Endocrinology

Is the science that deals with the study of hormones & their physiological effects on the body system.

Endocrine glands named so, because they don't have ducts, they pour their secretions directly into the circulation. There are so many endocrine glands in the body as hypothalamus, pituitary, thyroid, parathyroid, pancreas, gonads, ovary, testes.
Diabetes - MELLITUS ( DM )

In this lectures we will deal with the following :
1 - Definition & introduction .
2 - Epidemiology.
3 - Classifications .
4- Patho physiology & aetiopathogenesis .
5 - Clinical - features & complications (Hx + C/E ) .
   a) Acute
      * DKA
      * hyperosmolar non ketotic coma
      * Lactic - acidosis
   b) L . T . C
6 - Diagnosis.
7 - Aids of management.
8 - Prevention and advices .
Definition & Introduction: It is a clinical and metabolic disease characterized by hyperglycemias due to absolute or relative insulin-deficiency which can arise from loss of B-cell secretory capacity or resistance of peripheral tissues (end-organs) mainly skeletal muscles and adipose tissues to the insulin-effect due to multifactorial pathways. Lack of insulin effects the metabolism of carbohydrates, protein and lipid. It causes a significant change in water and electrolyte haemostasis. The disease is characterized also by unique macro and micro vascular angiopathy these by inducing ischaemia to various body organs mainly the eyes, kidneys, heart, nervous-system these by causing permanent and irreversible functional and structural changes in these organs. Death may result from either:

1-acute metabolic decompensations like DKA, hyperosmolas non-ketotic coma

2-organ damage like renal failure, IHD Heart - failure or C.V.A. in USA, DM is the leading cause of:

1-END-STAGE RENAL DISEASE (ESRD).
2-NON TRAUMATIC LOWER LIMB AMPUTATIONS.
3-ADULT - BLINDNESS.
4-MORBIDITY AND MORTALITY FOR THE FORESEEABLE - FUTURE.
D.M is a very serious disease, if unchecked, it can bring serious consequences including death. Fortunately, it can be managed but unfortunately most people who have diabetes don’t know that they have it and hence don’t treat it until it becomes very late. If you suspect you have it, it is very important that you get prompt professional attention and to determine whether you suffer from it. Over (100) million people suffer from DM in the world, in USA it is believed that over (14) million people suffer from DM, that includes all age-group from children to the elderly, the American Diabetes association (ADA) estimates that 6% of the general U.S population over 100million do have been found to have diabetes and an equal amount has not been diagnosed it. People with type (2) DM are at higher risk for vision and kidney problems, heart disease and nerve damage. More than 90% of the time, lifestyle changes such as losing weight, cutting back on fat and getting daily exercise can help keep your blood-sugar levels in line; so daily self care through scrupulous attention to a healthy-life style and a strong commitment to maintaining target blood sugar levels, diabetic people can slow down the degenerative process, but if left unchecked it shortens life and it is not a condition that goes away.
**Epidemiology:** the prevalence of DM is increasing over the past two decades. DM₂ is expected to rise more rapidly in the future due to:

- **a**- increase obesity
- **b**- decrease activity
- **c**- increase with ageing in both sexes but slightly more in (+) after age 60 years

<table>
<thead>
<tr>
<th>Age</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20 y.</td>
<td>0.19%</td>
</tr>
<tr>
<td>&gt; 20 y.</td>
<td>8.6%</td>
</tr>
<tr>
<td>&gt;65 y.</td>
<td>20.1%</td>
</tr>
</tbody>
</table>

d-geographical - factor : DM1 is the highest in Scandinavia e.g. 35/100.000/ Y. in Finland and it is much lower in Pacific Rim e.g. 1-3 /100.000/ Y.
in Japan and China, USA and Northern Europe 8-17/100.000/ Y. While DM2 and IGT are:
- **a**. highest in certain pacific - islands.
- **b**. intermediate in India and USA.
- **c**. relatively low in Russia and China. this variability is likely due to:
  1- genetic.
  2- environmental.
  3- behavioral factors.
The onset of DM2 occurs on average at an earlier age in ethnic-groups other than non Hispanic-white.
Risk - Factors are:

1- **Age**: All people are vulnerable to DM throughout their lives. However, the risk is higher as you grow older. There is a gradual increase in susceptibility with slight *peaks* at puberty and during pregnancy until we reach age 40. Then there is a rapid jump.

2- **Heredity**: If you have FHx of DM especially parents or siblings, you are near the top of the list in terms of risk. Heredity is the most important predisposing factor for DM especially DM$_1$. DM$_2$ also tends to run in families but since 80-85% of all cases occur among people over 40 and overweight obesity is considered more important in the development of DM$_2$.

3- **Obesity**: It is true that not all obese people have DM but overweight (obese) people set themselves up for DM is coming 10-20 years from now.

4- **Race**: In USA, DM is more common among African-American, Hispanics and American Indians. More than 40% of Pima Indians in USA have DM$_2$. However, that race alone doesn't predict DM; it must be combined with another factor such as obesity.

5- **Poverty**: Poor people in USA have the highest incidence of DM.

6- Impaired Glucose tolerance.

7- Hypertension & hypercholesterolemia $> 114.0$ ma% or more.

8- In women, having a history of G.D.m or, delivery of babies weighting $> 9$ pounds.

9- Polycystic ovary - syndrome or acanthosis - nigricans.

10- Hx of vascular - disease.
CLASSIFICATION OF DM

A. clinically is either:
   1. Type I DM or "IDDM"
   2. Type II DM "NIDDM"
   3. G.D.M
   4. D.M of the youth "M.O.D.Y"

B. etiologically is either
   - Type I 1. primary (idiopathic) or immune-mediated.
   - Type II 2. secondary
     a. pancreatic damage
        * chronic pancreatitis.
        * cystic-fibrosis.
        * Haemochromatosis.
        * CA pancreas.
        * Pancreatectomy.
b. excess insulin antagonistic hormones
   *increase growth-hormone
   (acromegally)
   *increase Thyroxin
   (Thyrotoxicosis)
   *increase steroids (Cushing's syndrome)
   *increase glucagons
   *increase catecholamine
   (phaeochromocytomas)

C. Anti insulin Abs.
d. Anti insulin receptors Ab. Drugs : 1. steroids . 2.Thiazides .3. phenytoin.
f. Associated with genetic diseases :
   1-Down's syndromes.
   2-klinefelter's syndromes .
   3-Turner's syndromes.
   4-Friedreich's ataxia.
   5-myotonia -dystrophica.

