Diabetes Mellitus

- Diabetes mellitus (**DM**) is a clinical syndrome characterized by chronic hyperglycaemia due to absolute or relative insulin deficiency or insulin resistance, or both leading to disturbance of metabolism of carbohydrate, protein, fat, water and electrolytes.
- DM is the leading cause of chronic renal failure, lower limb amputations and adult blindness.

Prevalence of DM:

Prevalence rates for type 1 DM are about 0.3%, it accounts for about 10% of D.M. prevalence rates for type 2 DM are 3-5% and 10-15% after age of 50 years, it accounts for about 85-90% of DM.

Diagnosis:

(Normally fasting plasma glucose < 110 mg/dL and post prandial < 140 mg/dL)

Criteria for the diagnosis of DM include:

1- Presence of the classic symptoms of D.M. e.g. polyuria, polydipsia, rapid weight loss + random plasma sugar ≥ 200 mg/dl.
2- Fasting plasma glucose ≥ 126 mg/ dl & post - prandial ≥ 200 mg/dl on more than one occasion.
3- Random plasma glucose ≥ 200 mg/dl (glucose measured in plasma is 10% greater than that of whole blood).

Impaired glucose tolerance (IGT) & impaired fasting glucose (IFG)

- Fasting < 126 mg/dL with post prandial value ≥ 140 and < 200 mg/dL.
- Impaired glucose fasting (fasting plasma glucose > 110 and < 126.
- IGT and IFG refer to intermediate states between normal glucose tolerance and D.M and appear to be risk factors for type 2 D.M.

Classification of Diabetes Mellitus

I- Type I diabetes (β cell destruction → absolute insulin deficiency)

(A) Immune – mediated
(B) Idiopathic

II- Type 2 diabetes (Insulin resistance with relative insulin deficiency)

III- Other specific types of diabetes:

(A) Genetic defects of β cell function causing maturity onset diabetes of the young (**MODY**) and its types (see later).
(B) Genetic defects in insulin action:
* Insulin resistance (Type A see later).
* Lipodystrophy syndromes.

(C) Pancreatic diseases:

* Pancreatitis
* Pancreatectomy
* Cystic fibrosis
* Haemochromatosis

(D) Endocrinopathies:

* Acromegally
* Cushing's syndrome
* Pheochromocytoma
* Hyperthyroidism

(E) Drugs:

* Glucocorticoids – beta blockers – thiazides – thyroxine – diazoxide.

(F) Other genetic syndromes sometimes associated with diabetes:

* Down's syndrome
* Klinefelter's syndrome
* Turner's syndrome
* Didmoad's syndrome
* Friedreich's ataxia
* Huntington's chorea.

IV- Gestational diabetes mellitus (GDM)

Type 1A DM (immune mediated):

- Type 1A DM develops as a result of the synergistic effects of genetic, environmental and immunologic factors that ultimately destroy the pancreatic beta cells.
- Features of diabetes do not become evident until a majority of beta cells are destroyed (about 80%). At this point, residual functional beta cells still exist but are insufficient in number to maintain glucose tolerance, then transition from glucose intolerance to frank diabetes will occur.

After the initial clinical presentation of type 1A DM, a (Honeymoon) phase may occur during which glycemic control is achieved with modest doses of insulin or, rarely, insulin is not needed. However, this fleeting phase of endogenous insulin production from residual beta cells disappears as the autoimmune process destroys the remaining beta cells, and the individual becomes completely insulin deficient.

- There is little or no endogenous insulin, so it is insulin dependant.
- Because of marked hypoinsulinemia, patients are usually presented with acute symptoms and complications: e.g. polyuria, polydipsia and ketoacidosis with or without precipitating factor **(ketoacidosis prone).**
- The age of onset is usually < 30 years, particularly childhood and adolescence, it may occur at any age !?.

Etiology: (The following abnormalities in both the humoral and cellular arms of the immune system have been identified) in type 1A DM.

Autoimmune reaction which may be provoked by viral infection!? → Destruction of Beta cells.

- Anti-islet cell antibodies (ICA) are present in >75 % of cases where pancreatic islet molecules targeted by the autoimmune process leading to ICA which include antibodies to insulin and GAD (glutamic acid decarboxylase). Also T lymphocytes are activated and proliferate when stimulated with islet proteins. Beta cells also seem to be susceptible to the toxic effects of TNF and IL_1.
- This autoimmune hypothesis may explain the HLA association and also how the cyclosporine therapy prolongs Beta-cells survival.

Pathology:

- The pancreatic islets are infiltrated with lymphocytes (in a process termed insulitis). After all beta cells are destroyed, the inflammatory process abates, the islets become atrophic and immunologic markers disappear. So antibodies may be detected in some individuals several years prior to the onset of diabetes.

Type 2 D.M.: (NIDDM)

- It is much more common than type I, the age of onset: > 40 years.
- It is mainly due to peripheral insulin resistance along with impaired insulin secretion and excessive hepatic glucose production.
- Because insulin ↓ is not marked, ketoacidosis usually occurs in presence of precipitating factor. e.g. infections, myocardial infarction or surgery.
- Some patients with Type II may progress to Type I **(late onset IDDM !?)**.
- *Patients with type II D.M may be:*

Non obese 20%	*Obese 80%*
- These patients may respond to dietary therapy alone ± hypoglycemic drugs. - Some patients show insulin resistance.	Obesity leads to insulin resistance, so insulin level is high. These patients need dietary therapy + hypoglycemic drugs.

Obesity, particularly visceral or central is very common in type 2 DM. Adipocytes secrete (leptin, TNF, free fatty acids, resistin and adiponectin) that modulate insulin secretion, insulin action and body weight and may contribute to the insulin resistance.

Markers of inflammation such as IL6 and c-reactive protein are often elevated in type 2 D.M.

Pathology:

- The pancrease contains islet amyloid deposition (amylin) which is co-secrted with insulin.

The terms insulin dependent D.M (IDDM) and non insulin dependent DM (NIDDM) are obsolete, because many individuals with type 2 DM eventually require insulin so, the use of the term NIDDM leads to a considerable confusion.

Also age is not a criterion in the classification system, although type 1 DM mostly develops before age of 30, it is estimated that between 5-10% of individuals who develop DM after age of 30 haye type IA DM.

It is known that type 2 DM more typically develops with increasing age, but it also occurs in children, particularly in obese adolescents.

