“MEAN PLATELET VOLUME IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND ITS CORRELATION ACROSS VARYING LEVELS OF ALBUMINURIA AND HBA1C LEVELS”

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CERTIFICATE

This is to certify that the dissertation entitled **"MEAN PLATELET VOLUME IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND ITS CORRELATION ACROSS VARYING LEVELS OF ALBUMINURIA AND HBA1C LEVELS"** is a bonafide work done **by DR.M.DEEPAN CHAKRAVARTHI**, Post graduate student, Institute of Internal Medicine, Madras Medical College, Chennai -03, in partial fulfilment of the University Rules and Regulations for the award of MD Branch – I Internal Medicine, under our guidance and supervision, during the academic year 2013 – 2016.

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I solemnly declare that the dissertation entitled " **MEAN PLATELET VOLUME IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND ITS CORRELATION ACROSS VARYING LEVELS OF ALBUMINURIA AND HBA1C LEVELS"** is done by me at Madras Medical College , Chennai – 03 during April 2015 to September 2015 under the guidance and supervision of **Prof.Dr.R.PENCHALAIAH**, to be submitted to the Tamilnadu Dr.M.G.R Medical University towards the partial fulfilment of requirements for the award of **M.D. DEGREE IN GENERAL MEDICINE BRANCH-I**

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Last but not the least, I wish to thank all the patients without whom the study would have been impossible.

CONTENTS

ABBREVIATION

ADA	:	American diabetes association
A1	:	normo albuminuria
A2	:	high albuminuria
A3	:	very high albuminuria
T2DM	:	type 2 diabetes mellitus
BMI	:	body mass index
TGL	:	triglycerides
CHOL	:	cholesterol
HDL	:	high density lipo proteins
TH1	:	t helper cell 1
APC	:	antigen presenting cells
TNF A	:	tumor necrosis factor alpha
IL	:	interleukin
MPV	:	mean platelet volume
VEGF	:	vascular endothelial growth factor
CAD	:	coronary artery disease

CVD	:	cardio vascular diseases
HT	:	hypertension
KDIGO	:	kidney disease improving global outcome
IDF	:	international diabetes federation
FBS	:	fasting blood sugar
PPBS	:	post prandial blood sugar

KEYWORDS

- Mean Platelet Volume
- Glycated hemoglobin
- Albuminuria
- Diabetes mellitus
- Body Mass Index
- Diabetic nephropathy
- Urine Albumin creatinine ratio
- Insulin Resistance

INTRODUCTION

Diabetes mellitus is a syndrome of altered carbohydrate metabolism characterised by deficiency of endogenous insulin production or defect in insulin secretion or peripheral resistance to insulin action

Mean platelet volume is one of the haematological parameters used to assess platelet function and activity. Large volumes correlates with increased platelet activity, and this in turn is associated with increased vascular complications in diabetes mellitus. Smaller mean platelet volumes on the other hand are associated with reduced platelet activity

Conventionally, microalbuminuria, defined as daily urine albumin excretion of 30-300 mg. It is one of the earliest indicators of diabetic nephropathy. However, according to the latest KDIGO guidelines, the term microalbuminuria should no longer be used and urinary albumin excretion should instead be categorised as A1, A2 and A3, which corresponds to daily albumin excretion of <30 mg, 30-300 mg, and >300 mg respectively[(1)]

The purpose of this study is to determine the correlation between platelet activity (as assessed by mean platelet volume), and diabetic complications, specifically diabetic nephropathy (as assessed by daily urine albumin excretion), and also glycaemic control (as assessed by HbA_{1C})

Glycaemic status of the patient is assessed by HbA_{1C} levels. Patients are grouped into two – those with levels less than or equal to 6.5%, and those with levels more than 6.5%, based on ADA criteria.[2] The HbA_{1C} is then compared with the mean platelet volume, to study its correlation.

AIMS

AND

OBJECTIVES

AIMS AND OBJECTIVES

PRIMARY OBJECTIVES

To estimate the mean platelet volume in an uncomplicated type 2 diabetes mellitus and to compare with normal controls

To determine the association between mean platelet volume across various levels of albuminuria, thereby relating its association with vascular complications of diabetes, specifically diabetic nephropathy

SECONDARY OBJECTIVES

To determine the association of mean platelet volume with the glycaemic status of the patient, as indicated by HbA_{1C}

To determine the correlation between mean platelet volume and fasting blood glucose, post-prandial blood sugar, duration of diabetes

REVIEW

OF

LITERATURE

REVIEW OF LITERATURE

HISTORICAL REVIEW

Diabetes is a disease of antiquity. Ancient Egyptian texts, dating back to 1500 BC describe a disease with “too great emptying of the urine”. Indian literature from the fifth and sixth centuries BC also described the same disease and gave it the name “madhumeha” which means honey urine, as it was found that urine would attract ants

The first use of the word diabetes was in 250 BC, by Apollonius of Memphis. “Mellitus” which means honey, was added in the 1600s by Thomas Willis in order to differentiate the condition from diabetes insipidus, which also causes polyuria.

Sushrutha and Charaka from India in 200-500 BC, described two variants of the disease – one associated with young age, and the other with obesity. This corresponds with our current classification of type 1 and type 2 diabetes mellitus.

Matthew Dobson (1735-1784) from Liverpool was the first to describe hyperglycaemia in a paper which he published in 1776. He collected the urine from his patient, Peter Dickonson, who had polyuria, and evaporated it into a white cake, which both smelled and tasted like sugar. The patient’s serum, likewise, was also found to have a sweetish taste. He therefore concluded that

sugar was not formed by the kidneys, but that the kidneys merely excreted the sugar which had previously existed in the blood

The scientific basis of diabetes began to be elucidated in the 18th century. It was Bouchardat of France who first linked diabetes and the pancreas together, and its associated was confirmed by Minkowski and Von Mering.

DIABETES MELLITUS

Diabetes mellitus is a heterogeneous group of disorders that have in common the metabolic defect of hyperglycaemia[3]. The mechanisms by which this hyperglycaemia is produced vary, and they may be acquired, genetic or environmental. This ultimately results in impaired pancreatic insulin secretion, impaired peripheral utilisation of glucose, and enhanced hepatic glucose production.

PREVALENCE

Diabetes prevalence has dramatically increased over the last few decades. The estimated number of cases of diabetes worldwide in 2013, is 382 million, with a projected increase to 592 million by 2035, according to the International Diabetes Federation [4]

The three countries with highest prevalence of diabetes in the world are India, China and US respectively [5]. Approximately 80% of all diabetics

reside in developing countries, with India and China having the largest contribution [6]

The prevalence of diabetes according to the WHO criteria was 5.6% among the urban areas and 2.7% among rural areas [7]

Although both types of diabetes show a trend of increasing prevalence, the number of cases of type 2 diabetes s increasing at a much faster rate than the number of cases of type 2 diabetes. The reason may be due to rising prevalence of obesity, industrialisation of countries, resulting in decreased physical activity and an ageing population

CLASSIFICATION

There are four clinical types [8]

- **Type 1** – occurs due to destruction of pancreatic ß-cells, usually culminating in complete insulin deficiency
- **Type 2** – occurs due to insulin resistance and progressive defect in insulin secretion
- **Other specific types** – genetic defects, disorders of exocrine pancreas, drug-induced
- **Gestational diabetes mellitus** – it is carbohydrate intolerance occurring during pregnancy

ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS

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 development or 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)
      5. HNF-1β (MODY 5)
      6. NeuroD1 (MODY 6)
      7. Mitochondrial DNA
      8. Subunits of ATP-sensitive potassium channel
      9. Proinsulin or insulin
      10. Other pancreatic islet regulators/proteins such as *KLF11, PAX4, BLK, GATA4, GATA6, SLC2A2* (GLUT2), *RFX6, GLIS3*
   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, mutations in carboxyl ester lipase
   D. Endocrinopathies—acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma
   E. Drug- or chemical-induced—glucocorticoids, vacor (a rodenticide), pentamidine, nicotinic acid, diazoxide, β-adrenergic agonists, thiazides, calcineurin and mTOR inhibitors, hydantoins, asparaginase, α-interferon, protease inhibitors, antipsychotics (atypicals and others), epinephrine
   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—Wolfram's syndrome, Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome

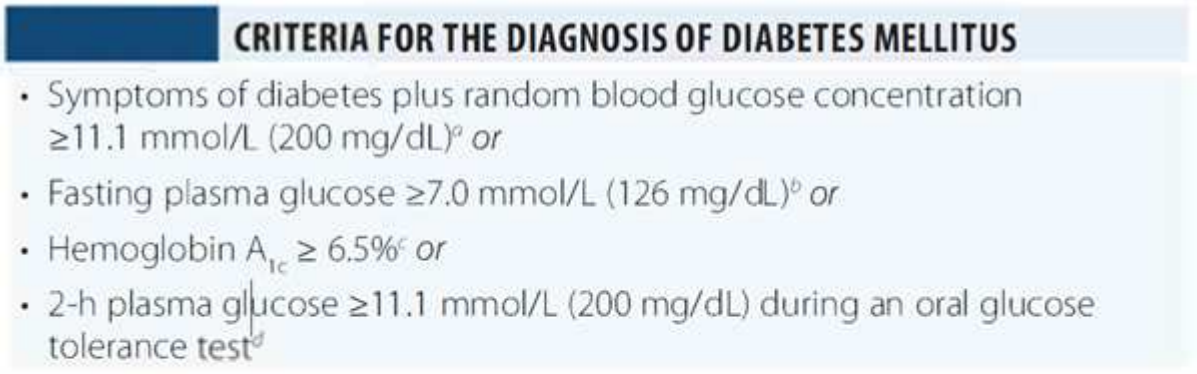
IV. Gestational diabetes mellitus (GDM)

DIAGNOSIS OF DIABETES MELLITUS

The classic symptoms of hyperglycaemia such as polyuria, blurred vision, increased thirst and recent weight loss should arouse clinical suspicion of diabetes mellitus

CRITERIA FOR DIAGNOSIS OF DIABETES MELLITUS [9]

- Random blood sugar >200 mg/dL, plus symptoms of diabetes
- Fasting blood sugar >126 mg/dL
- HbA_{1C}>6.5%
- 2-hour plasma glucose >200 mg/dL after an oral glucose tolerance test



CRITERIA FOR THE DIAGNOSIS OF DIABETES MELLITUS

- Symptoms of diabetes plus random blood glucose concentration ≥11.1 mmol/L (200 mg/dL)[a] *or*
- Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL)[b] *or*
- Hemoglobin A_{1c} ≥ 6.5%[c] *or*
- 2-h plasma glucose ≥11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test[d]

[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]Hemoglobin A_{1c} test should be performed in a laboratory using a method approved by the National Glycohemoglobin Standardization Program and correlated to the reference assay of the Diabetes Control and Complications Trial. Point-of-care hemoglobin A_{1c} should not be used for diagnostic purposes. [d]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.

As the various measures of glycaemia denotes different physiological phenomena, they will each identify different proportions of the diabetic population. For instance, switching the diagnostic criteria for diabetes, from fasting plasma glucose to HbA_{1C} would result in a decrease in the number of people diagnosed [10]

For example, the national health and nutrition examination survey (NHANES; 1999 to 2006), involve analysis of 6890 adults, with no prior history of diabetes. The prevalence of diabetes in this population using HbA_{1C} was 2.3%, but when fasting plasma glucose was used, the prevalence rose to 3.6% [11]

Overall, both criteria, whether HbA_{1C} or fasting blood glucose, resulted in 98% of the population being assigned the same classification. The American Diabetes Association, in 2003, recommended using fasting plasma glucose or a 75g oral glucose tolerance test to diagnose diabetes[12]. The International Expert Committee in 2009, recommended the use of HbA_{1C} with a value of 6.5% and above making the diagnosis of diabetes.

PLATELET BIOLOGY

PLATELET:

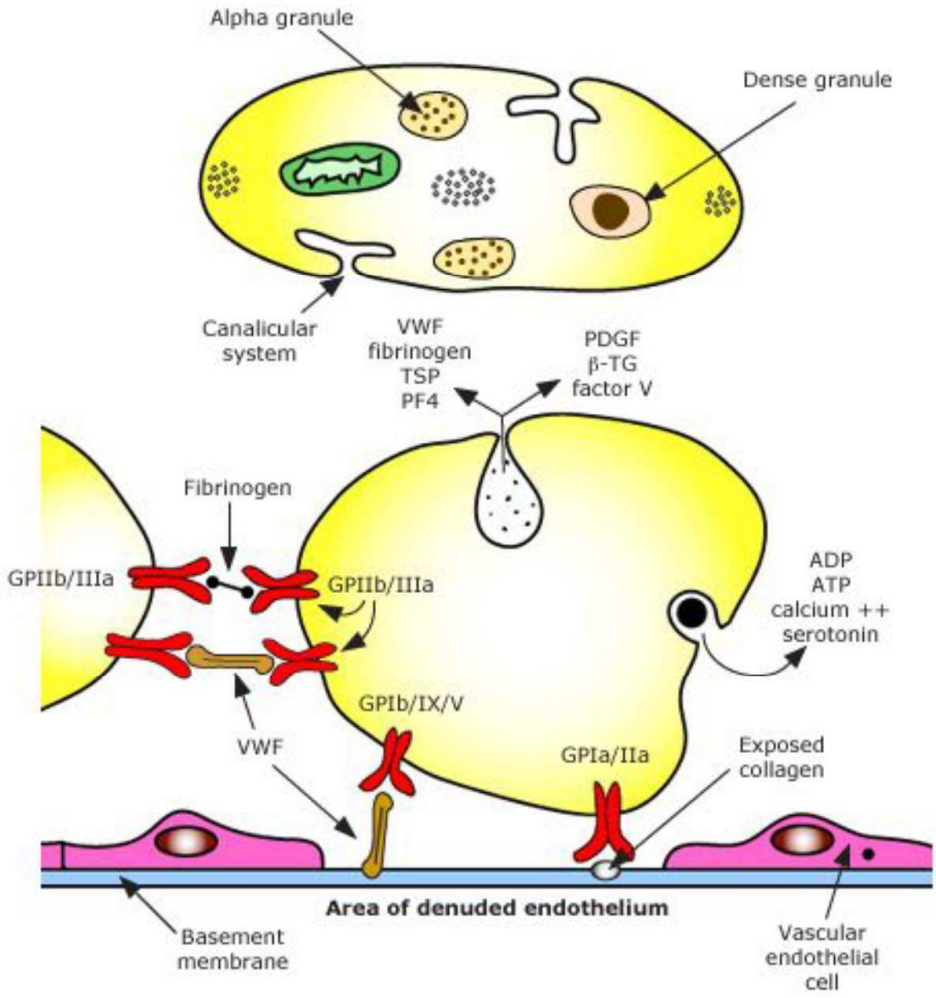
Platelets are anucleated, circulating, disc-shaped cells, which are responsible for the initiation of haemostatic mechanisms that repair vascular endothelial injury. They have four major functions

1. Platelet adherence
2. Activation and secretion
3. Platelet aggregation [13]
4. Interaction with coagulation factors

OVERVIEW OF FUNCTION:

Whenever there is a break in the integrity of vascular endothelial lining, platelets come into contact with the underlying connective tissue matrix, especially collagen fibrils. This activates signalling pathways, which cause the platelet to change shape and secrete thromboxane A2 and ADP, which is turn stimulate neighbouring platelets, producing further activation.

The platelet and its interactions



Activating platelets also directly bind fibrinogen, via the glycoprotein IIb/IIIa[14, 15]. A single fibrinogen molecule can bind to two GpIIb/IIIa receptors, thus cross-linking the platelets, producing platelet aggregation [16]. There are at least 40,000 to 80,000 copies of GpIIb/IIIa on each platelet, thus very large aggregates of platelets can be assembled at the sites of platelet activation [17, 18].

Besides these mediators, other agonists can also activate platelets. Tissue factor is present on all non-vascular cells. Whenever there is a disruption of endothelium, circulating blood is exposed to this tissue factor, which interacts with factor VIIa, and ultimately generates thrombin, which is the most potent platelet agonist. Platelets expedite this process as they contain procoagulant phospholipids, which promote the generation of thrombi. Thus the process of platelet activation and deposition of fibrin are closely intertwined.

PLATELET ACTIVATION:

Platelets may be activated by adherence to exposed collagen fibrils, or by exposure to circulating factors like thrombin and ADP[19]

SHAPE CHANGE:

When platelets are activated, their distinctive discoid shape is lost, and cytoskeletal rearrangements occurring within the platelets cause it to acquire an irregular morphology. There are three major cytoskeletal protein structures in the platelets

1. Actin network
2. Membrane-associated cytoskeleton
3. Marginal band of microtubule coil

Circulating platelets are unable to bind to fibrinogen or bind to each other. It is only after their activation that they are able to do so. This is because the platelet activation results in a change in the conformation of GpIIb/IIIa receptor, by a complex process known as inside-out signalling [20, 21] and it is this change in the conformation of the GpIIb/IIIa which allows fibrinogen binding.

SECRETION (GRANULE EXOCYTOSIS):

There are three types of platelet granules

1. Dense granules – these are platelet agonists, which promote platelet activation (eg. ADP, ATP, serotonin)
2. Alpha granules – von Willebran factor, fibronectin, fibrinogen, vitronectin
3. Lysosomal granules – glycosidases, proteases [22]

Mean platelet volume serves as the index of the activating and average size of the circulating platelets. Platelet with larger mean platelet volume are younger and tend to be more reactive and aggregable. When compared to platelets with smaller mean platelet volume, they possess denser granules, produce larger amounts of thromboxane A2, and secrete increased quantities of serotonin, and beta thromboglobulin[23, 24, 25]

All of these effects lead to a generalised procoagulant state. This results in greater thrombotic complications. There may therefore exist, a relationship between mean platelet volume (which is a measure of platelet function), and vascular complications in diabetes. Large mean platelet volume therefore is an indicator of the state of thrombogenesis[23, 26]

In diabetes, rupture of atherothrombotic plaques may result in small haemorrhages which lead to platelet hyperreactivity, recruitment of new

platelets, and stimulation of bone marrow. High mean platelet volume can therefore be viewed as a novel risk factor[27] for the various vascular complications in diabetes which is now being considered a prothrombotic state, having increased platelet reactivity. This platelet hyperreactivity has been documented both in vivo and in vitro in diabetes [26, 28]

The aetiology of platelet hyperreactivity in diabetes is multifactorial [24, 29, 30]. Some of the reasons are biochemical, such as hyperlipidaemia, and hypertriglyceridaemia, and increased expression of growth factors and lipoprotein receptors, insulin resistance and oxidant and inflammatory state [24, 29, 30]. Hyperglycaemia induces non-enzymatic glycation of various proteins on the platelet surface, thus increasing platelet reactivity by activation of protein kinase C and the osmotic effect of glucose [29, 31]. This glycation results in a decrease in the fluidity of the platelet membrane and an increase in platelet activation [29, 31].

There is also a functional insulin receptor, IR, on the platelet membrane, and by this mechanism insulin directly regulates platelet function. Experiments have revealed that insulin interferes with platelet interaction with collagen and reduces the pro-aggregant effects of agonists in non-obese healthy individuals [29, 31].

In inflammatory states, intra-platelet release of calcium, which occurs during platelet activation is increased by superoxide and this increases

platelet activity. Superoxide also decreases the activity of nitric oxide, as oxidative stresses reduce the endothelial function, thus decreasing nitric oxide and prostacyclin production. This effect of reduced nitric oxide activity causes increased platelet reactivity.

