PHC

432 Team

19 TBL: Diabetes

Done By:
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Objectives

Not given ☹

N.B: Doses are mentioned in the slides, you're not required to know them but if you want, you'll find them there

Classifications:

Type 1 Diabetes: absolute insulin deficiency - destruction of beta cells (autoimmune or other causes)

Type 2 Diabetes: insulin resistance with relative insulin deficiency – account for 90% diabetic patients

Gestational: develop after 30 weeks of gestation

Other types: complications of Cushing's, cystic fibrosis, drugs etc.

Type 2 Diabetes

Prevalence:

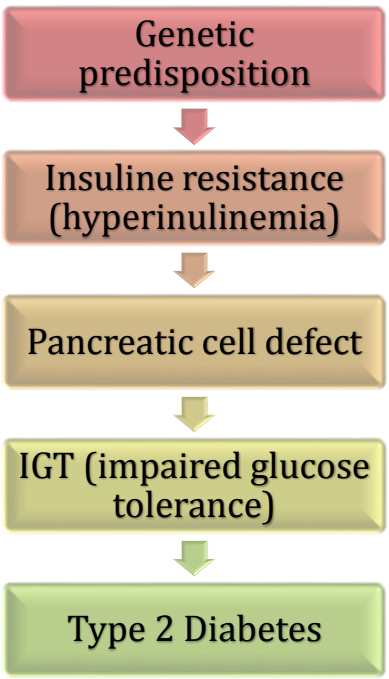
- A community based study of 17232 subjects conducted between 1995 and 2000 in KSA.
- The examining age group, 30-70 years of selected households during 5-year period
- The overall prevalence of DM obtained from this study is 23.7% in KSA.
- The prevalence in males and females were 26.2% and 21.5% respectively ($p<0.00001$).
- A large number of diabetics 1116 (27.9%) were unaware of having DM.

Stages of developing diabetes type 2:

First, those who are *genetically* prone to DM will have *insulin resistance*. Compensating to it, pancreatic cells will produce more and more insulin (hyperinsulinemia), those cells get *exhausted* with time and insulin level starts to drop → *impaired glucose tolerance*; if not controlled → *Diabetes*

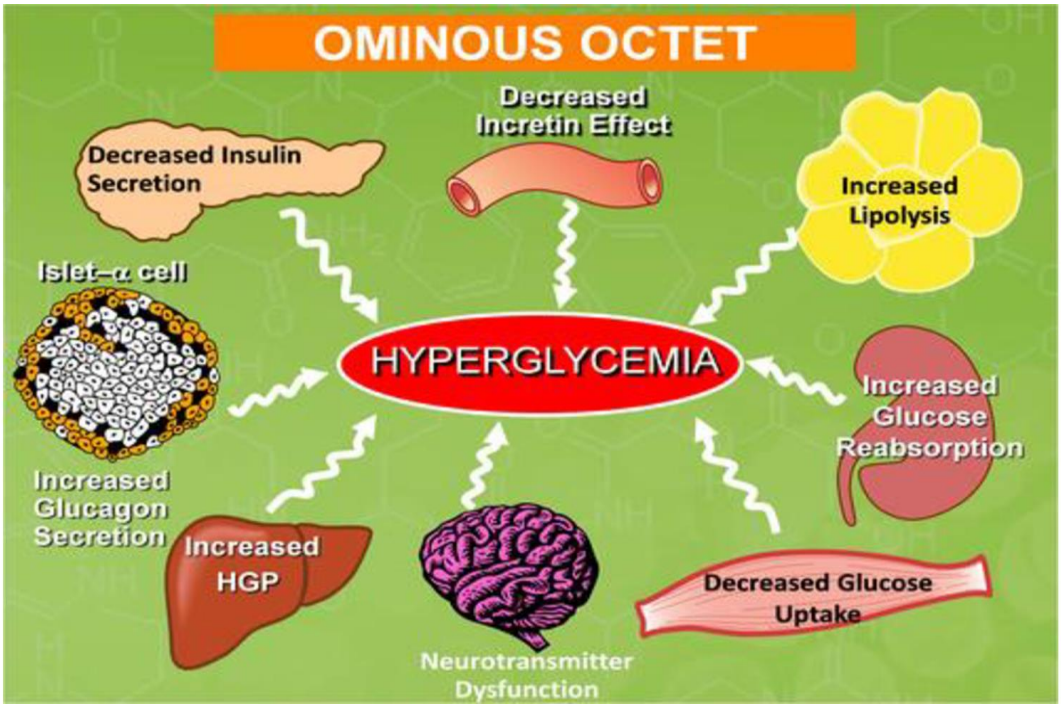
Yet, it's a *multifactorial* disease.

