

Diabetes Mellitus

By

Prof. Dr; Nabil Lamon

Definition:

- It is a clinical syndrome characterized by :
 - Chronic persistent hyperglycemia.
 - Disturbed metabolism of Ptn , Fat, CHO & Electrolyte.
 - Microangiopathy esp. in Retina, Glomeruli, & vasa nervosa.
- It is caused by: (absolute or relative lack of insulin)

Classification of DM

1. Type I diabetes

A. Immune mediated B. Idiopathic

2. Type 2 diabetes

3. Gestational DM

1. Other specific types:

-Genetic defects of B-cell function

-Genetic defects in insulin action

-Exocrine pancreatic causes

- Congenital cystic fibrosis
- Chronic pancreatitis, Hemochromatosis
- Fibrocalculous pancreatopathy (tropical DM - tropical malnutrition)

-Endocrinal causes

- Acromegaly, Pheochromocytoma
- Cushing syndrome, Conn's syndrome
- Somatostatinoma Glucagonoma,
- Thyrotoxicosis

-Infections:

- congenital rubella
- cytomegalovirus

-Drugs: interferon, Corticosteroids, CCP

-Other genetic syndromes: Down's syndrome - Klinefelter syndrome

-Uncommon forms of immune mediated diabetes: anti-insulin receptor Ab

N.B: (MODY type):** Mature Onset Diabetes in the Young:

- Represent 15 % of cases, autosomal dominant, in young obese people

-Treated by oral antidiabetics, less liable for microangiopathy

** (LADA): (Late onset Autoimmune Diabetes of Adult)

Pathophysiology of type1 DM:

- Type1 DM is the result of destruction of insulin-secreting beta cells of the islets of Langerhans in the pancreas. As beta-cell mass declines,

insulin secretion decreases until the available insulin no longer is adequate to maintain normal blood glucose levels.

- After 80-90% of the beta cells are destroyed, hyperglycemia develops and diabetes may be diagnosed.
- Patients need exogenous insulin to reverse this catabolic condition, prevent ketosis, decrease hyperglucagonemia, and normalize lipid and protein metabolism.
- Currently, autoimmunity is considered the major factor in the pathophysiology of type 1 DM.
- Approximately 85% of type 1 DM patients have circulating islet cell antibodies, and the majority also has detectable anti-insulin antibodies before receiving insulin therapy.
- The most commonly found islet cell antibodies are those directed against glutamic acid decarboxylase (GAD), an enzyme found within pancreatic beta cells.

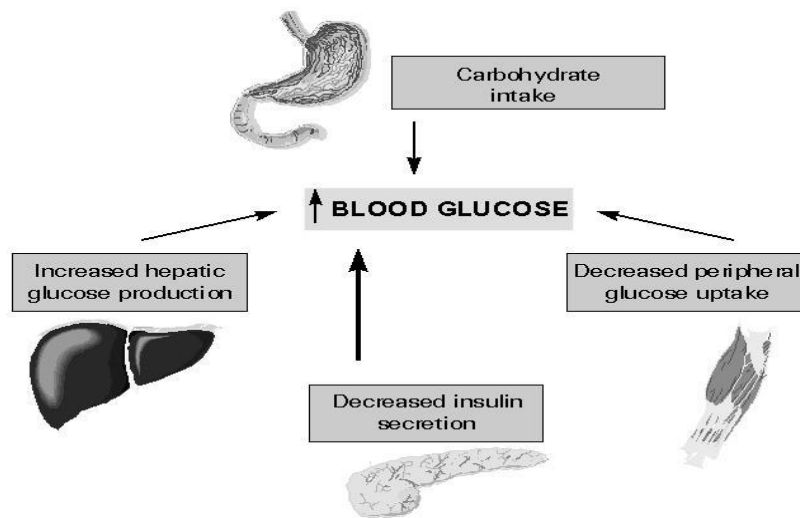
Etiology

- Type 1A DM results from autoimmune destruction of the beta cells of the pancreas and involves both genetic predisposition and an environmental component.
- From 90% to 95% of young children with type 1 DM carry HLA-DR3 or HLA-DR4. Carriage of both haplotypes (ie, DR3/4 heterozygotes) confers the highest susceptibility.
- Extragenetic factors also may contribute. Potential triggers for immunologically mediated destruction of the beta cells include viruses (eg, enterovirus, mumps, rubella, and coxsackievirus B4), toxic chemicals, and exposure to cow's milk in infancy, and cytotoxins.

Pathophysiology of type 2 DM

- Type 2 diabetes is characterized by a combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells.
- Beta-cell dysfunction develops early in the pathologic process and does not necessarily follow the stage of insulin resistance.
- Insulin resistance, which has been attributed to elevated levels of free fatty acids and proinflammatory cytokines in plasma, leads to decreased glucose transport into muscle cells, elevated hepatic glucose production, and increased breakdown of fat.
- A role for excess glucagon cannot be underestimated; indeed, type 2 diabetes is an islet paracrinopathy in which the reciprocal relationship

between the glucagon-secreting alpha cell and the insulin-secreting beta cell is lost, leading to hyperglucagonemia and hence the consequent hyperglycemia



Scheme for type 2 DM pathophysiology

- For type 2 diabetes mellitus to occur, both insulin resistance and inadequate insulin secretion must exist. For example, all overweight individuals have insulin resistance, but diabetes develops only in those who cannot increase insulin secretion sufficiently to compensate for their insulin resistance.
- In the progression from normal to abnormal glucose tolerance, postprandial blood glucose levels increase first. Eventually, fasting hyperglycemia develops as suppression of hepatic gluconeogenesis fails.

Etiology

- The etiology of type 2 diabetes mellitus appears to involve complex interactions between environmental and genetic factors. Presumably, the disease develops in a diabetogenic lifestyle (ie, excessive caloric intake, inadequate caloric expenditure, obesity) superimposed on a susceptible genotype.
- The genetics of type 2 diabetes are complex and not completely understood. Evidence supports the involvement of multiple genes in pancreatic beta-cell failure and insulin resistance.

The major risk factors for type 2 diabetes mellitus are the following:

- Age greater than 45 years (though, as noted above, type 2 diabetes mellitus is occurring with increasing frequency in young individuals)

- Weight greater than 120% of desirable body weight
- Family history of type 2 diabetes in a first-degree relative (eg, parent or sibling)
- Hispanic, Native American, African American, Asian American, or Pacific Islander descent
- History of previous impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) or A1C >5.7
- Hypertension (>140/90 mm Hg) or dyslipidemia (HDL cholesterol level < 35 mg/dL or triglyceride level >250 mg/dL)
- History of gestational diabetes mellitus or of delivering a baby with a birth weight of over 9 lb
- Polycystic ovarian syndrome (which results in insulin resistance)

Diagnosis of DM

-C/P - Investigation

-Complication -DD

■ Clinical Picture

A. **Asymptomatic:** in 1/3 of cases

B. **Classic symptoms:**

1. Polyuria : with nocturia
2. Polydypsia
3. Polyphagia with weight loss
4. Pruritis especially of vulva
5. Pains & paresthesia
6. Premature loosening of teeth
7. Blurred vision : due to osmotic swelling of lens

C. **Symptoms of complications:** acute, chronic.

Complication of DM

Acute complications

1. Diabetic comas
2. Infections
3. Complication related to systems
 - ARF
 - AMI
 - Acute neuropathy

Chronic Complication

- Neurological compl.
- Ocular Complication.
- CVS complication.
- Pul. complication
- GIT complication.
- Renal complication
- Genital complication.
- Skin complication.
- Diabetic Foot.
- Rheumatological comp
- Infection
- Psychiatric complication
- comp. of therapy

Differential Diagnosis

A) D.D. of reducing substance in urine

1. Glucosuria
 1. Renal glucosuria due to Low renal threshold:
 - Pregnancy
 - De-Toni Fanconi syndrome
 2. Alimentary glycosuria: Gastrectomy, liver cirrhosis
 3. Cerebral glucosuria : Sub arachinoid hge , Meningitis
2. Other Sugar in urine : Fructosuria , galactosuria, pentosuria
3. Other Reducing substances in urine : Vit.C , salicylates

B). D.D. of symptomatology

1. loss of weight inspite of good appetite:
 - Malabsorption syndrome
 - Parasitic infestation
 - Thyrotoxicosis
1. Other causes of Polyuria

C). 1ry from 2rv DM: (Cushing disease)

