Kg with a mean value of (170 ± 11) . Their body mass indexes ranged from 19 to 31 Kg / m² with a mean value of (25 ± 3.3) Kg / m². The all patients under medical control by specialized physician. All patients were randomly divided into two equal groups.

The study group was twenty five (19 male and 6 female) IDDM patients with autonomic neuropathy, Who practiced aerobic exercise training with a moderate intensity from 60 to 75 % of their HR_{max} for each patient three sessions /week for three months on an electronic treadmill for forty minutes to each session, and Control group include twenty five patients (17 male and 8 female) IDDM, all patients received their medical treatment.

Exclusion criteria: Patients with, Varicose veins, Severe ischemic heart diseases and Chest infection patients were excluded.

Before starting the study, a meeting was done for all patients to explain for all of them our study (patient information sheet PIS) and also to collect consent form of each patient and to record demographic data, fasting blood glucose, heart rate (HR) responses to valsalva maneuver, HR response to deep breathing, HR response to change of position, systolic blood pressure (BP) response to valsalva maneuver, systolic BP response to sustained hand grip and systolic BP response to change of position. ECG machine and its accessories will be used to do stress test for each patient by attending physician and to

monitor heart rate, rhythm, R-R interval and Q-T interval for each patient of both groups.

Each patient of study group was asked to perform aerobic exercise training on electronic treadmill with moderate intensity from 60 to 75 % of each individualized (HR_{max}), three times per week for three months for forty minutes of each session, accordingly to self limiting intensity of each patient the program started with:

Warming up phase; for 5 minutes on treadmill with low speed (0 watt) with horizontal line, then the speed of electronic treadmill increased to reach Active phase (Soligard et al., 2008).

Stimulus phase; in which each patient of group A performed self limiting exercises on treadmill with individualized moderate intensity from 60 to 75 % of HR_{max} . For 30 minutes (Laskowski., 2013)

Cool Down phase; about 5 minutes on treadmill with low speed (Woods et al., 2007).

Data were analyzed with SPSS software version 23. The level of significance was set at $P \leq 0.05$. Paired t-test was applied for each group to compare pre and

post values within the same group. Unpaired t-test was applied to compare pre and post values between both groups of the study.

III. RESULTS

Mean value of body mass index (BMI) had shown a significant improve by significantly decreased post exercise in study group (P value = 0.001) as compare to control group which increased significantly (P value = 0.047) (Table 1). In study group The value of Q-T interval had shown significant improve after exercise (P value = 0.001) but in control group had shown significant increase in Q-T interval (P value = 0.001) (Table 1). The reduction of Q-T interval was considered as improvement. In study group R- R interval had shown a significant improve post exercise (P value = 0.001) and no significant change in control group (Table 1). The increment of R- R interval was considered as improvement. The mean value of fasting blood glucose was shown high significant (decrease) improve post exercise (P value = 0.000) and control group had shown significant increase (P value = 0.002) (Table 1).

Table (1) : Changes of Body Mass Index (BMI), Q T interval ,R R interval and Fasting Blood Glucose Pre and Post Program within each group and between groups:

Variables	Study group			Control group			P value for both groups after program
	Pre program	Post program	P Value	Pre program	Post program	P Value	
	Mean \pm SD	Mean \pm SD		Mean \pm SD	Mean \pm SD		
BMI	29.2 \pm 2.6	27.7 \pm 2.3	0.001 S	28.8 \pm 1.7	29.2 \pm 1.8	0.047	0.018 S
Q T interval	448.8 \pm 47.3	414.6 \pm 45.3	0.001 S	426.2 \pm 34.8	450.4 \pm 39.3	0.001	0.023 S
R R interval	487.6 \pm 53.3	599.1 \pm 49.9	0.001 S	613.6 \pm 71.1	574.0 \pm 84.4	0.14	0.207
Fasting Blood Glucose	137.4 \pm 10.8	137.4 \pm 5.0	0.000 S	129.0 \pm 6.9	135.6 \pm 8.8	0.002	0.001 S

SD=Standard Deviation, Significant level: $P \leq 0.05$ S.

The mean value of systolic blood pressure responses to (change position, sustained hand grip and valsalva Maneuver) respectively had shown significant improve after exercise (P value = 0.003) (P value = 0.000) and (P value = 0.008) respectively but in control

group had shown significant increase in systolic blood pressure responses to change position, sustained hand grip (P value = 0.000) and (P value = 0.001) (Table 2) and no significant changes in response to valsalva Maneuver (P value = 0.098) (Table 2).

