CARDIOPULMONARY AND QUALITY OF LIFE RESPONSES OF INDIVIDUALS WITH TYPE 2 DIABETES TO THERAPEUTIC EXERCISES

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DECLARATION

With the exception of duly acknowledge references, I hereby declare that this research work was carried out by me at the Department of Physiotherapy, College of Medicine of the University of Lagos, under the supervision of my supervisors and has not been submitted to any other institution for the purpose of obtaining another degree.

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OSHO, OLUWASEYI ABIGAIL 17TH April 2012

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CERTIFICATION

This is to certify that the thesis:

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DEDICATION

This thesis is dedicated to all individuals with diabetes all over Nigerian, their families and care givers.

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ABSTRACT

BACKGROUND: Cardiopulmonary complications of diabetes mellitus contribute greatly to the morbidity, mortality, and reduced quality of life in people with type 2 diabetes (T2DM). These complications require multifactorial treatment which includes targeting hyperglycaemia, obesity, hypertension and reduced lung functions among other factors which had been shown to pose challenge to people with T2DM. The inclusion of an appropriate exercise program is thus critical for optimal health in individuals with diabetes.

OBJECTIVE: This study was designed to investigate the cardiopulmonary, biochemical, anthropometric and QoL of individuals with T2DM in response to therapeutic exercises. It was also aimed at determining the time frame when therapeutic effects of exercise interventions occur.

METHODOLOGY: Sixty individuals with T2DM, both male and female within the age range of 20-75years participated in this study. They were consecutively recruited and randomly allocated into two exercise groups and a control group. Therapeutic exercise interventions for groups I and II were existing exercise protocols which were aerobic exercises on treadmill and bicycle ergometer respectively at progressive moderate intensity of 60%, 70% and 80% of heart rate reserve combined with resistance exercises at moderate intensity of 50%, 60% and 70% of one repetition maximum. The outcome measures were obtained at baseline, 4^{th} week, 8^{th} week and 12^{th} week of the intervention period. These included cardiovascular parameters [resting arterial systolic (RASBP) and diastolic blood pressure (RADBP) and resting rate pressure product (RRPP)], pulmonary parameters [oxygen uptake (VO_2max), forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1)], anthropometric parameters (body mass index (BMI), waist hip ratio (WHR), and waist circumference (WC)) and QoL variables. The QoL was assessed using Diabetes Quality

of Life Clinical Trial Questionnaire-Revised. The biochemical parameter [glycosylated haemoglobin ($HbA1_C$)] of the subjects was assessed at baseline and at the end of the 12^{th} week. Descriptive and inferential statistics were utilized for data analysis. Level of significance was set at $p<0.05$.

RESULTS: Groups I and II recorded significant reduction in cardiovascular, biochemical and some anthropometric variables while pulmonary and QoL variables were significantly increased post intervention (<0.05). RASBP, RADBP, RRPP, HbA1c were significantly reduced while VO_2max, FEV1, and QoL were significantly improved in the two exercise groups when compared with the control group ($P<0.05$). However, FVC and WC were only significant in group I ($p=0.00$ and 0.03). Furthermore, Group I recorded better improvement in pulmonary function (FEV1 and FVC) when compared to group II. Therapeutic effect of moderate intensity combined aerobic and resistance exercise on some cardiopulmonary variables occurred as early as four week post exercise intervention (RRPP, VO_2max and FEV1), the trend of this effect continue to the eighth and twelfth week post intervention.

CONCLUSION: Weight bearing and non-weight bearing aerobic exercises when combined with resistance exercise both gave significant therapeutic benefits on the cardiopulmonary and QoL of people with T2DM. However, the choice of either should ultimately depend on the superior judgment of the clinicians; it should also depend on the outcome measures which the clinicians are aiming at improving on. In the absence of significant reduction of pulmonary variables, non-weight bearing exercises combined with resistance exercises will be suggested especially if there are contradicting foot pathologies which may be aggravated by weight bearing aerobic exercises combined with resistance exercises (WBARE). Otherwise, WBARE will be more beneficial in the absence of foot pathologies. In addition, assessment of RRPP, VO_2max and FEV1 in people with T2DM should commence after four weeks post intervention.

Key words: Weight bearing and non-weight bearing aerobic exercises, resistance exercise, cardiopulmonary, anthropometric, Glycosylated hemoglobin, Type 2 diabetes

CHAPTER ONE

INTRODUCTION

1.1 Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by high blood sugar (glucose) levels, which result from defects in insulin secretion, or action, or both (American Diabetes Association, 2003a). DM is diagnosed if fasting blood glucose levels are higher than 126 mg/dl on more than one occasion, if a random blood glucose level is higher than 200 mg/dl along with symptoms, or if an oral glucose tolerance test indicates blood glucose level higher than 200 mg/dl, two hours after drinking a beverage containing 75 grams of glucose dissolved in water (World Health Organisation (WHO), 2007). DM is a worldwide health problem predisposing to markedly increased cardiopulmonary morbidity and mortality (Arnalich *et al*., 2000; McKeever *et al*., 2005). Biochemical disorder such as poor glucose control significantly contribute to the increased risk of cardiovascular disease and other

morbidities in DM patients (George and Luduik, 2000; McKeever *et al*., 2005). Rates of cardiovascular diseases (CVD) morbidity and mortality are particularly high in this population thus representing a significant cost for health care systems.

There are two major types of DM, the type 1 formerly called insulin dependent or juvenile DM and the type 2 which is formerly known as non-insulin dependent DM which occurs mostly in adulthood (WHO, 2007; Paige, 2008). T2DM is caused by the decreased insulin production by the β cells of the pancreatic islet and an increased insulin resistance by the peripheral tissue. These cause hyperglycaemia (Patticia and Pellanda, 2007). Insulin is needed by the peripheral tissues to use the glucose in the body for energy. Without insulin the body is unable to use glucose causing body cells to starve, this results in complications in the other parts of the body (Kalofoutis *et al.*, 2007).

A study of the prevalence of DM showed that T2DM is the most common type of DM accounting for about 90% of cases (Snodlon *et al*., 1985; Familoni *et al*., 2008; National Institute of Health (NIH), 2011). Worldwide, approximately 200 million people have T2DM, a prevalence that has been predicted to increase to 366 million by 2030 (Wild *et al*., 2004; Kalofoutis *et al*., 2007). In 2005–2008, of adults ages 20 years or older in the united states with self-reported DM, 67% had blood pressure greater than or equal to 140/90 mmHg or used prescription medications for hypertension (NIH, 2011). Sixty two percent of persons with T2DM in the northern part of Nigeria were estimated to be hypertensive (Bello-Sani and Anumah, 2009). In 2004, heart disease was noted on 68% of DM-related death among people ages 65 years or older (NIH, 2011). Adults with DM have heart disease death rates about 2 to 4 times higher than adults without DM (NIH, 2011). DM affects 25.8 million people of all ages, 8.3 percent of the U.S. population, 18.8 million people are diagnosed while 7.0 million people are undiagnosed (NIH, 2011). One in every 16 people has DM and it was reported that nearly 3 million Americans are on insulin (Saul and Hoffer, 2003). Crude prevalence rates of

7.7 and 5.7% were estimated for males and females in Port Harcourt in Nigeria (Nyenwe *et al*., 2003). In Nigeria, the national prevalence of DM was estimated to be 6.8% in adult Nigerians older than 40 years (Abubakari and Bhopalb, 2008).

Many amputations and several deaths result from circulatory complication of DM (Saul and Hoffer, 2003). T2DM patients generally carry a number of risk factors for CVD, including hypertension, hyperglycaemia, abnormal lipid profiles, alterations in inflammatory mediators and coagulation/thrombolytic parameters, as well as other 'nontraditional' risk factors, many of which may be closely associated with insulin resistance (Kalofoutis *et al*., 2007). Therefore, successful management of CVD associated with DM represents a major challenge to the clinicians. Therapeutic approach is such that the blood pressure target is less than 130/80mmHg, or even lower if there are mitigating circumstances, such as the presence of renal disease (Laaksonen, 2003).

There is a growing body of evidence showing that hyperglycaemia is linked to increased cardiovascular risk (O'ke efe and Bell, 2007; Gavin, 2008). Anthropometric parameter such as high body mass index (BMI) has also been demonstrated to be significantly associated with heart diseases in people with DM. Atherogenic biochemical disorders are the major risk factors predisposing DM patients to cardiovascular diseases (Robert and Jonathan, 2003). The association of reduced lung function and DM has been described for many years although the clinical significance of this association is not known (Goldman, 2003; Ozoh *et al*., 2010; Tella and Sanni, 2005; Kaminski *et al.*, 2010). Possible links between respiratory impairment in people with DM have been attributable to increased body mass index, subsequent loss of respiratory compliance, neuropathies, loss of strength of the respiratory muscles, poor glucose control and other confounding variables (Kaminski *et al*., 2010). Therapeutic approaches is such that glycosylated haemoglobin level (HbA_{1c}) which is the

index of glucose control, be less than 7% or generally as close to normal (6%) as feasible without precipitating such adverse events as hypoglycaemia (Laaksonen, 2003).

Various medications are prescribed for management of glucose level in DM patients, these medications work in different ways to lower blood sugar. Most of them work by stimulating the pancreas to produce and release more insulin [Dipeptidyl-peptidase 4 (DPP-4) inhibitors, Glucagon-like peptide 1 (GLP-1) agonists, Meglitinides, Sulfonylureas]. Some work by inhibiting the production and release of glucose from the liver (Biguanide (Metformin), Thiazolidinediones). Others work by locking the action of stomach enzymes that break down carbohydrates or make tissues more sensitive to insulin **(**Alpha-glucosidase inhibitors) (Nathan *et al*., 2009). New classes of medications and numerous combinations have been demonstrated to lower glycaemia. However, current medications have failed to achieve and maintain the glycaemic levels most likely to provide optimal healthcare status for people with DM (Nathan *et al*., 2009).

Dietary advice is an accepted cornerstone of treatment for T2DM, but no quality data on the efficacy of diet intervention per se on glycaemic control, reduction in body weight, development of diabetic complications or quality of life (QoL) exists for the treatment of T2DM (Nield *et al*., 2007). Education programmes alone improves glycaemic control in some studies (Trento *et al*., 2002; Sarkadi and Rosenqvis, 2004), but not in all (Davies *et al*., 2008).

Physiotherapists as part of rehabilitation specialists play major roles not only in the prevention but also in the management of people with DM especially T2DM (Kalra *et al*., 2007). They utilize various measures in the management of people with T2DM. One of the modalities imbibed during management is therapeutic exercise. Therapeutic exercise is any exercise planned and performed to attain a specific physical benefit, such as maintenance of

the range of motion, strengthening of weakened muscles, increased joint flexibility, or improved cardiovascular and respiratory function (Kalra *et al*., 2007). Therapeutic exercise simply refers to the use of particular exercises as therapy for a health condition or as part of a regular fitness/conditioning program. It has been shown to be a valuable and economical therapeutic modality that may be considered as a beneficial adjunct for DM especially the type 2, non-insulin dependent DM (McAuley and Duncan, 993; Diloreto *et al.*, 2005; Isharwal *et al*., 2009).

Studies on the therapeutic effects of various exercise modes such as weight bearing aerobics on treadmill and non-weight bearing aerobic on bicycle ergometer when combined with resistance exercises on the cardiopulmonary, biochemical, anthropometric and QoL of people with T2DM are sparsely reported especially in African population (American College of Sport Medicine and American Diabetes Association (ACSM and ADA), 2010; Ferdowsi *et al*., 2011). This study was thus designed to investigate the cardiopulmonary, biochemical, anthropometric and QoL responses of individuals with T2DM to therapeutic exercises such as moderate intensity weight bearing and non-weight bearing aerobic when combined with resistance exercises. It also investigated changes in the cardiopulmonary, biochemical, anthropometric and QoL variables at specified duration in the intervention period.

1.2 Statement of the problem

DM is a global health problem predisposing individuals to markedly increased mortality and morbidity due the various complications associated with it (Zimmet *et al*., 1997). Therapeutic intervention in individuals with T2DM requires multifactorial treatment which should target obesity, hyperglycaemia and other comorbidities which affect the quality of life (QoL) of people with T2DM (Vinik *et al*., 2003).

Physiotherapists as part of rehabilitation specialists play major roles in the management of people with DM especially T2DM, utilizing therapeutic exercises (Odebiyi and Ohwovoriole, 2000, Tella and Sanni, 2005; Kalra *et al*., 2007). Either aerobics or resistance exercises had been established to be beneficial adjunct in the management of DM complications (Tella and Sanni, 2005; Arora *et al*., 2009). A combination of aerobics and resistance exercises have been established to be of greater beneficial adjunct for improvement of glycaemia in T2DM patients than either aerobics or resistance exercise alone (Arora *et al*., 2009; Isharwal *et al*., 2009). However, effect of combined moderate intensity aerobic and resistance exercise on the cardiopulmonary, biochemical and anthropometric variables at specified duration is yet to be established especially among African population (ACSM and ADA, 2010).

People with T2DM often develops foot pathologies (Akinbo, 2008) which necessitates the prescription of non-weight bearing aerobic exercise as against weight bearing aerobic exercise they regularly perform (Huo *et al*., 2006). Bicycle ergometer is usually the modality of choice (Marwick *et al*., 2009). Treadmill however simulate walking, which is a weight bearing exercise performed on day to day activities (Timothy and Connell, 2003). Inclination of this modality at a gradient of 1% had been established to give similar energy cost with outdoor walking as this gradient compensate for air resistance that will usually be present outdoor (Ramsbottom *et al*., 2007). However, whether a weight bearing aerobic exercise such as walking on treadmill or non-weight bearing aerobic exercise such as bicycle ergometer training when combined with resistance exercise will have superior benefit on the cardiopulmonary, biochemical and anthropometric measures of people with T2DM who may be compelled to undergo either of these mode of exercises due to their pathological condition is yet to be established.

The association of reduced lung function and DM has been described for many years (Goldman, 2003; Kaminski *et al*., 2010; Ozoh *et al*., 2010; Kaminski *et al*., 2010; Ferdowsi *et al*., 2011). Biochemical disorders such as abnormalities in glucose control (HbA1c) significantly contribute to the increased risk of cardiopulmonary diseases and other morbidities in individuals with T2DM (George and Luduik, 2000). Reduced lung volumes and airflow limitation have been reported to be chronic complications of T2DM. The severity of this reduction in lung volumes has been reported to relate to glycaemic exposure (Davis *et al*., 2002). Poor glucose control has been linked to microvascular complications and reduced ventilatory function of the lungs (Proffy, 2001; Davis *et al*., 2002). Airflow limitation is a predictor of death in T2DM after adjusting for other recognized risk factors (Davis *et al*., 2002). However, studies are needed to establish the effect of therapeutic exercises such as weight bearing aerobic and non-weight bearing aerobic exercise when combined with resistance exercise on the pulmonary functions in people with DM especially in African population (Kaminski *et al*., 2010; Ferdowsi *et al*., 2011).

The most widely used measure of adiposity is the body mass index (BMI) which gives a good index of overall adiposity (WHO, 2000). Waist circumference and the waist-hip ratio are measures for abdominal fat distribution. Obesity and abdominal fat distribution have been described to be predisposing factors to DM and its complications (Harris *et al*., 2000; Juhaeri *et al*., 2002). However, reports on the responses of these anthropometric variables to therapeutic exercises at moderate intensity range of combined aerobic and resistance exercise at specified duration using different exercise mode are sparse especially among African population.

Furthermore, studies are needed to give evidence on whether different mode of aerobic exercise when combined with resistance exercise may have specific or superior effect on the

cardiopulmonary, biochemical, anthropometric and QoL variables in individuals with T2DM in Nigerian population. The specific time when therapeutic effect of combined aerobic and resistance exercise begins is also yet to be established. This study was thus designed to investigate the cardiopulmonary, biochemical, anthropometric and QoL responses of individuals with T2DM to different modes of therapeutic exercises such as moderate intensity weight bearing aerobics on treadmill at 1% gradient and non-weight bearing aerobics on bicycle ergometer combined with resistance exercises with assessment at specified duration in the intervention period.

1.3 Aim of the study

The overall aim of this study was to determine the cardiopulmonary, biochemical, anthropometric and QoL changes in individuals with T2DM in response to therapeutic exercises.

1.4 Specific objectives

The specific objectives of this study were to:

1. Investigate the cardiovascular, pulmonary, biochemical, anthropometric and QoL changes in individuals with T2DM following combined weight bearing aerobic exercise on treadmill with resistance exercises.
2. Investigate the cardiovascular, pulmonary, biochemical, anthropometric and QoL changes in individuals with T2DM secondary to combined non-weight bearing aerobic exercise on bicycle ergometer with resistance exercises.
3. To compare the changes in the cardiovascular, pulmonary, biochemical, anthropometric and QoL of individuals with T2DM who undergone combined weight bearing aerobic exercise on treadmill with resistance exercises, those who undergone combined non-weight bearing aerobic exercise on bicycle ergometer with resistance exercises when compare with a control group with no exercise intervention.

4. Determine the time frame when therapeutic effect of combined aerobic and resistance exercises occur on the cardiovascular, pulmonary, biochemical, anthropometric and QoL variables of individuals with T2DM.

1.5 Significance of the study

The result of this thesis may guide therapists in exercise prescription, design and intervention in the management of patients with T2DM. It may also help to determine appropriate exercise programme which can be a safe and effective treatment strategy in reducing cardiopulmonary complications through enhancement of appropriate glycaemic control which is the major biochemical and metabolic disorder associated with DM.

The results of this thesis may also play a major role in determining appropriate exercise mode which may give a better therapeutic effect and a beneficial adjunct to bring about reduction in morbidity, mortality rate and in improving overall QoL of people with DM.

1.6 Scope of the study

This study was a randomized control study which was conducted at the Lagos University Teaching Hospital, Idi-Araba, Lagos, Nigeria and Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria. The subjects recruited for this study were male and female individuals with T2DM between 20 to 75 years of age.

1.7 Limitations of Study

Some subjects who started the study could not attend the exercise sessions regularly at the frequency specified for this study and were therefore excluded from the study. Most individuals with T2DM who were willing to participate did not meet the inclusion criteria for the study and could not participate in the study. Therefore the number of patients recruited for the study was fairly reduced.

1.8 Definition of terms

Aerobic exercises: These consist of rhythmic, repeated, and continuous movements of some large muscle groups for at least 10 min at a time (Ronald *et al*., 2007).

Anthropometric measurements: a set of noninvasive, quantitative techniques for determining an individual's body fat composition by measuring, recording, and analyzing specific dimensions of the body, such as height and weight; skin-fold thickness; and bodily circumference (Laaksonen, 2003).

Biochemical: Relating to biochemistry, the application of tools and concepts of chemistry to living organisms (Delmaris *et al*., 2008).

Cardiopulmonary: Having to do with both the heart and lungs. Cardio-heart, Pulmonary-lungs (Timothy and Connell, 2003).

Forced expiratory capacity in 1 second (FEV1): The forced expiratory flow rate in one second (FEV1) is the volume of air expired in the first second after a maximal inspiration (Ozoh *et al*., 2010).

Force vital capacity (FVC): The amount of air that can be maximally forced out of the lungs after a maximal inspiration (Ozoh *et al*., 2010).

Glycosylated haemoglobin (HbA_{1c}): The value (HbA_{1c}) is a reflection of the mean plasma glucose concentration over the previous 2 to 3 months (Ronald *et al*., 2007).

Health Related Quality of Life: The sense of total well-being that encompasses both the physical and psychosocial aspects of the patient's life (Polonsky, 2000).

Hyperglycaemia: High blood sugar level (Nathan *et al*., 2007).

Hypoglycaemia: Low blood sugar level (American Diabetes Association, 2003a).

Repetition maximum (RM): One repetition (1-RM) is the maximum weight that can be lifted by a muscle or group of muscles in a single time (Adeniyi *et al*., 2007).

Resistance exercises: Activities that use muscular strength to move a weight or work against a resistive load (Ronald *et al*., 2007).

Target heart rate: This is the ideal intensity level at which the heart is being exercised but not overworked. It is determined by finding the maximum heart rate and taking a percentage of it (60 to 85 percent, depending on fitness level) (American Heart Association (AHA), 2010).

1.8 List of abbreviations

DM	-	Diabetes mellitus
T2DM	-	Type 2 diabetes mellitus
QoL	-	Quality of life
CVD	-	Cerebrovascular diseases
MHR	-	Maximum heart rate
RASBP	-	Resting arterial systolic blood pressure
RADBP	-	Resting arterial diastolic blood pressure
RRPP	-	Resting rate pressure products
VO_2max	-	Oxygen uptake
FVC	-	Forced vital capacity
FEV1	-	Forced expiratory volume in one second
PF	-	Physical functioning
TF	-	Treatment flexibility
FS	-	Frequency of symptoms
HD	-	Health distress
E/F	-	Energy/fatigue
SF	-	Satisfaction
TS	-	Treatment satisfaction
MH	-	Mental Health
RAPA	-	Rapid assessment of physical activity
DQLCTQ-R	-	Diabetes Quality of Life Clinical Trial Questionnaire-Revised
H&E	-	Hematoxylin and Eosin
GLUT	-	Glucose Transporter Protein.
DMT	-	Dynamic measurement Technologies

CHAPTER TWO

LITERATURE REVIEW

2.1.1 Diabetes Mellitus

Diabetes Mellitus (DM) is a major worldwide health problem predisposing to markedly increased cardiovascular mortality and serious morbidity and mortality related to development of nephropathy, neuropathy and retinopathy (Laaksonen, 2003). DM is characterized by derangements in carbohydrate and lipid metabolism, and is diagnosed by the presence of hyperglycaemia (Gavin, 2008).

Type 2 diabetes (T2DM) formerly called non-insulin dependent diabetes mellitus (NIDDM) or adult - onset diabetes is a disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency (Slentz *et al.,* 2009). Traditionally considered a disease of adults, T2DM is increasingly diagnosed in children in parallel to rising obesity rates (NIH, 2008) due to alterations in dietary patterns as well as in life styles during childhood (Steinberger *et al.,* 2001). Unlike type 1 DM, there is very little tendency toward ketoacidosis in T2DM, though it is not unknown (Laaksonen, 2003). One effect that can occur is non-ketonic hyperglycaemia which also is quite dangerous, though it must be treated very differently (WHO, 2007). Complex and multifactorial metabolic changes very often lead to damage and functional impairment of many organs, most importantly the cardiovascular system in both types of diabetes (Kalofoutis *et al.,* 2007). This leads to substantially increased morbidity and mortality in both type 1 and T2DM patients, but the two have quite different origins and treatments despite the similarity in complications (Chiasson *et al.,* 2003)

Type 2 diabetes is the most common form of DM accounting for about 90% (American Diabetes Association, 2003a). Due to dietary habits and increasing obesity and sedentariness

in both western and developing countries, the prevalence of T2DM is growing at an exponential rate (WHO, 2000; Lovejoy, 2002). Type 2 diabetes is characterized by insulin resistance coupled with an inability of the pancreas to sufficiently compensate by increasing insulin secretion, with onset generally in middle or old age. Onset is insidious, and ketoacidosis is rare. The prevalence of T2DM among adults varies from less than 5% to over 40% depending on the population in question (Zimmet *et al.,* 1997). The pathogenesis of T2DM is still unclear, although multiple genetic and environmental factors clearly interplay to produce the disease. Although the pathophysiology is still unclear, variable defects of metabolism in skeletal muscle, fat, liver and pancreas contribute to increased insulin resistance and abnormal insulin secretion.

Type 2 diabetes is diagnosis when the fasting plasma glucose level >126 mg/dl (7.0 mmol./l) or a two-hour post-load level > 200mg/dl (11.1 mmol./l) in a 75-g oral glucose tolerance test as cutoffs for T2DM (Alberti and Zimmet, 1998; American Diabetes Association, 2003a). These criteria are similar to the American Diabetes Association criteria (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). The American criteria differ especially from previous criteria in that an oral glucose tolerance test is recommended only when the fasting glucose level is below 7.0 mmol/l but the suspicion of DM is high.

2.1.2 Classification of diabetes mellitus

The three main types of diabetes are;

- Type 1 DM
- Type 2 DM
- Gestational DM

Type 1 diabetes mellitus

Type 1 DM is an autoimmune disease. An autoimmune disease results when the body's system for fighting infection; the immune system, turns against a part of the body. In diabetes, the immune system attacks and destroys the insulin-producing beta cells in the pancreas. The pancreas then produces little or no insulin. A person who has type 1 DM must take insulin daily to live (WHO, 2007). Figure 1 shows the normal appearance of beta cell while Figure 2 shows the appearance of beta cells in type 1 DM.

At present, scientists do not know exactly what causes the body's immune system to attack the beta cells, but they believe that autoimmune, genetic, and environmental factors, possibly viruses, are involved. Type 1 DM accounts for about 5 to 10% of diagnosed diabetes in the United States. It develops most often in children and young adults but can appear at any age (WHO, 2007). Symptoms of type 1 DM usually develop over a short period, although beta cell destruction can begin years earlier. Symptoms may include increased thirst and urination, constant hunger, weight loss, blurred vision, and extreme fatigue. If not diagnosed and treated with insulin, a person with type 1 DM can lapse into a life-threatening diabetic coma, also known as diabetic ketoacidosis (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 2003; WHO, 2007).

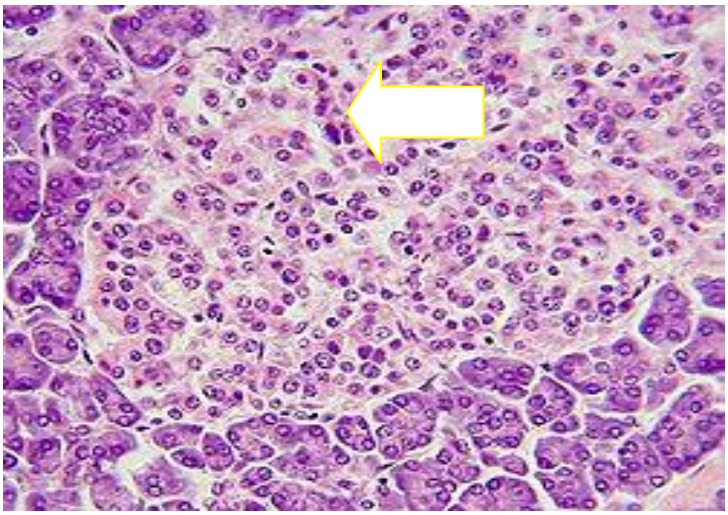

Figure 1: Appearance of normal beta cells

[HXE 400 (Francisco and La Rosa, 2000)]

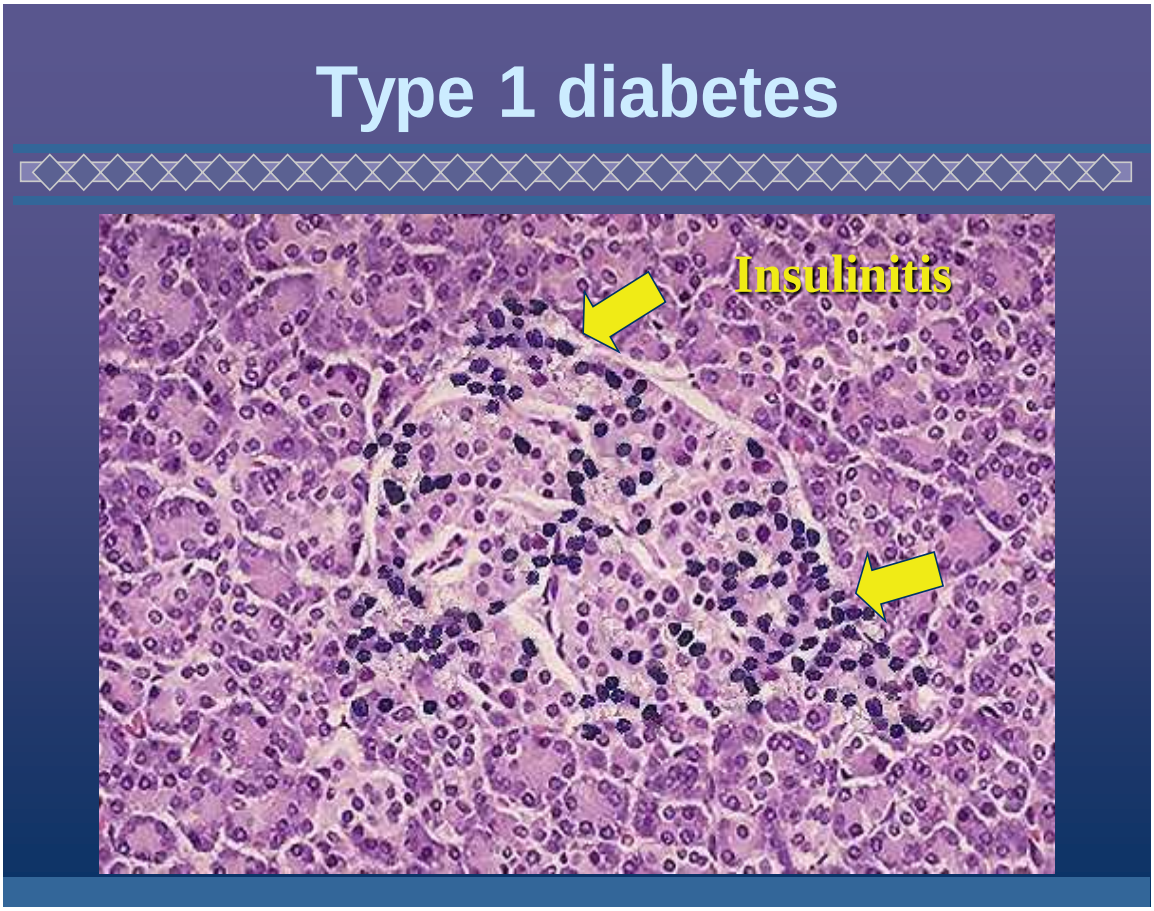

Figure 2: Destroyed beta cells in type 1 diabetes with accompanying insulitis

[H&E X 400 (Francisco and La Rosa, 2000)]

Type 2 diabetes

The most common form of DM is T2DM. About 90% of people with DM have type 2. This form of DM is most often associated with older age, obesity, family history of DM (Balletshofer *et al*., 2000), previous history of gestational diabetes, physical inactivity, and certain ethnicities. About 80% of people with T2DM are overweight.

T2DM is increasingly being diagnosed in children and adolescents, especially among African American, Mexican American, and Pacific Islander youth. When T2DM is diagnosed, the pancreas is usually producing enough insulin, but for unknown reasons the body cannot use the insulin effectively, a condition called insulin resistance. After several years, insulin production decreases. The result is the same as for type 1 DM, glucose builds up in the blood and the body cannot make efficient use of its main source of fuel (NIH, 2008).The symptoms of T2DM develop gradually. Their onset is not as sudden as in type 1 DM. Symptoms may include fatigue, frequent urination, increased thirst and hunger, weight loss, blurred vision, and slow healing of wounds or sores. Some people have no symptoms (WHO, 2007). Figure one shows the appearance of beta cell in T2DM

Gestational diabetes mellitus

Some women develop gestational DM late in pregnancy. Although this form of DM usually disappears after the birth of the baby, women who have had gestational DM have a 40 to 60 percent chance of developing T2DM within 5 to 10 years. Maintaining a reasonable body weight and being physically active may help prevent development of T2DM (Alberti and Zimmet, 1998). About 3 to 8% of pregnant women in the United States develop gestational diabetes. As with T2DM, gestational diabetes occurs more often in some ethnic groups and among women with a family history of DM. Gestational DM is caused by the hormones of pregnancy or a shortage of insulin. Women with gestational DM may not experience any symptoms (WHO, 2007; NIH, 2008).

