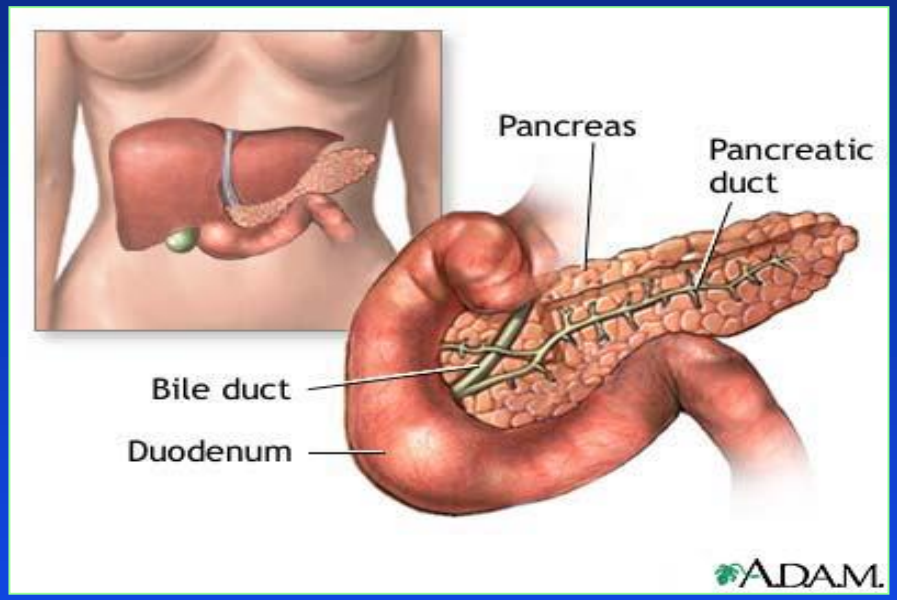
Diabetes Mellitus



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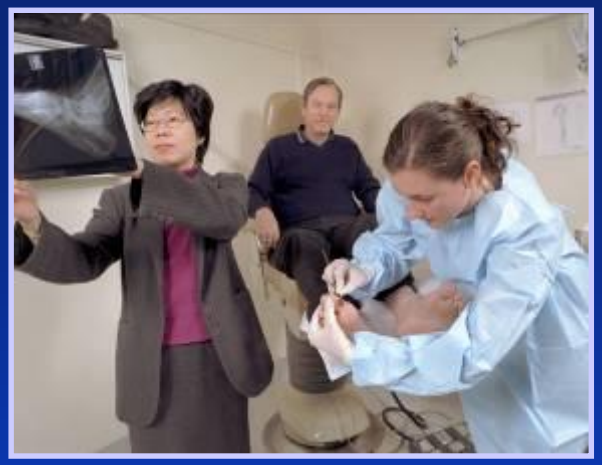
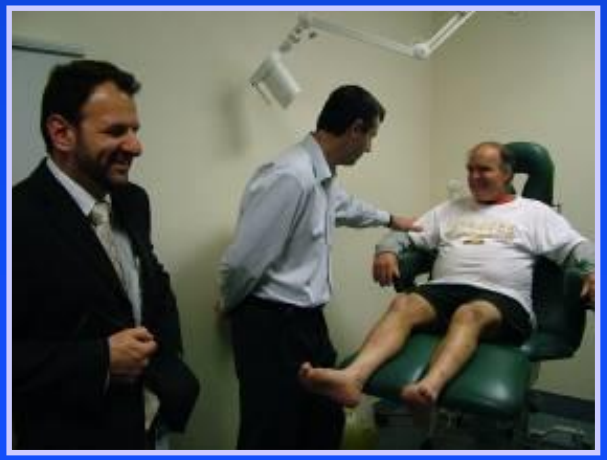
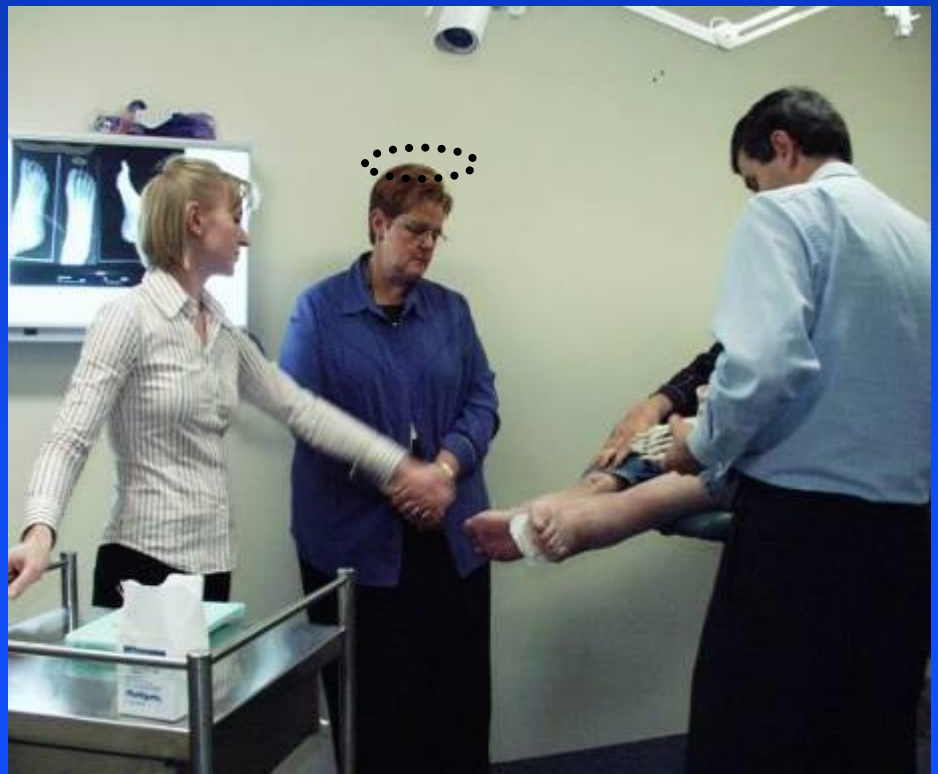
The Burden and Complexity of Diabetes







Burden of Diabetes

- The development of diabetes is projected to reach pandemic proportions over the next10-20 years.
- International Diabetes Federation (IDF) data indicate that by the year 2025, the number of people affected will reach 333 million –90% of these people will have Type 2 diabetes.
- In most Western societies, the overall prevalence has reached 4-6%, and is as high as 10-12% among 60-70-year-old people.
- The annual health costs caused by diabetes and its complications account for around 6-12% of all health-care expenditure.

Diagnosis of Diabetes Mellitus

Diagnosis

For nonpregnant individuals of any age, diagnosis of diabetes can be made when one of the following is present:

- Classic signs & symptoms + random plasma glucose≥ 200mg/dl
- FPG ≥ 126mg/dl
- Following std oral glucose challenge (OGTT): PG≥ 200mg/dl at 2 hrs.
- A1c≥ 6.5%

The diagnosis must be confirmed on a subsequent day

Diabetes

- Earliest abnormality:

  postprandial hyperglycemia

- Fasting hyperglycemia:

  80-90% reduced β cell mass

Clinical Presentation

• Type 1 DM

- Polyuria
- Polydipsia
- Polyphagia
- Weight loss
- Weakness
- Dry skin
- Ketoacidosis

• Type 2 DM

- Patients can be asymptomatic
- Polyuria
- Polydipsia
- Polyphagia
- Fatigue
- Weight loss
- Most patients are discovered while performing glucose screening

Pregnancy

Recommendations: Detection and Diagnosis of GDM

- Test for undiagnosed T2DM at the 1st prenatal visit in those with risk factors. B
- Test for GDM at 24–28 weeks of gestation in women not previously known to have diabetes. A
- Screen women with GDM for persistent diabetes at 4–12 weeks postpartum, using the OGTT. E

