Diabetes mellitus

429 medicine team

Type 1, Type 2 and Complications of diabetes

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Sources include: 427 team, Notes, Andreoli's Cecil, Step up and Kumar textbook of medicine.

Definition of diabetes:

- Is a group of metabolic disorders that is characterized by chronic hyperglycemia due to insulin deficiency or resistance or both.
- It affects carbohydrate, lipid and protein metabolism.
- The chronic hyperglycemia will ultimately cause complications related to many organs.
- Diabetes is classified into primary and secondary diabetes.
    - Primary diabetes accounts for 98% of cases and is
        - Type 1= 10%
        - Type 2= 90%
    - Secondary diabetes due to other causes like pregnancy or removal of the pancreas.

Epidemiology

- In the US:
    - Statistics for 2007 show that the total prevalence of diabetes in all ages was an estimated 23.6 million people (8% of the population).
    - Leading cause of end-stage renal disease (ESRD), new cases of blindness, and nontraumatic lower limb amputations in the United States.
- in KSA The prevalence in 1970 was 2.2 % and in 2004 it was 24.7 %
- 34% of all admitted patients are in the hospital due to diabetes or complications of diabetes
- In a CCU (cardiac care unit) study in Riyadh, almost 50% of patients were diabetic and 80% of those who died were diagnosed with diabetes.
- So high mortality and increasing incidence.

Normal Physiology:

- Blood glucose is maintained by insulin and glucagon.
- Insulin:
    - Produced by the beta cells of the islets of Langerhans and is coded for on chromosome 11
    - Released in the blood in response to high glucose levels in the blood
    - Insulin then takes the glucose into various cells of the body
- Glucagon:
    - Released from the alpha cells of the islets of Langerhans
    - Released in the blood in response to low glucose levels in the blood
    - Glucagon signals glycogen breakdown and then increase levels of glucose

Type 1 diabetes

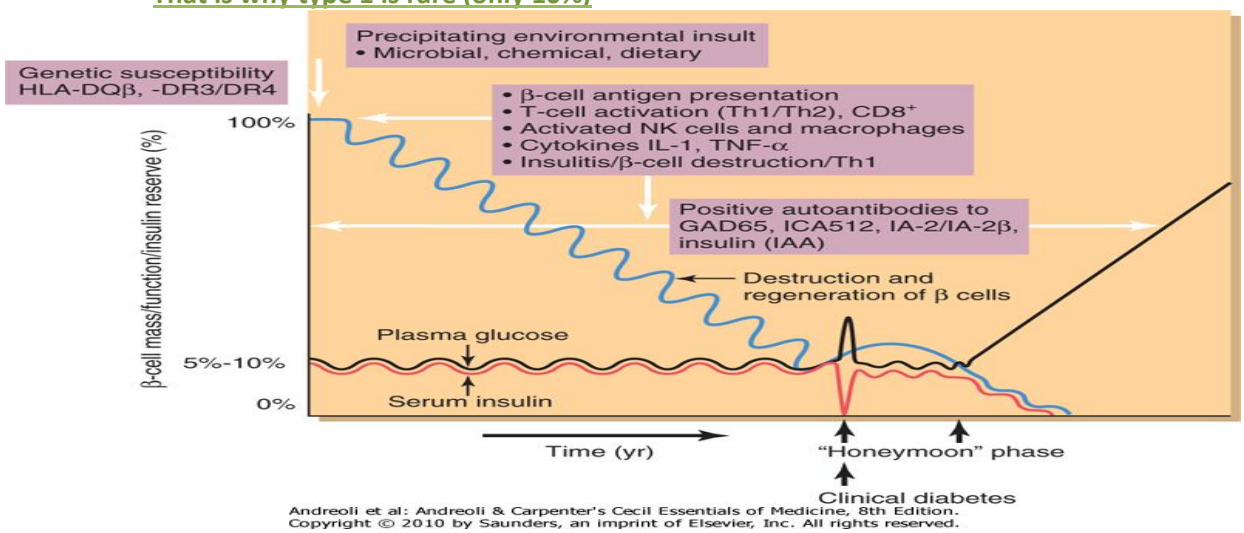
General considerations:

- 10% of all diabetic patients
- Immune mediated genetic disease
- Patients have ***NO or very low levels insulin***
- Patients ***require insulin to live*** and before the discovery of insulin in 1921 patients used to die
- Presents as:
    - Disease of young age usually <20 years old
    - Usually lean and thin
    - Classic acute symptoms of hyperglycemia
        - Polydipsia, polyuria
        - Weight loss due to the lypolysis of fat
        - Polyphagia

        - blurred vision
            - because of the increased glucose in the blood the water content of the eye will increase because glucose pulls water by osmosis and that leads to swelling up of the lens and altered focusing of the images away from the retina
            - ↑glucose → water ↑ → focus is disturbed due to lens swelling
        - Fungal infections due to increase glucose conditions
    - Severe hypoinsulinemia
    - ***1/3 of patients present as DKA (diabetic ketoacidosis) IMP***
        - Characteristic of ***type 1*** usually
        - When the body cannot utilize glucose and glucose doesn't enter the cells, the brain sends signals to the cells to start breaking down fat (lypolysis) as a result of this break down very harmful toxic acids like acetone and ketone bodies accumulate in the body.

