Postprandial Hyperglycaemia in Type2 Diabetes

Managing the peaks in Clinical practice

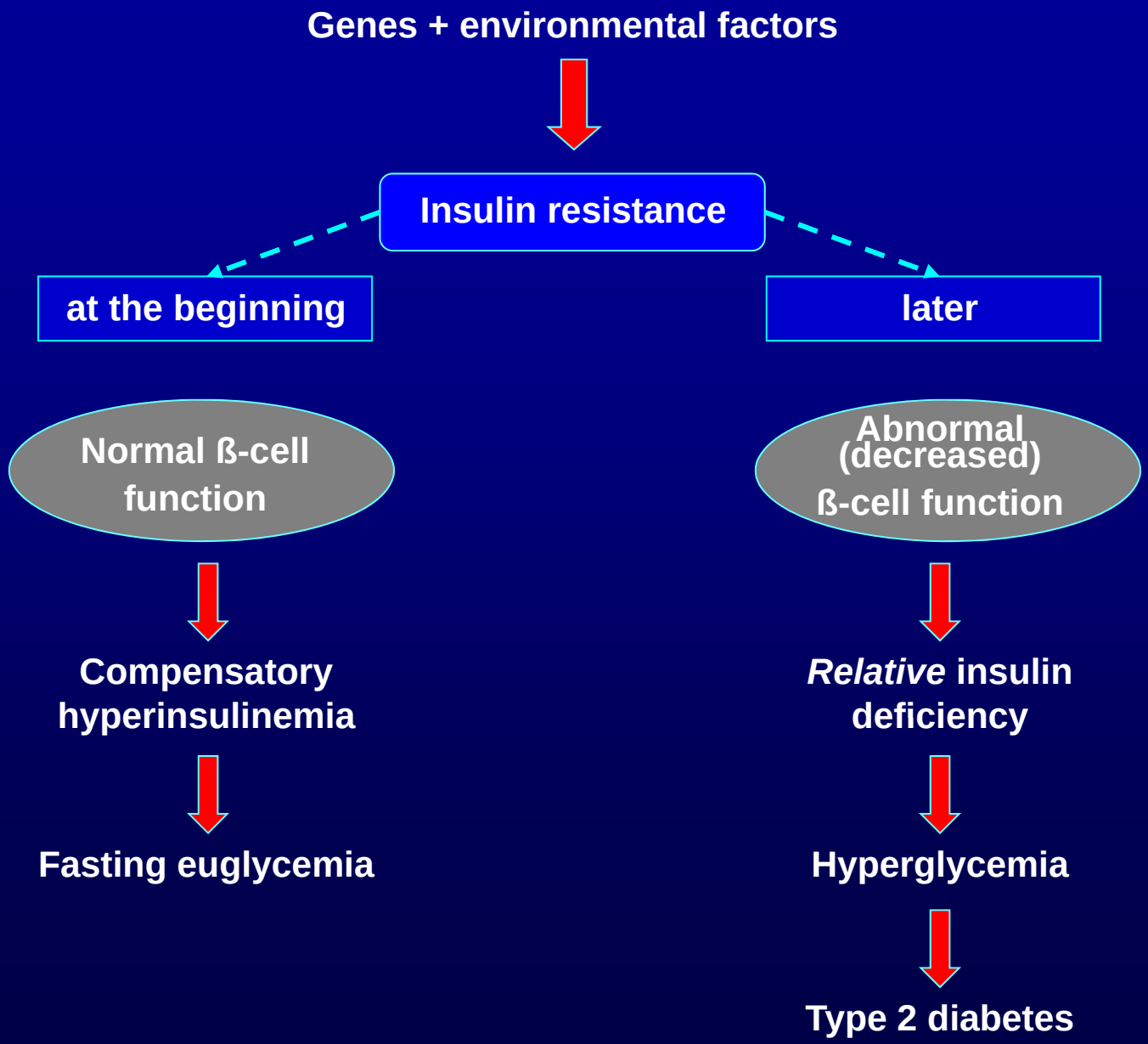
By

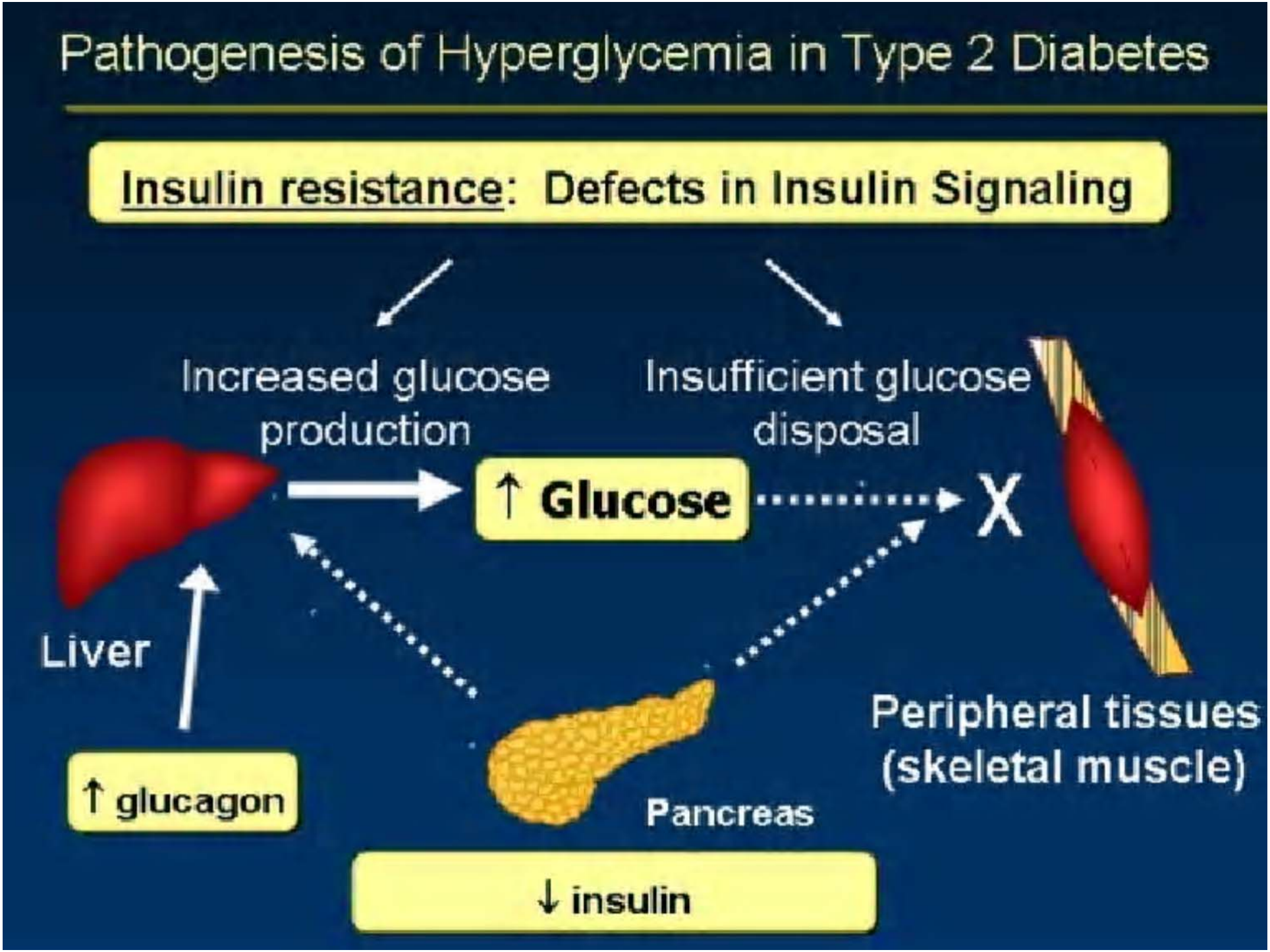
Dr Suleiman Shimjee

Overview

- Pathophysiology of Type2 Diabetes, role of PPH. Why is it relevant?
- Importance of managing postprandial hyperglycaemia. The Evidences.
- Clinical management of postprandial hyperglycaemia – the therapeutic agents

