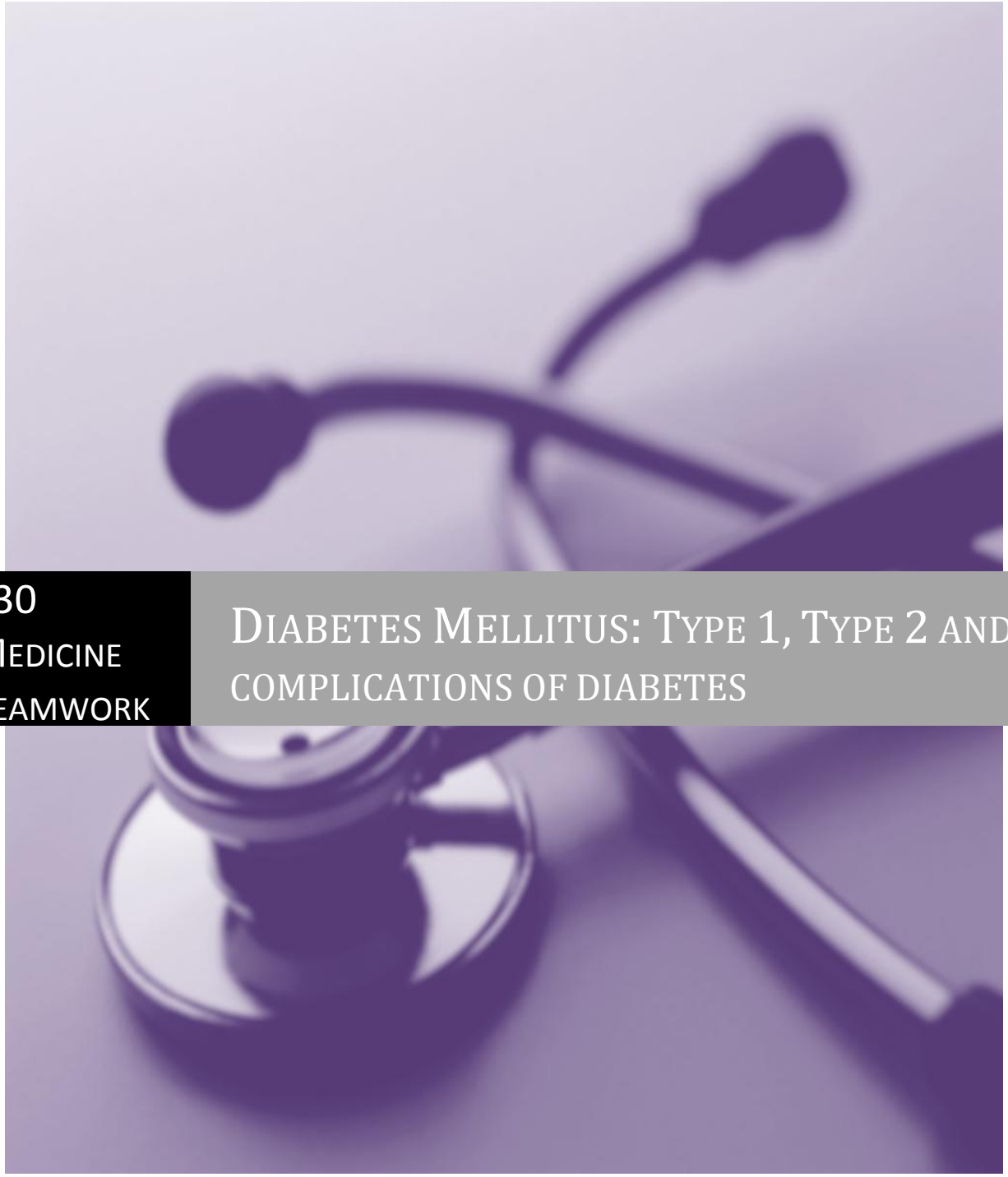
"He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all." – William Osler



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MEDICINE
TEAMWORK

DIABETES MELLITUS: TYPE 1, TYPE 2 AND COMPLICATIONS OF DIABETES

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Diabetes mellitus

What is diabetes?

- WHO's definition of DM: Diabetes is metabolic disease associated with glucose metabolism abnormalities as a result of insulin deficiency or insulin resistance that is also related to chronic complications affecting nerves, vessels and kidneys.
- Diabetes Mellitus is a disease of glucose metabolism abnormalities. It is a clinical syndrome characterized by hyperglycemia caused by insulin deficiency or insulin-resistance.
- Lack of insulin affects the metabolism of proteins, carbohydrates, fats and disturbances of electrolytes and water.
- Long standing metabolic derangement will lead to functional changes in the vascular system; these changes cause the complications of diabetes.
- The Incidence of Diabetes is rising gradually.
- The normal blood glucose level is tightly regulated and usually maintained between 80 and 120

Normal physiology: (For your understanding)

Insulin:

- Insulin is a hormone produced by the beta cells in the pancreas. Its secretion occurs in response to high blood glucose levels. Insulin regulates blood glucose levels and maintains it from going higher mainly by suppressing hepatic glucose production and stimulating glucose uptake by the skeletal muscles.

Insulin's effects on the liver:

- It inhibits gluconeogenesis, which is the synthesis of glucose from glycerol and amino acids, in order to decrease hepatic glucose production.
- It stimulates glycogenesis, which is the conversion of glucose to glycogen to store in the liver.
- Stimulates lipogenesis
- Inhibits lipolysis

Insulin's effects on the skeletal muscles:

- It promotes glucose uptake by the muscles.
- It enhances glycogen storage in the muscles.
- It stimulates protein synthesis in the muscles.

Insulin's effect on adipose tissue:

- **Insulin inhibits breakdown of fat in adipose tissue** by inhibiting the intracellular lipase that hydrolyzes triglycerides to release fatty acids.
- Insulin facilitates entry of glucose into adipocytes, and within those cells, glucose can be used to synthesize glycerol.
- Not only does it drive most cells to preferentially oxidize carbohydrates instead of fatty acids for energy, insulin indirectly stimulates accumulation of fat in adipose tissue.

What happens when you eat? (Doctor's notes)

- After meals:
    - Blood glucose level increases (the small intestine absorbs glucose and amino acids needed). Beta cells secrete insulin to lower blood glucose and maintain the normal level.
    - Insulin will transport glucose into the liver, muscles and adipose tissue.