Diabetic patients have platelets that contain increased amounts of GpIIa receptors, and surface P-selectin. They therefore possess greater sensitivity to stimulation when compared to platelets taken from persons without diabetes[30]

Platelet hyperreactivity is also seen in diabetics, because of dysregulated signalling pathways, resulted in greater aggregation and activation, while responding to a given stimulus. Activation of platelets plays an important role in the pathology of diabetes, as it triggers thrombus formation which in turn causes microcapillary embolization, and the relief of mitogenic constrictive and oxidative substances, such as vascular endothelial growth factor and platelet derived growth factor. These in turn result in an acceleration in the progress of local vascular lesions of diabetes, such as the neovascularisation of lens[31]

Another cause of increased mean platelet volume in diabetes may be the occurrence of an atherothrombotic event such an myocardial infarction. This results in rapid consumption of smaller sized platelets and causes a compensatory increase in the generation of reticulated platelets[32, 33]

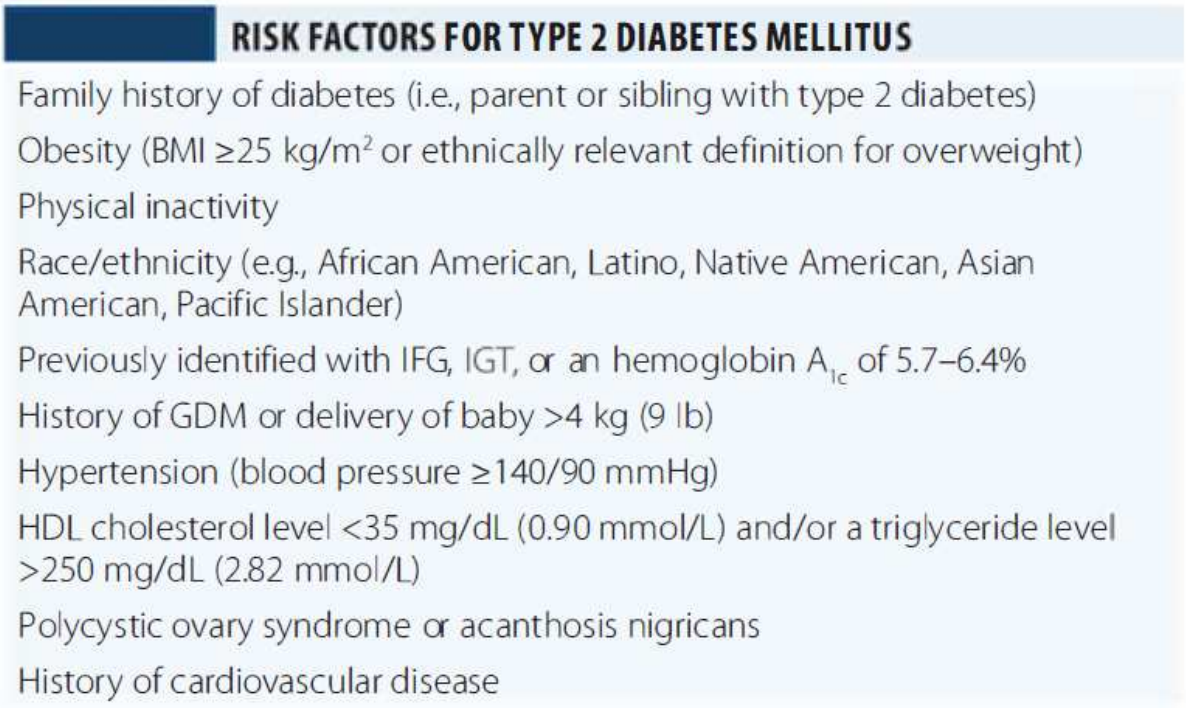
SCREENING FOR DIABETES

Screening for type 2 diabetes is recommended for the following reasons

1. Several individuals with diabetes mellitus are symptom-free and therefore unaware of the diagnosis
2. Studies have shown that type 2 diabetes mellitus might already exist for up to 10 years prior to the diagnosis
3. Some individuals have complications of diagnosis present at the time of diagnosis
4. Treatment of type 2 diabetes may have a favourable effect on the natural history of the illness

American Diabetes Association recommends that all individuals who are above 45 years of age should be screened for diabetes every 3 years. Screening should commence at an even earlier age, if they have obesity (ie. BMI >25 kg/m^2) or other risk factors for diabetes [42]

Unlike type 2 diabetes, where hyperglycaemia exists for a long asymptomatic period before the patient is diagnosed with the disease, in type 1 diabetes, such a long latent period is rare. Therefore, despite the availability of several immunological markers for type 1 diabetes, they have not been recommended for routine clinical use



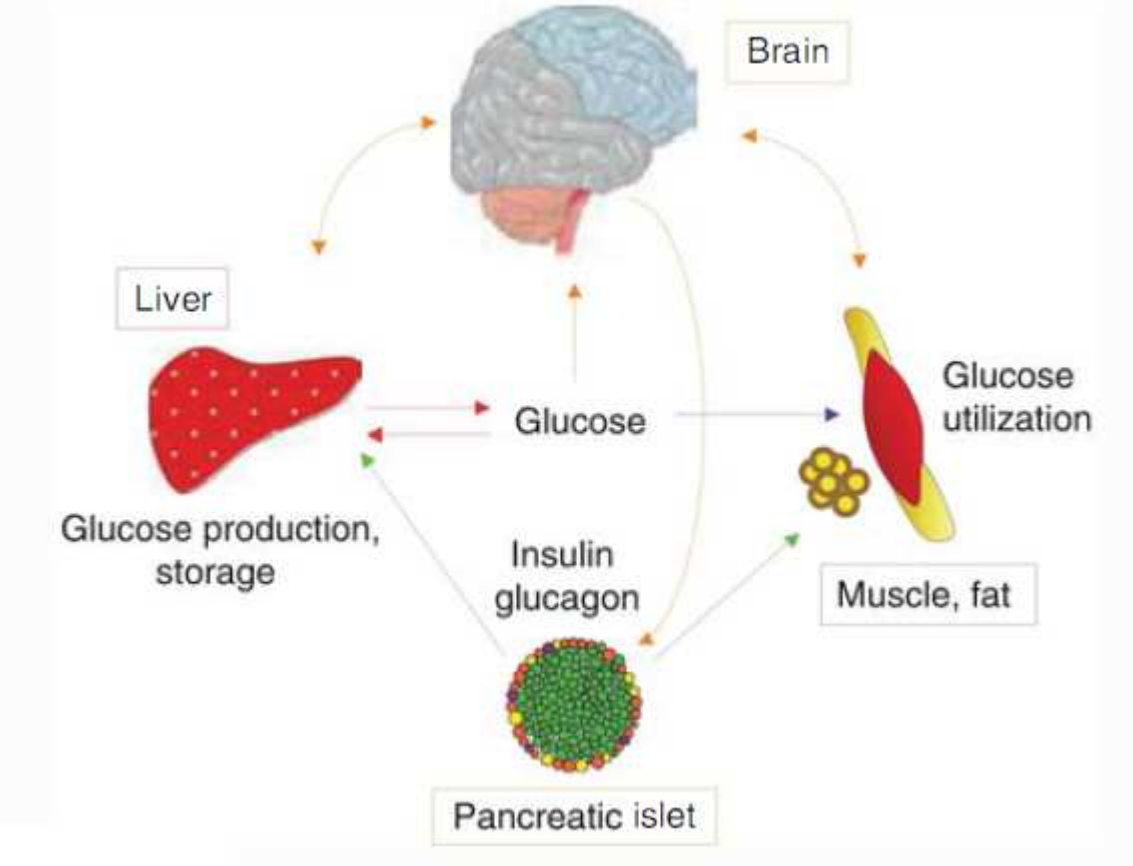
OVERALL REGULATION OF GLUCOSE HOMEOSTASIS:

Plasma glucose reflects the delicate balance between the peripheral glucose uptake and utilisation and the hepatic glucose production. This metabolic equilibrium is regulated by several components, with insulin being the most important one. During fasting, the decreased levels of insulin promotes hepatic glycogenolysis and gluconeogenesis, along with a decrease in the uptake of glucose by tissues that are insulin-sensitive (ie. skeletal muscle and fat).

This promotes the mobilisation of free fatty acids (lipolysis) and amino acids. Furthermore, when either the blood glucose or insulin levels are reduced, the pancreatic alpha cells secrete glucagon, and this stimulates gluconeogenesis and glycogenolysis in the renal medulla and in the liver.

Following a meal, the post-prandial glucose elevation produces a rising insulin, along with a simultaneous fall in glucagon, and this results in the reversal of this process. The large portion of post-prandial glucose is utilised by skeletal muscle, due to insulin-stimulated glucose uptake

REGULATION OF GLUCOSE HOMEOSTASIS

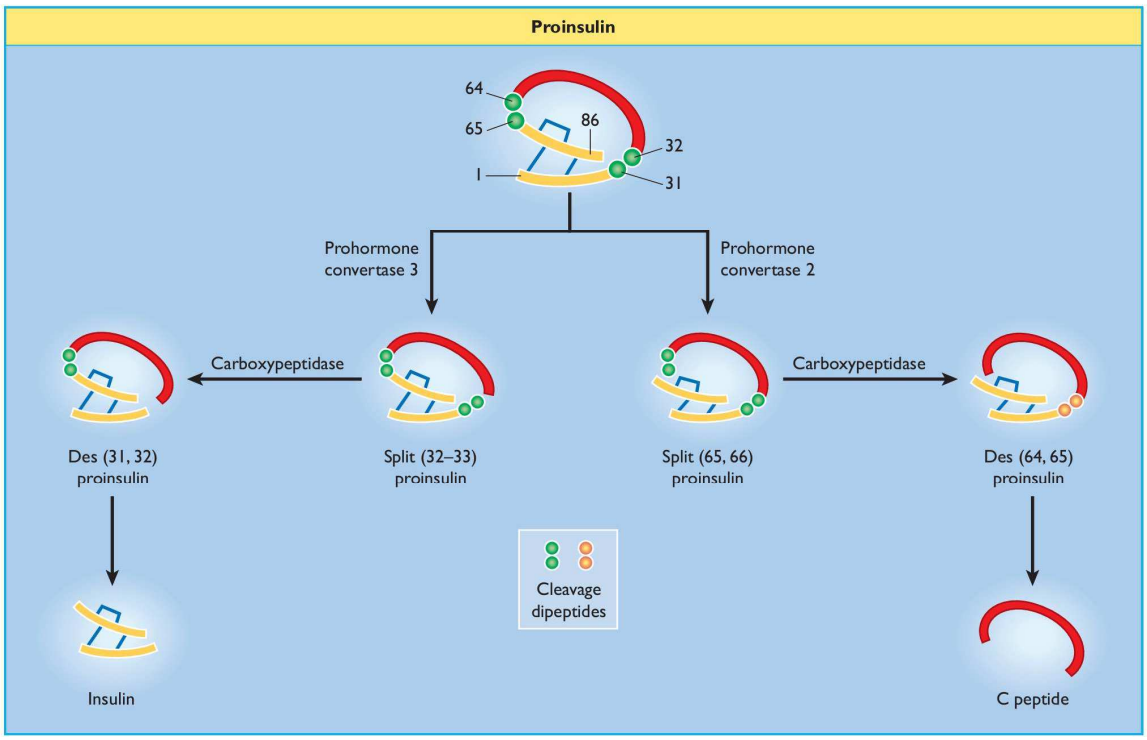


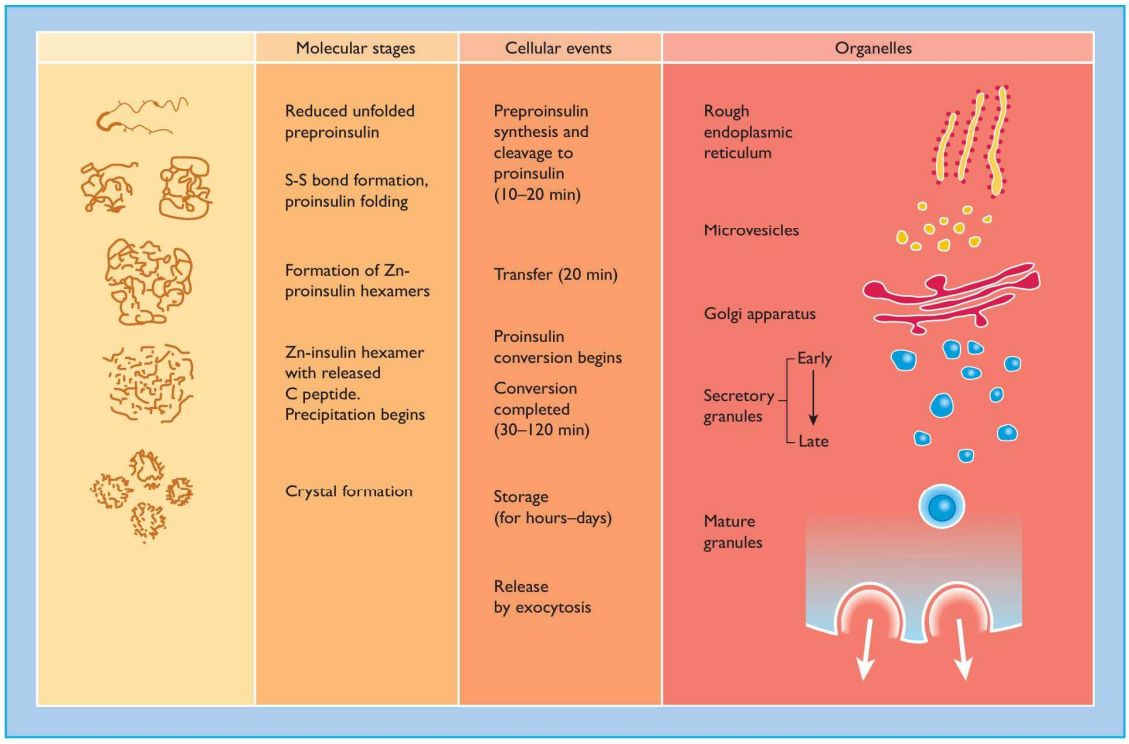
INSULIN BIOSYNTHESIS

Insulin is secreted in the islets of Langerhans by the pancreatic beta cells. It is initially secreted as preproinsulin, which is a single-chain polypeptide precursor with 86 amino acids. Subsequently, the amino-terminal signal peptide is removed by proteolysis, thus producing proinsulin, which structurally resembles the insulin-like growth factors 1 and 2. Further processing involves the cleavage of C-peptide residue with 31 amino acids, thus generating the A and B chains of insulin, that are linked by disulphide bonds.

The C-peptide is stored together with the mature insulin molecule, and they are both co-secreted from the beta cells. On account of larger half life of C-peptide, it is useful as an indicator of insulin secretion. It is also useful in the evaluation of hypoglycaemia, as it permits a differentiation between exogenous and endogenous sources of insulin secretion.

INSULIN BIOSYNTHESIS





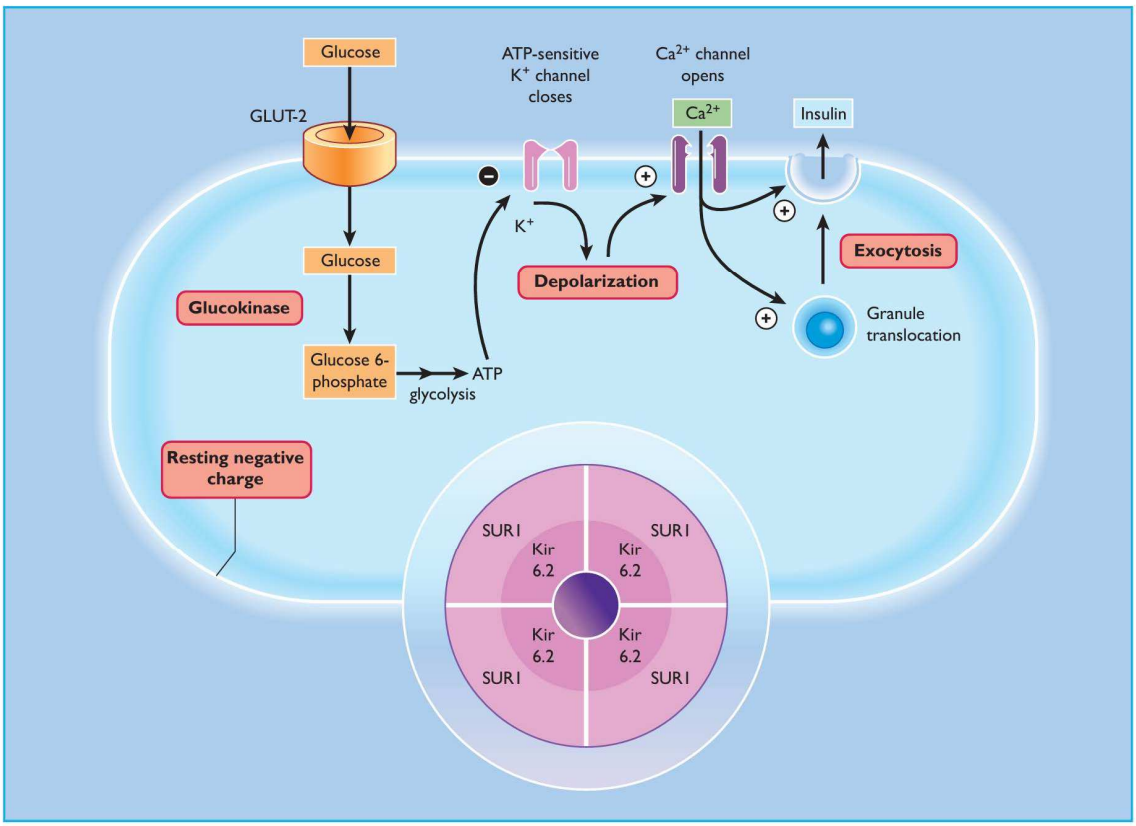
INSULIN SECRETION

Glucose levels greater than 70 mg/dL results in the stimulation of insulin synthesis. The glucose molecule is first transported by a facultative glucose transporter into the beta cell. Here it is phosphorylated by glucokinase, and enters glycolysis, thus generating ATP and this ATP inhibits the activity of the ATP-sensitive potassium channels.

When this channel is inhibited, it results in a depolarisation of the membrane of beta cell, and this results in the opening of voltage dependent calcium channels, thus resulting in an influx of calcium. It is this calcium which ultimately stimulates insulin secretion. Furthermore, incretins are secreted by neuroendocrine cells in the gastrointestinal tract. Their function is to amplify insulin secretion, and suppress glucagon secretion.

The most potent incretin is glucagon-like peptide 1 (GLP-1). It is secreted from the L-cells of the small intestine. It induces secretion of insulin only if the plasma glucose rises above the fasting level.

