

DIABETES MELLITUS

Roopa B.S
Lecturer, Department of Pharmacy Practice

- Diabetes mellitus is a metabolic disorder of fat, carbohydrate, and protein metabolism, which results from defects in insulin secretion, insulin sensitivity, or both.

Type 1 Diabetes

- cells that produce insulin are destroyed
- results in insulin dependence
- commonly detected before 30

Maturity-onset diabetes of youth (MODY) - Genetic inability to convert proinsulin to insulin.

Type 2 Diabetes

- blood glucose levels rise due to

1) Lack of insulin production

2) Insufficient insulin action (resistant cells)

- commonly detected after 40

- effects > 90%

eventually leads to β -cell failure
(resulting in insulin dependence)

Gestational Diabetes

3-5% of pregnant women develop gestational diabetes

Risk factors of developing GD

- Overweight prior to becoming pregnant
- Having sugar in your urine.
- Previously giving birth to a baby over 9 pounds
- Previously giving birth to a stillborn baby
- Having too much amniotic fluid (a condition called polyhydramnios)
- Member of a high risk ethnic group (Hispanic, Black, Native American, or Asian)
- Family history of diabetes
- Having gestational diabetes with a previous pregnancy

Complications of gestational diabetes

- Birth defects
- Affect major organs brain and heart
- Over-nutrition and excess growth of the baby.
- Fetal over-nutrition occurs
- Increased rate of miscarriage
- Large baby increases risks during labor and delivery

SCREENING

- **Type 1 diabetes Mellitus**: Acuteness of symptoms, screening is not recommended.
- **Type 2 Diabetes Mellitus** : Every 3 years in all adults beginning at age 45 years.
- **Children and Adolescents** : overweight (defined as BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal [50th percentile] for height) youths with at least two risk factors: a family history of type 2 diabetes in first- and second-degree relatives

- ⦿ Every 2 years starting at 10 years of age or at the onset of puberty.
- ⦿ **Gestational Diabetes** : first prenatal visit. initial screening is negative, retesting at 24 to 28 weeks of gestation

Testing

Fasting Plasma Glucose Test

(FPG) - (cheap, fast)

fasting B.G.L. 100-125 mg/dl
signals pre-diabetes

>126 mg/dl signals diabetes

Oral Glucose Tolerance Test (OGTT)

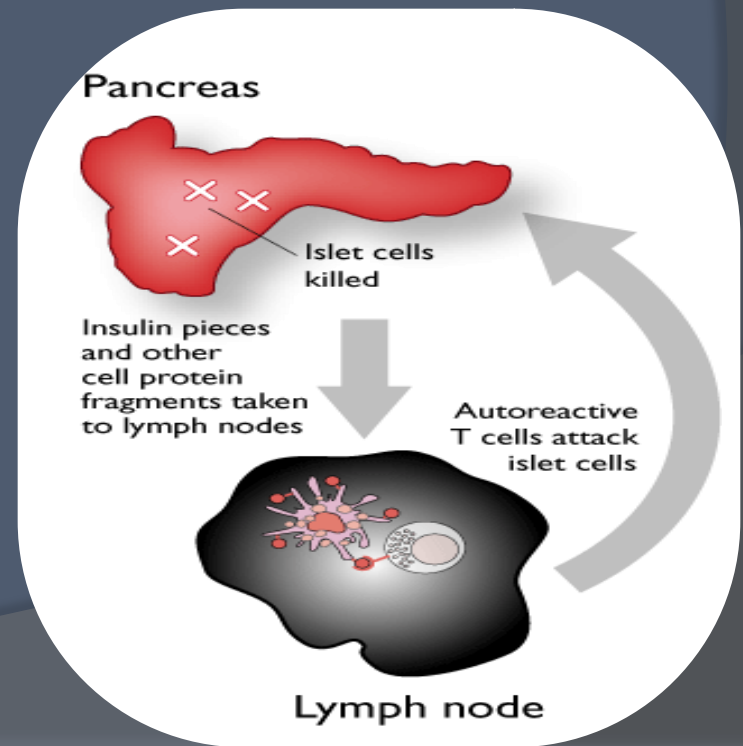
- * tested for 2 hrs after glucose-rich drink
- * 140-199 mg/dl signals pre-diabetes
- * >200 mg/dl signals diabetes

Glycated Hemoglobin tests A1C, result of 7% or less indicates good glucose control. A result of 8% or greater indicates that blood sugar levels are too high

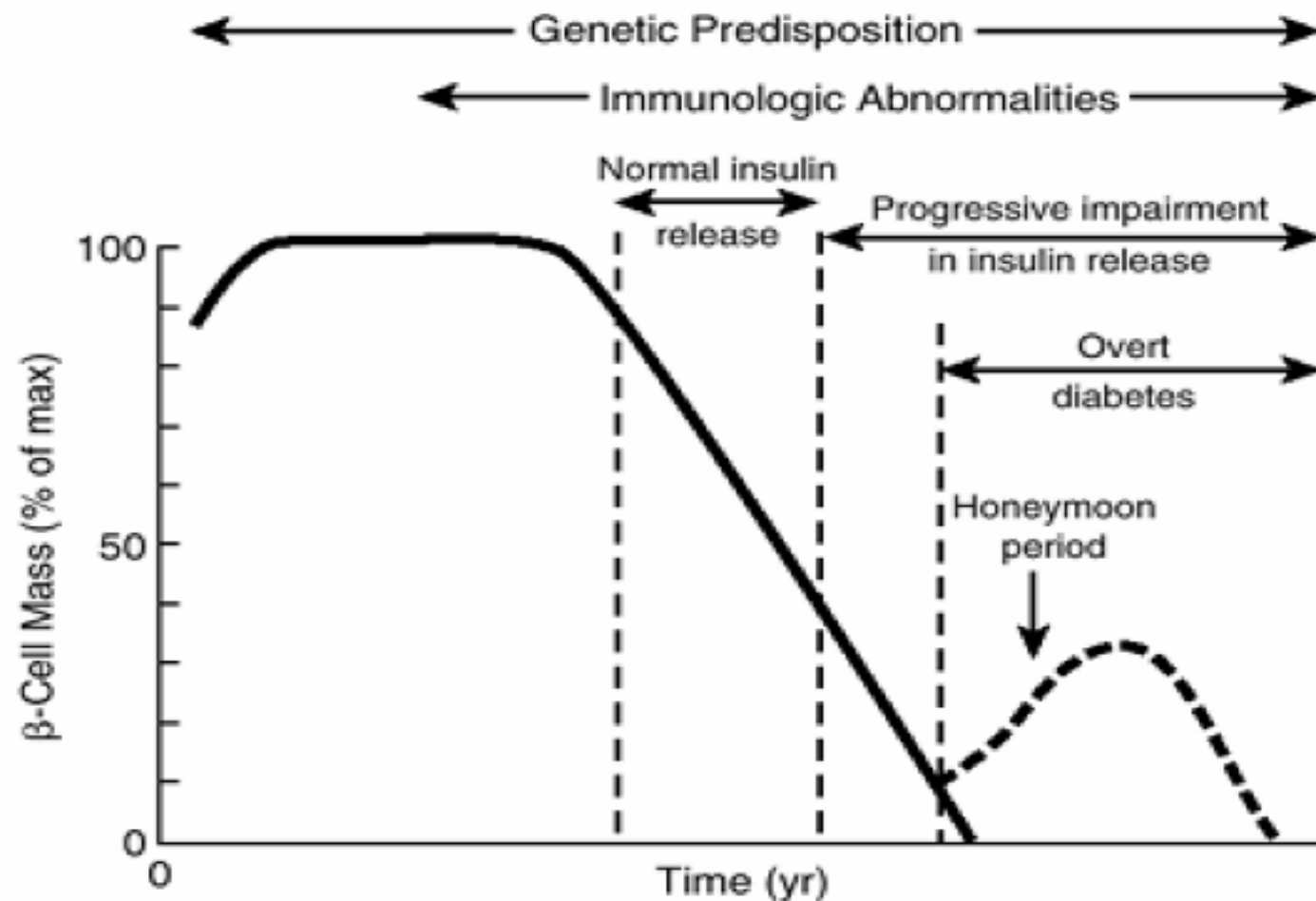
PATHOGENESIS

Type 1 Diabetes Mellitus

- Absolute deficiency of pancreatic β -cell *function*.
- Immune-mediated destruction of pancreatic β cells.



Proposed Scheme of Natural History of β -Cell Defect



Timing of trigger in relation to immunologic abnormalities is unknown. Note that overt diabetes is not apparent until insulin secretory reserves are <10–20% of normal.

Pathogenesis of Type 2 DM

Pancreatic Hormones

● Insulin (beta cells)

- stimulates the uptake of glucose by body cells thereby decreasing blood levels of glucose

● Glucagon (alpha cells)

- stimulates the breakdown of glycogen and the release of glucose, thereby increasing blood levels of glucose

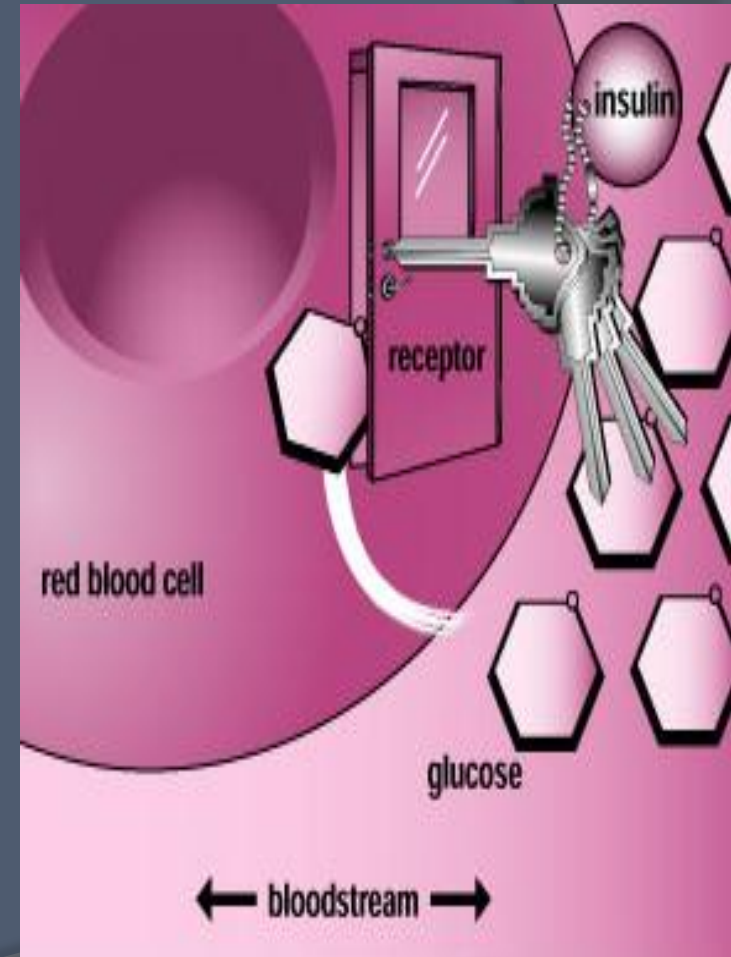
● Glucagon and insulin work together to regulate & maintain blood sugar levels

● Glycogen

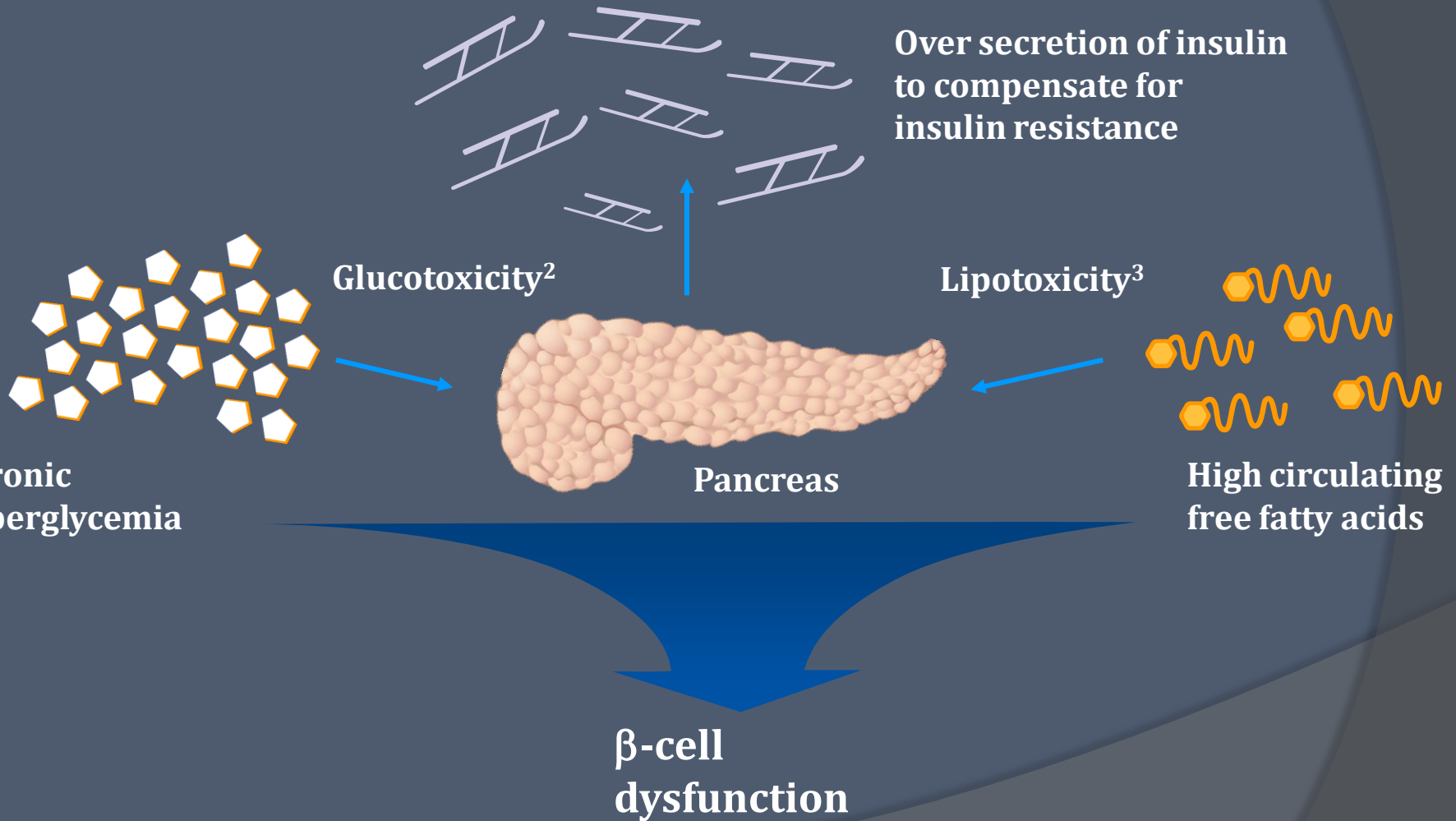
- Polysaccharide consisting of numerous monosaccharide glucoses linked together. Stored as an energy source in liver & muscles

