How to use Insulin for long term management of type 2 DM

Hemi Sinorita

Genetic factors

Obesity

Insulin resistance

Diet

Physical inactivity

Beta-cell

Appropriate compensation

Failure to compensate

Elevated insulin
Normal glucose

↑ Insulin secretion

↑ Beta-cell mass

↑ Proinsulin biosynthesis

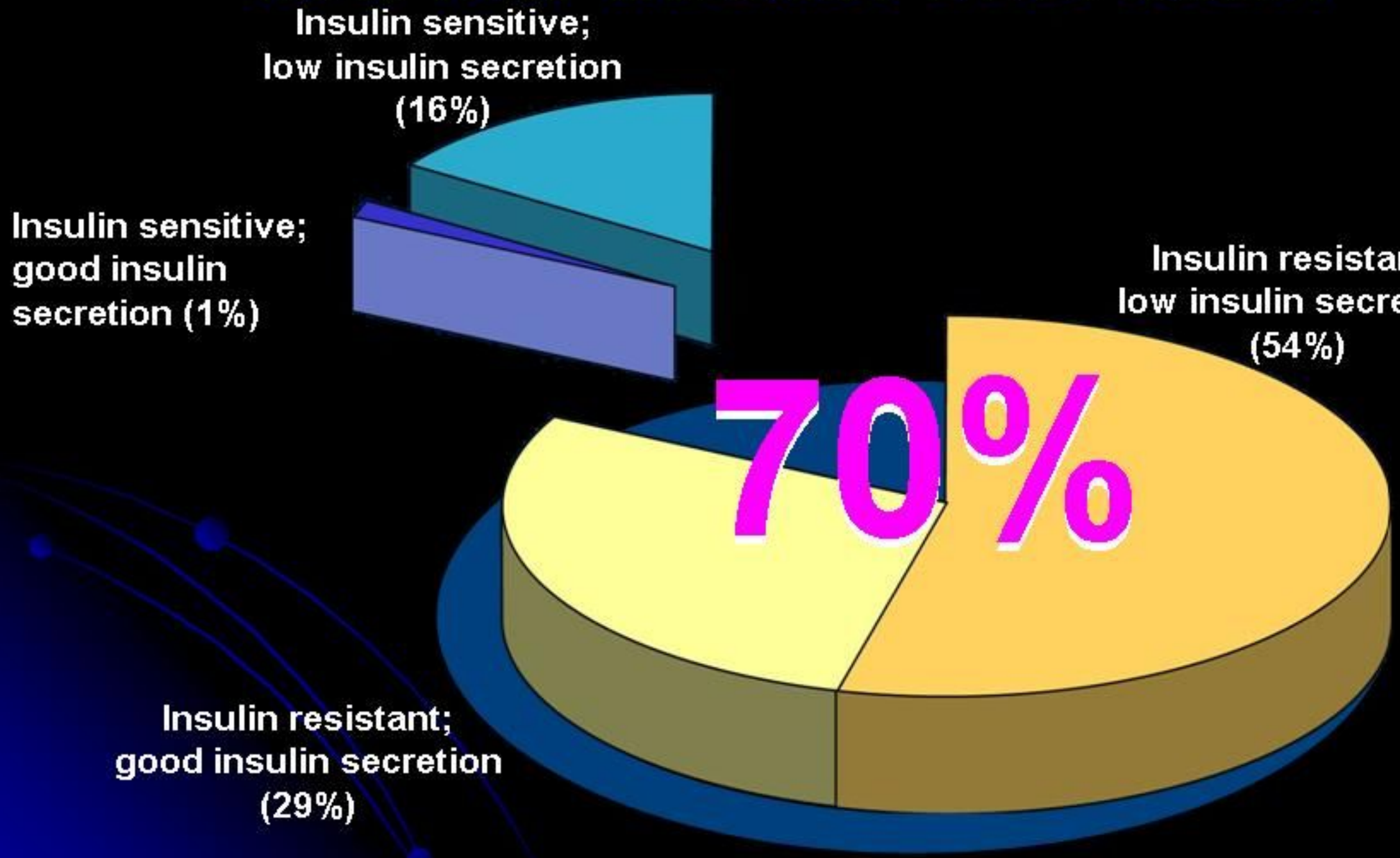
T2DM

↓ Insulin secretion

↓ Beta-cell mass

↓ Proinsulin biosynthesis

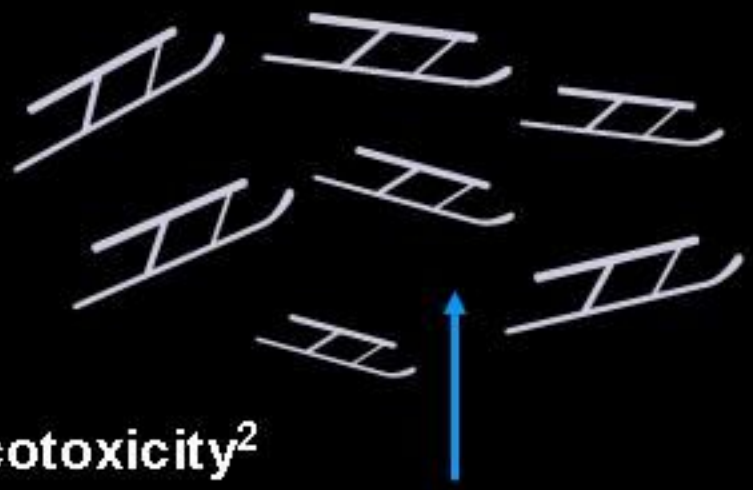
70% of patients type 2 diabetes are low insulin secretion



The 7-year follow-up of the San Antonio Heart Study

Haffner SM, *et al. Circulation* 2000; 101:975–980.

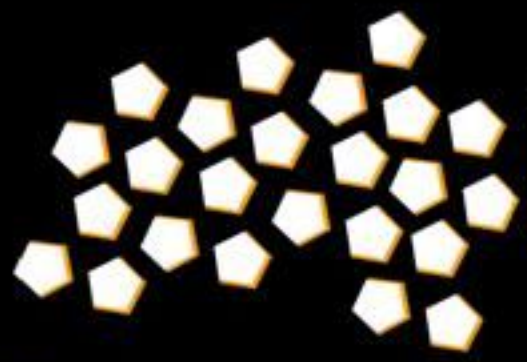
Why does the β-cell fail?

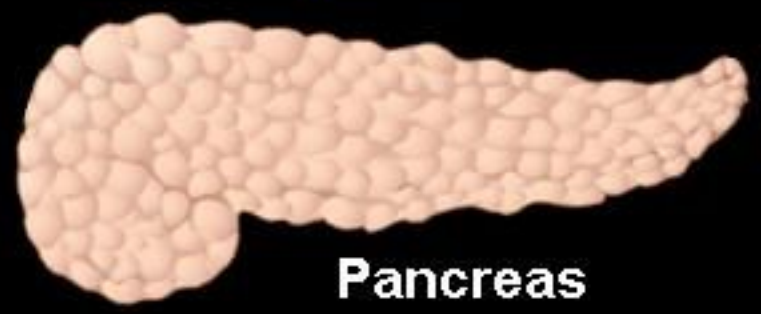


Oversecretion of insulin to compensate for insulin resistance[1,2]

Glucotoxicity[2]

Lipotoxicity[3]