At the time of diagnosis, 50% of β cell are not functioning. (Insulin deficiency)



Pathophysiology:

Ominous octet (ثمانيّة)



HGP: hepatic glucose production (increased because of insulin resistance)

Muscles: because of insulin resistance

Kidney (some new drugs can be given to increase glucose secretion)

Lipolysis: because of increase insulin resistance

In intestine: after eating carbs, L cells secrete GLP1 which work for 2-3 minutes and then get degraded by DPP (drugs can be used to block the action of DPP – *DPP4 inhibitors* – and prolong GLP1 – *GLP1 analogue* –) Incretin exogenous GLP1 actions: (pancreas stimulate insulin, inhibit glucagon secretion, delayed gastric emptying, brain feeling full) → weight loss.

Diagnosis: *(very important)*

Test	Prediabetes	Diabetes
FPG (fasting plasma glucose)	100 – 125 mg/dL (5.6 – 6.9 mmol/L) Impaired fasting glucose – **IFG**	≥126 mg/dL (7.0 mmol/L). fasting is defined as no caloric intake for at least 8 h
2-h PG (post-prandial glucose)	140 – 190 mg/dL (7.8 – 11 mmol/L) Impaired glucose tolerance – **IGT**	≥ 200 mg/dL (11.1 mmol/L) during an OGTT **?**. The test should be performed by using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.
A1C	5.7 – 6.4% (39-46)	≥6.5% (48 mmol/mol)
		Only one of the previous test is enough: symptomatic patient: one reading is enough asymptomatic: repeat the test, 2 positive readings are diagnostic

*additional way to diagnose Diabetes:

RPG (random plasma glucose)	In a patient with classic symptoms, one reading of ≥200 mg/dL (11.1 mmol/L) is diagnostic

- One repeating each test the possibility to get different results:
  - Fasting variability 7%
  - 2-h variability 50%
  - A1C is the less variable Less variable
- You can memorize both values: mg/dL and mmol/L ***or*** memorize one of them and know the formula: mmol/L × 18 = mg/dL

Screening:

Table 2.2—Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in all adults who are overweight (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) and have additional risk factors:
   - physical inactivity
   - first-degree relative with diabetes
   - high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - women who delivered a baby weighing >9 lb or were diagnosed with GDM
   - hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L) Dyslipidemia
   - women with polycystic ovary syndrome
   - A1C ≥5.7% (39 mmol/mol), IGT, or IFG on previous testing
   - other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
   - history of CVD
2. For all patients, testing should begin at age 45 years.
3. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly) and risk status.

- 2-h PG is the best for screening but you should do them all
- Symptoms appear when there is glucotoxicity (FPG is above 200, 2-h PG above 250, A1C above 9) Glucose is high in blood but cells can't benefit → Cell start to metabolize fat → weight loss and other symptoms appear. The benefit of screening is to prevent this.

Management:

1. **Prediabetes:** high risk to develop DM within few years

- Should be counseled on lifestyle changes.
- large studies of lifestyle intervention has shown sustained reduction in the rate of conversion to type 2 diabetes:
  - 43% reduction at 20 years in the Da Qing study.
  - 43% reduction at 7 years in the Finnish Diabetes Prevention Study (FDPS).
  - 34% reduction at 10 years in the U.S. Diabetes Prevention Program Study (DPPS) .
  - **Metformin** should be the choice of drug considered.

