Management of Diabetes

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Diabetes

Diabetes mellitus type 1

Lack of insulin. Insulin must be used

Diabetes mellitus type 2

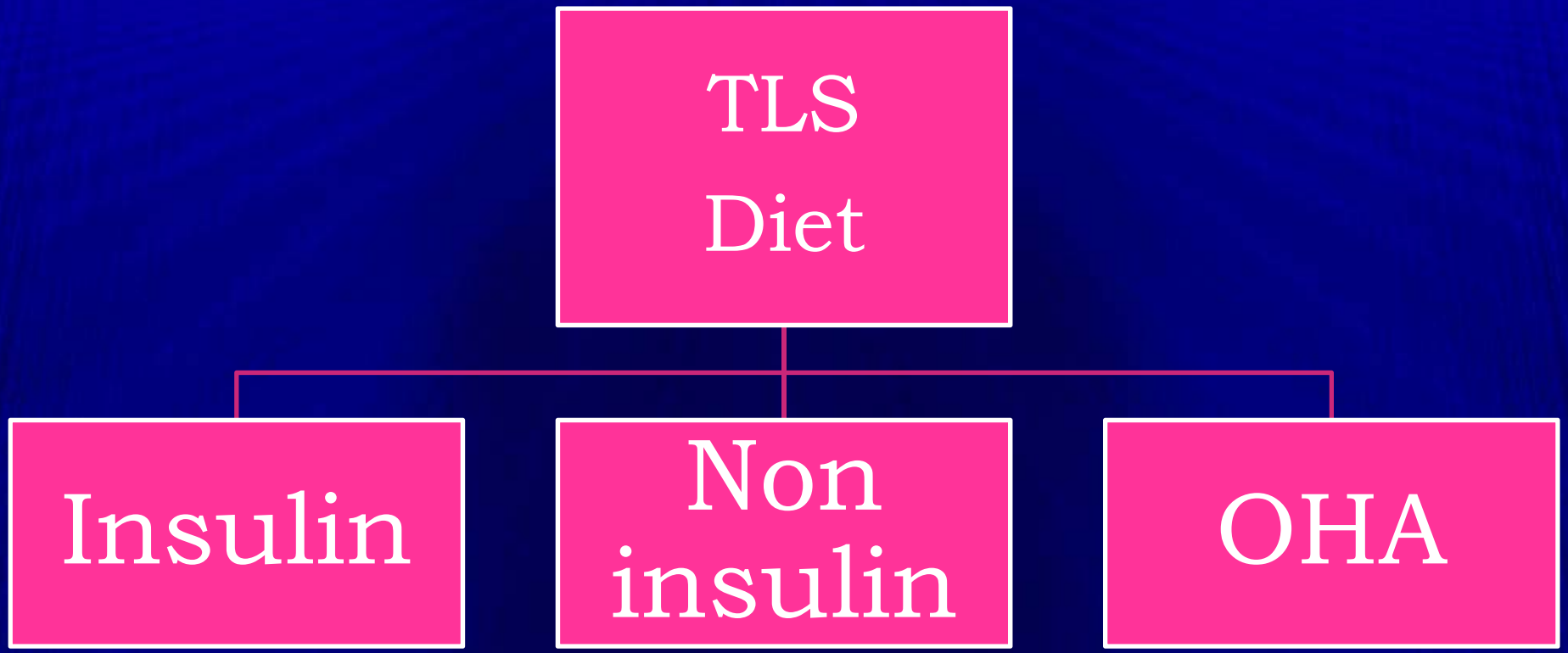
- Insulin resistance
- Treatments include

  (1) agents which increase amount of insulin secreted by pancreas,

  (2) agents which increase sensitivity of target organs to insulin,

  (3) agents which decrease rate of glucose absorbtion from gastrointestinal tract.