Chronic hyperglycemia

Pancreas

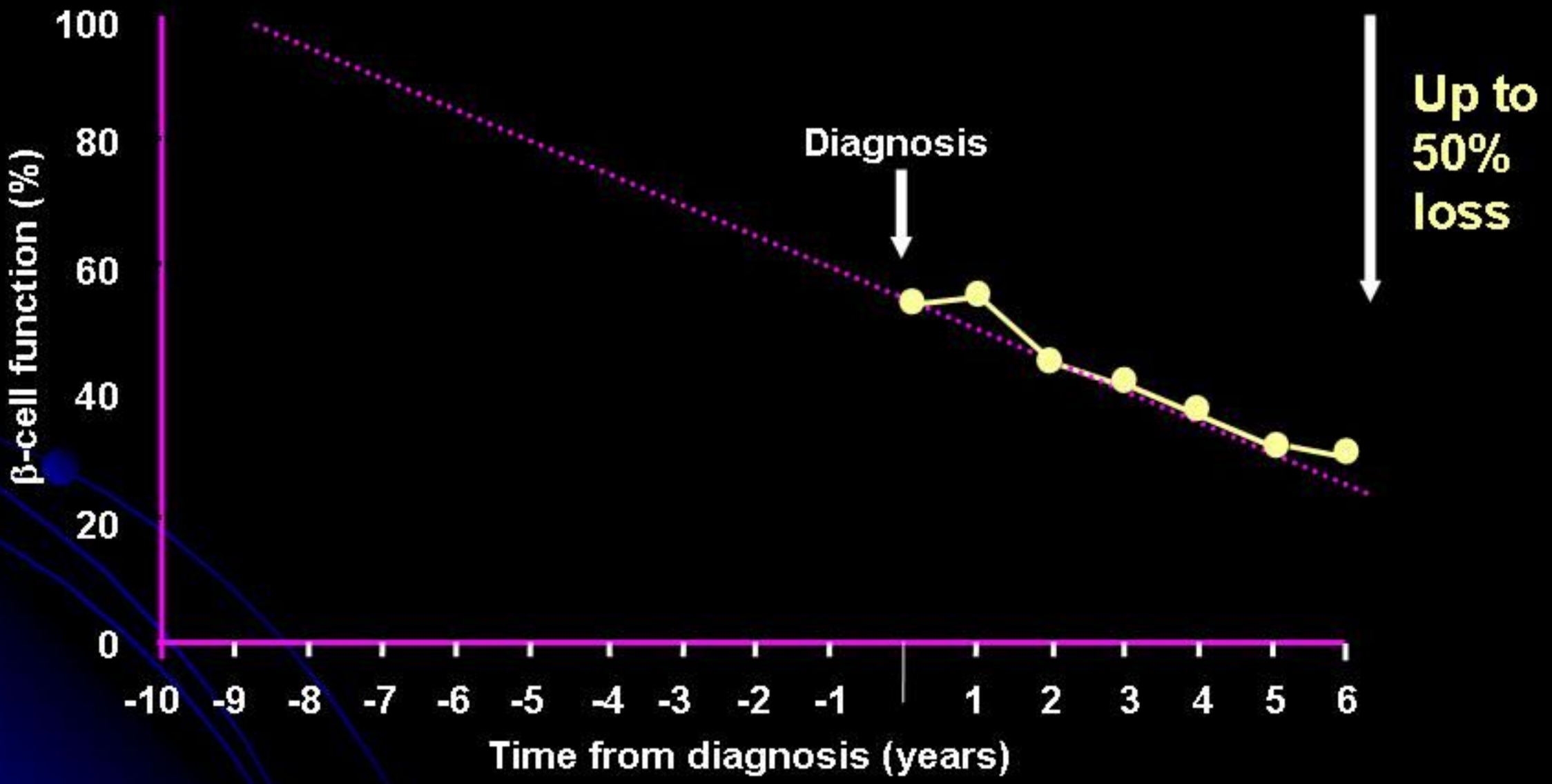
β-cell dysfunction

[1]Boden G & Shulman GI. *Eur J Clin Invest* 2002; 32:14–23.

[2]Kaiser N, *et al. J Pediatr Endocrinol Metab* 2003; 16:5–22.

[3]Finegood DT & Topp B. *Diabetes Obes Metab* 2001; 3 (Suppl. 1):S20–S27.

Loss of β-cell function occurs before diagnosis



Holman RR. *Diabetes Res Clin Prac* 1998; 40 (Suppl.):S21–S25

The different concentration of fasting blood glucose, fasting insulin level, insulin resistance and ß-cell function between obese non DM, obese pre DM and obese DM at Sardjito Hospital Yogyakarta

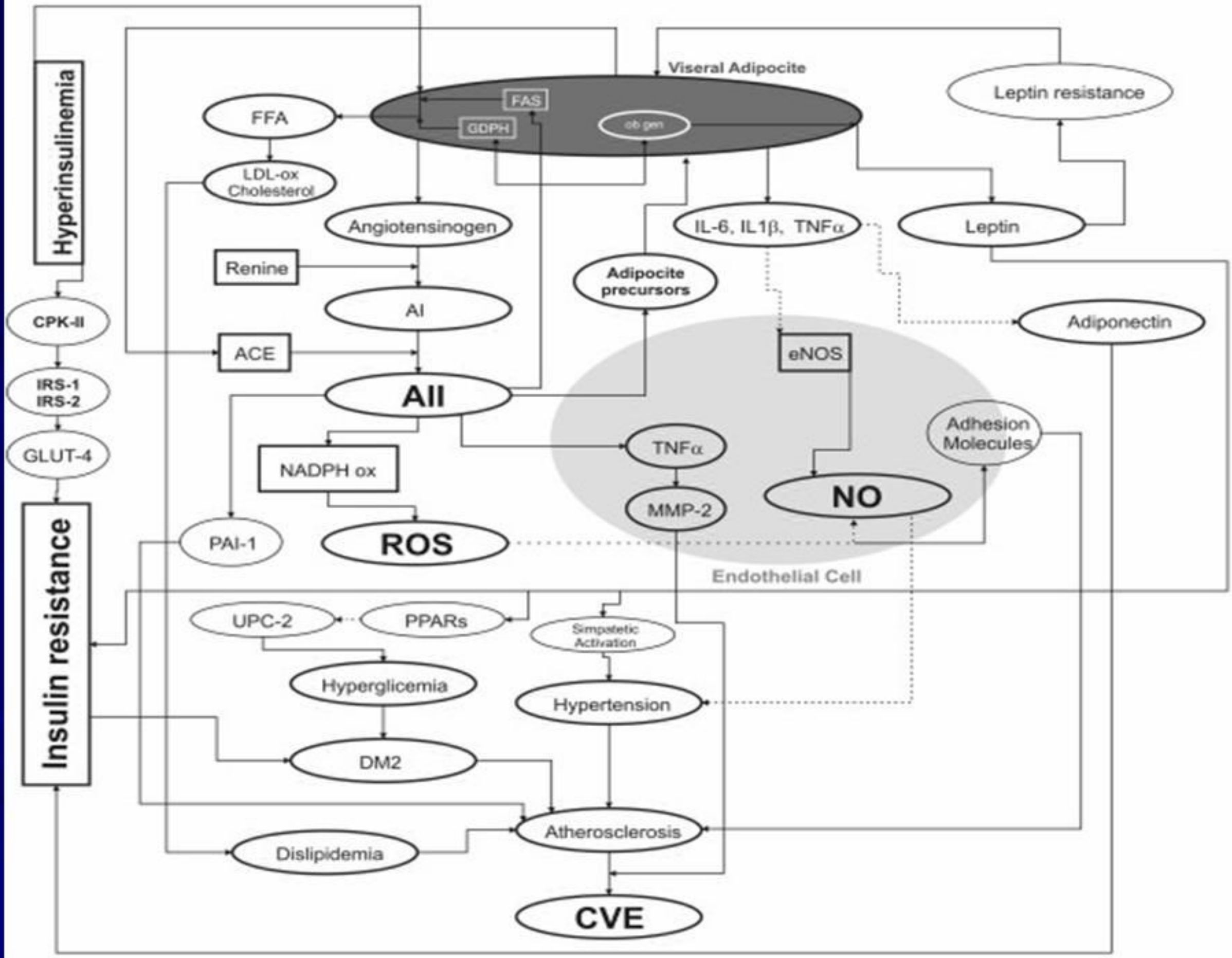
Variable	Obese Non DM (29)	Obese Pre DM (16)	Obes DM (30)	P*
FBG	90,57±9,15	102,18±10,03	159,71±46,57	<0,01
Insulin	8,32±7,14	20,95±37,08	10,34±5,99	0,16
HOMA-B	111,79±72,48	158,37±229,53	54,65±68,28	<0,01

* Kruskal Wallis test

When should we start insulin therapy in type 2 diabetes?

