Review of Literature
HISTORY OF DIABETES MELLITUS

Diseases with the cardinal feature of diabetes mellitus were recognized with antiquity. A polyuric state was described in an Egyptian papyrus dating from 1550 BC discovered by George Ebers and by Aretaeus of Cappadocia in the 2nd century AD. Aretaeus was also the first to use term 'diabetes', from the Greek word for a syphon, 'because the fluid does not remain in the body, but uses the man's body as a channel whereby to leave it'. His graphic account of the disease highlighted the incessant flow of urine, unquenchable thirst, the 'melting down of the flesh and limb into urine', and short survival.23

Few event in the history of medicine are more dramatic than the discover of insulin. Although the approximately attributed to Banting and Best, other provided important observation and techniques that made it possible. In 1869, a German medical student, Paul Langerhans, noted that pancreas contain two distinct group of cells, the acinar cells, which secret digestive enzymes, and cells that are clustered in island, or islet, which he suggested served a second function. Direct evidence for this function came in 1889, when Minkowski and Von mering showed that pancreatectomized dogs exhibit a syndrome similar to diabetes mellitus in humans.
There were numerous attempts to extract the pancreatic substance responsible for regulating blood glucose. In early 1900s, Gurg Zuelzer an pancreas. Although the patient improved temporarily, he sank back into a coma and died when the supply of extract was exhausted. E.L.Scott, a student at the University of Chicago, made another early attempt to isolate an active principle in 1911. Using alcoholic extracts of the pancreas (not so different from those eventually used by Banting and Best), Scott treated several diabetic dogs with encouraging results; however, he lacked clear measures of control of blood glucose concentration, and his professor considered the experiments inconclusive at best. Between 1916 and 1920, the Romanian physiologist Nicolas Paulesco found that injections of pancreatic extracts reduced urinary sugar and ketones in diabetic dogs. Although he published the results of his experiments, their significance was fully appreciated only years later.

Unaware of this work, Frederick Banting, a young Canadian surgeon, convinced J.J.R. Macleod, a professor of physiology in Toronto, to allow his access to laboratory to search for the antidiabetic principle of the pancreas. Banting assumed that the islets secreted insulin but that the hormone was destroyed by proteolytic digestion prior to or during extraction. Together with Charles Best, a fourth-year medical student, he attempted to overcome the problem by ligating the pancreatic ducts. The acinar tissue degenerated leaving the islets undisturbed; the remaining tissue then was extracted with ethanol and acid. Banting and Best thus
obtained a pancreatic extract that decreased the concentration of blood glucose in diabetic dogs.

The first patient to receive the active extracts prepared by Banting and Best was Leinard Thompson, aged 14. He presented by at Toronto general hospital with a blood sugar level of 500gm/dl(28mM). Despite rigid control of his diet (450 kcal/day), he continued to excrete large quantity of glucose, and without insulin, the most likely outcome would be death after a few months. The administration of Bating and Best’s extracts reduces the plasma concentration and urinary extraction of glucose. Daily injections were given. Glucose extraction was reduced from over 100 to as little as 7.5g/day and the patient demonstrated marked clinical importance. Thus replacement therapy with the new discovered hormone, insulin, had what was clearly an otherwise fatal metabolic disorder. Banting and Best faced many trials and tribulations during the subsequent year. It was difficult to obtain active extracts responsibly. This led to a great involvement of Macleod; Banting also sought help from J.B. Collip, a chemist with expertise in extraction and purification of epinephrine. Stable extracts eventually were obtained, and patient in many part of North America soon were being treated with insulin from porcine and bovine sources. Now, as a result of recombinant DNA technology, human insulin is used for therapy.
The noble prize in medicine and physiology was awarded to Banting and Macleod with remarkable rapidity in 1923, and a furor over credit followed Macleod did the same with Collip.\textsuperscript{24}

The oral hypoglycemic agents suitable for clinical use were the sulphonylureas, developed by Auguste Loubatieres in the early 1940's; carbutamide was introduced 1955 and tolbutamide in 1957. The biguanide phenformin became available in 1959, and metformin in 1960.\textsuperscript{23}

