Diabetes Mellitus

Diabetes is not a single disease. Rather, it is a heterogeneous group of syndromes characterized by an elevation of blood glucose level caused by a relative or .absolute deficiency of insulin

:Etiology of diabetes mellitus

Diabetes can be divided into two main groups based on :their requirement for insulin

A. Type 1 diabetes (IDDM): Insulin–dependent diabetes mellitus most commonly occurs in individual around the .time of puberty

Causes: Massive ß-cell destruction due to autoimmune-processes or an invasion of viruses or by the action of chemical toxins. As results of the ß-cell destruction, the pancreas fails to respond to glucose and the classic symptoms of insulin deficiency appear .(polydipsia, polyuria, and polyphagia and weight loss)

Frederick Banting

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J.J.R. Macleod

University of Toronto, 1923

- **Treatment:** Type 1 diabetic must depend on exogenous (injected) insulin to control hyperglycemia avoid ketoacidosis and maintain acceptable levels of glycosylated hemoglobin (HbA1c). The rate of formation of HbA1c is proportional to the average blood glucose concentration over the previous several months; **thus HbA1c provides a measure of how well treatment has normalized blood glucose in diabetics.** The goal in administrating insulin is to maintain blood glucose conc. .close to normal to avoid long-term complications

- Normal ß-cell function: Before ingesting a meal, low, basal levels of circulating insulin are maintained through constant ß-cell secretion. This is suppresses lipolysis, proteolysis and glycogenolysis. A burst of insulin secretion occurs within two minutes after ingesting a meal, in response to transient increases in the levels of circulating glucose and amino acids. This lasts up to 15 minutes and is followed by postprandial insulin secretion. However in type 1 diabetics, the ß-cell of pancreas can neither maintain a basal secretion level of insulin nor .respond in variation in circulating fuels

- **B-Type 2 diabetes (NIDDM) (maturity-onset):** Most diabetics are type 2 (80-90 %). The disease is influenced by genetic factors, aging, obesity, and peripheral insulin .resistance
- **Causes:** The pancreas in NIDDM retains some ß-cell function, but insulin secretion is insufficient to maintain glucose homeostasis. The ß-cell mass may become gradually reduced in type 2 diabetes. In contrast with type 1 diabetes, those with type 2 are often obese. Type 2 diabetes is frequently accompanied by the **lack of sensitivity of target organs to endogenous or exogenous insulin.** The resistance to insulin is considered the major cause of this type of .diabetes (sometimes referred to as "metabolic syndrome")
- **Treatment**: the goal of treatment of type 2 diabetes is to maintain blood glucose concentration within normal limits; most are dependent on administration of oral hypoglycemic agents. **Weight reduction, exercise, and dietary modification may decrease insulin resistance and correct .hyperglycemia of type 2 diabetics**

- **Type 3 (maturity-onset diabetes of the young-3 :(MODY)**

  Due to mutation of particular genes, resulting in deregulation of glucose levels and insulin secretion. **It occurs before 25 years of age. Patients with type 3 are not obese and insulin resistance is absent**

- **:Type 4 (Gestational diabetes) -4**

  It is a glucose intolerance associated with pregnancy. Tight glycemic control must be maintained close to normal range during pregnancy. Hyperglycemia .can lead to congenital abnormalities

  Diet, exercise, and/ or insulin administration are .effective in this case

:Clinical picture of diabetes in general

1. Polyurea (frequent urination especially during night).
2. Polydepsia (excessive thirst).
3. Polyphagia (increase appetite) with loss of weight.
4. General weakness and easy fatigue.
5. May present with symptoms of complications.

:Possible Complications in Diabetics

:CVS complications-1

Microangiopathy: which is the thickening of the- basement membrane of endothelium of capillaries, arterioles, and venules due to deposition of mucopolysaccharide materials causing narrowing of blood vessel (it is more pronounced in retina (retinopathy), glomeruli (nephropathy), vasa nervosa .(neuropathy)

Atherosclerosis of large vessel: Around 50% of- people with diabetes have disorders of lipid metabolism that is marked by high triglyceride levels or low High Density Lipoprotein (HDL) levels. If it deposited in cerebral blood vessel it produces **thrombosis with hemiplegia.** In coronary blood .vessel (angina with infarction)

