"AN INTERVENTIONAL STUDY OF PHYSICAL ACTIVITY ON HbA_{1C} AND VO_2Max IN TYPE 2 DIABETES MELLITUS."

BY

Dr. VINEETHA VITTAL, MBBS

DISSERTATION SUBMITTED TO
SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH,
TAMAKA, KOLAR, KARNATAKA
IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF MEDICINE
IN
PHYSIOLOGY

Under the guidance of

DR. VINUTHA SHANKAR.M.S. MD

DEPARTMENT OF PHYSIOLOGY
SRI DEVARAJ URS MEDICAL COLLEGE, KOLAR

2014

DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH,

TAMAKA, KOLAR, KARNATAKA.

DECLARATION BY THE CANDIDATE

I HEREBY DECLARE THAT THIS DISSERTATION/THESIS ENTITLED

"AN INTERVENTIONAL STUDY OF PHYSICAL ACTIVITYON HbA_{1C} AND VO_2Max IN TYPE 2 DIABETES MELLITUS"

IS A BONAFIDE AND GENUINE RESEARCH WORK CARRIED OUT BY ME UNDER THE DIRECT GUIDANCE OF

DR.VINUTHA SHANKAR.M.S, MD

PROFESSOR, DEPARTMENT OF PHYSIOLOGY,

SRI DEVARAJ URS MEDICAL COLLEGE, KOLAR

DATE:

PLACE: KOLAR

SIGNATURE OF THE CANDIDATE

DR. VINEETHA VITTAL

CERTIFICATE BY THE GUIDE

THIS IS TO CERTIFY THAT THE DISSERTATION ENTITLED

"AN INTERVENTIONAL STUDY OF PHYSICAL ACTIVITY ON HbA_{1C} AND VO_2Max IN TYPE 2 DIABETES MELLITUS"

IS A BONAFIDE RESEARCH WORK DONE

BY

DR. VINEETHA VITTAL

IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF

M.D IN PHYSIOLOGY

DATE:

PLACE: KOLAR

SIGNATURE OF THE GUIDE

DR.VINUTHA SHANKAR.M.S.MD
PROFESSOR
DEPARTMENT OF PHYSIOLOGY

ENDORSEMENT BY THE HOD, PRINCIPAL/HEAD OF THE INSTITUTION

THIS IS TO CERTIFY THAT THE DISSERTATION ENTITLED

"AN INTERVENTIONAL STUDY OF PHYSICAL ACTIVITY ON HbA_{1C} AND VO_2Max IN TYPE 2 DIABETES MELLITUS"

IS A BONAFIDE RESEARCH WORK DONE

BY

Dr. VINEETHA VITTAL

UNDER THE GUIDANCE OF

Dr. VINUTHA SHANKAR.M.S,

PROFESSOR,

DEPARTMENT OF PHYSIOLOGY.

SEAL & SIGNATURE OF THE HOD	SEAL & SIGNATURE OF THE PRINCIPAL
Dr. KARTHIYANEE KUTTY	**DR. M.B.SANIKOP**
DATE:	DATE:
PLACE: KOLAR	PLACE:KOLAR

COPYRIGHT

DECLARATION BY THE CANDIDATE

I HEREBY DECLARE THAT

SRI DEVARAJ URS UNIVERSITY, TAMAKA, KOLAR, KARNATAKA

SHALL HAVE THE RIGHTS TO PRESERVE,

USE AND DISSEMINATE THIS DISSERTATION / THESIS

IN PRINT OR ELECTRONIC FORMAT FOR ACADEMIC / RESEARCH PURPOSE.

DATE:
PLACE: KOLAR

SIGNATURE OF THE CANDIDATE

DR. VINEETHA VITTAL

SRI DEVARAJ URS MEDICAL COLLEGE, TAMAKA, KOLAR.

ETHICAL COMMITTEE

CERTIFICATE

THIS IS TO CERTIFY THAT, THE ETHICAL COMMITTEE OF SRI DEVARAJ URS MEDICAL COLLEGE, TAMAKA, KOLAR HAS UNANIMOUSLY APPROVED

DR. VINEETHA VITTAL,

POST GRADUATE STUDENT IN THE DEPARTMENT OF PHYSIOLOGY OF SRI DEVARAJ URS MEDICAL COLLEGE TO TAKE UP THE DISSERTATION WORK ENTITLED

"AN INTERVENTIONAL STUDY OF PHYSICAL ACTIVITY ON HbA_{1C} AND VO_2Max IN TYPE 2 DIABETES MELLITUS"

TO BE SUBMITTED TO THE
SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH,

TAMAKA, KOLAR.

MEMBER SECRETARY **PRINCIPAL**

ACKNOWLEDGEMENT

It is a pleasure to thank the people who made this thesis possible. I thank each and everyone for the knowledge they imparted to me & for the time they graciously gave me.

I wish to express my deepest gratitude to Dr. Vinutha Shankar, Professor, Department of Physiology, SDUMC, Kolar at the beginning of this study, who kindly suggested the subject of this study to me, who has the substance of a genius and who has been my teacher and supervisor in scientific work. I thank her for her excellent and tireless guidance, encouragement and patience throughout the years of the study.

No words can express my gratitude to Dr. Karthiyanee Kutty, Professor & HOD, Department of Physiology, who continually and convincely conveyed a spirit of adventure in regard to research. She showed and maintained a constant and most active interest during the entire period of this work. It was a pleasure to be associated with her contagious enthusiasm, persuasive and stimulating personality.

I wish to express my gratitude to Dr Anand Kumar, consultant and HOD of cardiology, for his guidance and advice throughout my study.

I also thank Dr. Sunanda Nayak., Professor, department of Physiology, for having been a source of inspiration. I am very fortunate to obtain benefit of her vast experience, valuable guidance, sincere suggestion, keen interest and constant encouragement at each step throughout my post-graduate career.

My special thanks to Dr Jagadamba, Dr Raja Reddy and Dr Geetha, Assistant Professors and Mrs. Usha Shenoy, lecturer, Department of Physiology for their invaluable guidance, kind support, co-operation and timely advice.

I render my hearty thanks to Dr. Ravi Shankar, Statistician, SDUMC for helping me in statistical analysis.

I wish to express my deepest gratitude to Dr.Ashwini priyanka, Dr.Sindhu, Dr. Sumitra, and Dr. Parasuraman for their help

I express my sincere heart felt gratitude to all the subjects for giving their willingness to participate in this study.

I thank all non teaching staff of the department for their kind co-operation.

Above all I am proud of my parents Dr. Peter Vittal and Dr.Jayanthi Vittal, my grandmother Dr Gnanasundari Amruthraj, my in-laws Mr Vijayananda H S and Mrs Sarvamangala S V for their constant encouragement, blessings, love & attention which has made me accomplish this work. They have formed the basis of this work without which it would not have seen the light of the day.

Of special value in this work was the appreciative support, love and co-operation of my husband Dr. Anil Kumar S V, who helped me throughout the thesis work.

In the end, I thank The Almighty for the blessing for the fulfillment of this work.

Date: **SIGNATURE**

Place: Kolar *(Dr. Vineetha Vittal)*

LIST OF ABBREVIATIONS

DM	-	Diabetes Mellitus
T2DM	-	Type 2 Diabetes Mellitus
HbA_{1c}	-	Glcosylated haemoglobin
MET	-	Metabolic Equivalent
IRS	-	Insulin receptor substrates
PI3K	-	Phosphatidylinositol 3-kinase
VO_2	-	Submaximal oxygen uptake
VO_2Max	-	Maximal oxygen uptake
MODY	-	Maturity Onset Diabetes Mellitus of the young
HPLC	-	High Performance Liquid Chromatography
HbA	-	Adult Haemoglobin
HR	-	Heart Rate
IGT	-	Impaired glucose tolerance
ADA	-	American Diabetes Association
IHD	-	Ischemic Heart Disease
BMI	-	Body mass index
WHR	-	Waist Hip Ratio
IGT	-	Impaired glucose tolerance
WHO	-	World Health Organisation
MET	-	Metabolic Equivalent
GLUT	-	Glucose transporter
NRF-1	-	Nuclear Respiratory Factor
TFAM-1	-	Mitochondrial Transcription factor A
PGC -1	-	Proliferator-Activated Receptor , coactivator

ABSTRACT

Background and objectives:

Type 2 diabetes is a global problem with devastating human, social and economic impact. India is one of the rapidly developing countries of the world. The rapid urbanization has brought along with it a sedentary lifestyle, which is an important contributor for diabetes.

Very few studies have analyzed the effect of sedentary life style on diabetes, so far. Worldwide, medications are prescribed by physicians for the control of diabetes but they neglect to prescribe a physical exercise regimen, which is very essential.

Physical activity and exercises cause an improvement of cardio-respiratory fitness .The best measure of cardio-respiratory fitness is VO_2Max, which is the rate of oxygen usage under maximal aerobic metabolism. Exercise prescription which may include a simple physical activity like brisk walking for half an hour, will improve the fitness of the body. The duration and type of physical activity will contribute to the efficiency of fitness. It has also been demonstrated that regular physical activity has beneficial effects in glycaemic control.[2] Glycaemic control is estimated by HbA_{1c}.

Most of the studies have used a combination of aerobic and resistance training, whereas fewer studies have been available regarding the effectiveness of aerobic fitness alone. As it is not feasible to apply resistance training in rural population, we have included only aerobic activity as a physical activity intervention in diabetics. This study was designed to evaluate the effect of this exercise prescription on VO_2Max and HbA_{1c} in type 2 diabetes mellitus patients.

Materials & Methods

Thirty patients with diagnosed type 2 diabetes mellitus without any obvious complications were selected considering the inclusion and exclusion criteria. Their VO_2Max was calculated using the Bruce protocol and HbA_{1c} was estimated by ion exchange chromatography with Bio-Rad $D_{10.}$ Then they were advised to follow an exercise prescription in the form of brisk walking 30mins/day for atleast 5 days/week for a duration of 6 months .After which they returned to check their VO_2Max and HbA_{1c}.The results obtained were statistically analysed.

Results:

In our study of 30 subjects, mean age was 45.33 $\pm$ 6.66 yrs and baseline VO_2Max was 32.67 $\pm$ 11.99 ml/kg/min(low for given age) and $HbA_{1C\ \%}$values were high (7.58$\pm$ 1.66) . Around 63.3% had poor cardio respiratory fitness. After a life style intervention in the form of walking it was found that VO_2Max increased and HbA_{1c} decreased significantly.

Conclusion:

Low cardio-respiratory fitness is prevalent in type 2 diabetics. Exercise improves cardio respiratory fitness as shown by increase in the VO_2 Max. Exercise lowers glycaemic index as shown by decrease in $HbA_{1C.}$ Hence, awareness regarding lifestyle modification in terms of increased physical activity should be emphasized. A suitable exercise regimen should be incorporated along with diet and drug prescription.

Key words: Type 2 diabetes, VO_2Max, $HbA_{1c,}$ Physical activity

CONTENTS

SL.NO	PARTICULARS	Page no
1	INTRODUCTION	1-2
2	AIMS & OBJECTIVES	3-4
3	REVIEW OF LITERATURE A. History of Diabetes B. History of Exercise physiology C. Cardio-Respiratory fitness D. Determinants of maximal oxygen consumption E. Role of physical activity in diabetes F. Complications of diabetes mellitus G. Exercise prescription H. Review of other works	5-56
4	MATERIALS AND METHODS	57-63
5	RESULTS AND ANALYSIS	64-67
6	DISCUSSION	68-72
7	CONCLUSION AND SUMMARY	73-77
8	BIBLIOGRAPHY	78-90
9	ANNEXURES	91
10	MASTER CHART	92

LIST OF TABLES

SL.NO	*DETAILS OF THE TABLE*	Page no
1	Bruce protocol	21
2	Bruce Protocol Norms for Men	61
3	Bruce Protocol Norms for Women	62
4	Baseline characteristics of the study group	65
5	Comparison of post interventional data with baseline data.	67

LIST OF GRAPHS

SL.NO	*DETAILS OF THE GRAPHS*	Page no
1	Chart showing the baseline cardiorespiratory fitness	65
2	Correlation between baseline HbA_{1C} and VO_2 Max	66
3	Chart showing the post interventional cardio-respiratory fitness	66
4	Correlation between post interventional HbA_{1C} and VO_2 Max	67

LIST OF FIGURES

SL.NO	*DETAILS OF THE FIGURES*	Page no
1	Relation between Insulin secretion and sensitivity	13
2	Electrocardiograph leads attached	21
3	Insulin signal transduction pathway in skeletal muscle	42
4	Mechanisms of glucose uptake into skeletal muscle	46
5	Alternative pathway for glucose transport in skeletal muscle	47

INTRODUCTION

INTRODUCTION:

Type 2 diabetes is a global problem with devastating human, social and economic impact. Today more than 240 million people worldwide are living with diabetes. Each year 7 million more people develop diabetes.[1] India is one of the rapidly developing countries of the world. The rapid urbanization has brought along with it a sedentary lifestyle, which is an important contributor for diabetes. And hence, India has the second highest diabetes prevalence in the world.

Very few studies have analyzed the effect of sedentary life style on diabetes, so far. Worldwide, medications are prescribed by physicians for the control of diabetes but they neglect to prescribe a physical exercise regimen, which is very essential.

Physical activity and exercises cause an improvement of cardio-respiratory fitness .The best measure of cardio-respiratory fitness is VO_2Max, which is the rate of oxygen usage under maximal aerobic metabolism. Exercise prescription which may include a simple physical activity like brisk walking for half an hour, will improve the fitness of the body. The duration and type of physical activity will contribute to the efficiency of fitness. It has also been demonstrated that regular physical activity has beneficial effects in glycaemic control.[2] Glycaemic control is estimated by HbA_{1c}.

Most of the studies have used a combination of aerobic and resistance training, whereas fewer studies have been available regarding the effectiveness of aerobic fitness alone. As it is not feasible to apply resistance training in rural population, we have included only aerobic activity as a physical activity intervention in diabetics. This study was designed to evaluate the effect of this exercise prescription on VO_2 Max and HbA_{1c} in type 2 diabetes mellitus patients.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

1. To assess baseline VO_2 Max as a measure of cardio respiratory fitness in type 2 diabetes mellitus.
2. To correlate VO_2 Max with HbA_{1c} levels, which is a marker of glycaemic control.
3. To prescribe aerobic activity for a period of 6 months (Exercise prescription as intervention).
4. To compare post interventional VO_2Max and HbA_{1c} levels with baseline values.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

A. HISTORY OF DIABETES

Diabetes is one of the oldest diseases known to mankind.

Up to 600 AD- It is described by physicians of ancient civilized world like Greece, India, China and Egypt. It was first mentioned by an Egyptian, Ebers on papyrus in 1500BC. He had a medical complication of diabetes and has described about polyuria. Then in 500 AD Sushruta described the comprehensive picture of the disease as Madhumeha (rain of honey) because of the sweet taste of urine which attracted ants and insects. Chinese physician Nezling in 400 BC and Greek celsus 30 BC to 50 AD also described important symptoms of the disease. Aretaeus of Cappedocia (Greece) is believed to have coined the term 'diabetes' conveying excessive water drinking and polyuria.[3]

Medieval period (600-1500) - Chhuan of China in 7th century AD and Arabian physician Avicenna described certain complications of diabetes like sexual dysfunction and gangrene.[3]

Advent of modern era (1500-1750) - Thomas Willis in 16th century and Matew Dobson in 1776 described the sweetness of urine. He evaporated the samples of urine and the residue which was left looked like brown sugar.

During 1850, Claude Bernard proposed hyperglycemia as the cardinal symptom of diabetes. In 1879, Paul Langerhans submitted his thesis to Berlin university. He described the presence of different kinds of tissue scattered among the acini (the islets) throughout the pancreatic gland.

The role of pancreas was established by Von Mering. He was especially interested in observing the role of pancreas in digestion. He sought the help of Minkowski who surgically removed the pancreas from 2 dogs. By the next day both dogs manifested with polyuria. Diabetes was diagnosed on testing the urine for sugar.

Minkowski demonstrated that grafting a piece of freshly removed pancreas under the skin of dogs prevented appearance of glycosuria as long as the graft was intact.

In 1902 Sterling proposed the hypothetical islet (insular) cell secretion as 'hormone'. One and half year later, Jean de Meyer applied the name insulin for the secretion.