The alpha-glucosidase (acarbose and miglitol) became more widely used in the 1980s. The thiazolidinediones were introduced in the 1990s, although troglitazone (Rezulin) was rapidly withdrawn because of hepatic toxicity; however, pioglitazone and rosiglitazone are now in widespread use. Other recent addition include the nonsulphonylureas repaglinide and nateglinide that work through pathways similar to those of the sulphonylureas but have shorter half lives.\textsuperscript{24}

In 1993, Diabetes Control and Complication Trail (DCCT) report is published. The DCCT result clearly demonstrate that intensive therapy (more frequent doses and self-adjustment according to individual activity and eating patterns) delays the onset and progression of long-term complications in individuals with type 1 diabetes.

In 1998, the United Kingdom Prospective Diabetes Study (UKPDS) is published. UKPDS result clearly identify the importance of good glucose
control and good blood pressure control in the delay and/or prevention of complications in type 2 diabetes. (http://www.cljhealth.com)

**EPIDEMIOLOGY**

The world is witnessing an epidemic of diabetes mellitus. Diabetes is an “iceberg” disease. Although increase in both prevalence and incidence of type 2 diabetes has occurred globally, they have been especially dramatic in societies in economic transition, in newly industrialized countries and in developing countries. Currently the number of cases of diabetes worldwide is estimated to be around 150 million. This number is predicted to double by 2025 (a prevalence rate of 5.4%) with the greatest number of cases being expected in China and India. In developing countries about 90% of diabetic is type 2 and less than 5% of all diabetic have type 1 diabetes mellitus.

**ASIA**

Type 2 diabetes (T2D) is one of the most common non-communicable disease in all regions of world. Asia is the exception as the number of people with T2D and obesity continue to increase in region. It is believed that asia will like become the center of this health epidemic, as two of the
most populous countries in the world, China and India, are located in this region.

The rising prevalence of diabetes in developing countries is closely related with industrialization and socio-economic development. It is estimated that 20% of the current global diabetic population resides in South east Asia region. The number of diabetic person in countries of this region is likely to triple by the year 2025 increasing from the present estimates of about 30 to 80 million.

**INDIA**

The prevalence of diabetes in India is currently reported around 13-15% and by 2025 it is estimated that approximately 55 million Indians will be diabetic.

The prevalence of diabetes is approximately twice in urban area than in rural population. The percentage of diabetics’ cases residing in urban area is projected to increase from 54% in 1995 to 73% by the year 2005. The prevalence of disease in adult was found to be 2.4% in rural and 4.0-11.6% in urban dweller.

The prevalence of diabetes is similarly in men and women throughout most age range but is slightly greater in men >60 year.

Its incidence is increasing rapidly and it is estimated that by the year 2030 this number will be double. Diabetes mellitus occur throughout the world but is more common (especially type 2) in the more developed countries. The greatest history in prevalence is however is expected to occur in Asia and Africa, where most patients will likely be found by 2030. The increase in incidence of diabetes in developing countries follow the trend of urbanization and lifestyle change, perhaps most importantly a 'western style' diet.

The most recent study (National Urban Diabetes Survey), carried out in six cities, found age-standardized prevalence rate of 12.1% for diabetes (with a slight male preponderance) and of 14% for IGT; subject under 40 year of age had prevalence of 5% (diabetes) and 13% (IGT). Diabetes was positively associated with increasing age, body mass index (BMI) and waist-hip ratio, and also with a family history of diabetes, a higher monthly income, physical inactivity. IGT showed associations with age, BMI and family history of diabetes. The city of Hyderabad showed the highest rate of both diabetes (17%) and IGT (30%); in Chennai, Mumbai, Bangalore and Hyderabad, the prevalence of IGT exceeded that of diabetes in Kashmir.
until a recent survey aged above 40, among whom diabetes affected 6% (less than one-third were previously diagnosed) and IGT 8%.25

ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS (AMERICAN DIABETIC ASSOCIATION, 2010)