Management



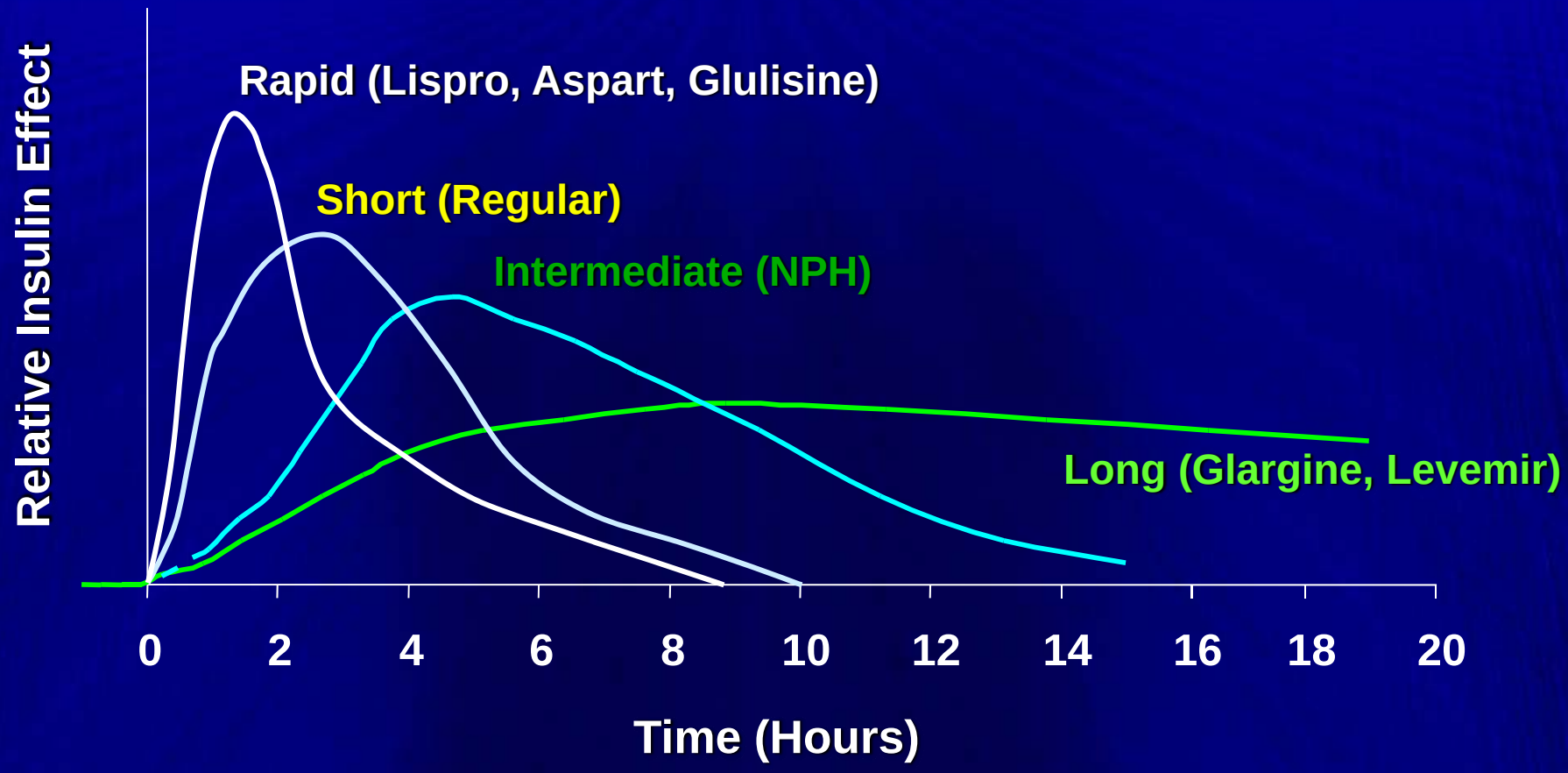
Insulin Preparations

- Current preparations are generated by recombinant DNA technology
- Consist of the amino acid sequence of human insulin or variations thereof
- Animal insulin (beef or pork) is no longer used
- Insulin is formulated as U-100 (100 units/mL), U-40 (40 units/mL)
- Routes – i.v. , s.c. , inhalational

Insulin Therapy

Type of Insulin	Onset of Action	Peak Action
Rapid Insulin		
Lispro	<15 min	0.5-1.5 h
Aspart	<15 min	0.5-1.5 h
Glulisine	<15 min	0.5-1.5 h
Regular	30-60 min	2-3h
Exubera**	<15 min	0.5-1.5 h
Basal Insulin		
Glargine	~1 h	peak less
Determir	1-2 h	peak less
NPH	2-4 h	6-10 h
Pre Mixed		
75/25, 50/50, 70/30	<15 min	Dual
70/30 NPH/Regular	0.5-1 h	Dual