INSULIN SECRETION:



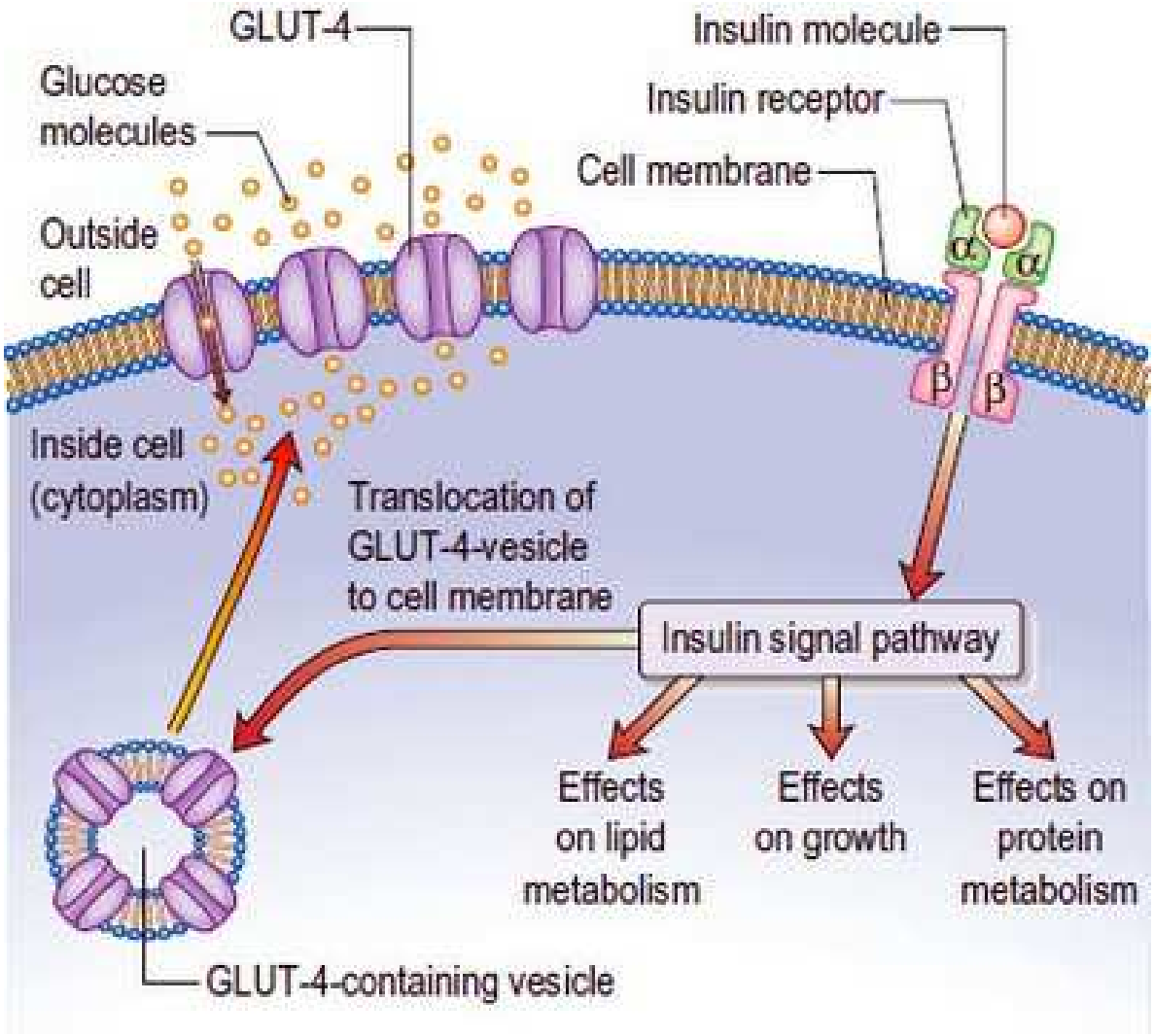
INSULIN ACTION

About half of total insulin which is secreted into the portal system is degraded by the liver. The remainder enters systemic circulation and binds to receptors on the target tissues. Binding to its receptor results in a stimulation of the intrinsic tyrosine kinase activity. This then leads to auto phosphorylation of receptors, and also the recruitment of various other intracellular second messengers, which include the insulin receptor substrate (IRS).

This results in a complex cascade of reactions involving phosphorylation and dephosphorylation, thus producing the widespread mitogenic and metabolic effects of insulin. Some of the effects include protein synthesis, glycogen synthesis, and lipogenesis. The expression of various genes are also regulated by insulin.

The action of insulin is regulated by three pathways that sense nutrition

1. Hexosamine biosynthetic signalling pathway
2. AMP-activating protein kinase signalling pathway
3. Mammalian target of rapamycin signalling pathway


GLUT-4
Insulin molecule
Glucose molecules
Insulin receptor
Cell membrane
Outside cell
α
α
β
β
Inside cell (cytoplasm)
Translocation of GLUT-4-vesicle to cell membrane
Insulin signal pathway
Effects on lipid metabolism
Effects on growth
Effects on protein metabolism
GLUT-4-containing vesicle

PATHOGENESIS

TYPE 1 DIABETES MELLITUS

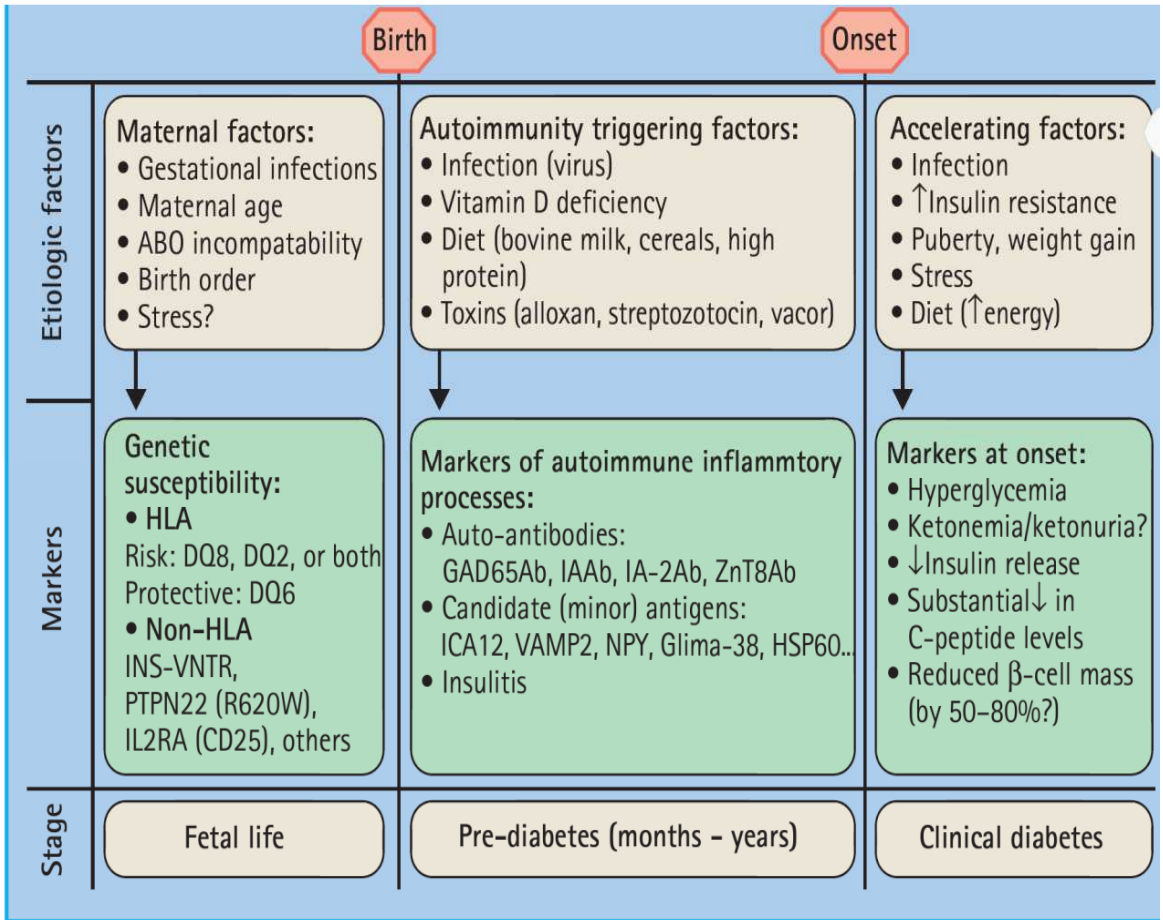
In patient with type 1 diabetes mellitus there will be beta cell secretory function defect due to selective loss of cells which are responsible for the secretory function by autoimmune mediated response. There will be infiltration of pancreatic islets causing insulitis. This is primarily mediated by CD8+ T cells which causes destruction of specific beta cells.

The etiology of type 1 diabetes mellitus is complex. It includes

- Genetic predisposition
- Environmental factors that triggers autoimmunity

In patients with genetic susceptibility having auto antibodies to islet cells various indicators such as insulin release abnormalities may predict the clinical onset. Based on these mechanisms various clinical trials are in progress which aims at stopping the autoimmune response there by halting the progression of disease.

PATHOGENESIS



GENETIC PREDISPOSITION

Multiple genes are involved in the pathogenesis of type 1 diabetic mellitus. In identical twins the occurrence of type 1 diabetic mellitus ranges from 40 to 60 %. It shows there are many other additional factors which are also involved in the occurrence of type 1 diabetic mellitus.

The major gene which is responsible for causing type 1 diabetic mellitus is present in chromosome 6 involving HLA complex. It encodes the necessary genes in the class II MHC molecule. These play a role in the antigen presentation to T helper cells which initiates the immune response. This ability of antigen presentation further depends on the aminoacid constituents of antigen binding sites.

Most of the type 1 diabetes mellitus patients consists of HLA DR3 or HLADR4 haplotype. Other haplotypes such as DQA10201, DQB10302 and DQ1310301 are also involved in the association of type 1 diabetes mellitus. Even though many individuals with these predisposing HLA types does not develop type 1 diabetes mellitus.

There are are various other genetic loci which are found to contribute to the development of type 1 diabetes mellitus. Also there are genes which protects against the development of type 1 diabetes mellitus. These are DQA101202 and DQB10602. These haplotypes are very rare in patients with

type 1 diabetes mellitus and are believed to confer protection against the development of type 1 diabetes mellitus.

PATHOPHYSIOLOGY

Even though the other cell types (such as alpha cells, delta cells, pancreatic polypeptide producing cells) islets of pancreas have functional and embryological similarity with the beta cells and almost have same protein, they are not involved in this autoimmune destruction.

Initially there will be lymphocytic infiltration of the beta cells that was followed by the destruction of beta cells. At a later stage the islets will become atrophic. Studies in the experimental models have shown that both humoural and cellular immunity plays a role in this autoimmune process.

The various abnormalities that are produced during this process are

1. Autoantibodies to islet cells
2. Lymphocytic infiltration of islets
3. Lymphnodes around peripancreatic area and activated lymphocytes in systemic circulation
4. Cytokine release within islets

These cytokines exert toxic effects especially to the beta cells. This action is mediated by nitric oxide metabolite formation apoptosis of islet beta cells. The destruction of beta cells is primarily T lymphocyte mediated

process and not because of autoantibodies to islet cells. These autoantibodies does not react with cell surface of islets and hence they do not transfer diabetes to animals.

The various molecules of islets that are targeted by these autoimmune mechanisms are insulin, glutamic acid decarboxylase (the enzyme responsible for GABA production) and a cell specific zinc transporter protein. Various theories suggests that these autoimmune process initiates destruction of one beta cell thereby producing a series of secondary autoantigens that will spread and cause the destruction of other islet molecule.

IMMUNOLOGIC MECHANISMS

The autoantibodies of islet cells comprises of various antibodies that target specific cell types of islets of pancreas such as insulin, znT8, GAD. These serve as useful markers of the autoimmune process involving type 1 diabetes mellitus. There are various commercially available assays to measure the levels of these antibodies.

These islet cell antibody testing (ICA) is very useful in differentiating type 1 diabetes mellitus from other types. It also identifies the patient at risk for developing type 1 diabetes mellitus. These ICAs are present in majority of

type 1 diabetes mellitus (>85%) in some of type 2 diabetes mellitus(5-10%) and rarely in gestational diabetes mellitus(<5%).

These ICAs are also present in first degree relatives of patient with type 1 diabetes mellitus. A combination of ICA and glucose tolerance test predicts > 50% risk of developing type 1 diabetes mellitus in 5 years.

ENVIRONMENTAL FACTORS

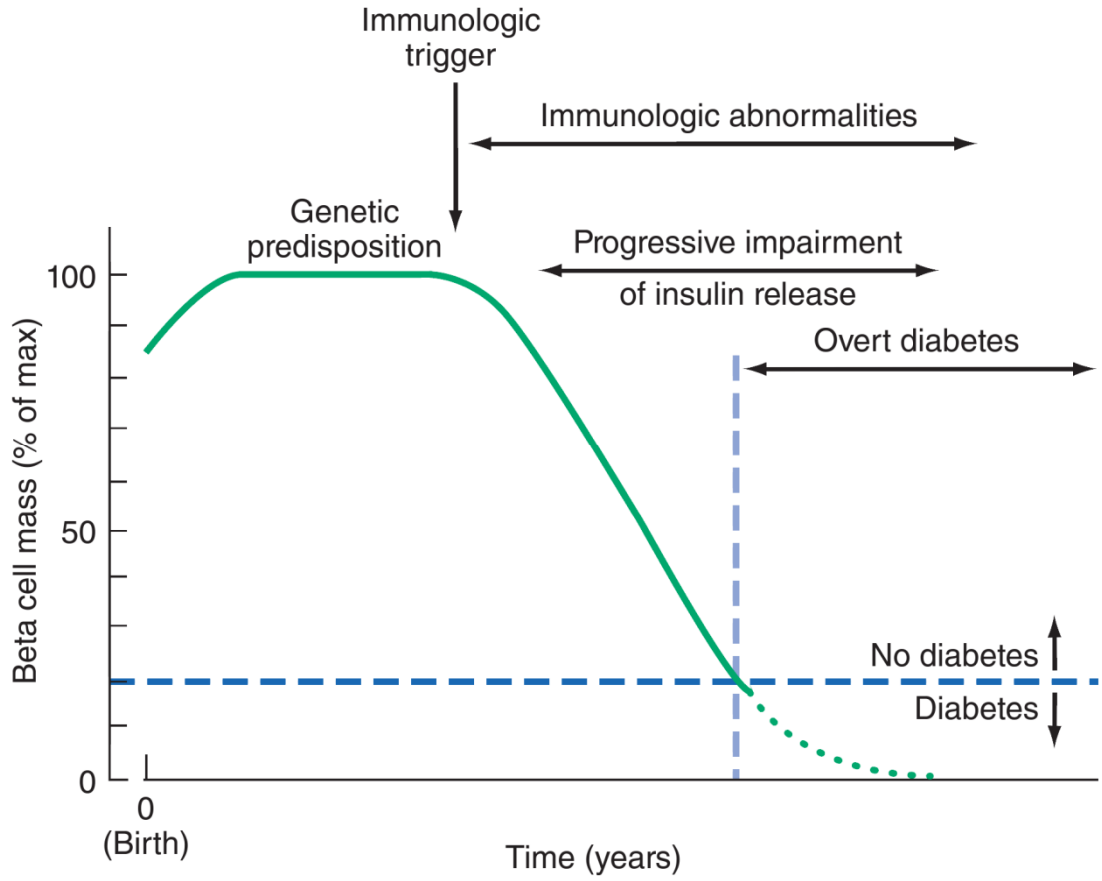
Various environmental factors are proposed in triggering the autoimmune process of type 1 diabetic mellitus. None has been confirmed by studies. These environmental factors includes

- Viral infections (coxsackie, rubella, enterovirus, most prominently)
- Proteins in bovine milk
- Compounds of nitrosurea

PREVENTION OF TYPE 1 DIABETIC MELLITUS

Various interventions has been proposed in experimental models for the prevention of type 1 diabetic mellitus, but none has been successful. Studies shown that IV insulin administration to at risk individuals for type 1 diabetic mellitus does not prevent it. Various clinical investigation is going on these process.

PATHOPHYSIOLOGY



TYPE 2 DIABETIC MELLITUS

To develop type 2 diabetic mellitus the major mechanisms responsible are

- Insulin resistance
- Abnormal insulin secretion

Even though many studies suggests that insulin resistance precedes the insulin secretion abnormality the diabetes become apparent only when there is inadequate insulin secretion. Type 2 diabetes mellitus comprises of various disorders that all share the phenotype of hyperglycemia.

Various studies suggests that south and east Asian ethnic groups develop diabetes at a more younger age and with a low BMI. There are certain group of patients with type 2 diabetes mellitus who are more prone to develop ketosis (often obese) and some who are ketone resistant. (often lean).

GENETIC CONSIDERATIONS

There is a strong genetic correlation with type 2 diabetic mellitus. The development of type 2 diabetes mellitus in concordant twins is between 70 and 90 %. The children of a type 2 diabetes mellitus individual have increased risk of getting diabetes. If both parents affected with type 2 diabetes mellitus then the risk arouses to 40%. Insulin resistance is present in many of the first degree relatives of a patient with type 2 diabetes mellitus.

Diabetes mellitus is a multifactorial and polygenic disorder. It involves genetic susceptibility, environmental factors (physical inactivity, diet, obesity). The genetic predisposition to type 2 diabetic mellitus are incompletely understood. Still most of the studies suggest that large number of genes contribute to a relatively small risk for the development of type 2 diabetic mellitus. The most important among these is a gene of transcription factor 7 variant.

The mechanisms by which these genetic alteration contributes to development of type 2 diabetic mellitus is still not clearly understood, but most of these interferes with function of islets or development of islets or secretory defect. The genetic susceptibility for the development of type 2 diabetic mellitus is under active investigation. Type 2 diabetes mellitus is mainly characterised by

- Impairment of insulin secretion
- Development of insulin resistance
- Increased gluconeogenesis from liver
- Fat metabolism abnormalities

Central obesity is frequently seen (>80%) in patients with type 2 diabetic mellitus. Even though there is insulin resistance, in the initial stage of type 2 diabetes mellitus the glucose tolerance remains within normal limits because of the increased insulin production to compensate for the insulin

resistance. With progression in insulin resistance, there will be compensatory hyperinsulinemia but at one stage the pancreatic islets are unable to sustain the increased production of insulin.