D). Type 1 DM from Type 2 DM:

	Type I DM = (IDDM)	Type 2= (NIDDM)
Incidence	5-15%	85%
Subtypes	Type I A : 80 % immune Type I B : 20 % idiopathic	Type 2-obese: 80 Type 2-non obese : 20

	Genetic locus	Chromosome 6 - recessive HLA DR3, DR4,B8,B15,	Chromosome 11 - multifactorial absent
	Pathogenesis	See before	See before
	Age of onset	< 30 years	> 30 years
	onset	sudden	Gradual
	symptoms	Severe, including coma	May be no symptoms
	Complication (DKA)	Ketolabile	Ketoresistant
Investigation	Insulin	Low or absent	- Abnormal - ↑↑ insulin resistance
	Glucagon	High and suppressed by insulin	High and resistant to insulin
	Auto Ab	ICA, ICSA, Anti-GAD	Absent
	C-peptide	deficient	increased
	Treatment	Insulin is a must	-Diet - OHD ± insulin

Investigations

A- To diagnose DM

	Normal (mg/dl)	Prediabetes	diabetes
Fasting	70 to less than 100	100-125 (IFG)	≥ 126
2 hr. PP	<140	140 -199 (IGT)	≥ 200
HbA1C	<5.7	5.7-6.4	≥6.5

■ IFG: "Impaired fasting glucose"

100 - 125 mg

■ IGT: "Impaired glucose tolerance"- 2h. P.P. 140 -199 mg

IGT Personnel: (rule of third)

1/3 remain IGT

1/3 develop frank DM,

1/3 return to normal plasma glucose

B- To diagnose type of DM

1. Plasma insulin level

■ it is low in type 1 DM & show early rise in type 2 DM

2. C -peptide level : assess endogenous insulin secretion

3. Auto antibodies:

■ Anti insulin receptorAb in immune mediated type 1 DM.

■ Anti GAD (glutamic acid decarboxylase)

■ ICA

4. For the cause

■ If 2 dry DM is suspected e.g. Cushing syndrome.

C- To monitor diabetic patients

■ Retinopathy: Fundus Exam.

■ Nephropathy : urine analysis for microalbuminuria

■ ECG

■ Lipid profile

D- To monitor diabetic patients

■ BLOOD:

1. Glycosylated proteins

a- Hb A1c:

Target in diabetics: < 7%

■ Formed due to non-enzymatic glycosylation of amino acid valine & lysine in β chain of HbA

■ Its % gives an estimate of diabetic control for the preceding 3 months.

■ The Normal level 4 - 6 % of total Hb

b- Other glycosylated proteins: fructosamine (glycosylated albumin) Factors interfering with measurement of A1c.

a- False high values: uremia, high concentrations of fetal hemoglobin (HbF), high aspirin doses (usually >10 g/day), or high concentrations of ethanol.

b- False low values: hemoglobinopathies, hemorrhage and hemolytic disorders.

Complication of diabetes

1- Neurologic complications:

Brain comp.

Cerebral Atherosclerosis

Diabetic Coma

▫ DKA coma

▫ HHNK coma

▫ Hypoglycemic coma

▫ Lactic Acid coma

Spinal cord

1. Pyramidal tract affection : diabetic lateral sclerosis
2. Anterior spinal artery occlusion
3. Diabetic pseudotabes

Nerve

- Peripheral neuropathy
- Autonomic neuropathy

Hypoglycemia

Definition:

1-In Patients with diabetes

Hypoglycemia is defined as all episodes of *an abnormally low plasma glucose* concentration (with or without symptoms) that expose the individual to harm, (at a self-monitored blood *glucose (SMBG) level* ≤ 70 mg/dL)

2-In Patients without diabetes

Whipple's triad :

- * Patient's symptoms of hypoglycemia.
- * Documented low patient's plasma glucose when the symptoms are present.
- * The symptoms can be relieved by administration of glucose.

Hypoglycemia mechanisms

1-Insulin secretion declines as the glucose declines to low-normal levels, around 80 mg/dl in venous blood.

Low insulin levels stimulate increases in hepatic and renal glucose production

2-Epinephrine is released by the adrenal medullae at mild levels of hypoglycemia (65–70 mg/dl). , And stimulates hepatic and renal glucose production and decreases glucose utilization by peripheral tissues

3-Glucagon release:

At glucose (65–70 mg/dl) Increases hepatic glucose production via glycogenolysis and gluconeogenesis.

4- Cortisol and growth hormone release

Contribute only if the hypoglycemia persists for several hours.

5-Neuroglycopenic symptoms

Develop If glucose levels to decline into the mid-50 mg/dl range.

Symptoms:

1-neurogenic (autonomic)

(Warning symptoms) Caused by sympathetic neural response to blood glucose <65

- Sweating
- Weakness
- Palpitations
- Tremor
- Nervousness
- Hunger
- Paresthesias

2- neuroglycopenia

- Confusion, Loss-of-consciousness.
- Cognitive impairment.
- Seizure.
- Focal neurologic deficits.
- Visual disturbances.

Signs

Diaphoresis and pallor .

Heart rates and systolic blood pressures are raised,

Neuroglycopenic manifestations

Outcome and complications

- The vast majority of episodes are reversed after the glucose level is raised to normal.
- Prolonged untreated hypoglycemia can lead to:

1- Transient neurological deficits , but Permanent neurological damage is rare.

2- Death

CAUSES OF HYPOGLYCEMIA

Drugs are the most common cause

A- In diabetes

Exogenous insulin and insulin secretagogue (sulfonylureas)

NB: Insulin sensitizers (metformin , thiazolidinediones), glucosidase inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and dipeptidyl peptidase IV inhibitors are much less common causes hypoglycemia.

B-Hypoglycemia in patients without diabetes

1-Drugs

- Insulin, sulfonylureas,
- Quinolones,
- Pentamidine ,
- Quinine ,
- Angiotensin-converting enzyme inhibitors,
- IGF-1
- Alcohol, Salicylates

2-Endocrine causes of hypoglycaemia

- Hypopituitarism,
- (ACTH) deficiency and Addison's disease

3-Endogenous hyperinsulinism

- A beta cell secretagogue, such as a sulfonylurea
- Insulinoma
- Insulin autoimmune hypoglycemia

Insulinoma

Pancreatic islet cell tumour that secrete insulin

Diagnosed by **Whipple's triad, plus**

Measurement of overnight fasting (16 hours) glucose and **insulin levels,. C-peptide or proinsulin** during a spontaneous **episode of hypoglycaemia.**

4- Tumours

Mesenchymal tumors, fibromas, carcinoid, myelomas, lymphomas, hepatocellular, and colorectal carcinomas.

Low glucose is caused by

- 1-Secretion of insulin-like growth factor-11.,
- 2-Excessive consumption of glucose by the tumour
- 3-True ectopic insulin secretion is extremely rare.

5-Critical illness

- Sepsis** Because of cytokine induced inhibition of gluconeogenesis in the setting of glycogen depletion .

- Chronic kidney disease**

Impaired gluconeogenesis, reduced renal clearance of insulin, and reduced renal glucose production.

- In fulminant liver failure,**
Gluconeogenesis is also impaired.

- Malnourishment**

As a result of substrate limitation of gluconeogenesis and glycogenolysis in the setting of glycogen depletion.

6-Postprandial hypoglycaemia

occurs within four hours after meals

After **gastric surgery,**

7-Factitious hypoglycemia

Measurement of C-peptide levels during hypoglycaemia should identify patients who are injecting insulin;

- Sulphonylurea abuse can be detected by chromatography of plasma or urine.

Special types of hypoglycemia:

1-Nocturnal hypoglycemia

Can lead to disruption of sleep and delays in correction of the hypoglycemia.

If high morning sugars preceded by an episode of Nocturnal hypoglycemia=
(**Somogyi effect**).

2-Hypoglycemia Unawareness

occurs in longstanding diabetes, especially type 1 diabetes .

It is an impairment of counter regulatory response to hypoglycemia (epinephrine and glucagon), so

Many patients will develop neuroglycopenic symptoms, without warnings symptoms of hypoglycemia which is dangerous .

DIFFERENTIAL DIAGNOSIS

D D of autonomic symptoms includes

- Postprandial syndrome,
- Cardiac disease (Arrhythmia, Valvular heart),
- Medications,
- Psychiatric disease,
- Hyperthyroidism, Pheochromocytoma

Management of hypoglycemia

APPROACH

1-Clinical evaluation

History including :

1. Timing of symptoms (particularly in relationship to meals),
2. Underlying illnesses or conditions
3. Medications taken by the individual by family members, and Social history.