·G.D.M
Patho physiology and aetiologypathogenesis
To get normal blood-glucose (3.5-6.5 m mol/l) there is a balance between hepatic glucose production with intestinally absorbed glucose and peripheral-utilization of glucose by the muscles & adipose tissue. A. continuous supply of glucose is essential for the brain that uses glucose as its principal fuel. When intestinal glucose absorption declines between meals, hepatic glucose output is increased in response to counter-regulatory hormones (glucagon and adrenaline) and it decreases during prolonged starvation as other metabolic-fuels derived from fat become more important. The liver produces glucose by:

1. glycogenolysis.
2. gluconeogenesis: from Amino acids (lactate, pyruvat, alanine) and fatty acids from adipose tissues through lipolysis.

**INSULIN** is the only an anabolic hormone and it has profound effects on the metabolism of carbohydrate, fat and protein. Insulin is secreted from pancreatic B cell into the portal circulation with a brisk increase in response to arise in blood-glucose after meals through neural mechanism.
**INSULIN** decrease blood - glucose by:

1- **Suppressing hepatic glucose production.**

2- **Increase peripheral glucose break-down.** Mediated by the glucose transporter, GLUT 4.

Adipocytes (and the liver) synthesize T.G from NEFAs & glycerol. Insulin stimulates lipogenesis & inhibits lipolysis so preventing fat-catabolism.

Lipolysis is mediated by T.G lipase, stimulated by catecholamines & liberates NEFAs which is oxidized by many times their partial oxidation in the liver provides Energy to drive gluconeogenesis & also produces Ketone-bodies (acetoacetate which is reduced to 3 hydroxybutyrate or decarboxylated to acetones) which are generated in hepatocytes-mitochondria. Ketone bodies are organic- acids which when in small amounts are oxidized & utilized as metabolic-fuel & in excess the liver can’t cob with it’s removal so causing hyperketonaemia. Ketogenesis is enhanced by insulin deficiency via increase Lipolysis & increase activity of lipase enzyme & release of the counter — regulatory hormones that stimulate lipolysis too.
So pathophysiological process in DM (I, II):

<table>
<thead>
<tr>
<th>Type 1 DM</th>
<th>Type 2 DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>No insulin (sever insulin def.)</td>
<td>Insulin resistance *hepatic &amp; peripheral *insulin stimulated (post prandial) glucose uptake impaired, especially in skeletal muscle</td>
</tr>
<tr>
<td>Increase counter regulatory hormones *gluconeogenesis, lipolysis &amp; ketogenesis *blocked peripheral glucose utilization</td>
<td>Increase glucagon *enhanced hepatic glucose output, impaired peripheral utilization.</td>
</tr>
<tr>
<td>Leads to keto-acidosis</td>
<td>Keto-acidosis rarely develops but hyperosmolar nonketotic coma will develop</td>
</tr>
<tr>
<td>Protein catabolism with muscle wasting (myopathy) &amp; negative nitrogen-balance</td>
<td>=</td>
</tr>
</tbody>
</table>
Pathophysiological: basis of the symptoms & signs of untreated / uncontrolled DM

*NORMALLY
Postprandial status is characterized by:
1-hyperglycaemia
2-hyperinsulinaemia

*BUT

*IN DIABETES
1-hyperglycaemia
2-not relative insulin secretion ↑
Aetio- pathogenesis

Type 1 DM: Type 1 A DM patients

A) I. There is genetic susceptibility which involves multiple genes. The concordance range in identical twins is 30 - 70 % they have HLA - DR$_3$ & / or DR$_4$ in 40% as compared to 2% in normal U.S population but presence of the haplotype HLA- D$_3$, HLA – D$_4$, in 20% is protection against DM as compared with < 1 % in normal U.S people.

2. incidence is increased ten folds in relatives of such patients.

3. don’t have first degree relative with this disorder.

B) Autoimmune - factors: * islet cell autoantibodies (ICAs) is present in >75% of type 1A DM pateints versus 5 - 10 % in type 2 DM & < 5 % in G.D.M & 3-4 % of 1st degree relative of i A DM so for the 1st degree relatives of patients with type la Dm to get the illness is relatively low.

*Anti GAD Ab. (glutamic - acid decarboxylase Ab).

*Insulitis (B cells infiltrated by lymphocytes) → B cells destruction & atrophy → Auto - Ab will disappear → insulin→ deficient islet → Frank DM.

C) Enviromental - factor: Coxsackie & rubella viruses, bovine milk proteins & nitrosurea compounds.

D) Stress: * increase secretion of glucagon& catecholamine.

*high immune activity.
Type 2 DM: genetic susceptibility & obesity via Leptin, TNF-alfa, FFA, resistin & adiponectin

Impaired insulin secretion + insulin resistance + increase hepatic glucose production

Type 2 DM

Decrease pancreatic insulin secretion

Clinical DM

It has strong genetic component: Polygenic & multifactorial, the concordance rate in identical - twin is 70-90% if both parents are diabetics the risk will be 40% chance to get 2 DM.
Clinical Features (symptoms & signs):

The illness may be symptomatic, being diagnosed accidentally through routine investigations or usually our patients are not aware of it & that is why large no. of patients seek medical advice when their disease is advanced & present with C/F related to it’s complications or the illness may herald it’s self by acute metabolic-decompensations. Diabetic-Ketoacidosis in type 1 DM & non Ketotic hyperosmolar coma which if untreated may lead to death, otherwise the main symptoms are:

<table>
<thead>
<tr>
<th>•Thirst &amp; dry mouth</th>
<th>•Blurring of vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>•Polyuria, candidiasis</td>
<td>•Pruritis - vulvae, balanitis</td>
</tr>
<tr>
<td>•Nocturia</td>
<td>•Nausea, headache</td>
</tr>
<tr>
<td>•Tiredness, fatigue, apathy &amp; irritability</td>
<td>•Hyperphagia, predilection for sweets</td>
</tr>
<tr>
<td>•Recent change in weight</td>
<td></td>
</tr>
<tr>
<td>C\F</td>
<td>TYPE 1</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Age at onset</td>
<td>&lt; 40 years</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>Weeks</td>
</tr>
<tr>
<td>Body - Weight</td>
<td>Normal or low</td>
</tr>
<tr>
<td>Ketonuria</td>
<td>+ve</td>
</tr>
<tr>
<td>Rapid death without insulin Rx</td>
<td>+ve</td>
</tr>
<tr>
<td>Auto antibodies</td>
<td>+ve</td>
</tr>
<tr>
<td>DM complications at Dx</td>
<td>No</td>
</tr>
<tr>
<td>FHx of DM</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Other autoimmune diseases</td>
<td>Yes</td>
</tr>
</tbody>
</table>
**Diabetic Ketoacidosis (DKA)**

**Diabetic Ketoacidosis:**

**Definition**
DKA is a major medical emergency and remains a serious of morbidity, mainly in patients with type 1 diabetes. (is emergency medical condition that can be life threatening if not treated properly).