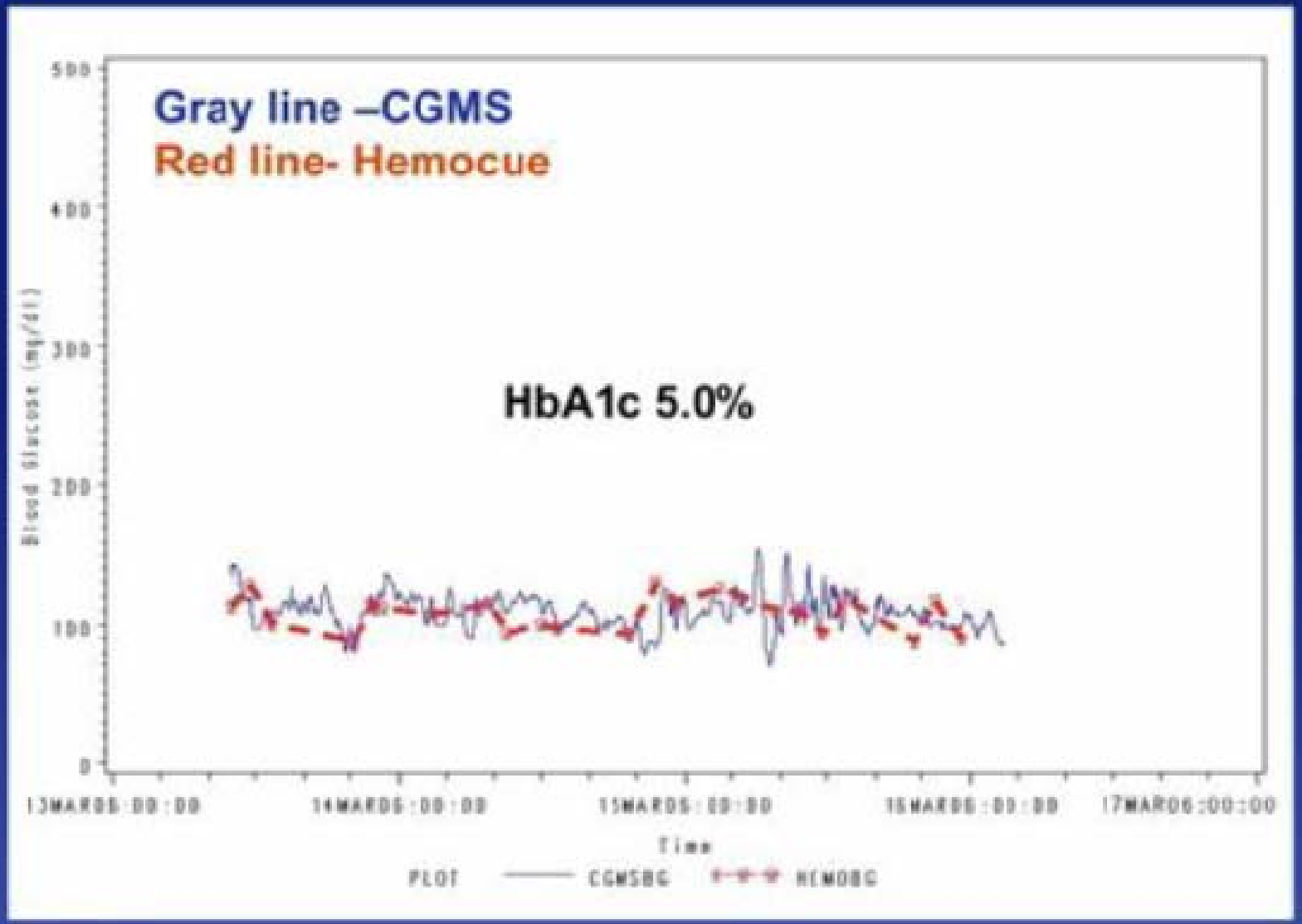
Etiology of type 2 diabetes




Pathogenesis of Hyperglycemia in Type 2 Diabetes
Insulin resistance: Defects in Insulin Signaling
Increased glucose production
Insufficient glucose disposal
↑ Glucose
X
Liver
Peripheral tissues (skeletal muscle)
↑ glucagon
Pancreas
↓ insulin