Clinical ex may explore the cause

2- Laboratory testing

1. Fasting or Postprandial evaluation for :
2. Glucose
3. Insulin
4. C-peptide
5. Beta-hydroxybutyrate
6. Proinsulin
7. Sulfonylurea and meglitinide screen

Determining the cause of hypoglycemia



In insulinoma, endogenous hyperinsulinism.

Plasma insulin, C-peptide, and proinsulin values are elevated .

Exogenous insulin:

Plasma insulin values are high .,
But plasma C-peptide and proinsulin values are low.

Nonislet cell tumors :

Plasma insulin, C-peptide, and proinsulin concentrations are not elevated.

3-localizing studies

Radiologic studies

Computed tomography, MRI, and ultrasonography can detect most insulinomas.

Hypoglycemia Prevention

1-Patient education

- Keeping a diary of low blood sugar symptoms
- Regular check of blood sugar

2--Modifying

- Diet (what, when, and how much you eat).
- The dosage or types of medicines.
- The timing and level of physical activity
- Glycemic targets for individual patients.

3-Hypoglycemia awareness :

Avoidance of hypoglycemia for several weeks may help to improve it.

4-Nocturnal hypoglycemia

Bedtime snacks

Take the intermediate insulin at bedtime rather than before supper

- Reducing the dose of soluble insulin before supper,
changing to a rapid-acting insulin analogue

Treatment of hypoglycemia

Treatment of acute hypoglycemia

For

Symptomatic diabetic with a low glucose value, <70 mg/dL.

Non diabetic with low glucose (<55 mg/dL) .

Symptomatic hypoglycemia but rapid blood glucose measurement is not available.

If the patient is conscious and able to drink and swallow , administer a rapidly-absorbed oral carbohydrate as

- 3 teaspoons of sugar (dissolved in water)
- 1-2 tablespoons of honey
- 3 or 4 glucose tablets
- 4-6 small hard candies
- 6 oz. regular (not diet) soda (about half a can)
- 4 oz. fruit juice

RULE of 15”

- ✓ Fast acting carbohydrates (**15g**).
- ✓ Check blood glucose **10-15** minutes after treatment
- ✓ Repeat treatment of **15** grams if blood glucose level remains low and recheck at another **15** minutes

If the patient has altered mental status, is unable to swallow, give an IV bolus of 12.5 to 25 gm of glucose (25 percent **dextrose**) Measure a blood glucose 10 to 15 minutes after the IV bolus. Readminister 12.5 to 25 grams of glucose as needed to maintain the blood glucose above 80 mg/dL.

If glucose cannot be given by parenteral or oral routes, give **glucagon** 1 mg IM or SQ. followed by careful glucose monitoring and oral or intravenous glucose administration.

Once the patient is able to ingest carbohydrate safely, providing a **mixed meal** .

Admit patients with ingestion of a long-acting hypoglycemic agent.

Treatment of the underlying cause

Adjust dose of antidiabetics

Surgical removal of the **insulinoma** is the Non islet tumours

oral glucocorticoids, diazoxide and octreotide, glucagon.

Replacement therapy for **addison disease**.

2- Diabetic ketoacidosis “DKA”

- Occurs in type 1 DM or type 2DM who have high levels of anti-insulin caused by intercurrent illness.

Causes

- Missed insulin
- Relative insulin deficiency
 - stress, steroid ttt, infection
 - Tissue damage : trauma, operation, burns, shock, stroke, MI
 - Pregnancy, labor & lactation
- ↑ ketone bodies Formation : as in Starvation, severe exertion or excess fat intake

Pathogenesis

- Glucose can't enter cells in absence of insulin → Hyperglycemia & glucosuria. Fat are mobilized for energy production → excess production of KB.
- (acetone, acetoacetic acid & B- hydroxyl Buteric acids)
 - ketosis,
 - ketonemia
 - ketonuria.
- Shift of K outside cells (in absence of insulin) which is then lost in urine.

Clinical Picture: (Effects of ketosis)

- Symptoms of uncontrolled DM for 2 - 3 days
- Respiration :
 - Kussmaul respiration deep rapid
 - Acetone breath
- CVS : shock, peripheral VD, dysrhythmias
- Dehydration
- Kidney : ketonuria + glucosuria → severe polyuria, polydypsia & dehydration (dry inelastic skin, sunken eye, thirst, low BP & low temp)
- GIT :
 - Acute abdomen (epigastric pain),
 - Nausea, vomiting, constipation & hematemesis
- Muscles: generalized weakness & ms pain due to absence of energy
- End stage : coma (due to acidosis, ketosis, dehydration & electrolyte imbalance)

Complications

- ARDS, (adult respiratory disorders syndrome)
- DIC, arterial and venous thrombosis,
- Pancreatitis,

- Brain edema

Investigations

- Blood
 - Hyperglycemia, ketonemia
 - Acidosis (T plasma HCO₃)
dehydration → ↑ PCV, ↑ serum creatinine c-T FFA & TG
 - Serum K : normal or high despite depletion of body K due to extracellular shift
 - leucocytosis and ↑ serum amylase
 - Euglycemic ketosis: when bl glucose is normal
- Urine : glucosuria , ketonuria, polyuria
- ECG, chest X-ray

D_D: from other types of comas in diabetics

		Hypoglycemia	DKA
History		excess ttt - missed meal	↓ttt - stress , infection
	-Onset of coma	rapid + irritable	slow + silent
	-Temperature	normal	subnormal
	-Respiration	normal	- Kuassmal (air hunger)
CIP			- acetone odour
	-Pulse	strong	weak & rapid
	BP	↑ systolic	low
	-Skin	wet	dry & cold
	-Tongue	moist	dry
	-Eyes	normal	sunken
	-Pupils	dilated	normal
	Urine	normal	sugar & acetone
Investigation	Blood	Hypoglycemia -ve -ve	Hyperglycemia Ketonemia Acidosis
Treatment	Oral sugar	Fluid + insulin	

Treatment

Aim:

- confirm diagnosis
- Search for and treat any ppt cause

- assess hydration and give fluid
- give insulin
- Monitor clinical signs and biochemistry

Lines of therapy:

1- Hospitalization better in ICU

2- Fluid replacement:

- Amount :
Guided by CVP (10cm H₂O)
1 L / hour till HR & BP return normal
- Type :
At 1st : isotonic saline
Then: glucose 5% when blood glucose drops < 250 mg (to avoid hypoglycemia)

Hypotonic saline with hypernatremia

3-Insulin

- Type : short acting
- Dose: low dose regimen 0.1 U / kg / h. continuous infusion or deep IM
- Follow up : by blood sugar every hour & give further insulin accordingly

4-ttt of acid base and electrolyte disturbances

- Metabolic acidosis: +- NaHCO₃
Indication : in severe case
Clinical : Kussmaul respiration),
Lab.: pH < 7.1 & HC03 <10 mEq
Dose : 1 L of 1/6 molar NaHC03 IV (till PH > 7.2
not reach 7.4 to avoid over correction → Alkalosis)

Correct plasma K⁺ level: K from the start

Hypo K⁺ : occurs with insulin ttt due to intracellular shift

Dose:

Add 10 ml KCL (20 mEq) to each 1 L of fluid given.