:Cerebral complications (diabetic coma) -2

:Diabetic ketoacidosis (DKA) -

DKA progresses from hyperglycemia to **ketosis,** which is a build-up of ketones in the body. Ketosis can lead to acidosis, which is a condition in which the blood has too much acid. When this happens it is known as diabetic ketoacidosis. **DKA is a potentially life-threatening complication of diabetes.** If left untreated the electrolyte and the acid-base disturbances can result in coma or death. Although DKA is generally seen in people with type-1 diabetes, it also has been described in patients with type-2 diabetes. DKA is identified by 3 clinical features: **Hyperglycemia, ketonuria or ketonemia, and acidosis**. By definition, the following laboratory values are present with DKA: serum blood glucose greater than 250 mg/dl, moderate or large ketonuria or ketonemia and an arterial blood ***pH below 7.3*** and/or .serum bicarbonate level below 15 mEq/L

Signs and symptoms: Feeling tired, excessive thirst and/or excessive urination, signs of dehydration such as dry mouth, confusion, rapid deep breathing, breathe that smells .fruity, fever, unconsciousness

Treatment: It's important to treat **dehydration** by replacing fluids that have been lost, so most likely IV therapy will be used. **Electrolyte imbalances** need to be corrected and insulin therapy started to control **hyperglycemia.** All of this must be done .under careful medical supervision

:Hypoglycemic Coma -

.It results from missing a meal or insulin overdose

Clinical picture include **hunger, sweating (moist tongue), dizziness, headache, irritability, shakiness, clammy skin, loss of coordinator, blurred vision, nausea, confusion, nightmares, heart palpitations or rapid heart rate, and numbness in the lips or tongue, dilated pupil, convulsion, coma.** If one doesn't take action as mild hypoglycemia develops, the lack of glucose may seriously impair brain function, causing delirium, seizures or loss of consciousness .(hypoglycemic coma)

Treatment: If one becomes hypoglycemic, he should take **10 to 15 grams of carbohydrate** as quickly as possible to boost blood glucose level and avoid falling into a hypoglycemic coma. All of the following contain 10 to 15 grams of carbohydrate: Two to three 5-gram glucose tablets. Four to six ounces of orange juice. Half a can of a cola or other soft .drink, Two teaspoons of sugar. Two teaspoons of honey

Diabetic Retinopathy (ocular complications) -3

The elevated blood sugar levels are the main factor in the development of damage and sclerosis to the endothelium of blood vessels. This is particularly marked in the **retina where the vessels are very thin.** If the management of DM is poor (no improvement in blood sugar levels or uncontrolled hypertension) significantly reduced vision or blindness may result from hemorrhage or retinal detachment In addition to .managing the DM laser treatment can be given

Diabetic nephropathy (renal complications)-4

This is caused by thickening of the basement membrane of tubules, inter-intra-capillaries causing damage to the kidneys. An early sign of this disorder is a **gradual loss of protein** through the excretion of tiny protein particles in urine, a condition known as "**microalbuminuria**". This early indication of diabetic. People diagnosed with diabetic nephropathy have a high risk of suffering further kidney damage and edema, .possibly leading to kidney failure requiring dialysis or transplant

:Diabetic foot syndrome

This may lead to ischemia (cyanosis-coldness), neuropathy (painless ulcer), infections (fungus infection):

combination of diabetic neuropathy (damage to the nerves) with resulting pain and insensitivity, plus a circulatory disorder is the reason for the high number of amputations that still have to be performed on people with diabetes. In most cases a minor injury to a neuropathic foot results in damage to the skin. Because the person feels no pain, they do not take the important step of relieving pressure on or immobilizing the foot so the lesion cannot heal. If a circulatory disorder such as occlusive arterial disease is an added factor, treatment of the wound can be a long process .and there is an increased risk of amputation

Genital complications: genital tract infection (puerperal-6 sepsis), impotence, menorrhagia (abnormally heavy bleeding .at menstruation), may be abortion, premature labor

:Diagnosis

:Urine analysis -1

Urine tests for detection of glucose in the urine using test-strips. These strips* .impregnated in the urine to detect glucose by specific color reaction

.Urine tests for detection of ketone bodies by ketostix or ketodiastix *

:**Blood glucose tests -2**

A-Fasting plasma glucose test: Overnight fasting then measuring plasma glucose level in the morning it should be (80-120 mg/dl) above 140 is .considered abnormal

B-Glucose tolerance test: Used in border-line case (i.e. fasting plasma glucose **120-140**). Fasting blood glucose level is determined and urine samples are collected, then 75 gm /100 ml glucose solution is taken orally, then samples from venous blood and urine are tested for glucose after 30, 60, 90, 120, 150 minutes of administration. Normal person blood glucose reach the peak level below **160** mg/dl in 30-60 min then return to fasting level again after 120-150 min. For diabetic person blood glucose reach the peak level above **180** mg/dl in 30-60 min then fails to return to its fasting level again after .(120-150 min. Renal threshold for glucose is 180 mg/dl