**Incidence and prevalence**
Some general points can be drawn from a large population based studies in Rhode Island, USA, an area with a well defined population, in which all cases of DKA were identified in one year. This study found that DKA

- Accounted for 125 of 9663 (1.6%) diabetic admission.
- Had an annual incidence of 46 per 10,000 diabetics.
- Had a female predominance of 2:1.
- Was the presenting feature of diabetes in 20% of cases.
- Was a recurrent problem in 15% of patients.
- Occurred most commonly in patients < 15 years old.

Most studies have found a striking increase in admission for uncontrolled diabetes in adolescence.
Pathophysiology

DKA results from the combined effects of insulin deficiency and increased counter regulatory hormones as the following Fig. The clinical picture can be worked out logically if you look at the biochemistry.

**Insulin deficiency** The effects of insulin deficiency are easily seen in studies of insulin withdrawal in patients with type 1 diabetes. Within one hour of intravenous insulin withdrawal, blood glucose concentrations increase as a result of:

- Increased hepatic glucose production from glycogen (*glycogenolysis*).
- Increased hepatic glucose from amino acids (*gluconeogenesis*).
- Reduced uptake of glucose into skeletal muscle and fat.
the resulting hyperglycaemia leads to an increased urine output owing to an osmotic diuresis which initially acts as a "safety valve". Increased losses of fluid in the urine stimulate thirst, which can help to maintain hydration as long as the patients is not vomiting. The critical factor is the onset vomiting, often related to worsening acidosis, which causes more rapid dehydration, pre-renal failure and further rise in blood glucose.

**Excess Counter-regulatory Hormones**
Glucagon concentrations are invariably raised and contribute to the speed of onset and severity of DKA. In the presence of severe insulin deficiency, glucagon stimulates hepatic gluconeogenesis and worsens hyperglycemia. Glucagon is also lipolytic and stimulates release of free fatty acids into the circulation, where they are used as a substrate for ketone body synthesis in the liver. There are three ketone bodies, all of which are organic acids:
- *Acetoacetone.*
- *Beta - hydroxybutyrate.*
- *Acetone.*
Ketone body concentrations increase within one to two hours of insulin withdrawal, and are the principle cause of metabolic acidosis. Usually all three are increased but occasionally beta - hydroxybutyrate concentrations are disproportionately elevated. This may create a diagnostic problem, since the nitroprusside reaction for ketones does not react with beta - hydroxybutyrate. In these circumstances, clinical and laboratory assessment are needed to excluded other causes of a metabolic acidosis (e.g. measurement of renal function, lactate and salicylate concentrations).
Fluid and Electrolyte Loss

Patients with DKA are always dehydrated mainly because of the osmotic diuresis. Vomiting may worsen fluid and electrolytes loss in some patients, as shown in the following table.

*Table (1) Losses of fluid and electrolytes in DKA*

<table>
<thead>
<tr>
<th>Fluid/electrolytes</th>
<th>Estimate deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body water</td>
<td>5-7 liters</td>
</tr>
<tr>
<td>Sodium</td>
<td>700 - 100 mmol/liter</td>
</tr>
<tr>
<td>Potassium</td>
<td>250 - 500 mmol/liter</td>
</tr>
<tr>
<td>Chloride</td>
<td>500 - 700 mmol/liter</td>
</tr>
<tr>
<td>Calcium</td>
<td>50 - 150 mmol/liter</td>
</tr>
<tr>
<td>Phosphate</td>
<td>50 - 150 mmol/liter</td>
</tr>
</tbody>
</table>

Causes and Precipitating Factors:

Most studies find similar underlying reasons for the reasons for the development of DKA but the proportion vary according to the age of the population studied, and the criteria for diagnosing intercurrent illness. A list of common precipitants is shown in table 2.
*Table 2: causes of DKA in 746 episodes in Birmingham UK, between 1971 and 1985.*

<table>
<thead>
<tr>
<th>Causes</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>28</td>
</tr>
<tr>
<td>Error in management by patient or medical adviser</td>
<td>13</td>
</tr>
<tr>
<td>Myocardial</td>
<td>1</td>
</tr>
<tr>
<td>Newly diagnosed type 1 diabetes</td>
<td>10</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>5</td>
</tr>
<tr>
<td>No cause found</td>
<td>43</td>
</tr>
</tbody>
</table>

**Infection - most common. Usually UTI, URI.**

*Other precipitating factors include:

- Pancreatitis (increased amylase seen in 2/3 of patient with DKA).
- Stroke.
- Trauma, surgery, psychological stress.

**Diagnosis**

A concise history and rapid clinical assessment are essential. In a “typical” presentation, the diagnosis is usually straightforward. There is usually a short period of 12-24 hours when the symptoms of hyperglycemia develop, followed by the onset of vomiting and acidotic breathing.
Clinical features of DKA include:

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyuria, thirst</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Weakness</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>Air hunger (Kussmaul breathing)</td>
</tr>
<tr>
<td>Leg cramps</td>
<td>Smell of acetone</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>Hypothermia</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Confusion, drowsiness coma (10%)</td>
</tr>
</tbody>
</table>

Clinical assessment (Box 1).
Patients with suspected DKA should be assessed quickly to conform the diagnosis so that treatment can be started as soon as possible. A brief history should be taken followed by a clinical examination looking for obvious precipitating illness. The typical patient is drowsy, flushed and dehydrated with kussmaul respiration.

*Box 1. : Clinical features indicating severe DKA.*

<table>
<thead>
<tr>
<th>Tachycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small volume pulse</td>
</tr>
<tr>
<td>Postural or supine hypotension</td>
</tr>
<tr>
<td>Cool peripheries</td>
</tr>
<tr>
<td>Peripheral cyanosis</td>
</tr>
<tr>
<td>Kussmaul respiration</td>
</tr>
<tr>
<td>Drowsiness</td>
</tr>
</tbody>
</table>
The ability to smell acetone on the breath is idiosyncratic and should not be relied upon as a substitute for measuring urine or plasma ketones. Dehydration is always present and measurement of pulse and blood pressure are essential to assess the extent of fluid loss. If possible, both supine and erect blood pressures should be recorded. Other features suggesting severe dehydration include: cold extremities, peripheral cyanosis, a thready pulse and oliguria.

<table>
<thead>
<tr>
<th></th>
<th>DKA</th>
<th>HYPOGLYCEMIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Gradual</td>
<td>Sudden</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td>Warm, dry</td>
<td>Cool, Clammy</td>
</tr>
<tr>
<td><strong>Respirations</strong></td>
<td>• Rapid and deep (Kussmaul)</td>
<td>• Not deep, but may be rapid</td>
</tr>
<tr>
<td></td>
<td>• Not as profound</td>
<td>• Very profound</td>
</tr>
<tr>
<td><strong>Breath Odor</strong></td>
<td>Sweet, fruity</td>
<td>Not found</td>
</tr>
<tr>
<td><strong>Investigation</strong></td>
<td>1. Blood sugar increase over 400mg/dl.</td>
<td>1. Blood sugar decrease below 50 mg/dl.</td>
</tr>
<tr>
<td></td>
<td>2. Urine for ketone bodies positive.</td>
<td>2. Urine for ketone bodies negative.</td>
</tr>
<tr>
<td></td>
<td>4. NaHC03 decrease.</td>
<td>4. NaHC03 Normal</td>
</tr>
<tr>
<td><strong>Response to glucose</strong></td>
<td>No response to administration of test dose of hypertonic Glucose.</td>
<td>The patient response and regain consciousness to adequate dose of hypertonic Glucose.</td>
</tr>
</tbody>
</table>
**Investigations:**

**1st: Essential**

1- Glucose: To support the diagnosis of DKA and provide a baseline to assess response to treatment.