I. Type 1 diabetes (ß-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 special types of diabetes
   A. Genetic defect of ß-cell function characterized by mutations in: Chromosome 12, Chromosome 7, Chromosome 20, Mitochondrial DNA, etc.
   B. Genetic defect in insulin action: Type 1 insulin defect, Leprechaunism, lipodystrophy syndromes, etc.
   C. Disease of the exocrine pancreas: Pancreatitis, Cystic fibrosis, Neoplasia, etc.
D. Endocrinopathies: Acromagaly, Cushing’s syndrome, Glucagonoma, Pheochromocytoma, etc.

E. Drug or other chemical induced: Vacor, Pentamidine, Nicotinic acid, etc.

F. Infection: Congenital rubella, Cytomegalovirus, etc.

G. Uncommon form of immune-mediated diabetes: “Stiff-man” syndrome, Anti-insulin receptor antibodies, etc.

H. Other genetic syndrome sometime associated with diabetes: Down syndrome, klinefelter’s syndrome, Turner’s syndrome, etc.

IV. Gestational diabetes mellitus (GDM)
INSULINE BIOSYNTHESIS, SECRETION, AND ACTION

Biosynthesis

Insulin in the beta cells of pancreatic islets. It is initially synthesized as a single-chain 86-amino-acid precursor polypeptide, preproinsulin. Subsequent proteolytic processing removes the aminoterminal signal peptide, giving rise to proinsulin. Proinsuline is structurally related to insulin like growth factor I and II , which bind weakly to the insulin receptor. Cleavage of an initial 31-residue fragment from proinsulin generates the C peptide and the A (21 amino acids ) and B (30 amino acids ) chains of insulin, which are connected by disulfide bonds. The mature insulin molecule and C peptide are stored together and cosecreted from secretory granules in the beta cells. Because the C peptide is cleared more slowly than insulin, it is a useful marker of insulin secretion and allow discrimination of endogenous and exogenous source of insulin in the evaluation of hypoglycemia. Pancreatic beta cells cosecrete islet amyloid polypeptide (IAPP) or amylin , a 37-aminoacid peptide, along with insulin .The role of IAPP in normal physiological is unclear , but is the major component of the amyloid fibrils found in the islets of patients with type 2 diabetes ,and an analogue is sometimes used in treating both type1 and type 2 DM. human insulin is now produced by recombinant DNA technology; structural alteration at one or
more residues are useful for modifying it physical and pharmalogical characteristics.

SECRETION

Glucose is the key regulator of insulin secretion by the pancreatic beta cell, although aminoacids, ketones, various nutrients gastrointestinal peptides and neurotransmitters also influence insulin secretion. Glucose levels $> 3.9$ mmol/L (70mg/dL) stimulate insulin synthesis, primarily by enhancing protein translation and processing. Glucose stimulation of insulin secretion begin with its transport into the beta cells by the GLUT2 glucose transporter. Glucose phosphorylation by glucokinase is the rate-limiting step that controls glucose regulated insulin secretion. Further metabolism of glucose-6-phosphate via glycolysis generates ATP, which inhibit activity of an ATP-sensitive K+ channel. This channel consist of two separate proteins: one is the binding site for certain oral hypoglycemic (eg. Sulfonylureas, meglitinides); the other is inwardly rectifying K+ channel induces beta cell membrane depolarization, which opens voltage dependent channels (leading to an influx of calcium), and stimulates insulin secretion. Insulin secretory profiles reveal a plusative pattern of hormone release, with small secretory burst occurin about every 10 min, superimposed upon greater amplitude oscillations of about 80-150 min. incretins are released from neuroendocrine cells of the gastrointestinal tract following food ingestion and amplify glucose-stimulated insulin
secretion and suppress glucagon secretion. Glucagon-like peptide 1 (GLP-1), the most potent incretin, is released from L cells in small intestine and stimulates insulin secretion only when the blood glucose is above the fasting level. Incretin analogues, such as exenatide, are being used to enhance endogenous insulin secretion.