- In addition to lifestyle counseling, Metformin is considered in IFG plus:
  - Hypertension
  - Low HDL cholesterol
  - Elevated triglycerides
  - Family history of diabetes (first-degree relative)
  - Obese
  - HX of GDM
  - Under 60 years of age
- Other drugs: pioglitazone, acarbose)
- Follow up each year

2. Diabetes

General principles:

- Diabetes management is a team work
- Individualize management
- Set Target goals

Glycaemic Targets	BP goals	Lipid goals

- Education (important to explain the progress of the disease)
  - Is associated with increased use of primary and preventive

1. Physical examination *(imp.)* *remember to screen for **microvascular** complications*

- Height and Weight (BMI)
- Blood Pressure (2 readings)
- Fundus Examination *(refer to ophthalmologist at the time of diagnosis, findings: Hard and soft exudates, new vessel formation, macular oedema….)*
- Cardiac examination
- Lower Limbs:
  - Skin Examination
  - Evaluation of pulses
  - Foot Examination *(Important in each visit)*
  - Neurologic Examination: monofilament test, if impaired then it is a stage before foot ulcer

2. Laboratory findings
    - FPG and 2-h PG
    - HbA1C (every 3 months for not controlled patients and on insulin / every 6 months for controlled)
    - ECG
    - Chest X-Ray
    - Lipid Profile (total cholesterol, LDL, HDL, and triglycerides)
    - Midstream Urine (for Ketones, protein, pus cells, etc)
    - Urea and Creatinine
    - Test for Microalbuminuria or Albumin to creatinine ratio / 24 hr urine collection for protein / Creatinine Clearance

3. Follow up – yearly check up:

› Investigations:

- HbA1C
- Urea and Creatinine
- Lipid Profile (Cholesterol, Triglyceride, LDL-C and HDL-C)
- **Albumin to creatinine ratio** (best) / 24 hour urine collection for protein (*Microalbuminuria 30 -299 mg, while Macroalbuminyria ≥ 300 mg*).

› Examination:

- Eye: Fundus Examination / eye referral
- Feet: Visual inspection and Neurovascular status

3. Medication (VERY VERY IMPORTANT)

› ***First, set a goal of your treatment:***

Current Treatment Goals for Glycemic Control: these are the goals you're aiming to reach when treating a diabetic patient

	American diabetes association (ADA) recommends:	**American College of Endocrinology (ACE) recommends:**
HbA1c	< 7.0% *(general goal)*	≤ 6.5%
Pre-prandial plasma glucose	70–130 mg/dL (3.9–7.2 mmol/L)	< 110 mg/dL (< 6.1 mmol/L)
Post-prandial plasma glucose	< 180 mg/dL (< 10.0 mmol/L)	< 140 mg/dL (< 7.8 mmol/L)

You only need to memorize *ADA recommendations.*

The goal is not appropriate or practical for some patients, and clinical judgment has to be applied for every patient. Factors such as life expectancy, risk for hypoglycemia, and the presence of cardiovascular disease need to be considered for every patient. (Individualize your treatment according to your patient. E.g. patient at risk of hypoglycemia, you can accept an HgA1c of 8%, or you can't accept a pre-prandial of 70 it should be higher).

Hypoglycemia in elderly, increase risk of MI

› **Second, choose the appropriate drug, or combination of drugs , again according to your patient:**

1. ***Oral drugs:***

A. Metformin *(1st and permanent choice always)*

› Features:

- Effective & well validated therapy
- Choice as initial therapy
- No hypoglycemia and mild weight loss

› **Mechanism of action**

- Mainly: Acts by reducing hepatic glucose production (gluconeogenesis)
- Other: Reduces appetite & may delay absorption, improves peripheral insulin sensitivity (hence sensitizer) → increase glucose uptake

› **Side effects :** B12 deficiency , GI disturbance , lactic acidosis.

› **C/I:** renal impairment because it can cause lactic acidosis. In this case calculate creatinine and GFR (less than 30 stop it).

› Start with 500 mg once or twice per day with meals and increase every few days until reach maximum dose of 2 gm per day.

Advantages	Disadvantages
▪ Oral	▪ GI disturbance
▪ Low cost	▪ B12 deficiency
▪ Decrease macrovascular complications?	▪ Lactic acidosis
▪ Decrease hepatic gluconeogenesis	▪ Contraindications
▪ Once daily dosing	

acarbos: good safty profile but GI, (acarbose is good with those having impaired post prandial cause it prevent absorption of glucose)

B. Sulphonylureas *(mechanism of action: increase secretion of insulin)*

Medications: Glibenclamide, Glipizide, Glimepiride, Gliclazide

Advantages	Disadvantages
▪ Oral	▪ Hypoglycaemia
▪ Low cost	▪ Weight gain
▪ Decrease microvascular complications	▪ β-cell failure?
▪ Once daily dosing	▪ CV risk?

