Chapter II

REVIEW OF RELATED LITERATURE

The literature in any field forms the foundation upon which all future work will be built. A search for the reference material would assist the investigator to determine the effectiveness of the various combinations of the variables, methodology used and the results obtained. The review of related literature scanning may serve as an important adjunct to the investigator by assisting in the interpretation of own study. Keeping in mind, the investigator has traced out different types of research works that have been undertaken by the physical educationists, sport scientists and health scientists on criterion variables related to the study.

The present chapter incorporates the research works conducted on the concept of the topic taking into consideration the composite view of different forms of exercises and physical activity protocols with respect to controlling of different biomarkers of the degenerative disease like diabetes mellitus and atherosclerosis in particular. Similar studies relating to biomarkers of degenerative diseases relating to vascular diseases and coronary heart disease were also presented. The present study tried to understand the effects of different intensities of aerobic running on resting state blood glucose, platelet count and plasma fibrinogen among type 2 diabetics.

In type 2 diabetic patients, aerobic running has been identified as the main treatment. Involving in the physical activity everyday contributes to
optimum health and qualitative of life. Through daily exercises the life styles can be changed to improve health and fitness. Aerobic running stimulates lungs and heart and all working group of muscles and produces beneficial changes in the body and in mind. Many physiological changes are determined by daily participation in aerobic running. Running might have a persistent effect on energy expenditure and fat oxidation, resulting in increased fat loss. The involvement of physical activities, it balances the intake of food and well as expenditure of the energy. However, even without loss of weight, exercise results in positive metabolic effects. It is necessary to participate in different forms of physical exercises especially the aerobic running to improve the preventive and curative capacity from diabetes and control other different degenerative diseases especially the cardiovascular diseases like, coronary heart diseases, hypertension and psychological problems.

**Studies Informing the Effect of Burden of Disease due to Increasing Diabetes and Cardio-vascular Diseases**

Growing awareness about the possible effects of diseases like diabetes mellitus and cardio-vascular problems like hypertension, and atherosclerosis on lifestyle is probably motivating the people towards lifestyle intervention programs more and more seriously. This is due to the various studies and estimates conducted across the world. These studies explain the importance of the lifestyle management with physical activity as a major lifestyle component to enhance the preventive capacity of persons from these diseases.
WHO predict that developing nations will bear the brunt of this epidemic of type II diabetes in the 21st century. Currently, more than 75% of people with diabetes live in low and middle income countries. An estimated 286 million people, corresponding to 6.4% of the world’s adult population, was lived with the diabetes mellitus in 2010. The number is expected to grow to 439 million by 2030, corresponding to 7.9% of the adult population. With an estimated 50.8 million people living with the diabetes mellitus in India, and India has become the world’s largest diabetic population nation, followed by China with 43.2 million. Diabetes is one of the most important causes of premature illness and death worldwide. Non-communicable diseases including diabetes mellitus account for 60% of all deaths around worldwide. The number of the deaths attributable to diabetes mellitus in 2010 shows a 5.6% increase over the estimates for the year 2007. This increase is largely due to a 30% increase in the number of deaths due to diabetes mellitus in the North America & Caribbean Region, a 12.5% increase in the South East Asia Region and an 11% increase in the Western Pacific Region. 80% of type II diabetes is preventable by changing diet, involvement in physical activities and improving the living environment. Yet, without effective prevention and control programmes the incidence of diabetes mellitus is likely to continue rising globally. Estimated global expenditures on the diabetes will be at least International Dollars 420 billion in 2010, and at least ID 562 billion in 2030. An estimated average of ID 878 per person will be spent on diabetes in 2010 globally. The World Health Organization (WHO) predicted net losses in national income from diabetes and
the cardiovascular disease of ID 557.9 billion in China, ID 303.3 billion in the Russian Federation, ID 336.7 billion in India, ID 49.2 billion in Brazil and ID 2.5 billion in Tanzania (2005 ID), in between the 2005 and 2015.

This is the right time that people realize the lifestyle compromises and financial burden due to the degenerative diseases and makes appropriate changes in their lifestyles. More and more research is essential to identify the preventive measures of such diseases mellitus. As physical activities and physical exercise has been recognized as a primary lifestyle intervention in achieving these changes, more research is desired in this direction to identify the exact exercise protocols in counteracting these challenges.

_Coccheri and Sergio (2008)_ found that diabetes mellitus affects about 8.5% of the adult population. The estimated number of patients with diabetes, presently about 175 million people, is expected to increase by 50-70.5% within the next 25 years.

_V Mohan, S Sandeep, R Deepa, et al., (2007)_ found that India leads the world with largest number of diabetic persons earning the dubious distinction of being termed the “diabetic capital of the world”. According to the Diabetes Atlas, 2007 published by the International Diabetes Federation, the number of people with diabetes mellitus in India currently around 41.5million is expected to rise to 70.5% million by 2025 unless urgent preventive measures are taken. The “Asian Indian Phenotype” refers to certain unique clinical and biochemical abnormalities in Indians which include improved insulin resistance, greater abdominal adiposity i.e., higher waist circumference despite lower body mass
index, (BMI), lower adiponectin and higher high sensitive C-reactive protein levels. This phenotype makes Asian Indians more prone to diabetes and premature coronary artery disease (CAD). At least a part of this is due to genetic factors that are from the heriditical transformation. Even though the prevalence of micro-vascular complications of diabetes like nephropathy and retinopathy are comparatively lower in Indians, the prevalence of premature coronary artery disease (CAD) is much higher in Indians compared to other ethnic group. However, the primary driver of the epidemic of diabetes is the rapid epidemiological transition associated with the changes in dietary patterns that is balanced diet and decreased physical training as evident from the higher prevalence of diabetes in the town/city/metropolitan population (urban population). The most disturbing trend is the shift in age of onset of diabetes to a younger age in the present years. This could have long lasting adverse effects on nation’s health and economic policies.

As a rising and powerful prospective economy, India must have more concern in monitoring and identifying the present challenges and makes appropriate governances in order to come out and face these inordinate and expensive challenges. The present study is appropriate in this regard and may provide constructive substantiation about how Aerobic running program of the experimentation would be useful in controlling the biomarkers of the cardiovascular diseases, and how the diabetes pathophysiology could be reversed.
Markku Laakso (2010) analyzed that the epidemic of diabetes, affecting about 4 – 6% of western population, is one of the main threats to human health in the 21st century. Changes in the human thinking, environment, behavior, and lifestyle have resulted in a dramatic enhancement in the incidence and prevalence of diabetes in people with genetic susceptibility to diabetes. The global number of people with diabetes was 152 million in 2000, and it is projected to increase to 223 million in 2010 (an increase of approximately 46.5%) both in developed and developing countries. Chronic hyperglycemia leads to many long-term complications in the nerves, heart, eyes, kidneys, and blood vessels. Individuals with pre-diabetes, undiagnosed type II diabetes and long-lasting type 2 diabetes are at high risk of all complications of macro-vascular disease, and micro-vascular diseases. More than 70% of patients with type II diabetes die of cardio-vascular causes. As a result, the epidemic of type II diabetes will be followed by an epidemic of diabetes-related cardio-vascular disease (CVD).

Nicholaos Kakouros Jeffrey J Rade (2011) observed that diabetes mellitus, that affects over 25 million of people in the US and an estimated 285 million worldwide, is associated with the significant burden of cardio-vascular and metabolic diseases. Patients with type II diabetes mellitus (DM2) have a 2 to 4 fold increased risk of premature coronary, cerebral, and peripheral vascular disease that together constitute the leading cause of death in the patients. Unlike the diabetes, neuropathy, nephropathy specific micro-vasculopathy, nephropathy, and the macro-angiopathic process in patients
with diabetes represents an accelerated but patho-physiologically similar process to atherosclerosis in non-diabetic persons. Thrombotic events of these vascular lesions, particularly in the coronary vasculature and cerebral and can be life threatening. Usually blood flow and thromboresistance is dependent on vasomotion, blood corpuscular elements (RBC & WBC), plasma components, and their interaction with the endothelial plane. Rupture of an atherosclerotic plaque exposes sub-endothelial material that promotes platelet activation and the local initiation of the coagulation cascade that it can leads to thrombus formation at the site of the endothelial disruption. Acute vascular events, such as the myocardial infarction and cardiac stroke, are due to such atherothrombotic events rather than gradual progression of luminal stenosis caused by atheromatous plaque. Platelet hyper reactivity and increased baseline activation in patients with diabetes is multifactorial and associated with biochemical factors such as hyperlipidemia and hyperglycemia, insulin resistance, and an inflammatory and oxidant condition. Patients with diabetes mellitus have an increased prevalence of the vascular disease. The Pathologic thrombosis associated with the atherosclerotic plaque rupture is a major cause of morbidity and mortality. Platelets are closely involved in the initiation and propagation of thrombosis. The facts were suggests that platelets from patients with type 2 diabetes have increased reactivity and baseline activation compared to the healthy controls. They reviewed the patho-physiology of platelet hyper reactivity in DM (diabetic mellitus) patients and its implications in clinical practice, with particular focus on the acute coronary syndromes, percutaneous
coronary intervention, and novel anti-platelet agents. Patients with diabetic mellitus (DM) have evidence of platelet hyper-reactivity and increased baseline platelet activation. These results as of a combination of factors are including the effects of oxidative stress, and inflammatory state, insulin, hyperglycemia, hyper-lipidemia, and endothelial dysfunction.