- Between meals:
    - When Intestinal glucose uptake decreases between meals, insulin level will decrease, therefore hepatic glucose output increases (stimulated gluconeogenesis and glycogen breakdown).
    - The brain needs continuous supply of glucose because it's the main fuel to the brain (brain can't oxidize fatty acids).
    - During starvation the body will depend on stored glycogen, after two days, the body starts breaking down its own fat (duration of this breakdown depends on the amount of fat the person has). Once done with the fats, the body will consume its own proteins leading to loss of color vision (rhodopsin will be gone causing vision loss, it usually occurs on day 45). Cardiomyopathy followed by heart failure may also occur.

Epidemiology: (Doctor's notes)

- The lowest percentages of the DM were recorded in rural area of Indonesia 0.2%.
- The highest percentage recorded in Pima India was 50%.

(Doctor's notes)

- DM Affects 5% of humans (Highest prevalence in any disease globally)
- Overall there are 5 types of Diabetes:
    - Type 1 DM (10%)
    - Type 2 DM (90%)
    - Impaired Glucose Tolerance (IGT)
    - Secondary DM
    - Gestational Diabetes

The prevalence of diabetes in KSA: (Doctor's notes)

- The prevalence in 1970 was 2.2 %.
- The prevalence in 1980 was 5.9 %.
- The prevalence in 1990 was 13.4 %.
- The prevalence in 2004 was 24.3 %.
- Patient admission is at 34% for diabetic patients, they are in the hospital either due to diabetes directly or to its complication.
- A survey was done among CCU patients in Riyadh; the result was 50 % – 53 % of the patients were diabetic. And after one week 80% of pts who died were diabetic.
- **We have very high mortality here in KSA**

Diabetes classification (Types)

1) Type I DM (10%):

- ***Definition***: Hyperglycemia caused by complete insulin deficiency due to destruction of the beta cells in the pancreatic islets.
- ***Etiology*** : Exact cause is unknown. But mostly, it is an autoimmune disease. These patients have had some type of an inflammatory process involving the beta cells called insulinitis. After developing this insulinitis, their beta cells get whipped out.
- Occurs early in life. (most often diagnosed in children, adolescents, or young adults)
    - The youngest case was reported to a fetus before delivery
- It takes many years to develop and usually signs and symptoms of hyperglycemia occur only if 70 to 90% of the beta cells have been destroyed.
- It has worse outcomes than type 2 diabetes because it is more aggressive.
- Patients with type 1 diabetes don't present with vascular diseases at diagnosing time. Patients are diagnosed in the early stages of the disease because they can't live without insulin for long time.

<u>These symptoms may be the first signs of type 1 diabetes, or may occur when the blood sugar is high:</u>

- Being very thirsty/Feeling hungry
- Feeling tired or fatigued
- Having blurry eyesight
- Losing the feeling or feeling tingling in your feet
- Losing weight without trying
- Urinating more often

Acute symptoms of hyperglycemia

- Polydipsia, polyuria
- Weight loss due to the lypolysis of fat
- Polyphagia

There are two peaks where patient's usually present: (Doctor's notes)

- 1st peak in age of 6-7 yr, & 2nd peak in age of 13-18 yr
- Insulin levels are usually very low, and they are prone to developing DKA
- This type of diabetes is **genetic disease** However type II DM is a **familial disease**
- Insulin is its only treatment.

Genetics of Type I DM: (Doctor's notes)

- Its gene located on the HLA of chromosome 6 (on the short limb), DR 3 & 4
- What happens in Type 1 DM is that for some environmental or unknown reasons the gene triggering occurs which will produce ICAs (islet cell antibodies), this will attack the beta cell of the pancreas, thus triggering of the gene which causes the diabetes occurrence either because of environmental factors OR spontaneously. Environmental factors include (Coxsackie B & mumps virus) which they trigger the gene expression of the ICA, because B lymphocytes produce antibodies against those viruses by activation of the gene adjacent to the gene which produces the ICA, leading to the possibility of activating the ICA gene.
- Having the gene does not mean you'll develop the disease if you have that bad gene. And activation of that gene does not mean you'll present with symptoms.
- Features: Young, Thin, HLA-DR 3&4 Activation.

DKA: (Doctor's notes)

- 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.

2) Type II DM (90%):

- ***Definition*** : Relative insulin deficiency due to impaired beta cells function. Also, resistance to the actions of the insulin in the liver and muscle tissues.
- Occurs later in life, it takes months to years to develop the symptoms.
- Patients usually present with complications.
- The problem in this type is insulin resistance (By peripheral tissues) → B-cells have to put more insulin to fight that resistance leading to an increase in Insulin levels. After a while, Beta cells get tired resulting in a fall in Insulin to normal levels & the glucose rise, resulting in mild hyperglycemia. If the patient is not treated, he/she will end up with a complete picture of DM, meaning they'll have hyperglycemia & hypoinsulinima. Patients with this type don't develop DKA. It is a familial disease. (Doctor's notes)
- ***Pathophysiology*** :
  Insulin resistance and Beta cells failure:
  - It is when the body's own sensitivity to insulin is reduced.
  - It is often associated with other disorders such as hypertension, dyslipidemia and central obesity.
  - (If Insulin-resistance, obesity and other risk factors occurred together, they increase the risk of developing cardiovascular disease, type 2 diabetes and strokes; known as "metabolic syndrome") .

Risk factors:

- Many risk factors contribute in developing type 2 diabetes, such as:
- ***Genetic predisposition:***
  - It's a familial disease. Many genes are involved in developing type 2 diabetes.
  - It is much more profound than in type 1 diabetes. It is very important to know the family history; if the parents have it then the kids would get it.
- ***Age*** → More common in middle aged and elderly people.
- ***Diet*** → High fat foods and food rich with carbohydrates.

- ***Obesity*** → It increases the risk of developing diabetes in genetically predisposed people. Around 70% of type 2 diabetics are obese
- Sedentary lifestyle
- It's associated with other disorders such as hypertension, dyslipidemia and central obesity.

How does obesity induce insulin resistance and cause beta cells failure?