C. Thiozolidinediones (TZD): **PIOGLITAZONE**

› Features:
- Used in combination with metformin and sulphonylurea
- Not preferred to be combined with insulin because both cause fluid retention → heart failure, still can be used with cautions
- Periodic monitoring of liver enzymes

› **Mechasnim of action:**
- Reduce insulin resistance (increase sensitivity) → promotes glucose uptake by skeletal muscles and adipose tissue, inhibits hepatic gluconeogenesis

› **Side effects:**
  - Osteoporosis (fractures), fluid retention, weight gain, slow effect may be after 2 months yet very strong

› **C/I:**
  - Not given in patients with heart failure (because of fluid retention)

Advantages	Disadvantages
▪ Target insulin resistance	▪ Fluid retention/CCF
▪ β-cell preservation?	▪ Weight gain
▪ Vascular protection?	▪ Bone fractures
▪ Decrease hepatic gluconeogenesis	▪ Bladder cancer?
▪ Once daily dosing	▪ Costly

1. ***Injections:***

A. Incretins: *good safety*

GLP1: *(drugs **mechanism of action** mimics the normal enzymes)*

› Secreted throughout the day by intestinal mucosa in response to oral glucose in the gut.

› Causes anabolic actions on the synthesis of insulin in beta cells by stimulating all steps of **insulin biosynthesis.**

› Provides continued and augmented release of insulin for secretion in response to glucose *without overproduction that could lead to hypoglycemia.*

› Acts on islet alpha cells, causing strong **inhibition** of postprandial **glucagon secretion**.

› Slows gastric emptying and acts on brain to promote early satiety with reduced food intake.

› Within minutes of secretion or exogenous administration, GLP-1 is rapidly degraded by ***dipeptidyl peptidase-4*** (DPP-4).

DPP-4: found in many body tissues, including liver, renal, and intestinal brush- border membranes; lymphocytes; and endothelial cells.

- *The incretin system is **impaired** in patients with **T2DM**, which, as a consequence of its insulinotropic actions, contributes to both **fasting and postprandial hyperglycemia.***
- *The impairment of **GLP-1** secretion varies directly with the degree of insulin resistance; those who are **more insulin resistant** have a lower rise in **GLP-1** in response to a meal.*

GLP-1 analogue: Liraglutide (subcutaneously once daily)	**DPP-4 inhibitor: Sitagliptin** (*Januvia*), Vildagliptin, Saxagliptin
› For overweight / obese type 2 patients › Combined with Metformin +/- Pioglitazone › GLP-1 exogenous more powerful reduction of A1C by 1.5%	› Type 2 diabetes only › **Monotherapy** or with Metformin or TZD › Weight neutral › Does not cause hypoglycemia
› Side effect: GI disturbance + sever nausea, weight loss, lower BP, increase heart rate › C/I: pancreatitis, pancreatic carcenoma › Choose according to: A1c, BMI, etc.	

GLP-1 analogues

Main advantages	Main disadvantages
Low risk of hypoglycaemia	Injection required
Weight loss	Limited long-term clinical experience at present
Lower blood pressure	Antibody formation (significance?)
CVD protective?	Link to pancreatic/medullary C-cell cancer and pancreatitis?
	Expensive

DPP4 –inhibitors

Main advantages	Main disadvantages
Low risk of hypoglycaemia	Limited long-term clinical experience
Weight neutral	Pancreatitis/Pancreatic Ca?
No drug interactions	Expensive
Fixed dose combinations with Metformin available	Heart Failure?

