“A COMPARATIVE STUDY OF INSULIN RESISTANCE IN OFFSPRINGS OF TYPE 2 DIABETES MELLITUS AND NON DIABETIC PATIENTS -A ONE YEAR CROSS SECTIONAL HOSPITAL BASED STUDY”

By

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Dissertation submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D. (MEDICINE)

Under the Guidance of

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MAY - 2010

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DECLARATION

I hereby declare that this dissertation entitled "A COMPARATIVE STUDY OF INSULIN RESISTANCE IN OFFSPRINGS OF TYPE 2 DIABETES MELLITUS AND NON DIABETIC PATIENTS - A ONE YEAR CROSS SECTIONAL HOSPITAL BASED STUDY" is a bonafide and genuine research work carried out by me under the guidance of Dr. ARATHI DARSHAN MD Associate Professor, Department of Medicine, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum – 590 010.

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LIST OF ABBREVIATIONS USED

Akt	-	Protein kinase B
ATP	-	Adenosine triphosphate
BMI	-	Body mass index
CAP/CBL/TC10	-	Cbl associated protein
CVD	-	Cardiovascular disease
DCCT	-	Diabetes control and complications trial
DM	-	Diabetes mellitus
DNA	-	De-oxy ribonucleic acid
ERK	-	Extracellular signal regulated kinases
FGIR	-	Fasting glucose insulin ratio
FPG	-	Fasting plasma glucose
GDM	-	Gestational diabetes mellitus
GLUT	-	Glucose transporter
GSK 3	-	Glycogen synthase kinase 3
GTT	-	Glucose tolerance test
HbA1c	-	Glycated hemoglobin
HDL	-	High density lipoprotein
HGO	-	Hepatic glucose output
HNF	-	Hepatocyte nuclear factor
HOMA – IR	-	Homeostasis model assessment – insulin resistance
HOMA	-	Homeostastis model assessment
IFG	-	Impaired fasting glucose
IGF	-	Insulin like growth factor
IGT	-	Impaired glucose tolerance

IPF	-	Insulin promotor factor
IRS	-	Insulin receptor substrate
MAPkinase	-	Mitogen activated protein kinase
Mek	-	Mitogen activated protein kinase / Extracellular signal regulated kinases
MODY	-	Maturity onset diabetes of young
NCEP : ATP III	-	National Cholesterol Education Programe – Adult Treatment Panel
NGT	-	Normal glucose tolerance
NIMGU	-	Non-insulin mediated glucose uptake
OGTT	-	Oral gluocse tolerance test
OPD	-	Out patient department
PEPCK	-	Phosphoenol pyruvate carboxy kinase
PFK	-	Phosphofructokinase
PI3kinase	-	Phophatidyl inositol – 3 kinase.
PKC	-	Protein kinase C
PP1	-	Protein phosphatase 1
PPARγ	-	Peroxisome proliferators activated receptor γ
PTEN	-	Phosphatase and tensin homolog
PTP 1B	-	Protein tyroine phosphatase 1B
QUICKI	-	Quantitative insulin sensitivity check index
SHIP1	-	Src homology 2 containing inositol phosphatase 1
SOS	-	Son-of-sevenless
WHO	-	World Health Organization

ABSTRACT

Background and objectives

Type 2 diabetes, is increasing worldwide in epidemic proportions. It has been estimated that the diabetic population will double from 150 to 300 million in the next 25 years. The objective of the present study was to assess the insulin resistance in offsprings of type 2 diabetes mellitus patients with offspings of non diabetic patients.

Methods

The present prospective cross sectional study, was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period January 2008 to December 2008. The study was approved by the Ethical and Research Committee of J. N. Medical College, Belgaum. Insulin resistance in offsprings of type 2 diabetic patients was compared with offsprings of non diabetic patients. Oral glucose tolerance test was performed according to World Health Organization criteria and patients with normal glucose tolerance were included in the study.

Results

Among the 71 subjects, 35 belonged to case group and 36 belonged to control group. The study was age, sex and BMI matched. The mean insulin levels in case group, was found to be higher (23.7 ± 19.77 mU/L) when compared to control group (9.9 ± 7.42 mU/L), which was statistically significant (p=0.000). Insulin resistance was calculated based on HOMA-IR index. A cut-off of more than or equal to 3.2 was taken. Mean HOMA-IR index was higher in case group

(5.8 ± 4.81) when compared to control group (2.2 ± 1.63). This was statistically significant (p=0.000). Insulin resistance among offpsrings, was found to higher in case group (48.6%) when compared to control group (19.4%). This was statistically significant (p=0.009).

Conclusions and interpretation

Hence, risk of insulin resistance is significantly more in offsprings of diabetic parents when compared to offpsrings of non diabetic parents.

Key words

Diabetes Mellitus; HOMA-IR Index; Insulin resistance;

CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

INTRODUCTION

Type 2 diabetes, is increasing worldwide in epidemic proportions. It has been estimated that the diabetic population will double from 150 to 300 million in the next 25 years.[1,2] The long term complications associated with diabetes are major causes of morbidity and mortality, imposing a high financial burden on health care systems. Type 2 diabetes will certainly be one of the major diseases of the 21st century.[3,4,5]

Type 2 diabetes mellitus (DM), is a heterogenous group of disorder characterized by variable degrees of insulin resistance, impaired insulin secretion and increased glucose production.

In contrast to other ethnic groups, Eastern-Asians and Asian Indians tend to develop type 2 diabetes, without the same degree of general adiposity and with a greater tendency to develop central obesity.[6,7,8]

Asian Indians, have an insulin resistant phenotype of obesity characterized by lean body mass index (BMI), high upper body obesity and high body fat percentage which confers a high risk of diabetes and cardiovascular diseases (CVD) in them.[9]

Insulin resistance, is a multifaceted syndrome responsible for future development of type 2 diabetes, obesity, hypertension, dyslipidemia and atherosclerotic CVDs.[10,11]

Prospective studies have shown that, insulin resistance predates the onset of type 2 diabetes by 10 to 12 years. There has also been a debate as to whether insulin resistance is the primary defect that precedes β-cell failure in the evolution of hyperglycemia in type 2 diabetes or vice versa. Obesity, especially visceral abdominal obesity, contributes to the development of insulin resistance, which may underlie a number of manifestations and cardiovascular complications of diabetes and the metabolic syndrome.

Insulin resistance, is associated with increased cardiovascular risk for developing overt diabetes. Therefore, early intervention to treat insulin resistance is an important preventive health strategy.[12,13]

Metabolic syndrome, is also common in the urban Indian population and insulin resistance is one of the major components, in the clusters of abnormalities. In view of important pathogenic role of insulin resistance in causation of diabetes and CVD in Indians, identification of insulin resistance by simple measurements, would facilitate selection of high risk individuals for primary prevention of these interrelated diseases.[14,15,16]

Anthropometry, plasma glucose and lipid profile including total cholesterol, high density lipoprotein (HDL) cholesterol and fasting triglycerides are routinely measured in screening procedures for diabetes or CVD. Plasma insulin is not routinely measured in most clinical laboratories. Insulin resistance is an important component of the metabolic syndrome and is likely to show an association, with other components of the syndrome.[9]

In the quest for a noninvasive measurement technique for insulin sensitivity, several fasting or 'homeostatic models' have been proposed. The homeostatic model assessment (HOMA), fasting glucose insulin ratio (FGIR) and quantitative insulin sensitivity check index (QUICKI) methods have been the most frequently used techniques, in clinical investigation. The fact that these tests require only a single venipuncture in the fasting state and do not call for concomitant intravenous access, makes them particularly attractive to patients and clinicians alike.[17,18,19,20]

First degree relatives, of people with type 2 diabetes have an increased risk of developing the disease, compared with people without diabetes heredity. They show signs of insulin resistance and insufficient insulin secretion, despite normal glucose tolerance. Early prevention of diabetes could be of great importance, in these individuals.[21]

Little is known, about the effectiveness of lifestyle intervention in the presumably motivated target group. Weight reduction cannot always be a primary goal because these individuals are not necessarily over weight.[21]

Thiazolidinediones, which act on insulin resistance, can slow and perhaps even prevent progression of type 2 diabetes. Treatment of insulin resistance with thiazolidinediones has been shown to ameliorate several complications associated with insulin resistance, such as hypertension, dyslipidemia, hyperinsulinemia, visceral fat, microalbuminuria and hypertension.[22]

In view of the above, the present study was undertaken, to compare the insulin resistance in offsprings of type 2 diabetic and non diabetic parents.

OBJECTIVES

The objective of the present study was to assess the insulin resistance in offsprings of type 2 diabetes mellitus patients, with offspings of non diabetic patients.

REVIEW OF LITERATURE

HISTORICAL REVIEW

Diabetes mellitus, is a disease that was recognized in antiquity, but its history has been characterized by numerous cycles of discovery, neglect and rediscovery. Its history, may be divided into four major periods that reflect different phases in the understanding and management of the disease. The 'ancient' period, witnessed the first clinical descriptions of diabetes and complications. The 16th to 18th centuries have been termed the 'diagnostic' period, as DM was then identified as a separate disease entity, while the mid to late 19th century may be regarded, as the first 'experimental' period, during which the glucoregulatory role of the pancreas became clear and the biochemical disturbances of diabetes were initially characterized.[23]

Finally, the 20th century has seen a dramatic increase in knowledge about diabetes. The discovery of insulin in 1921-22 has had profound scientific, clinical and social consequences. Some key developments in scientific and clinical understanding of diabetes may be summarized as follows;[24]

- Polyuric states, clinically resembling DM were described as early as 1550 BC in the ancient Egyptian papyrus discovered by George Ebers.
- The sweet taste of diabetic urine was noted in the fifth and sixth century AD by the Indian physicians (Sushruta and Charaka) and in the 17th century by Thomas Willis. The term 'Diabetes mellitus', an allusion to the honeyed taste of urine, was first used in the late 18th century by John

Rollo and others, to distinguish it from other polyuric states in which urine was tasteless.

- In 1776, Matthew Dobson discovered that diabetic serum as well as urine contained sugar, and concluded that diabetes was a systemic condition rather than a disease of kidneys.
- Claude Bernard, made numerous discoveries in the field of metabolism and diabetes during the mid to late 19th century, describing the storage of glucose in the liver as glycogen and hyperglycemia in experimental animals.
- In 1889, Oskar Minkowski and Josef Von Mering observed that total pancreatectomy produced diabetes in dogs.
- In 1893, Edovard Laguesse named the pancreatic islets after Paul Langerhans, who had described them in 1869, and suggested that they produced a glucose lowering substance. This then hypothetical hormone was named 'insulin' by Jean de Meyer in 1909, over a decade before its discovery.
- Various workers, including George Zuelzer (Germany) and Nicolas Paulesco (Romania), isolated active but impure hypoglycemic extracts from the pancreas during the first two decades of the 20th century; but toxic side effects precluded their formal testing in diabetic patients.
- Insulin, was discovered at the University of Toronto in 1921, through collaboration between Frederick G. Banting, Charles H. Best, James B. Collip and J.J.R. Macleod. Insulin was extracted from chilled pancreas in an acid / ethanol mixture; the extracts were found to lower blood glucose

levels in pancreatectomised dogs and were first tested in a human diabetic (Leonard Thompson) in January, 1922.

- Major advances in the understanding of diabetes and metabolism have included:

  A. The sequencing of insulin in 1955, by Frederick Sanger and elucidation of its three dimensional structure in 1969, by Dorothy Hodgkin.

  B. The measurement of insulin concentration using the first radio immunoassay, by Solomon Berson and Rosalyn Yalow in 1959.

  C. The isolation of proinsulin, in 1967 by Donald Steiner's group.

  D. Identification of specific insulin receptors by Pierre Freychet and colleagues, in 1971.

  E. The sequencing of the insulin receptor, in 1985.

- Mile stones in the management of diabetes have included,

  A. The development of long acting insulin preparations (isophane) in 1936, by Hans Christian Hagedorn and colleagues.

  B. The testing of sulfonylureas by Auguste Loubatieres, in 1944.

  C. First therapeutic use of a biguanide (phenformin) by G. Ungar, in 1957.

  D. Dry reagent test strips suitable for self monitoring of blood glucose, were introduced in the late 1970's.

  E. Definitive proof from the diabetes control and complications trial (DCCT) published in 1993, that strict glycemic control could slow or prevent, the development of diabetic microvascular complications.

EPIDEMIOLOGY

Type 2 DM, is the commonest form of diabetes accounting for 85 to 95% of all cases worldwide with its global prevalence increasing rapidly, as a consequence of westernized lifestyle and is destined to become one of the most costly diseases.

The prevalence is expected to increase by 122% (from 125 to 300 million) between 1995 and 2025. The developing world will suffer the most with a predicted 170% increase in cases that will mainly affect the 45 to 65 group, by contrast the diabetic population in the developed world will increase only by 40%, particularly among those aged more than 65 years.[26]

In the United State of America, 10 to 20% of diabetic children and adolescents now have type 2 DM with ethnic minorities, African Americans, Mexicans and Pima Indians having the highest prevalence. 85% of children with type 2 DM are obese.[27] Various study reports show that 74% to 100% of these children have a history of diabetes in the first and second degree relatives and the inheritance is polygenic.