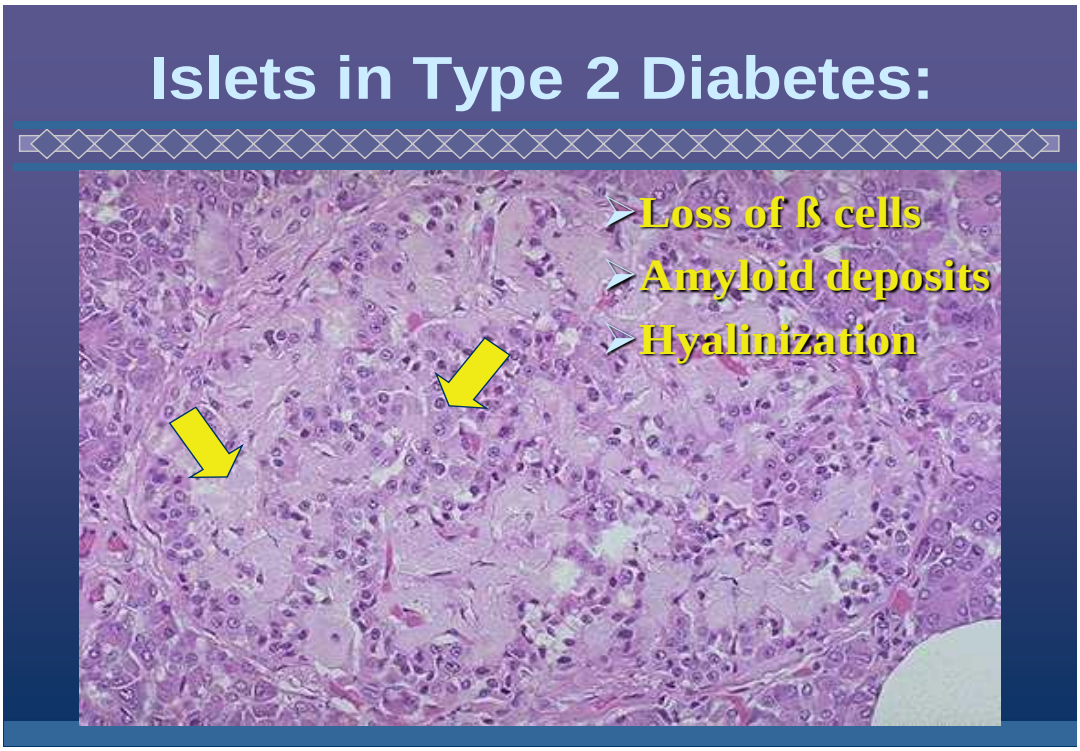

Figure 3: Appearance of beta cells in type 2 diabetes

[H&E X 400 (Francisco and La Rosa, 2000)

2.1.3 Epidemiology

Diabetes Mellitus is not contagious; however, certain factors can increase the risk of developing it. Type 1 DM occurs equally among males and females but is more common in whites (NIH, 2008). Data from the World Health Organization's Multinational Project for Childhood DM indicated that type 1 diabetes is rare in most African, American Indian, and Asian populations (Rewers *et al*., 1988). However, some Northern European countries, including Finland and Sweden, have high rates of type 1 DM (NIH, 2008). The reasons for these differences are unknown. Type 1 DM develops most often in children but can occur at any age (NIH, 2008).

Type 2 diabetes is more common in older people, especially in people who are overweight, and occurs more often in African Americans, American Indians, some Asian Americans, Native Hawaiians and other Pacific Islander Americans, and Hispanics/Latinos (Patrick *et al*., 1989). National survey data in 2007 indicate a range in the prevalence of diagnosed and undiagnosed diabetes in various populations ages 20 years or older in United States: Age 20 years or older recorded 23.5 million, or 10.7 percent, of all people in this age group have DM. Age 60 years or older recorded a prevalence of 12.2 million, or 23.1 percent, of all people in this age group. For men, 12.0 million or 11.2 percent, of all men ages 20 years or older have diabetes while the prevalence of DM in women was 11.5 million or 10.2 percent, of all women ages 20 years or older. Non-Hispanic whites have a prevalence of 14.9 million or 9.8 percent, of all non-Hispanic whites ages 20 years or older while non-Hispanic blacks recorded 3.7 million or 14.7 percent, of all non-Hispanic blacks ages 20 years or older (NIH, 2008).

Diabetes Mellitus prevalence in the United States is likely to increase for several reasons. First, a large segment of the population is aging. Also, Hispanics/Latinos and other minority groups at increased risk make up the fastest-growing segment of the U.S. population. Finally,

Americans are increasingly overweight and sedentary. According to recent estimates from the Centre for Disease Control (CDC), DM will affect one in three people born in 2000 in the United States. The centre for disease control (CDC) also projects that the prevalence of diagnosed DM in the United States will increase 165 percent by 2050 (NIH, 2008).There are an estimated 23.6 million people in the U.S. (7.8% of the population) with diabetes with 17.9 million being diagnosed (American Diabetes Association, 2009) 90% of whom are type 2 with prevalence rates doubling between 1990 and 2005, CDC has characterized the increase as an epidemic (Gerberding, 2007). According to CDC, about 23.613 million people in the United States, or 8% of the population, have DM (Gerberding, 2007). The total prevalence of DM increased 13.5% from 2005-2007(American Diabetes Association, 2008). It was thought that only 24% of DM is now undiagnosed, down from an estimated 30% in 2005 and from the previously estimated 50% in 1995 (Gerberding, 2007). About 90–95% of all North American cases of DM are type 2 and about 20% of the population over the age of 65 has T2DM (Zimmet *et al*., 1997).

The fraction of people with T2DM in other parts of the world varies substantially, almost certainly for environmental and lifestyle reasons, though these are not known in detail. DM affects over 150 million people worldwide and this number is expected to double by 2025 (Zimmet *et al*., 2001). Crude prevalence rates were 7.7 and 5.7% were estimated for males and females Port Harcourt in Nigeria. In Nigeria, the national prevalence of DM was estimated to be 6.8% in adult Nigerians older than 40 years (Abubakari and Bhopalb, 2008), making it the second common non-communicable disease after hypertension (Akinkugbe, 1997; Familoni *et al*., 2008).

2.1.4 Pathology

Diabetes Mellitus is characterized by hyperglycaemia due to disturbances in the metabolism of carbohydrate, fat and protein because of abnormalities in the availability of insulin or insulin-action (WHO, 2007). Even though DM is an endocrine disease in origin, its major manifestations are those of a metabolic disease. The characteristics symptoms are excessive thirst, polyuria, pruritus, and otherwise unexplained weight loss (American Diabetes Association, 2003a). DM also brings about the progression of secondary complications through the thickening of basement membrane (WHO, 2007). The most dominant feature of the metabolism in DM is an abnormally high concentration of blood glucose. This can be either due to an abnormally high rate of glucose production or of impaired glucose utilization. It is now accepted that the high blood glucose level is the result of combination of both these processes.

The secondary complications seen in patients with DM are found to involve alterations in vascular basement membrane composition as well as accumulation of glucose derived reaction products due to over utilization of glucose in insulin independent tissues (Laaksonen, 2003). Various authors have shown that hyperglycaemia leads to an increase in serum glycated proteins (Gordon *et al*., 2008; Delimaris *et al*., 2008) along with alterations in other atherogenic risk factors. Further, disturbances in mineral metabolism are also noticed (Walter, 1991; Ditzel and Lervang, 2009) and it is not known whether differences in trace element status are a consequence to the expression of the disease (Laaksonen, 2003).

Insulin resistance means that body cells do not respond appropriately when insulin is present. Unlike type 1 DM, the insulin resistance is generally "post-receptor", meaning it is a problem with the cells that respond to insulin rather than a problem with production of insulin (American Diabetes Association, 2003a).Other important contributing factors to T2DM are;

increased hepatic glucose production (e.g., from glycogen to glucose conversion), especially at inappropriate times (typical cause is deranged insulin levels, as those levels control this function in liver cells) (Laaksonen, 2003), decreased insulin-mediated glucose transport in (primarily) muscle and adipose tissues (receptor and post-receptor defects) and impaired beta cell function loss of early phase of insulin release in response to hyperglycaemic stimuli (Gavin, 2008). Figure 4 shows a schematic representation of regulation of blood glucose. These factors are more complex problem in T2DM, but is sometimes easier to treat, especially in the early years when insulin is often still being produced internally (Laaksonen, 2003). T2DM may go unnoticed for years before diagnosis, since symptoms are typically milder (*e.g.* no ketoacidosis, coma, *etc.*) and can be sporadic (Laaksonen, 2003). However, severe complications can result from improperly managed T2DM, including renal failure, erectille dysfunction, blindness, slow healing wounds (including surgical incisions), and arterial disease, including coronary artery disease. The onset of T2DM has been most common in middle age and later life (Zimmet *et al.*, 1997), although it is being more frequently seen in adolescents and young adults due to an increase in child obesity and inactivity (Zimmet *et al.*, 1997). There is also a strong inheritable genetic connection in T2DM. Having relatives (especially first degree) with T2DM increases risks of developing T2DM very substantially. In addition, there is a mutation to the Islet Amyloid Polypeptide gene that results in an earlier onset, more severe, form of diabetes (Jansson *et al*., 2002). About 55% of T2DM patients are obese (WHO, 2000). Long standing obesity leads to increased insulin resistance that can develop into diabetes. This can be attributed to the fact that adipose tissue (especially that in the abdomen around internal organs) is a source of several chemical signals to other tissues (hormones and cytokines). Other research shows that T2DM causes obesity as an effect of the changes in metabolism and other deranged cell behavior attendant on insulin resistance (Camastra *et al*., 1999). However, genetics play a

relatively small role in the widespread occurrence of T2DM. This can be logically deduced from the huge increase in the occurrence of T2DM which has correlated with the significant change in western lifestyle (Hu, 2003).

2.1.5 Symptoms

Early symptoms may be chronic fatigues, generalized weakness and malaise (feeling of unease), excessive urine production, excessive thirst and increased fluid intake, blurred vision (typically from lens shape alterations, due to osmotic effects, e.g., high blood glucose levels), unexplained weight loss, lethargy and itching of external genitalia (American Diabetes Association, 2003a).

2.1.6 Diagnosis of diabetes

The World Health Organization definition of DM is for a single raised glucose reading with symptoms, otherwise raised values on two occasions, of either the fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl) Or with a glucose tolerance test, two hours after the oral dose a plasma glucose ≥ 11.1 mmol/l (200 mg/dl) (WHO, 2007). The fasting blood glucose test is the preferred test for diagnosing diabetes in children and non-pregnant adults. The test is most reliable when done in the morning. However, a diagnosis of DM can be made based on any of the following test results, confirmed by retesting on a different day (WHO, 2007):

A blood glucose level of 126 mg/dL or higher after an 8-hour fast. This test is called the fasting blood glucose test. A blood glucose level of 200 mg/dL or higher 2 hours after drinking a beverage containing 75 g of glucose dissolved in water. This test is called the oral glucose tolerance test (OGTT) (Santaguida *et al*., 2005). A random blood glucose, taken at any time of day with blood glucose level of 200 mg/dL or higher, along with the presence of DM symptoms (WHO, 2007).

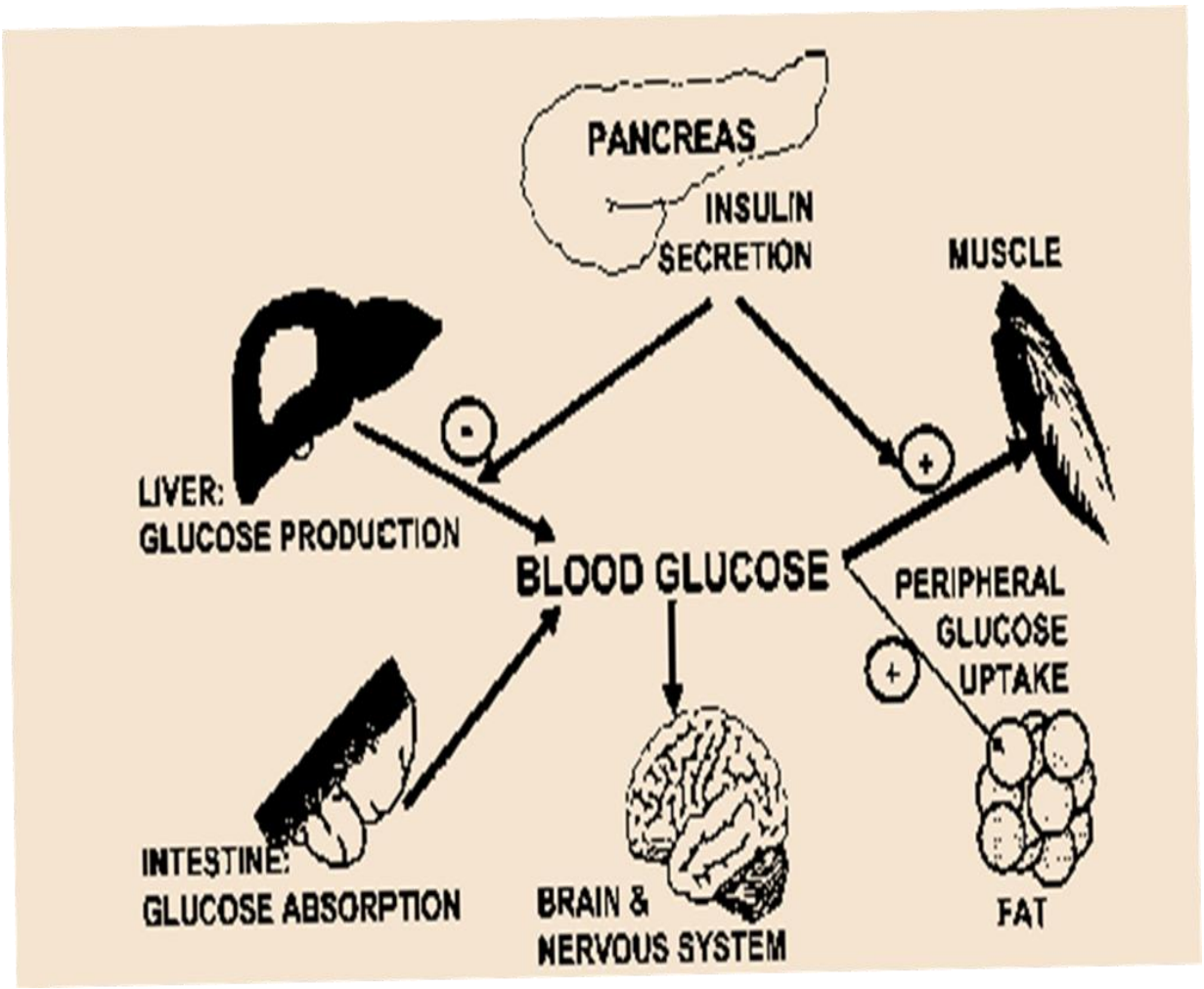

Figure 4: Schematic representation of regulation of blood glucose (Laaksonen, 2003)

Gestational DM is diagnosed based on blood glucose levels measured during the OGTT. Glucose levels are normally lower during pregnancy, so the cutoff levels for diagnosis of diabetes in pregnancy are lower. Blood glucose levels are measured before a woman drinks a beverage containing glucose. Then levels are checked 1, 2, and 3 hours afterward. If a woman has two blood glucose levels meeting or exceeding any of the following numbers, she has gestational DM: a fasting blood glucose level of 95 mg/dL, a 1-hour level of 180 mg/dL, a 2-hour level of 155 mg/dL, or a 3-hour level of 140 mg/dL (WHO, 2007).

2.1.7 Prevention

Onset of T2DM can often be delayed through proper nutrition and regular exercise (Lovejoy *et al*., 2002). Interest has arisen in preventing diabetes due to research on the benefits of treating patients before overt DM. Although the U.S. Preventive Services Task Force (USPSTF) concluded that "the evidence is insufficient to recommend for or against routinely screening asymptomatic adults for T2DM, impaired glucose tolerance, or impaired fasting glucose" (Harris *et al*., 2000). This was a grade A recommendation when published in 2003. However, the USPSTF does recommend screening for diabetes in adults with hypertension or hyperlipidemia (grade B recommendation). In 2005, it was reported by the Agency for Healthcare Research and Quality that there is evidence that combined diet and exercise, as well as drug therapy (metformin, acarbose), may be effective at preventing progression to DM in impaired glucose tolerance (IGT) subjects (Santaguida *et al*., 2005).

2.1.8 Benefit of early detection

Since publication of the USPSTF statement, a randomized controlled trial of prescribing acarbose to patients with high-risk population of men and women between the ages of 40 and 70 years with a body mass index (BMI), calculated as weight in kilograms divided by the square of height in meters, between 25 and 40. They were eligible for the study if they had

IGT according to the World Health Organization criteria, plus impaired fasting glucose (a fasting plasma glucose concentration of between 100 and 140 mg/dL or 5.5 and 7.8 mmol/L). USPSTF found 44 to be treated (over 3.3 years) in order prevent a major cardiovascular event (Chiasson *et al*., 2003). Other studies have shown that lifestyle changes, xenical and metformin can delay the onset of DM (Knowler *et al*., 2002; Ronald *et al*., 2007; ACSM and ADA, 2010).

2.2 Complications of diabetes mellitus

Persistent hyperglycemia is known to be responsible for serious damage to various organs and tissues in subjects with diabetes (Ronald *et al*., 2007; ACSM and ADA, 2010). The chronic complications of DM include: retinopathy, nephropathy, neuropathy and atherosclerosis. Diabetic retinopathy, a retinal disease in diabetes, is the leading cause of severe visual impairment in adults, disabling nearly 5000 patients per year in most countries (Laaksonen, 2003). Diabetic nephropathy, a kidney disease in DM, was the leading cause of end-stage renal failure at the end of 1998 in Japan after introduction of dialysis therapy and appears to still be so (Laaksonen, 2003). Diabetic neuropathy, a peripheral nerve disease in diabetes, is the most prevalent type of neuropathy in Japan and contributes to various disabled states in people with DM. Furthermore, atherosclerotic diseases such as cerebral infarction, myocardial infarction, and gangrene, though they are not specific to DM, are more prevalent and severe in patients with DM compared with patients with no DM. Figure 5 shows a schematic representation of some diabetic complications.

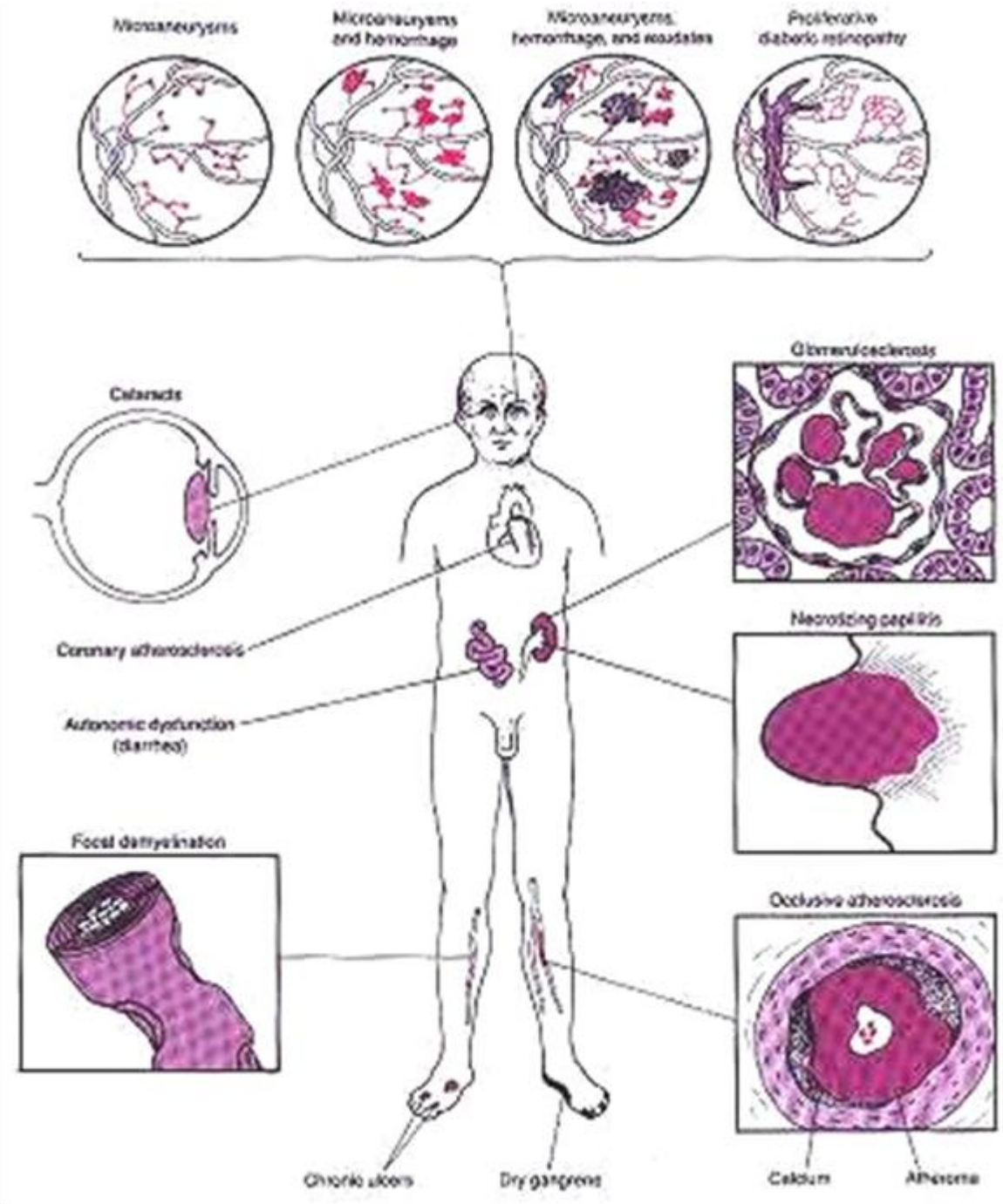

Figure 5*:* Schematic representation of some diabetic complications

(Francisco and La Rosa, 2000)

2.2.1 Pathogenesis of diabetic complications

The main lesion in diabetic complications resides in small and large vessels. The mechanism by which hyperglycemia causes vascular lesions appears to be multifactorial. The exaggerated glucose flux into vascular cells may cause a variety of metabolic derangements inside vascular cells such as activation of protein kinase C, sorbitol accumulation, and myo-inositol depletion (Laaksonen, 2003). Among these factors, evidence suggested that protein kinase C activation plays a major role in the development of diabetic complications since an inhibitor of protein kinase C is reported to be able to correct renal and retinal dysfunction in animal with diabetes (Laaksonen, 2003). It has been recently found that the inhibition of protein kinase C is able to prevent the accumulation of extracellular matrix proteins in renal glomeruli in spontaneously diabetic mice. This effect of protein kinase C inhibition appears to be transforming growth factor-beta mediated, that is, increased transforming growth factor-beta, which is a potent prosclerotic cytokine, may be protein kinase C dependent (Laaksonen, 2003). Furthermore, hyperglycemia increases the non-enzymatic glycation reaction between glucose and free amino groups in proteins, and therefore disturbs the biological function of various proteins. The products of non-enzymatic glycation such as advanced glycation end product (AGE) are known to induce various cytokines in vascular cells. These factors are likely to play some role in the development of diabetic complications (Brownlee *et al*., 2001).

Oxidative stress is increased in diabetes via either scavenger dysfunction or elevated production of reactive oxygen species. Heme oxygenase 1, which is a sensitive indicator protein for detecting oxidative stress, is increased in various tissues of experimental diabetic animals a few weeks after the induction of diabetes. Although the precise source of reactive oxygen species has not been clarified as yet, auto-oxidation of glucose per se, AGE-producing processes, mitochondrial dysfunction, and others have been reported as possible

sources. The mechanism by which oxidative stress causes diabetic complications has been extensively studied and there have been several reports suggesting that oxidative stress may injure endothelial cell function that may be related to the development of diabetic complications (Laaksonen, 2003).

2.2.2 Management of diabetic complication

Prevention or reduction in complications in the diabetic population is the most imminent issue in the field of clinical diabetology in many countries (NIH, 2008). Glycaemic control is the most effective means to prevent the appearance of diabetic complications (Laaksonen, 2003). Furthermore, a recent large-scale clinical study has indicated that blood pressure control is also effective in the prevention and treatment of diabetic complications. Tight blood pressure control (144/82 mmHg) have shown a significantly lower incidence of diabetes-related death, stroke and microvascular complications compared to those under less tight blood pressure control (154/87 mmHg) (Fang *et al*., 2004). It appears that blood pressure control may be more effective than glycaemic control in the management of various complications in T2DM. There is general agreement that diabetic patients should be more strictly controlled in respect of their blood pressure levels compared with their non-diabetic counterparts. As stated above, the pathogenic mechanisms of diabetic complications have been extensively studied, and various new therapies resulting from this basic research are under investigation (Fang *et al*., 2004).

In the early part of this century more effective and practical therapeutic means might be applied to the management of diabetic complications. However, the results from a survey recently conducted by the Ministry of Health and Welfare suggest that the majority of diabetic population have not been cared for in medical institutions in Japan however, it cannot be ascertained whether this is also the issue in Nigeria. Therefore, the most important

therapeutic means may be to encourage those diabetes patients to go to the doctor by convincing them of the importance of the regular management of DM (NIH, 2008).

2.3 Pulmonary function and Type 2 diabetes

The association between reduced lung function and DM has been described for many years (Goldman, 2003). Although the clinical significance of this association is not known, it is intriguing to think of the lung as another end organ adversely affected by DM. It is also interesting to consider that reduced lung function may be present before the clinical recognition of DM (Engstrom *et al*., 2002) or insulin resistance (Lazarus *et al*., 1998; Engstrom *et al*.,2003), suggesting that the lung may be involved in the pathogenesis of DM.

The issue of lung function and diabetes was addressed in the study by Davis *et al*., (2004). Taking advantage of an extensive population database in Western Australia, this group has conducted the largest prospective longitudinal survey to date of the pulmonary function of a cohort of patients with T2DM who had no history of lung disease. A total of 125 patients had spirometry measured at baseline and then again 7 years later. The key finding was that the average rate of decline of lung function as measured by FEV_1 was 71 ml/year compared with an expected decline in healthy nonsmokers of 25–30 ml/year. This change in lung function was similar whether or not smokers were included in the analysis, indicating its independence from smoking status. Although the follow-up group clearly represented healthy survivors, their lung function decline was still greater than expected, which would likely only underestimate the true rate of decline among all subjects with diabetes (Kaminsky, 2004). When explored by linear regression, the only predictor of reduced lung function was the level of glycaemic control. An increase of 1% in mean HbA_{1c} was associated with a decrease of 4% in predicted forced vital capacity (FVC) (Davis *et al*., 2004). Extrapolating back to 100% predicted (*i.e*., normal) lung function revealed that normal lung function predated the

diagnosis of DM by 1 to 2 years. In addition, of all factors identified, only reduced lung function was an independent predictor of all-cause mortality with a 10% reduction in FEV_1 associated with a 12% increase in all-cause mortality (Davis *et al*., 2004; Kaminsky, 2004).

This study adds to the growing body of literature that supports an association between reduced lung function and DM reviewed in Diabetes Care (Goldman *et al*., 2003). That glycaemic control may be a key factor in this association is highlighted not only by the current study, but also by the report on the Framingham Offspring Cohort, which examined the cross-sectional relationship of DM and the level of fasting glucose to pulmonary function among 3,200 subjects (Walter *et al*., 2003; Sreeja *et al*., 2003). The association of reduced lung function with other end-organ damage, such as retinopathy and renal vasculopathy (Goldman *et al*., 2003), and the improvement in lung function following intensive insulin therapy (Niranjan *et al*.,1997) further support the concept that the lung may be a target organ for damage in DM.

The study also speculated that abnormal lung function may precede the diagnosis of diabetes, suggesting that the lung may contribute to, or at least be commonly affected by, the factors involved in the pathogenesis of DM. In support of this idea are data from the Malmo Preventative Study (Engstrom *et al.,* 2003*)* and the Normative Aging Study (Lazarus *et al*., 1998). These studies found that non-diabetic subjects with reduced lung function were at higher risk of developing insulin resistance and hyperinsulinaemia. One explanation for this may be that inflammatory markers such as fibrinogen, which have been associated with reduced lung function in healthy individuals (Engstrom *et al*., 2002), have also been associated with the development of DM (Haffner, 2003).

The lung is one of the first organs to interact with the environment, so it is reasonable to expect that environmental toxins may first impinge on lung function before resulting in more

widespread effects. The link between reduced lung function and cardiovascular disease may be the elevation of serum markers of inflammation and increased insulin resistance (Engstrom *et al*., 2002; Engstrom *et al.,* 2003 Haffner, 2003). How reduced lung function relates to insulin resistance is unknown, but it has been attributed to underlying defects in skeletal muscle function (Lazarus *et al*., 1997) or to the mechanical effects of centripetal obesity both of which can affect ventilatory function (Weiss, 2001). Whatever the cause, the findings of Davis *et al*. (2004) supported the notion that lung function is an important marker of increased risk of death in patients with DM. Monitoring periodic lung function (FEV_1 and FVC) has been advocated as a general measure of overall health status as well as a prognostic indicator of premature death from all causes, including cardiovascular disease, chronic obstructive pulmonary disease, and lung cancer. If a low FEV_1 is a marker of DM or poor glycaemic control, then efforts should be focused on identifying and modifying known risk factors for cardiopulmonary disease and diabetes, such as smoking, lipid status, blood pressure, body weight, exercise, and periodontal disease. Glycaemic control should also be improved, perhaps by including use of insulin sensitizers that have been shown to reduce markers of subclinical inflammation (Haffner *et al*., 2003). If a low FEV_1 reflects a causative role played by the lungs in the development of diabetes, then optimizing lung health through smoking cessation, avoidance of irritant and toxic exposures, control of underlying airway inflammation, and promotion of physical activity seems warranted. Indeed, the spirometer should be added to the tools available for monitoring DM and its important sequelae (Kaminsky, 2004).

Hyperglycaemia in DM is known to have its effects on almost all body systems through alterations in structural and biochemical changes in tissues (Agarwal *et al*., 2009). The major cause is protein glycosylation which is responsible for thickening of basement membrane of various tissues leading to diffuse microangiopathy, demyelination and chromatolysis of axons

and Schwann cells. As the subjects with neuropathy were excluded from the study, it may be postulated that such changes in pulmonary functions might be the earliest sign of diabetic neuropathy leading to differential activation of inspiratory muscles (Goodman, 1996). Other reasons which may be ascribed are diminished elastic recoil of lungs (Sandler, 1990), some genetic factor involved for abnormal collagen structure linked to genetic predisposition of DM or age related changes in lung functions which might appear early in diabetic males than females due to some yet unexplained mechanisms (Agarwal *et al*., 2009).

A multifactorial pathophysiology that includes obesity-induced abnormalities of the chest wall, diabetic microangiopathy, and protein glycosylation may all contribute to the pulmonary end-organ effects of T2DM. Given the results of Yeh *et al* (2008) and others, the lungs are emerging as a body system that is significantly affected by T2DM. As with other end-organ disease, it is intriguing to speculate that improved glycaemic control could reduce the accelerated loss of lung function that is associated with T2DM (Teeter and Riese, 2008). Dyspnoea upon exertion in a patient with diabetes readily arouses suspicion of cardiovascular disease and/or physical deconditioning. The first development is the cumulative data that demonstrated a pattern of modest lung restriction in T2DM qualitatively similar to that in type 1 DM, with proportional decreases in FVC and FEV_1 that are directly related to glycaemia (Walter *et al*., 2003; Davis *et al*. 2004; Kaminsky *et al*., 2010). The FEV_1 is the maximum volume of air that can be forcibly blown out in the first second during the FVC manoeuvre, it is measured in litres. Along with FVC it is considered one of the primary indicators of lung function, a corresponding reduction in lung diffusing capacity (DLCO) (Davis *et al*. 2004), the primary noninvasive measure of alveolar gas exchange capacity. As the prevalence of T2DM approaches epidemic proportions and pulmonary function emerges as an independent predictor of incident DM, pathophysiology of lung involvement also assumes greater relevance (Davis *et al*. 2004).

The pathogenesis of diabetic complications is still a matter of debate and is thought to involve both a microangiopathic process and non-enzymatic glycosylation of tissue proteins (Marvisia *et al*., 2001). This process results in impaired collagen and elastin cross-linkage with a reduction in strength and elasticity of connective tissue. The presence in the lung of an abundant connective tissue and an extensive microvascular circulation raises the possibility that lung may be a 'target organ' in patients diabetes (Sandler, 1990; Marvisia *et al*., 2001).