Table (2) : Changes of systolic blood pressure responses to change position, sustained hand grip and response to valsalva Maneuver Pre and Post Program within each group and between groups:

Variables	Study group			Control group			P value for both groups after program
	Pre program	Post program	P Value	Pre program	Post program	P Value	
	Mean \pm SD	Mean \pm SD		Mean \pm SD	Mean \pm SD		
systolic B P response to change position	139.3 \pm 6.5	134.8 \pm 5.5	0.003 S	137.7 \pm 7.6	143.7 \pm 6.4	0.000 S	0.000 S
systolic B P response to sustained Hand Grip	139.6 \pm 6.1	134.1 \pm 5.9	0.000 S	138.4 \pm 6.8	142.9 \pm 7.1	0.001 S	0.000 S
systolic BP response to valsalva maneunver	137.6 \pm 6.4	134.2 \pm 5.8	0.008 S	134.4 \pm 8.5	136.7 \pm 5.6	0.098	0.135

SD=Standard Deviation, Significant level: $P \leq 0.05$ S.

in study group the mean values of the heart rate responses to (change position, Deep breathing and valsalva Maneuver) had shown significant improve post exercise (P value = 0.000), (P value = 0.000) and (P value = 0.001) respectively and in control group had

shown significant increase in heart rate responses to change position (P value = 0.009), Deep breathing (P value = 0.026), and no significant changes in heart rate responses to valsalva Maneuver (P value = 0.098) (Table 3).

Table (3) : Changes in Heart rate responses to (change position, Deep breathing and valsalva Maneuver) Pre and Post Program within each group and between groups:

Variables	Study group			Control group			P value for both groups after program
	Pre program	Post program	P Value	Pre program	Post program	P Value	
	Mean \pm SD	Mean \pm SD		Mean \pm SD	Mean \pm SD		
Heart Rate response to change position	98.3 \pm 7.6	93.9 \pm 5.7	0.000 S	98.3 \pm 6.7	101.6 \pm 2.7	0.009 S	0.001 S
Heart Rate response to Deep Breathing	92.6 \pm 6.4	88.5 \pm 5.6	0.000 S	84.2 \pm 6.7	86.7 \pm 6.1	0.026 S	0.005 S
Heart Rate response to valsalva maneuver	80.1 \pm 4.0	76.3 \pm 4.7	0.001 S	87.8 \pm 1.6	86.8 \pm 4.7	0.098	0.001 S

SD=Standard Deviation, Significant level: $P \leq 0.05$ S

IV. DISCUSSION

In this study, The mean value of BMI was significantly decreased post exercise from (29.2400 \pm 2.61852) to (27.76 \pm 2.38537). The mean value of fasting blood glucose pre exercise was (137.48 \pm 10.85557) and significantly reduced post exercise to (127.00 \pm 5.01664). The mean value of systolic blood pressure before exercise (change position, sustained hand grip and valsalva Maneuver) were (139.36 \pm 6.52482), (139.68 \pm 6.10137) and (137.60 \pm 6.45497) respectively which were significantly changed after exercise by decreasing to (change position, sustained hand grip and valsalva Maneuver) (134.80 \pm 5.50757), (134.16 \pm 5.91383) and (134.24 \pm 5.84009) respectively. The mean values of the heart rate responses to (change position, Deep breathing and valsalva Maneuver) were (98.36 \pm 7.65876), (92.68 \pm 6.47251) and (80.12 \pm 4.04475) respectively, That were significantly decreased post exercise to (93.96 \pm 5.78417), (88.56 \pm 5.61308) and (76.32 \pm 4.75850) respectively. The value of Q-T interval pre exercise was (448.88 \pm 47.39666). and significantly reduced post exercise to (414.68 \pm 45.37503) (Table 10). The reduction of Q-T interval was considered as improvement. R- R interval pre exercise was (487.60 \pm 53.32448) and significantly increased post exercise to (599.12 \pm 49.92438), The increment of R- R interval was considered as improvement.