ACTION

Once insulin is secreted into the portal venous system, nearly 50% is degraded in liver. Unexpected insulin enter the systemic circulation where it bind to receptors in the target sites. Insulin binding to its receptor stimulates intrinsic tyrosine kinase activity, leading to autophosphorylation and the recruitment of intracellular signaling molecules, such as insulin receptor substrates (IRS). IRS and other adaptor proteins initiate a complex cascade of phosphorylation reactions resulting in the widespread metabolic and mitogenic effects of insulin. As an example, activation of the phosphatidyl inositol-3-kinase (PI-3-kinase) pathway stimulates translocation of glucose transporters (eg. GLUT4) to the cell surface, an event that is crucial for glucose uptake by skeletal muscle and fat. Activation of other insulin receptor signaling pathway induces glucogen synthesis, protein synthesis, lipogenesis, and regulation of venous genes in insulin-responsive cell.

Glucose homeostasis reflects a balance between hepatic glucose production and peripheral glucose uptake and utilization. Insulin is the
most important regulation of this metabolic equilibrium, but neural input, metabolic signals, and other hormones (eg. Glucagon) result in integrated control of glucose supply and utilization. In the fasting state, low insulin level increase glucose production by promoting hepatic gluconeogenesis and glucogenolysis and reduces glucose uptake in insulin-sensitive tissue (skeletal muscle and fat), thereby promoting mobilization of stored precursor such as amino acid and free fatty acid (lipolysis). Glucagon secreted by pancreatic alpha cells when blood glucose or insulin level are low, stimulates gluconeogenesis and glucogenolysis by liver and renal medulla. Postprandial, the glucose load elicit a rise in insulin and fall of glucagon, leading to reversal of the process. Insulin, an anabolic hormone, promotes the storage of carbohydrate and fat and protein synthesis. The major portion of postprandial glucose is utilized by skeletal muscle, an effect of insulin-stimulated glucose uptake. Other tissue, most notably the brain, utilize glucose in an insulin-independent fashion.

Preparation of insulin commonly used are

a) rapid acting insulin like

1) Regular insulin and

2) Insulin analogues – insulin lispro, insuli aspart, insulin glulisine

b) Intermediate acting insulin; NPH insulin

c) Long acting insulin: Insulin Glargine and Insulin Detemir
d) Premixed insulin: 30/70, 50/50, 25/75 ratio of rapid and intermediate acting insulin adverse effect common observed with insulin used are:

- Hypoglycemia
- Weight gain
- Insulin allergy
- Lipodystrophy at the site of injection
- Insulin oedema
- Pain and infection at site of injection

Oral antidiabetic agents:

A) sulfonylurea:

These are most cost-effective glucose lowering agents\(^\text{30}\) and worldwide commonly used antidiabetic drug, increase insulin release from the pancreatic islets\(^\text{27}\).

It has two generation—

1) first generation-tolbutamide, acetohexamide, tolazomide, chlorpropamide.

2) Second generation—glibenclamide, glipizide, gliclazide, glimeperide.
The difference of this two generation primarily in their potency and adverse effect

All of them metabolized in the liver and metabolites are excreted through urine. They have variable elimination half life. 2nd generations have comparatively short half life (3 to 5 hrs), but the hypoglycemic effects evident for 12 to 24 hours, and can be administered once daily dose. The reason for this discrepancies is not clear properly.

Mechanism of action: They inhibit ATP sensitive potassium channel followed by depolarization of the β- cell membrane leading to activation of the voltage sensitive Calcium channel and entry of calcium resulting in release of insulin in the portal blood. This release of insulin is not modified by the plasma glucose and the sulfonylurea thus can cause hypoglycemia. Sulfonylurea reduces the hepatic clearance of insulin and thereby further increase insulin level

Sulfonylurea prime β cell membrane to glucose stimulus, may increase the number of insulin receptors, augement post receptor effect and also may increase insulin sensitivity.