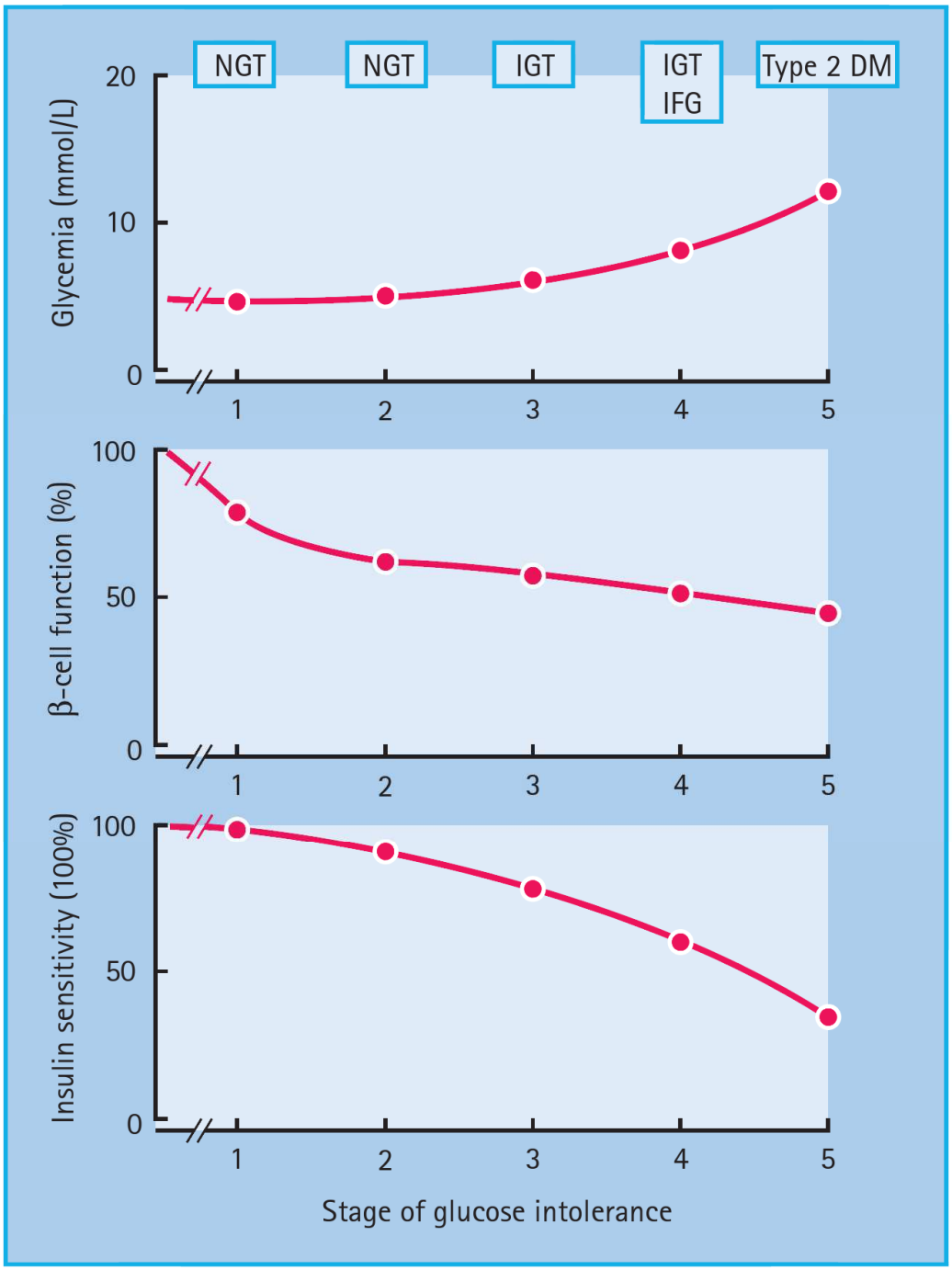
With this stage there will be development of impaired glucose tolerance which is characterised by increase in post prandial glucose. With further progression of disease, there is reduction in insulin secretion with increase in glucose production by the liver leading to a state of overt diabetes mellitus characterised by increase in fasting blood sugar. The relative contribution of both these processes (impaired insulin secretion and insulin resistance) varies from individual to individual.

INSULIN RESISTANCE SYNDROMES

It comprises various group of disorders with hyperglycemia as a common component. These include

- Metabolic syndrome
- Insulin resistance syndrome
- Syndrome X

STAGES OF GLUCOSE TOLERANCE



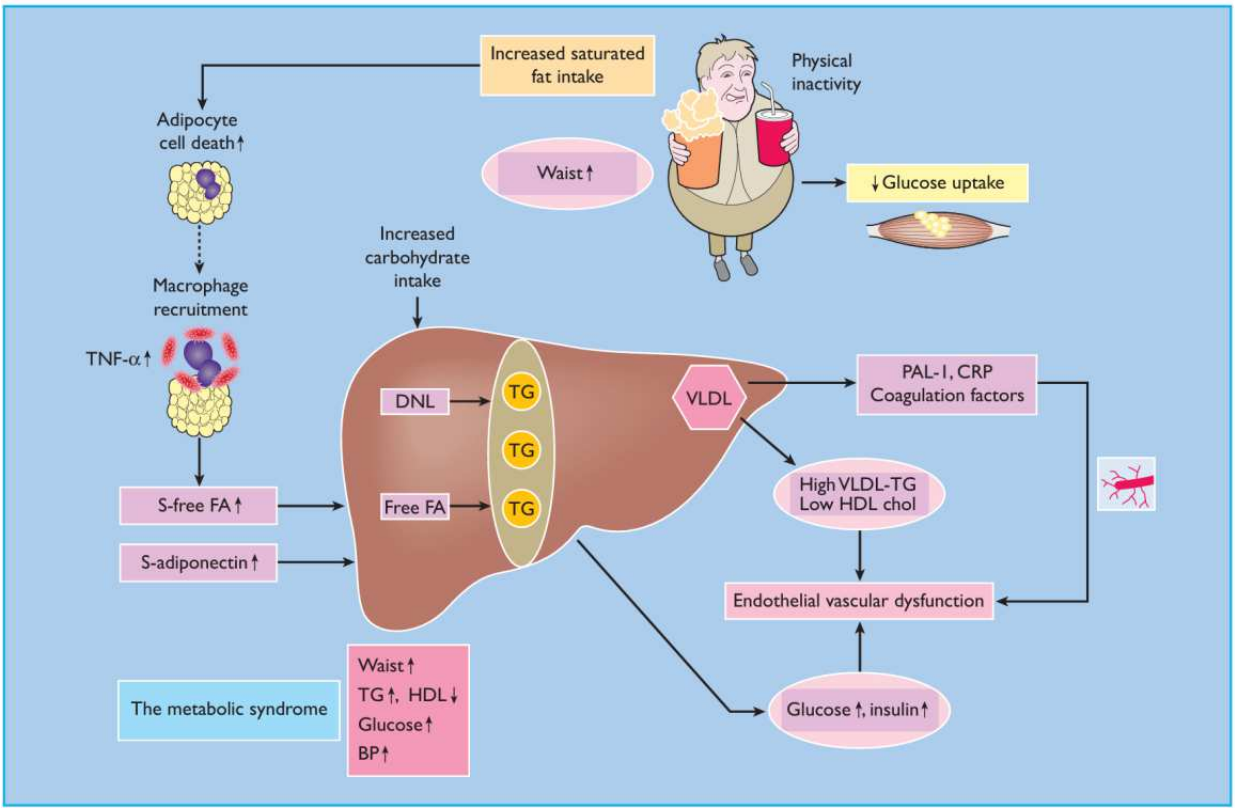
INSULIN RESISTANCE SYNDROMES

It comprises various group of disorders with hyperglycemia as a common component. These include metabolic syndrome, the insulin resistance syndrome and syndrome X which shares the various metabolic disorders that includes hypertension, central obesity, dyslipidemia, insulin resistance.

There are various other rare forms which comprises features of diabetes mellitus. Acanthosis nigricans and hyperandrogenism (characterised by acne, hirsutism, oligomenorrhoea in women) are also associated with these syndromes. Two distinct syndromes involving severe insulin resistance have been described in adults.

- Type A – defect in insulin signalling pathways, affects young females and have features of hyperandrogenism, obesity
- Type B – due to autoantibodies to insulin receptor, affects middle aged females, associated with other auto immune disorders.

Polycystic ovary syndrome is a disorder affecting premenopausal women with features of hyperandrogenism and chronic anovulation. Some group of women with PCOS have insulin resistance and increase in the risk of developing type 2 diabetic mellitus.


Increased saturated fat intake
Physical inactivity
Adipocyte cell death↑
Waist↑
↓Glucose uptake
Increased carbohydrate intake
Macrophage recruitment
TNF-α↑
DNL
TG
TG
TG
VLDL
PAL-1, CRP Coagulation factors
S-free FA↑
Free FA
High VLDL-TG Low HDL chol
S-adiponectin↑
Endothelial vascular dysfunction
The metabolic syndrome
Waist↑
TG↑, HDL↓
Glucose↑
BP↑
Glucose↑, insulin↑

MONOGENIC FORMS OF DIABETES

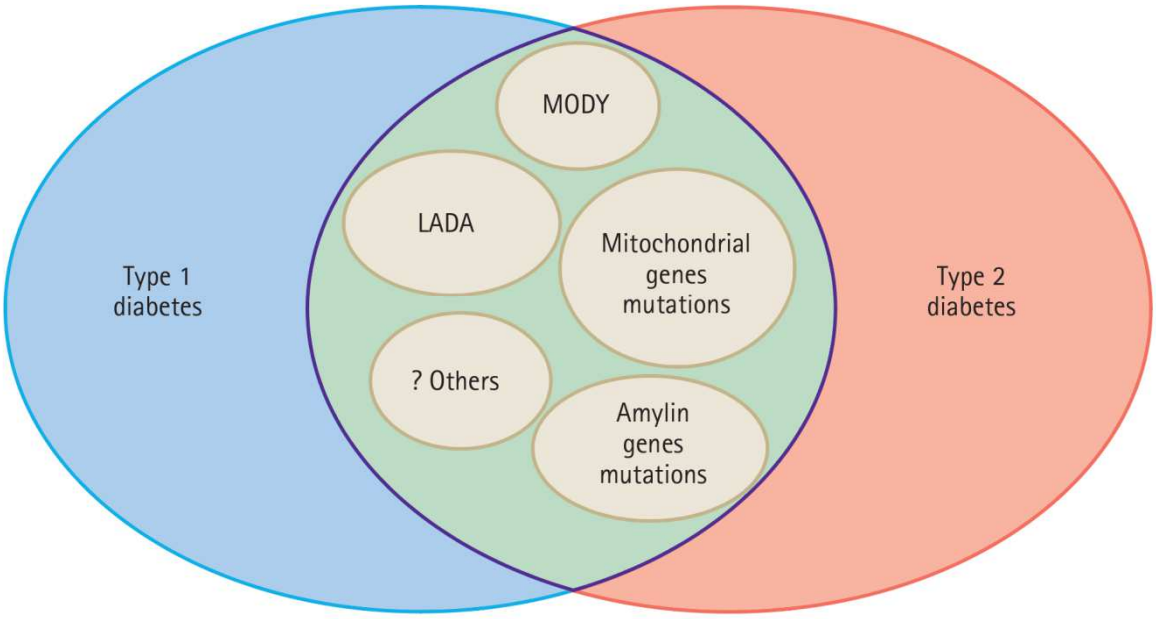
There are various monogenic forms of diabetes. Various variants of MODY have been identified. They are caused by mutation of genes encoding islet enriched transcription factor. These factors have a role in interfering with glucose stimulated secretion of insulin. They are transmitted as autosomal dominant forms. The affected individuals will often have other defects such as liver function abnormalities, renal cysts and pancreatic exocrine insufficiency.

Neonatal diabetes (onset < 12 months of age) is caused by genetic mutations. It is phenotypically similar to that of type 1 diabetes mellitus. The major mutations involved are

- ATP sensitive potassium channel subunits (kir 6.2 and ABCC8)
- Insulin gene defects

These individuals may be treated with sulfonylurea and usually respond well.

HETEROGENEOUS ETIOLOGY OF YOUNG ONSET DIABETES



COMPLICATIONS

Diabetes affects various organ systems leading to various complications. They include microvascular, macro vascular and nonvascular complications. The microvascular complications are retinopathy, neuropathy and nephropathy. Macro vascular complications are coronary heart disease, peripheral vascular disease, and cerebrovascular disease.

The various non vascular complications are gastroparesis, infections, hearing loss and skin abnormalities.

DIABETIC NEPHROPATHY

In our study we are correlating the mean platelet volume and the albuminuria levels in diabetic patients there by studying role of mean platelet volume in the development of vascular complications specifically diabetic nephropathy. High albuminuria (previously microalbuminuria)is an early indicator of diabetic nephropathy.

Diabetic nephropathy is the most important cause of chronic kidney disease and end stage renal disease. Albuminuria in diabetic individuals is also associated with an increased risk of cardiovascular disease. Usually the diabetic patients with diabetic nephropathy have associated diabetic retinopathy.

PATHOGENESIS

Due to chronic hyperglycemia there will be activation of soluble factors (growth factors, endothelin, angiotensin II, advanced glycation end products) alteration in the microcirculation of kidney (hyperfiltration, increased glomerular capillary pressure) and glomerular structural changes(mesangial expansion, fibrosis, thickening of basement membrane)

Initially during the first few years of diabetes mellitus there will be glomerular hyperperfusion, renal hypertrophy and thickening of glomerular basement membrane. Later after some 5 to 10 years individuals will began to loss small amounts of albumin in urine.

The KDIGO and ADA proposed in recent years that the microalbuminuria (30-299 mg/dl) and macro-albuminuria (>300mg/dl) should be replaced by high albuminuria and persistent albuminuria respectively as they better the continuous nature of urine albumin excretion and are risk factors for the development of diabetic nephropathy and cardiovascular disease.

This albuminuria levels should be detected at an early stage, as effective pharmacological therapy during this stage can delay the progression of diabetic nephropathy. Micro albuminuria levels should be assessed annually in patients with type 1 and type 2 diabetes mellitus. In patient with

type 1 diabetes mellitus screening for microalbuminuria should begin 5 years after diagnosis and in type 2 patients at the time of diagnosis.

Improvement in glycaemic control and use of ACE inhibitors or ARB's can reduce the albuminuria levels and also reduces intra glomerular pressure thereby delaying the progression of diabetic nephropathy.

MICROALBUMINURIA

Quantifying urine excretion of albumin is more sensitive than measuring general proteinuria. Albumin is normally excreted at a rate of <30 mg/day. When albumin excretion is persistently between 30-300 mg it is known as high albuminuria (previously known as microalbuminuria). When excretion exceeds 300 mg/day, it represents overt or dipstick positive proteinuria, and is known as very high albuminuria (previously known as macroalbuminuria).

In the case of type 1 diabetes, high albuminuria (previously microalbuminuria) might represent the earliest clinical manifestation of diabetic nephropathy, and usually begins to be seen five years after diagnosis. On the other hand, patients with type 2 diabetes, usually have high albuminuria at the time of diagnosis and this albuminuria probably represents underlying cardiovascular disease and not diabetic nephropathy in particular, as is the case in type 1 diabetes.

It is recommended that screening for high albuminuria be done at yearly intervals, in patients with both types of diabetes, starting at disease onset in type 2 diabetes, and five years after the disease onset in type 1 diabetes. While diagnosing high albuminuria, conditions causing transient elevation in albumin excretion should be excluded[34].

Such conditions include

- Exercise
- Fever
- Infection
- Poor glycaemic control
- Hyperlipidaemia
- Elevated blood pressure

URINE ALBUMIN CONCENTRATION

The gold standard for diagnosing high albuminuria is 24-hour urine collection. However, screening can be more easily achieved using an early-morning specimen, or a timed urine collection, in order to minimise urinary volume changes which occur during the day[34]. If the rate of albumin excretion in a timed urine collection is below 20 µg/min, or if the concentration of urine albumin in a random specimen is less than 20-30 mg/L, high albuminuria is unlikely.

Higher values, especially values just above these ranges could represent false positivity, and therefore, such samples need to be confirmed by repeating the measurement. Semiquantitative dipsticks are also available, which can detect high albuminuria in situations where a direct measurement of urine albumin excretion cannot be obtained.

The disadvantage of using urine albumin concentration or dipstick tests, is that false results may occur because urine albumin concentration depends not only on the amount of albuminuria, but also on the urine volume[35]. Thus, even if the rate of urine albumin excretion is constant, there may be a change in the urine albumin concentration if there occur substantial changes in urine volume. This confounding factor may be eliminated by performing repetitive measurements on early morning samples.

ALBUMIN-CREATININE RATIO

Measurement of urine albumin-to-creatinine ratio in a random sample of urine removes the confounding effect of urine volume on concentration of urinary albumin. Values of 30-300 mg/g of creatinine imply daily albumin excretion levels of 30-300 mg/day, corresponding to high albuminuria (previously microalbuminuria)[36].

Urinary albumin-creatinine ratio >300 mg/g of creatinine indicates very high albuminuria (previously macroalbuminuria). However, at least two

out of three specimens should have ACR levels without the high or very high ranges to make the diagnosis in order to eliminate false positives[36]

In one study, spot urine albumin-creatinine ratio and 24-hour urine collection were used to quantify urine albumin excretion. The study involved 13 individuals with type 1 diabetes, 12 individuals with type 2 diabetes, and 14 normal subjects[37]. Both measurements were found to give similar results. The presence of ACR more than 30 mg/g was 100% sensitive in detecting high albuminuria. These findings have been confirmed by the other studies as well[38].

LIMITATIONS OF URINARY ACR

Patients must be instructed to avoid vigorous exercise for 24 hours prior to being tested, as this can transiently raise the urinary albumin excretion[39]. Uncertainty exists regarding the optimal time to perform urine albumin-creatinine ratio. In one study, the highest correlation between urine ACR and 24-hour urine collection was seen when samples were taken after the first morning void and last sample before the bedtime[40]. However, a more large scale study, performed later, revealed a better correlation when first morning void was used. However, in this study, the differences which were noted with samples collected at other times were not found to be significant[41]. The test had reduced accuracy if excretion of creatinine is greatly different from expected values, especially when patients had

borderline values. The ratio will be reduced in muscular individuals because of high urinary creatinine excretion, and the ratio will be increased in emaciated individuals, where muscle mass and therefore urinary creatinine excretion, are significantly reduced.

DIABETIC RETINOPATHY

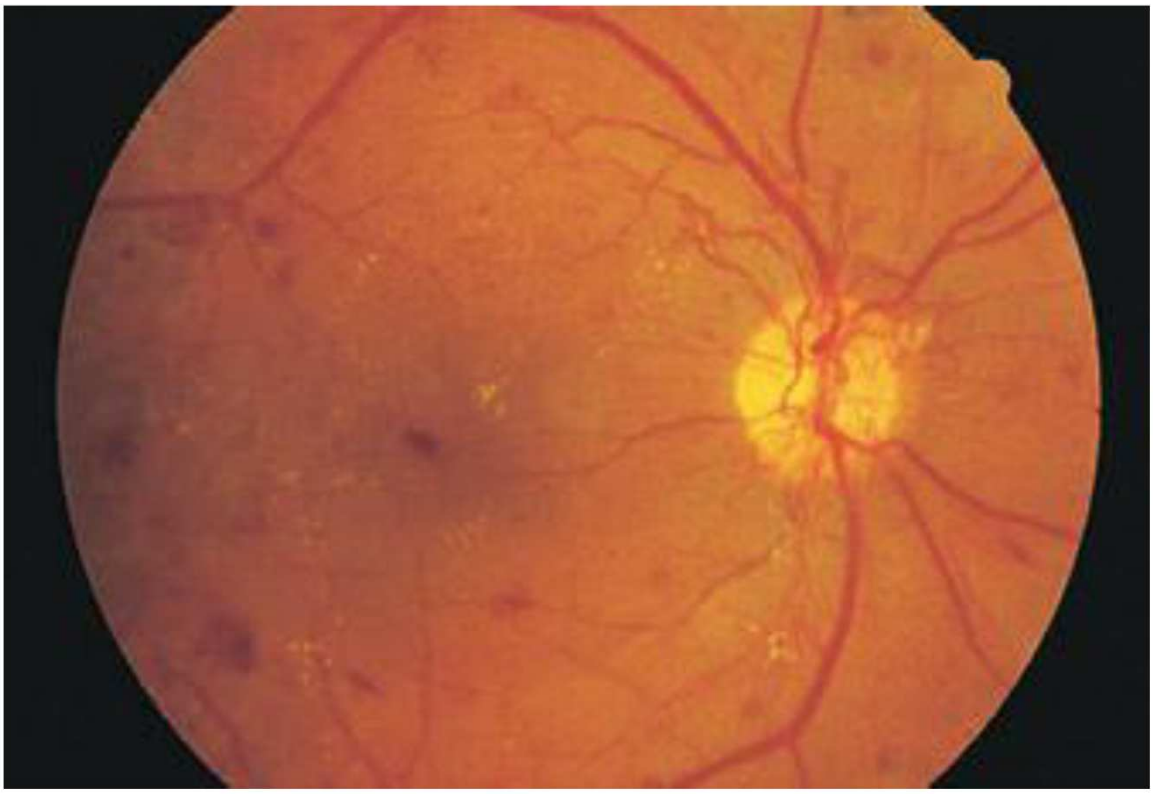
It comprises two stages.

