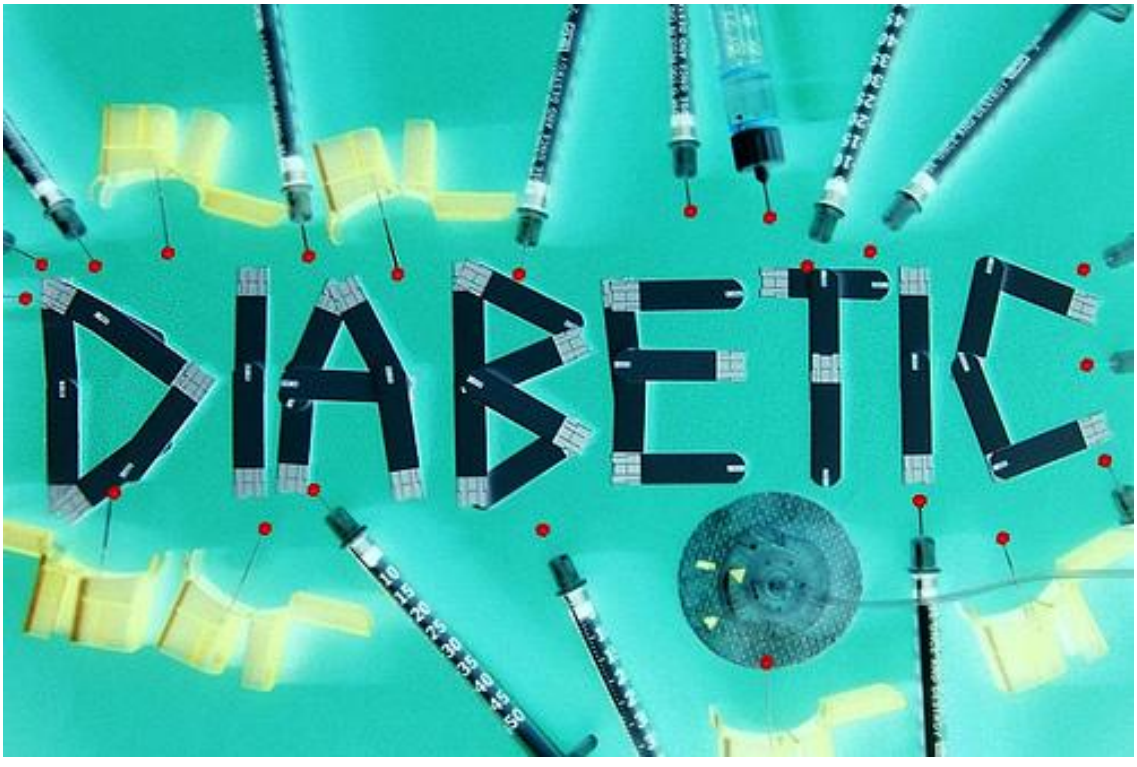
ENDOCRINE BLOCK



DIABETES MELLITUS, TYPE 1

Correction File

Case ..
A 14-year-old girl was admitted to a children's hospital in coma. Her mother stated that the girl had been in good health until approximately 2 weeks previously, when she developed a sore throat and moderate fever. She subsequently lost her appetite and generally did not feel well.
Several days before admission she began to complain of undue thirst and also started to get up several time during the night to urinate. However, on the day of admission the girl had started to vomit, had become drowsy and difficult to arouse, and accordingly had been brought to the emergency department. On examination: •She was dehydrated •Her skin was cold •She was breathing in a deep sighing manner (Kussmaul respiration) •Her breath had a fruity odor •Her blood pressure was 90/60 mmHg (N: 120/80) •Her pulse rate 115/min . •She could not be aroused

What is the most likely the diagnosis ?Insulin Dependent Diaeites mellitus

Talk about Diabetes mellitus Type 1?
It is autoimmune disease type IV hypersenstivity and affects childrean. it causes destruction in Beta cells of pancreas leads to no insulin → high glucagon → high production of glucose and ketones by liver

Mention the treatment of this condtion ?what du you think about her wight after tretment? Insulin injection . her wight will be incrased beacsue the insulin leads to increase glucose entery to fat tissue

Talk about type 3 and type 4 diabetes mellitus ?
Type 3: gastesional diabetes occurs in pregnancy usally around 24th week
Type 4 : Secondary diabetes mellitus which is caused by many diseases such as hyperthyrodism

What is diffrence between D	Type 1 	Type 2 
Age of onset	Childhood	Adult
Prevalence	< 10%	> 90%
Symptoms develop	Rapidly	Gradually
Weight	lean	overweight
Defect Or Deficiency	B-cell are destroyed, eliminating production of Insulin	Insulin resistance combined with inability of b-cell to produce appropriate quantities of insulin.
ketosis	common	Rare
plasma insulin	low	A-high early in disea B -low in diswase of long duration
Acute complication	Ketoacidosis	Hyperosmolar coma
Genetic predisposition	Moderate	Very strong
Use of oral hypoglycemic	Unresponsive	Responsive
Treatment	Insulin is always necessary	Diet, exercise, oral hypoglycemi +/- insulin

Anatomy

It is an elongated soft pinkish structure
(60-100) gram in weight & (6-10) inch in length

Why the Pancreas is Lobulated?