2-Electrolytes: Despite large urinary losses of sodium, plasma concentrations are usually normal or slightly low, ranging from 130 to 140 mmol/litre. Hyperglycaemia also contributes to the development of hyponatraemia, because the osmotic gradient moves water from the intracellular compartment and dilutes extracellular solutes. As a rule of thumb 1.5 mmol/litre should be subtracted from the measured sodium concentrations for every 5.0 mmol/litre of glucose over 5.5 mmol/litre in the patient’s sample.

Plasma potassium is usual at the upper end of normal or slightly increased (table 3). It is important to emphasise that the plasma potassium does not reflect the total body potassium deficit which is always present. However, patients with hypokalaemia at presentation are always severely potassium deficient and require energetic replacement therapy during treatment.

<table>
<thead>
<tr>
<th></th>
<th>DKA</th>
<th>NKHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketosis</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Blood sugar</td>
<td>Usually &lt; 600</td>
<td>Usually &gt; 900 Never &lt; 600</td>
</tr>
<tr>
<td>Osmolarity</td>
<td>Usually &lt; 350</td>
<td>Usually &gt; 350</td>
</tr>
<tr>
<td>Na+</td>
<td>Usually low</td>
<td>Usually high</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>Usually severe</td>
<td>Usually not severe (acidosis &lt; 7.35)</td>
</tr>
</tbody>
</table>
*Table. 3. percentage of patients with DKA who have disturbance of plasma potassium at presentation.*

<table>
<thead>
<tr>
<th>Plasma potassium</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypokalaemia</td>
<td>5-10</td>
</tr>
<tr>
<td>Normal potassium</td>
<td>70-8</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>10-20</td>
</tr>
</tbody>
</table>

3- Plasma urea: Usually raised as a feature of prerenal impairment secondary to dehydration.

4- Venous bicarbonate: To assess the severity of the acidosis. In many studies of a value of 15 mmol/litre is accepted to define DKA.

5- Urinary & plasma ketones: Best measured with a nitropruside-based reaction such as ketostix.

6- Blood culture: To identify possible underlying infection which may have precipitated DKA. Diagnosis of infection in DKA is difficult, since fever may not appear until after rehydration, and the white cell count us usually raised in the absence of infection.
2nd Optimal depending on clinical circumstance:

1- Arterial blood gases: Should be reserved for semiconscious patients or cases where there is no clinical improvement despite fluid and electrolyte replacement plus insulin after two to three hours.

2- Urine microscopy and culture: Not necessary if the urine is clear on gross inspection, but may be needed to confirm urinary tract infection in selected cases.

3- ECG: To exclude underlying silent myocardial infarction, especially in those > 40 years of age or with long duration of diabetes.

4- Chest X-ray: If there are signs of infection.

Potentially misleading:

1- White cell count: Often raised to 15000 - 20000 with a neutrophil Leucocytosis. Does not signify infection in the absence of obvious clinical signs.

2- Amylase: May be raised two to three fold, and is mainly of salivary gland origin. In a patient with abdominal pain from DKA, this may cause diagnostic confusion.

3- Creatinine: There is a potential risk of interference by raised plasma ketones, although modern methods have largely overcome this problem. If in doubt check with your local laboratory.
**Lipids**: Usually derange in uncontrolled diabetes. Triglyceride concentrations are usually raised but cholesterol remains normal. Occasionally, triglycerides maybe grossly elevated (> 50 mmol/liter), And the serum has a milky appearance from the accumulation of VLDL and chylomicrons (diabetic lipaemia). The major complication of diabetic lipaemia is *pancreatitis*, but the condition may also be associated with hepato-splenomegally eruptive xanthomata and memory impairment. The lipid abnormalities respond rapidly to *insulin therapy*.

*Table (4) Diagnostic criteria in DKA*

<table>
<thead>
<tr>
<th><strong>Blood glucose</strong>:</th>
<th>&gt; 250 mg per dL (13.9 mmol per liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PH</strong>:</td>
<td>&lt; 3.7</td>
</tr>
<tr>
<td><strong>Serum bicarbonate</strong>:</td>
<td>&lt; 15 mEq per liter</td>
</tr>
<tr>
<td><strong>Urinary Ketone</strong>:</td>
<td>&gt; 3+</td>
</tr>
<tr>
<td><strong>Serum Ketone</strong>:</td>
<td>Positive at 1:2 dilutions</td>
</tr>
<tr>
<td><strong>Serum osmolality</strong>:</td>
<td>Variable</td>
</tr>
</tbody>
</table>
**Treatment**

The therapeutic goals for diabetic ketoacidosis consist of: improving circulatory volume and tissue perfusion, reducing blood glucose and serum osmolality toward normal levels, clearing ketones from serum and urine at a steady rate, correcting electrolyte imbalances and identifying precipitating factors.

**Fluid Replacement:**
The severity of fluid and sodium deficits (table 1) is determined primarily by the duration of hyperglycemia, the level of renal function and the patient’s fluid intake. Dehydration can be estimated by clinical examination and by calculating total serum osmolality and the corrected serum sodium concentration. Total serum osmolality is calculated using the following equation:

\[
\text{Total serum osmolality (mOsm per kg of water)} + \text{Glucose (mg/dl) } 18 \\
+ \text{Blood urea nitrogen (mg/dl) } 2.8
\]
The measured serum sodium concentration can be corrected for the changes related to hyperglycemia by adding 1.6 mEq per L (5.6 mmol per L) to the measured sodium value for every 100 mg per dL (5.6 mmol per L) of glucose over the normal baseline of 100 mg per dL.

Corrected serum sodium concentrations of greater than 140 mEq per L (140 mmol per L) and calculated total osmolalities of greater than 330 mOsm per kg of water are associated with large fluid deficits. Calculated total osmolalities are correlated with mental status, in that stupor and coma typically occur with an osmolality of greater than 330 mOsm per kg of water.