- Adipose tissue releases large quantities of FFAs. They compete with glucose as a fuel supply for oxidation in muscles. This might induce insulin resistance. There will be an increase in blood glucose.
- In response to progressive insulin-resistance → blood glucose level increases → more insulin is secreted in order to maintain normal blood glucose levels → hyperinsulinemia → blood glucose level is still high because of insulin resistance in the liver and muscles tissues → beta cells will try to compensate by secreting more insulin → with time, beta cells get exhausted because of the constant insulin secretion. So, they won't be able to compensate adequately and their function will deteriorate → blood glucose rises → Hyperglycemia.
- Adipose tissue releases hormones that act on the sensitivity of insulin on other tissues.
- It has an influence on insulin sensitivity in the liver because visceral adipose tissues drain in the portal veins so it will affect gluconeogenesis and lipid metabolism.
- Elevated blood glucose and FFAs release toxins that effect beta cells function.
- In the early stages of the disease, you will find that patients have elevated insulin levels because of insulin resistance.
- Obesity is a permissive state. The more weight you gain, the more resistant your cells become to insulin, and the more insulin secreted to override this resistance. And this amount of rejected insulin will be increased in the blood with time and this won't allow the insulin to eliminate the predisposing factors of obesity.
- By the time the patient is diagnosed, around 50% of beta cells are lost.

Signs and symptoms:

- The classical symptoms of hyperglycemia are usually absent in type 2 diabetics. Usually they're asymptomatic or with non specific complaints such as fatigue.
- Type 2 diabetics will present with vascular complications once they're diagnosed because the disease has been quiet for years.
- Type 2 diabetics remains asymptomatic for many years, until they develop some symptoms or the doctor picks it up suddenly.
- Type 2 diabetics patients might complain of early microvascular diseases (the disease has been there for more than 5 to 10 years).
- Once a patient is diagnosed with type 2 diabetes, he should be screened right away for microvascular complications.

The Risk to develop Type DM II: (Doctor's notes)

- If there is no DM in the family your chance to be diabetic is 5%.
- If either your mother or father have 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 this percentage? (Doctor's notes)

- Yes, you can reduce it by exercising 20 min. a day, 3 times a week.
    - This will reduce 2/3 of the risk.
- If you maintain the normal body weight, you will reduce half of the risk.
- If you eat healthy foods, you will reduce 1/3 of the risk.

How familial diseases differ from genetic ones? (Doctor's notes)

- Familial disease are caused by an expression of multiple genes together, that's why it's called a polygenic disease, because there are many genes working together, like the obesity gene, insulin resistant gene and beat gene dysfunction.
- However in Genetic disease we have just one gene.
- **Type 2 DM is preventable while Type 1 is not.**

3) IGT (impaired glucose tolerance): (Doctor's notes)

- This is the stage before the person gets type II diabetes.
- Note: if you catch the patient in that golden phase you can prevent type II diabetes up to 80%.
- What can we do for them? Give them synthesizer or we ask them to lose weight & to exercise.
- It is a phase to type II diabetes.

4) Secondary DM: (Doctor's notes)

- Rare, usually secondary to trauma to the pancreas which lead to its surgical removal, recurrent pancreatitis, Cushing syndrome, glucagonoma, excess growth hormone secretion, acromigaly or very rare genetic diseases.

5) Gestational DM (temporary DM): (Doctor's notes)

- This is due to placenta secrete human lactogens
- This human lactogens (like growth hormone) induce insulin resistance
- This is temporary DM, meaning that when the pregnancy is over the diabetes will disappear, but there is a chance it continues after pregnancy.
- First pregnancy has a 7-8% chance of Diabetes, second pregnancy has a 30% chance (if she developed Diabetes in the first one) and the third has a 70% change (If she develops Diabetes in both the first and second)
- The effect (danger) of gestational diabetes will be on the baby not on the mother because it can cause congenital malformations and intrauterine death.
- When a person has sedentary life, the insulin resistance will begin AND when their calorie intake increases he/she will become obese, when those two occur (insulin resistance + obesity) he/she will develop type II DM.

- IGT is Rare
- Secondary DM is Rare
- Gestational DM is Temporary (Most of the time) (Is a risk for type 2 DM)

Investigations and Diagnoses:

- Diabetes is defined as: a fasting blood glucose level equal to or more than 126 mg on two different occasions on one to two weeks apart. Once these patients have that, they have diabetes and they carry the diagnoses for the rest of their lives.

Diagnostic Criteria: (Doctor's notes)

- If the patient is symptomatic, then diagnosis is confirmed by :
  - Random plasma glucose concentration equal to or more than 200 mg
  - Or fasting plasma glucose concentration equal to or more than 126 mg.
  - If patient is asymptomatic two samples are required.
- Oral glucose tolerance test is indicated when plasma glucose levels are elevated but not diagnostic of diabetes :
  - Random plasma glucose concentration between 140-199 mg
  - Fasting plasma glucose concentration between 110- 126 mg.
- Urine dipstick : glycosuria, ketonuria , albuminuria.
- **Hemoglobin A1C:** it is the best test to follow response to therapy over the last several months.
- (HbA1c) refers to HbA that has been modified by attachment of glucose to the N-terminal amino acid of the beta globin chain. Hemoglobin A1C is the part of hemoglobin that has glucose residues. If the patients' glycoselated hemoglobin is known, their mean sugar during the last several months will be detected. **Normal hemoglobin A1C = 6.5 and its equal to mean sugar of 125 mg.**

Management:

- Lifestyle modifications:
  - Exercising regularly: When type 2 diabetics lose weight, their cells become less insulin resistant.
  - Healthy diet: restricted carbohydrates, fat, and salt diet.
  - No smoking or alcohol consumption (alcohol suppresses gluconeogenesis so it can cause hypoglycemia in patients who are on insulin or oral hypoglycemic drugs).
- Oral hypoglycemic agents:
  - Physician can give one oral hypoglycemic agent a combination of hypoglycemic agents. It is only used in type 2 diabetes.

Beta cell implants:

- Very good modality of treatment
- The beta cells are separated off the exocrine cells (cadavers/doners)
- Pure beta cells are put in the liver
- Problems:
  - Pts must be continuously given immunotherapy
  - The half-life of beta cells is 5 years > Must be done every 5 yrs
  - To give 1 dose of beta cells, 2 donors must be available in order to concentrate the beta cell.
  - Only used in very complicated pts

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More on Treatment:

- *Sulphonylureas: (chloropropamide / tolbutamide / glipizide):*
  - Mechanism of action: they act on the beta cells to increase that secretion of insulin.
- All these drugs are excreted renally except tolbutamide, it is metabolized by the liver.
- Side effects:
  - Hypoglycemia: it is a common side effect especially in older patients who they forget to eat after taking the drug or overdose.
  - Weight gain: It is not preferred to use it in obese patients because it causes weight gain. (more insulin resistance, more medications needed)
- Indications/Contraindications:
  - Indicated in non obese patients with type 2 diabetes who didn't respond to dietary measures alone.
  - Contraindicated in patients with renal failure.
  - Not preferred in obese patients.
- *Biguanides:* metaformin – glucofag
  - It's the drug of choice and it's the first line drug .
  - It's the most important drug you can use for type 2 diabetes, they don't cause hypoglycemia or weight gain.
- Mechanism of action:
  - It blocks gluconeogensis and production of glucose by the liver
  - It suppresses the reabsorption of glucose from the GIT
  - Facilitates glucose into the muscle.
- Side effect:
  - GIT symptoms such as diarrhea, nausea and abdominal cramps. (start low doses then increase it, patient will get used to it)
  - Lactic acidosis: it's very uncommon but it is the most feared side effect. It occurs in patients with renal failure.
- Contraindications:
  - Contraindicated in patients with renal failure or impaired hepatic function.
  - Preferred in obese patient.
- *Thiazolidinediones : Glitazone (pioglitazone / rosiglitazone):*
  - Used as a 2nd line treatment in combination with metformin or with insulin.
- Mechanism of action: they sensitize the cells to insulin.
- Side effects: hepatotoxicity, sodium and water retention.
- Indications/contraindications :
  - Used in patients with renal insufficiency.
  - Contraindicated in patients with liver dysfunction.
  - Contraindicated in patients with cardiac failure.
- *Meglitinides*
- *Alpha- glucosidase inhibitors*
- *Insulin:*
  - Added if the patient is not controlled with oral hypoglycemic agents.
- There are four types:
  - Ultra short acting insulin (insulin lispro/aspart): taken right after meals.
  - Regular insulin.
  - intermediate insulin (NPH)
  - Long acting (Glargine): It provides a steady state of insulin for the entire day. Long acting dose of insulin is combined with insulin lispro after meals. This is the best way to control diabetes

Diabetic Complications

- **BLACK**: Doctor's notes
- **BLUE**: Extra notes
- **RED**: Important notes

Diagnosis:

What's the difference between Sensitivity & Specificity? (Doctor's notes)

- Sensitivity:
  - When +ve → Could be false.
  - When –ve → Definite
- Specificity
  - When +ve → Definitely true.
  - When –ve → Could be false.
- That's why for screening, we use sensitive tests. If we used specific tests, we might miss out on a lot of patients as normal. So we use specific tests as confirmatory tests instead.

(Imp.)	Sensitivity	Specificity
RBS	+	_
FBS	_	+
OGTT	+	+

Random Blood Sugar (RBS):

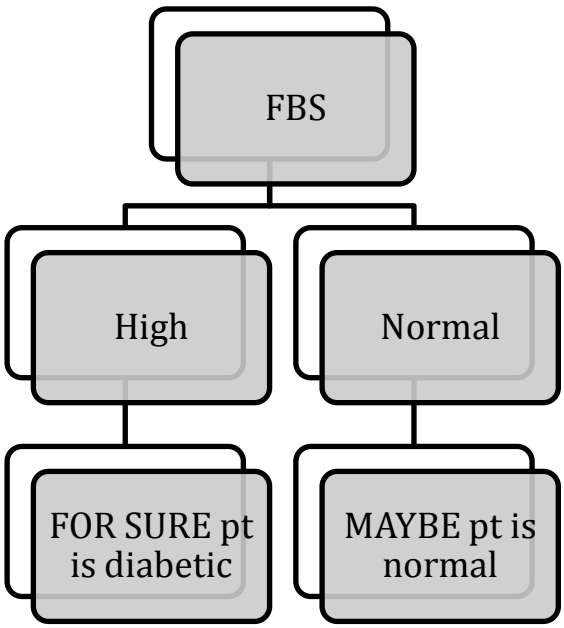
- **FIRST** LINE TEST: RBS (screening test) = Sensitive
- More than 11.1 mmol/L (200 mg/dL) is indicative of high BS (DM)
- If high and patient is symptomatic >> diagnostic of DM.
- If patient is ASYMTOMATIC, we must rely on 2 readings on different days.

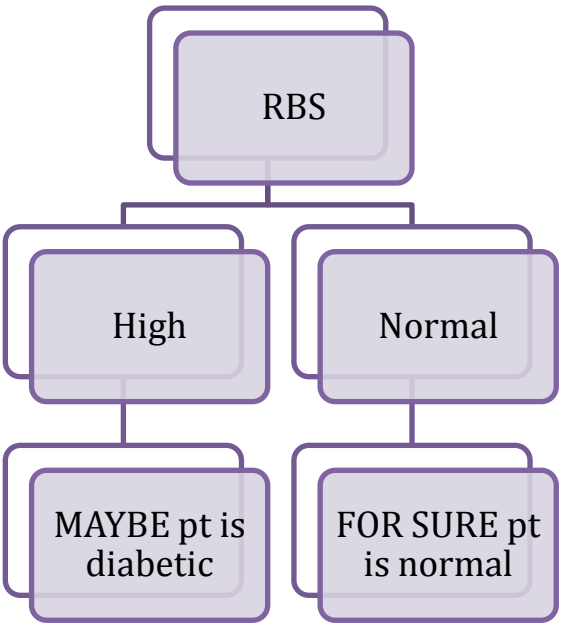
Fasting Blood Sugar:

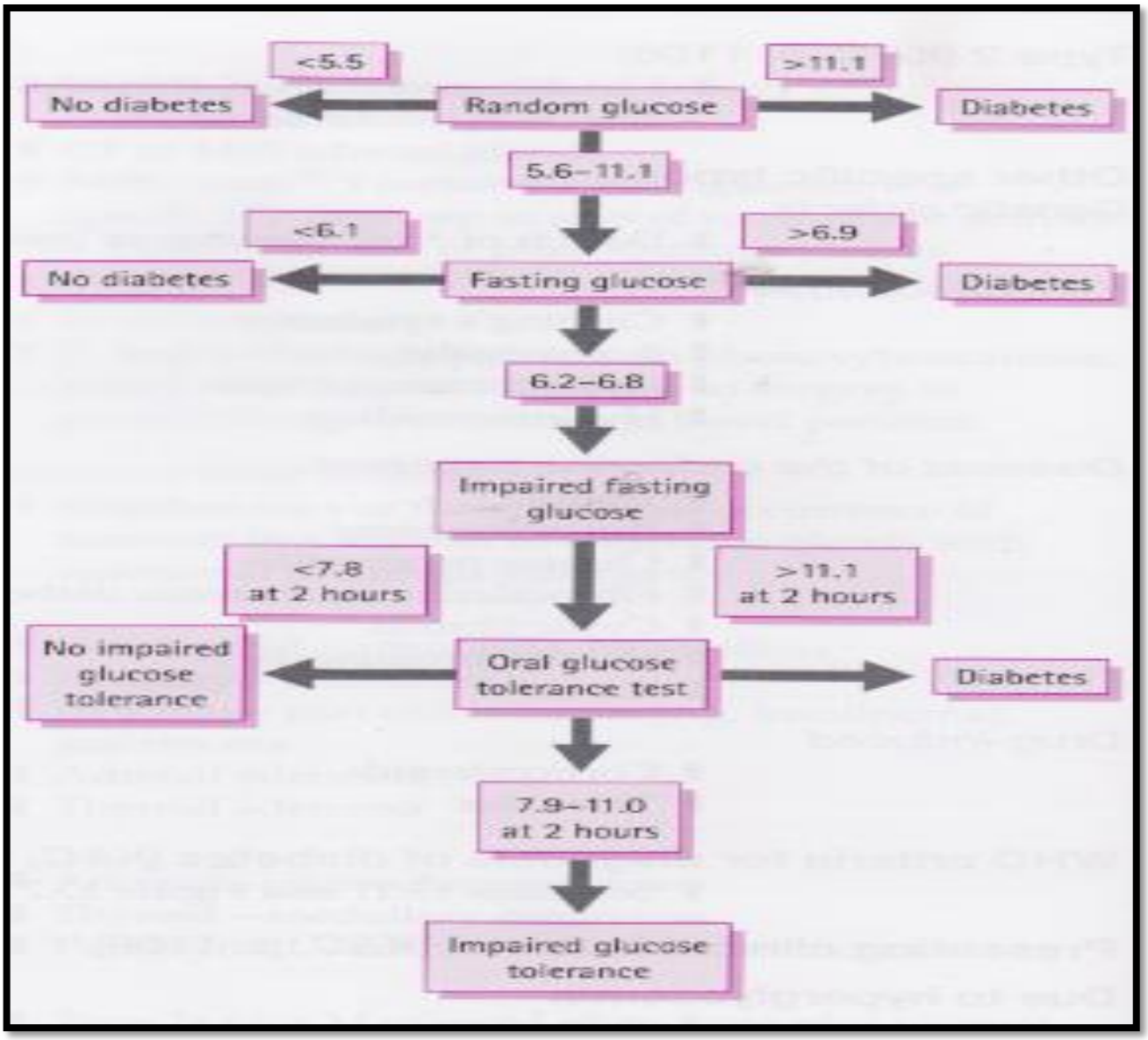
- If the result of the RBS is borderline, we do FBS to confirm = Specific.
- Above 7 mmol/L (126 mg/d/L) is diabetic.
- At least 2 readings are required & you rely on symptomatology + complications (polyuria, polydipsia, weight loss, blurring of vision, numbness…)

Oral Glucose Tolerance Test (OGTT):

- An oral glucose tolerance test (OGTT) is the **BEST TEST** to confirm the case and 1 reading is enough.
- That's why it's used in patients with risk factors (highly sensitive & specific).
- However, it's time consuming, requires trained staff and is more expensive. So, it's rarely required to confirm the Dx and SHOULD NOT be regarded as a 1st line investigation. (Must weigh things out properly)
- For an OGTT, we do a FBS when the patient comes, then give him a glucose load and measure again in 2 hours (you're basically covering 2 tests in 1).
- Above 11.1 mmol/L (200 mg/dL) is diabetic


FBS
High
Normal
FOR SURE pt is diabetic
MAYBE pt is normal


RBS
High
Normal
MAYBE pt is diabetic
FOR SURE pt is normal


<5.5
No diabetes
Random glucose
>11.1
Diabetes
5.6–11.1
<6.1
No diabetes
Fasting glucose
>6.9
Diabetes
6.2–6.8
Impaired fasting glucose
<7.8 at 2 hours
>11.1 at 2 hours
No impaired glucose tolerance
Oral glucose tolerance test
Diabetes
7.9–11.0 at 2 hours
Impaired glucose tolerance

MOST IMPORTANT TWO PRINICIPLES IN DM:

1- HbA1C:

- Glycated Hb - Result of the bond formation between the glucose and the Hb molecules. The rate at which this reaction occurs is related to the current glucose concentration. Glycated Hb is expressed as a percentage of the normal Hb(normal range 4–6.2%).
- This test provides an index of the average blood glucose concentration over the lifespan of the RBC (~ 6 weeks = 120 days). So if the HbA1C is high, then that means the pt was poorly controlled 3 months back.
- Used for rapid **ASSESSMENT OF GLYCEMIC CONTROL**
- It can be used for Dx because it's a sensitive test. If more than 6.5%>> maybe diabetic, so we have to challenge the pt (OGTT). [can go up to 16% in diabetics].
- The figure will be misleading if the lifespan of the RBC is reduced or if an abnormal Hb or thalassaemia is present.

Note:
We can actually take the patient's hair to check when has the peak of glycation exactly occurred to determine when have they developed diabetes.

2- Fructosamine:

- Glycated plasma proteins
- May also be measured as an index of control (compliance)
- Glycated albumin is the major component, and fructosamine measurement relates to glycaemic control over the preceding 2–3 weeks.
- Useful in patients with anaemia or haemoglobinopathy and in pregnancy (when haemoglobin turnover is changeable).

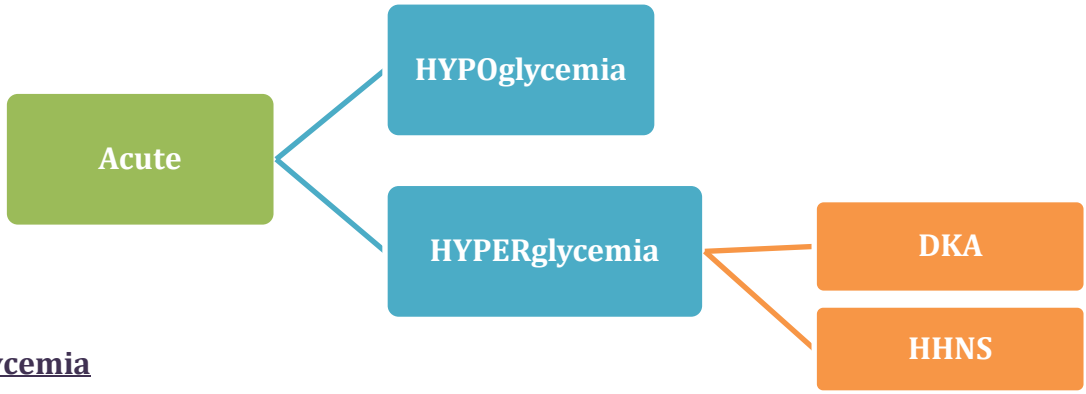
✓ Urine tests are NOT diagnostic of DM anymore

Extra:
The correlation between Urine Tests & simultaneous blood glucose is poor for these reasons:

- Changes in urine glucose lag behind changes in blood glucose.
- The mean renal threshold is around 10 mmol/L but the range is wide (7-13 mmol/L). The threshold also rises with age.
- Urine tests can give no guidance concerning BG levels below the renal threshold.