Adverse effect: hypoglycemia, weight gain, hypersensivity reaction (like rash, photosensitivity, agranulocytosis, transient leucopenia), nonspecific side effect (like nausea vomiting, flatulence, diarrhea, headache).
Nonetheless glibenclamide is one of the most commonly prescribed insulin secretagogues, even in the face of concerns about its potential cardiovascular toxicity\textsuperscript{13}

They can cause increased arrhythmic cardiovascular events due to blunting ischemic preconditioning a protective autoregulatory mechanism of the heart. This is a good reason to avoid high dose sulfonylurea\textsuperscript{14}

**b) BIGUANIDE**

It is an oral anti diabetic agent derived from plant Galega Officinalis. First derivative of this kind phenfomin, was discontinued due to its association with lactic acidosis. Metfomin approved by FDA in 1994 long after its appearance in Europe and Canada\textsuperscript{34}

Metformin is absorbed mainly from the small intestine after its oral administration. It is not metabolize in the body, excreted as such through kidney. Half life is 1.5 to 3 hrs.

The mechanism of action of metfomin is unknown. However suggested that it activate the AMP- activated protein kinase, implicated in the stimulation of skeletal muscle glucose uptake and in the inhibition of hepatic gluconeogenesis\textsuperscript{44}. It major clinical activity is to reduce hepatic insulin resistance, reduce gluconeogenesis, improve insulin sensitivity in
peripheral tissues\textsuperscript{31} it does not produce insulin and not related to hypoglycemia even in significant high doses.

The most common adverse effect is gastrointestinal: nausea, diarrhea, abdominal crampy pain and dysgousia. Such symptoms appear early in treatment, better start with low dose early then increase over weeks. At least 90% can tolerate this drug in the longterm treatment. It can cause less weight gain even associated with modest mean weight loss. Lactic acidosis is rare and develop only in high risk cases and not so recommended\textsuperscript{36}.

The antidiabetic action of MET attributed to anorexogenic effect, inhibition of intestinal absorption glucose, prevention of hepatic gluconeogenesis, increase the number of insulin receptors, increase the GLUT-4 glucose transports in insulin sensitive tissue.

According to ADA metformin should be initiated in all pts with t2dm, absent contraindications, at or near the time of diagnosis of diabetes\textsuperscript{37}.

Maximal dose of metformin is 2550mg\textsuperscript{31}

c) Thiazolidinedione

Thiazolidinediones were discovered in the late 1970s during screening for lipid-lowering agents. Ciglitazone was original compound noted to reduce hyperglycemia, hyperinsulinemia, and hypertriglyceridemia in rodent
model of insulin resistant diabetes. Troglitazone was the first to be marketed and removed from the market due to fatal idiosyncratic hepatic failure⁴⁰. Rosiglitazone and pioglitazone have been approved for the treatment of type2 diabetes since mid-1999⁴³. Thiazolidinedione MOA was discovered after the establishment of their clinical effectiveness. It is ligand of orphan receptor PPAR⁴¹. This receptor is a member of the nuclear receptor superfamily of ligand-activated transcription factors. It is a heterodimer consisting of two subunits; one binds thiazolidinediones and that binds retinoids. There are three subtypes of PPARs; PPAR-α, PPAR-δ and PPAR-γ. All three binds with specific response elements of the genes that have central roles in the storage and catabolism of fatty acid. PPAR-a present in liver, ligand is fibrate. PPAR-d is ubiquitous and has profound influence on lipoprotein metabolism. PPAR-g, to which thiazolidinedione binds, becomes activated and attaches to the PPAR-g response elements of genes that contain such element followed by incorporation of activator and inhibitor molecules, gene transcription is either activated or inhibited. PPAR-g responsive genes are numerous and involve the regulation of lipid metabolism, insulin action and adipose tissue differentiation. The major action of TZD are to increase insulin-mediated glucose uptake (decrease in insulin resistance) in muscle and to increase adipogenesis.⁴² PPAR-g receptors are expressed primarily in adipose tissue (>10 fold higher than in muscle), yet major quantitative effect in improving total body insulin sensitivity occurs in muscle. Thiazolidinedione
improve insulin action secondary to a primary action on adipose tissue, and appear to facilitate adiogenesis but in a way that improves insulin sensitivity. PPAR-γ are present in moderate concentration in macrophages, colonic epithelium, endothelial and vascular smooth muscle cells. Pioglitazone rapidly and well absorbed orally, metabolised extensively in liver by CYP4502c8&3a4, 2/3rd dose excreted in feces and 1/3rd in urine. t1/2 of pio and its active metabolites is 16 to 24hrs. can be safely administered in impaired renal function.