Till 1900, biochemical abnormalities of diabetes were not available. Benedict in 1911 published his method for detection and estimation of reducing sugar mainly glucose in the urine. Rothera devised a technique for detection of ketone bodies in urine during first decade of 20^{th} century.[3]

Diabetes mellitus- is a state of chronic hyperglycemia classically associated with symptoms of excessive thirst, increase in urine volume and if severe enough weight loss.[4]

The fundamental defect occurs in insulin secretion and/or action. In the classical young onset form of the disorder, there is near total insulin deficiency with inevitable widespread metabolic changes.

In older age onset form, there is diminished and/or delayed insulin secretion in response to glucose combined with varying degrees of diminished effectiveness of circulating insulin. When there is associated obesity, insulin resistance predominates.

Therefore diabetes can be defined as a state of diminished insulin action due to decreased availability or effectiveness in varying combinations.[4]

ETIOLOGIC CLASSIFICATION OF DM [5]

I. Type 1 diabetes (beta cell destruction, usually leading to absolute insulin deficiency) A. Immune-mediated B. Idiopathic
II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)
III. Other specific types of diabetes A. Genetic defects of beta cell function characterized by mutations in: 1. Hepatocyte nuclear transcription factor (HNF) 4α (MODY 1) 2. Glucokinase (MODY 2) 3. HNF-1α (MODY 3) 4. Insulin promoter factor-1 (IPF-1; MODY 4) B. Genetic defects in insulin action 1. Type A insulin resistance 2. Leprechaunism C. Diseases of the exocrine pancreas—pancreatitis, pancreatectomy, neoplasia D. Endocrinopathies - Acromegaly, Cushing's syndrome, glucagonoma, hyperthyroidism, E. Drug- or chemical-induced—glucocorticoids, β-adrenergic agonists F. Infections—congenital rubella, cytomegalovirus, coxsackievirus G. Uncommon forms of immune-mediated diabetes— "stiff-person" syndrome, anti-insulin receptor antibodies H. Other genetic syndromes sometimes associated with diabetes
IV. Gestational diabetes mellitus (GDM)

MODY – Maturity Onset Diabetes Mellitus of the young

Among these T2DM is the most common type and accounts for 90–95% of those with diabetes, previously referred to as non–insulin dependent diabetes or adult-onset diabetes, it encompasses individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency. Most patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance.[6]

Clinical presentation of diabetes-

The clinical presentation may be acute or sub acute. Thirst, polyuria and weight loss are usual features but medical attention is sought for such symptoms as lack of energy, visual blurring, impotence, delayed wound healing etc.

DIAGNOSTIC CRITERIA FOR DM

In 1979 and 1980, two groups, the National Diabetes Data Group in the United States and the World Health Organization (WHO), published reports addressing diabetes diagnostic criteria.[7]

Subsequently, in 1997 and 1999, two new reports on diabetes diagnostic criteria were published. The first was sponsored by the American Diabetes Association (ADA) and was the report of its Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. The second was from WHO, [8] in 2003, the Expert Committee published a follow-up report in which it carefully considered new data since its 1997 report.[6]

	YEAR OF REPORTS		
CRITERIA	1979 & 1980	1997 & 1999	2003
Fasting plasma glucose			
Diabetes	> 140 mg/dl	> 126 mg/dl	> 126 mg/dl
Impaired fasting glucose	Not considered	110 - 125 mg/dl	100 – 125 mg/dl
2 hour plasma glucose			
Diabetes	> 200 mg/dl	> 200 mg/dl	> 200 mg/dl
Impaired fasting glucose	140 - 199 mg/dl	140 - 199 mg/dl	140 - 199 mg/dl

Types of diabetes tissue damage

Microangiopathy (particularly retina, kidneys)

Macroangiopathy (ischaemic heart disease, cerebro-vascular disease)

Neuropathy (autonomic, sensory, motor)

Ocular cataracts

Inelastic collagen (Dupuytren's contractures) [4]

Glycosylated hemoglobin

Of all the glycosylated form of hemoglobin, HbA_{1C} is the most stable. More than 80 per cent of glycosylated form is $HbA_{1C.}$ Hence its measurement is taken to be the ideal parameter to understand the long term diabetic control. This is the most

important tool for monitoring diabetes. This test refers to hemoglobin component formed by interaction with glucose. Since life span of RBC is approx 120 days, a single HbA_{1c} determination can give information about glycaemic control in the preceding 8-12 weeks. It is estimated by HPLC method (High Performance Liquid Chromatography), which is considered to be the gold standard. The advantage is that this test does not require any dietary preparations and has low sensitivity but higher specificity compared to oral glucose tolerance test.

HbA_{1c} is formed by condensation of glucose with N- terminal Valine residue of β chain of HbA to form an unstable Schiff base. Glycosylation is the non enzymatic addition of sugar residue to amino groups of proteins. Human adult hemoglobin (HbA) usually consists of HbA_1 (97% of the total), HbA_2 (2.5%) and HbF (0.5%). HbA is made up of four polypeptide chains two alpha and two beta chains. Chromatographic analysis of HbA_1 identifies several minor hemoglobins, namely $HbA_{1a,}$ HbA_{1b} and HbA_{1c}. Formation of glycosylated hemoglobin (GHb) is essentially irreversible and the concentration in the blood depends on both the life span of the red blood cell (over 120 days) and its blood glucose concentration.

Because the rate of formation of GHb is directly proportional to the concentration of glucose in the blood, the GHb concentration represents the integrated values for glucose over the preceeding 8-12 weeks. This provides an additional criterion for assessing glucose control because GHb values are free of day to day glucose fluctuation and are unaffected by recent exercise or food ingestion.

Interpretation of results

The normal range of HbA_{1C} level in healthy persons is 4%-5.9%.

People with diabetes mellitus often have higher levels of $HbA_{1C.}$ A diabetic person with good glucose control has an HbA_{1C} that is close to or within 7% as per the American diabetes association. High HbA_{1C} represents poor glycemic control.

India leads the world in diabetes prevalence and hence, the allied complications are expected to find at their peaks in the country with a serious trend of westernized life style aggravating the ethnic susceptibility.

PATHOPHYSIOLOGY OF DIABETES [5]

Type 2 DM is characterized by impaired insulin secretion, insulin resistance, excessive hepatic glucose production, and abnormal fat metabolism. Obesity is very common in type 2 DM. In the early stages of the disorder, glucose tolerance remains near-normal, despite insulin resistance, because the pancreatic beta cells compensate by increasing insulin output. As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets in certain individuals are unable to sustain the hyperinsulinemic state. Impaired glucose tolerance (IGT) characterized by elevations in postprandial glucose then develops. A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycemia. Ultimately, beta cell failure ensues.

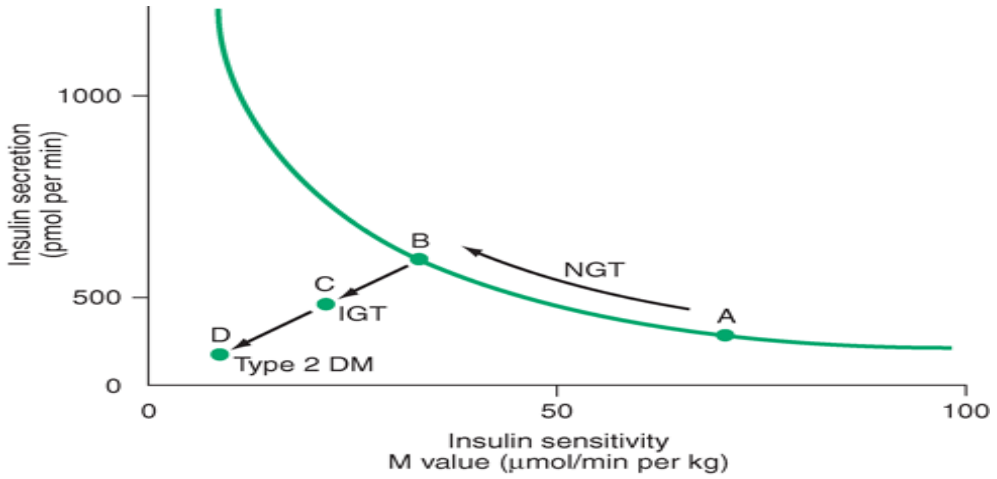
Impaired Insulin Secretion

Insulin secretion and sensitivity are interrelated (Figure 1). In type 2 DM, insulin secretion initially increases in response to insulin resistance to maintain normal glucose tolerance. Initially, the insulin secretory defect is mild and selectively involves glucose-stimulated insulin secretion. Abnormalities in proinsulin processing

are reflected by increased secretion of proinsulin in type 2 DM. Eventually, the insulin secretory defect progresses to a state of inadequate insulin secretion.

The reason for the decline in insulin secretory capacity in type 2 DM is unclear. The assumption is that a second genetic defect—superimposed upon insulin resistance—leads to beta cell failure. Beta cell mass is decreased in individuals with long-standing type 2 diabetes. Islet amyloid polypeptide or amylin is co-secreted by the beta cell and forms the amyloid fibrillar deposit found in the islets of individuals with long-standing type 2 DM. The metabolic environment of diabetes may also negatively impact islet function. For example, chronic hyperglycemia paradoxically impairs islet function ("glucose toxicity") and leads to a worsening of hyperglycemia.

Figure 1: Relation between Insulin secretion and sensitivity.



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

B.HISTORY OF EXERCISE PHYSIOLOGY:

Exercise physiology arose mainly in Greece and Asia Minor, although related topics were studied even earlier. The greatest influence on western civilization came from Greek physician Herodius (5^{th} century BC), Hippocrates (460-377 BC) and Galen (131-201 AD).

Sir Joseph Bar Croft (1872-1947) – pioneered fundamental work concerning the functioning of haemoglobin.

Austin Flint Jr. in 1877 published a text book of physiology where many topics related to exercise were discussed.

Christian Bohr (1884 – 1951) – studied solutioning of gases in various fluids including haemoglobin solution.

Otto Meyerth (1884- 1951), studied energy changes during cellular respiration.

A.V. Hill (1920) coined the term VO_2Max.

The formal exercise physiology laboratory was established in US in 1891 at Harvard University. George Wells Fitz played a major role in its establishment.

Olof Astrand from Karolinska institute medical school in Stockholm, Sweden in 1954 prepared data on the physical working capacity of both sexes aged 4 to 33 years. This important study was done in collaboration with his wife.

Irma Rhyming propelled Astrand to the forefront of experimental exercise physiology.

Robert A Bruce (1963), father of cardiovascular physiology, developed multistage treadmill test, known as Bruce protocol to predict VO_2Max.

Martti J Karnova (1991) devised the method to predict optimal exercise heart rate.

David Swain (1994) studied the relationship between %MHR (maximal heart rate) and % VO_2 Max.

C. CARDIO-RESPIRATORY FITNESS

Cardio-respiratory fitness is the ability of body's circulatory and respiratory system to supply fuel and oxygen during sustained physical activity.[9] Cardio-respiratory fitness is responsible for prolonged use of large muscles of the body which depends on cardiovascular and respiratory system. [10] Even though the strong association between physical inactivity and ill health is well documented, 60% of the population is inadequately active or completely inactive. Traditional methods of prescribing exercise have not proven effective for increasing and maintaining a program of regular physical activity. Hence in previously sedentary healthy adults, a lifestyle physical activity intervention is as effective as a structured exercise program in improving physical activity and cardio-respiratory fitness.

Indicators of cardio-respiratory fitness are maximal oxygen uptake (VO_2Max), endurance time and maximal power output. An international working party was convened in Toronto in the summer of 1967, under the auspices of the International Biological Programme and the parameter thus selected for measurement was the maximum oxygen intake (VO_2Max).

VO_2Max is most widely accepted parameter to evaluate cardio-respiratory fitness and is the first choice in measuring a person's cardiopulmonary status.[11] It is a fundamental measure of physiological functional capacity to exercise.[12-14] Cardio-respiratory fitness indicators other than VO_2Max suffer adverse effects of reduced exercise training capacity. In well trained endurance athletes, when training period was reduced to 1 hour 35 min sessions from a previous levels of 6 to 10 hrs a week over a four week period.[15] VO_2Max remained constant during the period of reduced training capacity while endurance capacity at 75% VO_2Max decreased.

Aerobic fitness is the ability to exercise continuously for extended periods without becoming tired or highest oxygen uptake the individual can attain during exercise while breathing air at sea level.[10]A person's aerobic fitness level is dependent on the amount of oxygen which can be transported by the body to the working muscles and efficiency of the muscle to use that oxygen. High aerobic fitness is associated with a reduction in risk factors related to cardiovascular diseases.[16] Fitness promotes muscle insulin sensitivity, [17]insulin mediated transport of glucose from blood to muscle,[18] improve nervous system function,[19] and lower heart rates. Increased lipoprotein lipases activity in skeletal muscle which results in an enhanced clearance rate of plasma triglycerides, increased transport of lipids and lipoproteins from the peripheral circulation and tissues to the liver, and enhanced high density cholesterol are mechanisms by which lipids may improve with fitness.[20]Earlier studies have demonstrated have demonstrated the importance of low cardio-respiratory fitness in young adulthood as a factor for developing cardiovascular co-morbidities later in middle age.[21]

Leibetseder et al studied the suitability of a simple running test to estimate cardio-respiratory fitness in 71 subjects from America. Each subject completed an

ergometric exercise test with continuous measurement of ventilation and expired gases. During test runs individual were instructed to adjust their speed to a specific HR. During first run HR was constrained to 70% VO_2Max from the prior laboratory incremental exercise test. The second run was constrained to a HR of 90% VO_2Max.It was suggested that this simple running test can be used to document training effects throughout with relatively high accuracy by VO_2Max prediction.[22]

Jack et al studied the use of the heart rate VO_2 relationship during graded exercise in the prescription of individualized exercise program. He concluded that, exercise can be successfully prescribed on an individualized basis outside the setup. Using the linear relationship between HR and VO_2, it is possible to establish a safe, meaningful, productive intensity or exercised based on HR equivalent of 75% of the aerobic capacity (VO_2Max).There is also greatest gain in cardio-respiratory endurance and efficiency as well in duration and frequency in three month program of prescribed exercise. There was 19.8% increase in aerobic capacity (VO_2Max) and slight increase in lean body weight (0.73kg) and substantial decrease in total body weight and relative fat (3.2%), serum cholesterol dropped slightly and triglyceride level .[23]

Blake et al studied how sedentary obese and normal weight women respond to exercise training and their fitness levels were compared. Both groups of women participated in a 14 week fitness program. They found that absolute VO_2Max was higher in obese than in normal weight. This suggests that obese women respond in a similar manner as normal weight women to exercise and weight loss is not necessary for improved fitness.[24]

Low cardio-respiratory fitness is a risk factor for cardiovascular disease mortality and morbidity. Lee et al studied the relationship between cardio-respiratory

fitness, body composition and all- cause mortality, cardiovascular disease mortality in men and found that unfit men had higher risk of all-cause and cardiovascular disease mortality compared to fit men, similarly unfit men with low waist girth less than 87cms had greater risk of all cause mortality than did men with high waist girths (>99cms).[25]

Mercedes et al investigated whether low cardiovascular fitness in young adults, estimated by short duration exercise treadmill test, was associated with the development of risk factors like hypertension, diabetes, metabolic syndrome and hyper-cholesterolemias and found that poor fitness in young adults is associated with the development of cardiovascular risk factors in middle age.[21]

Fox et al studied the relationship of physical inactivity or sedentary living habits to various chronic diseases. There is substantial evidence of an indirect nature that supports the connection that routine exercise is a necessary part of any program of preventive medicine. Fox and Haskel have concluded that it is highly prudent to incorporate programmes of increased habitual activity in an approach to the prevention of coronary heart disease.[26]

TESTS DONE TO ASSESS CARDIORESPIRATORY FITNESS:

The various tests done to assess cardio-respiratory fitness are-

- Queen's college step test
- Bicycle ergometer
- Treadmill graded exercise tests

METHODS OF VARIOUS TESTS:

QUEEN'S COLLEGE STEP TEST:

The Queens College Step test is one of many variations of step test procedures, used to determine aerobic fitness. This sub-maximal test provides a measure of cardio-respiratory or endurance fitness. The **advantages** of this test are minimal equipment and costs; little time required and can be self-administered. The **disadvantages** being biomechanical characteristics vary between individuals (e.g. taller people are at an advantage). Also, apparently the data was formulated from treadmill running, therefore their assumption is that stepping and treadmill running have the same oxygen cost.