2.4 Cardiovascular parameters and Type 2 diabetes

Blood pressure control has been reported to reduce the risk of cardiovascular disease among people with DM by 33 to 50 percent and the risk of microvascular complications—eye, kidney, and nerve diseases by about 33 percent (NIH, 2011). In general, for every 10 mmHg reduction in systolic blood pressure, the risk for any complication related to DM is reduced by 12 percent (NIH, 2011). No benefit of reducing systolic blood pressure below 140 mmHg has been demonstrated in randomized clinical trials (NIH, 2011). Reducing diastolic blood pressure from 90 mmHg to 80 mmHg in people with DM reduces the risk of major cardiovascular events by 50 percent (NIH, 2011).

Hyperinsulinaemia was associated with the incidence of hypertension and dyslipidaemia in the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) cohort of middle-aged men. Obesity and abdominal fat distribution also have a well-described association with hypertension (Harris *et al*., 2000; Juhaeri *et al*., 2002). Hypertension is a classic cardiovascular risk factor, as has been demonstrated by both longitudinal cohort studies and blood pressure medication trials (Psaty *et al*., 1997; Hung *et al*., 2004). However, the magnitude of the decrease in coronary morbidity and mortality is less than what would be predicted by epidemiological studies. This has been speculated to be due in part to adverse effects of (high-dose) diuretics and (non-selective) beta-blockers on insulin resistance,

dyslipidaemia and other factors related to the metabolic syndrome, or alternatively, that only part of the mortality associated with hypertension is due to blood pressure itself. Hypertension is also an independent risk factor for T2DM (Mykkanen *et al*., 1994; Perry *et al*., 1995).

Many other factors have also been found to be associated with the metabolic syndrome (Liese *et al*., 1998), including other lipid, lipoprotein and apolipoprotein abnormalities, such as increased small dense LDL lipoprotein (Festa *et al*., 1999), elevated apolipoprotein B and decreased apolipoprotein A-2 concentrations, haemostatic factors including fibrinogen (Sakkinen *et al*., 2000; Temelkova- Kurktschiev *et al*., 2002), inflammatory factors including C-reactive protein (CRP) (Chambers *et al*., 2001; Hak *et al*., 2001; Temelkova-Kurktschiev *et al*., 2002), hyperuricaemia (Costa *et al*., 2002), hyperleptinaemia (Jansson *et al*., 2002), endothelial dysfunction (Balletshofer *et al*., 2000), sleep apnea (Vgontzas *et al*., 2000) and alterations in sex homones including decreased testosterone levels in men, increased androgen levels in women and decreased sex hormone binding globulins in both sexes (Stellato *et al*., 2000; Jansson *et al*., 2002). Microalbuminuria has also been proposed to be related to the metabolic syndrome (Hodge *et al*., 2001; Mykkanen *et al*., 1994).

For the purpose of a general definition, however, abdominal obesity, disturbances in insulin and glucose metabolism, dyslipidaemia and hypertension as core components have been considered most appropriate (Alberti and Zimmet, 1998). Microalbuminuria was originally proposed by the WHO as a core component of the metabolic syndrome. Microalbuminuria in non-diabetic individuals is uncommon (Isomaa *et al*., 2001), however, and inclusion of microalbuminuria as a core component is controversial (Balkau and Charles, 1999). The National Cholesterol Education Program (NCEP) considered similar core components in their

clinically oriented definition of the metabolic syndrome, but did not include a measure of insulin resistance or hyperinsulinaemia, nor did they include microalbuminuria.

2.5 Anthropometric parameters and diabetes

Overweight and an abdominal fat distribution

The most widely used measure of adiposity is the BMI (kg/m2), which is dependent of height. Despite its crudeness, BMI provides a good index of overall adiposity at the population level (WHO, 2000). Somewhat more accurate calculations of percent body fat may be obtained from skinfold measures and bioelectrical impedance, but these measures require sex and age dependent norms that may vary from population to population. The most accurate and widely used measurements of adiposity are currently obtained through underwater weighing and dual-energy X-ray absorptiometry, although these methods are not practical for most epidemiological studies. The WHO and the National Institute of Health have defined overweight as BMI 25 kg m-2, and obesity as BMI 30 kg· m- 2 (National Institutes of Health. National Heart, 1998; WHO, 2000).

An abdominal distribution of fat appears to be particularly deleterious (Rexrode *et al*., 1998; Folsom *et al*., 2000). Waist and the waist-hip ratio are the most common anthropometric measures of abdominal fat distribution. Waist girth and even BMI correlate better than the waist-hip ratio with CT or MRI measures of abdominal obesity (Seidell *et al*., 1987). It has been suggested that the use of waist circumference should be preferred over waist-hip ratio (National Institutes of Health. National Heart, 1998; WHO, 2000), although the waist-hip ratio may offer additional information affecting health outcomes not related to abdominal fat distribution (Han *et al*., 1998). It should be noted, however, that as obesity increases, abdominal obesity also generally increases. Even BMI alone correlates nearly as well as waist circumference with abdominal fat as measured by computed tomography (Seidell *et al*.,

1987). Cut-offs of 94 cm and 102 cm for waist circumference has been suggested as action levels for intervention in men. These cut-offs are based on a large cross-sectional population based study in the Netherlands, in which those cutoffs corresponded to BMIs of 25 and 30 kg· m-2, and were associated with increased prevalence of chronic diseases and cardiovascular risk factors (Lean *et al*., 1998).

Visceral abdominal fat has been reported to be associated with insulin resistance independently of total body fat or subcutaneous abdominal fat (DeNino *et al*., 2001; Ross *et al*., 2002), but many other studies have found that subcutaneous abdominal adipose tissue is as strong or stronger correlate of insulin resistance (Abate *et al*., 1995; Hung *et al*., 2004). Adiposity and an abdominal fat distribution have also consistently loaded onto the factor explaining the greatest variance and having heavy loadings by measures of insulin and glucose metabolism in epidemiological studies employing factor analysis (Chen *et al*., 1999; Snehalatha *et al*., 2000; Hodge *et al*., 2001; Lindblad *et al*., 2001). Although insulin resistance has been considered to be the underlying abnormality of the metabolic syndrome, overweight and obesity are clearly the main triggering factors (Liese *et al*., 1998). An abdominal distribution of fat as measured by waist girth or waist-hip ratio has predicted cardiovascular endpoints even after adjustment for BMI (Folsom *et al*., 2000). Interestingly, the independent contribution of waist circumference or waist-hip ratio over BMI to the development of diabetes is not so clear (Chen *et al*., 1999; Wei *et al*., 1997).

2.6 Biochemical disorders and diabetes

For every biological process, there is a chemical explanation. Biochemical disorders involve an abnormality in the normal chemical processes within the tissues of T2DM patients. These lead to alteration in some vital biochemical substances which play a role in the normal chemistry of the system (Gordon *et al*., 2008). The major biochemical disorders in T2DM are

in lipid profile, glycaemic control, decreased haemostatic factors including fibrinogen, decreased inflammatory factors including C-reactive protein. Others include, hyperuricaemia, hyperleptinaemia, endothelial dysfunction, sleep apnea, alterations in sex hormones including decreased testosterone levels in men, increased androgen levels in women, decreased sex hormone binding globulins in both sexes and microalbuminuria (Frohlich *et al.*, 2000; Chambers *et al*., 2001; Hak *et al*., 2001; Temelkova-Kurktschiev *et al*., 2002).

2.6.1 Aetiology of biochemical abnormalities in Type 2 diabetes

Biochemical disorders in people with T2DM are due to; abnormalities in fat metabolism , metabolic syndrome associated with altered composition of lipoproteins, resulting in increased biochemical atherogenicity (Robert and Jonathan, 2003) and direct cellular damage from hyperglycaemia (Gavin, 2008).

Abnormal Fat Metabolism

The mechanism involved in abnormal fat metabolism relates insulin resistance to the presence of atherogenic dyslipidaemia. It was thought that insulin-resistant fat cells may increase the breakdown of triglycerides (TG) with release of free fatty acids into the circulation. Increased concentrations of free fatty acids cause fatty infiltration of liver, muscle and possibly pancreatic beta-cells (Kalofoutis *et al*., 2007; Gavin, 2008), this contributes to exacerbating insulin resistance in liver and muscle. This potentially reduces insulin secretion after long-term free fatty acid exposure. In the liver, increased TG synthesis and secretion of very low density lipoprotein (VLDL) increase fasting TG blood levels, through cholesteryl ester transfer protein (CETP), TGs from VLDL are exchanged for cholesterol found in HDL-c. VLDL becomes more cholesterol-rich, and the HDL particle becomes more cholesterol-depleted (low HDL-c). TG-rich LDL subsequently undergoes

hydrolysis by hepatic lipase or lipoprotein lipase; small dense LDL particles are produced, which are thought to be more atherogenic.

Direct Cellular Damage from Hyperglycaemia

In people with DM, all cells are bathed in blood that contains elevated levels of glucose. Most cells still manage to keep their internal glucose at normal levels, certain cells, particularly endothelial cells that line arteries and the capillaries of the retina and kidney - are unable to regulate glucose (Laaksonen, 2003), they therefore develop high internal levels of the sugar, which they cannot completely metabolize. As a result, glucose-derived "intermediate" metabolic products accumulate inside these cells; they activate pathways of cellular damage that can eventually lead to blindness and other complications.

Atherogenic biochemical disorders are the major risk factors predisposing patient with diabetes to cardiovascular diseases (Robert and Jonathan, 2003). This biochemical disorders manifested in lipid, lipoprotein and apolipoprotein abnormalities (Robert and Jonathan, 2003). Three main types of lipoproteins exist: high-density lipoprotein (HDL), low-density lipoprotein (LDL) and VLDL. All three types of lipoproteins come in different sizes. Each type contains a mixture of cholesterol, protein and triglyceride, but in varying amounts. LDL contains the highest amount of cholesterol. HDL contains the highest amount of protein. VLDL contains the highest amount of triglyceride, a blood fat. VLDL cholesterol is usually estimated as a percentage of triglyceride value. A normal VLDL cholesterol level is between 5 and 40 milligrams per deciliter. By lowering the triglyceride levels, one also lowers the VLDL cholesterol levels. HDL carries the so-called "good" cholesterol, large HDL removes cholesterol from the arteries while small HDL does not participate in this activity. LDL carries the so-called "bad" cholesterol. LDL comes in three sizes and the smallest size is thought to be the most dangerous type (Laaksonen, 2003). Small LDLs penetrate the artery

wall easier than large LDLs; they are also more easily trapped in the artery wall where their cholesterol can be released to cause plaque build-up. VLDLs mainly carry particles called triglycerides. Unlike HDL with one good size and one bad size, all LDL is bad. Large VLDL particles are the most dangerous. A combination of high numbers of both large VLDL particles and small HDL particles may place an individual at substantial increased risk for heart disease (Robert and Jonathan, 2003; O'ke efe and Bell, 2007).

Results from cross-sectional studies suggested that lipoprotein and apolipoprotein levels are also important cardiovascular risk factors in DM patient (O'ke efe and Bell, 2007). HDL has anti-inflammatory, antioxidant, antithrombotic and vasodilatory properties that may be relevant to this relationship (Gordon *et al*., 2008). One of the most important atheroprotective roles of HDL is reverse cholesterol transport, in which excess cholesterol in macrophage foam cells undergoes efflux and then is transported to the liver for excretion in the bile. Plasma high-density lipoprotein (HDL) levels are inversely related to the risk of atherosclerotic cardiovascular disease (Gavin 2008). In epidemiological studies employing factor analysis, fasting glucose and two-hour post-load glucose levels have also consistently associated with the factor explaining the greatest variance and having heavy loadings by measures of adiposity and fat distribution and insulin (Chen *et al*., 1999; Snehalatha *et al*., 2000; Lindblad *et al*., 2001). Both fasting and two-hour post-load glucose levels can therefore be considered a core component of the metabolic syndrome.

Type 1 and T2DM have a well-characterized two to four folds increased risk for CVD that is independent of known cardiovascular risk factors (Laakso, 2001). IFG and IGT also predict cardiovascular mortality (Gabir *et al*., 2000a). There is a graded increase in the cardiovascular risk of fasting and two hour post load glucose levels even in the normal range (Coutinho *et al*., 1999). Both IFG and IGT are strong predictors of future diabetes (Gabir *et*

al., 2000b). Low fasting serum HDL cholesterol levels and hypertriglyceridemia are consistently associated with the other components of the metabolic syndrome (Mykkanen *et al*., 1994). Other lipid subfractions such as apolipoprotein A1 and B levels, small dense LDL cholesterol and HDL subfractions are associated with the metabolic syndrome as well (Mykkanen *et al*., 1994; Liese *et al*., 1998).

Dyslipidemia has predicted the incidence of T2DM in several studies (Haffner *et al*., 1990; Perry *et al*., 1995). Low HDL cholesterol levels are a well established risk factor for CVD (Boden, 2000). The independent role of triglycerides as a cardiovascular risk factor is more controversial, although a meta-analysis suggests that triglycerides are an independent risk factor. The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial showed a decrease in cardiovascular events in men with low HDL cholesterol levels but normal LDL cholesterol levels who were treated with gemfibrozil, gemfibrozil is an HDL-elevating and triglyceride lowering drug, this study offers additional support for the importance of triglyceride and HDL levels as cardiovascular risk factors (Rubins *et al*., 1999).

Metabolic syndrome

Metabolic syndrome is a clustering of risk factors which includes hyperinsulinaemia, hypertension**,** obesity, hypertriglyceridaemia and impaired glucose tolerance. It is a strong predictor of coronary artery disease (CAD) (Adeniyi *et al*., 2007). NCEP set of guidelines to definition of metabolic syndrome were; elevated waist circumference for men equal to or greater than 40 inches (102 cm) and women equal to or greater than 35 inches (88 cm), elevated triglycerides equal to or greater than 150 mg/dL, reduced HDL ("good") cholesterol less than 40 mg/dL in men and less than 50 mg/dL in women. Elevated blood pressure ≥ 130/85 mm Hg or use of medication for hypertension, elevated fasting glucose ≥ 100 mg/dL

(5.6 mmol/L) or use of medication for hyperglycemia and WHR >0.90 or BMI 30 kg· m-2 (Laaksonen, 2003).

2.7 Relationship between the anthropometric, cardiovascular and biochemical parameters of individuals with diabetes

An abdominal distribution of fat appears to be particularly deleterious (Rexrode *et al*., 1998; Folsom *et al*., 2000). Abdominal fat can be divided into subcutaneous and visceral compartments that can be assessed with computed tomography or magnetic resonance imaging. Mainly experimental evidence suggests that abdominal obesity may mediate its deleterious effects on carbohydrate and lipid metabolism through the increased lipolytic activity of especially omental fat, which drains directly into the portal-venous system (Bjorntorp, 1991). This in turn results in higher non-esterified fatty acid concentrations, with consequent insulin resistance in the liver and skeletal muscle and dyslipidemia. According to this "portal hypothesis", because of the higher lipolytic activity of visceral than subcutaneous abdominal fat, visceral fat should be more closely associated with insulin resistance and its associated metabolic derangements (Bjorntorp, 1991). The pathophysiological significance of these subdivisions is unclear (DeNino *et al*., 2001).

The concept of ectopic fat deposition has been developed (Shulman, 2000). In addition to the quantity of abdominal subcutaneous and visceral fat, the degree of lipid storage in skeletal muscle and liver has also been shown to be powerful determinants of insulin sensitivity. Peripheral adipocytes have limited reserves for storing fat. Those reserves in turn depend in part on genetic and environmental factors. As the ability of the peripheral adipocyte to store fats exceeded, the fat cells become insulin resistant, resulting in increased lipolysis and release of fatty acids into the blood stream, and decreased uptake of fatty acids. This in turn

results in not only abdominal subcutaneous and visceral fat deposition, but also storage of lipids in liver and skeletal muscle (Laaksonen, 2003).

Triglyceride accumulation in the liver results in decreased hepatic insulin sensitivity and increased very low density lipoprotein (VLDL) production, which results in increased transfer of cholesterol esters from high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol to VLDL cholesterol in exchange for triglyceride (Ginsberg, 2000). This in turn impairs reverse cholesterol transport and results in a decrease HDL levels, a shift in balance to HDL3 cholesterol, and a shift from large buoyant LDL particles to small dense LDL particles. Increased hepatic insulin resistance also results in inappropriate gluconeogenesis postprandially (Laaksonen, 2003).

Skeletal muscle is a major determinant of whole-body glucose disposal (Kelley and Mandarino, 2000). More recent evidence suggests that intramuscular lipid deposits play a major role in decreasing glucose uptake in skeletal muscle (Ginsberg, 2000; Shulman, 2000). Intramuscular lipids appear to decrease glycogen synthesis and impair glucose transport by activating protein kinase C, which results in a cascade that phosphorylates insulin substrates 1 and 2, impairing the insulin receptor's ability to activate phosphatidylisositol kinase 3 and ultimately impairing glucose transport into the cell. Paradoxically, the ability to utilize fatty acids as an energy source in the resting state is impaired in insulin resistance, whereas in insulin-stimulated states, glucose oxidation is impaired (Kelley and Mandarino, 2000). As the metabolic syndrome becomes more severe, interplay between genetic susceptibility, insulin resistance and diet may lead to progressive cell failure and impaired insulin secretory capacity (Hu *et al*., 2001). As cell secretory capacity declines, impaired glucose tolerance (IGT) develops. IGT is common in older persons, up to 25% of individuals of European descent. Roughly 5-10% of persons with IGT convert to frank diabetes yearly, again with

weight gain, diet, genetic susceptibility and insulin resistance contributing to the progressive cell failure (Laaksonen, 2003).

The manifestations of cardiovascular risk factors such as dyslipidemia, hypertension, endothelial dysfunction, inflammation, hypercoagulability and impaired fibrinolysis, obesity and abnormal insulin and glucose metabolism predispose persons with the metabolic syndrome to development of another important end-stage consequence of the metabolic syndrome, cardiovascular disease (Liese *et al*., 1998). Disturbances in the adrenal-pituitary axis, inflammation and abnormal sex steroid metabolism (Laaksonen,, 2003) have all been proposed to contribute to or exacerbate the development of the metabolic syndrome, but evidence for these abnormalities as the primary mechanism for the pathogenesis of the metabolic syndrome is insufficient. Adipose tissue also produces hormones, cytokines and other peptides such as angiotensinogen, adipsin, acylation stimulating protein, adiponectin, retinol-binding protein, leptin, resistin, tumor neurosis factor, interleukin 6, plasminogen activator inhibitor-1 that may play a role in insulin resistance, inflammation and the development of diabetes and CVD (Pradhan and Ridker, 2002).

The pathophysiology behind the association of obesity and insulin resistance with hypertension is also poorly understood. Contributing mechanisms include resistance to insulin-mediated vasodilation and endothelial dysfunction (McFarlane *et al*., 2001), hyperinsulinemia mediated increased sodium and water absorption (Montani *et al*., 2002) and activation of the sympathetic nervous system (Montani *et al*., 2002). Environmental and genetic factors contribute to both the development of overweight and the propensity for insulin resistance and ectopic fat deposition and other manifestations of the metabolic syndrome Environmental factors include sedentary lifestyle and poor physical fitness (World Health Organization, 2000; Uusitupa, 2001), diet (Hu *et al.* 2001; Uusitupa 2001), low

childhood and adult socioeconomic status (Lawlor et al., 2002) and low birth weight an rapid childhood growth (Eriksson *et al*., 2002).

Results from cross-sectional studies suggested that lipoprotein and apolipoprotein levels are also important cardiovascular risk factors in DM patients (O'ke efe and Bell, 2007). HDL has anti-inflammatory, antioxidant, antithrombotic and vasodilatory properties that may be relevant to this relationship (Gordon *et al*., 2008). One of the most important atheroprotective roles of HDL is reverse cholesterol transport, in which excess cholesterol in macrophage foam cells undergoes efflux and then is transported to the liver for excretion in the bile. Plasma high-density lipoprotein (HDL) levels are inversely related to the risk of atherosclerotic cardiovascular disease (Gavin 2008). In epidemiological studies employing factor analysis, fasting glucose and two-hour post-load glucose levels have also consistently associated with the factor explaining the greatest variance and having heavy loadings by measures of adiposity and fat distribution and insulin (Chen *et al*., 1999; Snehalatha *et al*., 2000; Lindblad *et al*., 2001). Both fasting and two-hour post-load glucose levels can therefore be considered a core component of the metabolic syndrome.

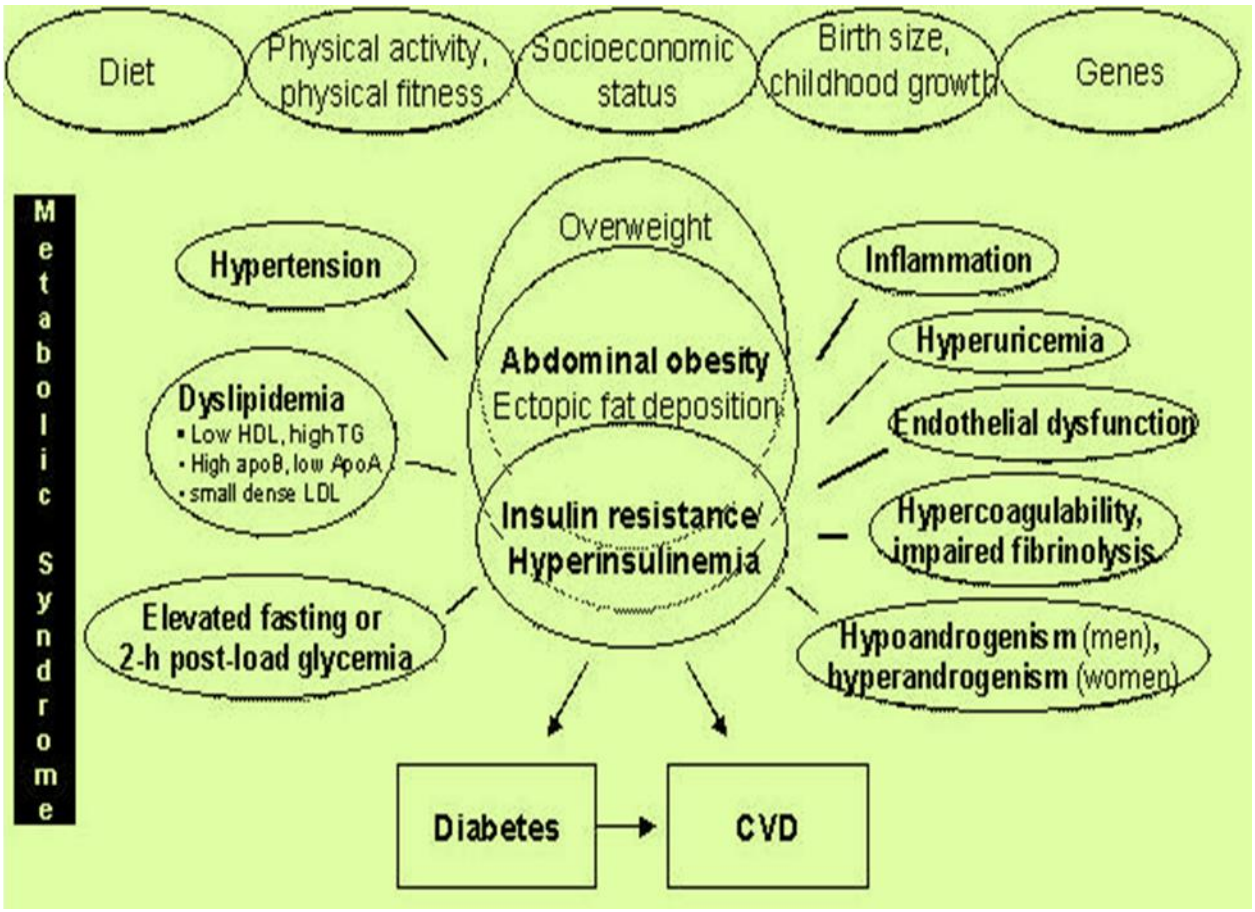

Figure 6: Schematic representation of the relationship between the anthropometric, cardiovascular and biochemical parameters of diabetic individuals (Laaksonen, 2003)

2.8 Management of diabetes mellitus

Before the discovery of insulin in 1921, everyone with type 1 DM died within a few years after diagnosis (NIH, 2008). Although insulin is not considered a cure, its discovery was the first major breakthrough in DM treatment. Today, healthy eating, physical activity, and taking insulin are the basic therapies for type 1 DM (National Center for Chronic Disease Prevention and Health Promotion, 2006). The amount of insulin must be balanced with food intake and daily activities. Blood glucose levels must be closely monitored through frequent blood glucose checking. People with DM also monitor blood glucose levels several times a year with a laboratory test called the HA_{1C}. Results of the HA_{1C} test reflect average blood glucose over a 2- to 3-month period (American Diabetes Association, 2003b).

Various drugs for DM work in different ways to lower blood sugar. Most of these drugs work by stimulating the pancreas to produce and release more insulin (Dipeptidyl-peptidase 4 (DPP-4) inhibitors, Glucagon-like peptide 1 (GLP-1) agonists, Meglitinides, Sulfonylureas), some work by Inhibiting the production and release of glucose from the liver (biguanide (metformin), Thiazolidinediones), others work by locking the action of stomach enzymes that break down carbohydrates or make tissues more sensitive to insulin **(**Alpha-glucosidase inhibitors) (Nathan *et al*., 2009). However, most of these drugs have numerous side effects which are either positive or negative. New classes of medications and numerous combinations have been demonstrated to lower glycaemia, current-day management has failed to achieve and maintain the glycaemic levels most likely to provide optimal healthcare status for people with diabetes (Nathan *et al*., 2009). Some experimental studies done on rat using seeds, fruit and leaf extract to address hyperglycaemia has also shown positive lowering effects of these extracts on blood glucose level and inference has been drawn on the likely possibility of them to have similar effect on human (Osinubi *et al*., 2003; 2005; 2006; 2007; 2008).

Healthy eating, physical activity, and blood glucose testing are the basic management tools for T2DM. In addition, many people with T2DM may require one or more diabetes medicines-pills, insulin, and other injectable medicine-to control their blood glucose levels. Adults with DM are at high risk for cardiovascular disease (CVD) (Kalofoutis *et al*., 2007). In fact, at least 65 percent of those with diabetes die from heart disease or stroke (ACSM and ADA, 2010). Managing DM is more than keeping blood glucose levels under control (American Diabetes Association, 2003a), it is also important to manage blood pressure and cholesterol levels through healthy eating, physical activity, and the use of medications, if needed (American Diabetes Association, 2003a). By doing so, those with diabetes can lower their risk.

People with diabetes must take responsibility for their day to day care. Much of the daily care involves keeping blood glucose levels from going too low or too high. When blood glucose levels drop too low, a condition known as hypoglycemia, a person can become nervous, shaky, and confused. Judgment can be impaired, and if blood glucose falls too low, fainting can occur (American Diabetes Association, 2003a). A person can also become ill if blood glucose levels rise too high.

2.8.1 Goals of management

The goal of DM management is to keep levels of blood glucose, blood pressure, and cholesterol as close to the normal range as safely possible (NIH, 2008). A major study, the Diabetes Control and Complications Trial (DCCT), sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), showed that keeping blood glucose levels close to normal reduces the risk of developing major complications of type 1 DM. The United Kingdom Prospective DM Study, a European study completed in 1998, showed that

intensive control of blood glucose and blood pressure reduced the risk of blindness, kidney disease, stroke, and heart attack in people with T2DM.

T2DM is a chronic, progressive disease that has no established cure (Kalofoutis *et al.,* 2007), but does have well-established treatments which can delay or prevent entirely the formerly inevitable consequences of the condition. Often, the disease is viewed as progressive since poor management of blood sugar leads to a myriad of steadily worsening complications (Kalofoutis *et al.,* 2007). However, if blood sugar is properly maintained, then the disease is effectively cured, that is, patients are at no heightened risk for neuropathy, blindness, or any other high blood sugar complication. There are two main goals of treatment (NIH, 2008): reduction of mortality and concomitant morbidity (from assorted diabetic complications) and preservation of QoL.

The first goal can be achieved through close glycaemic control (i.e., to near 'normal' blood glucose levels) (Santaguida *et al.,* 2005,); the reduction in severity of diabetic side effects has been very well demonstrated in several large clinical trials and is established beyond controversy (Santaguida *et al.,* 2005 Tuomilehto *et al.,* 2001; Knowler *et al.,* 2002) . The second goal is often addressed (in developed countries) by support and care from teams of diabetic health workers (usually physician, physiotherapists, nurse, dietitian or a certified diabetic educator). Endocrinologists, family practitioners, and general internists are the physician specialties most likely to treat people with DM. Knowledgeable patient participation is vital to clinical success, and so patient education is a crucial aspect of this effort (Kalra *et al.,* 2007). T2DM is initially treated by adjustments in diet and exercise, and by weight loss, most especially in obese patients (Bray *et al.,* 2002; ACSM and ADA, 2010). The amount of weight loss which improves the clinical picture is sometimes modest (2–5 kg or 4.4-11 lb) (Bray *et al.,* 2002), this is almost certainly due to currently poorly understood

aspects of fat tissue activity, for instance chemical signaling (especially in visceral fat tissue in and around abdominal organs) (Ronald *et al.,* 2007; Gordon *et al.,* 2008).

In many cases, such initial efforts can substantially restore insulin sensitivity. In some cases strict diet can adequately control the glycaemic levels (Yeh *et al.,* 2008). Treatment goals for patients with T2DM are related to effective control of blood glucose, blood pressure and lipids to minimize the risk of long-term consequences associated with diabetes. They are suggested in clinical practice guidelines released by various national and international diabetes agencies. The targets are: HAb1c of 6 % to 7.0 %, preprandial blood glucose: 4.0 to 6.0 mmol/L (72 to 108 mg/dl)(Brown *et al.,* 2003), two hour postprandial blood glucose: 5.0 to 8.0 mmol/L (90 to 144 mg/dl) (Clinical Practice Guidelines, 2008). In older patients, clinical practice guidelines by the American Geriatrics Society states "for frail older adults, persons with life expectancy of less than 5 years, and others in whom the risks of intensive glycaemic control appear to outweigh the benefits, a less stringent target such as [HbA1c of 8%] is appropriate".

2.8.2 Dietary management

Modifying the diet to limit and control glucose (or glucose equivalent, e.g., starch) intake, and in consequence, blood glucose levels, is known to assist T2DM patients, especially early in the course of the disease's progression. Additionally, weight loss is recommended and is often helpful in persons suffering from T2DM for the reasons discussed above (Lovejoy, 2002; Bray *et al.,* 2002). Several dietary modifications using dietary supplements are sometimes recommended to those with T2DM; there are studies suggesting that there is some beneficial effect for some of these (Saul and Hoffer, 2003).

2.8.3 Therapeutic exercise as physiotherapy modality in the management of Type 2 diabetes

The popular perception is that the role of physiotherapy is limited to management of DM complications such as neuromusculoskeletal problems which include cervical spondylosis, low back pain, joint stiffness, frozen shoulder, sensory neuropathy, weight gain, general debility, pectoral weakness, plantar fascitis/calcaneal spur, diaphragmatic weakness among others (Kalra *et al.,* 2007). However, physiotherapy plays a pivotal role in the prevention and management of diabetes apart from its complications (Kalra *et al*., 2007). Therapeutic exercise is a cornerstone of DM management prescribed and supervised by the physiotherapists. Physiotherapist holds a place of importance in helping people with DM to lead a better QoL through various therapeutic exercise interventions (Kalra *et al*., 2007; Ronald *et al*., 2007).

In September 2007, a joint randomized controlled trial by the University of Calgary and the University of Ottawa found that "Either aerobic or resistance training alone improves glycaemic control in T2DM, but the improvements are greatest with combined aerobic and resistance training than either alone (Ronald *et al.,* 2007). The combined program reduced the HbA1c by 0.5 percentage point. Other studies have established that the amount of exercise needed is not large or extreme, but must be consistent and continuing (Shephard *et al.,* 2001; Tuomilehto *et al.,* 2001; Williams *et al.,* 2001; Knowler *et al.,* 2002). Examples might include a brisk walk on every other day, cycling on bicycle ergometer which is an apparatus for measuring the muscular, metabolic and respiratory effects of exercise. It is a device with saddle, pedals, and some form of handlebars arranged as on a bicycle, but used as exercise equipment rather than transportation (Huo *et al*., 2006). Another aerobic exercise modality among several others is treadmill; it is an exercise machine for running or walking while staying in one place. The machine provides a moving platform with a wide conveyor belt and

an electric motor or a flywheel. The belt moves to the rear allowing a person to walk or run an equal, and necessarily opposite, velocity (Timothy and Connell, 2003).