Because it is surrounded by a fibrous tissue capsule from which septa pass into the gland & divide it into lobes. The lobes are divided into lobules.

The Location:

•It is a **Retro-Peritoneal** structure.
•It lies on the posterior abdominal wall in the: **Epigastrium & Left upper quadrant of the abdomen.**
•It extends in a transverse oblique direction at the **transpyloric plane (1st lumbar vertebral)** from the concavity of the duodenum on the right to the spleen on the left.

PARTS Because of its oblique direction the tail is higher than the head (at T12).

HEAD	NECK	BODY	TAIL
•It is disc shaped •Lies within the concavity of the duodenum •Related to the 2nd and 3rd portions of the duodenum. •On the right, it emerges into the neck. •On the left, it Includes **Uncinate Process** (an extension of the lower part of the head behind the superior mesenteric vessels) Structures Post. to the Head: (1) **Bile Duct** runs downwards & may be embedded in it. (2) **IVC** runs upwards.	•It is the constricted portion connecting the head & body of pancreas •**It lies in front of:** **1-Aorta** **2-Origin of Superior Mesenteric artery** **3-the confluence of the Portal Vein** •Its antero-superior surface supports the **pylorus of the stomach** •The **superior mesenteric vessels** emerge from its inferior border	•It runs upward & to the left. •It is triangular in cross section. •The **Splenic Vein** is embedded in its post. Surface •The **Splenic Artery** runs to the left along the upper border of the pancreas.	•A narrow, short segment ends within the splenic hilum •Lies in the **Splenicorenal ligament** •Anteriorly, related to: splenic flexure of colon**(May be injured during Splenectomy)**

RELATIONS OF PANCREAS

Anterior to (body & tail):	Posterior to (body & tail) :
•**Stomach** separated from by lesser sac •**Transverse colon** & transverse mesocolon	•Left Psoas muscle •Left Adrenal gland •Left Renal vessels •Upper 1/3rd of Left kidney •Hilum of the spleen

ARTERIAL SUPPLY

Celiac trunk	Superior mesenteric	Splenic arteries
CHA (R.Gastric & Hepatic)→ Gastroduadenal → **Superior pancreaticoduodenal**	**Inferior pancreaticoduodenal** TO HEAD	supplies the Body and Tail of pancreas by about 10 branches

VENOUS DRAINAGE

•Anterior and posterior arcades drain head and the body
•**Splenic vein** drains the body and tail .. Ultimately, ends into **Portal Vein**

LYMPHATIC DRAINAGE

•Rich network drains into nodes along the upper border of the pancreas
•Ultimately the efferent vessels drain into the **Celiac nodes.**
•Lymph vessels from the region of the Head pass to **Superior Mesenteric nodes**

NERVE SUPPLY

•**Sympathetic** from the **splanchnic nerves** , they have a predominantly inhibitory effect
•**Parasympathetic** from the **Vagus**, they stimulate both exocrine and endocrine secretions

Pancreatic DUCTS

Main P duct :
•Joins common bile duct & they open into a small hepatopancreatic ampulla in the duodenal wall **(Ampulla of Vater).**
•The ampulla opens into the lumen of the duodenum through **(Major Duodenal Papilla).**

Accessory P duct (of Santorini)
Drains superior portion of the head
•It empties separately into 2nd portion of duodenum at (minor duodenal papilla)

FUNCTIONS

The Exocrine portion
Small ducts arise from the lobules and enter the main pancreatic duct (which begins in the tail), & passes through the body and head where it meets the bile duct.

The Endocrine portion
(Islets of Langerhans) produce insulin & glucagon.

Glucose homeostasis . What does it mean ?
A process that Controls glucose metabolism & Maintains blood glucose level in the body
What is the organ that plays a key role in maintaining blood glucose level ? Liver

What is the major source of body's energy? Glucose
Dietary sources:

- Dietary CHO is digested in the GI to monosaccharides
- Starch provides glucose directly
- Fructose and galactose are converted to glucose in the liver

Metabolic sources (via gluconeogenesis): Glycerol, lactate, pyruvate, glucogenic amino acids

Write the steps of glucose metabolism in brief ?
1-Glucose, fractose and glactose "monosaccharides" go into blood stream.
2-From blood to periphral tissue to provide energy and it goes to liver "Liver removes about 70% of glucose load after a CHO meal".
3-When it goes to liver some of glucose used to make glycogen " glycogenesis" (for storage)
4-Excess glucose is converted to fatty acids and triglycerides in the liver , These are transported via VLDL to adipose tissue for storage. 5- when you are starving the gluconeogenesis will start .

Write 4 Hormones that Antagonize insulin action ?
1-Cortisol. 2-Growth Hormone. 3-Adrenaline. 4- Glucagon.

