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Effect of Exercise Training On Cardiovascular Responses In 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 be 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.

Key words: Aerobic Exercise, type 1 diabetes mellitus, cardiac autonomic neuropathy.

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[1.]

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)[2.]

Data from the 2008 Egypt Demographic and Health Survey (EDHS 2008) were used to show the Prevalence of diabetes for selected socio-demographic 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[3]**.**

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[4]**.**

CAN, manifested as changes in HRV, may be detected within 1year of diagnosis in type 2 diabetes and within 2 years of diagnosis in type 1 diabetes[5]

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[6.]

Diabetic autonomic neuropathy (DAN) is classified as subclinical or clinical depending upon the presence or absence of symptoms[7].

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[8.]

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[5] and contribute to mitochondrial uncoupling regional ventricular motion abnormalities, functional deficits, and cardio myopathy[9]**.**

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[10].

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 / m^2 with a mean value of (25 ± 3.3 Kg / m^2). 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 [11].

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 [12].

Cool Down phase; about 5 minutes on treadmill with low speed [(13)].

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.

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 ±SD	Mean ±SD		Mean ±SD	Mean ±SD		
BMI	29.2 ± 2.6	27.7 ± 2.3	0.001 S	28.8±1.7	29.2±1.8	0.047	0.018 S
Q T interval	448.8 ± 47.3	414.6 ± 45.3	0.001 S	426.2±34.8	450.4±39.3	0.001	0.023 S
R R interval	487.6 ± 53.3	599.1 ± 49.9	0.001 S	613.6±71.1	574.0±84.4	0.14	0.207
Fasting Blood Glucose	137.4 ± 10.8	137.4 ± 5.0	0.000 S	129.0±6.9	135.6±8.8	0.002	0.001 S

SD=Standard Deviation, Significant level: P≤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 ±SD	Mean ±SD		Mean ±SD	Mean ±SD		
systolic B P response to change position	139.3 ± 6.5	134.8 ± 5.5	0.003 S	137.7± 7.6	143.7± 6.4	0.000 S	0.000 S
systolic B P response to sustained Hand Grip	139.6 ± 6.1	134.1 ± 5.9	0.000 S	138.4± 6.8	142.9± 7.1	0.001 S	0.000 S
systolic BP response to valsalva maneunver	137.6 ± 6.4	134.2 ± 5.8	0.008 S	134.4± 8.5	136.7± 5.6	0.098	0.135

SD=Standard Deviation, Significant level: P≤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 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 ±SD	Mean ±SD		Mean ±SD	Mean ±SD		
Heart Rate response to change position	98.3±7.6	93.9±5.7	0.000 S	98.3± 6.7	101.6 ± 2.7	0.009 S	0.001 S
Heart Rate response to Deep Breathing	92.6±6.4	88.5±5.6	0.000 S	84.2 ± 6.7	86.7 ± 6.1	0.026 S	0.005 S
Heart Rate response to valsalva maneunver	80.1±4.0	76.3±4.7	0.001 S	87.8 ± 1.6	86.8± 4.7	0.098	0.001 S

SD=Standard Deviation, Significant level: P≤0.05 S

Discussion

In this study, The mean value of BMI was significantly decreased post exercise from (29.2400 ± 2.61852) to (27.76 ± 2.38537). The mean value of fasting blood glucose pre exercise was (137.48 ± 10.85557) and significantly reduced post exercise to (127.00 ± 5.01664) . 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 changed 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. 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. The value of Q-T interval pre exercise was (448.88 ± 47.39666). and significantly reduced post exercise to (414.68 ± 45.37503) (Table 10). 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.

Results of this study were supported by [19]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[3]. These results were supported by[15] 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[18]. [16]found that BMI and body fat percentage showed significant improvements in both training groups. [17]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[(16)]. The results of this study was similar to[15] who said both aerobic and resistance training have important roles in DM on glycemic contro [14]. Also [18]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[17]. Also, diabetic patients exercise had been useful adjunct to diet control in diabetic patients to reduce body weight and BMI[18]. Exercise improved body composition in diabetic patients that lead to weight loss and reduce BMI[19.] Fasting glucose values (FG) and body weight were significantly lower following 12 weeks of training[20.] Improvement in glycemic control reduces the incidence of CAN and slows the progression there of [21.] The results of this study were contradict with[23] 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.

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 [24] 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 [23]. [25]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 [24].

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[25]**.**

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. [27]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 [28] 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[(25)(26)].

As regarding to [29, 30, 28] their 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[26,27,28]. [31] concluded that When R-R interval measurements of the patient and control groups during resting and deep breathing were compared, no statistically significant difference between the groups was determined[29].