Pioglitazone has the capability of modestly reducing triglyceride and associated with modestly elevated HDL particle size and number can improve LDL particle size and number. It is critical to recognize that proven effects of pioglitazone and rosiglitazone to date are limited to improvements in glycemic control and changes in lipid parameters. TZD improve the secretory dynamics in subjects with diabetes and IGT. These observations provide hope for glitazone therapy in diabetes.

Adverse effects: weight gain, fluid retention, anaemia and risk of bone fracture. Weight gain is due to accumulation of fat in subcutaneous tissue and in fact there is reduction of visceral fat, hepatic fat and intramyocellular fat.

The usual dose of PIO is 15-30mg daily and approved as a monotherapy and in combination with metformin, insulin, and sulfonylurea for the treatment of t2dm.
Combination therapy: T2dm is a chronic and disease progressive disease which demands intense management from diagnosis through various stages of the disease. To reduce morbidity the effective treatment of hyperglycemia a top priority.

Combination of therapeutic agents (anti diabetic) are successful in the treatment of T2dm. The dosing of the agents in combination may be same as the agents are used alone. Due to different mechanism of action of the agents, they may produce synergistic effect. For that reason during titration it may be possible to use the lower of maximal dose to reach the desire therapeutic goal.
Insulin resistance: it is resistance to the metabolic effects of insulin and it indicates the presence of an impaired biologic response to either exogenously administered or endogenously secreted insulin, manifested by reduced insulin mediated glucose transport and metabolism in adipocytes and skeletal muscle and by impaired suppression of hepatic glucose output. It includes impaired action of insulin to the

a) Suppressive effects on glucose production
b) Stimulatory effect on glucose uptake and glycogenesis
c) Inhibitory effects on lipolysis

That results in consequent development of impaired glucose intolerance, type 2 diabetes mellitus, hypertension, dyslipidemia, atherosclerosis, cancer ultimately leading to increased mortality and morbidity.

Tissue specific insulin resistance:-

a) Skeletal muscle-- decrease glucose uptake by the muscle and decrease glycogenesis
b) Adipose tissue-- reduced suppression of lipolysis and thereby increase plasma free fatty acid level
c) Liver -- less suppression of gluconeogenesis from free fatty acid and amino acid
d) Brain—though the brain utilize the glucose in non insulin dependent manner; hypothalamus show resistance to the central appetite suppression effect and metabolic effects of insulin.

Contributors to the insulin resistance:-

a) Genetics—there is mutation in insulin receptors, peroxisome proliferator-activated receptor-ζ; and insulin mediated pseudo-acromegaly.
b) Environment—age, increase availability of food, reduced physical activity
c) Obesity—altered ratio of adiponectin, resistin, leptin. Increase release of inflammatory mediator as adipokines like CRP, TNF-α, IL-6, tranformation growth factor-β, monocyte chemoatratant. The relationship between inflammation and insulin resistance is actually causative. Central adipogenesis (intra-abdominal fat) is more strongly linked to insulin resistance because abdominal adipose tissue associated with a) greater component of adrenergic receptor b) resistant to antilipolytic effects of insulin c) high level of 11β-hydroxysteriod dehydrogenase type-I in mesenteric fat—so enhance conversion of inactive cortisone to active cortisol—increased lipolysis and altered production of adipokines.
Effects of insulin resistance: increased secretion of insulin to overcome insulin resistance, followed by β-cell dysfunction, impaired glucose tolerance developed, ultimately leads to type 2 diabetes mellitus.