- Not to soon

1. Defect in insulin secretion may not be primary defect.
2. Insulin therapy associated with higher risk for hypoglycemia.
3. Insulin therapy causes body weight gain and chronic hyperinsulinemia


Hyperinsulinemia
Viseral Adipocite
FAS
GDPH
ob gen
FFA
LDL-ox Cholesterol
Angiotensinogen
Renine
AI
ACE
AII
Leptin resistance
IL-6, IL1β, TNFα
Leptin
Adipocite precursors
Adiponectin
eNOS
CPK-II
IRS-1 IRS-2
GLUT-4
NADPH ox
TNFα
Adhesion Molecules
MMP-2
NO
PAI-1
ROS
Endothelial Cell
Insulin resistance
UPC-2
PPARs
Simpatetic Activation
Hyperglicemia
Hypertension
DM2
Atherosclerosis
Dislipidemia
CVE

…When should we start insulin therapy in type 2 diabetes?

- Not too late

1. May not ensure sufficient glicemic control.
2. May be refused by patient.

Diabetes Mellitus Treatment

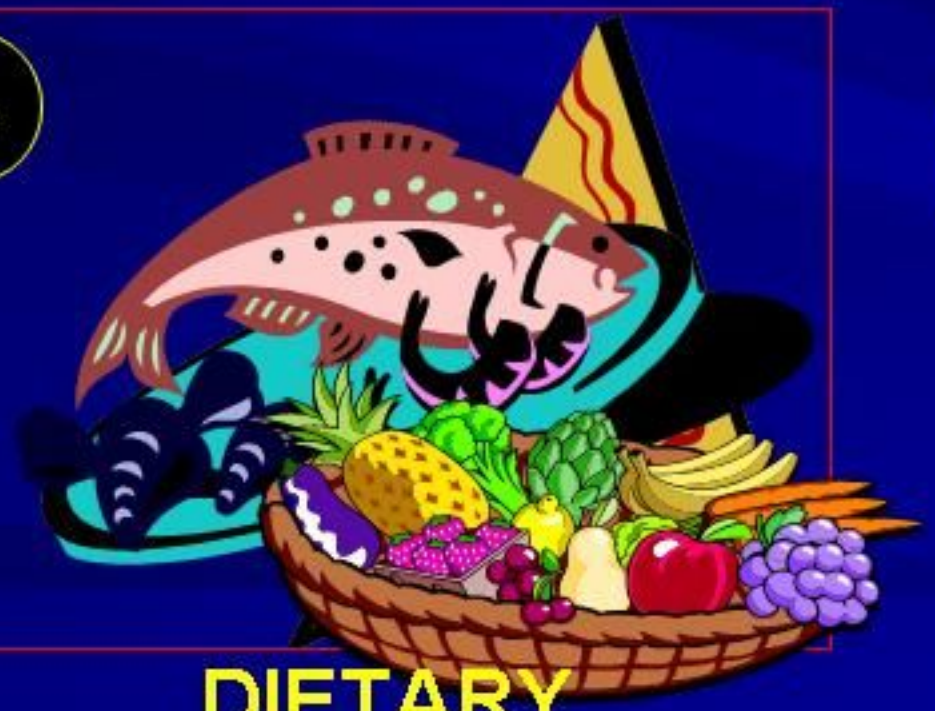
1

EDUCATION

2

EXERCISES

3



DIETARY

4

HYPOGLYCEMIC AGENT

Kriteria pengendalian

	Baik	Sedang	Buruk
Glukosa darah puasa (mg/dl)	80 - 109	110 - 125	≥ 126
Glukosa darah 2 jam (mg/dl)	80 - 144	145 - 179	≥ 180
A1C (%)	< 6,5	6,5 - 8	> 8
Kolesterol Total (mg/dl)	< 200	200 - 239	≥ 240
Kolesterol LDL (mg/dl)	< 100	100 - 129	≥ 130
Kolesterol HDL (mg/dl)	> 45		
Trigeliserida	< 150	150 - 199	≥ 200
IMT (kg/m^2)	18,5 - 22,9	23 - 25	> 25
Tekanan Darah	< 130/80	130-140 / 80-90	> 140/90

Algorithm for the metabolic management of Type 2 Diabetes

Tier 1: well-validated core therapies

Diagnosis:
Lifestyle + Metformin

Step 1

Step 2

- Lifestyle + Metformin + Basal insulin
- Lifestyle + Metformin + Sulfonylurea

Step 3

Lifestyle + Metformin + Intensive insulin

Tier 2: less well-validated core therapies

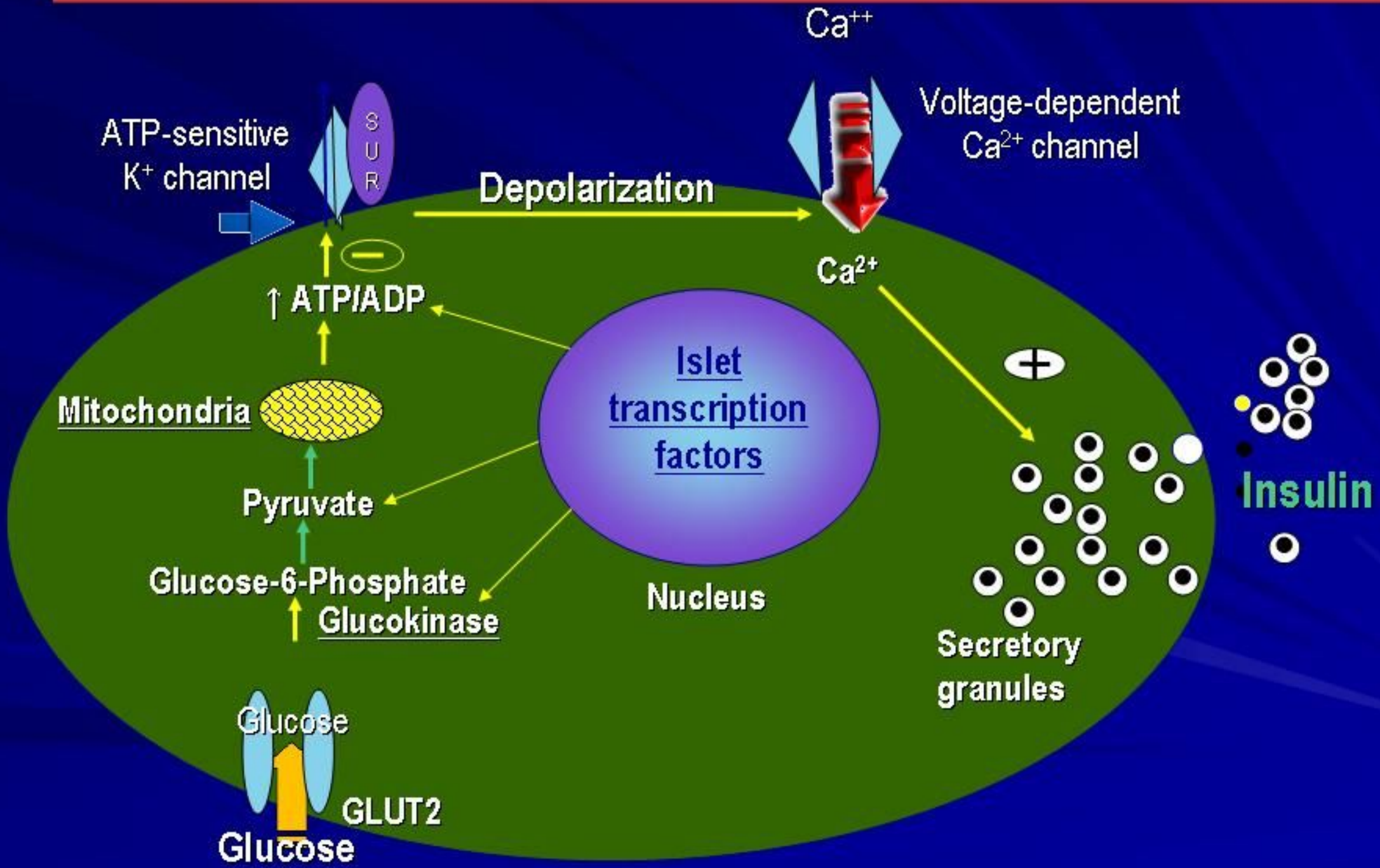
- Lifestyle + Metformin + Pioglitazone (no hypoglycemia /edema (CHF)/ bone loss)
- Lifestyle + Metformin + GLP-1 agonist [b] (no hypoglycemia/weight loss /nausea/vomiting)