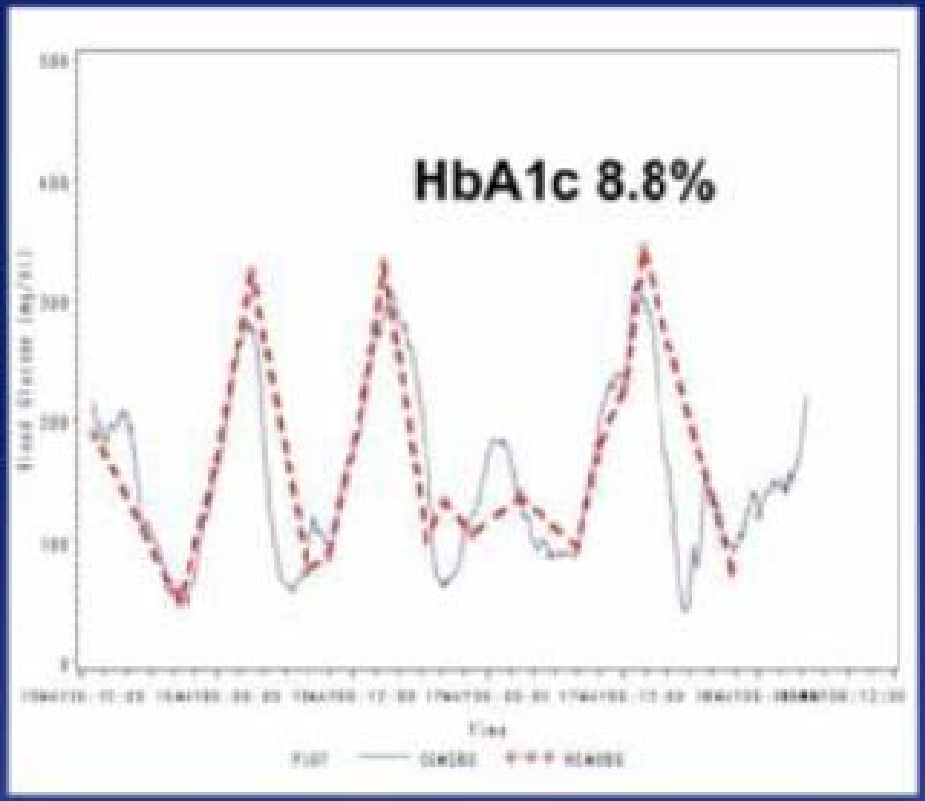
Glucose Fluctuations

Healthy Volunteer

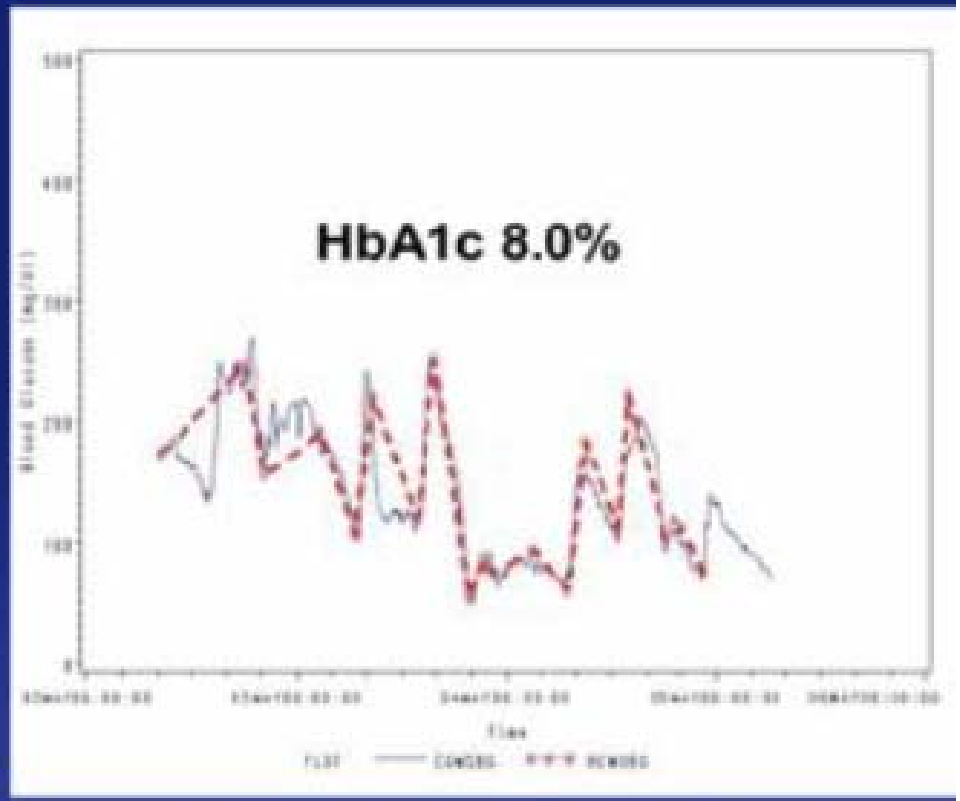


Glucose Fluctuations

Diabetes

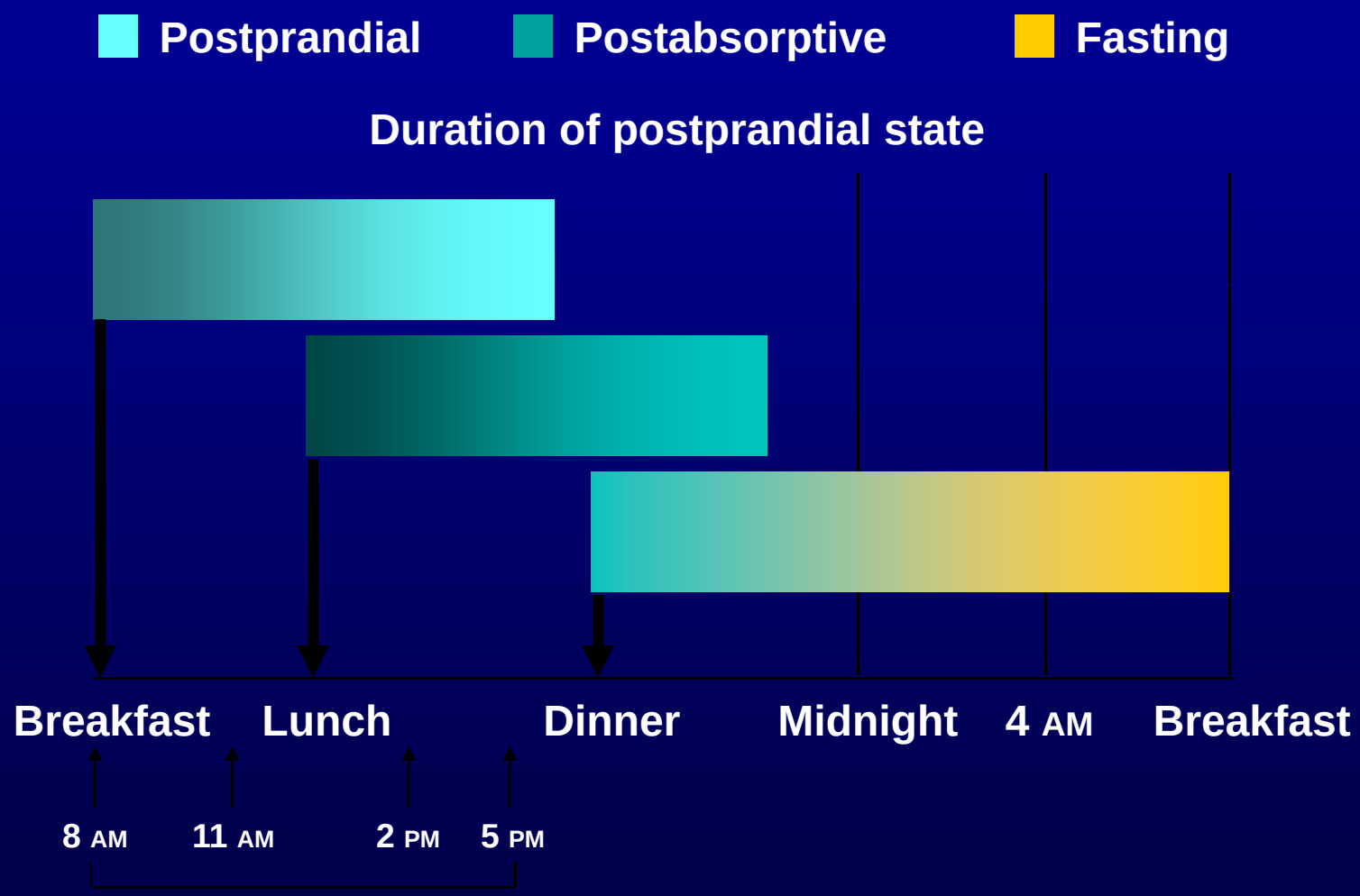


Type 2 Diabetic Subject



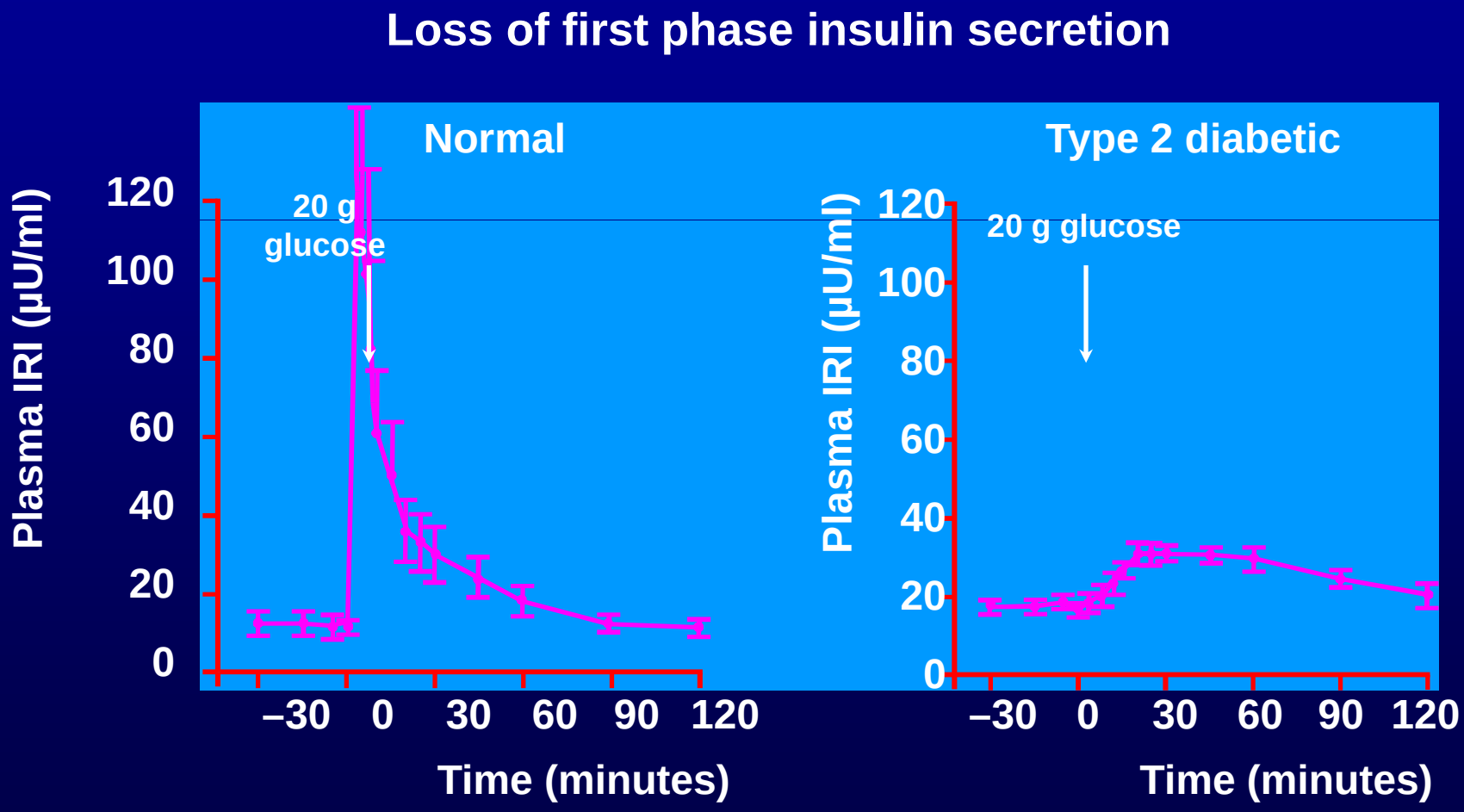
Type 1 Diabetic Subject