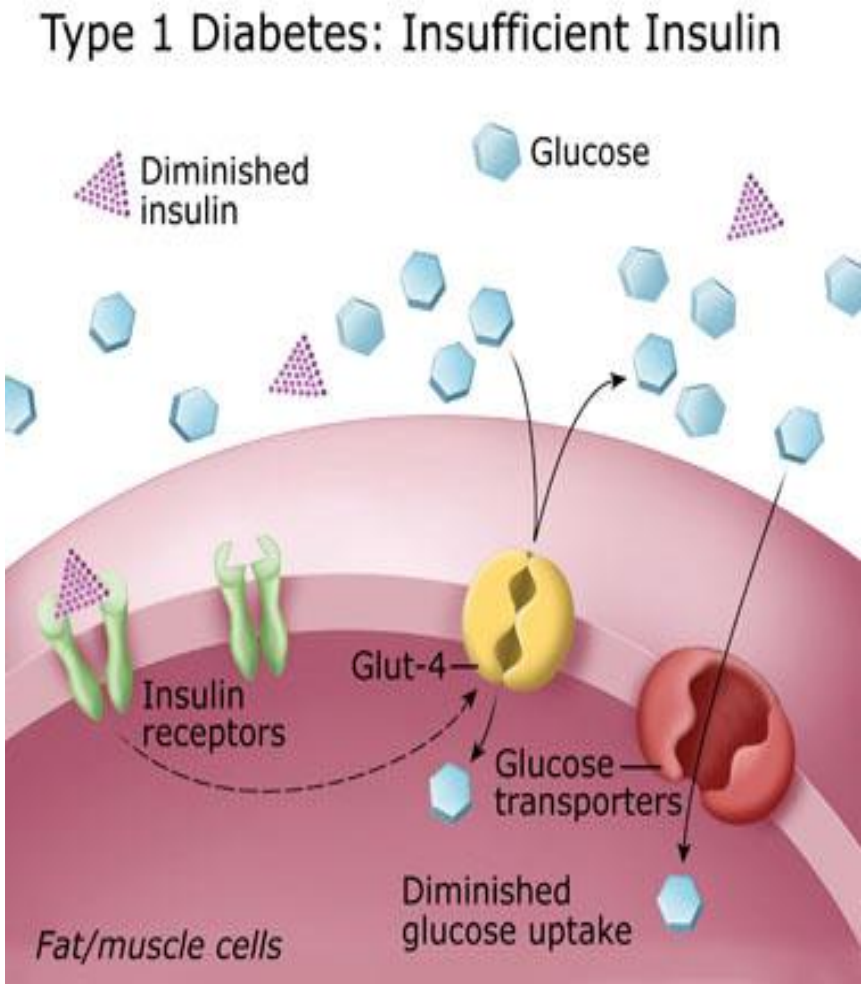
Pregnancy

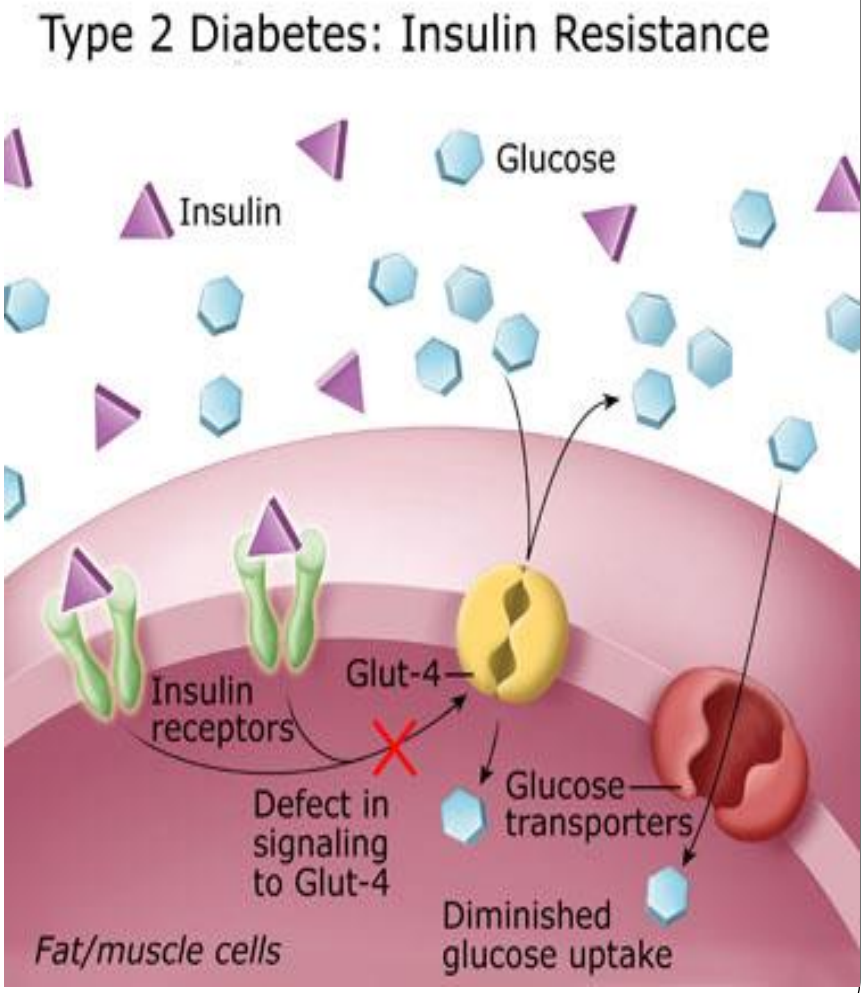
Criteria for very high risk:

- Severe obesity
- Prior history of GDM or delivery of large-for-gestational-age infant
- Presence of glycosuria
- Diagnosis of PCOS
- Strong family history of type 2 diabetes

	Fasting	2hr	A1C
Normal	<100	<140	
Impaired glucose tolerance		140-200	5.7-6.4%
Impaired fasting glucose	100-125		5.7-6.4%
Diabetes (nonpregnant)	≥126	≥200	≥6.5%

Type 1 or Type 2 ?





Characteristics	Type 1	Type 2
Percentage	5-10%	90%
Age at onset	usually<30 yrs	usually>40 yrs
Pancreatic func.	Usually none	Low, NRL or high Insulin
Pathogenesis	HLA types, ICA	Defect in Ins secretion, tissue resistance, ↑hepatic glucose output
Family history	usually not strong	Strong
Obesity	Uncommon	Common(60-90%)
Ketoacidosis	Often	Rare
Clinical presentation	Moderate to severe	Accidentally diagnosed

Special Situations

Diabetic ketoacidosis

- It is a true emergency

- Usually results from omitting insulin in type 1 DM or increase insulin requirements in other illness (e.g. infection, trauma) in type 1 DM and type 2 DM

- **Signs and symptoms:**
  - Fatigue, nausea, vomiting, evidence of dehydration, rapid deep breathing, fruity breath odor, hypotension and tachycardia

Diabetic ketoacidosis (Cont'd)

- **Diagnosis**
  - Hyperglycemia, acidosis, low serum bicarbonate, and positive serum ketones
- **Abnormalities:**
  - Dehydration, acidosis, sodium and potassium deficit
- **Patient education** is important

Diabetic ketoacidosis Management

- **Fluid administration:** Rapid fluid administration to restore the vascular volume,
- **IV infusion of insulin** to restore the metabolic abnormalities. Titrate the dose according to the blood glucose level.
- **Potassium and phosphate** can be added to the fluid if needed.

Follow up:

- Metabolic improvement is manifested by an increase in serum bicarbonate or pH.

Complications

- Glucose toxicity appears to contribute most to development and progression of microvascular complications
- Epidemiologic studies also show a relationship between degree of glocuse control and cardiovascular events
- Thus the primary goal for both types of diabetic patients is to bring glucose concentration as close to NRL value as possible

UKPDS

United kingdom Prospective Diabetes study

- The effect of tight blood glucose control on cardiovascular and microvascular complications of **type 2** diabetes was addressed

- Continuous relationship between risks of microvascular complications and glycemia: 1% reduction A1c⟶ 35% reduction in risk of complications

UKPDS group substudy

Tight blood pressure control (<130/85) reduced the risk of stroke by 44% and microvascular end points by 37%

UKPDS

Whether intensive therapy decreases the risk of macrovacular disease was less clear.

21% risk reduction of combined fatal and nonfatal MI and sudden death (P= 0.52)

Screening for type 2

- FPG is preferred over the OGTT as a screening test

- age≥ 45 yrs, particularly over weight:

every **3** years

- Consider testing for prediabetes in asymptomatic adults of any age w/ BMI ≥25 kg/m2 or ≥23 kg/m2 (in Asian Americans) who have 1 or more risk factors for diabetes.
- If tests are normal, repeat at a minimum of 3-year intervals

Risk factors for Prediabetes and T2D

- A1C ≥5.7% (39 mmol/mol), IGT, or IFG on previous testing
- first-degree relative with diabetes
- high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- women who were diagnosed with GDM
- history of CVD
- 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)
- women with polycystic ovary syndrome
- physical inactivity
- other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans).

Criteria for Testing for T2DM in Children & Adolescents

- Overweight plus any 2 :
  - Family history of type 2 diabetes in 1st or 2nd degree relative
  - Race/ethnicity
  - Signs of insulin resistance or conditions associated with insulin resistance
  - Maternal history of diabetes or GDM
- Age of initiation 10 years or at onset of puberty
- Frequency: every 3 years
- Test with FPG, OGTT, or A1C

American Diabetes Association Standards of Medical Care in Diabetes.
Classification and diagnosis of diabetes. Diabetes Care 2017; 40 (Suppl. 1): S11-S24

Secondary DM

- Acromegaly,
- Cushing syndrome,
- Thyrotoxicosis,
- Pheochromocytoma
- Chronic pancreatitis,
- Cancer
- Drug induced hyperglycemia:
  - Atypical Antipsychotics - Alter receptor binding characteristics, leading to increased insulin resistance.
  - Beta-blockers - Inhibit insulin secretion.
  - Calcium Channel Blockers - Inhibits secretion of insulin by interfering with cytosolic calcium release.
  - Corticosteroids - Cause peripheral insulin resistance and gluconeogensis.
  - Fluoroquinolones - Inhibits insulin secretion by blocking ATP sensitive potassium channels.
  - Naicin - They cause increased insulin resistance due to increased free fatty acid mobilization.
  - Phenothiazines - Inhibit insulin secretion.
  - Protease Inhibitors - Inhibit the conversion of proinsulin to insulin.
  - Thiazide Diuretics - Inhibit insulin secretion due to hypokalemia. They also cause increased insulin resistance due to increased free fatty acid mobilization.

Recommendation

- 5-10% weight loss

- 30 min of moderately intense physical activity per day

DPP

Diabetes Prevention Program Research Group

- Studied people at high risk for developing diabetes to determine if lifestyle intervention or metformin would prevent or delay the onset of type 2 diabetes.
- Early closure!