Also [24] found that exercise training lead to reduce BP. Also [32]found that in cardiac autonomic neuropathy there was increasing of SBP in response to exercise training. they found that patients with cardiac autonomic neuropathy have severely exaggerated increase in SBP and DBP[30]. 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 [18] found decreasing in resting HR after moderate aerobic exercise training on treadmill for 6 weeks in NIDDM patients. Also [30] 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[17,28].

[33]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[31]. 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[32]. [35]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 [33].

[36] 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 ischeamic 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[34]. [37] 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[35]. [38]said that Physical activity has the potential to yield several health benefits for people with diabetes. These benefits can include improvements in glucose control[(36)].

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.

References

1. Boulton AJ., Vinik AI.,: Position statement: Diabetes mellitus and exercise. American Diabetes Association, Diabetes Care 21(Suppl 1): S 40-44, (2010).
2. American Diabetes Association. Standards of medical care in diabetes—2006. Diabetes Care. 2006; 9 (suppl 1): S4–S42.
3. Stevens LK., Porta M., and Fuller JH., EURODIAB Prospective Complications Study Group. Relationship between risk factors and mortality in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study (PCS). Diabetes Care;31:1360–1366 (2008).
4. Naglaa Arafa, and Ghada Amin. "The epidemiology of diabetes mellitus in Egypt: Results of a national survey." Egyptian Journal of Community Medicine 28, no. 3 (2010).
5. Ewing DJ, Martyn CN, Young RJ, Clark BF. The value of cardiovascular autonomic function tests. Diabetes Care; 8: 5- (1985).
6. Drake-Holland AJ., Van d V., Roemen T., Hynd JW., Mansaray M., Wright ZM., and Noble MI. Chronic catecholamine depletion switches myocardium from carbohydrate to lipid utilisation. CardiovascDrugs Ther;15:111–117 (2006).
7. Young LH., Wackers FJ., Iskandrian AE., Wittlin SD., Filipchuk N., Ratner RE., and Inzucchi SE. DIAD Investigators. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. AMA;301:1547–1555 (2009).
8. Tesfaye S, Chaturvedi N, Eaton SE, et al. Vascular risk factors and diabetic neuropathy. N Engl J Med; 352:341- (2005).