Theoretically, exercise does have benefits in that exercise would stimulate the release of certain ligands that cause glucose transporter protein (GLUT) 4 to be released from internal endosomes to the cell membrane. Insulin though, which no longer works effectively in those afflicted with T2DM, causes glucose transporter protein GLUT 1 to be placed into the membrane. Though they have different structures, they both perform the same function of increasing intake of glucose into the cell from the blood serum. Exercise appears to acutely increase glucose uptake in part through the mechanistic action of contraction, perhaps partially mediated by increased translocation of GLUT 4 to the plasma membrane, increase tyrosine phosphorylation of the insulin receptor, insulin receptor substrate-1 is also increased (ACSM and ADA, 2010). This may explain in part increased insulin stimulated glucose transport in skeletal muscle, increase GLUT 4 protein expression and translocation, increase Insulin receptor autophosphorylation. The acute effects of exercise mostly disappear within 24 hours (ACSM and ADA, 2010).

More chronically, regular exercise appears to increase GLUT 4 protein expression and translocation, increase Insulin receptor autophosphorylation (American Diabetes Association 2003b; Ronald *et al*., 2007), increase insulin-stimulated glucose transport in skeletal muscle, and increase insulin whole body glucose disposal and glucose tolerance (Ronald *et al*., 2007). Mechanisms by which physical exercise may produce favorable changes more specifically in lipoprotein and lipid metabolism even in the absence of weight loss include decreasing hepatic triglyceride lipase activity increasing skeletal muscle lipoprotein lipase activity. Hepatic lipase activity seems to be inversely related to insulin sensitivity (ACSM and ADA, 2010) whereas skeletal muscle lipoprotein lipase activity may be positively related to insulin sensitivity.

Lifestyle interventions including regular physical activity have been shown to more than half the incidence of DM in persons with IGT (Tuomilehto *et al.,* 2001; Knowler *et al.,* 2002).Whether this would also apply to persons with the metabolic disorders such as biochemical abnormalities in general, or whether exercise alone would have a therapeutic effect has not been tested. Observational studies suggest that physical activity and cardiorespiratory fitness may decrease the risk for CVD both in people without DM and those with type 1and T2DM (Ronald *et al,* 2007; ACSM and ADA, 2010).

The relative benefit of vigorous physical activity compared with moderate-intensity physical activity has been debated. Although the trial and epidemiological data are not completely consistent, vigorous physical activity and high cardiorespiratory fitness seem to offer greater benefit against most cardiovascular and atherogenic risk factors than moderate physical activity or fitness (ACSM and ADA, 2010).

The shape of the dose-response relationship for the intensity of physical activity or cardiorespiratory fitness with respect to cardiovascular mortality in patients with diabetes has also been debated. (Shephard *et al,* 2001; Williams *et al,* 2001). Low-intensity leisure-time physical activity (LTPA) has consistently been less strongly associated with most chronic disease endpoints than moderate or vigorous exercise but may have other important functions, e.g. in weight control after weight loss in the obese (Hung *et al.,* 2004).

Anti-atherogenic effects of physical exercise on apolipoproteins B (apo B) and A-I (apo A-I) in individuals without DM have been less consistently observed, but appear to have been related mainly to weight loss (Williams *et al.,* 2001). Results from mainly small and uncontrolled studies testing the effects of regular aerobic exercise on the lipid profile in type 1 DM individuals have been variable (Bjorntorp 1991).

2.8.3.1 Exercise capacity in individuals with diabetes

Clinical and observational studies have shown that exercise capacity is a strong predictor of cardiovascular and overall mortality (Shephard *et al.*, 2001; Williams *et al.*, 2001). Patients with T2DM often complain of fatigue and reduced exercise capacity. Although these symptoms may be related to other disease conditions, such as hypertensive left ventricular (LV) hypertrophy or coronary artery disease, the presence of diabetes may independently contribute to the impaired exercise capacity. The causes of reduced exercise capacity in T2DM are unknown. Overt LV diastolic dysfunction, evidenced by abnormal transmitral flow, has been associated with impaired functional capacity in uncomplicated well-controlled T2DM (ACSM and ADA, 2010). However, primary myocardial disease may be present in many patients with T2DM, without overt systolic or diastolic dysfunction, independent of LV hypertrophy and coronary artery disease (Fang e*t al.*, 2004). Cardiac autonomic dysfunction may play an important role in the development of diabetic heart disease (Fang e*t al.*, 2004). Reduced heart rate recovery (HRR) immediately after exercise is an important indicator of cardiac autonomic dysfunction and contributes to cardiovascular morbidity and mortality in other diseases (ACSM and ADA, 2010).

Regular exercise has been recognized as an important component in the management of patients with DM. In addition to acutely lowering blood glucose, exercise training improves glucose tolerance and peripheral insulin sensitivity contributes to weight loss and reduces several risk factors for cardiovascular disease (Tuomilehto *et al*., 2001; Knowler *et al*., 2002). When proper precautions are taken to prevent hypoglycaemia, individuals with DM can enjoy the same benefits from exercise as non-diabetic healthy individuals. As a guideline, moderate intensity, aerobic endurance activities should be performed for 20 to 40 minutes at least 3 times a week (American Diabetes Association, 2003b). Blood glucose should be monitored, and insulin dose and carbohydrate intake adjusted based on the blood glucose response to the

type and duration of exercise (Ronald *et al*., 2007). During physical activity, whole-body oxygen consumption may increase by as much as 20-fold and even greater increases may occur in the working muscles. To meet its energy needs under these circumstances, skeletal muscle uses, at a greatly increased rate, its own stores of glycogen and triglycerides, as well as free fatty acids (FFAs) derived from the breakdown of adipose tissue triglycerides and glucose released from the liver. To preserve central nervous system function, blood glucose levels are remarkably well maintained during physical activity (American Diabetes Association 2003b).

Hypoglycaemia during physical activity rarely occurs in non-diabetic individuals. The metabolic adjustments that preserve normoglycaemia during physical activity are in large part hormonally mediated. A decrease in plasma insulin and the presence of glucagon appear to be necessary for the early increase in hepatic glucose production during physical activity, and during prolonged exercise, increases in plasma glucagon and catecholamines appear to play a key role (American Diabetes Association 2003b; Laaksonen, 2003). Conversely, the presence of high levels of insulin, due to exogenous insulin administration, can attenuate or even prevent the increased mobilization of glucose and other substrates induced by physical activity, and hypoglycemia may ensue. Similar concerns exist in patients with T2DM on insulin or sulfonylurea therapy; however, in general, hypoglycemia during physical activity tends to be less of a problem in this population. Indeed, in patients with type 2 diabetes, physical activity may improve insulin sensitivity and assist in diminishing elevated blood glucose levels into the normal range (American Diabetes Association 2003b).

2.8.3.2 Exercise capacity and diabetes control

Previous studies have shown that type 2 diabetes is associated with significant cardiopulmonary dysfunction (Kaminsky *et al*., 2010). The association of poor glycaemic control with worse exercise capacity in this study is consistent with a previous large study in asymptomatic type 2 diabetes (Ronald *et al*., 2007). Other studies have shown that A1C has an inverse correlation with maximum oxygen uptake, work capacity, or exercise duration (Fang *et al*., 2005; Ronald *et al*., 2007; ACSM and ADA). Importantly, chronic maintenance of near normoglycemia is associated with improved cardiopulmonary function (Fang *et al*., 2004), and exercise capacity increased 24% after improved glycaemic control was attained after initiating continuous subcutaneous insulin infusion (Fang *et al*., 2004).

The mechanism of the association between T2DM controls and exercise capacity is unclear. Poor glycaemic control has been associated with increased stiffness of large conduit vessels (Hung *et al*., 2004). The compliance of the aorta is believed to be of prime importance for modulating coronary artery blood flow, which has important consequences for myocardial work capacity and, therefore, exercise capacity. Poor DM control has been shown to be associated with subclinical LV dysfunction (Courtinho *et al*., 1999; Hung *et al*., 2004). Insulin resistance is associated with poor diabetes control, and previous studies demonstrated a negative correlation between insulin resistance and peak exercise capacity in diabetic patients (ACSM and ADA). However, impaired exercise capacity may be observed in mild and even pre-diabetic states, where insulin resistance may be an important contributor (Fang *et al*., 2004).

Glycosylation may impair the function of a number of proteins, and vascular or endothelial dysfunction may be a plausible connection between reduced exercise capacity and the metabolic disturbances associated with poor diabetes control, including abnormalities in

glucose transport and usage, increased free fatty acids, carnitine deficiency, and changes in calcium homeostasis (Fang *et al*., 2004).

2.8.3.3 Resistance training and Type 2 diabetes

Resistance exercises are activities that use muscular strength to move a weight or work against a resistive load (Ronald *et al*., 2007)**.** Clinical trials provided the strongest evidence for the value of resistance training in T2DM (ACSM and ADA). In these studies, the average age of participants was 66 years, and the resistance-training regimen involved multiple exercises at high intensity (three sets, three times per week), and absolute A1C declined 1.1–1.2% in resistance-training subjects versus no significant change in control subjects. Body composition changes were maintained, but exercise intensity and adherence were lower than in the first 6 months and the A1C difference between groups became statistically non-significant. Other published studies of resistance exercise in T2DM participants have used less intense exercise regimens (Cuff *et al.*, 2003; Kluding *et al*., 2010). Resistance training was reported to have positive changes in metabolic profile of adults with T2DM (Arora *et al*., 2009; Isharwal, *et al*., 2009.)

2.8.3.3.1 Safety of resistance training

Some medical practitioners have concerns about the safety of higher-intensity resistance exercise in middle-aged and older people who are at risk of CVD. Often, the main concern is that the acute rises in blood pressure associated with higher-intensity resistance exercise might be harmful, possibly provoking stroke, myocardial ischemia, or retinal hemorrhage (Ronald *et al*., 2007). No evidence has been found that resistance training actually increases these risks. No serious adverse events have been reported in any research study of resistance training in patients with T2DM, although the total number of subjects enrolled in these studies was small (Cuff *et al*., 2003; Arora *et al*., 2009; Isharwal, *et al*., 2009). A review of 12

resistance exercise studies in a total of 246 male cardiac rehabilitation patients found no angina, ST depression, abnormal hemodynamics, ventricular dysrhythmias, or other cardiovascular complications (Ronald *et al*., 2007). A study of 12 men with known coronary ischemia and electrocardiogram (ECG) changes inducible by moderate aerobic exercise found that even maximal-intensity resistance exercise did not induce ECG changes (Ronald *et al*., 2007). Therefore, moderate- to high-intensity resistance training was found to be safe even in men at significant risk of cardiac events.

2.9 Cardiorespiratory functions, glucose metabolism and therapeutic exercise in Type 2 diabetes

It has been demonstrated that persons with a clinical diagnosis of diabetes have impaired lung function, a finding that is consistent with previous work in this area (Davis *et al.*, 2000; Lawlor *et al*., 2004). These findings were not explained by obesity or increasing age. This relation was seen throughout the non-diabetic values of these markers of glucose autoregulation, which suggests that the relation between glucose and lung function is not just an association seen in persons with overt diabetes. A similar association was also seen between glycaemic markers and FVC but was not seen consistently with the FEV_1: FVC ratio; this suggests that the effect is primarily an effect on lung function and does not influence the development of obstructive lung disease (as seen in chronic obstructive pulmonary disease) (McKeever *et al*., 2005).

The absence of an effect of fasting plasma glucose on FEV_1 in the presence of a negative effect of increasing levels of other markers of poor glycaemic control is anomalous and difficult to explain. Over 95 percent of study population was in the non-diabetic ranges for fasting plasma glucose, and it was theorized that there may be greater random variation of fasting plasma glucose within these levels, while the other measures of glycaemic control

provide a more consistent measure of glycaemic control. Although researchers have been unable to find data in the literature to substantiate this, the association of a gradient of decreasing FEV_1 among persons with fasting plasma glucose levels in the "impaired" or diabetic ranges demonstrates a consistency with the rest of the data, suggesting that this may be the case. The mechanism by which impaired glycaemic control may lead to a reduction in lung function is uncertain, though it has been suggested that the increased systemic inflammation associated with diabetes (Arnalich *et al*., 2000) may result in pulmonary inflammation and hence airway damage (Walter *et al*., 2003). Alternatively, a reduction in antioxidant defenses resulting from increased oxidative activity associated with diabetes (McKeever *et al*., 20005) may lead to a secondary reduction in the antioxidant defenses of the lung and hence increased susceptibility to environmental oxidative insults, resulting in subsequent loss of lung function. In addition to an increase in intracellular oxidative stress, increased nuclear factor-κB, and inflammatory mediator expression, long-term hyperglycemia causes an increase in collagen molecule synthesis and cross-linking via the accumulation of advanced glycosylation end products, which may also adversely influence lung function (Brownlee, 2001). The observation that increasing insulin level and insulin resistance is associated with loss of lung function suggests that insulin may have a direct negative effect on airway function (McKeever *et al*., 2005).

Regular exercise leads to numerous and varied physiological changes that are beneficial from a health standpoint. They include improved cardio-respiratory function and skeletal muscle function; improved blood pressure, body composition, and bone improved glucose tolerance; enhanced performance of work, recreational activities and many positive psychological benefits all of which results in better quality of life (Kluding *et al*., 2010; ACSM and ADA 2010). Improved cardio-respiratory function means that the body is able to perform exercise much more efficiently. This results mainly from the body more effectively getting oxygen

into the blood stream and transporting it to the working muscles, where it is needed for the metabolic processing of energy. In other words, the regular exerciser's body is much more proficient at loading, transporting and utilizing oxygen (ACSM and ADA). He thus finds strenuous exercise far less strenuous than a person who does not exercise and is out of shape. Improvement in cardio-respiratory function has been reported not result from changes in the lung's ability to expand. In general individuals with type 2 diabetes who exercise regularly do not substantially change measures of pulmonary function such as the amount of air able to be blown out after taking the largest breath possible (FVC).

One of the largest differences between an exerciser and a non-exerciser concerns the heart's ability to pump blood and consequently deliver oxygen to working muscles (Guyton, 2000). Cardiac output is a major limiting factor for prolonged exercise. In addition, an exerciser typically has a larger blood volume, is better able to extract oxygen from the air in the lungs and is better able to extract oxygen from the blood at the working muscles than a sedentary individual is. Gas exchange involves not only oxygen delivery but also the removal of carbon dioxide, which is a byproduct of energy metabolism, and this process is also more efficient in an exerciser. Regular exercise thus produces numerous favorable changes that collectively result in the body being able to work in a far more efficient manner.

In intervention studies in persons without diabetes, aerobic physical exercise has in variable degrees and at least in the short term decreased weight and visceral fat accumulation (Hung *et al*., 2004), improved insulin sensitivity (Slentz *et al*., 2009), increased HDL cholesterol and decreased triglyceride levels and decreased blood pressure (ACSM and ADA, 2010) in addition to increasing cardiorespiratory fitness. These changes have often occurred independently of weight loss, although it is not completely clear how much of these favorable effects are independent of weight loss and changes in body composition. The mechanisms by which exercise may increase insulin sensitivity independently of weight loss are only partly

understood. Exercise appears to acutely increase glucose uptake in part through the mechanistic action of contraction, perhaps partially mediated by increased translocation of glucose transporter protein (GLUT) 4 to the plasma membrane (Baldi *et al*., 2010). Tyrosine phosphorylation of the insulin receptor and insulin receptor substrate-1 is also increased (Baldi *et al*., 2010), which may explain in part increased insulin stimulated glucose transport in skeletal muscle.

The acute effects of exercise mostly disappear within 24 hours. More chronically, regular exercise appears to increase GLUT 4 protein expression and translocation, insulin receptor autophosphorylation, insulin-stimulated glucose transport in skeletal muscle, whole body glucose disposal and glucose tolerance (Ronald *et al*., 2005). Other factors contributing to the mechanisms by which regular exercise may increase insulin sensitivity include effects on the interplay between skeletal muscle fiber type, oxidative capacity and intramuscular lipid content and blood flow and endothelial function. Mechanisms by which physical exercise may produce favorable changes more specifically in lipoprotein and lipid metabolism even in the absence of weight loss include decreasing hepatic triglyceride lipase activity and increasing skeletal muscle lipoprotein lipase activity. Hepatic lipase activity seems to be inversely related to insulin sensitivity, whereas skeletal muscle lipoprotein lipase activity may be positively related to insulin sensitivity (Ronald *et al*., 2005).

Lifestyle interventions including regular physical activity have been shown to more than half the incidence of diabetes in persons with IGT (Tuomilehto *et al*., 2001; Knowler *et al*., 2002). Whether this would also apply to persons with the metabolic syndrome in general, or whether exercise alone would have a therapeutic effect has not been tested.Observational studies suggest that physical activity and cardiorespiratory fitness may decrease the risk for CVD both in non-diabetic persons and those with type 1 and T2DM (Wei *et al*., 2000; ADA and

ACSM, 2010). Longitudinal cohort studies also show a decreased incidence of diabetes mellitus in persons who are fit or who engage in moderate or vigorous levels of physical activity compared to sedentary or unfit individuals (Wei *et al*., 2000; ADA and ACSM, 2010). The relative benefit of vigorous physical activity compared with moderate-intensity physical activity has been debated. Although the trial and epidemiological data are not completely consistent, vigorous physical activity and high cardiorespiratory fitness seem to offer greater benefit against most cardiovascular and metabolic risk factors than moderate physical activity or fitness.

The shape of the dose-response relationship for the intensity of physical activity or cardiorespiratory fitness with respect to cardiovascular mortality has also been debated. Some have argued that the relationship is curvilinear (Ronald *et al*., 2007; ACSM and ADA, 2010), with the most benefit gained in the low-fit or sedentary groups, whereas others have argued that at least for physical activity the relationship is linear (Williams, 2001), or even that a minimum threshold level in intensity around 6 METs is necessary for physical activity to be cardio-protective (Shephard, 2001). Low-intensity leisure-time physical activity (LTPA) has consistently been less strongly associated with most chronic disease endpoints than moderate or vigorous exercise but may have other important functions, e.g. in weight control after weight loss in the obese (Bjorntorp 1991). Based on the intervention and epidemiological evidence, the Center for Disease Control (CDC) and the American College of Sports Medicine (ACSM) have jointly published recommendations that adults engage in at least 30 min of moderate physical activity on most, and preferably all, days of the week. It is nonetheless acknowledged that further benefit may be gained by engaging in regular vigorous physical activity.

2.10 Diabetes and quality of life

When a person has a chronic disease like diabetes, their overall QoL can influence coping with their disease successfully in the short and over the long term (Borrott and Bush, 2008). Equally, the primary care management of their chronic disease can affect their overall quality of life beyond the illness itself. Therefore, being concerned about the quality of a person's life alongside clinical management of diabetes is good practice in primary care and significant to successful health care outcomes (Borrott and Bush, 2008). .

Several factors influence the QoL of a person with T2DM. These include the relationship between the patient and their health care givers, the individual's personality characteristics such as optimism and negative affectivity and acquisition of self-management skills and health behaviours. Effective T2DM management and improved QoL of individuals' are interrelated. The measurement of QoL is an important component in continuous improvement of chronic disease management in primary care settings. Although QoL has been defined in several different ways it is almost always regarded as being multidimensional and having several contributing factors. It is also usual to understand QoL from the individual's perspective. The multidimensionality of QoL has been described by Rose *et al*., (2002) and its elements are outlined along with influencing factors. Health Related Quality of Life (HRQOL) usually includes physical, psychological and social components and is influenced by aspects of the primary care setting such as the relationship with health professionals. It is also influenced by characteristics of the person such as self-efficacy and optimism and characteristics of the disease itself, including its progression. Knowledge and skills for self-management of the disease are by-products of these influencing factors and also contribute to HRQOL. The concept of QoL broadly encompasses how an individual measures the 'goodness' of multiple aspects of their life. These evaluations include one's emotional

reactions to life occurrences, disposition, sense of life fulfillment and satisfaction, and satisfaction with work and personal relationships (Diener *et al*., 1999).

2.11 Diabetes specific quality of life

Disease specific HRQOL is described by Polonsky (2000) as a multidimensional construct, of which each dimension can independently affect QOL. Diabetes-specific domains to be considered and included when considering HRQOL relate to how the disease is compromising an individual's sense of well-being psychologically, physically and socially. That is, what is the impact generated by diabetes on the individual, how much worry about anticipated effects of the disease occurs and how satisfied is the patient with themselves (Bradley *et al*., 1999). According to Polonsky (2000), aspects of living with diabetes such as coping styles, most elements of treatment satisfaction, and disease-related self-efficacy are more appropriately measured separately in a diabetes specific HRQOL instrument.

In summary, QoL instruments measure individuals' perceived sense of well-being, such as sense of satisfaction with life, work and personal relationships. These components are also combined with health related components of quality of life to form comprehensive HRQOL instruments. Finally, diabetes specific instruments assess individuals' HRQOL taking into account disease specific issues. The characteristics of a chronic disease like T2DM, affects a person's quality of life. Poor metabolic regulation leads to disease complications and ultimately secondary disease (National Health Priority Action Council, 2006). Yet, delivery of DM education to patients with T2DM in general practice has demonstrated significant reduced metabolic complications for patients (Deakin *et al*., 2005; Nathan *et al*., 2007; National Health Priority Action Council, 2006). The clinical parameters measured are collected by physical examination and blood pathology assay and include: Glycated

haemoglobin (HbA1c), fasting blood glucose, body weight/body mass index, blood pressure and Lipid profile.

The incidence of secondary disease processes, such as long-term complications of microvascular and macrovascular disease (CVD) (Nathan *et al*., 2007) including disorders such as diabetic nephropathy, limb ischaemia, diabetic neuropathy, diabetic autonomic neuropathy (National Health Priority Action Council, 2006) and periodontal disease (Diabetes Australia, 2006) is reduced when clinical parameters are stable. Decreased incidence of diabetes complications lessens the likelihood of poor QoL. While an individual's sense of well-being or QoL is related to self-perception and relationships with others (Trento *et al*., 2004), QOL may also be determined by pleasant and unpleasant evaluation of life events and satisfaction with life. Personality has been found a strong and constant predictor of subjective well-being and life satisfaction (Bornstein, 1998; Diener *et al*., 1999).

The Diabetes Quality of Life Clinical Trials Questionnaire Revised (DQLCTQ-R) was developed based on feedback from focus groups, expert clinicians, and literature searches. The questionnaire was validated using data from longitudinal clinical trials, which had the added benefit of showing responsiveness to change (Shen *et al*., 1999). The DQLCTQ-R incorporates previously validated scales which enhances the comprehensiveness of the instrument. The self-administered measure was revised to include 57 items comprising eight domains, Generic: physical function, energy/fatigue, health distress, mental health; and Diabetes specific (DQOL): treatment satisfaction, treatment flexibility, frequency of symptoms, satisfaction. Scaling responses include a range of 3-10 options including: 'all the time' to 'none of the time', 'very satisfied' to 'very dissatisfied', 'never' to 'all the time', and 'does not apply' to 'all the time'. This instrument has been found to be a valid and reliable way of measuring HRQOL of people with diabetes when new or alternative treatments have

been implemented (Shen *et al*., 1999). Herman *et al*. (2005) used the Disease QoL clinical trial questionnaire to assess patients' (with T2DM) treatment satisfaction and QoL in a randomized study of continuous insulin infusions and multiple daily insulin injection.

CHAPTER THREE

MATERIALS AND METHODS

3.1 Materials

3.1.1 Subjects selection

The subjects for this study were T2DM individuals who were recruited through referral from physicians at the Lagos University Teaching Hospital, Idi-Araba, Lagos and Lagos State University Teaching Hospital, Ikeja, Lagos, having been diagnosed to have T2DM. Prescreening test was done to either include or exclude the subjects from the study; this was partly done using the Physical Activity Readiness Questionnaire which is a seven item questionnaire which was self-reported by the patients. It was used to assess any cardiovascular or musculoskeletal risk factors which may make the prospective participant ineligible to take part in the study. If a prospective participant answered yes to one or more questions, a medical clearance along with information about specific exercise limitations were requested for before eligibility to join the intervention group based on the inclusion criteria. If the answered to all the PAR-Q questions is no, the prospective participant is cleared and eligible to join the intervention group.

Inclusion criteria

1. The subjects involved in this study were individuals with T2DM within the age range of 20 to 75 years old without severe complications of the DM *i.e* cardiovascular, renal, visual and cerebral.
2. Individuals who were sedentary in the past six months (score ≤ 3 on the RAPA questionnaire).
3. The subjects were non-smokers and non-alcoholics.

Exclusion criteria

Individuals excluded from the study were;

1. Those with resting blood pressure greater than 160mmHg for systole and 100mmHg for diastole.
2. Those with blood glucose level greater than 250 mg/dl were not allowed to participate in the exercise session on the day of episode of hyperglycaemia.
3. Patients who were not sedentary (score above 3 on the RAPA).
4. Patients with known history of acute or chronic respiratory infections, neuromuscular disease, malignancy, cardiopulmonary diseases, or recent history of major abdominal or chest surgery.
5. Those with wounds on feet.
6. Patients with gross abnormalities of the vertebral column or thoracic cage.
7. They were individuals without musculoskeletal limitations such as rheumatoid arthritis, severe osteoarthritis, and other joint problems so as not to aggravate the symptoms of these musculoskeletal diseases.

3.2 Ethical consideration

Ethical approvals were obtained from the Research and Ethics Committee of the teaching hospitals where the subjects were recruited *i.e.,* Lagos University Teaching Hospital (LUTH), Idi-Araba, Lagos and Lagos State University Teaching Hospital (LASUTH), Ikeja, Lagos (see appendix 5). Informed consent was also obtained from all subjects who participated in this study.

3.3 Instrumentation

The instruments utilized for this study were at the two study location were duplicated, were of the model and from the same manufacturer. They included;

1. Treadmill machine model 1110, 3.5 horsepower (Daily Youth, England).
2. Bicycle ergometer, ergofit 200 (Germany).
3. Sphygmanometer, Desk Top model no. 320 (W.A. Baum Co., Copiague, NY).
4. Stethoscope (Litmann)
5. Medical microsoft hand-held digital spirometer (Schiller, Switzerland).
6. Weights and sandbags of different sizes in kilograms.
7. Glucometer, Accucheck active brand (Roche, United States of America).
8. Glucose strips, Accucheck active brand (Roche, United States of America).
9. Combined weighing scale and height meter (Seradon, England).
10. Tape rule calibrated in centimeters and inches.
11. Stop watch and timer (Moron, England).
12. Rapid assessment of physical activity (RAPA) level questionnaire.
13. Diabetes Quality of Life Clinical Trial Questionnaire-Revised (DQLCTQ-R).
14. NycoCard HbA1c reader II, Axis Shield PoC, made in Norway

3.4 Research design

The study design was a randomized control trial.

3.5 Sample size determination

N represents the sample size for the study.

The sample size for comparative research studies is derived from the formula:

$$N = \frac{4\delta^2 (Zcrit + Zpower)^2}{D^2}$$ (John, 2003; Uitenbroek, 2003)

Zcrit = is the desired significance criterion at 0.05 = 1.960

Zpwr = is the desired statistical power at 80% = 0.842

D = is the minimum expected difference between two means of VO_2max values which is 28.41 kg/ml/min - 18.94 kg/ml/min, based on results from preliminary study.

δ = is the assumed SD of each group based on preliminary study= 6.753kg/ml/min.

$$N = \frac{4(6.753)^2 (1.960 + 0.842)^2}{(28.41-18.94)^2}$$

= 15.96

= 16

Each of the group should therefore have a minimum sample size of 16. All subjects in the three groups should not be less than 48.

3.6 Sampling technique

Sixty (64) consecutively referred individuals with T2DM were screened for eligibility and randomly assigned to the treatments and control groups. Subjects were made to pick from a bag which contained papers on which various groups have been written. The subjects were assigned to the group based on the paper picked. Four subjects who started the study could not attend the exercise sessions regularly at the frequency specified for this study due to their work schedules making the attrition rate 6.25%. Their data was therefore excluded from the data analyzed for this study.

Group I: Subjects who performed aerobic exercises on treadmill combined with resistance exercises.

Group II: Subjects who performed aerobic exercises on bicycle ergometer combined with resistance exercises.

Group III: Subjects who did not undergo exercise intervention, but who participated in educational sessions only.

3.7 Experimental procedures

Individuals with diabetes' previous activity level were assessed using the rapid assessment of physical activity (RAPA) level questionnaire adopted from a study by Topolski *et al*., (2006). Their background physical activity level was defined based on the score obtained from the total score of 10 points of the RAPA questionnaire. Only subjects with scores between 1-3 points which denoted sedentary and under-active life style were recruited for the study (appendix 1). All subjects maintain their medication and diet throughout the study period.

Sixty individuals with T2DM who qualified were randomly allocated into three groups as stated in the sampling technique above. The QoL of the subjects was assessed at baseline and at the end of 4^{th}, 8th and 12^{th} week of the intervention period using the DQLCTQ-R (appendix 2). The self-administered questionnaire was revised to include 57 items comprising eight domains which included generic: physical function, energy/fatigue, health distress, mental health; and Diabetes specific QoL (DQoL): treatment satisfaction, treatment flexibility, frequency of symptoms, satisfaction. Scaling responses included a range of 3-10 options including: 'all the time' to 'none of the time', 'very satisfied' to 'very dissatisfied', 'never' to 'all the time', and 'does not apply' to 'all the time'. This instrument had been found to be a valid and reliable way of measuring Health related QoL of people with DM when new or alternative treatments have been implemented (Shen *et al*., 1999; Polonsky, 2000).

3.7.1 Interventions

The researcher of the study recruited three research assistants who were assisting with the intervention protocols. They were trained appropriately in line with the standard and protocols for the study. However, the data collection for the outcome measures was the sole responsibility of the researcher for consistency and reliability purpose.

The exercise protocols for this study were adopted protocols from previous studies; Treadmill protocol at 1% gradient (Jones and Doust, 1996; Ramsbottom *et al*., 2007; Quinn, 2010), bicycle ergometer protocol at a load of 40 watt and a revolution of 60rpm (Huo *et al*., 2006; Adeniyi *et al*., 2007) and one repetition maximum (RM) for resistance exercise intensity assessment using free weights (Adeniyi *et al*., 2007). The heart rate of the subjects was clearly displayed on the monitoring screens of the treadmill and bicycle ergometer which have bilateral sensors which determine their heart rate once held with the hands during the aerobic exercise session.

The interventions for this study were aerobics exercises on treadmill combined with resistance exercises for the study group I and bicycle ergometer combined with resistance exercises for study group II. Group III was the control group who had no exercise intervention. However, subjects in this group participated in educational sessions as given to all other subjects in groups I and II during the study period.

3.7.1.1 Warm up exercises

All subjects in groups I and II performed 10 minutes warm up exercises which constituted flexibility exercises. This involved range of motion exercises to all joints of the upper and lower limbs and trunk. The warm up exercise was done caudio-cephally, starting from the joints of the feet up to the neck. Each joint was moved at ten repetitions each.

3.7.1.2 Aerobic exercises

The mode of aerobic exercise for group I was weight bearing exercise on treadmill while the mode for group II was non-weight bearing exercise on bicycle ergometer.

Intensity

The intensity of aerobic exercise was determined as a percentage of the heart rate reserved. The maximum heart rate (MHR) was obtained from the formulas:

MHR= 220-age in years (for men)

MHR= 226-age in years (for women) (Bumgardner, 2008).

Sixty to eighty percent of the value of the heart rate reserve which is the moderate intensity range was considered for each subject as the target heart rate for exercise.

Target Heart rate= 60-80% (MHR - Resting Heart Rate) + Resting Heart Rate (ACSM, 2006).

The Borg's rate of perceived exertion was also used as a check tool; subjects were instructed to indicate how they feel based on the scale. They were encouraged to exercise at moderate intensity range at point 12- 13 of the scale which denoted "somewhat hard" (figure 7).