BICYCLE ERGOMETER:

A cycle ergometer is a method to test aerobic fitness. Heart rate is measured every minute and the steady state heart rate is determined. The steady state heart rate is looked up on published tables (nomograms) to determine an estimation of VO_2Max. The advantage of this exercise is that it is non-weight bearing and less stressful on the lower body which is an added advantage for subjects who are obese or have orthopedic limitations. Disadvantages being the work rate on a cycle ergometer is self-paced and not as tightly controlled as on the treadmill, so subjects may perform more work than is intended and localized muscle fatigue in the legs can limit the ability of the subject to perform exercise at higher sub maximal intensities.

TREADMILL TEST:

Treadmill tests are used for conducting a cardiac stress. In a stress test, a patient is placed on a treadmill to run for a prescribed period of time. Clinicians measure how hard the heart is working under increasing speeds and inclines of the

treadmill. The results can indicate heart disease, and can also provide patients with an overall health profile so they know how much they can safely exert themselves during exercise.[27]

Treadmill protocols:

There are four primary methods or protocols developed specifically for conducting a cardiac stress test.

1. Bruce protocol

2. Modified Bruce protocol

3. Naughton protocol

4. Balke protocol

Each protocol targets a different patient population: Those who are considered fit, those who may have cardiac problems and those who have suffered from a cardiac event or who are elderly or unhealthy. The variables in the test are the speed of the treadmill, the incline settings and how they are adjusted throughout the test and rest periods during the test.

Bruce Protocol:

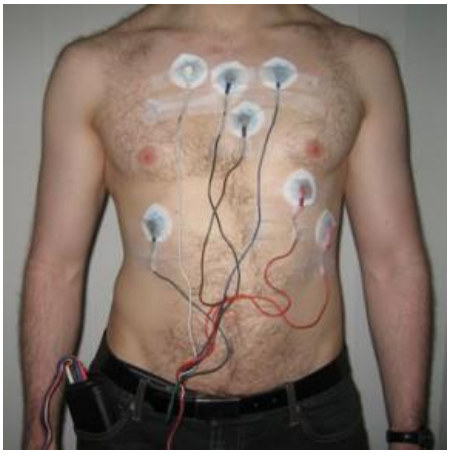
Dr. Robert A. Bruce designed this protocol in 1963, and it's the most common protocol for conducting a stress test. It's used for people who may have cardiovascular problems, and also to determine the cardio-respiratory fitness of healthy people. During this test, sticky electrocardiograph leads is wired to an ECG machine are attached to a person's chest (fig.2) and the heart rate is graphed during exercise in seven increasingly difficult three minute stages of effort on a treadmill. The treadmill

starts at 1.7 miles per hour at a 10 percent incline. The incline is increased by 2 percent every three minutes, while the speed is increased in stages until the maximum speed, 7.5 miles per hour, is achieved at a 28 percent incline[27].

Table 1: Bruce protocol

Stage	Speed (km/hr)	Speed (mph)	Gradient
1	2.74	1.7	10
2	4.02	2.5	12
3	5.47	3.4	14
4	6.76	4.2	16
5	8.05	5.0	18
6	8.85	5.5	20
7	9.65	6.0	22
8	10.46	6.5	24
9	11.26	7.0	26
10	12.07	7.5	28

Fig 2. Electrocardiograph leads attached



Procedure of the test:

1. This test requires the person to run for as long as possible on a treadmill whose speed and slope are increased by increments at timed intervals.

2. The athlete warms up for 10 minutes

3. The assistant sets the treadmill up with a speed of 2.74 km/hr. and an incline of 10% (Stage 1)

4. The assistant gives the command "GO", starts the stopwatch and the athlete commences the test

5. The assistant, at the appropriate times during the test, adjusts the treadmill's speed and slope as per the table (e.g. after 3 minutes the speed is adjusted to 4.02 km/hr and the slope to 12% and so on)

6. The assistant stops the stopwatch when the athlete is unable to continue and records the time (T).

Modified Bruce Protocol:

The Modified Bruce Protocol is an easier version of the Bruce Protocol. It's designed for people who are in poor health, have a history of cardiac troubles, or who are elderly. During this test, electrocardiograph wires are placed on a patient and he is placed on a treadmill that starts out at out at 1.7 mph --- the same standards of the Bruce Protocol. The difference between the two is that the incline during the test is increased at about half the rate as in the Bruce Protocol, making it a less stressful stress test[27].

Naughton and Modified Naughton Protocols:

The Naughton and Modified Naughton Protocols are the least stressful of the three most popular methods for conducting a cardiac stress test. They are designed for high-risk patients who might not be able to withstand the rigor of either Bruce protocol or modified Bruce protocol. In the Naughton Protocol, there are 10 stages of exercise of three minutes each. Each segment is followed by a three minute rest

period. In the Modified Naughton, the treadmill speed is set through the test at 2 mph. The stress comes from an incline that increases 3.5 percent every two minutes during the test until it gets to 21 percent, or until the patient asks to stop[27].

The Balke Protocol:

The protocol is slightly different for men and women. For men a constant speed of 3.3 mph and for women 3.0 mph are used. The timer is started when the subject is ready to begin the test. The test is begun by setting the incline at 0 percent. The incline is increased 2 percent after 1 minute and 1 percent thereafter every minute in case of a man and 2.5 percent every 3 minutes in case of a woman. The subject continues doing this as long as he/she can. The idea is to keep up the pace and increase the incline until exhausted and cannot be continued anymore. It is important to record the time, since it is used for the VO_2Max calculations.

VO_2Max:

VO_2Max is the greatest amount of oxygen a person can use while performing dynamic exercise involving a large part of total muscle mass. It represents the amount of oxygen transported and used in cellular metabolism. VO_2Max defines a person's functional aerobic capacity and is recognized as the "gold standard" for cardio-respiratory fitness[10]. It is measured by the volume of oxygen per kilogram of body weight per minute (ml/kg/min).[28]

In a study done in 1995 it was reported that VO_2Max was higher in men than in women ($p < 0.0001$), lower in sedentary than in physically active persons ($p < 0.001$ in men, < 0.01 in women), and diminished with age in cross-sectional comparisons. It was highly correlated with duration of exercise by the standardized

protocol. Accordingly, by regression equations average normal values for healthy persons could be predicted from sex, activity status, and age; values expected on testing could be estimated from the duration of exercise[29].

D. DETERMINANTS OF MAXIMAL OXYGEN CONSUMPTION:

In essence there are three major factors determining maximal oxygen consumption

1. Cardiovascular determinants.
2. Pulmonary determinants
3. Skeletal muscle mass.

1. CARDIOVASCULAR DETERMINANTS:

CARDIAC OUTPUT:

Cardiac output in an average male at rest is about 5L/min both for trained and untrained individuals. Resting cardiac output in an average female is about 4L/min. For an average sedentary person at rest with an average heart rate (HR) of 70 beats/min, usually sustains 5L of cardiac output. The calculated stroke volume equals 71.4ml.Stroke volume and cardiac output for women averages about 25% below the average values for men; in women, the average stroke volume at rest ranges from 50-60ml.During maximal exercise cardiac output increases 8 times the resting level.[30]

The physiological mechanisms responsible for increase in stroke volume during exercise are,

1. Intrinsic to the myocardium involves enhanced cardiac filling in diastole followed by a more forceful systolic contraction due to increase in venous return (hetero-metric regulation).

2. Greater systolic ejection occurs despite increased resistance to blood flow in the arterial circuit from exercise induced elevation of systolic blood pressure (after load) (homo-metric auto regulation).

3. Neuro-hormonal influence like norepinephrine, epinephrine involves normal ventricular filling with a subsequent forceful ejection and emptying during systole.[30].Training adaptations that expand blood volume and reduce resistance to blood flow in peripheral tissues.[30]There is an increase in 10-20% plasma volume following 3-6 aerobic training sessions. Intravascular expansion directly relates to increased synthesis and retention of plasma proteins. An increase in plasma volume enhances circulatory reserve and increase in diastolic volume, stroke volume, O_2 transport, VO_2Max and temperature regulating ability during exercise. Endurance training increases the compliance of the left ventricle to facilitate acceptance of blood in diastolic phase of the cardiac cycle.[15]

Whether endurance training enhances the myocardium's innate contractile state remains unclear. If this adaptation does not occur it too would contribute to a larger stroke volume.[30]

Cardiac output and oxygen consumption remain linearly related during graded exercise for men and women. However, females generally at any level of sub maximal oxygen consumption have 5-10% larger cardiac output than males. The 10% lower hemoglobin concentration in females explains gender differences in sub

maximal cardiac output. A proportionate increase in sub maximal cardiac output compensates for this small decrease in blood's oxygen carrying capacity.[30]

Low maximal oxygen consumption corresponds with the low maximum cardiac output. Proportionate increase in maximum cardiac output accompanies increases in VO_2Max with endurance training.

SYSTEMIC CIRCULATORY CHANGES:

The systemic cardiovascular response to exercise depends on the type of muscle contraction. With the start of an isometric muscle contraction, heart rate rises. The response to exercise involving isotonic muscle contraction is similar in that there is a prompt increase in heart rate but different in that a marked increase in stroke volume occurs.[31] There is a net fall in total peripheral resistance due to vasodilation in exercising muscles. Blood redistribution in specific tissues occurs during high intensity exercise. Blood flow to the skin, the primary heat exchange organ increases during light and moderate exercise in response to the rise in core temperature.[32]During maximal effort, the skin restricts its blood flow redirecting it to active muscles, even in a hot environment. The kidney and splanchnic tissue tolerate a considerably reduced blood flow before oxygen demand exceeds supply and compromise function. Visceral organs sustain a substantially reduced blood supply for more than 1 hour during intense exercise. The amount of blood mobilized from splanchnic area and other reservoirs may increase the amount of blood in the arterial portion of the circulation as much as 30% during strenuous exercise. With regular aerobic training the typical vasoconstrictor response of splanchnic and renal tissue to exercise diminishes.[33]At rest the heart extracts 70-80% of the O_2 from each unit of

blood delivered to it. Thus O_2 consumption is increased significantly only by increasing blood flow. A four to five fold increase in coronary circulation accompanies a similar increase in myocardial work during exercise. Cerebral blood flow increases during exercise by 25-30% of the resting flow.[30]

CIRCULATION TIME:

Depending on the velocity with which blood passes through metabolically active tissues oxygen levels in the blood can be below 3 millilitres per 100 millilitres. If the velocity of flow of blood is higher, the time required for gas exchange is decreased resulting in reduced extraction in metabolically active tissues and vice versa. The ability of the tissues to take oxygen from the blood is referred to as extraction of oxygen.[31]

2. PULMONARY AND HEMATOLOGICAL DETERMINANTS:

CHANGES IN VENTILATION:

Exercise increases pulmonary ventilation by increasing both rate and depth of breathing .During strenuous exercise, healthy young adults increase breathing rate to 35-45 breathes/min. Tidal volume of 2L and higher commonly occur during exercise. Minute ventilation increase up to 100L or more has been seen during strenuous effort in untrained individuals. In male endurance athletes, ventilation may increase to 160L/min during maximal exercise. Despite such large minute ventilations, tidal volume for trained and untrained rarely exceeds 60% of vital capacity.[34]

Full saturation of hemoglobin with oxygen does not occur. At sea level alveolar PO_2 of 100 mmHg, hemoglobin achieves 98% oxygen saturation (PaO_2=

97mmHg) due to slight admixture of venous blood that bypass the pulmonary capillaries (physiological shunt). During exercise, the amount of O_2 entering the blood from the lungs is increased because the amount of O_2 added to each unit of blood and the pulmonary blood flow per minute are increased. The PO_2 of blood flowing into pulmonary capillaries falls from 40 to 25 mm Hg or less, so that the alveolar capillary PO_2 gradient is increased and more O_2 can diffuse from alveoli into pulmonary capillary blood. Pulmonary blood flow is increased from 5.5L/min to as much as 20-35L/min. The total amount of O_2 entering the blood therefore increases from 250ml/min at rest to values as high as 4000ml/min. The amount of CO_2 removed from each unit of blood is increased, and CO_2 excretion increases from 200ml/min to as much as 8000ml/min. The increase in o_2 uptake is proportionate to workload up to a maximum. Above this maximum, O_2 consumption levels off and the blood lactate level continues to rise. The lactate comes from muscles in which aerobic resynthesis of energy stores cannot keep pace with their utilization and an oxygen debt is being incurred.[31]

VENTILATION PERFUSION RATIO:

Adequate gas exchange between alveoli and blood requires effective matching of alveolar ventilation to the blood perfusing the pulmonary capillaries. Approximately 4.2L of air normally ventilates the alveoli each minute at rest and an average of 5L of blood flows through pulmonary capillaries.

Ventilation perfusion ratio equals 0.84.In light exercise, the ventilation perfusion ratio remains approximately 0.8.In contrast, intense exercise produces a

disproportionate increase in alveolar ventilation and rise in ventilation perfusion ratio resulting in a relative fall in oxygenation of blood.

ARTERIOVENOUS DIFFERENCE OF OXYGEN

Resting metabolism uses an average of 5ml of oxygen from 20ml of oxygen in each deciliter of arterial blood that passes through the tissue capillaries. The difference of oxygen content of arterial and venous blood under resting conditions indicates an automatic reserve of oxygen for rapid use when metabolism increases suddenly.

Arterial blood oxygen content varies little from its resting throughout the full range of exercise intensity. In contrast mixed venous oxygen content varies between 12 and 15ml/dl during rest to a low of 2-4ml/dl during maximal exercise due to enhanced tissue extraction of O_2.

The progressive expansion of the arterio- venous difference to at least three times resting values results from reduced venous oxygen content. At maximal exercise aVO_2 differences approaches 20ml/dl in active muscle(all oxygen extracted).The oxygen content of mixed venous sample from pulmonary artery rarely falls below 2-4 ml/dl because blood returning from active tissues mixes with oxygen rich venous blood from metabolically less active organs.

The capacity of each unit volume of arterial blood to carry oxygen increases during exercise due to increase in number of red blood cells. Haemo-concentration results from the progressive movement of fluid from plasma to the interstitial space with the increase in capillary hydrostatic pressure as blood pressure rises and the metabolic byproducts of exercise metabolism osmotically draw fluid into tissue

spaces from plasma.[34]Increase in skeletal muscle microcirculation increases tissue oxygen extraction.[35]

OXYGEN CARRYING CAPACITY:

The hemoglobin concentration of normal blood is about 15gm/dl of blood. When fully saturated, each gram of normal hemoglobin can bind about 1.39 millilitres of oxygen. However, invivo, blood normally contains small amounts of inactive hemoglobin variants and so measured values are lower. A traditional value is 1.34 millilitres of oxygen combining with one gram of hemoglobin. Therefore 15grams/dl of hemoglobin carries about 20.1 millilitres of oxygen bound to hemoglobin when hemoglobin is 100% saturated.[31] Alterations in molecular structure of hemoglobin resulting from an increase in acidity, temperature, CO_2 concentration and red cell 2, 3 DPG reduce its affinity to hold oxygen. Exercise accentuates these factors, further facilitating oxygen's release to the tissues. Depending on the velocity with which blood passes through metabolically active tissues oxygen levels in the blood can be below 3 millilitres per 100 millilitres.

Significant decrease in iron content of red blood cells reduces oxygen carrying capacity. Iron deficiency anaemia diminishes person's capacity to sustain even mild intensity aerobic exercise.[34,36] In polycythemia, the increase in hemoglobin, has increased oxygen carrying capacity and so does the aerobic capacity.

3. TISSUE DETERMINANTS:

SKELETAL MUSCLE MASS:

One of the three factors determining maximal oxygen consumption the most important in terms of training adaptation is the role of skeletal muscle. The larger the mass of the exercising skeletal muscle the greater the potential for increasing whole body oxygen consumption. Also the manner in which skeletal muscle is trained and the muscle fiber type will influence the ability of the muscle to extract oxygen. Selective hypertrophy occurs in different muscle fiber types with specific and overload training.