Step 3

- Lifestyle + Metformin + Pioglitazone + Sulfonylurea [a]
- Lifestyle + Metformin + Basal insulin

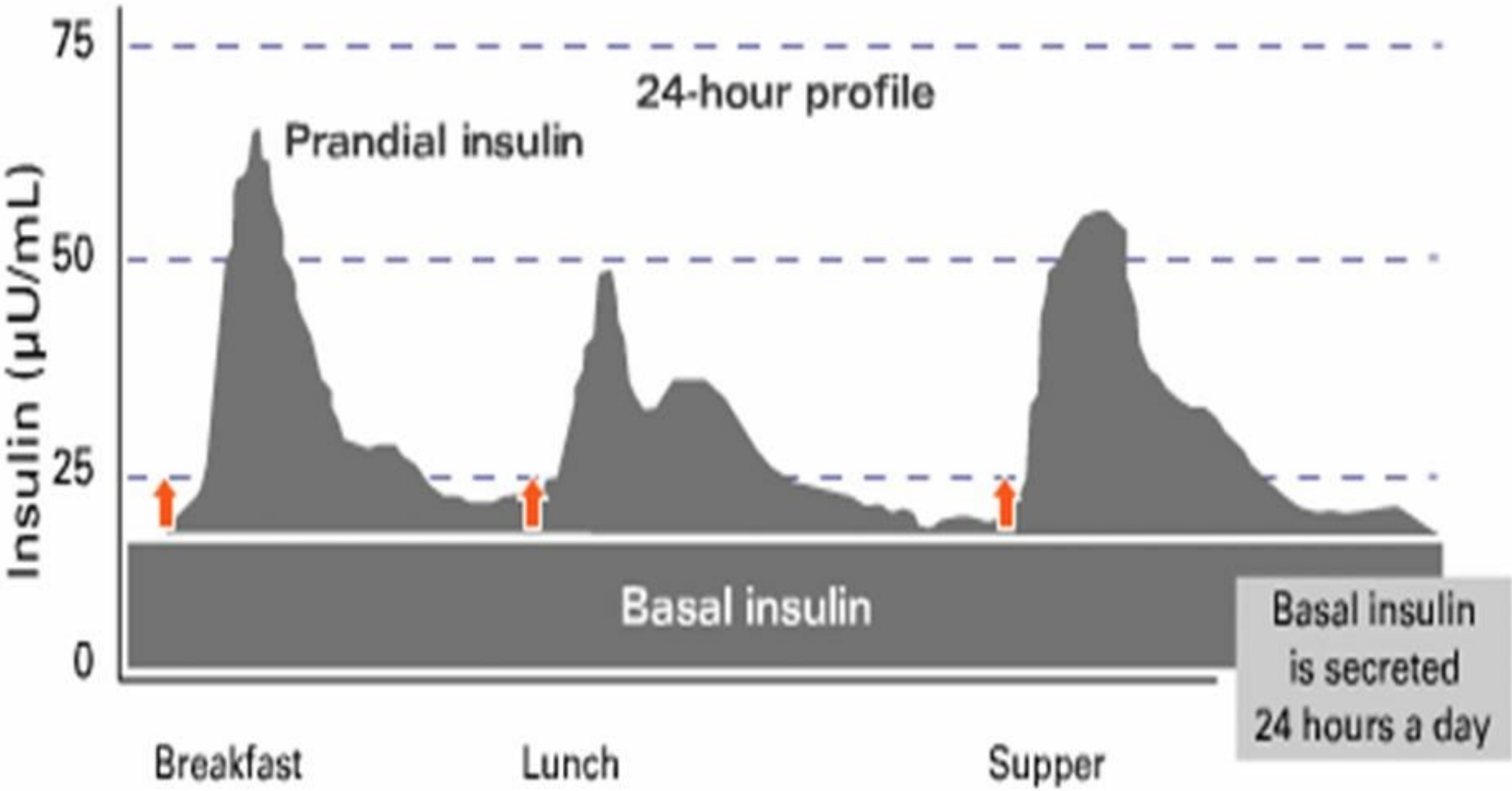
Nathan DM, et al. *Diabetes Care* 2008;31(12):1-11.