Indian problem

Several epidemiological studies in migrant Indians and India itself show that, the population has a high genetic predisposition for diabetes, which is precipitated by environmental factors such as urbanization.[28] The prevalence of diabetes is four to six fold lower in rural areas, which is probably attributed to a conventional lifestyle which has beneficial effect on glucose tolerance (IGT).

National Urban Diabetes Survey done in six cities, found age standardized prevalence rates of 12% for diabetes; with a slight male preponderance and 14% for impaired glucose tolerance. Subjects under the age of 40 years, had a prevalence of five percent for DM and 13% prevalence of impaired glucose tolerance.

Causes for diabetic pandemic

The type 2 DM epidemic is tightly and consistently linked to that of obesity, both geographically and chronologically. Many factors like, urbanization and mechanization, together with globalized pattern of western pattern of lifestyle, together with poverty, lack of education and low socio-economic status and inner city deprivation are emerging as significant risk factors for DM. Lack of breast feeding, low birth weight is associated with insulin resistance and type 2 DM in adult life (especially in subjects who become obese) due to long term metabolic response during poor fetal nutrition.[31]

Obesity

Prevention of obesity, in women of child bearing age, is another primary goal because exposure to environment of a diabetic pregnancy places the fetus at increased risk for future onset diabetes. About 80% of patients are obviously obese at the time of diagnosis, usually with a central fat distribution in and around the abdominal cavity. In addition, many of those who are not traditionally obese, by weight criteria have increased percentage of fat predominantly distributed in the abdominal region. It is the most obvious target to prevent DM.

Body mass index (BMI) and waist circumference

Three key anthropometric measurements are important to evaluate the degree of obesity – weight, height and waist circumference. The BMI, calculated as weight (kg)/height $(m)^2$, or as weight (lbs)/height$(inches)^2$ x 703, is used to classify weight status and risk of disease. Body mass index, is used since it provides an estimate of body fat and is related to risk of disease. Lower BMI thresholds for overweight and obesity have been proposed for the Asia-Pacific region since this population appears to be at risk at lower body weights for glucose and lipid abnormalities.

Excess abdominal fat, assessed by measurement of waist circumference or waist-to-hip ratio, is independently associated with high risk for DM and CVD. Waist circumference is a surrogate marker for visceral adipose tissue. It is measured in the horizontal plane above the iliac crest. Cut points, that define higher risk for men and women based on ethnicity have been proposed by the International Diabetes Federation (IDF).[32]

Table No. 1: Classification of weight status and risk of disease[33]

	BMI (Kg/m^2)	Obesity Class	Risk of Disease
Underweight	<18.5		
Healthy weight	18.5 – 24.9		
Overweight	25.0 – 29.9		Increased
Obesity	30.0 – 34.9	I	High
Obesity	35.0 – 39.9	II	High
Extreme Obesity	≥ 40	III	Extremely high

Table No. 2: Ethnic-specific values for waist circumference – IDF guidelines[34]

Ethnic Group	Waist Circumference
Europeans	
Men	>94cm (37in)
Women	> 80cm (31.5in)
South Asians and Chinese	
Men	> 90cm (35 in)
Women	> 80cm (31.5 in)
Japanese	
Men	> 85cm (33.5in)
Women	> 90cm (35 in)
Ethnic south and central Americans	Use south Asian recommendations until more specific data are available
Sub-Saharan Africans	Use European data until more specific data are available
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available

Metabolic syndrome

The metabolic syndrome (syndrome X, insulin resistance syndrome) consists of a constellation of metabolic abnormalities, that confer increased risk of CVD and DM. The criteria for the metabolic syndrome have evolved, since the original definition by the World health Organization (WHO) in 1998, reflecting growing clinical evidence and analysis by a variety of consensus conferences and professional organizations. The major features of the metabolic syndrome include

central obesity, hypertriglyceridemia, low HDL cholesterol, hyperglycemia and hypertension.[32]

National Cholesterol Education Programme: Adult Treatment Panel (NCEP: ATPIII) 2001 Criteria for metabolic syndrome

Three or more of the following;

1. Central obesity – Waist circumference more than 102cm (Male), more than 88 cm (Female).
2. Hypertriglyceridemia: Triglycerides more than or equal to 150mg/dL or specific medication.
3. Low HDL cholesterol: less than 40 mg/dL and less than 50 mg/dL males and females respectively, or specific medication.
4. Hypertension: Blood pressure more than or equal to 130 mm systolic or more than or equal to 85 mm diastolic or specific medication.
5. Fasting plasma glucose (FPG) more than or equal to 100 mg/dL or specific medication or previously diagnosed type 2 diabetes

Table No. 3: Indian Diabetes Federation criteria for metabolic syndrome

Waist Circumference		Ethnicity
Men	**Women**	
≥ 94cm	≥ 80cm	Europid, Sub-Saharan African, Eastern and Middle Eastern
≥ 90cm	≥80cm	South Asian, Chinese and ethnic South and Central American
≥ 85cm	≥ 90cm	Japanese

Two or more of the following :

Fasting triglycerides > 150mg/dL or specific medication

HDL cholesterol < 40mg/dL and <50mg/dL for men and women respectively or specific medication

Blood pressure >130 systolic or >85 mm diastolic or previous diagnosis or specific medication

Fasting plasma glucose ≥ 100mg/dL or previously diagnosed type 2 diabetes

Classification of diabetes and other categories of glucose regulation

Diabetes mellitus is classified on the basis of the pathogenic process that leads to hyperglycemia, as opposed to earlier criteria such as age of onset or type of therapy.[35]

Table No. 4: Spectrum of glucose homeostasis and diabetes mellitus

Type of diabetes	Normal glucose tolerance (NGT)	Impaired fasting glucose or impaired glucose tolerance	Hyperglycemia		
			Diabetes mellitus		
			Not insulin required	Insulin required for control	Insulin required for survival
Type 1					
Type 2					
Other Specific types					
Gestational diabetes					
Time (years)					
FPG (mg/dl)	< 100	100-125		≥ 126	
2-h plasma glucose (mg/dl)	< 140	140 – 199		≥ 200	

Etiologic classification of diabetes mellitus

I. Type 1 diabetes (-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 β-cell function characterized by mutations in :

1. Hepatocyte nuclear transcription factor (HNF) 4α maturity onset diabetes of young (MODY) 1
2. Glucokinase (MODY 2)
3. HNF – 1α (MODY 3)
4. Insulin promoter factor (IPF) 1 (MODY 4)
5. HNF – 1β (MODY 5)
6. Neuro D1 (MODY 6)
7. Mitochondrial deoxyribo nucleic acid (DNA)
8. Sub units of adenosine triphosphate (ATP) – sensitive potassium channel.
9. Proinsulin or insulin conversion

B. Genetic defects in insulin action.

1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipodystrophy syndromes.

C. Diseases of the exocrine pancreas – pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy.

D. Endocrinopathies – acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma

E. Drug or chemical induced – Vacor, pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, diazoxide, beta-adrenergic agonists, thiazides, phenytoin, α– interferon, protease inhibitors, clozapine, beta blockers.

F. Infections – congenital rubella, cytomegalovirus, coxsackie.

G. Uncommon forms of immune-mediated diabetes – "stiff-man" syndrome, anti-insulin receptor antibodies.

H. Other genetic syndromes sometimes associated with diabetes – Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Wolfram's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome.

IV. Gestational diabetes mellitus (GDM)

Type 2 DM

Insulin resistance and abnormal insulin secretion are central to the development of type 2 DM. Although the primary defect is controversial, most studies support the view that, insulin resistance precedes an insulin secretory defect and diabetes develops only when insulin secretion becomes inadequate.

Genetic Considerations

Type 2 DM has a strong genetic component. The concordance of type 2 DM in identical twins is between 70 and 90%. Individuals with a parent with type 2 DM have an increased risk of diabetes; if both parents have type 2 DM, the risk

approaches 40%. Insulin resistance as demonstrated by reduced glucose utilization in skeletal muscle is present in many nondiabetic, first degree relatives of individuals with type 2 DM. The disease is polygenic and multifactoral since in addition to genetic susceptibility, environmental factors (such as obesity, nutrition and physical activity) modulate the phenotype. The genes that predispose to type 2 DM are incompletely identified but recent genome-wide association studies have identified several genes that convey a relatively small risk for type 2 DM (relative risk of 1.1 to 1.5). Most prominent is a variant of the transcription factor 7-like 2 gene that has been associated with type 2 diabetes in several populations and with IGT in one population at high risk for diabetes. Genetic polymorphisms associated with type 2 diabetes have also been found in the genes encoding the peroxisome proliferators-activated receptor γ (PPAR-γ), inward rectifying potassium channel expressed in beta cells, zinc transporter expressed in beta cells, insulin receptor substrate (IRS) and calpain 10. The mechanisms by which these genetic alterations increase the susceptibility to type 2 diabetes are not clear, but several are predicted to alter insulin secretion, investigation using genome-wide scanning for polymorphisms associated with type 2 DM is ongoing.

Pathophysiology

Type 2 DM, is characterized by impaired insulin secretion, insulin resistance, excessive hepatic glucose production and abnormal fat metabolism. Obesity, particularly visceral or central (as evidenced by the hip-waist ratio), 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, 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 may ensue.[32]

Early onset type 2 diabetes was defined as type 2 DM with age at diagnosis between 25 to 39 years, history of late onset type 2 DM in both parents; history of several paternal and maternal uncles and aunts with DM; history of early onset type 2 diabetes in first sibling and progressive clinical severity towards insulin requirement and micro vascular complication over the course of treatment.[36,37,38]

INSULIN RESISTANCE

Normal physiology of glucose homeostatis

Maintenance of normal glucose levels depends upon, a closed feedback loop between the circulating glucose level and the pancreatic hormones, insulin and glucagons. In the fasting state, glucose is largely produced by the liver via glycogen breakdown and gluconeogenesis. Approximately 70% to 80% of the glucose produced by the liver is used by the brain (independent of insulin) and by other insulin-insensitive tissues, such as the gastrointestinal tract and erythrocytes. The insulin-sensitive tissues, principally muscle and fat, use only small quantities of glucose in the absence of increased insulin levels. Hepatic glucose output (HGO) in the short term (that is minutes to hours) is modulated by

insulin, glucagons, catecholamines and the glucose level itself. Growth hormone, thyroid hormone and cortisol (glucocorticoids) serve as longer-term modulators (that is hours to days) of hepatic glucose production.

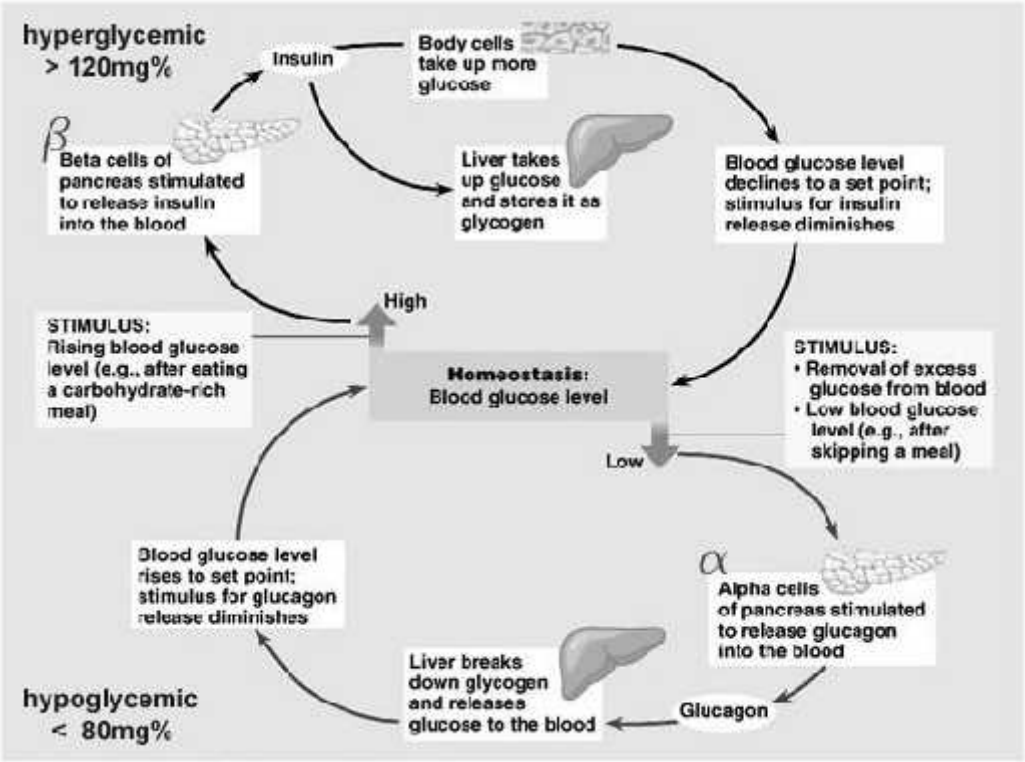


Figure No. 1: Normal physiology of glucose homeostatis

Insulin (from the pancreatic beta cell) exerts an inhibitory effect on hepatic glucose production. In contrast, glucagons (from the pancreatic alpha cell) stimulates hepatic glucose production. Thus, a reduction in insulin results in a slow rise in HGO. If the feedback loop is intact, as the serum glucose level rises, pancreatic insulin secretion would increase, and glucagons would decrease in order to maintain homeostasis. If peripheral insulin sensitivity changes, this would result in a change in serum glucose, which in turn would result in modulation of insulin and glucagons in order to maintain glucose levels.