Now it has become clearly evident from the available data; the burden of diabetes and consequent cardiovascular events on individuals is not only in phenotype specific countries like India and china but also to major economies like USA and other European counterparts. Developing countries and but also seems highly important to pass on the information to the individuals since the scientific attitude alone has answer in bringing up ideal lifestyles from the people of various countries.

**Studies on the Effect of Diabetes Mellitus on Healthy Lifestyle and Other Cardio-vascular Disease Events**

Vascular problems could bring abnormal negative changes in the lifestyle of persons or individuals as they are prone to different detrimental effects in their bodily processes. This makes these individuals not only to suffer but to compromise on many lifestyle issues making their life with compromised quality apart from financial issues or burdens.

**Ozlem Ucan, and Nimet Ovayolu (2010)** aimed to evaluate and compare the health-related quality of life of patients with diabetes mellitus (DM), obesity and hypertension in gaziantep, a south-eastern city in Turkey. In that study a cross-sectional, descriptive design was used. In this study, the research population included a total of 1605 diabetes mellitus, hypertension
and in obesity patients. To evaluate health-related quality of life of patients, short form - 36 (SF-36) was used. One-way ANOVA and chi-square analyses, student’s t-test were used for comparisons between the groups. As a results total, 18.1% of patients had combined obesity, diabetes mellitus, hypertension; 16.2% had hypertension and diabetes mellitus (DM). Approximately 16.1% had only hypertension; 15.3% had obesity and hypertension; 13.5% had diabetes mellitus; 12.8% had obesity and diabetes mellitus; and 8.5% had obesity. The health-related qualitative life physical component mean scores of patients with combined obesity and hypertension were lower than that of another groups (p < 0.05). Health-related physical fitness and quality of life physical component mean scores were determined as 34.5 (SD 0.4), and mental component mean scores were determined as 43.8 (SD 4.4). Health-related quality of life physical components mean scores of moderately active patients were higher, while older age and lower education and low income levels had a negative effect on health-related quality of life (p < 0.05). They concluded that hypertension, obesity and diabetes decrease patient health-related qualitative life while physical activity increases it. The co-existence of obesity and hypertension, in particular, has a more negative effect on health-related physical quality of life.

Prakash C Deedwania (2010) examined the effects of lifestyle intervention on changes in weight, fitness, and cardiovascular diseases (CVD) risk factors during a 4-year study. The Look AHEAD (Action for Health in Diabetes) trial is the multicenter randomized clinical trial comparing the effects
of an intensive lifestyle intervention (ILI), and diabetes support and tutoring (DSE; the control group) on the incidence of major coronary vascular diseases (CVD) events in 5145 overweight or obese individuals (59.5% female; mean age, 58.7 years) with type 2 diabetes mellitus. In each annual assessment, more than 93% of participants provided outcomes data. The ILI participants exhibited greater % of weight loss (-6.15% vs -0.88%; P < .001) than DSE participants at an average for four years and greater improvements in treadmill fitness (12.74% vs 1.96%; P < .001), hemoglobin A1c level (-0.36% vs -0.09%; P < .001), systolic (-5.33 vs -2.97 mm Hg; P < .001) and diastolic (-2.92 vs -2.48 mm Hg; P = .01) blood pressure, and levels of high-density lipoprotein cholesterol (3.67 vs 1.97 mg/dL; P < .001) and triglycerides (-25.56 vs -19.75 mg/dL; P < .001). Decrease in low-density lipoprotein cholesterol levels were lower in ILI participants than DSE (-11.27 vs -12.84 mg/dL; P = .009) owing to better use of medications to lessen lipid levels in the DSE group. After four years, ILI participants maintained better improvements than DSE participants in weight, fitness, hemoglobin A1c levels, systolic blood pressure, and also high-density lipoprotein cholesterol levels. They have come to a conclusion that the intensive lifestyle intervention can produce sustained weight loss and improvements in fitness, glycemic control, and CVD risk factors in individuals with diabetics having type-2 diabetes. Ultimately the differences in risk factors translate to decrease in CVD events will be addressed by the Look AHEAD trial.
José R Banegas, Esther López-García, Auxiliadora Graciani, et al., (2007) were intended to evaluate the collective effects of cardio-vascular risk factors on all the health-related quality of life dimensions among the elderly in this era of epidemic obesity and diabetes. The population-based experiment made of 3567 participants, representative from Spanish non-institutionalized population aged ≥ 60 years. Data was collected based up on home interviews and from the measurements of blood pressure and other anthropometric variables collected. Multiple linear regression was used to study the interaction between health-related quality of life, on each scale of the SF-36 questionnaire, and obesity (waist circumference > 102 cm in men and > 88 cm in women), hypertension (blood pressure ≥ 140/90 mmHg) and known diabetes, after adjusting for socio-demographic and lifestyle factors. In their experiment, they found that the patients suffering from obesity, hypertension, and diabetes, or a combination of these were, in general, connected with a worse health-related quality of life, on both the psychological and physical standards, than those without these factors, though statistical significance (P<0.05) was only established for some relationships. Obesity according to the scale, in women (−2.9 to −6.7 points) and diabetes in men (−6.1 to −16.4 points) were the factors most important and significantly associated with diminished health-related quality of life. According to the scale, Women who had all three factors showed the maximum decline in health-related quality of life (−10.2 to −17.7 points). They have concluded that the Obesity in diabetes in old men and old
women are the most influential factors adversely disturbing the health-related quality of life.

The obesity itself shows big impact on the health related quality independently. The experiments postulated that coexistence of many diseases like diabetes and hypertension which would result for deteriorate the health related quality of individuals to maximum extent. There were also experiments which tried to prove unearth the mechanisms in pathophysiology of diabetes leading to other cardiovascular problems. It is highly significant to individuals to understand the progressive effects of diabetes mellitus as this may lead to other cardiovascular problems like atherosclerosis of arteries making their health quality further deteriorated.

Han KA, Patel Y, et al., (2011) undertook a cross-sectional assessment of factors contributing to vascular function in 271 consecutive subjects, known as non-obese normal glucose tolerant (n = 115), non-obese dysglycaemic (n = 32), obese normal glucose tolerant (n = 57), obese dysglycaemic (n = 38), or type 2 diabetic (n = 29). Vascular function was measured invasively as leg blood flow reacts to methacholine chloride, an endothelium-dependent vasodilator. Categorical and continuous analyses were carried out to evaluate the reaction of hyperglycemia to vascular dysfunction. Even amid normoglycaemic subjects, obese subjects had impaired vascular function compared to non-obese subjects (p = 0.004). In non-obese dysglycaemic subjects (p=0.004) versus non-obese normoglycaemic subjects) Vascular function also impaired, to a level comparable to normoglycaemic
obese subjects. Within obese subject classifications, gradations of dysglycaemia including the presence of diabetes were not associated with further worsening of these vascular responses beyond the effect of obesity alone ($p = \text{not significant comparing all obese groups, } p < 0.001$ versus lean normoglycaemic subjects). After univariate and multivariable modeling analyses we found that effects of glycaemia were less powerful than effects of insulin resistance and obesity on vascular dysfunction and they have concluded that the dysglycaemia influences impaired vascular function in non-obese subjects, but obesity and insulin resistance are more important determinants of vascular function in obese and diabetic subjects.

De Haan JB, and Cooper ME (2011) found that diabetes remains a major cause of cardiovascular events even though intensive glycaemic and blood pressure control have decreased the risks of micro and macro vascular complications, end-stage renal failure, blindness and neuropathy. It is therefore essential for understanding the primary mechanisms and to ascertain effective treatments to prevent retard or reverse diabetic complications. One area of improved concentration is the diabetic vascular endothelium. Hyperglycaemia triggers a series of events, not least a raise in reactive oxygen species (ROS) causing to increase oxidative stress, which affects on endothelial function. In this experiment, we investigated a unifying hypothesis that an increase in glucose-mediated ROS causes endothelial dysfunction as the underpinning causative event triggering accelerated micro and macro vascular complications. Specially, the impact of shortage in the antioxidant enzyme,
glutathione peroxidase, on endothelial dysfunction as a trigger of diabetic micro and macro vascular complications, will be examined. Furthermore, novel antioxidant therapies will be highlighted. In particular, the use of Gpx1-mimetics holds well as a targeted antioxidant approach and an alternative adjunct therapy to control diabetic complications.

Hence, it is highly imminent to control the diabetes through proper lifestyle intervention so that other pathophysiological changes would be under control.