Maturity onset diabetes of the young (MODY)

It is an autosomal disease, Types:

* **(MODY 1)**: Mutation in Hepatocyte nuclear transcription factor (HNF4α). Presents after adolescence progressive managed by oral agents or insulin.
* **(MODY 2)**: Mutation in glucokinase (glucose sensor). There is mild hyperglycemia from birth, stable and treated by diet alone.
* **(MODY 3)**: Mutation in hepatic nuclear factor 1α (HNFα1). It is like type 1 but presents during adolescence.
* **(MODY 4)**: Mutation in insulin promotor factor 1 (IpF1). It is rare, presentation before 25 years is unsual.
* **(MODY 5)**: Mutation in hepatic nuclear factor 1β (HNF1β). It is rare, early onset diabetes. Renal cysts, proteinuria and renal failure can occur.

Gestational D.M

(It is a glucose intolerance state first detected during pregnancy and limited to pregnancy)

- It develops in 4% of pregnancies especially in the 3rd trimester.
- Beta cell reserve is apparently inadequate for the increased insulin requirement.
- Glucose level return to normal after few wks after labour, 30-60% develop D.M 5-15 years later.

Diagnosis of gestational diabetes **(fasting blood sugar > 126 mg/dL or by oral glucose to tolerance test as bellow)**

- Patients should be screened at 25 weeks of gestation with 50 gm glucose load, diabetes is suggested if the plasma glucose level 1 hour after glucose ingestion ≥ 140-150, this should be followed by a full 3 hour oral glucose tolerance test (OGTT).
- Criteria for gestational D.M by 3 hour OGTT after an oral glucose load of 100 gm are fasting ≥105, 1 hour ≥ 190, 2 hour ≥ 165 and 3 hour ≥ 145 mg/dl plasma.

Inheritance of D.M

I- Type I D.M

- A child of diabetic father has a chance of developing D.M **2,5-5%** than with diabetic mother **1.25-2.5%.**
- If one child in a family has type 1 DM each sibling has **5%** risk of developing D.M.
- Identical twin of a patient with type 1 DM has **30-35%** chance of developing the disease.

2- Type 2 DM

- Identical twins of a patient with type 2 DM have a greater than 90% chance of developing diabetes and about 25% of other patients have a first degree relative with type 2 DM. These data suggest genetic component.

	Type 1	***Type 2***
Age	Usually < 30 yrs	Usually > 40 yrs
Ketosis	Common (ketosis prone)	Uncommon
Body weight	Non obese (lean patients)	Obese 50 - 90 %
Insulin	↓ markedly	Moderate ↓ or insulin resistance (↑insulin)
HLA association	HLA DR3,4	No association
+ ve F. H.	Uncommon	Common
Associated autoimmune disease	+ ve e.g. thyroiditis	- ve
C-peptide	Disappearance of c-peptide	C peptide persists.
Treatment with insulin	Always necessary	Usually not required except after failure of oral hypoglycemics

Level of Insulin and other hormones in D.M

- Type I D.M → marked ↓↓ of insulin.
- Type II D.M → insulin level vary ↓ or ↑ (insulin resistance).
- ↑ Glucagon → glycogenolysis → ↑ glucose.
- Epinephrine ↑, cortisol ↑, and G.H ↑↑ during stress (anti insulin hormones).

Important terms:

- **Potential D.M.** → persons with normal GTT who have increased risk of developing DM for genetic reasons e.g a first degree relative with DM.
- **Latent D.M.**: Discovered by hyperglycemia following steroid GTT !?.
- **Chemical D.M.**: Accidental discovery of ↑↑ blood sugar without clinical symptoms.
- **Stress hyperglycemia**: Episodes of hyperglycaemia during severe illness e.g acute gastroenteritis,pneumonia, strokes or myocardial infarction.
- **Overt D.M.**: (Clinical D.M.) = symptoms of D.M.+ ↑ blood glucose.

Metabolic disturbances in D.M:

- ***Normally insulin tends to ↓ blood glucose through:***
  1- Increasing the cell membrane permeability to glucose except (brain).
  2- Stimulation of conversion of glucose into glycogen.
  3- Inhibiting gluconeogenesis.
- ***In D.M. insulin deficiency or resistance*** → hyperglycemia, if blood sugar exceeds renal threshold for glucose (180 mg %) this will lead to glucosuria.
  - As a result of defective glucose utilization, fatty acids are released from adipose tissue → deposited in the liver → fatty liver.
  - Part of fatty acids transformed into acetoacetic acid and beta hydroxy butyric acid (Ketone bodies) which become source of energy but if accumulate in blood → Ketosis → Ketoacidosis (↓ PH) → Coma
  - In severe cases, protein synthesis become inhibited & aminoacids are converted into → glucose → -ve nitrogen balance & muscle wasting.

Glucose toxicity: i.e Hyperglycemia impairs the function of β-cells and the action of insulin on peripheral tissue → further rise in serum glucose levels.

Causes and pathogenesis of diabetic complications:

1. **Polyol pathway,** where glucose is reduced to sorbitol by aldole reductase. ↑ Sorbitol → ⊖ of ATPase activity & myoinositol depletion. Also it might exert osmotic effects that could lead to cell injury. This will affect nerves, lens, kidney & blood vessels.
2. **Glycosylation** of proteins & collagens, this will affect Hb, plasma proteins & lens proteins, blood vessel walls, lipids & nucleic acids with formation of **advanced glycosylation end products (AGE)** with their undesired effects.
3. Glycosylated collagen becomes less soluble, this may lead to increase thickness of basement membrane of capillaries with narrowing of their lumens affecting the retinal blood vessels, renal glomeruli and vasa norvorum. Also the glycosylation will affects renal tubules & peripheral nerves.

Other mechanisms of vascular complications of D.M:

- ↓ RBCs deformability.
- ↑ Platelet aggregation.
- ↓ Fibrinolysis.
- Hyperlipidemia and hypertension.

} So diabetics are very liable to vascular complications e.g cerebrovascular and cardiovascular diseases.

Clinical Picture

1- Acute presentation:

- Polyuria (due to osmotic diuresis).
- Polydipsia (thirst) due to loss of fluid.
- Weakness or fatigue.
- Vulvovaginitis or pruritis.
- *Polyphagia* as ↓ insulin → inability of glucose to enter the satiety centre.
- *Weight loss* (due to fluid depletion and breakdown of fat and proteins).

Ketoacidosis may occur if the above symptoms are not recognized.

2- Sub-acute presentation:

- Blurring of vision due to glucose induced changes in refraction, pruritis vulvae (candida infection), in addition to polyuria and weight loss.

3- Complications as a presenting feature: (see later).

- Staph skin infection.
- Neuropathy.
- Impotence.
- Coronacy heart disease.
- Retinopathy.
- Urinary tract infection.

4- Asymptomatic diabetes:

Glycosuria or hyperglycemia discovered during routine Investigations.

