Modern Review
Introduction: India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the "diabetes capital of the world". The so called "Asian Indian Phenotype" refers to certain unique clinical and biochemical abnormalities in Indians which include increased insulin resistance, greater abdominal adiposity i.e., higher waist circumference despite lower body mass index, lower adiponectin and higher high sensitive C-reactive protein levels. This phenotype makes Asian Indians more prone to diabetes and premature coronary artery disease. At least a part of this is due to genetic factors. However, the primary driver of the epidemic of diabetes is the rapid epidemiological transition associated with changes in dietary patterns and decreased physical activity as evident from the higher prevalence of diabetes in the urban population.

Historical Perspective

For thousands of years, doctors have recognized diabetes is a disease, but did not understand its cause. An early Egyptian medical text written around 1550 B.C., called the Ebers Papyrus, describes a condition of "passing too much urine." The Greek physician Aretaeus, who lived in the second century A.D., gave diabetes its name, for a Greek word meaning "siphon" or "pass through." Aretaeus observed that his patients' bodies appeared to "melt down" into urine.

People observed early on that the urine from people with diabetes was very sweet. In fact, one way to diagnosed diabetes was to pour urine near an anthill. If the ants were attracted to the urine, it means that urine contained sugar. By the 18th century, physician added Latin term mellitus to diabetes, which describes its sugar taste.

Then in 1889 – more than 100 years after glucose was found in blood – German physiologist, Oskar Minkowski and Joseph von Mering, found quite by incident that the pancreas was involved in diabetes. While studying how fat is
metabolized in the body, they describe to remove the pancreas from a laboratory
dog. Much to their astonishment, the dog urinated again and again. Proving that
science rewards a prepared mind, the scientists had the foresight to test the dog's
urine for glucose. Sure enough, the dog had developed diabetes when its
pancreas was removed.

This led the scientists to suspect that some substance in pancreas
somehow prevented diabetes. As scientists embarked on a 30-year quest to find
the magic substance, people with diabetes were suspected to a host of so-called
cures, including bloodletting, opium and special diets. Unfortunately, none of these
measures helped the disease. Although some diets did seem to help some older
people with diabetes, they did nothing for severely affected young patients. These
patients typically died within several years of developing the disease.

Claude Bernard (France, 1845 – 55) made numerous discoveries in the
field of metabolism and diabetes, describing the storages of glucose in the liver as
glycogen and acute hyperglycemia that followed experimental damage to the
medulla oblongata.

In 1893, Edoward Laguesse named the pancreatic islets after Langerhans,
who has described in 1869, and suggests that they produce a glucose lowering
substance. The substance named "Insulin" by Jean de Meyer in 1909, over a
period before its discovery. Insulin was discovered at the University of Toronto in
1921 by Frederick G. Banting (Canada) and his colleague Prof. J.J.R. Macleod, an
authority on carbohydrate metabolism, from extraction of children pancreas in an
acid/ ethanol mixtures and were first tested in a human diabetes patient (Leonard
Thompson) in January, 1922. In 1923, Banting and Macleod were awarded the
Nobel Prize in Medicine for their discovery.

Major advanced in the understanding of diabetes and metabolism have
included understanding of insulin structure (Dorothy Hodkin, 1969), measurement
of insulin by Radio Immune Essay (Solomen Berson and Rosalyn Yalow, 1959),
isoalation of Pro-insulin (Donald steiners group, 1967), identification of specific
insulin receptor (Pierre Freychet and colleagues, 1971), autoimmune basis of
IDDM (Gian Franco Bottazzo etc. 1979).
From the management point of view development of long acting insulin preparation (Hans Christian Hagedornetc, 1936), testing of Sulphonylurea (AugusteLaubaTieres, 1944), first therapeutic use of Biaguanids (G.Unger, 1957). In 1980, WHO agreed diagnosing blood glucose limits for Diabetes and Impaired Glucose Tolerance (IGT).

**IMPORTANT LANDMARK IN THE HISTORY OF DIABETES**
(17th, 18th, 19th century)

<table>
<thead>
<tr>
<th>TIME</th>
<th>RESEARCHER</th>
<th>OBSERVATION</th>
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<tbody>
<tr>
<td>17th century</td>
<td>Thomas Willis (England)</td>
<td>Diabetic urine contains sugar</td>
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<tr>
<td>18th century</td>
<td>Mathew Dobson (England)</td>
<td>Diabetic serum contains sugar</td>
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<tr>
<td>1797</td>
<td>John Rolo (England)</td>
<td>First coin the term Mellitus</td>
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<tr>
<td>1815</td>
<td>Michel Chevereul (France)</td>
<td>Excess glucose found in DM</td>
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<tr>
<td>1857</td>
<td>WilhelmPetters (Germany)</td>
<td>Acetone found in diabetic urine</td>
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<tr>
<td>1869</td>
<td>Paul Langerhans (Germany)</td>
<td>Pancreatic islet identified</td>
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<tr>
<td>1874</td>
<td>Adolf Kussmaul (Germany)</td>
<td>‘Air hunger’ – acidotic breathing in diabetic coma.</td>
</tr>
<tr>
<td>1889</td>
<td>Minkowski and Von Mering (Germany)</td>
<td>Pancreatectomy causes DM in dog.</td>
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**IMPORTANT LANDMARK IN THE HISTORY OF DIABETES**
(20th century)

<table>
<thead>
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<tbody>
<tr>
<td>1907</td>
<td>Jean de Meyer (Belgium)</td>
<td>Hypothetical glucose lowering agent named INSULIN.</td>
</tr>
<tr>
<td>1922</td>
<td>Banting, Best, Macleod, Collip (Canada)</td>
<td>Isolation and first clinical use of insulin.</td>
</tr>
<tr>
<td>1922</td>
<td>Leonard Thompson</td>
<td>First patient successfully treated with insulin</td>
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<tr>
<td>1923</td>
<td>Jr. Murlin (US)</td>
<td>Discovered and named Glucagons.</td>
</tr>
<tr>
<td>1923</td>
<td>Banting and Macleod</td>
<td>Awarded Nobel prize</td>
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<table>
<thead>
<tr>
<th>Year</th>
<th>Name and Location</th>
<th>Contribution</th>
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<tbody>
<tr>
<td>1955</td>
<td>Frederic Sanger (England)</td>
<td>Identified primary structure of insulin</td>
</tr>
<tr>
<td>1969</td>
<td>Dorothy Hodgking (Eng)</td>
<td>Identified 3 dimensional structure of insulin</td>
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<tr>
<td>1959</td>
<td>R Yalow &amp; S Berson (USA)</td>
<td>Developed Radioimmunoassay for insulin</td>
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<tr>
<td>1970</td>
<td>Ralph De Frenzo (USA)</td>
<td>Developed the concept of insulin resistance</td>
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<tr>
<td>1971</td>
<td>Roth et al (USA)</td>
<td>Discovered insulin resistance</td>
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<tr>
<td>1977</td>
<td>Ulrich et al</td>
<td>Insulin gene cloned</td>
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<tr>
<td>1979</td>
<td>Deborah Doniach &amp; Gainfranco Bottazozo</td>
<td>Suggested autoimmune basis of type 1 diabetes.</td>
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PREVALENCE OF DIABETES

Diabetes is one of the most common non-communicable diseases (NCDs). It is the fourth or fifth leading cause of death in most high-income countries and there is substantial evidence that it is epidemic in many economically developing and newly industrialized countries. The epidemiological evidences suggest that the incidence of diabetes is increasing worldwide.

According to the International Diabetic Federation (IDF) as on 2013, about **382 million** people worldwide, or **8.3%** adults, are estimated to have Diabetes. About 80% live in low-and middle-income countries. If these trends continue, by 2035, some **592 million** people, or one adult in 10, will have Diabetes. This equates to approximately three new cases every 10 seconds or almost 10 million per year.

Mortality

Approximately 5.1 million people aged between 20 and 79 years died from diabetes in 2013, accounting for 8.4% of global all-cause mortality among people in this age group. This estimated number of death is similar in magnitude to the combined deaths from several infectious diseases that are major health priorities, and is equivalent to **one death in every six seconds**. Close to half (48%) of deaths due to diabetes are in people under the age of 60. The highest number of deaths due to diabetes occurred in countries with the largest numbers of people with the disease: China, India, USA and the Russia.
Age distribution
The majority of the 382 million people with Diabetes are aged between 40 and 59, and 80% of them live in low-and middle-income countries. All types of Diabetes are on the increase, type 2 diabetes in particular. As on 2013 in India there are 65.1 million of people with Diabetes (20 – 79 years).

Gender distribution
There is little gender difference in the Global numbers of people with diabetes for 2013 or 2035. There are about 14 million more men than women with diabetes (198 million men vs 184 million women).

Urban/rural distribution
There are more people with diabetes living in urban (246 million) than rural (136 million) areas as on 2013 although the numbers for rural areas are on the increase. In low-and-middle income countries, the number of people with diabetes in urban areas is 181 million, while 122 million live in rural areas. By 2035, the difference is expected to widen, with 374 million people living in urban areas and 145 million in rural areas.

Despite the predominantly urban impact of the epidemic, type 2 diabetes is fast becoming a major health concern in rural communities in low-and middle-income countries. No countries are escaping the diabetes epidemic, and in states and territories worldwide it is the poor and disadvantaged who are suffering most. Indigenous communities are among those especially vulnerable to diabetes.

Prevalence as per type of diabetes
Type 2 diabetes accounts for 85 to 95 % of all diabetes in high-income countries and may counts for an even higher percentage in low-and-middle-income countries. In most countries Type 2 diabetes has increased alongside rapid cultural and social changes: ageing populations, increasing urbanization, dietary changes, reduced physical activity and unhealthy behaviors.

Type 1diabetes, although less common than type 2 diabetes, is increasing each year in both rich and poor countries. In most high-income countries, the majority of diabetes in children and adolescents is type 1 diabetes.
Gestational diabetes: Additional 21 million cases of high blood glucose in pregnancy are estimated to contribute to the global burden of diabetes. That is equivalent to 17% of live births to women in 2013 that had some form of high blood glucose in pregnancy.

Prevalence of Impaired Glucose Tolerance

Impaired Glucose Tolerance (IGT), along with impaired fasting glucose (IFG), is recognized as being a stage preceding diabetes when blood glucose levels are higher than normal. Thus, people with IGT are at high risk of developing type 2 diabetes; although all people with IGT do not always go on to develop the disease. In more than one third of people with IGT, blood glucose levels will return to normal over a period of several years.

Some 316 million people worldwide, or 6.9% of adults, are estimated to have IGT. The vast majority (70%) of these people live in low-and-middle-income countries. By 2035, the number of people with IGT is projected to increase to 471 million, or 8.0% of the adult population.

According to the Indian Council of Medical Research-Indian Diabetes study (ICMR-INDIAB), a national diabetes study - 2013, India has 62.4 million people with diabetes. This is set to increase to over 100 million by 2030. The majority of people with diabetes (>90%) have Type 2 diabetes (T2DM). It affects the middle aged working group population and thus poses an even greater threat to the health & wealth of these individuals. This epidemic of diabetes is unfortunately paralleled by a corresponding increase in the prevalence of its complications, both micro vascular and macro vascular, which account for much of the premature morbidity and mortality due to diabetes in India.

DIABETES AND URBAN INDIANS

Diabetes is increasingly afflicting young and affluent urban people in India, reveals a survey of the diseases in 6 metros. The survey found that almost one in every eight person living in a metro is diabetic. Worse, half of them were less than 50 years old and at the peak of their working life. Worryingly, according to the survey, another 14% of metro residents—most of them below the age of 40 years showed a pre-diabetic condition i.e. Impaired Glucose Tolerance (IGT). This
implies that in the next two decades there may be a veritable explosion of the disease in India. In 1970 urban diabetes prevalence was 2.1% and now it is 12%. The prevalence of diabetes was the highest in the urban (12.4%) areas, followed by the midland (8.1%), highland (5.8%) and coastal division (2.5%).

**Diabetes and regional differences**

Epidemiological studies in the 1960's and 1970's using random and post-load blood glucose estimations reported diabetes prevalence varying from 1–4% in urban populations and 1–2% in rural populations. More standardized epidemiological studies since the 1990's reported prevalence rates that vary from 5–15% among urban populations, 4–6% in semi-urban populations and 2–5% in rural populations with large location-based disparities within urban and rural populations. At the turn of this century diabetes in adult urban Indian populations varies from a low of 5.4% in a northern state to a high of 12.3–15.5% in Chennai, South India, and 12.3–16.8% in Jaipur, Central India. Gene-environment interactions appear to be responsible for this rapid increase. The insulin-resistant state that was meant to be protective mechanism for regulation of calorie and fat metabolism at times of famine has turned deleterious as affluence has increased among these populations leading to diabetes epidemic. (Br J Diabetes V Dis 2007)

**Ten top countries for number of people with diabetes (20 – 79 years),**


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<td>98.4</td>
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<td>2. India</td>
<td>65.1</td>
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<td>109.0</td>
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<td>3. USA</td>
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<td>4. Brazil</td>
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<td>7. Indonesia</td>
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<td>10. Japan</td>
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DEFINITION OF DIABETES

Diabetes mellitus is a clinical syndrome with disordered metabolism and inappropriate hyperglycemia due to either an absolute deficiency of insulin or to a combination of insulin resistance and inadequate insulin secretion to compensate. It affects the metabolism of carbohydrate, fat, and protein. The effect of diabetes mellitus includes long term damage, dysfunction and failure of various organs.

INSULIN:

Insulin is a polypeptide (protein) anabolic hormone. It is composed of two amino acid chains connected to each other by disulphide linkages. The mature hormone consists of 51 amino acids and of the two chains, chain A contains 21 amino acids and chain B consist 30 amino acids. Insulin is an anabolic hormone which regulates the metabolism and storage of carbohydrates, proteins and fats. It secreted by islets of Langerhans of pancreas whenever there is abundance of energy giving diets like carbohydrates, proteins and fats.

ANATOMY OF THE ISLETS OF LANGERHANS:

The normal adult pancreas contains around 1-2 million islets. They vary in size from a few dozen cells to several thousands. They are most densely located in the tail region of the pancreas. The major cell types of islets are ‘A’ or α-cell, ‘B’ or β-cell, ‘D’ or δ-cell and ‘F’ or PP-cells secreting glucagons, insulin, somatoatatin and pancreatic polypeptide respectively. Some other islet cells products are pancreastatin, chromastatin and islets amyloid polypeptide. The β-cells constitute about 60% of all the cells of islets. Though the islets constitute only 2-3% of total pancreatic mass, they receive around 20% of the total pancreatic blood flow. In addition there are also rich innervations of islets from the celiac plexus by parasympathetic cholinergic, sympathetic adrenergic nerves.

SYNTHESIS AND SECRETION OF INSULIN:

ASSAY: Insulin is bioassayed by measuring blood sugar depression in rabbits (1 U reduces blood glucose of a fasting rabbit to 45 mg/dl) or by its potency to induced hypoglycemic convulsion in mice. 1 mg of International Standard of insulin is = 28 units. With the availability of pure preparations, it can now be assayed chemically also. Normal insulin secretory function is essential for
maintaining normal glucose tolerance, and abnormal insulin secretion is invariably present in patients with T2DM.

**Quantitation of βeta-cell Function**

The measurement of peripheral insulin concentration by radioimmunoassay is still the most widely used method for qualifying βeta-cell function in vivo. Although this approach provides valuable information, it is limited because 50% to 60% of the insulin produced by the pancreas is extracted by liver without ever reaching the systemic circulation. The standard radioimmunoassay for measuring insulin concentration is also unable to distinguish between endogenous and exogenous insulin, making it ineffective as a measure of endogenous βeta-cell reserve in the insulin-treated diabetic patients. Anti-insulin antibodies that may be present in patients treated with insulin interfere with the insulin radioimmunoassay, making insulin measurement in insulin-treated patients inaccurate. Conventional insulin radioimmunoassay is also unable to distinguish between levels of circulating proinsulin and true levels of circulating insulin.