The initial priority in the treatment of diabetic ketoacidosis is the restoration of extracellular fluid volume through the intravenous administration of a normal saline (0.9 percent sodium chloride) solution. This step will restore intravascular volume, decrease counter regulatory hormones and lower the blood glucose level. As a result, insulin sensitivity may be augmented. In patients with mild to moderate volume depletion, infusion rates of 7 mL per kg per hour have been as efficacious as infusion rates of 14 mL per kg per hour. The subsequent administration of a hypotonic saline (0.45 percent sodium chloride) solution, which is similar in composition to the fluid lost during osmotic diuresis, leads to gradual replacement of deficits in both intracellular and extracellular compartments.

When the blood glucose concentration is approximately 250 mg per dL (13.9 mmol per L), glucose should be added to the hydration fluid (i.e., 5 percent dextrose in hypotonic saline solution). This allows continued insulin administration until ketonemia is controlled and also helps to avoid iatrogenic hypoglycemia. Another important aspect of rehydration therapy in patients with diabetic ketoacidosis is the replacement of ongoing urinary losses.
Insulin Therapy:

Modern management of diabetic ketoacidosis has emphasized the use of lower doses of insulin. This has been shown to be the most efficacious treatment in both children and adults with diabetic ketoacidosis. The current recommendation is to give low-dose (short-acting regular) insulin after the diagnosis of diabetic ketoacidosis has been confirmed by laboratory tests and fluid replacement has been initiated.

It is prudent to withhold insulin therapy until serum potassium concentration has been determined. In the rare patient who presents with hypokalemia, insulin therapy may worsen the hypokalemia and precipitate life-threatening cardiac arrhythmias.

*Standard low-dose insulin therapy consists of an initial intravenous bolus of 0.15 unit of regular insulin per kg followed by the continuous intravenous infusion of regular insulin prepared in normal saline or hypotonic saline solution at a rate of 0.1 unit per kg per hour.*

In clinical situations in which continuous intravenous insulin cannot be administered, the recommended initial insulin dose is 0.3 unit per kg, with one half of the dose given as an intravenous bolus and the remainder given subcutaneously or intramuscularly. Subsequently, regular insulin should be given in a dosage of 0.1 unit per kg per hour until the blood glucose level is approximated 250 mg per dL.
If the blood glucose concentration does not fall by 50 to 70 mg per dL (2.8 to 3.9 mmol per L) in the first hour, the intravenous infusion rate should be doubled or additional intravenous 10-unit boluses of insulin should be given every hour. Either of these treatments should be continued until the blood glucose level falls by 50 to 70 mg per dL. Low-dose insulin therapy typically produces a linear fall in the glucose concentration of 50 to 70 mg per dL per hour.

More rapid correction of hyperglycemia should be avoided because it may increase the risk of cerebral edema. This dreaded treatment complication occurs in approximately 1 percent of children with diabetic ketoacidosis. The typical presentation is onset of headache and decreased mental occurring several after the start of treatment. Cerebral edema is associated with a mortality rate of up to 70 percent.

When a blood glucose concentration of 250 mg per dL has been achieved, the continuous or hourly insulin dosage can be reduced to 0.05 unit per kg per hour. The insulin and fluid regimens are continued until ketoacidosis is controlled. This requires the achievement of at least two of these acid-base parameters which are: a serum bicarbonate concentration of greater than 18 mEq per L, a venous PH of 3.7 or greater and an anion gap of less than 14 mEq per L.
What is insulin?

*Structure

source

natural

- Animal pancreas
- Human pancreas

synthetic

- Biosynthetic
- r DNA technology
*classification of insulin according to the onset and duration of action in to:
Prandial – insulin

<table>
<thead>
<tr>
<th>I- short acting</th>
<th>lispro</th>
<th>onset h.</th>
<th>duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>28th,29th amino acid lysine and proline reserved by rDNA technology</td>
<td>Aspart</td>
<td>&lt;0.25</td>
<td>3-4</td>
</tr>
<tr>
<td>regular</td>
<td>regular</td>
<td>0.5 – 1 given 1/2 h before meal</td>
<td>3-6</td>
</tr>
</tbody>
</table>

These insulin have full physiologic activities with less tendency to subcutaneous-aggregation rapid - absorption and onset of action and shorter – duration.

<table>
<thead>
<tr>
<th>II- intermediate</th>
<th>NPH</th>
<th>2-4</th>
<th>10-16</th>
</tr>
</thead>
<tbody>
<tr>
<td>lente</td>
<td>lente</td>
<td>3-4</td>
<td>12-18</td>
</tr>
<tr>
<td>III-long acting</td>
<td>Ultralente</td>
<td>6-10</td>
<td>18-20</td>
</tr>
<tr>
<td>glargine</td>
<td>glargine</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>IV- combination</td>
<td>Protamine+lispro 75%+25%</td>
<td>0.5 – 1</td>
<td>1 0-14</td>
</tr>
<tr>
<td>NPH+ regular 70%+30%</td>
<td>NPH+ regular 70%+30%</td>
<td>0.5 - 1</td>
<td>10-16</td>
</tr>
<tr>
<td>NPH+ regular 50%+50%</td>
<td>NPH+ regular 50%+50%</td>
<td>0.5 - 1</td>
<td>10-16</td>
</tr>
</tbody>
</table>
Note: glargine insulin is long acting biosynthetic human insulin (aspargine is replaced by glycine at 21th amino acid and two arginine residues are added to the C-terminus of B-chain) and it has lower incidence of hypoglycaemia (nocturnal).
*Route of insulin – administrations:
Single daily-dose of insulin-injection is not appropriate – therapy for diabetic – patients who need it. We should give $\frac{2}{3}$ of the dose at morning and $\frac{1}{3}$ of the dose at evening.
1-subcutaneous (s.c) injection or (csii), may cause lipo-atrophy or fat hypertrophy at the site of injections. What to do for it?
2-intramuscular (IM)
3-intravenous (IV)
4-insulin-pump: the main disadvantages are
   a. costly
   b. hypoglycaemia
   c. hyperglycaemia $\rightarrow$ DKA (pump-failure)
   e. infection at the site of the pump. $\rightarrow$ septicaemias.
   f. good IQ patients (experts)
5- insulin – pens: which may be more convient for some diabetic-patients.
Potassium Therapy:

Although the typical potassium deficit in diabetic ketoacidosis is 500 to 700 mEq (500 to 700 mmol), most patients are hyperkalemic at the time of diagnosis because of the effects of insulinopenia, hyperosmolality and academia. During rehydration and insulin therapies for diabetic ketoacidosis, the serum potassium concentration typically declines rapidly as potassium reenters the intracellular compartment. One protocol entails using insulin and intravenous fluid until the serum potassium concentration is less than 5.5 mEq per L (5.5 mmol per L). At this time, potassium chloride is added to intravenous fluid in the administered depends on the serum potassium concentration. When the serum potassium level is less than 3.3 mEq per L (3.3 mmol per L), the administration of 40 mEq per L of potassium is appropriate. If the serum potassium is greater than 3.3 mEq per L but less than 5.5 mEq per L, 20 to 30 mEq per L of potassium can be administered. The goal is to maintain the serum potassium concentration in the range of 4 to 5 mEq per L (4 to 5 mmol per L).
Bicarbonate Therapy:

In general, supplemental bicarbonate therapy is no longer recommended for patients with diabetic ketoacidosis, because the plasma bicarbonate concentration increase with insulin therapy.