- Nocturnal eneuresis may signal the onset of D.M. in children.
- Pruritis vulvae & vaginitis signal the onset of D.M. in adult female.
- Diabetes should be suspected in.
  - Obese patient with +ve F.H. of D.M.
  - Patient with peripheral polyneuropathy.
  - Female patient with large babies, polyhydramnios or unexplained fetal death.

Complications of D.M.

1- Skin complications:

- Fungal infection (mucocutaneous candidiasis).
- Bacterial infection → recurrent furuncles & carbuncles.
- Neuropathic foot ulcers (painless, planter).
- Xanthomas (yellow papules or nodules of the skin i.e. lipid deposition due to hyperlipidemia).

Specific diabetic dermatoses

1- Necrobiosis lipoidica

Patch of erythema over the shin of tibia which becomes yellowish, atrophic and may ulcerate.

2- Diabetic dermopathy (pigmented pretibial papules)

Begins as an erythematous area and evolves into area of circular pigmentation.

3- Diffuse granuloma annulare

Small papules that often turn into rings on the dorsum of hands and feet. They are slightly erythematous and become dusky with healing.

Acanthosis nigricans is sometimes a feature of severe insulin resistance and accompanying diabetes

2- Ocular complications:

- **Lids** → styes – xanthelasma (papules of lipid deposition confined to eyelids).
- **Iris** → new vessel formation (rubeosis iridis).
- **Lens** → cataract, also the lens may be affected by reversible osmotic changes in patient with acute hyperglycemia → blurring of vision.
- **External ocular palsy** especially of the sixth nerve.
- **Diabetic retinopathy**:
  - **Background retinopathy.**
  - **Pre-proliferative retinopathy.**
  - **Diabetic maculopathy.**
  - **Proliferative retinopathy.**

Diabetic Retinopathy

D.M causes increase thickness of capillary basement membrane with increased permeability of the retinal capillaries. Aneurysmal dilatation may occur in some vessels while others become occluded, these changes are first detectable by fluorescein angiography. Chronic retinal hypoxia stimulates production of vascular endothelial growth factor causing new vessel formation and increased vascular permeability causing exudative damage.

Background Retinopathy *(↑ capillary permeability)*	***Proliferative Retinopathy*** *(Hypoxia or ischemia of retina)*
- Microangiopathies. - Haemorrhages . - Exudate rich in lipids & proteins (hard exudates).	- Neovascularization due to retinal ischemia. - Vitreous haemorrhage. - Retinal detachment.

- **Diabetic maculopathy**, it may lead to blindness in absence of proliferation, there is macular edema –› macular damage.
- **Preproliferative retinopathy** with cotton wall spots and venous beading.

3- Neurological complications: see neurology (diabetic neuropathy)

- The vascular hypothesis postulates occlusion of the vasa nervorum as the primary cause.
- Also it may be due to accumulation of sorbitol within schwann cells. The earliest functional change in diabetic nerves is delayed nerve conduction velocity.
- Schwann cell injury, axonal damage and myelin degeneration will occur.

4- Vascular complications:

1. ***Microvascular disease*** (e.g. **Nephropathy – Retinopathy - Neuropathy**).
2. ***Macrovascular disease (Atherosclerosis)*** → Stroke, TIAs.
   → Coronary heart disease.
   → Peripheral ischaemia (e.g LL).
3. ***Gangrene of the foot*** (diabetic foot) → may occur with palpable dorsalis pedis artery indicating microangiopathy.
4. ***Angina*** - ***myocardial infarction*** may be painless due to neuropathy.

☆ Risk factors for macrovascular complications in D.M

- Duration
- Increasing age
- Hypertension
- Hyperinsulinism
- Hyperlipidemia
- Proteinuria

☆ Insulin resistance → Hyper insulinism, this leading to dyslipidemia (↑ VLDL, ↓ HDL) see later.

5- Renal complications: (see nephrology):

1. ***Urinary tract infection, pyelonephritis*** which may lead to (papillary necrosis)
2. ***Glomerular disease*** (**Diabetic nephropathy**).
   = Diabetic glomerulosclerosis → Nephrotic $.

Diabetic glomerulosclerosis may be diffuse or nodular. The latter is called as Kimmelstiel Wilson syndrome.

Microscopy of diabetic nephropathy:

- Increased mesangial matrix.
- Thick basement membrane.
- Hyalinization of affrent arteriole.
- Hyalinization of effrent arteriole.

6- Gastro-intestinal complications:

- Change in the bowel habits (autonomic neuropathy)
  - Constipation.
  - Diarrhea.
- Gastroparesis with gastric dyspepsia.

7- Hepatic complications:

1- Fatty infiltration in type II D.M. 2- Glycogen infiltration in type I D.M.

Liver and DM as above plus:

- NASH may occur in diabetics (see liver).
- Auto immune hepatitis may be associated with type 1 A diabetes.
- Haemochromatosis → D.M.
- Liver cirrhosis → Insulin resistance.
- Selection of oral hypolycemics in cases of liver cirrhosis (see later).

8- Genitourinary complications:

- Male: Impotence due to autonomic neuropathy and vascular complications.
- Female: Vulvovaginal infections, dyspareunia.
- Autonomic neuropathy may lead to cystopathy with inability to sense a full bladder and failure to void completely with post-void residual increase → hesitancy, incontinence and recurrent urinary tract infections, diagnosis by cystometry and urodynamic studies.

9- Diabetic foot:

- Amputations in diabetes can be delayed or prevented by patient education and medical supervision.
- Ischaemia, infection and neuropathy combine to produce tissue necrosis.
- It is important to distinguish between the ischaemic and the neuropathia foot.

	Ischaemia	*Neuropathy*
Symptoms	- Claudication - Rest pain	- Usually painless - Painful neuropathy may occur
Inspection	- Trophic changes	- High arch - Clawing of toes
Palpation	- Cold - Pulseless	- Warm - Pulse is present
Ulceration	- Painful - Heel and toes	- Painless - Plantar

Mangement of diabetic foot

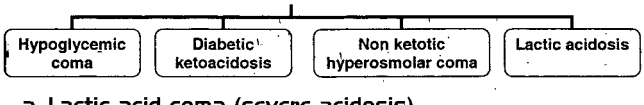
- Infection: early effective antibiotic therapy.
- Ischaemia: The feet are assessed with doppler ultrasound, the occluded vessels can be treated by pass surgery or angioplasty.

10- Diabetic infections:

Diabetics have a greater frequency and severity of infections due to abnormalities In cell mediated immunity and phagocytic function associated with hyperglycemic and diminished vascularization, also hyperglycemia aids the colonization and growth of a variety of organisms e.g candida and other fungal species.