Duration and progression of aerobic exercises on treadmill and bicycle ergometer

Participants performed aerobic exercises on treadmill (figure 8) and bicycle ergometer (figure 9) for 20 minutes per session. They commenced exercise at 60% of their heart rate reserve from the week 0 to week 4; they thereafter progressed to 70% from week 5 to week 8 and 80% from week 9 to week 12. This was done to allow for gradual adaptation to the moderate intensity training.

Frequency of aerobic exercises on treadmill and bicycle ergometer

The aerobic exercises was distributed over 3 days per week, making up to 3 sessions with no more than 2 consecutive days without aerobic exercise per week (Laaksonen, 2003). The total aerobic sessions was thus 36 sessions for the 12 weeks of the study.

3.7.1.3 Cool down exercises

Another 5 minutes for cool down was observed by the subjects after the aerobic exercise. They performed active full range of motion exercises of all joints of their upper limbs, lower

limbs and trunk. They thereafter rested for about 10 minutes before commencing resistance exercises (Arora *et al*., 2009).

Monitoring and safety tools

1. The glucose level of the subjects was checked using glucometer before exercise training as safety precaution against hypoglycemia.
2. Borg's rate of perceived exertion was also used to monitor the exercise intensity during aerobic exercise (figure 7).
3. Glucose was provided in case of unexpected hypoglycaemia.
4. Certified cardiopulmonary resuscitator is always present at the research locations during intervention protocols.
5. There was also provision for automatic defibrillators at the research locations.

3.7.1.4 Resistance exercises

Mode

Resistance exercises of the muscle groups were done by groups I and II subjects using dumb bells and sand bags of known weights at each exercise session. The resistance regimen was done for flexors and extensors of the elbows and knees (figure 10 and 11). Weights of different sizes which depended on the one repetition maximum (1-RM) of the muscle groups were considered suitable for the resistance exercises. The 1-RM was the maximum amount of weight that can be lifted once by the muscle groups. The participants also carried out strengthening exercises for both hands using rubber balls. They were encouraged to squeeze the ball as strongly as they could (Adeniyi *et al*., 2007), making 12 repetitions per set, three sets were considered for all the muscle group to be strengthened. A set of twelve repetitions of the abdominal curl ups, back extension and bilateral straight leg raisings were also carried out by the participants at speeds comfortable to them (Adeniyi *et al*., 2007).

Intensity of Resistance Exercise

Moderate intensity resistance which was 50%–70% of 1-RM was considered (Ronald *et al*., 2005). This was determined for flexors and extensors of the elbows and knees.

Duration, Frequency and Progression

The resistance exercises session commenced 10 minutes after the cool down exercises. The subjects performed resistance exercise three times per week for 12 weeks, making a total of 36 sessions for the study period. Each session lasted for a total duration of about thirty three minutes including one minute recovery period following performance of a set of resistance exercise by each muscle group (Kluding *et al*., 2010). Twelve repetitions were done per set and three sets were performed by these subjects for each muscle group exercised. Each set was followed by one minute recovery period. Each set of resistance exercise lasted for about 25-30 seconds. They started with 50% of 1-RM of flexors and extensors of the knees and elbows while lifting the weights at 12 repetitions at three sets per session at the early stage of the study period (week 0 to week 4). They thereafter progressed to 60% of 1-RM from week 5 to week 8 of the study period and finally 70% of 1-RM from week 9 to week 12 at the same repetitions and sets for the study period (Ronald *et al*., 2005). This was done to allow for gradual adaptation to the resistance exercises and also to prevent muscle soreness. The participants also carried out strengthening exercises for both hands using rubber balls, making 12 repetitions per set for three sets (Adeniyi *et al*., 2007). Three sets of twelve repetitions for the abdominal curl ups, back extension exercise and bilateral straight leg raisings were also carried out by the participants at speeds comfortable to them (Adeniyi *et al*., 2007).

Figure 7: Borg's rate of perceived exertion scale (Ronald *et al.*, 2007)

3.7.1.5 Education and counseling sessions

All subjects recruited for this study participated in group educational sessions. These were done every other week (fortnightly) within the twelve weeks of the intervention period. The topics for the educational session included:

1. Blood glucose monitoring and record keeping.
2. Recognition and management of hypoglycaemia and hyperglycaemia.
3. Medication adjustment based on nutrition and activity schedules.
4. Weight control and diet modification including meal plan.
5. Diabetes complications.
6. The importance of diabetes control.

Study Group I

The subjects for this study group were 20 individuals.

Pre-Intervention Assessment

The intensity of aerobic exercise was determined as a percentage of their heart rate reserve. The maximum heart was obtained from the formulas:

MHR= 220-age in years (for men)

MHR= 226-age in years (for women) (Bumgardner, 2008).

Sixty to eighty percent of the value of the heart rate reserve which is the moderate intensity range was considered for each subject as the target heart rate for exercise.

Target Heart rate= 60-80% (MHR - Resting Heart Rate) + Resting Heart Rate (ACSM, 2006).

The Borg's rate of perceived exertion scale was also a check tool; subjects were instructed to indicate how they feel based on the scale (figure 7). They were encouraged to exercise at moderate intensity range at points 12- 13 of the scale which denoted "somewhat hard".

Repetition Maximum Assessment

The 1-RM was assessed in order to determine the weight which can be lifted by the muscle groups during the resistance exercise intervention programme. This assessment was done for the muscle groups using dumb bells and sand bags of known weights. The assessment was done for flexors and extensors of the knees and elbows. Fifty percent to seventy percent which is the moderate intensity range was considered.

Procedures for Intervention:

The subjects in this group exercised on treadmill for a period of 20 minutes per session (figure 8). Subjects were initially required to walk on the treadmill at a speed of 1.5km/hr and at a gradient of 0% in order to get accustom with the treadmill (Ohuchi *et al.,* 1998), progression was then made to a gradient of 1% which had been established from previous studies to correlate with outdoor walking and to compensate for the lack of air resistance in the research ground (Jones and Doust, 1996; Ramsbottom *et al*., 2007; Quinn, 2010). The speed of the treadmill was increased to 3km/hr and thereafter gradually increased by 1km/hr every two minutes until the heart rate reaches 60 - 80% of the subjects' heart rate reserve (Jones and Doust 1996). This was displayed on the screen of the treadmill. The Borg's rate of perceived exertion which is a 6-20 point scale was also a monitoring tool; subjects' rate of perceived exertion was monitored at 12-13 point which denoted "somewhat hard", this being the moderate intensity range exercise range.

The subjects undergone this aerobic exercise at a progressive moderate intensity range of 60, 70 and 80% of their heart rate reserve calculated from their maximum heart rates which was deduced based on the value obtained from the formular; 220- age in years for male subjects and 226-age in years for female subjects (Bumgardner, 2008).

The resistance exercises were done at moderate intensity of 50, 60 and 70% of the RM of the major muscle groups to be exercised. The resistance exercises were done using dumbbells and sand bags of known weights at each exercise session. Each session lasted for a total duration of about thirty three minutes including one minute recovery period following performance of a set of resistance exercise by each muscle group (Kluding *et al.*, 2010). Twelve repetitions were done per set and three sets were performed by these subjects for each muscle group exercised followed by one minute recovery period. Each set of resistance exercise lasted for about 25-30 seconds. The resistance regimen was performed for flexors and extensors of the elbows and knees using weight of different sizes depending on the previously determined RM (figure 10 and 11). The participants also carried out strengthening exercises for both hands using rubber balls. They were encouraged to squeeze the ball as strongly as they could; making 12 repetitions at three sets (Adeniyi *et al*., 2007). A set of twelve repetitions of the abdominal curl ups, back extension and bilateral straight leg raisings were also carried out by the participants at speeds comfortable to them (Adeniyi *et al*., 2007).

Intervention duration and progression: The total intervention period for this study group was 12 weeks.

From week 0 to week 4: The subjects undergone 60% moderate intensity aerobic exercises combined with 50% moderate intensity resistance exercises.

From week 5 to week 8: The subjects progressed to 70% moderate intensity aerobic exercises combined with 60% moderate intensity resistance exercises.

From week 9 to week 12: Progression was made to 80% moderate intensity aerobic exercises combined with 70% moderate intensity resistance exercises.

Outcome measures: The outcome measures for this study group included: cardiovascular parameters (arterial systolic blood pressure and diastolic blood pressure, rate pressure product); pulmonary parameters [oxygen uptake (VO_2max), forced vital capacity and forced

expiratory volume in 1 second], and the anthropometric parameters [body mass index (BMI), waist circumference and waist hip ratio]. The subjects were assessed based on these outcome measures at the baseline, at the end of 4^{th}, 8^{th} and 12^{th} week of the study period. The QoL of the subjects were also assessed at baseline and at the end of 4th, 8^{th} and 12^{th} week of the study period using the DQLCTQ-R. Biochemical parameter (HbA1C) was assessed at baseline and 12^{th} week post intervention.

Study Group II

The subjects for this study group were 20 in number.

Pre-Intervention exercise Assessment

The intensity of aerobic exercise was determined as a percentage of the heart rate reserve.

The maximum heart rate (MHR) was obtained from the formulas:

MHR= 220-age in years (for men)

MHR= 226-age in years (for women) (Bumgardner, 2008).

Sixty to eighty percent of the value of the heart rate reserve which is the moderate intensity range was considered for each subject as the target heart rate for exercise.

Target Heart rate= 60-80% (MHR - Resting Heart Rate) + Resting Heart Rate (ACSM, 2006).

The Borg's rate of perceived exertion was also a check tool; subjects were instructed to tell how they feel based on the scale (figure 7). They were encouraged to exercise at moderate intensity range at points 12- 13 of the scale which denoted "somewhat hard".

Procedures for intervention: The subjects in this group were required to exercise for a period of 20 minutes per session on bicycle ergometer (figure 9). When sited on the bicycle, participants achieved free pedaling at a work load of 0watts until they have established regular and steady pedaling rate (Huo *et al*., 2006; Adeniyi *et al*., 2007). The workload was then gradually increased to 40watts (Huo *et al*., 2006; Adeniyi *et al*., 2007) while the

pedaling frequency was also gradually increased to 60 revolutions per minutes (rpm) (Travlos, 2009). Subjects were then instructed to continue pedaling at this rate until they attain the intensity relative to the calculate 60% of the heart rate reserve which was deduce from their maximum heart rate: 220- age in years for male subjects and 226-age in years for female subjects (Bumgardner, 2008).

The duration of this exercise protocol was 20 minutes (Adeniyi *et al*., 2007). Progression was then made to70 and 80% of their heart rate reserve as they got adapted to the exercise protocol during the study period. The resistance exercises were done at moderate intensity of 50, 60 and 70% of the RM of the major muscle groups exercised.

The same procedure for resistance exercises for group I was done for participants in group II.

Figure 8: Subjects performing aerobic exercises on treadmill

Outcome measures: The outcome measures assessed for this study group included: cardiovascular parameters (arterial systolic blood pressure and diastolic blood pressure, rate pressure product); pulmonary parameters [oxygen uptake (VO2max), forced vital capacity and forced expiratory volume in 1 second], and the anthropometric parameters (BMI, waist circumference and waist hip ratio). The subjects were assessed based on these outcome measures at the baseline, 4th, 8th and 12th week post therapeutic exercise intervention. The QoL of the subjects was also assessed at baseline and at the end of 4^{th}, 8th and 12^{th} week post therapeutic exercise intervention using DQLCTQ-R. Biochemical parameter (HbA1C) was assessed at baseline and 12th week post intervention.

Study group III

The subjects for this control group were 20 individuals. There was no exercise intervention for the subjects in this group. Their physical activity levels were assessed every at baseline, and end of 4th, 8th, and 12th week to ascertain that they were not engaging in exercises during the intervention period. They also participated in group educational sessions which were also given to exercise groups I and II. This was done every other week within the twelve weeks of the intervention period to reduce attrition. The topics for the educational session included:

1. Blood glucose monitoring and record keeping.
2. Recognition and management of hypoglycaemia and hyperglycaemia.
3. Medication adjustment based on nutrition and activity schedules.
4. Weight control and diet modification including meal plan.
5. Diabetes complications.
6. The importance of diabetes control.

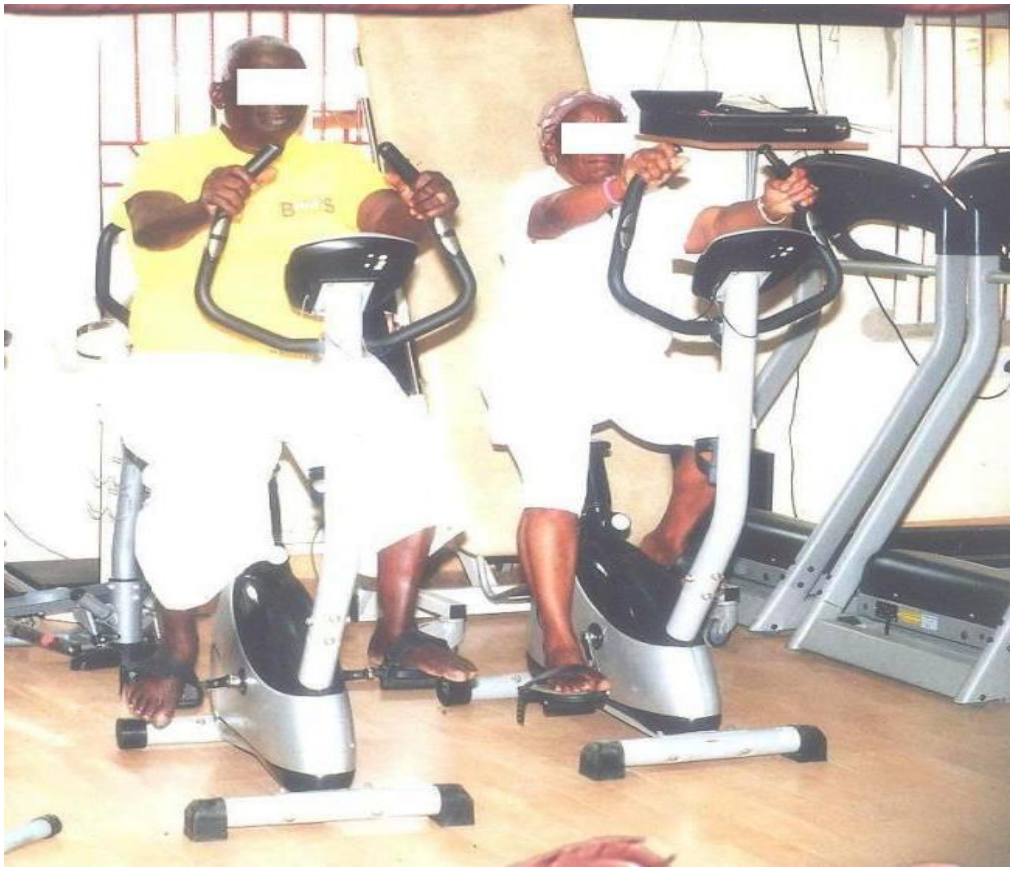

Figure 9: Subjects performing aerobic exercises on bicycle ergometer

Figure 10: Subjects performing resistance exercises to the upper limbs

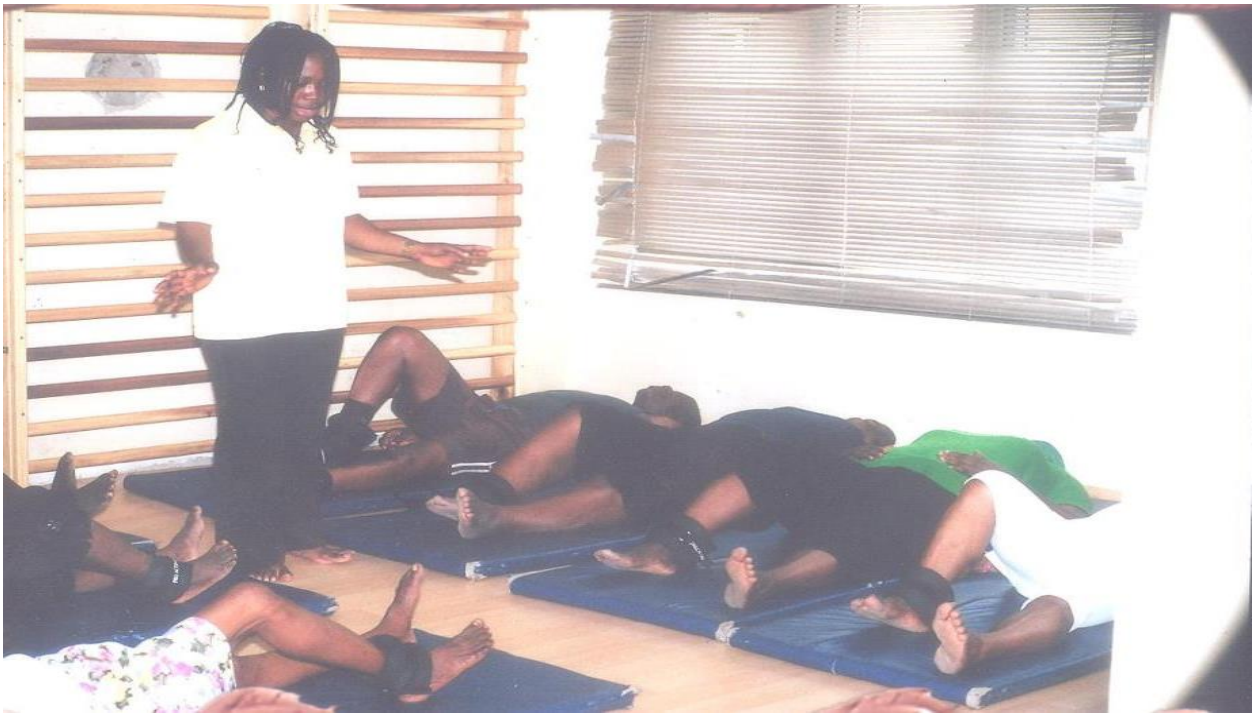

Figure 11: Subjects performing resistance exercises of the lower limbs

Outcome Measures: The outcome measures assessed for the subjects in this group were the same as those assessed in groups I and II. They included: cardiovascular parameters (arterial systolic blood pressure, arterial diastolic blood pressure, and rate pressure product); pulmonary parameters [oxygen uptake (VO_2max), forced vital capacity and forced expiratory volume in 1 second], and the anthropometric parameters (BMI, waist circumference and waist hip ratio). The subjects were assessed based on these outcome measures at the baseline and at the end of 4^{th}, 8^{th} and 12^{th} week of the study period. The QoL of the subjects were assessed at baseline and at the end of 4^{th}, 8^{th} and 12^{th} week of the study period using the DQLCTQ-R. Biochemical parameter (HbA1C) was assessed at baseline and 12th week post intervention.

3.8 Outcome measures

Socio-demographic data of all subjects were obtained at baseline; this included the age at last birthday, gender and duration of diabetes. All outcome measures for this study which included cardiovascular, pulmonary and anthropometric variables and QoL were assessed in groups I, II and III at baseline and at the end of the 4^{th}, 8^{th} and 12^{th} week. Biochemical variable (HbA1c) was assessed in all subjects at baseline and at the end of the 12^{th} week of the intervention period.

Anthropometric Measurements

The anthropometric measurements such as weight and height were taken without shoes but with light clothe (shorts or warm-up pants).

- Body mass index (BMI) (kg body weight· m^{-2} height) (meters squared) (Irwin *et al*., 2002), was determined from the measured body weight and height. It was deduced as body weight divided by height squared. Body weight was measured to the nearest kilogram using a weighing scale with incorporated height meter, manufactured by

Seradon, England. Height was measured to the nearest centimeter and was converted to meters.

- Waist circumference which is a measure of the central obesity was taken with tape rule in centimeter as the average of two measurements taken after inspiration and after expiration at the midpoint between the lowest rib and the iliac crest (Laaksonen, 2003).
- Waist-hip ratio was determined as the ratio of waist circumference and waist girth to the circumference of the hips measured at the trochanter major (Laaksonen, 2003).

The Cardiovascular Parameters;

The cardiovascular parameters included:

- **Resting arterial blood pressures** (systolic and diastolic) were obtained using mercury shygmanometer and stethoscope. The unit of measurement was mmHg. A mercury column sphygmomanometer (Baumanometer Desk Top model no. 320; W.A. Baum Co., Copiague, NY) was used to measure blood pressure. Subjects were required to be seated quietly for 20 minutes before measurements were taken. Blood pressure was taken two times on the right arm with subjects sitting with legs uncrossed using standardized methods recommended by the American Heart Association (NIH, 1993). The average of two systolic and diastolic blood pressure measures was recorded for data entry and analysis.
- **Resting Rate pressure product** was the product of arterial systolic blood pressure in mmHg and resting heart rate in beats per minutes measured using the stethoscope **(**Hermida *et al*,. 2001). The resting heart rate was obtained using stethoscope placed at the apex of the heart at the 5^{th} intercostal space, mid clavicular line.

The Pulmonary Parameters

These included oxygen uptake, forced vital capacity (FVC) and forced expiratory flow in 1 second (FEV1). The force vital capacity and the forced expiratory volume in one second were obtained using spirometer.

The FEV1 and FVC were obtained using hand held medical microsoft spirometer. These pulmonary function tests were done for each subject at a consistent time of the day. The precise technique in executing various lung function tests for the present study was based on the operating manual of the instrument with reference to the official statement of the American Thoracic Society of Standardization of Spirometry (1995) (American Thoracic Society, 1995). Subjects were trained about the entire maneuver, and were encouraged to practice it before doing the pulmonary function tests. The parameters measured included force vital capacity (FVC) and force expiratory volume in 1 second (FEV_1). The tests were performed with subjects in the standing position, blowing into the spirometer through disposable mouth pieces which were immediately disposed after usage. It was repeated three times after adequate rest. The values recorded were the largest of the three trials with less than 0.150L or 5% from the next largest. Subjects were asked to fully expire into the spirometer after maximal inspiration. Values obtain from the maximal expiration included FEV1 and FVC. This is clearly displayed on the crystal glass screen of the spirometer.

Oxygen uptake (VO2 max) for the subjects in groups I and II was obtained using Rockport one mile walk test. The subjects were required to walk for a mile as fast as they can on a track. The time taken to complete the one mile walk was recorded and the heart rate was immediately recorded on finishing the walk. The age, gender and age of the subjects were also documented. Figure 12 shows a subject undergoing the Rockport one mile test.

The VO2max of the subject was calculated using the formula;

132.853 - (0.0769 x W) - (0.3877 x Age) + (6.315 x Gender) - (3.2649 x T) - (0.1565 x HR)

(Kilne *et al*., 1987; O'Dea *et al*., 2001)

Where:

W= Weight was in pounds (lbs).

Gender Male=1 and Female= 0.

T= Time, expressed in minutes and 100th of the minutes.

HR= Heart rate was in beats per minutes.

Age was in years.

The Biochemical Parameter

Glycosylated Haemoglobin Level (HbA1c)

Blood samples were drawn from the subjects and sent for analyses at the chemical pathology laboratory. The blood samples were drawn in a fasting state from antecubital vein (Laaksonen, 2003) in the morning of the assessment days prior to the collection of other outcome measures. Subjects were required to fast for 12 hours before resting blood samples were collected from the antecubital vein using standard venipuncture methods. HbA1c was thereafter analysed using NycoCArd HbA1c test, the HbA1c values were obtained through the NycoCard reader II, Axis Shield PoC, made in Norway. The values were read post analysis and presented in % unit. The measuring range of the reader was 3-18% HbA1c, reference range was 4.5-6.3% HbA1c). The sample material was 5µL whole blood, and the level of precision was a coefficient of variation (CV) below 5% both within and between runs.

Quality of Life

The QoL of each subject in groups I, II, and III was assessed at baseline and at the end of 4th, 8th and 12th week of the study period. This was done using DQLCTQ-R. The self-administered questionnaire was revised to include 57 items comprising eight domains,

generic; physical function, energy/fatigue, health distress, mental health; and Diabetes specific (DQoL); treatment satisfaction, treatment flexibility, frequency of symptoms, satisfaction. Scaling responses included a range of 3-10 options including: 'all the time' to 'none of the time', 'very satisfied' to 'very dissatisfied', 'never' to 'all the time', and 'does not apply' to 'all the time'. This instrument had been found to be a valid and reliable way of measuring HRQoL of people with DM when new or alternative treatments have been implemented (Shen *et al*., 1999). Pretest was also done on twenty individuals with T2DM in LUTH to ascertain the content validity. All items were scored so that a high score defined a more favourable health state. In addition, each item was scored on a 0 to 100 range so that the lowest and highest possible scores were set at 0 and 100, respectively. Scores represent the percentage of total possible score achieved. Items in the same scale are averaged together to create the 8 scale scores. The eight scale scores represent the average for all items in the scale that the respondent answered. A score of 50 was rated average; 0-49 was rated below average; 51-100, above average. Scores below 50 indicated below average health status. (See appendix 2 for details and interpretation).

Figure 12: A subject undergoing the Rockport 1 mile test (V02max assessment)

3.9 Data analysis

Analysis of the socio-demographic data was done using descriptive statistics of mean and standard deviation. Chi-square test was used to compare the socio-demographic variables across the groups. To investigate the effects of a variable within a group; the Within - Subjects factors analysis was utilized (repeated measure analysis of variance (ANOVA) and the effects between the groups; Between - Subjects analysis were used according to Two Way ANOVA with a 95% confidence interval. Two Way ANOVA was applied to detect differences among groups (I, II and control). The Tukey's Honestly Significant Difference (Tukey HSD) available in SPSS was used for post hoc comparison. Level of significance was set at $p<0.05$ .Paired t test was used to compare the baseline and 12^{th} week values of the biochemical variable within the groups. Friedman test was used for the analysis of the QoL between baseline and end of 4^{th}, 8^{th} and 12^{th} week values within the group and Kruskal-Wallis H for across group comparison of QoL. Level of significance was set at $p<0.05$.

CHAPTER FOUR

RESULTS

4.1 Physical characteristics of the study groups

Table 1 shows the socio-demographic data and physical characteristics of the subjects in groups I, II and III, the gender, age, weight, height and duration of diabetes of the subjects were similar at baseline across the groups.

Table 1: Physical characteristics of the study groups

	Group I	Group II	Group III	X^2, F and p value
Gender	**n= 20**	**n= 20**	**n= 20**	
Female	**12(60%)**	**7(35%)**	**9(45%)**	**X^2=2.55, p=0.28**
Male	**8(40%)**	**13(65%)**	**11(55%)**	
Total	**20(100%)**	**20(100%)**	**20(100%)**	
Age (years)	**62.85±6.03**	**61.40±8.20**	**61.90±2.1**	**F=0.30, p=0.74**
Duration of diabetes(years)	**5.90±3.88**	**6.95±4.07**	**4.70±4.75**	**F=1.40, p=0.25**
Weight (kg)	**75.20±8.92**	**77.900±11.57**	**88.05±8.77**	**F=2.12, p= 0.13**
Height (m)	**1.63±0.06**	**1.59±0.09**	**1.63±0.05**	**F=2.19, p= 0.12**

3.2 Cardiopulmonary, Biochemical and Anthropometric Variables of Subjects in Group I

Table 2 shows the changes in cardiopulmonary, biochemical and anthropometric variables of subjects in group I at baseline, 4^{th}, 8^{th} and 12^{th} week post exercise intervention. Analysis of variance was used for data processing of the cardiopulmonary and anthropometric variables while paired t test was used for the biochemical variable; HbA1c. There were significant reduction in the resting arterial systolic blood pressure (RASBP), resting arterial diastolic blood pressure (RADBP), resting rate pressure product (RRPP) and HbA1c while oxygen uptake (VO2max), forced expiratory volume in one second (FEV1), forced vital capacity (FVC) were significantly increased. Waist circumference (WC) was also significantly reduced. No significant difference was observed in BMI and waist hip ratio (WHR).

Figure 13 shows a schematic representation of the post hoc analysis of the cardiopulmonary variables which were significant in group I. Comparison was made between the cardiopulmonary variables at baseline and 4^{th}, 8^{th} and 12^{th} week. The significant difference in the RSBP, RDBP, VO_2max, FVC and FEV1 occurred in the subjects between the baseline and 8^{th} week and baseline and 12^{th} week.

Figure 14 shows the schematic representation of the post hoc analysis of the RRPP which was significantly reduced in groups I and II. The significant change actually occurred in the subjects in group I between the baseline and 4^{th}, baseline and 8^{th} week and baseline and 12^{th} week while it occurred between baseline and 8^{th} week and baseline and 12^{th} week in group II. Figure 15 shows the schematic representation of the post hoc analysis of waist circumference which was significant in groups I and II. The significant change occurred between the baseline and 4^{th} in group I while it occurred between baseline and 12^{th} week in group II.