Pathogenesis

- Type 1 diabetes mellitus is genetic disease meaning there is a problem in the genes.
- Beta cells of the islet of Langerhans are destroyed so insulin cannot be secreted. Let's find out how they are destroyed:
    - On the short arm of chromosome 6 there is a HLA area (human leukocyte antigen) and this area is segmented into different parts (A, B, C, D, etc)
    - One of these areas is HLA-DR3 and HLA-DR4
    - Some <u>environmental</u> OR <u>unknown factors</u> then activate this gene and mRNA bind to the gene and produces proteins
    - Those proteins are ICA (islet cells antibodies) and they start attacking the beta cells and then there is no secretion of insulin
    - So why does Coxsackie virus and mumps trigger diabetes? Because the gene that encodes for their antibodies is near DR3 and DR4
- This type of diabetes doesn't run in families and therefore it cannot be transmitted to children, but gene susceptibility can be transmitted in up to a 5% chance but still needs a factor to activate it
- ***Type two on the other hand runs in families***
- Note this:
    - Having the DR3 or DR4 gene doesn't mean you will get DM in fact 45% of the population have it
    - Having the ICA antibodies doesn't mean you will get DM (only in 30% of people ICA antibodies will attack the beta cells, in the other 70% it will not attack)
    - ***You must have the genes + have the ICA antibodies + these antibodies must attack the beta cells***
        - <u>That is why type 1 is rare (only 10%)</u>



Type 2 diabetes mellitus

General considerations:

- 90% of all diabetic patients
- Familial disease that ***can be transmitted through families***
- Patients have ***normal or high levels of insulin*** but they can diminish over the years
- Subtle disease that may show after 4-7 years after development of insulin resistance has started and complications are occurring
- Presents as:
    - Can be Found incidental on screening tests
    - Can present with the Classical symptoms (polyuria, poluphagia, etc...)
    - Patients are usually overweight
    - Happens in older patients (older than 30)
    - There is no DKA in type II because of the remaining insulin level is enough to fight against DKA (but not enough to lower the glucose level)
    - In patients who don't routinely check up it could reach complications and patients can present with complications
        - As many as 50% have an established cardiovascular complication at the time of diagnosis
    - Example: patient came to you saying he was diagnosed 3 months ago with diabetes but he is not taking the medication, is the patient type I or type II?
        - He is type II. Type I will end in ER with DKA

Pathogenesis

Risk factors:

- Obesity
    - Associated with increased plasma levels of free fatty acids which make muscles more insulin resistant, reducing glucose uptake.
    - Therefore obesity exacerbates insulin resistance
    - Exercise makes muscles more insulin sensitive
- Genetics
- Age
- Family history
    - If there is no DM in the family your chance to be diabetic is 5%.
    - If either your mother or father has DM your chance to be DM will be 15%.
    - If your mother & father have DM your chance to be DM will be 45%.
    - If either your mother or father & one of the brother or sister have DM your chance to be DM will be 70%.
- Can we reduce the risk?
    - Yes, you can reduce that by running 20 min. 3 times a week this will reduce 2/3 of the risk.
    - If we maintain the normal body weight this will reduce the half of the risk.
    - If you eat a healthy food this will reduce 1/3 of the risk.
    - **Example :**a person has 45% risk to develop DM… we ask him to run every week 3 times for 20 min, this will reduce the risk to 15%. And we ask him to maintain his normal body weigh this will reduce the risk to the 7.5%, and finally we ask him to eat healthy food this will reduce the risk to 2.5%.

The problem type II is the peripheral tissue insulin resistance

- Pancreatic beta cells have to put more insulin to fight that resistance
    - Patients first have normal glucose level with high insulin level
- But after time the beta cell get fatigued and the insulin will fall to the normal levels

- (Now we will get normal insulin and hyperglycemia).
- If the patient was not treated he will develop the complete picture of DM
  - (hyperglycemia and hypoinsulinemia)
- If the glucose level is very low body starts to break down protein as a source of energy. First protein to be broken down is rhodopsin (eye protein) > so vision is affected in early stage
- Type II diabetes is familial. How do familial diseases differ from the genetic diseases?
  - The familial diseases are caused by expression of multi-genes together, that's why they call it a polygenic disease because there are many genes that work together like obesity gene, insulin resistance gene, and they beat normal gene function
  - However in Genetic disease we have just one gene

Others

1. Impaired glucose tolerance
   a. Also known as pre diabetes, which is not a clinical entity but rather a risk factor for DM type 2 and cardiovascular complications
   b. This is the stage before the person gets type II diabetes.
      i. Note: if you catch the patient in that golden phase you can prevent type II diabetes up to 80%of times.
      ii. Obesity and lack of physical activity makes it develop to DM type 2
   c. Lab tests of fasting blood glucose are between 110-126 mg/dl
2. Secondary diabetes for reasons like:
   a. Removal of the pancreas
   b. Trauma
   c. Acromegaly
   d. Cushing syndrome
3. Gestational diabetes
   a. This is due to the placenta which secretes human lactogens that act like growth hormone that induces insulin resistance.
   b. Usually it is temporary that terminates at delivery, but there is a chance to continue after pregnancy.
   c. The effect (danger) of gestational diabetes will be on the baby not on the mother only because it can cause congenital malformation, intrauterine death.

Comparison between T1DM & T2DM

	Type 1	**Type 2**
Onset	Sudden	Gradual
Age of onset	Young <20 years old	Older >30 years old
Presentation	Classic, DKA	Incidental, classic or over 4-6 years
Insulin	Low or absent	Normal or high
ketones	DKA is common	Rare
Familial	Negative	Positive
genetic	Positive DR3 and DR4 gene	----
Body habitus	Thin	obese
Antibodies	Positive antibodies	No ICA antibodies
Acute complications	DKA & hypoglycaemia	Hyperosmolar coma & hypoglycaemia

Diagnosis and screening:

- Diagnosis and screening is very important in diabetic patients because complications are very serious and need to be prevented early on
- Different laboratory tests can be used besides the clinical symptoms to diagnose diabetes
- If the patient presents with the classic or overt symptoms then diagnosis can be made clinically
- Remember: there is no such thing as mild diabetes, if you have high blood glucose you are liable to developing complications
- Clinical symptoms and any of the lab tests that test positive on 2 different occasions is enough for diagnosis
- Diagnosing type 1 and type 2 is important because the management is different in both (type 1 need insulin)