Functions of insulin

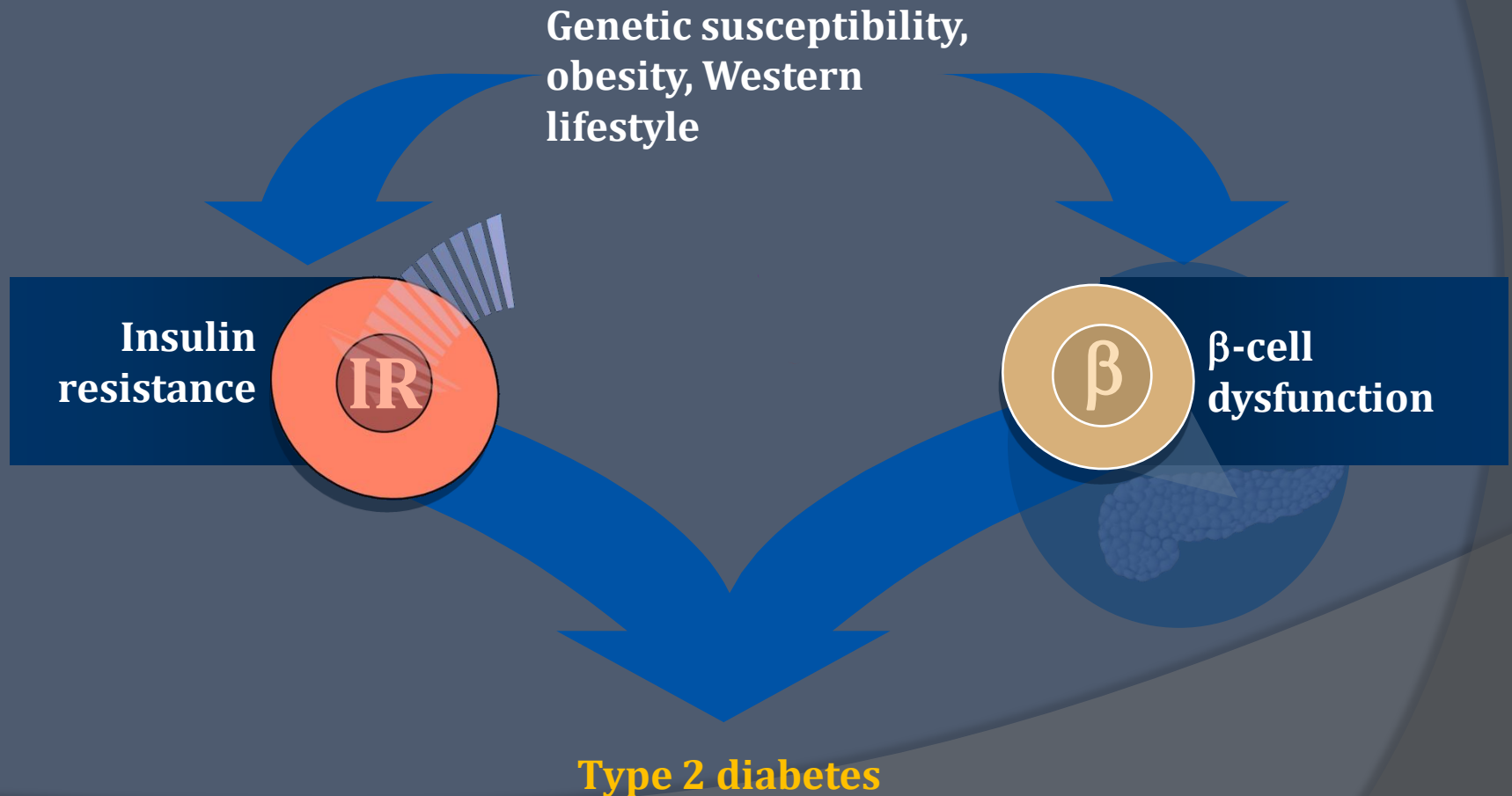
- ⦿ Enables glucose to be transported into cells for energy for the body
 - Glucose is the preferred fuel of the body cells and the only fuel that the brain can use
- ⦿ Converts glucose to glycogen to be stored in muscles and the liver
- ⦿ Facilitates conversion of excess glucose to fat
- ⦿ Prevents the breakdown of body protein for energy



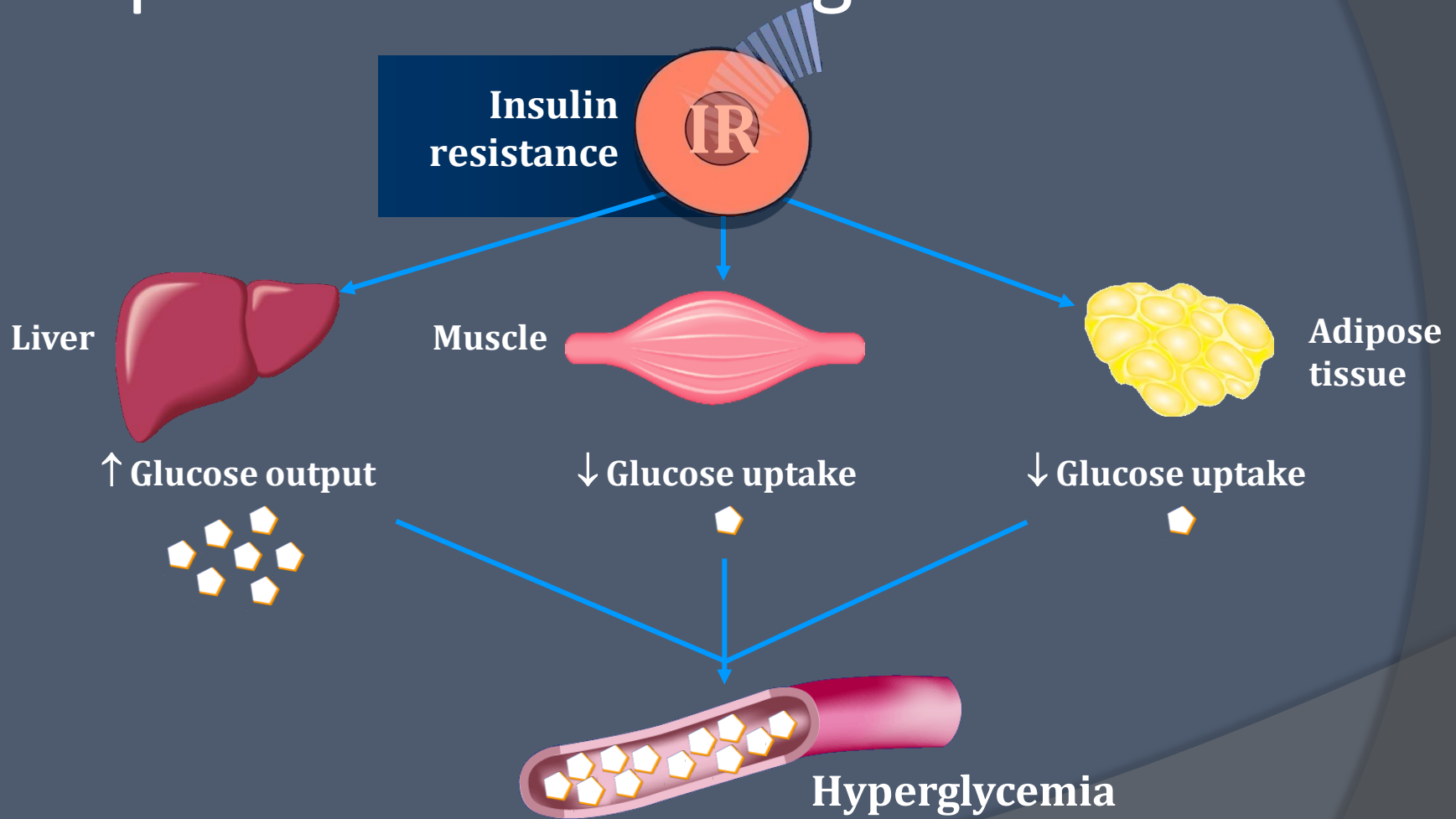
Why does the β -cell fail?



Insulin resistance and β -cell dysfunction are core defects of type 2 diabetes



Insulin resistance – reduced response to circulating insulin



Clinical Presentation

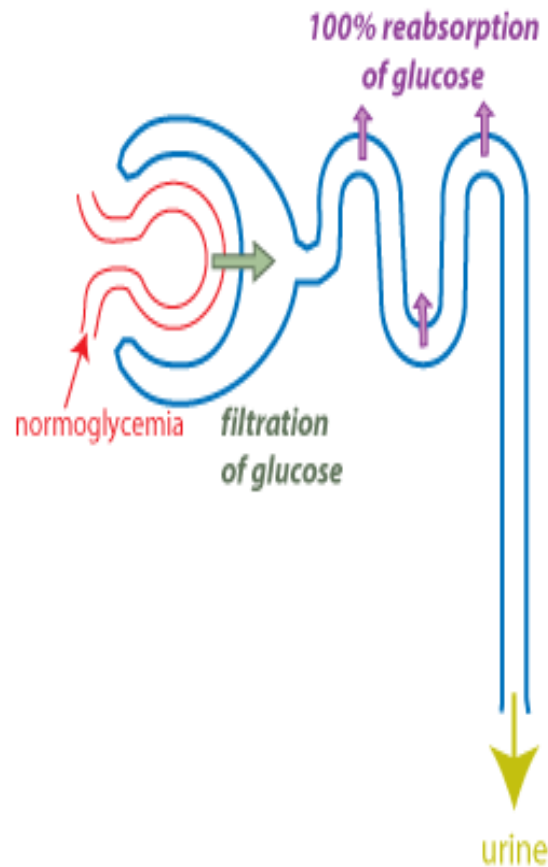
Diabetes Mellitus Type 1

⦿ Clinical Manifestations:

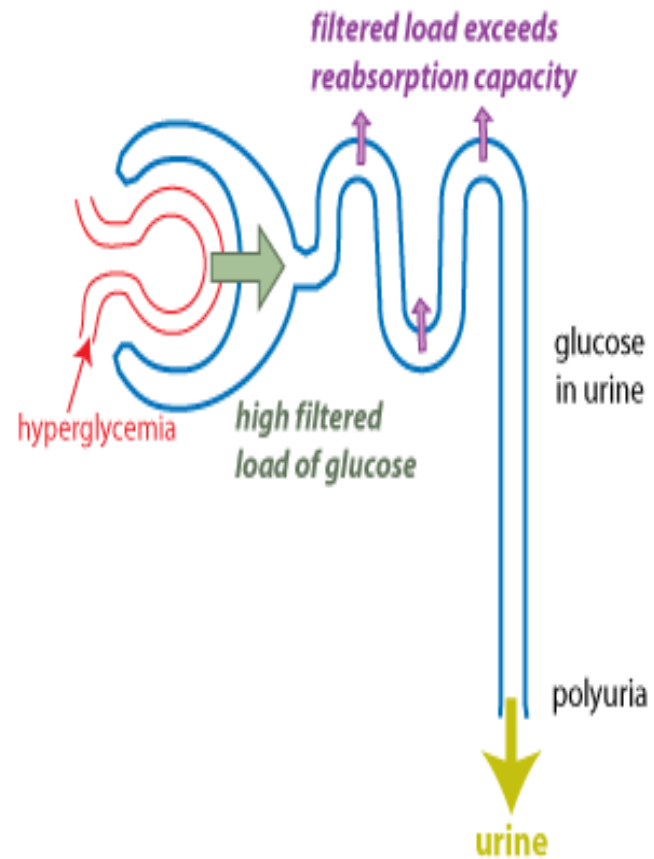
- Polyuria - increased urine
- Polydipsia - increased thirst
- Polyphagia - increased hunger
 - 3 'Ps"
- Weight loss
- Fatigue
- Nausea, vomiting

⦿ Ketoacidosis may be a presenting sign

normal glucose handling:



in diabetes mellitus:



Diabetes Mellitus Type 1

- Usually develop symptoms over a short period of time, and the condition is often diagnosed in an emergency setting
- In addition to high glucose levels, acutely ill type 1 diabetics have high levels of ketones.
 - As cells cannot get glucose, they burn fats as an alternate energy source
 - Ketones are produced by the breakdown of fat and muscle, and are toxic at high levels
 - Ketones in the blood cause a condition called "acidosis" or "ketoacidosis" (low blood pH)
 - Urine testing detects ketones in the urine
 - Blood glucose levels are also high.

Diabetes Mellitus Type 2

◎ Type 2 Clinical Manifestations:

- Polydipsia - increased thirst
- Polyuria - increased urine
- Polyphagia - increased hunger
- Fatigue
- Blurred vision
- Slow healing infections
- Impotence in men

<i>Characteristics</i>	Type 1	Type 2
Percentage of diabetic population	5–10%	90%
Age at onset	Usually <30 yr; peaks at 12–14 yr	Usually >40 yr, but increasing prevalence among obese children
Pancreatic function	Usually none, although some residual C-peptide can sometimes be detected at diagnosis, especially in adults	Insulin present in low, “normal,” or high amounts
Pathogenesis	Associated with certain HLA types; presence of islet cell antibodies suggests autoimmune process	Defect in insulin secretion; tissue resistance to insulin; ↑ hepatic glucose output
Family history	Generally not strong	Strong
Obesity	Uncommon unless “overinsulinized” with exogenous insulin	Common (60–90%)
History of ketoacidosis	Often present	Rare, except in circumstances of unusual stress (e.g., infection)

<i>Characteristics</i>	Type 1	Type 2
Clinical presentation	Moderate to severe symptoms that generally progress relatively rapidly (days to weeks): polyuria, polydipsia, fatigue, weight loss, ketoacidosis	Mild polyuria, fatigue; often diagnosed on routine physical or dental examination
Treatment	Insulin, Diet, Exercise	Diet, Exercise, Oral antidiabetic agents (α -glucosidase inhibitors, biguanides, non-sulfonylurea insulin secretagogues, sulfonylureas, thiazolidinediones) and Insulin

Vascular Complications of Type 2 Diabetes

- Vascular complications are the major cause of morbidity and mortality in Type 2 diabetes

Microvascular

nephropathy
retinopathy
neuropathy

Macrovascular

cardiovascular disease
peripheral vascular disease
cerebrovascular disease

- Findings from UKPDS show that intensive glycaemic control in the treatment of Type 2 diabetes results in a decrease in diabetes-related microvascular complications

Vascular Complications

Ways to reduce risks

- Control cholesterol, blood pressure
- No smoking
- Maintain good blood glucose levels
- Get regular exercise
- Aim for healthy body weight
- Medical checks including electrocardiograph (ECG)

MICROVASCULAR

Diabetic Nephropathy

- In people with diabetes, the nephrons thicken and slowly become scarred over time.
- The kidneys begin to leak and protein (albumin) passes into the urine.
- The exact cause is unknown.
- Medicine to use are **ACE inhibitors and angiotensin receptor blockers (ARBs)**.