- **Skin** → Staph infections, mucocutaneous candidiasis.
- **Gall bladder** → Emphysematous cholecystitis.
- **Urinacy tract** → Pyelonephritis, perinephric abscess and emphysematous pyelonephritis.
- **Lung** → Tuberculosis.
  → Staph, pneumococcal or gm –ve bacterial pneumonia.
- **Rhinocerebral mucormycosis** is a rare fungal infection.

11- Coma = (Acute diabetic complications):



a. Lactic acid coma (severe acidosis)

- It occurs as a result of accumulation of lactic acid in blood (> 5 mmol/L)
- Patients present with a severe metabolic acidosis without significant hyperglycemia or ketosis This may occur in diabetic patients under biguanides therapy with high doses.
- High risk with biguanides therapy with advanced liver or renal dysfunction.
- Treatment by rehydration + infusion of isotonic bicarbonate 1.26%.

b. Hyperosmolar coma: (It is characteristic of uncontrolled type 2 DM)

- **Marked rise of blood glucose (> 600 mg/dl)**. There is minimal insulin level which is not enough to ⊖ hyperglycemia but enough to ⊖ ketogenesis in the liver. This will lead to hyperglycemia without significant ketosis, **hyperosmolarity > 320 mOsm/L → dehydration**, stupor and coma. The hyperosmolar state may predispose to stroke or myocardial infarction.
- Common precipitating factors include: consumption of glucose rich fluid, steroid therapy.

$$\text{Plasma osmolarity} = 2\,[\text{Na} + \text{K mEq/L}] + \frac{\text{Plasma Glucose mg/dl}}{18}$$

Normally it is 285-300 mOsm/L, Value > 320 mOsm/L = hyperosmolarity.

c. Hypoglycemic coma:

- It results from big doses of Insulin with uncorresponding amount of diet **(Insulin shock)**. It usually occurs in patients under Insulin therapy, also it can be caused by oral hyoglycemics (see hypoglycemia).

d. Diabetic ketoacidosis (DKA):

Diabetic ketoacidosis is the hall mark of type 1 DM. Its main causes are:

- Undiagnosed diabetes.
- Stress of intercurrent illness.
- Interruption of insulin therapy.

Pathogenesis

- In the absence of insulin, hepatic glucose production accelerates, and peripheral uptake by tissues such as muscles is reduced.
- High glucose levels lead to osmotic diuresis with loss of fluid and electrolytes leading to dehydration.
- Plasma osmolarity rises and renal perfusion falls.
- Absence of glucose utilization leading to lipolysis → elevation of free fatty acids in blood, this will lead to conversion of fatty acids into ketone bodies in

mitochodria of the liver **(ketogenesis)** giving acetone, acetoacetate and β hydroxy butyrate.

- Accumulation of ketone bodies produces metabolic acidosis.
- The excess ketones are excreted in the urine, also appear in breath. Ketone bodies → vomiting → further fluid loss.
- Respiratory compensation for the acidosis → hyperventilation (air hunger).
- Progressive dehydration impairs renal excretion of hydrogen ions and ketones aggravating the acidosis.

Clinical Picture of diabetic ketoacidosis

- Hyperventilation **(kussmaul breathing).**
- Nausea, vomiting.
- Deterioration of level of consiousness.
- Dry skin (dehydration).
- Superimposed infection.
- Sometimes acute abdomen may occur.

Investigations:

1- High blood glucose, acidosis.
2- Ketonaemia or heavy ketonuria.
3- Acidosis.

Complications of DKA

- Cerebral edema due to rapid reduction of blood glucose and use of hypotonic saline.
- Acute respiratory distress $
- Thromboembolism
- Disseminated intravascular coagulation.
- Acute circulatory failure.
- Serious infections e.g mucormycosis.

	Hypoglycemic coma	***Ketotic coma***
1- Patient	Follow the treatment	Neglect the treatment
2- Onset	Acute	Gradual
3- Pulse	Tachycardia + good volume	Weak & rapid
4- Blood pressure	High (↑ C.A)	Low (dehydration + acidosis)
5- Skin	Sweaty, pale	Dry & inelastic
6- Breath	Normal	Acetone odour
7- Pupils	Dilated	Not dilated
8- Respiration	Normal	Acidotic
9- Tongue	Normal	Dry (under surface of the tongue)
10- Urine	No sugar	+ve Sugar & acetone.
11- IV glucose	Rapid recovery if early	No effect
12- Coma	Irritable	Not irritable
13- Temperature	Normal, hypothermia may occur	Subnormal

Q ***Acute diabetic complications*** = Diabetic comas & Infections

Q ***Chronic diabetic complications*** = Diabetic triopathy & atherosclerosis

Q Electrolyte deficiency in D.M

- Hyponatremia with uncontrolled diabetes and DKA leading to lethargy and weakness.
- Hypomagnesemia → muscle spasms and tetany.
- Hypophosphatemia → Osteomalacia and muscle weakness.

Investigations of a case of Diabetes

1- Urine for glucosuria: (qualitative rather than quantitative)

Dipstick methods:

Glucose is detected in urine in cases of D.M, renal glycosuria, alimentary glycosuria (gastrectomy, thyrotoxicosis), lactosuria and in the presence of reducing agents in urine e.g. vitamin C and aspirin.

2- Urine for Ketonuria:

- Qualitative detection of ketones bodies can be done by "Nitroprusside test ", dipstick test is available.
- Heavy ketonuria can inhibit some dipstick tests for glucose.

3- Blood sugar tests:

Fasting: Normally 75 - 115 mg /dl

- Fasting ≥ 126 mg/dl is diagnostic.
- If < 126 mg/dl in suspected patient oral glucose tolerance test can be done.

Two hours post - prandial blood sugar: normally < 140 mg/dl

- It usually returns to normal after 2 hours (after intake of 75 gm glucose).
- If ≥ 200 mg/dl, the diagnosis is confirmed.

Random blood sugar ≥ 200 is also diagnostic

Oral Glucose tolerance test (OGTT):

- It is performed only in borderline or suspected cases, diagnosis of impaired glucose tolerance and diagnosis of gestational diabetes.
- Patient should take normal sufficient diet for at least 3 days before the test.

Method:

1- Fasting venous sample of plasma sugar is determined.

2- Bladder is then emptied.

3- 75 gm glucose are then taken orally for adult and 100 gm for pregnant female

4. Samples of venous blood & urine are tested for glucose: at zero, 1/2 hour, 1 hour, 2 hours and 3 hours.

- Normal glucose tolerance is considered when fasting is < 126 mg/dl and PP. < 140 mg with no value between zero time & 2 hours exceeding 200 mg/dl (i.e. peak < 200 mg/dl). All urine samples are -ve for glucose.
- Because of difficulties in interpreting & the lack of standards related to aging, it is replaced generally by fasting hyperglycemia, post - prandial hyperglycemia and randome hyperglycemia as means of diagnosis of D.M.
- ***Abnormalities in OGTT***: (see also DD of glycosuria)
  - Renal glycosuria.
  - Alimentary glycosuria.
  - Impaired glucose tolerance.
  - Flat response i.e. (the difference between the peak level and fasting < 20-25 mg/dl) e.g. malabsorption, insulinoma and adrenal hypofunction.