C- Two-hours postprandial blood glucose: fasting plasma glucose level was determined then a meal or 75 gm /100 ml glucose solution is taken orally. After 2 hours plasma glucose level is detected. It should return to normal fasting level after 2 hours in normal subject. If it is above **130** mg/dl so its .suggestive. If it is above **180** mg/dl so it is diagnostic

Glycosylated hemoglobin (HbA1c): (normal level -3 3.9-6.9%)

This glycosylated hemoglobin is formed by non-enzymatic glycosylation reaction between glucose and N-terminal amino acid of β-chain of the hemoglobin molecule. It becomes stable for 6-8 weeks throughout the life span of RBCs (120 days). It is level is high in diabetics, reflecting the state of hyperglycemia over the preceding 8 weeks, so it is useful to asses the efficiency of diabetic control but it is not diagnostic. All red blood cells have some glucose bound to them. With normal blood glucose levels, glycated hemoglobin is expected to be 3.9 % to 6.9 %. As blood glucose concentration rise, however, more binding occurs. Poor blood sugar control over time is suggested when the glycated hemoglobin .measure exceeds 8.0%

Management of Diabetes

I. Treatment with insulin

Chemistry of insulin: Insulin hormone is protein in nature consists of two polypeptide chains, A and B. chain A is composed of **21 amino acids** while chain B consists of **30 amino acids.** The chains are connected by two disulphide linkages (S-S), which is essential for the .biological activity of insulin

Source of insulin secretion: Insulin is the hormone secreted by the **ß** (beta) cells of the islets of Langerhans. Glucagon hormone secreted from **α** (alpha) cell of pancreas and somatostatin is secreted from **δ** (delta) cells .of pancreas

Synthesis of insulin: The beta cells of the pancreatic islets synthesize insulin from a single chain precursor termed proinsulin. In the process of conversion of human proinsulin to insulin, 4 amino acids and the remaining connector or C peptide are removed by proteolysis. Insulin and C peptide are secreted in equimolar amounts in response to any .stimulant

Regulation of insulin secretion: The beta cells receive a :dual autonomic nerve supply

The parasympathetic: which reaches the beta cells as**-1** postganglionic vagal nerve endings upon stimulation; **it enhances the release of insulin,** an effect which can be .blocked by **atropine**

The sympathetic: which feeds both α and ß2-receptors:**-2** stimulation of α-receptors inhibits the release of insulin, whereas stimulation of ß2-receptors promotes its release. Adrenaline had a predominant effect on the α-receptors of the islets. **It therefore inhibits release of insulin.** However, if the α-receptors are blocked by drugs e.g. phentolamine, adrenaline would act mainly on the .ß2-receptors to enhance release of the hormone

Stimulants of insulin secretion: Normally, the release of insulin is controlled by the **blood glucose level**, which directly stimulate insulin release, as well as its synthesis. Insulin secretion is also increased by certain **amino acids (e.g. arginine, and leucine)** and by GIT hormones such as **secretin, gastrin, pancreozymin gastric-inhibitory peptide (GIP).** On the other hand **adrenalin is a potent inhibitor of .insulin secretion**

Mechanism of insulin secretion: Secretion is most commonly triggered by high blood glucose which is taken up by the glucose transporter into beta-cells of pancreas. There, it is phosphorylated by glucokinase, which acts as a glucose sensor. The products of glucose metabolism enter the mitochondrial respiratory chain and generate adenosine k triphosphate (ATP). The rise in ATP levels causes a block of channels, leading to membrane polarization and an influx of .Ca++, which results in pulsatile insulin exocytosis

Glucose-induced insulin secretion appears to occur in two :phases

An initial-burst phase, which peaks in minutes then .1 **.rapidly declines**

.A slow phase, which takes an hour to reach a peak .2

:Insulin receptors

They are highly specific glycoprotein complexes, consisting of **two α subunits** (on the external surface of the cells) and **two ß subunits** (across the cell membrane) linked together by disulphide bonds. When insulin binds to the α subunits a tyrosine residue on the inner ß subunits undergoes autophosphorylation, leading to activation of kinase which become capable of phosphorylation of other proteins and enzymes. **This initiates a cascade of events, facilitating glucose entry into the cells as well as transporting of amino acids and certain ions.** Insulin receptors vary in number inversely with insulin concentration to which they are exposed. Thus with low insulin concentration, the number of receptors increases (up regulation) and with high insulin concentration, the .number of receptors decreases.(down regulation)