Complete adaptation actually does not occur and thus, a new higher steady-state glucose level is reached. One must account for each variable that contributes to this regulatory system - HGO, pancreatic endocrine function and peripheral tissue glucose uptake - in order to appropriately evaluate abnormalities in glucose homeostasis.

At the cellular level, the mechanism of insulin action, involves a cascade of biochemical interactions. The initial event begins with insulin binding to a cell surface receptor, which activates the receptor's intrinsic tyrosine kinase activity. Tyrosine kinases phosphorylate intracellular substrates, including themselves (autophosphorylation). The phosphorylation triggers a molecular phosphorylation /dephosphorylation signaling cascade. Proteins such as IRS-1 and IRS-2 are phosphorylated and ultimately result in the activation of three major pathways: the phosphatidylinositol-3 (PI3) kinase pathway, the Cb1 activated protein/Cbl/Tc10 pathway and the extracellular signal regulated kinase (ERK) pathway.[39] Much research studies enzymes such as protein tyrosine phosphatase (PTP) 1B, PI-3 kinase, protein kinase B (Akt) and glycogen synthase kinase 3 (GSK3), among others, in order to understand the nature of the post-receptor defects seen in type 2 diabetes.[39] The ultimate result of the signaling cascade is the recruitment and translocation of the glucose transporter 4 (GLUT4) protein from an intracellular pool to the cell membrane, which facilitates the influx of glucose into the cell for subsequent metabolism.

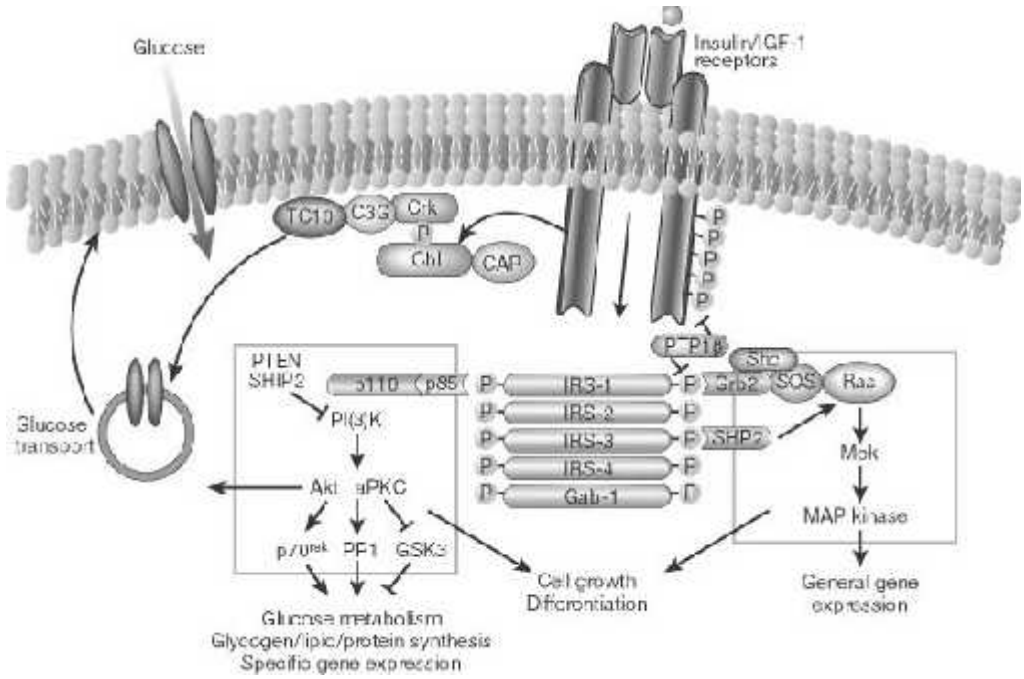


Figure No. 2: Insulin signaling pathway

Components of insulin signaling pathway

- Insulin receptor – IRS-1 and IRS-2 (Liver)
- PTP1B
- p110-p85
- PI3K pathway – GSK3, Akt, phosphofructokinase 2 (PFK2) (Liver), Phosphoenolpyruvate carboxykinase (PEPCK) gene (Liver), p70S6K
- CAP / Cbl / Tc10 pathway
- ERK pathway

Natural history and epidemiology of insulin resistance

Insulin resistance is present in approximately 90% of patients with type 2 diabetes.[40] Insulin resistance is often associated with a cluster of metabolic abnormalities (known as the metabolic syndrome, also known as the

dysmetabolic syndrome, insulin resistance syndrome, syndrome X, and Reaven's syndrome). Glucose intolerance and hyperglycemia, hypertension, dyslipidemia, abdominal (central) obesity, endothelial dysfunction, impaired vascular reactivity, vascular inflammation and a hypercoagulable state with impaired fibrinolysis compose the metabolic syndrome. Some or all of these components may be present in any given patient.

The role of insulin resistance in the genesis of the metabolic syndrome remains controversial, but there is a strong association. Insulin resistance also occurs in persons who are not diabetic. Up to 25% of nondiabetic patients have a lower degree of insulin sensitivity, similar to those with type 2 diabetes who have good glycemic control. The severity of insulin resistance is quite variable from person to person and is usually progressive over time. Investigations of various populations in which insulin resistance, IGT, and type 2 diabetes are prevalent have provided insight into the factors, that influence the development and progression of these metabolic derangements.

A higher prevalence of glucose intolerance and type 2 diabetes has been observed among certain ethnic groups, such as Pima Indians and other Native Americans, Hispanic Americans, Pacific Islanders and African Americans. For example, the Pima Indians of Arizona have the highest rate of diabetes in the world. About 50% of the Pima Indian population between the ages of 30 and 64 years of age has type 2 diabetes. The severity of insulin resistance is one of the strongest predictors of type 2 diabetes in these high-risk groups. Similar observations have been made in the Mexican American population and in children of diabetic parents who have signs of insulin resistance years before the

onset of diabetes. Additionally, the likelihood of insulin resistance increases along with other cardiovascular risk factors, such as coagulation and fibrinolytic abnormalities, in first-degree relatives of patients with type 2 diabetes.

Although more prevalent in older people, insulin resistance is not limited to adults. An increasing number of children and teenagers are found to have insulin resistance. Obese adolescents, can manifest features of the metabolic syndrome such as hypertension, dyslipidemia, acanthosis nigricans and glucose intolerance, including frank type 2 diabetes.

Generally, insulin resistance gradually progresses and worsens over a period of years. With worsening insulin resistance, insulin is less able to dispose of glucose from the circulation. As a result, compensatory hyperinsulinemia ensues in order to maintain euglycemia. However, beta cell dysfunction gradually manifests, leading to inability to maintain a sufficient hyperinsulinemic state to overcome the insulin resistance, which eventually leads to prediabetes (IGT) and then type 2 diabetes with overt hyperglycemia.

Although it is clinically challenging, our goal as clinicians should be to identify persons who are at risk as early as possible in the natural history, where interventions are likely to be most efficacious. Ethnicity, family history, features of the metabolic syndrome and postprandial hyperglycemia even with normal fasting glucose may be helpful in identifying these at-risk persons.

Patients with type 2 DM, share a pathophysiology that involves the pancreatic beta cells, the liver and the major insulin-sensitive peripheral target tissues, namely skeletal muscle and adipose tissue.

Insulin resistance

Insulin resistance is defined as a condition of low insulin sensitivity in which the ability of insulin to lower circulating glucose is impaired. The genetic predisposition for the development of insulin resistance, while unquestionably present,[41] is largely undefined, but observations of decreased insulin sensitivity among relatives of people with type 2 diabetes suggest a genetic association. Genetic determinants likely interact with other factors, such as obesity, aging, elevated free fatty acids and hyperglycemia, to contribute to the development of a pathologic, insulin-resistant state. The underlying biochemical and molecular basis of insulin resistance, in most persons with type 2 diabetes remains to be determined.

Insulin resistance in muscle, adipose and liver tissue arises from multiple complex metabolic abnormalities. Biochemical defects, that provoke insulin resistance involve impaired insulin signaling (a biochemical cascade of events) and reductions in glucose transport in insulin-sensitive tissue.

From a clinical standpoint, early insulin resistance results in compensatory hyperinsulinemia with the maintenance of euglycemia as discussed earlier in the natural history of type 2 diabetes. At this stage, measurement of fasting glucose and random glucose usually remains within normal limits, is asymptomatic and thus is often undetected. On physical examination, one might detect acanthosis nigricans, which can occur in association with severe insulin resistance. Excessive skin tags may also be seen in association with insulin resistance.

Hepatic Insulin Resistance

Basal rates of HGO, have been described as increased or inappropriately normal in type 2 diabetes. The degree of abnormality in HGO positively and strongly correlates with the degree of fasting hyperglycemia. This suggests that the rate of HGO has a major role in contributing to fasting glucose levels. The increased rate of HGO, results from impaired effects of insulin and glucose to normally suppress glucose release from the liver. The insulin dose-response curve for suppression of HGO is right shifted, in type 2 diabetic subjects, studied at euglycemia. No reduction is seen in the maximum suppressive response at supraphysiologic insulin levels. In other words, the liver is insulin resistant, but given enough insulin, HGO can be completely suppressed. This is consistent with a decrease in hepatic insulin receptor number. However, other studies show that a defect in the ability of glucose, to inhibit its own release from the liver is another factor, contributing to hepatic glucose overproduction. Elevated glucagons can also contribute to reducing the suppressive effects of insulin and glucose on HGO.

In the fed state, the liver continues to play a crucial role in maintaining glucose homeostasis. After a meal, glucose and insulin enter the liver via the portal circulation and change liver function from its role in the fasting state as a glucose-producing organ to that of storage. During feeding, glucose is stored in the form of glycogen in the liver. However, because there are defects in hepatic sensitivity to glucose and insulin, there is a delayed reduction in HGO suppression in the type 2 diabetic patient. This is a major contributor to the post

prandial hyperglycemia, that is noted early in the course of insulin resistance and the prediabetic state.

Peripheral Insulin Resistance

It is well established that, subjects with type 2 diabetes exhibit peripheral insulin resistance in target tissues, such as skeletal muscle.[42] The hyperinsulinemic-euglycemic clamp technique, a research method for measuring peripheral insulin resistance, shows that the glucose disposal rate is usually reduced by at least 50% in subjects with type 2 diabetes. Two abnormalities are observed in the insulin dose-response curve; a right shift (as seen in hepatic insulin resistance) and a decrease in maximal response.

The rightward shift in the curve, is consistent with a decreased number of insulin receptors. The decrease in maximal response implies a post binding (intracellular) defect of insulin action. The exact underlying intracellular defects continue to be determined. Putative defects in IRS-1, PI3 kinase,[43,44,45] GSK3 and other factors have been demonstrated and are the subject of current research efforts.

The deficiency of peripheral glucose uptake after oral glucose ingestion, is also defective in type 2 diabetic subjects. In normal subjects, after cellular uptake, glucose normally undergoes both oxidative and nonoxidative metabolism. At low insulin concentrations, the major route of peripheral glucose disposal is via glucose oxidation (i.e. using glucose as metabolic fuel). At higher insulin levels, an increasing fraction of disposal occurs via glycogen synthesis i.e. glucose is removed from the circulation and stored. Glycogen synthesis is the

major component of nonoxidative glucose metabolism. However, in type 2 diabetic subjects, the deficiency of glucose disposal by both these processes is reduced, primarily in the nonoxidative pathway.

Glucose Resistance and Noninsulin – Mediated Glucose Uptake

Aside from insulin resistance and beta cell dysfunction, glucose uptake that is not mediated by insulin (insulin-independent glucose uptake or glucose-mediated glucose uptake) is important in determining glucose use. Noninsulin-mediated glucose uptake (NIMGU) plays an important role in the rate of glucose disappearance. About 80% of tissue glucose uptake in the fasting state occurs via insulin-independent mechanisms, primarily in central nervous system tissue and to a much lesser degree in peripheral tissues, such as muscle and adipose tissue.

In the fasting state, NIMGU is the major pathway for glucose disposal in both type 2 diabetic subjects and in normal controls. Furthermore, for a particular glucose level, the efficiency of NIMGU (defined as NIMGU – serum glucose) is equal in both type 2 diabetic subjects and normal controls. However, the absolute basal rate of NIMGU is higher in type 2 diabetic subjects compared with normal controls due to an elevated basal rate of glucose disposal. It is thought that, this elevated basal rate of NIMGU in subjects with type 2 diabetes, plays a role in the pathogenesis of type 2 diabetes.