There are three laboratory tests

1. Fasting blood sugar (FBS)
    a. Ask the patient to fast then measure his blood glucose:
        i. Normally it should be less than 5.6 mmol/L (100 mg/dl)
        ii. Impaired fasting glucose test is when the result is between 5.6 and 7 mmol/L (100-126 mg/dl)
        iii. Above 7 mmol/L (126 mg/dl) is diabetic
    b. Sensitivity and specificity
        i. This is a specific test: If a patient has high glucose in FBS test then he definitely has diabetes
        ii. This is NOT a sensitive test: if a patient has normal blood glucose on FBS he might have diabetes and he might be normal
    c. So this is a specific test which means it is good **for confirming the diagnosis of diabetes**
    d. Remember that you need to take 3 different readings on different occasions
2. Random blood sugar (RBS)
    a. Take a random sample: If it is more than 11.1 mmol/L (200 mg/dL) then it means high glucose in the blood
    b. Sensitivity and specificity:
        i. This is a sensitive test: If the patient has normal levels of glucose then he is definitely NOT diabetic
        ii. This is NOT a specific test: If the patient has high blood glucose then he might be diabetic and might be normal
    c. So this is a sensitive test which means it is **good for SCREENING of diabetes**
3. Oral glucose tolerance test (OGTT)
    a. We take a measure when the patient is fasting then, We give the patient glucose and then take measures after 2 hours:
        i. Normally it should be less than 7.8 mmol/L (140 mg/dL)
        ii. Impaired glucose tolerance test is when the result is between 7.8 -11 mmol/L (140-200 mg/dL)
        iii. Above 11.1 mmol/L (200 mg/dL) is diabetic
    b. ***This is the best test! Most specific and most sensitive***.

	Normal	Impaired fasting glucose	Impaired glucose tolerance	Diabetes mellitus
FBS	<5.6 mmol/L (<100)	5.6-7 mmol/L (100-126)	----------	>7.0 mmol/L (>126)
RBS	--------	---------		>11.1 mmol/L (>200)
OGTT	<7.8 mmol/L (<140)	----------	7.8-11 mmol/L (140-200)	>11.1 mmol/L (>200)

Screening

- Screening for T1DM:
  - Measurement of autoantibody markers (antibodies to islet cells, insulin, glutamic acid decarboxylase, and tyrosine phosphatase)
  - It is not done widely for reasons like: lack of established cut-off values for immune markers, lack of consensus regarding effective therapy for patients with positive test results, and lack of cost-effectiveness.
- Screening for T2DM:
  - Early diagnosis and treatment may reduce the burden of this disease, its complications (particularly microvascular and macrovascular disease), and associated co morbidities, such as dyslipidemia, hypertension, and obesity.
  - Recommendations:
    - Screen all adults over the age of 45 years every 3 years.
    - For persons with risk factors start screening earlier; risk factors include ((BMI > 25), sedentary life style, family history, hypertension, hyperlipidemia, history of gestational diabetes, on previous testing impaired glucose tolerance or impaired fasting glucose.

Follow up:

- The markers for follow up of diabetes are HbA1c and fructose amine, and they show the level of glucose in the blood for a period of time in the past. So we can say it reflects glycemic control:
  - HbA1C
    - When glucose is exposed to protein in the blood they undergo a process named "non-enzymatic glycation" which is binding of the glucose to the protein molecule.
      - Haemoglobin + glucose = HbA1C
    - In the blood haemoglobin gets glycated and is normally less than 5% of all haemoglobin
    - When glucose levels are high in the blood for a long time more Haemoglobin gets glycated and the levels go up.
    - ***Because the life of RBC's are 120 that means HbA1C reflects glycemic control for the past 3 months***
    - Ideally should be kept under 7% but under 8% is also accepted
  - Fructose amine
    - Here albumin undergoes "non-enzymatic glycation" and produces fructose amine. (Albumin + glucose = fructose amine)
    - ***Represents glycemic control for the past 3 weeks***
    - Good for pregnancy (short term changes)
    - Good for patients with haemolytic anaemia in which RBC life is short
- ***Both HbA1C and fructose amine are linked with incidence of complications! IMP***

Complications of diabetes

- We can classify complications into long term and short term (acute and chronic)
- Acute complications depend on the type of DM (type 1 or 2) and Chronic complications depend on the duration of the disease
- Acute complications of DM include DKA (diabetic ketoacidosis), hypoglycaemia and Hyperosmolar non-ketotic coma

Hypoglycaemia

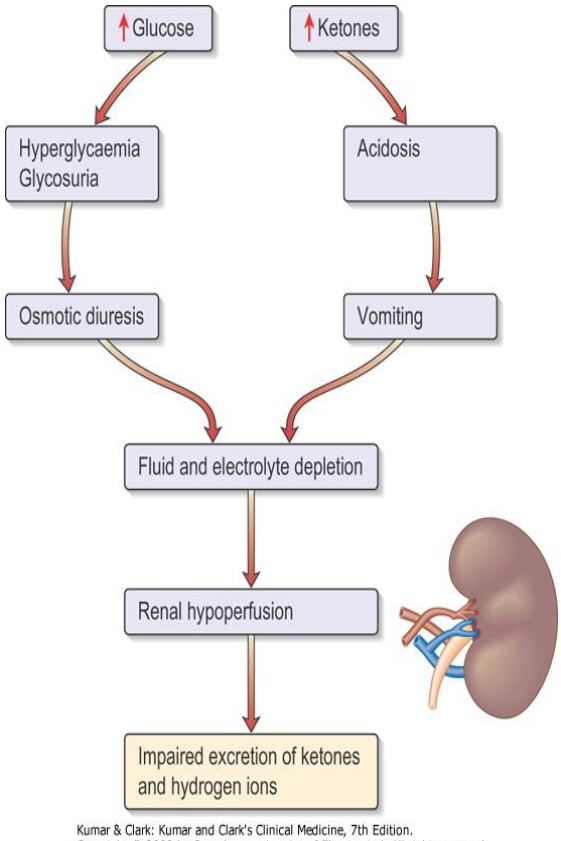
- General considerations and clinical features :
  - ***The commonest acute complication of diabetes***