Results of this study were supported by **Neil J et al 2006**, who studied the Differences among the effects of aerobic, resistance, and combined training on HbA_{1c} (A1C) were trivial for training lasting ≥ 12 weeks, in diabetic patients. There were generally moderate benefits for other measures of glucose control. For other risk factors, although combined training was generally superior to aerobic and resistance training. but there

were small additional benefits of exercise on glucose control with increased disease severity. They concluded that All forms of exercise training produce benefits in the main measure of glucose control: A1C. The effects are similar to those of dietary, drug, and insulin treatments. These results were supported by **Thomas H et al 2009** who said that both aerobic and resistance training have important roles in DM. Recent work comparing the individual and combined effects of aerobic and/or resistance training revealed that both forms of exercise were equally beneficial for glycemic control, although aerobic training had a greater effect on body composition, also **Sarika Chaudhary et al 2010** found that BMI and body fat percentage showed significant improvements in both training groups.

Jamie F. Burr 2012 who concluded that Aerobic exercise has significant and particular benefits for people with type 1 diabetes. It increases sensitivity to insulin, improves cholesterol levels, and decreases body fat. The results of this study was similar to **Thomas H et al 2009** who said both aerobic and resistance training have important roles in DM on glycemic control. Also **Alsayd et al, (1999)** who found that after six weeks of exercise training on treadmill with moderate intensity in diabetic patients there was a significant reduction in body weight and BMI. Also **Wing et al; (1988)** found that in diabetic patients exercise had been useful adjunct to diet control in diabetic patients to reduce body weight and BMI. **Klem et al; (1997)** found that exercise improved body composition in diabetic patients that lead to weight loss and reduce BMI. Also **Koullam. Parpa et al 2009** found that fasting glucose values (FG) and body weight were significantly lower following 12 weeks of training. also **Didangelos T et al 2006** said that Improvement in glycemic control reduces the incidence of CAN and slows the progression there of.

The results of this study were contradict with **Lehmann et al; (1995)** they found that moderate exercise training resulted in considerable decrease of body fat particularly in abdomen region but this decrease of the body fat wasn't accompanied with weight loss or reduction of BMI. Also **Poirier et al; (1996)** found that exercise training for six months in NIDDM didn't significantly changed body weight or BMI. In the current study this reduction of body weight and BMI in group (A) may be attributed to the walking training program was associated with some advises about diet control and weight reduction.

The results of this study showed a significant reduction in fasting blood glucose (FBG) level of group (A) after exercise program while a significant increased in FBG in group (B). This current positive response of FBG in NIDDM patients was supported with the most of the recent studies. These result were supported by **Russell et al; (1999)**, they found that exercise training with moderate intensity lead to increase insulin sensitivity and so reduced blood sugar level and regular exercise improve glycemic control that leads to reduce hypertension and normalized lipid in type II D.M. Also **Alsayd et al, (1999)** found that moderate aerobic exercise training on treadmill for 6 weeks reduced FBG in type-II diabetic patients. **Roger et al; (1988)** found that after one week of aerobic exercise, The FBG had been improved via improvement of glucose tolerance test. Also result of **Anna Chudyk et al 2011** supported our result who said that 645 articles retrieved, 34 met our inclusion criteria; most investigated aerobic exercise alone, and 10 reported combined exercise training. Aerobic alone or combined with resistance training (RT) significantly improved HbA_{1c} -0.6 and -0.67%, respectively (95% CI -0.98 to -0.27 and -0.93 to -0.40, respectively), systolic blood pressure (SBP) -6.08 and -3.59 mmHg, respectively (95% CI -10.79 to -1.36 and -6.93 to -0.24, respectively), and triglycerides -0.3 mmol/L (95% CI -0.48 to -0.11 and -0.57 to -0.02, respectively). Waist circumference was significantly improved -3.1 cm (95% CI -10.3 to -1.2) with combined aerobic and resistance exercise. they concluded that Aerobic exercise improves glycemic control, SBP, triglycerides, and waist circumference in diabetic patients. **Hordern M D et al 2009** proved that resisted exercise training for 6 weeks significantly increased rate of glucose disposal and insulin sensitivity in sedentary NIDDM patients, they concluded that discrepancy of blood sugar response to exercise is most likely due to the difference in intensity, volume and duration of exercise. Similler result were founb by **Landary and Allen (1992)** who found that in diabetic patients after 6-12 weeks of an aerobic exercise, the FBG had been improved, and **Schneider et al; (1990)** found that after exercise training improve of glucose tolerance and reduce blood sugar level. **Lampman et al; (1991)** also concluded that after exercise training the

FBG had been lowered. **Beernbaum et al; (1989)** found that after exercise training for 6-12 weeks on a stationary bicycle in Diabetes Mellitus type II the blood glucose level decreased and there was no relationship between the degree of autonomic neuropathy and level of blood glucose fall.

