ENDOCRINE BLOCK

OBESITY , METABOLIC SYNDROME & DMT2

Correction File

Case..
30-year-old African-American woman with a history of hypertension presents to her new primary care physician for a physical examination. She claims to be in good health but has noticed she is urinating more frequently and has had several urinary tract infections in the past year. Her family history is significant for premature coronary artery disease and diabetes in multiple first-degree relatives. Her heart rate is 70/ min and her blood pressure is 140/90mm Hg. Physical examination is notable for morbid obesity (body mass index: 48 kg/m2), and a urine dipstick reveals 2+ glycosuria.

What is the most likely diagnosis?
Non-insulin-dependent (type 2) diabetes mellitus (NIDDM).

What are the diagnostic criteria for this condition?
Random plasma glucose → 200 mg/dL with symptoms or Fasting plasma glucose → 126 mg/dL on two separate occasions or Plasma glucose → 200 mg/dL 2 hours after a glucose tolerance test .

What is the production and structure of insulin?
Insulin is originally produced as pre-proinsulin in the pancreas. During posttranslational processing, a signal peptide is removed, producing proinsulin. Proinsulin contains two polypeptide chains connected by two sulfhydryl bonds (cysteine to cysteine) and a C-peptide. In the conversion from proinsulin (the zymogen) to active insulin, the C-peptide is cleaved off (Figure 6-9). Synthetic insulin lacks the C-peptide. Therefore, measuring C-peptide is useful in patients in whom surreptitious insulin injection is suspected (factitious hypoglycemia).

What is the most appropriate treatment for this patient?
The number one reason this patient has NIDDM is her obesity. Therefore, nonpharmacologic treatments such as diet, weight reduction, and exercise must be employed. However, these have limited long-term success. Pharmacologic treatment for type 2 DM includes oral hypoglycemic agents. Only in refractory cases is insulin added to the regimen (Table 6-4 lists common drugs for both type 1 and type 2 DM). Tight glucose control markedly reduces microvascular and neurologic complications of DM. The goal is a hemoglobin A1c level of 7%.

Talk about the mechanism of action of Insulin secretagogues?
↑ Hyperglycemia → Blockade of ATP dependent K+channels → Opening of voltage-dependent Ca++channels → ↑ intracellular calcium in the beta cells → ↑ Insulin release.

Talk about level of inslulin in Type 2 DM ?
Early is high but later will be low. Type 2 DM occurs due insulin resistence that mainly caused by obesity, lack of phsical activity and genatic.

What is difference in the managment type 1 and type 2 DM ?
Type 2 DM can be treated by excresice, diet, oral hypoglycemia and insulin while type 1 DM only by insulin.

14-year-old Hispanic-American boy with a family history of obesity & hypertension presents to the pediatrician for a mandatory school physical examination. He has no medical complaints. Social history is notable for a sedentary lifestyle. His diet consists of pizza, sandwiches, potato chips, & 2 cups of soda daily. Physical examination reveals a male with an abdominal circumference > 40 inches. His body mass index is 36 kg/m2, pulse is 100/min, & blood pressure is 140/95 mm Hg. Skin examination reveals velvety, darkly pigmented patches in the skin folds at the nape of his neck & axilla .

What is the most likely diagnosis?

Metabolic syndrome, also known as dysmetabolic syndrome, syndrome X, and insulin resistance syndrome.

What are the diagnostic criteria for this condition?

The National Cholesterol Education Program Adult Treatment Panel III defines metabolic syndrome as the presence of any three of the following five traits:
Abdominal obesity (male > 40 inches; female > 35 inches).
Hypertriglyceridemia (≥ 150 mg/dL).
Low levels of high-density lipoprotein (HDL) cholesterol (male < 40 mg/dL; female < 50 mg/dL). Blood pressure ≥ 130/85 mm Hg.
Fasting glucose ≥ 110 mg/dL.

What do the skin findings represent?

Acanthosis nigricans is a common physical sign of insulin resistance, particularly in Hispanics and African Americans. It may be due to high levels of circulating insulin or insulin-like growth factor receptors in the skin. Other conditions with acanthosis nigricans include polycystic ovarian syndrome and some visceral malignancies.