Diabetic Retinopathy

- ② Over accumulation of Glucose damages the tiny blood vessels in the retina.
- ② Treatment : Laser treatment

Diabetic neuropathy

◎ **Polyol pathway : Sorbitol accumulates.**

- Extra glucose is shunted into the polyol pathway and converted to sorbitol and fructose by the enzymes aldose reductase and sorbitol dehydrogenase.
- **Advanced glycation end products.**
- **Oxidative stress**

Diabetic neuropathy

- ◎ **Symptoms include** : Loss of sensory function in lower extremities, pain and paresthesias
- ◎ **Treatment** : Analgesic (ibuprofen 600 mg) and antidepressants (Imipramine, amitriptyline (10 to 25 mg bedtime ,Desipramine combination of fluphenazine plus nortriptyline), topical capsaicin, CBZ, phenytoin, lidocaine and mexiletine.

- **Anticonvulsant, topiramate**, has shown promise in the reduction of symptoms, with the positive side effect of weight loss in type 2 diabetes patients, although tolerability is problematic

- ◎ **New Drug approved recently : Tapentadol (NUCYNTA)**
- ◎ Extended-release tablets, an oral analgesic taken twice daily.
- ◎ **The first and only opioid approved** by the FDA for neuropathic pain associated with DPN. **Aug 2011-**
- ◎

◎ **Tapentadol : Contraindicated in**

1. Respiratory depression
2. Acute or severe bronchial asthma or hypercarbia
3. Hypersensitivity

Diabetic neuropathy management

Pregnancy

- At the end of the third trimester, the physician can prescribe amitriptyline, gabapentin, and other medications as indicated if the benefit clearly outweighs the risk to the fetus.

◎ Staging scale of diabetic polyneuropathy is as follows :

1. N0 - No neuropathy
2. N1a - Signs but no symptoms of neuropathy
3. N2a - Symptomatic mild diabetic polyneuropathy; sensory, motor, or autonomic symptoms; patient able to heel walk
4. N2b - Severe symptomatic diabetic polyneuropathy (as in N2a, but patient unable to heel walk)
5. N3 - Disabling diabetic polyneuropathy

Macrovascular

Cardiovascular Disease

- ② The high glucose in the bloodstream damages the arteries, causing them to become stiff and hard.
- ② Fatty material that builds up on the inside of these blood vessels can eventually block blood flow to the heart or brain, leading to heart attack or stroke.

Peripheral Vascular Disease and Foot Ulcers

- ⦿ Narrowing of the lumen of arteries in the legs, causing a reduction in circulation.
- ⦿ Claudication, rest pain or vascular ulceration



Figure 41-10 Neuropathic ulcers occur on pressure points in areas with diminished sensation in diabetic polyneuropathy. Pain is absent (and therefore the ulcer may go unnoticed).

Diabetes Management

- Healthy eating
- Exercise
- Monitoring
- Medication/Insulin
- Health Care Team

Management of Diabetes

Type One: Insulin + Healthy Eating + Exercise

Type Two:

Healthy eating + exercise

then Healthy eating + exercise + tablets

then Healthy eating + exercise + tablets + insulin

Healthy Eating

◎ Snacks for all?

- People on sulphonyureas and conventional insulin therapies may need snacks to avoid hypos
- Newer oral hypoglycaemic agents and insulins make snacks less necessary
- Snack advice should be individualised and the person advised to blood glucose monitor

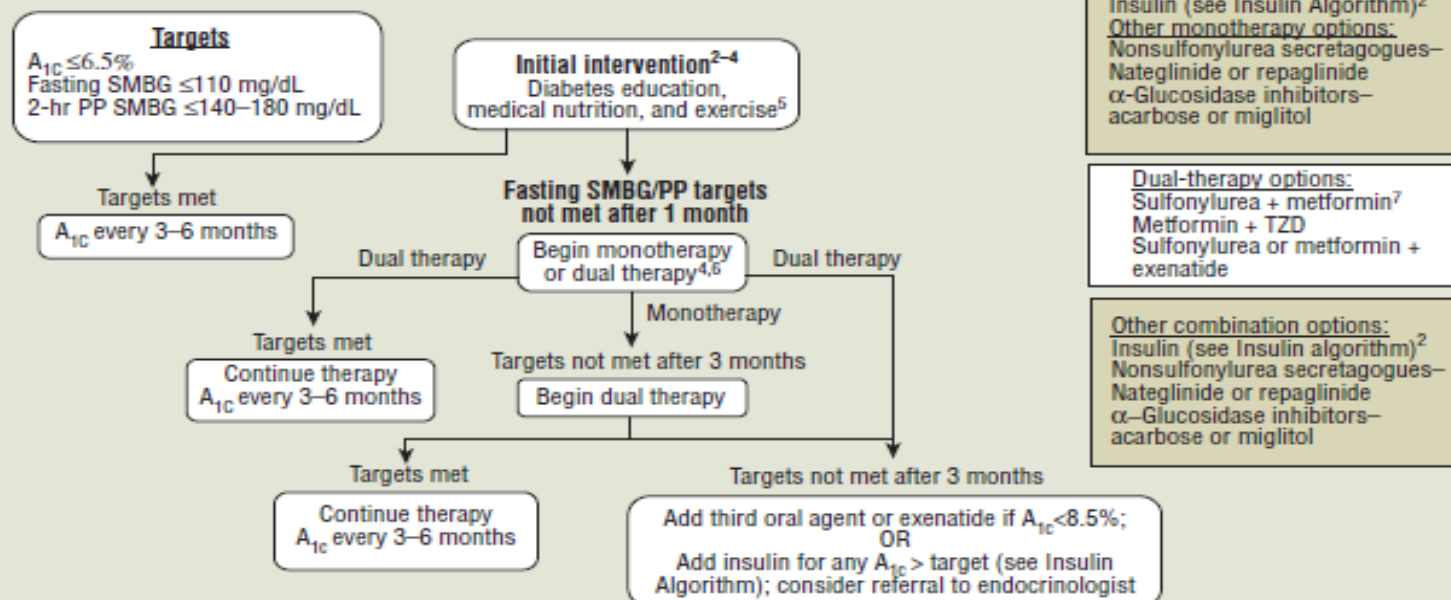
Exercise & Weight Loss

◎ Benefits of a 10kg weight loss

- Fall of 50% in fasting glucose
- Fall of 10% total cholesterol
- Fall of 15% LDL
- Fall of 30% triglycerides
- Rise of 8% HDL
- Fall of 10 mmHg systolic, 20 mmHg diastolic


Glycemic Control Algorithm

Glycemic Control Algorithm for Type 2 DM in Children¹ and Adults



¹Metformin is the only FDA-approved oral diabetic agent in children (\geq age 10); other agents may be used at the discretion of the clinician. ²See Insulin Algorithm for Type 2 Diabetes Mellitus in Children and Adults. ³If initial presentation with glucose ≥ 260 mg/dL in symptomatic patient, consider insulin or insulin analog as initial intervention, probably with dual therapy. ⁴Monotherapy with sulfonylurea or metformin does not sustain HbA_{1c} reductions (UKPDS study); dual therapy certainly indicated if initial glucose ≥ 210 mg/dL or $HbA_{1c} \geq 9.0\%$. ⁵These interventions should be maintained lifelong; see Medical Nutrition, Weight Loss, and Exercise Algorithms. ⁶If initial dual therapy is initiated, decide on add-on therapy options within 3 months if glycemic targets are not met. ⁷Sulfonylureas and metformin are the most studied and least expensive oral diabetes agents; glipizide ER and glimepiride have a lower incidence of hypoglycemia than glyburide. **Publication #45-11265.**

FIGURE 77-9. Glycemic control algorithm for type 2 diabetes mellitus (DM) in children and adults. See www.texasdiabetesCouncil.org for current algorithms. (A_{1c} , glycosylated hemoglobin; ER, extended release; PP, postprandial; SMBG, self-monitoring of blood glucose; TZD, thiazolidinedione; UKPDS, United Kingdom Prospective Diabetes Study.) (Reprinted with permission from the Texas Diabetes Council.)

Secretagogues	Insulin sensitizers	Alpha-glucosidase inh
Sulfonylureas	Biguanides e.g. Metformin	Alpha-glucosidase Inhibitors
Meglitinides 	Glitazones - Thiazolidinediones	
Peptide analogs		
AMYLIN AGONISTS -Anti-hyperglycemic Synthetic Analogs	DPP-4 INHIBITORS - Dipeptidyl peptidase-4 inhibitor -Gliptins	Glucagon-like peptide-1 (GLP-1) AGONIST - Incretin Mimetics

Oral Hypoglycaemics

- Type 2 diabetes generally results from either a decrease in:
 - Insulin resistance (activity)
 - Insulin secretion
- The use of oral medications with diet & exercise can manage the problem but oral hypoglycaemics are **NOT insulin** & therefore cannot replace insulin
- Hypoglycaemics help the body better utilise or make insulin
 - Beta cells must make enough insulin to work, otherwise combination with insulin is necessary.

Classes of Oral Hypoglycaemic Agents

◎ *Target insulin secretion*

- Sulphonylureas (glibenclamide)
- Meglitinides (repaglinide)

◎ *Target insulin resistance*

- Biguanides (metformin)
- (Thiazolidinediones) (rosiglitazone)

◎ *Target glucose absorption from intestine*

- Alpha glucosidase inhibitors (acarbose)

Biguanides: Metformin

- ⦿ Decreases hepatic glucose output
- ⦿ Increases peripheral uptake of glucose into cells
- ⦿ Monotherapy or adjunct
- ⦿ Does not produce weight gain, useful in obese patients.
- ⦿ Dose:
 - 500mg daily increasing gradually to 500mg three times a day
 - Max dose 3g - most only tolerate 2g daily

Metformin

- ⦿ Reduces HbA1C by 1-2%
- ⦿ **Contraindications:**
 - **May provoke lactic acidosis**
 - Contraindicated with Renal impairment
 - Liver & heart failure
 - Severe dehydration
- ⦿ **Side effects**
- ⦿ Nausea, vomiting, diarrhoea, abdominal discomfort, **impaired B₁₂ absorption** – People of 50 and older consume 2.4 micrograms of vitamin B12 daily from either fortified foods or supplements.

Sulphonylureas

- Stimulate beta cells to release insulin from functioning pancreatic cells
- First Generation : Acetohexamide, Chlorpropamide, Tolazamide, and Tolbutamide.

Examples:

- Glibenclamide
 - Widely used, long acting
 - Avoid in elderly, Renal impairment
- Gliclazide
- Glipizide
- Glimepiride
- Dose: varies per drug
- Drug interactions: multiple

Sulphonylureas

- Reduces HbA1C by 1-1.5%
- Choice of agents available (dependent on onset, duration of action & elimination)
- 1st choice in lean patients
- Drugs broken down in liver so avoid in people with liver and renal impairment
- Adverse Effects:
 - GI disturbances, headache
 - Mild skin reactions, photosensitivity, mild alcohol intolerance.
 - Hypoglycaemia
 - Weight gain
- 5-10% secondary failure rate / year

Sulphonylurea

⦿ Long Term Side Effects

- Beta cell exhaustion
 - Secondary failure of treatment
- Therefore, use
 - Short-acting versions
 - Lowest effective doses
- After many years of treatment
 - Secondary failure inevitable

- ⦿ Glipizide – 2.5 – 5 MG
- ⦿ Glyburide -1.25–2.5mg
- ⦿ Glimepiride 2 mg
- ⦿ Duration of action up to 24 hrs.

Alpha Glucosidase Inhibitors

- Glucosidase inhibitors are competitive, reversible inhibitors of pancreatic α -amylase and membrane-bound intestinal α -glucosidase hydrolase enzymes. The drugs leads to blocking the enzymatic degradation of complex carbohydrates in the small intestine. Thus, less carbohydrate is absorbed and the carbohydrate that is absorbed is delayed.
- Only effective if taken at same time as food, as drug needs to reach intestines at same time as food to work.
- Example:
 - Acarbose and Miglitol ,Voglibose
- Monotherapy or adjunct

Alpha Glucosidase Inhibitors

◎ Dose:

- 50mg daily increasing gradually to three times a day, if necessary up to 200mg three times a day
- Take with or just prior to meal
- Treat hypo with glucose

◎ Side effects:

- flatulence, diarrhoea, abdominal distension & pain

◎ Contraindications

- Pregnancy / breast-feeding
- Liver and severe renal impairment
- Inflammatory bowel disease & intestinal obstruction

Alpha Glucosidase Inhibitors

● In therapy:

- Add-on to treatment with metformin or sulphonylureas
- Part of triple therapy
- Monotherapy
- With insulin in Type 1 diabetes
- Reduces HbA1C by 0.5%
- Safe
- Weight neutral
- Dose coupled with meals
- Monitor LFTs during 1st 6-12mths

Meglitinides

- **Prandial Glucose Regulators** (PGR's)
- Stimulate beta cells to release insulin, response however is glucose dependent
- Following meals there is an early phase insulin release
- In Type 2 diabetes, this is lost causing post prandial spikes
- PGR mimic release of physiological insulin, as they are short acting and do not stimulate the beta cells constantly