Improvement of FBG can be explained by several mechanisms as exercise training improve impairment of the muscular glucose transport protein system and the decreased of enzymatic activity, which regulate storage and oxidation of glucose in the skeletal muscle (**Ebeling et al; 1995**). Also exercise training increase the conversation of low oxidative type (II a) fibers that have a greater capillary density and high concentration of the muscle glucose transport system that make them exhibit a greater response to insulin action than type (II b) fibers (**Ivy, 1997**).

In this study The value of Q-T interval pre exercise was (448.88 ± 47.39666) . and significantly reduced post exercise to (414.68 ± 45.37503) .The reduction of Q-T interval was considered as improvement. R- R interval pre exercise was (487.60 ± 53.32448) and significantly increased post exercise to (599.12 ± 49.92438) , The increment of R- R interval was considered as improvement. **Mathur et al 2006** said that QTc prolongation in diabetic subjects stands favourably as an autonomic dysfunction parameter as compared to other autonomic neuropathy function test (ANF) tests. Further, QTc prolongation has linear positive correlation with the degree of CAN. It is inferred from the present observations that QTc prolongation in diabetics with an otherwise normal heart can be used as a diagnostic test for assessment of cardiac autonomic neuropathy and may even be considered as a cardiac autonomic function test with prognostic significance. These results were supported by **Veglio et al; (2000)** who assessed the relationship between QT interval prolongation and mortality in type 1 diabetic patients. Data on survival after 5 years were obtained from 316 of 379 patients (83.3%) who took part in a study on the prevalence of diabetic neuropathy and QT interval prolongation. They found that mortality at 5 years was 6.32%, patients who survived were significantly younger, had a shorter duration of diabetes, had lower systolic and diastolic blood pressure levels, and had a shorter QT interval corrected for the previous cardiac cycle length (QTc) than subjects who died. In univariate analysis, patients had a higher risk of dying if they had a prolonged QTc or if they were affected by autonomic neuropathy. QTc prolongation was the only variable that showed a significant mortality they concluded that the first cohort-based prospective study indicating that QTc prolongation is predictive of increased mortality in type 1 diabetic patients.

As regarding to **Oka et al; (1996)**, **Khan et al; (1987)**, **Veglio et al; (2000)** and **Ewing et al; (1991)**, thier studies had been shown that aerobic exercise training at

moderate intensity of 60–75 % of maximal HR leads to improve and decrease Q-Tc interval in diabetic patients with autonomic neuropathy, This may be due to improvement of sympathetic and parasympathetic nervous system.

Oka et al, (1996) had attempted to clarify the relationship of Q-T interval to alpha and beta sympathetic, as well as, parasympathetic function tests including spectral analysis of R-R interval and systolic blood pressure. Q-T interval in 76 diabetic patients and 76 ages matched healthy control whose R-R interval was comparable. They also investigated the relationship of Q-T interval to various clinical features of diabetes mellitus and to autonomic function tests, Q-T interval in diabetic patients was significantly greater than in healthy control, but were prolonged in patients with long duration of disease as compared with short duration one. There were a significant correlation between Q-T interval and postural hypotension, also between Q-T interval and both high and low frequency component of spectral analysis of R-R interval, whereas, no relation was observed with spectral analysis and systolic blood pressure. An abnormal Q-T interval is an indicator of cardiac sympathetic and parasympathetic nervous dysfunction, but not vasomotor dysfunction.