- Non proliferative stage
- Proliferative stage

Non proliferative stage is characterised by microaneurysms, blot haemorrhage and cotton wool spots. Proliferative retinopathy is characterised by neovascularisation of retina which occurs due to retinal hypoxia. These new vessels are very fragile and rupture easily causing vitreous haemorrhage, fibrosis and culminating in retinal detachment.

Regular ophthalmic examination is necessary in all patients with type 2 diabetes mellitus to prevent diabetic retinopathy. Laser photocoagulation will be useful in later stages.

DIABETIC RETINOPATHY



DIABETIC NEUROPATHY

Various manifestations such as mononeuropathy, polyneuropathy and autonomic neuropathy can occur. Distal symmetric polyneuropathy is the most common form. Paresthesia or hyperaesthesia may occur. Usually pain presents at rest and worsens at night. Polyradiculopathy is characterised by involvement of one or more nerve root.

VARIOUS COMPLICATIONS OF DIABETES

- Microvascular
  - Eye disease
    - Retinopathy (nonproliferative/proliferative)
    - Macular edema
  - Neuropathy
    - Sensory and motor (mono- and polyneuropathy)
    - Autonomic
  - Nephropathy (albuminuria and declining renal function)
- Macrovascular
  - Coronary heart disease
  - Peripheral arterial disease
  - Cerebrovascular disease
- Other
  - Gastrointestinal (gastroparesis, diarrhea)
  - Genitourinary (uropathy/sexual dysfunction)
  - Dermatologic
  - Infectious
  - Cataracts
  - Glaucoma
  - Cheiroarthropathy[a]
  - Periodontal disease
  - Hearing loss

MONITORING DIABETES

The most important goal in diabetes management is to attain normal physiological levels of glucose without leading to hypoglycaemia.[42] The two most commonly used glycaemic measures are blood glucose and HbA1c (glycated haemoglobin).

HbA1c levels indicatesthe overall glycaemic control in the previous 8 - 10 weeks thereby assessing the therapeutic response. While the blood glucose levels gives information about day to day control levels and subjected to wide variation other than fasting blood glucose.

The haemoglobin present in the blood combines with glucose non enzymatically to form glycated derivatives. This glycation reaction in turn depends on the concentration of glucose in the blood. This reaction occurs between beta chain of haemoglobin A molecule and glucose forming HbA1c. It is now widely used as a standard measurement to monitor glycaemic control.

TREATMENT OF DIABETES MELLITUS

Life style modification such as healthy diet, increased physical activity plays an important role in diabetes management. Insulin is recommended in all patients with type 1 diabetes mellitus and also useful in type 2 diabetes mellitus. The patient should be encouraged to self-monitorthe blood glucose levels there by preventing hypoglycaemia related complications.

All measures should be taken to prevent diabetic complications by routine screening for complications. The associated diseases like hypertension and dyslipidaemia should be addressed. There are various antidiabetic drugs available and the choice of one depends on the blood sugar levels and patient condition. Combination of drugs can be used if the patient is having severe hyperglycaemia.

The most dangerous complication of therapy with diabetes is hypoglycemia. Weight gain is another adverse effect. Recurrent hypoglycemia necessitates modification of treatment regimen and glycaemic control for the patient.

TREATMENT OF DIABETES MELLITUS

	Mechanism of Action	Examples[a]	HbA_{1c} Reduction (%)[b]	Agent-Specific Advantages	Agent-Specific Disadvantages	Contraindications
Oral						
Biguanides[c,e]	↓ Hepatic glucose production	Metformin	1–2	Weight neutral, do not cause hypoglycemia, inexpensive, extensive experience, ↓ CV events	Diarrhea, nausea, lactic acidosis	Serum creatinine >1.5 mg/dL (men) >1.4 mg/dL (women) (see text), CHF, radiographic contrast studies, hospitalized patients, acidosis
α-Glucosidase inhibitors[c,e,g]	↓ GI glucose absorption	Acarbose, miglitol, voglibose	0.5–0.8	Reduce postprandial glycemia	GI flatulence, liver function tests	Renal/liver disease
Dipeptidyl peptidase IV inhibitors[c,e,g,h]	Prolong endogenous GLP-1 action	Alogliptin, Anagliptin, Gemigliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin, vildagliptin	0.5–0.8	Well tolerated, do not cause hypoglycemia		Reduced dose with renal disease; one associated with increase heart failure risk; possible association with ACE inhibitor–induced angioedema
Insulin secretagogues: Sulfonylureas[c,e]	↑ Insulin secretion	Glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glyburide, glyclopyramide	1–2	Short onset of action, lower postprandial glucose, inexpensive	Hypoglycemia, weight gain	Renal/liver disease
Insulin secretagogues: Nonsulfonylureas[c,e,g,h]	↑ Insulin secretion	Nateglinide, repaglinide, mitiglinide	0.5–1.0	Short onset of action, lower postprandial glucose	Hypoglycemia	Renal/liver disease
Sodium-glucose cotransporter 2 inhibitors[c,e,g]	↑ Urinary glucose excretion	Canagliflozin, dapagliflozin, empagliflozin	0.5–1.0	Insulin secretion and action independent	Urinary and vaginal infections, dehydration, exacerbate tendency to hyperkalemia	Limited clinical experience; moderate renal insufficiency
Thiazolidinediones[c,e,g]	↓ Insulin resistance, ↑ glucose utilization	Rosiglitazone, pioglitazone	0.5–1.4	Lower insulin requirements	Peripheral edema, CHF, weight gain, fractures, macular edema	CHF, liver disease
Parenteral						
Amylin agonists[c,d,e,g]	Slow gastric emptying, ↓ glucagon	Pramlintide	0.25–0.5	Reduce postprandial glycemia, weight loss	Injection, nausea, ↑ risk of hypoglycemia with insulin	Agents that also slow GI motility
GLP-1 receptor agonists[c,e,g,h]	↑ Insulin, ↓ glucagon, slow gastric emptying, satiety	Exenatide, liraglutide, dulaglutide	0.5–1.0	Weight loss, do not cause hypoglycemia	Injection, nausea, ↑ risk of hypoglycemia with insulin secretagogues	Renal disease, agents that also slow GI motility; medullary carcinoma of thyroid
Insulin[c,d,e,g,i]	↑ Glucose utilization, ↓ hepatic glucose production, and other anabolic actions	See text and Table 418-4	Not limited	Known safety profile	Injection, weight gain, hypoglycemia	
Medical nutrition therapy and physical activity[e]	↓ Insulin resistance, ↑ insulin secretion	Low-calorie, low-fat diet, exercise	1–3	Other health benefits	Compliance difficult, long-term success low	

[a]Examples are approved for use in at least one country, but may not be available in the United States or all countries. Examples may not include all agents in the class. [b]HbA1c reduction

EMERGING THERAPIES

Pancreas transplantation is an important option in patients with type 1 diabetic mellitus with end stage renal disease. But immunosuppression is needed. Newer pharmacological therapies includes glucokinase activators, GPR40 agonists, monoclonal antibodies to inflammation and 11 beta hydroxysteroid dehydrogenase inhibitors for type 2 diabetes mellitus patients.

Bariatric surgery has been recommended in obese individuals with type 2 diabetes mellitus. ADA recommends bariatric surgery in type 2 diabetes individuals with Body Mass Index > 35 kg /m2.

MATERIALS

AND

METHODS

MATERIALS AND METHODS

PATIENT SELECTION

All patients were explained about the diabetes and its complications. They were informed about the study proceedings and the usefulness of the study in their own language. All the subjects gave consent before participating in the study.

DESIGN OF THE STUDY

Cross sectional study

STUDY CENTRE

Institute of internal medicine and

Institute of diabetology

Madras medical college and Rajiv Gandhi government general hospital, Chennai

STUDY DURATION

April 2015 to September 2015 – total 6 months

INCLUSION CRITERIA

1. Confirmed cases of type 2 diabetes mellitus
2. Non diabetic controls without coronary artery disease

EXCLUSION CRITERIA

1. Patients on antiplatelet drugs such as aspirin and clopidogrel.
2. Patients with abnormal platelet counts (thrombocytosis or thrombocytopenia)
3. Type 1 diabetes mellitus patients
4. Type 2 diabetes mellitus with macrovascular complications
5. Diabetes complicating pregnancy
6. Conditions causing transient urinary albumin excretion such as infection, heart failure, exercise and uncontrolled hypertension

SAMPLE SIZE

A total of 140 patients which includes 90 diabetics and 50 controls. Healthy subjects who attended routine master health check ups were taken as control group

METHOD OF DATA COLLECTION

All the patients involved in the study are subjected to following parameters.

1. History of patient
2. General examination
3. Systemic examination
4. Laboratory investigations
5. Electrocardiogram

METHODOLOGY

HISTORY

A detailed history on diabetes and other comorbid illness were collected

The history includes

Age

Sex

Duration of diabetes

History of chestpain, claudication pain and stroke

History of blurring of vision

History of comorbid illness such as hypertension

Treatment history

History of smoking and alcohol, if present the details of that

GENERAL EXAMINATION

The following parameters were assessed in all subject

1. BMI based on weight and height using the formula weight/height in meter square
2. Blood pressure was measured in the right arm with the patient in sitting position
3. Other general examination was done

SYSTEMIC EXAMINATION

The following systems were examined to detect any complications of diabetes

CARDIOVASCULAR

RESPIRATORY

CENTRAL NERVOUS SYSTEM

ABDOMEN

LABORATORY INVESTIGATIONS

All the patients were subjected to the following investigations

- Mean platelet volume
- Urine albumin creatinine ratio

- Fasting blood glucose
- Post prandial blood glucose
- Glycosated haemoglobin levels(HbA1c)
- Platelet count
- Total cholesterol
- Haemoglobin
- Serum creatinine

Mean platelet volume is measured by an automatic blood counter using venous blood samples which were taken in a test tube mixed with EDTA and tested within 1 hour of collection. HbA1c was measured using automated high performance liquid chromatography.

Serum glucose was measured by hexokinase enzymatic method. Albuminuria is measured by early morning urine albumin creatinine ratio. The diabetic patients are subdivided into three groups based on albuminuria levels

- A1 (<30 mg/gm) - normoalbuminuria
- A2(30-300 mg/gm) - high albuminuria
- A3(>300mg/gm) – very high albuminuria

Mean platelet volume is assessed and compared in the above groups. Then based on HbA1c levels patient is again subdivided into (according to ADA criteria)

- HbA1c ≤ 6.5 %
- HbA1c > 6.5%

Again mean platelet volume is compared in the above mentioned groups thereby assessing its relation with glycaemic status of the patient.

ANALYSIS PLAN

Statistical analysis was done using SPSS software version 17.0

SPONSORSHIP

No

CONFLICT OF INTEREST

None

OBSERVATION

AND

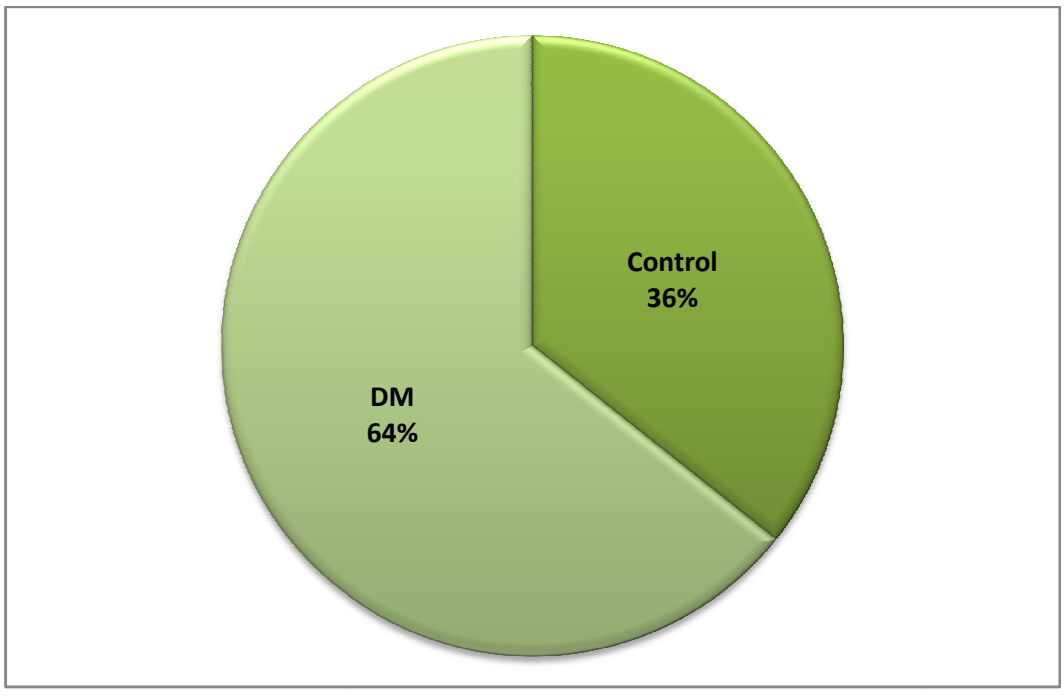
RESULTS

OBSERVATION AND RESULTS

A total number of 140 patients participated in our study that includes 90 (64 %) type 2 diabetes mellitus patients and 50 (36%) age matched healthy controls. Among them 88 (63 %) are males and 52 (37%) are females. They are distributed in age group of 40 to 70 years.

FIGURE 1

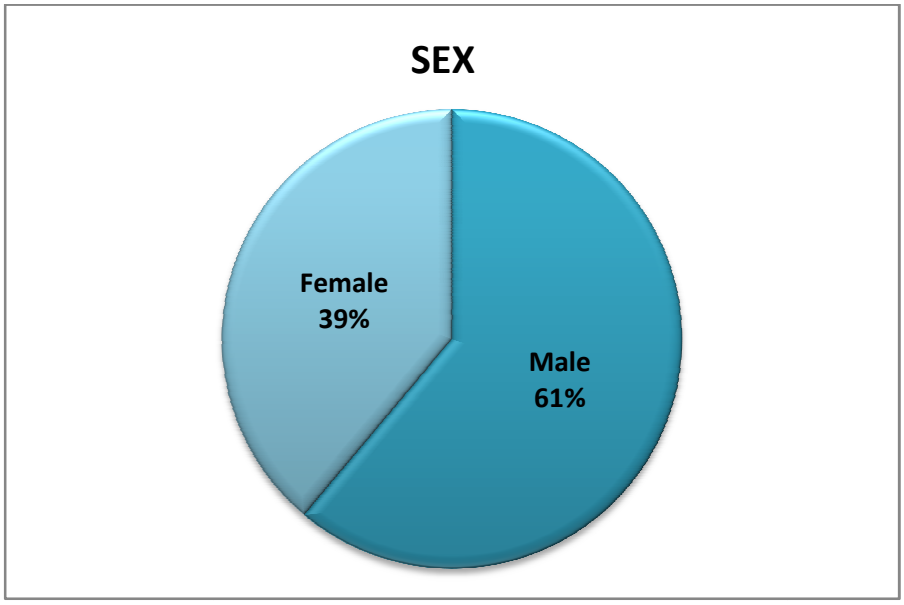
DISTRIBUTION OF PATIENTS IN OUR STUDY



Our study includes 140 subjects among which 90 (64%) are type 2 diabetes mellitus patients and 50 controls.

FIGURE 2

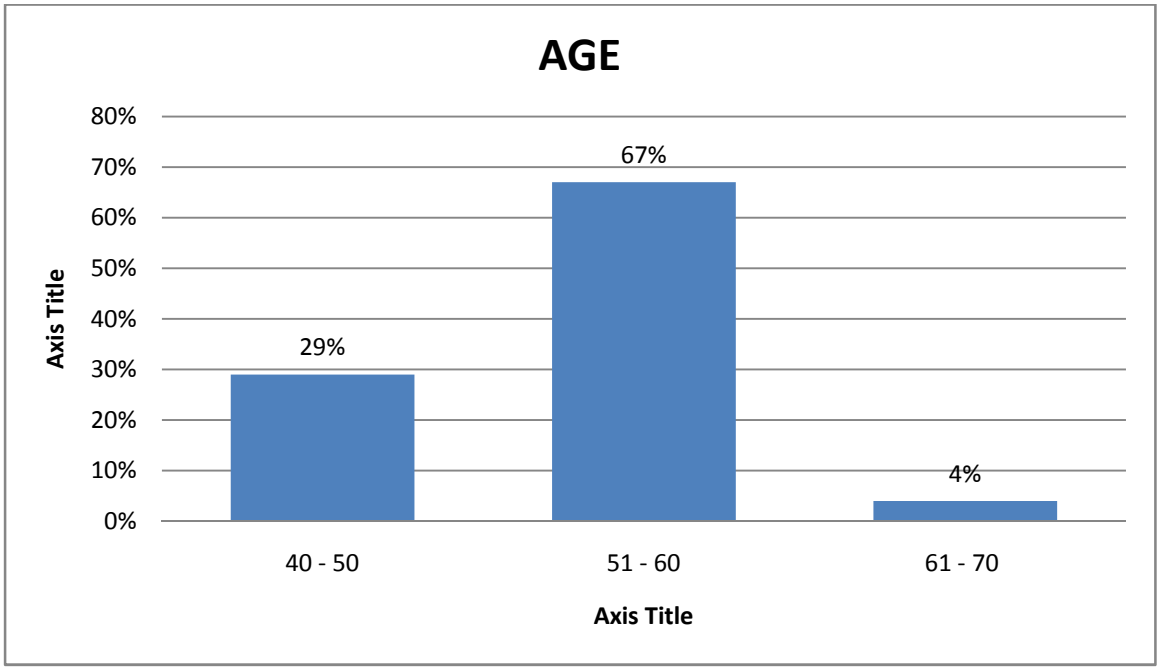
SEX WISE DISTRIBUTION OF DIABETES PATIENTS



In our diabetes group, 55 patients(61%) are males and 35 patients(39%) are females

FIGURE 3

AGE WISE DISTRIBUTION OF DIABETES PATIENTS



In our study group 29% belongs to the age group 40-50, 67 % belongs to age group 51-60 and 4% belongs to more than 60 age group.

TABLE 1

COMPARISON OF VARIOUS PARAMETERS BETWEEN THE DIABETIC AND NONDIABETIC CONTROLS

Independent sample t test

	Control		**DM**		**P value**
	Mean	**SD**	**Mean**	**SD**	
Age	52.58	4.26	51.93	4.51	0.409
Duration of DM	N/A	N/A	5.57	1.98	N/A
BMI	26.48	1.36	30.99	2.42	**<0.0001**
MPV	7.93	0.24	8.8	0.36	**<0.0001**
Urine albumin creatinine ratio	N/A	N/A	213.48	189.27	N/A
Platelet	3.8	0.48	3.59	0.43	0.009
Hb	14.68	14.12	12.37	0.77	0.124
Total cholesterol	180.54	18.99	216.86	54.77	**<0.0001**
Serum Creatinine	1.2	0.34	1.46	0.29	**<0.0001**
FBS	89.6	9.73	171.35	53.02	**<0.0001**
PPBS	129.68	9.75	248.51	84.81	**<0.0001**

MPV was significantly higher (8.8± 0.36) in the diabetes patients when compared to control(7.93± 0.24) group and is stastically significant ($p<0.0001$) by independent sample t test.