Physiology of insulin secretion

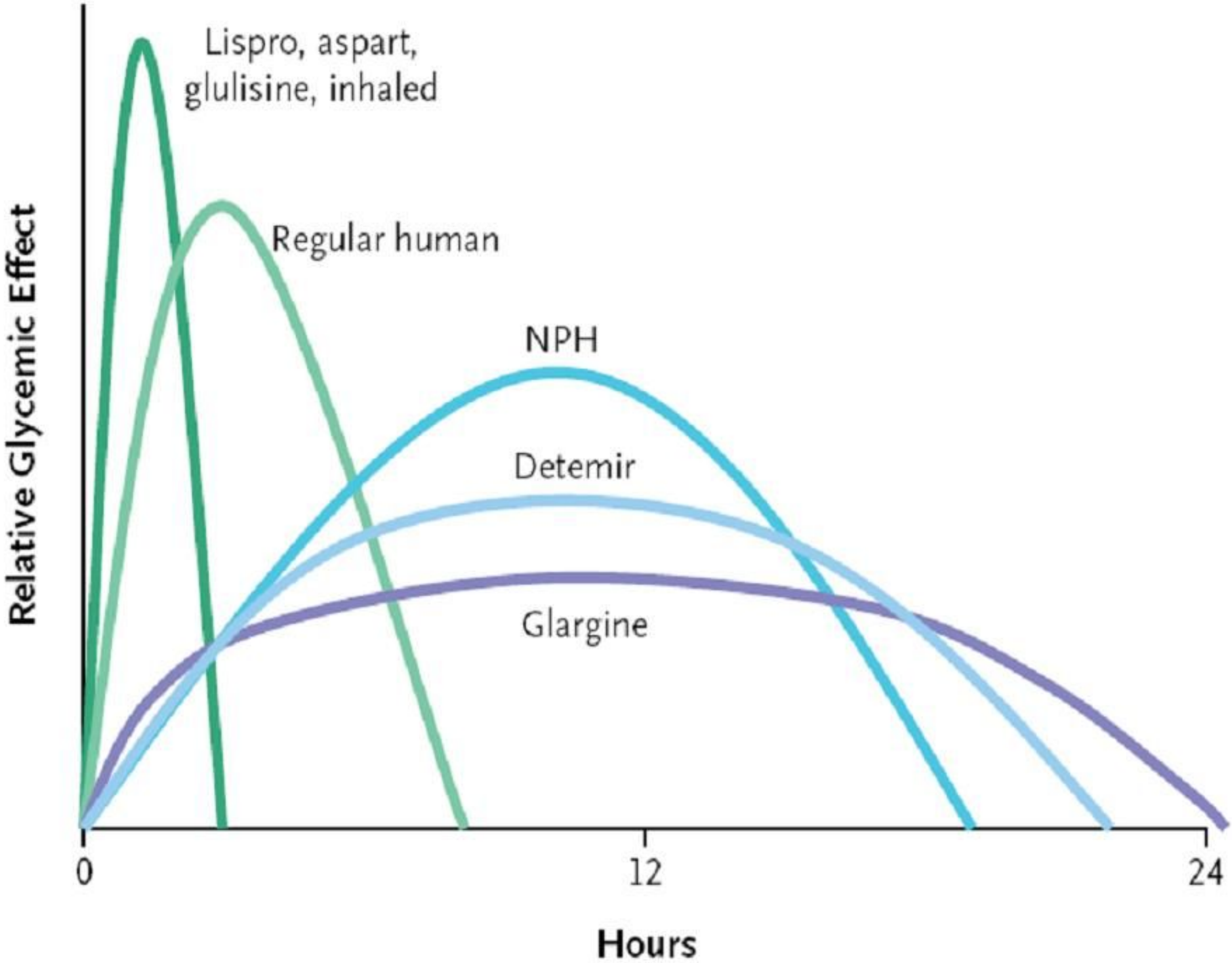


1. Type 1 diabetes
2. Uncontrolled type 2 diabetes.
3. Gestasional diabetes
4. Liver/renal insufficiency.
5. Acute infection (celulitis, gangren), TBC, stroke/AMI.
6. KAD/HHS
7. Major surgery
8. Under weight, MRDM
9. Grave's disease
10. Cancer
11. Corticosteroid treatment

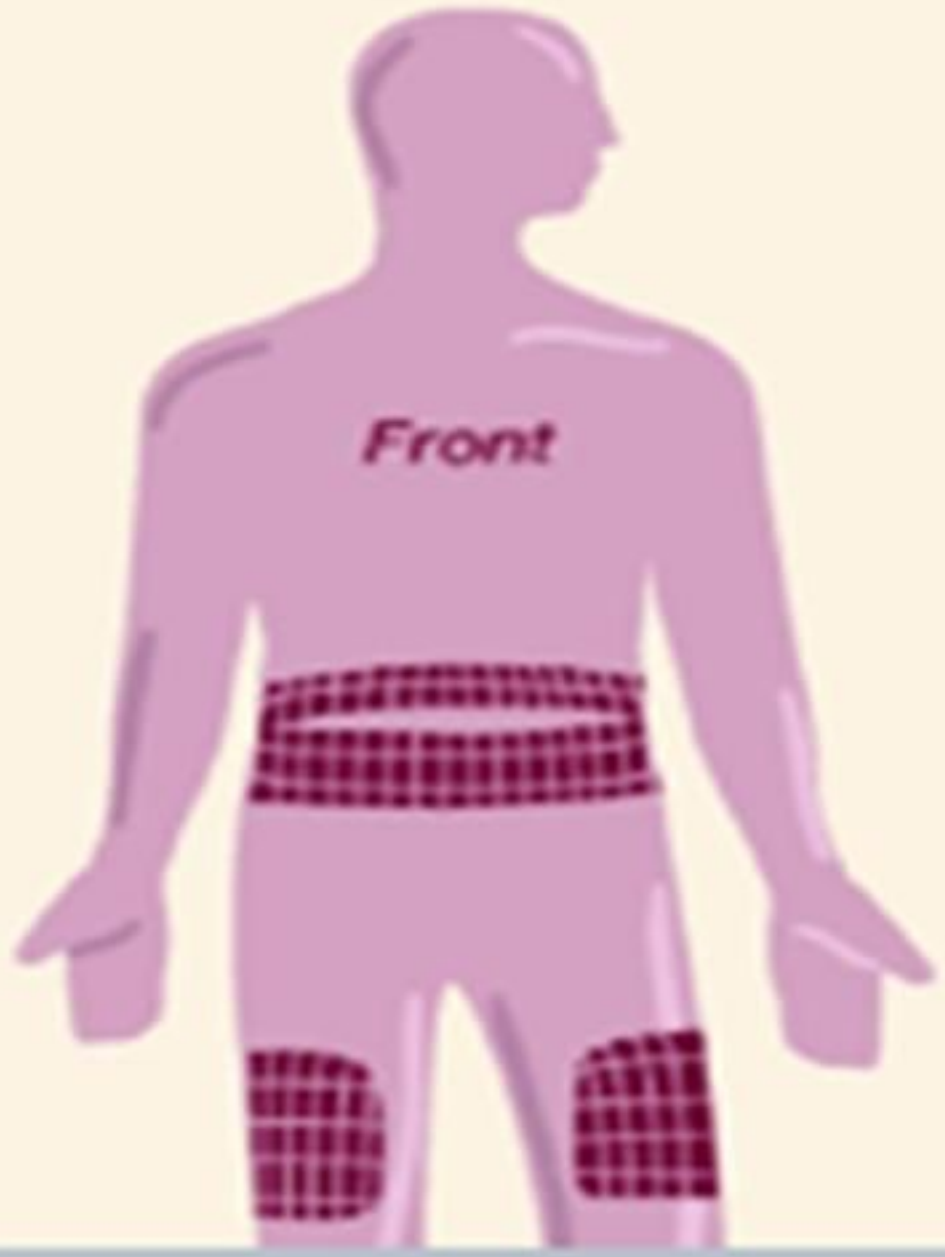
Physiologic insulin secretion[15]



Conceptual depiction of insulin profiles.


Lispro, aspart,
glulisine, inhaled
Regular human
NPH
Detemir
Glargine
Relative Glycemic Effect
0
12
24
Hours