Average time between developing DM & Symptomatology:

COMPLICATIONS:



1] Hypoglycemia

- The commonest acute complication of DM
- Primary organ at risk is the brain because it uses glucose as a main source of energy >> Neuroglycopenic symptoms

2] Hyperglycemia

- **Diabetic Ketoacidosis:**

➢ Due to severe insulin deficiency in T1DM, the body starts to rely on fatty acids for energy instead of Kreb's cycle. This will result in the production of acetone (ketone bodies) which are very toxic to the brain, liver, cardiac muscle, etc… That's why the mortality in DKA is very high.

➢ The moment the patient arrives to the ER, they will be extremely dehydrated so we give insulin ASAP + IV lines.

➢ As soon as they're given the 1st dose, there will be switch off of FA energy production and switch on of Kreb's cycle. So acetone bodies will start to be eliminated through respiration & the kidneys.

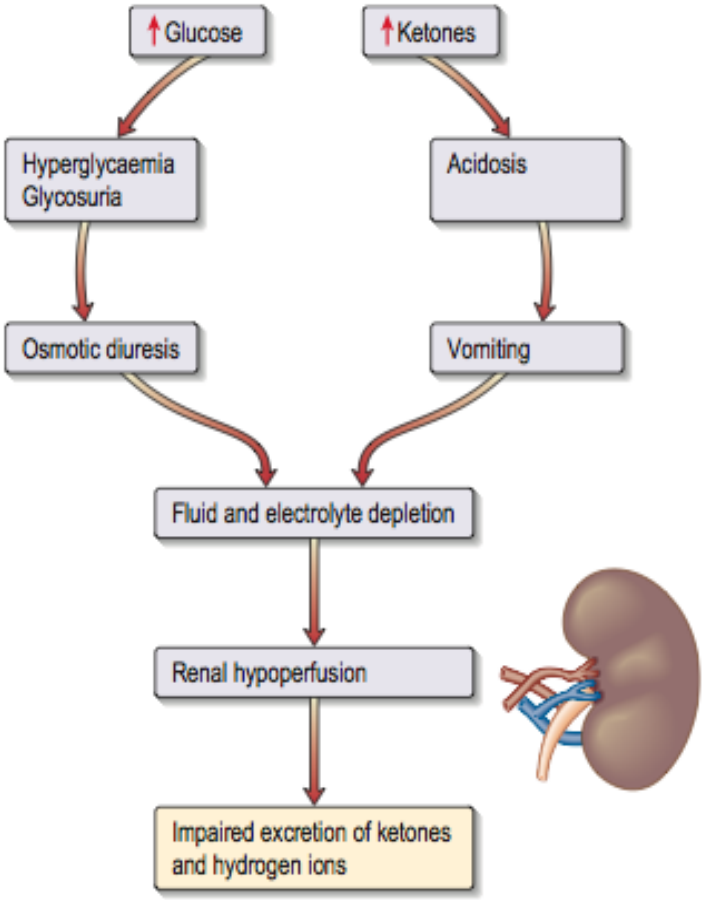
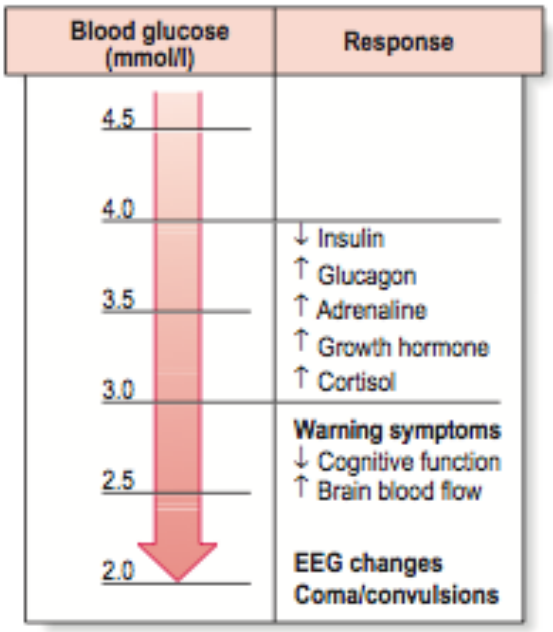


TABLE 1.4 Cardinal clinical features of diabetic ketoacidosis
• Marked polyuria and polydipsia
• Nausea and vomiting
• Dehydration
• Reduced level of consciousness
• Acidotic (Kussmaul) respiration

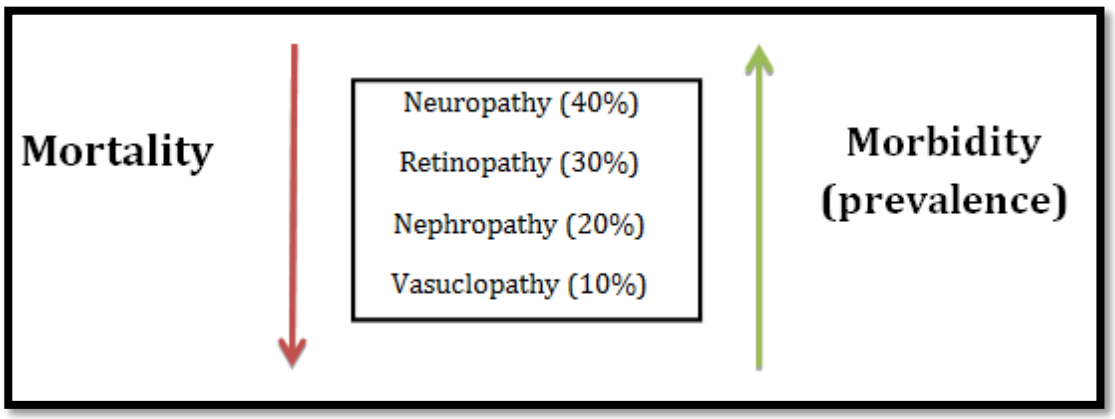
- **Hyperosmolar Hyperglyceminc Non-Ketotic Syndrome:**