It is also seen that, in the presence of baseline hyperglycemia, physiologic insulin levels had a diminished ability to suppress HGO and to stimulate peripheral glucose disposal in type 2 diabetic subjects. As previously discussed, basal HGO is elevated in patients with type 2 diabetes, which might serve to

maintain the level of hyperglycemia needed to compensate for this observed decrease in peripheral insulin action (e.g. mass action). Moreover, this study showed that fasting hyperglycemia exerted a suppressive effect on HGO, but it did not completely compensate for the decrease in hepatic insulin action seen in type 2 diabetic patients. The exact underlying biochemical and cellular mechanisms, behind these findings remain uncertain, but they likely involve multiple defects in the intracellular enzymes involved in glucose entry and use within the cell, as well as abnormalities of the glucose transporter proteins.

Genetic causes of insulin resistance

A strong genetic basis for insulin resistance is suggested by high prevalence in certain populations, particularly in Nauru Islanders of the Pacific, Pima Indians of Arizona, high incidence in "westernized" lifestyle characterized by high calorie intake and sedentary life style.[41,46] Some of the diseases are associated with insulin receptor gene mutations, Leprechaunsim is the most extreme form, characterized by intrauterine growth retardation. Type A insulin resistance, is the mildest form characterized by insulin resistance, acanthosis nigricans and hyperandrogenism (in females).[47]

Mutations in PPARγ, results in the clinical features of severe insulin resistance and partial lipodystrophy of buttocks, sparing the face and central abdominal depots.[48,49]

Adiponectin, is a 30-kDa adipose specific secretory protein that appear to enhance insulin sensitivity. Decreased circulating levels of adiponectin is associated with obesity and insulin resistance.[50]

Leptin protein is derived from adipose tissue. Circulating leptin concentrations, are associated closely with fasting insulin concentrations and the percentage of body fat, making it as a marker of obesity and insulin resistance. Resistin is a adipose tissue specific hormone, causes insulin resistance by increase in the rate of glucose production, suggesting it has rapid inhibitory effects on hepatic rather than peripheral insulin sensitivity.[51,52]

Measurement of insulin resistance

The standard technique, for assessment of insulin sensitivity is the hyperinsulinemic euglycemic clamp; it is often combined with the hyperglycemic clamp to determine the adequacy of compensatory β-cell hypersensitivity.[53,54,55,56] Although, clamp technology has been applied to the study of insulin sensitivity and insulin secretion during childhood, it is too invasive for general epidemiologic studies. Because no intravenous access is needed, the oral glucose tolerance test (OGTT) is better suited for assessment of large populations. Although, OGTTs are more difficult to perform than simple measurements of fasting glucose and insulin levels, the OGTT is a minimal-risk procedure that is applicable, for large-scale screening and for repeat studies for individual subjects.[57]

In the quest for a noninvasive measurement technique for insulin sensitivity, several fasting or “homeostatic” models have been proposed and each has correlated reasonably well with clamp techniques.[18,19,20] The HOMA, FGIR and QUICKI methods have been the most frequently used techniques, in clinical investigations. The fact that, these tests require only a single venipuncture in the

fasting state and do not call for concomitant intravenous access makes them particularly attractive to patients and clinicians alike.

The HOMA approach, has been widely used in clinical research to assess insulin sensitivity. Rather than using fasting insulin levels or FGIR, the product of the fasting concentrations of glucose (expressed as milligrams per deciliter) and insulin (expressed as microunits per milliliter) is divided by a constant. The constant 405 should be replaced by 22.5 if the glucose concentration is expressed in System International units. Unlike insulin levels and the FGIR, the HOMA calculation compensates for fasting hyperglycemia. The HOMA and insulin values increase for insulin-resistant patients, whereas the FGIR decreases.

The QUICKI method, can be applied to normoglycemic and hyperglycemic patients. The index is derived by, calculating the inverse of the sum of logarithmically expressed fasting glucose and insulin concentrations. As insulin concentrations decrease, QUICKI values increase.

Low birth weight and family history

- Low birth weight is associated with and increased occurrence of type 2 DM in later life. Paternal diabetes is associated with low birth weight in babies. The risk of diabetes associated with low birth weight is strongly related to the development of paternal diabetes, suggesting a genetic link between low birth weight and later diabetes.[58]
- Familial clustering, was rather stronger in non obese probands than in overweight or obese, as estimated by family history index which operates on a simple assumption, that genetic loading of type 2 diabetes increases

with number of relatives who have the disease and with genetic proximity of those relatives.

- Insulin sensitivity, can be predicted from measurements in the fasting state and during an oral glucose tolerance test.

Diagnosis of diabetes[32]

Criteria for the Diagnosis of Diabetes Mellitus[32]

- Symptoms of diabetes plus random blood glucose concentration more than or equal to 11.1 mmol/L (200 mg/dL)[a] *or*
- Fasting plasma glucose more than or equal to 7.0 mmol/L (126 mg/dL)[b] *or*
- Two-hour plasma glucose more than or equal to 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test[c]

[a]Random is defined as without regard to time since the last meal.
[b]Fasting is defined as no caloric intake for at least 8 h.
[c]The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; not recommended for routine clinical use.
Note: In the absence of unequivocal hyperglycemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.

Glucose tolerance is classified into three categories based on the FPG:

1. FPG less than 5.6 mmol/L (100 mg/dL) is considered normal;
2. FPG equal to 5.6–6.9 mmol/L (100–125 mg/dL) is defined as IFG; and
3. FPG more than or equal to 7.0 mmol/L (126 mg/dL) warrants the diagnosis of DM.

Oral glucose tolerance test

The test uses the following procedures.

- It first employs an FPG test.

- A blood test is then taken two hours after drinking a 75 g anhydrous glucose solution.

Based on the OGTT, IGT is defined as plasma glucose levels between 7.8 and 11.1 mmol/L (140 and 199 mg/dL). Diabetes is defined when plasma glucose is more than 11.1 mmol/L (200 mg/dL), 2 h after a 75 g oral glucose load.

The current criteria, for the diagnosis of DM emphasize that the FPG is the most reliable and convenient test for identifying DM, in asymptomatic individuals. A random plasma glucose concentration more than or equal to 11.1 mmol/L (200 mg/dL) accompanied by classic symptoms of DM (polyuria, polydipsia, weight loss) is sufficient for the diagnosis of DM.

Hemoglobin A1C (HbA1c) was advocated as a diagnostic test for DM. Though there is a strong correlation between elevations in the plasma glucose and the A1C, the relationship between the FPG and the A1C in individuals with normal glucose tolerance or mild glucose intolerance is less clear, and thus the use of the A1C is not currently recommended to diagnose diabetes.[32]

METHODOLOGY

The present study, was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on offsprings of type 2 DM and non diabetics during the period of January 2008 to December 2008.

Study design

One year cross-sectional study.

Study period

The present study was conducted during January 2008 to December 2008.

Method of collection of data

Source of Data

Offsprings of diabetic and non diabetic patients, attending outpatient department or admitted patients in Medicine Wards, at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Sample size

Offsprings of 30 diabetic and 30 non diabetic patients.

Sampling procedure

The study included offsprings of 30 diabetic and 30 non-diabetic patients. As there was no data available in KLES Dr. Prabhakar Kore Hospital and

Medical Research records section particularly regarding the study subjects, the sample size of 30 cases and 30 controls were randomly selected on account of previous literature. This was a cross sectional study and the power of the study was not compromised with the sample size.

Selection criteria

Inclusion Criteria

- Case group – off springs of patients diagnosed to have type 2 diabetes after 30 years of age.
- Control group – off springs of non-diabetic individuals.

Exclusion Criteria

- Off springs of type 1 DM patients.
- Off springs of patients diagnosed to have type 2 DM before 30 years of age.
- History of drug consumption believed to after plasma glucose levels.

Procedure

The study was approved by the Ethical and Research Committee of Jawaharlal Nehru Medical College, Belgaum. During the study period, all patients presenting with and fulfilling the inclusion criterion were included in this study after obtaining informed written consent (Annexure–I). Oral glucose tolerance test, was performed according to WHO criteria and patients with normal glucose tolerance were included in the study.

Detailed relevant history and clinical examination was done according to predesigned and pretested proforma (Annexure-II). Fasting blood sample was drawn for measuring plasma insulin levels. Homeostosis model assessment was calculated as;

$$\frac{\text{Fasting Insulin mU/L X Fasting plasma glucose m mol/L}}{22.5}$$

Further, insulin resistance was compared in both the groups. Subjects also underwent other investigations like fasting lipid profile.

Statistical methods

Mean age, insulin levels, Homeostosis model assessment-insulin resistance (HOMA-IR) and BMI of the two groups were compared using unpaired 't' test. Chi – square test and Kruskal Wallis test were used to test the association between two or more variables in case of frequency distribution. Correlation co-efficient was used to find the association between insulin and other variables. A p value of less than 0.05 was considered as significant.

RESULTS

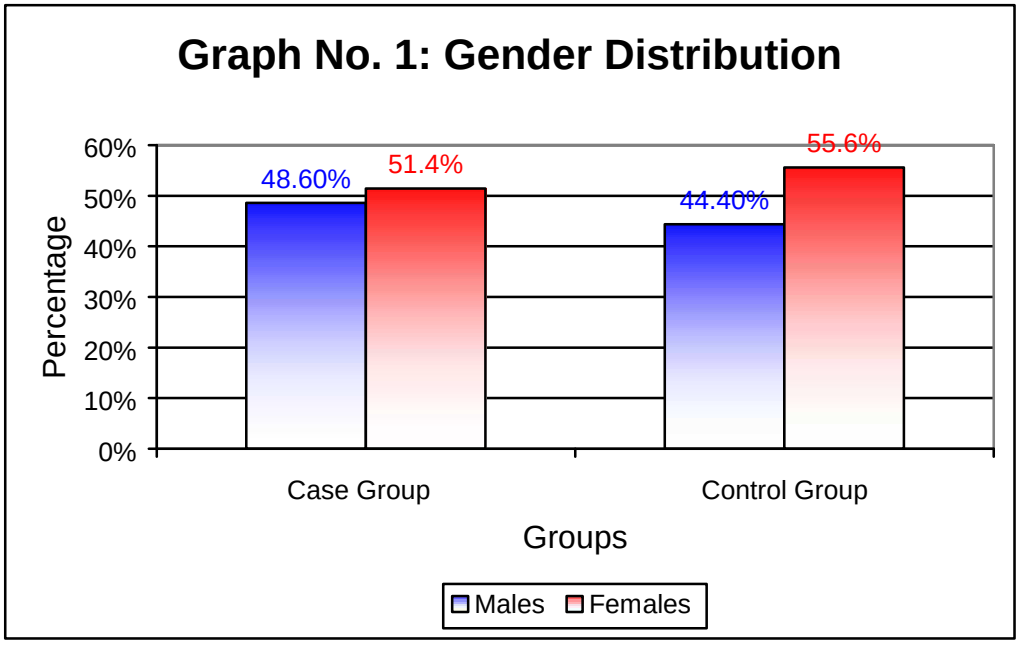
The present study, was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on 35 offsprings of type 2 DM (Case Group) and 36 offsprings of non diabetics (Control group). The data obtained was tabulated as below.

BASIC DEMOGRAPHIC CHARACTERISTICS

Table No. 5: Gender distribution

Gender	Case group		Control group	
	Number	Percentage	Number	Percentage
Male	17	48.6%	16	44.4%
Female	18	51.4%	20	55.6%

$X^2 = 0.122$ df = 1 p = 0.727



In the present study, male subjects comprised of 17 (48.6%) in case group and 16 (44.4%) in control group, female subjects comprised 18 (51.4%) in case group and 20 (55.6%) in control group. There was no difference in the sex distribution of two groups.

Table No. 6: Age distribution

Age (Years)	Case group		Control group	
	No.	**%**	**No.**	**%**
15-20 years	06	17.1%	09	25.0%
21-25 years	12	34.3%	12	33.3%
26-30 years	11	31.5%	05	13.9%
31-35 years	02	5.7%	05	13.9%
36-40 years	02	5.7%	03	8.3%
> 40 years	02	5.7%	02	5.6%
Total	35	100%	36	100%

$X^2 = 3.837$ df = 3 p = 0.280

The above table, shows the distribution of subjects according to age. Most of the subjects were in age group 21 to 25 (In case group 34.3%, in control group 33.3%) and age group more than 40 had the least number of subjects (In case group 5.7%, in control group 5.6%). There was no difference in the age distribution of two groups.

Table No. 7: Mean age and body mass index

Gender	Case group		Control group		X^2	df	p value
	Mean	S.D.	Mean	S.D.			
Mean age (Years)	25.9	6.71	26.1	7.72	0.147	69	0.883
Mean BMI (Kg/m^2)	23.2	2.79	22.2	3.03	0.668	69	0.506

In the present study, the mean age in case group was 25.90 ± 6.71 years and 26.10 ± 7.72 years in control group (p=0.883). The mean BMI in case group was 23.20 ± 2.79 kg/m^2 and 22.20 ± 3.03 kg/m^2 in control group (p=0.506). Hence the mean age and BMI was comparable between the two groups.