Phase	
I- Well fed state	•Glucose is mainly supplied by dietary CHOs •Liver removes about 70% of glucose load after a CHO meal •All body tissues use dietary glucose for energy in this phase •Some glucose is converted to glycogen for storage in the liver (glycogenesis) •Excess glucose is converted to fatty acids and triglycerides in the liver •These are transported via VLDL (very low density lipoproteins) to adipose tissue for storage •Gluconeogenesis is inhibited in this phase •Cori and glucose-alanine cycles are inhibited
II- Glycogenolysis	•starts during early fasting when dietary glucose supply is exhausted •Hepatic glycogenolysis maintains blood glucose level in this phase •Glycogenolysis is the major source of blood glucose in this phase
III-Gluconeogenesis	•starts when glycogen stores in liver are exhausted (within 20 hours) •Duration of phase III depends on 1- Feeding status 2- Hepatic glycogen stores 3- Physical activity •Hepatic gluconeogenesis from lactate, pyruvate, glycerol and alanine maintains blood glucose level •Gluconeogenesis is the major source of blood glucose in this phase
IV- Glucose & KB oxidation"	•Several days of fasting leads to phase IV •Gluconeogenesis starts to decrease •KB accumulation increases which enter the brain for energy production •Brain uses both glucose and KB for energy
V- FA & KB oxidation	•Prolonged fasting leads to phase V •Less dependence on gluconeogenesis •All body tissues use FA and KB oxidation for energy production •Gluconeogenesis somewhat maintains blood glucose level in this phase •High KB conc. and glucose levels inhibit proteolysis in muscle (conservation of muscle) •When all fat and KBs are used up body uses muscle protein to maintain blood glucose level

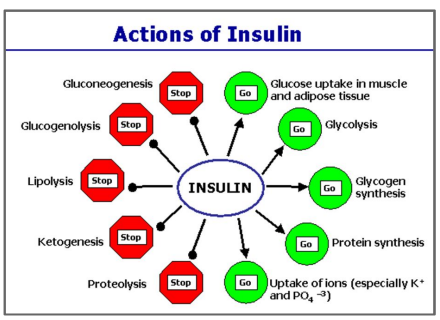
Hormones that regulate glucose metabolism	
Insulin	•Plays a major role in glucose homeostasis •Synthesized by the b-cells of islets of Langerhans of pancreas •A small protein composed of two chains •Formed as prepro-insulin and converted to pro-insulin upon secretion •Rise in blood glucose level stimulates insulin secretion •Promotes entry of glucose into cells
Glucagon	•A peptide hormone secreted by a-cells of pancreatic islets •Secreted in response to hypoglycemia •↑glucose levels •Stimulates glycogenolysis •Activates hepatic gluconeogenesis
Cortisol	•Cortisol is a steroid hormone secreted by adrenal gland • Contributes to glucose homeostasis •Maintains normal glucose levels in fasting •Stimulates gluconeogenesis in the liver •Mobilizes amino acids for gluconeogenesis •Inhibits glucose uptake by cells •Stimulates fat breakdown in adipose tissue
Growth hormone	•A protein hormone secreted by anterior pituitary gland •Maintains blood glucose levels by: 1-Inhibiting insulin action 2-Stimulating gluconeogenesis in the liver
Epinephrine	•A catecholamine hormone secreted by adrenal gland •Stimulates lipolysis in adipose tissue when glucose blood levels fall •Promotes glycogenolysis in skeletal muscle

Mechanism of action (INSULIN)

•The insulin receptor is present on the plasma membrane of cell , Composed of
2a-subunit (extracellular)
2b-subunit (cytoplasmic)
•Binding of insulin to a-subunit causes phosphorylation of b-subunit This activates the receptor
•The activated receptor then phosphorylates intracellular proteins generating a biological response

Insulin and CHO metabolism

•Glucose is diffused into cells through hexose transporters such as GLUT4
•GLUT4 is present in cytoplasmic vesicles
•Insulin binding to its receptor causes vesicles to diffuse into plasma membrane
•GLUT4 is inserted into the membrane allowing glucose transport into the cell
•Brain and liver have non-insulin dependent glucose transporter
•Stimulates glycogen synthesis •↑glycolysis • Stimulates protein synthesis
•Insulin deficiency causes diabetes mellitus
•Hyperinsulinemia is due to insulin resistance in: Diabetes mellitus or Metabolic syndrome



Talk briefly about the pancreas function?

1- It has an exocrine gland which helps to produce enzymes that help in digestion
2- Endocrine gland .. produce hormones

Which types of cells dose Islets of Langerhans secrete?

a. β (B) cells: secrete insulin. (The most one in islets cells) leads to decrease blood glucose
b. α (A) cells: secrete glucagon leads to increase Blood glucose level
c. δ (D) cells: secrete somatostatin lead to inhibt exocrine and endocrine seretions
d. G cells: secrete gastrin leads incraese HCL formation by pariteal cells in Stomache
e. PP cells or F cells : secrete pancreatic polypeptide leads to inhibt exocrine seretion

What is glucagon and from where it produced ?

A 29-amino-acid polypeptide hormone that is a potent hyperglycemic agent - Produced by α cells

Describe the synthesis of glucogan ?

DNA in α cells (chromosome 2) → mRNA → Preproglucagon → proglucagon → glucagon

Talk about the of Insulin ?

Insulin is protien hormone so it is formed from mRNA → mRNA translation to protien (Preproinsulin) which has (signal peptide and A,B and C chains) → Enters to endoplasmic reticlum which signal peptide is removed and converted to proinsulin(A,B and C chains) → travles to golgi appartus which modifies the protien by removing C peptide and remains A and B chins that is connected by disulfide bond insulin.