  (incidence of diabetes was reduced by 58% and 31% in the intensive lifestyle and metformin groups)

Metformin

Very high risk for diabetes:

- Age<60
- BMI≥35
- Combined IFG & IGT
- At least 1 risk factor

Treatment

Desired outcome

- Relieve symptoms
- Reduce mortality
- Improve quality of life
- Reduce the risk of microvascular and macrovascular disease complications
  - **Macrovascular complications:**

    Coronary heart disease, stroke and peripheral vascular disease
  - **Microvascular Complications:**

    Retinopathy, nephropathy and neuropathy

Treatment

- Diet
- Drugs: Insulin, oral hypoglycemic or antihyperglycemic
- Exercise

Diet

- **For type 1 the goal is to regulate insulin administration with a balanced diet**

- **In most cases, high carbohydrate, low fat, and low cholesterol diet is appropriate**

- **Type 2 DM patients need caloric restriction**
- Meal plans emphasize normalizing plasma glucose and lipid levels as well as maintaining normal BP to prevent cardiovascular morbidity

- **Artificial sweeteners:**
  - e.g. Aspartame, saccharin, sucralose, and acesulfame
  - Safe for use by all people with diabetes

- **Nutritive sweeteners:**
  - e.g. fructose and sorbitol
  - Their use is increasing except for acute diarrhea in some patients

Exercise

- **In Insulin dependent patients:** hyperglycemia, normoglycemia, or hypoglycemia can occur

- **In type 2 diabetic patients:**

  plasma glucose Conc Usually decrease. symptomatic hypoglycemia is uncommon

Goals of therapy

- Keep patients free of symptoms associated with hyper or hypoglycemia
- Try to achieve target blood glucose goals
- Maintain normal growth and development in children (intensive therapy is not recommended for <7 yrs)
- Eliminate or minimize all other cardiovascular risk factors.
- Improve patient's knowledge of this disease

Treatment
Glycemic goals

TABLE 72–7. Glycemic Goals of Therapy

Biochemical Index	ADA	ACE and AACE
Hemoglobin A_{1c}	<7%[a]	≤6.5%
Preprandial plasma glucose	90–130 mg/dL (5.0–7.2 mmol/L)	<110 mg/dL
Postprandial plasma glucose	<180 mg/dL[b] (<10 mmol/L)	<140 mg/dL

[a] Referenced to a nondiabetic range of 4.0–6.0% using a DCCT-based assay. More stringent glycemic goals (i.e., a normal HbA_{1c}, <6%) may further reduce complications at the cost of increased risk of hypoglycemia (particularly in those with type 1 diabetes).

[b] Postprandial glucose measurements should be made 1–2 hours after the beginning of the meal, generally the time of peak levels in patients with diabetes.

ADA, American Diabetes Association; ACE, American College of Endocrinology; AACE, American Association of Clinical Endocrinologists; DCCT, Diabetes Control and Complications Trial.

Treatment
Complication monitoring

- Annual eye examination
- Annual microalbuminuria
- Feet examination
- BP monitoring
- Lipid profile

ADA goals for diabetic adults

• A1c	<7%
• Preprandial BS	80-130 mg/dl
• Postprandial BS	<180 mg/dl
• Blood pressure	<130/80 mmHg
• LDL	<100 mg/dl
• TG	<150 mg/dl
• HDL	
Men	>40 mg/dl
women	>50 mg/dl

Methods of monitoring

- Urine ketone testing
- Plasma glucose
- SMBG
- Hgb A1c
- Glycated serum protein & Alb; fructosamine

Treatment
Nonpharmacological therapy

Activity

- **Exercise improves insulin resistance and achieving glycemic control.**
- **Exercise should start slowly for patients with limited activity.**
- **Patients with CV diseases should be evaluated before starting any exercise**


SMOKING

Self-Care

- Patients should be educated to practice self-care. This allows the patient to assume responsibility and control of his / her own diabetes management. Self-care should include:

  - Blood glucose monitoring
  - Body weight monitoring
  - Foot-care
  - Personal hygiene
  - Healthy lifestyle/diet or physical activity
  - Identify targets for control
  - Stopping smoking

Insulin

Indications:

- Type 1 diabetic patients
- Type 2 diabetic patients when their symptoms cannot be controlled with diet alone or oral antidiabetic agents
- Type 2, during pregnancy or periods of intercurrent illness or stress (eg., surgery)

Insulin, Generic Name (Brand)	Onset	Peak	Effective Duration
Rapid-acting			
Insulin aspart injection (NovoLog)	5-15 min	30-90 min	<5 h
Insulin lispro injection (Humalog)	5-15 min	30-90 min	<5 h
Insulin glulisine injection (Apidra)	5-15 min	30-90 min	<5 h
Insulin human (rDNA origin) Inhalation Powder (Exubera) (2)	5-15 min	30-90 min	5-8 h
Short-acting			
Regular	30-60 min	2-3 h	5-8 h
Intermediate, basal			
NPH	2-4 h	4-10 h	10-16 h
Long-acting, basal			
Insulin glargine injection (Lantus)[ab]	2-4 h[c]	No peak	20-24 h
Insulin detemir injection (Levemir)[ab] (3)	3-8 h	No peak	5.7-23.2 h
Premixed			
75% insulin lispro protamine suspension/25% insulin lispro injection (Humalog Mix 75/25)	5-15 min	Dual	10-16 h
50% insulin lispro protamine suspension/50% insulin lispro injection (Humalog Mix 50/50) (4)	5-15 min	Dual	10-16 h
70% insulin aspart protamine suspension/30% insulin aspart injection (NovoLog Mix 70/30)	5-15 min	Dual	10-16 h
70% NPH/30% regular	30-60 min	Dual	10-16 h

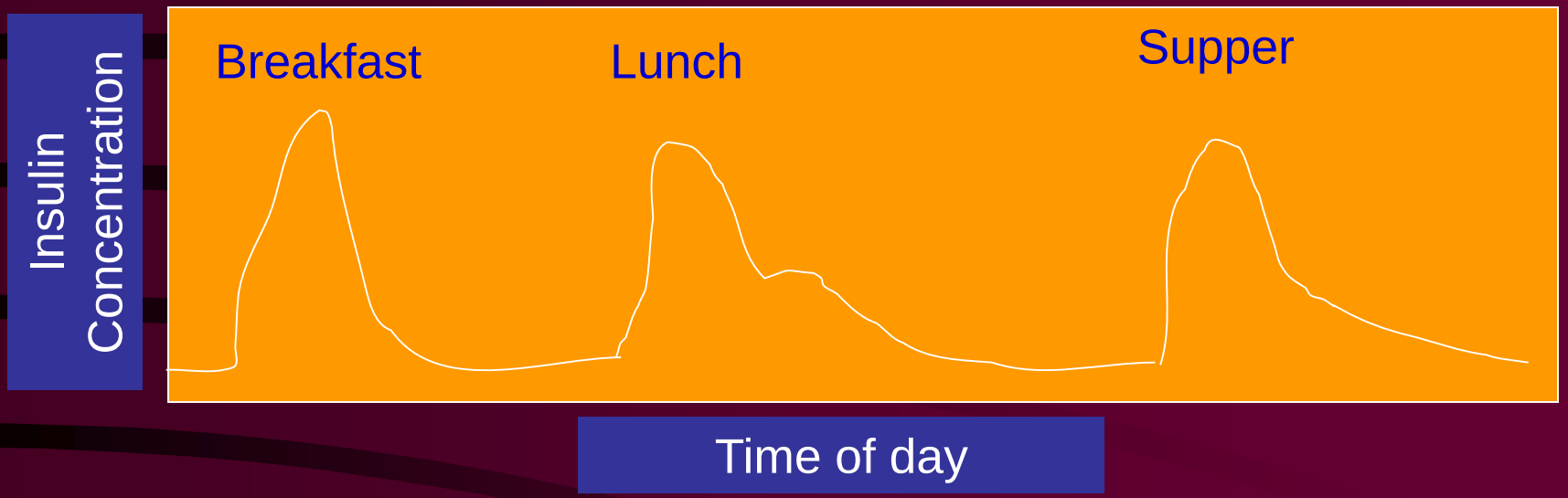
Abbreviation: NPH, neutral protamine Hagedorn

[a]May require 2 daily injections in patients with type 1 diabetes mellitus.

[b]Assumes 0.1-0.2 U/kg per injection. Onset and duration may vary significantly greatly by injection site.