9. Schumer MP, Joyner SA, Pfeifer MA. Cardiovascular autonomic neuropathy testing in patients with diabetes. Diabet Spectr.; 11: 227–223:(1998).
10. Pop-Busui R, Kirkwood I, Schmid H, Marinescu V, Schroeder J, Larkin D, Yamada E, Raffel DM, Stevens MJ. Sympathetic dysfunction in type 1 diabetes: association with impaired myocardial blood flow reserve and diastolic dysfunction. J Am Coll Cardiol.; 44: 2368–2374-(2004).
11. Colberg S, Swain D, Vinik A. Use of heart rate reserve and rating of perceived exertion to prescribe exercise intensity in diabetic autonomic neuropathy. Diabetes Care.; 26: 986–990-(2003).
12. Soligard T., et al. Comprehensive warm-up programme to prevent injuries in young female footballers: Cluster randomized controlled trial. BMJ; 337:a2469 (2008).
13. Laskowski ER., (expert opinion). Mayo Clinic, Rochester, Minn. July 9, (2013).
14. Woods K., et al. Warm-up and stretching in the prevention of muscular injury. Sports Medicine.;37:1089 (2007).
15. Thomas H. Marwick, Matthew D. Hordern, Todd Miller, Deborah A. Exercise Training for Type 2 Diabetes Mellitus: Impact on Cardiovascular Risk: A Scientific Statement From the American Heart AssociationCirculation June 30, 119:3244-3262- (2009).
16. Sarika Chaudhary, Manpreet Kaur Kang, and Jaspal Singh Sandhu, : The Effects of Aerobic Versus Resistance Training on Cardiovascular Fitness in Obese Sedentary Females Asian J Sports Med.; 1(4): 177–184 (2010 Dec).
17. Jamie F. Burr, Physical activity in type 1 diabetes mellitus Assessing risks for physical activity clearance and prescription Can Fam Physician. 58(5): 533–535 (2012).
18. Alsayed, A A: Effect of exercise on macro and micro circulating blood flow in diabetic patients. Doctoral thesis, Faculty of physical therapy, Cairo university.126-36 (1999).
19. Wing, R.R., Epstein, L.H., and Paternostro-Bayles, M. Exercise in a behavioral weight control program for obese patients with Type 2 (non-insulin-dependent) diabetes. Diabetologia;31(12):902-909 (1988).
20. Klem, M.L., Wing, R.R., McGuire, M.T., Seagle, H.M., and Hill, J.O. A descriptive study of individuals successful at long-term maintenance for substantial weight loss. Am -J -Clin -Nutr 66:239-46, (1997).
21. KOULLAM. PARPA, MARCOS A. MICHAELIDES, BARRY S. BROWN Effect of High Intensity Interval Training on Heart Rate Variability in Individuals with Type 2 Diabetes Journal of Exercise Physiologyonline (JEPonline) Volume 12 Number 4 – (August 2009).
22. Didangelos TP, Arsos GA, Karamitsos DT, Athyros VG, Georga SD, Karatzas ND. Effect of quin april or losartan alone and in combination on left ventricular systolic and diastolic functions in asymptomatic patients with diabetic autonomic neuropathy. J Diabetes Complications.; 20: 1–7 (2006).
23. Lehmann, R., Vokae, A., and Agosti, K. Loss of abdominal fat and improvement of the cardiovascular risk profile by regular moderate exercise training in patients with NIDDM. Diabetolgia. 38: 1313-1319 (1995).
24. Russell, D., White, M. D., and Carl, S. Exercise in Diabetes Management The Phyisi-Sport-Med. April: (4) 27 (1999).
25. Hordern M D , Coombes J S , Cooney L M, Jeffriess L , Prins J B ,T H Marwick Effects of exercise intervention on myocardial function in type 2 diabetes: Heart :;95:1343-1349 – (2009).
26. Ebeling, P., Tumoinen , J. A. , and Bourey, R. Athletes with NIDDM exhibit imparted metabolic control and increased lipid utilization with no increase in insulin sensitivity. Diabetes: 44: 472-477 (1995).
27. Mathur CP, Deepak Gupta QTc Prolongation in Diabetes Mellitus an Indicator of Cardiac Autonomic Neuropathy JIACM; 7(2): 130-2 (2006).
28. Veglio, M., Sivieri, R., Chinaglia, A., Scaglione, L., and Cavallo-Perin, P. QT interval prolongation and mortality in type 1 diabetic patients. a 5-year cohort prospective study. Neuropathy Study Group of the Italian Society of the Study of Diabetes, Piemonte Affiliate, Diabetes Care, Vol. 23, Issue 9: 1381-1383 (2000).
29. Oka, H., Mohio, S., Sato, K., and Katayama, K. Prolongation of Q-T interval and Autonomic Nervous Dysfunction in Diabetic Patients. Diabetes-Res-Clin-Pract. 31(1-3): 63-70 (1996).
30. Kahn, J.K., Sisson, J.C., and Vinik , A.I. QT interval prolongation and sudden cardiac death in diabetic autonomic neuropathy. J-Clin- Endocrinol -Metab. 64:751-54, (1987).
31. Abdulkadir Tunc , Hatice Kubra Avcı Gulen, Ufuk Emre Research of R-R Interval Recording Sensitivity in Diabetic Autonomic Neuropathy. Diagnosis İstanbul Med J; 16: 89-92- (2015).

32. Donckier, J.E., De-coster, B.M., Buysschear, M., Pieters, D.P., Cauwe, F.M., Robert, A., Brichabnt, C.M., Ketelslegers, J.M. Exercises and posture related changes of arterial natriuretic factor and cardiac function of diabetes. Diabetic Care. Jul- Aug; 12 (7): 475-80 (1989).
33. Sheri R. Colberg, Ronald J. Sigal, Judith G. Regensteiner, Bryan J. Blissmer, Richard R. Rubin, Lisa Chasan-Taber, : Exercise and Type 2 Diabetes The American College of Sports Medicine and the American Diabetes Association: joint position statement Diabetes Care.; 33(12): e147–e167 (2010 Dec).
34. Marrero, D., and Sizemore, J.M. Motivating patients with diabetes to exercise. American Diabetes Association. 554-559 (1996).
35. Aaron I. Vinik, MD.; Roy Freeman, , Tomris Erbas, :Diabetic Autonomic Neuropathy Seminars in Neurology Semin Neurol. ; (4) 23- (2003).
36. Scognamiglo, R., Fasoli, G., Ferri, M. and Nistri, S. Myocardial dysfunction and an abnormal left ventricular exercise response in autonomic diabetic patients. Clin-Cardiol. May ;18 (5): 276-82 (1995).
37. Bottini, P., Tantucci, C., Scionti, L., Dottrorini, M.L., Puxeddue, E. Reboldi, G., Bolli, G.B., Casucci, G., Santeusanio, F., Sorbin, C.A. Cardiovascular responses in diabetes: influence of autonomic neuropathy of different severity. Diabetologia. Feb; 38 (2): 244-50 (1995).
38. Lampman, R.M., and Schteingart, D.E. Effects of exercise training on glucose control, lipid metabolism, and insulin sensitivity in hypertriglyceridemia and non-insulin dependent diabetes mellitus. Med Sci Sports Exercise 23:703-12, (1991).

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