Insulin is derived from single chain 86-amino acid precursor polypeptide i.e. preproinsulin. Within Golgi bodies of pancreatic Beta-cell, proinsulin is cleaved by converters to form insulin, C peptide, and two paired of basic amino acids. Insulin is subsequently released into the circulation at concentrations equimolar with those of C peptide. In addition, small amounts of intact proinsulin and proinsulin conversion intermediates can be detected in the circulation, where they constitute 20% of total circulating insulin like immunoreactivity. In vivo, proinsulin has a biologic potency that is only about 10% of that insulin, and the potency of split proinsulin intermediates is between that of proinsulin and that of insulin. C peptide has no known conclusive effects on carbohydrate metabolism, although certain physiologic effects of C peptide have been proposed. Unlike insulin, C peptide is not excreted by the liver and is excreted almost exclusively by the kidneys. Its plasma half-life of approximately 30 minutes contrasts sharply with that of insulin, which is approximately 4 minutes.

Because C peptide is secreted in equimolar concentration with insulin and is not excreted by the liver, many investigators have used levels of C peptide as a
marker of beta-cell function. The use of plasma C peptide level as an index of beta-cell function depends on the critical assumption that the mean clearance rate of C peptide is constant over the range of C peptide levels observed under normal physiologic conditions. This assumption has been shown to be valid for dogs and humans, and this approach can be used to derive rates of insulin secretion from plasma concentrations of C peptide under steady-state conditions, however, because of long plasma half-life of C peptide under non-steady-state conditions (e.g. after the glucose infusion), peripheral plasma levels of C peptide do not change in proportion to the changing insulin secretion rate.

**Signaling Pathways in the Beta-cell and Insulin Secretion**

The signaling pathways in the pancreatic beta cell are involved in the stimulus secretion coupling of insulin release. These pathways provide the mechanism whereby insulin secretion rates responds to changes in the blood glucose concentrations. Glucose enters the pancreatic beta cell by a process of facilitated diffusion mediated by the glucose transporter GLUT2. Although levels of GLUT2 on the beta-cell membrane are reduced in diabetic states for various reasons, it is not currently believed that this is a rate-limiting step in regulation of insulin secretion.

The first-limiting step in this process is the phosphorylation of glucose to glucose-6-phosphate. This reaction is mediated by the enzyme glucokinase. There is considerable evidence that glucokinase, by determining the rate of glycolysis, functions as the glucose sensor of the beta cell and that is the primary mechanism by which the rate of insulin secretion adapts to changes in blood glucose. According to this view, as glucose level increase, more glucose enters the beta cell, the rate of glycolysis increases, and the rate of insulin secretion increases. A fall in blood glucose levels results in a fall in the rate of glycolysis and a reduction in the rate of insulin secretion.

Glucose metabolism produces an increase in cytosolic ATP, the key signal that initiates insulin secretion by causing blockade of the K\textsubscript{ATP} channel on the beta-cell membrane. Blockade of this channel induces membrane depolarization, which leads to an increase in cytosolic Ca\textsuperscript{2+} and insulin secretion. The biochemical study of *Lagerstroemia speciosa* (L.) Pers as a Hypoglycemic Agent.
events that link the increase in glycolysis to an increase in ATP are complex. Dukes and co-workers proposed that glycolytic production of NADH during the oxidation of glyceraldehyde-3-phosphate is the key process because NADH is subsequently processed into ATP by mitochondria through the operation of specific shuttle systems.

The rate of pyruvate generation has also been proposed as an explanation for the link between glucose metabolism and increased insulin secretion. According to this view, pyruvate generated by glycolytic pathway enters the mitochondria and is metabolized further in the TCA cycle. Electron transfer the TCA cycle to the respiratory chain by NADH and the reduced from the flavin adenine dinucleotide (FADH$_2$) promotes the generation of ATP, which is exported into the cytosol. The increase in ATP closes ATP-sensitive K$^+$ channels, which depolarizes the beta cell membrane and opens the voltage dependent Ca$^{2+}$ channels leading to an increase in intracellular Ca$^{2+}$; the increase in cytosolic Ca$^{2+}$ is the main trigger for exocytosis, the process by which insulin containing secretory granules fuse with the plasma membrane, leading to the release of insulin into the circulation. The increase in ATP not only closes K$_{ATP}$ channels but also serves as a major permissive factor for movement of insulin granules and for priming of exocytosis.

Cyclic AMP also plays an important role in beta cell signal transduction pathways. This second messenger is generated at the plasma membrane from ATP and potentiates glucose-stimulated insulin secretion, particularly in response to glucagon, glucagon-like peptide 1 (glp1), and gastric inhibitory polypeptide (also known as glucose-dependent insulinotropic peptide (GIP). The cAMP-dependent pathways appear to be particularly important in the exocytotic machinery.

K$_{ATP}$ channel plays an essential role in beta cell stimulus-secretion coupling: an excellent review was published by Aguilar-Bryan and colleagues. K$_{ATP}$ channels include sulfonylurea receptors (SURs) and potassium inward rectifiers (KIR6.1 and KIR6.2), and which assemble to form a large octameric channel with a (SUR/KIR6.x) stoichiometry. In the pancreatic beta cell, the SUR1/KIR6.2 pairs constitute the K$_{ATP}$ channel. K$_{ATP}$ channels control the flux of
potassium ions driven by an electrochemical potential. Opening of these channels can set the resting membrane potential of beta cells below the threshold for activation of voltage-gated Ca$^{2+}$ channels when plasma glucose levels are low, thus reducing insulin secretion. Changes in the cytosolic concentration of ATP and ADP lead to closure of the channels and depolarization of the beta cell membrane. Mutation in both components of beta-cell $K_{ATP}$ (i.e. SUR and KIP6.2) have been shown to lead to hypertension of insulin, resulting clinically in either a recessive form of familial hyperinsulinemia or persistent hyperinsulinemic hypoglycemia of infancy.

**REGULATION OF INSULIN SECRETION**

Glucose is the key regulator of insulin secretion by beta cells of pancreas. In addition other factors like amino acids, lipid derivatives, various nutrients, gastrointestinal peptides and neurotransmitters also stimulate insulin secretion.

Under basal condition ~1 U insulin is secreted per hour by human pancreas. Much larger quantity is secreted after every meal. Secretion of insulin from $\beta$ cells is described below:

**Role of blood glucose level**- When the glucose level is >70 mg/dl (3.9 mmol/L), it stimulates insulin synthesis primarily by enhancing protein translation and processing as well as inducing insulin secretion. Glucose stimulates insulin secretion through a series of regulatory steps that begin with transport into the beta cells by the GLUT 2 glucose transporter. Glucose phosphorylation by glucokinase is the rate limiting step that controls the glucose regulated insulin secretion. The metabolism of glucose-6 phosphate via glycolysis generates ATP, which inhibit the activity of ATP sensitive $K^+$ channel. This inhibition induces $\beta$-cell membrane depolarization, opening of voltage dependent calcium channels leading to an influx of calcium, and stimulation of insulin secretion.

**Role of amino acids**- the excess amino acids in the blood also stimulates insulin secretion. The potent amino acids are arginine and lysine. Without any increase in the blood glucose level, the amino acids alone can cause a slight increase in insulin secretion. However, the amino acids potentiate the action of glucose on the
Factors and conditions which increase/decrease insulin secretion-

<table>
<thead>
<tr>
<th>Increase insulin secretion</th>
<th>Decrease insulin secretion</th>
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<tbody>
<tr>
<td>■ Increased blood glucose</td>
<td>■ Decrease blood glucose</td>
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<tr>
<td>■ Increased free fatty acids</td>
<td>■ Fasting</td>
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<tr>
<td>■ Increased amino acids</td>
<td>■ Somatostatin</td>
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<tr>
<td>■ Gastrointestinal hormones (gastrin, cholecystokinin, secretin, gastric inhibitory peptide)</td>
<td>■ α-adrenergic activity</td>
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<tr>
<td>■ Glucagon, growth hormone, cortisol</td>
<td>■ Leptin</td>
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<tr>
<td>■ Parasympathetic stimulation, acetylcholine</td>
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<tr>
<td>■ β-adrenergic stimulation</td>
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<td>■ Insulin resistance, obesity</td>
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ACTION OF INSULIN:

Insulin is the important hormone that is concerned with regulation of carbohydrate metabolism and blood sugar level. It also concerned with metabolism of proteins and fats.

Carbohydrate metabolism-

i. Transportation and peripheral utilization of glucose-

Insulin is the only metabolic hormone secreted in the body which is anti-diabetic, i.e. the only hormone which reduces blood sugar. After a carbohydrate rich meal, blood sugar level raises leading to secretion of insulin by the pancreas. Now this insulin binding to the receptor stimulates intrinsic tyrosine kinase activity, leading to receptor auto phosphorylation and the recruitment of intracellular signaling molecules, such as intrinsic receptor substrate (IRS) 1 and 2. These and other adaptor proteins initiate a complex cascade of phosphorylation and dephosphorylation reactions, ultimately resulting in widespread metabolic and mitogenic effects of insulin. Activation of the phosphatidylinositol-3 kinase pathway stimulates translocation of glucose transporters (GLUT 4) to the cell surface, which is essential for transportation of glucose into the cells. Insulin promotes the peripheral utilization of glucose, as in presence of insulin glucose inside the cell oxidized immediately.
Chapter 3

ii. Storage of glucose-
Insulin promotes the rapid conversion of glucose into glycogen which is stored in liver and muscles by activating the enzymes which are essential for glycogenesis. In liver when the glycogen content increases beyond its storage capacity, insulin converts glucose into fatty acids.

iii. Inhibition of glycogenolysis-
Insulin prevents the breakdown of glycogen into glucose in muscle and liver.

iv. Inhibition of gluconeogenesis-
Insulin prevents gluconeogenesis by inhibiting the release of amino acids from muscle and by inhibiting the activities of enzymes involved in gluconeogenesis.

Protein metabolism-
Insulin facilitates the synthesis and storage of proteins and inhibits the cellular utilization of proteins. It facilitates the transport of amino acids into the cells from blood by increasing permeability of cell membranes for amino acids. By influencing the transcription of DNA and increasing translation of mRNA, it accelerates the protein synthesis. Insulin prevents catabolism of proteins by decreasing the activity of cellular enzymes.

Fat metabolism-
Insulin stimulates the synthesis of fat. It promotes the transport of excess glucose into the cells particularly liver cells where this glucose is utilized for synthesis of lipids by the insulin activated enzymes. Moreover insulin facilitates the transport of fatty acids into the adipose tissue and storage of fat by inhibiting the enzymes which degrades the triglycerides.

Growth of the body-
Along with growth hormone, insulin promotes growth of body by its actions on the anabolism of protein. It enhances the transportation of amino acids into the cell and synthesis of protein in the cell.
Fate of insulin:

Insulin is distributed only extra-cellularly. It is a peptide; gets degraded in the GIT if given orally. Injected insulin or that released from pancreas is metabolized primarily in liver and to a smaller extent in kidney and muscles. Nearly half of the insulin entering portal vein from pancreas is inactivated in the first passage through liver. Thus liver is normally exposed to a much higher concentration (4 – 8) fold of insulin than are other tissues. As noted above, degradation of insulin after receptor mediated internalization occurs to variable extents in most target cells. During biotransformation the disulfide bonds are reduced – A and B chains are separated. These are further broken down to the constituents amino acids. The plasma t½ is 5– 9 min.

ETIOLOGICAL CLASSIFICATION OF DIABETES MELLITUS: (HPI MED)

The advancement in understanding of the etiology and pathogenesis of diabetes mellitus (DM) has leads to a revised classification rather insisting on the classification based on therapy or age of onset. The present classification is based on the pathogenic process that leads to hyperglycemia are prepared by an international expert committee sponsored by American Diabetes Association and later endorsed by WHO.

Classification of DM based on etiology-

I. Type 1 diabetes (β-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 secretory defect with insulin resistance)

III. Other specific types
   A. Genetic defect of β-cell function characterized by mutation in
      1. Hepatocyte nuclear transcription factor (HNF) 4α (MODY 1)
      2. Glucokinase (MODY 2)
      3. HNF - 1α (MODY 3)
      4. Insulin promoter factor (IPF) 1 (MODY 4)
      5. HNF 1β (MODY 5)
Chapter 3  Modern Review

6. Mitochondrial DNA
7. Proinsulin or insulin conversion.

B. Genetic defect in insulin action
   1. Type A insulin resistance
   2. Leprechaunism
   3. Rabson-Mendenhall Syndrome
   4. Lipotrophic diabetes

C. Disease of the exocrine pancreas
   1. Pancreatitis
   2. Pancreatectomy
   3. Neoplasia
   4. Cystic fibrosis
   5. Hemochromatosis
   6. Fibrocalculuspancreatopathy

D. Endocrinopathies
   1. Acromegaly
   2. Cushing’s syndrome
   3. Glucagonoma
   4. Pheochromocytoma
   5. Hyperthyrodism
   6. Somatostatinoma
   7. Aldosteronoma

E. Drug or Chemical induced
   1. Glucocorticoids
   2. Thyroid hormone
   3. Nicotinic acid
   4. Thiazides
   5. β-adrenergic agonist
   6. α-interferon
   7. Protease inhibitor
   8. Clozapines
   9. β-Blockers
Chapter 3

F. Infection
1. Congenital rubella
2. Cytomegalo virus
3. Coxackie

G. Uncommon forms of Immune-mediated diabetes
1. ‘Stiff-man’ syndrome
2. Anti-insulin receptor antibodies

H. Other genetic syndrome sometimes associated with diabetes
4. Wolfman’s syndrome, etc..

IV. Gestational diabetes mellitus (GDM).

TYPE 1 DIABETES MELLITUS: (API MED)

The type 1 diabetes results from destruction of β cell loss and or severe insulin secretary deficiency, to the extent that these patients require insulin replacement for survival and also to prevent the development of keto acidosis, coma and death. This occurs as a result of synergistic effect of genetic, immunological and environmental factors. This type of severe insulin deficiency is divided in to type 1A and type 1B. Type 1A constitutes 90% of type 1 population and is immune mediated, characterized by islets auto-antibodies (ICA –islet cell antibody, GAD –glutamic acid decacboxylase antibody, IA insulin auto-antibody). Antibodies mediated insulitis leads to selective destruction of the islet β-cells, sparing glucagon producing α-cells of islets. Type 1A diabetes is strongly associated with specific human lecocyte antigen (HLA) alleles and almost always progresses to severe insulin deficiency. Individual with a genetic susceptibility (having HLA DR3/ or D4 haplotype) begins to loose β-cells as the autoimmune process starts, which thought to be triggered by an infection, puberty or environmental stimulus with increase insulin requirement. Often the immunological markers (ICA, GAD Ab, IA) appear after the triggering event and before diabetes is clinically evident and disappears after most of the β-cells are destroyed, inflammatory process abates and the islets become atrophic. The rate of decline of β-cells varies widely among individuals, with some patients progressing rapidly to...
clinical diabetes and others evolving more slowly. Features of diabetes do not become evident until majority of beta cells are destroyed (>80%). After the initial clinical presentation type 1 D.M. "honey moon phase" may ensure during which only highlighted glycemic control is achieved with modest dose of insulin or rarely insulin is needed. However as the residual \( \beta \)-cells destroyed by the autoimmune process, the individual becomes completely insulin deficient.