[c]Time to steady state

Pharmacotherapy :Type 1 DM



Normal insulin secretion during he day

- **Constant background level (basal)**
- **Spikes of insulin secretion after eating**

Drugs used in diabetes mellitus…
Insulins

- Insulin Regular (Crystal) (Insulin R)
- Vial: 100 IU/ml 10 ml

Insulins …

- Insulin NPH (Isophane) (Insulin N)
- Vial: 100 IU/ml 10 ml

Insulins …

- Insulin 70/30 (70 NPH / 30 Regular)
- Vial: 100 IU/ml 10 ml

Insulins …

- Insulin Aspart (Novorapid)
- Pen: 100 IU/ml 3 ml

Insulins …

- Insulin **glulisine** (Apidra)
- Pen: 100 IU/ml 3 ml

Insulins …

- Insulin (Novomix) (70 NPH / 30 Aspart)
- Pen: 100 IU/ml 3 ml

Insulins …

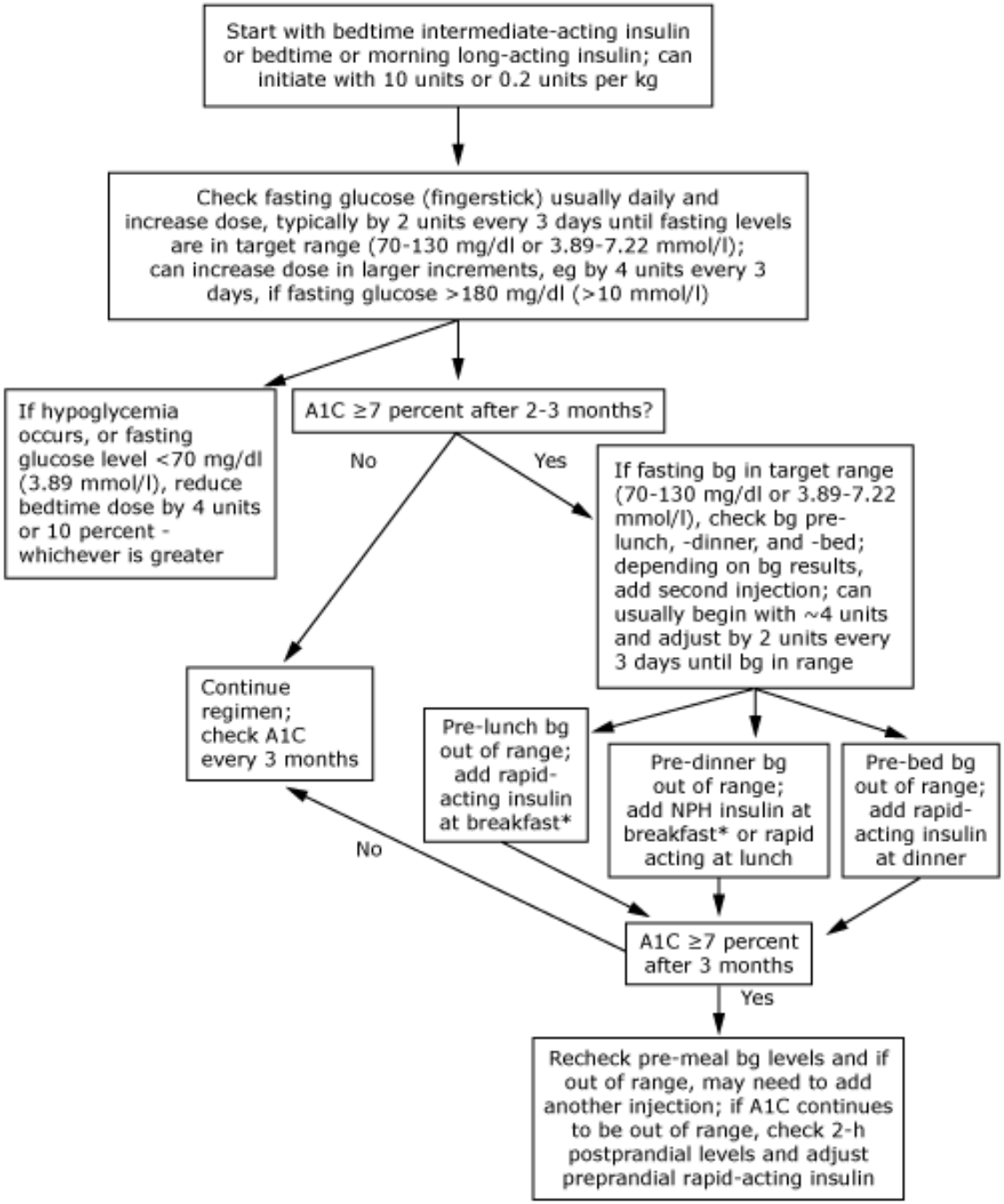
- Insulin Glargine (Lantus Solostar) (Abasaglar)
- Vial: 100 IU/ml 10 ml
- Pen: 100 IU/ml 3 ml

Insulins …

- Insulin **Detemir** (LEVEMIR®)
- Pen: 100 IU/ml 3 ml

Insulin as initial therapy

- A1C >10 percent
- fasting plasma glucose >250 mg/dL
- random glucose consistently >300 mg/dL
- ketonuria
- unplanned weight loss in association with hyperglycemia


Start with bedtime intermediate-acting insulin or bedtime or morning long-acting insulin; can initiate with 10 units or 0.2 units per kg
Check fasting glucose (fingerstick) usually daily and increase dose, typically by 2 units every 3 days until fasting levels are in target range (70-130 mg/dl or 3.89-7.22 mmol/l); can increase dose in larger increments, eg by 4 units every 3 days, if fasting glucose >180 mg/dl (>10 mmol/l)
If hypoglycemia occurs, or fasting glucose level <70 mg/dl (3.89 mmol/l), reduce bedtime dose by 4 units or 10 percent - whichever is greater
A1C ≥7 percent after 2-3 months?
No
Yes
If fasting bg in target range (70-130 mg/dl or 3.89-7.22 mmol/l), check bg pre-lunch, -dinner, and -bed; depending on bg results, add second injection; can usually begin with ~4 units and adjust by 2 units every 3 days until bg in range
Continue regimen; check A1C every 3 months
Pre-lunch bg out of range; add rapid-acting insulin at breakfast*
Pre-dinner bg out of range; add NPH insulin at breakfast* or rapid acting at lunch
Pre-bed bg out of range; add rapid-acting insulin at dinner
No
A1C ≥7 percent after 3 months
Yes
Recheck pre-meal bg levels and if out of range, may need to add another injection; if A1C continues to be out of range, check 2-h postprandial levels and adjust preprandial rapid-acting insulin

Insulin (Cont'd)

Drugs interfering with glucose tolerance

- **The most significant interactions are with drugs that alter the blood glucose level:**

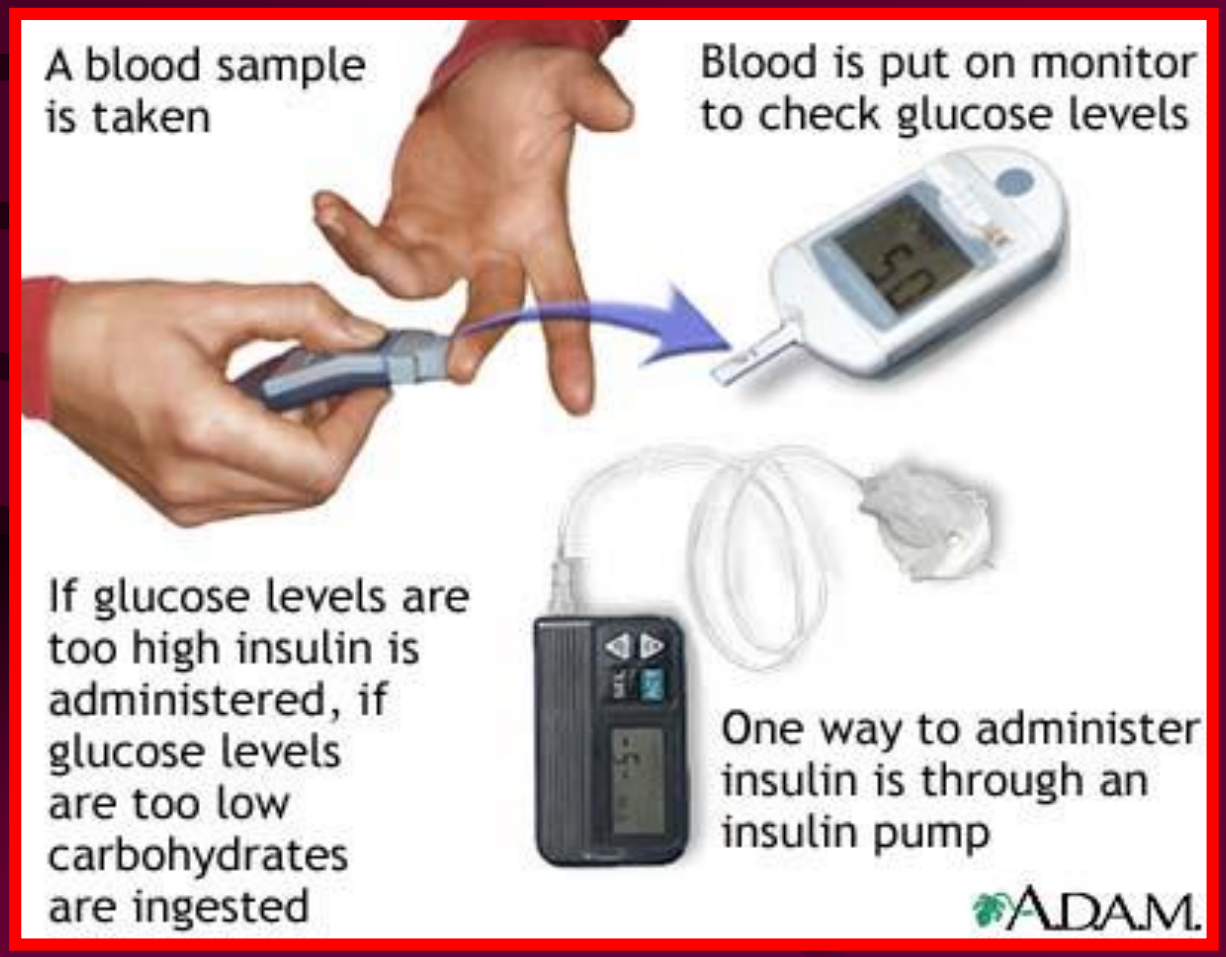
- Diazoxide
- Thiazide diuretics
- Corticosteroids
- Oral contraceptives
- Phenytoin

- **All these drugs increase the blood glucoseconcentration.**
- **Monitoring of BG is required**

Pharmacotherapy :

- -The insulin regimen has to mimic the physiological secretion of insulin
- With the availability of the SMBG and HbA1C tests adequacy of the insulin regimen can be assessed
- More intense insulin regimen require more intense monitoring

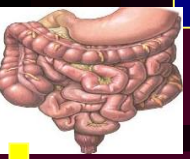
Monitoring


A blood sample is taken
Blood is put on monitor to check glucose levels
If glucose levels are too high insulin is administered, if glucose levels are too low carbohydrates are ingested
One way to administer insulin is through an insulin pump
A.D.A.M.