Six factors, genetic, exercise, nutritional, hormonal, environmental and neural interact to regulate skeletal muscle mass and corresponding strength development with resistance training. Muscle overload increases strength and selectively stimulates muscle fiber hypertrophy. Muscle hypertrophy induced increased protein synthesis with myofibrillar thickening, connective tissue cell proliferation and an increase in number of satellite cells around each fiber. Muscle hypertrophy entails structural changes within the contractile apparatus of individual fibers, particularly fast twitch fibers and increased aerobic energy stores. The genetic code exerts the great influence on muscle fiber composition is fixed before birth.[15]

METABOLIC MACHINERY

Increasing the size and number of mitochondria and augmenting aerobic enzyme activity improve a muscle's metabolic activity in exercise. Local vascular and metabolic improvements within the muscle enhance its capacity to produce ATP

aerobically. These include enlarged mitochondrial structure and enhanced enzyme activity which occurs with training in subsarcolemmal and inter-fibrillar muscles. Increase in mitochondrial protein by a factor of two exceeds the typical 10 – 20% increase in VO2 max with endurance training. These local training adaptations translate to an increase in oxygen extraction capacity. [15]

Mitochondrial potential and not oxygen supply limits the muscle oxidative capacity of untrained individuals. Endurance trained skeletal muscle contains larger and more numerous mitochondria than less active muscle fibres.[15]

MYOGLOBIN

The iron protein pigment myoglobin in skeletal and cardiac muscle provides an "extra" oxygen store to release oxygen at low PO_2. Myoglobin facilitates oxygen transfer to the mitochondria when intracellular PO_2 in active skeletal muscle decreases dramatically as seen during intense exercise and in beginning of exercise.[34]

Unlike adult haemoglobin, the shape of myoglobin-O_2 dissociation curve is not sigmoid but a rectangular hyperbola. myoglobin binds oxygen more readily than adult haemoglobin at low oxygen pressures. During rest and moderate exercise, myoglobin maintains high oxygen saturation. At PO_2 of 40 mmHg, myoglobin retains 95% of its oxygen. The greatest quantity of oxygen releases from MbO_2 when tissue PO_2 declines below 5 mm Hg. Acidity, carbon dioxide and temperature do not affect myoglobin's oxygen binding affinity, so it does not exhibit Bohr effect.[34]

Muscles containing type 1 fibres are called red muscles because they are darker than other muscles due to presence of large amount of myoglobin. The red

muscles, which respond slowly and have a long latency, are adapted for long, slow, posture maintaining contractions. White muscles, which contain mostly type 2 fibres, have short twitch duration and are specialized for fine skilled movement. Slow twitch muscle fibres have high capacity to generate ATP aerobically. Muscles myoglobin content relates to their level of physical activity. Whether regular exercise exerts any effect on myoglobin levels in humans remains undetermined.[15]

MUSCLE BLOOD FLOW

Muscle blood flow at rest at a thermo-neutral environment, the typical 5L cardiac output distributes to tissues in proportion to their metabolic activity. Environmental stress, level of fatigue, exercise mode and intensity affect regional blood flow, but the major portion of the blood flow during exercise diverts to active muscles. Muscle blood flow at rest is 4-7 ml/min/100gms of muscle which is about 20%of the cardiac output. The cardiac output flow increases steadily in graded exercise, with active muscle receiving 50-70ml/min/100gms of muscle blood flow, which is about 80% of the cardiac output during maximal exertion.[37, 38] Blood flow to active muscle is highly regulated. The greatest quantity of blood is diverted to the oxidative portions of the muscle at the expense of those areas with high glycolytic capacity.[39]

SIZE OF THE MUSCLE

The fibre size in untrained women and men on the average cross sectional area for slow twitch fibre in women is approximately 70% of men's size; for fast twitch

fibres it is about 85% the scatter is very large; however there is no sex difference in proportion to the fibre type. The demand on the oxygen transporting functions varies with the size of the active muscles, the isometric contractions hinder the local blood flow and dynamic exercise facilitates the circulation, so that a greater oxygen uptake can be obtained during dynamic exercise. Usually exercise involves both static and dynamic muscle contraction. Static exercise produces relatively high heart rate and arterial pressure.

The highest oxygen consumption arm exercise are 20-30% lower than the leg exercise. The intra-arterial blood pressure during arm exercise is higher than in leg exercise at given oxygen uptake or cardiac output and the heart rate is also higher. These differences relate to the relatively smaller muscle mass activated in arm exercise.[40]

When combining arm and leg exercise the highest oxygen uptake that can be attained depends upon the relative loads on the arms. It was noticed that the oxygen uptake was same in maximal running as in arms plus les exercise. The physical limitations that restrict the rate at which energy can be released aerobically are dependent upon the chemical ability of the muscular cellular tissue system to use oxygen in breaking down the fuel and the combined activity of cardio-vascular and pulmonary system to transport oxygen to the muscular tissue system.[10]

TYPE OF EXERCISE

The increase oxygen uptake in the beginning of exercise is explained by the sluggish adjustment of the respiration and circulation. That is the sluggish adjustment

of the oxygen transporting systems. So the exercise, during the first 2-3 mins there is an oxygen deficit.

In light exercise the energy output during the first minute of exercise can be delivered aerobically, since oxygen is stored in the muscles bound to the myoglobin and in the blood perfusing the muscles. During the more severe exercise, anaerobic process must supply part of the energy during the early part of the exercise. The heavier the rate of exercise, the steeper is the increase in oxygen uptake.

Factors Affecting VO_2Max:

There are many physiological factors that combine to determine VO_2Max such as age, gender, genetics, handrail support during treadmill exercise, physical activity levels, altitude, body mass and composition, form of exercise. Two theories have been proposed:

Utilization Theory

This theory maintains that aerobic capacity is limited by lack of sufficient oxidative enzymes within the cell's mitochondria [41]. It is the body's ability to utilize the available oxygen that determines aerobic capacity. Proponents of this theory point to numerous studies that show oxidative enzymes and the number and size of mitochondria increase with training. This is coupled with increased differences between arterial and venous blood oxygen concentrations (a-VO_2 difference) accounting for improved oxygen utilization and hence improved VO_2Max.

Presentation Theory

Presentation theory suggests that aerobic capacity is limited not predominantly by utilization, but by the ability of the cardiovascular system to deliver oxygen to

active tissues. Proponents of this theory maintain that an increase in blood volume, maximal cardiac output (due to increased stroke volume) and better perfusion of blood into the muscles account for the changes in VO_2Max with training.

Genetics:

Genetic make-up has a very strong influence over VO_2Max and it is ultimately what defines upper limit for VO_2Max improvements. The capacity of circulatory system to deliver oxygenated blood to muscles and also the specific physiology of muscles are both genetically predetermined to a certain extent. For example, in regards to the circulatory system, hemoglobin (the molecule in blood that binds and carries oxygen) concentrations are genetically influenced. As for muscle physiology, the relative proportion of fast twitch and slow twitch fibers in your muscles is also genetically predetermined, and slow twitch muscle fibers are able to consume more oxygen than fast twitch muscle fibers.

Effects of Aging on VO_2Max:

VO_2Max decreases with age. The average rate of decline is generally accepted to be about 1% per year or 10% per decade after the age of 25. One large cross sectional study found the average decrease was 0.46 ml/kg/min per year in men (1.2%) and 0.54 ml/kg/min in women (1.7%).[42, 43]

Usually, the decline in age-related VO_2Max can be accounted for by a reduction in maximum heart rate, maximal stoke volume and maximal a-VO_2 difference i.e. the difference between oxygen concentration arterial blood and venous blood.[44]

Vigorous training at a younger age does not seem to prevent the fall in VO_2Max if training is ceased altogether. Elite athletes have been shown to decline by 43% from ages 23 to 50 (from 70 ml/kg/min to 40 ml/kg/min) when they stop training after their careers are over. In some cases, the relative decline is greater than for the average population - as much as 15% per decade or 1.5% per year.[45]

However in comparison, master athletes who continue to keep fit only show a decrease of 5-6% per decade or 0.5-0.6% per year. When they maintain the same relative intensity of training, a decrease of only 3.6% over 25 years has been reported and most of that was attributable to a small increase in bodyweight.

It seems that training can slow the rate of decline in VO_2Max but becomes less effective after the age of about 50. [41]

Effects of gender on VO_2Max:

There is an inherent disparity in the VO_2Max capabilities of men and women. Men have roughly 10% to 25% higher VO_2Max capabilities than women, even when experimental adjustments are made to eliminate and/or minimize differences in total body mass, fat free mass, training history, or even differences in hemoglobin concentrations. The available data suggests that the differences are biologically predetermined and largely due to size differences in contracting muscles.

Form of Exercise:

Since oxygen is ultimately consumed in the muscles during exercise, it follows that VO_2Max, when measured, will vary in accordance with the specific form of exercise performed. For example, there is usually more total muscle mass active during running than during swimming, and so VO_2Max will generally be greater

when measured during a running test than it would be if measured during a swimming test. Treadmill running type tests typically return the highest VO_2Max scores.

VO_2Max at Altitude:

VO_2Max decreases as altitude increases above 1600m (5249ft). For every 1000m (3281ft) above that, maximal oxygen uptake decreases further by approximately 8-11%.[41] A person with a VO_2Max lower than 50 ml/kg/min would struggle to survive at the summit of Everest without supplemental oxygen. The decrease is mainly due to a decrease in maximal cardiac output. Recall that cardiac output is the product of heart rate and stroke volume. Stoke volume decreases due to the immediate decrease in blood plasma volume. Maximal heart rate may also decrease and the net effect is that less oxygen is "pushed" from the blood into the muscles[44].

Determining VO_2Max:

VO_2Max can be determined through a number of physical evaluations. These tests can be **direct** or **indirect**.

Direct testing requires sophisticated equipment to measure the volume and gas concentrations of inspired and expired air. There are many protocols used on treadmills, cycle ergometers and other exercise equipment to measure VO_2Max directly.

VO_2Max can also be **estimated** by many indirect tests. Some are more reliable and accurate than others but none are as accurate as direct testing. The Bruce Treadmill Test is most commonly used for testing VO_2Max in healthy men, athletes or for signs of coronary heart disease in high risk individuals. It estimates VO_2Max

using Bruce formula (as opposed to direct tests that use gas analysers to measure respired gases). In order to evaluate peak cardio-respiratory function and accurately prescribe endurance exercise, VO_2peak, when available, should be assessed.

E. ROLE OF PHYSICAL ACTIVITY IN DIABETES

Physical activity is defined as any bodily movement produced by skeletal muscles that result in energy expenditure beyond resting expenditure. Exercise is a subset of physical activity that is planned, structured, repetitive, and purposeful and improvement or maintenance of physical fitness is the objective.[46]

Aerobic exercise: This consists of rhythmic, repeated, and continuous movements of the same large muscle groups for at least 10 min at a time. Examples include walking, bicycling, jogging, continuous swimming, water aerobics etc. When performed at sufficient intensity and frequency, this type of exercise increases cardio-respiratory fitness. [47]

Resistance exercise: Activities that involve moving a weight or working against a resistive load. Examples include weight lifting and exercises using weight machines. When performed with regularity and moderate to high intensity, resistance exercise increases muscular fitness. [47]

MET (metabolic equivalent): A MET is a unit of intensity, equal to energy expenditure at rest. Physical activity at 3 METs uses three times as more energy as stationary sitting. [47]

The current human genome was moulded and refined through generations of time. The basic framework for physiologic gene regulation was selected during an era

of obligatory physical activity, as the survival of our late Palaeolithic (50000–10000 BC) ancestors depended on hunting and gathering. A sedentary lifestyle in such an environment probably meant elimination of that individual. The phenotype of the present day *Homo sapiens* genome is much different from that of our ancient ancestors, primarily as a consequence of expressing evolutionarily programmed late Palaeolithic genes in an environment that is predominantly sedentary. So, human genome is maladapted, resulting in abnormal gene expression, which in turn frequently manifests itself as clinically overt disease. Some of these genes still play a role in survival by causing premature death from chronic diseases produced by physical inactivity. These disruptions in cellular homeostasis are diminished in magnitude in physically active individuals compared with sedentary individuals due to the natural selection of gene expression that supports the physically active lifestyle displayed by our ancestors. Genes evolved with the expectation of requiring a certain threshold of physical activity for normal physiologic gene expression, and thus habitual exercise in sedentary cultures restores perturbed homeostatic mechanisms towards the normal physiological range of the Palaeolithic *Homo sapiens.* [48]

The genetic basis of diabetes was proposed by geneticist James V. Neel in 1962 in **thrifty gene hypothesis**. Thrifty genes are genes which enable individuals to efficiently collect and process food to deposit fat during periods of food abundance. According to the hypothesis, the 'thrifty' genotype would have been advantageous for hunter-gatherer populations because it would allow them to fatten more quickly during times of abundance. Fatter individuals carrying the thrifty genes would thus better survive times of food scarcity. However, in modern societies with a constant abundance of food, this genotype efficiently prepares individuals for a famine that never comes. The result is widespread chronic obesity and related health problems

like diabetes. [49] Neel suggested that genes which predispose to diabetes (called 'thrifty genes') were historically advantageous, but they became detrimental in the modern world. In his words they were "rendered detrimental by progress".

Thrifty gene hypothesis is based on an analysis of the pattern and level of mortality during famines. Despite much anecdotal evidence used to suggest that famines cause substantial mortality, real data available from famines involve rather low levels of mortality and there is no evidence that fat people survive famines better than lean people. Mortality actually falls mostly on groups such as the very young and very old where differential mortality in relation to body composition is highly unlikely. Another alternative to the thrifty gene hypothesis is the **drifty gene hypothesis** proposed by the British biologist John Speakman. The main feature of this idea was that the current pattern of obesity did not suggest that obesity under strong positive selection for a protracted period of time. Instead that the obesity came about because of genetic drift in the genes controlling the upper limit on our body fatness. Such drift might have started because around 2 million years ago ancestral humans effectively removed the risk from predators, which was probably a key factor selecting against fatness. [50]

MECHANISMS REGULATING GLUCOSE UPTAKE INTO SKELETAL MUSCLE[5, 51, 52]

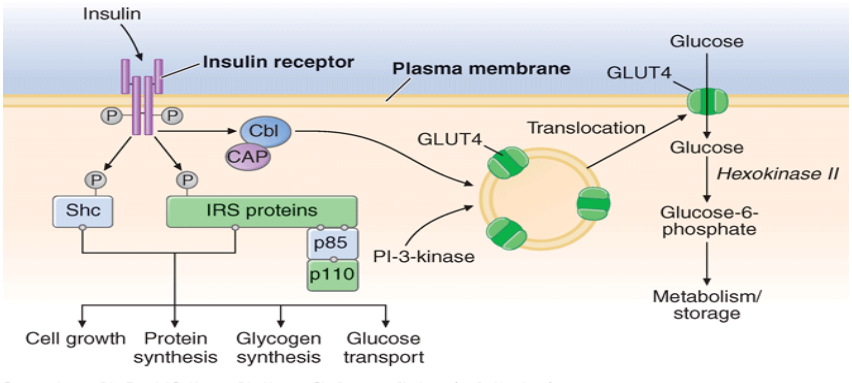
Skeletal muscle glucose uptake is mediated by glucose transporter 4, the major isoform that is responsive to hormones such as insulin, and by energy-demanding conditions such as exercise and hypoxia. Like insulin, muscle contraction (in vitro or in situ) and exercise increase glucose uptake into skeletal muscle. However, the contraction/exercise pathway of glucose uptake in skeletal muscle is an independent

pathway to that of insulin. Indeed, skeletal muscle glucose uptake is normal during exercise in those who suffer from insulin resistance and diabetes. Thus, the pathway of contraction-mediated glucose uptake into skeletal muscle provides an attractive potential target for pharmaceutical treatment and prevention of such conditions, especially as skeletal muscle is the major site of impaired glucose disposal in insulin resistance.

Activation of the insulin receptor substrates (IRS)/phosphatidylinositol 3-kinase (PI3K) axis is indispensable to insulin-stimulated GLUT4 translocation and glucose uptake. Similarly, 2 serine/threonine kinases participate in mediating insulin's metabolic actions in skeletal muscle and fat. In adipose cells, c-Cbl-associated protein (CAP), adaptor protein associated with pleckstrin homology and Src homology2 (SH2) domain (APS) and the small GTPase TC10 may also be involved in mediating insulin regulation of GLUT4 traffic and glucose uptake.

The mechanisms regulating skeletal muscle glucose uptake during contraction have not been fully elucidated. Potential regulators include Ca21 (via CaMK's and/or CaMKK), AMPK, ROS, and NO signaling, with some redundancy likely to be evident within the system.

Figure 3: Insulin signal transduction pathway in skeletal muscle.