4- Glycosylated Hb:

- It is produced by a reaction between glucose & the terminal valine of the B-chain of the hemoglobin molecule.
- Normally, it is 4-8 % of the total Hb.
- In diabetics it reaches about 20%, so it is ↑↑ in diabetics with chronic hyperglycemia; it reflects their metabolic control over the preceding 6 weeks.
- Glycosylated plasma proteins **(fructosamine)** may also be measured as an index of control. Glycosylated albumin is the major component, fructosamine measurement related to glycaemic control over the preceding 1-3 weeks.

5- Self glucose monitoring: (home blood glucose monitoring by finger prick)

- Capillary blood glucose measurerments performed by the patients themselves.
- It is useful in patients in whom tight metabolic control is required.
- Patients asked to take regular profiles (e.g. four daily samples on two days each week) and to note these in a record book.
- Blood is taken from the side of a finger not from the tip which is densely innervated.

6- Hyperketonemia

Serum levels of acetoacetate, acetone, and Beta hydroxybutyrate can be done.

All investigations for complications of D.M should be done e.g urine analysis, kidney function tests, serum electrolytes, blood pH, fundus examination, duplex scane for lower limb arteries and CT/MRI for brain.

Differential Diagnosis of glycosuria (melituria)

1- Renal glycosuria:

- Due to ↓↓ renal threshold of glucose, so at some point in the OGTT there is glycosuria inspite of the fact that plasma glucose below renal threshold.

- This is usually a hereditary tubular defect.

2- Lag - storage curve:

i.e. (**alimentary glycosuria**) due to rapid absorption e.g. after gastrectomy (late dumping syndrome) & thyrotoxicosis. There is sharp early rise in plasma glucose > 200 mg/dl + glycosuria, but P.P. is below fasting level.

3- Transient hyperglycemia & glycosuria:

May occur during stress.

4- Reducing substances in urine: (false +ve test)

As salicylates, chloral hydrate.

Renal threshold of glucose is 180 mg/dl.

- Renal glycosuria is a benign asymptomatic condition where glucose appears in urine despite a normal blood level of glucose.
- As many as 50 % of pregnant women normally have demonstrable glucose in urine during the 3rd & 4th months but in late weeks of pregnancy lactose may be present (lactosuria).

Treatment of Diabetes mellitus

Insulin

- Insulin is a polypeptide, formed of 2 chains (A,B) linked by disulfide bonds.
- It is synthesized as preproinsulin which is then converted into proinsulin. The later is hydrolyzed into insulin & C peptide which are secreted in equimolar amount.
- C peptide measurement gives a better index of pancreatic B-cell function than peripheral insulin.
- *Insulin secretion is:*

Increased by	*Decreased by*
• Glucose, sulfonylurea	• Somatostatin, beta blockers
• Amino acids (AA) specially arginine	• Thiazides.

- The main sites of inactivation are the liver & kidney.

Actions of insulin

A- Rapid (transport effects)	B- Gradual (anabolic effects)
- ↑ Entery of glucose, AA, K into the cells - Glucose uptake by the brain is obligatory and is not dependent on insulin, other tissue such as muscles and fats are facultative glucose consumers so insulin facilitates glucose uptake by these tissues.	***Carbohydrates*** - ↑Glycogen storage. - ↑Peripheral Utilization of glucose. - ↓Gluconeogenesis. ***Fat*** - ⊖ Lipogenesis. - ↓ Ketogenesis by the liver. ***Protein*** - ↑ AA transport to the cell. - It has a protein sparing effect.

Mechanism of action of insulin

- The insulin receptor consists of two α subunits which include the binding sites for insulin and two β subunits which traverse the cell membrane.
- When insulin binds to the α subunits this triggers tyrosine kinase activity of the β subunits, leading to migration of a glucose transporter ($GLUT_4$) to the cell surface → increase glucose transport into the cell.

Preparations of insulin

- Insulin was discovered in 1921.
- Bovine and porcine insulin have been the main stays of therapy until the introduction of synthetic human insulin.
- Beef insulin differs from human insulin by three amino acids so induces antibody formation, whereas pork insulin differs by one amino acid so it is relatively non immunogenic
- Human insulin is now available from 2 sources.

  a- **Semisynthetic** i.e. chemical substitution of alanine of porcine insulin by threonine.

  b- Total synthesis of A&B chains separately by recombinant DNA.
- Conventional insulin preparations (bovine, porcine) contain potentially antigenic components. New procedures have been devised to prepare purer preparations. e.g. single mono component (M.C) insulin.
- Soluble insulin can be formulated with protamine or zinc to retard its action.

Type	Trade names	Action
A- *Rapidly acting or soluble (clear solution)* It is also called crystalline insulin or regular insulin. It is given by S.C, I.M, I.V injection.	- Insulin Actrapid. - Humulin R. Each 1 ml = 20 units.	Onset: 30 min. Peak: 2-4 hrs. Duration: 6-8 hrs.
B- *Intermediate acting* Isophan insulin (cloudy solution). It is called NPH (neutral protamine hagedorn). It is given by S.C injection only.	- Insulin NPH. - Humulin N. - Monotard. - Lente. Each 1 ml = 40 units.	Onset: 2 hrs. Peak: 5-10 hrs. Duration: 16-24 hrs.
C- *Long acting* Protamine zinc insulin (PZI). It is given by S.C injection only.	- Insulin ultra-lente. - Insulin ultratard. - Humulin L. Each 1 ml = 40 units.	Onset: 6 hrs. Peak: 10-20 hrs. Duration: 24-28 hrs.

N.B **Recently most insulin preparations are in the form of 100 unit/1ml.**

Insulin mixtures

- Premixed combination of 30% soluble with 70% NPH is the most widely used **(humulin mixtard)** or initard (50/50) are acceptable and convenient for patients.
- Zinc and protamine insulin can be mixed in the syringe with soluble insulin immediately prior to injection.

Indications of insluin:

1- Type 1 DM.

2- D.M not adequately controlled with diet and oral agent (type 2 DM).

3- Hyperglycemic ketoacidosis, hyperosmolar coma.

4- Critical episodes in type 2 DM e.g. operation, infection, ischemia, trauma &pregnancy.

5- Insulin test of hypothalamic hypophyseal adrenal axis.

6- Hyperkalemia.

7- Insulin stimulation test for GH assessment.