Oral antidiabetic agents

Pharmacological Treatment of Type 2 DM

Strategy for Controlling Hyperglycemia



Absorption from Diet

Biosynthesis in Liver

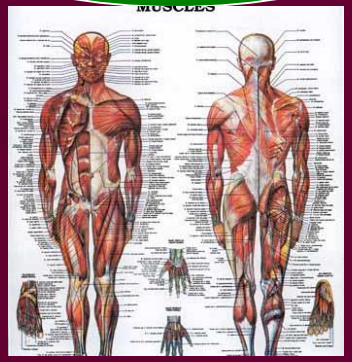
α-Glucosidase Inhibitors

Biguanides

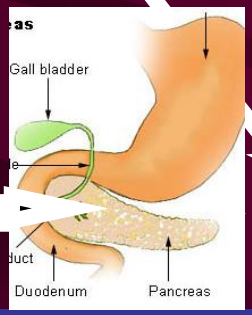
Serum Sugar

Cellular Uptake

Biguanides; thiazolidinediones



Pancreas



Insulin

Sulfonylureas

Meglitinide

Biguanides

- Metformin (Glucophage) (Brot)
- Tab: 500, 1000 mg

Metformin

- Lowers FPG by decreasing gluconeogenesis
- Improve peripheral sensitivity to insulin
- Lipids: ↓chol(5-10%); ↓TG(10-20%)
- Weight loss

Metformin

- Eliminated entirely by kidney unchanged
- ADR: diarrhea, abdominal discomfort, metallic taste, nausea, anorexia
- Slowly titrating, taken with food

Contraindications & Precautions

B12 deficiency in long-term metformin use
Recommendation: periodic measurement of B12 levels & supplementation as needed.

- **Renal impairment**
- **Hepatic disease**
- **CHF requiring pharmacologic treatment**
- **Acute or chronic metabolic acidosis**
- **History of lactic acidosis**
- **Predisposing: Excessive alcohol intake, shock, dehydration, sepsis, surgery**

Drug interactions

- Alcohol
- Cimetidine
- Iodinated materials: AKI or severe CKD (GFR< 30) => 48 hrs

Efficacy

- A1c 1.5-1.7 %
- FBG 50-70 mg/dl
- PPG 83 mg/dl

Dosage

- Initially 500mg once or twice daily
- Weekly or biweekly increments of 500mg/d
- Dose 2-3 times daily
- Max: 2550mg
- SrCr and LFT at baseline and annually

Sulfonylureas

- First generation: acetohexamide, chlorpropamide, tolazamide, tolbutamide (shortest acting)
- 2nd generation: glipizide, gluburide, glimepride
- 2nd generation 100 times more potent, but no evidence that they are more effective

Sulfonylureas (Cont'd)

Classification

- **First generation**
  - Lower potency, more potential for drug interactions and side effects
- **Second generation**
  - higher potency, less potential for drug interactions and side effects
- **All sulfonylurea drugs are equally effective in reducing the blood glucose when given in equipotent doses.**

Major Pharmacokinetic Properties of Sulfonyl Ureas

	Eqv. Dose (mg)	Duration (h)	Active metabolites
First Generation			
Tolbutamide	1000-1500	12-24	Yes (p-OH derivative)
Chlorpropamide	250-375	24-60	Yes (2'-OH and 3'OH groups)
Tolazamide	250-375	12-24	No (4-COOH derivative)
Second generation			
Glipizide	10	10-24	No (cleavage of pyrazine ring)
Glyburide (glibenclamide)	5	16-24	Some (trans + cis 4'-OH groups)
Third generation			
Glimepiride	1-2	24	Yes (-OH on CH3 of R' group)

Pharmacokinetics

- Highly protein bound

- Food does not impair the extend of absorption but delay the time to peak levels of some agents

Glyburide

- Initial: 2.5mg/d

  elderly 1.25mg/d

  increase by 1.25 or 2.5mg Q 1-2 wks

- Max: 20 mg

Continue

- Some studies showed little or no improvement in glucose control at dosage **≥10mg/d** of gliburide
- Max dose **20 mg** for glyburide & **320 mg** for gliclazide
- Addition of a 2nd oral agent or insulin may be indicated for pts no longer respond to doses ≥10 mg

Glyburide

- Longer acting t ½ (4-13 hrs), duration **12-24** hrs
- Single dose: <10 mg/d
- Metabolized to active compounds

ADRs

- Hypoglycemia, weight gain
- GI, rare blood dyscrasias, allergic dermatologic reactions, hepatotoxicity, hypothyroidism, disulfiram reaction

Relative contraindications for Sulfonylureas

Type 1

Pregnancy

Surgery

Severe infections

Severe stress or trauma

Severe hepatic or renal failure

Insulin therapy should be used in all of these

Sulfonylureas

- Chlorpropamide (Diabinese)
- Tab: 250 mg

Drugs used in diabetes mellitus

- Glibenclamide (Glyburide) (Daonil)
- Tab: 5 mg

Gliclazide (Diamicron) (Diabezid)

Tab: 80 mg

Tablet, Extended Release: 30mg, 60 mg

Dosing: Individualized

- The 30 mg modified-release tablet equals the 80 mg immediate-release tablet.
- Immediate-release tablet: Initial: 80 mg twice daily; titrate based on blood glucose levels. Usual dosage range: 80 to 320 mg/day (maximum dose: 320 mg/day); dosage of ≥160 mg should be divided into 2 equal parts for twice-daily administration.
- Modified-release tablet: Initial: 30 mg once daily with breakfast; titrate in 30 mg increments every 2 weeks based on blood glucose levels. Maximum dose: 120 mg once daily

Drugs used in diabetes mellitus…

- Glipizide (Glucotrol) (Minidiab)
- Tab: 5 mg

Thiazolidinediones

- Decrease insulin resistance in muscle and liver
- Food does not alter their absorption
- The action relies on gene transcription and protein production
- Onset: 1-3 wks
- Max effect: after 8-12 wks
- No dose adjustments required in pts with RF

Thiazolidinediones

- Reduction of inflammatory mediators
- Inhibition of vascular smooth muscle cell proliferation, improved endothelial function

ADR

- **Hepatotoxicity**: monitor LFT at baseline and periodically thereafter

- Increase in plasma volume(6-7%) and vascular edema(5-7%)

Continued

- Incidence of peripheral edema is greatly increased when TZDs are used in combination with insulin(15%)
- Should not be used in CHF **NYHA class III, IV**
- Used cautiously in pts with CRF and impaired cardiac function

Contraindications & Precautions

- Type 1
- Pre-existing hepatic disease:
  should no be used if **ALT>2.5 times** NRL,
  ALT>3 times discontinue, Bil rise, symptoms
- Severe CHF
- Premenopausal anovulatory women

Drug interactions

- Pioglitazone induces CYP 3A4: estrogens, terfenadine, cyclosporine, tacrolimus, statins, OCPs

- Rosiglitazone does not appear to inhibit any of the major CYP enzymes

Efficacy

- Effects are intermediate between that of acarbose and sulfonylureas or metformin

- 25% of individuals are unresponsive

Thiazolidinediones

- Pioglitazone (Actos) (Pitoze) (Glutazone)
- Tab: 15, 30, 45 mg

Pioglitazone

- **Monotherapy:**

  15mg or 30mg once daily increased to

  Max 45 mg/d

- **Combination:**

  initiated at 15 or 30mg

  no adequate data on >30 mg/d

Meglitinides

- Close ATP sensitive k Channel
- Unlike sulfonylureas, rapid onset and shorter duration of action
- Postprandial glucose

ADR

- Hypoglycemia
- Weight gain

Drug interactions

- **Gemfibrozil & repaglinide**

Efficacy

- Efficacy of repaglinide is compareable to metformin and sulfonylureas

- Netaglinide less potent

Clinical use

- Monotherapy or combination with metformin, TZDs

- **Combination with sulfonylureas, no additional benefit**

Repaglinide

- **Initial:** naïve or A1c<8%; 0.5 mg with each meal

  failed to sulfonyl or A1c>8% 1-2 mg with each meal

- Taken 0-30 min before meal
- Severe renal dysfunction: initiated at 0.5 mg dose
- Liver dysfunction: titrated cautiously

Meglitinides

- Repaglinide (Novonorm) (Newbet)
- Tab: 0.5, 1, 2 mg

α- Glucosidase inhibitors

- Reversibly inhibit glucosidase
- Lowering postprandial blood glucose
- Acarbose: F 0.5-1.7%

  metabolized by GI amylases to inactive

Clinical use

- Monotherapy or combination with sulfonylurea, metformin, insulin
- Initial dose: 25mg TDS
- Dose increased 25mg/meal Q 4-8 wk
- Max dose: ≤60 kg 50mg TDS

  >60 kg 100mg TDS
- Max response at 6 months

Efficacy

- Postprandial: 25-50 mg/dl
- FPG: 20-30 mg/dl (↓glu tox)
- HgA1c: 0.5-1%
- No effect on weight or lipid profile