The risk of developing type 1A diabetes increases ten-fold in relatives (of type 1 diabetes) having haplotypes DQA1 0301, DQB1 0302, DQA1 501 and DQB1 0201. The concordance of type 1 DM in identical twins ranges between 30-70% indicating that additional modifying factors must be involved in determining whether DM develops.

Type 1B DM are those minor group constituting ~10% of type 1 diabetes lacking the evidence of immunological markers indicative of an autoimmune destruction of \( \beta \)-cells. This idiopathic group also characterized by insulin deficiency as well as a tendency to develop ketosis and many of these individuals are either African-American or Asian in heritage.

Certain HLAs are strongly associated with the development of type 1 diabetes. About 95% patients with type 1 diabetes possess either HLA-DR3 or HLA-DR4. HLA-DQ genes are more specific markers of type 1 susceptibility, since a particular variety (HLA-DQB1 *0302) is found in the DR4 patients with type 1, while a "protective" gene (HLA-DQB1 *0602) is often present in the DR4 controls. In addition, most patients with type 1 diabetes at diagnosis have circulating antibodies to islet (islet cell antibodies, ICA), insulin (IAA), glutamic acid decarboxylase (GAD65), and to tyrosine phosphatases (IA-2 and IA2-\( \beta \)). These antibodies facilitate screening of siblings of affected children as well as adults with atypical features of type 2 for an autoimmune cause of their diabetes.

A. Immune-mediated type 1 diabetes mellitus: Immune-mediated type 1 diabetes is believed to result from an infectious or toxic insult to persons whose immune system is genetically predisposed to develop a vigorous autoimmune response either against altered pancreatic B cell antigens or against molecules of the B cell resembling the vital protein (molecular mimicry). Extrinsic factors that

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Study of Lagerstroemia speciosa (L.) Pers as a Hypoglycemic Agent" Page 64
affects B cell function include damaged caused by virus such as mumps or coxsackie B4 virus, by toxic chemical agents, or by destructive cytotoxins and antibodies released from sensitized immunocytes. Specific HLA immune response genes are believed to predisposed patients to a destructive autoimmune response against their own islet cells (auto aggression), which is mediated primarily by cytotoxic T cells. Amelioration of hyperglycemia in patients given an immunosuppressive agent shortly after onset of type 1 diabetes leads further support to the pathogenic role of autoimmunity.

B. **Idiopathic type 1 diabetes mellitus**: Fewer than 10% of subjects have no evidence of pancreatic B cell autoimmunity to explain their insulinopenia and ketoacidosis. This subgroups has been classified as "idiopathic type 1 diabetes" and designated as "type 1B". This diabetes is suspected as homozygous for a mutation in PAX-4 (Arg133Trp) – a gene that is essential for the development of pancreatic islets.

**Pathogenesis of type 1 diabetes**
2. Type 2 diabetes mellitus: (CMDT – 2007)

Type 2 DM is a heterogeneous disorder with a complex etiology that develops in response to genetic and environmental influences. Central to the development of type 2 DM are insulin resistance and abnormal insulin secretion. Though controversy remains regarding the primary defect, most studies support the view that insulin resistance precede insulin secretory defects. Type 2 DM has a strong genetic component and major genes that predispose the disease are yet to be identified. The concordance of type 2 DM in identical twins is between 70-90%. Individual with a parent with type 2 DM have an increased risk of diabetes, if both parents have it; the risk increases up to 40%. Type 2 DM is characterized by three pathophysiologic abnormalities viz. impaired insulin secretion, peripheral insulin resistance, and excess hepatic glucose production. Here hyperglycemia may be associated with hyper insulinemia and β-cell function may be normal or pancreatic islet become unable to sustain the hyper insulinemia produce IGT (Impaired glucose tolerance). Obesity, particularly visceral or central, is very common and the adipocytes secretes a numbers of biological products like leptin, tumour necrosis factor α, free fatty acids etc. modulate the processes such as insulin secretion action, and body weight may contribute to insulin resistance in type 2 DM. In most case of this type of diabetes, the cause is unknown. Attempts to identify genetic markers for type 2 have as yet been unsuccessful, although linkage to a gene on chromosome 2 encoding a cysteine protease, calpain-10, has been reported in a Mexican-American population.

Tissue insensitivity to insulin has been noted in most type 2 patients irrespective of weight and has been attributed to several interrelated factors. These include an undefined genetic factor, which is aggravated in time by additional enhancers of insulin resistance such as aging, a sedentary life style, abdominal - visceral obesity. In addition, there is an accompanying deficiency in the response of pancreatic B cells to glucose. Both the tissue resistance to insulin and the impaired B cell response to glucose appear to be further aggravated by
increased hyperglycemia (glucose toxicity), and both defects are enriched by treatment that reduced the hyperglycemia towards normal.

Patients with this most common form of diabetes have insensitivity to endogenous insulin. When an associated defect of insulin production prevents adequate compensation for this insulin resistance, non-ketotic mild diabetes occurs. Hyperplasia of pancreatic B cells is often present and probably accounts for the fasting hyperinsulinism and exaggerated insulin and proinsulin responses to glucose and other stimuli seen early in the disease.

**Pathogenesis of Type 2 Diabetes Mellitus (T2DM)**

The pathogenesis of T2DM is complex and involves the interaction of genetic and environmental factors. A number of environmental factors have been shown to play a critical role in the development of diseases, particularly excessive calorie intake leading to obesity and a sedentary lifestyle. The clinical presentation is also heterogeneous, with a wide range in age of onset, severity of associated hyperglycemia and degree of obesity. From a pathophysiologic standpoint, persons with T2DM consistently demonstrate three cardinal abnormalities.

1. Resistance to the action of insulin in peripheral tissues, particularly muscle and fat but also liver.
2. Defective insulin secretion, particularly in response to a glucose stimulus.
3. Increased glucose production by the liver.

Recently, it has been suggested that the list of cardinal abnormalities in diabetes should be expanded to eight, adding accelerated lipolysis in the fatty cells, hormone deficiency and resistance, hyperglucagonemia, increased renal tubular reabsorption, and the role of the central nervous system in metabolic regulation.

**Insulin Resistance and the risk of Type 2 Diabetes (T2DM)**

**Insulin Resistance:**

Insulin resistance plays a major role in the development of IGT and finally diabetes. Insulin resistance is a consistent finding in patients with T2MD.

The term insulin resistance indicates the presence of an impaired biological response to either exogenously administered or endogenously secreted insulin.
Insulin resistance is manifested by decreased insulin-stimulated glucose transport and metabolism in adipocytes and skeletal muscle by impaired suppression of hepatic glucose output.

Increased hepatic production of glucose and resistance to the action of insulin in muscle are invariable in obese and non-obese patients with type 2 diabetes. Insulin resistance may be due to any one of three general causes: an abnormal insulin molecule, an excessive amount of circulating antagonists, or target tissue defects and so there is impair glucose utilization by the insulin sensitive tissue. The last is the most common cause if insulin resistance in type 2 diabetes and seems to be the predominant abnormality in those with more severe hyperglycemia.

**Causes insulin resistance**

There are probably several causes of insulin resistance and there is thought to be a strong genetic factor (an inherited component), some medications also can lead to insulin resistance. In addition, insulin resistance is seen often in the following conditions:

- Themetabolic syndrome
- Obesity
- Pregnancy (GDM)
- Infection or severe illness
- Stress
- Duringsteroid use
- Polycystic ovary syndrome (PCOS)

**Obesity and Type 2 Diabetes**

The association of obesity with T2DM has been recognized for decades. A close association between obesity and insulin resistance is seen in all ethnic groups and is found across the full of body weight, across all ages, and in both sexes. A large number of epidemiological studies have shown that the risk of diabetes, and presumably that of insulin resistance, rises as body fat content
increases from very lean to the very obese, implying that the absolute amount of body fat has an effect on insulin sensitivity across a broad range. However, central (intra-abdominal) adiposity is more strongly linked to insulin resistance and to a number of important metabolic variables, including plasma glucose, insulin, total plasma cholesterol and triglyceride concentrations, and decreased plasma high-density lipoprotein (HDL)-cholesterol concentrations, than is total adiposity. In addition, the effect of accumulation of abdominal fat on glucose tolerance is independent of total adiposity.

A number of hypotheses for the reason for the relationship between intra-abdominal fat and abnormal metabolism have been proposed. First, abdominal fat is more lipolytically active than subcutaneous fat, perhaps because of its greater complement of adrenergic receptors. In addition, the abdominal adipose store is resistant to the antilipolytic effects of insulin, including alterations in lipoprotein lipase activity; this leads to increased lipase activity and a greater flux of fatty acids load. Finally, the high levels of 11β - hydroxysteroid dehydrogenase type1 (HSD11B1) in mesenteric fat could result in enhanced conversion of inactive cortisone to active cortisol, resulting in increased cortisol production. This might change adipocytes to increase lipolysis and alter the glucose metabolism.

**Nutrient overload and Insulin resistance**

Cells have developed a number of ways to sense incoming nutrients, including direct and indirect activation of transcription factors and protein kinases. These pathways integrate with incoming hormonal signals to modulate cellular metabolism, increasing anabolic reactions in times of nutrient surfeit and catabolic reactions in postprandial or nutrient deficit states. In a sense, the reaction of different tissues to obesity may be a relatively normal physiologic response to excess nutrient delivery, with prolonged activation leading to unintended and pathologic states that result in insulin resistance, inflammation, and even cell death. A variety of interacting factors functioning within and between tissues determine the final phenotypic response of a person to continued nutrient overload. An
individual can be obese with normal objective findings related to glucose and lipid homeostasis or other cardiovascular risk factors, whereas another person can be only slightly above normal weight ands yet harbor a distinctly abnormal physiology.

**Adipose tissue and Insulin Resistance**

To maintain metabolic homeostasis, nutrient intake exceeding expenditure must be converted to biologic precursors to increase cellular mass or it must be stored. Most excess nutrients whether carbohydrate, protein or lipid are stored as fatty acids in the form of triglyceride in adipose tissue. This storage segregates the excess nutrients in a form that is mobilizable in times of energy deficit. If the storage capacity of adipose tissue is exceeded, lipids and other nutrients enter nonstorage tissues, such as myocytes, hepatocytes, vascular cells, and beta cells, and trigger a variety of adaptive and nonadaptive cellular responses that lead to insulin resistance and cellular dysfunction.

Adipocytes are more than storage cells; they regulate the uptake and release of fatty acids; participates in the glycerol free fatty acid cycle; release leptin and other hormones that signal the energy status of the body and secrete and ever expanding number of cytokines that have hormonal, paracrine and autocrine actions. The adipocytes itself can be adversely affected by accumulation of excess nutrients, leading to the events that can have adverse consequences on the body. As adipocytes surface area increases in obesity, there is increased expression leptin, interleukin(IL-6),IL-8, monocyte chemo attractant protein 1, and granulocyte colony-stimulating factors. These and possibly other cytokines attract pro-inflammatory macrophages(M1 type), which release factors such as tumor necrosis factor (TNF-α) that have local and systemic inflammatory effects.

**mTOR**

The mammalian target of rapamycin (mTOR) may be part of the integration of excess nutrient accumulation and insulin resistance. mTOR is a part of a multisubunit serine/threonine protein kinase complex, called TORC, that integrates...
signalling from the insulin and other growth factor receptors and regulates many cells processes including growth, autophagy, apoptosis, protein synthesis and transcription. The TORC1 complex is activated by growth factors including insulin and insulin-like growth factors as well as nutrients, primarily the essential branched-chain amino acid leucine and fatty acids, the later via formation of phosphatidic acid.

**Unfolded protein response**

In states of over feeding and obesity, evidence for activation of unfolded or malfolded protein response (UPR) can be seen in liver, adipose tissue, pancreatic beta cells, and other tissues. The UPR response to overnutrition is thought to have several effects, including activation of the janus kinase (JNK) and nuclear factors-kB (NF-kB)/inhibitor of kB kinase (IKK) pathways leading to decreased IRS1 (A) activity, increased levels of endogenous inflammatory mediators, alteration in sterol regulatory element-binding protein 1 (SREBP1)-mediated transcription. Reduction in hepatic gluconeogenesis and after prolonged activation, cellular dysfunction and apoptosis.

**Fatty Acids and insulin resistance**

Elevated free fatty acids (FFA) predict the progression from IGT to diabetes. In the periphery FFAs might not be markedly elevated because of efficient extraction by the liver and skeletal muscle. Therefore, normal or minimally elevated FFA levels might not reflect the true exposure of fatty acids to the peripheral tissues. Increased fatty acid flux to skeletal muscle related to increased visceral lipolysis has been implicated in the inhibition of muscle glucose uptake.

**Hyperinsulinemia and insulin Resistance**

Hyperinsulinemia is one of the cause of insulin resistance. Elevated concentrations of insulin can cause insulin resistance by downregulating insulin receptors and desensitizing postreceptor pathways. Del prato and associates showed that 24 and 72 hours of physiologic hyperinsulinemia in normal person
insulin resistance. Other interventions to decrease NTF-α actio result in increased insulin sensitivity.

**Metabolic syndrome (Syndrome X; Insulin resistance syndrome)**

According to the World Health Organization (WHO) have criteria for the metabolic syndrome:

1. **High insulin levels**, an elevated fasting blood glucose or an elevated post meal glucose alone with at least 2 of the following criteria (hyperinsulinemia).
2. **Abdominal obesity** as defined by a waist to hip ratio of greater than 0.9, a body mass index of at least 30 kg/m² or a waist measurement over 37 inches.
3. **Cholesterol** panel showing a triglyceride level of at least 150 mg/dl or HDL cholesterol lower than 35 mg/dl (dyslipidemia).
4. **Blood pressure** of 140/90 or above (or on treatment for high blood pressure) (hypertension).

**Pathogenesis of type 2 diabetes**

![Pathogenesis of type 2 diabetes diagram](image-url)
3. **Other specific types of diabetes mellitus:**

Maturity onset diabetes of young (MODY) – The MODY variety comprises a phenotypically and genetically heterogeneous subtype of DM and is a relatively rare monogenic disorder characterized by non-insulin-dependent diabetes with autosomal dominant inheritance and an age onset of 25 years or younger. Patients are non-obese, and their hyperglycemia is due to impaired glucose-induced secretion of insulin. Five different varieties of MODY, due to mutation in genes encoding islet cell transcription factors of glucokinase have been identified so far.

Abnormalities at their genetic loci on different chromosomes of the β-cell have been identified which causes defect in β-cell and insulin secretion decreased in amount. Some of the gene identified in the insulin receptors of the target cell produced peripheral insulin resistance by subsequent alteration in insulin receptor functions.

Any process that diffusely injures the pancreas (pancreatitis, trauma, pancreatic carcinoma, infection) damage the pancreas leads to precipitation of diabetes. Several hormones (GH, cortisol etc) can cause diabetes after excessive secretion which antagonized insulin action and revolves when the hormone excess is removed.
Somatostatin and aldosterone – induced hypokalemia, can cause diabetes by inhibiting insulin secretion. Many drugs can also impair insulin secretion. The “stiff man syndrome” is an autoimmune disorder of the central nervous system, characterized by stiffness of the axial muscle with painful spasm has high titer of GDA antibody and develops diabetes.