Patients With Type 2 Diabetes May Spend More Than 12 Hours per Day in the Postprandial State



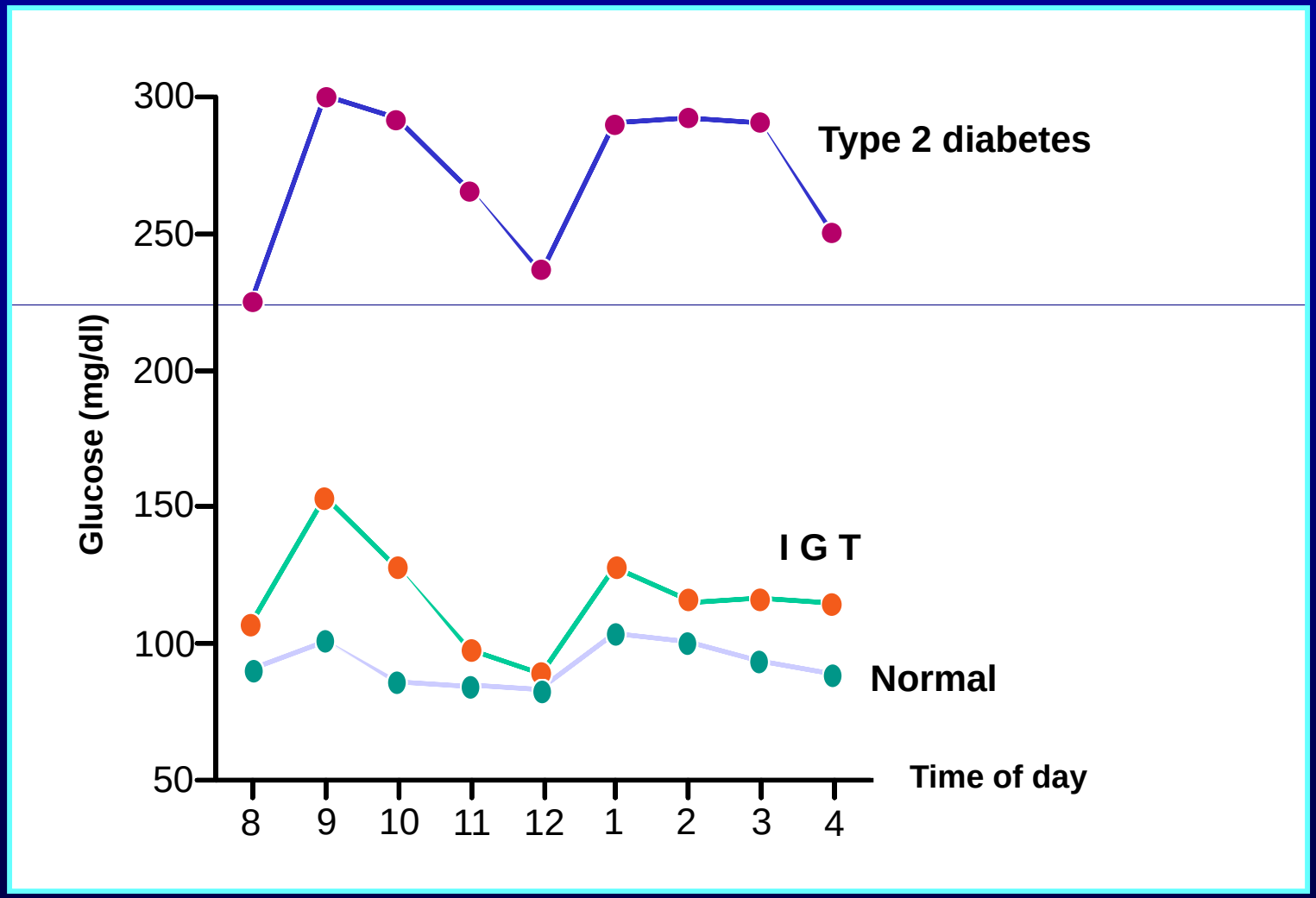
Adapted from Monnier L. *Eur J Clin Invest.* 2000;30(suppl 2):3-11.

Pattern of insulin secretion is altered early in type 2 diabetes



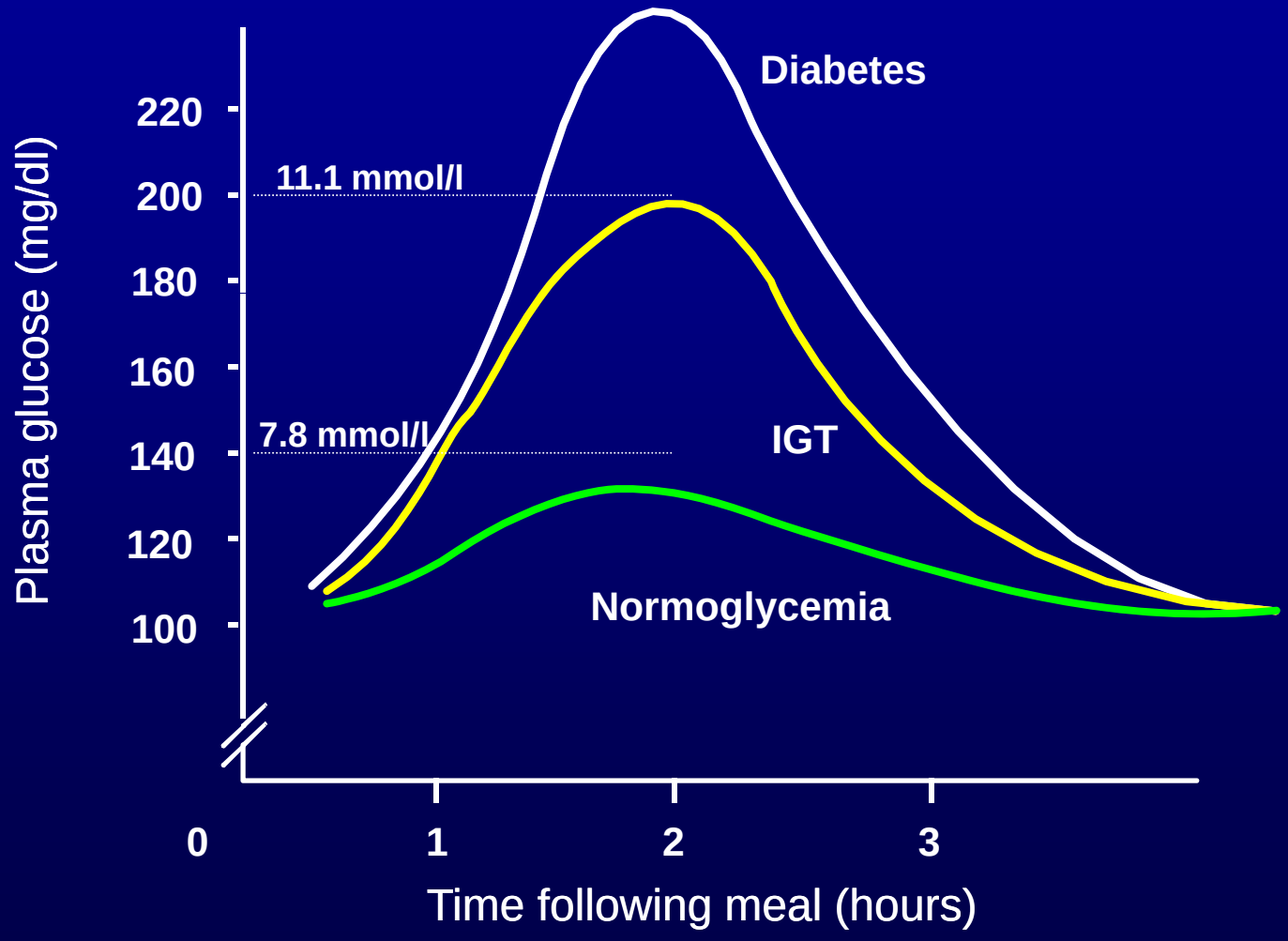
Ward WK, et al. *Diabetes Care* 1984;7:491–502.