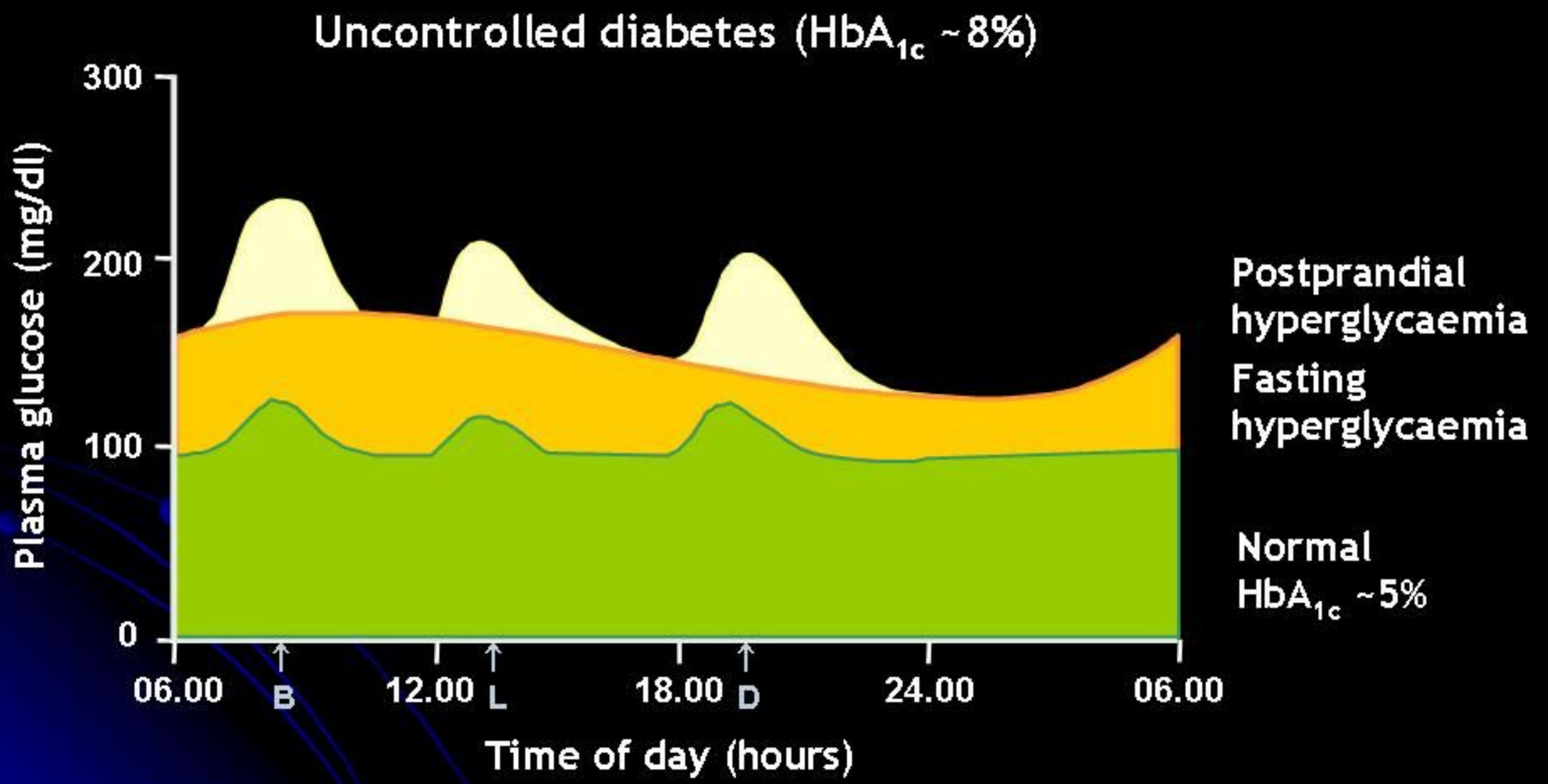
Insulin Injection Areas




Sterile
250
200
150
100
50
12

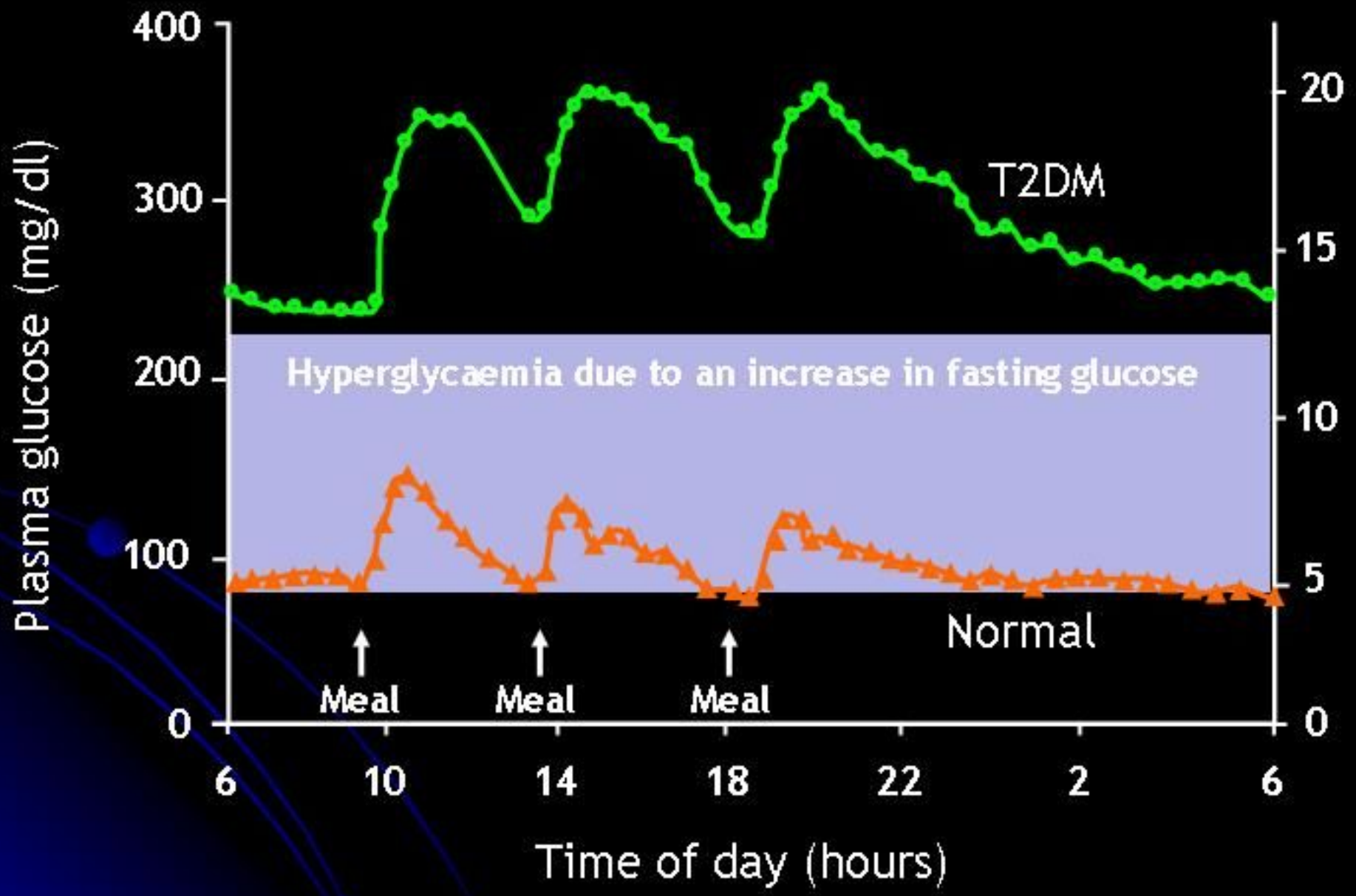
15496-09dg fotosearch.com

Both fasting and postprandial blood