- Usually patients recover and do not die of hypoglycaemia, but rather from the circumstances like swimming or driving etc...
- Primary organ at risk of hypoglycaemia is the brain because it uses glucose as a main source for energy
- Having said that, this produces neuroglycopenic symptoms like: CNS dysfunction, irritability, weakness, drowsiness, headache, confusion, coma and even death.
- Symptoms occur at a blood glucose of 40-50 mg/dL
- Symptoms related to increase epinephrine like high blood pressure, tremors , sweating, anxiety and palpitations
- Taking too much insulin is another common cause
- Diagnosed by low blood glucose. (Whiples triad is used in cases of insulinoma)

- Normally:
  - Plasma glucose is maintained on a day-to-day basis within a narrow range of 72 to 144 mg/dL (4 to 8 mmol/L) and is kept at that by the action of insulin and glucagon
  - As glucose levels decrease glucagon increases and increases blood sugar levels
  - The second hormone to increase is epinephrine and after that cortisol in order to maintain blood sugar levels
- Treatment:
  - If the patient can eat, give sugar-containing foods; if not, give intravenous dextrose (50ml of 50% dextrose into a large vein).
  - Intramuscular glucagon acts rapidly by mobilizing hepatic glycogen, and is useful in when intravenous access in difficult.
  - So it is revisable with glucagon and/or glucose

DKA (Diabetic ketoacidosis)

- DKA is an acute, life-threatening medical emergency that can occur in both type I and type II diabetic patients. But is the hallmark of type 1 diabetes.
- 1/3 of DM patients present with DKA
- Remember this: DKA= hyperglycemia + acidosis + ketonemia
- Pathogenesis:
  - Insulin deficiency
    - leads to high blood glucose
    - Increased ketogenesis from the liver = ketosis
  - Glucagon increase also leads to high levels of sugar in the blood
  - Severe hyperglycemia then leads to osmotic dieresis which causes dehydration and volume depletion
  - So DKA will cause: hyperglycemia (greater than 250 mg/dL), ketonemia, metabolic acidosis (pH less than or equal to 7.3), and volume depletion.
    - And that is what you look for in diagnosis
  - Hyponatremia and potassium abnormalities may also occur
- Precipitating factors:
  - Inadequate insulin administration
  - Any type of stress or illness (e.g., infectious process, trauma, myocardial infarction, stroke, recent surgery, sepsis, GI bleeding)
- Clinical features:
  - Nausea and vomiting
  - Kussmaul's respiration (rapid and deep) due to metabolic acidosis
  - Marked dehydration, orthostatic hypotension, tachycardia secondary to water and electrolyte loss from the kidney.



- "Fruity" (acetone) breathe odour. “you can smell it from the ER door”
- Abdominal pain (more common in children) that may mimic surgical acute abdomen.
- Altered consciousness, drowsiness, and frank coma may occur if not treated.

- Treatment
  - Give insulin IV once diagnosis is established and make sure the patient is not hypokalemic because that will make it worse. Switch to subcutaneous insulin when anion gap is closed and patient cane at again.
  - Replace fluid with normal saline once diagnosis is established. Add 5% glucose once the blood glucose reaches 250 mg/dL to prevent hypoglycaemia.
    - If glucose levels decrease too rapidly that will cause cerebral edema
  - Replace potassium prophylactically 1-2 hours after beginning insulin. Ensure adequate renal function (urine output) before administering.

Hyperosmolar hyperglycemic nonketotic syndrome (HHNS)

- Occurs almost exclusively in patients with T2DM, who are usually elderly.
- A state of severe hyperglycemia, hyperosmolarity, and dehydration **without significant ketosis**
- Pathogenesis:
  - Similar to that of DKA but may be distinguished from it by the more marked hyperglycemia, the relative absence of acidosis and ketonemia, and the greater degree of dehydration.
  - There is no ketonemia because there is still a little insulin to prevent ketogenesis and the effect of glucagon
  - **Severe dehydration** is due to continued hyperglycemic (osmotic) diuresis. The patient's inability to drink enough fluids (either due to lack of access in elderly/bedridden patients or to inadequate thirst drive) to keep up with urinary fluid losses exacerbates the condition
- Clinical features:
  - Signs of extreme dehydration and volume depletion → hypotension, tachycardia.
  - Thirst, oliguria.
  - CNS findings and focal neurologic signs are common e.g. seizures (secondary to hyperosmolarity).
- Diagnosis:
  - Hyperglycemia: serum glucose > 600 mg/dL.
  - Hyperosmolarity.
  - Serum pH .7.3 (no acidosis)
- Treatment:
- Fluid replacement is most important (normal saline).
- Low dose Insulin infusion

DKA vs. HHNS

	DKA	HHNS
Blood glucose	250-600 mg/dL	Usually >600 mg/dL
Acidosis	pH <7.3 (acidosis)	pH >7.3 (no acidosis)
Ketonemia	+ for ketosis	No ketosis
osmolarity	Usually <320 mOsm/kg	Severe hyperosmolarity >320
Dehydration	Present	More severe
Treatment	Insulin, IV fluids, potassium	IV fluids (IMP), insulin
CNS	No focal CNS symptoms	Focal neurological symptoms (seizures)

Chronic complications of DM

- Chronic complications of DM are dependent on the duration of the disease.
- DM is the leading cause of IHD, stroke, blindness, ESRF, dialysis and amputation.

As you go down the mortality and morbidity increases.

That means vasculopathy has the highest mortality (it's what kills the patients)

Neuropathy (40%)
Retinopathy (30%)
Nephropathy (20%)
Vasculopathy (10%)

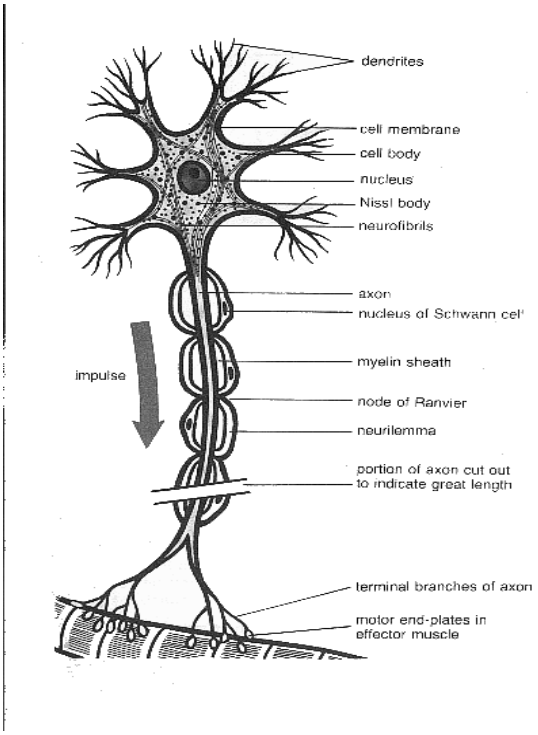
As you go up prevalence increases.