Insulin administration inhibits ongoing lipolysis and ketone production and also promotes the regeneration of bicarbonate. Retrospective reviews and prospective randomized studies have failed to identify changes in morbidity or mortality with sodium bicarbonate therapy in patients who presented with a PH of 6.9 to 7.1. Therefore, the use of bicarbonate in a patient with PH greater than 7.0 is not recommended. Furthermore, bicarbonate therapy carries some risks, including hypokalemia with overly rapid administration, paradoxic cerebrospinal fluid acidosis, and hypoxia.

Some authorities, however, recommend bicarbonate administration when the PH is less than 7.0, for the purpose of treating the possible adverse hemodynamic effects of profound academia. If bicarbonate is used, it should be given as a nearly isotonic solution, which can be approximated by the addition of one ampule of sodium bicarbonate in 300 ml of sterile water. The bicarbonate solution is administered over a one-hour period.

A small percentage of patients who have diabetic ketoacidosis present with metabolic acidosis and a normal anion gap. Therefore, they have fewer ketones available for the regeneration of bicarbonate during insulin administration. Bicarbonate therapy may be warranted in this subset of patients.
Phosphate Therapy

Osmotic diuresis leads to increased urinary phosphate losses. During insulin therapy, phosphate reenters the intracellular compartment, leading to mild moderate reductions in the serum phosphate concentration.

Adverse complications of hypophosphatemia are uncommon and occur primarily in patients with severe hypophosphatemia (a serum phosphate concentration of less than 1.0 mg per dl [0.32 mmol per L]). Prospective studies have indicated no clinical benefit for phosphate replacement in the treatment of diabetic ketoacidosis, and excessive phosphate replacement may contribute to hypocalcaemia and soft tissue metastatic calcification. Although the replacement of phosphate per se is not routinely recommended, it may be useful to replace some potassium as potassium phosphate. One protocol is to administer two thirds of the potassium as potassium chloride and one third as potassium phosphate. The use of phosphate for this purpose reduces the chloride load that might contribute to hyperchloremic acidosis and decreases the likelihood that a patient will develop severe hypophosphatemia during insulin therapy.
<table>
<thead>
<tr>
<th>Complication</th>
<th>Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute gastric dilatation or erosive gastritis</td>
<td>Vomiting of blood or &quot;coffee - ground&quot; material</td>
</tr>
<tr>
<td>Cerebral edema</td>
<td>Obturation or coma with or without neurological sign, especially if occurring after initial improvement.</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Adrenergic or neurological signs: rebound ketosis.</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td>Infection</td>
<td>Fever</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Unremitting acidosis after 4-6 h of adequate therapy.</td>
</tr>
<tr>
<td>Myocardial ischaemia</td>
<td>Chest pain, appearance of heart failure, appearance of hypotension despite adequate fluids.</td>
</tr>
<tr>
<td>Mucomycosis</td>
<td>Facial pain, bloody nasal discharge blackened nasal turbinates, blurred vision properties.</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>Hypoxemia in the absence of pneumonia</td>
</tr>
</tbody>
</table>
Prognosis:
Most patient with DKA recover when probably treated. While the mortality rate in large series is reported to be around 10 percent, most deaths result from late complication of DKA rather than from ketaacidosis itself. The major causes are infarction and infection, particularly pneumonia. Poor prognostic signs on admission include:
1- Hypotension.
2- Azotemia.
3- Deep coma.
4- Associated illness.
In children cerebral edema is a common cause of death (less frequent in adults).

Non ketotic hyperosmolar diabetic COMA:
It is acute metabolic complication in elderly diabetic patients acute metabolic complication in elderly diabetic patients which is characterized by:
1- Sever hyperglycaemia > 50 mmol/litre.
2- Sever dehydration.
3- Sever pre-renal ischaemia - uraemia.
4- No significant hyperketonaemia.
5- Mortality rate > 50%.
6- Hyperosmoality N= 280 - 300 mmol/kg.
Plasma - osmolality = 2[ Na⁺ + k⁺ ] + [ Glucose ] + [ urea ]
7- Look for a source of infection like pneumonias.
**Treatment:**
1. Soluble Insulin Iv (0.45%).
2. 1/2 strength saline until plasma-osmolality becomes normal then continue with normal saline Iv (0.9%).
3. Antibiotic when indicated.
5. Thrombo-embolic complications are common & prophylactic subcutaneous heparin is recommended.

**Lactic Acidosis:**
This metabolic abnormality usually occurs in Type 2 DM & on metformin. It is characterized by:
1. Coma.
2. Patient is very ill.
3. Over-breathing.
4. Mild dehydration.
5. No smell of acetones.
6. Ketonuria is mild or negative.
7. Plasma HC03 decrease, PH < 7.2.
8. Diagnosis is confirmed by very high plasma, Lactic - acids > 5 mmol/litre.
Treatment:
*Iv NaHC03+
*Insulin + .
*Glucose .
*Sodium dichloroacetate .

Prognosis: is very poor & mortality rate > 50 %.

Long term complication of DM:
Are mainly related to:
A- Macro-vascular changes—► atherosclerosis —► (Macro-angiopathy)
hyperinsulinaemia ( INSULIN —► Resistance ) enhances atherogenic effect of smoking , Blood pressure increased , hyperlipidaemia causing mortality rate = 70% due to CHD (MI & CVA) that occurs early in life & being more extensive & sever but aggressive Rx of diabetic - patients with CVD can improve outcome .
B- Micro vascular changes ( diabetic micro angiopathy) which is specific for DM & it causes death by diabetic - nephropathy leading to chronic renal failure ( ESRD).
Both types of vascular disease cause morbidity & disability which is mainly related to:
*blindness due to " diabetic-retinopathy"
*feet ulcers ” diabetic foot”
*gangrene & intermittent - claudication due to atherosclerosis .
*IHD “Angina " & heart - failure .
*Autonomic - neuropathy : Bowel & bladder dysfunction (diabetic cystopathy ).
According to many studies it was concluded that both micro & macro vascular complication can be prevented in 60% of diabetic patients who get strict-glycaemic- control (HbA₁C ≤ 6.5%) as indicated by DCCT (Diabetic control & complication Trials) in Type I DM.

The disadvantage of this was:
1. Weight gain.
2. Hypoglycaemia episodes thus intensive glycaemic control is not indicated in:
   1. patients with impaired awareness of hypoglycaemia.
   2. patients with MI or CVA history.
   3. elderly.
   4. children (pre-school age).