glucose levels are elevated in T2DM

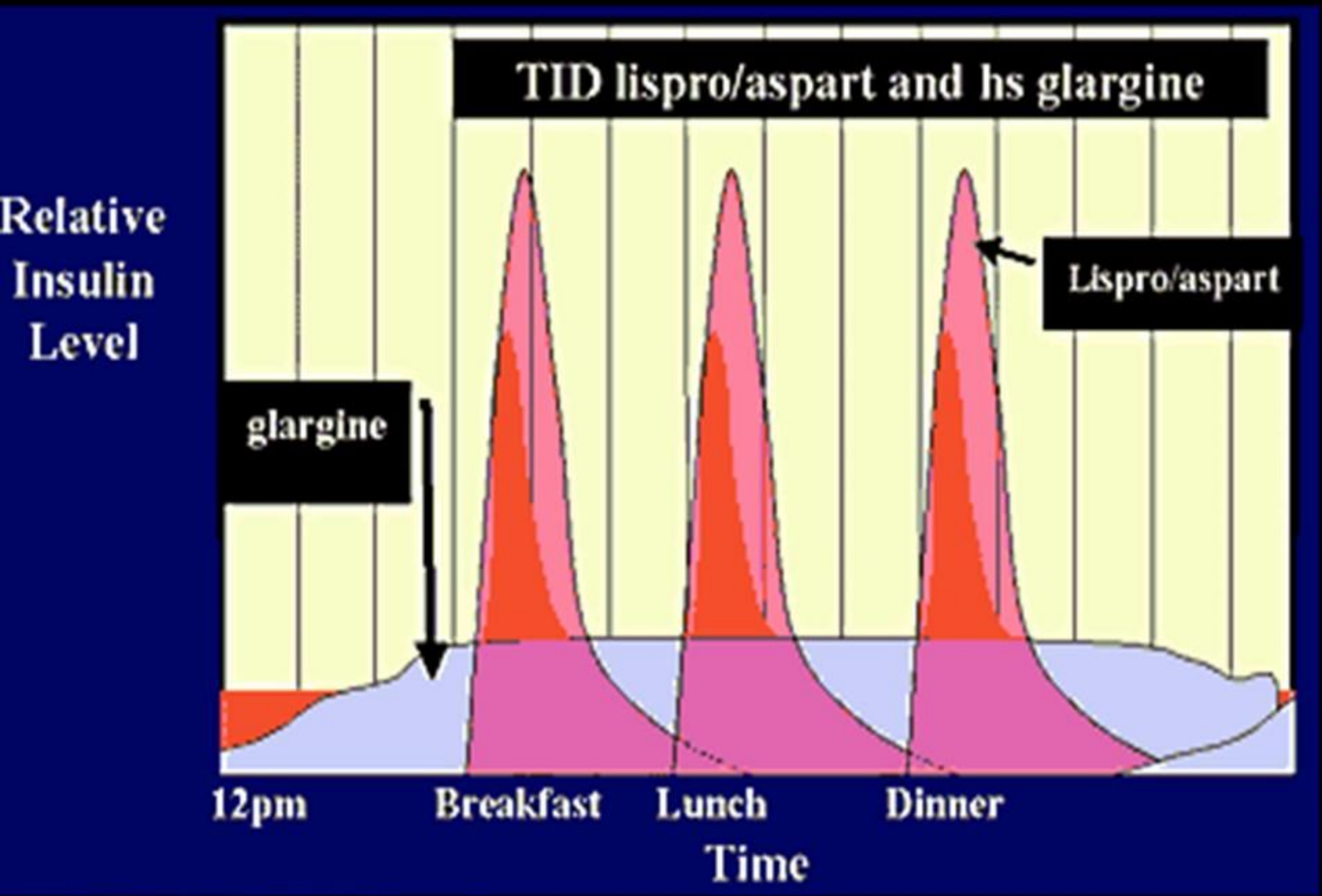


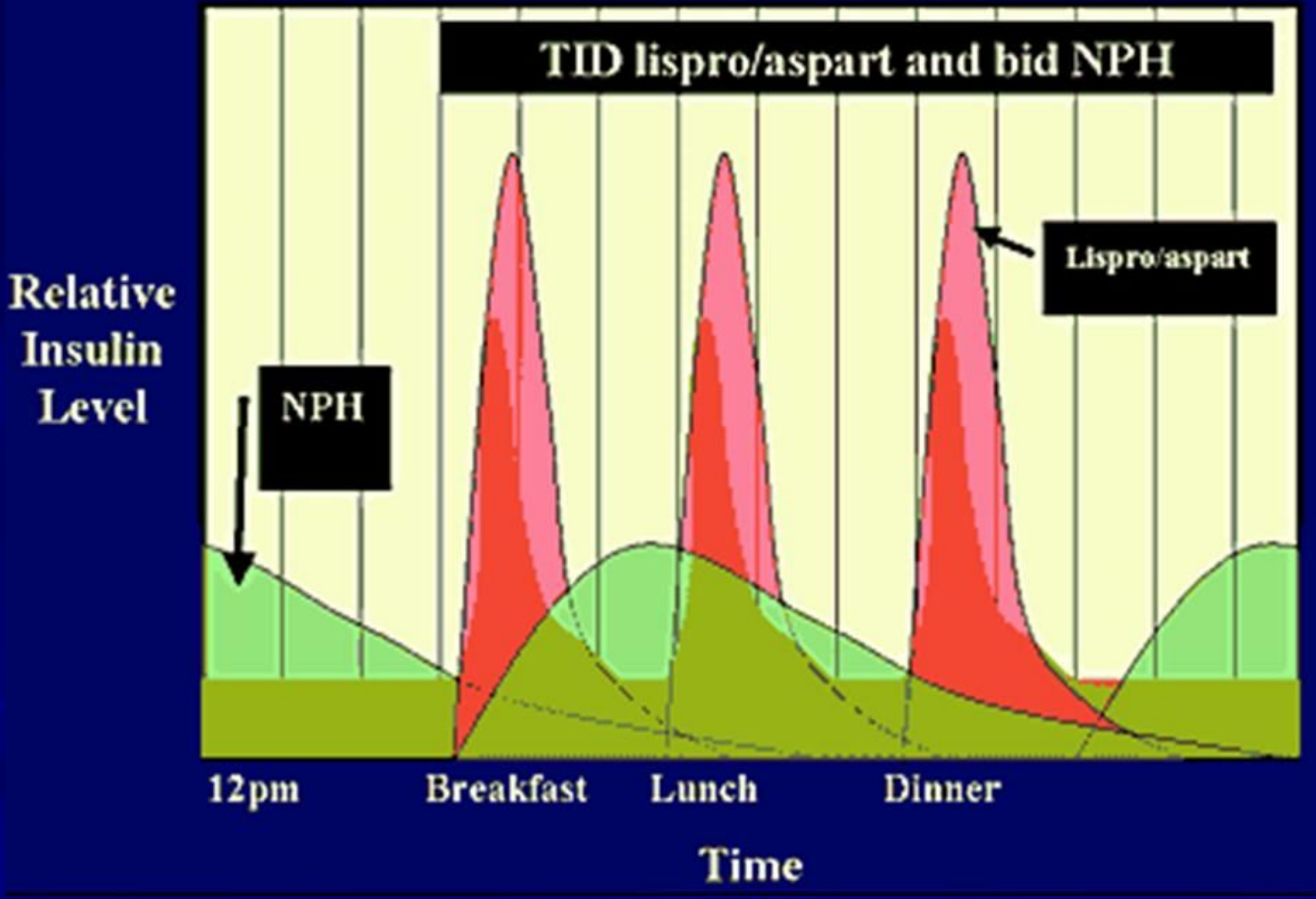
B=breakfast; L=lunch; D=dinner.
Adapted from Riddle M. Diabetes Care 1990;13:676–86.