B. Insulin

- Powerful agent
- Necessary in 20-30% of patients
- Inexpensive
- High level of patient fear (they don't prefer insulin)
- Side effect:
  - Weight gain
  - Hypoglycaemia
  - Fluid retention

Indication:

C. If HbA1c is ≥ 9% (you can start at anytime, but if A1c ≥ 9 then you have to. after reduction you can stop it)

D. After **maximum metformin** and **suphonylurea**

E. You should consider adding **Insulin** and taper the Sulphonylurea.

Insulin in our body is secreted in 2 patterns:

- basal each 10-15 minutes to control blood sugar
- After meals: post prandial

Drugs are working same way:

- **Rapid acting**: start within 5 mins and last for 5 hours (for post prandial) e.g. Lispro /Aspart
- **Regular**: start within 30 mins
- **Background** long acting insulin: start after 1-5 h, e.g. NPH, Levemir (twice daily) Lantus/glargine (once daily) can't be combined with

Treatment regimens:

a. Conventional Insulin Therapy
   - Two injections per day of NPH and Regular Insulin

b. Mixed Insulin
   - Two injections per day of 70/30 or 60/40 or 50/50 (ratio between long and short acting insulin mixed together in **one injection**, taken twice daily after large meals to control both basal and post-prandial blood sugar)

c. Multiple Insulin Injections
   - 1 or 2 injections of NPH plus 3 injections of Regular or Rapid Insulin.
   - One injection of Glargine or Detemir plus 3 injections of rapid insulin (Lispro /Aspart).

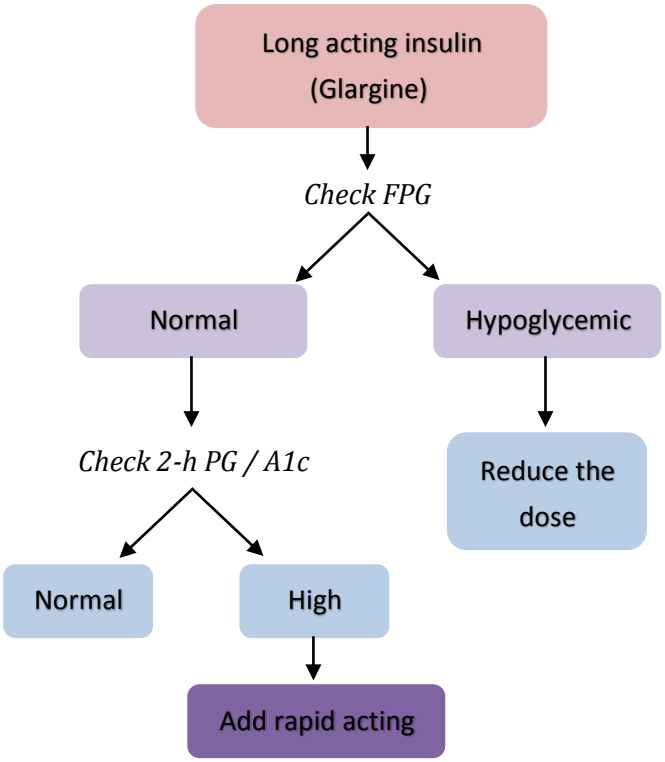
Insulin glargine (lantus) alone	Glargine with Lispro
• The first clear long-acting insulin • Acidic (pH of 4) when injected it is neutralized by the body, causing Glargine crystals to be precipitated and slowly absorbed. • It is taken *once a day* • Being acidic, cannot be mixed with other insulin	• Avoids fasting hyperinsulinaemia and hypoglycemia • Can mimic pancreatic ß-cell insulin secretion • 36% had hypoglycemia vs 50% on NPH. • Dose: Glargine 50% and Lispro 50%

Guide on how to use insulin

1. Give a long acting insulin (Glargine) at bedtime 10 U or 0.2 U/Kg
2. Check FG regularly, increase the dose by 2 U every 3-4 days until FG 80 – 130 mg/dl
3. If hypoglycaemia occurs, or FG < 70 mg/dl reduce bedtime by 4 units or 10 % which is greater.

If FG in range, check 2 hrs after breakfast, lunch and dinner and add rapid (Aspart) insulin. Begin with 4 U before each. Adjust by 2 U every 3-4 days Untill 2hpp < 180 mg/dl.

Usually the dose of rapid insulin is near equal or higher than the long acting insulin.