**Studies on Obesity Pathogenesis and Diabetic Predisposition**

Obesity is closely linked to the development of diabetes and adversely affects the life expectancy. At early stages of obesity, within fat depots that support tissue expansion, gene programs are activated, which arises as a combined result of the hypertrophic growth of adipocytes and the recruitment of adipocyte precursors to the adipogenic process. Both adipocytes and adipocyte precursors are enveloped by a dense network of type 1 collagen within adipose tissues. This collagenous web is supposed to give adipose tissues with structural integrity and elasticity needed to maintain best form and function. Matrix metalloproteinase (MMP)14 (MT1-MMP) is a peri-cellular type-I collagenous that is critical for the postnatal development of the mesenchyme, in addition to adipose tissues. Whether the developmental role of MMP14 during adipogenesis is applicable to the pathogenesis of adult obesity remains unclear. The premature morbidity and mortality noticed in MMP14 knockout mice preclude tries to evaluate the role of nutritional interventions on
adult obesity among these animals. Also, it has not been confirmed whether
the diet-induced expansion of fat mass is functionally related to the remodeling
of the type-I collagen network.

**Tae-Hwa Chun, Mayumi Inoue, Hiroko Morisaki, et al., (2010)** demonstrated that the type 1 collagen architecture of adipose tissues
undergoes fast degradative remodeling in reaction to a high-fat diet challenge
in vivo via a proteolytic process mediated by MMP14. A decrease in MMP14
dosage avoids the diet-induced cleavage of the type I collagen network in vivo in
addition, it disrupts the regulation of the transcriptional programs linked to
adipo-genesis and lipo-genesis. Consistent with insights got from analyses of
genetically modified mice, human MMP14 single nucleotide polymorphisms
(SNPs) are known that positively associate with human obesity and diabetes
traits. Taken together, these results hold a new model wherein MMP14 not only
participates in obesity pathogenesis but also serves as a potential genetic
modifier of obesity and diabetes predisposition in humans.

The pathogenesis of obesity has apparent symptoms that the obese
individuals to turn out to be further obese may be likely and this causes to
increase in the diabetes predisposition in humans.

**Paul Poirier, Thomas D Giles, George A Bray, et al., (2006)** observed
that obesity is becoming a global epidemic in both adults and in children. It is
associated with the numerous co-morbidities such as cardio-vascular diseases
(CVD), type II diabetics, sleep apnea/sleep-disordered, breathing, abets, and
hypertension, certain cancers, and also mortality as well as decreases life
expectations. Besides this, an altered metabolic profile, a variety of adaptations/alterations in cardiac structure and function occur in the individual as adipose tissue accumulates in excess amounts, even in the absence of the co morbidities. Therefore, obesity may affect the heart through its influence on known risk factors such as hypertension, glucose intolerance, inflammatory markers, dyslipidaemia, obstructive sleep apnea/hypoventilation, and the prothrombotic conditions.

For this reason, the obesity is an increasing danger as observed and also is a possible door way for more degeneration leading to hypertension and glucose intolerance and hypertension. It is also extensively talk about that obesity itself may not be a dangerous medical condition, but it causes disturbance in the metabolic pathways of the individuals causing metabolic syndrome and if uncared for blows into Diabetes. The management of the diseases has become lot more expensive in modern times and managing and treatment of certain degenerative diseases like cardiovascular diseases and diabetes become lifetime leading to enormous financial burdens to individuals and to various nations.

**Analysis Verifying the Result of Diabetes Mellitus on the Cardio-vascular Events likes Hypertension, Aggravated Atherosclerosis, etc.**

The diabetes mellitus hereafter was seen as a medical condition which has not aggravated consequences in predisposition of diabetes among humans, but the latest study on this issue seems worrying and remarkable. Presence of
excess amounts of glucose in the blood, i.e. hyperglycemia could lead to many changes in the biochemical conditions of the humans leading to palpable changes. This could cause further complications and consequent events could swift the cardiovascular problems.

Demirtenc R, et al., (2009) indicated that more plasma viscosity in diabetics could aggravate the platelet aggravation and fibrinolytic activity and hence the glycemic control in diabetics should be the important. Platelet activity and aggregation potential, which are necessary components of thrombogenesis and atherosclerosis, are more vital when the glycemic control is not done.

Studies in Understanding the Role of Blood Platelets and Fibrinogen on Precipitation of Atherogenesis with Special Reference to Diabetics

As previously been examined, the platelets though necessary to plug the damaged layer of the endothelium, they now and then over activate to bring extra damage to the artery by causing to extend larger plaques thereby lessening the lumen. The presence of additional platelets or fibrinogen may also be a severe biomarker for the atherosclerotic condition to develop much rapidly.

Karthik Balasubramaniam, Girish N Viswanathan, et al., (2012) have conducted a meta analysis approach to examine patients with diabetes mellitus presenting with acute coronary syndrome have a higher risk of cardio-vascular complications and recurrent ischemic events when compared to non-diabetic counterparts. Different mechanisms including endothelial dysfunction, platelet hyperactivity, and abnormalities in coagulation and fibrinolysis have been
implicated for this increased atherothrombotic risk. Platelets play an important role in atherogenesis and its thrombotic complications in diabetic patients with acute coronary syndrome. Hence, potent platelet inhibition is of paramount importance in order to optimise outcomes of diabetic patients with acute coronary syndrome. They found the increased thrombotic burden in diabetes and acute coronary syndrome, DM patients have increased atherothrombotic risk and recurrent ischaemic events following acute coronary syndrome and PCI despite being on currently recommended dual antiplatelet therapy, when compared to the nondiabetic population. This may partly be due to abnormal endothelial function, abnormal platelet haemostasis resulting in platelet hyperactivity, and dysregulation in the coagulation processes. GP IIb/IIIa inhibitors and bivalirudin have shown to improve acute outcomes in DM patients with ACS. Current dual antiplatelet therapy has proved successful in improving the outcomes in DM patients with ACS and remains the main stay of treatment for long-term secondary prevention and reduction of stent thrombosis. However, in the presence of DM, platelet activity and recurrent thrombotic events remain significantly high in spite of the currently recommended antiplatelet and antithrombotic therapies. Therefore, more potent antithrombotic therapies are warranted for this group of high risk patients. Clinical studies with novel therapies may provide important treatment alternatives in the future to tackle this thrombotic burden.

José Luis Ferreiro (2010) recognized that patients with diabetes mellitus (DM) have high atherosclerosis, which the main is primary factor
resulting the high risk of atherothrombotic events in such patients. Atherothrombotic problems are the principal cause of morbidity and mortality in patients with DM. Among factors contributing to the prothrombotic condition which characterise patients with DM, platelet hyperreactivity plays a pivotal role. Platelets of DM patients are characterised by dysregulation of several signaling pathways leading to intensified adhesion, activation and aggregation. Many mechanisms are formulated in platelet dysfunction of patients with DM, which can be divided as follows: a) hyperglycaemia, b) insulin deficiency and resistance, c) associated metabolic conditions, and d) other cellular abnormalities.

**Doina Popov (2010)** reviewed that hyperglycemia, the hallmark of diabetes mellitus, is a main threat for endothelial dysfunction and vascular problem. Recently, for couple of years, considerable achievements have been established in accepting endothelial cell dysfunction triggered by high glucose concentration. This collection of conclusion evident that the clinical observation that diabetes is a hypercoagulable state. This conclusion and the accepted roles played by hyperglycemia and hyperinsulinemia and its development is to be examined with much rigorous lines to recognize scientific answers.

**Paolo Gresele, Giuseppe Guglielmini, et al., (2003)** have conducted a cross-over, randomized, double-blind study. 12 patients with T2DM underwent 4 h of either acute hyperglycemia (13.9 mmol/l, 250 mg/dl) or euglycemia (5.5 mmol/l, 100 mg/dl). Shear stress-induced platelet activation,
P-selectin and lysosomal integral membrane protein (LIMP) expression on platelets in the bleeding-time blood, urinary 11-dehydro-thromboxane B2 (TxB2) excretion, von Willebrand factor:antigen (vWF:Ag), and von Willebrand factor:activity (vWF:activity) were measured before and after hyperglycemia or euglycemia. Through this study they can found short-term hyperglycemia induces an increased activation of platelets exposed to high shear stress conditions in vitro (filtration method) or in vivo (bleeding time). In vivo platelet activation is reflected by an increased urinary excretion of 11-dehydro-TxB2. The increased levels of vWF in the circulation correlate with the increase in platelet activation markers and may indicate some degree of causation. Acute, short-term hyperglycemia in T2DM may precipitate vascular occlusions by facilitating platelet activation.