:Types of insulin preparations

:Regular insulin (1

It is a short acting, clear aqueous soluble, crystalline zinc insulin. It is **rapid in action** but **short in duration.** Therefore, it should frequently administered daily to control DM. It is usually injected subcutaneously 30 minutes before meals but can be also given intravenously in emergency, e.g., diabetic acidosis. The ultrashort acting insulins, e.g., Lispro, aspart and glulisine have more rapid absorption than regular insulin, so it is usually injected 15 minutes prior to meals. Peaks after 30-90 minutes of its injection with shorter duration of activity. Injected subcutaneously and intravenously in emergency usually in combination .with long acting insulin to assure proper glucose control

Protamine Zinc Insulin (PZI): (Long-acting insulin) (2

The combination of **crystalline zinc insulin and excess protamine** causes the formation of large crystals. Therefore this preparation is sparingly soluble. When injected this formulation serves as a tissue depot, producing **a slow absorption** and **longer duration** of action lasts up to **36 hours.** Because it contains excess protamine it should not be combined in the same syringe with soluble insulin to .avoid its binding with excess protamine

Isophane insulin [Neutral Protamine Hagedorn NPH)] (3

It is a suspension of **crystalline zinc insulin combined at neutral pH with just enough protamine (but no excess).** This **intermediate** acting insulin due to delayed absorption of insulin because of its conjugation with protamine. It should be given subcutaneously (never IV). It can be administered in the same syringe with soluble insulin without .fear of binding with excess protamine

:Lente Insulin (4

Lent insulin formulations do **not contain protamine**; their insolubility results from the **addition of excess zinc in an acetate buffer** rather than a phosphate buffer. The onset of action depend on the physical .state, the ambient zinc concentration, and the pH

a) **Semi-lente insulin**: a microamorphous crystalline form known as prompt insulin zinc suspension. Its onset after 1 hour and has duration .of action of 12-16 hours. It can considered as fast acing insulin

,b) **Ultra-lente insulin:** A large crystalline form with high zinc content known as extended insulin zinc suspension. It is long acting insulin .with an onset of 4-6 hours and a duration of 20-36 hours

-c) **Lente insulin**: Combining 7 parts of ultra-lente and 3 parts of semi ,lente produces insulin zinc suspension. It is intermediate acting insulin .similar to NPH in its onset (1-2 hrs) and in its duration (18-28 hrs)

Insulin glargine: The isoelectric point of insulin glargine is lower than that of human **(5** insulin, leading to precipitation at the injection site, so extending its action. It has a .flat prolonged hypoglycemic effects, that is, it has no peak

:Insulin Combination

Various premixed combinations of human insulins, such as 70% NPH and 30% .regular insulin. 50% of each of these is also available

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:Sources of insulin

Recently human insulin has been produced either by enzymatic modification of pork or bacterial synthesis involving recombinant DNA technique. Human insulin produced by recombinant DNA technique (Humulin) is available in several formulations: regular, NPH, Lente, Ultra-lente. It is largely replaced most of the clinically used insulin which is derived from either **beef (cow)** (differs by 3 AA from human) and pork (differs by 1 AA from human). The beef insulin is slightly more antigenic than pork in .humans

:Adverse effects of insulin

:Hypoglycemia .1

The worst sequela of hypoglycemia is insulin shock. The early symptoms of the hypoglycemia is the sympathetic overactivity such as **sweating, tachycardia, tremors, palpitations, restlessness and hunger** are thought to be occurred by the compensatory secretion of epinephrine. Then hypoglycemia affects the CNS causing mental confusion, motor incoordination, loss of consciousness with or without convulsion. Hypoglycemia is best treated by **administrating glucose** (5% IV) or **glucagon** (1 mg **soluble** vial, IV, IM, SC.) or by giving **oral fruit juice**, or **.carbohydrate**

Local reactions: Irritation at the injection site can **.2** leads to lipoatrophy or lipodystrophy. Site of injection should be rotated. Subcutaneous infusion .can results in infection and local allergic reactions

:Antigenic response (insulin resistance) .3

With the development of new, more highly purified animal insulins and the advent of human insulin, the production of insulin antibodies and .hypersensitivity reactions are less of a problem