4. **Gestational Diabetes mellitus (GDM):**

Gestational diabetes mellitus is defined as carbohydrate intolerance of any degree with onset or first recognition during pregnancy. Pregnancy is associated with increased tissue resistance to insulin, resulting in increased level of blood insulin as well as glucose and triglycerides. In most of the cases the glucose intolerance returns to normal in post-partum. Glucose metabolism deteriorates to some degree in all pregnant women, only a minority of women develops gestational diabetes. The pathogenesis of vast majority of GDM cases more closely resembles that of type 2 diabetes, i.e. there is defect in β-cell insulin secretion along with insulin resistance. The insulin resistance is probably enhanced due to combined effect of human placental lactogen, estrogen, progesterone, free cortisol and degradation of insulin by the placenta.

The insulin secreting cells of the pancreatic islets may be unable to meet this increased demand in women genetically predisposed to develop either of the primary types of diabetes. The term “gestational diabetes” refers to hyperglycemia occurring for the first time during pregnancy and typically, it presents in the second half of pregnancy and remits after childbirth. It occurs in individuals who have an inherited predisposition to develop diabetes and may take the form of either type 1 or type 2 diabetes. Repeated pregnancy may increase the likelihood of developing permanent diabetes, particularly in obese women. The hyperglycemia may not disappear after delivery. It is associated not only with increased rate of perinatal mortality and neonatal morbidity but also with a high incidence (possibly 80%) of subsequent clinical diabetes (both type 1 & type 2) in the mother. Normalization of metabolism, whether by treatment with dietary measures alone or, more commonly, with additional treatment usually in the form of insulin, undoubtedly reduces the fetal risk of subsequent diabetes is less.
Risk factors for gestational diabetes

1. Older women
2. Women with a history of glucose intolerance
3. Women with a history of large-to-gestational-age babies
4. Women from certain high risk ethnic groups (East Asian, Pacific island ancestry)
5. Women who have had glycosuria during previous pregnancy
6. Women who are overweight or obese
7. Women with a pregnancy complicated by polyhydramnios
8. Women with a family history of DM in first degree relative

Recommendations from 2013 WHO guidelines on diagnosing hyperglycemia in Pregnancy –

Diabetes in pregnancy should be diagnosed if one or more of the following criteria are met:
• Fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dl)
• 2 – hour plasma glucose ≥ 11.1 mmol/L (200 mg/dl) following a 75 g oral glucose load.
• Random plasma glucose ≥ 11.1 mmol/L (200 mg/dl) in the presence of diabetes symptoms.

Gestational diabetes mellitus should be diagnosed at any time in pregnancy if one or more of the following criteria are met:
• Fasting plasma glucose 5.1 – 6.9 mmol/L (92 - 125 mg/dl)
• 2 – hour plasma glucose 8.5 – 11.0 mmol/L (153 - 199 mg/dl) following a 75 g oral glucose load.
DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS:

The diagnosis of diabetes mellitus depends on the measurement of glycaemia. Because plasma glucose concentration ranges as a continuum, the criteria are based on estimates of the threshold for the complication of diabetes. All three tests – fasting plasma glucose (FPG), 2-hour plasma glucose (2-hour PG) and Glycosylated hemoglobin (HbA\textsubscript{1C}) – are able to predict the glucose levels that are diagnostic of diabetes. Furthermore, there is a relationship between elevated levels of all three markers and cardiovascular diseases, although the relationship is generally stronger for HbA\textsubscript{1C}.

<table>
<thead>
<tr>
<th>Test</th>
<th>Normoglycemia</th>
<th>Increased Risk</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Impaired Fasting Glucose</td>
<td>Impaired Glucose Tolerance</td>
</tr>
<tr>
<td>Fasting PG (mg/dl)</td>
<td>&lt;100</td>
<td>100 – 125</td>
<td></td>
</tr>
<tr>
<td>2-hour PG (mg/dl)</td>
<td>&lt;140</td>
<td>140 – 199</td>
<td></td>
</tr>
<tr>
<td>HbA\textsubscript{1C} (%)</td>
<td></td>
<td></td>
<td>5.7 – 6.4</td>
</tr>
<tr>
<td>Random PG (mg/dl)</td>
<td></td>
<td></td>
<td>&gt;200 mg/dL plus symptoms of diabetes</td>
</tr>
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</table>

Although the oral glucose tolerance test (OGTT) is an invaluable tool in research, it is not recommended for routine use in diagnosing diabetes. It is inconvenient for patients and in most cases the diagnosis can be made on the basis of elevated fasting plasma glucose (FPG), 2-hour plasma glucose (2-hour PG), an elevated random glucose and/or elevated Glycosylated hemoglobin % (HbA\textsubscript{1C}) determination in the presence of hyperglycemic symptoms.
## Some essential diagnostic points: (CMDT 2008)

<table>
<thead>
<tr>
<th>Type 1 diabetes</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Polyuria, polydipsia and weight loss associated with random plasma glucose ≥ 200 mg/dl.</td>
<td>• Most patients are over 40 years of age and are obese.</td>
</tr>
<tr>
<td>• Plasma glucose of 126 mg/dl or higher after an overnight fast, documented on more than one occasion.</td>
<td>• Polyuria, polydipsia. Ketonuria and weight loss generally are uncommon at the time of diagnosis. Candidal vaginitis in women may be an initial manifestation. Many patients have few or no symptoms.</td>
</tr>
<tr>
<td>• Ketonemia, ketonuria, or both.</td>
<td>• Plasma glucose of 126 mg/dl or higher after an overnight fast on more than one occasion. After 75 g oral glucose, diagnostic values are 200 mg/dl or more 2 hours after the oral glucose.</td>
</tr>
<tr>
<td>• Islet autoantibodies are frequently present.</td>
<td>• Hypertension, dyslipidemia, and atherosclerosis are often associated.</td>
</tr>
</tbody>
</table>

## Some other laboratory findings:

Other than serum glucose level some other laboratory investigations are done in diabetes, but these are not for diagnostic and usually used for screening/research or therapeutic evaluation.

1. Urine analysis-

   a) Glucosuria :- A specific and convenient method to detect glucosuria is the paper strip impregnated with glucose oxidase and a chromogen system (Clinistix, Diastix), which is sensitive to as little as 0.1% glucose in urine. Diastix can be directly applied to the urinary stream, and differing color response of the indicator strip reflects glucose concentration. For better test for urinary glucose should be performed 1-2 hour after a meal. The greatest disadvantage of using urinary glucose as diagnostic or screening is the individual variation of renal threshold.

   b) Ketonuria :- Ketone bodies in urine can be identified by the nitroprusside reaction, which is primarily specific for acetoacetate and usually carried out using tablet or test papers. Ketonuria is not pathognomic of diabetes, but if associated with glycosuria, the diagnosis of diabetes is practically certain. Although these...
tests do not detect β- hydroxybutyric acid, which lacks a ketone group, the semi quantitative estimation of ketonuria thus obtained is nonetheless usually adequate for clinical purpose.

c) Microalbuminuria : It is defined as the excretion of 30 – 300 mg of albumin in urine per day. It may be noted that microalbuminuria represents and intermediary stage between normal albumin exertion (2.5 – 30 mg/dl) and microalbuminuria>300 mg/dl. The small increase in the albumin excretion predicts impairment of renal function in diabetic patients. Microalbuminuria severs as a signal of early reversible renal damage. Increased microalbuminuria correlates with increased levels of blood pressure and increased LDL cholesterol, and this may explain why increased proteinuria in diabetic patients is associated with an increase in cardiovascular deaths even in the absence of renal failure. ACE inhibitors/ ARBs prevent and decreased the microalbuminuria both in normotensive and hypertensive patients.

2) Glycosylated Hemoglobin (HbA1c):- Hemoglobin becomes glycosylated by ketoamine reactions between glucose and other sugar and the free amine groups on the α and β chains. Only glycation on the N-terminal valine of the beta chain imparts sufficient negative charge to the hemoglobin molecule to allow separation by charge dependant technique. These charge separated hemoglobin's are collectively referred as hemoglobin A1 (HbA1). The major form of HbA1 is hemoglobin A1C (HbA1C) where glucose is the carbohydrate. The hemoglobin A1C fraction is abnormally elevated in diabetic persons with chronic hyperglycemia.

Since glycohemoglobins circulates within the red blood cells whose life span lasts up to 120 days, they generally reflect the state of glycaemia over the preceding 8 – 12 weeks, thereby providing an improve method of assessing diabetic control. The reference ranges is 4-6% and mean plasma glucose levels of 170, 205, 240 and 275 mg/dl approximately correlates with HbA1c values of 7, 8, 9, and 10% respectively. A decline of Glycosylated hemoglobin from elevated initial values by 1% per 10 days indicated sudden and sustained reduction in hyperglycemia. Studies indicated that no subjects whose mean level of HbA1C was
1.1 time upper limit of normal range had retinopathy or increased albuminuria. Measurement of HbA1c has commonly been used to monitor the glycemic control of persons already diagnosed with diabetes. It has a great advantage, that blood specimen can be taken at any time and patient need not for fast. According to American Diabetic Association quarterly HbA1c testing in type 1 and once or twice yearly in type 2 diabetes, is necessary.

3) **Serum fructosamine** :- Measurement of serum fructosamine is a simple and reliable method for the estimation of glycated serum proteins. Serum fructosamine is formed by non-enzymatic glycosylation of serum proteins (predominantly albumin). Since serum albumin has a much shorter half life than hemoglobin. Serum fructosamine generally reflects the state of glycemic control for only the preceding 1 – 2 weeks. Reductions in the serum albumin (eg. Nephritic state or hepatic disease) will lower the serum fructosamine value. When abnormal hemoglobin’s or hemolytic state affect the interpretation of glycohemoglobin or when a narrower time frame is required, such as for ascertaining glycemic control at the time of conception in a diabetic woman who has recently become pregnant, serum fructosamine assays offer some advantage. Any pathological state which decreases the serum protein will also decrease the serum fructosamine level. The normal reference range is 1.5-2.4 mmol/l in relation to serum albumin level 5 g/dl.

4) **Lipoprotein abnormalities in diabetes** :-

Circulating lipoproteins are just as dependant on insulin as is the plasma glucose. In type 1 diabetes, moderately deficient control of hyperglycemia is associated with only a slight elevation of LDL cholesterol and serum triglycerides and little if any change in HDL cholesterol. Once the hyperglycemia is corrected, lipoprotein levels are generally normal. However in obese patients with type 2 diabetes, a distinct “diabetic dyslipidemia” is characteristic of insulin resistance syndrome. Its features are a high serum triglycerides level (300 – 400 mg/dl), a low HDL cholesterol (less than 30 mg/dl), and a qualitative change in the LDL particles, producing a smaller dense particle whose membrane carries supranormal amounts of free cholesterol. These smaller dense LDL particles are more susceptible to oxidation, which renders them more atherogenic. Since low...
HDL cholesterol is a major feature predisposing to macrovascular disease, the term “dyslipidemia” has preempted the term “hyperlipidemia”, which mainly denoted the elevated triglycerides. Measures designed to correct the obesity and hyperglycemia, such as exercise, diet and hypoglycemic therapy, are the treatment of choice for diabetic dyslipidemia, and in occasional patients in whom normal weight was achieved, all features of lipoprotein abnormalities cleared.

**Screening for Type 2 Diabetes Mellitus (T2DM)**

Undiagnosed T2DM is common, accounting for almost 20% of diabetes cases. Subjects at high risk for diabetes and with undiagnosed T2DM are at significantly increased risk for coronary disease, stroke, and peripheral vascular disease. Delay in diagnosis of T2DM causes an increase in microvascular and macrovascular disease. In addition, affected individuals have a greater likelihood of having dyslipidemia, hypertension, and obesity. Therefore, it is important for the clinician to screen for diabetes in a cost-effective manner in subjects who demonstrate major risk factors for diabetes.

<table>
<thead>
<tr>
<th>Major risk factors for Type 2 Diabetes Mellitus</th>
</tr>
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<tbody>
<tr>
<td>• Overweight (BMI ≥25 kg/m²)</td>
</tr>
<tr>
<td>• Physical inactivity</td>
</tr>
<tr>
<td>• First-degree relatives with diabetes</td>
</tr>
<tr>
<td>• Members of a high-risk ethnic population (e.g. African American, Latino, Native American, Asian American, Pacific Islander)</td>
</tr>
<tr>
<td>• Female with a history of delivering a baby weighing &gt;9 lb or diagnosed as GDM</td>
</tr>
<tr>
<td>• Hypertension (≥149/90 mm Hg or under Anti-hypertensive medication)</td>
</tr>
<tr>
<td>• HDL cholesterol level &lt;35 mg/dL or Triglyceride level &gt;250 mg/dL or both</td>
</tr>
<tr>
<td>• Female with polycystic ovarian syndrome</td>
</tr>
<tr>
<td>• Impaired glucose tolerance, or impaired fasting glucose on previous testing</td>
</tr>
<tr>
<td>• History of cardio-vascular diseases</td>
</tr>
<tr>
<td>• Other clinical conditions associated with insulin resistance (e.g. obesity etc)</td>
</tr>
</tbody>
</table>

Study of *Lagerstroemia speciosa* (L.) Pers as a Hypoglycemic Agent
### Summary of Major Recommendation for T2DM Screening

- Testing to detect T2DM and to assess risk for future diabetes should be considered in asymptomatic adults for any age who are overweight or obese (BMI \( \geq 25 \text{ kg/m}^2 \)) and who have one or more additional risk factors for diabetes.
- In those without risk factors for T2DM, testing should begin at the age 35 – 40 years.
- If test results are normal, repeat testing should be carried out at 3 to 5 years interval.
- Any of the following tests is appropriate: HbA\(_{1c}\), FBS, 2-hr 75-gm OGTT
- In those found to have increased risk for future diabetes, identify and, if appropriate, treat other CVD risk factors.

### CLINICAL FEATURE OF DIABETES

The presenting features of diabetes vary widely according to the age, nature of the types, duration of illness and association with the other complaints. Even most of the diabetic patients are asymptomatic and are diagnosed either during routine investigation or when complications are developed. The common symptoms are divided in to two groups:

| Osmotic symptoms-       | • Polyuria,  
|                        | • polydipsia,  
<table>
<thead>
<tr>
<th></th>
<th>• polyphagia.</th>
</tr>
</thead>
</table>
| Non-osmotic symptoms-   | • Weakness,  
|                        | • Fatigue,  
|                        | • Giddiness,  
|                        | • Weight loss,  
|                        | • Blurring of vision,  
|                        | • Muscle pain,  
|                        | • cramps,  
|                        | • Paresthesia,  
|                        | • Itching etc.  |
The early symptoms of untreated diabetes are related to elevated blood sugar levels, and loss of glucose in the urine. High amounts of glucose in the urine can cause increased urine output and lead to dehydration. Dehydration causes increased thirst and water consumption.

The inability of insulin to perform normally has effects on protein, fat and carbohydrate metabolism. Insulin is an anabolic hormone, that is, one that encourages storage of fat and protein. A relative or absolute insulin deficiency eventually leads to weight loss despite an increase in appetite.

Some untreated diabetes patients also complain of fatigue, nausea and vomiting.

Patients with diabetes are prone to developing infections of the urinary bladder, skin, and vaginal areas.

Fluctuations in blood glucose levels can lead to blurred vision. Extremely elevated glucose levels can lead to lethargy and coma.

Though most of the features are common in Type 1 & Type 2 diabetes but there is some variability among the symptoms. Bellow comparisons of the features of both types are given.