Earliest abnormality of type 2 diabetes: postprandial hyperglycemia



Adapted from: Reaven GM, *et al*. *J Clin Endocrinol Metab* 1993; **76**: 44–48.

Postprandial glucose in normal, IGT and diabetic subjects

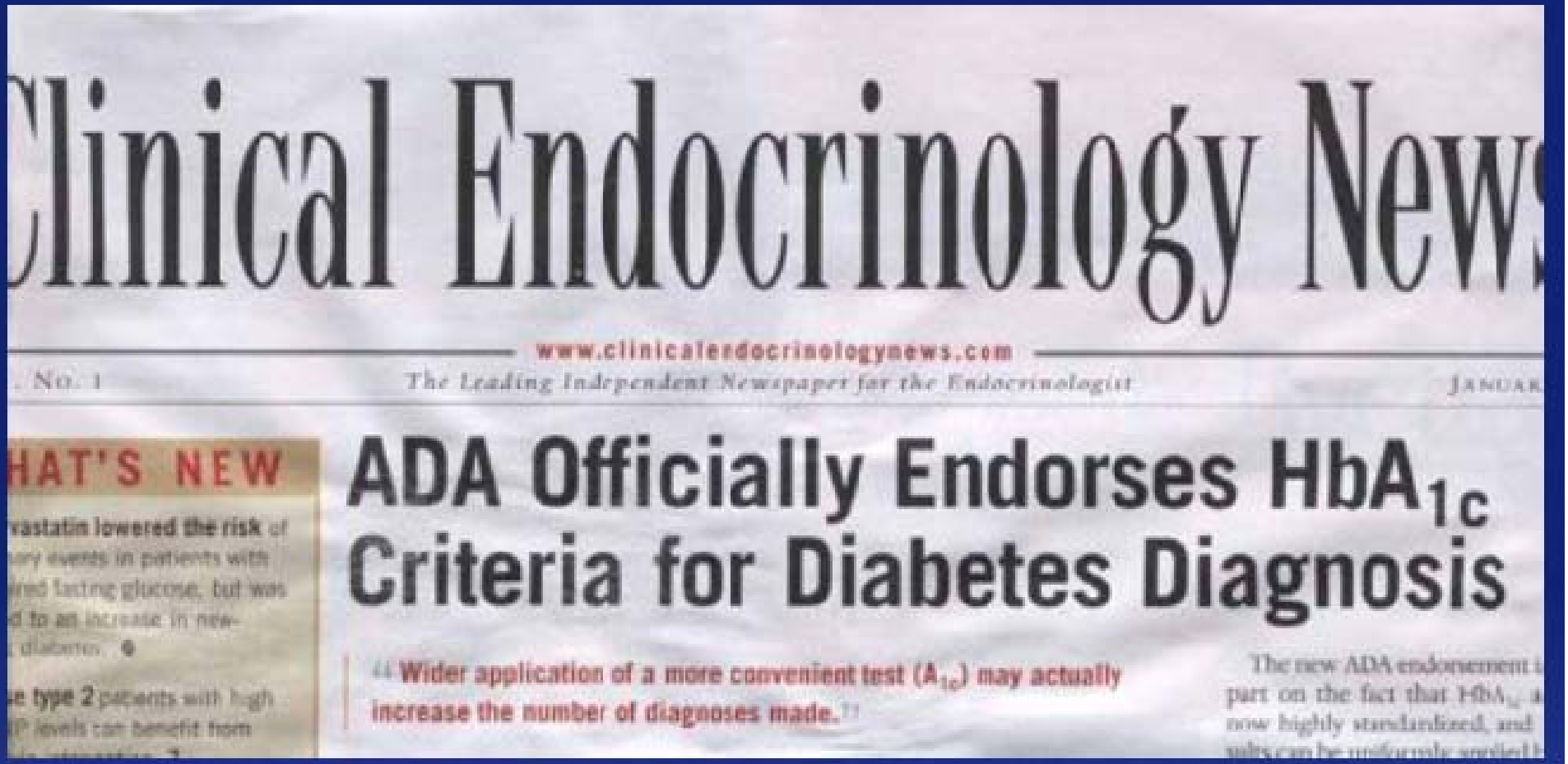


Harris MI *Diabetes Care* 1993; **16**: 642-52

Early diabetes is a postprandial disease

Role of PPG in the progression of Type2 diabetes

- PPG rise before fasting
- High PPG -> down regulate insulin receptors -> increase insulin resistance (Bell 2001)
- Glucotoxicity -> accelerated loss if βcell (*Miedler al 2002*)
- Lipotoxicity -> obesity -> raised fatty acid -> ↑PPG