Weight gain: Is an undesirable effect of intensive **.4** .insulin therapy

Oral Hypoglycemic Drugs

A- Insulin Secretagogues: These agents are :useful in

Patients with Type 2 diabetes that can not-1 .managed by diet alone

Patients who develop diabetes after the age -2 of forty, and had diabetes

.less than five years

Sulfonylureas .1

1st generation: Tolbutamide (8 hr)

:2nd generation

Glibenclamide (Daonil) (18 hr), Gliclazide (Diamicron) (20 hr)

Glipizide (Minidiab) (20 hr), Glimepiride (Amaryl) (24 hr)

Mechanisms of action

Stimulation of insulin secretion from ß-cells of pancreas (by blocking ATP-sensitive **(1** K+ channels resulting in depolarization and Ca++ influx)

.Reduction of serum glucagon level (2

.Increase binding of insulin to target tissues and receptors (3

Pharmacokinetic

.Given orally, metabolized by liver, excreted by kidney

Adverse Effects

Hyperinsulinemia and hypoglycemia

.Weight gain- GIT disturbance

.Contraindicated in renal and hepatic insufficiency as accumulation may occur

.Cross placenta and cause insulin depletion

Meglitinid .2

Nateglinide (Starlix) (2 hr)

Repaglinide (NovoNorm) (2 hr)

Mechanisms of action

Like sulfonylurea blocking ATP-sensitive K+ channels **(1**

In contrast to sulfonylurea they have **rapid onset and short (2 .duration**

Particularly effective in the early insulin release that occur **(3** after a meal (postprandial glucose regulator)

Pharmacokinetic

Effective orally and inactivated by liver CYP3A4, excreted in bile

Adverse Effects

.Low incidence of hypoglycemia compared to sulfonylurea

Drugs that inhibit CYP3A4 (erythromycin, ketoconazole) may cause hypoglycemia whereas drugs that increase level of this enzyme (barbiturate, carbamazepine, rifampin) may .have the opposite effect

:B- Insulin Sensitizer

These agents lower blood sugar by improving target cell response to insulin without increasing pancreatic insulin secretion. This group includes two classes, Biguanides and .Thiazolidinediones

Biguanides(Metformin (6 hr) .1
(Cidophage, Diaphage)
Mechanisms of action

Reduction of hepatic gluconeogenesis **(**

.Slow intestinal glucose absorption **(2**

Reduction of hyperlipidemia (LDL, VLDL **(3** cholesterol conc., fall and HDL cholesterol .concentration rise

Metformin is DOC for newly diagnosed Type 2 **(4** .diabetics as it reduce cardiovascular mortality

Metformin requires insulin for its action, but it dos not **(5** promote insulin secretion (hyperinsulinemia is not a .problem)

Metformin is effective in treatment of polycystic ovary **(6** diseases, by lowering insulin resistance in these .women so can results in ovulation and pregnancy

Pharmacokinetic

Given orally, not bound to plasma proteins and not metabolized by liver, excreted mainly in the urine.

Adverse Effects

Contraindicated in sever infection, pregnancy, renal and hepatic insufficiency as accumulation may occur.

(2 Long-term use may interfere with vitamin B12 absorption.

(3 The drug should be discontinued in patients requiring IV radiographic contrast agents. Fatal lactic acidosis may occur.

(4 Increased risk of lactic acidosis in patients treated with heart failure medications.

Thiazolidinediones (TZDs) (Glitazones)

Pioglitazone (Glustin) (>24 hr) Rosiglitazone ((Rosizone) >24 hr

Mechanisms of action

Regulate adipocyte production and secretion of fatty acids as well as glucose metabolism, resulting in increased insulin sensitivity in adipose tissues, liver, .skeletal ms

.LDL levels have increased with rosiglitazone **(2**

.HDL levels increase with both drugs **(3**

TZDs lead to an expansion in the subcutaneous **(4** .tissues

They also effective in treatment of polycystic ovary **(5** diseases, by lowering insulin resistance in these .women so can results in ovulation and pregnancy

Pharmacokinetic

inactivated Effective orally, bound to serum albumin and .by liver CYP450, excreted in urine and bile

Adverse Effects

Hepatotoxicity with troglitzone **(1**

Weight gain (due to increase in subcutaneous fat or **(2** .due to fluid retention)

.The latter may lead to or worsen heart failure **(3**

.Headache and anemia **(4**

Women taking oral contraceptives and TZDs may **(5** become pregnant (reduce plasma conc., of estrogen-containing contraceptives

Alpha 2 inhibits insulin release from pancrease but it stimulate glucagon release