<table>
<thead>
<tr>
<th>Features</th>
<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual age of onset (years)</td>
<td>Common between 5-10 yrs may diagnosed at 90 yrs also</td>
<td>36 - 65 years</td>
</tr>
<tr>
<td>Sex</td>
<td>M : F = 1 : 1</td>
<td>F &gt; M (India : M &gt; F)</td>
</tr>
<tr>
<td>Prevalence</td>
<td>1 % in India</td>
<td>90-95% of all diabetics</td>
</tr>
<tr>
<td>Genetic</td>
<td>Hereditary + strong autoantibody to pancreas</td>
<td>Hereditary + no autoantibody</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Non-obese</td>
<td>Often obese</td>
</tr>
<tr>
<td>Usual onset</td>
<td>Rapid</td>
<td>Slow, insidious</td>
</tr>
<tr>
<td>Ketosis</td>
<td>Prone</td>
<td>Rare</td>
</tr>
<tr>
<td>Insulin lack</td>
<td>++++</td>
<td>±</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Rare, secondary if present</td>
<td>+ particularly in obese</td>
</tr>
<tr>
<td>Polyuria and Thirst</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>
Weakness and Fatigue | ++ | +
---|---|---
Polyphagia & weight loss | ++ | -
---|---|---
Recurrent blurred vision | + | ++
---|---|---
Vullovaginitis or pruritus | + | ++
---|---|---
Peripheral neuropathy | + | ++
---|---|---
Nocturnal enuresis | ++ | ±
---|---|---
Often asymptomatic | - | ++
---|---|---
Common cause of death | Nephropathy, CHD, keto-acidosis, hyperglycemia etc | CHD, nephropathy, stroke, gangrene etc

SIGN AND SYMPTOMS (CMDT – 2007)

1. **Type 1 diabetes**: Increase urination is a consequence of osmotic diuresis secondary to sustained hyperglycemia. This results in a loss of glucose as well as free water and electrolytes in the urine. Thirst is a consequence of the hyperosmolar state, as is blurred vision, which often develops as the lenses are exposed to hyperosmolar fluids.

   Weight loss despite normal or increased appetite is a common feature in type 1 when it develops sub acutely. The weight is initially due to depletion water, glycogen, and triglycerides; thereafter reduced muscle mass occurs as amino acids are diverted to form glucose and ketone bodies.

   Lowered plasma volume produced symptoms of postural hypotension. Total body potassium loss and general catabolism of muscle protein contribute to the weakness.

   Paresthesias may be present at the time of diagnosis, particularly when the onset is sub-acute. They reflect a temporary dysfunction of peripheral sensory nerves, which clears as insulin replacement restores glycemic levels closer to normal, suggesting neurotoxicity from sustained hyperglycemia.

   When absolute insulin deficiency is of acute onset, the above symptoms develop abruptly. Keto acidosis exacerbates the dehydration and hyper osmolarity by producing anorexia, nausea and vomiting, interfering with oral fluid replacement.
The patient's level of consciousness can vary depending on the degree of hyperosmolarity. When insulin deficiency develops relatively slowly and sufficient water intake is maintained, patient remains relatively alert and physical findings may be minimal. When vomiting occurs in response to worsening ketoacidosis, dehydration progresses and compensatory mechanisms before inadequate to keep serum osmolarity below 320 – 330 mosm/L. Under these circumstances, stupor or even coma may occur. The fruity breath odor of acetone further suggests the diagnosis of diabetic ketoacidosis.

2. **Type 2 diabetes:** While many patients with type 2 diabetes present with increased urination with thirst, many others have an insidious onset of hyperglycemia and are asymptomatic initially. This is particularly true in obese patients, whose diabetes may be detected only after glycosuria or hyperglycemia is noted during routine laboratory studies. Occasionally, type 2 patients may present with evidence of neuropathic or cardiovascular complications because of occult disease present for some time prior to diagnosis. Chronic skin infections are common. Generalized pruritus and symptoms of vaginitis are frequently the initial complaints of women. Diabetes should be suspected in women with chronic candidal vulvovaginitis as well as in those who have delivered large babies (> 4.1 kg) or have had polyhydramnions, preeclampsia, or unexplained fetal losses.

Standardized tables of waist-to-hip ratio indicate that ratios of “greater than 0.9” in men and “greater than 0.8” in women are associated with and increased risk of diabetes in obese subjects. Mild hypertension is often present in obese diabetics. Eruptive xanthomas on the flexor surface of the limbs and on the buttocks and lipemiatetinalis due to hyperchylomicronemia can occur in patients with uncontrolled type 2 diabetes who also have a familiar form of hypertriglyceridemia.
COMPLICATIONS OF DIABETES MELLITUS:

Diabetes is a disease of complication involves in multi organs. It is two in one disease i.e. there is presence of metabolic abnormalities and vascular complications. Within 7 years of diagnosis of diabetes, there is 5 - 10% prevalence of diabetic renal disease in patient over 40 years of age. CAD mortality 2 - 4 times higher and neuropathy 20 - 80%. In the preinsulin era, infections and ketoacidosis accounted for major cause of mortality in diabetes.

The trend has been changed in last 50 years. Today the major concern is of long term chronic micro and macro vascular complications. Degree of hyperglycemia is most important factor for the incidence of complications.
Acute complications

A. Infections:
   Poor wound healing – foot, skin, other organs.

B. Metabolic:
   - Hypoglycemia (mainly a complication of drug therapy in DM)
   - Diabetic Ketoacidosis (DKA)
   - Hyperosmolar nonketotic coma (HONKC)
   - Lactic acidosis.

Diabetic foot

People with diabetes may develop a number of different foot problems as a result of damage to nerves and blood vessels. These problems can easily lead to infection and ulceration, which increase a person’s risk of amputation. People with diabetes face a risk of amputation that may be more than 25 times greater than that in people without diabetes. However, with proper management, a large proportion of amputation can be prevented. People with diabetes must examine their feet regularly.

DIABETIC KETOACIDOSIS:

Diabetic ketoacidosis (DKA) is one of the most serious acute metabolic complications of diabetes. It was a common cause of death before the introduction of insulin. The patients may present with ketosis, ketoacidosis, ketoacidotic precoma or coma. It occurs typically in untreated patients of type 1 DM with absolute insulin deficiency and also in patients with relative insulin lack such as type 2 DM and inadequately treated type 1 DM.

Pathophysiology: (HPI MED, API MED)

In diabetic ketoacidosis the insulin deficiency is coupled with concomitant elevation of counter regulatory hormones i.e. glucagon, catecholamines, growth hormone & cortisol resulting alteration of normal metabolic homeostasis. This alteration is dominated by catabolic effect of the increased hormones to promote glycolysis, gluconeogenesis, glycogenolysis and inhibition of peripheral glucose utilization and simultaneous acceleration of protein break down and lipolysis. All
these results in hyperglycemia, increased free fatty acid, glycerol, amino acids and lactate. The \( \beta \) oxidation of excess free fatty acids in the liver increases production of ketone bodies namely acetoacetate, betahydrate, betahydroxy butyrate and acetone and results in hyperketonemia. Ketones are strong organic acid which lowers the physiological pH and alters fluid balance of the body. As ketones are fat soluble they excreted through the lungs and produces acetone breath. Thus the hormone metabolic disturbances results in severe and sustained hyperglycemia, ketonemia, aminoacidomia, and lipaemia. The consequence of hyperglycemia and heavy glucosuria is osmotic diuresis and electrolyte loss, producing severe dehydration, hypotension and shock. Normal plasma ketones level is 0.1-0.15 mmol/l and in DKA it increases 15-30 mmol/l.

**Manifestations of diabetic ketoacidosis:** (HPI Med)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Nausea, vomiting, thirst, polyuria, abdominal pain, altered mental function, shortness of breath.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precipitating events</td>
<td>Inadequate insulin administration, infections, and drugs.</td>
</tr>
<tr>
<td>Physical findings</td>
<td>Tachycardia, dry mucous membranes, reduced skin turgor, dehydration, hypotension, tachypnea, Kussmaul respiration, respiratory distress, abdominal tenderness, fever, lethargy, cerebral edema, possibly coma.</td>
</tr>
</tbody>
</table>

**NONKETOTIC HYPEROSMOLAR STATE:**

Hyperglycemic nonketotic hyperosmolar state (NKHS) is an acute metabolic complication seen in middle aged and elderly diabetics. Its most prominent feature include polyuria, orthostatic hypotension and a variety of neurological like altered mental status, lethargy, seizure and possibly coma.

**Pathophysiology:** (HPI MED)

Insulin deficiency and inadequate fluid intake are the underlying causes of NKHS. Insulin deficiency increases hepatic glucose production through glycogenolysis and gluconeogenesis and impairs glucose utilization in skeletal muscle. The raised serum glucose increases osmolality in extra cellular fluid and cause shift of water from intracellular to extracellular space resulting intracellular dehydration. The osmotic diuresis leads to profound intravascular volume loss.
depletion, which is exacerbated by inadequate fluid intake. The absence of ketosis
is probably due to the relative or less severe insulin deficiency and lower level of
counter regulatory hormones like glucagon etc.

**Manifestations of nonketotic hyperosmolar state:** *(API MED)*

Patient typically presents with drowsiness or in confused state or in coma. Polyurea and increased thirst may be present for days or week prior to the development. Profound dehydration, rapid and shallow breathing, elevated osmolality with variable neurological signs like seizure, paresis, muscle fasciculation, hemianopea, nystagmus are the other features.

Below distinguishing features of diabetic ketoacidosis (DKA) and Nonketotic hyperosmolar state (NKHS) are given with comparison.

<table>
<thead>
<tr>
<th></th>
<th>DKA</th>
<th>NKHS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td><strong>Respiration</strong></td>
<td>Hyperventilation, deep</td>
<td>Normal, shallow</td>
</tr>
<tr>
<td><strong>Dehydration</strong></td>
<td>+ to ++</td>
<td>++ to +++</td>
</tr>
<tr>
<td><strong>Consciousness</strong></td>
<td>Diminished</td>
<td>Comatose</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>Normal or low</td>
<td>May be raised</td>
</tr>
<tr>
<td><strong>Blood glucose</strong></td>
<td>&gt;250 mg/dl</td>
<td>&gt;600 mg/dl</td>
</tr>
<tr>
<td><strong>Blood urea</strong></td>
<td>42-70 mg/dl</td>
<td>60-180 mg/dl</td>
</tr>
<tr>
<td><strong>Serum sodium</strong></td>
<td>125-140 mmol/l</td>
<td>130-155 mmol/l</td>
</tr>
<tr>
<td><strong>Serum potassium</strong></td>
<td>3-6.5 mmol/l</td>
<td>3-5 mmol/l</td>
</tr>
<tr>
<td><strong>Bicarbonate</strong></td>
<td>&lt;14 mmol/l</td>
<td>16-30 mmol/l</td>
</tr>
<tr>
<td><strong>Ketones</strong></td>
<td>++ to +++</td>
<td>0 to +</td>
</tr>
<tr>
<td><strong>Osmolality</strong></td>
<td>300-380 mmol/l</td>
<td>350-450 mmol/l</td>
</tr>
</tbody>
</table>

*(API MED 8th ed)*

**Chronic complications of diabetes mellitus:** *(HPI MED)*

The chronic complications of DM affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. Chronic complications are divided mainly into vascular and nonvascular complications. The vascular complications are further subdivided into microvascular and macrovascular.
### Chronic Complication of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Micro vascular</th>
<th>Macro vascular</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye disease</strong></td>
<td><strong>Coronary artery disease (MI)</strong></td>
</tr>
<tr>
<td>• Retinopathy</td>
<td>• Peripheral vascular disease (PVD)</td>
</tr>
<tr>
<td>• Macular edema</td>
<td>• Cerebro vascular disease</td>
</tr>
<tr>
<td>• Cataracts</td>
<td>• Transient ischemic attract</td>
</tr>
<tr>
<td>• Glaucoma</td>
<td><strong>Others</strong></td>
</tr>
<tr>
<td><strong>Neuropathy</strong></td>
<td>• Gastrointestinal (Gastroperesis, diarrhea, constipation etc.)</td>
</tr>
<tr>
<td>• Peripheral polyneuropathy (sensory loss and motor weakness)</td>
<td>• Genitourinary (Uropathy, Sexual dysfunction)</td>
</tr>
<tr>
<td>• Radiculopathy</td>
<td><strong>Nephropathy</strong></td>
</tr>
<tr>
<td>• Mononeuropathy</td>
<td>• Microalbuminuria</td>
</tr>
<tr>
<td>• Amyotrophy</td>
<td>• Macroalbuminuria</td>
</tr>
<tr>
<td>• Autonomic neuropathy (postural hypotension and GI problems etc.)</td>
<td><strong>Foot disease: Ulceration, Athropathy</strong></td>
</tr>
<tr>
<td><strong>Nephropathy</strong></td>
<td><strong>Dematological</strong></td>
</tr>
<tr>
<td>• Microalbuminuria</td>
<td>• Fungal lesion and curbancle</td>
</tr>
<tr>
<td>• Macroalbuminuria</td>
<td><strong>Others</strong></td>
</tr>
<tr>
<td><strong>Mechanism of complications:</strong> (HPI MED)</td>
<td></td>
</tr>
</tbody>
</table>

Although chronic hyperglycemia is an important etiologic factor leading to complication of diabetes, the mechanisms are not clear. Three major theories, which are not mutually exclusive, have been proposed to explain how hyperglycemia might lead to the chronic complications of DM.

1. Formation of advanced glycosylation end products (AGEs) via non-enzymatic glycosylation of cellular proteins.
2. Hyperglycemia increases glucose metabolism via sorbitol pathway.
3. Formation of diacylglycerol leading to activation of certain isoforms of protein kinase C (PCK).
Chapter 3

Pathogenesis:

When glucose level goes high, glucotoxicity occurs. Increased glucose is used by either of two pathways:

**Enzymatic pathway:** Diabetic complications occur in tissue which do not require insulin for glucose uptake, such as kidney, eye, and nerves. When there is hyperglycemia, glucose entered the above mentioned organs. In normoglycemia, the level of glucose and thus the level of sorbitol and fructose are maintained within the cells. Myoinositol competes for glucose and glucose at normal level of glucose; sufficient myoinositol is available within the cells. Increased level of fructose, within the cells, drains water and leads to cellular damage. The pathway for conversion of glucose to sorbitol and fructose is called as the polypol pathway. Increased sorbitol level reduced myoinositol in the cells and it leads to decreased phosphoinositidibiphosphate (PIP₂), and via the diacyl glycerol pathway (DAG) increase the level of protein kinase C (PKC). Thus increased level of PKC inhibits Na⁺K⁺ATPase leading to increased permeability, basement membrane thickening etc. Matrix cells proliferation occurs in all cell responds to hyperglycemia in different i.e.

- Red blood cells → Reduced contractibility → Ischemia of tissue
- Platelet → Platelet hypersensitivity → Increased coagulability
- Glomerular basement membrane → Thickened but not compact / coherent → Leaks of protein.
- Retinal capillaries aneurism (due to loss of pericytes) → Ischemia to retina → Increased fragile neovascularization leads to hemorrhage.

**Non-enzymatic pathway:** This refers to process by which glucose chemically attach to the amino groups of proteins without the aid of enzyme. Glucose forms chemically reversible glycosylation products with protein (named as Schiff bases) that may rearranged to form Amadori type early glycasylated products, which are also chemically reversible. The degree of glycosylation is directly proportional to the blood glucose level. Early glycosylation products on collagen and other long lived protein in interstitial tissues and blood vessel wall leads to formation of irreversible advanced glycosylated end products (AGE). AGE formation occurs
with protein, lipids, nucleic acid and collagen. AGE bind to receptors and many cells type endothelium, macrophages, etc and induced a variety of biological activity.

**Pregnancy complications**

Women with any type of diabetes during pregnancy risk a number of complications if they do not carefully monitor and manage their conditions. Women with diabetes require details planning and close monitoring before and during pregnancy to minimize complications. High blood glucose during pregnancy can lead to fetal abnormalities and cause it to gain excess size and weight, and overproduce insulin. These can lead to problems at delivery, injuries to the child and mother, and a sudden drop in blood glucose (hypoglycemia) in the child after birth. Children who are exposed for a long time to high blood glucose in the womb are at higher risk of developing type 2 diabetes later in life.