What is insulin resistance?

Insulin resistance (IR) is the state in which endogenous or exogenous insulin produces a less-than-expected biological effect. Patients have elevated blood glucose with normal to elevated insulin levels. Today, IR is nearly universal in obese individuals and is correlated with amount of intra-abdominal fat. Several mechanisms of IR in obesity have been proposed:
1-Insulin receptor downregulation.
2-Intracellular lipid accumulation.
3-Increased free fatty acids that impair insulin action.
4-Cytokines and “adipokines,” which modify the effect of insulin.
Treatment with metformin can be initiated to increase insulin responsiveness.

What class of drugs should be avoided in patients with this condition?

Atypical antipsychotics, such as clozapine, are associated with the metabolic syndrome, particularly weight gain and hypertriglyceridemia. Even for patients without weight gain, the effect on serum triglycerides increases the risk for adverse cardiovascular events.

What is the metabolic syndrome?

A combination of metabolic abnormalities which↑ the risk of heart disease, DM & other diseases

What are the features of metabolic syndrome?

- Obesity (Signals from adipocytes in obesity cause metabolic abnormalities such as:

Dyslipidemia -Glucose intolerance - Insulin resistance - Hypertension).

•High serum triglycerides (TGs) •Low HDL cholesterol

•Hyperglycemia •Insulin resistance (hyperinsulinemia))

Insulin resistance :

- ↓ Cells responsive to insulin → ↑plasma insulin → hyperglycemia
- Hydrolysis of stored fats → ↑ plasma FFAs →
- ↓ of glucose uptake/use by cells → ↓ glycogenesis → hyperglycemia
- Compensatory hyperinsulinemia causes down regulation of insulin receptor → Defects in insulin receptor

Dyslipidemia:

1-Insulin resistance in adipocytes → ↑ activity of hormone-sensitive lipase → ↑ plasma FFAs

2-FFAs → TGs/cholesterol in the liver:

↑ VLDL in the blood ↓ HDL levels

What is the early indicator of insulin resistance? Dyslipidemia

What are the markers of metabolic syndrome?

•Lipoproteins (LDL, HDL) •Adipokines (Leptin, adiponectin)

•Inflammatory markers: c-reactive protein, TNF-a

•Hemostatic marker : Plasminogen activator inhibitor-1

What are the risk factors for metabolic syndrome?

•Obesity •Alcoholism •Sedentary Lifestyle •Smoking

•Hypercortisolism (Steroid use/Cushing's disease)

•Drugs (Rifampicin, isoniazid, etc.) •Mutations in insulin receptor

Metabolic syndrome is linked to:

•Heart disease •Type-2 diabetes mellitus •Kidney disease

•Reproductive abnormalities in women (Polycystic ovarian syndrome , Impaired ovulation and fertility, Irregular menstruation)

•Nonalcoholic steatohepatitis (fatty liver disease)

•Obesity is a major risk factor for cancer of esophagus, colon and rectum, liver, gall bladder

Diagnosis – WHO criteria:

•Impaired glucose tolerance •Diabetes mellitus •Insulin resistance

PLUS any of these two:

1-Hypertension 2- Dyslipidemia 3-Central or General obesity 4-Microalbuminuria

Managing Metabolic Syndrome:

•Primary intervention (Lifestyle changes) : -Weight reduction -Smoking cessation

•Secondary intervention: Medication to treat existing risk factors

Management of:

•Blood pressure (anti-hypertensive drugs) , Low dose diuretics , ACE inhibitor

•Lipids (statins, fibrates)

•Blood glucose (metformin, TZDs)

•Aspirin to treat clotting disorders

Obesity: is a disorder of body weight regulatory systems ,Causes accumulation of excess body fat

What are the risk factors associated with Obesity ?

•Diabetes mellitus • Hypercholesterolemia • High plasma triglycerides •Heart disease • Hypertension •Cancer • Gallstones, arthritis, gout • mortailty

BMI is an indirect measure of obesity Correlates height, weight and amount of body fat in an individual

What are the different site at which the fat deposts in the Body?