➢ In T2DM patients, they are fighting for energy and their BS keeps going higher & higher until they reach a stage where they're going to have severe hyperosmolarity. This will lead to a lot of problems that are correlated to the high viscosity of blood (like honey flowing in your arteries). It has a very high mortality >> IHD problems – lactic acidosis…



	DKA	HHNS
Pathogenesis	Insulin deficieny > hyperglycemia, ketosis, acidosis, dehydration	Insulin deficieny > hyperglycemia, hyperosmolarity, profound dehydration
Lab Findings	Hyperglycemia (>250) Metabolic Acidosis (anion gap), serump pH < 7.3 Ketosis	Hyperglycemia (>600) Hyperosmolarity Serum pH > 7.3 (no acidosis)
Treatment	Insulin, IV fluids, Potassium	Aggressive IV fluids, Insulin

Chronic Complications:



✓ Chronic complications depend on the duration of uncontrolled glycaemic control.

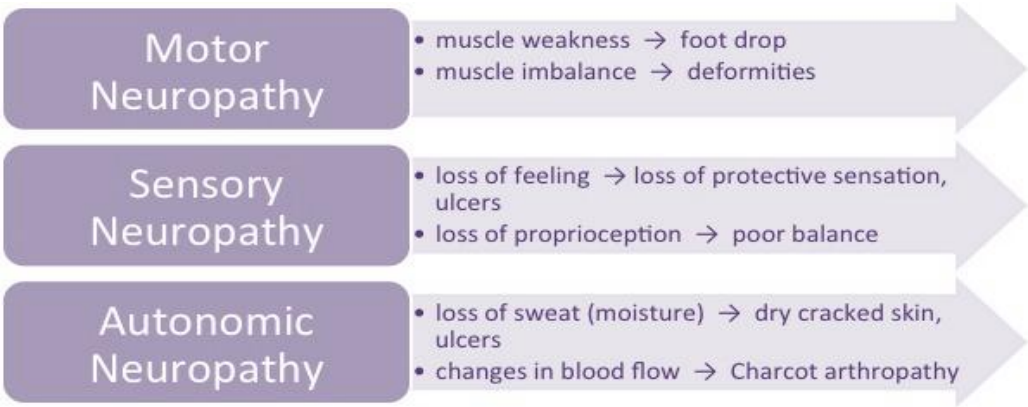
✓ DM → Leading cause of IHD, stroke, blindness, ESRF, dialysis & amputation.

Neuropathy:

- Neurons do not need insulin to take up glucose like the other cells. However, they ARE encircled by Schwann cells which DO need insulin to take up glucose.
- Schwann cells are responsible for insulation & fast conductance.
- Sugar from the blood enters into the nerve to give the nerve energy; this sugar, glucose, is converted into another sugar, called sorbitol (very viscid).
- When sorbitol is used up as energy, this will lead to sorbinil deposition.
- This will attract water molecules to be drawn into the nerve causing the nerves in a diabetic to be swollen.
- If a nerve swells in a place that is already tight, then the nerve becomes pinched, or compressed. [Tingling →Neuritis → Numbness = Very slow-progressing & very common].
- If the pt is not treated, he will lose the axon → loss of sensation.
- If you give insulin to the Schwann cell, it will switch off the Sorbitol pathway → Sorbinil will decrease → Swelling of Schwann cell will decrease → pt. will start to feel pain in his feet → a good sign indicating the pt. has regained sensation in his feet (pressure released off axon)
- If we didn't reach the stage of axon destruction, we can still treat the patient and use preventative measures. It's too late (irreversible) to intervene if the axon is cut (diabetic foot, ulcers = late stage).
- DCCT + UKPD: When you have your DM controlled, you can decrease the rate of neuropathy by more than 60%.

DCCT: Diabetes Control & complications Trial (T1DM)

UKPDS: United Kingdom Prospective Diabetes Study (T2DM)



Retinopathy:

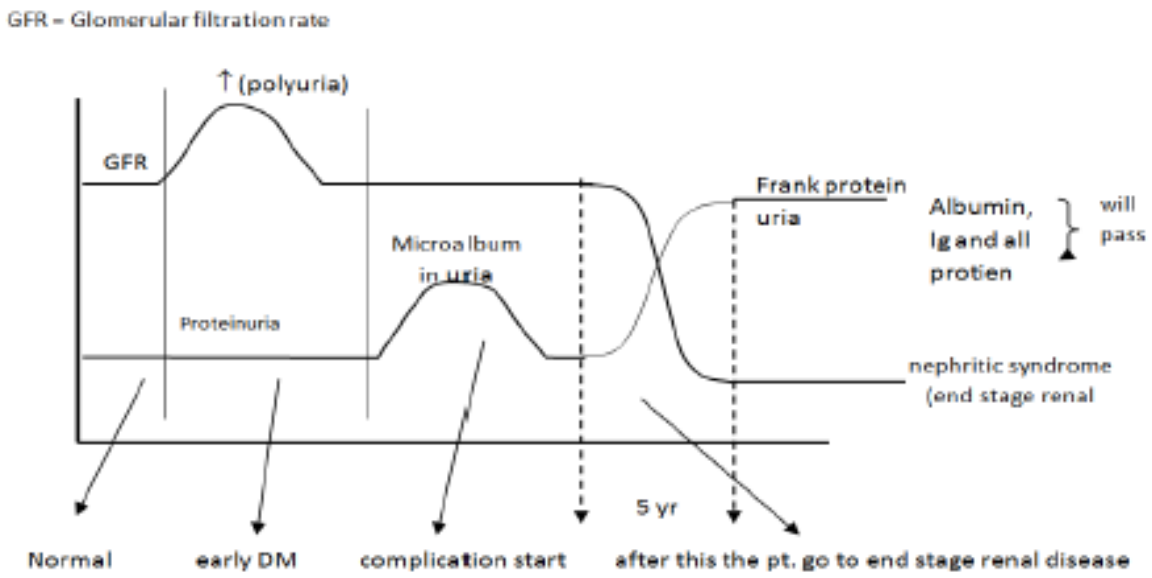
- The vessels come out of the optic disc branching out to different places in the retina
- Most active metabolic cells in the body are the Rods and Cons, even when sleeping → because they send millions of signals in fractions of a second (25-30% of your total energy is taken up by them = very high metabolic cell rate)
- Low insulin → Retina starts to form new blood vessels to supply itself with more blood , especially around the macula (neovascularization)→ these new branches of the Retinal artery will be providing the retina with more glucose & energy [Proliferative Retinopathy]
- However, these new blood vessels are fragile (lacking of endothelial tight junctions → prone to spontaneous bleeding). So any minimal trauma (head bump) can cause hemorrhage in the posterior chamber of the eye [Vitreous Hemorrhage]
- Bleeding → clot → fibrous band → pulls on retina → Retinal Detachment → blindness (4000-6000 pt/yr go blind due to DM in KSA)

Note: Retinal detachment Sx: Bright flashes of light, blurred vision, floaters in the eye, shadow or partial blindness.