**R Barazzoni, M Zanetti, G Davanzo, et al., (2000)** in their study fibrinogen production was determined in six male type 2 diabetic patients having no detectable micro- and macrovascular consequences (age, 45 ± 4 yr; body mass index, 27 ± 0.9 kg/m2) and in seven non-diabetic matched controls using leucine isotope precursor-product relationships. Insulin (P < 0.05), Plasma glucose (P < 0.001) and glucagon concentrations (P < 0.01) were more in the patients. Diabetic patients also had greater plasma fibrinogen concentration (+50%; P < 0.01) and pool (+40%; P < 0.01) as well as fractional (+35%; P = 0.08) and absolute (+100%; P < 0.01) synthetic rates. The plasma glucagon concentration was directly related (P < 0.005 or less) to the fibrinogen concentration as well as to fractional and absolute synthetic rates.
Thus, fibrinogen production is distinctly increased, and this change is likely to determine the noticed hyperfibrinogenemia in type 2 diabetic patients. Hyperglucagonemia may cause the fibrinogen production increased. These results in normoalbuminuric patients without clinical difficulties hold the hypothesis that increased fibrinogen production and plasma concentrations may come first and perhaps contribute to the onset of clinical cardiovascular complications in type 2 diabetes. Finally, we assess that the fibrinogen formation is apparently increased in type 2 diabetic patients, and this difference is likely to play an vital role in this increased fibrinogen concentrations in type 2 diabetes. Increased plasma glucagon concentrations may leads to the enhanced fibrinogen production. These results in normoalbuminuric patients without noticeable vascular complications also specify that increased fibrinogen formation and plasma absorption may precede the onset of clinical cardiovascular disease and might therefore leads to the increased cardiovascular risk in type 2 diabetes.

In addition, the mean platelet value among diabetics is comparatively more as observed by (Hekimsoy Z, et al., (2004) and Taj Muhammad Khan, Mumtaz Ali Marwat, et al., (2005)) aided to conclude the role of fibrinogen absorption in the growth of complications in Pakistani diabetics. Around 120 subjects in the range of age between 40 years and 70 years from the staff members of Saidu Medical College, Swat and diabetics from the Medical OPD of Saidu Group of Teaching Hospitals were chosen. Parameters like fibrinogen absorption, body weight, height, body mass index, and serum glucose
absorption were calculated and compared with all the groups according to the
addition and elimination criteria. Data indicated a exceedingly important raise
in the parameters like body weight, fibrinogen absorption and plasma viscosity
in diabetics with complications than diabetics without complications and
healthy manage subjects. They completed that fibrinogen concentration and
plasma viscosity is extensively prominent in diabetics with complications. It
seems to act as a risk factor in the increased complications in diabetes.

As already examined the viscosity of the blood in diabetics along with
increased values of fibrinogen due to inhibition of fibrinolysis over diabetics,
seems a many complications leading to the quicker problem of cardiovascular
events similar to atherosclerosis.

**Yoshimasa Aso, Sachiko Matsumoto, et al., (2002)** have studied 112
type 2 diabetic patients (66 lean, 46 obese) and 69 age-based healthy subjects
(46 lean, 23 obese). We calculated plasma portions of fibrinogen and
prothrombin F1+2 (F1+2) as signifying coagulation activity and plasmin-
antiplasmin complex (PAP) and D dimer as signifying fibrinolytic activity.
Plasma PAI-1 portions also were noticed. Plasma portions of F1+2, PAP, D
dimer, and PAI-1 were advanced in diabetic patients than in control subjects.
Plasma fibrinogen and F1+2 were alike between lean and fat diabetic patients,
but plasma PAP and D dimer were noticeably less in obese than lean diabetic
patients (P [lt ] .0001, P = .0194, respectively). By multivariate analysis, plasma
PAI-1 and body mass index (BMI) were independent factors in diabetic patients
predicting PAP, while BMI and glycosylated hemoglobin (HbA1c) independently
predicted D dimer. Plasma PAI-1 concentrations were considerably more in obese than lean diabetic patients (P < .0001). They have arrived at both coagulation and fibrinolytic systems are improved in lean and obese type 2 diabetic patients compared with healthy subjects. Even though the degree of activation of coagulation was same between lean and obese diabetic patients, the fibrinolytic activity was less in obese than lean patients. Fibrinolytic substitution for hypercoagulation is partial in obese patients with type 2 diabetes, partly because of elevated PAI-1 in the blood. Hypofibrinolysis is a state that is commonly observed in type 2 diabetic patients, a finding also perhaps related to obesity and insulin resistance.

Atherogenesis leads complex results between platelets and monocytes (platelet-monocyte crosstalk) and with endothelial cells. Especially, Platelets are activated in cases of diabetes mellitus. During atherogenesis, incomplete functions of platelets other than those inhibited by aspirin, as a cyclooxygenase inhibitor, or by adenosine diphosphate receptor P2Y(12) antagonists, such as thienopyridines, are similar. Particularly during platelet-monocyte crosstalk, vital role is played by adhesion receptors such as selectins and integrins. Also, ESA roots platelet activation by direct and indirect mechanisms. Antagonistic thereto is a renal bleeding tendency in cases of severe CKD, due to platelet dysfunction, which can be substituted with appropriate renal replacement therapy and administration of ESA in order to reach a hemoglobin (Hb) level of 10 g/dl. However, if the Hb level exceeds 10 g/dl, the even concentrated platelet activation caused by ESA, united with the activation caused by
diabetes, leads to a prothrombotic state, which in patients with severe atherosclerosis can result in sharp atherothrombotic complications, in the genesis of which platelets play a key role. This would be one premise evidence for the improved occurrence of strokes in the TREAT study.

It is evident that the increase in platelets and fibrinogen levels is one of the main events causing more aggravated atherogenesis over patients having diabetes.

Carr ME (2001) found that diabetes mellitus is a hypercoagulable state. Eighty percent of patients with diabetes mellitus die a thrombotic death. Seventy-five percent of these deaths are due to cardiovascular complications, and the remainder is due to cerebrovascular events and peripheral vascular complications. Vascular endothelium, the primary defense against thrombosis, is abnormal in diabetes. Endothelial consequences definitely play a vital role in the increased platelets and clotting factors seen in diabetes. Coagulation activation markers, such as prothrombin activation fragment 1+2 and thrombin–anti-thrombin complications are eminent in diabetes. The plasma levels of many clotting factors including fibrinogen, factor VII, factor VIII, factor XI, factor XII, kallikrein, and von Willebrand factor are eminent in diabetes. On the contrary, the level of the anticoagulant protein C (PC) is lessened. In the fibrinolytic system, the main resources of removing clots, is comparatively reserved in diabetes due to abnormal clot structures that are more resistant to deprivation and the raise in plasminogen activator inhibitor type 1 (PAI-1). Increased circulating platelet aggregates, increased platelet aggregation in
reaction to platelet agonists, increased platelet contractile force (PCF), and the presence of higher plasma levels of platelet release products, such as β-thromboglobulin, platelet factor 4, and thromboxane B2, demonstrate platelet hyperactivity in diabetes.

Reid HL, Vigilance J, Wright-Pascoe RA, et al., (2000) have conducted a study to find out the effect of hyperglycaemia on hyperfibrinogenaemia and its significance on plasma viscosity was examined in 69 diabetic patients in the course of hypoglycaemic treatment. Glycaemic effect was predicted by calculation of glycosylated haemoglobin (HbA1). Plasma fibrinogen concentration (PFC) was estimated by a clot-weight technique. The relative plasma viscosity (RPV) was counted by capillary viscometry. The average PFC and RPV were considerably ($p < 0.001$) eminent in the diabetic patients as compared with a non-diabetic control group. Both PFC and RPV exhibited a unique, step-wise raise with progressively not as good as glycaemic effect. The data firmly specify that continual hyperglycaemia is allied with a frank hyperfibrinogenaemia and hyperviscous plasma in all the diabetic patients experimented. These irregular haemorrheological variations could affect harmfully on both the haemostatic process and circulation in diabetic patients.

Studies Supporting the General Physical Activity in Improving the Preventive Capacity from Cardio-vascular Diseases and Diabetes Mellitus
Constant physical activity and exercise has been postulated as a powerful intervention in controlling the biomarkers of several degenerative diseases and to arrest the pathogenesis of these diseases.

Balducci S, Zanuso S, Cardelli P, Salvi L, Mazzitelli, et al., (2012) have stated that physical activity/exercise - induced increases in fitness, particularly muscular, predict improvements in cardio-vascular risk factors in subjects with type 2 diabetes independently of weight loss, thus indicating the need for targeting fitness in these individuals, particularly in subjects who struggle to lose weight. They conducted a study on sedentary patients with type 2 diabetes (n = 606) were enrolled in 22 outpatient diabetes clinics and randomized to twice-a-week supervised aerobic and resistance training plus exercise counseling versus counseling alone for 12 months. Baseline to end-of-study changes in cardio-respiratory fitness, strength, and flexibility, as assessed by (VO₂ max) estimation, a 5-8 maximal repetition test, and a hip/trunk flexibility test, respectively, were calculated in the whole cohort, and multiple regression analyses were applied to assess the relationship with cardiovascular risk factors. They found changes in (VO₂ max), upper and lower body strength, and flexibility were significantly associated with the variation in the volume of physical activity, HbA(1c), BMI, waist circumference, high-sensitivity C-reactive protein (hs-CRP), coronary heart disease (CHD) risk score, and inversely, HDL cholesterol. Changes in fitness predicted improvements in HbA(1c), waist circumference, HDL cholesterol, hs-
CRP, and CHD risk score, independent of study arm, BMI, and in case of strength, also waist circumference.