Insulin Time Action Curves

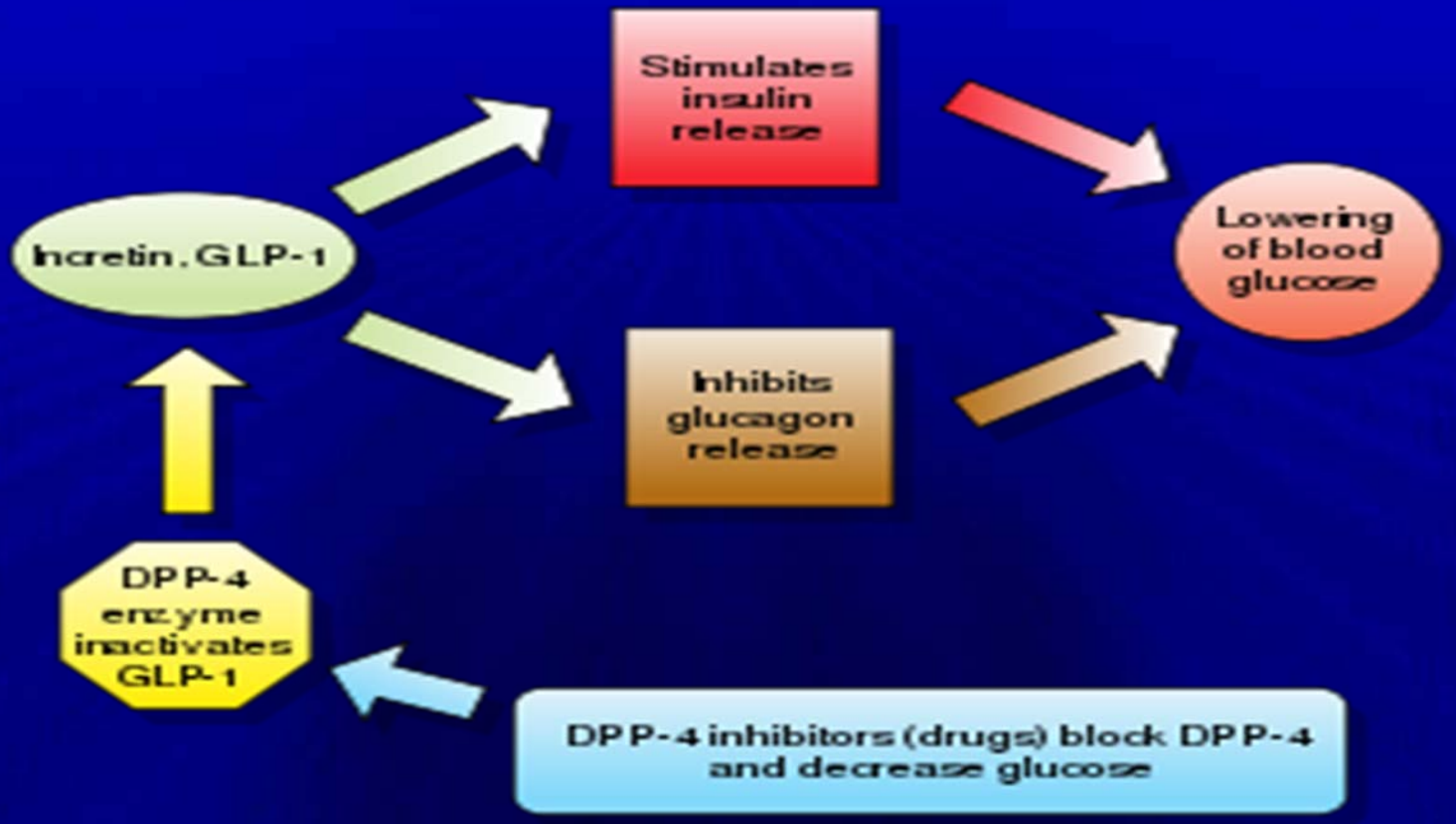


Non insulin injectables

Pramlintide

- Analogue of amylin, a small peptide hormone that is released into blood by β-cells of pancreas along with insulin, after a meal
- Like insulin, amylin is deficient in diabetes
- By augmenting endogenous amylin, pramlintide aids in the absorption of glucose by slowing gastric emptying, promoting satiety and inhibiting inappropriate secretion of glucagon
- Approved by FDA for use by Type 1 and Type 2 who use insulin
- Administered s.c.
- MC A/E nausea
- A1C reductions 0.5-1.0%

Incretin mimetics



- Incretins are insulin secretagogues
- Glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP)

Glucagon-Like Peptide-1 (GLP-1)

- Peptide hormones secreted by enteroendocrine cells in the GI tract
- Release is rapid in response to meals
- Binds to membrane GLP receptor causing increase insulin release from beta cells
- Increases insulin secretion in a glucose-dependent manner
- Decreases glucagon secretion
- Increases insulin-sensitivity in both alpha cells and beta cells
- Increases beta cells mass and insulin gene expression

Glucagon-Like Peptide-1 (GLP-1)

- Inhibits acid secretion and gastric emptying in the stomach
- Decreases food intake by increasing satiety in brain.
- Exenatide - GLP agonist
- Typical reductions in A1C values are 0.5-1.0%
- Liraglutide, a once daily human analogue
- Taspoglutide is presently in Phase III clinical trials with Hoffman-La Roche.

Oral hypoglycemics

Classes of OHA

- **Sensitizers** help the body use insulin
  - Biguanides
  - Thiazolidinediones
- **Secretagogues** stimulate pancreas to release more insulin
  - Sulfonylureas
  - Nonsulfonylurea
- **α-glucosidase inhibitors** block breakdown of starches and sugars
- **DDP IV inhibitors** increase blood concentration of incretin GLP-1

Biguanides (Metformin)

- MOA: reduce hepatic glucose output & increase uptake of glucose by periphery, including skeletal muscle
- Usually first-line for treatment of T2DM
- Cons: Lactic Acidosis, Contrast media, diarrhea
- Pros: weight neutral/ loss, ↓ hypoglycemia
- A1C reduction is 1.5-2.0%
- Dosing 500 mg - 2000 mg daily

Thiazolidinediones

- MOA: Enhance peripheral insulin sensitivity. Bind to PPARγ, nuclear regulatory protein regulating glucose and fat metabolism
- Rosiglitazone : suspended due to ↑ CV risks
- Pioglitazone
- Cons: Weight gain, slow onset, liver toxicity
- Pros: Insulin sensitizer, ↓ hypoglycemia
- A1C reduction is 1.5-2.0%
- Dosing 15 mg - 45 mg daily

Sulfonylureas

- MOA: close ATP / K+ channel in the B-cell → Insulin release
- Only useful in Type II diabetes
- Can be safely used with most other drugs/ insulin
- Cons: Hypoglycemia, weight gain
- Pros: Low cost, rapid BS reduction
- A1C reduction is 1.0-2.0%
- Second-generation agents
  - glipizide (5-40 mg/day)
  - Glyburide/ glibenclamide (1.25-20 mg/day)
  - Glimepiride (1-8 mg/day)
  - Gliclazide (40-240 mg/day)

Nonsulfonylurea secretagogues (Meglitinides)

- They act on same K+ channels as SU, but at different binding site enhancing insulin secretion
- They are taken with meals to boost insulin response to each meal
- Cons: High cost, frequent dosing
- Pros: ↓Risk of hypoglycemia, short-acting, meal-adjusted dosing
- A1C reduction is 0.5-1.0%
- Nateglinide (180 to 360 TDS)
- Repaglinide (1.5 to 16 TDS)

Alpha-glucosidase inhibitors

- Not technically hypoglycemic agents
- Slow digestion of starch in small intestine, so glucose of meal enters the blood more slowly, and can be matched more effectively by impaired insulin response
- Cons: flatulence and bloating, frequent dosing
- Pros: ↓Risk of hypoglycemia, non systemic action, weight loss
- A1C reduction is 0.5-1.0%
- Acarbose (150 to 300 mg TDS)
- Miglitol (150 to 300 mg TDS)

Dipeptidyl peptidase-4 inhibitors

- MOA: increase blood concentration of GLP-1 by inhibiting its degradation by DDP IV
- Cons: increased risk for infection and headache, weight gain and/or hypoglycemia with SU
- Pros: ↓Risk of hypoglycemia, weight neutral, no CNS side effects, oral
- A1C reduction is 0.7-1.0%
- Vildagliptin (100 mg/ day)
- Sitagliptin (100 mg/ day)
- saxagliptin (2.5-5 mg/ day)
- linagliptin (5 mg/ day)
- Alogliptin (not yet approved)

Treatment goals

A1C	<7.0%
Preprandial capillary plasma glucose	70–130 mg/dl
Postprandial capillary plasma glucose	<180 mg/dl

ADA. V. Diabetes Care. *Diabetes Care* 2011;34(suppl 1):S21. Table 10.