- If the pt is still in the proliferative stage, we resort to laser therapy to cauterize the roots of the new vessels, thus, preventing them from bleeding out.
- If a pt presents with severe proliferative retinopathy and we control his DM, his disease can still be regressed. The irreversible point is retinal detachment.
- The DCCT & UKPDS both demonstrated that intensive glycaemic control reduces the risk of onset of diabetic retinopathy (by ~40%), progression of pre-existing ones and the need for laser for pts with T1DM (DCCT) & T2DM (UKPDS).

Nephropathy:

- The basement membrane is responsible for filtration.
- Leakage of proteins → microalbuminuria (MA) → fibrosis on bowman's side → bigger pores → proteinuria → overt proteinuria (nephrotic syndrome) → complete fibrosis → glomerular sclerosis → Renal Failure
- First, GFR will start to increase in DM because there's polyuria & polydipsia. Then it goes back to normal.
- After a while MA will occur → ACEIs and dietary modification should be started at this stage.
- The chronic albumin leakage from Bowman's capsule will lead to bigger pores (fibrosis). The pt will start to have overt proteinuria which leads to the decrease in GFR. (This takes up an average of 5-7 yrs to develop)
- Screening for Diabetic Nephropathy by MA (very sensitive): If +ve → we start dietary modification & ACEIs.
- We can delay the disease almost 15 years by ACEIs → thus preventing Renal Failure
- If they reach proteinuria, usually not much can be done
- When the patient starts to develop renal failure, they're put on dialysis. (1/3 billion SR/yr – 8000 pts/yr → very costly)
- Strong correlation between retinopathy & nephropathy. That's because if tight glycaemic control is attained, both cases will improve.



Vasculopathy:

- CAD: (11%)
  - Main problem (commonest) → highest mortality
  - CABG, Stents
  - 20,000 die every yr from CAD due to DM
- CVD: (7%)
  - It will compromise the pt (strokes)
  - Manifests as amnesia, cranial nerve disease…
  - Medical Rx
- PVD: (2%)
  - Patient complains of foot gangrene (Pain → Discoloration → Bluish black)
  - Bypass (can't do anything else at that stage)

Management: [Principles of therapy = Diet + Exercise]

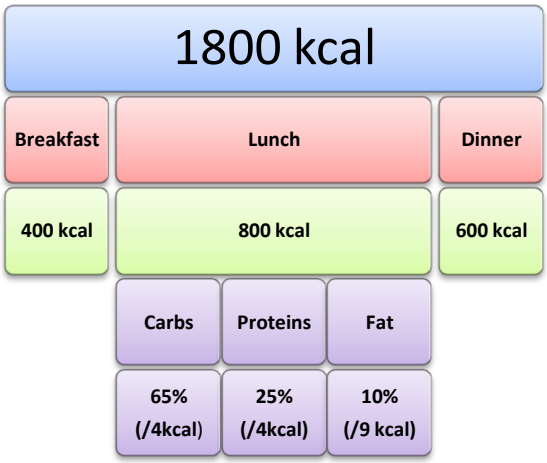
- Educating patients
- Self-assessment of glycemic control

Exercise:

- Due to the high levels of FAs in obesity, the muscles are desensitized to insulin → increasing insulin resistance
- This can be undone with exercise which will make the muscles more sensitive to insulin → decreasing insulin resistance
- Walking decreases HbA1C by 1% (better than most meds)

Diet:

- In order to calculate the daily calorie intake needed for a person, we need to know their body weight first because it will change accordingly.
- If a person is in their ideal BW, we count up30 kcal/kg/day.
- If we divide the average daily requirement to 3 meals and divide it accordingly, taking in consideration the patient's "main meal", lunch in this example, we'll have:
  - Breakfast: 400 kcal
  - Lunch: 800 kcal
  - Dinner: 600 kcal
- If we took up each meal (eg: lunch)and broke it down to 3 different portions for C, P & F to prepare a healthy diet, we'll have:
  - 65% for carbohydrates
  - 25% for proteins
  - 10% for fat
- Next, you have to know the calorie yield for each main nutrient:
  - Each gram of carbohydrates yields 4 kcal/gram
  - 1 gm of proteins yields 4 kcal/gram
  - 1 gm of fat yields 9 kcal/gram



- Now, you'll be able to direct your patient to a diabetic diet by dividing the calorie percentage for each nutrient by the calorie yield index.

Extra

About the DCCT & the UKPDS:

- The DCCT in the USA compared standard and intensive insulin therapy in a large prospective controlled trial of young patients with type 1 diabetes. Despite intensive therapy, mean blood glucose levels were still 40% above the non-diabetic range, but even at this level of control, the risk of progression to retinopathy was reduced by 60%, nephropa-thy by 30% and neuropathy by 20% over the 7 years of the study. Near-normoglycaemia should, therefore, be the goal for all young patients with type 1 diabetes. The unwanted effects of this policy include weight gain and a two- to three-fold increase in the risk of severe hypoglycaemia. Control should be less strict in those with a history of recurrent severe hypoglycaemia.
- The UKPDS compared standard and intensive treatment in a large prospective controlled trial of type 2 diabetes patients. There was a 25% overall reduction in microvascular disease end-points, a 33% reduction in albuminuria and a 30% reduction in the need for laser treatment for retinopathy in the more intensively treated patients. This study also showed blood pressure control to be equally necessary in the prevention of retinopathy. However, a recent UKPDS study shows that good blood pressure control needs to be continued to maintain the benefits (i.e. there is no 'legacy'effect). There appeared to be little difference in outcome between the agents used to achieve good metabolic control (metformin, sulphonylurea or insulin). Intensive blood pres-sure control very considerably reduced the cardiovascular risk.

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