What is the actions of Glucagon ? It has opposite actions of Insulin

1-Glycogenolysis 2- Gluconeogenesis 3- Lipid oxidation (to produce keto acids "ketone bodies").
4- Release of Glucose from hepatocytes to blood 5- Acts on adipose tissue but not in muscles.

Which kind of tests can use them for diagnose diabetes or pre-diabetes?

1-fasting plasma glucose test (FPG) 2- The oral glucose tolerance test (OGTT):

	Normal glucose tolerance	Impaired glucose tolerance	Diabetes
FPG	<110	110-125	≥126
2-h PG (OGTT)	<140	140-199	≥200

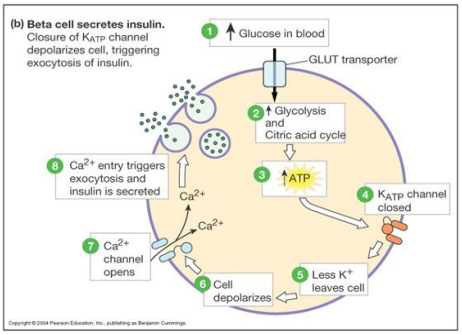
Actions of Insulin		
Adopose tissue	Muscle	Liver
+Glucose entery + Fatty acids synthisis + Glycerol phosphate synthisis +Triglceride depostion + Lipoprotien lipase + K uptake - Hormone senstive lipase	+Gluscose entery + Glycogen synthesis + Protien synthisis + K uptake + Amino acid Uptake + Ketone Uptake - Protien catabolism - Relasing gluconeogenic amino acids	+Glycogen synthesis +Protien synthesis +Lipid synthesis +Glycolysis -Ketogenesis -Gluconeogenesis

insulin: Insulin receptors belongs to the large class of tyrosine kinase receptors, Made of two alpha subunits and two beta subunits

Mention factors that increase and decrease secretion of insulin fron beta cells of pancreas ?

Regulators of insulin secretion

Stimulators of insulin secretion	Inhibitors of insulin secretion
↑ Serum glucose	↓ Glucose
↑ Serum amino acids	↓ Amino acids
↑ Serum free fatty acids	↓ Free fatty acids
↑ Serum ketone bodies	
Hormones	Hormones
Gastroinhibitory peptide (GIP)	Somatostatin
Glucagon	Epinephrine (α-receptor)
Gastrin	
Cholecystokinin (CCK)	
Secretin	
Vasoactive intestinal peptide (VIP)	
Epinephrine (β-receptor)	
Parasympathetic nervous system	Sympathetic nervous system stimulation



Effects on Glucagon Secretion

Stimuli for Glucagon Secretion

↓ Blood glucose
↑ Serum amino acids (arginine, alanine)
Sympathetic nervous system stimulation
Stress
Exercise

Inhibitors of Glucagon Secretion

Somatostatin
Insulin
↑ Blood glucose

Talk Brifely about Mechanism of insulin secretion in case of too much glucose in blood ?

1-Glucose enters B cell by facilitated diffusion via GLUT-2.
2-Glucose is phosphorylated to glucose-6-phosphate by Glucokinase *((rate limiting enzyme))
3-Oxidation of glucose-6-phosphate generates ATP. (by glycolysis)
4- ATP acts on ATP-sensitive K+ channel , closing it. (sulfonylurea drug for diabetics works by closing this channel↑ insulin)
5- Reduced exit of K+ depolarizes membrane.
6- Depolarization opens voltage-gated Ca+2 channels.
7- Ca+2 enters B cell.
8-Ca+2 triggers exocytosis of insulin vesicles.
9- Insulin is secreted

Action of insulin:

Rapid (seconds) (+) transport of glucose, amino acids, K+ into insulin-sensitive cells

- intermediate (minute)

(+) protein synthesis
(-) protein degradation
(+) of glycolytic enzymes and glycogen synthase
(-) phosphorylase and gluconeogenic enzymes

- Delayed (hours) (+) mRNAs for lipogenic and other enzymes

Mention Glucose Transport:

- ❏ GLUT1 (erythrocytes, brain) insulin dependent)
- ❏ GLUT2 (liver, pancreas, small intestines and kidney) insulin indepndent
- ❏ GLUT3 (brain) insulin independent
- ❏ GLUT4, insulin sensitive transporter (muscle, adipose tissue) insulin dependent

- Gluconeogenesis - Synthesis of glucose from noncarbohydrate precursors, Lactic acid, glycerol, amino acids, liver cells synthesis glucose when carbohydrates are depleted.
- Glycogenesis - Formation of glycogen, glucose stored in liver and skeletal muscle as glycogen, important energy reserve.
- Glycogenolysis – breakdown of glycogen (polysaccharide) into glucose molecules (monosaccharide)
- Glycolysis - the breakdown of glucose into pyruvate by cells for the production of ATP

Why diabetic patients are at increased risk to have infections?

Because of Host related factors & Organisms related factors for the ↑infections among diabetic.

List & describe the Host related factors in DM infection ?