The mean BMI in control group (26.48±1.36) was also lower than the diabetes group (30.99±2.42) and also stastically significant.

The mean fasting blood sugar and post prandial blood sugar in the control group was (89.6± 9.73) and (129.68±9.75) while in the diabetes group it was (171.35± 53.02) and (248.51±84.51) respectively.

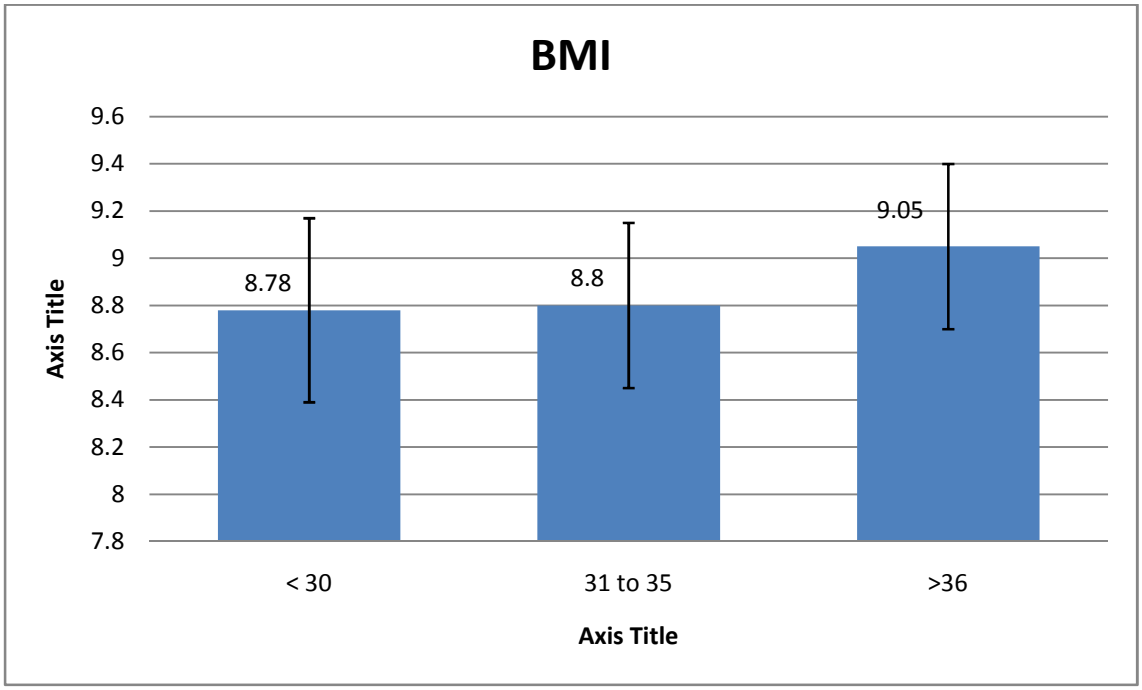
The mean total cholesterol level in control group was (180.54±18.99) while in the diabetes group it was (216.86±54.77)

The mean age of patients in control group was (52.58±4.26) while in the diabetes group it was (51.93±4.51)

The mean platelet count in diabetes was (3.59± 0.43) while in the control group it was (3.8±0.48)

FIGURE 4

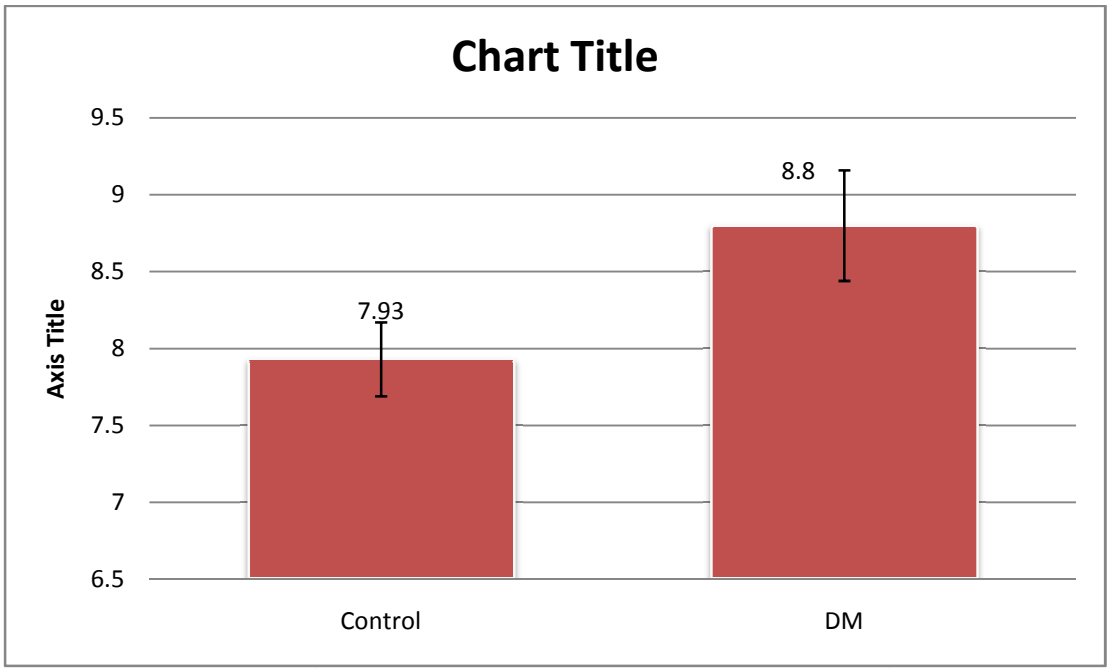
CORRELATION OF MEAN PLATELET VOLUME WITH BMI



Mean platelet volume shows a positive correlation (p value – 0.042) with BMI in our study. The correlation coefficient calculated by Pearson correlation coefficient shows only weak correlation (0.215)

FIGURE 5

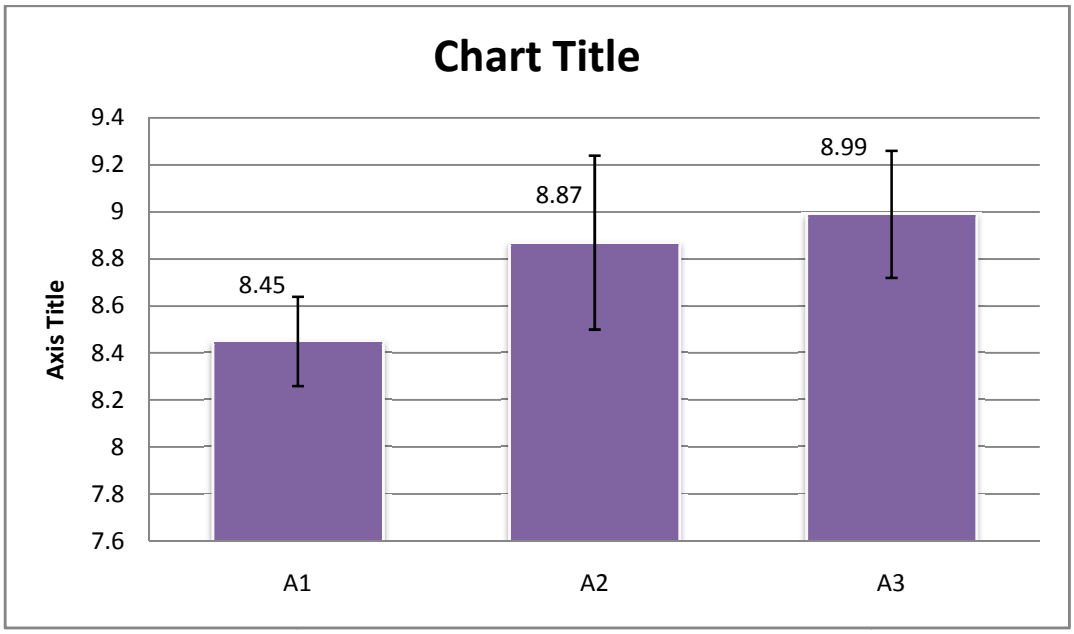
CORRELATION OF MPV IN CONTROLS AND DIABETES PATIENTS



The mean platelet volume in diabetes group(8.8± 0.36) is significantly higher than the control group(7.93± 0.24) and independent sample test shows a significant correlation(p <0.0001)

FIGURE 6

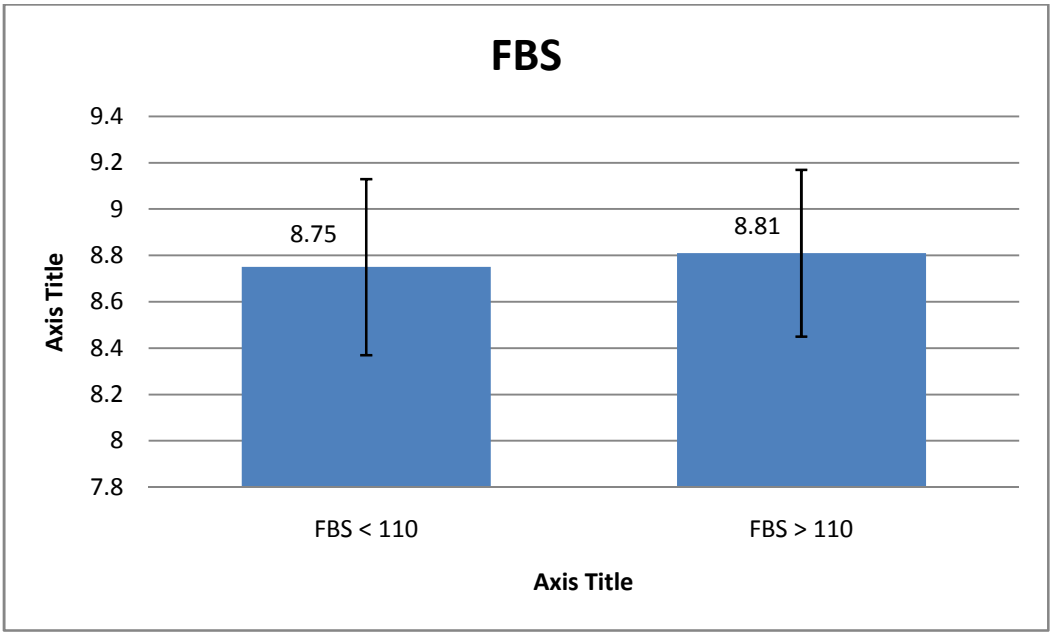
CORRELATION OF MPV ACROSS VARYING LEVELS OF ALBUMINURIA IN DIABETES PATIENTS



The mean MPV in A1 group is (8.45± 0.19) which was lower than A2(8.87± 0.37). both groups were lower than A3 (8.99±0.27).statistical significance exists between A1 and other two groups. ($p < 0.0001$) but A2 and A3 does not show any statistical significance by independent t test.

FIGURE 7

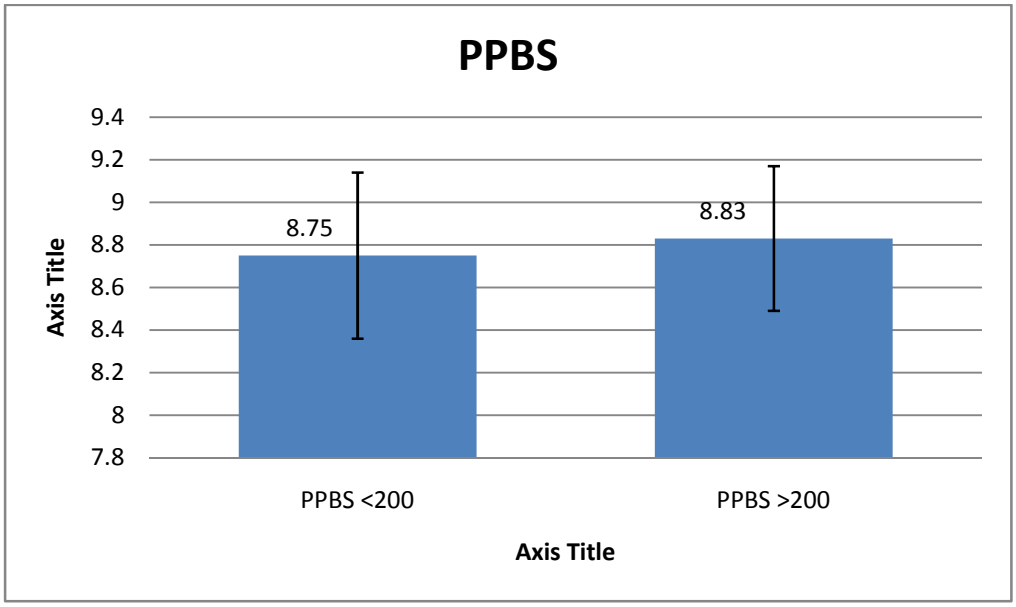
CORRELATION OF MPV WITH FBS



There is no significant correlation between MPV and Fasting blood sugar (p value- 0.236) in diabetes patientsevaen though MPV is slightly higher in patients with FBS more than 110.

FIGURE 8

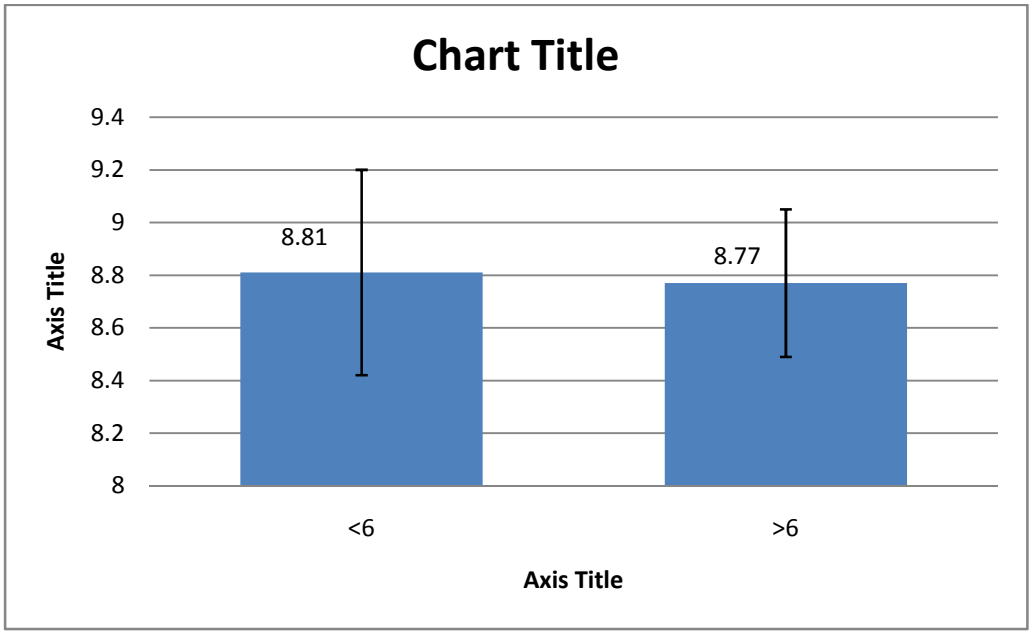
CORRELATION OF MPV WITH PPBS



In diabetes patients with postprandial blood sugar more than 200 MPV is slightly on the higher side but still not statistically significant (p- 0.124)

FIGURE 9

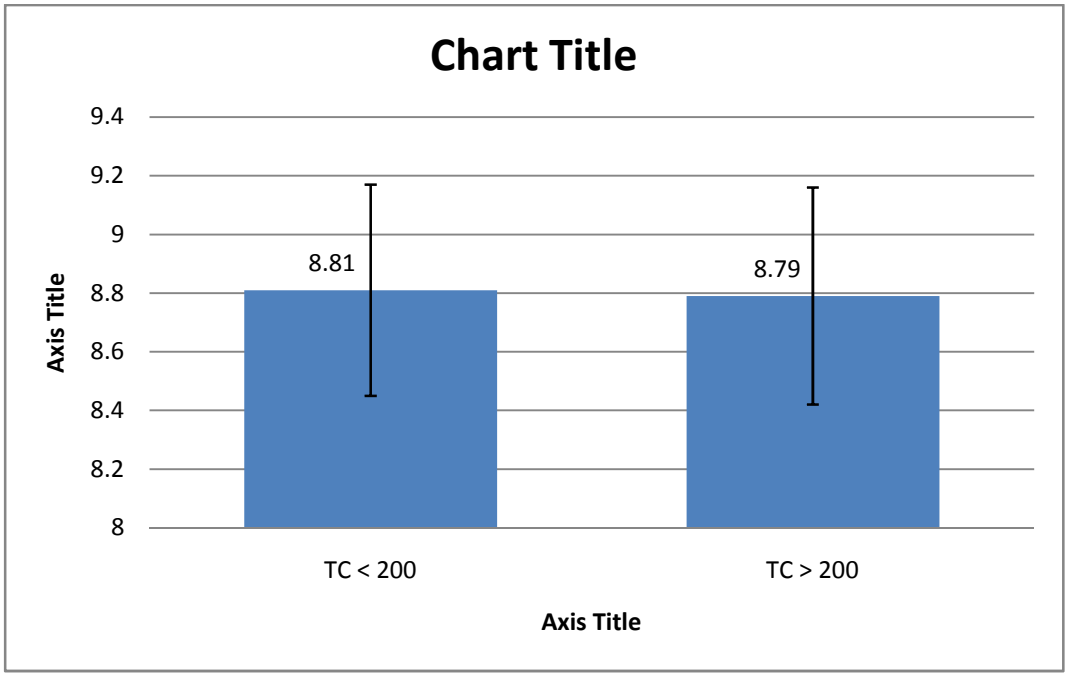
CORRELATION OF MPV WITH DURATION OF DIABETES



There is no correlation between MPV with duration of diabetes (p – 0.648)

FIGURE 10

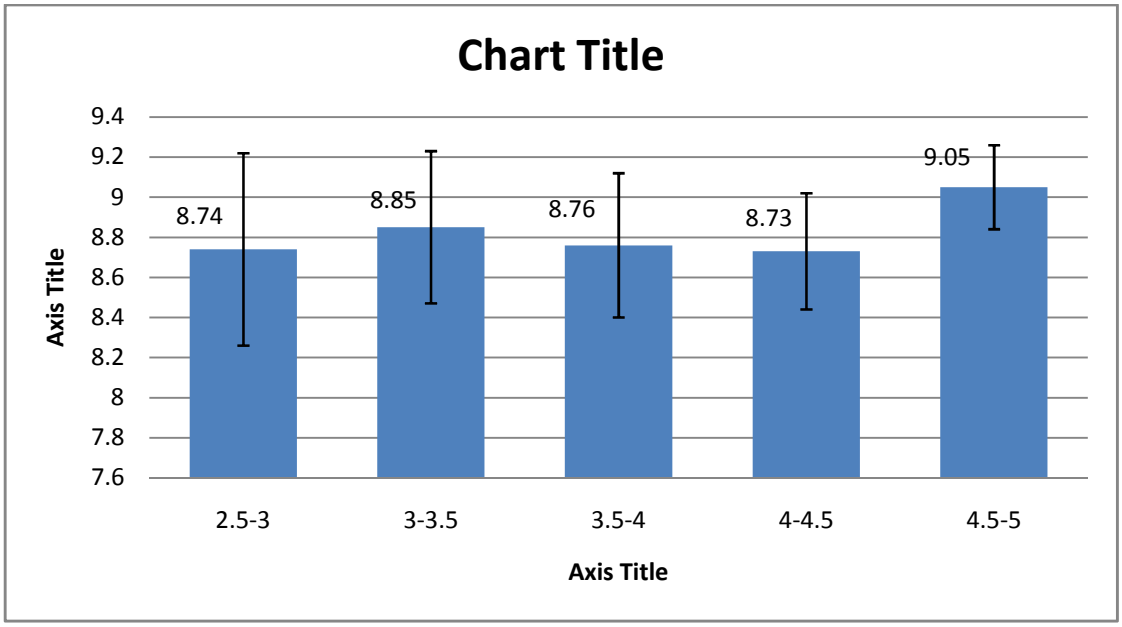
CORRELATION OF MPV WITH TOTAL CHOLESTROL