Insulin analogues:

- Insulin lispro **(Humanlog)** is a regular insulin analogue which dissociates much more rapidly and thus enter the circulation more rapidly than soluble insulin.

Special problems in D.M:

1- Infection: There is increased demand for insulin. Also, regular insulin should be used.

2- Pregnancy & labour:

- Oral antidiabetic are contraindicated.
- Single dose insulin is changed into multiple doses.

3- Surgery: (↑ insulin demand)

- Preoperatively: shift to regular insulin.
- Postoperatively: continue insulin therapy.

Complications of insulin therapy:

1- Hypoglycemia is the most common complication (see hypoglycemia)

2- Insulin allergy:

- Local reaction as pruritic erythematous indurated lesion.
- Angioedema, anaphylaxis
- Allergy can be avoided by changing the source of insulin. Antihistaminic & topical steroids are helpful.

3- Insulin resistance **(insulin antibodies)** with dyslipidemia and hypertension. The insulin requirement is increased up to 200 unites/d or more.

4- Weight gain:

- Patients who are non compliant are predisposed to weight gain with insulin therapy (insulin makes you feel hungry).

5- Pseudo insulin resistance **(Somogyi phenomenon);**

- Occurs in patients over treated with insulin → hypoglycemia with release of anti insulin hormones → rebound hyperglycemia.

Treatment: reduction of insulin dose and dietary control.

6- Insulin lipodystrophies:

Atrophy or hypertrophy of S.C. fatty tissue at the site of insulin injection.

7- Peripheral edema due to salt and water retension.

Insulin resistance: It is a clinical condition characterized by increased serum insulin level with high or normal blood glucose with development of the metabolic $ or syndrome x (see later).

Causes:

- Surgery, infections, acromegaly, Cushing's syndrome, acanthosis nigricans and polycystic ovary syndrome
- Insulin antibodies **(prereceptor resistance),** obesity **(receptor resistance),** failure to activate receptor tyrosine kinase **(post receptor resistance).**

Treatment:

- Change to human preparations, treatment of the cause, immunosuppression by corticosteroids in cases of insulin antibodies, weight reduction.
- Manifestations of the metabolic syndrome or syndrome x include hyperinsulinemia, hypertension. Dyslipidemia (↓ HDL and ↑ VLDL), central obesity, type 2 DM or impaired glucose tolerance (IGT) or impaired fasting glucose and accelerated cardio vascular disease.

Dawn phenomenon:

Early morning rise in plasma glucose requiring increased amounts of insulin. It is independent of Somogyi mechanism. The nocturnal surge of growth hormone release may be a factor.

Oral antidiabetics

They are particularly used in type 2 DM without ketosis when an initial trials on diet alone has failed to control symptoms and hyperglycemia.

They are 2 groups: **a. Sulfonylurea.** **b. Biguanides.**

A- Sulfonylurea

Mechanism of action:

1- Stimulate insulin release from β cells (**insulin secretagogues**) through closure of ATP-sensitive potassium channels on the B-cell membrane; this will promote calcium influx, leading to insulin release.
2- They increase insulin sensitivity in peripheral tissues!?.
3- They reduce the hepatic release of glucose.

Indications:

1- NIDDM.
2- Tolbutamide test to diagnose insulinoma.
3- Chlorpropamide in treatment of nephrogenic diabetes insipidus.

Adverse reactions:

1- Hypoglycemia. 2- Alcohol intolerance, allergy.
3- Chlorpropamide causes → hyponatremia.
4- GIT upset, cholestatic jaundice.

Sulfonylureas should be used with care in patients with liver disease, and only those primarily excreted by the liver should be given to patients with renal impairment.

B- Biguanides

Mechanism of action:

1- ↓Absorption of glucose from the gut.
2- ↑Anaerobic metabolism of glucose to lactate.
3- ↑Insulin sensitivity (upregulation of insulin receptors). i.e they are insulin sensitizers.
4- ↓ Hepatic production of glucose by inhibiting gluconeogenesis.

Indications:

1- As a supplement to a sulfonylurea when this with dietary advice fail to control blood sugar.
2- Over weight diabetics.
3- To ↓ insulin requirement where insulin resistance is not due to antibodies.

Adverse effects:

1- Lactic acidosis may occur especially in patients with severe hepatic or renal disease.
2- GI upset: Anorexia, vomiting, epigastric discomfort and diarrhea.

Unlike sulphonylureas, biguanides do not induce hypoglycemia in non diabetic individuals.

Preparations & doses

Drug	Trade name	Dose (mg/d)	Half life (hours)
1- Sulfonylureas:			
1st generation:			
- Chlorpropamide	**Pamidine** (100 mg, 250 mg) tab	100-500	36
- Tolbutamide	**Diamol** (500 mg) tab	500-3000	4
2nd generation: (less drug interactions)			
- Glibenclamide	**Euglucone or Doanil** (5 mg) tab	2.5-15	12
- Gliclazide	**Diamicron** (80 mg) tab	40-240	10
- Glipizide	**Minidiab** (5 mg) tab	2.5-30	3.5
- Glimepiride	**Amaryl** (1mg, 2mg, 3mg) tab. It's duration of action is 24 hr	1-8	
2- Biguanides:			
- Metformin	Cidophage or Glucophage (850 mg, 500 mg) tab	850-2250	5

- **Glibenclamide:** long half life, renal excretion, avoid in renal impairment. It is prone to induce severe hypoglycemia. It should be avoided in elderly.
- **Gliclazide:** fairly long half life, mainly metabolized by liver, can be used in renal impairment. It cause few side effects.
- **Chlorpropamide:** long acting, renal excretion, avoid in renal impairment.
- **Tolbutamide**: short half life preferred in old age, metabolized by liver, can be used in renal impairment.
- **Glimepiride** has low incidence of hypoglycemia and can be administrated once daily.

Other recent oral hypoglycemic drugs

1- Glucosidase inhibitors e.g. Acarbose (Glucobay) 50 mg tab TDS

- These drugs inhibit the enzymes involved in the breakdown of carbohydrate in the intestine → ↓ glucose absorption.
- They will reduce the postprandial rise in blood glucose. It can be used in patients with liver disease.

Side effects: - Abdominal discomfort, flatulence and diarrhea.

2- Repaglinide, (Novonorm)

- It stimulates insulin production at meal times, 0.5 mg or 1 mg before meal times.

3- Pioglitazone (Glustin) 15-30 mg/D one dose, it reduces insulin resistance i.e insulin sensitizer, also it reduces hepatic glucose production by inhibiting gluconeogenesis.