Subcutaneous fat" 80% to 90 % of Total body fat : which is fat stored under skin in abdominal and gluteal-femoral region

Visceral Fat : Composed of omental & mesenteric fat present in close association with digestive tract

Android,apple-shaped,or upper body obesity	Gynoid,pear-shaped, or lower body obesity
Excess body fat deposited in the central abdominal area •Associated with risk of hypertension, insulin resistance, diabetes, dyslipidemia, and coronary heart disease	•Fat deposited around the hips or gluteal region •Associated risks are lower

Abdominal fat	Gluteal Fat
Smaller cells	Larger cells
More responsive to hormones (visceral &SC)	Less responsive to hormones
Release substances via portal vein to the liver	Release substances to circulation with no effect on the liver

Adipocyte

Triacylglycerols are deposited in adipocytes (fat cells) which can ↑ in size up to a limit

↡

Prolonged overnutrition stimulates

↡

Pre-adipocytes in adipose tissue

↡

Proliferation / differentiation into mature fat cells

↡

↑ adipocyte number

Thus obesity is due to a combination of increased fat cell size (hypertrophy) and number (hyperplasia)

•Fat cells, once gained, are never lost

•Reduction in weight causes adipocytes to ↓ in size

Class	BMI	GRADE
Under weight	≤ 18.5	
Normal	18.5-24.9	
Over weight	25.0-29.9	
Obese	30.0-34.9	I
Obese	35.0-39.9	II
Highly obese	≥ 40	III

Define the ectopic fat ? Excessive calories that cannot be stored in adipose tissue "spill over" into other tissues such as muscle and liver , that is strongly associated with insulin resistance.

Factors contributing to obesity

•Genetic: familial tendency •Environmental and behavioral –Sex: women more susceptible

–Activity: lack of physical activity –Psychogenic: emotional deprivation/depression –Smoking

–Alcohol: problem drinking •Drugs: e.g. tricyclic derivatives

What are the Causes of weight Gain?

•Energy imbalance:calories consumed not equal to calories used
•Over a long period of time •Due to a combination of several factors:
–Individual behavior –Social interaction –Environmental factors –Genetics
•More in and less out = weight gain / •More out and less in = weight loss
•Hypothalamus : Control center for hunger and satiety •Endocrine disorder : Hormonal imbalance

What are the factors lead to increase appetite ?

afferent neural signals, circulating hormones, and metabolites.
•These signals cause the release of hypothalamic peptides and activate efferent neural signals
•Adipocytes also function as endocrine cells
•They release many regulatory molecules: Leptin, adiponectin, resistin

What is the leptin and how it's secretion is regulated ?

A protein hormone produced by adipocytes that is required to keep the body weight under control , Leptin secretion increase in well-fed state and reduce in starvation.
•Signals the brain about fat store levels
•Regulates the amount of body fat by: Controlling appetite and energy expenditure
•Leptin causes overweight mice to lose weight and maintain weight loss

Name a mutation which lead to leptin resistance ?

Mutation in **db** gene causes leptin resistance.
•Leptin increases metabolic rate and decreases appetite in humans
•Plasma leptin level in obese humans is usually normal for their fat mass
•Resistance to leptin has been found in obese humans
•Leptin resistance may have some role in human obesity –Dieting decreases leptin levels
–Reducing metabolism, stimulating appetite

What is the adiponectin and action of it ?

A protein hormone secreted from adipocytes.
Action of adiponectin : increase uptake and oxidation of fatty acids and glucose by muscle and liver.
Blocks the synthesis of fatty acids and gluconeogenesis by hepatocytes
Net effect is to increase the sensitivity to insulin, and improve glucose tolerance.
•Adiponectin levels are inversely correlated with body fat percentage and parallels with HDL levels
•Low levels are seen in metabolic syndrome and diabetes mellitus

What are drugs used to decrease body weight ? Orlistat , Lorcaserin.

What are metabolic changes in obestity ?