MPV does not show any statistical significance with cholesterol level (p -0.402)

FIGURE 11

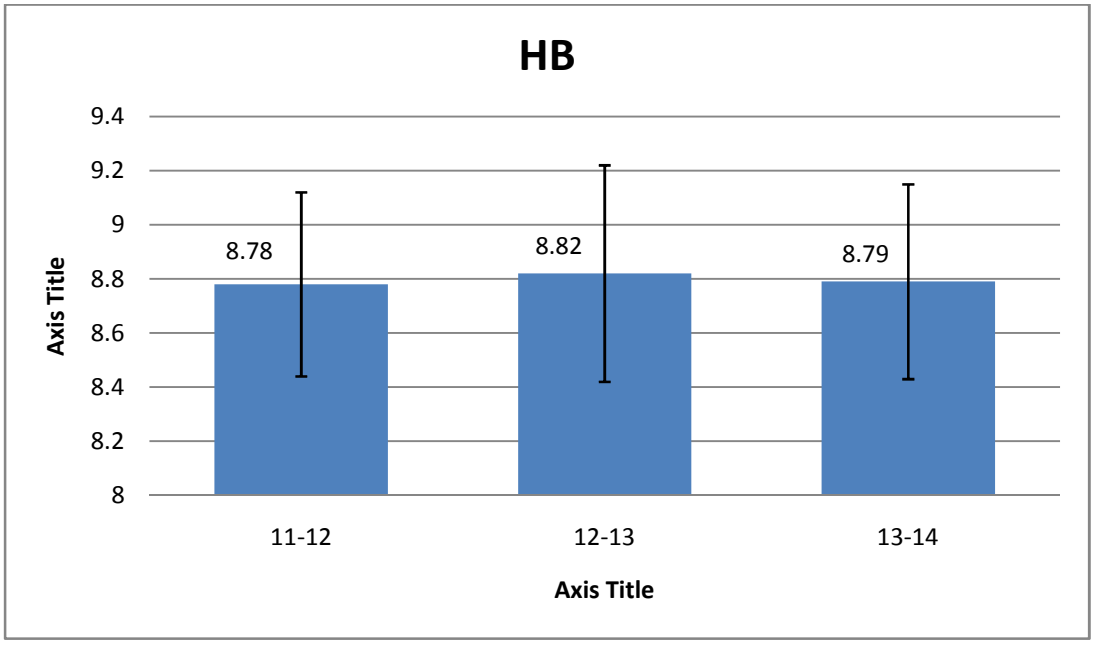
CORRELATION OF MPV WITH PLATELET COUNT



We grouped the patient according to platelet count into five groups. MPV does not show any significant correlation (p -0.122)

FIGURE 12

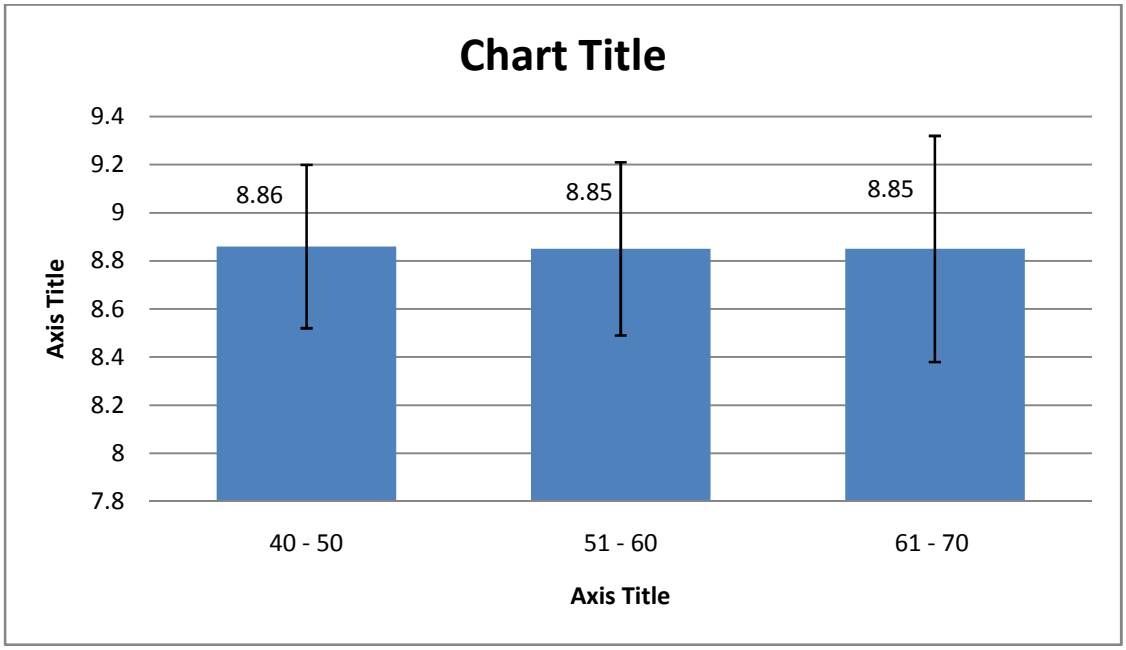
CORRELATION OF MPV WITH HB



There is no signicant correlation between MPV and haemoglobin levels. (p- 0.688)

FIGURE 13

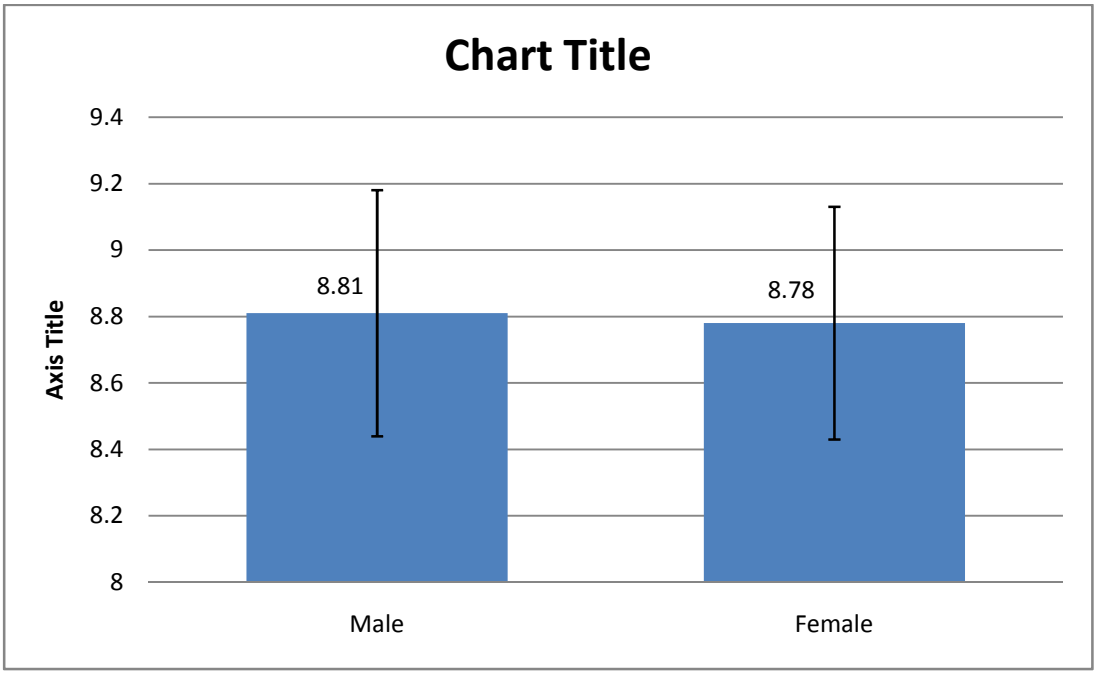
CORRELATION OF MPV WITH AGE OF DIABETES



There is no significant correlation exists between age and MPV in diabetes patients. (p- 0.069)

FIGURE 14

CORRELATION OF MPV WITH GENDER



There is no significant correlation exists between diabetes and gender of the diabetes patients. (p -0.677) even though MPV is slightly higher in males when compared to females.

TABLE 2

CORRELATION OF MPV IN DIABETES PATIENTS AND CONTROLS

	MPV			
	Mean	SD	P value	
Control	7.93	0.24	<**0.0001**	Independent sample t Test
DM	8.8	0.36		

CORRELATION OF MPV ACROSS VARYING LEVELS OF ALBUMINURIA IN DIABETES PATIENTS

	MPV			
	Mean	SD	P value	One way Anova
A1	8.45	0.19		
A2	8.87	0.37	<**0.0001**	Post hoc test Bonferroni
A3	8.99	0.27	<**0.0001**	

CORRELATION OF MPV WITH HbA1c

MPV	Correlation coefficient	P value
HbA1c	0.145	0.174

Pearson correlation test

CORRELATION OF MPV WITH VARIOUS PARAMETERS IN DIABETES PATIENTS

	Correlation coefficient	P value
Age	-0.193	0.069
Gender	-0.045	0.677
BMI	0.215	**0.042**
Duration of DM	-0.049	0.648
Urine albumin creatinine ratio	0.403	**<0.0001**
Platelet count	0.228	0.122
Hemoglobin	-0.043	0.688
HbA1C	0.145	0.174
Total cholesterol	0.089	0.402
Serum Creatininine	0.155	0.145
Fasting Blood Sugar	0.126	0.236
Post Prandial Blood Sugar	0.226	0.124

Pearson correlation test

DISCUSSION

DISCUSSION

Once the platelets gets activated mean platelet volume tends to increase and also changes its disc shape into swollen spheres. Larger platelets have tendency to be more adhesive and aggregative then the smaller ones. They also produce larger amounts of prothrombotic factors.[43,44,45] This increase in mpv, aggregative capacity and large amounts of vasoactive molecule production is previously documented[45,46,47]

The mechanisms causing this has not been clearly defined yet there are theories which suggests that this increase in MPV may be either due to osmotic swelling of megakaryocytes[48] or due to the effect of insulin which forces the platelet to change its structure[49] another postulation is that there will be increased platelet turnover and so the presence of younger megakaryocytes.[50]

High albuminuria (previously microalbuminuria) is one of the earliest indicator of diabetic nephropathy. In our study we aimed at comparing mean platelet volume in controls and diabetics. Also we correlated MPV with various levels of albuminuria and HbA1c levels.

Our study shows that MPV was significantly higher in diabetes patients than controls. This was similar to previous studies.[51-53] In the diabetes patients it was significantly higher in patient with group A2 i.ehigh albuminuria (previously called microalbuminuria) and group A3 i.every high albuminuria (previously called macroalbuminuria) when compared to patients with group A1 i.enormoalbuminuria. Some studies shows higher MPV in patients with microalbuminuria when compared to normoalbumiuria.[46,54,55]

Some other studies fails to show this coorelation of MPV with albuminuria levels[45,56,57]This differences may be due to variations in size of the sample, type of anticoagulation used and other methodological variations such as fasting or fed state. Our study also implies that there is no much difference between group A2 (high albuminuria) and group A3(very high albuminuria) even though both groups have increased MPV.

Unubol, Ayhan, Guney et al showed a significant positive relationship between mean platelet volume and microalbuminuria. Lutfullahcakir, GulaliAktas et al showed that mean platelet volume increases in type 2 diabetes mellitus independent of HbA1c levels[71]

In our study there is no correlation between MPV and HbA1c levels. Various studies has been done which shows the same results[58,59,60,61,62-67] some studies suggests a positive correlation between MPV and HbA1c levels[51,53,61] and also states improvement in glycaemic control leads to decrease in MPV[53,60]kodiatte et al 2012 showed MPV is increased in patients with diabetes and had a positive correlation with fasting blood sugar, post prandial blood sugar and HbA1c levels[68]

Also our study does not show any correlation of MPV with gender and duration of diabetes which is same as previous studies[58,63] This suggests the fact once vascular damage starts it will be constant and continues for the duration of disease independent of both duration and glycaemic control.

Coban et al states MPV was found to have a significant correlation with BMI.[69] It also proves that implementing diet treatment will reduce the MPV[70] Our study also shows a significant positive correlation of MPV with BMI. Many previous studies suggests a conflicting results with MPV and BMI[58,48] We need to do larger studies with more patients to find the correlation.

Study done by turgutalp et al showed significant positive correlation of MPV with serum creatinine and negative correlation with GFR in diabetic nephropathy patients[55] Another study by barbek et al showed that MPV was higher in patients with low creatinine clearance[45] Our study shows no correlation between MPV and creatinine. This was explained by the fact we excluded patient with low GFR.

CONCLUSIONS

CONCLUSIONS

Mean platelet volume is significantly higher in diabetes mellitus patients than healthy controls.

In diabetes mellitus patients, Mean platelet volume is significantly higher in those with high albuminuria (previously microalbuminuria) and very high albuminuria (previously macroalbuminuria) when compared with patients having normoalbuminuria.

It suggests platelet may have a role in causing the vascular complications of diabetes particularly diabetic nephropathy. Mean platelet volume is a simple, easy and affordable investigation. In our study there is a positive correlation exists between MPV and BMI.

Also our study suggests no correlation of mean platelet volume with HbA1c, fasting blood sugar, postprandial blood sugar, serum creatinine, total cholesterol, duration of diabetes, age and sex. Further larger studies are needed to show its correlation in the future.

LIMITATIONS

LIMITATIONS

The presence and absence of other diabetic complications was not analysed in the study.

The study includes only moderate size sample

Effects of the medications such as insulin and oral antihyperglycaemic on MPV was not included in this study.

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ANNEXURES

PROFORMA

MEAN PLATELET VOLUME IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND ITS CORRELATION ACROSS VARYING LEVELS OF ALBUMINURIA AND HBA1C LEVELS

Name : Patient ID :

Age :

Sex :

Duration of diabetes :

H/O chest pain :

H/O claudication pain :

H/O blurring of vision :

H/O chest pain :

Past H/O : h/o CAD , CVA , HTN

Personal H/O : h/o smoking , alcohol

General examination :

- BMI
- BP
- Pallor

Systemic examination :

- CVS
- RS
- ABDOMEN
- CNS

Investigations :

- Mean platelet volume
- Albumin creatinine ratio
- Fasting blood glucose
- Post prandial blood sugar
- HBA1C
- Platelet count
- Total cholesterol
- Haemoglobin
- Sr creatinine

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

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CERTIFICATE OF APPROVAL

To
Dr.Deepan Chakravarthi
Postgraduate M.D.(General Medicine)
Madras Medical College
Chennai 600 003

Dear Dr.Deepan Chakravarthi,

The Institutional Ethics Committee has considered your request and approved your study titled **"Mean Platelet volume in patients with Type 2 diabetes mellitus and its correlation across varying levels of albuminuria and HbA1c levels" No.10052015.**

The following members of Ethics Committee were present in the meeting held on 12.05.2015 conducted at Madras Medical College, Chennai-3.

1. Prof.C.Rajendran, M.D.,	: Chairperson
2. Prof.P.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.B.Vasantha, M.D., Prof. of Pharmacology, MMC	: Member
5. Prof.P.Ragumani, M.S., Professor of Surgery, MMC	: Member
6. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
7. Prof.K.Srinivasagalu, M.D.,Director, I.I.M. MMC, Ch-3	: Member
8. Thiru.S.Rameshkumar, B.Com., MBA	: Lay Person
9. Thiru.S.Govindasamy, B.A., B.L.,	: Lawyer
10. Tmt.Arnold Saumia, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

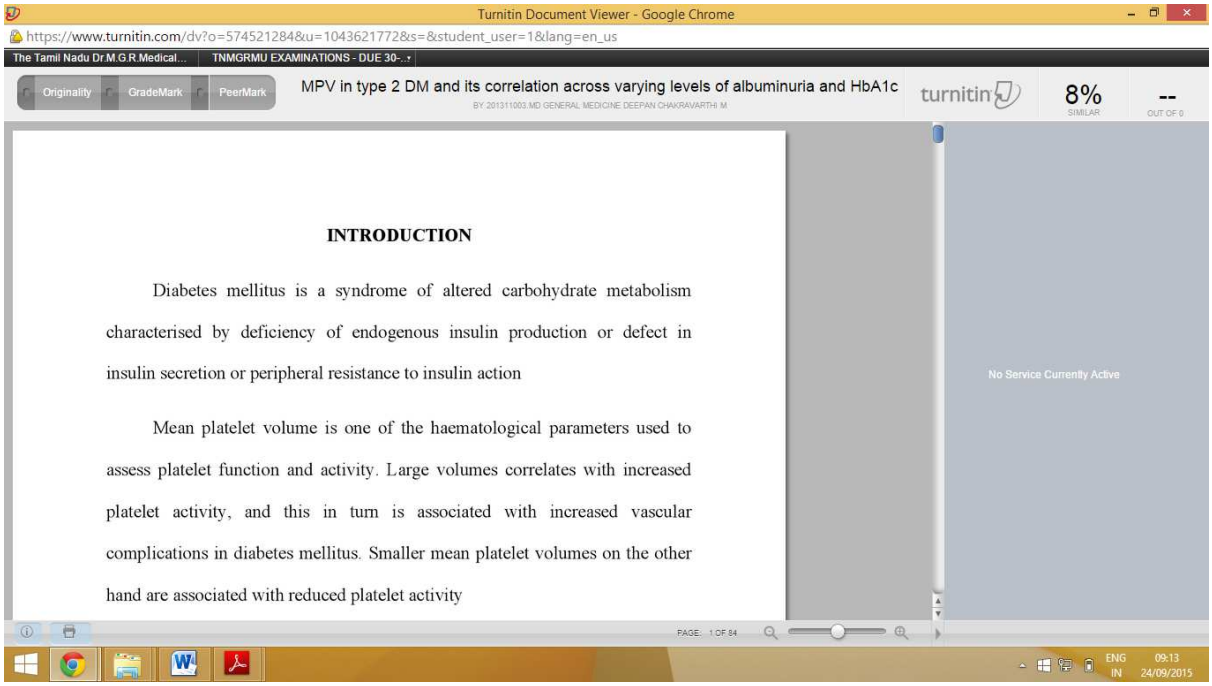
The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

10/6/15

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

TURNITIN PLAGIARISM SCREENSHOT



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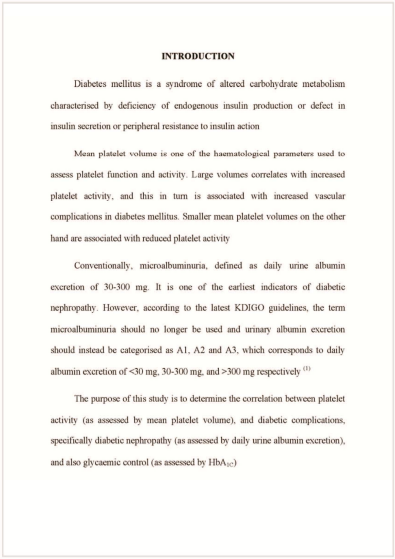

INTRODUCTION

Diabetes mellitus is a syndrome of altered carbohydrate metabolism characterised by deficiency of endogenous insulin production or defect in insulin secretion or peripheral resistance to insulin action

Mean platelet volume is one of the haematological parameters used to assess platelet function and activity. Large volumes correlates with increased platelet activity, and this in turn is associated with increased vascular complications in diabetes mellitus. Smaller mean platelet volumes on the other hand are associated with reduced platelet activity

Conventionally, microalbuminuria, defined as daily urine albumin excretion of 30-300 mg. It is one of the earliest indicators of diabetic nephropathy. However, according to the latest KDIGO guidelines, the term microalbuminuria should no longer be used and urinary albumin excretion should instead be categorised as A1, A2 and A3, which corresponds to daily albumin excretion of <30 mg, 30-300 mg, and >300 mg respectively [1]

The purpose of this study is to determine the correlation between platelet activity (as assessed by mean platelet volume), and diabetic complications, specifically diabetic nephropathy (as assessed by daily urine albumin excretion), and also glycaemic control (as assessed by HbA_{1C})

INFORMATION SHEET

We are conducting a study on **"MEAN PLATELET VOLUME IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND ITS CORRELATION ACROSS VARYING LEVELS OF ALBUMINURIA AND HBA1C LEVELS"** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to assess the mean platelet volume in type 2 Diabetes Mellitus and correlate across varying levels of albuminuria and HbA1C levels.