Therapeutic Lifestyle Changes

Medical nutritional therapy

- Decrease fat content and total calories
- Decrease saturated fat, substitute mono/polyunsats
- Low glycemic index CHOs/ calorie counting
- Increase dietary fiber
- Decrease salt for hypertension
- Carbohydrates mainly from fruits, vegetables, whole grains, legumes, and low-fat or skim milk

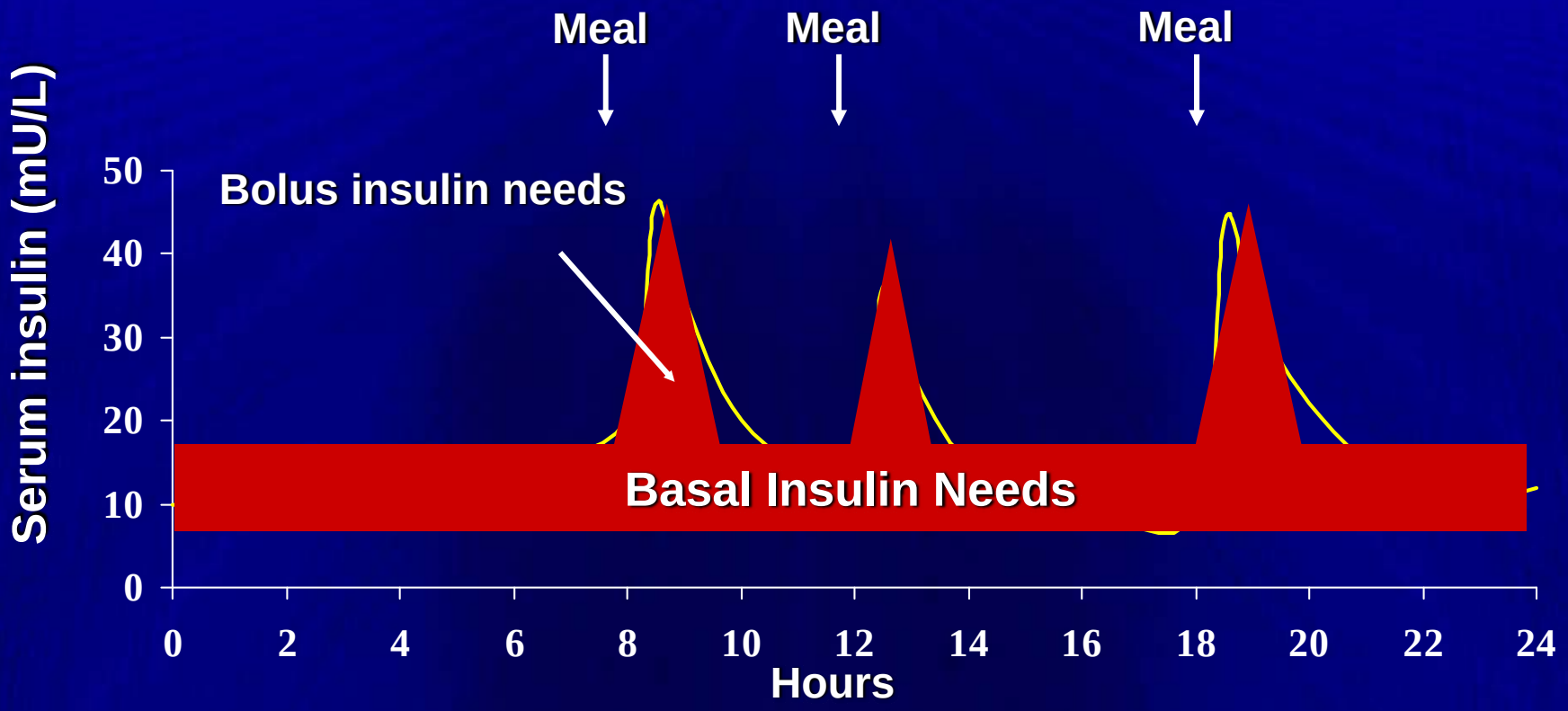
weight management

sufficient physical activity

Treatment of T1 DM

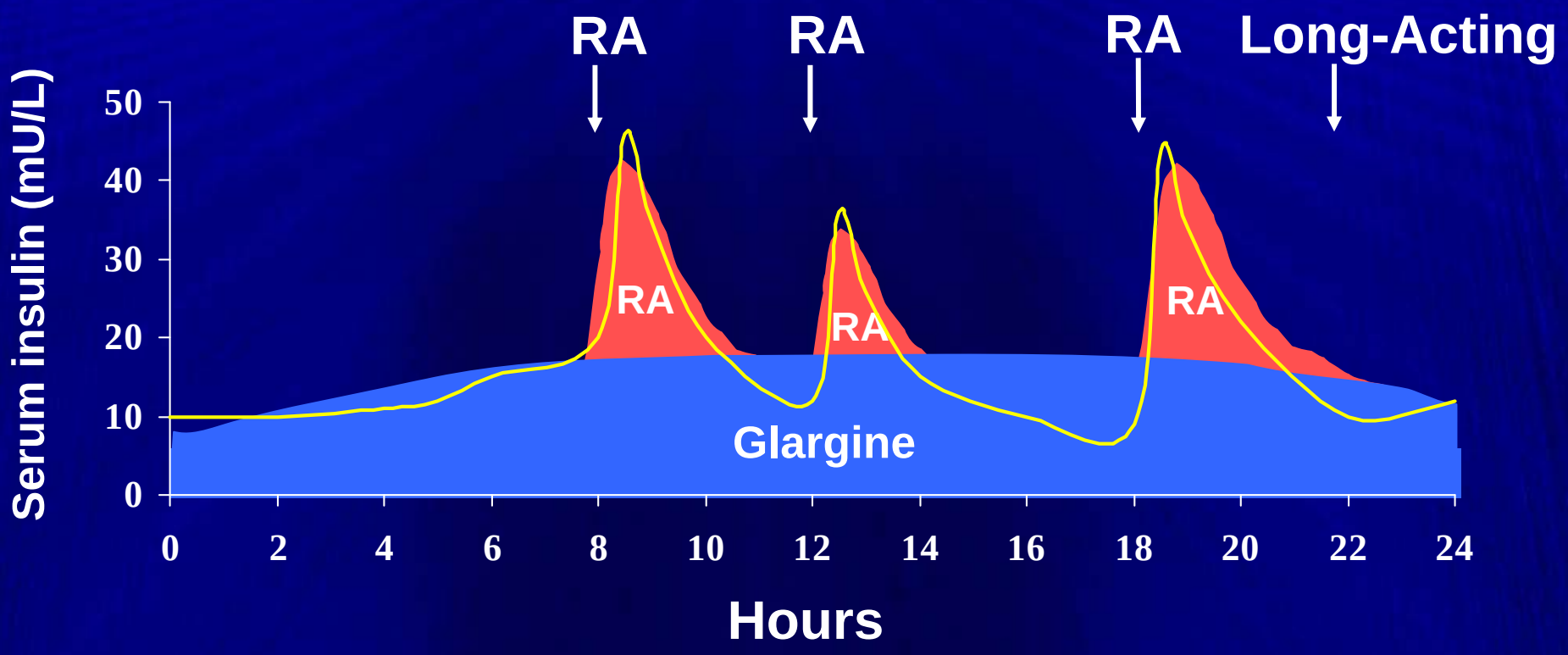
- Insulin
- Sensitizers
- Pramlintide
- AGI
- 1 u/kg/day – 1.3 u/kg/day in puberty

Normal Insulin Secretion



Kendall DM. *N Engl J Med* 322:898, 1990

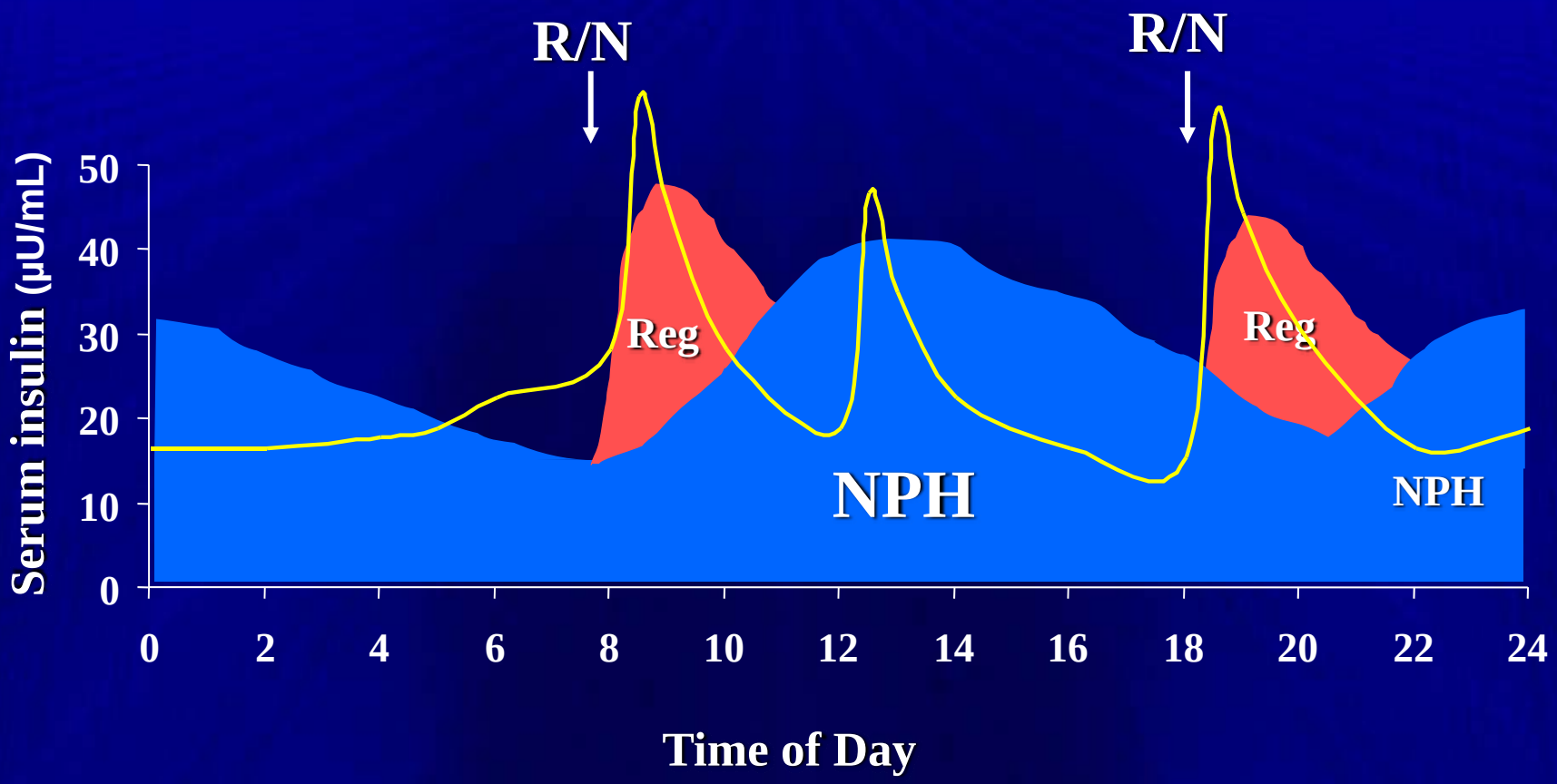
Flexible Insulin Regimen: RA - RA - RA – LA