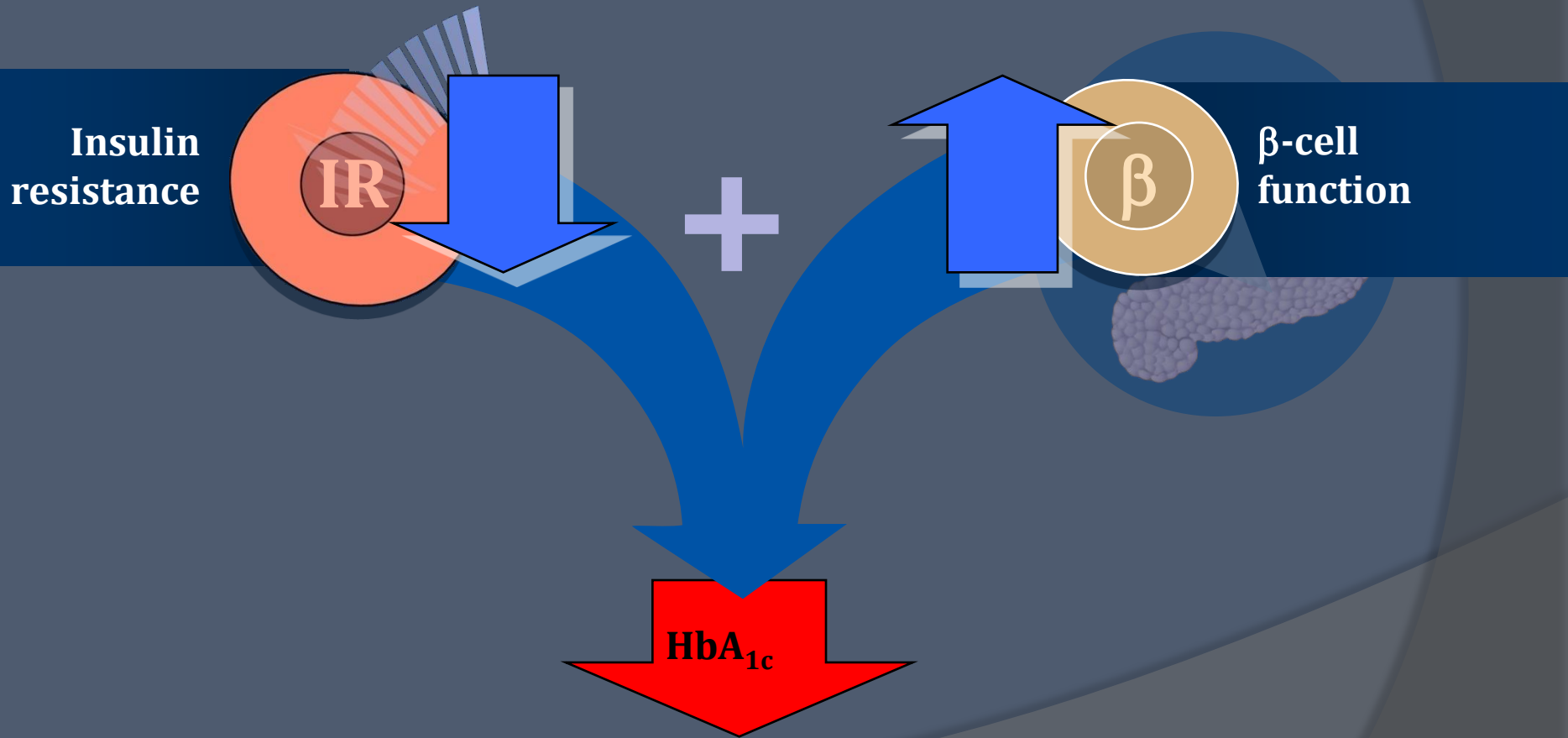
Meglitinides -Non-sulfonylurea secretagogues

- **Repaglinide AND Nateglinide**
- Dose: initially 500mcg, up to 4mg as a single dose
- Must be taken within 30 mins before a main meal
- Contraindications
 - Diabetic ketoacidosis
 - Pregnancy & breast feeding
 - Type 1 diabetes
 - Severe hepatic impairment (repaglinide only)
 - Monitoring: LFTs periodically

Meglitinides

- ⦿ Quickly lowers post prandial glucose levels (no lag before response)
- ⦿ ↓HbA₁C 0.5-2%
- ⦿ Short half life
- ⦿ Meal time flexibility
- ⦿ ↓Risk of weight gain

The dual action of thiazolidinediones reduces HbA_{1c}



Thiazolidinediones

- Improves insulin sensitivity skeletal muscle, adipose tissue & liver, thereby promoting uptake of fatty acids & glucose at these sites
- Actions
 - Counteract insulin resistance
 - Reduces HbA_{1c} by 1-2%
 - ? Alternative to insulin (Type 2 DM only)
 - Beneficial effect on lipids
- Examples:
 - Pioglitazone, Rosiglitazone
 - Adjunct with either metformin or SU
- Dose: varies per drug
 - Pioglitazone (Actos): 15-30mg once daily
 - Rosiglitazone (Avandia): 4 mg/day, or + metformin 8 mg/day

Thiazolidinediones

⦿ **Contraindications**

- Pregnancy / breast-feeding
- Liver impairment
- Heart failure

⦿ **Side-effects:**

- Oedema, weight gain, GI disturbances, headache, dizziness

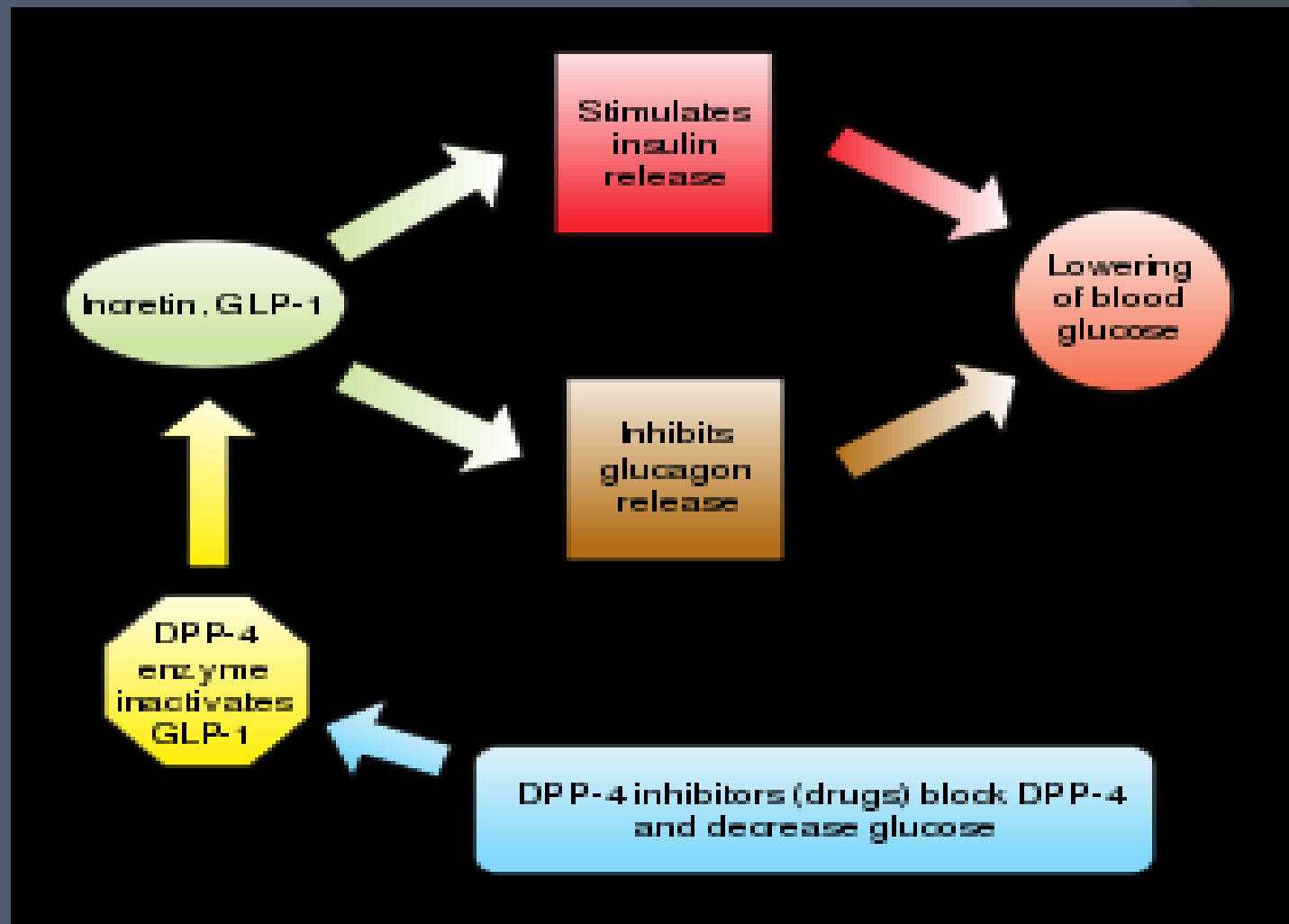
INCRETINS

- **Exenatide** : 5 micrograms subcutaneously twice daily within the 60 minute period before the morning and evening meals. Exenatide should not be administered after a meal.

Dipeptidyl peptidase 4 Inhibitors

- ⦿ **DPP-IV inhibitors : Sitagliptin AND Vildagliptin**
- ⦿ prolong the half-life of an endogenously produced glucagon-like peptide-1 (GLP-1).
- ⦿ The average reduction in HbA1c with vildagliptin or sitagliptin is approximately 0.7% to 1% at a dose of 100 mg a day.
- ⦿ **Dose :** Vildagliptin will be dosed orally, at 50 mg to 100 mg daily.
- ⦿ Sitagliptin is dosed orally at 100 mg daily unless renal insufficiency is present.

- ◎ **ADR's** ∴ Mild hypoglycemia
- ◎ No significant increases in peripheral edema, hypertension, or cardiac outcomes have been noted to date.



Selective Inhibitor of Low-Affinity Sodium Glucose Cotransporter (SGLT2)

- **Canagliflozin** blocks the reabsorption of glucose by the kidney, increasing glucose excretion and lowering blood glucose levels.
- New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) seeking approval for the use of **canagliflozin**, an investigational, oral, once-daily, selective sodium glucose co-transporter 2 (SGLT2) inhibitor, for the treatment of adult patients with type 2 diabetes.

- ◎ Dapagliflozin (FORXIGA) : Positive CHMP opinion.
- ◎ BREAST AND BLADDER CANCERS
- ◎ Empagliflozin: Boehringer and Lilly

Amylin Agonist

- ⦿ **Pramlintide** : reductions in A1C values
- ⦿ 0.5 - 1.0%.
- ⦿ Given at mealtimes.
- ⦿ 60 pen-injector for doses of 15 mcg, 30 mcg, 45 mcg, 60 mcg.
- ⦿ 120 pen-injector for doses of 60 mcg and 120 mcg.

Optimal Glycaemic Control

- One of the primary goals in treating diabetes is to 'treat to target' in terms of HbA_{1c}
- With long term treatment, 75% of patients do not maintain optimal glycaemic control (<7% HbA_{1c}) with monotherapy alone
- Optimal combinations of oral therapy to treat diabetes need to be found to achieve this target
- Combination therapy used when monotherapy fails

Combination With Insulin

- ⦿ Insulin therapy, or
- ⦿ Insulin therapy + metformin, or
- ⦿ Insulin therapy + sulphonylurea
- ⦿ Monitor glycaemic control
 - Target HbA1C = 7%
- ⦿ Many oral treatment options
- ⦿ Change therapy in response to poor control

Oral Hypoglycaemics

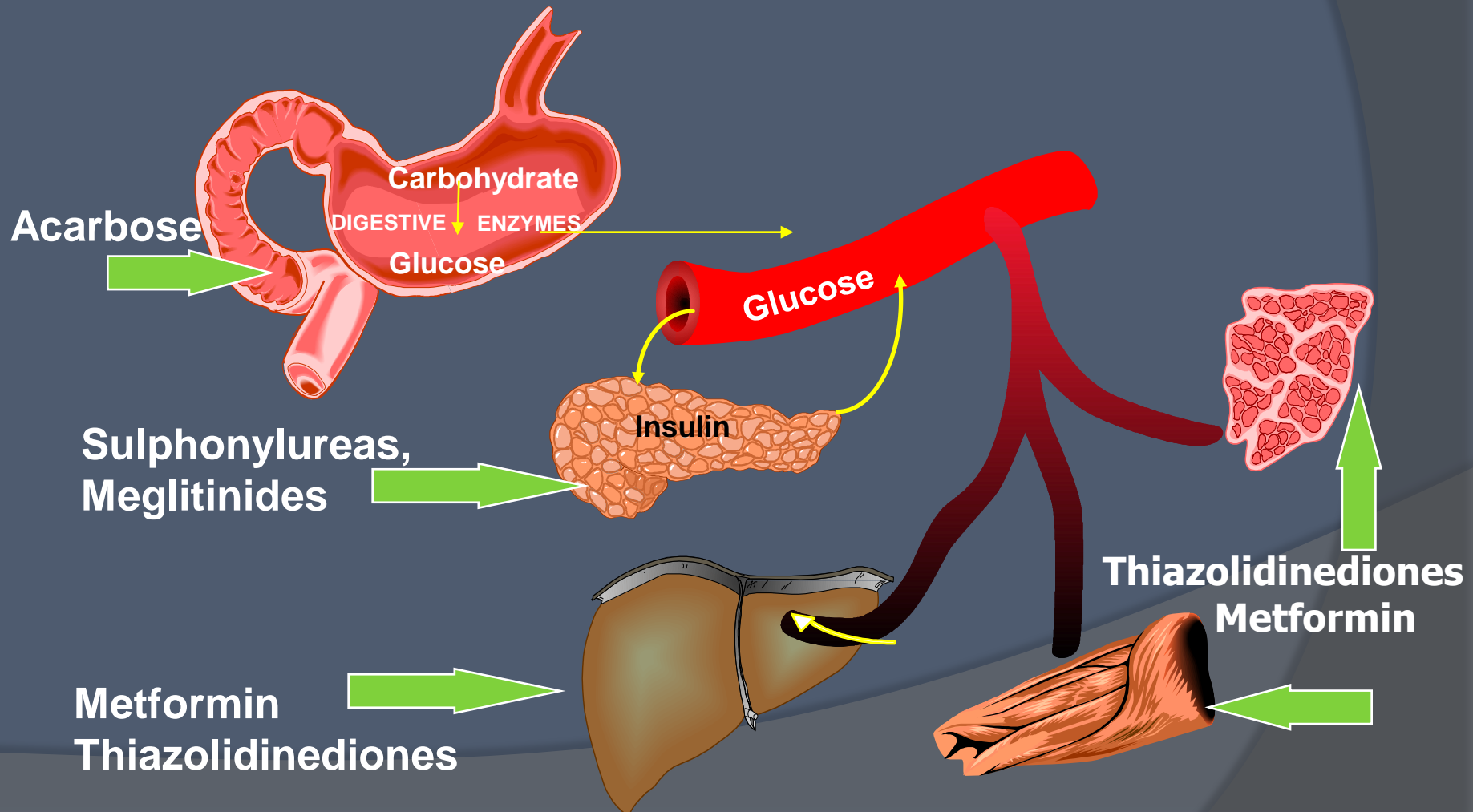


Table 1. Anti-Hyperglycemic Medications for Type 2 Diabetes Mellitus

Agent	Mechanism of Action	Expected HbA1c Reduction, %	Adverse Effects	Cardiovascular Issues
Sulfonylureas Glyburide Glipizide Glimepiride	Bind to sulfonylurea receptors on pancreatic islet cells, closing K _{ATP} channels, stimulating insulin release; relatively long duration of action	≈ 1–2	Hypoglycemia, weight gain	Hypoglycemia may precipitate ischemia, arrhythmia; cardiac K _{ATP} channel closure may impair ischemic preconditioning
Glinides Nateglinide	Bind to sulfonylurea receptors on pancreatic islet cells, closing K _{ATP} channels, stimulating insulin release; relatively short duration of action	≈ 1–2	Hypoglycemia, weight gain	Hypoglycemia may precipitate ischemia, arrhythmia; cardiac K _{ATP} channel closure may impair ischemic preconditioning
Biguanides Metformin	Decrease hepatic glucose production	≈ 1–2	Diarrhea, nausea, lactic acidosis, decreased B12 levels	May improve CVD outcomes (UKPDS ⁴²); should not be used in acute or unstable HF because of lactic acidosis risk
α-Glucosidase inhibitors Acarbose Miglitol	Slow gut carbohydrate absorption	≈ 0.5–1.0	Gas, bloating	Improves postprandial glucose excursions, which are more tightly associated with CVD than fasting glucose; may reduce MI risk (STOP-NIDDM ⁴³)
Thiazolidinediones Rosiglitazone Pioglitazone	Activate the nuclear receptor PPAR-γ, increasing peripheral insulin sensitivity; also reduces hepatic glucose production	≈ 1–1.5	Weight gain; edema; possible bone loss in women	May precipitate clinical HF in predisposed individuals; contraindicated in NYHA class III–IV HF (because of fluid retention.); not recommended in class II HF ⁴⁴ ; pioglitazone may reduce MI, stroke risk (PROactive ⁴⁵); rosiglitazone may increase MI risk ^{46,47}
Incretin modulators GLP-1 mimetics Exenatide	Increase glucose-dependent insulin secretion, decrease glucagon secretion, and delay gastric emptying; inhibit degradation of endogenous GLP-1 (and GIP-1), thereby enhancing these effects of these incretins (see above)	≈ 1	Nausea, vomiting	Very preliminary data suggest possible benefit in patients with cardiomyopathy ^{20,21}
DPP-4 inhibitors Sitagliptin		≈ 0.6–0.8	---	
Amylin analogues Pramlintide	Decrease glucagon secretion and delay gastric emptying	≈ 0.4–0.6	Nausea, vomiting	---
Insulins Glargine, detemir NPH, lente Regular Lispro, aspart, glulisine Premixed	Increase insulin supply	No limit (theoretically)	Hypoglycemia; weight gain; edema (at high doses)	Retrospective data in HF suggests worse clinical outcomes in HF patients who require and are treated with insulin.