The following tests:

1. Mean Platelet volume 2. Urine Albumin Creatinine ratio 3. Fasting blood sugar
4. Post Prandial blood sugar 5. HBA1C levels are to be performed.

We are selecting certain cases and if you are found eligible, we may be using your blood samples to do certain tests which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator Signature of Participant

Date:
Place:

ஆராய்ச்சி தகவல் தாள்

சென்னை ராஜீவ்காந்தி அரசு பொது மருத்துவமனையின் பொது மருத்துவத்துறையில் "நீரிழிவு நோயில் இரத்த வட்டுக்களின் கொள்ளளவையும், ஆல்புமினூரியாவின் பல்வேறு நிலைகளையும் ஹீமோகுளோபின் ஏ1சி அளவையும் ஒப்பிட்டு ஆராய்தல்" பற்றிய ஆய்வு நடைபெறுகிறது.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இதனால் தங்களது சிகிச்சையில் பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த ஆய்வில் தங்களுக்கு மருத்துவபரிசோதனை, இரத்த வட்டுக்களின் கொள்ளவு ஆல்புமினூரியா, ஹீமோகுளோபின் ஏ1சி உள்ளிட்ட இரத்தப் பரிசோதனை மற்றும் சிறுநீர் பரிசோதனை செய்யப்படும்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின்போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதை தெரிவித்துக்கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின்பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின்போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :
இடம் :

PATIENT CONSENT FORM

Study Detail : "**MEAN PLATELET VOLUME IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND ITS CORRELATION ACROSS VARYING LEVELS OF ALBUMINURIA AND HBA1C LEVELS**"

Study Centre : Rajiv Gandhi Government General Hospital, Chennai.

Patient's Name :

Patient's Age :

Identification Number :

Patient may check (√) these boxes

a) I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ❑

b) I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

c) I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

d) I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❑

e) I hereby consent to participate in this study. ❑

f) I hereby give permission to undergo detailed clinical examination and blood investigations as required. ❑

Signature thumb impression Signature of Investigator

Patient's Name and Address Study Investigator's Name

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சியின் தலைப்பு

நீரிழிவு நோயில் இரத்த வட்டுக்களின் கொள்ளளவையும், ஆல்புமினூரியாவின் பல்வேறு நிலைகளையும் ஹீமோகுளோபின் ஏ1சி அளவையும் ஒப்பிட்டு ஆராய்தல்

ஆய்வு நிலையம் : பொது மருத்துவத்துறை,
சென்னை மருத்துவக் கல்லூரி சென்னை - 3.

பங்கு பெறுபவரின் பெயர் :

உள்நோயாளி எண் :

பங்குபெறுபவர் இதனை (✓) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கின்றேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன், இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிகிறேன். ☐

இந்த இரு அறுவை சிகிச்சை முறைகளும் ஒப்புக்கொள்ளப்பட்ட முறைகள் என்பதையும் இதனால் உடலுக்கு எந்தவிதமான உபாதைகளும் இருக்காது என்பதை அறிந்துகொண்டு இந்த ஆய்வில் பங்குபெற முழு மனதுடன் சம்மதிக்கிறேன். ☐

பங்கேற்பவரின் கையொப்பம் ..... இடம்..... தேதி.....

இடது கை பெருவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம்..... தேதி.....

ஆய்வாளரின் பெயர் .....

MASTER CHART

PATIENTS WITH DIABETES MELLITUS

Sl.No	Age	Sex	BMI	Duration of diabetes	Investigations									
					Mean platelet volume	Urine albumin creatinine ratio	Albuminuria group	Platelet count	Hemoglobin	HbA1C	Total cholestrol	Serum Creatininine	Fasting Blood Sugar	Post Prandial Blood Sugar
1	62	Male	31.2	8	8.5	20	A1	2.87	13.8	6.4	212	1.2	118	148
2	59	Male	21.6	6	8.4	22	A1	2.73	12.7	7.2	190	0.8	142	198
3	60	Female	30.1	8	8.3	12	A1	3.12	13.4	8.2	234	1.5	234	298
4	54	Male	28.2	5	8.5	13	A1	2.87	11.9	5.5	200	1.3	102	145
5	51	Male	29.2	6	8.7	23	A1	2.76	11.4	6.9	224	1.1	168	198
6	58	Female	32.4	7	8.6	15	A1	3.42	12.9	7.2	286	1.7	168	254
7	56	Female	26.3	6	8.4	21	A1	2.97	13.9	6.4	234	1.1	103	143
8	42	Male	32.4	5	8.4	22	A1	4.23	12.4	7.3	223	1.6	198	254
9	54	Male	34.1	4	8.2	12	A1	3.93	13.4	8.4	254	1.5	204	267
10	56	Female	34.4	3	8.3	14	A1	3.76	11.9	6.3	190	1.3	121	145
11	65	Male	27.8	6	8.5	23	A1	4.21	13.6	7.6	234	1.5	198	265

12	59	Female	32.1	5	8.6	11	A1	3.65	11.6	7.4	222	1.2	197	299
13	58	Male	30.7	6	8.5	15	A1	3.87	12.7	8.3	187	1.7	234	334
14	54	Female	31.4	7	8.4	13	A1	3.98	13.7	5.5	165	1.1	97	132
15	49	Male	32.1	8	8.5	11	A1	3.76	12.7	6.1	187	1.3	113	143
16	47	Female	34.4	11	8.7	16	A1	3.76	11.3	6.4	198	1.3	102	132
17	54	Male	29.7	4	8.9	13	A1	3.54	13.7	7.3	143	0.8	154	198
18	61	Female	28.7	3	7.9	12	A1	3.43	11.2	7.3	203	0.6	176	232
19	46	Male	27.7	5	8.3	11	A1	3.31	12.6	6.3	165	1.3	112	143
20	53	Male	29.4	6	8.4	15	A1	3.34	11.4	6.1	187	1.7	87	132
21	52	Male	29.3	7	8.4	17	A1	3.42	12.7	7.7	234	1.9	198	265
22	51	Male	30.4	6	8.5	18	A1	3.11	13.4	8.1	222	1.5	232	398
23	55	Male	30.7	6	8.6	22	A1	3.17	13.1	6.6	165	1.3	113	175
24	56	Female	30.8	5	8.5	15	A1	4.12	11.9	6.2	187	1.2	117	154
25	46	Male	32.1	4	8.9	45	A2	3.87	13.7	7.3	132	1.7	187	232
26	55	Male	30.5	7	9.2	53	A2	4.43	12.5	7.1	165	1.4	198	265
27	53	Female	33.2	4	9.1	56	A2	3.65	11.8	6.2	187	1.3	112	176
28	54	Male	34.7	5	8.9	54	A2	3.45	12.4	7.1	203	1.6	198	287

29	51	Female	34.1	6	8.5	43	A2	3.56	11.5	7.7	265	1.5	212	324
30	64	Male	32.1	5	9.3	109	A2	4.76	12.7	8.2	235	1.3	287	398
31	52	Male	36.3	6	9.6	232	A2	4.86	13.7	7.2	198	1.3	187	254
32	55	Male	29.6	4	8.3	134	A2	3.36	13.2	6.1	176	1.2	197	236
33	49	Female	28.7	2	8.6	57	A2	3.65	11.1	6.3	186	1.7	132	165
34	47	Male	31.2	1	8.9	87	A2	4.43	13.8	7.2	302	1.4	199	236
35	43	Male	28.7	7	9	68	A2	4.23	12.3	7.1	202	1.9	197	287
36	52	Female	29.6	6	9.2	90	A2	4.12	11.5	7.4	243	1.3	202	298
37	53	Male	29.9	8	9	112	A2	4.13	12.3	8.1	212	1.9	256	387
38	54	Female	28.2	9	9.1	243	A2	4.12	12.2	6.4	176	1.3	154	219
39	52	Male	28.4	12	8.5	256	A2	3.87	11.7	7.1	198	1.2	198	287
40	51	Female	32.3	6	8.9	187	A2	3.12	11.3	7.2	234	1.7	232	287
41	49	Female	32.6	5	8.8	115	A2	3.32	11.9	6.2	154	1.2	112	165
42	54	Female	32.7	6	9	156	A2	3.34	11.3	6.1	176	1.4	86	143
43	55	Female	32.6	4	9.4	143	A2	3.45	11.4	8.2	165	1.5	123	198
44	54	Female	32.6	6	9.2	254	A2	3.65	11.6	7.2	154	1.2	135	234
45	51	Male	32.8	7	9.2	232	A2	3.54	12.6	7.4	176	1.7	232	342

46	43	Male	31.7	5	9.4	124	A2	3.23	12.5	7.1	187	1.3	211	323
47	48	Male	32.9	7	9.2	187	A2	3.21	13.4	7.2	165	1.2	236	343
48	49	Male	32.4	5	9.2	169	A2	3.53	13.3	8.1	176	1.8	276	387
49	52	Female	32.5	9	9	199	A2	3.32	12.5	6.4	176	1.3	132	176
50	51	Male	32.9	2	8.7	232	A2	3.73	13.4	6.1	187	1.2	84	154
51	52	Male	32.6	3	8.8	145	A2	3.21	12.8	6.3	198	1.3	102	143
52	55	Male	32.4	4	8.8	87	A2	3.31	13.4	7.3	345	1.3	165	298
53	53	Male	37	7	8.9	76	A2	3.26	12.7	7.5	365	1.3	212	356
54	53	Male	31.2	6	8.1	112	A2	3.14	12.6	7.3	234	1.8	213	298
55	52	Female	29.6	5	8.5	169	A2	3.12	12.4	6.1	198	1.4	102	143
56	51	Female	25.7	3	8.6	238	A2	3.87	11.2	6.9	176	1.3	121	165
57	51	Male	28.7	5	8.7	234	A2	3.12	12.4	7.1	143	1.9	222	298
58	48	Female	30.8	6	8.1	221	A2	3.11	11.2	6.6	187	1.3	187	254
59	49	Male	29.4	9	8	143	A2	4.34	12.5	6.7	167	1.2	143	198
60	54	Male	28.9	4	8.9	150	A2	4.32	12.2	7.7	198	1.3	198	267
61	52	Male	31.2	4	9.1	434	A3	4.35	11.9	7.2	178	1.5	212	302
62	45	Female	33.3	5	9.2	387	A3	3.98	11.5	6.2	167	1.3	112	165

63	49	Male	31.9	6	8.9	543	A3	3.76	12.5	7.4	154	1.8	198	234
64	51	Female	31.7	5	8.8	487	A3	3.76	12.7	7.2	178	1.7	178	287
65	53	Male	31	3	8.8	587	A3	3.76	12.8	7.7	232	1.1	198	343
66	52	Female	32.9	2	9.1	345	A3	3.54	12.2	8.2	254	0.9	276	443
67	55	Male	29.8	4	9.2	462	A3	3.56	11.9	6.4	345	1.6	123	187
68	53	Male	34.5	5	8.8	543	A3	3.78	11.8	5.9	365	1.7	89	118
69	49	Male	29.3	6	9.2	376	A3	3.76	11.7	6	234	1.8	98	123
70	42	Female	33.1	8	8.9	432	A3	3.43	11.5	7.1	231	1.9	187	285
71	45	Female	32.9	7	9	387	A3	3.36	12.3	7.5	187	1.4	202	298
72	54	Male	27.8	9	9.1	568	A3	4.11	12.5	7.4	235	1.7	245	324
73	53	Male	28.7	8	8.3	678	A3	3.98	12.4	7.2	265	1.9	254	302
74	52	Male	27.6	6	9.1	365	A3	3.26	11.9	7.1	178	1.8	198	287
75	51	Female	32.4	7	9	443	A3	3.58	12.8	8.2	243	1.7	254	443
76	49	Female	33.7	8	8.6	467	A3	3.42	11.7	7.8	187	1.5	276	387
77	48	Male	28.7	4	8.7	543	A3	3.23	11.5	6.5	222	1.4	123	187
78	45	Male	32.1	2	8.9	442	A3	3.76	11.4	6.4	287	1.9	121	176
79	54	Male	33.5	1	8.6	365	A3	3.43	12.7	6.9	302	2.1	145	187

80	55	Female	33.7	5	8.7	387	A3	3.27	13.2	6.4	332	1.9	112	165
81	53	Male	33.5	4	9.3	398	A3	3.18	12.9	6.5	187	1.2	105	156
82	51	Female	33.2	4	9.2	421	A3	3.17	11.7	6.7	176	1.4	143	187
83	46	Male	32.1	6	9	442	A3	3.15	13.2	7.7	176	1.3	187	342
84	45	Female	29.4	5	8.9	467	A3	3.19	11.3	7.4	167	1.9	165	298
85	47	Male	29.7	7	8.9	465	A3	3.45	12.9	7.9	298	1.8	197	387
86	46	Female	29.4	6	9.1	441	A3	3.65	11.3	8.1	287	1.7	232	443
87	55	Female	29.1	5	9.2	442	A3	3.76	11.2	7.5	323	1.9	197	287
88	54	Male	29.3	6	9.7	324	A3	3.87	12.8	7.2	298	1.6	187	278
89	51	Male	28.7	5	9.2	432	A3	3.36	12.7	7.1	345	1.5	167	305
90	52	Male	28.3	6	9.3	543	A3	3.65	12.9	6.2	298	1.5	113	165

CONTROLS

Sl.No	Age	Sex		Duration of diabetes	Investigations									
			BMI		Mean platelet volume	Urine albumin creatinine ratio	Albuminuria group	Platelet count	Hemoglobin	HbA1C	Total cholestrol	Serum Creatininine	Fasting Blood Sugar	Post Prandial Blood Sugar
1	48	Male	29.5		7.7			3.12	11.5		187	1.2	87	132
2	49	Female	24.5		8			3.65	12.5		134	0.9	78	143
3	54	Male	23.6		8.1			3.54	14.3		165	0.7	98	112
4	55	Male	25.8		7.9			3.43	13.7		204	1.4	102	140
5	53	Male	26.4		7.8			4.32	12.9		234	1.3	78	102
6	51	Female	27.3		7.5			4.51	11.3		127	1.1	102	132
7	56	Male	28.4		7.6			2.95	12.5		165	0.7	98	123
8	55	Female	26		7.7			3.23	11.9		187	0.9	87	132
9	54	Male	25.4		8.5			3.43	12.8		198	1	78	123
10	49	Male	24.6		8			4.12	12.8		165	1.2	65	112
11	55	Male	26.2		7.9			3.65	11.9		158	1.9	102	136

12	52	Male	23.4		7.7			3.87	112.4		176	0.7	78	102
13	51	Male	27.8		7.4			4.12	13.9		179	0.9	89	123
14	57	Male	29.2		7.9			4.35	13.4		187	1.2	98	132
15	58	Female	28.7		8			4.76	11.5		234	1.1	86	129
16	48	Male	26.7		8.1			4.65	14.3		176	1.5	79	124
17	49	Male	29		8.2			4.53	13.2		169	1.4	97	134
18	47	Female	28.9		8.2			4.32	11.8		176	1.7	99	132
19	56	Male	27.6		8.2			4.31	13.2		190	1.2	102	136
20	51	Male	27.4		8.1			4.21	12.5		204	1.1	78	103
21	52	Female	27.5		8			3.78	12.3		176	1.2	87	132
22	53	Male	26.4		7.9			3.98	13.5		187	1.4	98	138
23	57	Male	25.7		8.6			3.65	13.1		189	1.3	89	137
24	58	Female	24.7		7.8			3.43	12.4		167	1.2	76	129
25	53	Male	25.8		7.7			3.65	13.6		178	0.8	86	132
26	54	Female	25.3		8			3.87	11.6		165	0.7	97	127
27	55	Male	26.4		7.9			3.21	13.2		176	0.5	104	139
28	57	Female	27.5		7.6			3.54	11.4		168	0.7	95	137

29	53	Female	26.7		7.5			3.65	12.2		187	1.2	86	134
30	52	Male	26.8		7.6			3.53	13.4		169	1.3	76	123
31	49	Male	26.8		7.7			3.65	13.7		158	1.4	84	129
32	47	Male	25.7		7.9			3.23	12.7		178	1.5	83	132
33	49	Male	24.9		8			3.56	12.5		176	1.2	75	129
34	46	Male	25.2		7.9			4.43	12.3		167	0.7	96	138
35	42	Male	25.7		8.1			4.23	12.7		167	0.8	99	139
36	44	Male	25.8		8.2			4.31	13.6		187	1.3	96	137
37	52	Female	25.3		8.3			3.76	12.3		176	1.6	103	129
38	58	Female	26.3		8.1			3.65	11.6		169	1.3	96	127
39	57	Male	26.2		8			3.34	11.6		187	1.3	94	124
40	59	Female	26.1		8.1			4.41	12.4		197	1.8	93	126
41	56	Male	27.2		7.9			4.46	13.2		176	1.6	92	132
42	47	Female	28.3		7.6			4.35	11.6		187	1.5	98	135
43	59	Male	27.5		7.9			4.31	12.5		196	1.3	103	145
44	60	Female	26.9		7.8			2.92	12.4		187	1.2	87	132
45	52	Male	25.4		8			3.12	13.6		197	1.1	98	136

46	48	Female	26.8		8.1			3.76	12.2		186	1.7	86	146
47	47	Female	25.6		8.2			3.54	11.7		178	1.8	75	132
48	52	Male	26.4		8			3.32	12.7		178	1.9	86	126
49	57	Male	26.2		7.8			3.57	13.2		198	0.9	85	128
50	56	Male	26.9		7.9			3.15	14.5		205	0.8	76	132

KEY TO MASTER CHART

S.NO	:	serial number
BMI	:	body mass index
FBS	:	fasting blood sugar
PPBS	:	post prandial blood sugar
A1	:	normo albuminuria (< 30 mg/gm of creatinine)
A2	:	high albuminuria (30- 300 mg/gm of creatinine)
A3	:	very high albuminuria (> 300 mg/gm of creatinine)
TC	:	total cholesterol
HB	:	haemoglobin
PLT	:	platelet count
HBA1C	:	glycated haemoglobin
URINE ACR	:	urine albumin creatinine ratio
MPV	:	mean platelet volume
M	:	male
F	:	female