On the other hand, **Laptev DN et al 2012** Studied effect of graded physical exercise on glycemia level and interval QT duration in children and adolescents with type 1 diabetes mellitus. they found that there were two periods of significant and prolonged lowering of glycemia: in 120-420 min and 19-21 hours after exercise. Lowering of glycemia after physical exercise was associated with prolongation of QT interval. Also **Zravenboer et al, (1993)** investigated the corrected QT interval as a test for diagnosing autonomic dysfunction in 60 type I diabetic patients with proven peripheral neuropathy, Significant increase in QTc interval was observed after dynamic exercise, however, no change in QTc was observed following static exercise, and hence we conclude that static exercises may not be useful in assessing the cardiovascular status of an individual or in predicting cardiovascular events. they concluded that the corrected QT interval should not be used for the diagnosis of the severity of diabetic autonomic neuropathy. The result of study of **Suarez GA et al 2005** came in contradict with our result, they studied the relationship between cardiac autonomic neuropathy (CAN) and major cardiovascular events in 2 prospective studies. Specifically, the relationship between baseline CAN and the subsequent incidence of a fatal or nonfatal cardiovascular event, defined as an myocardial infarction MI, heart failure, resuscitation from ventricular tachycardia or fibrillation, angina, or need for coronary revascularization, was examined. The relative risks associated with CAN in these studies were 2.2 and 3.4, respectively, with the latter result just achieving statistical significance ($P < 0.05$). There seems to be an

association between CAN and major cardiovascular events, but given the small number of events that occurred in each of these studies, The significance of CAN as an independent cause of sudden death has, however, been questioned recently. They suggested that although CAN could be a contributing factor, it was not a significant independent cause of sudden death. Heart failure is, however, common in individuals with diabetes; it is identified in these patients by the presence of neuropathy, even in those without evidence of coronary artery disease or LV dysfunction. Several long-term studies have demonstrated a consistent beneficial effect of regular exercise training on carbohydrate metabolism and insulin sensitivity, which can be maintained for at least 5 years. These studies used exercise regimens at an intensity of 50–80% Vo_{2max} three to four times a week for 30–60 min a session. Improvements in HbA_{1c} were generally 10–20% of baseline and were most marked in patients with mild type 2 diabetes and in those who are likely to be the most insulin resistant. It remains true, unfortunately, that most of these studies suffer from inadequate randomization and controls, and are confounded by associated lifestyle changes. Data on the effects of resistance exercise are not available for type 2 diabetes although early results in normal individuals and patients with type 1 disease suggest a beneficial effect. It now appears that long-term programs of regular exercise are indeed feasible for patients with impaired glucose tolerance or uncomplicated type 2 diabetes with acceptable adherence rates. Those studies with the best adherence have used an initial period of supervision, followed by relatively informal home exercise programs with regular, frequent follow-up assessments. A number of such programs have demonstrated sustained relative improvements in Vo_{2max} over many years with little in the way of significant complications.

Takebayashi K et al 2002 concluded that QTc intervals showed a significant positive correlation with systolic and diastolic blood pressure although it did not correlate with serum lipid concentrations. QTc also tended to be long in obese diabetic subjects (body mass index > 25 and QTc intervals might also be affected by other factors such as arteriosclerotic macroangiopathy and obesity, and not only autonomic nerve function. Therefore it might be considered as an overall index for complications, and not for pure autonomic impairment.

In this study The mean value of systolic blood pressure before exercise (change position, sustained hand grip and valsalva Maneuver) were (139.36 ± 6.52482) , (139.68 ± 6.10137) and (137.60 ± 6.45497) respectively which were significantly improved after exercise by decreasing to (change position, sustained hand grip and valsalva Maneuver) (134.80 ± 5.50757) , (134.16 ± 5.91383) and (134.24 ± 5.84009) respectively.