**Balducci S, Zanuso S, Fernando F, Fallucca S, et al., (2009)** have found that the effects of cardio-respiratory fitness is inversely related to the development of type 2 diabetes and cardio-vascular morbidity and mortality. Trials in individuals with impaired glucose tolerance have highlighted the role of physical activity/exercise in the prevention of type 2 diabetes. Moreover, physical activity and exercise training have been recognized as treatment options for patients with type 2 diabetes. Both aerobic and resistance training were shown to produce beneficial effects by reducing HbA1c, inducing weight loss and improving fat distribution, lipid profile and blood pressure in patients with type 2 diabetes. Mixed aerobic and resistance training was recently shown to be more effective than either one alone in ameliorating HbA1c. However, further research is needed to establish the volume, intensity and type of exercise that are required to reduce cardiovascular burden and particularly to define the best strategy for promoting long-term compliance and durable lifestyle changes in individuals with type 2 diabetes. The Italian Diabetes Exercise Study (IDES) is a prospective Italian multicentre randomized controlled trial, of larger size and longer duration than previously published trials. It has been designed to assess the combined effect of structured counselling and supervised mixed (aerobic plus resistance) exercise training, as compared with counselling alone, on HbA1c and other cardiovascular risk factors as well as fitness parameters in individuals with type 2 diabetes and the
metabolic syndrome. This study was also aimed at testing a sustainable strategy for promoting and maintaining a sufficient level of physical activity among individuals with type 2 diabetes to be implemented at the population level.

Yates T, Khunti K, et al., (2007) have reviewed that the physical activity is extensively reported to reduce the risk of type 2 diabetes in individuals with prediabetes, some experiments have examined this issue separately of other lifestyle changes. The intend of this examination is to perform a systematic review of controlled trials to establish the exclusive effect of exercise on glucose levels and risk of type 2 diabetes among people with prediabetes (IGT and/or IFG). A thorough investigate of MEDLINE (1966-2006) and EMBASE (1980-2006) established 279 potentially significant studies and eight out of which met the inclusion criteria for this analysis. These eight experiments were controlled trials among individuals with impaired glucose tolerance and seven experiments used a multi-component lifestyle intervention that included exercise, diet and weight loss goals and one used a structured exercise training intervention. Four experiments used the occurrence of diabetes over the course of the study as an outcome change and four depends up on 2-h plasma glucose as an outcome count. In the four experiments that considered the occurrence of diabetes as an outcome, the risk of diabetes was decreased by around 50% (range 42-63%); as these experiments revealed only few variations in physical activity levels, the lessened risk of diabetes is probable to be attributable to factors other than physical activity. In the
remaining four studies, only one reported significant improvements in 2-h plasma glucose except one revealed little to moderate increases in maximal oxygen uptake.

These outcomes specify that the role of physical activity independent of dietary or weight loss changes to the prevention of type 2 diabetes in people with prediabetes is equivocal.

**Li S Zhao JH, and Luan J (2010)** aimed to review the impact of a physically active lifestyle on the genetic predisposition to obesity in a huge population-based experiment. They genotyped 12 SNPs in obesity-susceptibility loci in a sample of population-based with 20,430 individuals (aged 39–79 y) from the European Prospective Investigation of Cancer (EPIC) - Norfolk cohort at 3.6 years, an average follow-up duration. A genetic predisposition score was measured for every individual by adding the BMI i.e. body mass index, increasing alleles among the 12 SNPs. Physical activity was estimated with a help of self-administered questionnaire. Linear and logistic regression models were used to observe key effects of the genetic predisposition score and its relations with physical activity on BMI/obesity risk and BMI change over time, assuming an additive effect for every added BMI-increasing allele carried. Each additional BMI-increasing allele was coupled with 0.154 (standard error [SE] 0.012) kg/m² (p = 6.73×10^{-37}) increase in BMI (equivalent to 445 g in body weight for a person 1.70 m tall). This involvement was extensively (pinteraction = 0.005) more manifest in inactive people (0.205 [SE 0.024] kg/m² [p =
3.62×10−18; 592 g in weight]) than in active people (0.131 [SE 0.014] kg/m2 [p = 7.97×10−21; 379 g in weight]). Similarly, each additional BMI-increasing allele increased the risk of obesity 1.116-fold (95% confidence interval [CI] 1.093–1.139, p = 3.37×10−26) in the whole population, but considerably (pinteraction = 0.015) extra in inactive individuals (odds ratio [OR] = 1.158 [95% CI 1.118–1.199; p = 1.93×10−16]) than in active individuals (OR = 1.095 [95% CI 1.068–1.123; p = 1.15×10−12]). Constant with the cross-sectional observations, physical activity personalized the involvement between the genetic predisposition score and change in BMI during follow-up (pinteraction = 0.028). They have arrived that a living physically active lifestyle is related with a 40% decrease in the genetic predisposition to regular obesity, as expected by the number of risk alleles carried for any of the 12 recently GWAS-identified loci.

Even though the regular involvement in physical activity may not the required level of intensity and length may improved regulate the pathophysiology of these degenerative illness.

**Stefano Balducci, Silvano Zanuso, Antonio Nicolucci, et al., (2010)** intended to examine and evaluate the efficacy of an intensive exercise involvement strategy in motivating physical activity (PA) and improving hemoglobin A1c(HbA1c) level and additional modifiable cardiovascular risk factors in patients having type 2 diabetes mellitus (T2DM). For this experiment, 691 suitable sedentary patients with T2DM and the metabolic syndrome were selected and 606 were enrolled in 22 outpatient diabetes clinics in entire Italy
and randomized by center, age, and diabetes treatment to supervised aerobic and resistance training plus structured exercise counseling (exercise group) vs counseling alone (control group), two times in a week, for 12 months. End points included HbA1c level (primary) and other cardiovascular risk factors and coronary heart disease risk scores (secondary). Observations in their study, the mean (SD) volume of PA (metabolic equivalent hours per week) was considerably higher (P < .001) in the exercise (total PA [nonsupervised conditioning PA + supervised PA], 20.0 [0.9], and nonsupervised, 12.4 [7.4]) vs control (10.0 [8.7]) group. Supervised exercise produced significant improvements (mean difference [95% confidence interval]) in physical fitness than the control group; HbA1c level (–0.30% [–0.49% to –0.10%]; P < .001); systolic (–4.2 mm Hg [–6.9 to –1.6 mm Hg]; P = .002) and diastolic (–1.7 mm Hg [–3.3 to –1.1 mm Hg]; P = .03) blood pressure; high-density lipoprotein (3.7 mg/dL [2.2 to 5.3 mg/dL]; P < .001) and low-density lipoprotein (–9.6 mg/dL [–15.9 to –3.3 mg/dL]; P = .003) cholesterol level; waist circumference (–3.6 cm [–4.4 to –2.9 cm]; P < .001); body mass index; insulin resistance; inflammation; and risk scores. In control groups, these parameters improved marginally improved. They have arrived that this exercise intervention strategy was effective in promoting PA and improving HbA1c and cardiovascular risk profile. On the contrary, counseling alone, though successful in achieving the currently recommended amount of activity, was of partial efficacy on cardiovascular risk factors, suggesting the need for a larger volume of PA in these high-risk subjects.
Sheri R Colberg, Ann L Albright, Bryan J Blissmer, et al., (2010) have claimed that the (PA) physical activity, including suitable stamina and resistance training, is a major therapeutic modality for type 2 diabetes. Unfortunately, besides often physical activity is insignificant therapy. Constructive changes in glucose tolerance and insulin sensitivity usually worsen within 72 h of the last exercise session; as a result, regular physical activity is essential to sustain glucose-lowering effects and improved insulin sensitivity. Individuals with type 2 diabetes should struggle to achieve a minimum cumulative total of 1000 kcal·wk⁻¹ from physical activities. Those with type 2 diabetes generally have a lower level of fitness (VO₂max) than non-diabetic individuals, and therefore exercise intensity should be at a comfortable level (RPE 10–12) in the beginning of training and should progress carefully as tolerance for activity improves. Resistance training has the likely to improve muscle strength and endurance, improves flexibility and body composition, reduce risk factors for cardiovascular disease, and result in better glucose tolerance and insulin sensitivity. Exercise type and/or intensity changes may be required for whom suffered with diabetes with the heart rate response and as a result, ratings of apparent physical exertion relatively than heart rate may need to be used for moderating intensity of physical activity. They have come to a conclusion that exercise plays most important role in the avoidance and control of insulin resistance, pre-diabetes, GDM, T2DM, and diabetes-related health problems. Both aerobic and resistance training recover insulin action, at least acutely, and can assist with the management of BG levels, lipids, BP, CV
risk, mortality, and QOL, but exercise must be undertaken regularly to have constant benefits and likely include regular training of changing types.