1. Vascular insufficiency result in local tissue ischemia that **enhances the growth** of microaerophilic & anaerobic organisms while **depressing the O2 dependent bactericidal functions** of leukocytes with impairment of the local **inflammatory response&** absorption of **antibiotics.**

2. Sensory peripheral neuropathy. Minor local trauma may result in skin ulcers, which leads to diabetic foot infections.

3. Autonomic neuropathy: Diabetic patients may develop urinary retention and stasis that ,in turn, predisposes to develop UTIs.

4. Hyperglycemia and metabolic derangements in diabetes may facilitate infection.

5. Immune defects in diabetes such as:

-Depressed Neutrophil function
-Affected adherence to the endothelium.
-Affected chemotaxis and phagocytosis
-Compromised intracellular bactericidal activity.
-opsonization
-Depressed cell mediated immunity

6. Increased skin and mucosal colonization

Diabetics on insulin have asymptomatic nasal & skin colonization with S.aureus ,particularly MRSA. Colonization predisposes to skin infection & transient bacteraemia which may result in distal sites infection such as damaged muscle.

In type 2 diabetes :mucosal colonization with C.albiacns is common. Vulvovaginitis caused by non-albicans Candida spp. is common in patients with poor glycemic control

7. Surgical site infections associated with postoperative hyperglycemia which is related to deleteriuos effect on chemotaxis, adherence & phagoctosis by granulocytes

List the Common infections in DM patients ?

1- Upeer & lower respiratory tract infections 2- Priodental infections 3- Abdominal infections
4-Genitourinary infections 5- Skin & soft tissue infections & diabetic foot.

List and describe the organsims related factors in DM infections ?

1- Candida albicans : Glucose inducible protein impairs phagocytosis give the organsim the advantge over the host

2- Rihzopus spp : ketoacidosis allow rihzopus to thrive in high glocuse acidic conditions which cause mucormycosis.

List the causitive organsims of the most common infections in DM ?

Most common infections	Causitive organsims	Clinical presntations
Otitis externa	P,aerugenosa	Pain , otorrhea , hearing loss
Rihnocerberal Mucormycosis	Rihzopus	facial &ocular pain
Pneumonea	S,aerus , S,pneumonea , TB	short of breath , continous cough
Celullitis	Group B strepto , S,aerus , GAS	tender , erthematuos lesion
Chronic osteomylitis	Group B strepto , S,aerus ,	fever , foul disgharge
Necrotizing facitis	GAS	pain , discoloration
Deep tissue infection	GAS	acute pain in limbs
Genitourinary	E.coli , C.albicans	Asymptomatic
Vulvoginitis	C.albicans	pain , itching

Upper Respiratory Tract Infections

Diagnosis: CT and MRI studies to define the extent of bone destruction.

Treatment: surgical debridement & IV antipseudomonas antibiotics.(ceftazidime)

Rhinocerebral Mucormycosis

Diagnosis: biopsy of necrotic tissue

Treatment: surgical debridement and prolonged IV therapy with Amphotericin B .

Genitourinary infections

Diagnosis: flank mass & crepitus . CT show gas in the renal tissues.

Management: supportive & IV antibiotics , nephrectomy may be needed.

Necrotizing fasciitis

Management :aggressive surgical debridement & IV antibiotics.

The most common and most important soft tissue infection in diabetic patients, why ?

because it is related to peripheral neuropathy & compromised microvascular circulation which limits the access of phagocytic cells to the infected area & poor concentration of antibiotics in the affected area. Complicated by chronic Osteomyelitis, gas gangrene, amputation & death.

Pathophysiology: microvascualr disease limits blood supply to the superficial and deep structures. Pressure from ill fitting shoes ,trauma compromises local blood supply predisposing foot to infection.

Organisms involved in diabetic foot infections

- **Cellulitis:** beta-hemolytic streotococci (group A,B streptococi), S.aureus, Entertobacteriacae (E. coli, Klebsiella, Proteus spp.) in chronic ulcers.
- **Macerated ulcer or nail injury (sinus) :** P.aeruginosa .
- **Deep soft tissue infections** (necrotizing fasciitis, or myositis).GAS & gas producing gram positive bacilli (Clostridium).
- **Chronic Osteomyelitis:** GAS and Group B.sterptococci, S.aureus, Enterobacteriacae (E.coli ,Proteus mirabilis , K.pneumoniae.) ,Bacteroides fragilis

Clinical presentations of diabetic foot infections

- **Cellulitis:** tender, erythematous nonraised skin lesion on the lower limb ,may be accompanied with lymphangitis which suggests GAS.
  Bullae suggests S.aureus ,occasionally GAS.
- **Deep skin and soft tissue infections:** patient acutely ill, with painful induration of the limb especially the thigh . Foot may be involved. Wound discharge suggest anaerobes
- **Acute Osteomyelitis**:pain at the involved bone, fever, adenopathy.
- **Chronic Osteomyelitis:** fever ,foul discharge ,may be pain, no lymphangitis, deep penetrating ulcer , &sinuses on the planter surface of the foot

Diagnosis of foot infections

- Thorough examination to evaluate the patient's vascualr and neurological status.
- Radiological examination including doppler ultrasonography ,transcutaneous oxymetery, MR angiography.
- CT scan ,MRI and gallium -67 scan for soft tissue and bone evaluation.
- Exploration of ulcer to determine its depth and presence of sinus tract.
- Deep specimens (tissues) for culture and susceptibility testing

List the managment of Diabetic foot infections ?