That means that neuropathy has the highest prevalence

(Prevalence rates are in brackets)

First: neuropathy:

- Pathogenesis
  - Nerve cells are independent of insulin so they do not need insulin to enter glucose into the cell
  - On the other hand Schwann cells need insulin to utilize glucose.
  - And in DM Schwann cells lack glucose and they switch to the polyol (sorbitol) pathway to produce energy.
  - This pathway produces sobrbinil which is very concentrated and that increases viscosity and then increase water content so the cell well swell up
  - Swelling of the Schwann cells in different locations will lead to pressure symptoms like tingling and eventually more pressure will lead to complete loss of sensation if the Schwann cells cut the nerve
- Neuropathy is reversible unless the nerves are cut.
- So to reverse neuropathy you have to give insulin and after that Schwann cells turn off the sorbitol pathway and reduce swelling.
  - Patients will usually feel pain after giving them insulin but that is a good sign because it means sensation is back>
- ***The commonest type of neuropathy is sensory*** neuropathy due to the long length of the sensory neurons, meaning they have more Schwann cells.
- Clinically:
  - Peripheral neuropathy:
    - Occurs in a "glove/stocking" pattern (which means hands and feet are affected 1st)
    - Sensory numbness and tingling
    - Loss of sensation leads to ulcer formation, Charcot's joints and ischemia of pressure points
    - Painful diabetic neuropathy – hypersensitivity to light touch that is hard to tolerate
  - Cranial nerve palsy (mononeuritis) – most commonly the occulomotor nerve CN3; causes diabetic third nerve palsy:
    - Blood supply problem
    - Eye pain, diplopia, ptosis, inability to adduct the eye



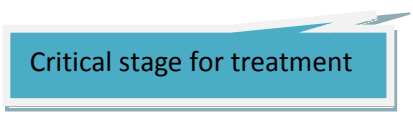
        - ***The pupils are spared*** (contract to light stimuli)!! Ischemia and reduced blood supply of the nerves affects the inner side of the nerve first; because the pupil fibers are located on the outside of the nerve so ischemia affects it very late and they are spared
    - Mononeuritis Multiplex:
        - Here the problem is in the blood supply to the nerve – the vasa nervosa!
        - You can get diplopia from CN3 palsy or drop hand (ulnar nerve palsy)
        - Do not treat it! Collaterals will usually fix the problem; just make sure insulin intake is good.
    - Autonomic neuropathy: This is a major problem that reduces the quality of life; it can manifest as:
        - ***Impotence in men (most common)***
        - Neurogenic bladder- retention and incontinence
        - Gastroparesis
        - Constipation and diarrhea

Second: retinopathy:

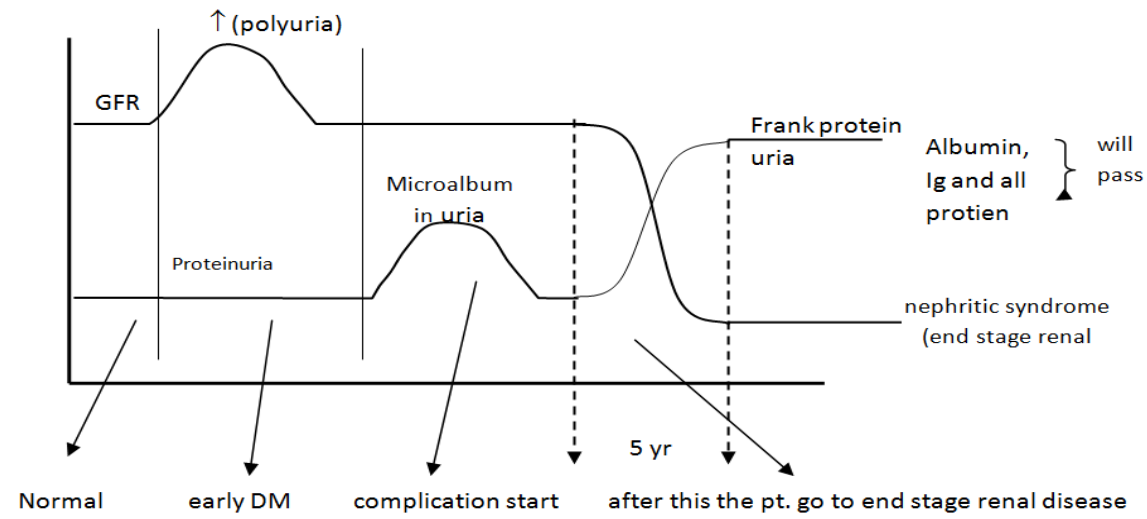
- Many eye pathologies can occur due to DM like 3rd cranial nerve palsy, cataracts, glaucoma and lens swelling. That is why an annual visit to an ophthalmologist is recommended for all diabetic patients
- But the ***most common cause of diabetic retinopathy is retinal detachment*** due to proliferative retinopathy; let's see how that happens:
    - Rods and cones of the retina are very active cells that require energy all the time
    - In absence of insulin the rods and cones don't receive glucose so they signal proliferation of new blood vessels (they think that they aren't receiving blood)
    - These new proliferations are very delicate and therefore liable to bleeding from the minimal of things like coughing
    - If these proliferations bleed they will bleed in the posterior chamber and cause vitreous hemorrhage which then will turn into a clot
    - After a while this clot will undergo fibrosis and it will start pulling the retina thus causing retinal detachment and bleeding
- Insulin is used to control DM and laser therapy can be used to prevent further bleeding