It is evident that the physical activity and exercise training on regular basis like a logical and scientific intervention answer to manage the state of diabetes and also to prevent this state. It is also clear that the exercise training is postulated as a preventive measure for other cardiovascular biomarkers. Even though general physical activity has been known as a preventive measure from different degenerative diseases and their biomarkers, it is necessary to realize the different types of exercise methods in arriving the preferred results. There were several experiments’ results favoring the Aerobic running training as an effective preventive intervention for control and prevention of diabetes mellitus and several cardiovascular events.

Studies on the Effect Aerobic Running and Training on the Reversibility of Pathophysiology of Diabetes Mellitus and CVDs

Numerous experiments hold across the globe recommended strongly that aerobic running training on regular basis like a scientific answer for manage of many factors of diabetes mellitus and cardiovascular biomarkers. But, it is necessary to recognize the effect of different intensities and periods of aerobic training on these influences. Also, there are a lot of exercise procedures like anaerobic sprint training, resistance form of training etc, which control different metabolic pathways and carry special variations in the serviceable levels of different systems of the body.
The area under the insulin concentration curve (insulin area under the curve) reduced by 23.3% (12 781.7 ± 7454.2 vs 9799.0 ± 4918.6 µU·min/mL before and after intervention, respectively; \(P = .03\)). Insulin sensitivity was better with no changes in body weight (preintervention, 67.9 ± 14.5 kg; postintervention, 68.3 ± 14.0 kg) or percent body fat (preintervention, 41.4% ± 4.8%; postintervention, 40.7% ± 5.2%). The lower limb fat-free mass increased by 6.2% (\(P < .01\)) as a result of training, and changes in lower limb fat-free mass were correlated with changes in the insulin area under the curve (\(r = -.68; P < .01\)). Serum adiponectin, IL-6, and CRP concentrations did not change (preintervention vs postintervention: adiponectin, 9.57 ± 3.01 vs 9.08 ± 2.32 µg/mL; IL-6, 1.67 ± 1.29 vs 1.65 ± 1.25 pg/mL, CRP, 3.21 ± 2.48 vs 2.73 ± 1.88 mg/L) while insulin-like growth factor-1 was lower after training (preintervention, 453.8 ± 159.3 ng/mL; postintervention, 403.2 ± 155.1 ng/mL; \(P < .05\)). They felt that a twelve week of aerobic training increased insulin sensitivity in overweight and obese girls without change in body weight, percent body fat, and circulating concentrations of adiponectin, IL-6, CRP, and other inflammatory markers.

These conclusions suggest that more physical activity may improve the metabolic abnormalities coupled with obesity in children with a mechanism except the parameters cited earlier.

Okada S, et al., (2010) and Zanuso S, et al., (2010) have found that the endurance training has been accepted as best possible form of exercise for
diabetics to bring modifications in glycemic activity and definite fibrinolytic activities to prevent atherosclerosis in arteries.

**Lockard M, et al., (2007)** have found that the exercise training particularly endurance training considerably manages the fibrinolytic activity connected factors. It is exclusively significant over the diabetics as the pro thrombogenic factors like plasma prothrombin element, platelet count, fibrinogen etc are seen at high. It is imminent to diabetics to control the glycemic activation of pro thrombogenic conditions through apt form of exercise.

Patience training has a considerable impact on the coagulation cascade, lessining coagulation activity in the general pathway and thrombin formation at rest while increasing the activation potential of the intrinsic pathway.

**Timothy S Church, Steven N Blair, Shannon Cocreham, et al., (2010)** intended to observe the benefits of aerobic training alone, resistance training alone, and a combination of both on hemoglobin A1c (HbA1c) in individuals with type 2 diabetes. A randomized controlled trial in which 262 sedentary men and women in Louisiana with type 2 diabetes and HbA1c levels of 6.5% or higher were enrolled in the 9-month exercise program between April, 2007 and August, 2009. 41 participants were meant for the nonexercise control group, 73 to resistance training 3 days in a week, 72 to Aerobic running out of which they expended 12 kcal/kg per week; and 76 to combined aerobic and resistance training in which they expended 10 kcal/kg per week and
engaged in resistance training twice in a week. Modifications are made in HbA1c level. Secondary outcomes incorporated procedures of anthropometry and fitness. The experiment is with 63.0% women and 47.3% nonwhite participants who were a mean (SD) age of 55.8 years (8.7 years) with a baseline HbA1c level of 7.7% (1.0%). As per the control group, the absolute mean change in HbA1c in the combination training exercise group was −0.34% (95% confidence interval [CI], −0.64% to −0.03%; P = .03). The mean varies in HbA1c were statistically unimportant in either the resistance training (−0.16%; 95% CI, −0.46% to 0.15%; P = .32) or the aerobic (−0.24%; 95% CI, −0.55% to 0.07%; P = .14) groups when compared with the control group. Only the mixed exercise group enhanced maximum oxygen consumption (mean, 1.0 mL/kg per min; 95% CI, 0.5-1.5, P < .05) compared with the control group. All exercise groups lessened waist circumference from −1.9 to −2.8 cm when compared with control group. The resistance training group lost a mean of −1.4 kg fat mass (95% CI, −2.0 to −0.7 kg; P < .05) and mixed training group lost a mean of −1.7 (−2.3 to −1.1 kg; P < .05) when compared with control group. They felt that among patients with type 2 diabetes mellitus, a combination of aerobic and resistance training compared with the non exercise control group improved HbA1c levels. This was not achieved by aerobic or resistance training alone.

There may be many results by different researchers which may be credited to the phenotype of population, methods, intensities and period used etc. A combined aerobic training with resistance training is also a protective
exercise intervention. But, it is ideal to appreciate the different concepts of resistance training before incorporating this into the exercise intervention.

Studies on the Effect of Combined Exercise Training on the Reversibility of Pathophysiology of Diabetes Mellitus and CVDs

It is also relevant to understand the impact of various exercise procedures and their amalgamation on the protective status of diabetes and consequent cardiovascular events.

O'Hagan C, De Vito G, Boreham CA, et al., (2013) have found that exercise is an effective treatment for type 2 diabetes mellitus, resulting in stabilization of plasma glucose in the acute phase and improvements in body composition, insulin resistance and glycosylated hemoglobin with chronic exercise training. However, the most appropriate exercise prescription for type 2 diabetes has not yet been established, resulting from insufficient evidence to determine the optimum type, intensity, duration or frequency of exercise training. Furthermore, patient engagement in exercise is suboptimal. There are many likely reasons for low engagement in exercise; one possible contributory factor may be a tendency for expert bodies to prioritize the roles of diet and medication over exercise in their treatment guidelines. Published treatment guidelines vary in their approach to exercise training, but most agencies suggest that people with type 2 diabetes engage in 150 min of moderate to vigorous aerobic exercise per week. This prescription is similar to the established guidelines for cardiovascular health in the general population. Future possibilities in this area include investigation of the physiological effects
and practical benefits of exercise training of different intensities in type 2 diabetes, and the use of individualized prescription to maximize the health benefits of training.

**Geidl W and Pfeifer K (2011)** stated that the health-enhancing effects of endurance and resistance training, recommendations for exercise interventions for persons with type 2 diabetes and different co morbidities are derived to optimize the benefits of exercise. The authors have conducted a hierarchic, systematic literature analysis and found Aerobic training, resistance training, and combined training programmes hold equal potential to reduce the HbA1c by about 0.5-0.8. Endurance training improves cardio-respiratory fitness and cardiovascular risk factors. Compared to resistance training it will lead to superior effects on hypertension and blood lipids. Combined training is generally a little superior to aerobic and resistance training showing greater improvements for body weight, HDL-cholesterol and blood pressure. Health-enhancing effects are found for a broad range of exercise types, intensities and scope. Persons with type 2 diabetes should perform at least 90 min per week of vigorous (> 65% of VO\textsubscript{2max}) aerobic exercise or 150 min per week of moderate-intensity (40-65% of VO\textsubscript{2max}) aerobic physical activity. Performing at least 240 min of physical activity per week is associated with greater cardiovascular disease risk reductions as well as with less cardio-vascular events compared with lower volumes of activity. Optimizing therapeutic benefits with different types and doses of exercise in combination with dietary and drug treatments needs further research.
Anna Chudyk, MSC1,2 and Robert J. Petrella (2011) have made a
efficient review of the documents between 1970 and 2009 in representative
databases for the effect of aerobic or resistance exercise training on clinical
markers of CV risk, including glycemic control, dyslipidemia, blood pressure,
and body composition in patients with type 2 diabetes. Of 645 articles
retrieved, 34 reached our inclusion criteria; most investigated Aerobic running
alone, and 10 reported combined exercise training. Only aerobic or mixed with
resistance training (RT) drastically improved HbA1c −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 limits was extensively
improved −3.1 cm (95% CI −10.3 to −1.2) with combined aerobic and resistance
exercise, although fewer experiments and more heterogeneity of the responses
were noticed in the latter two markers. Exclusive Resistance exercise or
combined with any other form of exercise, not established to have any
considerable impact on CV markers. They have stated that only Aerobic
running or along with RT improves glycemic control, SBP, triglycerides, and
waist circumference. The result of resistance exercise exclusively on CV risk
markers in type 2 diabetes remains not clear.