ADRs

- Flatulence(42-77%), diarrhea(30%),abdominal pain (10-20%)
- Slowly titrating
- Acarbose ≥300mg/d; transient increase in transaminases
- Monitoring Q 3 mon for the first year & periodically thereafter

Contraindications & precautions

- Malabsorption, IBD, Intestinal obstruction
- SrCr> 2 mg/dl
- Hypoglycemia: sucrose not be used

α glucosidase inhibitors

- Acarbose (Glucobay) (Acarbex)
- Tab: 50, 100 mg

Incretin based therapies

- Insulinotropic hormones secreted from small intestine in response to CHO.
- Glucose dependent insulinotropic polypeptide (GIP) and Glucagon like peptide-1 (GLP-1)
- Stimulate β-cells in glucose dependent manner
- GLP-1 inhibits α-cells
- Cleavaged by DPP-4

GLP-1 Mimetics/Analogs

- Exenetide is a synthetic form of exendin-4 (Gila monster)
- Exendin-4 shares 50% of amino acid sequence
- Similar affinity for receptor, strong resistance DDP4
- Liraglutide

Mechanism of action

- Augment first-phase insulin response
- Moderate glucagon secretion
- Decrease hepatic glucose production
- Do not impair normal glucagon response to hypoglycemia
- Slow gastric emptying
- Suppress appetite (wt loss

Exenetide

- Injection site does not alter kinetic
- Eliminated by glomerular filtration & proteolytic degradation
- Mean terminal half life 2.4 hr
- BD SC dosing
- Liraglutaide: highly protein bound (›98%), t1/2 10-14, once daily

Adverse effects

- GI side effects, common, dose dependent
- Mild to moderate nausea 40%, vomiting and/or diarrhea 15%
- Starting on low dose, slowly titration
- Decreased appetite, injection site reaction
- Rarely: hypersensitivity reactions, acute pancreatitis, reversible renal impairment or failure
- Antibody in 40-50% pts, failure

Contraindications & precautions

- Hypersensitivity
- Severe GI disease
- Severe renal impairment (CrCl ‹30 ml/min)

Drug interactions

- Increased risk of hypoglycemia with hypoglycemic agents
- Reduce the rate & extend of absorption (antibiotics, OCPs)
- Take medication at least 1 hour before exenatide
- Case reports: increased INR

Efficacy

- Max dose plus SFU or metformin or TZD:

  FBS 20-80 mg/dl

  2h-PP 60-70 mg/dl

  HbA1c 0.8-1%

  wt loss 4-5 kg

- Liraglutide

  FBS 30-60 mg/dl

  HbA1c 0.6-1.75%

  wt loss 2-3 Kg

Clinical use

- Add on agents in T2DM, failed on monotherapy or combination with oral oral agents and/or insulin
- Helpful in obese pts
- Starting dose: 5 mcg Sc (abdomen, thigh, arm) BD, 60 min before morning and evening meal
- Severe GI side effects: just before meals
- After one month max dose 10 mcg Sc BD

Human glucagon-like peptide-1 (GLP-1) analogue

- **Liraglutide** (Victoza)

- 6 mg/ml solution for injection in pre-filled pen
- 18 mg liraglutide in 3 m

ADR

- Nausea (39%), diarrhea (21%), constipation (19%), vomiting
- Increased heart rate ;Headache (14%); Hypoglycemia
- Fatigue (8%), dizziness (7%), Weakness
- Injection site reactions, Itching
- **Acute renal failure**, angioedema, asthma, benign gastrointestinal neoplasm (colorectal), bronchospasm, carcinoma (papillary thyroid), cholecystitis, cholestasis, chronic renal failure (exacerbation), dehydration, dysgeusia, facial edema, first degree atrioventricular block, hepatitis, hypersensitivity reaction, increased liver enzymes, increased serum calcitonin, increased serum creatinine, increased susceptibility to infection, left bundle branch block, malaise, malignant neoplasm (including colorectal carcinoma), malignant neoplasm of breast, **medullary thyroid carcinoma**, **Pancreatitis, suicidal behavior**

Dipeptidyl Peptidase-4 Inhibitors

- Sitagliptin
- Linagliptin
- Valdagliptin
- Saxagliptin
- Denagliptin

DPP-4 inhibitors

- Inhibit degradation of GIP and GLP-1 upon entering GI vasculature
- Sitagliptin & vildagliptin reduce DPP-4 activity by 80%
- Some inhibition maintain for up to 24 hrs after an oral dose

Sitagliptin

- Rapidly absorbed, bioavailability 87%
- Absorption unaffected by food
- Terminal half life 12.4 hr
- 79% excreted unchanged in urine
- Metabolised by CYP3A4

Adverse effects

- Common side effects:

Increased risk of infection (nasopharyngitis, upper Respiratory tract infections, sinusitis, UTI, headache)

- Hypersensitivity reactions (anaphylaxis, STJ, angioedema) after first dose to 3 mon

Dipeptidyl peptidase-4 (DPP-4) inhibitor

- **Sitagliptin (ziptin, sitavix) (Januvia)**
- Tab: 25, 50, 100 mg
- **سیتافورمین ® (سیتاگلیپتین- متفورمین)- زیپمت**
- Tab: 50 - 500 mg
- Tab: 50- 1000 mg

- **دسته دارویی :**
مهار کننده دی پپتیل پپتیداز تیپ چهار

مکانیسم اثر:
مهار کننده آنزیم دی پپتیدیل پپتیداز تیپ ۴ (DPP-4)است که در کنار رژیم غذایی و ورزش درکنترل قند خون بیماران دیابتی تیپ IIمورد استفاده قرار میگیرد. این دارو با مهار آنزیم دی پپتیل پپتیداز تیپ چهار مانع از تجزیه اینکریتین (Incretin)در بدن میشود. اینکریتین که به نام Glucagon-like peptide -1شناخته میشود فاکتوری است که می تواند با کنترل ترشح انسولین و کاهش ترشح گلوکاگون بر روی هموستاز گلوگز موثر باشد. کاهش ترشح گلوکاگون میتواند بر روی روند گلوکونئوژنز در کبد نیز موثر باشد، به همین دلیل سیتاگلیتپین با مهار این جریان فیزیولوژیک بدن، به شکل موثری قند خون را کاهش میدهد. با توجه به ترشح هورمون اینکریتین در پاسخ به حضور غذا در دستگاه گوارش، سیتاگلیتین با مهار تجزیه این هورمون، هنگام غذا خوردن یا در ساعات اولیه بعد از آن، اثرگذار خواهد بود.

Sitagliptin

- Used with caution in combination with antidiabetic agents, hypoglycemia

Efficacy

- FBS 15-30 mg/dL
- A1c 0.62%-0.85%
- 2-hpp 63-71 mg/dL
- Long term preservation β-cell function

Dosage

- Add on therapy; SFU, biguanide, TZD, insulin
- Sitagliptin 100mg once daily, ±food
- Renal function assessment baseline and periodically thereafter
- Dose reduction in moderate to severe renal insufficiency and ESRD requiring dialysis
- CrCl 30-50 mg/dl ; 50 mg/d
- CrCl <30 mg/dl; 25 mg/d
- Administered without regard timing of hemodialysis

Linagliptin

- Tab 5 mg

Drugs used in hypoglycemia

- Glucagon **(GlucaGen® HypoKit®)**
- Prefilled syringe : 1 mg

Usual Adult Dose for Hypoglycemia

- Less than 20 kg: 0.5 mg (0.5 unit) subcutaneous, IM or IV.
- 20 kg or more: 1 mg (1 unit) subcutaneous, IM or IV.

Diazoxide

- Slowing the release of insulin from the pancreas
- **Usual Adult Dose for Hypoglycemia**
- 3 to 8 mg/kg/day orally in divided doses every 8 or 12 hours.
- Higher dosages (up to 15 mg/kg/day) have been used in refractory hypoglycemia.

Drugs used in hypoglycemia…

- Diazoxide (Proglicem) (Eudemine)
- Cap, Tab: 25, 50, 100 mg

Rational use of drugs

World Health Organization

Type 2 diabetes treatment

Tier 1 algorithm

- Step1: lifestyle & metformin

  Metformin should be titrated to its maximally effective dose at 1-2 mon

- Step 2: add either insulin or sulfonylurea

  Within 2-3 mon of step1 or any time when target A1c is not achieved or metformin is contraindicated or not tolerated

  A1c>8.5% or hyperglycemic symptoms, insulin

- Step 3: starting or intensifying insulin therapy

Secondary failure

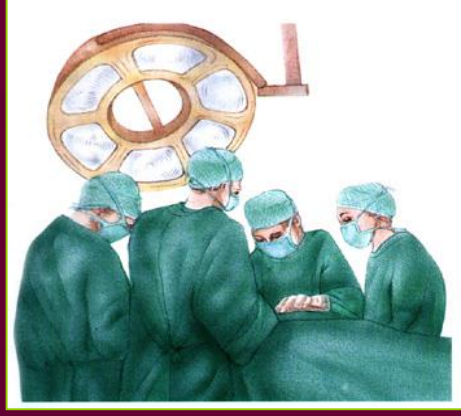
- Is fairly common and occurs at a rate of approximately 5-10% per year
- Progressively poor glucose control that occurs after one month to several yrs periods of good response
- May be related to progressive pancreatic failure, poor compliance, exogenous diabetogenic factors

Treatment

- Identifying and correcting diabetogenic factors (obesity, illness, drug)

- Should always add another agent rather than switch to another

II. Surgery



- Islet transplantation has been investigated as a treatment for type 1 diabetes mellitus in selected patients with inadequate glucose control despite insulin therapy.