**Other complications**

**Oral Health**

Diabetes can pose a threat to oral health. For example, there is an increased risk of inflammation of gum (gingivitis) in people with poor glucose control. Gingivitis in turn is a major cause of tooth loss and may also increase the risk of cardiovascular disease.

**Sleep apnoea**

Recent research demonstrates the likelihood of a relationship between type 2 diabetes and obstructive sleep apnoea. Estimates suggest that up to 40% of people with sleep apnoea have diabetes, although the incidence of new diabetes in people with sleep apnoea is not known. In people with type 2 diabetes, sleep apnoea may have effects on their ability to control blood glucose.
To summarize the consequences of hyperglycemia and involvement of enzymatic and non-enzymatic pathway are shown in the following figures -

**Cellular damage**
- Accumulation of water in the cells
- Reduced Na⁺, K⁺ ATPase
- Decrease PIP₂+PKC
- Decrease Myo-inositol in cells
- Increase sorbitol in cells

**Enzymatic Pathway**
- Aldose reductase

**Hyperglycemia**
- High affinity for O₂ → Hb
- Impaired O₂ delivery
- Ischemia
- Decreased deformability

**Non enzymatic glycosylation of protein**
- Collagen
- LDL, S. albumin
- Decreased clearance
- Increased cholesterol

**Conformation change**
- Lens protein → Cataract

**Neuropathy**
- Leakage

**CV Disease**

**Retinopathy**

Study of Lagerstroemia speciosa (L.) Pers as a Hypoglycemic Agent
### Prevention/treatment

- **Strict glycemic control**
- Diagnosed patient referred for ophthalmological examination at least once in a year.
- Developed retinopathy (early stage) referred for laser photocoagulation therapy.
- Treat high BP etc.
- Improve glycemic control with diet, physical activity, antidiabetic, neural vitamin supplement (B1, B2).
- Prevention is only treatment.

### Findings

- **Peripheral neuropathy**: Numbness, tingling sensation, sharp pain, cramps, joint pain, loss of balance and coordination, changes in autonomic function, postural hypotension, heart palpitations, delayed gastric emptying, gastroparesis, constipation, gastrectomy, diarrhea, UTI, retinopathy.
- **Autonomic neuropathy**: Autonomic functions such as blood pressure regulation, heart rate, digestion, bowel function, urination, sexual function.

### Type 1:

- **181 years**: Acute renal hypertrophy/hyperfunction - Increased GER - polyuria
- **1.5 years**: Normal GFR - Increased BP (1 mm of Hg/year) - No symptoms
- **5.15 years**: Incipient nephropathy - Microalbuminuria (30-300 mg/dl/day)
- **15-25 years**: Overt nephropathy - Proteinuria - Increased BP (5 mm of Hg/year) - Decreased GFR (10 ml/min/year)
- **25-30 years**: End stage renal disease - Decreased GFR, develop CRF. Chest pain, other IHD-like features. Ulceration in the foot, gangrene, infection etc., leads to amputation. (Diabetic foot)

### Pathological Hallmarks

- Retinal vascular Microaneurism
- Neuronal hypoxia
- Fragile neovascularization
- Macular edema
- Decreased myoinositol in neuron
- Narrowing of blood vessels supplying the nerves
- Interaction of soluble factor (growth factor, angiotensin II, endothelin, AGES, etc.)
- Microlumina in renal structural changes in glomeruli
- Formation of atherosclerosis
- Loss of pressure sensation in the foot due to peripheral neuropathy
- Atherosclerotic hypoxia in the periphery
- Altered superficial blood flow due to autonomic neuropathy

### Complication

- **Retinopathy**
- **Neuropathy**
- **Nephropathy**
- **Coronary heart disease (CHD)**
- **Diabetic foot**

### Modern Review

#### GUIDELINE FOR CHRONIC DIABETIC COMPLICATION

<table>
<thead>
<tr>
<th>Findings</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy</td>
<td></td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td></td>
</tr>
</tbody>
</table>

#### Drug therapy for hypertension and elevated cholesterol

- Life style modification
- Drug therapy for hypertension
- Lose weight (if necessary)
- Lower fat, fiber intake
- Antibiotics, antidiabetic, neural vitamin supplement (B1, B2)

#### Prevention measures same as CHD

- Proper foot care, by using fitted shoe, removed any calluses or corns, looks for any abrasions or small ulceration, wear clean socks (not too tight) and regularly check for any growth in the foot after removing of shoe.

---

*Study of Lagerstroemia speciosa (L.) Pers as a Hypoglycemic Agent*
MANAGEMENT OF DIABETES MELLITUS:

The management of diabetes mellitus aims to achieve a good control of several metabolic parameters and a euglycemic state to avoid acute and chronic complications of DM. Diet, exercise, oral hypoglycemic agents, insulin and patients education are the vital aspects which require due consideration in the management of DM.

Exercise increases the effectiveness of insulin, and moderate exercise is an excellent means of improving utilization of fat and carbohydrate in diabetic patients. A judicious balance of the size and frequency of meals with moderate regular exercise can often stabilize the insulin dosages in diabetics who tend to slip out of control easily.

All diabetic patients must receive adequate instruction of personal hygiene, especially with regard to care of the feet, skin and teeth. All infections (especially pyogenic ones) provoke the release of high levels of insulin antagonists such as catecholamines or glucagons and thus bring about a marked increase in insulin requirements. Supplemental regular insulin is often required to correct hyperglycemia during infection.

GOALS OF DIABETES MANAGEMENT: (API MED 8TH ED)

➤ Individualization of treatment regimen.
➤ Achievement of metabolic status at normal or as close to normal as possible, especially blood glucose and lipid concentration.
➤ Achievement and maintenance of normal or reasonable body weight.
➤ Adhere to a sound, realistic and appropriate diet and exercise programme.
➤ Attainment of normal quality of life without symptoms referable to diabetes.
➤ Attainment of utility towards society and family.
➤ Prevention of acute complications and an attempt towards prevention or progression of chronic complications.
➤ Patient’s education for successful long term management.
LIFESTYLE INTERVENTION

The components of lifestyle intervention include nutrition counseling, exercise recommendation and comprehensive diabetic education with the purpose of changing the paradigm of care of diabetes from providers focused to patients focused to get rid of diabetic complications and also improve the quality of life.

Patient Education

Diabetes education may be cost-effective as diabetes is a lifelong disease, and healthcare have almost no controls over the extent to which patients adhere to the day-to-day treatment regimen. The appropriate role of healthcare provider is to serve as a coach to the patient, who has primary responsibility for the delivery of daily care. As a result, health care providers must carefully engage patients as partners in the therapeutic process. It is critical for the healthcare professional to understand the context in which patients are taking care of their disease. A prescriptive approach, in which patients are told to do, can work in some situations but fails more often than not because of unrecognized barriers to the execution of a particular plan.

As defined by ADA, diabetes self-management education is the process of providing to the person with diabetes knowledge and skill needed to perform self-care, manage crisis, and make lifestyle changes. As result of this process, the patient must become a knowledgeable and active participant in the management of his/her disease. To make this goal successful, patients and healthcare providers have to work together in a long-term. Minimal diabetes education should be universally provided and individualized with emphasis on the core issues.

Points to addressed in diabetes self-management education

- Pathophysiology of the patient's diabetes and its relationship to treatment option.
- Incorporating appropriate nutritional management.
- Incorporating physical activity into lifestyle.
- Using medications (if applicable) for therapeutic effectiveness.
- Monitoring blood glucose and (when appropriate) urine ketones and using the results to improve control.
• Preventing, detecting, and treating acute complications including sick day rules and hypoglycemia,
• Preventing (through risk detection), detecting and treating chronic complications.
• Goal-setting to promote health and problem-solving for daily living.
• Integrating psychological adjustment into daily life.
• Promoting preconception care, management during pregnancy, and gestational diabetes management (if applicable).

**DIETARY MANAGEMENT:**

Dietary management is the first line of treatment in all types of diabetes to achieve the overall therapeutic goals and normal metabolism. Modification of diet is the most important aspect in the therapeutic plan for diabetic patients. Diet therapy consists of maintenance of proper nutrition and monitoring of total calories ingested, individual food sources that make up these calories and distribution of calories throughout the day. Dietary recommendation is depends upon current eating habits, lifestyle, age, occupation, presence of hyperlipidemia, hypertension, other medical conditions and type and time of insulin secretions. Thus selection, moderation and restriction as per lifestyle and work are the keys of planning diabetic diet. Daily calorie requirement as per lifestyle are tabulated below.

<table>
<thead>
<tr>
<th>Lifestyle</th>
<th>Daily calorie requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedentary</td>
<td>20-25 Kcal/kg of IBW</td>
</tr>
<tr>
<td>Moderate activity</td>
<td>26-30 Kcal/kg of IBW</td>
</tr>
<tr>
<td>Strenuous</td>
<td>31-35 Kcal/kg of IBW</td>
</tr>
</tbody>
</table>

The ideal body weight of a person is calculated as:

\[
\text{Ideal body weight (IBW) (Kg)} = \{\text{Height (cm)} - 100\} \times 0.9
\]

The obese and overweight must be encouraged to reduce weight as attainment of optimal body weight results in marked reduction of hyperglycemia and increase in target cell response to insulin. An energy deficit of 500 calorie daily will help the patients to reduce 500 gm weight every week. Any person above 50 years may require 10% less calories for each decade. The American diabetic association
Modern Review

(ADA) recommends about 45-65% of total calories in the form of carbohydrates, 25-35% in the form of fats and 10-35% in the form of protein to the DM patients. In type 2 DM patients limiting the carbohydrate intake and substituting some of the calories with mono-saturated fats, such as olive oil, rapeseed oil or oils of nuts, can lower triglycerides and increase HDL cholesterol. The current recommendation for both type of DM patients continue to limit cholesterol to 300 mg daily, and individuals with LDL cholesterol more than 100 mg/dl should limit to 200 mg daily. High protein intake may cause progression of renal disease in patients with diabetic nephropathy. For these patients a reduction in protein intake to 0.8 kg/day or about 10% of total calories daily is recommended.

Weight loss is necessary both for IDDM and NIDDM patient to achieve the normal basic metabolic index (BMI : 20 – 25 kg/m^2). Benefit of acute long term energy restriction with or without weight loss are shown in the following table.

<table>
<thead>
<tr>
<th>Acute energy restriction without marked weight loss</th>
<th>Long term energy restriction with significant weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Reduced hepatic glucose output</td>
<td>• Improve insulin secretion</td>
</tr>
<tr>
<td>• Fall in blood glucose level</td>
<td>• Enhance insulin sensitivity</td>
</tr>
<tr>
<td>• Symptomatic improvement.</td>
<td>• Further fall in blood glucose</td>
</tr>
<tr>
<td></td>
<td>• Reduced atherogenicity in blood lipid profile</td>
</tr>
<tr>
<td></td>
<td>• Fall in blood pressure</td>
</tr>
<tr>
<td></td>
<td>• Reduced thrombogenic factors.</td>
</tr>
</tbody>
</table>

American Diabetes Association (ADA) recommendations – The current recommendations for both type of diabetes continue to limit cholesterol to 300 mg daily and advised to daily protein intake of 10 – 20% of total calories. They suggest that saturated fat be no higher than 8 – 9% of total calories with a similar proportion of polyunsaturated fat and that the remainder of caloric needs be made up of an individualized ratio of monounsaturated fat and of carbohydrate containing 20 – 30 g of dietary fiber. Poultry and fish continue to be recommended as a substitute of red meats for keeping saturated fat contains low. The present ADA position statement proffers no evidence that reducing protein intake below 10% of intake (about 0.8 g/kg/day) is of any benefit in patients with nephropathy and renal impairment.
Dietary fiber —

Plant components such as cellulose, gum and pectin are indigestible by humans and are termed dietary fiber. Insoluble fibers such as cellulose or hemicellulose, as found in bran, tend to increase intestinal transit and may have beneficial effects on colonic functions. In contrast, soluble fibers such as gum and pectins, as found in beans, oatmeal or in apple skin, tend to retard nutrients absorption rates so that glucose absorption is slower and hyperglycemia may be slightly diminished. Although its recommendations do not include insoluble fiber supplements such as added bran, the ADA recommends foods such as oatmeal, cereals, and beans with relatively high soluble fiber content as staple components of the diet in diabetics. High soluble fiber content in the diet may also have favorable effect on blood cholesterol levels.

Artificial sweeteners —

The latest position statement of the ADA concludes that all nonnutritive sweeteners that have been approved by the Food and Drug Administration (FDA) — such as Aspartame (180 times sweeter than sucrose, not heat stable = 2-4 mg/day) and Saccharin (30% sweeter than sucrose, heat stable so used in cooking) are safe for consumption by all people with diabetes. Two other nonnutritive sweeteners have been approved by the FDA as safe for general use: sucralose and acesulfame potassium. These are both highly stable and, in contrast to aspartame, can be used in cooking and banking.

Glycemic Index (GI) —

GI of a food is the measure of the relative amount and speed rise in blood glucose level that occurs after the given carbohydrate containing food is eaten.

High GI food causes a higher and faster rise in blood sugar. It is important to know that no food should be taken on free food and in unlimited quantity.

Quality of Diet —

- Fiber in plenty: Approx 20 – 30 g/ day
- Fats: Total fat intake should not exceed 25% of the total calories. Animal fats (saturated) should be limited.
• Simple sugar need to be avoided: Cane, sugar, glucose, sweet, softdrinks, cokes, ice-creams as they are rapidly absorbed and causes sudden rise in the blood glucose.

Meal plans in type 1 diabetes mellitus:
Total daily food intake should be distributed consistently throughout the day, especially for carbohydrate intake.

Daily meals should be regular:
• 3 main meals – breakfast, lunch and dinner
• 2-3 snacks – mid morning snack, afternoon snack etc.
• Bedtime snack is important to avoid nocturnal hypoglycemia

Timing and amount of food will depend on type of insulin, physical activity, lifestyle and result of blood glucose monitoring. Frequent small feeds are better.

Meal plan in type 2 diabetes mellitus:
Meals should be regular and distributed throughout the day.

Daily meals should be regular:
• 3 main meals – breakfast, lunch and dinner
• Snacks should not be encouraged
• The obese should be on appropriate caloric restriction to favour a gradual weight correction programme.

Timing and amount of food will depend on type of drug/insulin, physical activity, lifestyle and results of blood glucose monitoring. Frequent small feeds are better.