(2010) have critically reviewed the more relevant evidence on the
interrelationships between exercise and metabolic outcomes. The research
questions addressed in the recent specific literature with the most relevant randomized controlled trials, meta-analysis and cohort studies are presented in three domains: aerobic exercise, resistance exercise, combined aerobic and resistance exercise. From this review appear that the effects of aerobic exercise are well established, and interventions with more vigorous aerobic exercise programs resulted in greater reductions in HbA(1c), greater increase in VO(2max) and greater increase in insulin sensitivity. Considering the available evidence, it appears that resistance training could be an effective intervention to help glycemic control, especially considering that the effects of this form of intervention are comparable with what reported with aerobic exercise. Less studies have investigated whether combined resistance and aerobic training offers a synergistic and incremental effect on glycemic control; however, from the available evidences appear that combined exercise training seems to determine additional change in HbA(1c) that can be seen significant if compared with aerobic training alone and resistance training alone.

Irvine C and Taylor NF (2009) have investigated on progressive resistance exercise, people with type 2 diabetes mellitus. The primary outcome was glycaemic control measured as percentage glycosylated haemoglobin (HbA1c). Secondary outcomes were body composition (lean body and fat free mass in kg), and muscle strength (% change in 1RM, dynamometry, change in maximum weight lifted). The search yielded nine relevant trials that evaluated 372 people with type 2 diabetes. Compared to not exercising, progressive resistance exercise led to small and statistically significant absolute reductions
in HbA1c of 0.3% (SMD -0.25, 95% CI -0.47 to -0.03). When compared to aerobic exercise there were no significant differences in HbA1c. Progressive resistance exercise resulted in large improvements in strength when compared to aerobic (SMD 1.44, 95% CI 0.83 to 2.05) or no exercise (SMD 0.95, 95% CI 0.58 to 1.31). There were no significant changes in body composition. Progressive resistance exercise increases strength and leads to small reductions in glycosylated haemoglobin that are likely to be clinically significant for people with type 2 diabetes. Progressive resistance exercise is a feasible option in the management of glycaemia for this population.

Savvas P Tokmakidis, et al., (2004) have experimented the short term and long term impact of a both strength and aerobic training program on glycemic control, insulin action, exercise ability and muscular strength in postmenopausal women with type 2 diabetes. 9 postmenopausal women having age 55.2 (6.7) years, with type 2 diabetes involved in a supervised training program for four months duration for two strength training sessions (3 sets of 12 repetitions at 60% one-repetition maximum strength) and two aerobic training sessions (60–70% of maximum heart rate at the beginning, and 70–80% of maximum heart rate after two months). Anthropometrical dimensions, percentage glycated hemoglobin, a 2-h oral glucose tolerance test, exercise stress testing and maximum strength were calculated in the beginning, and after a four and sixteen week of the exercise program. Important reductions were noticed in both i.e. glucose (8.1% P<0.01) and insulin areas under the curve (20.7%, P<0.05) after 4 weeks of training. These implementations were
further better after a 16 week (glucose 12.5%, insulin 38%, P<0.001). Glycated hemoglobin was considerably reduced after a four week [7.7 (1.7) vs 7.1 (1.3)%, P<0.05] and after 16 weeks [7.7 (1.7) vs 6.9 (1.0)%, P<0.01] of exercise training. Also, exercise period and muscular strength were considerably improved after a four week (P<0.01) as well as after 16 weeks (P<0.001) of training. Body mass and body-mass index, however, were not drastically changed during the experiment. They have strongly felt that both training program of strength and aerobic running could induce positive adaptations on glucose control, insulin action, muscular strength and exercise tolerance in women with type 2 diabetes.

M Vona, et al., (2009) have experimented in coronary artery illness, exercise training (ET) is associated with an development in endothelial function, but little is known about the relative effect of different types of training. The purpose of this research was to prospectively evaluate the impact of different types of ET on endothelial function in 209 patients after a first recent acute myocardial infarction. Endothelial purpose was evaluated before and after 4 weeks of different types of ET and after a month of detraining by measuring flow-mediated dilation and von Willebrand factor levels at baseline and after ET. Patients were randomly divided into 4 groups viz. 1st group: aerobic ET (n=52); 2nd group: resistance training (n=54); 3rd group: resistance plus aerobic training (n=53); and 4th group: no training (n=50). At baseline, flow-mediated dilation was 4.5±2.6% in group 1, 4.01±1.6% in group 2, 4.4±4% in group 3, and 4.3±2.3% in group 4 (P=NS). After Exercise Training, flow-
mediated dilation increased to 9.9±2.5% in 1st group, 10.1±2.6% in 2nd group, and 10.8±3% in 3rd group (P<0.01 versus baseline for all groups); it also increased in group 4 but to a much lesser extent (to 5.1±2.5%; P<0.01 versus trained groups). The von Willebrand factor level after ET decreased by 16% (P<0.01) similarly in groups 1, 2, and 3 but remained unchanged in 4th group. Detraining returned flow-mediated dilation to baseline levels (P<0.01 versus post training). They have come to a conclusion that the patients with recent acute myocardial infarction, ET was associated with better endothelial function independently of the type of training, but this effect disappeared after 1 month of detraining.

**Ronald J Sigal, Glen P Kenny, Normand G Boulé, et al., (2007)** aimed to establish the impacts of exclusive aerobic training, resistance training alone, and combined exercise training on hemoglobin A1c values in patients with type 2 diabetes. Randomized, controlled trial Setting with 8 community-based facilities and selected 251 patients adults aged between 39 to 70 years with type 2 diabetes. A negative result over a stress test or clearance by a cardiologist, and adherence to exercise during a 4-week run-in period, were necessary before randomization. Interventions: Aerobic training, resistance training, or both types of exercise (combined exercise training) where a sedentary control group was also included. Exercise training was conducted three times in a week for twenty weeks (weeks 5 to 26 of the study). The main outcome was the difference in hemoglobin A1c value at 6 months. Next results were variations in body composition, plasma lipid values, and blood pressure.
The complete variation in the hemoglobin A1c value in both the exercise training group and the control group was −0.51 percentage point (95% CI, −0.87 to −0.14) in the aerobic training group and −0.38 percentage point (CI, −0.72 to −0.22) in the resistance training group. Combined exercise training resulted apart from change in the hemoglobin A1c value of −0.46 percentage point (CI, −0.83 to −0.09) compared with aerobic training alone and −0.59 percentage point (CI, −0.95 to −0.23) compared with resistance training alone. Variations in blood pressure and lipid values did not statistically differ importantly among groups. Unpleasant events were more common in the exercise groups. Restrictions: The generalizability of the results to patients who are not as much adherent to exercise programs is uncertain. The participants were not blinded, and the total length of exercise was larger in the combined exercise training group than in the aerobic and resistance training groups. They have come to a conclusion that either aerobic or resistance training alone improves glycemic control in type 2 diabetes, but the improvements are greatest with combined aerobic and resistance training.

Robin L Marcus, Sheldon Smith, Glen Morrell, et al., (2008) have made a experiment to compare the outcomes of a diabetes exercise training program using combined aerobic and high-force eccentric resistance exercise and a program of Aerobic running only. For that experiment, fifteen participants with type 2 diabetes mellitus (T2DM) were involved in a 16-week supervised exercise training program: 7 (mean age=50.7 years, SD=6.9) in a combined aerobic and eccentric resistance exercise program (AE/RE group)
and 8 (mean age=58.5 years, SD=6.2) in a program of Aerobic running only (AE group). Outcome measures included thigh lean tissue and intramuscular fat (IMF), glycosylated hemoglobin, body mass index (BMI), and 6-minute walk distance. Both groups experienced decreases in mean glycosylated hemoglobin after training (AE/RE group: −0.59% [95% confidence interval (CI)=−1.5 to 0.28]; AE group: −0.31% [95% CI=−0.60 to −0.03]), with no significant between-group differences. There was an communication between group and time with respect to modify in thigh lean tissue cross-sectional area, with the AE/RE group gaining more lean tissue (AE/RE group: 15.1 cm² [95% CI=7.6 to 22.5]; AE group: −5.6 cm² [95% CI=−10.4 to 0.76]). Both groups experienced decreases in mean thigh IMF cross-sectional area (AE/RE group: −1.2 cm² [95% CI=−2.6 to 0.26]; AE group: −2.2 cm² [95% CI=−3.5 to −0.84]) and increases in 6-minute walk distance (AE/RE group: 45.5 m [95% CI=7.5 to 83.6]; AE group: 29.9 m [95% CI=−7.7 to 67.5]) after training, with no between-group differences. There was an interaction between group and time with respect to variation in BMI, with the AE/RE group experiencing a greater decrease in BMI. Important advancements in long-term glycemic control, thigh composition, and physical performance were demonstrated in both groups after participating in sixteen weeks exercise schedule. Subjects in the AE/RE group demonstrated additional improvements in thigh lean tissue and BMI. Improvements in thigh lean tissue may be vital in this population as a means to increase resting metabolic rate, exercise tolerance, protein reserve and functional mobility. They felt that one of the most commonly used interventions
in physical therapy is therapeutic exercise. Exercise is obviously useful for individuals with T2DM, even though very often this group does not readily take part in exercise. People with T2DM often demonstrate low exercise tolerance and lessened physical activity. This often results in more BMI and more total and regional storage of fat, along with reduces in lean tissue. Exercise can ease these detrimental body composition variations. Using eccentric resistance exercise may be ideally fitted for maximize lean tissue results, at a fraction of the cardiovascular cost of concentric and isometric resistance exercise. Based on these results, they suggest that therapeutic exercise for people with T2DM comprise both aerobic and resistance components and that eccentric resistance exercises should be included.