Muscle Glycogen Concentration:

Skeletal muscle glucose uptake in exercising humans has been reported to be either enhanced or unaffected by low muscle glycogen levels. In vitro studies have shown that glucose transport is elevated in response to low muscle glycogen content in fast-twitch (glycolytic), but not slow-twitch (oxidative) muscle fibers. Because GLUT4 is hypothesized to be structurally bound to glycogen particles, it has been speculated that depleting glycogen releases GLUT4 to facilitate glucose transport. If muscle glycogen has some influence on contraction mediated glucose uptake, it is likely to be via one or more of the signaling pathways.

Alternative pathways leading to glucose uptake: [51, 52]

As with exercise, hypoxia also enhances glucose transport into skeletal muscle and muscle cells in culture. Hypoxia is imposed on isolated cells or isolated skeletal muscle by oxygen deprivation and its effects are mimicked by pharmacological interference with the mitochondrial oxidative chain. DNP is a mitochondrial uncoupler that transiently reduces cellular adenosine triphosphate (ATP) levels. DNP stimulates glucose uptake into both L6 myotubes and isolated fast-twitch muscle independently of PI3K activity. Hence, exercise, hypoxia and DNP are said to engage "alternative" signaling pathways.

Role of 5'-AMP-activated protein kinase (AMPK) in stimulation of muscle glucose uptake:

The heterotrimeric enzyme AMPK has been proposed as an "energy sensor" that is rapidly phosphorylated and activated during exercise/contraction in skeletal muscle. As muscle glucose transport correlated well with AMPK activity, it was

proposed that AMPK might be a signal in exercise/contraction-stimulated glucose transport into skeletal muscle. Hypoxia and DNP also increased AMPK activity in L6 myotubes and in isolated skeletal muscle, providing further support for a link between AMPK activation and glucose uptake.

Role of cytosolic Ca^{2+} in the stimulation of muscle glucose uptake:

A hallmark of muscle contraction is Ca^{2+} release from the sarcoplasmic reticulum (SR) that is induced through depolarization of the adjacent transverse tubules. Increased cytosolic Ca^{2+} stimulates glucose uptake independently of contraction. The plasma membrane depolarization caused by high extracellular K+ elevates glucose uptake into L6 muscle cells and this effect is completely inhibited by dantrolene, an inhibitor of Ca^{2+} release from the SR. It can be concluded hypoxia may induce Ca^{2+} release from the mitochondria. Indeed, glucose uptake into hypoxic muscle was also completely inhibited by dantrolene. Similarly, a role for Ca^{2+} in DNP-stimulated glucose uptake was suggested from the partial inhibition of uptake in L6 myotubes upon cytosolic Ca^{2+} chelation.

AS160 (Akt substrate of 160 kDa): in the regulation GLUT4 traffic:

Activation of the PI3K target Akt by muscle contraction/exercise remains equivocal and appears to be rapid, transient, muscle fibre-type specific and to exhibit lower activation in muscle that is contracted in vitro compared with in vivo. Interestingly, both in vitro muscle contraction and AICAR increased the phosphorylation of AS160, a recently identified Akt substrate that functionally participates in insulin regulation of GLUT4 traffic in 3T3-L1 adipocytes and L6 skeletal muscle cells.

Regulation of glucose uptake by adiponectin

Adiponectin (Ad), a recently identified adipokine, is proposed to be an endogenous insulin sensitizer. Liver appears to be the major target tissue of adiponectin, where it enhances insulin suppression of endogenous hepatic glucose production. Ad also increased glucose uptake and GLUT4 translocation in L6 muscle cells. Ad-induced AMPK phosphorylation in skeletal muscle and in muscle cells in culture, and transfection of myocytes with a dominant-negative AMPK mutant attenuated the stimulatory effects of gAd and Ad on glucose uptake. These results suggest that adiponectin engages ≥1 "alternative pathways" to regulate glucose uptake.

Nitric Oxide

The mu neural isoform of NOS (nNOSl) is the primary isoform expressed in skeletal muscle. nNOSl is constitutively active and its activity, and therefore NO production, increases by 1.5–2-fold with contraction. The NO donor sodium nitroprusside (SNP) increases NO production in isolated skeletal muscle and enhances glucose transport independently of insulin. The NO donor, SNP appears to increase glucose uptake in muscle through a cGMP-PKG (cGMP-dependent protein kinase) dependent pathway. NO is known to also exert its effects via cGMP-independent signaling such as through the formation of peroxynitrite ($ONOO^-$) from superoxide (O_2^-). In adipocytes, NO increases GLUT4 translocation and glucose uptake independent of the cGMP/PKG pathway and AMPK activation, with the s-nitrosylation of proteins appearing to be responsible. Thus, there is building evidence that NO plays a critical role in signaling glucose uptake during contraction.

Reactive Oxygen Species (ROS)

Physiological levels of ROS may be important signaling molecules regulating various cellular processes, metabolism and gene expression. Seemingly contrasting dynamics of ROS is likely to be a product of duration and extent of exposure, with chronic low level oxidative stress or acute large increases in ROS generation having deleterious effects on muscle cells and acute modest changes initiating signaling cascades. Exogenous hydrogen peroxide can increase basal glucose uptake in isolated rat epitrochlearis muscle implicating ROS in the regulation of glucose uptake during contraction. In support of H_2O_2 being the primary ROS associated with the regulation of glucose uptake, the anti-oxidant catalase (which reduces H_2O_2 to H_2O) but not SOD, inhibits the increase in rat EDL (Extensor Digitorum Longus) muscle glucose uptake in response to the superoxide generating system hypoxanthine1xanthine oxidase.

Figure 4: Mechanisms of glucose uptake into skeletal muscle. (A) insulin-stimulated glucose uptake, (B) Potential mechanisms involved in contraction-stimulated glucose uptake. 1) Glucose delivery to the muscle cell, 2) glucose transport through the membrane 3) glucose phosphorylation and therefore flux through metabolism.

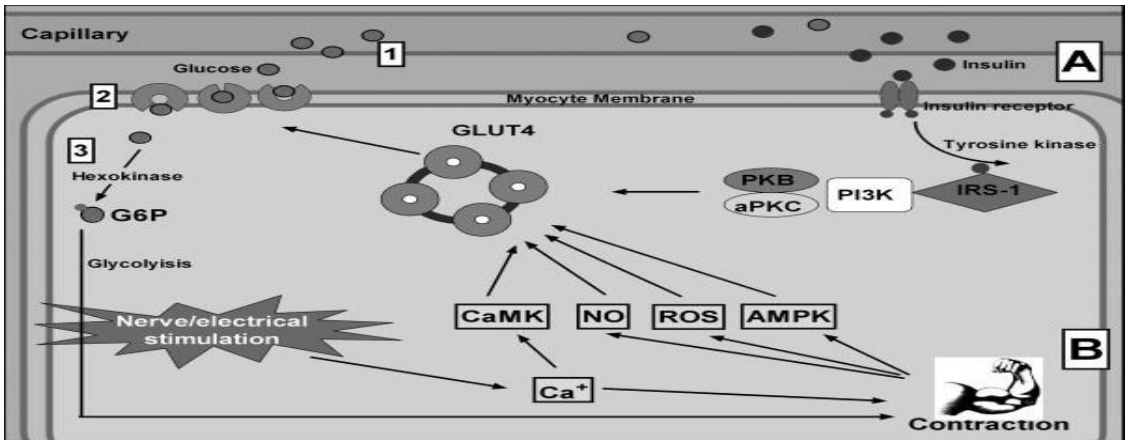
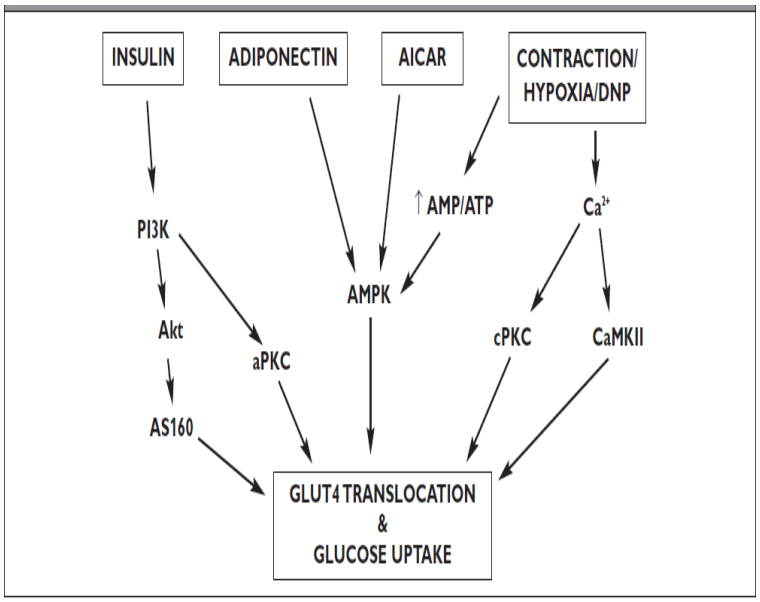


Figure 5: Alternative pathway for glucose transport in skeletal muscle



*AICAR = 5-amino imidazole-4-carboxamide ribonucleoside
*AMPK = 5'-AMP-activated protein kinase
*aPKC = atypical PKC
*CaMKII = Ca^{2+}/calmodulin-dependent protein kinase
*cPKC = conventional protein kinase C

Many studies done earlier have shown the importance of physical activity in controlling obesity and hence occurrence of diabetes mellitus. Even in diabetic patients physical activity reduces the blood sugar levels effectively through pathways independent of insulin as explained above.

There was a strong positive association between obesity (BMI) and increased risk for diabetes in both genders. The prevalence of diabetes was significantly lower for subjects who reported at least 30 min per day of sport activity. This substantially reduced the risk of diabetes in physically active subjects and remained significant after adjusting for age, BMI, WHR, cardiovascular disease and educational level.[53]

Researchers have showed that recommended physical activities have great role in decreasing important variables such as: fasting blood sugar, postprandial blood sugar and hemoglobin A_{1c} (HbA_{1c}). The intake of medicine and insulin didn't have significant difference (i.e., medication didn't differ) but doing physical activity according to the recommended pattern caused the above variables to decrease

significantly. So, physical activity and exercises are critical components of diabetes management. The recommended physical activity can affect most in controlling the complications of diabetes mellitus. If any individual in regard to his physical condition cannot do physical activity, respecting a proper dietary pattern is in the second place of importance. [54]

Structured exercise training that consists of aerobic exercise, resistance training, or both combined is associated with HbA_{1c} reduction in patients with type 2 diabetes. Structured exercise training of more than 150 minutes per week is associated with greater HbA_{1c} declines than that of 150 minutes or less per week. Physical activity advice is associated with lower HbA_{1c}, but only when combined with dietary advice. [55, 56] Higher physical activities are associated with reduced risk of dysglycemia over 5 years even after accounting for BMI. [57]

The total sitting time was more closely related to BMI than total physical activity time and subjects with a higher weight status were more sedentary. Specific group of diabetic or pre-diabetic patients with overweight or obesity had the total sitting time been more closely related to BMI than total PA time. Subjects with high sitting time had a higher BMI, even after correction for total PA time. Even those diabetics or pre-diabetics who meet public health guidelines for leisure time PA may be at risk for co-morbidities if they spend a large proportion of their residual leisure time in sedentary activities. [58]

Beyond the effect of activity on body mass and composition, physical activity may reduce the risk for type 2 diabetes directly through improvements in insulin sensitivity.

F. COMPLICATIONS OF DIABETES MELLITUS

The major long-term complications relate to damage to blood vessels. Diabetes doubles the risk of cardiovascular disease. The main "macrovascular" diseases (related to atherosclerosis of larger arteries) are ischemic heart disease (angina and myocardial infarction), stroke and peripheral vascular disease.

Diabetes also causes "microvascular" complications—damage to the small blood vessels. Diabetic retinopathy, which affects blood vessel formation in the retina of the eye, can lead to blindness. Diabetic nephropathy can lead to scarring changes in the kidney tissue, loss of protein in the urine, and eventually chronic kidney disease requiring dialysis. Diabetic neuropathy, most commonly causes numbness, tingling and pain in the feet and also increasing the risk of skin damage due to altered sensation. Together with vascular disease in the legs, neuropathy contributes to the risk of diabetes-related foot problems (such as diabetic foot ulcers) that can be difficult to treat and occasionally require amputation.[59]

Molecular basis of diabetic complications [60]

Hyperglycaemia causes overproduction of superoxide by the mitochondrial electron-transport chain. The metabolism of glucose through glycolytic pathway and the tricarboxylic acid cycle produces reducing equivalents that are used to drive ATP synthesis via oxidative phosphorylation in the mitochondria. Byproducts of mitochondrial oxidative phosphorylation include free radicals such as superoxide anion and their generation is increased by high glucose levels. Glucose auto oxidation also creates free radicals that can damage cellular proteins as well as mitochondrial DNA. Increased oxidant stress reduces nitric oxide levels, damages cellular proteins

and promotes leukocyte adhesion to the endothelium while inhibiting its barrier function causing various vascular, renal and neurological complications.

G. EXERCISE PRESCRIPTION:

Exercise prescription commonly refers to the specific plan of fitness-related activities that are designed for a specified purpose, which is often developed by a fitness or rehabilitation specialist for the client or patient. Due to the specific and unique needs and interests of the client/patient, the goal of exercise prescription should be successful integration of exercise principles and behavioral techniques that motivates the participant to be compliant, thus achieving their goals.

Components of exercise prescription

An exercise prescription generally includes the following specific recommendations:

- Type of exercise or activity (eg, walking, swimming, cycling)
- Specific workloads (eg watts, walking speed)
- Duration and frequency of the activity or exercise session
- Intensity guidelines – Target heart rate (THR) range and estimated rate of perceived exertion (RPE)
- Precautions regarding certain orthopedic (or other) concerns or related comments

Benefits of physical activity: Regular physical activity -

- Controls/ prevents the development of diabetes

- Improves the strength of heart which makes the heart to work more efficiently during exercise and at rest. The more activities the people perform, the greater is their capacity for exercise and the stronger is the heart which keeps away any heart problem. This leads to reduction of high blood pressure, controlling blood cholesterol levels, controlling diabetes by improving the body's ability to metabolize glucose.
- Helps weight reduction by mobilizing excess fat from the body.
- Decreases total and LDL cholesterol
- Raises HDL cholesterol
- Increases energy store in the body
- Increases tolerance to anxiety, stress and depression
- Helps building healthy bones, muscles and joints.
- Decreases risk of orthopedic injury by improving flexibility
- Improves flexibility and builds muscle.
- Indirectly encourages people to quit smoking for maintaining proper health and fitness.
- Reduces the risk of cancer.