While in type 2 DM, intensive & strict glycaemic - control & Blood pressure control (140/80) proved to be effective & important to reduce (prevent) the progression of both vascular changes as indicated by (UKPDS & comommoto's studies). 1% reduction in HbA₁C will reduce events (vascular) by 37%.
Pathophysiology of LTC includes:

A. Biochemical events of hyperglycaemia:
   • Non enzymatic - glycation.
   • Oxidative — reductive.
   • Increase polyol - pathway activity.
   • Intracellular myo- inositol depletion.
   • Increase diacylglycerol synthesis.
   • Increase protein - kinase activity.

B. Functional & anatomical abnormalities:
   • Haemodynamic - disturbances.
   • Haemorrhheological & coagulation abnormalities.
   • Micro vascular - hypertension.
   • Endothelial - dysfunction.
   • Increase capillary - permeability.

L.T.C. micro vascular induced diabetic complications include:
1- Diabetic - retinopathy.
2- Diabetic - nephropathy.
3- Diabetic - neuropathy.
4- Diabetic – foot.

These complication are related to hyperglycemia of long duration as evidenced by four supposed theories and to prevent or delay these complications we need to do strict glysemic control as following s
Hyperglycemia

↑ Intracellular glucose

1. ↑ AGEs
   - Abnormal protein function
   - Altered cell function
     - Renal, vascular, connective tissue effects
     - Cytokines, growth factors

2. ↑ Circulating AGEs

3. ↑ Sorbitol
   - Alterations in redox potential, ROS

4. ↑ DAG
   - PKC activation

5. ↑ Fruc-6-P
   - Flux in hexosamine pathway

Complications of diabetes

Intensive control
Diabetic — Retinopathy: 30% in female presenting problem. This is the most common cause of blindness in adults between 30-65 years of age in developed countries but retinal photocoagulation therapy when applied in early stage when the patient is usually a symptomatic, is very effective. So regular Fundoscopy is mandatory in all diabetic patients.

C\F. The earliest changes are retinal-capillary bed abnormalities (cap dilatation & closure).

A) Simple (Background):
1- Micro-aneurysm.
2- Retinal-hemorrhage.
3- Exudates.
4- Cotton wool spots.
5- Venous-changes
6- Prognosis: No immediate threat to vision
7- Rx:
   a. intensive glycaemic control
   b. intensive lipid & BP control
   c. Stop smoking, alcohol
   d. fundoscopy: 6-12 months
   e. consult the ophthalmologist if rate of progression increase significantly.
   f. Laser.

B) Malignant (proliferative):
1- Neovascularisation.
2- Pre-retinal-hemorrhage.
3- Vitreous-hemorrhage.
4- Fibrosis-hemorrhage.
5- Exudative-maculopathy.
6- Prognosis: Slight-threatening of vision
7- Rx:
   refer the case to ophthalmologist urgently to interfere otherwise vision may be lost.
*Photocoagulation therapy will reduce severe visual loss by 85% & maculopathy by 50%*

*Vitrectomy is *indicated* in: 1) recurrent vitreous-hemorrhage that doesn't clear. 2) retinal-detachment due to retinitis-proliferans.

*Other causes of blindness in diabetic patients type 2:

◊ 50% due to non-diabetic causes:  
   a) macular degeneration.  
   b) retinal vein thrombosis.  
   c) retinal arterial occlusion.  
   d) ischaemic optic-neuropathy.  
   e) glaucoma.

◊ Diabetic - causes:  
   a) Snow flake cataract.  
   b) proliferative-retinopathy.  
   c) maculopathy.

*Cataract* is Rx by lens-extraction (*extra capsular* - method) with implantation of an intra-ocular-lens.

*Diabetic retinopathy needs 4-7 years history of uncontrolled DM2 to develop, the longer the duration of DM2 the higher the chance of diabetic-retinopathy to occur.*

**DIABETIC - NEPHROPATHY:**

It is among the most common causes of E.S.R.F (CRF) in developed countries as it is usually associated with other LTC, Rx is frequently difficult, so prevention is very great full.

It occurs in type 1 DM after 20 years in 30% but the risk after this time will be less than 1% per year.

Over all the incidence is decrease due to improved standards of diabetic control.
**Risk-factors to develop D.nephropathy include :-**

1) Poor control of blood glucose .
2) Long - duration of diabetes.
3) Presence of other micro - vascular complication .
4) Ethnicity (e.g. pima-Indians, Asian-races).
5) Pre-existing hypertension .
6) Family Hx of diabetic nephropathy.
7) Family Hx of hypertension .

**Pathological lesion are :-**

1) Minimal change glomerulonephritis
2) Focal / segmental glomerulosclerosis (Kimmelstiel - Wilson nodule: Is the characteristic diabetic glomerulosclerosis)
3) Diffuse glomerulosclerosis .
4) Acute & chronic pyelonephritis .
5) Acute papillary – necrosis.

**Clinically : - either :**

1) Asymptomatic proteinuria (micro - macro albumenuria).
2) Hypertension - states.
3) Nephrotic - syndrome .
4) End stage chronic renal failure(E.S.C.R.F)

*We can reduce the risk of nephropathic - progression by*

1) Improved control of blood glucose .
2) Aggressive decrease of Blood pressure.
3) Starting **ACE inhibitors therapy** (Captopril, Enalopril) or angiotensine type 2 receptors – blockers (Micardis) or diltiazem- verapamil as alternatives .
**Treatment:**
1-Supportive.
2-Kidney - transplantation it may recur in the implanted graft but this is a too - slow process to be a serious problem , yet CHD is the major cause of death .
Pancreatic transplantation can be done at the same time but it’s availability is difficult & limited.
Microalbumenuria is an imp. indicator of risk of overt D.nephropathy, *so that the progressively increasing albumenuria or albumenuria accompanied by hypertension is more likely occur in D.nephropathy*

**Diabetic - neuropathy:**
1. It is a relatively early & common LTC 30% in DM
2. It is usually - symptom less .
3. It is either involving :-
   a) CNS.
   b) Cranial nerves ( reversible except facial nerve palsy ).
   c) Peripheral nerves (sensory-motor) :classified into
      * mono - neuropathy .
      * poly - neuropathy which is treated by {_Tricyclic Antidepressant ( TCA ) ,Tegretol, Gabapentin, capsaicin "topically" }.
   d) Autonomic nerves system : In
      * CVS .   * Sudomoter     * GIT      * Vasomotor
      * Genitourinary     * Pupillary
Histopathology:
1- axonal - degeneration.
2- thickening of schwann cell basal - lamina.
3- patchy segmental demyelination.
4- thickening of basement - membrane & mitochondria in intraneural capillaries.

Autonomic diabetic neuropathy:-
1. **CVS:**
   - postural hypotension is treated by { stockings, fludrocortisone, Alfa – agonist ” midodrine ”, NSAIDs }.
   - resting tachycardia.
   - fixed heart rate.