Oral r given after recovery

Phosphate: as K

5- Care of comatosed Pt.: (see neurology)

6- ttt cause & ppt factors

7-Monitoring:

state of hydration, urine output, conscious level, plasma glucose , K and ABG

8-Others

Prophylactic antibiotic

Nasogastric tube : to aspirate gastric content

Heparin IV in old & dehydrated patients to guard against DIC - Frusemide IV in oliguric patients

O₂ if PO₂ < 80mmHg

9-Insulin therapy: conventional after control DKA

10- Prevention of recurrence:

Avoid reduction of insulin dose during intercurrent illness

3- hyperglycemia hyperosmolar non-ketotic state

- Causes : occurs in old type 2 DM due to
 - Absence of fat reserve or fat mobilization (relative lack of GH or cortisol)
 - Insensitive thirst center in old age lead to dehydration aggravated by use of diuretics
 - PPt factors : infection, infarction
- C/P
 - Severe polyuria, polydypsia & dehydration (main symp.)
 - No or little ketosis
 - Prerenal uremia may occur due to dehydration
 - Neurologic symptoms : convulsions, coma, hemiparesis, stupor
- Investigations
 - **Blood** :
 - severe hyperglycemia often > 1000mg
 - ↑ PCV, ↑ Na, ↑ plasma osmolality (N. 290 mosm/L)
 - Urine: glucose without ketone bodies
- Treatment : as DKA without bicarbonate
 - **Fluids**
 - Type : 1/2 normal saline (1/2 molar)
 - Amount : IL / hour not faster to avoid cerebral edema
 - Insulin : smaller amount than ketoacidosis
 - Heparin : since there is ↑ incidence of DIC

3- diabetic lacticacidosis

4- Cause

- Tissue hypoxia : pneumonia, myocardial infarction
- Diabetics taking biguanides

5- CIP : of acidosis

- Kussmaul respiration
- Late CNS, CVS inhibition

6- Investigations

- ↓pH & bicarbonate
- ↑ plasma lactate

7- Treatment

- Correct hypoxia
- NaHCO₃ -Insulin-glucose combination
- Dialysis may be needed

N.B:

- Other causes of coma in diabetics:

- Cerebral stroke
- Uremic coma in patient with diabetic neuropathy
- Rhino cerebral mucormycosis (fungal infection)
- Associated causes of coma e.g. hepatic encephalopathy.

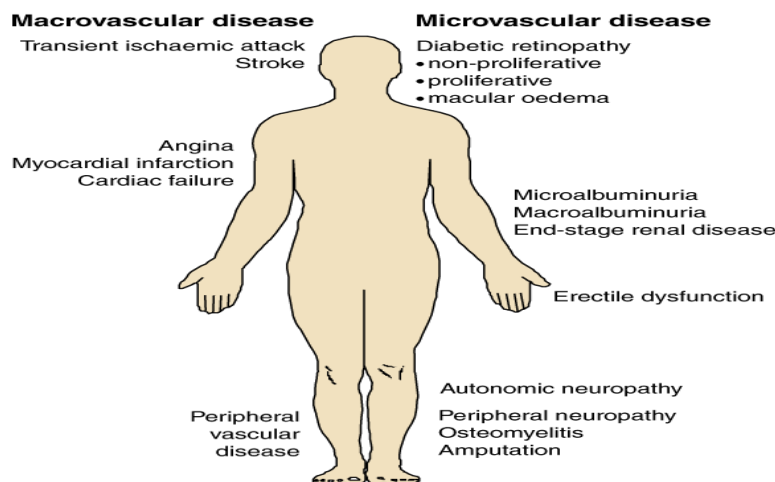
Macrovascular Complication of DM

By

Prof Dr; Omnia State

The people with diabetes have a significantly greater risk of macrovascular complication than that of the non-diabetic population. Diabetes is a risk factor in the development of atherosclerosis. Meanwhile, diabetic risk factors of macrovascular complication are:

- Duration of diabetes
- Increasing age
- Systolic hypertension
- Hyperinsulinaemia due to insulin resistance associated with
- obesity and syndrome X (metabolic syndrome)
- Hyperlipidaemia, particularly hypertriglyceridaemia/low HDL
- Proteinuria (including microalbuminuria)



The people with diabetes have a significantly greater risk of macrovascular complication than that of the nondiabetic population:

Atheromatous lesion in diabetes:

- Atheromatous lesions tend to be more severe, extensive and run more aggressive in diabetes than non-diabetic people
- Pathogenesis :
 - a. Hyperglycemia, hyperlipidemia, smoking etc. leads to monocyte and/or platelet adhesion
 - b. Monocytes migrate into the artery wall between the endothelial cells, become macrophages and accumulate lipid to form "foam cells"

- c. Release of growth factors and cytokines leads to migration and proliferation of smooth muscle cells which produce large amount of connective tissue in the atherosclerotic plaque

1- Caoronary heart disease:

- Myocardial infarction is three to five times more among diabetic people
- Women with diabetes lose their premenopausal protection from coronary artery disease.
- Painless angina and myocardial infarction may be due to neuropathic damage to the autonomic nerves serving the myocardium.
- Atypical presentation of angina and myocardial infarction (malaise, sweating, dyspnea and syncope which may be confused with hypoglycemia.
- Long term mortality from MI are increased in diabetes may be due to increased risk of HF in diabetes
- Management of MI is similar to non- diabetic population with more caution with usage of thromolytic therapy because of the risk of intraocular haemorrhage in the patient with retinopathy.

2- Cardiomyopathy :

Diabetes can cause a cardiomyopathy even without coronary artery atheroma
Left ventricular contractility abnormalities detected by echocardiology is the main subclinical feature

3- Hypertension :

- Hypertension is twice more in diabetics than non- diabetic
- Hypertension is closely associated with metabolic syndrome X, Insulin resistance or hyper insulinaemia

• Hyper insulinaemia lead to hypertension through:

- 1- Stimulation of kidney reabsorption of sodium and water
- 2- Stimulation of calcium and sodium in the vascular smooth muscle which enhance contractility causing hypertrophy of vascular smooth muscles ;and stimulation of sympathetic nervous systems

• Control of hypertension in diabetes is important due to:

- 1- Hypertension is major CVS risk factors
- 2- Hypertension can accelerates microvascular complication as nephropathy and retinopathy

Investigation:

Hypertensive diabetic patients should be investigated for:

- 1- Secondary hypertension (Cushing's, Conn's disease and Pheochromocytoma)
- 2- Renal damage (protienuria or microalbuminuria, urine microscopy, serum creatinine and elcterolytes)
- 3- CV damage (ECG, chest x-ray for left ventricular hypertrophy)
- 4- Other CV risk factors eg. hyperlipidaemia, poor glycemc control

Treatment:

- ACE inhibitors are the first choice due to:
 - 1- It delay the progression of diabetic retinopathy and reduce microalbuminuria
 - 2- It has no adverse effect in lipid profile or glycemic control
- A thiazide should be used at low dose to avoid worsening of glycemic control and aggravation of dyslipidemia
- Beta-adrenoceptors can aggravate hyperglycemia, dyslipidemia and impotence.

5- Peripheral arterial disease PAD:

Symptoms:

1. Asymptomatic
2. Intermittent claudication calf pain on walking
3. Buttock pain may occur if iliac vessels is affected
4. Decreasing claudication distance and rest pain denote critical ischemia
5. Unhealed skin wound

Signs:

1. Absence of pedal pulse (8% dorsalis pedis 2% posterior tibialis)
2. Cold extremities
3. Pale or bluish colour of the skin
4. thin ,shiny skin with scanty hair
5. dystrophic toenail

Investigation:

1. Doppler US
2. Ankle Brachial Index (ABI) : normal value 0.98 - 1.31
3. Angiography

Prevention of macrovascular complication:

1. Early control of blood glucose
2. Strict control of hypertension produces
3. Stop smoking
4. Treatment of lipid abnormalities : to the lowest achievable level
5. ACE inhibitors/angiotensin II receptor antagonists : 25–35% lowering of the risk of heart attack, stroke, overt nephropathy or cardiovascular death
6. Low dose aspirin: can reduce macrovascular risk, but is associated with a morbidity and mortality from bleeding.

6- Cerebral stroke :

- Stroke is twice higher in diabetic population than non-diabetics
- Mortality and disability from stroke are also worse in the diabetic person compared to non- diabetic people (May because of elevation of blood glucose level following stroke)

Microvascular Complications of Diabetes Mellitus

By

Prof Dr; Mamdouh El-Nahas

Microvascular disease is specific to diabetes. Small blood vessels throughout the body are affected but the disease process is of particular danger in three sites: Retina, Renal glomerulus and Nerves

Pathophysiology of Microvascular Complications

Chronic Hyperglycemia leads to:

- Non-enzymatic glycosylation of a wide variety of proteins, e.g. hemoglobin, collagen, LDL. This leads to an accumulation of advanced glycosylated end-products causing injury and inflammation via stimulation of pro-inflammatory factors, e.g. complement, cytokines.
- Polyol pathway: The metabolism of glucose by increased intracellular aldose reductase leads to accumulation of sorbitol and fructose. This causes changes in vascular permeability, cell proliferation and capillary structure via stimulation of protein kinase C and TGF-*B*
- Abnormal microvascular blood flow impairs supply of nutrients and oxygen. Microvascular occlusion is due to vasoconstrictors, e.g. endothelins and thrombogenesis, and leads to endothelial damage.
- Other factors include the formation of reactive oxygen species and growth factors stimulation (TGF-*B*) and vascular endothelial growth factor (VEGF). These growth factors are released by ischaemic tissues and cause endothelial cells to proliferate.
- Haemodynamic changes, e.g. in kidney.