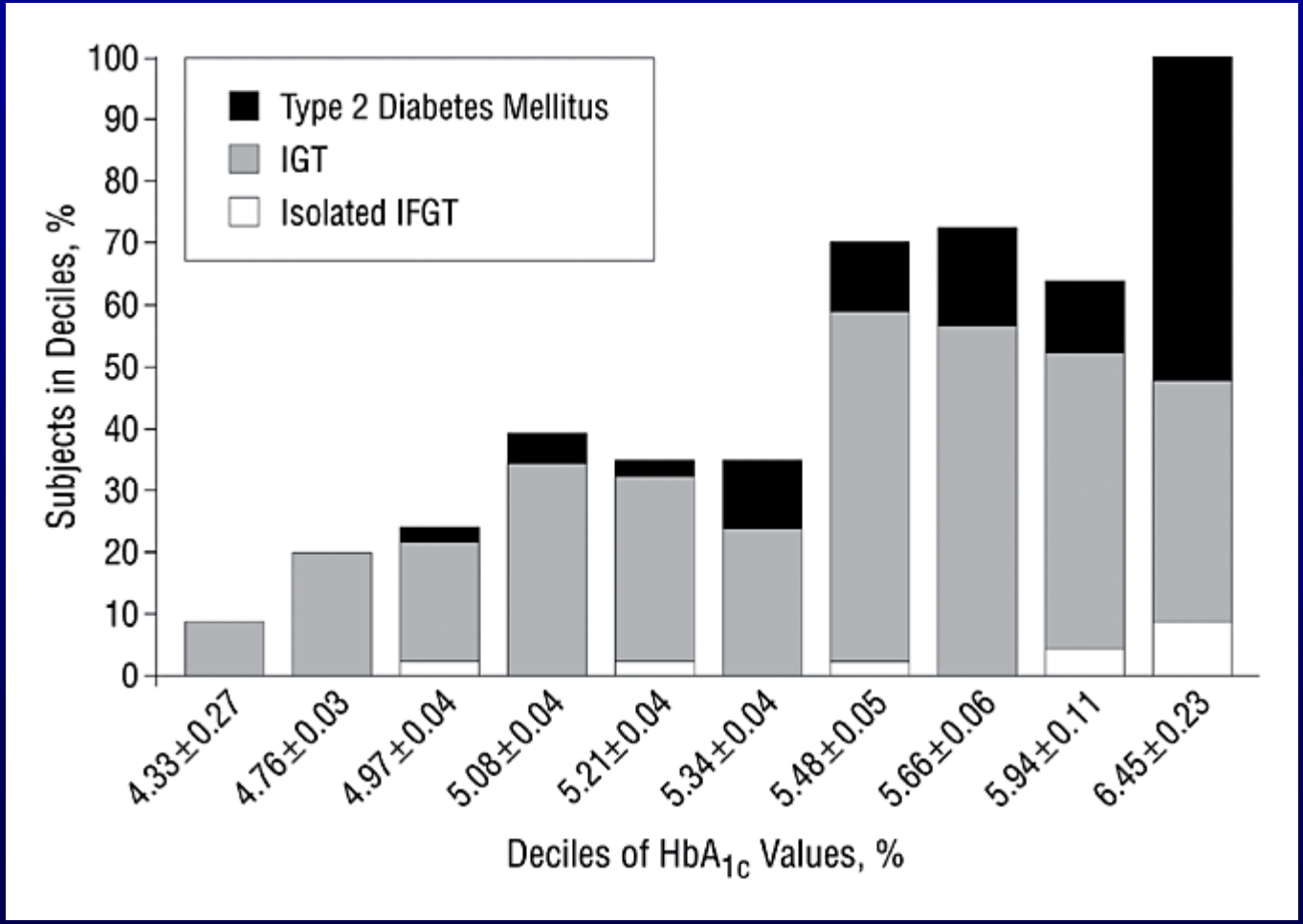


IDF, EASD, WHO and other groups considering adoption of recommendations of Committee

PPG contribution to HBA1C

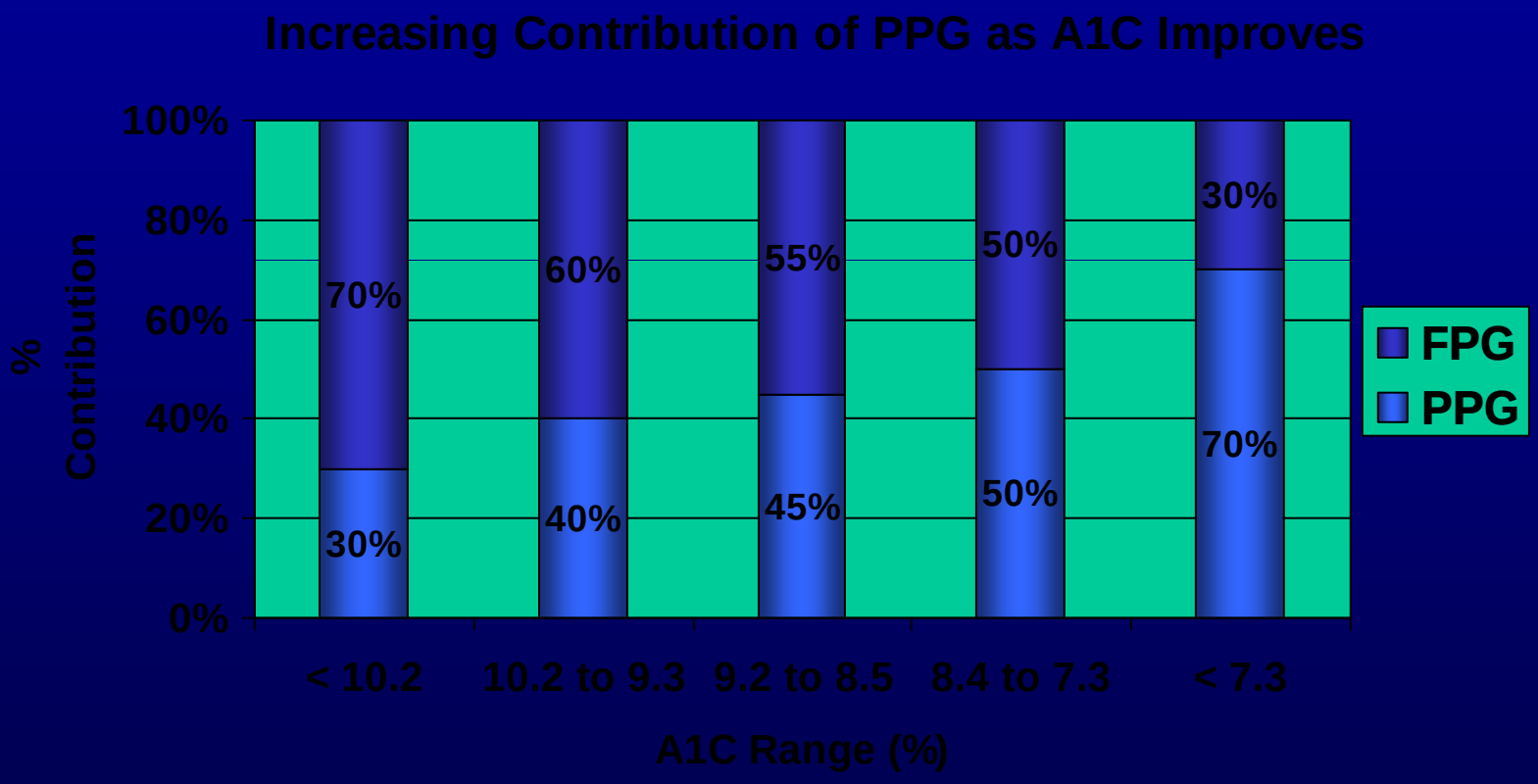
- HBA1C - fasting and post-prandial hyperglycaemia
- DCCT -> ↑HBA1C -> ↑complications
- Early disease -> normal fasting glucose but raised HBA1C
- Post lunch glucose related to HBA1C (*1997 Avignon*)
- Contribution of PPG to overall control
  - HBA1C < 7.3% -> PPG 69.&%
  - HBA1C > 10.2% -> PPG 30.5% (*Monnier et al 2003*)

In Individuals with HbA1C <6.5%, Postload Dysglycemia Predominates



Woerle HJ et al Arch Intern Med. 2004;164:1627-1632.