Agree with this result **Roy et al; (1989)** found that in diabetic patients who maximally exercised on bicycle, there was an increase in Systolic blood pressure SBP. Also **Alsaydet al, (1999)** found a significant decrease in SBP and DBP in type II D.M patients as a response to moderate aerobic exercise training on treadmill for 6 weeks. Also **Russell et al; (1999)** found that exercise training lead to reduce BP and that similar to finding of **Schreider and Ruderman (1990)**. Also **Lehmann et al; (1995)** found that cycling exercise training program for three months in diabetic patients significantly reduce SBP and DBP and it was correlated significantly with the change in the physical activity and **Lehmann et al; (1995)** found that a highly significantly reduction in the SBP and DBP by exercise training to normal range particularly in those diabetic patients who prone to develop neuropathy. **Hilsted et al; (1979)** found that blood pressure response to exercise training didn't increase to expected level in diabetic autonomic neuropathy patients, and lowered mean SBP and DBP response to comparable relative exercise training in patient with autonomic neuropathy compared with diabetic patients without autonomic neuropathy. **Harald E M et al 2012** said that Aerobic interval training is an effective method to lower blood pressure and improve other cardiovascular risk factors. Our result were supported by **Jamie F. Burr 2012** who concluded that Aerobic exercise has significant and particular benefits for people with type 1 diabetes. It increases sensitivity to insulin, lowers blood pressure, improves cholesterol levels, and decreases body fat. patients with type 1 diabetes who are physically more active have a lower overall risk of cardiovascular events than their sedentary counterparts. Also **Gail and Francis, (1984)** concluded that physical exercise training altered the cardiovascular responses to exercise training as decreased heart rate and pressure load on myocardium. Also **Gert-van-Dijk et al (1994)** confirmed that aerobic exercise training is currently promoted as life style modification that lowers the resting BP especially in persons with elevated BP, it was supported with that the dynamic exercise training reduces resting SBP and DBP by approximately 3% and 4 % respectively. On the other hand **Campainge and Lampman, (1994)** found that patients with type 2DM displayed a greater SBP in response to exercise training. Also **Donckier et al; (1989)** found that in cardiac autonomic neuropathy there was increasing of SBP in response to exercise training. **Vinik et al; (1995)** found that patients with cardiac autonomic neuropathy have severely exaggerated increase in SBP and DBP. Also **Bottini et al; (1995)** found that in diabetic autonomic neuropathic patients, SBP was significantly increased in response to exercise training. **Pamella Karoline et al** concluded that a single session of aerobic exercise resulted in 24 h BP reductions in individuals with T2D, also **2015 Radice et al; (1996)** found that in diabetic autonomic neuropathic patients in response to exercise

training there was no significant difference in blood pressure either at rest or at peak of exercise training between diabetic patients with autonomic neuropathy and diabetic patients without autonomic neuropathy and during exercise training diabetic patients showed lower values of SBP and DBP. Agreed with these results, **Thomas H et al 2009** who said that both aerobic and resistance training have important roles in DM. Recent work comparing the individual and combined effects of aerobic and/or resistance training revealed that both forms of exercise were equally beneficial for glycemic control, although aerobic training had a greater effect on body composition (except with regard to increasing muscle cross-sectional area). Caution should be used when interpreting these results given double the volume of exercise performed in the combined training. It is recommended that patients with Type 2 Diabetes Mellitus (T2DM) perform both aerobic and resistance training. They concluded that Exercise training in patients with T2DM is feasible, well tolerated, and beneficial to improve cardiovascular risk. It is recommended that patients with T2DM accumulate a minimum of 150 minutes per week of at least moderate-intensity and/or 90 minutes per week of at least vigorous-intensity cardiorespiratory exercise.

The mean values of the heart rate responses to (change position, Deep breathing and valsalva Maneuver) were (98.36 ± 7.65876), (92.68 ± 6.47251) and (80.12 ± 4.04475) respectively, That were significantly decreased post exercise to (93.96 ± 5.78417), (88.56 ± 5.61308) and (76.32 ± 4.75850) respectively This improvement of hemodynamic responses come in agreement of **Alsayd et al, (1999)** he found decreasing in resting HR after moderate aerobic exercise training on treadmill for 6 weeks in NIDDM patients. Also **Kahn et al; (1986)** found that during exercise training program of diabetic cardiac autonomic neuropathy patients there were lower resting HR, although cardiac autonomic neuropathy have higher resting HR. **Wiese et al; (1990)** studied heart rate variability (HRV) in diabetic patients with and without autonomic neuropathy in response to orthostatic load and found significant lower in HRV in diabetic patients with autonomic neuropathy. Also **Clarie and David (1981)** found that strengthening exercise training program for 6 months significantly decreased HR. **Gail and Francis, (1984)** reported that exercise training program was associated with cardiovascular impairment. This was supported with reducing the HR after the exercise training program. On the other hand, **Oka et al; (1995)** found that in diabetic with mild autonomic neuropathy the R-R of low frequency component wasn't different from those of healthy subject control or from patients without autonomic neuropathy and R-R of high frequency component was significantly smaller than that of healthy ones. **Roy et al; (1989)** found that in diabetic patients who maximally