PPAR indicates peroxisome proliferator-activated receptor; NYHA, New York Heart Association; and NPH, neutral protamine Hagedorn.

INSULIN THERAPY

..\education videos\Mechanism of action of insulin -
YouTube.mp4

INSULIN ALGORITHM FOR TYPE 2 DIABETES MELLITUS IN CHILDREN¹ AND ADULTS

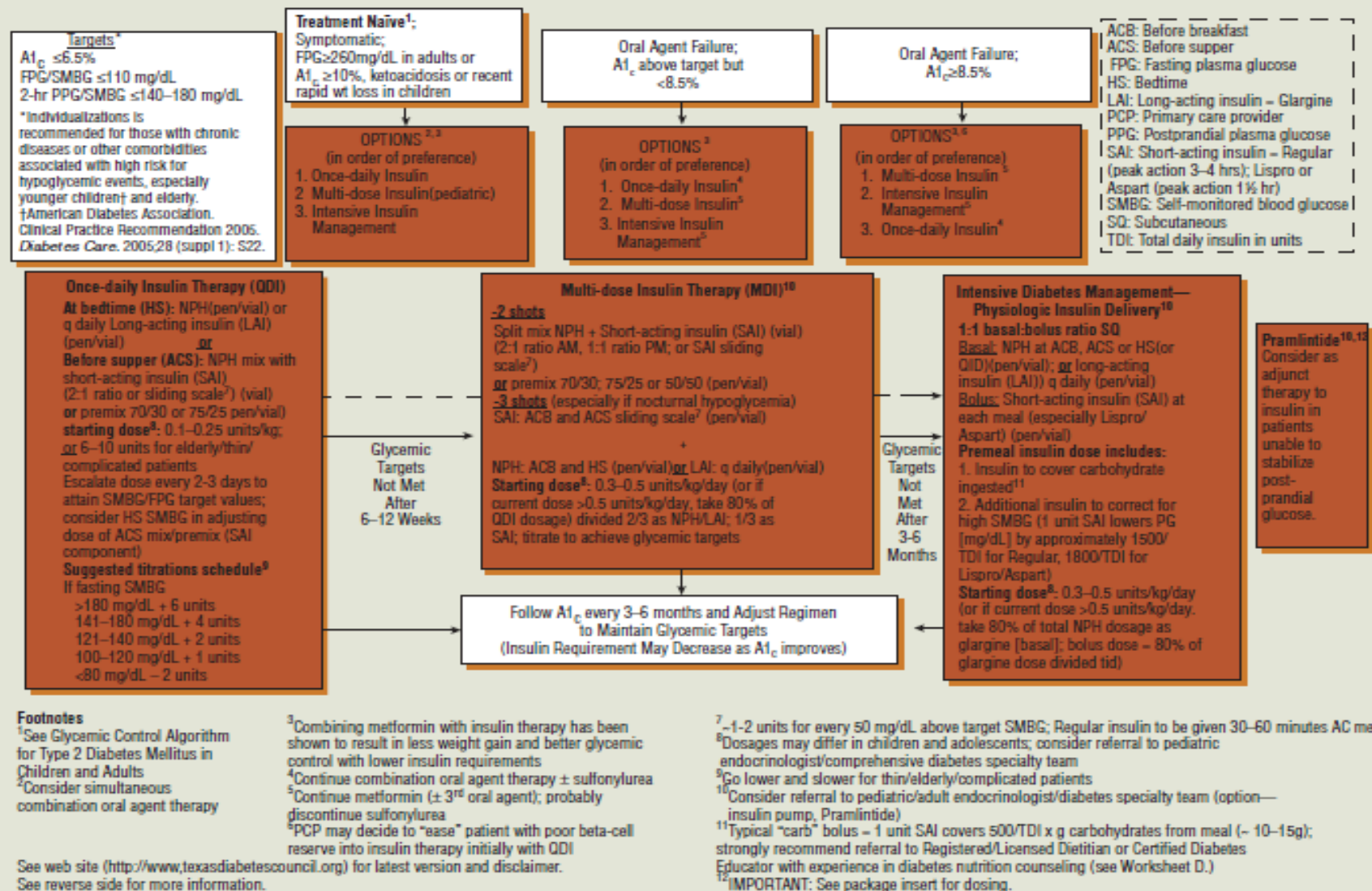


FIGURE 77-10. Insulin algorithm for type 2 diabetes mellitus (DM) in children and adults. See www.texasdiabetesCouncil.org for current algorithms. (Reprinted with permission from the Texas Diabetes Council.)

Who should have insulin therapy?

- ⦿ Newly Diagnosed Type 1
- ⦿ The Type 2 diabetic on maximum tablets
- ⦿ The Type 2 diabetic with contraindications to OHA e.g renal failure, poor tolerance
- ⦿ Pregnancy
- ⦿ Post acute MI
- ⦿ Acute illness/ infection

Control of BGL essential to minimise long term complications

Types of Insulin

⦿ **Source**

- Animal sources
- Recombinant DNA = human insulin

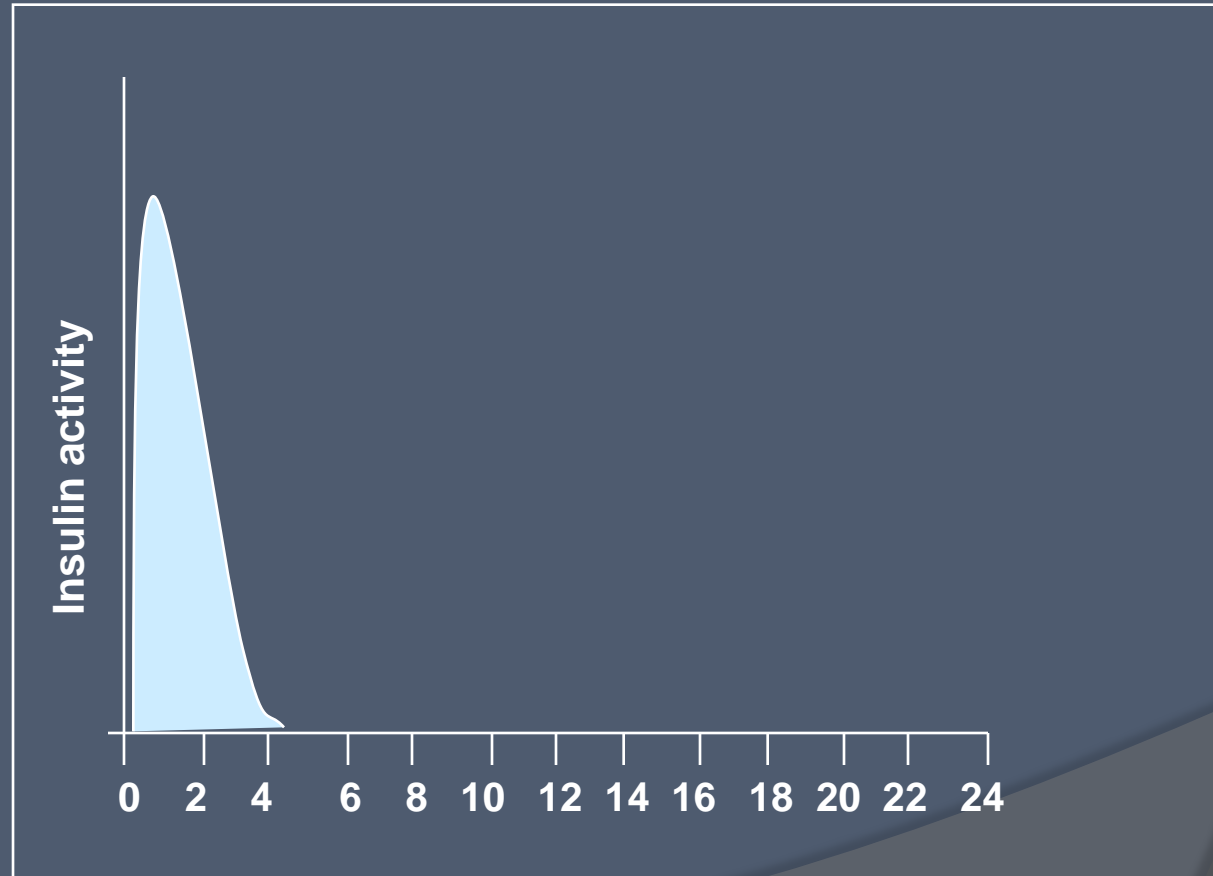
⦿ **Duration of action**

- Rapid acting
- Short acting
- Intermediate acting
- Long-acting
- Biphasic

Rapid-acting Insulin

- ⦿ Examples
 - Humalog (Lilly)
 - Novorapid (Novo Nordisk)
- ⦿ Very rapid onset approx 15 mins;
 - ensure food intake after administration
- ⦿ Peak action 1 hour, duration of action 4 hours
- ⦿ Can be administered just before or even after meals
- ⦿ Hypoglycaemic effect over in < 3 hours
- ⦿ Clear solution
- ⦿ Only form that can be given IV
- ⦿ May be combined with longer acting insulin

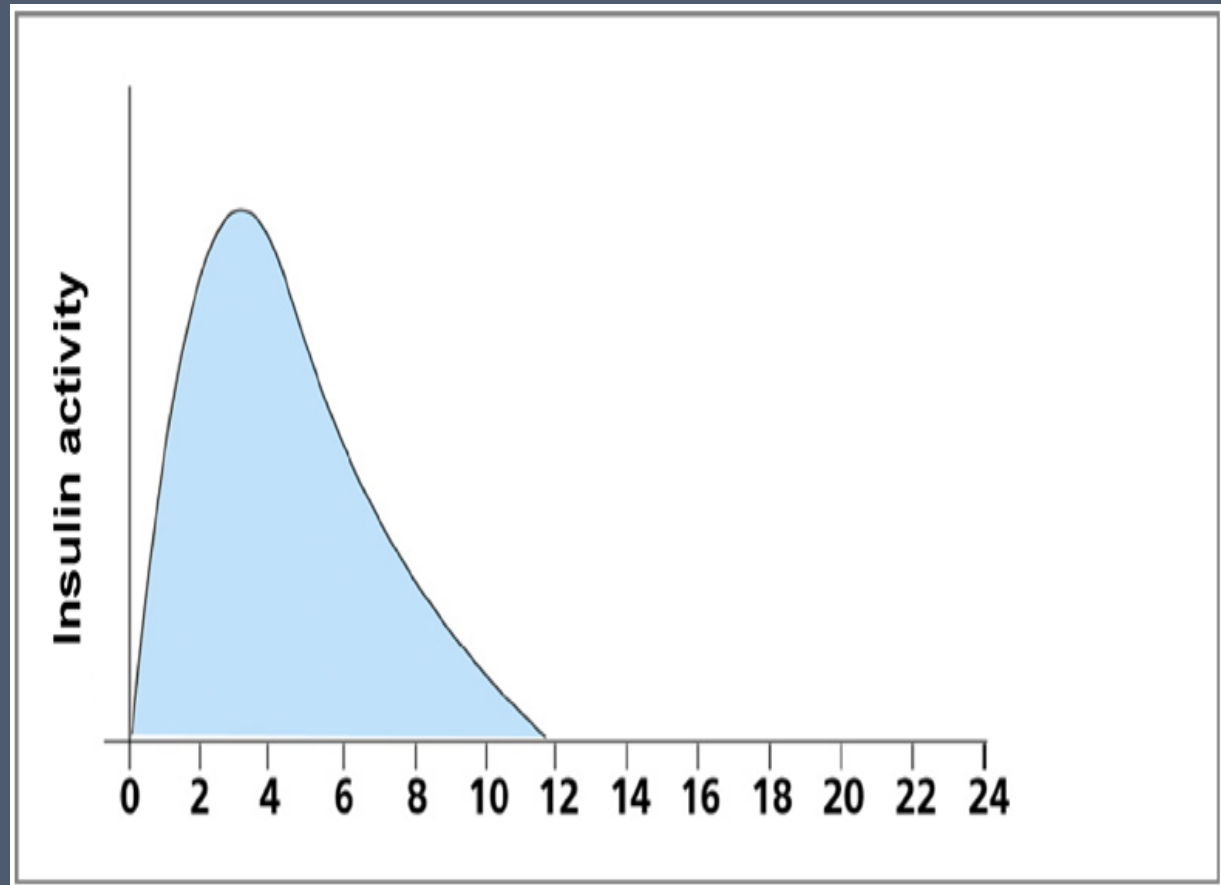
Rapid acting



Short-acting Insulin

- ⦿ Short acting = soluble or neutral insulin
- ⦿ Rapid onset of action (30-60 mins)
 - ensure food intake $\frac{1}{2}$ hour after administration
- ⦿ Peak 2-4 hours, duration 6-8 hours
- ⦿ **Examples**
 - Human Actrapid (Novo Nordisk)
 - Humulin R (Lilly)
 - Hypurin Neutral (Beef) (Aspen)
- ⦿ Injected < 30 mins before meals
- ⦿ Clear solution