Diabetic Neuropathies

Classifications:

A- Focal and multifocal neuropathies e.g. mononeuropathy, amyotrophy, radiculopathy, entrapment neuropathy, mononeuritis multiplex.

B- Symmetrical neuropathies e.g. diabetic peripheral neuropathy and autonomic Neuropathy.

Mononeuropathies: Affect peroneal, median or ulnar nerves. It tends to occur at sites of entrapment or external compression. Peroneal nerve palsy is characterized by weakness or paralysis of foot and toe dorsiflexors, foot drop and foot eversion. Impaired sensation over the dorsum of the foot and the lower anterior aspect of the leg. The ankle reflex is preserved as is foot inversion.

Cranial nerve palsies: Often affect III, VI, IV and rarely VII nerves. III nerve palsy is characterized by: acute onset and Intact papillary reactions: pupilloconstrictor fibres located peripherally so they are affected in lesions that produce compression e.g. aneurysm.

Entrapment Neuropathies

1-Carpal tunnel syndrome: found in 5.8 % of diabetic patients. It has a less favorable outcome after surgical decompression, as diabetes slows nerve regeneration.

2- Ulnar neuropathy at the elbow affects 2.1% of diabetic patients

3- Peroneal neuropathy at the fibular head affects 1.4–13% of diabetic patients.

4- Lateral cutaneous nerve of the thigh (meralgia paresthetica) affect 0–1.0% of diabetic patients.

Autonomic Neuropathies:

The most common effect of autonomic neuropathy is erectile dysfunction, which affects 40% of males with diabetes. Only a small number develop severe GI and bladder dysfunction.

Clinical features

- Impotence
- Postural hypotension, giving dizziness and syncope in up to 12%
- Resting tachycardia or fixed heart rate/loss of sinus arrhythmia in up to 20%
- Gustatory sweating—sweating after tasting food
- Dysphagia with delayed gastric emptying, nausea/vomiting
- Constipation or diarrhea
- Urinary retention or overflow incontinence
- Anhidrosis—absent sweating on the feet is especially problematic as it increases the risk of ulceration
- Abnormal pupillary reflexes

Assessment

At least annually check the following:

- Lying and standing BP (measure systolic BP 2 minutes after standing; normal is <10 mmHg drop, >30 mmHg is abnormal)
- Pupillary responses to light

Other less commonly performed tests to consider if the diagnosis is uncertain or in high-risk patients include the following:

- *Loss of sinus arrhythmia:* Measure inspiratory and expiratory heart rates after 5 seconds of each (<10 beats/min difference is abnormal, >15 are normal).

Loss of heart rate response to Valsalva maneuver: Look at the ratio of the shortest R–R interval during forced expiration against a closed glottis compared to the longest R–R interval after it (<1.2 is abnormal).

- *BP response to sustained hand-grip:* Diastolic BP prior to the test is compared to diastolic BP after 5 minutes of sustaining a grip equivalent to 30% of maximal grip. A diastolic BP rise >16 mmHg is normal, <10 mmHg is abnormal. A rolled-up BP cuff to achieve the required hand-grip may be used.
- For *gastric symptoms* consider a radioisotope test meal to look for delayed gastric emptying.

Peripheral neuropathy

The presence of *symptoms* and/or *signs* of peripheral nerve dysfunction in people with diabetes after *exclusion* of other causes of peripheral neuropathy. It affects 25-35% of diabetic patients, had gradual onset and progressive course with predominant sensory manifestations. Diagnosis depends on loss of perception of pain, touch, vibration and pressures in glove and stocking pattern. Manifestation of peripheral neuropathy:

Usually insidious onset with numbness or paresthesia, often found on screening rather than as a presenting problem

- Starts in the toes and on the soles of the feet, and then spreads up to mid-shin level, mostly in a symmetrical fashion. Less often, it also involves the fingers and hands.
- Affects all sensory modalities and results in reduced vibration perception thresholds, pinprick, fine touch, and temperature sensations.
- D Vibration sensation and absent ankle reflexes are often the first features found. Another risk factor for ulceration is the inability to feel a 10 g monofilament.
- Less often, the skin is tender or sensitive to touch (hyperesthesia), or frank pain can occur.
- Painful neuropathy affects up to 5% of a general clinic population.

This pain may be sharp, stabbing, or burning in nature and at times very severe.

- There may also be some wasting of the intrinsic muscles of the foot with clawing of the toes.

Management of peripheral neuropathy: Tight glycemic control. Alpha Lipoic Acid and Benfotiamine can help to improve nerve functions. Drugs that reduce pain e.g. tricyclic antidepressants, gabapentin, pregabalin and serotonin noradrenaline reuptake inhibitors. Protect a foot that lost its natural protective mechanisms is essential to prevent progression of neuropathy into a more advanced foot pathology.

Diabetic eye diseases

Diabetic eye diseases include:

1. Diabetic retinopathy
2. Cataract which develops earlier in diabetes than in the general population. . However with high levels of blood sugar often associated with a degree of ketosis an acute cataract may develop (snowflake cataract) which comes on very rapidly and does not clear.
3. Error of refraction due to fluctuations in blood sugar leading to osmotic changes within the lens.
4. Ocular Nerve palsies: The sixth and the third nerve are the most commonly affected. These nerve palsies usually recover spontaneously within a period of 3–6 months

Diabetic retinopathy: Diabetic retinopathy is the commonest cause of blindness worldwide. Diabetic retinopathy increases with the duration of diabetes. Progression of retinopathy often accelerated with poor control of diabetes and blood pressure. Diabetic retinopathy is asymptomatic until become advanced, so fundus examination should be routinely done at least annually. It can be either background (Nonproliferative) or Proliferative. Diabetic Maculopathy: If the oedema extends into the macula then the retina becomes thickened, visual function deteriorates and there is loss of central vision.

Renal affection in Diabetes

Renal affection in Diabetes leads to increased risk of:

- Renal atherosclerosis
- Urinary tract infections, papillary necrosis
- Glomerular lesions, e.g. from basement membrane thickening and glomerulosclerosis (Diabetic nephropathy).

Diabetic nephropathy: Approximately 40% of patients with type 1 and 20% with type 2 diabetes develop nephropathy. Some centers have reported a falling incidence rate of diabetic nephropathy in type 1 diabetes. This may reflect good-quality local care for diabetes. Diabetic nephropathy is the most common cause of chronic kidney failure and end-stage kidney disease worldwide.

The earliest functional abnormality in the diabetic kidney is renal hypertrophy associated with a raised glomerular filtration rate. As the kidney becomes damaged by diabetes, the afferent arteriole becomes vasodilated to a greater extent than the efferent glomerular arteriole. This increases the intraglomerular filtration pressure. This increased intraglomerular pressure leads to increased shearing forces locally which are thought to contribute to mesangial cell hypertrophy and increased secretion of extracellular mesangial matrix material. This process eventually leads to glomerular sclerosis. The initial structural lesion in the glomerulus is thickening of the basement membrane. Associated changes result in disruption of the protein cross-linkages which normally make the membrane an effective filter. In consequence, there is a progressive leak of large molecules (particularly protein) into the urine.

Stages of Diabetic nephropathy

1. Elevated glomerular filtration rate with enlarged kidneys
2. Intermittent Microalbuminuria
3. Microalbuminuria
4. Proteinuria and Nephrotic syndrome.
5. ESRD

Clinical features are usually absent until advanced chronic kidney disease develops. Therefore, we should evaluate urinary albumin excretion (microalbuminuria) annually in all subjects with diabetes.

Management of Diabetic Nephropathies: Optimal control of blood glucose and blood pressure. Avoid high protein intake. ACE inhibitors should be started and titrated to full dose in all patients with confirmed nephropathy (including those with microalbuminuria alone). If ACE inhibitors are not tolerated, angiotensin II receptor antagonists should be substituted. Avoid taking Contrast agents containing Iodine and NSAIDs.

Diabetic Foot complications

By

Prof Dr; Mamdouh El-Nahas

The term diabetic foot indicates any foot pathology that results directly from diabetes or its long-term complications.

In the past, the term diabetic foot was used to indicate gangrene and amputations. Then, it was realized that Diabetic gangrene doesn't occur suddenly but is preceded by several stages.