exercised on bicycle, there was an increase in HR and SBP, they concluded that increasing in resting work product and decrease cardiac output in response to exercise training program in diabetic patients due to decrease parasympathetic activity, While **Bottini et al; (1995)** found that diabetic autonomic neuropathy in response to exercise training program there was a significant increase in HR. Also **lrace et al; (1991)** found a significant increase in HR in response to exercise training program and higher in diabetic autonomic neuropathy than in diabetic without autonomic neuropathy. Also **Howorka et al; (1997)** concluded that in diabetic patients with mild or no autonomic neuropathy who regularly performed endurance exercise training program as stationary bicycle, there was increasing in HR, whereas in definite or severe autonomic neuropathy no effect on HR variability. **Radice et al; (1996)** they studied cardiovascular response to exercise training program in middle aged NIDDM patients with and without autonomic neuropathy, and found that diabetic autonomic neuropathy patients had significant slower recovery of HR and significant higher proportion of blunted increase of HR. **Koullam Parpa et al 2009** studied Effect of High Intensity Interval Training on Heart Rate Variability in Individuals with Type 2 Diabetes. The purpose of their study was to examine the effect of high intensity interval training (HIIT) on cardiovascular autonomic function as determined by HRV, in individuals with diabetes. Their Results demonstrated a statistically significant difference in HRV pre (HRV: 52.80 ± 8.5 ms) compared to post training (HRV: 62.60 ± 11.00 ms), $t(13) = -7.46$, $p = 0.0001$. In addition, systolic blood pressure (SBP), diastolic blood pressure (DBP), resting heart rate (RHR), fasting glucose values (FG) and body weight were significantly lower following 12 weeks of training. The beneficial effect on autonomic regulation as a result of exercise training may have clinical importance in preventing adverse cardiovascular events in individuals with diabetes.

Didangelos T et al 2006 said that Improvement in glycemic control reduces the incidence of CAN and slows the progression there of. Glycemic control with a reduction of HbA1c from 9.5 to 8.4 has also been shown to improve HRV with mild autonomic abnormalities; this was not so in cases of advanced autonomic abnormalities. The use of aldose reductase inhibitors such as sorbinil improved resting and maximum cardiac output, and improved MIBG uptake and HRV in patients with mild abnormalities but not in those with advanced CAN. **Vinik A ET AL 2003** concluded that a further decrease in exercise capacity and blood pressure BP is seen in patients with both vagal CAN and orthostatic hypotension. The severity of CAN correlates inversely with the increase in heart rate at any time during exercise and with the maximal increase in heart rate. Thus, CAN contributes to diminished exercise tolerance. Therefore, autonomic testing offers a useful tool to

identify patients with potentially poor exercise performance and may help prevent hazards when patients are introduced to exercise training programs. Prolonged QTc causes premature action potentials during the late phases of depolarization. This increases the risk of developing ventricular arrhythmias or fatal ventricular fibrillations. Higher rates of prolonged QTc are seen in females, older patients, high systolic blood pressure or heart rate, and short stature (**Panoulas VF et al 2014**).

Pamella Karoline et al 2015 studied the effects of different intensities of aerobic exercise on 24-hour blood pressure (BP) responses in individuals with type 2 diabetes mellitus (T2D) and prehypertension. [Subjects and Methods] Ten individuals with T2D and prehypertension (55.8 ± 7.7 years old; blood glucose 133.0 ± 36.7 mg·dL⁻¹ and awake BP $130.6 \pm 1.6/80.5 \pm 1.8$ mmHg) completed three randomly assigned experiments: non-exercise control (CON) and exercise at moderate (MOD) and maximal (MAX) intensities. Heart rate (HR), BP, blood lactate concentrations ([Lac]), oxygen uptake (VO₂), and rate of perceived exertion (RPE) were measured at rest, during the experimental sessions, and during the 60 min recovery period. After this period, blood pressure was monitored for 24 h. thier results indicate that [Lac] (MAX: 6.7 ± 2.0 vs. MOD: 3.8 ± 1.2 mM), RPE (MAX: 19 ± 1.3 vs. MOD: 11 ± 2.3) and VO_{2peak} (MAX: 20.2 ± 4.1 vs. MOD: 14.0 ± 3.0 mL·kg⁻¹·min⁻¹) were highest following the MAX session. Compared with control group, only MAX elicited post-exercise BP reduction that lasted for 8 h after exercise and during sleep. They concluded that a single session of aerobic exercise resulted in 24 h BP reductions in individuals with T2D, especially while sleeping, and this reduction seems to be dependent on the intensity of the exercise performed.