Third: nephropathy:

- Diabetic nephropathy is the most common cause of ESRD in developed countries (about 30% of cases)
- The mere presence of protienuria in the urine is a risk linked with cardiovascular complications
- Pathogenesis:
    - In DM oncotic pressure in the glomerulus increases causing more fluid to be filtered and that increases GFR after that the glomerulus cannot handle it, this is initially not accompanied by histological changes.
    - The first thing to happen to the patient after that is microalbuminuria which is the first sign and here glycemic control is very helpful to reduce progression
    - Further glycosylation of the basement membrane and glomerulosclerosis occur (two types; 1. Nodular glomerular sclerosis (kimmelstiel- Wilson syndrome) 2. Diffuse golmerular sclerosis (also seen in HTN))
    - After this stage frank protienuruia and nephritic syndrome occurs and here the patient has 5 years before he develops ESRD
- HTN increases the risk of progression of diabetic nephropathy
- ACE inhibitors should be initiated
- In short: Hyperglycemia →↑GFR→ Microalbuminuria→ Protienuria→↓GFR→ESRD



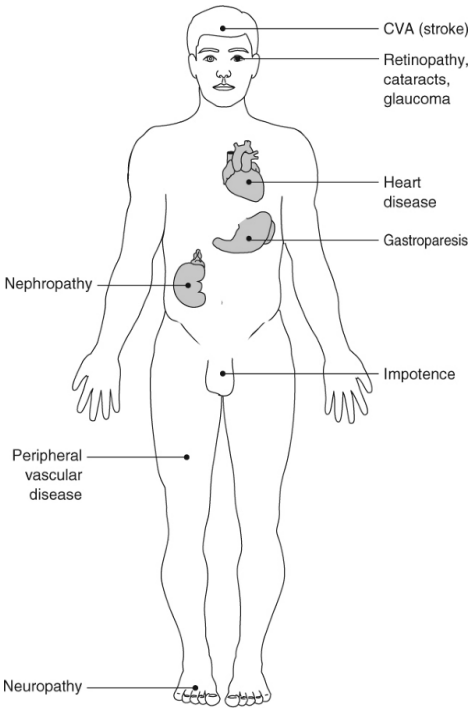
GFR = Glomerular filtration rate



- Figure explanation:
  - Normal : GFR is normal and protein is almost zero
  - Early DM: at first GFR increases to compensate for the increase in fluid load on the glomerulus
  - Complications start: here microalbuminuria starts to appear and it is very important to start treatment with ACEI to stop the progression of the disease.
    - ACEI decrease the hydrostatic pressure from the glomerulus. When you decrease the hydrostatic pressure the protein will not leak so you will decrease the sclerosis in the same time, so you can delay the proteinuria.
    - You can delay ESRD by 15 years with proper treatment
  - 5 year phase: is when frank protienuria appears and here the patient has 5 years before he develops ESRD

Fourth: Vasculopathy:

- Classified into microvascular and macrovascular
- Microvascular's examples are from the previous (nephropathy, retinopathy)
- Macrovascular complications:
  - IHD, stroke and limb ischemia are common
  - ***The commonest complications are cardiac followed by cerebrovascular***
  - Patients usually have hyperlipidemia + hyperglycemia + HTN
    - So any DM patient must have a full cardiac profile check up
  - Cardiac disease:
    - The main problem is ***accelerated atherosclerosis.***
    - The manifestations of atherosclerosis include the following:
      1. Coronary artery disease (CAD) :
         - Risk of CAD is <u>two to four</u> times greater in diabetic than in non-diabetic persons.
         - ***Most common cause of death in diabetic patients.***
         - Silent myocardial infarctions are common.
      2. Peripheral vascular disease—in up to 60% of diabetic patients



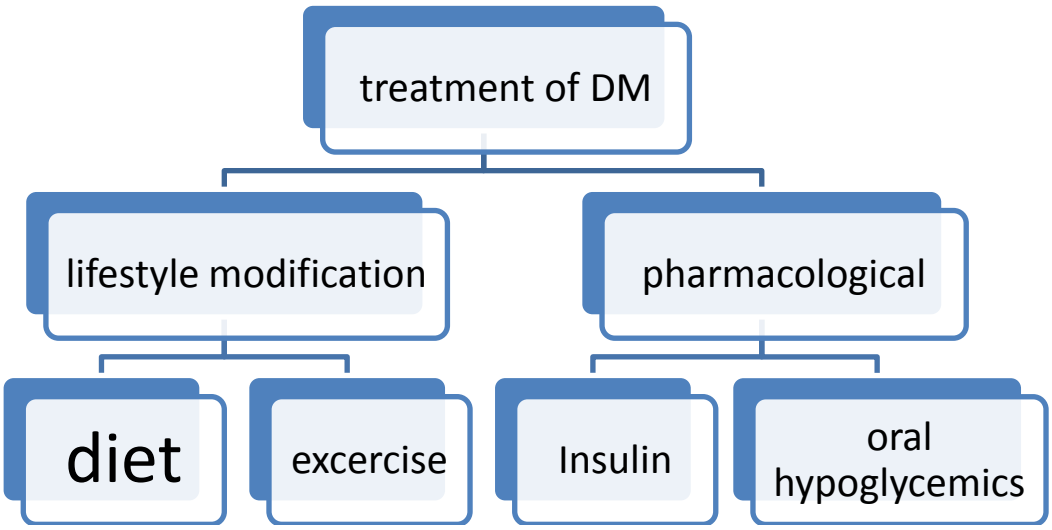
3. Cerebrovascular disease (strokes).

- The risk of coronary events is greatly reduced if the patient can eliminate or reduce other major cardiovascular risk factors (smoking, HTN, hyperlipidemia, obesity).