Tested by:
- a) H. rate variation during deep - breathing .
- b) H. rate response to standing .
- c) H. rate changes during the valsalva manoeuvre .
- d) B.P response to standing .
- e) B.P response to sustained hand- grip .

2. **GIT:**
   - dysphagia
   - N /V/ Abdominal fullness : diabetic gastroparesis which is treated by { plasil , domperidone , erythromycin }.
   - nocturnal diarrhea ± faecal incontinence treated by { loperamide, antibiotics , clonidine , octreotide }.
   - constipation - pseudo-intestinal obstruction ( colonic - atony)
3. **Genitourinary:**
   - diabetic cystopathy - U.T.I is treated by \{ intermittent self- catheterization \}
   - impotence, retrograde ejaculation.

4. **Sudomotor:**
   - Gustatory - sweating is treated by \{ Anticholinergics - propantheline, clonidine, topical antimuscarinic agent "glycopyrrolate" \}
   - Nocturnal sweating without hypoglycaemia.
   - Anhidrosis, fissures in the feet.

5. **Vasomotor:**
   - Cold feet.
   - dependent oedema.
   - bullous formation

6. **Pupillary:**
   - decreased pupil size.
   - resistance to mydriatics.
   - delayed or absent reflexes to light.

➢ IMPORTENCE ( Erectile dysfunction ) is treated by:
   - Sildenafil (Viagra) : phosphodiesterase inhibitor
   - papaverine or prostoglandin E1 (Alprostadil) injected into corpus — cavernosum.
   - Vacuum tumescence devices.
   - Implanted penile prosthesis.
   - psychological - counselling.
It is a frequent complication that is why foot care is particularly important. Tissue necrosis is a common reason for hospital admission in diabetics which will be long & often ends with amputation.

<table>
<thead>
<tr>
<th>C\F</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathy</td>
<td>negative paraesthesiae</td>
</tr>
<tr>
<td>Pain</td>
<td>numbness</td>
</tr>
<tr>
<td>ischaemia</td>
<td>negative Ulcer - Trophic ulcer</td>
</tr>
<tr>
<td>Claudication</td>
<td>sepsis</td>
</tr>
<tr>
<td>Rest- pain</td>
<td>gangrene</td>
</tr>
<tr>
<td>Structural damage</td>
<td>ulcer</td>
</tr>
<tr>
<td></td>
<td>sepsis</td>
</tr>
<tr>
<td></td>
<td>Abscess</td>
</tr>
<tr>
<td></td>
<td>osteomyelitis</td>
</tr>
<tr>
<td></td>
<td>digital - gangrene</td>
</tr>
<tr>
<td></td>
<td>charcot joint (ankle)</td>
</tr>
</tbody>
</table>
• Treatment of diabetic - foot:

• Remove callus - skin.
• Treat infection.
• Avoid weight - bearing.
• Ensure good glycaemic - control.
• Angiographic study to check for vascular- reconstruction where indicated.

Therefore practically prevention is the most — effective way of dealing with diabetic foot tissue - necrosis. Educate diabetics to take care or their feet.

Orthotic - foot ware is required to prevent ulcerations & protect feet with charcot – arthropathy
Hyperosmolar non ketotic diabetic coma

Definition: it is usually a complication of type 2 DM. It is a syndrome of profound dehydration resulting from sustained hyperglycemic–diuresis in which the patient cannot drink water to keep up with urinary–fluid loss.

*Ppt. factors

1. stroke
2. infection
3. P.D a haemodialysis, tube-feeding with high protein formulas, high carbohydrate infusion.
   b. phenytoin
   c. steroid
   d. immune suppressive drugs
   e. diuretics.
*C/f: the reason for -ve DKA in type 2 DM is not known. F.F.A. are lower than in DKA.
- extreme hyper glycaemiaes  1000mg\dl
- hyper osmolarity
  \[ \text{Osmol.} = 2 \{[\text{Na}^+]+[\text{K}^+]\} + \text{glucose/18} + \text{BUN/2.8} \] Mosmol/l

- volume – depletion
  a. pre-renal azotaemica (Bu and creat. ↑)
  b. plasma HCO3- 20 meq/l (acidosis is due to:
     1. starvation – ketosis.
     2. retension of inorganic acid due to azotaemia
     3. ↑lactic –acid due to volume depletion

- CNS features: 1. confusion
  2. drowsiness
  3. coma
  4. seizure jaksonian type transient hemiplegia

- pneumonia and G-ve sepsis
  Urine and blood and CSF --- culture
- dehydration viscosity ↑, thrombosis-----Dic
- acute – pancreatic may occur
- MR ≥50 %
*R1
1. IVF (10 litters) initially isotonic salt ---- 2-3 lit in 1-2 h. then 1/2 strength NaCl. When glucose become normal then 5% dextrose to supply free water
2. insuline --- small dose or large dose + (K) replacement
3. when there is lactic acidosis --- NaHCO3 is give iv
4. antibiotic is given for infection.
Management of Diabetic Ketoacidosis

Initial evaluation (perform immediately):
- History and physical examination
- Laboratory tests: arterial blood gases, complete blood count with differential, urinalysis, blood glucose, blood urea nitrogen, creatinine, electrolytes (chem)
- Electrocardiogram
- Chest radiograph and cultures as needed
- Start IV fluid: 1 L of 0.9% sodium chloride per hour initially (15 to 20 mL/kg)

Diagnostic criteria for diabetic ketoacidosis:
- Blood glucose level >250 mg/dL (13.9 mmol/L)
- Arterial pH <7.3
- Serum bicarbonate level <15 mEq/L
- Moderate ketonuria and ketonemia

IV fluids
- Determine hydration status
- Hypovolemic shock
  - Administer 0.9% sodium chloride (1 L/hour) and/or plasma expander
- Nonhypovolemic shock
  - Administer regular insulin, 0.15 U/kg as IV bolus
  - Monitor hemodynamic monitoring
- Evaluate corrected serum sodium level
  - Serum sodium level high
    - Administer 0.45% sodium chloride (7 to 14 mL/kg/hour), depending on hydration status
  - Serum sodium level normal
  - Administer 0.9% sodium chloride (11 to 14 mL/kg/hour) until hydration status is normalized
  - When serum glucose reaches 250 mg/dL (13.9 mmol/L)
- Serum sodium level low
  - Administer 0.9% sodium chloride (7 to 14 mL/kg/hour), depending on hydration status

Insulin

Potassium
- If serum potassium level is <3.5 mEq/L, hold insulin and give 40 mEq of potassium per hour (two thirds as potassium chloride and one third as potassium phosphate) until potassium level is ≥3.5 mEq/L
- If serum potassium level is ≥3.5 mEq/L, do not give potassium but check level every 2 hours

Figure 2. Protocol for the management of patients with diabetic ketoacidosis.
(IV=intravenous SC=subcutaneous; IM=intramuscular)