As Patients Get Closer to A1C Goal, the Need to Successfully Manage PPG Significantly Increases



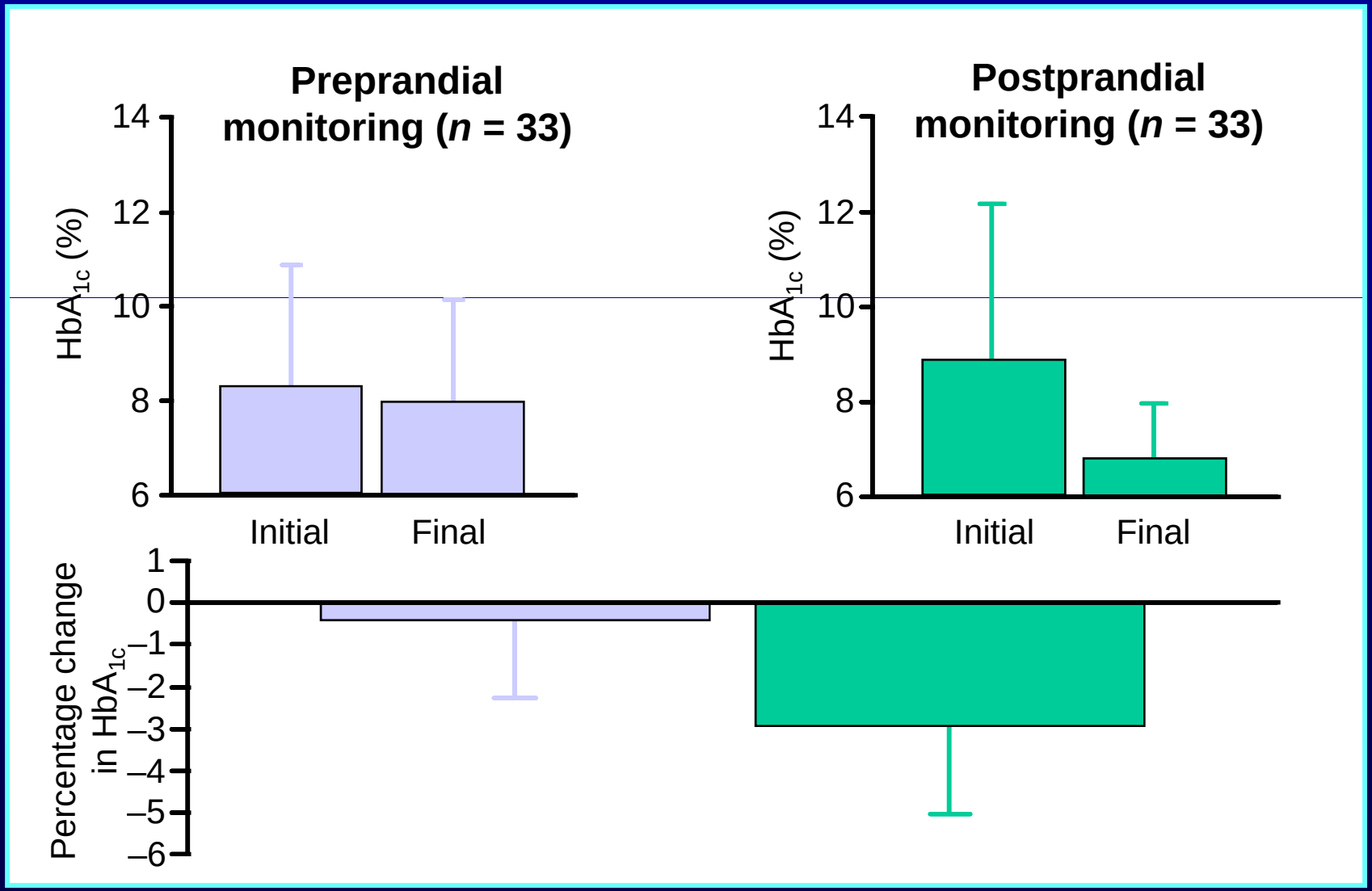
Adapted from Monnier L, Lapinski H, Collette C. Contributions of fasting and postprandial plasnma glucose increments to the overall diurnal hyper glycemia of Type 2 diabetic patients: variations with increasing levels of HBA(1c). *Diabetes Care.* 2003;26:881-885.

PPG, but not FPG distinguishes patients with HbA1C Between 6.0-7.0%

Characteristics	HbA1C Group (%) 6.0-6.5	6.6-7.0
# of patients	37	16
Gender	14/23	8/8
Age	54.6	49.6
BMI	27.8	27.9
FPG	111	113 (p=0.88)
2hPPG	198	226 (p=0.03)
Mean HbA1C	6.26	6.73

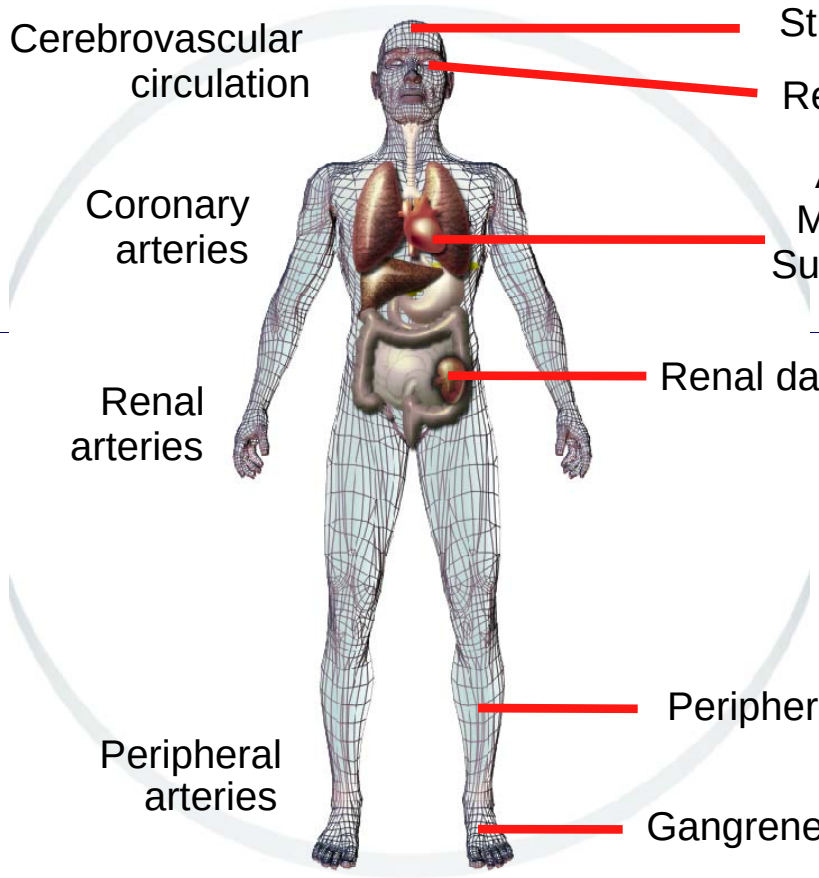
Woerle HJ et al Arch Intern Med. 2004;164:1627-1632.

Effect of pre- *vs.* postprandial glucose monitoring on HbA1c in gestational diabetes



De Veciana *et al*. *New Engl J Med* 1995; **333**; 1230

Macro- and microvascular complications



*Causes of death in diabetic population

Is postmeal hyperglycaemia harmful?