Management

- The treatment of DM starts at preventing it by reducing risk factors
- General rules of management
  - Type 1 diabetic patients require insulin to live
  - Type 2 diabetics are started with a 6 month trial of diet and exercise, then oral hypoglycaemics are administered if they are irresponsive
    - Many cases of T2DM can be managed with diet and exercise specially in obese patients
    - We administer insulin to type 2 patients in cases of
      - DKA
      - In those younger than 40 years of age
      - When hypoglycemic agents did not achieve satisfactory control of type II diabetes
  - ***ALL diabetics require diet and exercise***
  - The two main "wings of therapy" are diet and exercise
- We can classify them into:
  - Short term: treatment of acute complications and presentation (DKA, etc...)
    - If patient with type II came with 700 mg/dl glucose we give him short period of insulin just to relive his high glucose
  - Long term: control of hyperglycemia + prevention of complications

- Remember that many diabetic patients have other disease like (HTN, dyslipidemia, etc...)
- Smoking has very bad effect in getting Macrovascular problems. Smokers with diabetes are in at a very high risk of getting amputation. So smoke cessation is necessary.
- If patient has Macrovascular disease : give also ACEI – Aspirin – statin (statin even if the patient has normal cholesterol he will benefit from it in reducing inflammatory process in vessels
- **The Target in the management:**
  - The target is HB_{A1C} 7 or less. For elderly patient, Microvascular disease, latent DM we can accept up to 8.
  - 1% percent reduction in HB_{A1C} give a great benefit



First: diet therapy

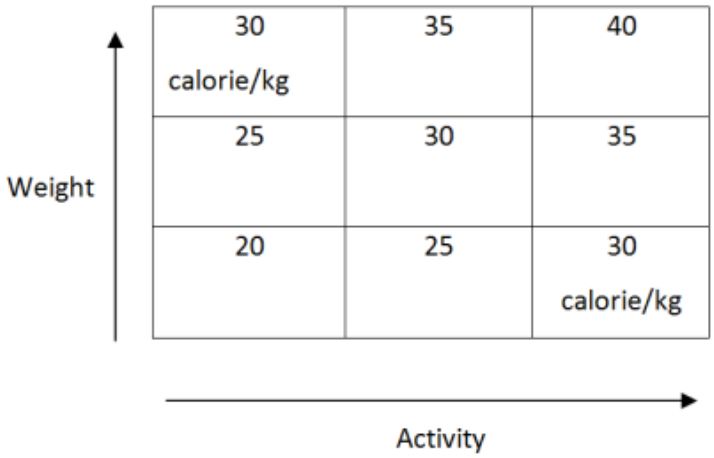
- 1800-2000 kcal is the regular daily requirement to maintain the BMR
- We can break that down into
  - 600 kcal for breakfast
  - 800 kcal for lunch
  - 400 kcal for dinner
- A normal diet should be 65% carbohydrates, 15% protein and 10% fat
- Calories gained from diet
  - 1 gram of protein yields 4 calories
  - 1 gram of carbohydrates yields 4 calories
  - 1 gram of fat yields 9 calories
- A diabetic diet should be:
  - Low in sugar – not sugar free
  - High in starchy carbohydrates (slower absorption)
  - High in fibre
  - Low in fat (specially saturated fat)
- After knowing all these numbers you can choose the appropriate diet for your patient
- The nutrient load should be spread throughout the day (three main meals with snacks in between and at bed time), which reduces swings in blood glucose.

Second: exercise:

- Remember that in obesity high levels of fatty acids desensitizes the muscle to insulin and increases insulin resistance
- Exercise actually makes the muscles MORE insulin sensitive thus decreasing resistance
- Amount:
  - People with diabetes should accumulate a minimum of 150 minutes of moderate to vigorous-intensity aerobic exercise each week
  - spread over at least 3 days of the week
  - with no more than 2 consecutive days without exercise
- Walking decrease HB_{A1C} "the target" by 1 % (better than many of the medications) – (running 20 min. 3 times a week this will reduce 2/3 of the risk)
- Maintain normal body weight will reduce the half of the risk
- 10% loss weigh is enough to get rid of large amount of visceral fat

A table from the doctor to describe relation between calorie changes and activity:

- Normal is the middle box which is 30 calories/kg
- If you increase activity then you should increase calorie intake
- If you decrease activity then you should decrease calorie intake



Third: pharmacological: (attached with the folder is MJW table for drugs)

Insulin: administered mainly to type 1 patients

- Insulin has the strongest effect in lowering glucose
- Method of administration

- Self-administered subcutaneously
- IV in case of emergencies

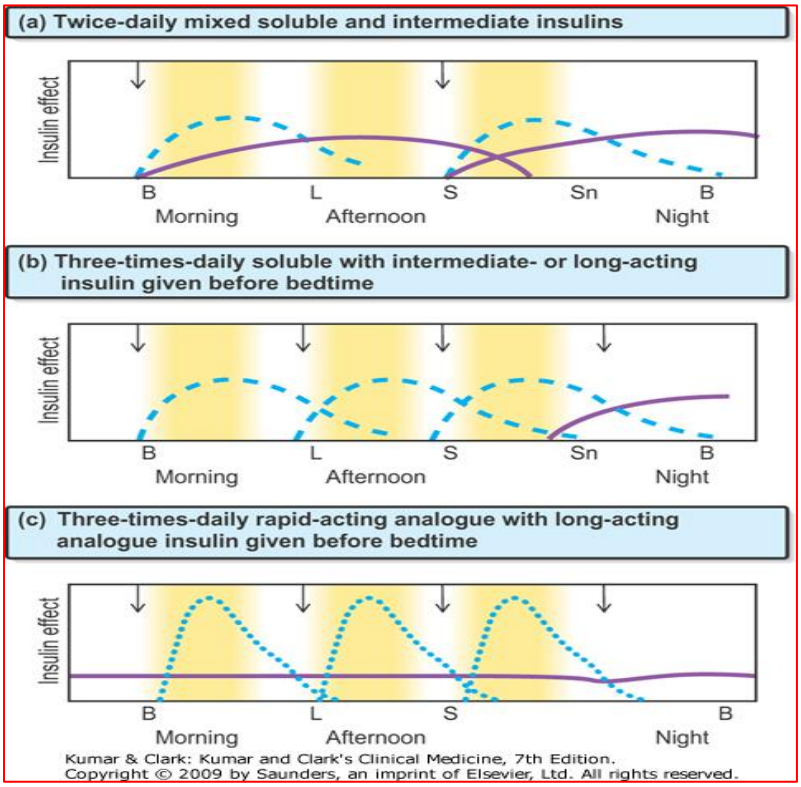
- Types of insulin
  - Rapid-acting insulin: e.g. insulin aspart and insulin lispro.
    - The onset of action is within 15 minutes.
    - Short duration of action (2-4 hours).
    - Clear solution at natural pH.
    - They are the preferred insulin preparation for pre meal bolus.
  - Short-acting insulin: e.g. regular insulin.
    - The onset of action: 30-60 minutes.
    - They last for 4-6 hours.
    - Clear solution at natural pH.
    - They are the only insulin used in emergencies such as ketoacidosis or for surgical operations.
  - Intermediate acting insulin: Isophane (NPH).
    - The onset of action: 1-2 hours.
    - They last for 13-18 hours.
    - Given once or twice daily.
  - Long- acting insulin : e.g. insulin glargin
    - Onset of action: 2-4 hours.
    - They last for about a day.
    - They are slowly released from the site of injection and thus do not produce a peak after administration, so there is no risk of hypoglycemia.