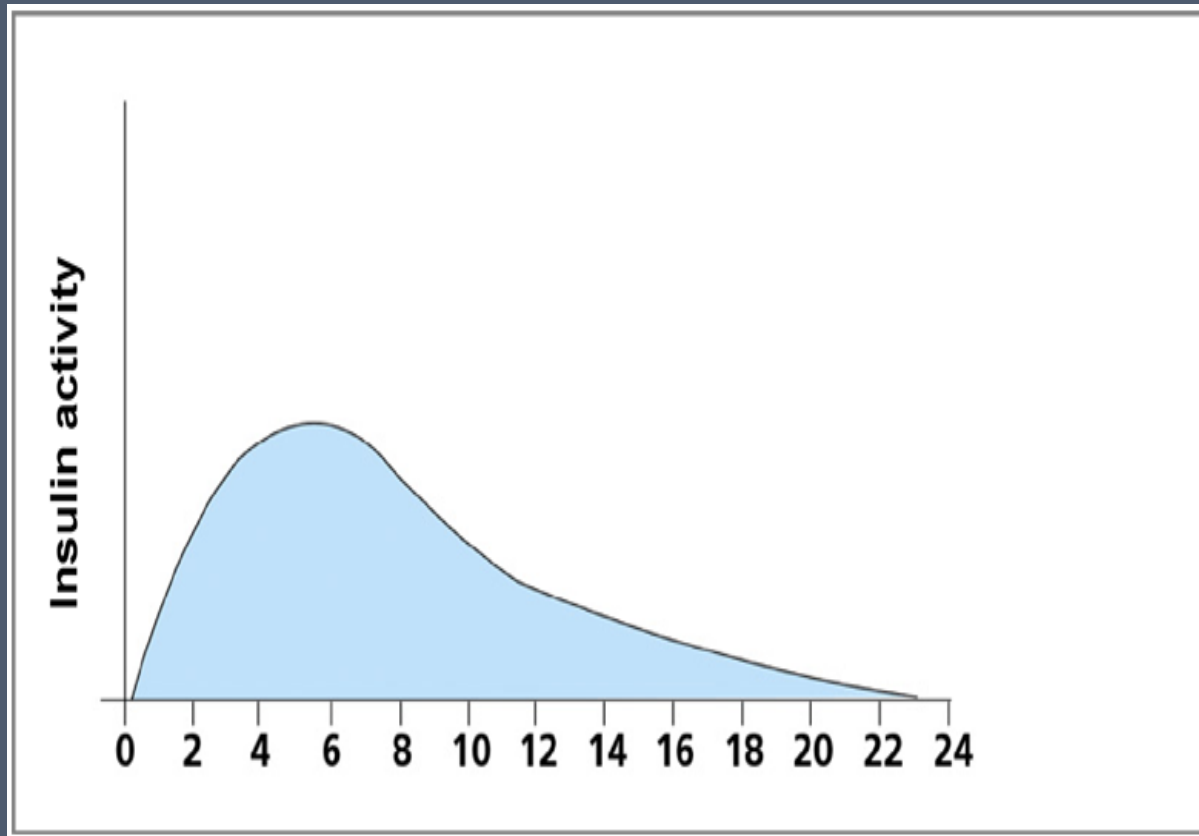
Short acting / soluble insulin



Intermediate-acting Insulin

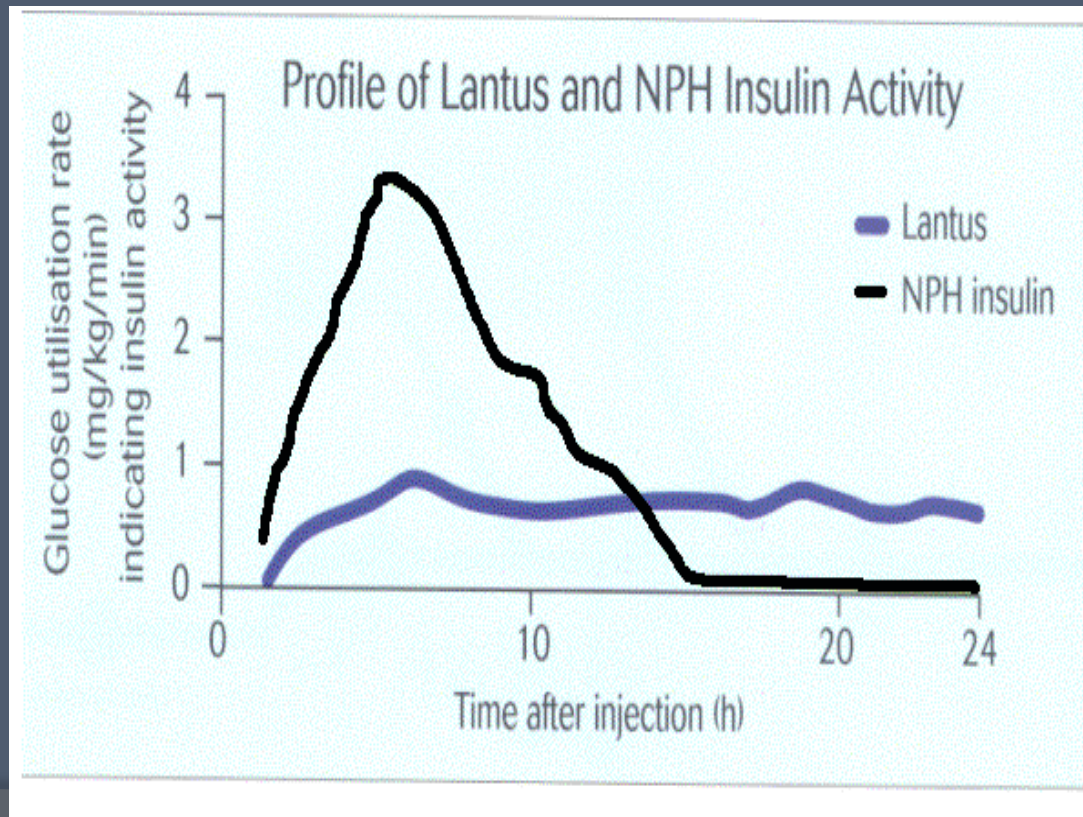
- ⦿ Intermediate acting = isophane insulin (NPH - neutral protamine hagedorn)
- ⦿ Cloudy due to the addition of a protein
 - (isophane or zinc)
- ⦿ Must be mixed well before use
- ⦿ Examples
 - Humalin NPH
 - Hypurin Isophane
 - Protophane
 - Levemir - Detemir
- ⦿ Retarded onset = 1-2 hrs, Peak 4-12 hours
- ⦿ Prolonged duration of action lasting 8-20 hrs
- ⦿ Always draw up clear before cloudy if 2 types of insulin are required

Intermediate-acting Insulin



Long-acting Insulin

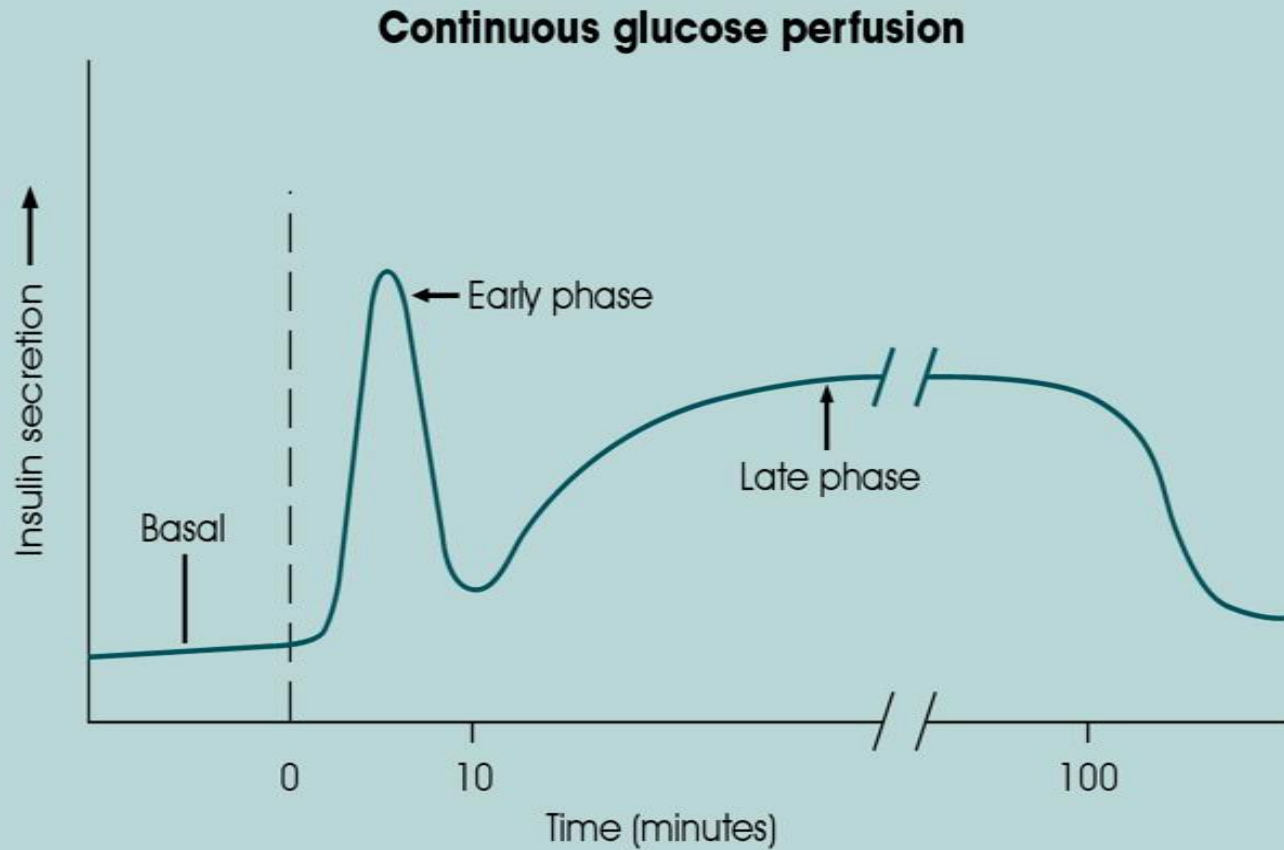
- Lantus –Glargine Insulin- Once daily
- Duration of action 24 hrs; Peakless (Clear)



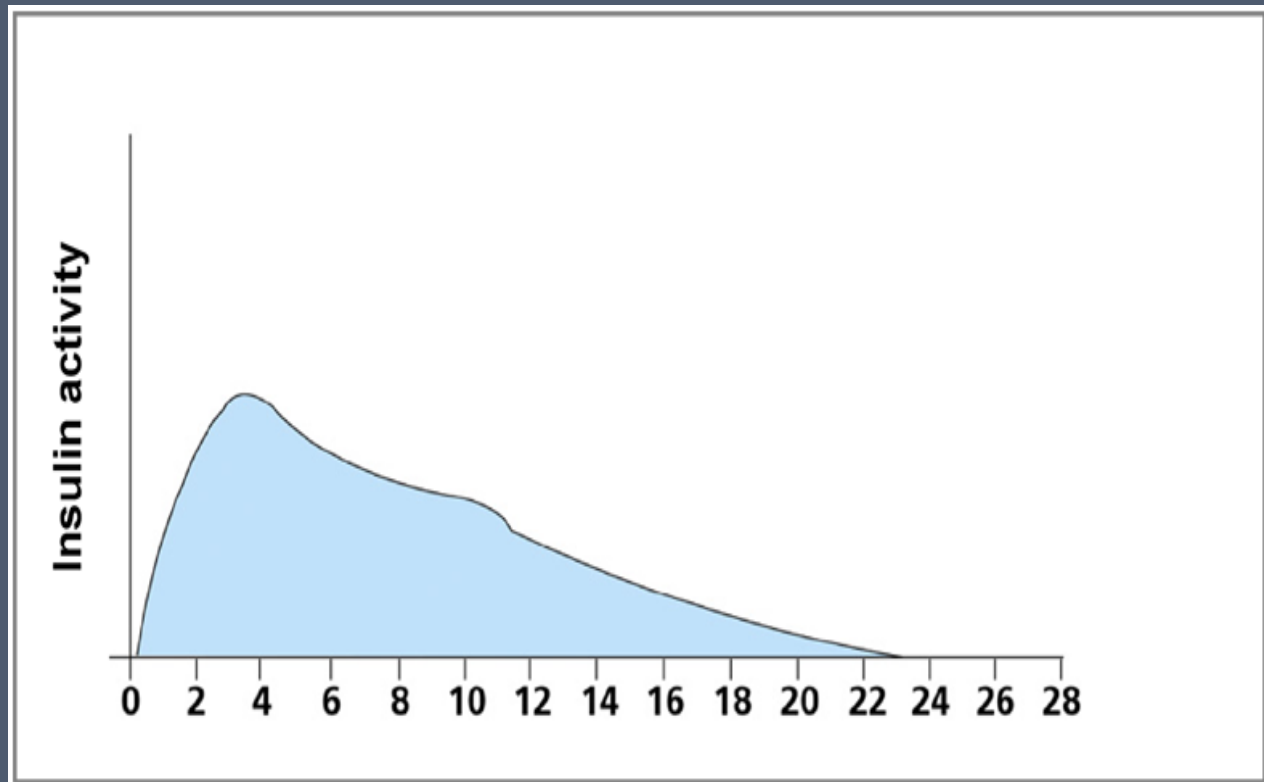
Biphasic Insulin

- ⦿ Mixture of isophane and soluble or analogue insulins
- ⦿ Offer dual insulin release profiles from one injection
 - Depending on proportion of soluble, or analogue, component to isophane
- ⦿ Examples
 - Humalog Mix 25 or Mix 50 (Lilly)
 - Human Mixtard 10/20/30/40/50 (Novo Nordisk)
 - Novomix 30 (Novo Nordisk)

The Biphasic Insulin Response



Human insulin mixtures



Insulin Regimens

- ⦿ Variety of insulin regimens
 - Tailored to meet the needs of different people with diabetes
- ⦿ Treatment option chosen reflects
 - Type of diabetes
 - Person's lifestyle, age and ability to self-test blood glucose
 - Presence of obesity
 - Choice
- ⦿ Goal is insulin release profile most similar to physiological state.

Insulin Pump Therapy

- Insulin aspart is FDA approved for use in the insulin pump and approval of insulin lispro is pending.
- If rapid-acting insulins are used, meal-related boluses are given 0 to 15 minutes before eating.

Estimating Total Daily Insulin Requirements

These are initial doses only; they must be refined using SMBG results. Patients may be particularly resistant to insulin if their blood glucose concentrations are high (glucose toxicity); once glucose concentrations begin to drop, insulin requirements often decrease precipitously. The weight used is actual body weight. Insulin dose requirements can change dramatically over time depending on circumstances (e.g., a growth spurt, modest weight gain or loss, illness).