H. REVIEW OF OTHER WORKS:

In a follow up study of 6 yrs in 8633 non diabetic men, cardio-respiratory fitness and fasting plasma glucose was monitored, 149 patients developed type 2 diabetes and 593 patients developed impaired fasting glucose. It was found that those with low fitness had a 1.9 fold risk for impaired fasting glucose and 3.7 fold risk for diabetes compared to those in the high fitness group. This study showed that low

cardio respiratory fitness was associated with risk for impaired fasting glucose, type 2 diabetes and also may contribute to the progression of the disease.[17]

A cohort study conducted on 11,627 individuals aged 20-79 yrs were measured for cardio respiratory fitness. In this 5.5 year follow up study, 572 of them developed type 2 diabetes and those with parental history had a 1.40 fold higher risk for developing type 2 diabetes but those with low cardio respiratory fitness with no parental history was 1.79 times more likely to develop type 2 diabetes. The risk of diabetes in those who had parental history of diabetes was 2.37 times higher in unfit and only 1.41 times higher in fit. Hence in this study it was concluded that though high cardio respiratory fitness didn't fully attenuate the risk of diabetes associated with parental history, being fit reduces diabetes risk regardless of parental history.[61]

Another study of 12 weeks duration was done that evaluated the ability of structured exercise training or physical activity advice to decrease HbA_{1c} levels as compared with control group in patients with type 2 diabetes. Stuctured exercise duration of more than 150 mins per week was associated with decrease in HbA_{1c} of 0.89% while duration of 150 mins or less per week was associated with reduction of only 0.36%.Physical activity alone was not associated with HbA_{1c} changes but physical activity when combined with dietary advice was associated with decrease in HbA_{1c}.[55]

In a18 year follow up study conducted in Columbia on 23444 men aged 20- 85 yrs. The walking/jogging/running group had 40% lower risk of developing diabetes when compared to sedentary group. The moderate and high cardio respiratory fitness group had a 38% and 63% lower risk of developing diabetes compared to the low fitness group. Thus they concluded that those who participated in fitness activity had a

lower risk of developing type 2 diabetes compared to sedentary and higher levels of fitness was associated with an inverse gradient of diabetes.[62]

A step wise regression study was conducted to find out the different risk factors that cause elevated plasma glucose levels in men and women. It was revealed that high density lipoprotein cholesterol was predictive of 2 hr plasma glucose levels in women and cardio respiratory fitness was predictive in men. This study showed that increase in cardio respiratory fitness was more beneficial in prediabetic men than women. [63]

In a study done in Canada at the university of Ottawa, they allocated 251 type 2 diabetes patients to aerobic, resistance (strength) training and combined training. In this study it was concluded that cardio respiratory fitness with aerobic training is a better predictor of changes in HbA_{1c} than improvement in strength.[64]

Another study in the university of Ottawa, Canada checked for changes in cardio-respiratory fitness and HbA_{1c} for different types of training in 2 sets of age group –younger- 39-54yrs and older 55-70 yrs. It was concluded that in younger age groups combined training didn't provide additional benefits when compared to aerobic and resistance training alone but in older subjects there was greater fitness with combined versus aerobic alone.[65]

A study done on 32 metabolic syndrome patients showed that aerobic training was superior to combined training in enhancing the endothelial function ,insulin signaling in fat and skeletal muscle and excitation contraction coupling and decrease in blood glucose and lipogenesis in adipose tissue.[66]

Since there was a significant association between insulin resistance and low cardio-respiratory fitness in nondiabetic subjects, a study done in USA investigated VO_2 Max as an early marker of impaired insulin sensitivity so as to device early interventions to prevent the development of insulin resistance syndrome and type 2 diabetes. It was a cross sectional analyses of 369 people at risk for insulin resistance syndrome and type 2 diabetes aged 20-65 yrs from the Community Diabetes Prevention project in Minnesota. It was revealed that individuals at risk had a VO_2 Max 15% lower than control group and it was concluded that decrease VO_2 Max is among the earliest indicators of insulin resistance syndrome and type 2 diabetes. Therefore important risk factor for disease progression.[67]

A study done on the urban and rural adults in Cameroon, to examine the independent association between objectively measured free living physical activity energy expenditure (PAEE) and metabolic syndrome. Here each KJ/kg/day of PAEE was associated with 2.1% lower risk of prevalent metabolic syndrome. So 6.5 KJ/kg/day difference in PAEE equivalent to 30min/day of brisk walking corresponds to 13.7% lower risk of prevalent metabolic syndrome.

This study showed that urban compared to rural residence is associated with lower PAEE and higher prevalance of metabolic syndrome. So, PAEE is strongly independently associated with prevalent metabolic syndrome. Hence population wide change in PAEE may be significant benefit in terms of reducing the emerging burden of metabolic disease in sub-Saharan Africa.[68]

A 7 year follow up study on 4,187 Japanese men free from Diabetes, was undertaken to study the fitness over a period of time and the maximum oxygen uptake was monitored at least 4 times in these 7 years. The study group was divided into

quartiles. Here 274 developed diabetes and it was concluded that long term trends in fitness is a strong predictor of the incidence of type 2 diabetes in Japanese men.[69]

A randomised control trial was done to identity the effect of 1 yr exercise intervention on myocardial dysfunction in patients with type 2 diabetes. Here 223 type 2 diabetes patients without occult coronary artery disease aged 18-75 years were randomised to an exercise training group(n= 111) or a usual care group (n= 112). Here the changes in myocardial function were not different between groups but there was an improvement in waist circumference, fat mass, blood glucose, HbA_{1C} and VO_2Max in the intervention group. This study concluded that exercise leads to improvement in metabolic function.[70]

An American heart association concluded that exercise training in patients with type 2 diabetes is feasible, well tolerated and beneficial and that sedentary behavior should be minimized. To decrease the cardiovascular risk patients with type 2 diabetes should accumulate a minimum of 150mins/week of a least moderate intensity or 90 mins per week of at least vigorous intensity. Also resistance training should be encouraged. Long term exercise training should be implemented with telephone exercise counseling.[71]

A study was done in 13 adolescent boys with previous type 2 diabetes to examine whether their cardio respiratory fitness and physical activity is reduced in them compared to their overweight controls. Here cardio-respiratory fitness was assessed on electronically braked cycle ergometer and physical activity was estimated from a 7 day physical activity recall. This study showed that youth with type 2 diabetes performed less than 60% moderate physical activity compared to their non-diabetic counterparts. Also diabetic youth exhibit significantly lower cardio-

respiratory fitness compared to controls. Hence this study concluded that cardio-respiratory fitness and physical activity are reduced in youth with type 2 diabetes.[72]

An U.S.A based study on 375 children (193 girls and 182 boys) aged 7-9 yrs to examine the combined influence of aerobic fitness and BMI on metabolic syndrome score in children. Here children were classified as being normal weight, at risk for overweight and overweight on the basis of BMI and aerobic fitness. Here it is found that those with normal weight- high fit group possess the lowest metabolic syndrome score and the overweight unfit group had the highest metabolic syndrome score. Also those children who were overweight and had high fitness level had lower scores than the overweight low fit group. Hence in this study it was concluded that high fitness level modified the impact that BMI had on metabolic syndrome score in children. So increasing the child's fitness level could be one method of reducing the risk of obesity related comorbidities.[73]

MATERIALS AND METHODS

METHODOLOGY:

SOURCE OF DATA:

University ethical clearance was obtained.

The study group comprised of 29 diabetic subjects.

The subjects were recruited from Narayana Hrudayalaya unit of R.L Jalappa hospital and research centre, Tamaka, Kolar.

- **Basis for sample size**:

Estimation of sample size for the circumstance – one sample paired t test.

$$n = \left[\frac{\left(\frac{z_{1-\alpha}}{2} + z_{1-\beta}\right)\sigma}{d}\right]^2$$

where, z_1-α/2 = 1.96

z_1-β = power of 0.95 = 1.645

σ = SD = 1.5

d = change in HbA_{1c} before and after the experiment = 1

So,

n = 29

CRITERIA FOR SELECTION OF STUDY GROUP:

a. Inclusion criteria:

1. Diabetic subjects with sedentary lifestyle.

2. Subjects with duration of diabetes more than 6 months.

3. The diabetic subjects >30 years of age.

b. Exclusion criteria

1. Subjects with any clinical complications of diabetes mellitus.

2. Subjects with type 1 diabetes mellitus and gestational diabetes mellitus.

3. Patients with current insulin therapy.

4. Previously exercising subjects.

5. Subjects with restriction of activity due to medical conditions like IHD.

6. Subjects with BP >160/100mmHg and other medical illness.

METHOD OF COLLECTION OF DATA

Data was collected from the subjects volunteering for study after taking informed consent. The study comprised of 29 patients diagnosed with type 2 diabetes mellitus attending the Narayana hrudayalaya unit of R.L Jalappa hospital and research centre, Tamaka, Kolar.

Physical activity profile was studied using standardized questionnaire and average duration of the activity per day was calculated.[74] (Annexure 1)

Physical Activity Level is given by the formula:

24 hour energy expenditure /basal metabolic rate.

24 hour Energy expenditure = ∑ MET **x** Average duration of activity per day (min/day) **x** Basal metabolic rate.

Physical activity Level (PAL) values:

- < 1.4 - Sedentary
- 1.4 – 1.75 - moderate physical activity
- >1.75 - heavy physical activity

Only those with physical activity levels less than 1.4 were chosen since only sedentary subjects were required. Then the patient's blood was drawn and sent for HbA_{1c}, so that the patient's baseline HbA_{1c} was obtained by ion exchange chromatography with Bio-Rad D_{10}. The results obtained were statistically analyzed. The dietary history was taken.

The cardio-respiratory fitness (VO_2 Max) was found out using the Bruce protocol.

Firstly, the subject was made to run for as long as possible on treadmill, whose speed and slope increments at timed intervals were changed. The time at which the subject was unable to continue was recorded. This time was substituted in a formula which is different for males and females and VO_2 Max was calculated[75].

Men: $\mathbf{VO_2\ Max = 14.8 - (1.379 \times T) + (0.451 \times T^2) - (0.012 \times T^3)}$

Women: $\mathbf{VO_2\ Max = 4.38 \times T - 3.9}$

There are standard and normal values of VO_2Max for different age groups and gender. With this standard value we were able to find out and associate if there was a

decrease or increase in VO_2Max values in these diabetic subjects. The results obtained were also statistically analyzed for correlation between VO_2Max and HbA_{1c}.

Table 2: Bruce Protocol Norms for Men [75]

VO_2 Max Norms for Men - Measured in ml/kg/min						
Age	**Very Poor**	**Poor**	**Fair**	**Good**	**Excellent**	**Superior**
13-19	<35.0	35.0-38.3	38.4-45.1	45.2-50.9	51.0-55.9	>55.9
20-29	<33.0	33.0-36.4	36.5-42.4	42.5-46.4	46.5-52.4	>52.4
30-39	<31.5	31.5-35.4	35.5-40.9	41.0-44.9	45.0-49.4	>49.4
40-49	<30.2	30.2-33.5	33.6-38.9	39.0-43.7	43.8-48.0	>48.0
50-59	<26.1	26.1-30.9	31.0-35.7	35.8-40.9	41.0-45.3	>45.3
60+	<20.5	20.5-26.0	26.1-32.2	32.3-36.4	36.5-44.2	>44.2

Table 3:Bruce protocol Norms for Women[75]

VO_2Max values for Women as measured in ml/kg/min						
Age	**Very Poor**	**Poor**	**Fair**	**Good**	**Excellent**	**Superior**
13-19	<25.0	25.0-30.9	31.0-34.9	35.0-38.9	39.0-41.9	>41.9
20-29	<23.6	23.6-28.9	29.0-32.9	33.0-36.9	37.0-41.0	>41.0
30-39	<22.8	22.8-26.9	27.0-31.4	31.5-35.6	35.7-40.0	>40.0
40-49	<21.0	21.0-24.4	24.5-28.9	29.0-32.8	32.9-36.9	>36.9
50-59	<20.2	20.2-22.7	22.8-26.9	27.0-31.4	31.5-35.7	>35.7
60+	<17.5	17.5-20.1	20.2-24.4	24.5-30.2	30.3-31.4	>31.4

Then the patients were subjected to a physical activity intervention for 6 months. Exercise prescription included the following; He/she had to walk briskly for 30mins/day and a minimum of 5 days a week that is he/she had to walk more than 150 mins/week. Subjects were encouraged to take the stairs instead of elevator. The subjects were followed up by regular phone calls, messages to motivate them to adhere to this walking schedule. The subjects were asked to return to check their VO_2Max and HbA_{1c} after a physical activity intervention of 6 months. The results obtained was tabulated and statistically analyzed to assess the effectiveness of physical activity on cardio respiratory fitness and glycaemic control in diabetics.


TREADSTAR XP

RESULTS AND ANALYSIS

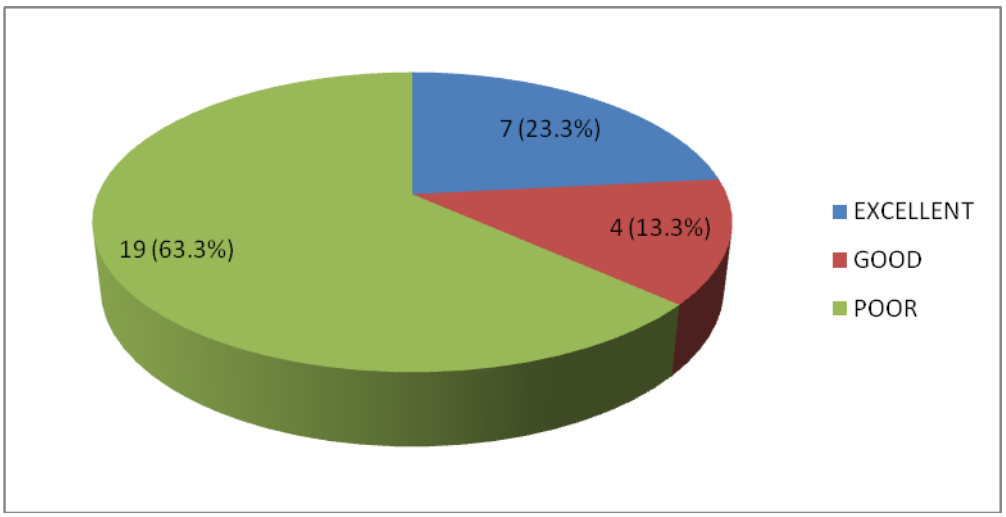
RESULTS

Table 4: BASELINE CHARACTERISTICS OF THE STUDY GROUP

BASELINE CHARACTERISTICS	MEAN ±S.D
Age(years)	45.33 ± 6.66
VO_2Max(ml/kg/min)	32.67±11.99
$HbA_{1C\ (\%)}$	7.58±1.66

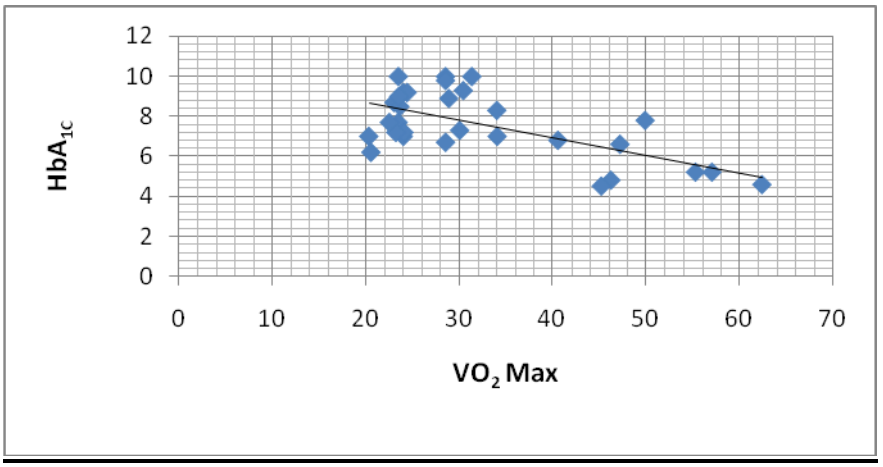
As shown by table 4, the mean age of the study group at baseline was 45.33 ± 6.66, the mean VO_2Max (ml/kg/min) was 32.67 ± 11.99 and mean $HbA_{1C\ (\%)}$ was 7.58 ± 1.66.

Pie chart 1(Graph 1): CHART SHOWING THE BASELINE CARDIORESPIRATORY FITNESS



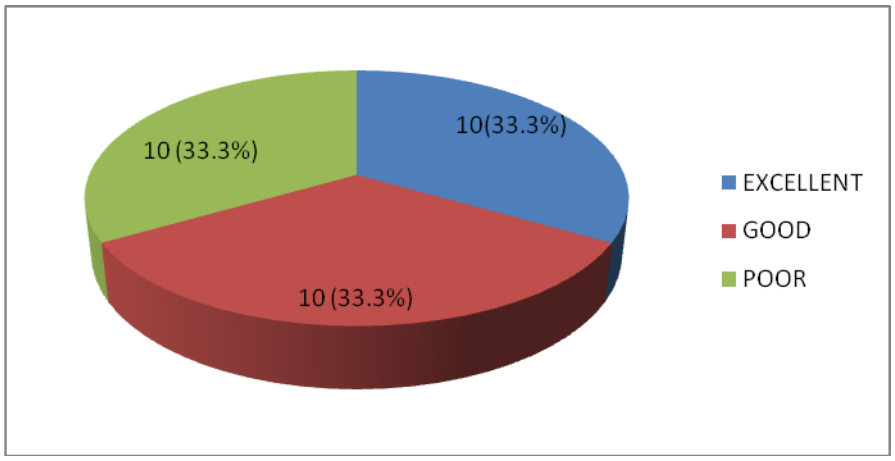
At the onset, out of 30 subjects, 63.3% had poor, 23.3% had excellent and 13.3% had good cardio respiratory fitness. (Pie chart 1)

Graph 2: CORRELATION BETWEEN BASELINE HbA_{1C} AND VO_2 Max



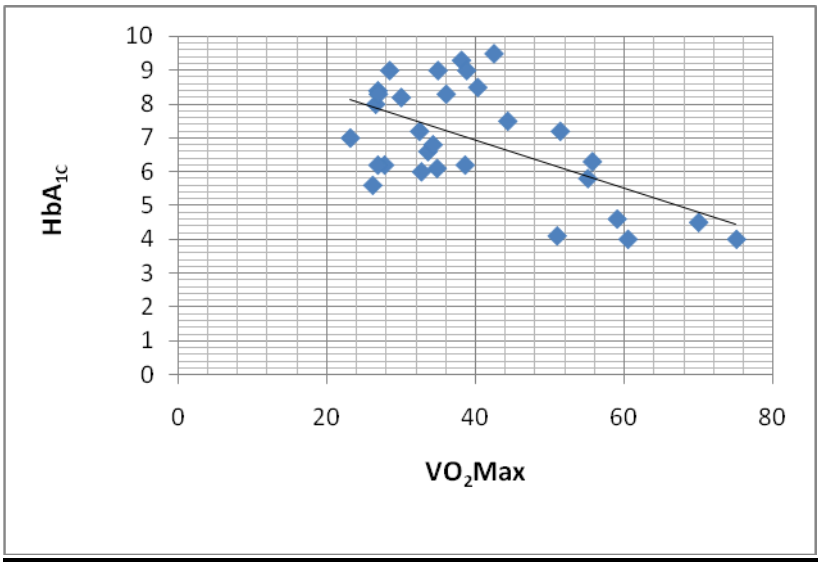
There is a significant negative correlation between Heb_{raic} and VO_2Max(r=-0.636, p< 0.001) (Graph 2)

Pie chart 2(Graph 3): CHART SHOWING THE POST INTERVENTIONAL CARDIO-RESPIRATORY FITNESS



After the exercise intervention 33.3% had excellent, good and poor cardio respiratory fitness each. (Pie chart 2).