Administration

- *Do not mix Glargine with other insulin products.*
- Insulin site should be clean, but wiping with alcohol is not needed.
- Syringe reuse acceptable but with meticulous attention
- Cleanliness is needed.
- Insulin pens improve the dose accuracy.
- Injection site rotation reduces the lipoatrophy.
- Abdomen region has a faster absorption rate than the Arm, which is faster than the leg.

Summary of drugs contraindications

Chronic Kidney Failure	Metformin, Acarbose,Sitagliptin, Insulin & SUs (reduced dosage)
Heart Failure	TZDs
Osteoporosis:	TZDs
Myocardial Infarction	Hypoglycemias should be avoided when Insulin or SUs are taken.
Elderly people (>70 years)	Hypoglycemias should be avoided when Insulin or SUs are taken.

Type 2 Obese Patients

- Exercise and Diet control
- Bariatric Surgery for BMI ≥ 35
- First choice: Metformin 2- 2.5 gm per day
- Second choice: if still not controlled, Add Pioglitazone 15 -30 mg
- Third choice:
  a. Liraglutide 1.2 mg or (3 mg) SC daily (First choice)
  b. Basal / Bolus Insulin (this will lead to increase in weight)

Next topics are included in the slides but the doctor skipped them, maybe because of the lack of time! Yet go through them just incase

Antiplatelet agents

- Consider **Aspirin** therapy (75–162 mg/day) as a **primary prevention** strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk 10%).
- This includes most **men 50 years** of age or **women 50 years** of age who **have at least one additional major risk factor** (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria).

Statins and Diabetes

- Diabetics < 40 years with no CV risk factors, No statin.
- Statin therapy should be added to lifestyle therapy, for diabetic patients with no additional atherosclerotic CV disease risk factors 40-75 years (**A**) and < 40 years (**B**).
- For patients with diabetes aged 40–75 years with additional atherosclerotic cardiovascular disease risk factors, consider using high-intensity statin and lifestyle therapy. (**B**)
- The addition of **Ezetimibe** to moderate-intensity statin has been shown to provide additional CV benefit compared with moderate-intensity statin alone and may be considered for patients with a recent acute coronary syndrome with LDL cholesterol > 50 mg/dL (1.3 mmol/L) or for those patients who cannot tolerate high intensity statin therapy. (**A)**

(IMPROVE-IT)

Table 8.1—Recommendations for statin and combination treatment in people with diabetes

Age	Risk factors	Recommended statin intensity*
<40 years	None	None
	ASCVD risk factor(s)**	Moderate or high
	ASCVD	High
40–75 years	None	Moderate
	ASCVD risk factors	High
	ASCVD	High
	ACS and LDL cholesterol >50 mg/dL (1.3 mmol/L) in patients who cannot tolerate high-dose statins	Moderate plus ezetimibe
>75 years	None	Moderate
	ASCVD risk factors	Moderate or high
	ASCVD	High
	ACS and LDL cholesterol >50 mg/dL (1.3 mmol/L) in patients who cannot tolerate high-dose statins	Moderate plus ezetimibe

*In addition to lifestyle therapy.
**ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, overweight and obesity, and family history of premature ASCVD.

Statin and Fibrate

- Statin and Fenofibrate may be considered for men with both triglyceride level ≥ 204 mg/dL (2.3 mmol/L) and HDL cholesterol level < 34 mg/dL (0.9 mmol/L). (**B**)
- Combination therapy (statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone and may increase the risk of stroke and is not generally recommended. (**A**)

Vaccination

- Influenza vaccine (yearly)
- Pneumococcal vaccine (once in lifetime)

Targets in DM

- *BP < 140 / 90*
- *HbA1C ≤ 7 % (European Diab. Soc. ≤ 6.5 %)*
- *LDL-C < 100 mg/dl (2.6 mmol/L)*
- *HDL-C > 40 mg/dl (males), > 50 mg/dl (females)*
- *TG < 150 mg/dl (1.7 mmol/L)*
- Mixed z: NPH 70% + regular 30% (twice daily) before main meals
- When you use rapid + long Stop all medication except metformin
- Long acting minimal dose if FPG less than 30 continue, if not inc the dose
- If less than 30 with A1c high, problem is post prandial, add rapid and after 2 injection stop all drugs except metformin

Don't forget to go through the already distributed MCQ.. good luck ☺

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