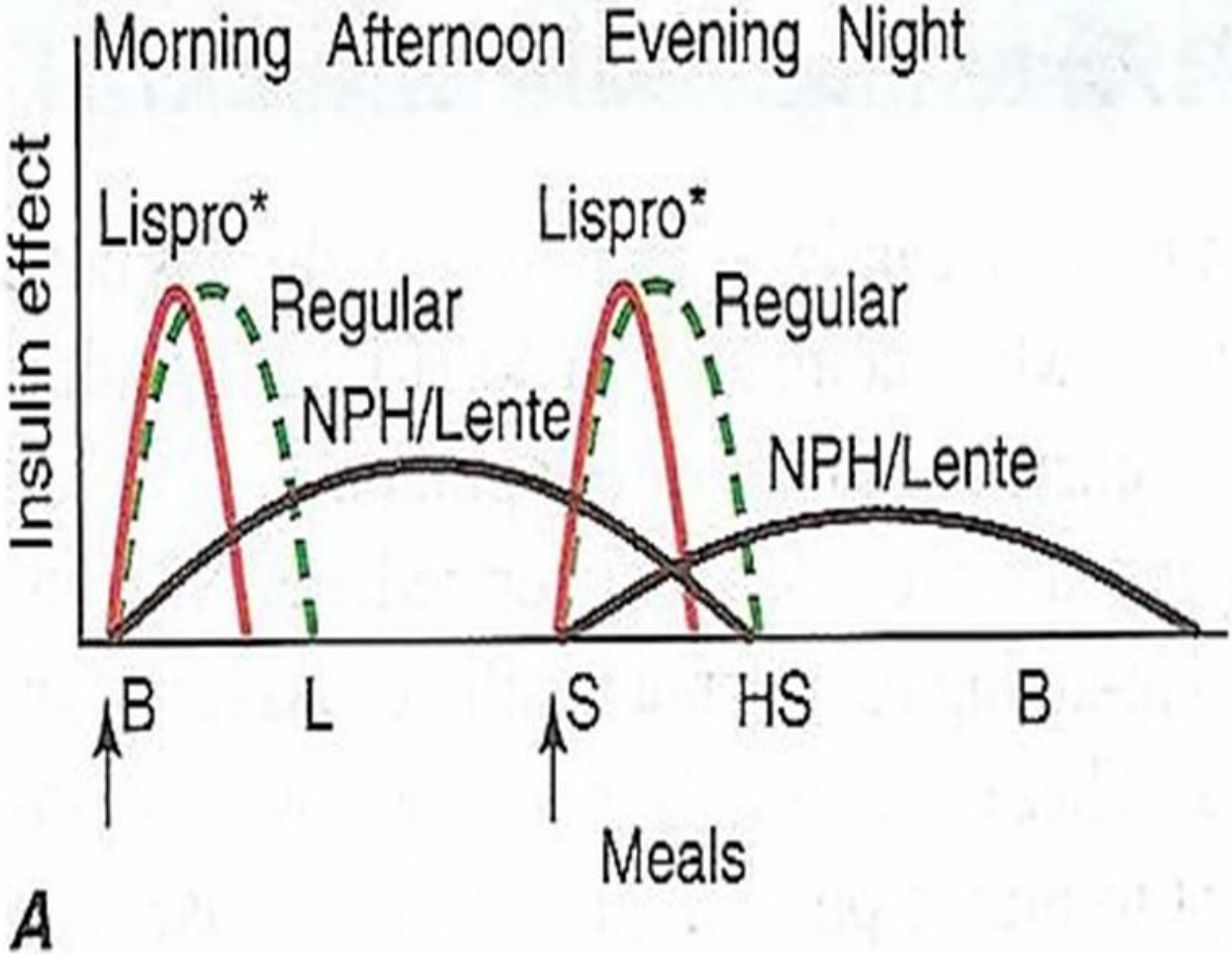
Treating fasting hyperglycaemia lowers the entire 24-hour plasma glucose profile



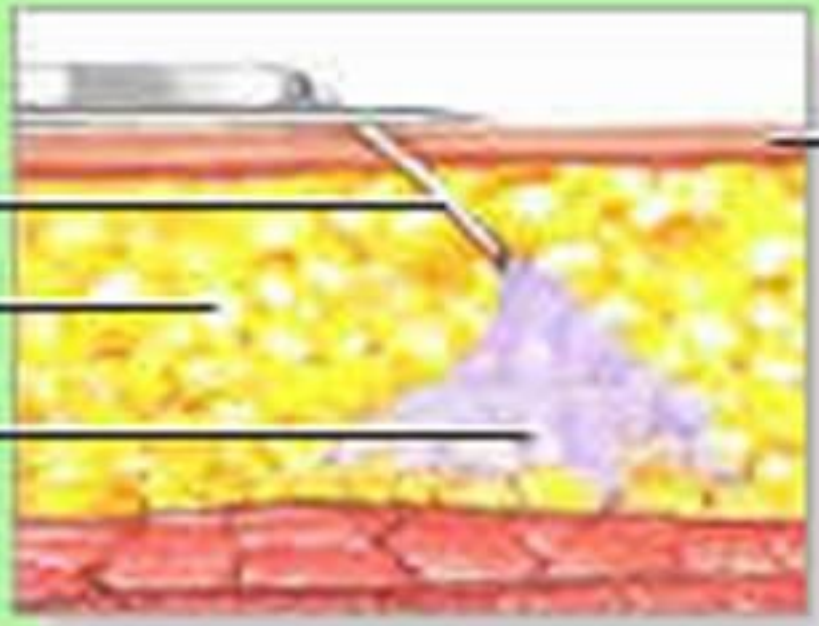
Comparison of 24-hour glucose levels in control subjects vs patients with diabetes ($p<0.001$).
Adapted from Polonsky K, et al. N Engl J Med 1988;318:1231–9.


TID lispro/aspart and hs glargine
Lispro/aspart
glargine
Relative Insulin Level
12pm
Breakfast
Lunch
Dinner
Time


TID lispro/aspart and bid NPH
Lispro/aspart
NPH
Relative Insulin Level
12pm
Breakfast
Lunch
Dinner
Time


Morning Afternoon Evening Night
Insulin effect
Lispro*
Regular
NPH/Lente
Lispro*
Regular
NPH/Lente
B
L
S
HS
B
Meals

A



Dosage instructions are entered into the pump's small computer and the appropriate amount of insulin is then injected into the body in a calculated, controlled manner

Insulin pump

Initiation and Adjustment of Insulin Regimens

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 consistently in target range (3.9–7.2 mmol/l [70–130 mg/dl]). Can increase dose in larger increments, e.g., by 4 units every 3 days, if fasting glucose is >10 mmol/l (180 mg/dl)

If hypoglycemia occurs, or fasting glucose level <3.9 mmol/l (70 mg/dl), reduce bedtime dose by 4 units or 10% - whichever is greater

A1C ≥7% after 2-3 months

No

Yes

If fasting bg is in target range (3.9–7.2 mmol/l [70–130 mg/dl]), check bg before lunch, dinner, and bed. Depending on bg results, add second injection as below. Can usually begin with ~4 units and adjust by 2 units every 3 days until bg is in range

Pre-lunch bg out of range. Add rapid-acting insulin at breakfast [a]

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 [a]

Continue regimen. Check A1C every 3 mo

No

A1C ≥7% 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

[a] See speaker notes

Nathan DM, et al. *Diabetes Care* 2008;31(12):1-11.

Side effect :

1. Hypoglycemia
2. Hypokalemia
3. Urticaria
4. Peripheral edema
5. Weight gain

~90% of people with type 2 diabetes are overweight or obese

World Health Organization, 2005. http://www.who.int/dietphysicalactivity/publications/facts/obesity

Obesity Changes the Function of the Adipose Tissue

Adiponectin ↓

- FFA
- Leptin
- Angiotensinogen
- Resistin
- CRP
- TNF-α
- PAI-1
- Serum Amyloid-A
- IL-6, IL-1
- Estrogens
- Cortisol
- Visfatin
- SAA
- MCP-1
- RBP-4

Modified from Caballero AE. *Current Diabetes Reports* 2004;4:237-246.

Insulin

r = 0.342; p=0.014

Leptin

r = 0.279; p = 0.048

Adiponectin

r = -0.346; p = 0.014

Free Fatty Acid

r = -0.395; p = 0.004

Vivastin

r = -0.376; p = 0.006

Aldosterone

terima kasih