Multiple Dose Insulin Intensive Therapy

- Most physiological
- Basal dose suppresses hepatic glucose output
- Bolus dose enhances postprandial glucose uptake
- Basal dose about 50%
- Bolus doses 10-20% before meals

Basic Insulin Therapy
Split Mixed Insulin (R/N)



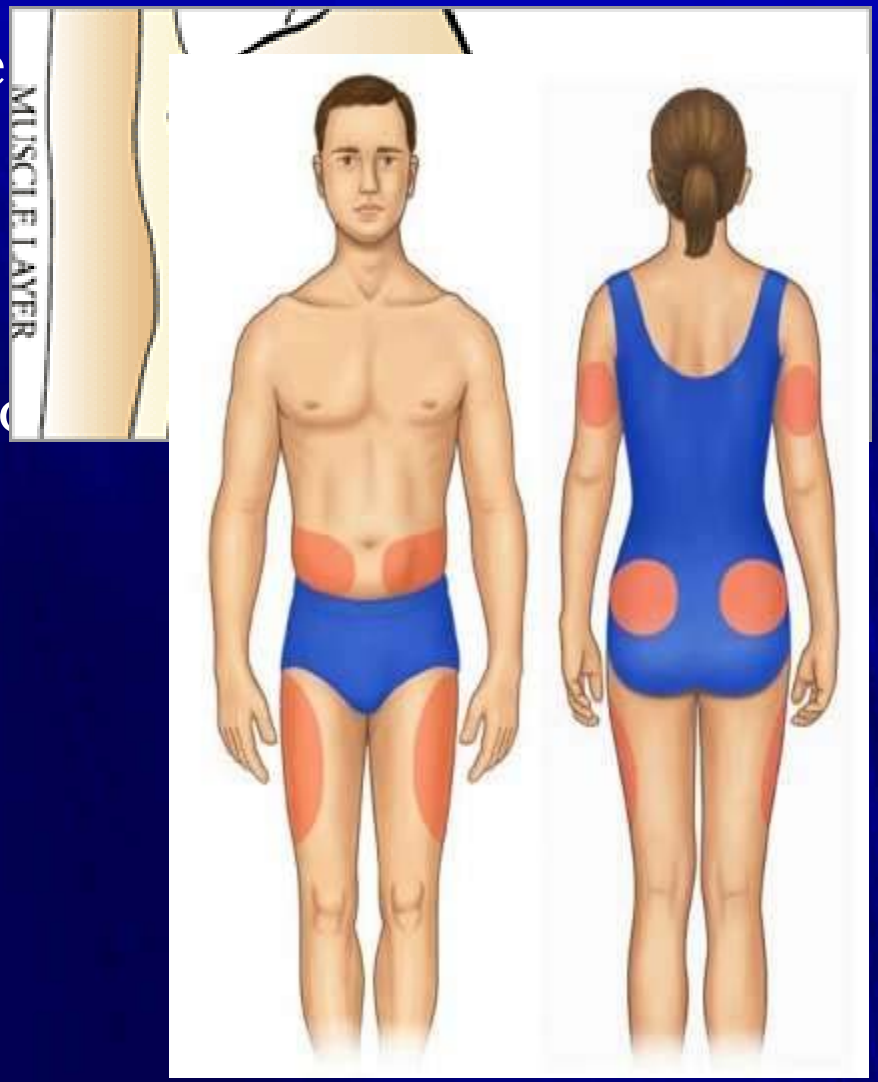
Twice daily Insulin Therapy

- Most commonly used
- Morning dose 2/3 in AM of which 2/3 NPH and 1/3 regular (70/30 mix)
- 1/3 in PM of which 50% NPH and 50% regular (50/50 mix)

A 70 kg man dosed at 0.5 Units/kg/day would get
  - AM 16 Units NPH, 8 Units Regular
  - PM 6 Units NPH , 6 Units Regular

Insulin use

- Rapid, short-acting, glargine clear
- Rest uniformly cloudy
- Rotate it every time you inje
- Stomach and upper arm absorb insulin more quickly than thighs and buttocks
- Vials of insulin not in use should be refrigerated
- pinch, pull, inject

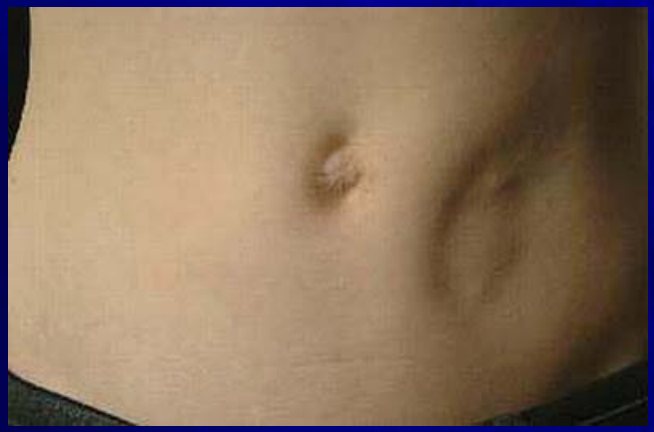


Insulin Side Effects

Allergy: human insulin free of this risk

Insulin resistance: > 1.5-2 u/kg or 200 u/ day

Lipodystrophy (fat redistribution)