Graph 4: CORRELATION BETWEEN POST INTERVENTIONAL HbA_{1C} AND VO_2Max.



There is a significant negative correlation between HbA_{1C} and VO_2Max (r= -0.587, p= 0.001) (graph 4)

Table 5: COMPARISON OF POST INTERVENTIONAL DATA WITH BASELINE DATA.

VO_2 Max Mean± SD		t	P	HbA_{1C} Mean± SD		t	p
Before	**After**			**Before**	**After**		
32.6 ±11.99	**40.05±13.75**	**-10.475**	**<0.001**	**7.58±1.66**	**6.91±1.66**	**19.94**	**<0.001**

When a comparison of post interventional data with the baseline data was done using the paired t test, it was found that there was a significant improvement in the mean VO_2Max from 32.6 ±11.99 to 40.05±13.75.Also there was a significant improvement in the mean HbA_{1C} from 7.58±1.66 to 6.91±1.66.(table 5)

DISCUSSION

DISCUSSION

Type 2 diabetes mellitus (DM) is a global problem with devastating human, social and economic impact and fast turning into an epidemic even in the developing countries .Though primary prevention should be the target, the burden of DM should be reduced too. The important principles in the management of diabetes mellitus are drugs, diet and exercise. Once developed these patients are also prone to many micro-vascular complications including cardiovascular changes. They are known to have decreased response to sub-maximal graded exercise even without cardiovascular changes[76].

VO_2Max can be used clinically to assess the cardiovascular limitations of the subject to graded exercise. This study was designed to assess the cardio-respiratory fitness of the diabetic subjects recruited for the study and assess if 30 minutes of walking per day for 5 days a week for 6months would improve their cardio-respiratory fitness.

Baseline VO_2Max was estimated by treadmill using Bruce protocol. Bruce protocol classifies cardio-respiratory fitness based on VO_2Max into superior, excellent, good, fair, poor, very poor. The VO_2Max of subjects were compared to these standards and it was found of 30 subjects, 7 had excellent cardio respiratory fitness, 4 had good cardio respiratory fitness and 19(63%) had poor cardio respiratory fitness (pie chart 1). Earlier studies too have documented similar findings of poor cardio respiratory fitness in diabetes as indicated by their observation of lower VO_2Max.[77, 73, 78]

Glycosylated hemoglobin values, a measure of glycemic control was found to be 7.58$\pm$1.66% in the subjects before the intervention which was high indicating

inadequate glycemic control. Studies have shown that improving the cardio respiratory fitness will improve the glycemic control.[77]

The VO_2Max is largely dependent on the amount of oxygen available to the exercising muscles. In type 2 diabetics, higher levels of HbA_{1C} could negatively affect tissue oxygenation.[79] This may be due to the addition of glucose molecule at the N terminal valine of β chains which interfere with the binding of 2,3DPG, an important physiological regulator of hemoglobin function.[80] Hence, improving glucose disposal during exercise in turn reduces HbA_{1C} levels enabling 2,3DPG to bind normally with haemoglobin. This reduces hemoglobin's affinity for oxygen, making oxygen readily available to exercising tissues. Various other studies also report similar findings [17].

Two factors influence the blood glucose levels. They are the amount of insulin secreted by pancreatic β cells in response to blood glucose and responsiveness of liver and skeletal muscle to the above mentioned insulin. Blood levels of insulin and responsiveness of liver and skeletal muscle to the released insulin have a significant role in the development of type 2 diabetes mellitus. Mitochondrial activity in turn influences the above mentioned factors. Hence mitochondrial dysfunction or impaired mitochondrial activity is seen as an early step towards the development of type 2 diabetes.[81] Normal functioning of mitochondria is essential for the production of ATP. Mitochondrial dysfunction leads to impaired production of ATP which in turn leads to reduced cardio respiratory fitness.

Regular walking is a lifestyle change that anyone can adopt and is economic, convenient, and feasible and can be performed at one's own pace. The study subjects were encouraged to walk for 30 minutes a day, for at least 5 days a week, for a period

of 6 months. Subjects were followed up by regular phone calls, messages to motivate them to adhere to their walking schedule. They were also asked to give a missed call after their daily walk.

6 months of physical activity intervention resulted in a significant increase in VO_2Max from 32.6 $\pm$ 11.99 to 40.05 $\pm$ 13.75 (an increase of 22.5%) and significant decrease in $HbA1_C$ from 7.58 $\pm$ 1.66 to 6.91 $\pm$ 1.66 (a decrease of 8.84%).

The American diabetes association has observed that several long term studies have demonstrated a consistent beneficial effect of regular physical activity and training on carbohydrate metabolism and insulin sensitivity which can be maintained for at least 5 years. These studies used physical activity regimen at an intensity of 50-80% VO_2Max, 3 - 4 times a week, for 30-60 minutes a session, and the improvement of HbA_{1C} was 10- 20% from the baseline.[82]This conclusion is similar to the results of the studies done in Canada and Finland .[64, 83] In a study done in Glasgow, UK with 16-week-long exercise intervention, the VO_2Max increased by 35%.[66]A Japanese cohort study showed a strong inverse relationship between long term trends in fitness and development of type 2 diabetes. Another Japanese study has shown improvement with walking similar to our study but they prescribed a minimum of 10,000 steps which would take more than 30 minutes.[84]

This may be explained by the fact that in insulin-resistant subjects and models, exercise improves insulin action and glucose tolerance by influencing mitochondrial biogenesis.[85,86] Substantial evidences exist which indicate that aerobic exercise stimulates mitochondrial biogenesis by increasing gene expression of PGC-1, NRF-1, and TFAM.[87]Endurance exercise training increases mitochondrial size, number, and oxidative activity contributing to improved whole-body glucose

metabolism.[88]Mitochondrial biogenesis may also be stimulated by increased expression of eNOS brought on by physical activity. [89, 90]Aerobic exercises also restore age associated reduction in expression of mitochondrial genes and mitochondrial biogenesis .[91] Thus, exercise can improve glucose and lipid metabolism by activation of AMPK and PGC-1α that increase mitochondrial biogenesis and function.

Insulin and muscle contraction cause a net gain of GLUT4 at the plasma membrane to increase glucose uptake, but they utilize distinctly different signaling molecules and mobilize GLUT4 from different pools: exercise/muscle contraction stimulates glucose uptake into skeletal muscle independently of insulin. That explains why humans with insulin resistance can increase muscle glucose transport in response to acute bout of exercise.

The muscle contraction that occurs during exercise can recruit Glut 4 to plasma membrane and this occurs independent of insulin. There is Rab 4, a small GTP binding protein that has been implicated in regulation of Glut 4 translocation in adipose cells. The studies of Rab 4 suggest that there are distinct exercise-stimulated and insulin-stimulated Glut 4 containing vesicles that utilize different molecular switches for mobilization.[92]

We have been able to demonstrate that lifestyle change wherein an inclusion of just 30 minutes of walk 5 times a week could significantly improve cardiovascular fitness and glycemic control. Good glycemic control seemed to be an important motivator to adherence to physical activity in the form of a walk for 30 minutes.

CONCLUSION

CONCLUSION

From this study it was concluded that;

1. Low cardio respiratory fitness is prevalent in type 2 diabetics.

2. Exercise improves cardio respiratory fitness as shown by increase in the VO_2Max.

3. Exercise lowers glycemic index as shown by decrease in $HbA_{1C.}$

Hence, awareness regarding lifestyle modification in terms of increased physical activity should be emphasized. A suitable exercise regimen should be incorporated along with diet and drug prescription. So exercise prescription should be kept in mind and patient enquired about adherence to exercise on OPD visits.

SUMMARY

SUMMARY

Diabetes, a major non-communicable disorder, is a lifelong and life altering illness with no proven cures and demands only management. Although it has been pointed out that the main cardiovascular risk factors in diabetes are dyslipidemias, hypertension and smoking; very few studies have analyzed the effect of other risk factors such as sedentary life style. Worldwide medications are prescribed by physicians for the control of diabetes but they neglect to prescribe an exercise regimen.

30 diabetic subjects were enrolled in this interventional study to assess the effect of physical activity on cardio respiratory fitness and glycemic index in type 2 diabetics. The best measure of cardio-respiratory fitness is VO_2Max, which is the rate of oxygen usage under maximal aerobic metabolism. The glycaemic level was estimated by HbA_{1c}. Their VO_2Max was calculated using the Bruce protocol and HbA_{1c} was estimated by ion exchange chromatography with Bio-Rad $D_{10.}$Then they were advised to follow an exercise prescription in the form of brisk walking 30mins/day for at least 5 days/week for a duration of 6 months .Subjects were encouraged to take the stairs instead of elevator. The subjects were followed up by regular phone calls, messages to motivate them to adhere to this walking schedule. After 6 months they returned to check their VO_2Max and HbA_{1c} .The results obtained were statistically analysed to assess the effectiveness of physical activity on cardio respiratory fitness and glycaemic control in diabetics.

Most of subjects had low cardio respiratory fitness and high glycemic index when recruited for the study .But after the exercise intervention the cardio respiratory fitness significantly improved and glycemic index significantly decreased. So, awareness regarding lifestyle modification in terms of increased physical activity should be emphasized in type 2 diabetics in addition to treating them with medications.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Silink M. UN resolution 61/225: a gift to the diabetic world. Pact Diab Int 2007; 24: 387-388.

2 .Lazarevic G, Antic S, Cvetkovic T, Vlahovic P, Tasic I, Stefanovic V. A physical activity programme, its effects on insulin resistance and oxidative defense in obese male patients with type 2 diabetes. Diabetes Metab 2006; 32: 583 –590.

3. Tripathy BB, Rastogi SS, Moses A, Moses SGP. Land marks in history of diabetes. RSSDI textbook of diabetes mellitus 1st edition. Hyderabad: RSSDI, 2002: 1-32.

4. Bell JI, Hockaday TDR. Diabetes mellitus. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. Oxford Textbook of Medicine. Vol 2. 3rd ed. New York: Oxford University Press; 1996:1448-1504.

5. Powers AC. Diabetes Mellitus. In: Longo DL, Kasper DL, Jameson JL, Fauci AS, Hauser SL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 18thed. New York: Mc Grawhill; 2012: 2968-3002.

6. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2010; 33: s62-69.

7. World Health Organization. WHO Expert Committee for Diabetes. Geneva: WHO; 1980. 80 p.

8. World Health Organization, Department of Non-communicable Disease Surveillance. Definition, diagnosis and classification of diabetes mellitus and its complications. Geneva: WHO; 1999. 59p.

9. Jain AK, Jain SK, Bhatnagar OP. Cardio respiratory response to steady state exercise in sedentary men 20 – 39 years old men. Indian J Chest Dis Allied Sci 1983; 25:172-185.

10. Astrand PO and RodahlK. Textbook of work physiology. Physiological basis of Exercise (3rd edi), Singapore Mac-Graw-Hill International edition.

11. Fox E. Differences in metabolic alterations with sprint versus endurance interval training. Metabolic adaptation to prolonged physical exercise. Basel, Switzerland Birkhauser Verlig. 1975; 119 -126.

12. McArdle WD, Katch FI, Pechar GS, Jacobson L, Ruck S. Reliability and interrelationship between maximum oxygen intake, physical work capacity and step-test scores in college women. Med Sci Sports 1972; 4:182-186.

13. Taylor HL, Buskirk E, Henschel A. Maximal O_2 intake as an objective measure of cardio respiratory performance. J Appl Physiol 1955; 8:72 - 80.

14. Wilmore JH. The assessment and variation in aerobic power in world class athletes as related to specific sports. Am J Sports Med 1984; 12:120-127.

15. Mc Ardle WD, Katch FI, Katch VL. Training for anaerobic and aerobic power in exercise physiology. Energy, Nutrition and human performance 6thedition. Lippincott Williams and Wilkins.2007; 469-507.

16. Ozcelik O, Aslan M, Ayar A, KelestimurH. Effects of body mass index on maximal work production capacity and aerobic fitness during incremental exercise. Physiol Res 2004; 53:165-170.

17.Wei M, Gibbons LW, Mitchell TL, Kampert JB, Lee CD, Blair SN. The association between cardio-respiratory fitness and impaired fasting glucose and type 2 diabetes mellitus in men. Ann Intern Med 1999; 130:89-96

18.Perseghin G, Price TB, Petersen KF, Roden M, Cline GW, Gerow K et al. Increased glucose transport-phosphorylation and muscle glycogen synthesis after exercise training in insulin-resistant subjects. N Engl J Med 1996; 335:1357-1362.

19. Melanson EL, Freedson PS. The effect of endurance training on resting heart rate variability in sedentary adult males.Eur J Appl Physiol 2001;85:442-449.

20. Hager RL, Tucker LA, Seljaas GT. Aerobic fitness, blood lipids, and body fat in children. Am J Public Health 1995; 85:1702-1706.

21 Carnethon MR, Gidding SS, Nehgme R, Sidney S, Jacobs DR Jr, Liu K. Cardio-respiratory fitness in young adulthood and the development of cardiovascular disease risk factors. JAMA 2003; 290:3092-3100.

22. Mc Ardle WD,KatchFI,KatchVL. Training the anaerobic and aerobic energy systems in essentials of exercise physiology.2nd edition.Lippincott Williams and Wilkins: 2000; P362.

23.Wilmore JH and Haskell WL. Use of the heart rate- energy expenditure relationship in the individualized prescription of exercise. Am J Clin Nutr 1971; 24:1186-1192.

24. Blake A, Miller WC, Brown DA. Adiposity does not hinder the fitness response to exercise training in obese women. J Sports Med Phys Fitness 2000; 40:170-177.

25. Lee CD, Blair SN, Jackson AS. Cardio-respiratory fitness, body composition, and all-cause and cardio-vascular disease mortality in men. Am J Clin Nutr 1999; 69:373-380.

26. Fox EL.A simple, accurate technique for predicting maximal aerobic power. J Appl Physiol 1973; 35:914-916.

27. Glenn K, editor. Treadmill protocols [monograph on the internet]. [Last updated on 04/08/11] Available from: http://www.livestrong.com/article/41681treadmill-protocols.

28. Quinn E, editor. The Bruce Treadmill Test Protocol- A fitness evaluation used to measure VO_2Max [monograph on the internet]. Cited 2008 June 09. Available from: http://www.sport-fitness-advisor.com/bruce-treadmill-test.html

29. Reid M, Lachs M, Feinstein A. Use of methodological standards in diagnostic test research. Jam Med Assoc 1995; 274:645–651.

30. Mc Ardle WD, KatchFI, KatchVL. Functional Capacity of cardiovascular system in exercise physiology, energy, nutrition and human performance.6th edition. Lippincott Williams and Wilkins: 2007; 352-363.