I - Control blood sugar and hyderation
II - Evaluation of nuropathy and vasculoropathy
III - Mild cases : debredment of necrotic tissue and treat with proper antibiotic
IV - modreate to sever cases : places the foot at risk of amputation. Needs hospitalization ,IV antibiotics and surgical intervention if needed

Prevention

- is the cornerstone of diabetic foot care.
- It is multidisciplinary including family physician, social worker, home care nurse and specialist.
- Patient education about the control and complication of diabetes.
- Blood sugar should be controlled promptly (shift to insulin if oral hypoglycemic agents were not effective),wt. reduction, a diet low in fat and cholesterol.
- Proper foot care, using protective footwear and pressure reduction.
- Self examination and family member of foot.

Case:
A women who has just completed a course of antibiotic , present with white , flaky, cheesy exudate on her oral mucosa and soft palate.

What is the most likely diagnosis?
Candidiasis.The fungus Candida albican.

Describe the organism.
Candiada is a unicellular yeast fungus which reproduced by budding and has Pseudohyphae.

Mention other candida species ?
1- Candida parapsilolosis , 2- candida tropicalis , 3- candida glabrata , 4- candida ksusei

Where is the microorganism that causes this condition is normally found?
A) Oral cavity
B) Skin
C) Gastrointestinal tract
D) Genitourinary tract

What are the mucous membrane infections that this microorganism can cause?
A) Thrush (oropharyngeal candidiasis)
B) Esophagitis
C) Vulvoaginitis

What laboratory tests can help confirm the diagnosis?
1-Specimen
2-Direct Microscopy: A potassium hydroxide preparation (KOH) ,budding yeast cells and psuedohyphae will be in stained smear or KOH by Giemsa Gram stain
3-Culture: SDA and blood agar at 37c, Creamy moist colonies in 24-48 hr
4-Blood culture: espicially for systemic infections.
5- Serology : A-Antigen such as mannan antigen by elisa, B- Antibodies
6- PCR

What populations other than immunocompromised patients are at risk for serious forms of this condition?
Intravenous drug users are at higher risk for candidal endocarditis.

What are the appropriate treatments for this condition?
Fluconazole or nystatin is used for superficial infections, and amphotericin B or fluconazole can be used for systemic infections.
(C.glabrata and C.krusei are resistant to fluconazole)

In which conditions does the antifungal susceptipility testing done?
A)for fungi isolated from sterile sample
B)If the patient is not responding to treatment
C)In case of recurrent infections

Mention the routes of transmission of the candidiasis ?
1- Endogenous
2- Exogenous : can be happan during hospitlization

TYPE 1 DIABETES MELLITUS

A. Insulin deficiency leading to a metabolic disorder characterized by hyperglycemia

B. Due to autoimmune destruction of beta cells by T lymphocytes

1. Characterized by inflammation of islets
2. Associated with HLA-DR3 and HLA-DR4
3. Autoantibodies against insulin are often present (sign of damage) and may be seen years before clinical disease develops.

C. Manifests in childhood with clinical features of insulin deficiency

1. High serum glucose—Lack of insulin leads to decreased glucose uptake by fat and skeletal muscle.
2. Weight loss, low muscle mass, and polyphagia—Unopposed glucagon leads to gluconeogenesis, glycogenosis and lipolysis, which further exacerbates hyperglycemia.
3. Polyuria, polydipsia, and glycosuria—Hyperglycemia exceeds renal ability to resorb glucose; excess filtered glucose leads to osmotic diuresis.
4. Treatment involves lifelong insulin.

D. Risk for diabetic ketoacidosis

1. Characterized by excessive serum ketolies
2. Often arises with stress (e.g., infection); epinephrine stimulates glucagon secretion increasing lipolysis {along with gluconeogenesis and glycogenolysis),

I. increased lipolysis leads to increased free fatty acids (FFAs).

ii. Liver converts FFAs to ketone bodies (|3-hydroxybutyric acid and acetoacetic acid).

3. Results in hyperglycemia (> 300 mg/dl.), anion gap metabolic acidosis, and hvperkalemia
4. Presents with Kussmaul respirations, dehydration, nausea, vomiting, mental status changes, and fruity smelling breath (due to acetone.)
5. Treatment is fluids (corrects dehydration from polyuria), insulin, and replacement of electrolytes (e.g., potassium).

Complications for type 1 and type 2:

1- Nonenzymatic glycosylation (NEG) oflhe vascular basement membrane, NEG of large- and medium-sized vessels leads to atherosclerosis and its resultant complications,

2- Cardiovascular disease is the leading cause of death among diabetics.

3- Peripheral vascular disease in diabetics is the leading cause of nontraumatic amputations.