Treatment of type 1 diabetes

Diet

- Caloric recommendations are 36 kcal/kg for males and 34 kcal/kg for females.
- Carbohydrate contents is 50-60%, (4 Kcal/gm), proteins 15%, (4 Kcal/gm) fats 30-35% (9 Kcal/gm) of total energy intake. Polyunsaturated fats are preferred. Salt restriction for hypertensive diabetics.
- The minimal proteins requirement for good maturation is 0.9 g/kg.
- The use of non-nutritive sweeteners e.g aspartame is useful.

Interventions in prediabetic stage (+ve islet's Abs) to prevent type 1A DM!?

- Neonatal and early infancy cow milk deprivation.
- Immune suppression by cyclosporine or azathioprine.
- Antioxidant.

The side effects and risk of long term immunosuppression are felt to be greater than the risk of diabetes.

Insulin therapy

The usual required insulin dose in most insulin deticient diabetics is about 0.5 to 0.8 unit per kg/D, it can be given by the different following methods (with trial and error!?) with initial daily dose 0.3 units/kg/D. Sometimes the required insulin is higher.

A- Conventional insulin therapy:

- We can give one or two injections/day of intermediate acting insulin with or without the addition of small doses of regular insulin.
- Adults of normal weight may be started on 15-20 units/day, obese patients may be started on 25-30 units/day. Changes should be no more than 5-10 units/step.
- Single insulin injection provides adequate control in patients with residual insulin secretion.
- Poorly controlled patients should be placed on twice daily insulin injections with about two thirds of the total insulin given before breakfast and the remainder before supper using mixtard insulin as below.

Example: Most patients on twice daily insulin injections treated with a mixture of intermediate and regular insulin e.g. 20 units NPH plus 10 units of regular before breakfast and 10 units of NPH plus 5 units of regular before supper using **mixtard insulin** (70/30 each 1 ml = 40 or 100 units).

B- The multiple subcutaneous insulin injection technique:

- Administration of intermediate or long acting insulin in the evening as single dose together with regular insulin prior to each meal.
- One approach is to give 25% of the daily dose as intermediate insulin with the other 75% given as regular insulin divided such that 40, 30 and 30 percent is given 30 minute before breakfast, lunch and supper respectively.
- The introduction of **(pen injection)** devices has made this approach much more acceptable to patients.

C- Infusion devices:

- **CSII (continuous subcutaneous insulin infusion)**; insulin is delivered by a small pump strapped around the waist.
- Insulin is delivered at a basal rate continuously throughout the day via a needle in the subcutaneous tissue of abdominal wall.
- Mealtime doses are delivered when the patient touches a button on the side of the pump.

D- Pancrease /Islet transplantation:

- Because of long term Immunosuppression pancrease/islet transplantation is at present an option for only a select group of patients, mainly for type 1 D.M requiring renal transplantation, this is also more effective in preventing nephropathy in the grafted kidney.

Treatment of type 2 diabetes

Diet: (similar to diet in type I DM but !?)

- The majority of type 2 DM, patients are obese, the main goal of diet therapy is therefore weight loss.
- In thin type 2 DM, patients calories should not be restricted.
- The diet of all patients with type 2 DM should be limited in fat & cholesterol.

Prevention of type 2 DM

It is indicated in individuals with a strong family history of DM or those with impaired glucose tolerance (IGT) or impaired fasting glucose.

- Diet control and exercise to maintain normal body mass index (BMI).
- Metformin is helpful in prevention or delaying of D.M!?
- Ramipril (ACE) and pravastatin (cholesterol lowering) are also helpful !?

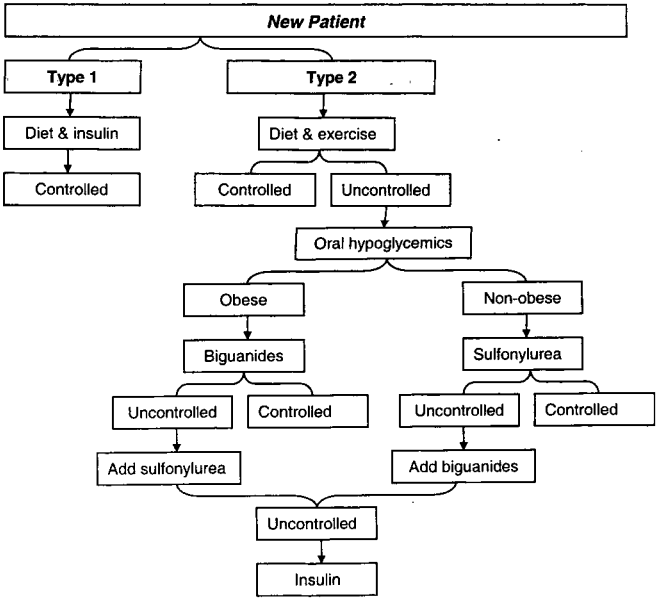
Oral antidiabetic drugs:

- In patients with type 2 D.M with no successful metabolic control with dietary therapy alone, the next therapeutic step is oral antidiabetic + diet.

Insulin: Some patients with type 2 DM require insulin therapy.

- Acceptable metabolic control may not be achieved from the start with oral antidiabetic **(1ry failure),** or a patient who initially responded to oral agent may with time fail to respond **(2ry failure).**
- The use of insulin in type 2 diabetes is similar to that described in type I diabetes, except that because of the presence of insulin resistance, higher doses may be needed.
- Because of some residual endogenous insulin secretion, a single daily dose of an intermediate insulin may be enough.

Treatment Pathway for D.M.:



The ideal goals for glycemic control:

- Fasting plasma glucose (90-130 mg/dL).
- Peak post prandial plasma glucose < 180 mg/dL.
- Glycosylated Hb < 7%.

Management of diabetic ketoacidosis:

Insulin therapy (crystalline)	*Fluid therapy*	*K therapy by infusion*
• Start I.V insulin, 5u/h. • When blood sugar <250 mg/dL reduce insulin to 1-4 u/h.	• Start I.V 0.9% saline 1 liter in 30 minutes. • Then 0.5 liter 0.9% saline in 30 minutes. • Then 0.5 liter 0.9% saline in 1 hour. • Then 0.5 liter 0.9% saline in 2 hours. • Then change to glucose 5% 0.5 liter/2h when blood sugar < 250 mg/dL.	• There is total body K deficit, although the initial levels may not be low due to acidosis. • Insulin therapy leads to K influx into the cell, so K therapy must be started with initiation of insulin therapy, as follows: - If plasma K > 5.5 meq/l give no K. - If K 3.5-5.5 give 20 meq for each liter of infused fluids. - If K < 3.5 give 40 meq for each liter of infused fluids.