Diabetic gangrene is usually preceded by advanced foot pathology e.g. Diabetic Foot ulcers, diabetic foot Infections, critical limb ischemia and Charcot foot. Also, advanced foot pathology didn't occur suddenly but is preceded by risk factors for the more severe foot pathology.

The high risk foot is the foot that has developed one or more of the following risk factors:

- Peripheral Neuropathy
- Peripheral arterial disease
- Foot Deformity
- Trauma
- Callus
- Skin and Nail pathology

For prevention of foot problems the diabetic patients should:

1. Achieve tight control of blood glucose levels
2. Annual foot screening
3. Report any changes in his or her feet immediately to healthcare professional.
4. Engage in a simple daily foot care routine by washing and drying between toes, moisturizing and checking for abnormalities.

DM & other systems affected

By

Dr; Ibrahim El-Sayed

1-Infections and diabetes

1.1- Why diabetes increases risk of infections?

Due to abnormalities in cell mediated immunity and phagocytic function, hyperglycemia, diminished vascularity and autonomic dysfunction.

1.2- Effects of infections on diabetes:

A- Increasing insulin resistance leading to bad glycemic control.

B- Precipitation of diabetic ketoacidosis.

1.3- Common infections in diabetes:

A- Skin: staphylococcal infections (boils, abscesses, carbuncles) and mucocutaneous candidiasis.

B- Gastrointestinal: periodontal disease and cholecystitis (including emphysematous cholecystitis).

C- Urinary tract: cystitis, pyelonephritis (including emphysematous pyelonephritis) and perinephric abscess.

D- Lung: pneumonia and tuberculosis.

E- Bone: osteomyelitis.

F- ENT: rhino-cerebral mucormycosis and malignant otitis externa.

1.4- Prevention of diabetic infections:

Good glycemic control, good hygiene and vaccination with pneumococcal and influenza vaccines.

1.4- Treatment of diabetic infections:

A- Proper diagnosis and early start of antimicrobial.

B- Use insulin during infection period if patient is on oral treatment.

2- Gastrointestinal complications of diabetes

2.1- Mouth: periodontal disease with looseness of the teeth and gum inflammation.

2.2- Esophagus: gastroesophageal reflux disease (GERD) caused by autonomic neuropathy with decreased lower esophageal sphincter (LES) pressure or delayed gastric emptying.

2.3- Gastroparesis:

* Clinical symptoms that suggest gastroparesis include early satiety, nausea, vomiting, bloating, and postprandial abdominal fullness in addition to unexplained poor glycemic control despite strong therapeutic efforts.

* The presence of residual food in the stomach after an overnight fast during upper gastrointestinal endoscopy supports the diagnosis.

* The traditional "gold standard" to establish the diagnosis of gastroparesis is scintigraphic measurement of gastric emptying.

* Treatment: small meals, avoid fatty meals, use of prokinetics eg metoclopramide and avoid use of GLP-1 based therapies in treatment of diabetes.

2.4- Diabetic enteropathy:

Presented by diarrhea which is watery and painless, occurs at night, and may be associated with fecal incontinence. Bouts of diarrhea can be episodic with intermittent normal bowel habits or even alternating with periods of constipation in addition steatorrhea can occur due to bacterial overgrowth.

2.4.1- Management:

* Exclude other causes of diarrhea especially infectious one.

* Correction of water and electrolyte imbalances, tight control of blood glucose, and restoration of possible nutritional deficiencies.

* Symptomatic therapy: antidiarrheal agents such as loperamide.

2.5- Liver: Non alcoholic fatty liver including non alcoholic steatohepatitis.

2.6- Gall bladder: cholecystitis including emphysematous cholecystitis.

3- Skin and diabetes

3.1- Acanthosis nigricans: Velvety hyperpigmented plaques in neck, back and body folds.

3.2- Necrobiosis lipoidica diabetorum: Painful violaceous plaque with central yellowish area surrounded by brownish border usually on shin of the leg. Central ulceration may occur.

3.3- Diabetic dermopathy: Painless reddish papules usually on the shin of the tibia heal leaving atrophic scarred hyperpigmented macules.

3.4- Bullosis diabetorum: Non-inflamed bullae with sterile fluid heal within 2-3 weeks without residual scarring.

3.5- Granuloma annulare: Ring shaped papules with depressed centers usually on dorsum of the hand and arm.

3.6- Diabetic thick skin:

* Fingers and hands: inability to do non islamic praying.

* Scleroderma diabetorum: marked thickening of the skin in posterior aspect of the neck and upper back.

3.7- Carotenemia: Yellow skin and nails.

3.8- Skin ulcers: Vascular and neuropathic ulcers.

3.9- Hyperlipidemia:

* Eruptive xanthoma: yellow papules or nodules usually on extensor surfaces.

* Xanthelasma: yellow plaques that usually appear on the medial aspects of the eyelids.

3.10- Skin infections:

* Fungal: Candidal intertrigo and paronychia, dermatophytes causing powdery white lesions especially between fingers.

* Bacterial: Carbuncles, furuncles, abscesses, cellulitis, erysipelas.

3.11- Skin and anti-diabetic medications:

* Insulin: Lipoatrophy and lipohypertrophy.

* Sulphonylurea: Drug eruptions.

Diabetes and pregnancy

By

Dr; Ibrahim El-Sayed

Classification:

A- Pregestational diabetes either type 1 or type 2 diabetes.

C- Gestational diabetes: carbohydrate intolerance that begin in pregnancy.

Risk factors for developing gestational diabetes:

* Family history of diabetes

* Past history of gestational diabetes.

* Age >25 years.

* Previous delivery of a baby > 4 kg.

* Polycystic ovary syndrome

* Current use of glucocorticoids.

* Certain ethnic groups eg, African-American, South or East Asian.

* Prepregnancy body mass index >30 kg/m².

Effects of pregnancy on diabetic state:

* Hyperinsulinemia and increased insulin resistance due placental secretion of diabetogenic hormones eg corticotropin releasing hormone, placental lactogen, and progesterone, as well as decreased exercise.

* Diabetic retinopathy worsens.

* Diabetic nephropathy: Pregnancy is not associated with permanent worsening of renal function in the majority of diabetic women in the absence of uncontrolled hypertension or baseline serum creatinine concentration above 1.5 mg/dL.

* Pregnancy does not affect the course of somatic or autonomic neuropathy.

Effects of diabetes on pregnancy:

Fetal and neonatal complications:

* Congenital malformations: eg congenital heart defects, caudal dysgenesis and neural tube defects.

* Macrosomia with associated shoulder dystocia and increasing likelihood of cesarean delivery.

* Neonatal: Hypoglycemia, erythrocytosis, hyperbilirubinemia, prematurity with respiratory problems.

Maternal complications:

* Spontaneous abortion.

* Hypertension/preeclampsia.

* Polyhydramnios.

* Infections: eg urinary tract infections.

* Recurrence of gestational diabetes in subsequent pregnancies.

* Gestational diabetes increases risk of developing type 2 diabetes.

Screening and diagnosis:

Whom to screen: Universal screening for all pregnant women is better than screening women who have at least one risk factor for development of gestational diabetes.

Whom and how to screen:

* First prenatal visit: Fasting plasma glucose or HbA1c to exclude overt diabetes (Fasting plasma glucose ≥ 126 mg/dL, or A1C ≥ 6.5 percent).

*** 24 to 28 weeks of gestation:**

A- One step approach: 75 gram two hour oral glucose tolerance test, a diagnosis of gestational diabetes can be made in women who meet either of the following criteria (fasting plasma glucose ≥ 92 mg/dL but < 126 mg/dL or one hour ≥ 180 mg/dL or two hour ≥ 153 mg/dL).

B- Two step approach: if one hour plasma glucose after a 50 gram oral glucose ≥ 130 mg/dL go to 75 gram two hour oral glucose tolerance test.

Management:

Target blood glucose:

* Fasting glucose concentrations ≤ 95 mg/dL.

* Preprandial glucose concentrations ≤ 100 mg/dL.

* One-hour postprandial glucose concentrations ≤ 140 mg/dL.

* Two-hour postprandial glucose concentrations ≤ 120 mg/dL.

* Glucose levels should not decrease to less than 60 mg/dL.

4.6.2- Diet:

* Weight loss in pregnancy is not generally recommended, so the aim of diet is to prevent excessive weight gain.