4- NEG of small vessels (arterioles) leads to hyaline arteriolosclerosis:

A-Involvement of renal arterioles leads to glomerulosclerosis, resulting in small, scarred kidneys with agranular surface

B-Preferential involvement of efferent arterioles leads to glomerular hyperhitration injury with microalbuminuria that eventually progresses to nephrotic syndrome; characterized by Kimmelstiel-Wilson nodules in glomeruli

5- Glucose freely enters into Schwann cells (which myelinate peripheral nerves), pericytes of retinal blood vessels, and the lens.

6- Leads to peripheral neuropathy, impotence, blindness, and cataracts; diabetes is the leading cause of blindness in the developed world.

Increase risk of DM ?

- FPG 5.6-6.7mmol\L
- 2-h PG in the 75-g OGTT 140mg\dL to 199 mg\dL
- A1C (5.7-6.4%)

Criteria for Diagnosis of DM ?

- FPG 7mmol\L
- A1C ≥ 6.5%
- 2-h PG in the 75-g OGTT≥200mg\dL
- Patient with classic symptoms of hyperglycemia/crisis, random plasma PG≥200mg\dL

What is Hg A1C ?

- It's a non enzymatic covalent glycosylation of Hb.
- It is used to estimate glycemic control in the last 1-2 months
- Recently, A1C is recommended for the detection of T2DM
- A1C and fasting plasma glucose (FPG) were found to be similarly effective in diagnosing DM
- A1C values also correlate with the prevalence of retinopathy
- Assays for A1C has to be standardized according to the (NGSP).

What are the metabolic effects of DM ?

they are relative to insulin deficiency :¯ glucose uptake by tissue and increase glucose

Mechanisms of ⬆ Hepatic Glucose Output

⬇ Insulin
⬇ Inhibitory effect on glucagon secretion
⬆ Glucagon
⬆ Gluconeogenesis & glycogenolysis (Liver)
⬆ plasma glucose

Mechanisms of ⬇ of Peripheral Glucose Uptake Muscle

⬇ Insulin
⬇ Glucose & amino acid uptake
⬆ Protein breakdown
⬆ Plasma glucose
⬆ Plasma amino acids

Adipose Tissue

⬇ Insulin
⬇ Glucose uptake
⬆ Plasma glucose

What are the mechanisms of DM microvasular complication ?

- ⬆ AGEs production (advanced glycosylation end products)
- ⬆ intracellular sorbitol
- ⬆ Reactive oxygen species ROS

Mechanism of each ?

•AGEs : chronic hyperglycemia lead to non enzymatic combination of glucose and AA which form AGEs that cross link with collagen and cause problems . Also it might react with ROS and cause inflammation.

•Sorbitol (polyol) glucose is metabolized to sorbitol by aldose reductase, sorbitol production will consume NADPH lead to oxidative stress. Sorbitol accumulation ⬆ intracellular osmotic pressure and cause cell swelling .Alteration in the activity of PKC altered VEGF activity altered vascular permeability

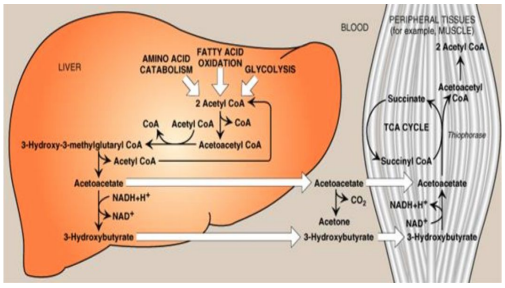
What are the microvascular complication of DM ?

•Diabetic retinopathy :major cause of morbidity → Blindness (after 20y all T1DM & 50-80% of T2DM)
•Diabetic nephropathy (earliest complication) ⬆ GFR –microalbuminuria-protenuria
⬇ GFR- end stage renal disease
•Diabetic neuropathy :loss of myelinated and unmyelinated nerves(correlate with duration & glycemic control of DM)

FPG: Fasting plasma glucose; PG: post glucose; OGTT: Oral glucose tolerance test

What are the medical emergencies that could a diabetic patient have?

A)Diabetic Ketoacidosis
B)Hyperosmolar hyperglycemic state
C)Hypoglycemia



Diabetic Ketoacidosis is a triad of what?

A)Hyperglycemia
B)High anion gap metabolic acidosis
C)Ketonemia
(DKA is more associated with T1DM)

Talk brifely about ketone bodies synthesis(Mechansim of DKA) ?

Occurs in heptocyres mitochondria so In uncontrolled DM there is lipolysis in adipose tissue this will lead to increase [FFA] and mobilization of FFA to liver and this is will lead to increase hepatic FA oxidation to acetyle CoA which will be utilized in KB synthesis (Ketogenesis) , then will be ketonemia , ketouria and ketoacidosis. The first Ketone bodies is synthesized to acetoacetate then this can be either reduced to B-Hydroxybutyrate or spontaneously decarboxylated to acetone.

Talk about ketolysis (ketone bodies utilization)?

It occurs in mitochondria of extrahepatic tissues ,so can not occur in RBC. it also **can not** occur in liver
lacks thiophorase enzyme required for ketolysis). B-hydroxybutyrate is oxidized to acetoactate by dehydrogenase. Acetoacetate is converted to acetoacetyl CoA that is catalyzed by thiophorase. Acetoacetyl CoA is converted to acetyl CoAs.