**Studies on the Effect of Intensity of Exercise Training on the Reversibility of Pathophysiology of Diabetes Mellitus and CVDs**

Aerobic running exercise with various intensities might involve in different metabolic pathways yields various impacts on the pathophysiology of diabetes mellitus. Therefore, it is necessary to identify with the effect of different intensities of aerobic training on these subjects.

**Eric Arthur Gulve (2008)** have suggested that training, along with dietary intervention, represents first-line therapy for diabetes mellitus. Aerobic running is suggested for its useful action on glucose control as well as its capabilities to slow down the progression of other co morbidities common in patients with diabetes, such as cardiovascular disease. The ability of aerobic running to get better glycemic manage in diabetes is well documented,
although adherence to exercise regimens is difficult. Very recently, the glucose-lowering impact with resistance training have also been documented. However diabetes exercise can also present considerable challenges to glycemic control. An understanding of the interactions between specific antidiabetic medications and various forms and intensities of exercise is necessary to optimizing glycemic control while minimizing the potential for sensitive derangements in plasma glucose levels. Contrary, exercise protocols is characterized by high intensity are more likely yields hyperglycemia.

The episodes of hyperglycemia with increased intensity aerobic training may be a possibility; it is not yet acknowledged very constructively. There may be certain other possible modalities like duration of the high intensity Aerobic running might bring many effects.

**Thomas H Marwick, Matthew D Hordern, Todd Miller, et al., (2009)** have studied the impact of exercise training in patients with T2DM is feasible, well tolerated and useful. Personalized exercise prescription offers an ideal opportunity to account for both cardiac and non-cardiac considerations in T2DM. 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 cardio-respiratory exercise and conflict training should be encouraged apart from this. This strategy can be achieved with flexible contributions of moderate- to vigorous-intensity cardio-respiratory exercise. Patients should participate in at least three nonconsecutive days in a week to make best use of
benefits. Personage sessions should last for not less than 10 minutes. Sedentary behaviors should be lessened. Exercise training should be conducted for long-term with telephone exercise counseling identified as a strategy that is inexpensive, practical, and effective. This counseling provides the prospect to judge exercise levels, adjust exercise prescriptions, and provide motivation and support. Contact frequency can decrease over time, because maintenance of initial high-frequency contact may not be required.

**Arnt Erik, Tjønna, et al., (2008)** have found that individuals with the metabolic syndrome are three times more probable to die of heart disease than healthy counterparts. Exercise training lessens several of the complications of the syndrome, but the exercise intensity that results the maximal useful adaptations is in dispute. Moderate and high exercise intensity are compared with regard to variables associated with cardiovascular function and prognosis in patients with the metabolic syndrome. 32 metabolic syndrome patients of age, 52.3±3.7 years; maximal oxygen uptake [VO2max], 34 mL · kg⁻¹ · min⁻¹) were randomly chosen for equal volumes of either moderate continuous moderate exercise (CME; 70% of highest measured heart rate [Hfmax] or aerobic interval training (AIT; 90% of Hfmax) three times in a week upto sixteen weeks or to a control group. VO2max increased more after AIT than CME (35% versus 16%; P<0.01) and was associated with removal of more risk factors that constitute the metabolic syndrome (number of factors: AIT, 5.9 before versus 4.0 after; P<0.01; CME, 5.7 before versus 5.0 after; group difference, P<0.05). AIT was better to CME in enhancing endothelial function (9% versus 5%;
P<0.001), insulin signaling in fat and skeletal muscle, skeletal muscle biogenesis, and excitation-contraction coupling and in lessening blood glucose and lipogenesis in adipose tissue. The two exercise programs were uniformly successful at lowering mean arterial blood pressure and reducing body weight (~2.3 and ~3.6 kg in AIT and CME, respectively) and fat. Exercise intensity was an significant factor for improving aerobic ability and reversing the risk factors of the metabolic syndrome. Individuals suffering with the metabolic syndrome are three times more likely to die of heart disease than healthy counterparts. Exercise training decreases many of the symptoms of the syndrome. They have compared both moderate and high exercise intensity with respect to variables associated with cardiovascular function and prognosis in patients with the metabolic syndrome.

They arrived at exercise intensity was an vital cause for improving aerobic ability and reversing the risk factors of the metabolic syndrome. These conclusions may have significant implications for exercise training in rehabilitation programs and future experiments. The increment in aerobic capacity is postulated as a optimistic measure in the conduct of high intensity aerobic training for prevention of diabetes and other degenerative diseases. Post prandial hyperglycemic conditions noticed in some of the elite athletes need not be a serious consequence here.

**Bajpeyi S, Tanner CJ, Slentz CA, et al., (2009)** in their experiment intended to establish whether exercise prescriptions contradictory in volume or intensity also change in their capacity to retain insulin sensitivity during an
ensuing period of training cessation. Sedentary, overweight/obese subjects were assigned to one of three 8-mo exercise programs: 1) low volume/moderate intensity [equivalent of approximately 12 miles/wk, 1,200 kcal/wk at 40-55% peak O(2) consumption (Vo(2peak)), 200 min exercise/wk], 2) low volume/vigorous intensity (approximately 12 miles/wk, 1,200 kcal/wk at 65-80% Vo(2peak), 125 min/wk), and 3) high volume/vigorous intensity (approximately 20 miles/wk, 2,000 kcal/wk at 65-80% Vo(2peak), 200 min/wk). Insulin sensitivity (intravenous glucose tolerance test, S(I)) was calculated when subjects were sedentary and at 16-24 h and 15 days after the concluding training bout. S(I) increased with training compared with the sedentary condition (P ≤ 0.05) at 16-24 h with all of the exercise prescriptions. S(I) decreased to sedentary, the relevant values after 15 days of training cessation in the low-volume/vigorous-intensity group. On contrary, at 15 days S(I) was drastically high compared with sedentary (P ≤ 0.05) in the prescriptions utilizing 200 min/wk (low volume/moderate intensity, high volume/vigorous intensity). In the high-volume/vigorous-intensity group, indexes of muscle mitochondrial density followed a pattern paralleling insulin action by being elevated at 15 days compared with pre-training; this trend was not evident in the low-volume/moderate-intensity group. Based up on these findings they propose that in overweight/obese subjects a relatively chronic persistence of enhanced insulin action may be obtained with endurance-oriented exercise training; this persistence, however, is dependent on the characteristics of the exercise training performed.
High intensity high volume aerobic running protocols are highly positive in bringing the required modifications in the pathophysiology of diabetics.

Maria Polikandrioti1 and Helen Dokoutsidou (2009) have experimented the role of exercise and nutrition in type II diabetes mellitus. In couple of recent years, the relationship between physical activity and type II diabetes mellitus management has been estimated by many studies. It is well recognized that physical activity leads general and specific health advantages for diabetic patients. The fundamental principles of an effective exercise program are the intensity, time and frequency of exercise in an suitable environment. Typically, low-intensity and long-duration exercise programs are measured as the most suitable for diabetic patients. Regarding dietary choices, it is extensively acknowledged that healthy nutrition is the root for the treatment of type II diabetes since it leads positively to the maintenance of blood glucose within normal range and controls the complications of the disease.

Some analysis are conserving with high intensity aerobic training for offsetting the Diabetes Mellitus environment in human beings, where as the intensities used in these studies are not made evident rather. There are not scientifically proven for incorporating high intensity aerobic training very near to the Lactate Threshold level or Anaerobic Threshold level. As this intensity might also carry advancements in aerobic capacity of the humans, which further could increase the exercising ability of the individuals. Hence, the present experiment made to appreciate the effect of very high intensity aerobic
training that could bring enhancements in aerobic ability of the individuals and its effect on the bio markers of diabetes mellitus and atherosclerosis among diabetics.