Notes

- The insulin regimen can be started by 10-20 u I.M followed by 5 u/h I.M.
- Average fluid deficit = 6 liters
  - 3 L for extra-cellular compartment, replaced by saline.
  - 3 L for intracellular compartment, replaced by glucose.
- The patient may need urinary catheter (if no urine is passed after 2 hr), nasogastric tube (if drowsy), antibiotic (if infection is likely).
- If plasma Na > 155 meq/L give saline 0.45 % rather than 0.9% until Na falls to 140 meq/L.
- If PH < 7 give 300-500 ml 1.26% sodium bicarbonate over 30 minutes.
- Monitor blood glucose, Na, K, pulse, blood pressure, urine output, respiration, plasma osmolarity and PH.
- Continue with the above regimen until fluid deficit is replaced, ketonuria abolished and adequate oral intake can be started.

Treatment of hyperosmolar coma (non ketotic):

- The therapy for the hyperosmolar coma is very similar to that for DKA, with the administrations of insulin, fluids & K.
- This coma is complicated sometimes with: **M.I – stroke – infection – pulmonary emboli.**
- Small dose of insulin is required to prevent rapid lowering of blood sugar, to prevent brain edema **(desequilibrium syndrome).**
- Low molecular weight heparin may be required to prevent thrombotic complications.

Brittle diabetes

This term is used to describe unpredictable fluctuations of blood glucose with recurrent episodes of hyperglycaemia with or without ketoacidosis and/or recurrent hypoglycaemic episodes.

Causes of recurrent hypoglycaemia:

- Over treatment with insulin.
- Low renal thereshold for glucose.
- Endocrine causes e.g pituitary or adrenal insufficiency.
- Gastroparesis due to autonomic neuropathy leading to mismatch between the time of absorption and the peak of insulin action.
- Renal failure.
- Uncooperative, unintelligent patient.

Causes of recurrent ketoacidosis:

- Inappropriate insulin combinations.
- Intercurrent illness e.g unsuspected infections.
- Unknown aetiology.

Causes of recurrent hyperglycemia:

- As ketoacidosis plus somogyi and dawn phenomena.

Factitious disorders and malingering behaviour may be also responsible for blood glucose fluctuations.

Management of brittle diabetes

(1) Hospitalization, careful evaluation of the patient.
(2) Treatment of cause.
(3) Use crystalline insulin at regular interval e.g every 6 hours.
(4) Insulin pump.

Hypoglycemia

Definition and diagnosis of hypoglycemia is based on the presence of a triad called ***whipple's triad:***

1) A low plasma glucose concentration (< 45-50 mg/dl).

2) Symptoms consistent with hypoglycemia.

3) The improvement of these symptoms following an increase in plasma glucose.

Glucose thresholds for hypoglycemia induced symptoms and physiologic responses vary widely so, whipple's traid is important for diagnosis.

Causes of hypoglycemia:

Fasting Hypoglycemia

- Insulinoma, hepatoma.
- Critical illness e.g extensive hepatic dysfunction, chronic renal failure, malnutrition or anorexia nervosa.
- Drugs: Insulin, oral hypoglycemics (it may be factitious).
- Hormonal deficiency: (GH, Epinephrine, Cortisol).

Postprandial (reactive) hypoglycemia:

- Alimentary hypoglycemia (reactive) e.g dumping syndrome after gastric surgery (see GIT)
- Functional hypoglycemia.
- Reactive hypoglycemia of diabetes, sometimes occurs with early diabetes (late but excessive release of insulin after a carbohydrate diet).
- Galactosemia, fructose intolerance, ethanol induced.

Important Causes of Hypoglycemia and approach to the patients

1) Insulinoma:

- Relatively rare tumors between age of 40-70 years.
- Diagnosis by low glucose level (< 45 mg/dl) in presence of high plasma insulin (6 U/ml or more).
- It is also helpful to measure plasma C peptide (high).
- CT scan, celiac or superior mesenteric arteriography for diagnosis.

Treatment:

- Surgical removal.
- Medical to prevent insulin release e.g by diazoxide, octreotide.

2) Insulin therapy

- The presence of hypoglycemia, high insulin levels and low C peptide indicate excess exogenous insulin.

3) Oral hypoglycemics

- Common with long acting drugs.
- This occurs especially in patients with renal & hepatic diseases.
- Insulin level is high, C peptide is high like insulinoma, so search for a hypoglycemic agent in blood or urine.

4) Postprandial Hypoglycemia (reactive hypoglycemia)

- Observed in patients after gastrectomy **(alimentary hypoglycemia)** this is due to rapid glucose absorption with excessive insulin release, glucose metabolized rapidly but insulin levels remain high resulting in hypoglycemia 1-2 hours postprandially.

- Idiopathic postprandial hypoglycemia.

Postprandial hypoglycemia should be treated with frequent small meals that are low in carbohydrate, rich in protein.

Clinical presentation of Hypoglycemia:

1) ***Secondary to catecholamine release*** **(Adrenergic)** this occurs with rapid decrease in glucose level:

- Sweating	- Anxiety	- Tachycardia.
- Tremors	- Hunger	- Fainting.

2) ***Secondary to CNS Dysfunction*** **(neuroglycopenic symptoms)** occurs with slow decrease of glucose level.

- Confusion	- Headache.	- visual disturbance
- Irritability	- Convulsions	- Coma.

3) ***Nocturnal hypoglycemia*** (usually due to excessive insulin therapy)

- Morning headache	- Seizures during sleep.
- Night mares	- Restlessness.

4) ***Hypoglycemia may be asymptomatic.***

Grades of hypoglycemia

Mild: Patient is aware of hypoglycemia, he responds and treat himself with oral glucose or sucrose.

Moderate: Patient is also aware but cannot respond or treat himself, recovery is by oral glucose or sucrose.

Severe: There is coma or semicoma, recovery by I.V glucose, glucagon S.C or I.M can be used

Treatment of severe hypoglycemia:

- Initial treatment of a confused or comatosed patient with severe hypoglycemia is to infuse a bolus of 50 ml of 50%. Glucagon 1mg IM or S.C can be used.
- Then give continuous infusion of 10% of glucose at a rate sufficient to keep the glucose level greater than 100 mg/dl.
- In many situations especially following long acting insulin or oral hypoglycemic drugs, the hypoglycemia will last for an extended period of time, so continue the treatment with close observation.

Mild to moderate cases can by treated by oral glucose or sucrose or 100 ml of sweet drink.

Q. Causes of Hypoglycemia in patients taking insulin or sulphonylurea ?.

- Missed, delayed or inadequate diet.
- Unexpected or unusual exercise
- Errors in doses or schedule
- Poorly designed insulin regimen.
- Gastroparesis (autonomic neuropathy).
- Malabsorption or dumping.
- Unrecognized other endocrine disorder e.g Addison's disease
- Factitious.