Table No. 8: Comparison of age with mean BMI

Age (Years)	BMI (Kg/m^2)	
	Mean	S.D.
15-20 years	21.7	2.55
21-25 years	23.3	2.88
26-30 years	23.1	2.66
31-35 years	22.1	4.05
36-40 years	23.9	2.31
> 40 years	26.1	1.31

F= 5.65 df = 1.929 p = 0.101

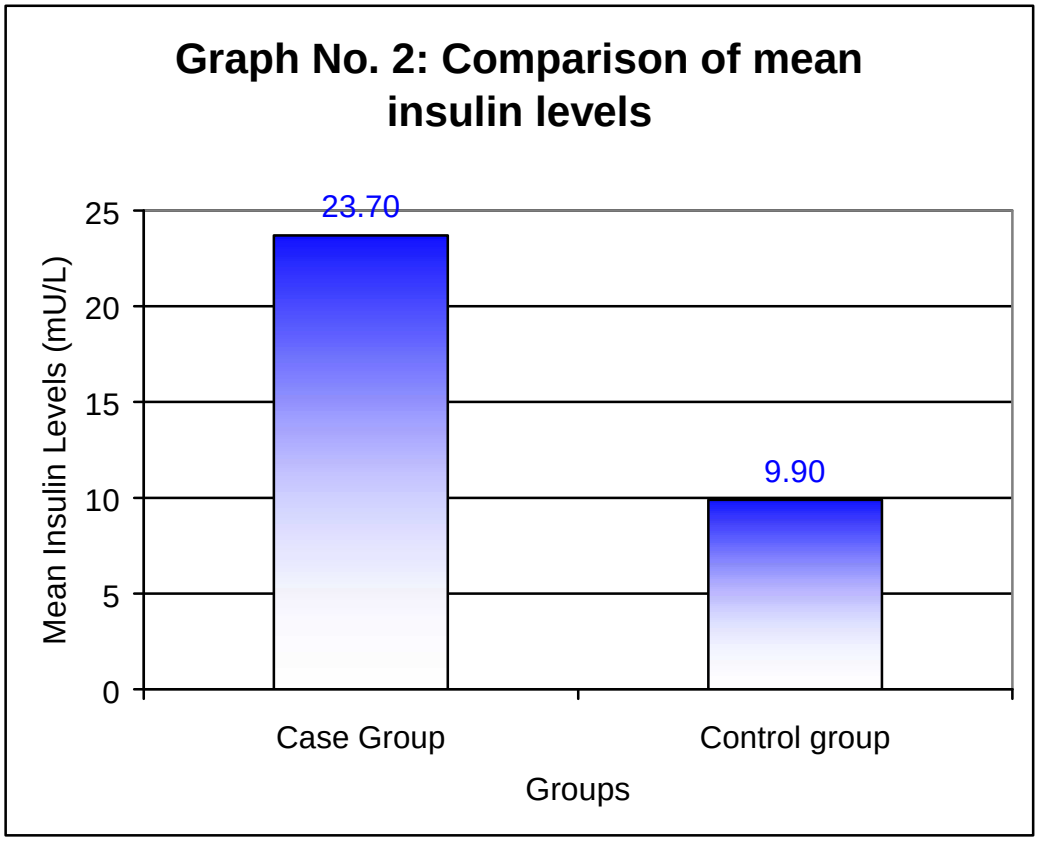
In the present study, the mean BMI was maximum in age group more than 40 years (26.10 ± 1.31 kg/m^2) and least in age group of 15 to 20 years (21.7 ±

2.55 kg/m^2). There was no difference of mean BMI in various age groups, statistically as calculated by Kruskal Wallis Test (p=0.101).

Table No. 9: Comparison of insulin levels

Insulin levels	Case group		Control group	
	Mean	**S.D.**	**Mean**	**S.D.**
Mean insulin levels (mU/L)	23.7	19.77	9.9	7.42

t = 0.3903 df = 69 p = 0.000

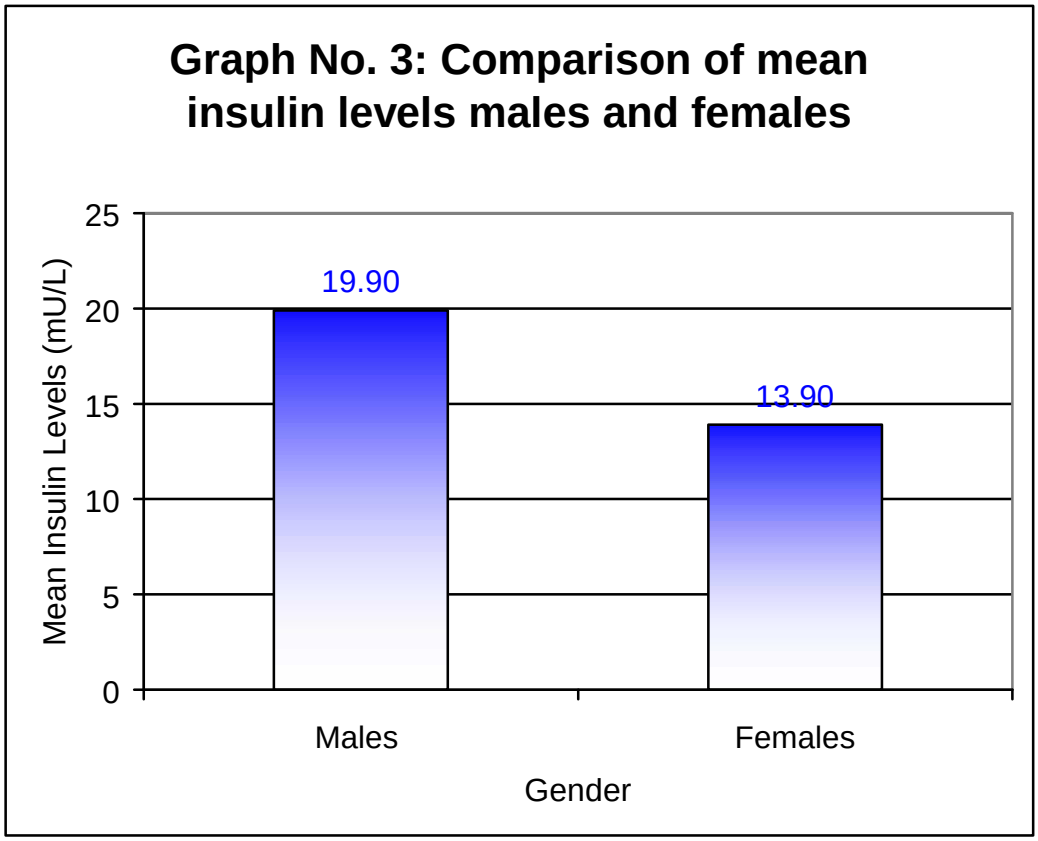


In the present study, the mean insulin level in case group was 23.7± 19.77 mU/L and in control group was 9.90 ± 7.42 mU/L. This difference between two groups was statistically significant (p=0.000).

Table No. 10: Comparison of insulin levels in males and females

Insulin levels	Males		Females	
	Mean	**S.D.**	**Mean**	**S.D.**
Mean insulin levels (mU/L)	19.9	21.0	13.9	10.16

t = 1.574 df = 69 p = 0.120



In the present study, the mean insulin levels in males was 19.9 ± 21.0 mU/L and in females was 13.9 ± 10.16 mU/L. There was no difference in insulin levels statistically, between males and females (p=0.120).

Table No. 11: Age and mean insulin levels

Age (Years)	Insulin Level (mU/L)	
	Mean	**S.D.**
15-20 years	21.40	19.2
21-25 years	15.50	18.76
26-30 years	19.30	11.59
31-35 years	7.40	4.33
36-40 years	14.00	15.21
> 40 years	16.00	19.50

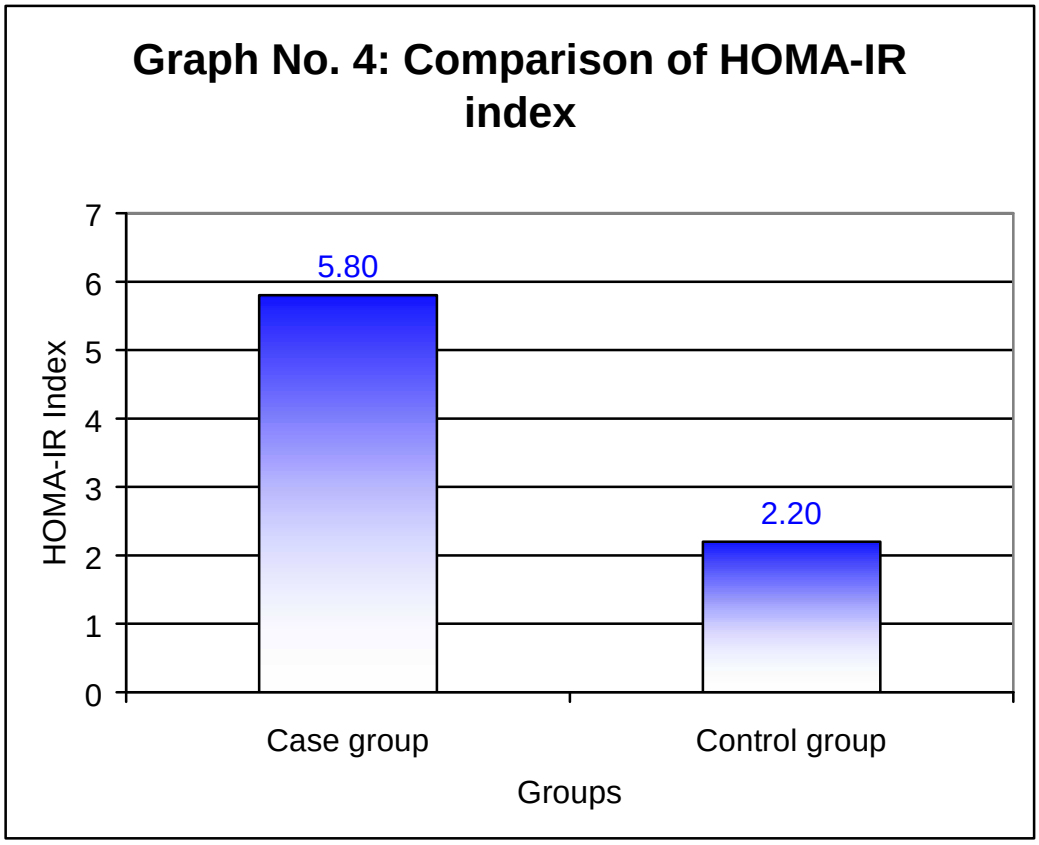
$F_{3,65} = 0.833$ p=0.531

The above table, shows the mean insulin levels in various age groups. Mean insulin level was maximum in 26 to 30 year age group (19.30 ± 11.59 mU/L), and least in 31 to 35 years age group (7.40 ± 4.33 mU/L). However, statistically there was no difference in the insulin levels in various age groups (p=0.531).

Table No 12: Comparison of HOMA-IR index

HOMA-IR Index	Case group		Control group	
	Mean	**S.D.**	**Mean**	**S.D.**
Mean HOMA IR index	5.80	4.81	2.20	1.63

t = 3.772 df = 69 p = 0.000

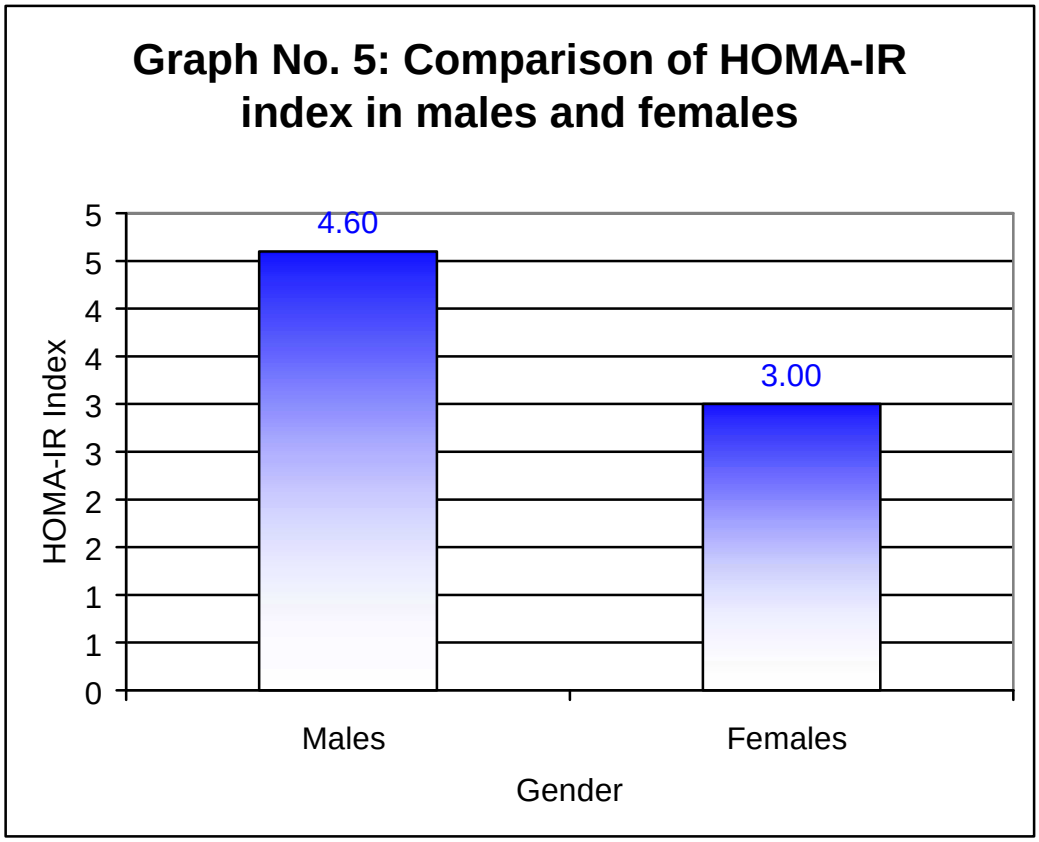


In the present study, the mean HOMA-IR index in case group was 5.80 ± 4.81and in control group was 2.20 ± 1.63. This difference was statistically significant (p=0.000).