* For women who are at ideal body weight during pregnancy, the caloric requirement is 30 kcal/kg/day; for women who are overweight and obese, the caloric requirement is 22 to 25 kcal/kg/day; and for morbidly obese women, the caloric requirement is 12 to 14 kcal/kg/day.

Insulin: regular insulin, NPH insulin, insulin aspart, insulin lispro and insulin detemir have acceptable safety profiles, while insulin glargine has not been studied extensively in pregnancy.

Oral medications:

* Glyburide and metformin can be given if patient refuse taking insulin.

* Women with polycystic ovary syndrome who get pregnant and taking metformin can continue it during pregnancy.

Management of DM

By

Prof Dr; Megahed Abu El-Magd

1. **Life style modification**(including medically assisted weight loss)
2. **Oral anti-diabetic agents**
3. **Insulin**

Therapeutic Lifestyle Changes

- **Weight loss** (for overweight and obese patients): Reduce by 5% to 10%
- **Physical activity:** 150 min/week of moderate-intensity exercise (eg, brisk walking) plus flexibility and strength training.
- **Diet:**
 - Eat regular meals and snacks; avoid fasting to lose weight
 - Consume plant-based diet (high in fiber, low calories/glycemic index, and high in phytochemicals/antioxidants)
 - Understand Nutrition Facts Label information
 - Incorporate beliefs and culture into discussions
 - Use mild cooking techniques instead of high-heat cooking
 - Keep physician-patient discussions informal.
- **Healthful Eating Recommendations:**
 - **Carbohydrate:**
 - ✓ Specify healthful carbohydrates (fresh fruits and vegetables, legumes, whole grains); target 7-10 servings per day
 - ✓ Preferentially consume lower-glycemic index foods (glycemic index score <55 out of 100: multigrain bread, pumpernickel bread, whole oats, legumes, apple, lentils, chickpeas, mango, yams, brown rice)
 - **Fat**
 - ✓ Specify healthful fats; containing poly-unsaturated fatty acids (nuts, avocado, certain plant oils, fish)

- ✓ *Limit saturated fats (butter, fatty red meats, tropical plant oils, fast foods) and trans fat; choose fat-free or low-fat dairy products.*
- **Protein:**
- ✓ *Consume protein in foods with low saturated fats (fish, egg whites, beans); there is no need to avoid animal protein*
- ✓ *Avoid or limit processed meats*
- **Micronutrients**
- ✓ *Routine supplementation is not necessary; a healthful eating meal plan can generally provide sufficient micronutrients*
- ✓ *Chromium; vanadium; magnesium; vitamins A, C, and E; and CoQ10 are not recommended for glycemic control*
- ✓ *Vitamin supplements should be recommended to patients at risk of insufficiency or deficiency.*

Insulin

Insulin therapy is appropriate for patients with type (1) and type (2) diabetes. The absolute insulin deficiency of established type (1) diabetes can only be treated effectively with multiple daily insulin injections

Indications of insulin therapy in type (2) diabetes:

- 1- Patients unable to adequately control their blood glucose levels with maximum dose combinations of oral glucose lowering medications.
- 2- Patients undergoing surgery
- 3- Patients with renal or hepatic disease or allergies that preclude the use of oral glucose lowering medications.
- 4- Women who are planning pregnancy or who are already pregnant.
- 5- Critically ill hospitalized patients.

Insulin therapy is often instituted early for type (2) diabetes patients who:

- Can't control their diabetes with diet and exercise
- Are highly symptomatic with marked catabolic state.
- Are newly diagnosed with very high glucose level

The first step in choosing an insulin regimen is to establish glycemic goals for most patients; this means that one half of SHBG results of all within the following ranges:

Preprandial	90-130 mg/dl
Bedtime	100-140 mg/dl
Postprandial (1-2h)	<180mg/dl

Insulin by comparative action table;

Type of Insulin & Brand Names	Onset	Peak	Duration	Role in Blood Sugar Management
Rapid-Acting				
Humalog or lispro	15-30 min.	30-90 min	3-5 hours	Rapid-acting insulin covers insulin needs for meals eaten at the same time as the injection. This type of insulin is used with longer-acting insulin.
Novolog or aspart	10-20 min.	40-50 min.	3-5 hours	
Apidra or glulisine	20-30 min.	30-90 min.	1-2½ hours	
Short-Acting				
Regular (R) humulin or novolin	30 min. -1 hour	2-5 hours	5-8 hours	Short-acting insulin covers insulin needs for meals eaten within 30-60 minutes
Velosulin (for use in the insulin pump)	30 min.-1 hour	2-3 hours	2-3 hours	
Intermediate-Acting				
NPH (N)	1-2 hours	4-12 hours	18-24 hours	Intermediate-acting insulin covers insulin needs for about half the day or overnight. This type of insulin is often combined with rapid- or short-acting insulin.
Lente (L)	1-2½ hours	3-10 hours	18-24 hours	
Long-Acting				
Ultralente (U)	30 min.-3 hours	10-20 hours	20-36 hours	Long-acting insulin covers insulin needs for about one full day. This type of insulin is often combined, when needed, with rapid- or short-acting insulin.
Lantus	1-1½ hour	No peak time; insulin is delivered at a steady level	20-24 hours	
Levemir or detemir	1-2 hours	6-8 hours	Up to 24 hours	
Pre-Mixed*				
Humulin 70/30	30 min.	2-4 hours	14-24 hours	These products are generally taken twice a day before mealtime.
Novolin 70/30	30 min.	2-12 hours	Up to 24 hours	
Novolog 70/30	10-20 min.	1-4 hours	Up to 24 hours	
Humulin 50/50	30 min.	2-5 hours	18-24 hours	
Humalog mix 75/25	15 min.	30 min.-2½ hours	16-20 hours	
*Premixed insulins are a combination of specific proportions of intermediate-acting and short-acting insulin in one bottle or insulin pen (the numbers following the brand name indicate the percentage of each type of insulin).				

(ADA) recommendations:

- ✓ It is Very important to individualize the patient’s age, health states, and history of significant hypoglycemia, life styles and personal goals.
- ✓ For example, it would be reasonable to modify preprandial goal to 100-140mg/dl or higher for a type (1) diabetes patients with severe or hypoglycemia unawareness.
- ✓ Pregnant women with either type(1) or type (2) diabetes require meticulous glycemc control, whole blood goals should be modified to <95mg/dl fasting , >140 mg/dl postprandial (1h),<120 mg/dl (2h) postprandial.

Insulin regimen:

2 injections /day

Advantages: Two Injections /day

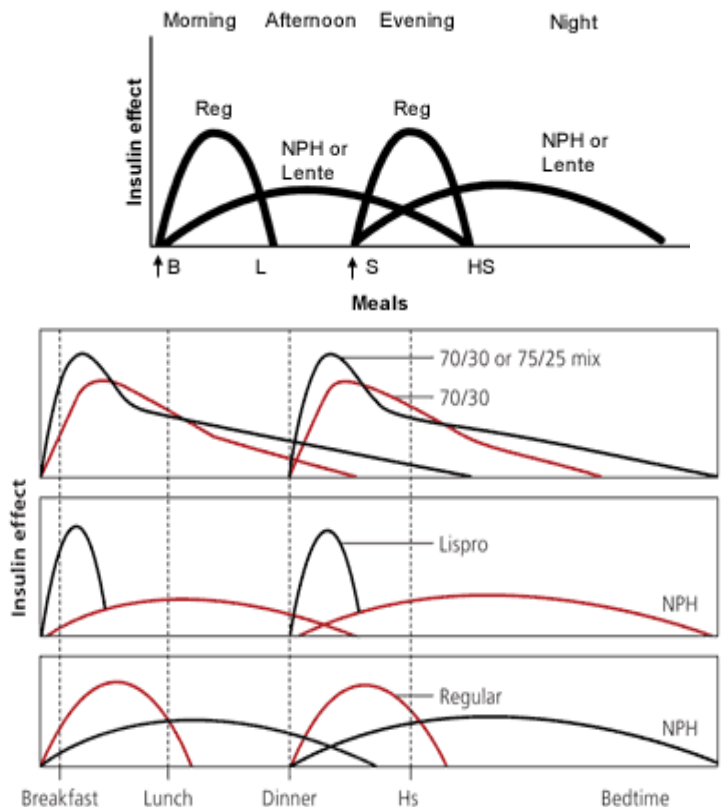
Disadvantages: NPH given at supper peaks during the night

And often not last overnight until breakfast

Leading to nocturnal hypoglycemia and/or

And high breakfast glucose levels.