Sarika Chaudhary et al 2010 evaluated the effects of aerobic and strength training on cardiac variables such as blood pressure, heart rate (HR), and metabolic parameters like cholesterol, high density lipoprotein (HDL), triglycerides and anthropometric parameters of obese women. Their findings of the study indicate statistically significant differences in recovery heart rate [Pre-exercise: 97.40 ± 5.378 (mean±standard deviation (SD)), post-exercise: 90.70 ± 4.599 , $t=8.066$, $P<0.001$] and in post-diastolic blood pressure [Pre-exercise: 85 ± 3.265 , post-exercise: 86.20 ± 2.820 , $P<0.001$] in aerobic training and in systolic blood pressure [Pre- and post-exercise] in both training groups ($P<0.001$). Significant differences were observed in very low-density lipoprotein [pre-exercise: 28.10 ± 1.415 , post-exercise: 26.86 ± 0.760 , $t=5.378$] and HDL [pre-exercise: 45.40 ± 3.533 , post-exercise: 53.60 ± 3.134 , $t=6.318$] levels in aerobic training group with $P<0.001$. BMI and body fat percentage showed significant improvements in both training groups they concluded that Aerobic training is more beneficial and

can be used as a preventive measure in patients who are at risk of developing cardiovascular diseases due to obesity.

Sheri Colberg 2013 said that if cardiac autonomic neuropathy (CAN) is present, the heart rate response is abnormal at rest, when standing, and when during strain related to holding the breath (Valsalva maneuver). Blood pressure responses can be abnormal when changing positions or performing isometric exercise. Moreover, the potential for exercise-related dehydration is a concern, as is impaired thermoregulation during activities in environmental extremes, and extra fluids may need to be consumed to protect against both dehydration and hyperthermia. Care must be taken with all components of the exercise prescription. In addition to developing a safe exercise prescription and considering exercise precautions for those with autonomic neuropathy, attention must be given to factors that will assist patients in maintaining a regular physical activity program. Marrero and Size more have developed the Ease of Access Index and Ease of Performance Index to help patients determine how realistic their activity selections are (**Marrero DGet al 1996**).

Aaron I. Vinik et al 2003 concluded that, knowledge of early autonomic dysfunction can encourage patient and physician to improve metabolic control and to use therapies such as ACE inhibitors and β -blockers, proven to be effective for patients with CAN.

The insulin sensitivity, lipid profile, blood pressure, coagulation properties, body composition, and psychological well be improved in diabetic patients by aerobic exercisxes (**Mayer et al; 1998**).

Scognamiglio et al; (1995) they investigated role of myocardial contractility recruitment in determining an abnormal left ventricular response to isometric and isotonic exercise in 14 diabetic patients with autonomic neuropathy (A.N), they studied left ventricular and myocardial functions at rest and during exercise by two-dimensional echocardiography, they excluded ischemic heart diseases by the absence of left ventricular wall motion abnormalities induced by exercises and by coronary angiography, they found that there was an abnormal response of left ventricular ejection fraction to isometric and dynamic exercise in these patients.

Bottini et al; (1995) investigated cardiovascular and plasma catecholamine response during incremental exercise and recovery in diabetic patients with and without autonomic neuropathy, all the patients underwent a submaximal or symptom limited incremental exercise test using a cycle ergometer, air flow and respiratory gases fractions were sampled at the level of the mouth allowing a breath-by-breath analysis of oxygen consumption (VO_{2max}), the heart rate and systolic blood pressure were recorded and venous samples were obtained from the patients at rest and

during each minutes of exercise and recovery to measure to measure epinephrine and nor-epinephrine plasma level, the heamodynamic parameters and plasma catecholamine were completed at rest and at 25, 50, 75 and 100 % of the peak of (VO_{2max}), they found that during exercise heart rate, systolic blood pressure, nor-epinephrine, and epinephrine increase was different among diabetic groups being significantly blunted in diabetic patients with autonomic neuropathy.

(Lampman, 1991) said that Physical activity has the potential to yield several health benefits for people with diabetes. These benefits can include improvements in glucose control

V. CONCLUSION

The result of this study support the importance of using exercise training program as general and especially walking training for IDDM with autonomic neuropathy.

The aerobic exercise training has a positive effect on blood glucose level, heart rate, blood pressure, R-R interval and Q-T interval in IDDM patients with autonomic neuropathy. So the exercise training generally should be recommended as a protective factor against the major risk factors.

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