Free Foods –
• Salads i.e. Cucumber, Cabbage, Lettuce, Onion, Tomato, Capsicum, Radish, Carrot, Garlic etc.
• Green leafy vegetables and kerela, Jika, Patol, Bhol, Kachkal, Kaldil, Panilaw, Outenga, Methi, Narasingha (curry leaf), Bhendi (ladies finger) ...
• Plain tea or coffee without sugar or milk
• Plain clear soups, plain lemon juice in water without sugar.
Foods to avoid totally –

- Sugar, jaggery, Honey, Sherbet, Sweet, Cake, Jam, Jelly, Ice-cream, Pastries, Sugarcane etc.
- Salted nuts, Potato chips, Mixture, Bhujia, Namkin, Kachuri, Pakoras, Puri, Samosa, Paratha, Roll, Chowmein, Momo, Fried rice etc.
- Soft drinks, cold drinks, carbonated drinks, orange/ mango squashes
- Chocolates, Bournvita, Butter, Ghee, Cream, Horlicks, Drinking chocolates
- Dry fruits – Peanuts, Cashew nuts, Kismis, Khejur ...
- Raw or ripe fruits – Mango, Leechi, Grapes, Banana, Jackfruits, Pineapple, Coconuts...
- Potato, sweet potato, Tapioca, Pumpkin, Milk powder, Buffalo/ Goats milk
- Alcohol, Beer, Sweet wine, Tobacco, Khaini, Jarda, Pan masala, Smoking.
- Red meat e.g. Pork, Beef, Broiler chicken, Mutton, Duck, Pigeon, Deer

Foods that can be taken in Restricted amount –

- Milk/ curd fresh from cows only. The top creamy layer from the milk/ curd is to be skimmed off before it is consumed.
- Protein – local chicken allowed. Big fish can be taken but only occasionally, small fish should be preferred can be taken daily. Egg – only chicken eggs to be taken – either poached or boiled but avoid fried eggs (maximum 2 / week)
- Fruits – one small sized orange, half of an apple, one mauumbai, onenachpati, half of guava, black berry (Jamu), Amlakhi, Dalim...
- Snacks/ Biscuits – Aakhoi, Muri, but not Chira, Cream cracker Biscuits, Almond, Chapati (Ruti) from wheat flour only.

In the past, the need to restrict carbohydrate, especially sugars and patients finally rejected their dietary patterns, they are likely avoid carbohydrate food and therefore satisfied their appetite with extra fats. These results high prevalence of vascular disease because if more fat are eat.

- Dietary fat converted to TG and stored in adipose tissue leads to limited capacity of fat oxidation.
- Less diet induced thermogenicity of fat than carbohydrate and protein.
So BMR is lowered with fatty diet.

- Fatty diet causes hyperinsulinemia due to GPI, leading to insulin resistance, which may favor TG deposition in adipose tissue.
- Fat rich diet are highly palatable but are less satisfactory because their energy density high and fiber contains are low, which tends to encourage over eating.

Dietary fibers are coarse vegetable cell wall material that is resistant to digest by the alimentary enzymes of human. Only soluble fibers have useful metabolic effect in diabetic patient, the insoluble fibers merely acts as fecal bulking agent, and perhaps to enhance the satisfying properties by increasing the volume in the stomach. Soluble fiber flatten the blood glucose level after eating, and cause parallel reduction in postprandial insulin concentrations; insulin sensitivity increased and lower the serum lipid level. Daily requirement is 15 – 20 gm/1000 kcal. Dietary fibers are available in green leafy vegetables, pulses, fruits, legumes, barley, grain cereals, etc.

Fat recommendation implies an overall shift away from animal and diary fats to those derived from vegetables which contain monounsaturated fat. So avoid more meat and eggs and eat more vegetables and on and off fish.

W.H.O. recommends 400 gm/day fruits and vegetables for diabetic patient. Protein intake should be restricted in diabetic Nephropathy (<0.8 g/kg body wt)

A general guideline for diabetic diet (API MED 8th ed)

<table>
<thead>
<tr>
<th>Energy</th>
<th>25-30 Kcal/kg in IBW, reduce in obese and increase in underweight.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>0.8 gm/kg body wt. supplement provided for pregnancy, lactation &amp; growth. A small quota of animal proteins- fish, milk, yoghurt and appropriate food intake recommended. Avoid cattle meat and eggs.</td>
</tr>
<tr>
<td>Fats</td>
<td>20-25% of total calories.</td>
</tr>
<tr>
<td></td>
<td>Saturated fats- 6-7% of total calories.</td>
</tr>
<tr>
<td></td>
<td>Cooking oil- 0.5 kg/month/person.</td>
</tr>
<tr>
<td></td>
<td>Total fat intake in the form of cholesterol 300 mg/day.</td>
</tr>
</tbody>
</table>
Carbohydrates  |  55-60% of total calories. To encourage complex carbohydrates i.e. mainly whole grain cereals, pulses, beans, vegetables and salads. Avoid simple & refined carbohydrates like bakery products and deep fried items.
---|---
Fruits  |  Fresh fruits up to 400 gm/day, avoid juices.
Dietary fiber  |  30-40 gm/day preferably from natural sources; avoid loss from refining and processing. Indian diet is generally rich in fiber and does not require addition of fiber supplement.
Common salt  |  Up to 6-8 gm/day. Reduce intake to 4 gm/day in presence of hypertension, renal failure & heart problems.
Condiments & spices  |  Provide anti-oxidants, trace elements, minerals, and n-3 fatty acids.
Artificial  |  Use of saccharine & aspartame in limited amount is acceptable. Avoid in pregnancy and lactation.
Alcohol  |  Strictly restricted.
Tobacco  |  Avoid smoking or its use in any form.

Designing a diet and the steps involved and there rationale are shown in algorithmic form:

---
Study of *Lagerstroemia speciosa* (L.) Pers as a Hypoglycemic Agent*
Calculate subjects acceptable weight range at BMI <20-25kg/m²

Calculate target wt after 3 months (optimal less rate 1-2 kg/month)

Calculate subject's current energy intake

Apply standard dietary guideline

Assess eating pattern of subjects and his or her family

Designing individual regimen
- Energy deficit of 500k. cal/day
- Modification of eating behaviour
- Advice about smoking and alcohol
- Encourage appropriate exercise

Regular review
- Body weight, BMI, waist circumference
- Glycaemia and lipid control
- Quality of life
- Compliance

Target achieved
- Maintain contact
- Revise targets if necessary

Target not achieved
- Review approach, education and compliance
- Consider additional treatment
- Very low caloric diet
- Anti-obesity drugs
- Non-pharmacological method

Maintenance programme
Following flow charts shows the management approach in diabetes mellitus –
EXERCISE:

Energy for muscular work is divided initially from the breakdown of muscle glycogen and later forms the circulating glucose and non-esterified fatty acid; muscle uptake of glucose may be increased 20 times during exercise. Exercise enhances insulin delivery to muscle and opens up previously non-perfused capillaries, these increase both the effect of insulin and the surface area for glucose transport.

In IDDM, glycemic changes during exercise depend largely on blood insulin level and therefore on the type of the insulin used and the interval between insulin administration and exercise. So patient with IDDM can reduce the risk of hypoglycemia by taking 20 – 40 gm extra carbohydrate before and hourly during exercise or by reducing pre-insulin doses by 30 – 50%.

In NIDDM patients exercise not only increases peripheral glucose uptake but also decreases endogenous insulin secretion, hypoglycemia is therefore rare and extra carbohydrate is not necessary. Exercise also increased peripheral and hepatic insulin sensitivity, increased muscle GLUT-4 and also decreased the risk of CVD and PVD (peripheral vascular disease).

Guide line of exercise by A.D.A. with other's recommendation:

Contraindication:
- If receiving insulin – sports where hypoglycemia would be dangerous (e.g. driving, climbing etc.)
- If proliferative retinopathy.

Indication with caution:
- CAD (specially in NIDDM)
- Peripheral neuropathy, Peripheral Arterial Disease (PAD)

General advice:
- Take daily exercise, daily if possible.
- Heavy exercise is not necessary.
- Tailor exercise schedule to the pt’s individual needs and physical fitness.
- Use proper foot wear and inspect the foot regularly after exercise.
• Avoid exercise during poor metabolic control and in extreme cold and hot climate.

For IDDM, monitor glycaemia before, during and after exercise. Avoid hypoglycemia during exercise by taking extra carbohydrate, during non exercising site for insulin injection and reduced pre exercise insulin dose by 30 – 50% if necessary.

In NIDDM, exercise used to reduced weight should be combined with dietary measurement.

Exercise prescription:
• What kind of exercise? – Best exercise is walking, jogging, bicycling, swimming etc..
• How often? – Three to five times per week is preferable with not more than 2 days rest between exercise day.
• How long? – 15 to 60 minutes is advised depending on the person capacity and the type of exercise.

Walking schedule (for older patient)

<table>
<thead>
<tr>
<th>Week</th>
<th>Distance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>1 mile/ 30 min</td>
</tr>
<tr>
<td>2nd</td>
<td>2 mile/ 30 min</td>
</tr>
<tr>
<td>3rd</td>
<td>1 mile/ 15 min</td>
</tr>
<tr>
<td>4th</td>
<td>2 mile/ 30 min</td>
</tr>
<tr>
<td>5th</td>
<td>3 mile/ 45 min</td>
</tr>
<tr>
<td>6th</td>
<td>14 mile/ 60 min</td>
</tr>
</tbody>
</table>

• Benefits of exercise in Type 2 DM
  ➢ Lowers plasma glucose levels and increase insulin sensitivity.
  ➢ Increase burning calories so reduce body weight.
  ➢ Improves circulation. Toning of heart muscles.
  ➢ Lowers blood pressure.
  ➢ Improves cardiac fitness.
  ➢ Lowers lipid levels.
  ➢ Relives STRESS – Mental sense of well being and Relaxation.
Calories burnt in various activities –

Require to burn 7700 calories to loss 1 kg body weight.

<table>
<thead>
<tr>
<th>Action</th>
<th>Calories burnt / hour</th>
<th>Action</th>
<th>Calories burnt / hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting in bed</td>
<td>60</td>
<td>Recreational</td>
<td>120</td>
</tr>
<tr>
<td>Sitting, Playing card</td>
<td>72</td>
<td>Driving, Tailoring</td>
<td>168</td>
</tr>
<tr>
<td>Eating, Writing</td>
<td>84</td>
<td>Horse riding</td>
<td>180</td>
</tr>
<tr>
<td>Standing relax</td>
<td>84</td>
<td>Dancing</td>
<td>300</td>
</tr>
<tr>
<td>Conversation</td>
<td>84</td>
<td>Gardening</td>
<td>236</td>
</tr>
<tr>
<td>House work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweeping floor</td>
<td>102</td>
<td>Other physical activities</td>
<td></td>
</tr>
<tr>
<td>Washing hand</td>
<td>150</td>
<td>Walking 5 km/hr speed</td>
<td>180</td>
</tr>
<tr>
<td>Washing cloth</td>
<td>252</td>
<td>Walking 7 km/hr speed</td>
<td>270</td>
</tr>
<tr>
<td>Ironing cloth</td>
<td>180</td>
<td>Walking 9 km/hr speed</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cycling</td>
<td>350 – 450</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tennis</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Badminton</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Football</td>
<td>480</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jogging</td>
<td>480</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Running</td>
<td>600 – 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Table tennis</td>
<td>330</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Swimming 3 km/hr</td>
<td>600</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Light exercise</td>
<td>150</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate exercise</td>
<td>240</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Strong exercise</td>
<td>400</td>
</tr>
</tbody>
</table>
ORAL HYPOGLYCEMIC AGENT (OHA): (API MED)

The oral hypoglycemic agents are used in type 2 DM in case of failures of diet and exercise management.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Action(hrs)</th>
<th>Duration of dose/day</th>
<th>Daily dose</th>
<th>No. of dose/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Insulinotropic agent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Sulphonyl urea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1&lt;sup&gt;st&lt;/sup&gt; generation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Tolbutamide</td>
<td>6 – 8</td>
<td>0.5 – 3 mg</td>
<td>2 – 3</td>
<td></td>
</tr>
<tr>
<td>b) Chlorpramide</td>
<td>36 – 48</td>
<td>0.1 – 0.5 mg</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>c) Tolazamide</td>
<td>18 – 24</td>
<td>0.125 – 1 gm</td>
<td>1 – 2</td>
<td></td>
</tr>
<tr>
<td>(2&lt;sup&gt;nd&lt;/sup&gt; generation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Glibenclamide</td>
<td>18 – 24</td>
<td>5 – 15 mg</td>
<td>1 – 2</td>
<td></td>
</tr>
<tr>
<td>b) Glipizide</td>
<td>12 – 18</td>
<td>5 – 20 mg</td>
<td>1 – 2</td>
<td></td>
</tr>
<tr>
<td>c) Gliclazide</td>
<td>12 – 24</td>
<td>25 – 150 mg</td>
<td>1 – 3</td>
<td></td>
</tr>
<tr>
<td>d) Glyburide</td>
<td>12 – 24</td>
<td>1.25 – 20 mg</td>
<td>1 – 2</td>
<td></td>
</tr>
<tr>
<td>e) Glimepride</td>
<td>24</td>
<td>1 – 6 mg</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>B. Meglitinide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Repaglinide</td>
<td>2 – 6</td>
<td>0.5 – 16</td>
<td>2 – 4</td>
<td></td>
</tr>
<tr>
<td>b) Nateglinide</td>
<td>2 – 3</td>
<td>60 – 120</td>
<td>3 – 4</td>
<td></td>
</tr>
<tr>
<td>2. Hepatic gluconeogenesis inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biguanides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Metformin</td>
<td>6 – 8</td>
<td>0.5 – 2 gm</td>
<td>2 – 4</td>
<td></td>
</tr>
<tr>
<td>3. Inhibitor of rapid glucose absorption</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α Glucosidase inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Acarbose</td>
<td>-</td>
<td>50 – 300 mg</td>
<td>1 – 3</td>
<td></td>
</tr>
<tr>
<td>b) Miglitol</td>
<td>-</td>
<td>75 – 300 mg</td>
<td>1 – 3</td>
<td></td>
</tr>
<tr>
<td>4. Insulin sensitizer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Pioglitazone</td>
<td>-</td>
<td>15 – 45 mg</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>b) Rosiglitazone</td>
<td>-</td>
<td>2 – 8 mg</td>
<td>1 – 2</td>
<td></td>
</tr>
<tr>
<td>5. Incretins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Exenatide</td>
<td>-</td>
<td>5 – 10 mcg</td>
<td>2 – 4</td>
<td></td>
</tr>
</tbody>
</table>
# IMPORTANT FEATURES OF ORAL HYPOGLYCAEMICS:

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Examples</th>
<th>Anticipated reduction in HbA1c%</th>
<th>Agent specific advantages</th>
<th>Agent specific disadvantages</th>
<th>Contra indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphonylureas (SU)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulate insulin secretion in a biphasic action. The insulin-trophic effect of SU is augmented by glucose, &amp; they apparently increase β-cell sensitivity to glucose and non-glucose stimuli. SU do not increase insulin synthesis by β-cell.</td>
<td>Repaglinide</td>
<td>1 - 2</td>
<td>Short onset of action, lower postprandial glucose</td>
<td>Hypoglycemia</td>
<td>Renal liver diseases</td>
</tr>
<tr>
<td>Meglitinide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulates insulin secretion from pancreatic β-cell by closing ATP sensitive potassium channels on cell membrane. Prandial glucose regulator.</td>
<td>Metformin</td>
<td>1 - 2</td>
<td>Weight loss improved lipid profile, no hypoglycemia</td>
<td>Lactic acidosis, diarrhoea, nausea, possible increased cardiovascular mortality</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Biguanides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease hepatic glucose production, weight loss, increase glucose utilization</td>
<td>Acarbose, Miglitol</td>
<td>0.5 - 1.0</td>
<td>No risk of hypoglycemia</td>
<td>GI flatulence, increase liver function test</td>
<td>Serum creatinine&gt;1.5mg dl(men), &gt;1.4 mg dl (women) radiographic contrast studies, seriously ill patients acidosis.</td>
</tr>
<tr>
<td>α Glycosidase inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delays the digestion and absorption of carbohydrates in the gut by competitively and reversibly inhibiting alpha glucosidase enzymes in the proximal small intestine.</td>
<td>Rosiglitazone, Pioglitazone</td>
<td>1 - 2</td>
<td>Decrease insulin and sulphonyl urea requirement, decrease triglycerides</td>
<td>Frequent hepatic monitoring for idiosyncratic hepatocellular injury</td>
<td>Liver disease, congestive heart failure</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Promote glucose uptake in skeletal muscle, adipose tissue, and liver. These actions are thought to be mediated via a specific nuclear receptor -peroxisome proliferator's activator receptor-gamma (PPAR-γ). Direct effects on intracellular glucose transporters are also postulated.</td>
<td>Low Calorie, low fat diet exercise</td>
<td>1 - 2</td>
<td>Other health benefits</td>
<td>Compliance difficult, long term success low</td>
<td></td>
</tr>
<tr>
<td>Medical nutrition therapy and physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
INSULIN

Insulin has been commercially available since 1921 and is arguably still the mainstay of therapy for most people with DM. In 1921, Canadian scientist Frederick Banting and medical student Charles Best isolated a substance from the pancreas of dogs, which they named isletin – and which is now known as insulin. In a series of experiments, they found that a pancreactomised dog could be kept alive with injections of isletin. The following year, after much laboratory work to purify with insulin extracted from a fetal calf, a 14 years old boy called Leonard Thompson became the first person with diabetes to receive an insulin injection, and his conditions improved significantly. Prior to discovery of insulin, people with diabetes were put a starvation diet and had no hope for survival.