Table No 13: Comparison of HOMA-IR index in males and females

HOMA-IR Index	Males		Females	
	Mean	**S.D.**	**Mean**	**S.D.**
Mean HOMA IR index	4.60	5.08	3.00	2.29

t = 1.690 df = 69 p = 0.096



In the present study, the mean HOMA-IR index in males was 4.60 ± 5.08 and in females it was 3.00 ± 2.29. There was no statistically significant difference in HOMA-IR index between males and females (p=0.096).

Table No. 14: Age and HOMA-IR index

Age (Years)	HOMA-IR Index	
	Mean	**S.D.**
15-20 years	4.70	4.57
21-25 years	3.50	4.51
26-30 years	4.30	2.84
31-35 years	1.60	2.84
36-40 years	3.20	3.84
> 40 years	3.70	4.55

$F_{3,65} = 0.713$ $p = 0.616$

The above table shows, mean HOMA-IR index in various age groups. The mean HOMA-IR was found to be highest in 15 to 20 years age group (4.70 ± 4.57) and least in 31 to 35 years age group (1.60 2.84). However statistically, there was no difference in HOMA-IR index in various age groups (p=0.616).

Table No. 15: Comparison of insulin levels in offsprings (more than one offsprings) of type 2 diabetics and non diabetics

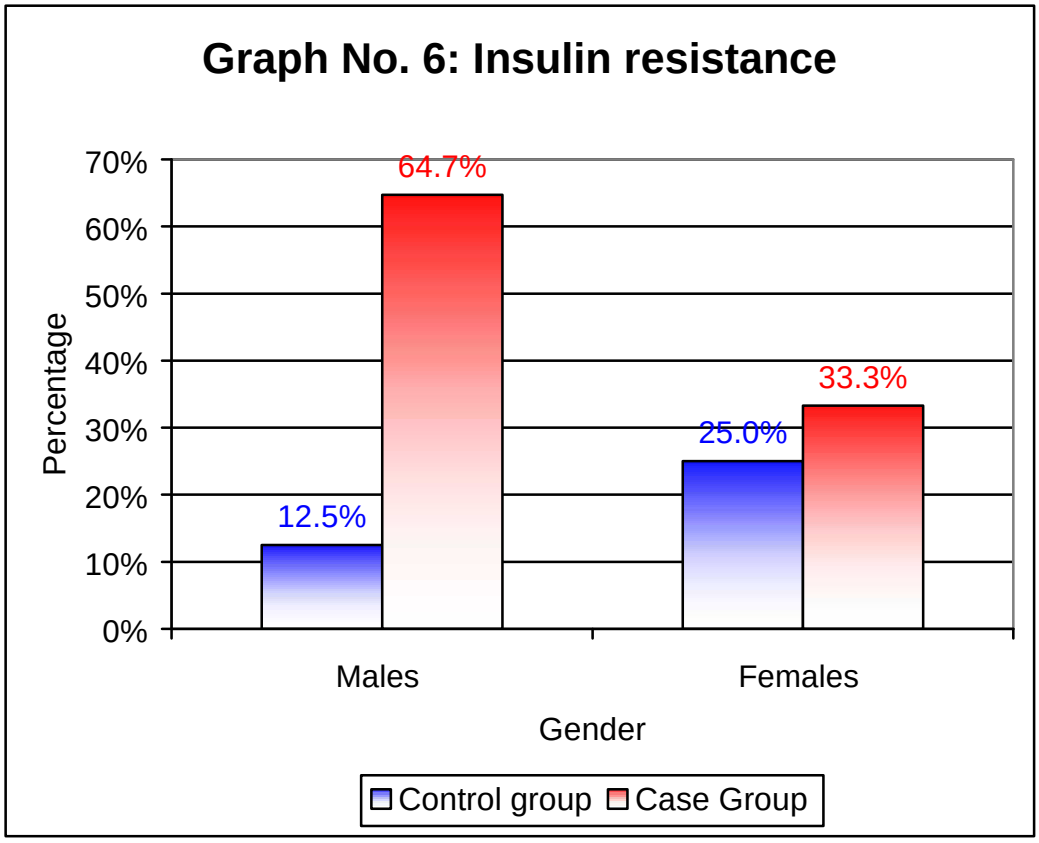
Case group			Control group			
Cases	**Insulin levels in Offsprings**		**Controls**	**Insulin levels in Offsprings**		
	1	**2**		**1**	**2**	**3**
1	36.2	34.20	1	4.20	4.90	0.00
2	12.20	14.20	2	6.00	6.20	0.00
3	10.00	6.00	3	8.20	10.40	9.20
4	29.00	5.90	4	2.90	3.70	0.00
5	40.80	13.40	5	3.40	6.50	0.00
t=1.498 df=8 p=0.172			t=0.968 df=8 p=0.361			

The above table shows, insulin levels in offsprings (more than one offsprings) of diabetic and non diabetic parents. It was observed that the offsprings in case group had higher insulin levels compared to control group.

Table No. 16: Insulin resistance

Groups	**Males**			**Females**			**Total**
	No.	**HOMA IR ≥ 3.2**	**Percent**	**No.**	**HOMA IR ≥ 3.2**	**Percent**	
Case group	17	11	64.7%	18	06	33.3%	48.5%
Control group	16	02	12.5%	20	05	25%	19.4%

X^2=6.728 df=1 p=0.009

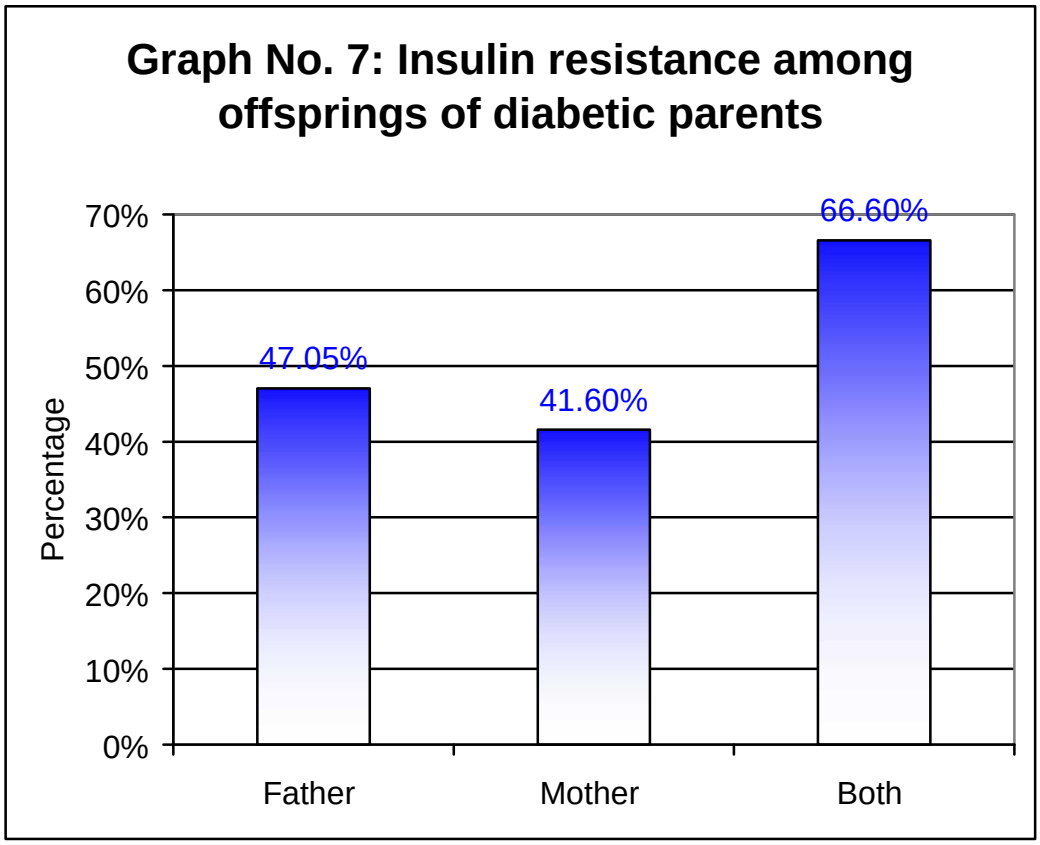


In the present study, insulin resistance was found in 48.5% in case group and 19.4% in control group. This difference was statistically significant (p=0.009). Insulin resistance was seen in 64.7% male offsprings in case group, when compared to 12.5% offsprings in control group. Insulin resistance was seen in 33.3% female offsprings in case group, when compared to 25% offsprings in control group.

Table No. 17: Insulin resistance among offsprings of diabetic parents

Diabetic parent	No. of Offsprings	Insulin resistance	Percentage
Father	17	08	47.05%
Mother	12	05	41.60%
Both	06	04	66.60%

X^2=1.031 df=2 p=0.597



In the present study, insulin resistance was seen in 47.05% offsprings whose father was a diabetic, 41.6% offsprings whose mother was a diabetic and 66.6% offsprings had history of both parents being diabetic. However, the p value was not statistically significant (p=0.597).

Table No. 18: Correlation co-efficient between insulin levels and variables (r and p values)

Variables	Correlation co-efficient	p value
Triglyceride	0.528	0.000
Triglyceride / HDL ratio	0.381	0.001
Mean BP	0.495	0.000
BMI	0.037	0.762
Waist girth	0.154	0.199

The above table, shows the correlation co-efficient between insulin levels and various variables. It was found that, there was a statistically significant association between insulin levels and triglycerides (p=0.000), triglyceride / HDL ratio (p=0.001) and mean BP (0.000). However, there was no statistically significant association between insulin levels and BMI (0.762) and waist girth (p=0.199).

DISCUSSION

The determination of insulin resistance, in offsprings of type 2 diabetics has a great clinical and epidemiological importance. Insulin resistance, not only puts them at a high risk of developing frank diabetes in future but it has also has been associated with a number of clinical and metabolic abnormalities.[10]

The present study, comprised of 35 offsprings of type 2 diabetics (case group) and 36 offsprings of non diabetics (control group). The total subjects in present study, were 71. Out of which, 33 were males and 38 were females.

The case group comprised offsprings of patients, diagnosed to have diabetes after 30 years of age and they were not on any drugs believed to alter plasma glucose levels. The control group, comprised offsprings of non-diabetic individuals.

This was in accordance with a study done in 2005, which evaluated insulin resistance in 172 first degree relatives and 178 controls.[10]

Most of the subjects in the present study, were between 15-30 years of age, who comprised 82.9% of sample size in case group and 72.2% of sample size in control group.

The mean age of the subjects in the present study, was 25.9 ± 6.71 years in case group and 26.1 ± 7.72 years in control group (p=0.883).

Height and weight of subjects was measured and BMI was calculated.

The mean BMI in case group, was 23.2 ± 2.79 kg/m^2 and in control group was 22.2 ± 3.03 kg/m^2 (p=0.506). Hence, both the groups were sex, age and BMI matched.

A cohort study done in Chennai in 2005, studied insulin resistance and serum triglycerides in age and BMI matched groups.[9] Another study in 2003, compared insulin resistance in 17 lean offsprings whose parents had type 2 diabetes with 17 age, sex and BMI matched subjects, without family history of diabetes as controls.[59]

The mean fasting insulin levels in the present study, were higher in normoglycemic offsprings of diabetic parents (23.7 ± 19.7 mU/L) than the corresponding values in controls (9.9 ± 7.42 mU/L). This was statistically significant (p=0.000), indicating that there was hyperinsulinemia in offsprings of diabetic parents.

A study in Catalonia showed that basal insulin levels were higher in first degree relatives of type 2 diabetic parents (24±4 mU/L) than the corresponding values in controls (21±6 mU/L).[60] A case control study done in Lucknow in 2005, on 172 first degree relatives of diabetics and 178 controls, also showed higher mean fasting insulin levels in normoglycemic first degree relatives (31.2 ± 4.5 mU/L) than the corresponding values in controls (14.4 ± 4.08 mU/L).[10] Another study done in Poland, also found that offsprings of type 2 diabetic parents had hyperinsulinemia ($p<0.05$).[59]

The present study, also compared mean insulin levels in male and female subjects. Mean insulin levels were 19.9 ± 21 mU/L in male subjects and 13.9 ±

10.6 mU/L in female subjects. There was no statistical difference in insulin levels, between the two genders (p=0.120).