Adipocytes send signals that cause abnormal metabolic changes such as: Dyslipidemia, Glucose intolerance & Insulin resistance

Other hormones :

Ghrelin: A peptide hormone secreted by stomach :Stimulates appetite, ↑food intake , ↓ energy expenditure & fat catabolism
Cholecystokinin: Peptides released from the gut after a meal Sends satiety signals to the brain
Insulin: Promotes metabolism

Benefits of weight loss in obesity

Weight loss ↓risk factors for obesity leading to: •↓blood pressure •↓serum triacylglycerols
•↓blood glucose levels •↑in HDL levels •↓mortality •Beneficial changes in BMR
•↓energy requirement •Slow weight loss is more stable

What are the types of diabetes?
1- Type 1 insulin depended (5-10%)
2- Type 2 insulin non depended (90-95%).
3- Gestational diabetes.
4- Secondary diabetes.
5- pre-diabetes.

What are the symptoms of diabetes?
1- Thirst.
2- Passing lots of urine.
3- Malaise.
4- Infections (thrush).
5- Weight lost.

Write three complications of diabetes?
1- Cardiovascular. 2- Eyes. 3- Feet.

***Prevalence worldwide is increasing**
- 2.8% in 2000 (171 million).
- 4.4% in 2030 worldwide.(366 million).

***Amputation are at least 10 times more common in people with diabetes.**

***diabetes is a leading cause of blindness and visual impairment.**

*** Diabetes is responsible for over one third of end-stage renal disease requiring dialysis.**

What are the risk factors for type 2 DM?
1- Obesity. 2- genetic . 3- life style.

***Pregnancy causes weight gain and increases levels of estrogen and placental hormones which antagonize insulin.**

What are the medications which are known to antagonize the effect of insulin?
1- Thiazide diuretics.
2- Adrenal corticosteroids.
3- Oral contraceptives.

Genetic factors may play a part in development of all types; autoimmune disease and viral infections may be risk factors in Type I DM.

Physiologic or emotional stress: causes prolonged elevation of stress hormone levels (cortisol, epinephrine, glucagon and growth hormone), which raises blood glucose levels, placing increased demands on the pancreas.

Why is diabetes is so important ?
Due Complications :
- Cardiovascular
- Eyes
- Renal - Hypertension, renal failure
- Feet
- Skin, infections, sexual, psycho-sexual, depression
- Quality of life
- Premature mortality

Mention the Primary and secondary causes of obesity ?

Primary : Dietary intake ,Physical Inactivity,Eating patterns ,Eating environment ,Food availability , Food packaging and Fast food linked to increased adiposity.

Secondary: Hypothyroidism,Cushing's Syndrome .Hypothalamic Obesity ,Polycystic Ovarian Syndrome ,Growth Hormone deficiency ,Oral Contraceptives .Pregnancy related ,Genetic Syndromes ,Medication Related and Eating Disorder

Mention other causes of obesity ?

1- Gentic :defective :A mutant gene that leads A defective gene to produce Leptin ; a satiety hormone that influences the appetite control in hypothalamus such as : A defective ob gene causes inadequate leptin production. Thus, the brain receives an under assessment of body's adipose stores and urge to eat.

2- **Characteristics of fast food** linked to increased adiposity:

Higher energy density
Greater saturated fat
↓ complex carbohydrates & fiber
↓ fruits and vegetables.

Mention obesity syndrome componets ?

- Glucose intolerance
- Insulin resistance
- Dyslipidemia
- Type 2 diabetes
- Hypertenision
- Elevated plasma leptin concentration
- Increased visceral adipose tissue
- Increased risk of CHD & some cancers

Mention the clinical steps that you should follow to appraoch to obesity?

- A full history with a dietary inventory and an analysis of the subject's activity level.
- Screening questions to exclude depression
- Screening for eating disorders as 30% of patients suffer from them
- Determine any co-morbidities;
- Exclude the possible and rare secondary causes
- Requirements of treatment and belief to fulfill
- Behavior assessment for readiness
- Family support, time and financial considerations

What is diffrence between overwight and obesity ?

Overweight is defined as a BMI at or above the 85th percentile and lower than the 95th percentile for children of the same age and sex.
Obesity is defined as a BMI at or above the 95th percentile for children of the same age and sex.

Mention some of the Psychosocial Factors?