Insulin is indicated for type 1 diabetic patients as well as for type 2 patients with insulinopenia whose hyperglycemia does not respond to diet and exercise therapy either alone or combined with other hypoglycemic agent.

Insulin from two animal species, bovine and porcine are used therapeutically. Bovine insulin differs from human insulin by three amino acids and porcine insulin by only one at B-30. Thus insulin synthesize from bovine sources are more antigenic. Human insulin is manufactured by two processes—semisynthetic human insulin (enzyme modified porcine insulin) and recombinant DNA techniques (biosynthetic human insulin). Presently east cultures are genetically engineered to yield human insulin which is more rapidly absorbed and has a shorter duration of action.

Current insulin preparations (Human insulin) are having the same amino acid sequence of human insulin and are generated by recombinant DNA technology in Escherichia coli – ‘proinsulin recombinant bacterial’ (prb) and in yeast – ‘precursor yeast recombinant’ (pyr), or by ‘enzymatic modification of procaine insulin(emp). In USA and Europe the use of human insulin has rapidly overtaken that of purified animal insulin’s: in Britain now > 90% diabetics who use insulin are taking human insulin are analogues. Human insulin is more water soluble as well as hydrophobic than procaine or bovine insulin. It has a slightly
more rapid s.c. absorption, earlier and more defined peak and slightly shorter duration of action.

So many insulin preparations are available and they are classified as short acting, intermediate acting and long acting in general, individuals with type 1 diabetes require 0.5 – 1.0 U/kg per day insulin divided into multiple dose, according to the necessity. One commonly used regimen consists of twice daily injections of Intermediate Insulin (NPH or lente) mixed with a short acting insulin before the morning and evening meal (2/3 in the morning and 1/3 in the evening). This type of regimen restricts the patient in a constant diet and behavioral activities. So if diet and exercise or activities are different day to day than other regimen should be advised after keeping the following condition in mind – fasting blood glucose controlled by evening (previous day) intermediate insulin, pre lunch glucose controlled by morning short acting insulin, pre evening glucose controlled by morning intermediate insulin and bed time glucose controlled by pre evening short acting insulin.

Calculation of mealtime Insulin

One unit of insulin = 10 g or 40 kcal of carbohydrate.
0.5 unit of insulin = 100 kcal of protein or fats.
10 g of glucose increased blood sugar by approx 36 mg/dl.

### Indications for insulin therapy

<table>
<thead>
<tr>
<th>Long term permanent insulin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ IDDM or type 1 DM</td>
</tr>
<tr>
<td>✓ NIDDM or type 2 DM with primary and secondary failures of OHA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intermittent insulin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Type 2 DM subjects during</td>
</tr>
<tr>
<td>• Acute infections</td>
</tr>
<tr>
<td>• Major surgery, perioperatively</td>
</tr>
<tr>
<td>• Acute myocardial infarction, stroke</td>
</tr>
<tr>
<td>• Acute metabolic emergencies, e.g. ketocacidosis etc.</td>
</tr>
<tr>
<td>➢ Gestational diabetes mellitus (GDM)</td>
</tr>
</tbody>
</table>
Types of insulin preparations, insulin analogues and their pharmacokinetic -

Commercially available insulin's are divided into three major categories based on their therapeutic action profile; short acting, intermediate acting and long acting.

<table>
<thead>
<tr>
<th>Insulin class</th>
<th>Time of action (hours)</th>
<th>Species of origin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Onset</td>
</tr>
<tr>
<td>Short acting insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monomeric</td>
<td>&lt;0.5</td>
<td>0.5-4.5</td>
</tr>
<tr>
<td>Regular</td>
<td>0.2-0.5</td>
<td>1.0-3.0</td>
</tr>
<tr>
<td>Intermediate acting insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH-Isophane</td>
<td>1.0-2.0</td>
<td>4.0-6.0</td>
</tr>
<tr>
<td>Lente</td>
<td>1.0-2.0</td>
<td>4.0-8.0</td>
</tr>
<tr>
<td></td>
<td>1.0-3.0</td>
<td>5.0-10.0</td>
</tr>
<tr>
<td>Long acting insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultra lente</td>
<td>2.0-3.0</td>
<td>4.0-8.0</td>
</tr>
<tr>
<td>Glargine</td>
<td>2.0-4.0</td>
<td>6.0-12.0</td>
</tr>
<tr>
<td>Biphasic premixed insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH+regular in various</td>
<td>0.5-1.0</td>
<td>2.0-10.0</td>
</tr>
<tr>
<td>ratios (75/25;70/30; 50/50)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

H- Human, B- Bovine P- Porcine NPH- Neutral Protamine Hagedom (API MED)

To effectively control diabetes it is necessary to combine short acting with intermediate acting insulin. Presently, stable premixed insulin in various proportions of regular and NPH are available. The frequently used premixed insulin preparations are ‘30/70’ i.e. 30% regular and 70% NPH, ‘50/50’ i.e. 50% regular and 50% NPH. Insulin is available in various strengths. In India two strengths namely 40 and 100 units per ml are available, but in western countries usually 100 units per ml are marketed.

Insulin therapy is generally started with regular insulin given s.c. before each major meal. The requirement assessed by testing urine or blood glucose levels (glucose oxidase based spot tests and glucometers are available). Most type 1 patients requires 0.4 – 0.8 U/ kg/ day. In type 2 patients, insulin dose varies...
(0.2 – 1.6 U/ kg/ day) with the severity of diabetes and body weight. Obese patients requires proportionally higher dose due to relative insulin resistance.

For administration of insulin methods used are:

For injection of insulin U-40 and U-100 disposable syringes are used to 40 units/ml and 100 units/ml respectively. Insulin pen devices are user friendly, convenient to carry and highly suitable for multiple injections in a day. Insulin pumps are programmable device for continuous subcutaneous insulin infusion as said earlier. Inhaled insulin is a novel method for delivering a preprandial powdered form of insulin by inhalation and has been approved by the FDA.

A number of innovations have been made to improve easy and accuracy of insulin administration as well as achieve tight glycemia control. These are:

1. **Insulin syringes**: Prefilled disposable syringes contain specific types or mixtures of regular and modified insulin.

2. **Pen devices**: Fountain pen like: use insulin cartridges for s.c. injection through a needle. Preset amounts (in 2 U increments) are propelled by pushing a plunger; convenient in carrying and injections.

3. **Inhaled insulin**: Recently, an inhaled human insulin preparation has been marked in Europe and USA. The fine powder is delivered through a nebulizer, absorption is rapid. Peak action occurs at ~2 hours and duration of action is 6 – 7 hours. It is used to control mealtime glycemia, but it is not suitable for round-the-clock basal effect. Less than 10% of inhaled insulin is absorbed.

4. **Insulin pump**: Portable insulin devices connected to a subcutaneously placed canula: proved continuous subcutaneous insulin infusion (CSII). Only regular insulin is used. They can be programmed to delivered insulin at a low basal rate (approx. 1U/ hour) and premeal boluses (4 – 15 times the basal rate) to control the post-prandial glycemia. Though theoretically more appealing, no definite advantages of CSII over multi dose s.c. injections has been demonstrated. Moreover, cost, strict adherence to diet, exercise, care of the device and canula, risk of pump failure, site infection, are on demanding by the patients.

5. **Implantable pumps**: Consist of an electromechanical mechanism which regulates insulin delivery from a percutaneously refillable reservoir.
Mechanical pumps, fluoro-carbon propellant and osmotic pumps are being developed.

6. **External artificial pancreas**: This is a microprocessor controlled devices connected through i.v. lines, which measures blood glucose and then infuses appropriate amounts of insulin in a continuous feedback manner. Its size, cost and other problems limit use to only researcher institutions.

7. **Other routes of insulin delivery**: Intraperitoneal, oral (by complexing insulin into liposomes or coating it with impermeable polymer) and rectal routes are being tried. These have the advantages of providing higher concentrations in the portal circulations, which is more physiological.

**Steps in the management of the diabetic patient** (CMDT – 2007)

1. **Type 2 diabetics** –
   a) **The obese patient with type 2 diabetes** –
      b) **Weight reduction** – Treatment is directed toward achieving weight reduction, and prescribing a diet is only one means to this end. Behavior modification to achieve adherence to the diet – as well as increase physical activity to expend energy – is also required. Cure can be achieve by reducing adipose stores, with consequent restoration of tissue sensitivity to insulin.

      b) **Hypoglycemic agents** – If the patient is not able to achieve target glycemic control with weight management and exercise, then pharmacological therapy is indicated. The choice of initial agent is depends on a number of factors, including morbid conditions, adverse reactions to the medications, ability of the patient to monitor for hypoglycemia, drug cost, and patient and physicians preferences.

      **Metformin** is advantageous because apart from lowering glucose without the risk of hypoglycemia, it also lowers triglycerides and promotes some modest weight loss. The drug, however, can't be used in patients with renal failure, and Gl side effects develop in some patients at even the lowest dose.

      **Thiazolidinediones** improves peripheral insulin resistance and lowers glucose without causing hypoglycemia. They have been reported to improve nonalcoholic fatty liver disease, have beneficial effects on the lipid profile and...
some other cardiovascular risk factors, decreased microalbuminuria. These drugs, however, can cause fluid retention and are contraindicated in patients with heart failure and active liver disease. They also increase weight.

**Sulphonylureas** have been available for many years and their use in combination with metformin is well established. They do, however, have the propensity of causing hypoglycemia and weight gain. The α-glucosidase inhibitors have modest glucose lowering effects and GI side effects.

**Exenatide** has a lower risk of hypoglycemia than the sulphonylureas and promotes weight loss. However, it needs to be given by injections.

For most obese patients with mild type 2 diabetes Metformin is the first line agent. If it doesn't gives satisfactory result, than a second agent should be added. If two agents are inadequate, then a third agent is added, although data regarding efficacy of such combine therapy are limited.

When the combination of oral agents fails to achieve euglycemia in patients with type 2 diabetes, various insulin regimens may be effective. There is no consensus about how insulin therapy should be instituted. One proposed regimen is to continue the oral and then simply add a bed time dose of NPH or long-acting insulin analog to reduce excessive nocturnal hepatic glucose output and improve fasting glucose levels. If the patient dose not achieve target glucose levels durian the day, then daytime insulin treatment can be initiated. A convenient insulin regimen under these circumstances in a split dose of 70/30 NPH/ regular mixture before breakfast and before dinner. If the regimen fails to achieve satisfactory glycemic goal or is associated with unacceptable frequency of hypoglycemic episodes, then a more intensive regimen of multiple insulin injections can be instituted as in patients with type 1 diabetes.

Metformin principally reduce hepatic glucose output and the thiazolidinediones improves peripheral insulin resistance, so it is a reasonable option to continue these drugs when insulin therapy is instituted. The sulphonylureas also have been shown to be of continued benefit. Thus, the continued use of the oral drugs may permit the use of lower doses of insulin and simpler regimens.
B) The non-obese patient with type 2 diabetes – Non-obese patients with type 2 diabetes frequently have increased visceral adiposity – the so called metabolically obese normal weight patient – and the treatment algorithm is much the same as in the obese patient except there is not as much emphasis on weight loss. However, exercise remains an important aspect of important. Person who does not have central obesity or insulin resistance should be evaluated for other types of diabetes for other types of diabetes such as latent autoimmune diabetes of adulthood (LADA) or MODY. Patients with LADA can initially be treated with OHA but require insulin within a few years.

2. Type 1 diabetes –

In general individuals with type 1 DM require 0.5-1.0 U/kg per day of insulin in divided doses. Initial insulin regime should be conservative; approximately 40-50% of the insulin should be given as basal insulin. The commonly used regimen consist of twice daily injections of an intermediate (NPH or Lente) mixed with a short acting insulin before the morning and evening meal. Such regimens usually prescribe two thirds of the total daily insulin dose in the morning and one third before the evening meal. A combination of rapid-acting insulin analogs and long acting insulin analogs allows for more physiologic insulin replacement. The rapid-acting insulin analogs have been advocated as a safer and much more convenient alternative to regular human insulin for preprandial use. In a study comparing regular with insulin lispro, daily insulin dosages and HbA1c levels were similar, but insulin lispro improved postprandial control, reduced hypoglycemic episodes, and improves patients convenience compared with regular insulin.

However, because of their relative short duration (3 – 4 hr), the rapid acting insulin analogs need to be combined with longer-acting insulin to provide basal coverage and avoid hyperglycemia prior to the next meal.

Another multiple component insulin regimen is continuous subcutaneous insulin injection (CSII). Sophisticated devices are available for this, which can accurately deliver small doses of insulin as programmed. A preprandial insulin bolus is delivered by the insulin infusion device based on the instructions from the
patient, which follow individualized algorithms that account for prandial plasma glucose and anticipated carbohydrate intake.

Multiple injections of NPH insulin can be mixed in the same syringe as the insulin lispro, insulin aspart, and insulin glulisine. Insulin glargine is usually given once in the evening to provide 2h hour coverage. This insulin can't be mixed with any of the other insulins and must be given as a separate injection. There are occasional patients in whom insulin glargine does not seem to last for 24 hours, and in such cases it needs to be given twice a day. Insulin detemir may be also needs to give twice a day to get adequate 24 hour basal coverage.

Example of intensive insulin regimens using rapid-acting insulin analogs (insulin lispro, aspart, or glulisine) and NPH, or insulin glargine in a 70 kg man with type 1 diabetes.1,3

<table>
<thead>
<tr>
<th></th>
<th>Pre-breakfast</th>
<th>Pre-lunch</th>
<th>Pre-dinner</th>
<th>At bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting insulin analogs</td>
<td>5 units</td>
<td>4 units</td>
<td>6 units</td>
<td>-</td>
</tr>
<tr>
<td>NPH insulin</td>
<td>3 units</td>
<td>3 units</td>
<td>2 units</td>
<td>8 – 9 units</td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid-acting insulin analogs</td>
<td>5 units</td>
<td>4 units</td>
<td>6 units</td>
<td>-</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>15 – 16 units</td>
</tr>
</tbody>
</table>

1Assumes that patient is consuming approximately 75 g carbohydrate at breakfast, 60 g at lunch and 90 g at dinner.
2The dose of rapid-acting insulin can be raised by 1 or 2 units if extra carbohydrate (15 – 30 g) is ingested or if premeal blood glucose is > 170 mg/dl. Rapid acting insulin can be mixed in the same syringe with NPH insulin.
3Insulin glargine (or insulin detemir) can't be mixed with any of the available insulin and must be given as a separate injection. NPH = neutral protamine Hagedom.