A study in 2006, found mean insulin levels of 14 mU/L in Asian Indian men and 10.5 mU/L in Asian Indian women.[6]

The present study, showed comparable insulin levels in all age groups (p=0.531).

Various studies, are used for measurement of insulin resistance. Euglycemic insulin clamp test done for measuring insulin resistance, is regarded as gold standard in research. Because of infeasibility of this test, various studies across the globe have regarded homeostasis model assessment (HOMA) method to be gold standard, for measuring insulin resistance in clinical practice and population based research studies.[61] It had been demonstrated that, there was a strong positive correlation, between HOMA-IR and Euglycemic insulin clamp-IR in type 2 diabetic subjects.[62,63] So in the present study, HOMA-IR has been taken as standard method, for measuring insulin resistance.

The HOMA-IR cut off point for diagnosis of insulin resistance was taken as 3.2 in the present study.[17]

In this study, the mean HOMA-IR index was higher in normoglycemic offsprings of diabetic parents (5.8 ± 4.81) than the corresponding values in controls (2.2 ± 1.63). This was statistically significant (p=0.000), indicating a high risk of insulin resistance, in offsprings of diabetic parents.

A study in Poland, in the year 2003, found offsprings of type 2 diabetic parents were insulin resistant ($p<0.005$).[59] Another study found, mean HOMA-IR of 7.462 ± 5.218 in first degree relatives of diabetics compared to HOMA-IR 4.335 ± 2.279 in first degree relatives of non diabetics.[10]

Mean HOMA-IR in male subjects in the present study, was 4.6 ± 5.08 and 3.0 ± 2.29 in female subjects. There was no statistically significant difference in HOMA-IR index between the two groups.

A study done in 2006 found, mean HOMA-IR of 3.29 in Asian Indian men and mean HOMA-IR of 2.3 in Asian Indian women.[6]

In the present study, HOMA-IR index was comparable in all age groups ($p=0.616$).

In the present study, five parents in the case group, that is five diabetic parents, had two offsprings each. The insulin levels were comparable in these offsprings ($p=0.172$). Similarly four parents in control group, had two offsprings each and one had three offsprings. The insulin levels were comparable in these offsprings also ($p=0.361$).

In the present study, insulin resistance was calculated by HOMA-IR and it was found that insulin resistance in normoglycemic offsprings of case group was 48.5%, when compared to that of control group (19.4%). This was statistically significant ($p=0.009$). Hence, risk of insulin resistance was more in the case group compared to control group.

A study of 154 healthy normoglycemic first degree relatives of type 2 DM patients in 1999, showed the prevalence of insulin resistance to be 40%.[64] Another study of 1,988 normoglycemic relatives of type 2 DM patients of age 35 to 70 years in 2001, showed the prevalence of insulin resistance as 25%.[65] A study done in Lucknow in 2003, showed the prevalence of insulin resistance, in normoglycemic first degree relatives as 30.2%, as measured by HOMA-IR index.[10]

The higher percentage of insulin resistance, in the present study, was probably due to the reason that, only offsprings were taken as study subjects. Whereas, other studies were done in first degree relatives (siblings and offsprings).

This study, also compared insulin resistance in offsprings of whose either father or mother or both were diabetic. Insulin resistance, was seen in 47.05% offsprings (8 out of 17) whose father was a diabetic, 41.6% (5 out of 12) offsprings, whose mother was a diabetic and 66.60% (4 out of 6) offsprings whose both parents were diabetic. However, this was not statistically significant ($p=0.597$).

The present study, also studied association between insulin levels with triglycerides and triglyceride/HDL ratio. Correlation co-efficient, of 0.528 was found between insulin levels and triglycerides ($p=0.000$) and 0.381 between insulin levels and triglyceride/HDL ratio ($p=0.001$). Hence fasting hyperinsulinemia, was associated with fasting hypertriglyceridemia.

A study done in Chennai, in 2005, also found that triglycerides (r=0.18, p=0.007) showed significant correlation with insulin resistance.[9] Another study found that increased prevalence in insulin resistance, in the Asian Indian men was associated with increased hepatic triglyceride content.[6] Study done at Lucknow, showed higher prevalence of hyeprtriglyceridemia, in insulin resistant first degree relatives, than in insulin resistant controls (80.64% Vs 0%, p=0.000). The serum HDL levels (75.5% Vs 14.28%; p=0.070) were also lower.[10]

The association, between insulin levels and mean blood pressure in the subjects was studied and a correlation coefficient of 0.495 was observed, between the two. This was statistically significant (p=0.000). Many subjects with hyperinslinemia, were in prehypertensive group.

A study in 2004 at Chennai, found that, prevalence of hypertension increased with an increase in quartiles of fasting insulin levels (p=0.035) and HOMA-IR (p=0.030).[66]

In the present study, association of insulin levels with BMI and waist girth was also studied. A correlation co-efficient, of 0.037 was found between BMI and insulin levels (p=0.762) and 0.154 between waist girth and insulin levels (p=0.199) respectively. There was no association between obesity and hyperinsulinemia in the present study, indicating that lean individuals are also prone for insulin resistance. This inference was contradicting to many studies.

A study done in African Americans, showed that, obesity had strong association with insulin resistance (p=0.92) in first degree relatives.[67] A study of 154 healthy glucose tolerant first degree relatives, found absolute

hyperinsulinemia and higher prevalence of insulin resistance in obese first degree relatives, as compared to non obese relatives.[64] Another study, showed higher prevalence of insulin resistance, in obese first degree relatives (43.87%) than in controls (15.2%), as per waist hip ratio estimation.[10] Whereas a study at Poland, has shown that insulin resistance was present even in young lean subjects were at a high risk to develop type 2 diabetes. Thus suggesting that, insulin resistance may be a primary abnormality, in the pathogenesis of this disease.[59]

However, the same study on a larger population, may throw light on the exact prevalence of insulin resistance in offsprings of type 2 diabetics. It may also provide additional information, of association of insulin resistance with obesity.

CONCLUSION

1. Basal insulin levels are higher in normoglycemic offsprings of type 2 diabetic patients, than the corresponding values in controls.

2. Insulin resistance is more in offsprings of diabetic parents.

3. There is no association between obesity and insulin resistance.

4. There is a strong association of insulin levels, with hypertriglyceridemia and mean blood pressure, suggesting that insulin resistance, is a marker of dyslipidemia and hypertension.

5. Lifestyle interventions, can be started in offsprings with insulin resistance to prevent the development of overt diabetes, in future.

SUMMARY

Offsprings, of type 2 diabetics patients are at a high risk for developing diabetes in future. It is well established fact that, insulin resistance has been associated, with a number of clinical and metabolic abnormalities.

The present, prospective cross sectional study, was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum, during the period of January 2008 to December 2008. Insulin resistance, in offsprings of type 2 diabetic patients was compared, with offsprings of non diabetic patients.

Among the 71 subjects, 35 belonged to case group and 36 belonged to control group. Of the 35 offsprings in case group, 17 were males and 18 were females. In the control group, 16 were males and 20 were females out of 36 offsprings. The mean age of subjects in case group, was 25.9 ± 6.71 years and 26.1 ± 7.72 years, in control group. The mean BMI in case group, was 23.2 ± 2.79 kg/m^2 and 22.2 ± 3.03 kg/m^2, in control group. The study was age, sex and BMI matched.

The mean insulin levels, in case group was found to be higher (23.7 ± 19.77 mU/L), when compared to control group (9.9 ± 7.42 mU/L), which was statistically significant (p=0.000).

Insulin resistance was calculated based on HOMA-IR index. A cut-off, of more than or equal to 3.2, was taken. Mean HOMA-IR index was higher in case

group (5.8 ± 4.81), when compared to control group (2.2 ± 1.63). This was statistically significant (p=0.000).

Insulin resistance, among offpsrings was found to higher in case group (48.6%), when compared to control group (19.4%). This was statistically significant (p=0.009). Hence, risk of insulin resistance is significantly more in offsprings of diabetic parents, when compared to offpsrings of non diabetic parents.

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ANNEXURE I - CONSENT FORM

"A COMPARATIVE STUDY OF INSULIN RESISTANCE IN OFFSPRINGS OF TYPE 2 DIABETES MELLITUS AND NON DIABETIC PATIENTS -A ONE YEAR CROSS SECTIONAL HOSPITAL BASED STUDY".

Objective and purpose of the study

This research, is intended to study the prevalence of insulin resistance in offsprings, of type 2 diabetes mellitus and non diabetic patients. The principal investigator of the study is Dr. Vikas S. Patil under the guidance of Dr. Arathi Darshan. My co-operation, will be of great help in prevention of diabetes mellitus in offsprings of diabetic patients in future.

Procedure

If I agree, to be part of the research study, I will be asked the relevant history and will be subjected, to relevant clinical examination and investigations. I, will also have to give blood sample for fasting insulin levels, FBS and PPBS.

Risk and Benefits

The only risk and possible discomfort I might get is while taking blood from my arm, for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn.

Alternatives

Taking part in this study is voluntary. I may choose not to take part in this study, or if I decide to take part, I can later change my mind and withdraw from the study. My decision will not change the present or future health care or other services that I receive. The study doctor or sponsor, may stop my participation in this study any time. If I choose not to take part in the study, I will receive the standard treatment for patients with my condition.

Privacy and confidentiality

All information collected about me during the course of this study, will be kept confidential, to the extent permitted by law. The code numbers will identify me, in this research record. Information from this study may be published but my identity will be confidential, in any publication.

Institution / Sponsor's policy

Does not apply to this research

Financial incentives for participation

I will not be paid/offered any gifts/incentives for participating in the study.

Authorization to publish the results

The results of the study, would be forwarded to the KLE University, Belgaum, as part of requirement towards the completion of MD degree, review and publishing.

If I, have any questions about my rights as a participant, I may call Dr. V. D. Patil, Principal and Chairman, J.N.M.C Ethical Committee and contact Human Research phone number 0831-2471350.

Consent Statement

I voluntarily agree to take part in this study, by signing below. I may withdraw at any time. I am, not giving up any of my legal rights by signing this form. My signature below indicates that I have read, or this entire consent form has been read to me, and have had all my questions answered.

Name of the Participant or legally authorised representative: _____

Signature / Thumb print _____

In case of the queries, during study or in future, you may contact following person -

Principal investigator : Dr. Vikas S. Patil

Guide : Dr. Arathi Darshan

Name of the Witness _____

Signature _____

Investigator Name and Signature _____

Date: Place:

ANNEXURE II

PROFOMA

Name : IP No :

Age (In Years): Sex :

Date : Occupation:

Name of the patient: Group :

Relation with patients:

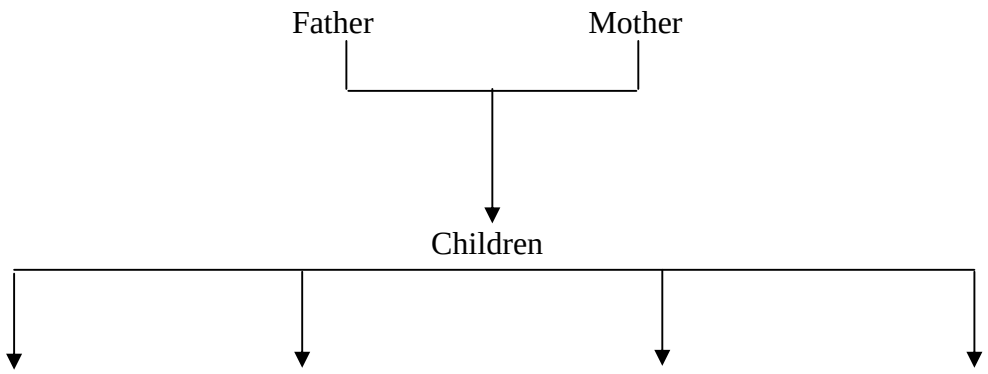
HISTORY:

Present history

Polyuria	Present /Absent
Polyphasia	Present /Absent
Polydispia	Present /Absent
Fatigue	Present /Absent
Blurred vision	Present /Absent
Slow healing	Present /Absent
Weight gain/loss	
Any other significant history	

Past history

Family history



Treatment history

H/o of intake of drugs which alter plasma glucose levels Present / Absent

General Physical Examination

Built and nourishment:

Pulse : /min Peripheral pulses:

Blood Pressure:

Lying down : mm Hg Standing: mm Hg

Examination of Foot/nail:

Anthropometry

Height (in Cms): Weight (in Kgs):

Hip girth (in Cms): Waist girth (in Cms):

Waist Hip ratio:

Systemic examination

C.V.S.:

R.S.:

Per Abdomen:

C.N.S.:

Investigations

Fasting plasma glucose: mg/dL

Post Prandial plasma glucose: mg/dL

Fasting insulin levels: mu/L

Inference

ANNEXURE III - MASTER CHART

CASE GROUP

CONTROL GROUP

KEY TO MASTER CHART

B	:	Both father and mother
BMI	:	Body Mass Index
Cms	:	Centimeters
DBP	:	Diastolic blood pressure
F	:	Female
FBS	:	Fasting blood sugar
FR	:	Father
HbA_1C	:	Glycated hemoglobin
HDL	:	High density lipoprotein
HOMA-IR	:	Homeostasis model assessment – Insulin resistance
IP/OP No.	:	Inpatient/Outpatient Number
Kg	:	Kilograms
Kg/m^2	:	Kilograms per meter square
LDL	:	Low density lipoprotein
M	:	Male
mg	:	Milligrams
mg/dl	:	Milligrams per deciliter
mm of Hg	:	Millimeter of mercury
MR	:	Mother
mU/L	:	Milli units per liter
PPBS	:	Postprandial blood sugar
SBP	:	Systolic blood pressure
Sr. No.	:	Serial Number

Sr. No.	IP / OP. No.	Demo-graphy		History of DM in parents	Physical examination						Investigations										
		Gender	Age (Years)		Waist Girth (Cms)	Hip Girth (Cms)	Waist Hip Ratio	Height (Cms)	Weight (Kg)	Body Mass Index (Kg/m^2)	SBP (mm Hg)	DBP (mm Hg)	Mean Blood Pressure (mm Hg)	FBS (mg/dL)	PPBS (mg/dL)	Insulin Levels (mU/L)	HOMA-IR Index	Triglycerides (mg/dL)	Cholesterol (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	HbA1c (mg%)
1	253809	M	18	FR	87.5	95.0	0.9	177.5	72.0	24.9	132	88	102.6	99	111	67.30	16.45	162	142	130	44	5.8
2	254024	M	26	B	90	97.5	0.9	184.0	80.0	24.6	130	88	102.0	96	127	36.20	8.50	192	130	110	44	5.6
3	780661	F	27	B	65	89.0	0.8	170.0	55.0	19.0	132	82	98.6	98	130	34.20	8.28	180	110	84	42	5.6
4	781052	M	23	FR	85	102.0	0.8	177.5	84.0	29.0	132	74	93.3	94	100	12.00	2.78	210	162	132	38	5.0
5	790061	F	26	MR	92	92.0	0.7	164.0	56.0	21.5	124	82	96.0	74	112	14.20	2.59	80	122	70	32	5.2
6	256019	M	20	MR	72	96.0	0.8	168.0	57.0	20.2	110	70	83.3	80	109	16.20	3.20	182	110	102	42	5.4
7	262880	M	45	MR	85	94.0	0.9	168.0	78.0	27.6	140	80	100.0	95	122	45.00	10.50	214	168	88	37	5.9
8	841742	F	19	FR	64	82.0	0.8	156.0	50.0	22.2	110	70	83.3	92	130	10.00	2.27	63	129	80	40	5.0
9	266006	F	22	FR	68	89.0	0.8	160.0	56.0	21.8	122	80	92.6	66	138	6.00	0.97	43	122	70	43	5.1
10	849732	F	30	FR	69	89.0	0.8	168.0	62.0	21.9	136	80	98.6	94	110	29.00	6.73	82	132	90	34	5.2
11	267668	M	32	FR	84	100.0	0.8	177.0	80.0	25.5	122	80	92.6	92	132	5.90	1.34	71	114	63	37	5.7
12	266880	M	23	MR	72	89.0	0.8	165.0	60.0	22.1	110	70	83.3	86	110	13.60	2.75	162	110	46	32	6.1
13	266769	M	21	B	70	89.0	0.8	164.0	58.0	21.6	100	74	82.6	99	122	4.60	1.13	95	128	77	32	5.5
14	271730	F	37	B	65	82.0	0.8	153.0	56.0	24.0	130	80	92.6	84	140	10.80	2.22	172	157	91	31	5.5
15	271130	F	21	MR	82	96.0	0.9	160.0	66.0	25.7	120	80	93.3	99	138	7.10	1.75	73	129	74	39	5.0
16	268307	F	15	MR	60	80.0	0.8	157.0	44.0	17.8	120	70	86.6	80	102	37.50	7.40	162	80	25	23	4.4
17	263092	M	36	FR	78	89.0	0.9	162.0	62.0	24.0	142	80	100.6	99	132	40.80	10.07	93	219	148	52	5.2
18	827678	F	28	FR	70	86.0	0.8	156.0	54.0	22.2	130	80	96.6	89	112	13.40	2.94	90	190	120	44	5.2
19	264953	F	23	FR	75	99.0	0.8	158.0	48.0	19.2	112	82	92.0	88	112	10.30	2.23	69	141	89	38	5.6
20	264929	F	24	MR	74	94.0	0.8	162.0	56.0	21.3	110	80	90.0	91	108	8.00	1.79	45	107	70	28	5.9
21	264767	M	43	FR	86	94.0	0.9	173.0	74.0	24.7	128	72	90.6	90	110	9.90	2.20	129	185	129	30	5.7
22	277108	M	19	B	68	90.0	0.8	176.0	70.0	22.6	142	90	107.3	92	122	42.70	9.69	156	143	120	45	5.0
23	277037	F	20	FR	69	86.0	0.8	162.0	62.0	23.6	132	82	98.6	94	114	47.80	11.09	158	152	86	46	5.5
24	277131	F	28	FR	67	92.0	0.7	168.0	56.0	19.8	124	80	94.6	94	112	14.00	3.24	110	171	114	35	5.8
25	280841	M	30	B	70	86.0	0.8	170.0	64.0	22.1	138	84	102.0	90	110	28.20	6.26	145	116	48	39	5.9
26	281864	M	27	MR	82	101.0	0.8	150.0	64.0	28.4	130	80	96.6	76	102	10.20	1.91	104	160	110	38	5.6
27	284960	F	21	MR	66	94.0	0.7	164.0	60.0	22.3	106	74	84.6	94	111	9.20	2.13	58	142	86	46	5.5
28	285973	M	24	FR	79	100.0	0.8	158.0	62.0	24.8	128	82	97.3	89	108	21.20	4.65	159	138	72	38	5.1
29	301304	M	23	MR	86	94.0	0.9	167.0	74.0	26.6	128	88	101.3	98	120	95.70	23.15	167	154	72	27	6.1
30	300953	M	26	FR	78	96.0	0.8	172.0	62.0	21.0	124	82	96.0	96	124	38.00	9.00	89	187	140	29	6.0
31	311970	F	28	MR	89	104.0	0.9	148.0	62.0	28.3	112	80	90.6	92	110	8.90	2.02	89	127	80	38	5.8
32	313865	F	27	FR	67	98.0	0.7	160.0	58.0	22.6	138	84	102.0	78	108	22.40	4.31	124	132	62	34	5.5
33	315528	F	32	FR	83	101.0	0.8	150.0	61.0	27.1	102	70	80.6	76	112	12.60	2.36	61	71	32	27	5.7
34	315505	F	21	MR	66	90.0	0.7	158.0	54.0	21.8	100	70	80.0	87	107	12.30	2.64	84	59	29	18	5.8
35	327358	M	21	MR	72	92.0	0.8	174.0	68.0	22.5	132	80	97.3	89	101	34.30	7.53	186	102	28	27	5.1

Sr. No.	IP / OP. No.	Demo-graphy		Physical examination						Investigations										
		Gender	Age (Years)	Waist Girth (Cms)	Hip Girth (Cms)	Waist Hip Ratio	Height (Cms)	Weight (Kg)	Body Mass Index (Kg/m^2)	SBP (mm Hg)	DBP (mm Hg)	Mean Blood Pressure (mm Hg)	FBS (mg/dL)	PPBS (mg/dL)	Insulin Levels (mU/L)	HOMA-IR Index	Triglycerides (mg/dL)	Cholesterol (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	HbA1c (mg %)
1	254161	F	18	78	98.5	0.79	150.0	56.0	24.8	122	80	96.0	94	110	4.3	0.99	90	160	122	46	6.0
2	254004	M	40	83	98.0	0.84	170.0	70.0	24.2	122	80	93.3	91	121	5.9	1.33	96	192	130	44	6.0
3	780947	F	32	74	94.0	0.78	162.0	60.0	22.9	110	70	92.7	78	110	4.2	0.8	90	140	92	46	5.2
4	256194	F	24	60	82.4	0.72	160.0	48.0	18.75	128	80	96.0	97	130	18.0	4.3	52	120	82	43	5.2
5	254246	M	35	60	84.0	0.71	170.0	45.0	15.5	100	70	90.0	94	120	4.3	0.99	103	169	122	26	5.5
6	255741	F	22	65	78.0	0.83	150.0	56.0	24.8	122	80	93.3	96	127	6.0	1.42	111	104	61	21	5.5
7	781942	M	29	82	102.0	0.8	162.0	68.0	25.9	120	80	92.7	84	110	6.2	1.28	106	100	68	32	5.2
8	261092	F	19	75	93.0	0.8	156.0	52.0	21.6	132	80	97.3	80	120	16.1	3.18	40	144	99	37	5.0
9	257613	F	27	70	90.0	0.78	156.0	56.0	23.04	110	70	92.7	80	130	10.4	2.05	116	207	144	40	5.7
10	759138	M	23	80	90.0	0.88	170.0	76.0	26.2	122	80	93.3	79	122	8.2	1.59	110	182	110	42	5.0
11	759129	F	29	74	98.0	0.75	162.0	58.0	22.13	130	80	96.7	85	116	9.2	1.93	122	184	110	39	5.2
12	257629	M	16	65	87.0	0.74	172.0	60.0	20.3	124	70	97.0	94	130	3.7	0.86	40	124	78	38	5.5
13	800148	M	15	62	80.0	0.77	140.0	36.0	18.36	110	70	92.7	79	112	2.9	0.51	82	110	94	42	5.0
14	272781	F	22	70	89.0	0.78	156.0	48.0	19.75	130	80	96.7	78	110	19.9	3.83	58	149	100	37	5.1
15	263671	F	23	69	85.0	0.81	160.0	60.0	23.4	124	80	94.7	88	108	1.1	0.24	35	100	73	20	5.2
16	272289	M	45	82	102.0	0.81	152.0	59.0	25.5	132	80	94.0	98	124	6.5	1.6	76	110	69	25	5.5
17	860359	F	38	73	94.0	0.77	150.0	46.0	20.4	122	80	94.0	92	120	3.4	0.77	74	104	72	40	5.2
18	271820	M	42	88	96.0	0.92	159.0	68.0	26.9	138	80	97.3	98	132	2.8	0.67	97	128	74	34	5.3
19	271493	F	23	69	86.0	0.8	162.0	62.0	23.6	124	82	93.3	98	128	12.0	2.96	73	139	94	30	6.0
20	271311	F	32	60	78.0	0.76	163.0	48.0	18.1	108	70	89.3	88	110	2.8	0.6	95	143	90	34	5.8
21	268538	F	31	67	87.0	0.77	162.0	60.0	22.9	132	80	97.3	90	134	13.9	3.08	97	131	79	33	5.9
22	263625	F	34	68	86.0	0.79	150.0	52.0	23.1	112	80	90.7	99	140	7.9	1.93	125	149	92	32	5.6
23	276823	F	20	69	86.0	0.8	162.0	62.0	23.6	110	70	93.3	84	110	8.8	1.82	38	176	115	53	5.7
24	276805	M	18	78	92.0	0.84	174.0	80.0	26.4	124	72	97.3	92	118	6.7	1.52	128	111	51	14	5.3
25	277134	M	25	87.5	95.0	0.92	177.5	82.0	26.19	112	80	90.7	91	122	7.1	1.59	40	122	73	41	5.5
26	278103	M	36	90	108.0	0.83	170.0	78.0	26.9	114	68	98.7	86	114	9.2	1.95	100	110	94	42	5.4
27	281027	F	21	74	94.0	0.78	156.0	48.0	19.7	132	82	100.0	87	116	26.0	5.58	90	148	104	46	5.6
28	281424	F	19	70	92.0	0.76	168.0	56.0	19.85	136	80	98.7	90	110	10.0	2.2	106	142	100	45	5.2
29	281512	M	30	89	109.0	0.81	184.0	80.0	23.6	130	80	96.7	96	126	30.2	7.15	126	144	92	30	5.2
30	285625	M	22	82	102.0	0.8	152.0	64.0	27.7	112	76	92.0	91	110	7.6	1.7	97	128	74	34	5.8
31	305995	F	26	75	94.0	0.79	150.0	56.0	24.5	100	80	86.7	94	112	4.3	0.99	90	162	124	46	5.3
32	309972	M	17	70	90.0	0.77	172.0	58.0	19.6	134	80	98.0	79	122	24.2	4.72	148	164	89	30	5.8
33	310343	F	23	78	101.0	0.77	158.0	60.0	24.09	130	80	96.7	89	112	20.4	4.48	111	104	61	31	5.5
34	316778	M	21	76	96.0	0.79	162.0	70.0	26.7	112	70	94.0	94	110	5.9	1.36	108	122	74	40	5.4
35	322543	M	25	67	88.0	0.76	162.0	52.0	19.84	102	80	82.3	89	109	5.3	1.16	124	91	39	27	5.2
36	327504	F	19	60	80.0	0.8	148.0	44.0	20.07	108	74	91.3	92	118	22.4	5.08	139	134	66	40	5.2