Table 2: Cardiopulmonary, Biochemical and Anthropometric Variables of Subjects in Group I

VARIABLES	BASELINE	END OF 4TH WEEK	END OF 8TH WEEK	END OF 12TH WEEK	F value	p value
CARDIOVASCULAR						
RASBP (mmHg)	**135.70±18.39**	**127.15±13.31**	**124.90±13.19**	**120.55±11.88**	**3.91**	**0.01***
RADBP (mmHg)	**80.50±6.74**	**75.45±6.68**	**75.85±5.27**	**71.35±5.35**	**7.64**	**0.00***
RRPP (beats/min/mmHg)	**10570.10±1818.34**	**9513.45±1379.44**	**9456.00±1728.71**	**8228.00±929.74**	**8.10**	**0.00***
PULMONARY						
VO2max (ml/kg/min)	**21.32±5.33**	**23.19±4.82**	**26.05±4.58**	**28.64±4.88**	**8.58**	**0.00***
FVC (Litres)	**1.50±0.22**	**2.06±0.49**	**2.18±0.53**	**2.13±0.57**	**8.78**	**0.00***
FEV1 (Litres)	**1.42±0.27**	**1.94±0.44**	**2.14±0.54**	**2.32±0.45**	**15.89**	**0.00***
BIOCHEMICAL						
HbA1C (%)	**7.38±1.23**			**6.07±0.86**	**t=15.28**	**0.00***
ANTHRPOMETRIC						
BMI (kg/m2)	**31.10±1.20**	**27.79±3.27**	**29.97±11.96**	**28.73±3.16**	**0.98**	**0.41**
WC (cm)	**100.53±9.99**	**93.40±6.77**	**95.81±6.45**	**98.61±8.05**	**3.11**	**0.03***
WHR	**0.96±0.03**	**0.97±0.05**	**0.93±0.10**	**0.96±0.11**	**1.05**	**0.38**

Key: RASBP= Resting Arterial Systolic BP, RADBP= Resting Arterial Diastolic BP, RRPP = Resting rate pressure product, VO2max= oxygen uptake, FVC= Forced vital capacity, FEV1= Forced Expiratory Volume in one second, HbA1c= Glycosylated haemoglobin, BMI= Body mass index, WC= Waist circumference, WHR= Waist hip ratio *= significant at $p<0.05$

GROUP 1

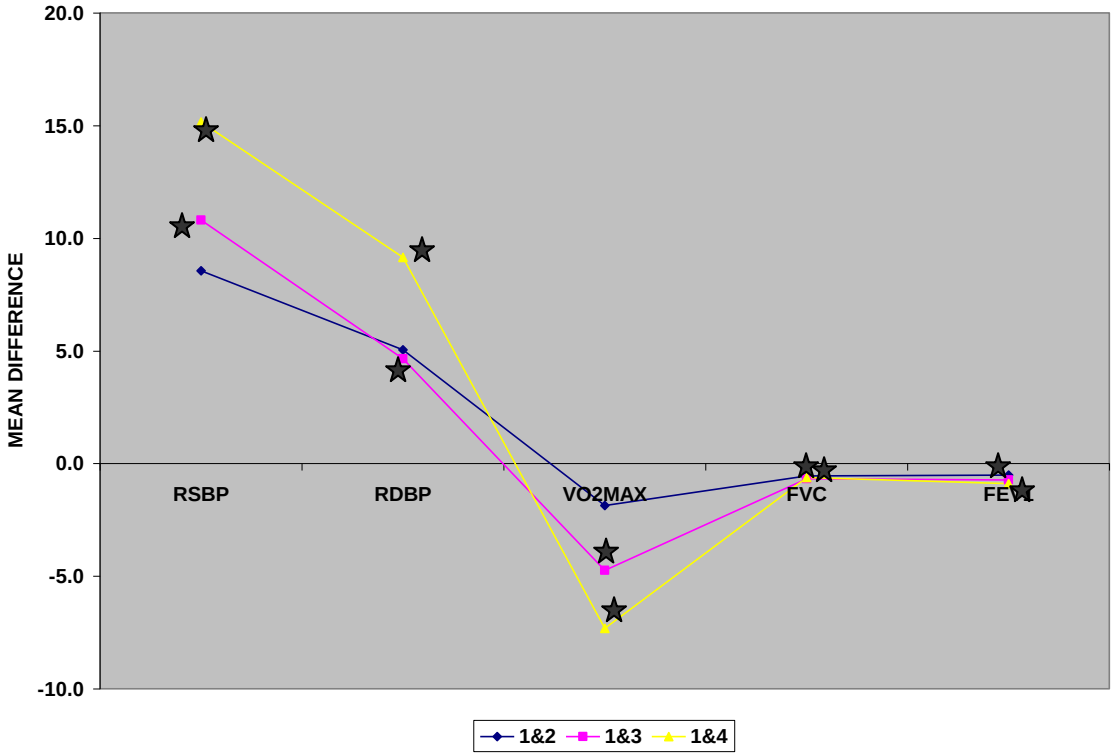

Figure 13: Schematic representation of post hoc analysis of the cardiopulmonary variables in group I

Key: RASBP= Resting arterial systolic blood pressure, RADBP= Resting arterial diastolic blood pressure, VO_2max= oxygen uptake, FVC= Forced vital capacity, FEV1= Forced expiratory volume in one second 1= baseline, 2= 4^{th} week, 3= 8^{th} week, 4= 12^{th} week, ★ = significant at $p<0.05$

GROUP I & II

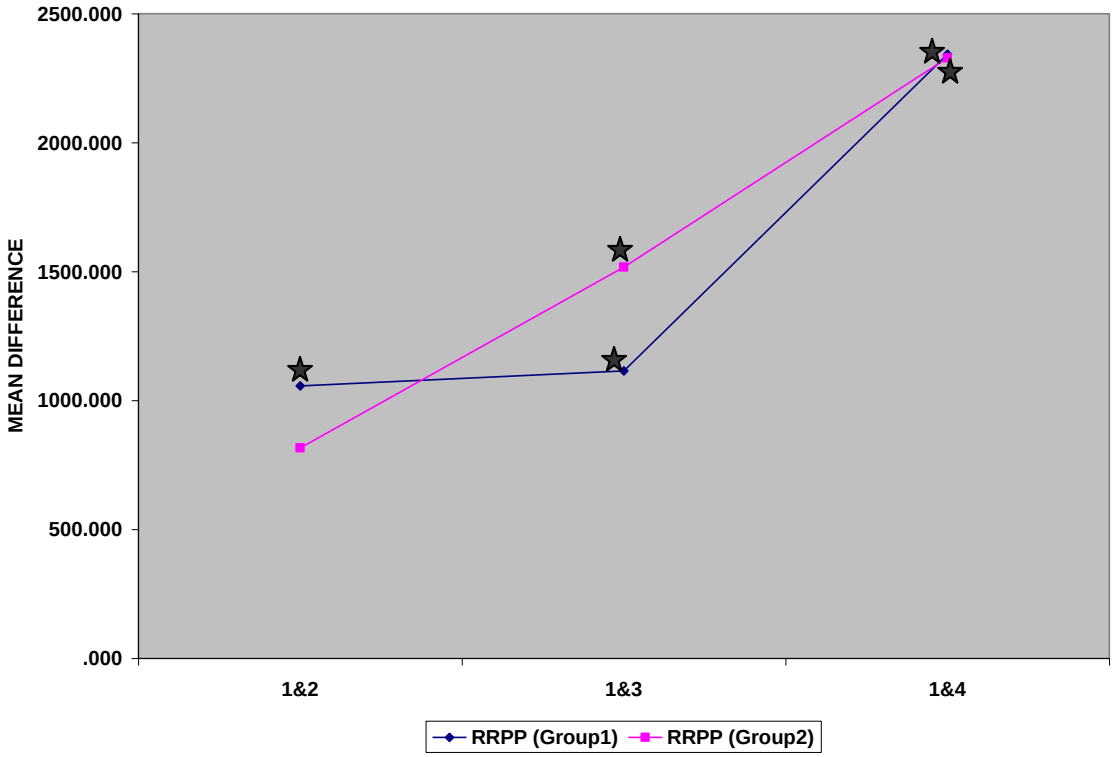

Figure 14: Schematic representation of post hoc analysis of the resting rate pressure products in groups I and II

Key: RRPP = Resting rate pressure product, 1= baseline, 2= 4th week, 3= 8th week, 4= 12th week

★ = significant at $p<0.05$

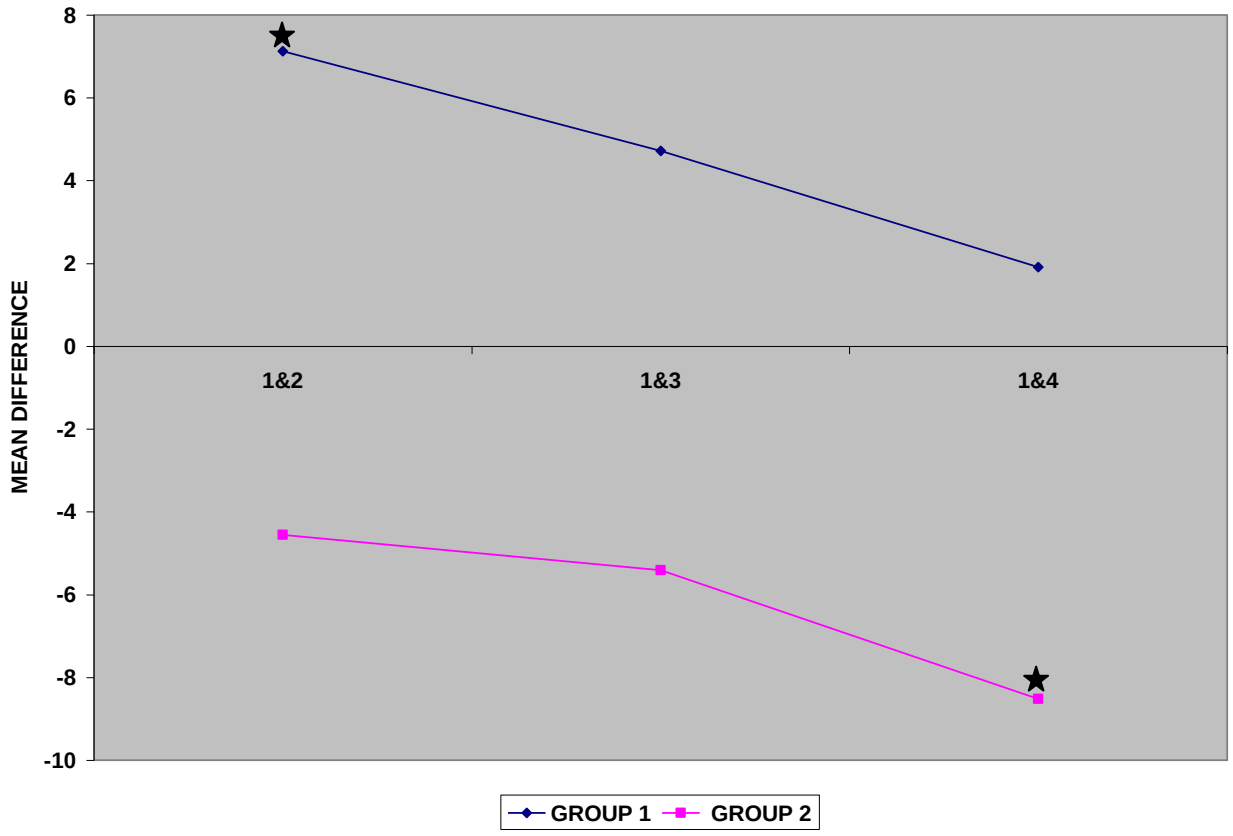

Figure 15: Schematic representation of post hoc analysis of the waist circumference in groups I and II

4.3 Quality of Life Variables of Subjects in Group I

Table 3 shows the changes in QoL variables of subjects in group I. Friedman test was used for data processing. The overall QoL of the subjects at baseline was 44.2 which signified a QoL below average while the overall QoL value post 12^{th} weeks exercise intervention was 64.09 which signified a QoL above average. There were significant increase in the physical functioning, treatment flexibility, frequency of symptoms, energy/fatigue, health distress, treatment satisfaction, mental health and treatment satisfaction scales of the subjects. In addition, the values of the various aforementioned domains in the QoL increases progressively from the baseline values to the 12^{th} week post exercise intervention. The p values of their overall QoL when comparison of baseline and 4^{th}, 8^{th} and 12^{th} week intervention values were done also signify that there were significant difference, $p<0.05$

Table 3: Quality of Life Variables of Subjects in Group I

QoL	baseline	End of 4th week	End of 8th week	12th week	X^2 value	p value
PF	**41.85**	**55.90**	**61.65**	**62.55**	**41.19**	**0.00***
FS	**51.02**	**61.26**	**65.81**	**66.60**	**29.46**	**0.00***
TS	**38.75**	**52.38**	**56.78**	**64.75**	**37.93**	**0.00***
HD	**46.18**	**53.76**	**57.86**	**63.80**	**43.32**	**0.00***
SF	**43.35**	**53.85**	**59.33**	**65.78**	**26.66**	**0.00***
TF	**43.18**	**55.17**	**59.12**	**62.70**	**20.833**	**0.00***
EF	**46.18**	**53.76**	**57.86**	**63.80**	**34.32**	**0.00***
MH	**43.14**	**59.54**	**62.44**	**62.70**	**11.216**	**0.01***
Overall QoL	**44.20**	**55.70**	**60.12**	**64.09**	**31.20**	**0.00***

Key: QoL= Quality of life, PF= Physical function, FS= Frequency of symptom , TS= Treatment satisfaction, HD= Health distress, TF= Treatment flexibility, MH= Mental health, SF=Satisfaction, E/F= Energy/Fatigue , X^2 is the Friedman test value *= significant at $p<0.05$

3.3 Cardiopulmonary, Biochemical and Anthropometric variables of subjects in group II

Table 4 shows the changes in cardiopulmonary, biochemical and anthropometric variables of subjects in group II at baseline, 4^{th}, 8^{th} and 12^{th} week post exercise intervention. Analysis of variance was used for data processing of the cardiopulmonary variables while paired t test was use for the biochemical variable; HbA1c. There were significant reduction in the RASBP, RADBP, RRPP, and HbA1c, VO2max FEV1 were significantly increased. No significant difference was observed in the FVC, BMI and WHR. WC, though significant, did not follow a particular trend.

Figure 15 shows a schematic representation of the post hoc analysis of the cardiopulmonary variables which were significant in group I. Comparison was made between the cardiopulmonary variables at baseline and 4^{th}, 8^{th} and 12^{th} week. The significant difference in the RSBP, RDBP, VO2max and FEV1 occurred in the subjects between the baseline and 8^{th} week and baseline and 12^{th} week.

Table 4: Cardiopulmonary, Biochemical and Anthropometric Variables of Subjects in Group II

VARIABLES	BASELINE	END OF 4TH WEEK	END OF 8TH WEEK	END OF 12TH WEEK	F value	p value
CARDIOVASCULAR						
RASBP (mmHg)	**136.20±16.81**	**135.00±14.40**	**125.30±13.06**	**123.90±13.00**	**3.94**	**0.01***
RADBP (mmHg)	**82.75±8.33**	**80.75±5.84**	**75.20±5.47**	**71.55±5.84**	**12.54**	**0.00***
RRPP (beat/min/mmHg)	**11307.75±2002.74**	**10492.35±1540.40**	**9791.05±1570.99**	**8979.90±1816.44**	**6.49**	**0.00***
PULMONARY						
VO2max (ml/kg/min)	**21.55±2.44**	**22.01±3.62**	**27.35±3.76**	**28.02±4.17**	**18.57**	**0.00***
FVC (litres)	**1.54±0.39**	**1.55±0.39**	**1.72±0.45**	**1.86±0.52**	**2.46**	**0.07**
FEV1(litres)	**1.36±0.41**	**1.46±0.43**	**1.68±0.33**	**1.77±0.39**	**4.71**	**0.00***
BIOCHEMICAL						
HbA1C (%)	**6.97±0.90**			**6.02±0.74**	**t=13.32**	**0.00***
ANTHROPOMETRIC						
BMI kg2/m	**31.68±4.06**	**31.35±4.28**	**31.61±4.10**	**31.58±4.07**	**0.03**	**0.99**
WC (cm)	**97.73±8.93**	**102.29±9.76**	**103.15±9.61**	**102.35±9.23**	**3.15**	**0.03***
WHR	**1.00±0.08**	**0.99±0.77**	**0.98±0.07**	**0.90±0.33**	**1.45**	**0.23**

Key: RASBP= Resting arterial systolic BP, RADBP= Resting arterial diastolic BP, RRPP= Resting rate pressure product, VO2max= oxygen uptake, FVC= Forced vital capacity, FEV1= Forced expiratory volume in one second, HbA1c = Glycosylated haemoglobin, BMI= Body mass index, WC= Waist circumference, WHR= Waist hip ratio *= significance at $p<0.05$

GROUP II

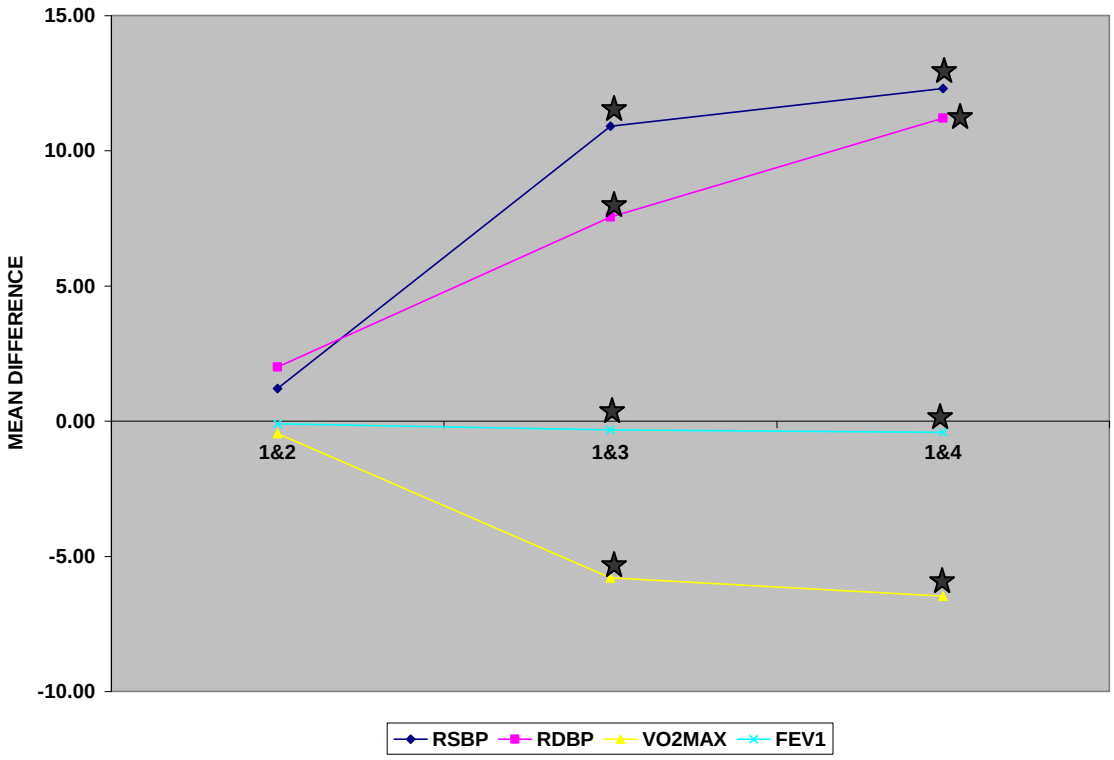

Figure 16: Schematic representation of post hoc analysis of the cardiopulmonary in group II

Key: RASBP= Resting Arterial Systolic Blood, RADBP= Resting Arterial Diastolic Blood Pressure, VO2max= Oxygen Uptake, FEV1= Forced Expiratory Volume in one second, 1 = baseline, 2= 4th week, 3= 8th week, 4= 12th week, ★ = significant at $p<0.05$

4.5 Quality of life variables of subjects in group II

Table 5 shows the changes in QoL variables of subjects in group I, Friedman test was used for data processing, all the scales in the QoL domain showed significant increase. The overall QoL of the subject at baseline was 43.23 which signified a QoL below average while the overall QoL value post 12^{th} weeks exercise intervention was 60.93 which signified a QoL above average. The values of their ranking in the aforementioned scales were higher after 12 week exercise intervention when compared with their baseline values. The p value of their overall QoL when comparison of baseline and post 12 week intervention value was done was greater than 0.05 which is thus not significant.

Table 5: Quality of Life Variables of Subjects in Group II

QoL	Baseline	End of 4th week	End of 8th week	12th week	X^2 value	p value
PF	**45.85**	**55.60**	**63.40**	**64.70**	**30.80**	**0.00***
FS	**48.90**	**50.95**	**54.91**	**63.80**	**16.45**	**0.00***
TS	**40.00**	**49.23**	**51.43**	**58.55**	**28.96**	**0.00***
HD	**43.90**	**58.20**	**59.50**	**67.65**	**30.01**	**0.00***
SF	**45.00**	**40.23**	**44.98**	**52.58**	**14.54**	**0.00***
TF	**32.47**	**42.02**	**53.38**	**61.45**	**64.16**	**0.00***
EF	**48.39**	**53.68**	**55.38**	**61.15**	**19.39**	**0.00***
MH	**40.21**	**44.31**	**47.01**	**57.60**	**23.03**	**0.00***
Overall QoL	**43.09**	**49.28**	**53.50**	**60.93**	**22.13**	**0.00***

Key: QoL= Quality of life, PF= Physical function, FS= Frequency of symptom, TS= Treatment satisfaction, HD= Health distress, TF= Treatment flexibility, MH= Mental health, SF=Satisfaction, E/F= Energy/Fatigue, X^2 is the Friedman test value *= significant at $p<0.05$

4.6 Cardiopulmonary, biochemical and Anthropometric variables of subjects in group III

Table 6 shows the changes in cardiopulmonary and biochemical anthropometric variables of subjects in group III at baseline, 4^{th}, 8^{th} and 12^{th} week post exercise intervention. Analysis of variance was used for data processing of the cardiopulmonary variables while paired t test was use for the biochemical variable; HbA1c. There were no significant differences in the RASBP, RADBP, RRPP, VO2max, FVC, FEV, HbA1c BMI, WC and WHR. However, mean HbA1c was reduced from 6.95±1.34 to 6.77±0.71 (about 2.6%) in the subjects.

Table 6: Cardiopulmonary Biochemical and Anthropometric Variables of Subjects in Group III

VARIABLES	BASELINE	END OF 4TH WEEK	END OF 8TH WEEK	END OF 12TH WEEK	F value	p value
CARDIOVASCULAR						
RASBP (mmHg)	**134.60±8.82**	**125.80±12.43**	**128.80±6.57**	**130.90±12.14**	**2.59**	**0.06**
RADBP (mmHg)	**78.90±3.45**	**77.50±7.13**	**79.80±4.45**	**77.00±6.16**	**1.08**	**0.36**
RRPP(beats/min/mmHg)	**11509.00±765.83**	**10833.60±1397.40**	**11745.50±488.36**	**11103.60±1784.09**	**1.95**	**0.13**
PULMONARY						
VO2max (ml/kg/min)	**21.43±5.27**	**18.07±2.41**	**18.17±2.86**	**19.94±6.15**	**2.57**	**0.06**
FVC (Litre)	**1.81±0.82**	**1.80±0.77**	**1.78±0.73**	**2.08±0.68**	**0.69**	**0.56**
FEV1 (Litre)	**1.39±0.56**	**1.47±0.57**	**1.61±0.53**	**1.48±0.55**	**0.53**	**0.66**
BIOCHEMICAL						
HbA1C (%)	**6.95±1.34**			**6.77±0.71**	**t= 0.28**	**0.60**
ANTHROPOMETRIC						
BMI (kg2/m)	**33.00±2.45**	**34.83±7.04**	**32.96±2.47**	**32.95±2.57**	**1.01**	**0.39**
WC (cm)	**100.93±11.00**	**105.91±8.46**	**106.00±8.31**	**105.88±7.31**	**1.59**	**0.20**
WHR	**0.92±0.35**	**0.90±0.32**	**1.03±0.19**	**1.06±0.35**	**1.18**	**0.32**

Key: RASBP= Resting arterial systolic BP, RADBP= Resting arterial diastolic BP, RRPP= Resting rate pressure product, VO2max= oxygen uptake, FVC= Forced vital capacity, FEV1= Forced expiratory volume in one second, HbA1c= Glycosylated haemoglobin, BMI= Body mass index, WC= Waist circumference, WHR= Waist hip ratio *= significanT at p< 0.05.

4.7 Quality of life Variables of Subjects in Group III

Table 7 shows the changes in QoL variables of subjects in group III. Friedman test was used for data processing; there were significant improvement in the treatment flexibility (TF) and mental health (MH) of the subjects in group III, all other scales in the QoL domain showed no significant difference. The overall QoL of the subjects at baseline was 41.61 which signified a QoL below average while the overall QoL value post 12^{th} weeks exercise intervention was 46.60 which showed a QoL below average. However, the values of their ranking in the aforementioned scales were higher after 12 week exercise intervention when compared with their baseline values.

Table 7: Quality of Life Variables of Subjects in Group III

QoL	baseline	End of 4th week	End of 8th week	12th week	X^2 value	p value
PF	**45.00**	**45.15**	**47.20**	**47.12**	**0.73**	**0.87**
FS	**44.53**	**44.68**	**45.73**	**45.05**	**0.71**	**0.87**
TS	**35.20**	**35.15**	**40.55**	**40.93**	**2.60**	**0.46**
HD	**40.75**	**40.30**	**41.55**	**45.10**	**1.49**	**0.69**
SF	**43.15**	**43.35**	**42.75**	**47.10**	**3.280**	**0.35**
TF	**33.13**	**43.18**	**41.79**	**47.94**	**10.04**	**0.02***
EF	**47.10**	**47.15**	**46.76**	**50.78**	**1.14**	**0.77**
MH	**44.05**	**44.25**	**44.25**	**48.40**	**8.13**	**0.04***
overall QoL	**41.61**	**42.90**	**43.82**	**46.60**	**3.51**	**0.57**

Key: QoL= Quality of life, PF= Physical function, FS= Frequency of symptom , TS= Treatment satisfaction, HD= Health distress, TF= Treatment flexibility, MH= Mental health, SF=Satisfaction, E/F= Energy/Fatigue, X^2 is the Friedman test value *= significant at $p<0.05$

4.8 Cardiovascular Variables of Study Groups

Table 8 shows the comparison of cardiovascular variables across groups I, II and III at baseline, 4^{th} week, 8^{th} week and 12^{th} week post exercise intervention. The RADBP and RRPP were significantly reduced from 4^{th} week to 8^{th} and 12^{th} week while the RASBP was significantly reduced at 12^{th} week.

Figure 16 shows the schematic representation of the post hoc analysis of the cardiovascular variables which were significant when comparison of groups I, II and III were done. Analysis between groups I and II shows significant reduction in RADBP at 4^{th} week only, comparison between groups I and III shows no significant difference in RASBP while significant reduction in RADBP was recorded at 8^{th} and 12^{th} week. Comparison between group II and III show a significant reduction in RADBP at 8^{th} and 12^{th} week, the significant change in RASBP occurred at 4^{th} and 12^{th} week.

Figure 17 shows the schematic representation of the post hoc analysis of the cardiovascular variable RRPP which was significant when across group comparison of groups I, II and III were done. Analysis between groups I and II shows significant difference in RRPP at 4^{th}, 8^{th} and 12^{th} week, comparison between groups I and III shows significant reduction in RRPP at 4^{th}, and 12^{th} week. Comparison between group II and III show a significant reduction in RRPP at 8^{th} week only.

Table 8: Cardiovascular Variables of the Study Groups

	CARDIOVASCULAR VARIABLES	GROUP I	GROUP II	GROUP III	F value	p VALUE
BASELINE	**RASBP (mmHg)**	**135.70±**	**136.20±16.81**	**134.60±8.82**	**0.06**	**0.94**
	RADBP (mmHg)	**80.50±6.74**	**82.75±8.33**	**78.90±3.85**	**1.73**	**0.19**
	RRPP (beats/min/mmHg)	**10570.10±1818.34**	**11307.75±2002.74**	**11509.00±765.83**	**1.86**	**0.17**
4TH WEEK	**RASBP(mmHg)**	**127.15±13.31**	**135.00±14.40**	**125.80±12.43**	**2.75**	**0.07**
	RADBP(mmHg)	**75.45±6.68**	**80.75±5.84**	**77.50±7.13**	**3.31**	**0.04***
	RRPP(beats/min/mmHg)	**9513.45±1379.44**	**10492.35±1540.40**	**10833.60±1397.40**	**4.52**	**0.02***
8TH WEEK	**RASBP (mmHg)**	**124.90±13.19**	**125.30±13.06**	**128.80±6.57**	**0.71**	**0.49**
	RADBP (mmHg)	**75.85±5.27**	**75.20±5.47**	**79.80±4.25**	**4.90**	**0.01***
	RRPP (beat/min/mmHg)	**9456.00±1728.71**	**9791.05±1570.99**	**11745.50±488.36**	**12.99**	**0.00***
12TH WEEK	**RASBP(mmHg)**	**120.55±11.88**	**123.90±13.00**	**130.90±12.14**	**3.66**	**0.03***
	RADBP (mmHg)	**71.35±5.35**	**71.55±5.84**	**77.00±6.16**	**6.13**	**0.00***
	RRPP (beats/min/mmHg)	**8228.00±929.74**	**8979.90±1816.44**	**11103.60±1784.09**	**18.16**	**0.00***

Key: RASBP= Resting arterial systolic BP, RADBP = Resting arterial Diastolic BP, RRPP= Resting rate pressure product,*= significant at P<0.05.

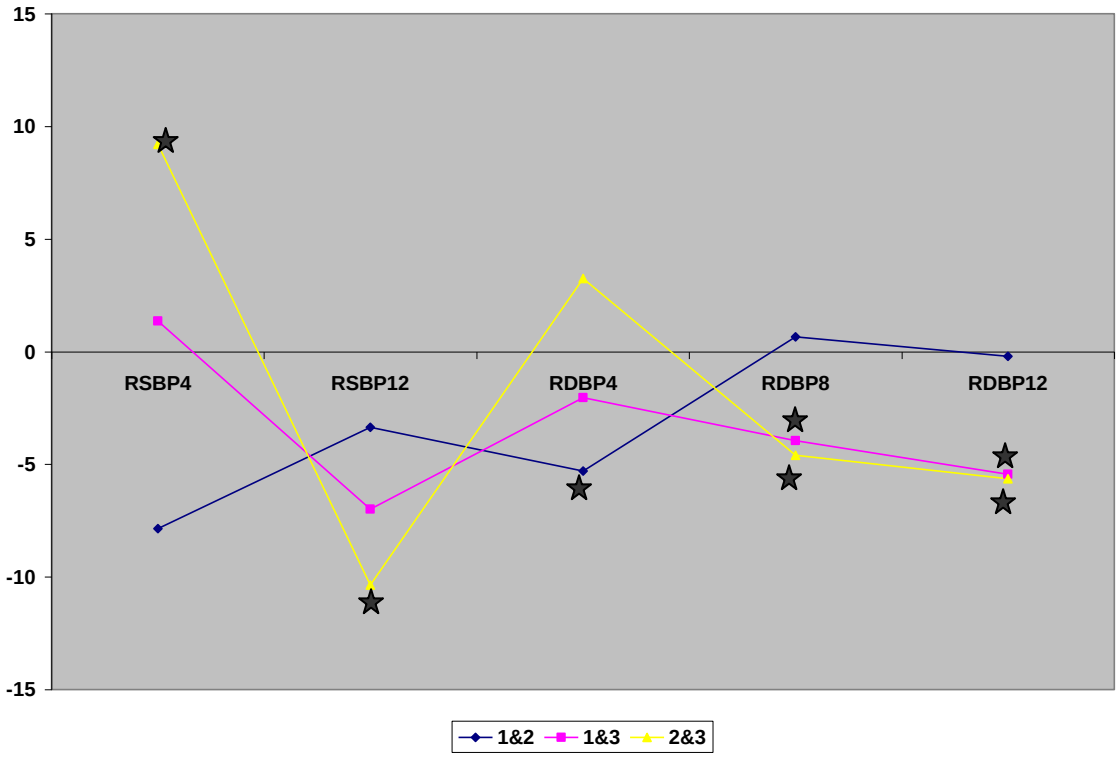

Figure 17: Schematic representation of post hoc analysis of the resting arterial systolic and diastolic blood pressure across the groups

Key: RSBP4 = Resting arterial systolic blood pressure at 4th week, RSBP12= Resting arterial diastolic blood pressure at 12th week, RDBP4= Resting arterial diastolic blood pressure at 4th week, RDBP8= Resting arterial diastolic blood pressure at 8th week, RDBP12= Resting arterial diastolic blood pressure at 12th week, 1= group I, 2= group II, 3= group III, ★ = significant at $p< 0.05$

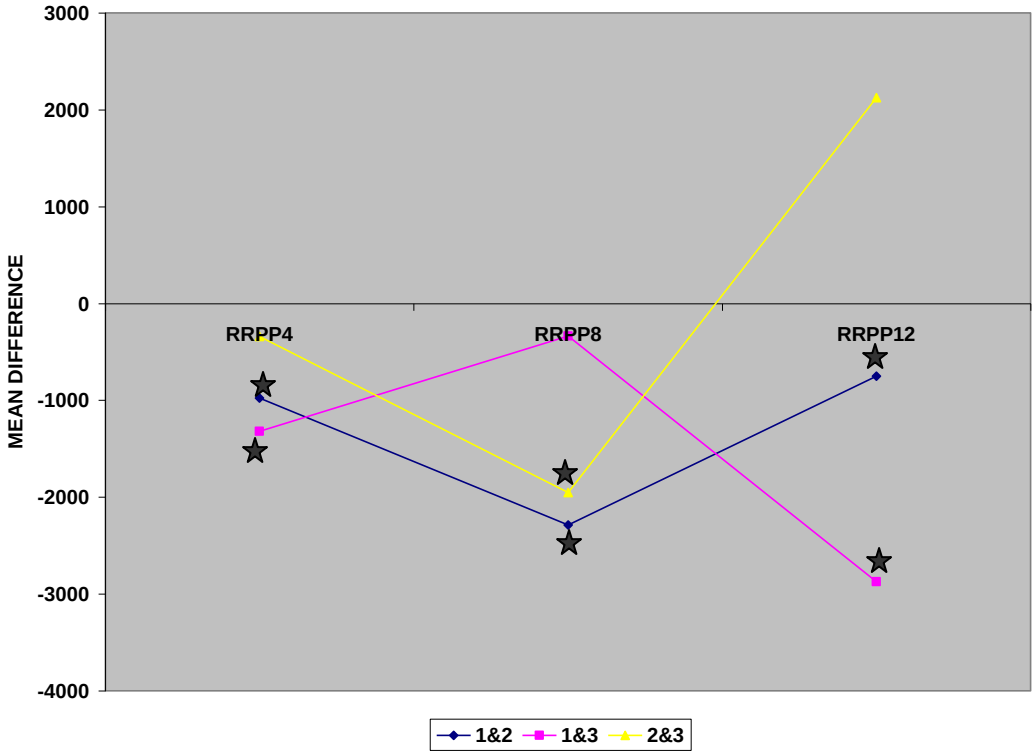

Figure 18: Schematic representation of post hoc analysis of the resting rate pressure product across the groups

Key: RPP4 = Resting rate pressure product at 4th week, RPP8= Resting rate pressure product at 8th week, RPP12= Resting rate pressure product at 12th week, RDBP8= Resting diastolic blood pressure at 8th week, RDBP12= Resting diastolic blood pressure at 12th week, 1= group I, 2= group II, 3= group III, ★ = significant at $p < 0.05$

4.9 Pulmonary Variables of Study Groups

Table 9 shows the changes in pulmonary variables across groups I, II and III at baseline, 4^{th} week, 8^{th} week and 12^{th} week post exercise intervention. Analysis of variance was used for data processing. The VO_2max and FEV1 were significant at 4^{th} week, 8^{th} week and 12^{th} week, while the FVC was significantly increased at 4^{th} week, 8^{th} week but not at 12^{th} week.