Type 1 Diabetes

Initial dose	0.5–0.8 U/kg
Honeymoon phase	0.2–0.5 U/kg
With ketosis, during illness, during growth	1.0–1.5 U/kg

Type 2 Diabetes

With insulin resistance	0.7–1.5 U/kg
-------------------------	--------------

Estimating Basal Insulin Requirements

These are empiric doses only and should be adjusted using appropriate SMBG results (fasting or premeal). Basal requirements vary throughout the day, often increasing during the early morning hours. The requirement also is influenced by the presence of endogenous insulin, the degree of insulin resistance, and body weight. The range is 0.3 to 1.4 U/hr.

Approximately 50% of total daily dose

Approximately 0.7 U/hr for a 70-kg person (154 lb)

Estimating Premeal Insulin Requirements

The "500 Rule" estimates the number of grams of carbohydrate (CHO) that will be covered by 1 unit of rapid-acting insulin.⁵⁶ The rule is modified to the "450 Rule" if using regular insulin.

$500/\text{total daily dose of insulin (TDD)} = \text{number of grams covered}$

Example: For a patient using 50 units per day, $500/50 = 10$. Therefore, 10 g carbohydrate would be covered by one unit of insulin lispro or insulin aspart. This equation works very well for type 1 patients in estimating their premeal insulin requirements. Because patients with type 2 diabetes have insulin resistance, the rule may underestimate their insulin requirements.

Availability

100 or 500 units/ml (U-100 or U-500; 1 unit = ~36 micrograms of insulin) 500 units per ml.

Calculating Insulin Dosing: A general rule of thumb

- General rule of thumb: total daily dose (TDD) of insulin = Weight in pounds / 4
 - Example: a patient weighs 200 pounds; then the TDD = 50 units (200 / 4)
- Of the TDD, 50% should be basal (given overnight) and 50% given for carbohydrate (CHO) coverage with meals (bolus insulin)
 - Example: of the 50 units, 25 units are given as insulin glargine (Lantus) at HS; and ~ 25 units are divided among the meals
 - To estimate the amount of rapid-acting insulin (e.g Humalog, Novalog) to give with meals to cover the CHO consumed, use the **Rule of 500**; which is 500 divided by the TDD. This gives an estimate of how much rapid-acting insulin to give to cover the carbohydrate (CHO) in meals
 - Example: $500/\text{TDD} \rightarrow 500/50 = 1$ unit for every 10 g CHO; if 60 grams of CHO are consumed, then 6 units of short acting insulin should be given with the meal
 - Sometimes patients have high blood sugar before they eat, to correct for high blood sugar prior to a meal, use the **Rule of 1800**; which is 1800 divided by the TDD. In this example $1800 / 50 = 36$; this means that you can expect a drop in the blood sugar of 36 for each unit of rapid-acting insulin. So if the patient has a pre-prandial sugar of 220, and it should be 120 pre-prandial, add 3 more units to the rapid-acting insulin (6 to cover for the CHO consumed, and 3 to correct the high blood sugar = 9 units total)

Total Daily Insulin Requirement

The general calculation for the body's daily insulin requirement is:

$$\text{Total Daily Insulin Requirement (in units of insulin)} \\ = \text{Weight in Pounds} \div 4$$

Alternatively, if you measure your body weight in kilograms:

$$\text{Total Daily Insulin Requirement (in units of insulin)} \\ = 0.55 \times \text{Total Weight in Kilograms}$$

Example 1:

If you are measuring your body weight in pounds:

- Assume you weigh 160 lbs.

In this example:

$$\text{TOTAL DAILY INSULIN DOSE} = 160 \text{ lb} \div 4 = 40 \text{ units of insulin/day}$$

Example 2:

If you are measuring your body weight in kilograms:

- Assume your weight is 70Kg

- ⦿ **If hypoglycemia occurs**
- ⦿ Decrease dose by > 4 units or 10% (if dose > 60 units)
- ⦿ **If HBA1C < 7% after 2 months**
- ⦿ Continue regimen, check HbA1c every 3 months
- ⦿ **If HBA1C > 7% after 2 months**
- ⦿ Check blood sugar pre-lunch; pre-dinner and pre-bedtime
 - If pre-lunch blood glucose is elevated add rapid acting insulin with breakfast
 - If pre-dinner blood glucose is elevated add rapid acting insulin with lunch OR NPH insulin with breakfast
 - If pre-bedtime blood glucose is elevated add rapid acting insulin with dinner

Determining the “Correction Factor”

Supplemental doses of rapid-acting insulin are administered to acutely lower glucose concentrations that exceed the target glucose concentration. These doses must be individualized for each patient and again are based on the degree of sensitivity to insulin action. For example, if the premeal or bedtime blood glucose target is 140 mg/dL and the patient's value is 190 mg/dL, additional units of insulin might be added to the premeal dose or an additional supplemental bedtime dose of lispro might be given. The correction factor determines how far the blood glucose drops per unit of insulin lispro or insulin aspart given and is known as the “1800 Rule”.⁶⁵ For regular insulin, the rule is modified to the “1500 Rule”. The equation is as follows:

$$1800/\text{TDD} = \text{point drop in blood glucose per unit of insulin}$$

Example: If a patient uses 30 units of insulin per day, their correction factor (or insulin sensitivity) would be $1800/30 = 60$ mg/dL. Therefore, the patient can expect a 60 mg/dL drop for every unit of rapid acting insulin administered. Patients with a higher sensitivity factor have lower insulin requirements. Individuals with a lower sensitivity factor (higher insulin requirements) typically achieve a smaller reduction in blood glucose per unit of insulin.

CHO, carbohydrate; SMBG, self-monitored blood glucose; TDD, total daily dose.
Adapted from reference 60.

The dawn phenomenon

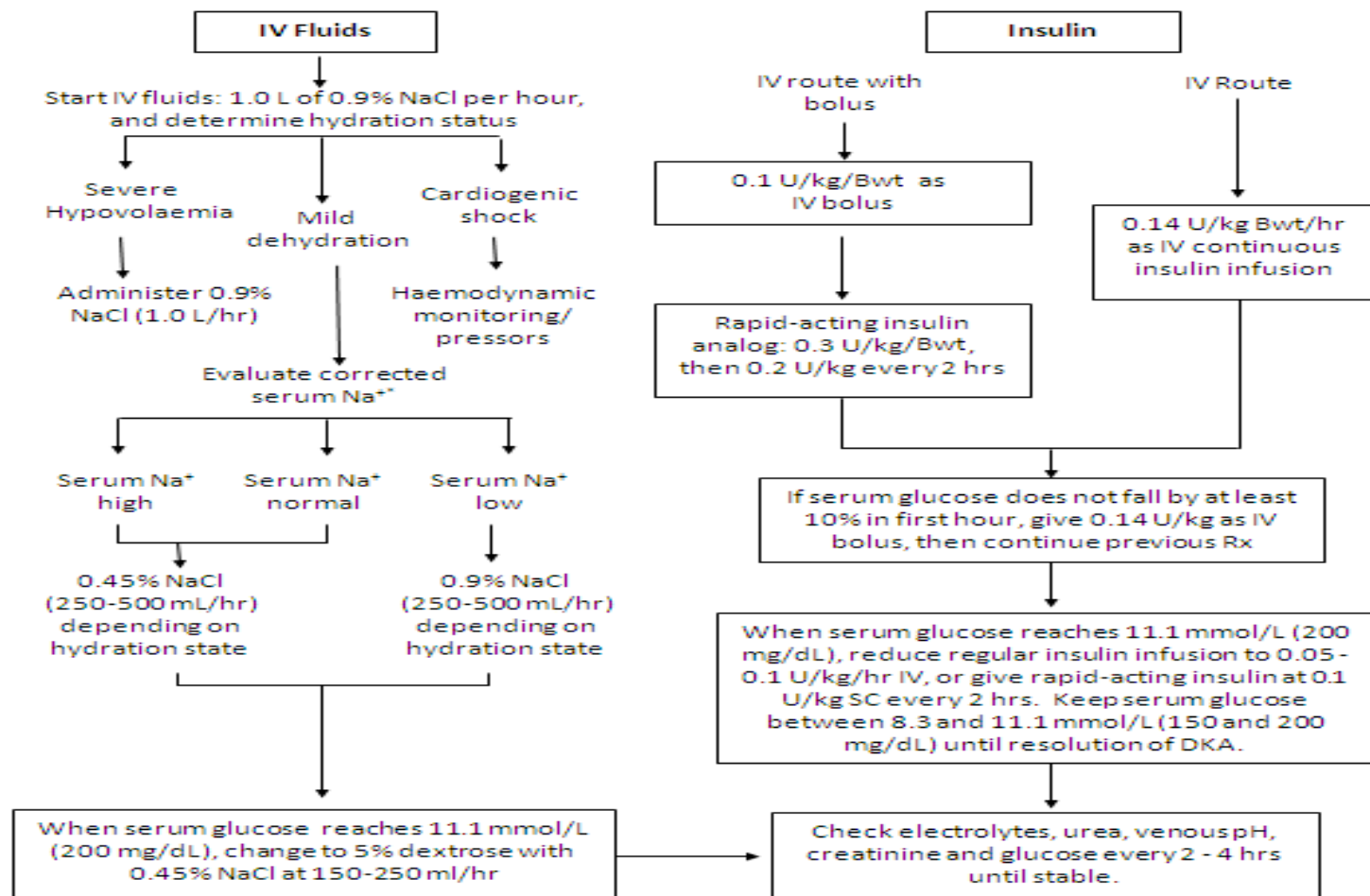
- A rise in the blood glucose concentration that occurs between 4 and 8 AM after a physiologic nadir in the blood glucose concentration that occurs between midnight and 3 AM

- **Renal Failure** : decreased clearance of endogenous and exogenous insulin, resulting in increased plasma concentrations of insulin.
- Thus insulin requirements may diminish as her renal disease progresses.

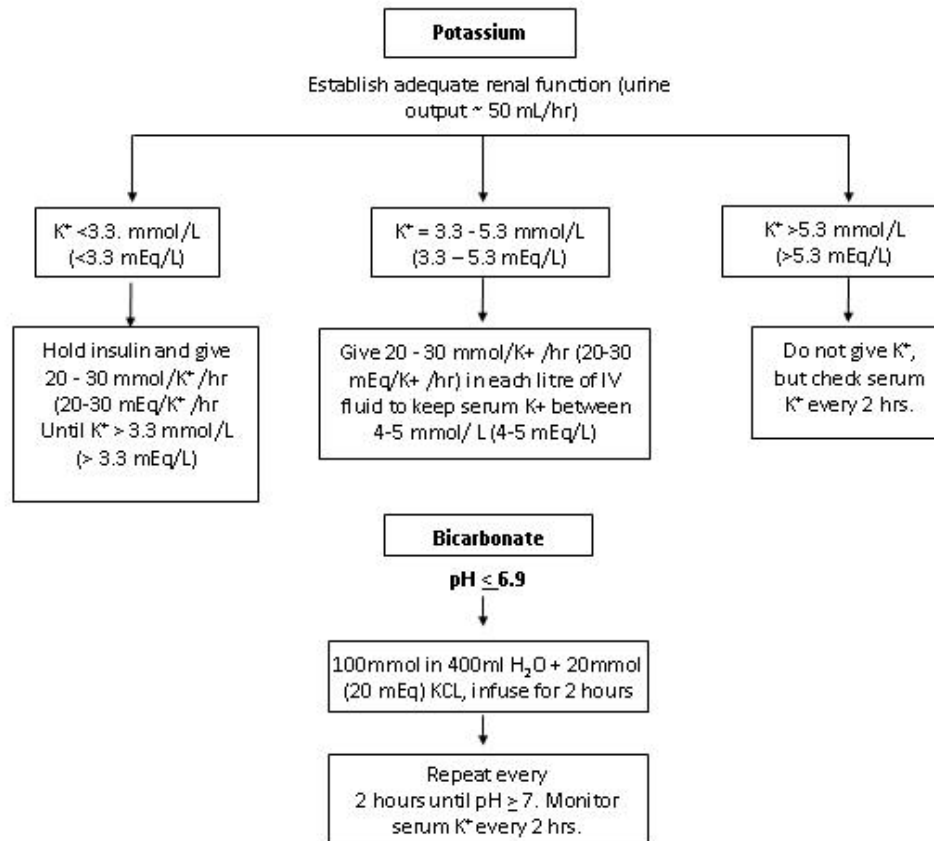
Diabetic Ketoacidosis

- ◎ **Aim** : correction of intravascular volume, dehydration, fluid and electrolyte losses, and hyperosmolarity .

Diabetic Ketoacidosis



Diabetic Ketoacidosis



Diabetic Ketoacidosis

- ◎ **Phosphate therapy** : Phosphate replacement has not resulted in clinical benefits .
 1. To avoid cardiac, respiratory, and skeletal muscle dysfunction, OR incardiac dysfunction (e.g., with signs of left ventricular dysfunction),
 2. Symptomatic anaemia
 3. Respiratory depression (e.G., Decreased oxygen saturation), and
 4. In those with a serum phosphate concentration <1.0 mg/dl

Diabetic Ketoacidosis

- Management and monitoring should continue until resolution of DKA. Criteria for resolution are:
- plasma glucose <11.1 mmol/L (200 mg/dL) (at this point, insulin can be decreased by 50%)
- serum bicarbonate >18 mmol/L (18 mEq/L)
- venous pH >7.3
- anion gap <10 .