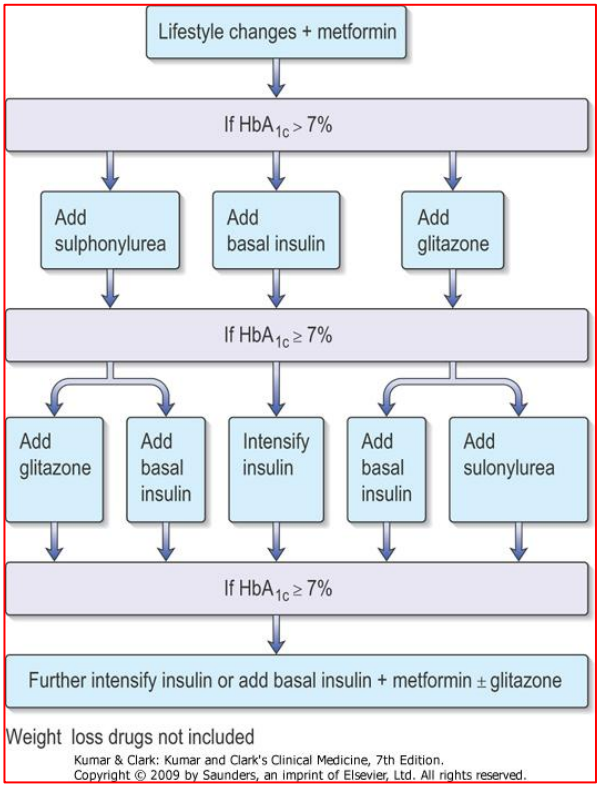
Oral hypoglycaemics:

- Remember: strongest effect in lowering glucose is insulin (the more you increase the dose, the more the effect – unlike Oral hypoglycemics they have a limited effect)
- Use these in type II diabetic patients when conservative therapy (diet and exercise) fails.
- Start with one agent (metformin or sulfonylurea are common choices). If monotherapy fails, use two agents from different classes in combination.
- Each agent has advantages and disadvantages, so clinical judgment is required in selecting the initial agent.
- They are of two types:
  - Sensitizers : increase insulin sensitivity
  - Secretagogues: stimulate insulin secretion
- Classes of oral hypoglycemics:
  - **Biguanides**: e.g. Metformin
    - increases insulin sensitivity
    - site of action is the liver
    - it doesn't affect insulin secretion hence it doesn't cause hypoglycaemia
      - if a patient who uses metformin comes to you with hypoglycaemia then he probably took herbal medications that contain sulfonylurea
    - no weight gain because it doesn't affect insulin secretion
    - **ADRs**: GI symptoms(N&V, diarrhoea, etc...) , lactic acidosis, metallic taste
  - **Sulfonylureas** : e.g. Glibenclamide, Tolbutamide
    - Stimulate pancreas to produce insulin
    - Site of action is pancreas
    - They can cause hypoglycemia which could be fatal
    - Causes weight gain due to insulin anabolic effect
    - Sulfonylureas should be used with care in patients with liver disease. Patients with renal impairment should only be given those primarily excreted by the liver.
    - Tolbutamide is the safest drug in the very elderly because of its short duration of action
  - **Alfa-glucosidase inhibitors:** e.g. acarbose.

- Slow down the breakdown of complex sugar into simple sugar in gut so delay glucose absorption and thus reduce postprandial glucose peak.
- Site of action is Gut
- **ADRs:** bloating, flatulence, and diarrhea

- **Thiazolidinediones" glitazones"**: e.g. rosiglitazones.
  - They enhance insulin sensitivity.
  - Site of action is Fat and muscle!
  - They reduce hepatic glucose production and also enhance peripheral glucose uptake.
  - **ADRs:** Weight gain, Edema, hepatotexicity.
  - They are contraindicated in heart failure and hepatic impairment
- **GLP-1 "Glucagon like peptidase-1"** and Incertin:
  - Stimulate insulin and inhibit glucagon release.
  - GLP-1are inhibited in type II diabetes - either give them GLP-1 or prevent the breakdown of what they have by giving "DDP-4 inhibitors"
  - Injectable GLP-1 is more effective than oral one and have suppressor appetite affect (new and expensive)
- **DDP-4 inhibitors "dipeptidyl peptidase inhibitor**" : reduce breaking down of GLP-1





Insulin regimens. Profiles of soluble insulins are shown as: dashed lines; intermediate- or long-acting insulin as solid lines (purple); and rapid-acting insulin as dotted lines (blue). The arrows indicate when the injections are given. B, breakfast; L, lunch; S, supper; Sn, snack (bedtime).

A treatment pathway for T2DM