Figure 18 shows the schematic representation of the post hoc analysis of the pulmonary variables which were significant when across group comparison of groups I, II and III were done. Analysis between groups I and II shows a significant increase in VO2max at 8^{th} week only. Comparison between groups I and III shows real significant difference in VO2max at 4^{th} 8^{th} and 12^{th} week, FVC was significant at 4^{th} and 8^{th} week while FEV1 recorded significant increase at 4^{th}, 8^{th} and 12^{th} week. Comparison between group II and III show a significant increase in VO2max at 4^{th}, 8^{th} and 12^{th} week, FVC shows no significant difference while FEV1 was significant at 12^{th} week only.

Table 9: Pulmonary Variables of Study Groups

	PULMONARY VARIABLES	GROUP I	GROUP II	GROUP III	F value	p VALUE
BASELINE	**VO2max(ml/kg/min)**	**21.32±5.33**	**21.55±2.44**	**21.43±5.27**	**0.01**	**0.99**
	FEV1 (Litre)	**1.42±0.27**	**1.36±0.41**	**1.39±0.56**	**0.09**	**0.92**
	FVC(Litre)	**1.50±0.22**	**1.54±0.39**	**1.81±0.82**	**1.95**	**0.15**
4TH WEEK	**VO2max (ml/kg/min)**	**23.19±4.82**	**22.01±3.62**	**18.07±2.41**	**10.22**	**0.00***
	FEV1(Litre)	**1.94±0.44**	**1.46±0.43**	**1.47±0.57**	**6.36**	**0.00***
	FVC(Litre)	**2.06±0.49**	**1.55±0.39**	**1.80±0.77**	**4.02**	**0.02***
8TH WEEK	**VO2max(ml/kg/min)**	**26.05±4.58**	**27.35±3.76**	**18.17±2.86**	**34.15**	**0.00***
	FEV1 (Litre)	**2.14±0.54**	**1.68±0.33**	**1.61±0.53**	**7.44**	**0.00***
	FVC(Litre)	**2.18±0.53**	**1.72±0.45**	**1.78±0.73**	**3.56**	**0.04***
12TH WEEK	**VO2max (ml/ kg/min)**	**28.64±4.88**	**28.02±4.17**	**19.94±6.15**	**17.87**	**0.00***
	FEV1 (Litre)	**2.32±0.45**	**1.77±0.39**	**1.48±0.55**	**16.21**	**0.00***
	FVC (Litre)	**2.13±0.57**	**1.86±0.52**	**2.08±0.68**	**1.12**	**0.33**

Key: VO2max= oxygen uptake, FVC= Forced vital capacity, FEV1= Forced expiratory volume in one second, *= significant at $p< 0.05$

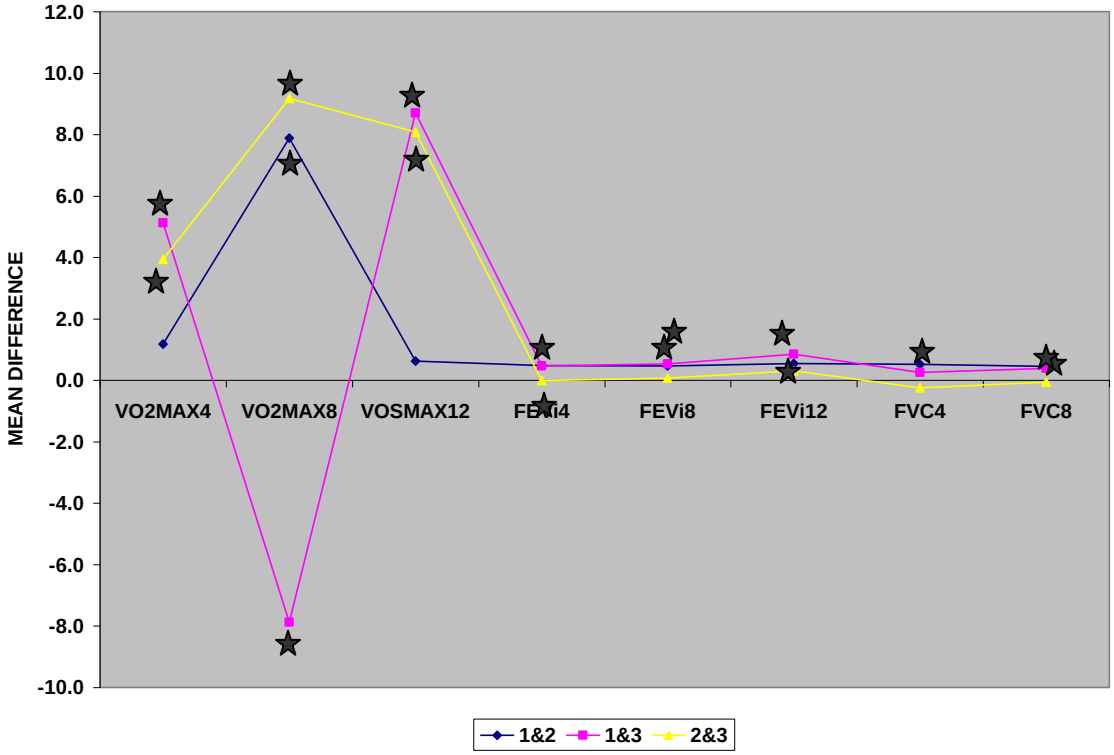

Figure 19: Schematic representation of post hoc analysis of the pulmonary variables across the groups

Key: VO2max4= Oxygen Uptake at 4th week, VO2max8= Oxygen Uptake at 8th week, FEV14= Forced Expiratory Volume in one second at the 4th week, FEV18= Forced Expiratory Volume in one second at 8th week, FEV12 = Forced Expiratory Volume in one second at the 12th week,FVC4= Forced vital capacity at 4th week, FVC8= Forced vital capacity at 8th week, FVC12= Forced vital capacity at 12th week 1= group I, 2= group II, 3= group III, ★ = significant at $p < 0.05$

4.10 Biochemical Variable; Glycosylated Haemoglobin of Study Groups

Table 10 shows the changes in the biochemical variable, HbA1c across groups I, II and III at baseline and 12th week post exercise intervention. Analysis of variance was used for data processing. There was significant reduction in HbA1C across the groups.

Figure 19 shows the schematic representation of the post hoc analysis of the biochemical variable; HbA1c which was significant when across group comparison of groups I, II and III were done. The significant reduction was actually observed between I and III and between II and III (figure 20).

Table 10: Biochemical Variable; Glycosylated Haemoglobin of Study Groups

BIOCHEMICAL VARIABLES	GROUP I	GROUP II	GROUP III	F VALUE	p VALUE
HbA1c (%) (BASELINE)	7.38±1.23	6.97±0.90	6.95±1.34	0.84	0.44
HbA1c (%) (12^{TH} WEEK)	6.07±0.86	6.02±0.74	6.77±0.71	5.95	0.00*

Key: HbA1c= Glycosylated haemoglobin,*= significant at $p<0.05$

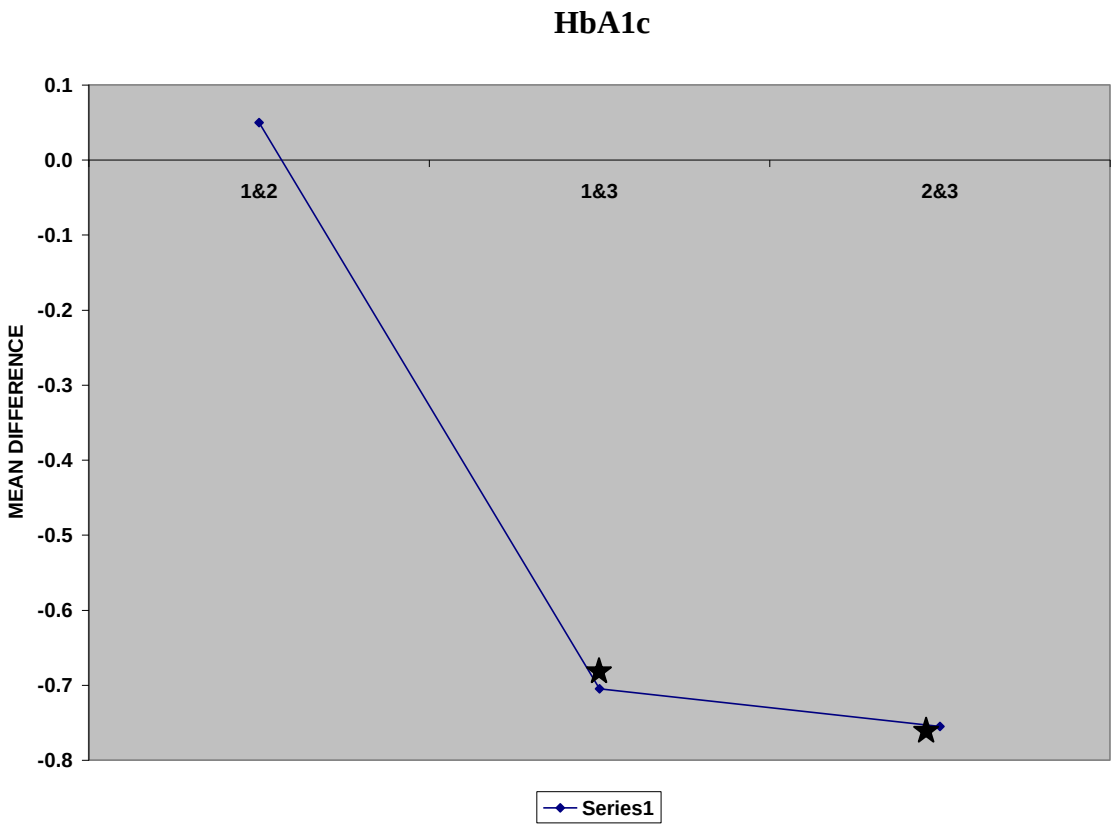

Figure 20: Schematic representation of post hoc analysis of the glycosylated haemoglobin across the groups

Key: HbA1c= Glycosylated haemoglobin, 1= group I, 2= group II, 3= group III,

★ = significant at $p < 0.05$

4.11 Anthropometric variables of subjects

Table 11 shows the changes in anthropometric variables BMI, WHR and WC across the groups I, II and III at baseline, 4^{th}, 8^{th} week and 12^{th} week post exercise intervention. Analysis of variance was used for data processing. BMI and WC were significant reduced when across group comparison was done; BMI was significantly reduced at 4^{th} and 12^{th} week while WC was significantly reduced at 4^{th}, 8^{th} and 12^{th} week. WHR was not significant throughout the assessment periods.

Figure 20 shows the schematic representation of the post hoc analysis of the anthropometric variables which were significant when across group comparison of groups I, II and II were done. Analysis between groups I and II shows significant reduction in BMI at 4^{th} and 12^{th} week while WC was significant at 4^{th} and 8^{th} week. Comparison between groups I and III shows significant reduction in BMI at baseline, 4^{th} and 12^{th} week, WC was significant reduced at baseline, 4^{th}, 8^{th} and 12^{th} week. Comparison between group II and III show a significant reduction in BMI at 4^{th} week only. Greater difference was observed when comparison was done between group I and control group III (figure 21).

Table 11: Anthropometric Variables of Subjects

	ANTHROPOMETRIC VARIABLES	GROUP I	GROUP II	GROUP III	F value	p VALUE
BASELINE	**BMI (kg/m2)**	**31.10±1.20**	**31.68±4.06**	**33.00±2.45**	**2.50**	**0.09**
	WC (cm)	**100.53±9.99**	**97.73±8.93**	**100.93 ±11.00**	**0.61**	**0.55**
	WHR	**0.96±0.03**	**1.00±0.08**	**0.92±0.35**	**0.72**	**0.50**
4TH WEEK	**BMI(kg/m2)**	**27.79± 3.27**	**31.35±4.28**	**34.83±7.04**	**9.46**	**0.00***
	WC (cm)	**93.40± 6.77**	**102.29±9.76**	**105.91±8.46**	**5.72**	**0.01***
	WHR	**0.97 ±0.05**	**0.99±0.07**	**0.90±0.32**	**2.17**	**0.12**
8TH WEEK	**BMI(kg/m2)**	**29.97±11.96**	**31.61±4.10**	**32.96±2.47**	**0.81**	**0.45**
	WC (cm)	**95.81±6.45**	**103.15±9.61**	**106.00±8.31**	**7.75**	**0.00***
	WHR	**0.93±0.09**	**0.98±0.07**	**1.03±0.19**	**2.50**	**0.09**
12TH WEEK	**BMI(kg/m2)**	**28.73±3.16**	**31.58±4.07**	**32.95±2.57**	**8.35**	**0.00***
	WC (cm)	**98.61±8.05**	**102.35±9.23**	**105.88±7.31**	**3.92**	**0.03***
	WHR	**0.96±0.11**	**0.90±0.33**	**1.06±0.35**	**0.83**	**0.44**

Key: BMI= Body mass index, WC= Waist circumference, WHR= Waist hip ratio, *= significant at p< 0.05

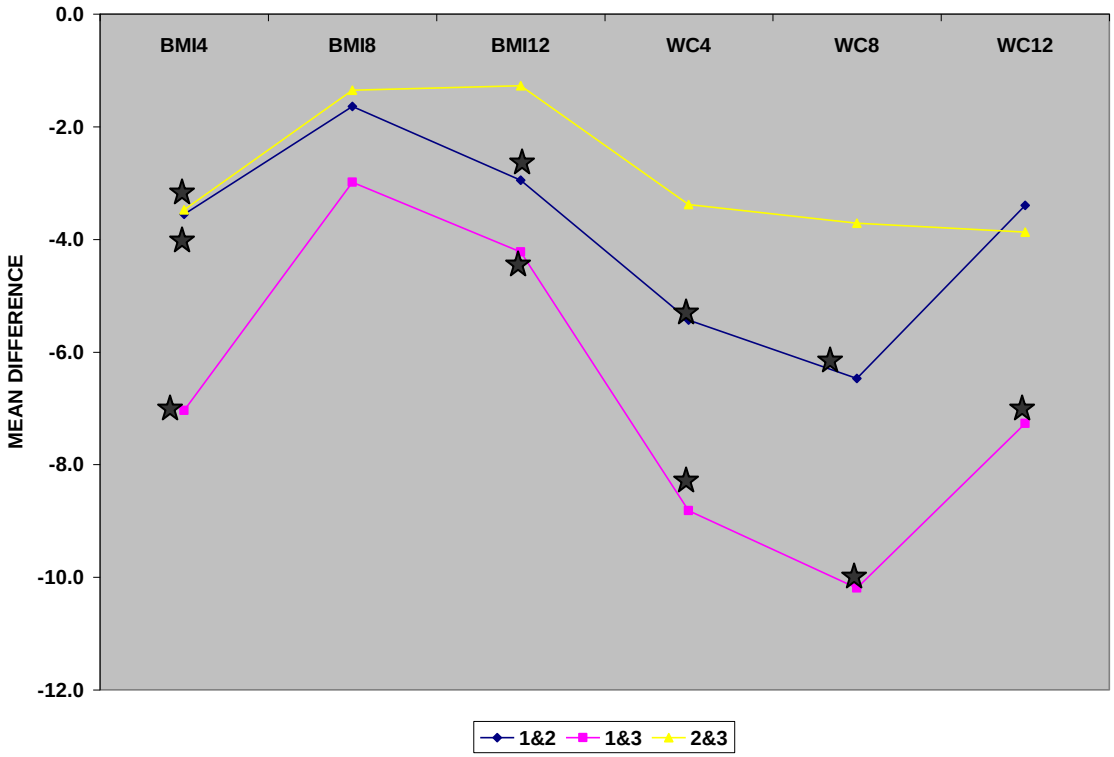

Figure 21: Schematic representation of post hoc analysis of the anthropometric variables across the groups

Key: BMI= Body mass index at baseline, BMI4= Body mass index at 4th week, WC= Waist circumference at baseline, WC4 =Waist circumference at 4th week, WC8= Waist circumference at 8th week, WC12= Waist circumference at 12th week, 1= group I, 2= group II, 3= group III

★ = significant at $p< 0.05$.

4.12 Quality of Life Variables of Study Groups and Correlation Between Glycosylated haemoglobin level and the Cardiopulmonary Variables

Table 12 shows the changes in QoL variables of subjects in group I. Kruskal-Wallis H test was used for data processing. The p value of the overall QoL of the subjects at baseline was 0.11 which signified no significant difference, the p value of the overall QoL after the 12^{th} week of the study period was 0.00 which showed a significant difference across the groups. The overall QoL was significantly increased across the group at the end of the 4^{th}, 8^{th} and 12^{th} post intervention.

Table 13 shows the Correlation between glycosylated haemoglobin level and the cardiopulmonary variables post 12 week intervention. There are significant negative correlation between HbA1c and RRPP, RADBP, VO2max and FEV1 while there is positive correlation between HbA1c and RASBP including FVC.

Table 12: Overall Quality of Life Variables of Study Groups

	GROUP I	GROUP II	GROUP III	X^2 VALUE	p VALUE
Baseline	**56.2**	**56.1**	**55.5**	**0.10**	**0.95**
End of 4th week	**55.2**	**50.0**	**42.9**	**32.20**	**0.00***
End of 8th week	**59.6**	**54.1**	**43.8**	**41.20**	**0.00***
End of 12th week	**64.2**	**61.5**	**46.6**	**40.60**	**0.00***

Key: X^2= value of Kruskal-Wallis H test *= significant at $p<0.05$

Table 13: Correlation between Glycosylated Haemoglobin Level and the Cardiopulmonary Variables post 12 week intervention.

	Correlations	RASBP	RADBP	RRPP	V02max	FVC	FEV1
HbA1c	**Pearson Correlation**	**0.722**	**-0.576**	**-0.043**	**-0.128**	**0.342**	**-0.621**
	Sig. (2-tailed)	**0.001**	**0.010**	**0.357**	**0.007**	**0.561**	**0.001**

RRASBP= Resting arterial systolic BP, RADBP= Resting arterial Diastolic BP, RRPP= Resting rate pressure product, VO_2max= Oxygen uptake, HbA1c= Glycosylated haemoglobin, FVC= Forced vital capacity, FEV1= Forced Expiratory Volume in one second, *= significant at $p<0.05$

CHAPTER FIVE

DISCUSSION, CONCLUSION AND RECOMMENDATION

5.1 Discussion

Diabetes mellitus is a worldwide health problem predisposing to markedly increased cardiopulmonary morbidity and mortality with resultant poor QoL (Zimmet *et al*., 1997; Vinik *et al*., 2003). It requires multifactorial treatment with focus on obesity, hyperglycaemia and other comorbidities which affect the QoL of people with T2DM (Vinik *et al*., 2003). Studies are needed to give evidence on whether different exercise mode may have specific or better therapeutic effect on the cardiopulmonary, biochemical, anthropometric and QoL parameters of individuals with T2DM. Disorders in these parameters have been known to lead to complications and various assaults to vital functioning of the body of people with T2DM (Vinik *et al*., 2003; Kaminski *et al*., 2010).

People with T2DM often develop foot pathologies (Akinbo, 2008) which necessitates the prescription of non-weight bearing aerobic exercise as against weight bearing aerobic exercise they usually perform (Huo *et al*., 2006). It is thus necessary to determine the effect of either mode of aerobic exercises when combined with resistance exercises on people with T2DM. Assessment and progress monitoring of people with T2DM post exercise prescription is also paramount for optimal feedback on patient's progress and development of motivational measures in people with T2DM.

With regards to the demographic and descriptive characteristics, subjects who reported for this study were between the age range of 40 and 75 even though the inclusion criteria permitted individuals between the age range of 20 to 75 years. In addition, the mean age of the subjects in

this study across the groups ranges between a minimum value of 61.40±8.20 (group II), and 62.85±6.03 (group I). This is in conformity with the report of previous findings which reported that the prevalence of DM increases with age and those adults over the age of 40 years are more likely to develop DM than younger adults (Abubakaria and Bhopalb, 2008).

The mean values of the cardiopulmonary and the QoL variables recorded for the study groups in the study at baseline were not within the normal values predicted for the age range of these subjects (Ozoh *et al*., 2010). The pulmonary functions tests especially the FEV1 and FVC of the subjects in this study at baseline (FEV1=1.42±0.27L, 1.36±0.41L, 1.39±0.56L for groups I, II, and III respectively and FVC=1.50±0.22L, 1.54±0.39L, 1.81±0.82L for groups I, II, III respectively) were below predicted normal values even for African population (FEV1= 2.99L±0.56 and FVC=3.70L±0.73) having standardized for weight and gender (Ozoh *et al*., 2010). The VO_2max values across the groups at baseline (group I; 21.32±5.33 ml/kg/min, group II; 21.55±2.44 ml/kg/min and group III; 21.43±5.27 kg/ml/min,) were also below the normal predicted values for their age range (25-27 ml/kg/min) (Ozoh *et al*., 2010) while the QoL measures were below average value at baseline. The finding is this study suggested that people with T2DM in our population do not have normal values of cardiopulmonary and QoL variables. The reduction in their baseline cardiopulmonary value may be as a result of the inflammatory effect of hyperglycaemia on the cardiovascular system and the lungs which are stimulated by the pathways induced by hyperglycaemia since the subjects recorded fairly high glycosylated level before the research protocols. With the high internal levels of the sugar, which cannot be completely metabolize, glucose-derived "intermediate" metabolic products accumulate inside these cells of these vital organs; they activate pathways of cellular damage that can eventually lead to complications particularly in the endothelial cells that line arteries and the capillaries of these organs including the lung (Laaksonen, 2003).

Effect of Weight Bearing Aerobic Exercise Combine with Resistance Exercises on the Cardiopulmonary, Biochemical, Anthropometric and Quality of Life of individuals with Type 2 Diabetes

This study showed that moderate intensity weight bearing aerobic exercise such as treadmill walking when combined with resistance exercises have significant therapeutic effect on the cardiopulmonary and biochemical variables of the studied T2DM subjects. This was demonstrated by the significant reduction in mean resting arterial systolic and diastolic blood pressure and resting rate pressure product in the subjects who performed treadmill walking combined with resistance exercises. The increase mean VO_2max, FVC and FEV1 values of the subjects who had these exercise modes as intervention also demonstrated these therapeutic benefits. Significantly reduced glycosylated haemoglobin level and waist circumference in the subjects was also a positive suggestion to this beneficial effect. These significant changes occurred in these variables as early as fourth week especially in the RRPP as recorded in post hoc analysis post exercise intervention while the trend continue through the eighth and twelfth week in other cardiopulmonary variables. However, anthropometric variables such as BMI and WHR were not significant. The QoL of these subjects also improved significantly.

These findings are partly in conformity with the study of Robert and Jonathan (2003) who reported that individuals with T2DM, who performed walking exercise for two hours a week, lowered their mortality rate by 39%. Olawale *et al* (2011) and Ferdowsi *et al* (2011) concluded that walking lowered high blood pressure, improved circulation and ventilatory function, and may also help the body respond to insulin with better control of blood glucose. Walking was also reported to reduce stress and enhance mood and thus improve QoL (Bradley *et al*., 1999).

The findings in this study is contrary to the findings of Bibi *et al*., (2010) who reported that walking did not significantly improve HbA1c in T2DM patients studied, and that QoL was not improved in their subjects. The result obtained in this study can be attributed to the fact that

exercising on treadmill simulates walking (Timothy and Connell, 2003). Exercising on treadmill at a gradient of 1% had been established from previous studies to correlate with outdoor walking and to compensate for the lack of air resistance in the research ground (Jones and Doust, 1996; Ramsbottom *et al*., 2007; Quinn, 2010). Brisk walking is a form of weight bearing exercise performed in day to day activities and when combined with resistance exercise gives greater therapeutic values (Jones and Doust, 1996). The improvement seen in glycaemic control in subjects in this group can be explained on the basis that whole body aerobic exercise performed on treadmill machine improves insulin action predominantly in majority of the skeletal muscles which were brought to action during this form of exercise. Additional benefit and enhancement in therapeutic effect is also experienced when combined with resistance exercises. The mechanism behind this phenomena included several adaptations like increased capillary density and GLUT4 content, a shift towards more insulin sensitive fibre types, possibly changes in the phospholipids composition of the sarcolema, increase glycolytic and oxidative enzymatic activity and increase in glycogen synthase activity (Kravitz, 2010; ACSM & ADA, 2010).

A reduction in WC as observed in this group had been found to be associated with reduction in cardiovascular risks factors (Bello-Sani and Anumah, 2009). The reduction in the arterial systolic and diastolic blood pressure may also be attributed to the fact that during upright exercise such as treadmill exercise, the normal blood pressure response initially observed is a progressive increase in systolic blood pressure with no change or even a slight decrease in diastolic blood pressure (Kravitz, 2010; Olawale *et al*., 2009; Olawale *et al*., 2011). The slight decrease in diastolic blood pressure was said to be due primarily to the vasodilation of the arteries from the exercise bout, this leads to the expansion in arteries size and consequently the lowering of blood pressure during the diastolic phase (Shenoy *et al*., 2009). Following exercise, systolic blood pressure progressively declines during an active recovery. With a passive (such as seated) recovery, systolic blood pressure may drop abruptly due to the pooling of blood in the

peripheral areas of the body (Olawale *et al*., 2011; Kravitz, 2010). There may also be a drop in diastolic blood pressure, during the recovery phase of exercise due to the vasodilation (Kravitz, 2010). Meta-analysis of randomized controlled trials have also concluded that progressive resistance exercise is efficacious for reducing resting systolic and diastolic blood pressure in adults and therefore suggested that patients with hypertension can safely participate in, and likely benefit from resistance training (Shenoy *et al*., 2009). With chronic and regular exercise session as perform in this study, the arterioles may consistently experience the bouts of vasodilation and thus adapt to the increase in size, hence, the probable explanation for the significant decrease in systolic and diastolic blood pressure observed in the subjects in this group as early as four weeks post intervention with continuous trend through the eighth and twelfth week of the intervention period.

Aerobic exercise on treadmill had been reported to have significant improvement and increase on lung functions such as FVC, FEV1 and VO2max in overweighed male students (Ferdowsi *et al.,* 2011). It was also reported that aerobic exercise can reduce the resistance of airways and thus increase lung volumes such as FVC and FEV1 (Jones and Magdalene, 2006). FVC and FEV1 are known to depend on the lungs elastic and airways resistance (Guyton, 2005). Some studies reported that they are affected by the strength of the respiratory muscle especially the expiratory muscles such as the abdominal muscles (Jones and Magdalene, 2006; Ferdowsi *et al*., 2011). Therefore, improvement in respiratory muscle strength and endurance will in turn increase the FVC. A study also reported that abdominal muscle strengthening does not appear to be an effective means of improving FVC and FEV1 in healthy subjects (Simpson, 1983). The subjects in this study performed resistance exercises of the trunk muscles especially the abdominal muscles; however, assessment of respiratory muscle strength was outside the scope of this study hence we cannot objectively ascertain whether the improvement in mean FVC and FEV1 which were significantly increased was as a result of improvement in expiratory muscle

strength. Improved glucose control as reported in the subjects in this group might have brought about a reduction in microvascular complication in the lung and the consequence reduction in inflammation of the lung tissues might have enhance the improvement in lung function (Kaminski *et al*., 2010).

Effect of Non Weight Bearing Aerobic Exercise Combine with Resistance Exercises on the Cardiopulmonary, Biochemical, Anthropometric and Quality of Life of individuals with Type 2 Diabetes

This study also established that moderate intensity non-weight bearing bicycle ergometer exercise when combined with resistance exercises substantially brought about significant improvement in the cardiopulmonary, biochemical and QoL variables in the group which had these interventions. However, no significant change was recorded in FVC in this group as observed in their group I counterpart who underwent treadmill walking combined with resistance exercise. Likewise, the changes in mean WC which was significant in this group did not follow a regular pattern of increase or decrease but fluctuated within the group during the study period. Post hoc analysis also recorded the significant changes from eighth week post intervention in all the significant cardiopulmonary variables. Bicycle ergometer is a non-weight bearing exercise often prescribed for patients with DM due to the high prevalence of foot pathologies (Akinbo, 2008). It is often prescribed for obese DM patients and those with joint pathology. It is less expensive, easy to maintain, needs less space in the laboratory, and is less intimidating to elderly patients with DM when compared with treadmill (Piepoli *et al*., 2010). However, It has been reported to be less effective than treadmill for secondary prevention of cardiopulmonary morbidity through cardiac rehabilitation (Piepoli *et al*., 2010), since this modality relies primarily on the quadriceps muscle group. It was reported that acute leg fatigue may limit performance before the cardiorespiratory fitness is reached (Piepoli *et al*., 2010).

The finding in this study may be attributed to the fact that bicycle ergometer apart from being an aerobic exercise modality, may also help in improving the strength of lower extremities muscles especially the quadriceps muscles (Hung *et al*., 2004, Kennedy *et al*., 2003). Lower extremity strengthening program as part of pulmonary rehabilitation as in bicycle ergometer has been reported to improved quadriceps muscle strength, endurance and functional status as well as overall QoL (Kennedy *et al*., 2003). Lower extremities strength assessment was not done in this study. However, the QoL of the subjects which was assessed was significantly improved.

The reduction in the blood pressure recorded in the group may be partly attributed to the increased metabolic activity in the lower extremities during exercise. Cells are known to produce by-products called metabolites, when tissue activity in the lower trunk and lower extremities increases during non-weight bearing aerobic exercise such as bicycle ergometer, the production of metabolites will also increase. Blood flow to the exercising area thus remains constant in the face of these changes, and then the metabolites will build up in the tissues. The major metabolites that build up include carbondioxide, Adenosine Di Phosphate, extracellular potassium (K+) and organic acids (Kravitz, 2010). These metabolites directly stimulate the vasodilation of local arterioles in the skeletal muscles which are abundantly found in the lower extremities. There is also moderate accumulation of these metabolites in other skeletal muscles in other parts of the body which were also moderately put into action during this mode of exercise; this is also partly enhanced by the accompanying increased cardiac output and stroke volume (Shenoy *et al*., 2009; Kravitz, 2010). Beta-adrenergic stimulation by epinephrine which occurs during exercise has also been known to cause vasodilation of arterioles in skeletal muscles during exercise (Guyton 2000; Kravitz, 2010). The overall resultant effect is increasing blood flow and with regular exercises, the arterioles become adapted to the vasodilation. The stretching of the blood vessels also stimulates neural control; the baroreceptors send impulses to the vasomotor centre in the brain. This in turn reduces the excitatory impulses that are usually

sent from the vasomotor centre via the sympathetic nerves to the arterioles. The overall effect of this is vasodilatation of the arterioles and reduced blood pressure (Guyton, 2000). With regular bouts of exercise, the chronic effect is a long lasting reduction in blood pressure (Shenoy *et al*., 2009; Kravitz, 2010).

The predominant significant difference in scales and domains of the QoL in this group may be attributed to an increased ability to perform activities of daily living, apart from the physiological and psychosocial effect of the exercise intervention (Osho *et al*., 2009). The combined complementary and beneficial strengthening effect of the resistance exercises performed by the subjects may also be paramount in improvement of overall glucose control (Laaksonen, 2003; Hung *et al*., 2004, Kennedy *et al*., 2003). Improved cardio-respiratory function and skeletal muscle function which helps in glucose control and enhanced performance of work including recreational activities are often accompanied by positive psychosocial benefits which may results in better QoL above average as observed in the subjects this group.

Comparison of Cardiopulmonary, Biochemical, Anthropometric and Quality of Life Variables of individuals with T2DM Following Combined Weight Bearing Aerobic Exercise with Resistance Exercises and Combined Non-Weight Bearing Aerobic exercise with Resistance Exercises

This study suggested that individuals with T2DM who undergo weight bearing aerobic exercise on treadmill combined with resistance exercise and those who undergo non-weight bearing exercise on bicycle ergometer may not have a lesser or superior benefit over each other in terms of positive responses in their cardiorespiratory functions and glucose control (HbA1C). However better pulmonary functions; FVC and FEV1 and reduction in waist circumference may be recorded in those who undergo weight bearing aerobic exercise on treadmill combined with resistance exercise.