31. Ganong WF. Review of Medical Physiology.21st edition. Boston: McGraw Hill; 2003.

32. Johnson JM. Physical training and control of skin blood flow. MedSci Sports Exerc 1998; 30:382-386.

33. McAllister RM. Adaptations in control of blood flow with training: splanchnic and renal blood flows. Med Sci Sports Exerc 1998; 30:375-381.

34. Mc Ardle WD, KatchFI, KatchVL. Gas exchange and transport in exercise physiology energy, nutrition and human performance.6th edition. Lippincott Williams and Wilkins: 2007; 260-311.

35.Coyle EF, Martin WH , Sinacore DR, Joyner MJ, Hagberg JM, Holloszy JO. Time course of loss of adaptations after stopping prolonged intense endurance training. J Appl Physiol Respir Environ Exerc Physiol 1984; 57:1857-1864.

36. Beard J,TobinB. Iron status and exercise. Am J ClinNutr 2000; 72:594S-597s.

37. Rowell LB. Human cardiovascular control. Cary, NC: Oxford University Press, 1994.

38. Rowell LB. Human circulation, regulation during physical stress. New York: Oxford University Press, 1986.

39. DelpMD. Differential effects of training on the control of skeletal muscle perfusion. Med Sci Sports Exerc 1998; 30:361-374.

40. Mc Ardle WD, KatchFI, KatchVL. Essentials of exercise physiology:5thedition.Philadelphia, PA: Lippincott Williams and Wilkins 2001.

41. Wilmore JH, CostillDL. Physiology of Sport and Exercise. 3rd edition. Champaign: 2005.

42. Jackson AS, Beard EF, Wier LT, Ross RM, Stuteville JE, Blair SN. Changes in aerobic power of men, ages 25-70 yr. Med Sci Sports Exerc 1995; 27: 113-120.

43. Jackson AS, Wier LT, Ayers GW, Beard EF, Stuteville JE, Blair SN. Changes in aerobic power of women, ages 20-64 yr. Med Sci Sports Exerc 1996; 28: 884-891.

44. McArdle WD, Katch FI and Katch VL. Essentials of Exercise Physiology.2nd Edition. Philadelphia: Lippincott Williams & Wilkins: 2000.

45. Loftin M, Sothern M, Warren B and Udall J. Comparison of VO_2 peak during treadmill and cycle ergometry in severely overweight youth. J Sports Sci and Med 2004; 3: 254- 260.

46. Thompson PD, Buchner D, Pina IL, Balady GJ, Williams MA, Marcus BH et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease. Circulation 2003; 107:3109-3116.

47. Sigal RJ, Kenny GP, Wasserman DH, Sceppa CC. Physical Activity/Exercise and Type 2 Diabetes. Diabetes Care 2004; 27:2518-2539.

48. Booth FW, Chakravarthy MV, Spangenburg EE. Exercise and gene expression. Physiological regulation of the human genome through physical activity. J Physiol 2002; 543:399–411.

49. Neel JV. Diabetes Mellitus: A "thrifty" genotype rendered detrimental by "progress"? Am J Hum Genet 1962; 14:353–362.

50. Speakman JR. Thrifty genes for obesity, an attractive but flawed idea, and an alternative perspective: the 'drifty gene' hypothesis. Int J Obes 2008; 32:1611-1617.

51. Wijesekara N, Thong FSL, Antonescu CN, Klip A. Diverse signals regulate glucose uptake into skeletal Muscle. Canadian J Diabetes 2006; 30:80-88.

52. Merry TL, McConell GK. Skeletal muscle glucose Uptake during exercise: A focus on reactive oxygen species and nitric Oxide signaling. IUBMB Life 2009; 61:479–484.

53. Defay R, Delcourt C, Ranvier M, Lacroux A, Papoz L. Relationships between physical activity, obesity and diabetes mellitus in a French elderly population: the POLA study. Int J Obes Relat Metab Disord 2001; 25:512-518.

54. Syed ME, Shakeri MT, Rajabian R, Vafaee A. Role of physical activity and nutrition in controlling Type 2 diabetes mellitus . J Biol Sci 2007; 8:794–98.

55. Umpierre D, Ribeiro PA, Kramer CK, Leitão CB, Zucatti AT, Azevedo MJ et al. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes. JAMA; 305:1790-1799.

56. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care 2011; 34:S11-S61.

57. Ponsonby AL, Sun C, Ukoumunne OC, Pezic A, Venn A, Shaw JE et al. Objectively measured physical activity and the subsequent risk of incident dysglycemia. Diabetes Care 2011; 34:1497–1502.

58. Helmink JH, Kremers SP, Brussel-Visser FN, de VriesNK. Sitting time and body mass index in diabetics and pre-diabetics willing to participate in a lifestyle intervention. Int J Environ Res Public Health 2011; 8:3747-3758.

59. Boussageon R, Angoulvant TB, Elahi MS, Lafont S, Bergeonneau C, Kassaï B et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and micro vascular events in type 2 diabetes: meta-analysis of randomised controlled trials. Br J Med [serial on the Internet]. 2011 July 26. [cited 2012 Aug 4]; 343: [about 12 pages]. Available from: http://www.bmj.com/content/343/bmj.d4169.

60. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature 2001; 414:813-820.

61. Goodrich KM, Crowley SK, Lee DC, Sui XS, Hooker SP, Blair SN. Associations of cardio-respiratory fitness and parental history of diabetes with risk of type 2 diabetes. Diabetes Res Clin Pract 2012; 95:425-431.

62.Sieverdes JC, Sui X, Lee DC, Church TS, McClain A, Hand GA et al. Physical activity cardio-respiratory fitness and the incidence of type 2 diabetes in a prospective study of men.Br J Sports Med 2010;44:238-244.

63. Gatterer H, Ulmer H, Dzien A, Somavilla M, Burtscher M. High cardio-respiratory fitness is more beneficial in pre-diabetic men than women. Clinics 2011; 66:747-751.

64.Larose J, Sigal RJ, Khandwala F, Prud'homme D, Boulé NG, Kenny GP. Associations between physical fitness and HbA_{1c} in type 2 diabetes mellitus. Diabetologia 2011; 54:93-102.

65. Larose J, Sigal RJ, Boulé NG, Wells GA, Prud'homme D, Fortier MS et al. Effect of exercise training on physical fitness in type II diabetes mellitus.Med Sci Sports Exerc 2010;42:1439-1447.

66. Tjonna AE, Lee SJ, Rognmo O, Stolen TO, Bye A, Haram PM et al. Aerobic Interval training versus continuous moderate exercise as a treatment for the metabolic Syndrome. Circulation 2008; 118:346-354.

67. Leite AO, Monk AM, Upham PA, Chacra AR, Bergenstal RM. Low cardio-respiratory fitness in people at risk for type 2 diabetes: early marker for insulin resistance. Diabetol Metab Syndr 2009; 1:8z.

68. Assah FK, Ekelund U, Brage S, Mbanya JC, Wareham NJ.Urbanization, Physical Activity, and Metabolic Health in sub-Saharan Africa. Diabetes Care 2011; 34: 491–496.

69. Sawada SS, Lee IM, Naito H, Noguchi J, Tsukamoto K, Muto T et al. Long-term trends in cardio respiratory fitness and the incidence of type 2 diabetes. Diabetes Care 2010; 33:1353–1357.

70. Hordern MD, Coombes JS, Cooney LM, Jeffriess L, Prins JB, Marwick TH. Effect of exercise intervention on myocardial function in type 2 diabetes mellitus. Heart 2009; 95: 1343-1349.

71. Marwick TH, Hordern MD, Miller T, Chyun DA, Bertoni AG, Blumenthal RS et al. Exercise training for type 2 diabetes mellitus: impact on cardiovascular risk: a scientific statement from the American heart association. Circulation 2009; 119:3244-3262.

72. Shaibi GQ, Faulkner MS, Weigensberg MJ, Fritschi C, GoranMI. Cardio-respiratory fitness and physical activity in youth with type 2 diabetes. Pediatr Diabetes 2008; 9: 460 – 463.

73. DuBose KD, Eisenmann JC, Donnelly JE.Aerobic fitness attenuates the metabolic syndrome score in normal-weight, at-risk-for-overweight, and overweight children. Pediatrics 2007; 120:1262-1268.

74. Vaz M. Evaluating Habitual Physical Activity Patterns. State Level Workshop on Human Experiments in Physiology – Setting up innovative experiments with minimal equipment and expenditure. 2000 Jan 28-29; Bangalore. p. 70-81.

75. Vivian H. Heyward, Advance Fitness Assessment & Exercise Prescription, 3rd Edition, the Cooper Institute for Aerobics Research, Dallas TX, 1998.

76.Macanancy O, Reilly H, Oshea D, Cgana M, Green S. Effect of type 2 diabetes on the dynamic response characteristics of the leg vascular conductance during exercise. J Appl physiol 1998;85:310-317.

77. Sawada SS, Lee IM, Muto T, Matuszaki K, Blair SN. Cardio-respiratory fitness and the incidence of type 2 diabetes: prospective study in Japanese men. Diabetes Care 2003; 26: 2918-2922.

78. Regensteiner JG, Sippel J, McFarling ET, Wolfel EE, Hiatt WR. Effects of non-insulin-dependent diabetes on oxygen consumption during treadmill exercise. Med Sci Sports Exerc 1995; 27:875-81.

79. BrownleeM,CeramiA.The biochemistry of the complications of diabetes mellitus. Annu Rev Biochem 1981; 50:385-432.

80. Mc Donald JM,DavidJE. Glycosylatedhemoglobins and diabetes mellitus. Hum Pathol 1979; 10:279-291.

81. Petersen KF, Dufour S, Befroy D, Garcia BA, Shulman GI. Impaired Mitochondrial Activity in the insulin-resistant Offspring of Patients with Type 2 Diabetes. N Engl J Med 2004; 350: 664-671.

82. American Diabetes association. Physical activity/Exercise and diabetes. Diabetes care 2003; 26:S73-S77.

83. Vanninen E, Ususitupa M, Siitonen O, Laitinen J, Lansimies E. Habitual physical activity, aerobic capacity and metabolic control in patients with newly- diagnosed

type 2 diabetes mellitus: effect of 1 year diet and exercise intervention. Diabetologia1992; 35: 340-346.

84. Yamanouchi K, Shinozaki T, Chikada K, Nishikawa T, Ito K, Shimizu S et al. Daily walking combined with diet therapy is a useful means for obese NIDDM patients not only to reduce body weight but also to improve insulin sensitivity .Diabetes care 1995;18:775-778.

85. Hughes VA, Fiatarone MA, Fielding RA, Kahn BB, Ferrara CM, Shepherd P et al. Exercise increases muscle GLUT-4 levels and insulin action in subjects with impaired glucose tolerance. Am J Physiol 1993; 264: E855–E862.

86. Henriksen EJ. Invited review: effects of acute exercise and exercise training on insulin resistance. J Appl Physiol 2002; 93: 788–796.

87. Toledo FG, Menshikova EV, Ritov VB, Azuma K, Radikova Z, DeLany J et al. Effects of physical activity and weight loss on skeletal muscle mitochondria and relationship with glucose control in type 2 diabetes. Diabetes 2007; 56: 2142–2147.

88. Short KR, Vittone JL, Bigelow ML, Proctor DN, Rizza RA, Coenen-Schimke JM et al. Impact of aerobic exercise training on age-related changes in insulin sensitivity and muscle oxidative capacity. Diabetes 2003; 52: 1888–1896.

89. Suvorava T, Lauer N, Kojda G. Physical inactivity causes endothelial dysfunction in healthy young mice. J Am Coll Cardiol 2004; 44: 1320–1327

90. Menshikova EV, Ritov VB, Toledo FG, Ferrell RE, Goodpaster BH, Kelley DE. Effects of weight loss and physical activity on skeletal muscle mitochondrial function in obesity. Am J Physiol Endocrinol Metab 2005; 288: E818–E825.

91.Reznick RM, Zong H, Li J, Morino K, Moore IK, Yu HJ et al. Aging-associated reductions in AMP-activated protein kinase activity and mitochondrial biogenesis. Cell Metab 2007; 5: 151–156.

92. Shibata H, Omata W, Suzuki Y, Tanaka S, Kojima I. A synthetic peptide corresponding to the Rab4 hyper variable carboxyl-terminal domain inhibits insulin action on glucose transport in rat adipocytes. J Biol Chem 1996; 271:9704 - 9709.

ANNEXURE 1

Questionnaire for Physical Activity

1. On an average how many hours per day do you spend at work?

2. On an average how many hours do you sleep in a day?

3. How do you normally travel to and from work?

4. Apart from work how do you spend time?

Type of activity	**Average duration in min**	**Daily**	**Weekly**
Sports /exercise			
Hobbies involving manual activity like gardening			
Household chores –cooking, sweeping			
Sedentary activity – reading, watching TV			
Eating			
Brushing and bathing			
Dressing			
Socializing (talking)			

MASTER CHART

	AGE	SEX	TOTAL EXER TIME min(PRE)	VO_2Max PRE ml/kg/min	PRE RATING	TOTAL EXER TIME min (POST)	VO_2Max POST ml/kg/min	POST RATING	HbA_{1C} PRE %	HbA_{1C} POST %	HEIGHT cms	WEIGHT KG
1	52	M	9.35	31.4	FAIR	12	42.46	EXCELLENT	10	9.5	167	66
2	51	M	11.59	40.6	GOOD	15.9	55.7	SUPERIOR	6.8	6.3	165	65
3	42	M	16.9	62.38	SUPERIOR	22.8	75.1	SUPERIOR	4.58	4	167	72
4	52	M	7.38	24.09	VERY POOR	9.4	32.7	FAIR	7	6	170	84
5	53	M	7.3	24.09	VERY POOR	9.72	34.92	FAIR	9.2	9	168	66
6	57	M	8.59	28.6	POOR	10.58	38.09	GOOD	10	9.3	173	68
7	45	M	8.59	28.6	VERY POOR	9.71	34.8	FAIR	6.7	6.1	186	86
8	45	M	7.1	23.54	POOR	9.35	32.44	GOOD	7.7	7.2	159	55
9	38	M	6.1	20.4	VERY POOR	7.81	27.74	FAIR	7	6.2	165	69
10	40	M	7	23.09	VERY POOR	8.57	29.98	VERY POOR	8.7	8.2	162	60
11	47	M	10	34.07	POOR	11.86	44.31	GOOD	8.3	7.5	177	79
12	40	M	8.6	28.6	POOR	10.68	38.79	FAIR	9.8	9	168	76
13	48	M	9.1	30.5	POOR	11.29	40.27	GOOD	9.3	8.5	175	64
14	38	M	12.9	46.26	EXCELLENT	16.23	60.49	SUPERIOR	4.8	4	172	115
15	40	M	15.5	57.05	SUPERIOR	19.2	70	SUPERIOR	5.2	4.5	168	58
16	47	M	7.2	24.16	POOR	9.52	33.57	POOR	7.2	6.6	173	88
17	40	F	7.3	28.95	FAIR	9.7	36.03	EXCELLENT	8.9	8.3	153	45
18	48	M	6.11	20.63	POOR	7.54	26.14	VERY POOR	6.2	5.6	179	94
19	44	M	10	34.11	FAIR	11.5	38.58	FAIR	7	6.2	167	69
20	31	M	7.25	24.49	VERY POOR	8.6	26.84	VERY POOR	9.2	8.4	164	74
21	35	M	8.59	30.11	VERY POOR	10.2	34.25	POOR	7.3	6.8	164	64
22	36	M	12.39	45.23	EXCELLENT	14	50.96	SUPERIOR	4.5	4.1	172	70
23	53	M	13.45	49.91	SUPERIOR	14.6	51.38	SUPERIOR	7.8	7.2	159	65
24	56	M	12.67	47.23	EXCELLENT	15	55.09	SUPERIOR	6.6	5.8	156	67
25	47	M	7.3	23.29	VERY POOR	8.6	26.84	VERY POOR	7.2	6.2	173	63
26	47	M	7.11	23.72	VERY POOR	8.1	26.55	VERY POOR	8.5	8	168	84
27	55	M	6.3	22.6	POOR	7	23.13	VERY POOR	7.7	7	167	64
28	39	M	7.9	23.61	VERY POOR	8.79	26.9	VERY POOR	9	8.3	151	60
29	46	M	15.3	55.29	SUPERIOR	16	59.04	SUPERIOR	5.2	4.6	154	55
30	48	M	7.8	23.56	VERY POOR	8.32	28.42	VERY POOR	10	9	161	64