- Observations in patients with type 1 diabetes indicate that islet transplantation can result in insulin independence with excellent metabolic control

Ref. Shapiro A.M. J., et al. N Engl J Med 2000; 343:230-238, Jul 27, 2000

Diabetes Mellitus Complications

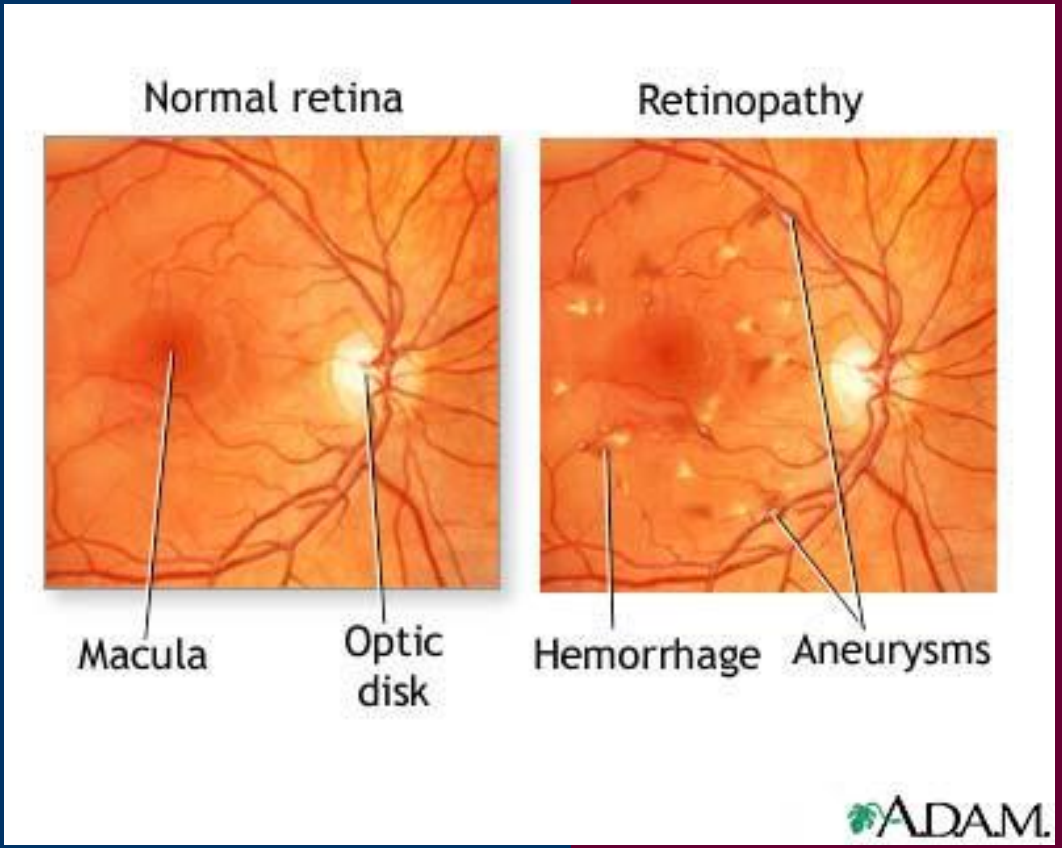
1. Hypoglycemia

- **Cause:** Missing meals or excessive exercise or too much insulin
- **Symptoms:** Tachycardia, palpitation, sweating, nausea, and vomiting. Progress to mental confusion, bizarre behavior and coma
- **Treatment:** Candy or sugar
  IV glucose
  Glucagon

Diabetes Mellitus Complications

2. Diabetes retinopathy

- Microaneurysm
- Hemorrhage
- Exudates
- Retinal edema
- other



Retinopathy

- Type1 pts should have a dilated retinal examination within 3-5 yrs of diagnosis, evaluation is not necessary before 10 yrs of age
- Type 2 soon after diagnosis
- ADA recommend annual examination

Diabetes Mellitus Complications

3. Diabetes nephropathy

- 30-40 % of all type 1 DM patients develop nephropathy in 20 years
- 15-20 % of type 2 DM patients develop nephropathy
- Manifested as:
  - Microalbuminuria
  - Progressive diabetic nephropathy leading to end-stage renal disease

Diabetes Mellitus Complications

Diabetes nephropathy (Cont'd)

- All diabetic patients should be screened annually for microalbuminurea to detect patients at high risk of developing progressive diabetic nephropathy
- Tight glycemic control and management of the blood pressure can significantly decrease the risk of developing diabetic nephropathy.
- ACE-inhibitors are recommended to decrease the progression of nephropathy

Nephropathy

- Hyperglycemia causes intraglumerular HTN and renal hyperfiltration then is followed by microalbuminuria with minimal glomerulosclerosis, which is still potentially reversible

- Progression can be accelerated in the presence of HTN

- Lipid abnormality also may contribute to progression of glumerulosclerosis

Albuminuria

- Microalbuminuria: >30mg/24 hr
  Macro >300 mg/24 hrs

- At least 2 of 3 urine samples in 3-6 mon period

Screening

- Type1 :

  annually after 5 yrs or at onset of puberty

- Type2:

  annually from the time of diagnosis

False elevation

- Exercise
- Excessive protein intake
- Uncontrolled diabetes
- Uncontrolled HTN
- UTI

Management

- Early detection
- Tight glucose control
- ACEIs & ARB
- Aggressive management of HTN, dyslipidemia and smoking cessation

Diabetes Mellitus Complications

4. Diabetes neuropathy

- **neuropathy**: loss of sensation due to damage of nerve fibres (e.g. heat, cold, pain)

- high blood glucose changes the metabolism of nerve cells

- reduced blood flow

Autonomic neuropathy:

- **Manifested by orthostatic hypotension, diabetic diarrhea, erectile dysfunction, and difficulty in urination.**

Peripheral neuropathy

- Metabolic disturbance of neurons, microangiopathy, autoimmune

- Symptomatic peripheral neuropathy occurs in 25% of pts: parasthesia, pain in lower extremities

Treatment

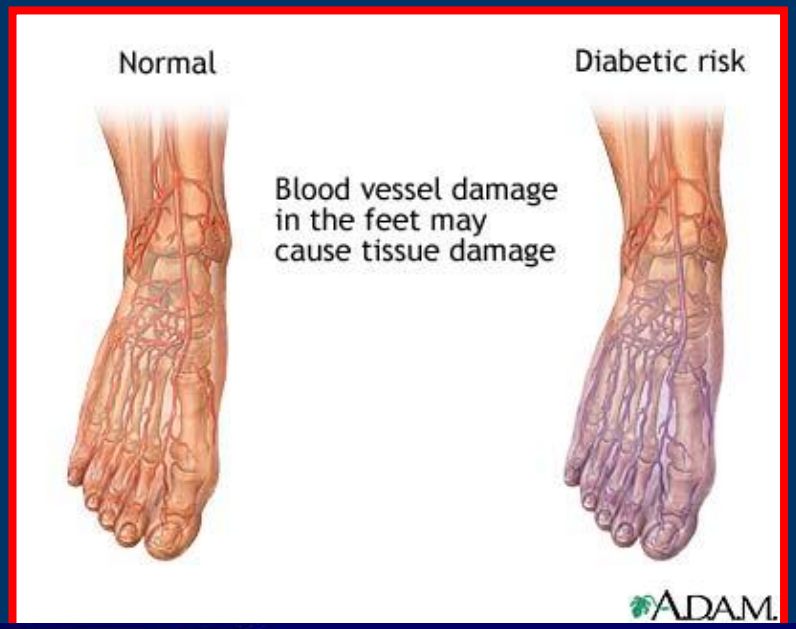
- Simple analgesics
- TCAs
- CBZ
- Gabapentin
- Lamotrigine, topiramate, tramadol, capsaicin, mexiletine, lidocaine, clonidine

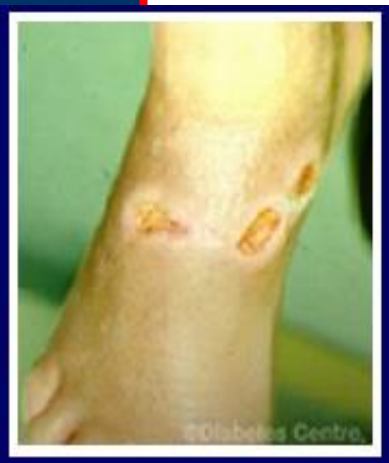
Diabetes Mellitus Complications

5. Peripheral vascular disease and foot ulcer

Incidence of gangrene of the feet in DM is 20 fold higher than control group due to:

- **Ischemia**
- **Peripheral neuropathy**
- **Secondary infection**





HTN

- Is the main determinant of life expectancy and complications in diabetic pts
- HTN in a pts with Type 1 usually is of renal paranchymal origin (1-2 yr after onset of microalbuminuria)
- In type 2 is part of metabolic syndrome

HTN

- Patients with a SBP 130-139 mmHg or a DBP 80-89 mmHg may be given lifestyle therapy alone for a maximum of 3 months

- Patients with more severe hypertension (SBP ≥ 140 mmHg or DBP ≥90 mmHg) at diagnosis or follow-up should receive pharmacologic therapy in addition to lifestyle therapy.

Treatment

- For patients without albuminuria, any of the four classes of blood pressure medications (**ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers)** that have shown beneficial cardiovascular outcomes may be used.