- 1) Inflexibility in dealing with midday glucose levels.



3 Injections / Day

-Using NPH and short or rapid acting analog before breakfast and short or rapid acting insulin at supper and NPH at bed time.

-Advantages: Better overnight glucose control

-Disadvantages: still injectable at midday.

4 injections/day

Using short or rapid acting insulin and long acting.

Advantages: allows meal to meal adjustment.

Determining total insulin dose:

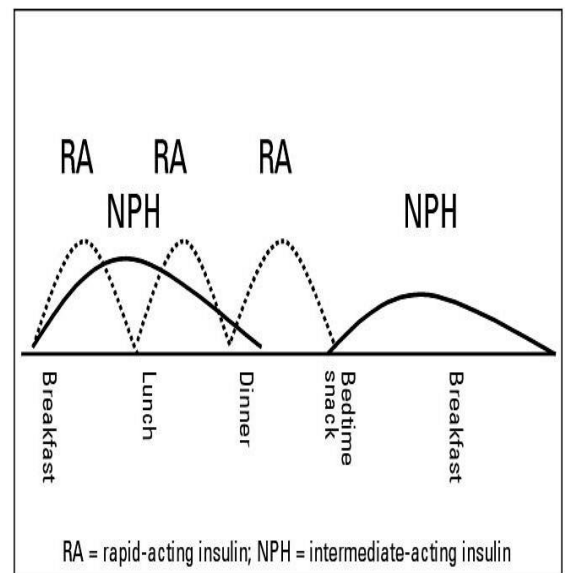
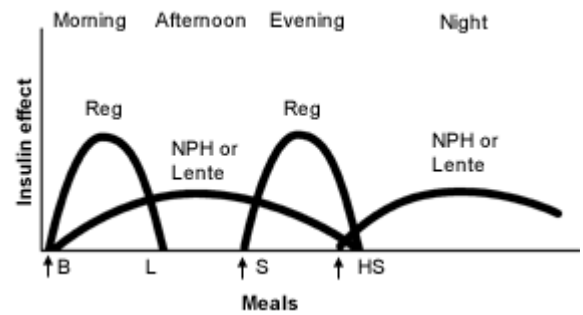
About one-half to two-thirds of the total-daily insulin dose is given to cover basal-needs and should be longer acting insulin.

The other one-third to one-half of the total daily insulin dose should be rapid or short acting insulin given before each meal to control postprandial glycemia,

When initiating insulin therapy, base line total daily dose is often calculated as 0.6 X body weight in kilograms.

Correction insulin dose:

Adjusting insulin dose:



If glucose are out of target at	Adjust this insulin component
Postbreakfast/ prelunch	Prebreakfast rapid/ short insulin
postlunch/ presupper	Prelunch rapid/ short insulin and /or morning NPH
Midafternoon	Morning NPH or long-acting insulin analog
Postsupper/ bedtime	Presupper rapid/ short insulin
Early morning	Every NPH or long-acting insulin analog

$$\frac{1500}{BW} = X \text{ (correction factor)}$$

BW

$$\frac{\text{Current Blood Sugar} - \text{Target Blood Sugar}}{\text{Correction Factor (X)}} = \text{Correction Insulin Dose}$$

Example:

80-kg patient who is 60 mg/dl above target glucose level would require 3-unit supplement based on equation:

$$1500/80\text{kg}=18.72$$

$$(200-140\text{mg/dl})/18.75=\sim 3\text{units}$$

Initial insulin dose type-1 diabetes patient:

Dose (unit/kg/day)	patient
0.5	Conditioned athletes
0.6	Motivated exercisers or women in follicular phase of menses
0.7	Women in last week luteal phase of menses or in 1 st trimester of pregnancy, child starting puberty, adult ill with a virus
0.8	Women in 2 nd trimester of pregnancy, child in mid-puberty, adult with a severe or localized viral infection
0.9	Women in 3 rd trimester of pregnancy, adult ill with bacterial infection
1.0	Women at term pregnancy, adult with a severe bacterial infection or illness, child at peak pubescence
1.5-2.0	Child at peak pubescence who is ill

Oral Hypoglycemic Agents:

-Insulin sensitizers

- Metformin
- Thiazolidinedione

-Insulin secretagogues.

- Sulphonylureas and glinides.
- Dpp4 inhibitors.

Classes:

- Biguanides eg metformin.
- Sulphonylureas e.g gliclazide ,glimpride.
- Meglitinides eg repaglinide.
- Thiazolidinediones eg pioglitazone.
- Dipeptidylpeptidase 4 inhibitors eg sitagliptin,vildagliptin.
- Alpha glucosidase inhibitors e.g. Acarbose.

1. Biguanides

MOA: -act directly against insulin resistance and reduce hepatic glucose output.

It is considered as the corner stone in treatment of type (2) Diabetes in all guidelines.

Advantages:

- Cheap
- No weight gain
- No or minimal episodes of hypoglycemia.
- Beneficial cardiovascular outcomes.

Side effects: Gastro-intestinal like flatulencies and diarrhea.

2. Sulphonylureas:

MOA: triggering insulin release by inhibiting KATP channels of the pancreatic B-cells.

Typical reduction in A1C values for SU is 1.0-2.0 %.

First Generation:

- 1) Tolbutamide
- 2) Acetohexamide
- 3) Chlorpromide

Second or new generation:

- 4) Glipizide
- 5) Glyburide (glibenclamide)
- 6) Glimipride (amaryl)
- 7) Gliclazide (diamicron)
- 8) Gliquidone (glurinorm)

Side effects:

- 1) Hypoglycemia
- 2) Weight gain

Advantages:

- 1) effective reduction of A1C
- 2) Not Expensive.

Contraindications:

- 1) Pregnancy
- 2) Type (1) diabetes.
- 3) Patients with acute or end-stage liver disease
- 4) Patients with end-stage renal diseases.

3. Non-sulphonylurea secretagogues

Meglitinides

MOA: Short acting secretagogues

Act on the same potassium channels of Sulphonylureas. Enhance insulin secretion.

Examples: 1- Repaglinide

2- Nateglinide.

3- Mitiglinides

-They are called prandial glucose regulators as these drugs act mainly on the postprandial glucose excursions

-Typical reduction in A1C 0.5-1.0%.

Side-effects:

- 1) Hypoglycemia
- 2) Weight gain.

4. Thiazolidinediones:

E.g. pioglitazone dose (15-45mg/day)

MOA: binds to PPAR γ nuclear receptors lead to transcription of genes regulating glucose and fat metabolism

Typical reduction in A1C (1.0-1.5%)

Advantages: no or minimal hypoglycemia.

Disadvantages:

1. Weight gain
2. Oedema both L.L
3. Bad effect on bone metabolism especially in postmenopausal females.

Contra-indications:

4. Pregnancy
5. Advanced heart failure
6. Hepatic cell failure
7. Acute liver injury

5. Dipeptidyl peptidase-4 inhibitors (DPP4I)

MOA: inhibits destruction of endogenous GLP-1 (glucagon like polypeptide 1) and cause increase in incretin level which stimulates insulin release from pancreatic B-cells in a glucose dependant manner

E.g.

- 1) Sitagliptin (januvia)
- 2) linagliptin
- 3) alogliptin.
- 4) saxagliptin.
- 5) vildagliptin.

Advantages:

1. No hypoglycemia
2. No weight gain
3. Well tolerated drugs.

Disadvantages: Costly (expensive)

Side effects: Minimal like nasopharyngitis, headache and nausea.

6. Alpha-glucosidase inhibitors:

E.g. Acarbose

MOA: inhibits the upper gastrointestinal enzymes that convert dietary starch and other complexes into simple sugar which can be absorbed.

It causes mild to moderate reduction in postprandial glucose.

Advantages:

1. no hypoglycemia
2. no weight gain

Side effects:

Usually cause flatulence and diarrhea.

7. Sodium –Glucose co transporter inhibitors: (SGLT2I)

MOA: Inhibits glucose re-absorption from proximal convoluted tubules of the kidney

E.g. 1) Canagliflozin

2) Dapagliflozin

Advantages:

1. No hypoglycemia
2. Mild reduction in systolic blood pressure
3. Decrease body weight

Disadvantages:

1. Expensive drugs
2. with mild to moderate reduction in A1C

Side effects:

1. Urinary-tract infections
2. Ketoacidosis