Once-Daily

- Intermediate- or long-acting basal insulin
- Given at breakfast
- Simplest regimen
- Sufficient for many elderly Type 2 people
- Often used in combination with OHA
- Obese Type 2 person uncontrolled on maximal doses of oral therapies
 - **Example: Metformin + once daily insulin**

Twice-Daily

- Twice-daily biphasic insulin
- Very popular regimen
- Often used in treatment of Type 2 diabetes
- Administered in morning and at teatime
- Can be quite restrictive as meal times cannot be varied

Basal-Bolus

- Four daily injections
 - Before meals (bolus)
 - 3 short- or rapid-acting insulin doses
 - Bedtime (basal)
 - once-daily intermediate-acting insulin
- Flexibility
 - Can adjust bolus injections for eating patterns

Three Times Daily

- Mixture of short- and intermediate-acting insulins before breakfast or
- Mixture of short-acting insulin before the evening meal or
- Intermediate-acting insulin at bedtime
- Regimen often adjusted depending on the person's circumstances
- Flexibility offered to the prescriber

Regimens

Regimen	Advantages	Disadvantages	Comments
BD isophane	Simplicity	Lack of flexibility; rarely achieves good control	Sometimes useful at start of treatment
BD mixture	Simplicity	Lack of flexibility; nocturnal hypo episodes	Useful if glycaemic targets are not tight
Metformin with OD	Simplicity; may limit weight gain	Poor control of post prandial glucose	Maybe useful in overweight people
Basal bolus	Flexibility	Regular HBGM; requires 4 injections a day	Closest (except pump) to physiological insulin production

Initiating Intravenous Insulin Therapy Regimen

1. Commence an intravenous infusion as follows:
 - o 1 litre Glucose 5% containing 20 mmol potassium at 125 ml/hr
 - or
 - o 1 litre Sodium Chloride 0.9% containing 20 mmol potassium at 125 ml/hr if initial blood glucose is greater than 13.0 mmol/litre

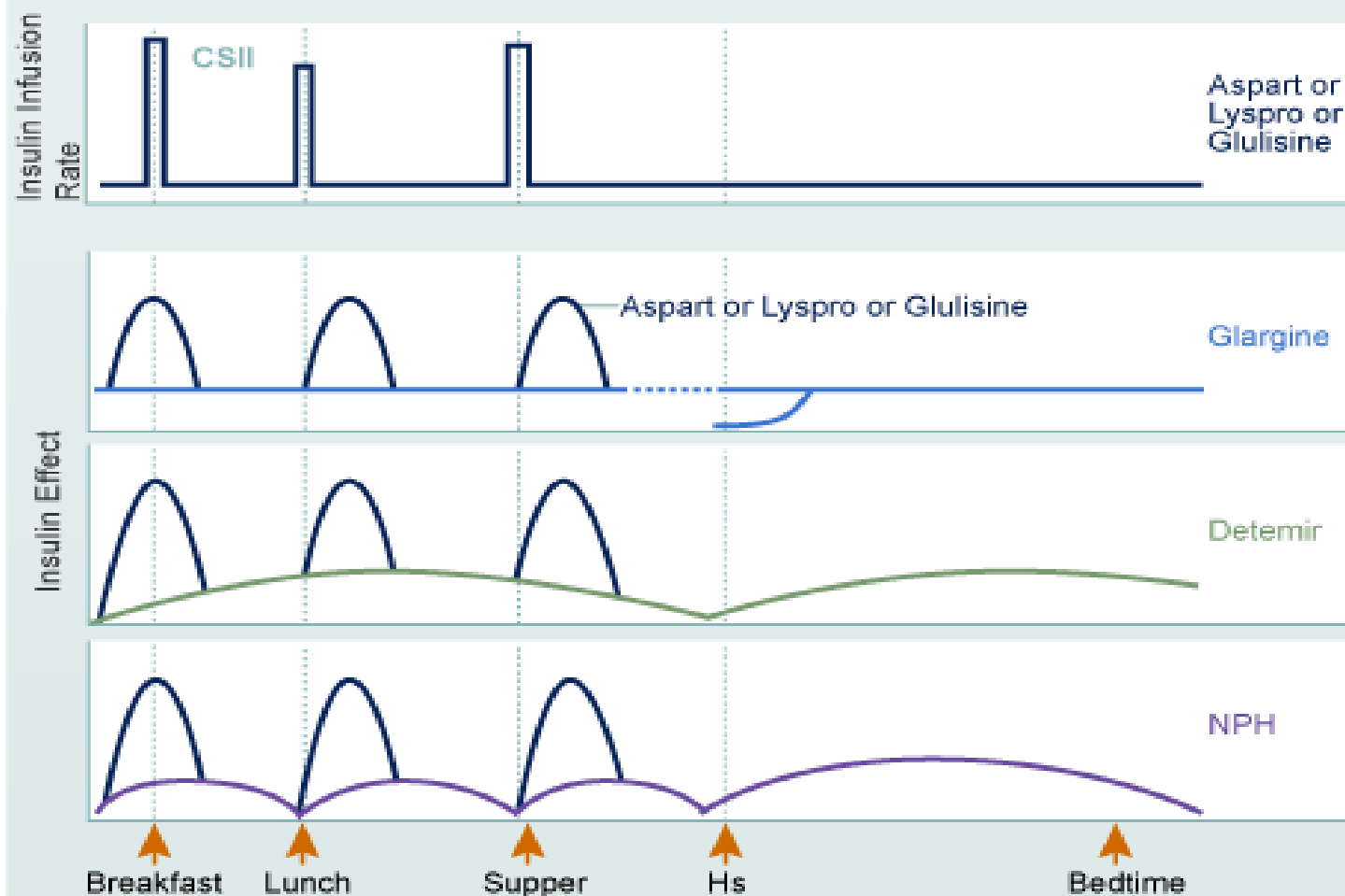
If a sodium chloride 0.9% infusion is started it should be switched to Glucose 5% when blood sugar is less than 13.0 mmol/litre. Do not switch back if blood sugar goes back above 13.0 mmol/litre.

2. Set up a syringe driver with 50 units of soluble insulin (Actrapid®) made up to 50 ml with sodium chloride 0.9%, i.e. 1unit per ml.
3. Start the insulin infusion at the rate corresponding to the blood glucose as outlined in the table and adjust as per blood glucose measurements.

Blood glucose (mmol/L)	Insulin Dose (mls/hour)
Greater than 22 If repeated blood glucose is greater than 22mmol/litre not falling seek advice	7
19.1-22.0	6
16.1-19.0	5
13.1-16.0	4
10.1 – 13.0	3
7.1 – 10.0	2

Measure and chart blood glucose hourly for 6 hours adjusting insulin infusion rate as appropriate then, if stable (Blood Glucose 5 - 10mmol/L) every 2-3 hours. A fresh insulin infusion should be prepared every 12 hours for immediate use.

Current Intensive Insulin Regimens for Type 2 Diabetes



Adverse Effects of Insulin

- ⦿ Hypoglycaemia : Confusion, Dizziness, Feeling shaky, Headaches, Sudden hunger, Sweating, Weakness
- ⦿ Allergic reactions,
 - usually local site & usually diminish
 - less likely with human insulin
- ⦿ Insulin lipodystrophy
 - Atrophy or hypertrophy of subcutaneous fat at injection sites
 - Rotate within sites to prevent
- ⦿ Insulin insensitivity or resistance
 - Requires higher doses of insulin

Insulin Therapy in Type 2 Diabetes

Reasons for use of insulin

- Progression of Type 2 diabetes over time
- People uncontrolled with maximal doses of OHA therapy who are insulin resistant
- Preconception and in pregnancy (oral therapy contraindicated)
- Patients with organ failure for whom oral therapy is contraindicated
- Acute illness/surgery in type 2 diabetes

Table 1: Pharmacokinetics and Estimated Costs of Selected Insulin Products

Category	Insulin	Time to Onset	Time to Peak	Duration of Action	Approximate retail cost (brand-name, 10-ml vial)*
Long-acting	Glargine	2–4 hours	No distinct peak	20–24 hours	\$104.00
	Detemir	1–3 hours	6–8 hours	18–22 hours	\$103.00
Intermediate-acting	NPH	2–4 hours	4–10 hours	10–18 hours	\$54.00
Short-acting	Regular	30–60 minutes	2–3 hours	5–8 hours	\$54.00
Rapid-acting	Aspart	5–15 minutes	0.5–1.5 hours	3–5 hours	\$112.00
	Lispro	5–15 minutes	0.5–1.5 hours	3–5 hours	\$103.00
	Glulisine	5–15 minutes	0.5–1.5 hours	3–5 hours	\$102.00

**Approximate costs based on prices listed by an online retailer 10 March 2009*

Hypoglycaemia

Hypoglycaemia or low blood glucose occurs

- when the blood glucose level falls to below the level where signs and symptoms occur

Hypoglycaemia can only occur if people are taking tablets for diabetes or insulin

- ⦿ Hypoglycemia – following glucose levels
- ⦿ < 50 mg/dL in men
- ⦿ < 45 mg/dL in women
- ⦿ < 40 mg/dL in infants and children

Hypoglycaemia

Causes

- too much insulin/tablets
- delayed or missed meal
- not enough carbohydrate in a meal
- more exercise than usual - exercise can have a glucose lowering effect for 12 or more hrs afterwards
- alcohol
(especially if not taken with food)

Hypoglycaemia

Signs and Symptoms

- weakness, tremor, sweating
- palpitations, anxiety, pallor
- headache, dizziness
- feeling hungry
- lack of concentration, vagueness
- numbness and tingling around lips
- irritability, behaviour changes
- if not treated, can lead to convulsions and coma

Hypoglycaemia

Treatment - must be immediate

Quickly check BGL if able. If in doubt, treat as a hypo (low BGL)

If conscious and safely able to swallow

- 5 - 7 jelly beans or 15g glucose tablets
- 3 teaspoons glucose powder/sugar
- 150 ml of other glucose energy drinks

Hypoglycaemia

- If no improvement within 5 – 10 minutes, repeat the high GI(quick acting carbohydrate) food/drink
- Once improvement has occurred (feeling better, BGL rising if testing is available) then follow with a low GI snack

eg glass of milk

yoghurt

sandwich

piece of fruit

meal if it is due

Hypoglycaemia

If drowsy and unable to swallow safely

- do not try to give food or fluids
- lie person on their side
- Glucagon if able to administer

Glucagon

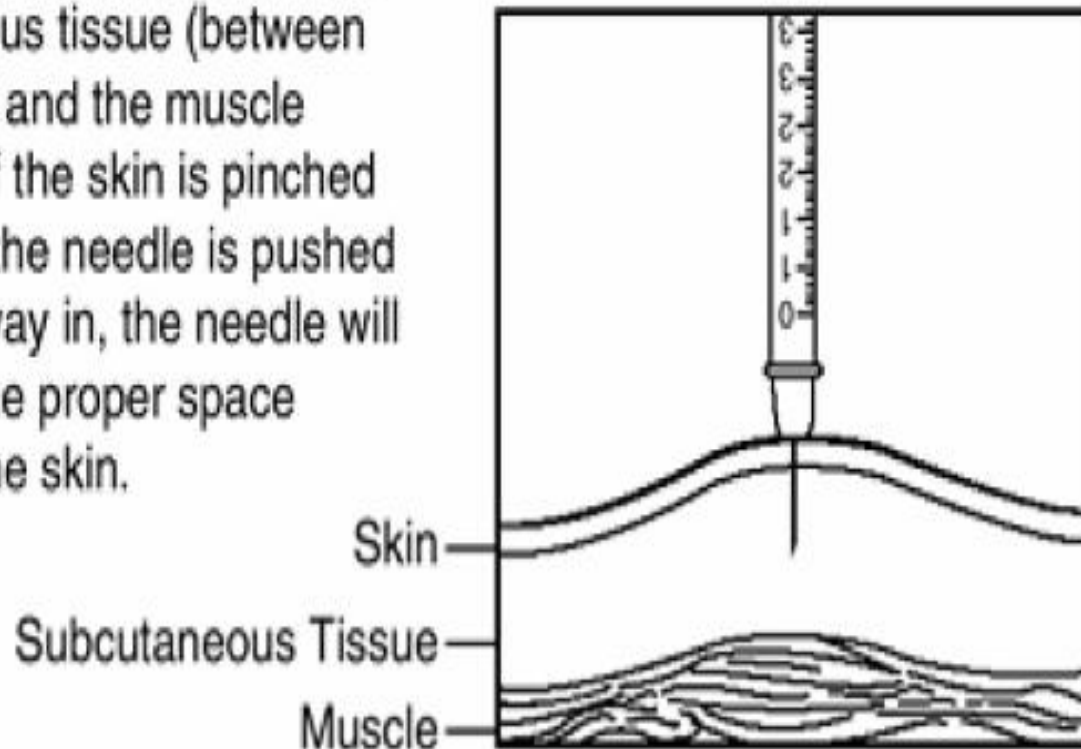
- ⦿ Glucagon is a hormone which functions in the opposite direction to insulin, and breaks down the stored glycogen into glucose for use as required between meals when blood glucose decreases
- ⦿ In a person without diabetes, this system keeps the blood glucose level within a narrow margin
- ⦿ (Glucagon) can be used in an emergency
- ⦿ Dose 0.5-1 mg IM; onset 5-15 mins IM

Future Developments

- ⊙ Beta cell transplantation
- ⊙ Non-injectable formulations of insulin
 - Inhaled insulin
 - replace short acting insulin for some people
 - injections of intermediate- or long-acting insulin will remain
 - Inhaled (nasal)
 - Intradermal
 - Oral

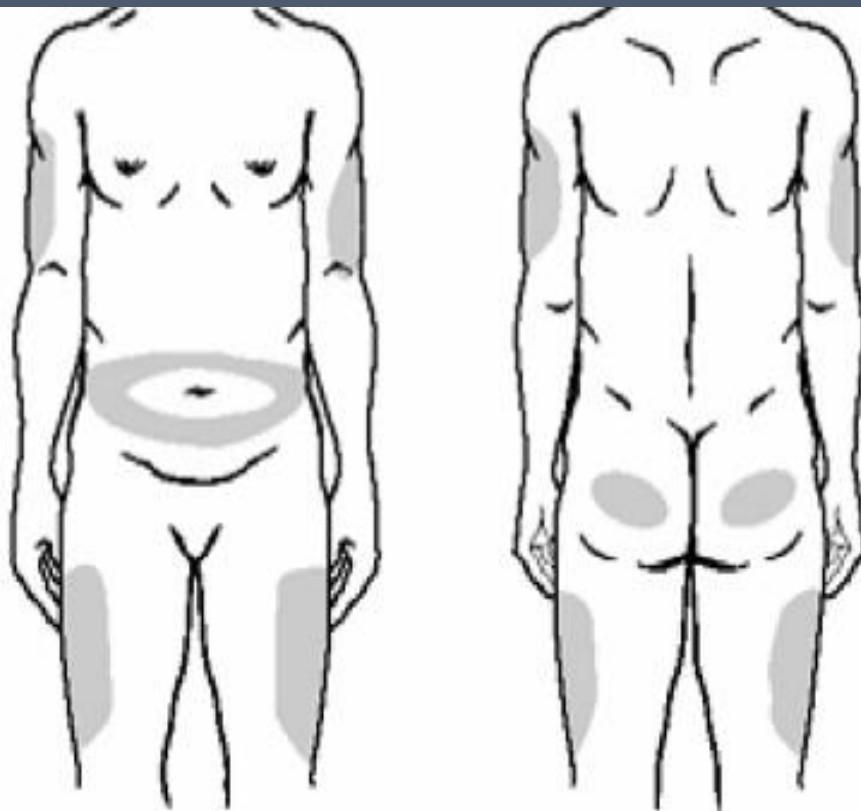
Administration sites

Insulin is injected in the subcutaneous tissue (between the skin and the muscle layer). If the skin is pinched up and the needle is pushed all the way in, the needle will reach the proper space under the skin.



Administration sites

The actual point of injection should be varied each time within a chosen body area. Give injections at least one inch apart (Patients should consult with their physician or diabetes educator about which area is most appropriate for use.)



Rotation

- Rotation between different sites (e.g. abdomen to arm) no longer recommended
- Choose one site to maintain day to day consistent absorption
- Rotation *within* site must occur to prevent lipoatrophy
- Inject at appropriate angle (45-90) depending on depth of subcutaneous tissue



Dosage: various regimes

- Short acting 15-30 mins before a meal & intermediate acting at night
- May be given at set doses at set times e.g. BD
- May be given according to BGL (sliding scale).
Short acting insulin only
- Aim to keep BGL in a range (4-9mmol)
- HbA1c provides an index of control, should be below 8.8%

Holman and Turner

- $(\text{FPG (mg/dl)} - 50)/10,$