- ACEIs and ARBs :development and progression of nephropathy

- Thiazide diuretics are also associated with clear treatment benefits and improved outcomes (don't exceed **25**mg/d HCTZ)

Cardiovascular disease

- CHD is the leading cause of premature death in type2 and accounts for 50% of deaths in diabetics
- Relative to nondiabetics, are 2-3 times more likely to develop CHD
- Women with diabetes, regardless of their age or menopausal status, have equal risk for CHD to that of nondiabetic men

Lipids

- The most common abnormality in type 2 is **hypertriglyceridemia** with low levels of HDL

- Adults with diabetes should be screened annually for serum lipoprotein levels

- ADA recommends **statin** therapy in pts over the **age** of **40** with a TC≥135mg/dl regardless of baseline LDL levels

Statins

Statin should be added regardless of baseline lipid level for pts:

- With overt CVD
- Without CVD who are over the age of 40 and have 1 or more other CVD risk factors
- LDL :100 mg/dl
- Multiple CVD risk factors or Long duration of diabetes

Gastroparesis

- Conventional antiemetic therapy is usually not helpful
- Prokinetic agents are considered first line
- Metoclopramide 10 mg QID
- Domperidone, cisapride, erythromycin

Peripheral arterial disease

- ↓foot pulse, intermittent claudication, skin ulcers, gangrene

- Elimination of risk factors:

  smoking, dyslipidemia, HTN, hyperglycemia, antiplatelet therapy, exercise

Asprin

Aspirin therapy (75-162 mg/ day) as a primary prevention strategy:

This includes most men >50 years / women >60 years of age who have at least one additional major risk factor:

- Family history of CVD
- Hypertension
- Smoking
- Dyslipidemia
- Albuminuria

مرور اصول درمان دارویی دیابت

تعریف دیابت

Table 2.2—Criteria for the diagnosis of diabetes
FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).
*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

- نکته : بیمار مطرح شده دو معیار آزمایشگاهی همزمان به نفع دیابت دارد پس نیاز به تکرار تست قند خون نیست.

- انتخاب دارو بر اساس ویژگی های بیمار (شدت هیپر گلیسمی)، وجود یا عدم وجود نارسایی کلیه و مشکل قلبی عروقی، وزن بیمار، وضعیت مالی و... متفاوت است. مثلا در بیمار چاق ارجح این است که از داروهایی استفاده کنیم که اثر مثبت در کاهش وزن دارند یا اثرشان روی وزن خنثی است مثل متفورمین یا سیتاگلیپتین.

- در شروع درمان، درمان **ارجح** در بیماران **قرص متفورمین** است (در صورت فقدان کنتراندیکاسیون و تحمل بیمار).

بی‌گوانید	**متفورمین** (۵۰۰ ، ۱۰۰۰ میلی گرم)	از طریق کاهش آزاد شدن قند از کبد به کنترل قند خون کمک می‌کنند.	مصرف دارو قبل از غذا مؤثرتر است ولی در صورت بروز عوارض گوارشی، بعد از غذا مصرف شود. در صورت حذف وعده غذایی، دارو باید مصرف شود. معمولاً ۳-۱ بار در روز تجویز می‌شود.	تهوع، نفخ، اسهال، بی‌اشتهایی	نارسایی کلیوی شدید، کتواسیدوز دیابتی، بیماری کبدی شدید، بیماری قلبی(نارسایی قلبی شدید)، کودکان زیر ۱۰ سال (برای انواع پیوسته‌رهش کمتر از ۱۷ سال)، سوختگی شدید، جراحی. در صورت نیاز به تصویر برداری با ماده حاجب نیاز به رعایت احتیاطات خاص هست.	۲۵۵۰ میلی گرم	دارد
	متفورمین پیوسته رهش (۵۰۰، ۱۰۰۰ میلی گرم)		به همراه وعده غذایی شام مصرف شود. در صورت حذف وعده غذایی، دارو مصرف شود . معمولاً ۲-۱ بار در روز تجویز می‌شود.			۲۰۰۰ میلی گرم	ندارد

- در مبتلایان به دیابت تیپ ۲ لازم است در همان ویزیت اول اقدامات لازم برای بررسی عوارض دیابت شامل عوارض چشمی، کلیوی و قلبی (در صورت علامت دار بودن) انجام شود و در فاصله۳ ماه ویزیت مجدد انجام شده و در مورد ادامه درمان و یا تجویز داروی دوم تصمیم گیری میشود.

- درمان دیابت تیپ ۲ داروی خوراکی یا انسولین است. قدم اول در درمان دارویی دیابت، تجویز یکی از داروهای خوراکی ضد دیابت است با دو استثنا :

۱. در بیماران مبتلا دیابت تیپ ۲ که به تازگی تشخیص داده شده و علامت دار هستند (پلی اوری پلی دیپسی و ناکچوری) و A1C بالای ۱۰ یا BS بالای ۳۰۰ دارند باید انسولین شروع شود.

۲. در بیماران مبتلا به دیابت تیپ ۲ که A1C بالای ۹ دارند باید درمان دارویی با ۲ داروی خوراکی شروع شود.

- انتخاب دارو بر اساس ویژگی های بیمار (شدت هیپر گلیسمی)، وجود یا عدم وجود نارسایی کلیه و مشکل قلبی عروقی، وزن بیمار، وضعیت مالی و... متفاوت است. مثلا در بیمار چاق ارجح این است که از داروهایی استفاده کنیم که اثر مثبت در کاهش وزن دارند یا اثرشان روی وزن خنثی است مثل متفورمین یا سیتاگلیپتین.

- در مبتلایان به دیابت تیپ ۲ که با اضافه کردن درمان دارویی خوراکی نیز به هدف کنترل قند نرسیدیم (Hb A1C بیمار ۱,۵ تا از عدد هدف در این فرد بالاتر بود) باید انسولین شروع شود .در صورت شروع انسولین، درمان با قرص متفورمین (در صورت فقدان کنترااندیکاسیون و تحمل بیمار) باید ادامه یابد و سایر داروهای خوراکی قطع شود.

- **نکته:** در مبتلایان به دیابت تیپ ۲ که ASCVD (عوارض قلبی عروقی) شناخته شده دارند بعد از شروع تغییر سبک زندگی و متفورمین اگر به هدف کنترل قند دست نیافتیم باید داروهایی که با کاهش عوارض قلبی همراه هستند (Liraglutide / empagliflozin) شروع شود. این داروها در بازار ایران وجود دارند ولی گران قیمت هستند و امکان تهیه آن در بسیاری از افراد وجود ندارد. در صورت عدم امکان تهیه این داروها می توان از سایر داروها استفاده کرد.

سولفونیل-اوره	**گلی‌کلازید** (۸۰ میلی گرم)	ترشح انسولین را از لوزالمعده افزایش داده و از این طریق قند خون را کاهش می-دهند.	۳۰ دقیقه قبل از غذا مصرف شود. در صورت عدم مصرف وعده غذایی، این دارو نباید مصرف شود. معمولاً ۳-۱ بار در روز تجویز می‌شود.	افت قند خون، افزایش وزن	اسهال شدید، انسداد روده، استفراغ طولانی مدت، بیماری کبدی یا کلیوی شدید، بارداری	۳۲۰ میلی گرم	دارد
	گلی‌کلازید پیوسته‌رهش (۳۰، ۶۰ میلی گرم)		۳۰ دقیقه قبل از غذا مصرف شود. در صورت عدم مصرف وعده غذایی، این دارو نباید مصرف شود. معمولاً ۲-۱ بار در روز تجویز می‌شود.			۱۲۰ میلی گرم	۳۰ میلی گرم دارد ۶۰ میلی گرم ندارد
	گلی‌بنکلامید (گلیبوراید) (۵ میلی گرم)		۳۰ دقیقه قبل از غذا مصرف شود. در صورت عدم مصرف وعده غذایی، این دارو نباید مصرف شود. معمولاً ۲-۱ بار در روز تجویز می‌شود.		بیماری کبدی یا کلیوی شدید، سوختگی شدید، اسیدوز، اغما، پورفیری	۲۰ میلی گرم	دارد

مهار کننده آنزیم دی پپتیدیل پپتیداز ۴	**سیتاگلیپتین** (۲۵، ۵۰ میلی گرم	بهبود (افزایش) مقدار انسولین بعد از صرف غذا و کاهش تولید قند.	این دارو با غذا تداخلی ندارد و می‌توان آن را همراه غذا و یا بدون غذا مصرف نمود. این داروها باید در ساعت مشخصی از روز مصرف شوند. معمولاً ۲-۱ بار در روز تجویز می‌شود.	سردرد، علایم شبیه آنفلوآنزا، گلودرد	پانکراتیت در بیماری کلیوی و گوارشی شدید با احتیاط مصرف شود.	۱۰۰ میلی گرم	ندارد
	لیناگلیپتین (۵ میلی گرم)				حساسیت به دارو، نارسایی قلبی و یا پانکراتیت	۵ میلی گرم	ندارد
مگلیتینید	**رپاگلیناید** (۰/۵، ۱، ۲ میلی گرم)	تحریک آزاد شدن انسولین از لوزالمعده پس از صرف غذا	۳۰ دقیقه تا بلافاصله قبل از غذا مصرف شود. در صورت عدم مصرف وعده غذایی، این دارو نباید مصرف شود. معمولاً ۴-۲ بار در روز تجویز می‌گردد.	افت قند خون ، افزایش وزن	اختلال کبدی شدید و افراد حساس به دارو	۱۶ میلی گرم	دارد

The Italian Way

If you never never go, you will never never know

Rome was burnt in one day in AD 64