Atrophy, hypertrophy

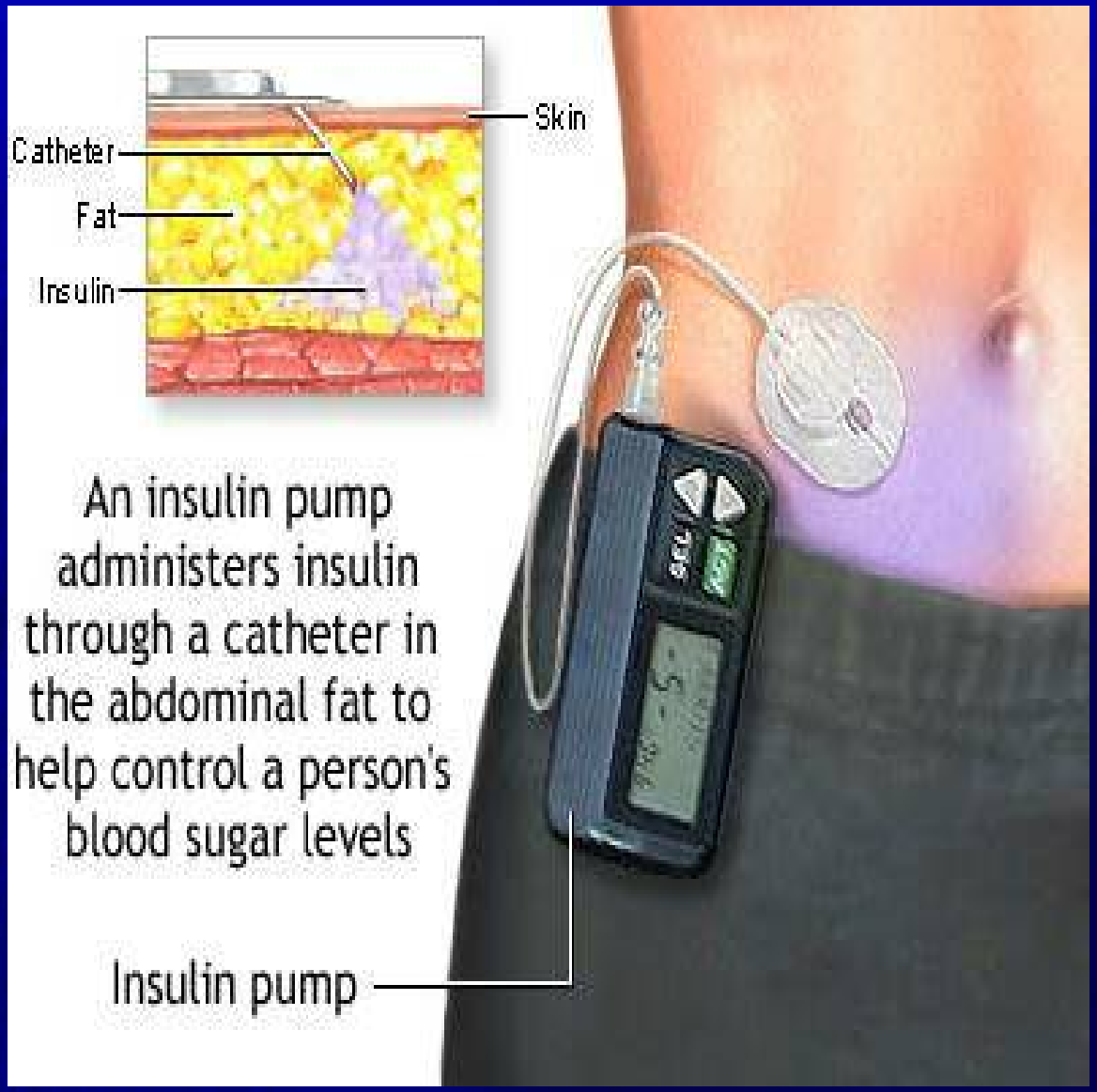
Local abscess

Injection site pain

Visual disturbances at the start

Insulin edema/ weight gain

Insulin pump

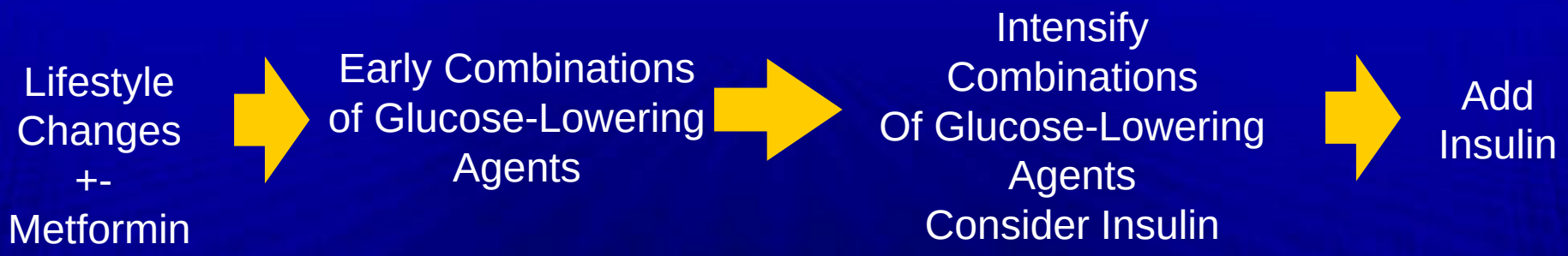


Useful in motivated and DM-educated patients with T1DM, children and in certain insulinopenic patients with T2DM who are unable to achieve optimal glycemic control