Manifestations of DKA:

A)Fruity odor on the breath (acetone)
B)Acidosis (low PH of blood because KBs are acids)
C)Dehydration (due to glucosuria)

What is the rate limiting enzyme for ketogenesis?

HMG CoA synthase (Hydroxymethylglutaryl CoA synthase)

What are the electolyte abnormalities that are frecuently seen in DKA?

A)It is associated with depletion of total body potassium stores through osmotic diuresis.
B)Water loss secondary to glycosuria.
C)Acidosis due to increase production of ketone bodies.

Talk about hyperosmolar hyperglycemic state.

- Little or no accumulation of ketone bodies
- Serum [glucose] is often >50 mmol/L
- Plasma osmolality may reach 380 mosmol/Kg (normal 275-295)
- Neurological abnormalities are frequently present
- Insulin levels are insufficient to allow appropriate glucose utilization but are adequate to prevent lipolysis and subsequent ketogenesis
- Usually occurs in elderly patients with T2DM
- Has a substantially higher mortality than DKA (up to 15%)

What are the manifestations of hypoglycemia?

A) CNS Symptoms (confusion, aberrant behavior, or coma)
B)Low blood [Glucose]
C)Symptoms resolved within minutes following the administration of glucose

Why hypoglcemia is a medical emergency?

A)The brain has absolute requirment for a continous supply of glucose
B)Transient hypoglycemia lead to cerebral dysfunction
C)Severe,prolonged hypoglycemia lead to brain death

Case..

A 14 years old patient is brought to the ER with nausea, vomiting, hyperventilation, hyperglycemia, ketonemia and dehydration.

What is the most likely diagnosis? Mention the symptoms in this case ?

Diabetes Mellitus type 1 .

1-Ketogenesis 2- Dehydration 3- Hyperglycemia 4- nephropathy-Thirst, Polyuria- Polydipsia- Nausea - Tachycardia -Kussmaul–Kien respiration (rapid & deep), Ketotic breath (fruity, with acetone smell).

What are the mechanisms DKA ?

Fat → free fatty acids → acetyl-CoA → ketone bodies → Ketonemia → Ketonuria & Acidosis.

Acetoacetic acid, β-hydroxybutyric.

Acid and acetone (↑ ketogenesis).

Describe the Treatment of diabetic ketoacidosis ? (briefly)

1- Fluid therapy (Rehydration) for dehydration .Dehydration means ECF. So we have to restore blood volume and perfusion of tissues by **infusion of isotonic saline (0.9% sodium chloride)**

2- Potassium therapy to correct the serum potassium concentration

3- Insulin therapy (Short acting insulin) to stop lipolysis, promotes degradation of ketone bodies

4- Bicarbonate therapy to correct metabolic acidosis

Talk in general about Hypoglycemia ?

Its a **serious acute emergency situation** with a risk of coma led to death .

A characteristic feature of **type II** (especially during stress)

Causes ?

Overdose of insulin, or oral hypoglycemic drugs such as **(sulfonylureas and meglitinides)**

- Excessive physical exercise
- Missed or delayed meal

Characters

Autonomic features sympathetic: tachycardia, palpitation, sweating, tremor, **parasympathetic**: nausea, vomiting Neurological defects: Headache, visual disturbance, slurred speech, dizzinessTremors, mental confusion, convulsions - **Coma** due to blood glucose to the brain

The treatment

1. Conscious patient: Sugar containing beverage or food

2. Unconscious patient: Glucagon (1 mg S.C. or I.M.) . Or 20-50 ml of 50% glucose solution I.V. infusion **(risk of possible phlebitis)**

What are the Precautions in DM ?

- Monitoring of blood glucose level (blood sugar level should be checked routinely).
- Patients should carry **glucose tablets or hard candy** to eat if blood sugar gets too low
- Diabetic patient should wear a **medical ID bracelet** or carry a card
- Patient should not skip meals or eat partial meals
- Patient should eat extra carbohydrates if he will be active than usual

What are the routs of adminstrations of the exogenus insulin ؟

1- insulin syrings
2-portable pin injector
3- insulin pump
4- I.V = emergency

Types of insulin differ in pharmacokintiks proparties by ?

1- Onset of action
2- duration of action

What are the groups of insulin that can be use during emergency cases e.g: DKA ?

1- Ultra short acting insulins (Lispro , aspart , glusilin)
2- Regular insulins (Humolin R ,Novolin R)

List the onset of actions and duration for each group.

1- Ultra / onset (5-15 m) / duration (3-5 hr)
2- regular / onset (30-45) / duration (6-8)
3- Intermideate / onset (1-2) / duration (13-15)
4- Long / onset (1-3) / duration (13-20)

Advanteges of the Ultra & regular inslin groups over the other tow groups

1-Rapid onset of action (due to rapid absorption)
2-Reduced risk of postprandial hypoglycemia

Advanteges of the long acting insulin group over the intermidate group

1- No peak (peak less)
2- Produce prolonged hypoglicimic effect
3- safer than the intermidate group (no nocturnal hypoglicymia)

List the complications of insulin therpey

1- Hypoglicymia
2- insulin recsistance
3- weight gain
4- Hypokalimia
5- Hypersensitivty

THANK YOU FOR CHECKING OUR TEAM..

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