During whole-body aerobic exercise such as treadmill walking, whole-body oxygen consumption increases by as much as 20-fold and even greater increases occur in the working muscles with additional resistance exercise (American Diabetes Association 2003b). To meet its energy needs under these circumstances, skeletal muscle uses, at a greatly increased rate, its own stores of glycogen and triglycerides, as well as free fatty acids (FFAs) derived from the breakdown of adipose tissue triglycerides and glucose released from the liver leading to decreased blood glucose level (American Diabetes Association 2003b). With improved glucose control and negative correlation between HbA1c and pulmonary variables recorded in subjects in this study post intervention, microvascular complications and inflammations of lung tissue are probably averted. The result is thus an increased and improved lung function which was observed in the FEV1, FVC and VO2 max values as predominantly recorded in the subjects in groups I and in VO2max and FEV1 which was also recorded in group II who had exercise interventions.

Improvement in cardio-respiratory function has been reported not to result from changes in the lung's ability to expand (Baldi *et al*., 2010). In general, individuals with T2DM who perform aerobic exercise regularly do not substantially change measures of pulmonary function such as the amount of air able to be blown out after taking the largest breath possible (FVC) (Baldi *et al*., 2010). This may explain the insignificant FVC values reported at 12^{th} week post intervention in the across group comparison despite significant improvement in FEV1 in both exercise groups I and II during the intervention period. In addition, increase expiratory muscle strength has been linked to increased FEV1 and FVC (Jones and Magdalene, 2006). However, assessment of strength of abdominal muscles which were the major expiratory muscles exercised during the resistance exercises in the study was not done and thus we could not accurately ascertain this report. However, the significant reduction in the waist circumference is a positive sign of improvement in abdominal muscle tone and reduction in fats.

No physiological changes were significantly associated with scores on the QoL survey in a study with aerobic exercise intervention on sedentary persons with DM (Holton, 2003).In addition, neither training nor the presence of T2DM significantly affected the physical or mental component scores on the QoL survey (Holton, 2003). Significant improvement noted in the domains of the QoL of the studied DM subjects using the multidimensional scales of the Diabetes Quality of Life Clinical Trial Questionnaire- Revised was in support of the findings of Rose *et al* (2002) who reported substantial improvements in the QoL of T2DM patients post training. It is also partly in support of the study by Miu *et al*., who reported significant improvement in physical function but not on mental component (Miu *et al*., 2008).

However, QoL is multi-dimensional; it depends largely on how individuals view their physical and psychosocial well-being. Several factors influence it in T2DM patients (Borrott and Bush, 2008). Exercise had been reported to be one of the active coping strategies for an improved QoL in people with DM (Rose *et al*., 2002). The significant difference in QoL of the subjects when across group comparison was done in the study may be partly attributed to the significant improvement in the cardiopulmonary and biochemical variables. The clinical parameters collected by physical examination and blood pathology assay in the studied people with DM which include glycated haemoglobin (HbA1c), body weight/body mass index, blood pressure, FEV1, FVC and VO_2max had been reported to be useful measure of incidence and progression of secondary disease processes such as complications of microvascular and macrovascular disease (CVD) including disorders in people with DM (Nathan *et al*., 2007). Reduction in occurrence of these complications had been linked to stability in these clinical parameters (Borrot and Bush 2008). Decreased incidence of these complications of which cardiopulmonary complication is one, lessens the likelihood of poor QoL (National Health Priority Action Council, 2006). Hence, the probable explanation of the significant improvement in the QoL of individuals with T2DM in this study after the twelve week study period, especially those who

had exercise intervention. They might have been positively influenced by the significant reduction in mean blood pressure (both systolic and diastolic), rate pressure product, glucose control (HbA1c) and increase VO_2max, FVC and FEV1 which occurred in these subjects.

In addition, improved cardiorespiratory function especially in VO_2max means that the body is able to perform exercise much more efficiently. The body can thus effectively get oxygen into the blood stream and transport it to the working muscles, where it is needed for the metabolic processing of energy. In other words, subjects in the exercise groups I and II will thus finds strenuous exercise and physical activity far less strenuous with less experience of fatigue than those who do not exercise. Vitality may therefore be improved and the overall resultant effect is improvement in QoL above average apart from the additional psychosocial benefits which therapeutic exercise intervention may bring.

Determination of Time Frame When Therapeutic Effect of Combined Aerobic and Resistance Exercises Occur on the Cardiovascular, Pulmonary, Biochemical, Anthropometric and Quality of Life Variables of Individuals with T2DM.

In comparing the weight bearing aerobic exercise on treadmill and non-weight bearing aerobic exercise on bicycle ergometer when combined with resistance exercise with a control group with no exercise intervention, significant changes in cardiovascular variables; RADBP and RRPP occurred as early as fourth week of the study period. These trends continue to the eighth and 12^{th} week except in the RASBP which was only at the 12^{th} week. Likewise in the pulmonary variables, significant changes was observed in VO2max, FVC and FEV1 as early as the fourth week with the trend continuing to the eighth and twelfth week when exercise group I was compared with the control group with no exercise intervention. Improvement was also noted in the, WC and QoL variables as early as the 4^{th} week of the study period and in the biochemical variable (HbA1c) values post 12 weeks intervention in the exercise groups. Greater

improvement in the pulmonary variables was recorded in group I as revealed in the post hoc results in FEV1 which recorded significant increase at 4^{th}, 8^{th} and 12^{th} week while been significantly increased in group II only at 12^{th} week. FVC was also significantly increased in group I at end of 4^{th} and 8^{th} week while it was not significant at all in group II. In addition post hoc test shows significant difference in waist circumference at 4^{th}, 8th, and 12^{th} week while no significant difference was recorded at in group II.

Studies have established that exercise must be consistent and continuous for therapeutic effect to occur (Ronald *et al*., 2007; Gordon *et al*., 2008). The result of this study showing a positive effect of the combined therapeutic exercises as early as 4^{th} week as recorded in the exercise groups suggested the combined effects that these form of exercises may have on the physiological and biochemical processes of the body of the studied DM patients. There is also skeletal muscle disposition of glucose produced in the process and the untoward effect on the overall glucose control might have been responsible for this early significant improvement observed (American Diabetes Association, 2002b). In addition to its role in preserving musculoskeletal function and independence, resistance exercise has been shown to favourably influence several metabolic and cardiovascular disease (CVD) risk factors that were traditionally thought to be exclusively associated with aerobic exercise (Ronald *et al*.,2005; Ronald *et al*., 2007). Findings from previous studies have supported resistance exercises as being comparable to aerobic exercises in ameliorating CVD risk factors for more than a decade now (Ronald *et al*., 2007). A meta-analysis of randomized controlled trials also concluded that progressive resistance exercise is efficacious for reducing resting systolic and diastolic blood pressure in adults (Shenoy *et al*., 2009), the author to this meta-analysis study admitted that reductions in blood pressures were modest, this study further effectively disputes the myth that resistance exercises are a detriment to blood pressure control.

The improvement observed in the pulmonary functions FEV1, FVC and VO2max in the exercise groups as early as 4th week post intervention (especially in the exercise group I) when across group comparison was done in this study may be attributed to the improvement in glucose metabolism which has been reported to occur acutely and immediately after exercise thus producing its effect even till 48 hour post exercise session (Davis *et al*., 2004; Kaminsky *et al*., 2010). The resultant effect of this is an improved glucose control as consistent exercise sessions continue. In addition, since the subjects in the exercise groups in this study performed combined aerobic and resistance exercises thrice per week for twelve week (three months), this might have enabled adequate glucose control (HbA1c) which usually is measured estimated within three month. Reduced lung volumes and airflow limitation has been reported to be chronic complications of T2DM. The severity of this decrease has been reported to relate to glycaemic exposure (Davis *et al*., 2000). Poor glucose control has been linked to microvascular complications and reduced ventilatory function of the lungs. Airflow limitation is a predictor of death in T2DM after adjusting for other recognized risk factors (Davis *et al*., 2000).

This study suggested that individuals with T2DM who undergo weight bearing aerobic exercise on treadmill combined with resistance exercise and those who undergo non-weight bearing exercise on bicycle ergometer may not have a lesser or superior benefit over each other in terms of positive responses in their cardiorespiratory functions and glucose control (HbA1C). However better pulmonary functions; FVC and FEV1 and reduction in waist circumference may be recorded in those who undergo weight bearing aerobic exercise on treadmill combined with resistance exercise. In addition, therapeutic effect of moderate intensity combined aerobic and resistance exercise occur as early as fourth week post exercise intervention, assessment of patients response in terms of therapeutic effect and improvement on the cardiopulmonary, biochemical, anthropometric and QoL variables following prescription of combined aerobic and

resistance exercises should thus commence as early as the fourth week post intervention in people with T2DM.

5.2 Summary of Findings

1. Weight bearing aerobic exercise using treadmill at 1% gradient when combined with resistance exercise brought about significant improvement in cardiopulmonary, biochemical and QoL variables. An anthropometric variable WC was also improved in the studied people with T2DM. FVC was significantly increased
2. Non-weight bearing aerobic exercises using bicycle ergometer when combined with resistance exercises brought about improvement in cardiopulmonary, biochemical, and QoL of the subjects who had these interventions.
3. Significant beneficial effect of aerobic exercise when combined with resistance exercises on the cardiopulmonary, biochemical and QoL variables was recorded in the exercise groups I and II when compared with the control group III. However, better pulmonary functions; FVC and FEV1 and reduction in waist circumference was recorded in those who undergone weight bearing aerobic exercise on treadmill combined with resistance exercises.
4. Therapeutic effect of moderate intensity combined aerobic and resistance exercise on the cardiopulmonary (RRPP, VO_2max and FEV1) and QoL variables occurred as early as fourth week post exercise intervention, the trend of this effect continue through the eighth and twelfth week post intervention.

5.3 Contributions to Knowledge

1. Weight bearing aerobic exercise on treadmill at 1% gradient when combined with resistance exercises brought about significant improvement in cardiopulmonary, biochemical, anthropometric and QoL variables of the studied T2DM patients.

2. Non-weight bearing aerobic exercises on bicycle ergometer when combined with resistance exercises brought about significant improvement in the cardiopulmonary, biochemical and QoL variables of the studied T2DM patients.
3. Non-weight bearing aerobics combined with resistance exercise can be as beneficial as weight bearing aerobic combined with resistance exercise. However, in the existence of pulmonary dysfunction such as low lung volumes, the advantage of weight bearing aerobic combined with resistance exercise should be considered in the absence of foot pathology and if the advantages of such prescription outweighs the disadvantages. In the absence of significant reduction in the pulmonary variables, Non-weight bearing aerobics combined with resistance exercise will be suggested.
4. Therapeutic effect of moderate intensity combined aerobic and resistance exercise on some cardiopulmonary and QoL variables occurred as early as the fourth week post exercise intervention, the trend of this effect continued with consistence exercise intervention.

5.4 Conclusion

T2DM is a worldwide health problem predisposing to markedly increased cardiopulmonary morbidity and mortality (Zimmet *et al*., 1997) with resultant poor QoL (Vinik *et al*., 2003). It requires multifactorial treatment which should target obesity, hyperglycaemia and other comorbidity which affect the QoL of people with T2DM. Regular exercise leads to numerous and varied physiological, biochemical and psychosocial changes that are beneficial from a health standpoint in people with T2DM.

Aerobic exercise when combined with resistance exercise either on treadmill or bicycle ergometer both gave significant therapeutic effects. Neither one each is superior over the other.

However, better improvement in pulmonary function may be recorded in individuals who perform aerobic exercise on treadmill combined with resistance exercises.

Improvement in the cardiopulmonary functions, glycaemic control, QoL may be brought about by the combined effect of both aerobic and resistance exercises. These modes of therapeutic exercises should thus be the cornerstone of exercise program for people with T2DM. Prescribed correctly and with adequate considerations of the barriers, motivation and medical concerns facing people with DM, combined exercise can be a safe and effective treatment strategy in T2DM patients. Progress monitoring should resume as early as four weeks after prescription of exercise especially in patient with T2DM who recorded abnormality in cardiopulmonary functions at baseline of assessment. Motivational measures to stimulate continuity and consistence performance of therapeutic exercise in patient with T2DM may thus be enhanced once the early therapeutic benefit is established in patient clinical parameters.

5.5 Recommendations

Physiotherapists should work as part of rehabilitation team involved in the management of cardiopulmonary complications of people with T2DM. Therapeutic exercise prescription to individuals with T2DM should involve a combination of aerobic and resistance exercises. Adequate assessment of the condition of the lower extremities, especially the feett should be taken into consideration in order to ascertain the appropriate mode of aerobic exercise which should be prescribed.

Non-weight bearing aerobics combined with resistance exercise can be as beneficial as weight bearing aerobic combined with resistance exercise. However, in the existence of pulmonary dysfunction such as low lung volumes the advantage of weight bearing aerobic combined with resistance exercise should be considered in the absence of foot pathology and if the advantages of such prescription outweighs the disadvantages.

Assessment of cardiopulmonary functions of people with T2DM post exercise prescription should commence as early as four weeks post intervention for the purpose of progress monitoring and development of motivational measures for patients with T2DM.

5.6 Implications for further studies

Cardiopulmonary complications and reduction in QoL are major issues which pose significant challenges and economic burden to people with T2DM. Several risk factors have been attributable to these complications in T2DM patients; one of such is obesity. Further studies may thus be needed to evaluate the fat body composition of people with T2DM using underwater weighing or DXT scan post exercise prescription in other to accurately ascertain the anthropometric indices of the subjects in response to therapeutic exercises. Future studies may also need to assess the respiratory muscle strength of the T2DM patients in response to therapeutic exercises.

Many rehabilitation approaches may play major roles in enhancing therapeutic benefits in people with T2DM, therefore, other studies may need to evaluate the effect of other modes of aerobic and resistance exercises on the cardiopulmonary, biochemical and QoL variables of individuals with T2DM. In conclusion further studied may consider a biweekly assessment of outcome measures post intervention rather than the monthly basis assessed in this study.

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APPENDIX 1

INFORMED CONSENT

TITLE OF STUDY: Cardiopulmonary and Quality of life responses of individuals with Type 2 Diabetes to therapeutic exercises

INVESTIGATOR(S): OSHO Oluwaseyi A (mrs)

CONTACT PHONE NUMBER: 08063315130

Purpose of the Study

You are invited to participate in a research study. The purpose of this study is to show more light on the responses of people with diabetes to controlled and monitored exercises.

Participants

You can participate in the study if you are a patient with diabetes of duration between 1 to 10 years. If you are between ages 20-70 years old with no muscle or joint problems, non-smoker and non-alcoholic.

Procedures

If you volunteer to participate in this study, you will be asked to do some exercises which will increase the rate at which you breathe and at which your heart is beating.

Benefits of Participation

There may/may not be direct benefits to you as a participant in this study. However, we hope to learn more on how exercises help people with diabetes to live a healthier life with an improved quality of life. This research may also guide us in design and prescription of exercises to individuals with diabetes.

Risks of Participation

Your safety is guaranteed during participation in this study as it carries minimal risk. However, you may become tired after walking on a treadmill or after pedaling the bicycle ergometer which are some of the equipment to exercise with in this study. Your blood sample will also be taken for analysis at the chemical pathology laboratory. All this procedures and feeling are normal, not life threatening and should not cause any harm or negative after effect to your health.

Cost /Compensation

There will not be financial cost to you to participate in this study. The study will take 30 to 45 minutes per session, three times in a week between 10a.m to 2p.m from Monday to Friday. It will last for duration of 12 weeks.

Contact Information

If you have any questions or concerns about the study, you may contact the above named investigator on the stated phone number. For questions regarding the rights of research subjects, any complaints or comments regarding the manner in which the study is being conducted you may contact department of Physiotherapy, College of Medicine of the University of Lagos, Idi-Araba, Lagos.

Voluntary Participation

Your participation in this study is voluntary. You may refuse to participate in this study or in any part of this study. You may withdraw at any time without prejudice to your relations with the hospital. You are encouraged to ask questions about this study at the beginning or any time during the research study.

Confidentiality

All information gathered in this study will be kept completely confidential. No reference will be made in written or oral materials that could link you to this study. All records will be stored in a locked facility at University of Lagos and the teaching hospitals from which you are recruited.

Participant Consent:

I have read the above information and agree to participate in this study. I am at least 20 years of age. A copy of this form has been given to me.

Signature of Participant	**Date**
Participant Name	

APPENDIX 2

DATA COLLECTION FORM

HOSPITAL NUMBER ……

GROUP ……

AGE …….

GENDER ……..……...

EDUCATIONAL LEVEL ……..

DATE OF ASSESSMENT …….

DURATION OF DIABETES …….

MODE OF MANAGEMENT ……

MEDICATION RECORD ……..

NATIONALITY ……..

RELIGION ……..

TELEPHONE NUMBER ……

Anthropometric variables	Baseline	End of 4th Week	End of 8th Week	End of 12th Week
Weight (kg)				
Height (m)				
Waist circumference (cm)				
Hip circumference (cm)				
Waist hip ratio				
BMI				
Cardiovascular variables				
Resting arterial systolic BP (mmHg)				
Resting arterial diastolic BP(mmHg)				
Resting heart rate (b/m)				
Rate pressure product b/min.mmHg				
Pulmonary variables				
FVC (litres)				
FEV1 (litres)				
VO_2max (kg/ml/min)= 132.853 - (0.0769 x W) - (0.3877 x Age) + (6.315 x Gender) - (3.2649 x T) - (0.1565 x HR) W= Weight = Gender , male=1, female= 0 T= Total time spent to walk for 1 mile= HR= Heart rate attained after completion of 1 mile test=…….b/min Age at last birthday…….years				
Biochemical variable				
HbA1c (%)				
Quality of Life records				
Physical functioning				
Frequency of symptom				
Treatment satisfaction				
Health distress				
Satisfaction				
Treatment satisfaction				
Energy and fatigue				
Mental health				
Overall QoL				

APPENDIX 3

INTERVENTION RECORD FORM

Aerobic exercise intensity record

Calculated Maximum Heart Rate: Male; 220- Age in years=

: Female; 220- Age in years=

Calculated Target heart rate

Target Heart rate= 60-80% (MHR - Resting Heart Rate) + Resting Heart Rate=

Heart rate for Intensity range:

60%=

70%=

80%=

		Week 0 to 4	Week 5-8	Week 9-12
Target heart		60%	70%	80%
	1RM	50%	60%	70%
Elbow				
Flexor/extensors				
Knee				
Flexors/extensors				

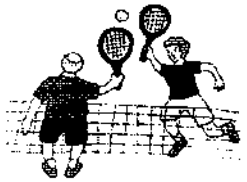
APPENDIX 4

RAPID ASSESSMENT OF PHYSICAL ACTIVITY QUESTIONAIRRE

Physical Activities are activities where you move and increase your heart rate above its resting rate, whether you do them for pleasure, work, or transportation.

The following questions ask about amount and intensity of physical activity you usually do. The intensity of the activity is related to the amount of energy you use to do these activities.

Examples of physical activity intensity levels:

Light activities • your heart beats slightly faster than normal • you can talk and sing	 Walking Leisurely  Stretching  Vacuuming or Light Yard Work
Moderate activities • your heart beats faster than normal • you can talk but not sing	 Fast Walking  Aerobics Class  Strength Training  Swimming Gently
Vigorous activities • your heart rate increases a lot • you can't talk or your talking is broken up by large breaths	 Stair Machine  Jogging or Running  Tennis, Racquetball, Pickleball or Badminton

HOW PHYSICALLY ACTIVE ARE YOU?

(Check one answer on each line)

RAPA 1	1.	I rarely or never do any physical activities	Yes ☐	No ☐
	2.	I do some **light** or **moderate** physical activities, but not every week.	Yes ☐	No ☐
	3.	I do some **light** physical activity every week.	Yes ☐	No ☐
	4.	I do **moderate** physical activities every week, but less than 20 minutes a day or 5 days a week.	Yes ☐	No ☐
	5.	I do vigorous physical activities every week, but less than 20 minutes a day or 3 days a week.	Yes ☐	No ☐
	6.	I do 30 minutes or more a day of **moderate** physical activities, 5 or more days a week.	Yes ☐	No ☐
	7.	I do 20 minutes or more a day of **vigorous** physical activities, 3 or more days a week.	Yes ☐	No ☐

RAPA 2 3 = both 1&2	1.	I do activities to increase muscle **strength,** such as lifting weights or calisthenics, once a week or more	Yes ☐	No ☐
	2.	I do activities to improve **flexibility,** such as stretching or yoga, once a week or more.	Yes ☐	No ☐

SCORING INSTRUCTIONS

RAPA 1: Aerobic

To score, choose the question with the highest score with an affirmative response. Any number less than 6 is suboptimal.

For scoring or summarizing categorically:

Score as sedentary:

1. I rarely or never do any physical activities.

   Score as under-active:

2. I do some light or moderate physical activities, but not every week.

   Score as under-active regular – light activities:

3. I do some light physical activity every week.

   Score as under-active regular:

4. I do moderate physical activities every week, but less than 30 minutes a day or 5 days a week.

5. I do vigorous physical activities every week, but less than 20 minutes a day or 3 days a week.

   Score as active:

6. I do 30 minutes or more a day of moderate physical activities, 5 or more days a week.

7. I do 20 minutes or more a day of vigorous physical activities, 3 or more days a week.

RAPA 2: Strength & Flexibility

I do activities to increase muscle strength, such as lifting weights or calisthenics, once a week or more. (1)

I do activities to improve flexibility, such as stretching or yoga, once a week or more. (2)

Both. (3)

None (0)

APPENDIX 5

QUALITY OF LIFE ASSESSMENT: Diabetes Quality of Life Clinical Trial Questionnaire-Revised

Physical functioning (6 questions)	LIMITED FOR MORE THAN FOUR WEEKS	LIMITED FOR FOUR WEEKS OR LESS	NOT LIMITED AT ALL
Q-1. For how long (if at all) has your health limited:			
a. The kinds or amounts of vigorous activities you can do, like lifting heavy objects, running or participating in strenuous sports?	a. 1	2	3
b. The kinds or amounts of moderate activities you can do, like moving a table, carrying groceries or bowling?	b. 1	2	3
c. Walking uphill or climbing a few flights of stairs?	c. 1	2	3
d. Bending, lifting, or stooping?	d. 1	2	3
e. Walking one block?	e. 1	2	3
f. Eating, dressing, bathing or using the toilet?	f. 1	2	3

Energy/Fatigue (5 questions)	**(CIRCLE ONE NUMBER ON EACH LINE)**					
	ALL OF THE TIME	MOST OF THE TIME	A GOOD BIT OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
Q-2. How often during the past four weeks:						
a. Did you feel worn out?	a. 1	2	3	4	5	6
c. Did you have a lot of energy?	c. 1	2	3	4	5	6
e. Did you feel full of pep?	e. 1	2	3	4	5	6
g. Did you have enough energy to do the things you wanted to do?	g. 1	2	3	4	5	6
i. Did you feel tired?	i. 1	2	3	4	5	6
Health Distress (6 questions)						
Q-3. How often during the past four weeks:						
d. Were you discouraged by your health problems?	d. 1	2	3	4	5	6
e. Did you feel weighed down by your health problems?	e. 1	2	3	4	5	6

f. Were you afraid because of your health?	f. 1	2	3	4	5	6
h. Was your health a worry in your life?	h. 1	2	3	4	5	6
j. Were you frustrated about your health?	j. 1	2	3	4	5	6
k. Did you feel despair over your health problems?	k. 1	2	3	4	5	6

	(CIRCLE ONE NUMBER ON EACH LINE)					
	ALL OF THE TIME	MOST OF THE TIME	A GOOD BIT OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
Mental Health (5 questions)						
Q-4. How much of the time, during the past four weeks:						
a. Have you been a very nervous person?	a. 1	2	3	4	5	6
b. Have you felt calm and peaceful?	b. 1	2	3	4	5	6
c. Have you felt downhearted and blue?	c. 1	2	3	4	5	6
d. Have you been a happy person?	d. 1	2	3	4	5	6
e. Have you felt so down in the dumps that nothing could cheer you up?	e. 1	2	3	4	5	6

	(CIRCLE ONE NUMBER ON EACH LINE)				
	Very Satisfied	Moder-ately Satisfied	Neither Satisfied Nor Dissatis-fied	Moder-ately Dissatis-fied	Very Dissatis-fied
DQOL Satisfaction (15 questions)					
Q-5. Currently, how satisfied are you with:					
a. The amount of time it takes to manage your diabetes?	a. 1	2	3	4	5
b. The amount of time you spend getting check-ups? The time it takes to determine your	b. 1	2	3	4	5
sugar level?		2	3	4	5
d. Your current treatment?	d. 1	2	3	4	5
e. The flexibility you have in your diet?	e. 1	2	3	4	5
f. The burden your diabetes is placing on your family	f. 1	2	3	4	5
g. Your knowledge about your diabetes?	g. 1	2	3	4	5
h. Your sleep?	h. 1	2	3	4	5
i. Your social relationships and friendships?	i. 1	2	3	4	5
j. Your sex life?	j. 1	2	3	4	5
k. Your work, school, and household activities?	k. 1	2	3	4	5
l. The appearance of your body?	l. 1	2	3	4	5
m. The time you spend exercising?	m. 1	2	3	4	5
n. Your leisure time?	n. 1	2	3	4	5
o. Life in general?	o. 1	2	3	4	5
	Very Satisfied	Moder-ately Satisfied	Neither Satisfied Nor Dissatis-fied	Moder-ately Dissatis-fied	Very Dissatis-fied
Treatment Satisfaction (3 questions)					
Q-6. Your opinions about your current treatment for diabetes.					
a. How controlled do you feel your diabetes has been in the past four week?	a. 1	2	3	4	5
b. How satisfied have you been in the past four weeks with your treatment?	b. 1	2	3	4	5

c. How willing would you be to continue with your present treatment?	c. 1	2	3	4	5
	(CIRCLE ONE NUMBER ON EACH LINE)				
	A GREAT DEAL OF CHOICE	A LOT OF CHOICE	SOME CHOICE	A LITTLE CHOICE	NO CHOICE
Treatment Flexibility (10 questions)					
Q-7. During the past four weeks, how much choice do you have in:					
a. How often you have to eat your meals or snacks?	a. 1	2	3	4	5
b. Eating your meals or snacks away from home?	b. 1	2	3	4	5
c. The timing of your meals or snacks?	c. 1	2	3	4	5
d. The kinds of food you eat?	d. 1	2	3	4	5
e. The amounts of food you eat?	e. 1	2	3	4	5
f. Planning your physical activities (e.g., walking, sports)?	f. 1	2	3	4	5
g. Planning your social activities (e.g.,, parties, visiting with family and friends)?	g. 1	2	3	4	5
h. Planning your daily activities (e.g., work, school, taking care of the house)?	h. 1	2	3	4	5
i. Participating in activities at the spur of the moment?	i. 1	2	3	4	5
j. Changing your plans at the spur of the moment?	j. 1	2	3	4	5

	(CIRCLE ONE NUMBER)					
	ALL SOME OF THE TIME	MOST OF THE TIME	A GOOD BIT OF TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
Frequency of Symptoms (7 questions)						
Q-8. How much of the time in the past weeks have you had these problems?						
a. Blurred vision (not correctable with glasses)	a. 1	2	3	4	5	6→
b. Nausea	b. 1	2	3	4	5	6→
c. Fatigue	c. 1	2	3	4	5	6→
d. Thirst/dry mouth	d. 1	2	3	4	5	6→
e. Excessive hunger	e. 1	2	3	4	5	6→
f. Frequent urination	f. 1	2	3	4	5	6→
g. Paresthesia (pins and needles of feet and hands)	g. 1	2	3	4	5	6→

How bothered have you been by these problems (Q8) in the past weeks?					
(CIRCLE ONE NUMBER)					
VERY BOTHERED				NOT AT ALL BOTHERED	
a.	1	2	3	4	5
b.	1	2	3	4	5
c.	1	2	3	4	5
d.	1	2	3	4	5
e.	1	2	3	4	5
f.	1	2	3	4	5
g.	1	2	3	4	5

Scoring instruction for Diabetes Quality of Life Clinical Trial Questionnaire-Revised

The survey produces 8 scale scores:

- Physical Functioning (PF)
- Treatment flexibility (TF)
- Frequency of symptoms (FS)
- Health distress (HD)
- Energy/fatigue (E/F)
- Satisfaction (SF)
- Treatment satisfaction (TS)
- Mental Health (MH)

• Scale scores are a sum of all items in the specific scale and do not require further standardization or weighting

- Scores are standardized to a 0-100 range converting the lowest possible score to 0 and the highest to 100
- Scores are norm-based: Mean = 50, Standard

Deviation = 10

Score Interpretation

• 50 is average; 0-49 is below average; 51-100 is above average. Scores below 50 indicate below average health status and should trigger further investigation, with increasing deviations providing higher need for further assessment.

APPENDIX 6

PAR-Q - The Physical Activity Readiness Questionnaire

Answer yes or no to the following questions:

1. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?
2. Do you feel pain in your chest when you do physical activity?
3. In the past month, have you had chest pain when you were not doing physical activity?
4. Do you lose your balance because of dizziness or do you ever lose consciousness?
5. Do you have a bone or joint problem that could be made worse by a change in your physical activity?
6. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?
7. Do you know of any other reason why you should not do physical activity?

If a prospective participant answered yes to one or more questions, a medical clearance along with information about specific exercise limitations were requested for before eligibility to join the intervention group based on the inclusion criteria. If the answered to all the PAR-Q questions is no, the prospective participant is cleared and eligible to join the intervention group.

APPENDIX 7

LAGOS UNIVERSITY TEACHING HOSPITAL

PRIVATE MAIL BAG 12003, LAGOS, NIGERIA

Chairman:
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REF. NO. ADM/DCST/221

13th September, 2010

Osho Oluwaseyi Abigail (Mrs.)
Ph.D Degree Student
u. f. s. Prof. & Head
Dept. of Physiotherapy
LUTH/CMUL

APPROVAL OF RESEARCH PROPOSAL

I wish to refer to your request on the above stated subject.

Approval has been granted to you to continue with the study title **"CARDIOPULMONARY AND BIOCHEMICAL RESPONSES OF INDIVIDUALS WITH TYPE 2 DIABETES TO THERAPEUTIC EXERCISES".**

Wishing you all the best in your study.

Thank you.

D. J. AKPAN
FOR: CHAIRMAN, RESEARCH & ETHICS COMMITTEE

APPENDIX 8

LAGOS STATE UNIVERSITY TEACHING HOSPITAL, IKEJA

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DIRECTORATE OF CLINICAL SERVICES AND TRAINING

HEALTH RESEARCH AND ETHICS COMMITTEE

REG. NO. NHREC 04/04/2008

PROJECT TITLE: "CARDIOPULMONARY AND BIOCHEMICAL RESPONSES INDIVIDUALSNWITH TYPE 2 DIABETES TO THERAPEUTIC EXERCISES".

REF: NO.: LREC/10/04/131

PRIN. INVESTIGATOR: MRS OSHO, OLUWASEYI

ADDRESS: DEPARTMENT OF PHYSIOTHERAPY, LUTH

DATE OF RECEIPT OF VALID APPLICATION: 30/04/10

DATE OF APPROVAL: 08/06/2010

This is to inform that the research described here in the submitted protocol, the consent forms, advertisements and other participant information materials have been reviewed and given full approval by the Health Research & Ethics Committee.

This approval dates from **08/06/2010 to 08/06/2012**. If there is any delay in starting the research, please inform the HREC so that the dates of approval can be adjusted accordingly. Note that no participant accrual or activity related to this research may be conducted outside of these dates. All inform consent forms used in this study must carry the HREC assigned number and duration of HREC approval study. In multiyear research, endeavor to submit your annual report to the HREC early in order to obtain renewal of your approval and avoid disruption of your research.

The National code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the code including ensuring that all adverse events are reported promptly to the HREC. No changes are permitted in the research without prior approval by the right HREC except in circumstances outlined in the code. The HREC reserves the right to conduct compliance visit to your research site without previous notification.

PROF. OGUNDIPE.O

Chairman, HREC-LASUTH

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