- Social support (adherence).
- Self-efficacy – feel they can handle the regimen and control the disease.
- Stress – causes less insulin and more glucose production.

Note that ..

- Early adolescence (age range 11-14 yrs.) Am I normal.
- Mid-adolescence (age 14-16 yrs.) Independence/self image.
- Late adolescence (age 17-older yrs.) Future oriented, intimacy /career goals.

What are the Psychological Complications of Chronic Illness?

- Chronic disorder.
- Treatment requirements.
- Hospitalization.
- Surgery or other procedures.

List the Developmental Complications of Chronic Illness.

- Body image issues.
- Developing independence.
- Relationship with peers.

What are Compliance with Medical Treatment?

- Daily lives.
- Mental disorders.
- Challenge.

What are the obstacles affecting transition to health care system for the adolescents ?

- Dependent behavior.
- Immaturity.
- Severe illness or disability.
- Psychopathology.
- Lack of support systems.
- Lack of trust in caregivers.
- Poor adherence to treatment regiment.
- Parental involvement.

List the obstacles to health care for family or caregivers

- Excessive need for control.
- Emotional dependency.
- Parenting styles/overprotective.
- Heightened perception of disease severity.
- Lack of trust in caregivers.
- Denial about the severity of the disease.

A patient with renal disease came to you with hyperglycemia what is the best oral hypoglycemic drug for him? Tolbutamide

What are the advantages of second generation sulfonylureas over the first?
1)More potent than first generation. 2) Have longer duration of action. 3)Less frequency of administration.4) Have fewer adverse effects Have fewer drug interactions

A baby girl had fetal hypoglycemia at birth, what drug most likely her mother was taking? Sulfonylureas.

What drug of oral hypoglycemic its absorption is reduced with food? Glipizide
What are the Adverse effects of Meglitinides? Hypoglycemia and weight gain.

What are the actions of metformin?
1)Increases peripheral glucose utilization (tissue glycolysis) 2) Reduces insulin resistance.
3)Inhibits hepatic gluconeogenesis 4)¯LDL &VLDL 5)- HDL

An obese patient who have diabetes type 2 need an oral hypoglycemic what is the recommended drug for him? Metformin (Biguanides > Insulin sensitizers)

What are the Adverse effects of metformin?
-GIT disturbances: nausea, vomiting, diarrhea and metallic taste in the mouth
- Lactic acidosis.
-Interference with vitamin B12 absorption (long term use).

What are the contraindications of metformin?
Renal disease, Liver disease, Alcoholism, Cardiopulmonary dysfunction and Pregnancy.

A diabetic patient who is in a very high risk of hypoglycemia due to unstable diet, what drug would you advise him to take? metformin or glitazones

What is the mechanism of action Insulin sensitizers Thiazolidinediones?
Activate peroxisome proliferator-activated receptor -g (PPAR-g), Increase glucose uptake and utilization in muscle and adipose tissue, Increase sensitivity of target tissues to insulin.

A diabetic lady who was on contraceptives came to you pregnant with increased numbers of ALT and AST, what oral hypoglycemic she is most likely taking?
Glitazones (Insulin sensitizers Thiazolidinediones).

What is the mechanism of action of a-Glucosidase inhibitors?
Reversible inhibitors of intestinal a-glucosidases in intestinal brush border that are responsible for carbohydrate digestion (lower postprandial glucose level).

Who are the contraindications of a-glucosidase inhibitors?
-irritable bowel syndrome.
-Inflammatory bowel disorders.
-Intestinal obstruction.

What is the mechanism of action of Dulaglutide?
Incretins (GLP-1) mimetics > Stimulate insulin secretion & decrease glucagon secretion.

A type 2 diabetic patient has high glucose levels even though he is taking oral medicine, What would be the beast drug to give it to him now?
Dulaglutide > Incretins (GLP-1) mimetics subcutaneously

What is the net effects of Sitagliptin? Inhibit DPP-4 enzyme thus increase incretin hormone (GLP-1).

THANK YOU FOR CHECKING OUR TEAM..

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"When they develop their own gravitational field it's a clear warning sign of getting type 2 diabetes."