Insulin Therapy in Type 2 DM

- Not 1st line, except initially in some
- 50% need eventually
- Can be combined with oral agents
- Hospitalization, associated illness
- Renal failure/hepatic failure/pregnancy
- Type 2 DM –
    - 0.3 - 0.6 U/kg/day for most patients
    - 0.6 - 1.0 U/kg/day if insulin resistant

Current Treatment Paradigm Pathophysiology-Oriented Approach



- Combination therapy from the outset
- Treatment designed to address the underlying pathophysiology
- Vigorous effort to meet glycemic targets
- Simultaneous rather than sequential therapy
- Early stepwise titrations to meet glycemic targets

American Diabetes Association , *Diabetes Care* 2009;32:193

T2DM

Monotherapy

MET	DPP4	GLP-1	TZD	AGI

↓ *2 - 3 Mos.*

Dual Therapy

MET	+	GLP-1 or DPP4
		TZD
		Glinide or SU
TZD	+	GLP-1 or DPP4
MET	+	AGI

↓ *2 - 3 Mos.*

Triple Therapy

MET + GLP-1 or DPP4	+	TZD
		Glinide or SU

→ *2 - 3 Mos.* → **INSULIN ± Other Agent(s)**

AACE December 2009 Update.

Diabeic Ketoacidosis

- Occurs in type 1 DM >>> type 2 DM
- Severe insulin deficiency and activation of counter regulatory hormones (e.g. glucagon)
- Precipitation- interruption of insulin, sepsis, etc
- Clinical features - polyuria, nausea, vomiting, vaguely localized abdominal pain, Kussmaul respiration
- Dehydration is invariable and respiratory distress, shock, and coma can occur
- Labs will show metabolic acidosis and positive serum ketones, elevated plasma glucose

Diabeic Ketoacidosis

- Therapeutic priorities are fluid replacement, adequate insulin, potassium repletion, monitoring
- Fluid deficits of several liters are common. Restoration done using isotonic (0.9%) saline
- Sufficient insulin to turn off ketogenesis and correct hyperglycemia
- Potassium deficit always be assumed or anticipated, regardless of plasma levels
- Insulin therapy - rapid shift of K+ into intracellular compartment

Nonketotic Hyperosmolar Syndrome

- Occurs primarily in patients with type 2 DM
- Ketoacidosis is absent because insulin levels may effectively prevent lipolysis and subsequent ketogenesis yet are inadequate to facilitate peripheral glucose uptake and to prevent hepatic residual gluconeogenesis and glucose output.
- Precipitating factors - stress, infection, stroke, noncompliance with medications etc
- In contrast to DKA, onset of NKHS is usually insidious. Clinical evidence of severe dehydration is the rule. Some alterations in consciousness and focal neurologic deficits may be found
- Clinical findings include (a) hyperglycemia, often >600 mg/dL; (b) plasma osmolality >320 mOsm/L; (c) absence of ketonemia; and metabolic acidosis

Nonketotic Hyperosmolar Syndrome

- The goals of therapy are:
  - Restoration of hemodynamic stability and intravascular volume by fluid replacement
  - Compared to DKA, much more fluid replacement
  - Correction of electrolyte abnormalities
  - Gradual correction of hyperglycemia
  - Treatment of underlying disease /precipitations
  - Complications - thromboembolic events (cerebral and myocardial), cerebral edema, ARDS

Hypoglycemia

- Low serum glucose (<60 mg/Dl) + symptoms of sympathoadrenal activation (sweating, anxiety, tremor, palpitations)
- Neuroglycopenia (fatigue, dizziness, headache, visual disturbances, drowsiness, difficulty speaking, inability to concentrate, confusion, LOC or seizures)
- Usually complicates therapy with insulin or SU
- Risk factors – skipped meals, unaccustomed physical exertion, alcohol ingestion, drug overdose.
- Readily absorbable carbohydrates, IV dextrose, Glucagon IM/SC

Pregnancy & diabetes / GDM

- Miscarriage, birth anomalies CVS, CNS, macrosomia, RDS, extreme prematurity
- FPG concentration >92 mg/dL; 1-hour glucose value ≥180 mg/dL; or 2-hour value ≥153 mg/dL
- All pregnant women should be screened for GDM at 24 to 28 weeks' gestation

Pregnancy & diabetes / GDM

- Regular or rapid-acting insulin analogues are preferred
- Basal insulin needs can be provided by using rapid-acting insulin via CSII or by using long-acting insulin (eg, NPH)
- Metformin and glibenclamide - effective alternatives without adverse effects

Newer advances (Insulin)

Inhalation

- Exubera, withdrawn by maker in 2007, lack of acceptance

Transdermal

- Pulsatile insulin uses microjets
- Electricity using iontophoresis and ultrasound make skin porous

Intranasal insulin

- CPEX Pharmaceuticals phase 2a trial Nasulin

Newer advances (Insulin)

Oral insulin

- Novo Nordisk phase 1 trial (NN1952)
- Biodel, VIAtab, administered sublingually.
- Biocon, phase III trials (IN-105)

Pancreatic transplantation

- Often performed in conjunction with liver or kidney transplant, transplantation of only beta cells. transplanting genetically engineered non-beta cells to secrete insulin

Newer advances (Oral)

- **Piragliatin** - Novel glucokinase activator, shown to improve beta cell function
- **Dapagliflozin** - Renal sodium-glucose transporter-2 (SGLT 2) inhibitor targeting renal gluconeogenesis and absorption
- **Bromocriptine quick release** - dopamine-D2 receptor agonist
- Produces its effects without increasing insulin concentrations, by altering activity of hypothalamic neurons to reduce hepatic gluconeogenesis
- **Metabolic surgery** include gastroplasty, laparoscopic adjustable gastric banding, sleeve gastrectomy, gastric bypass, and biliopancreatic diversion

Thank you

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