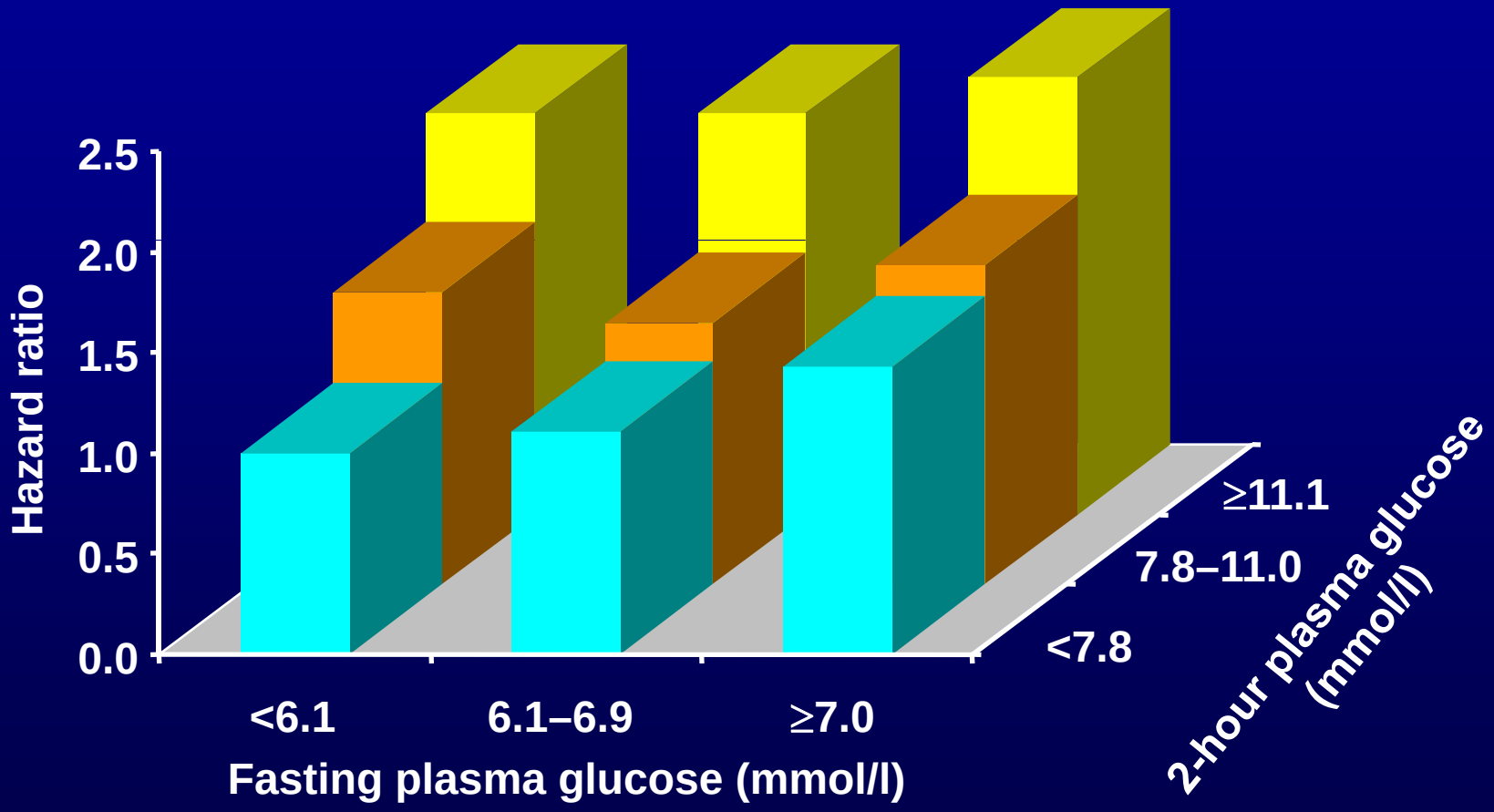
- Epidemological studies → strong association between post-meal glycaemia & cardiovascular risks and outcomes
- Growing evidence → relationship between PPH and:
  - Oxidative stress
  - Corotid IMT
  - Endothelial dysfunction

  Which are all markers of CVD
- PPH →
  - Retinopathy
  - Cognitive dysfunction in elderly people
  - Certain cancers

DECODE & DECODA Study

- Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) and in Asia (DECODA)
- 25000 people with newly diagnosed type 2 diabetes
- 2000 deaths
- Mean follow up 7.3 years
- Suggested the 2 hour post prandial blood glucose was associated with increased mortality
- 2 hour plasma glucose better predictor of cardiovascular and all cause mortality than fasting glucose
- European – 6.6% with IGT developed DM
- Asian - 18.9 %with IGT developed DM

Relative risk for death increases with 2-hour blood glucose irrespective of the FPG level



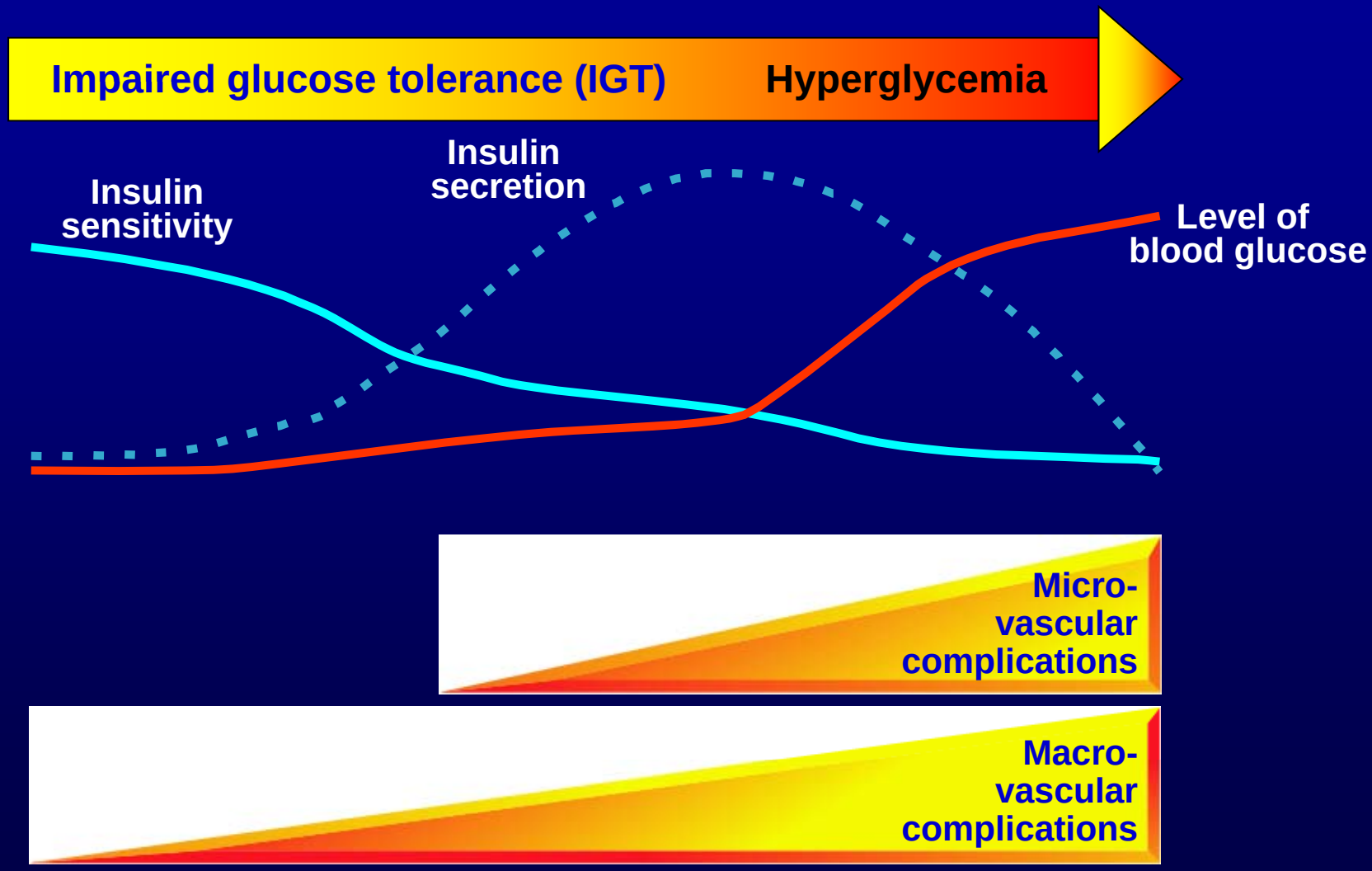
Adjusted for age, center, sex

DECODE Study Group. Lancet 1999;354:617–621

Development of type 2 diabetes

FPG 6.1 - 7.0mmol/L
2h ppBG 7.8 - 11.1 mmol/L

FPG >7.0mmol/L
2h ppBG >11.1 mmol/L



RETINOPATHY & PPH

- Limited evidence PPH and microvascular disease
- JAPAN Study (*Biochem Biophys Res Commun 2005; 336(1):339-345*)
- PPH better that HBA1C

RISK OF PANCREATIC CANCER

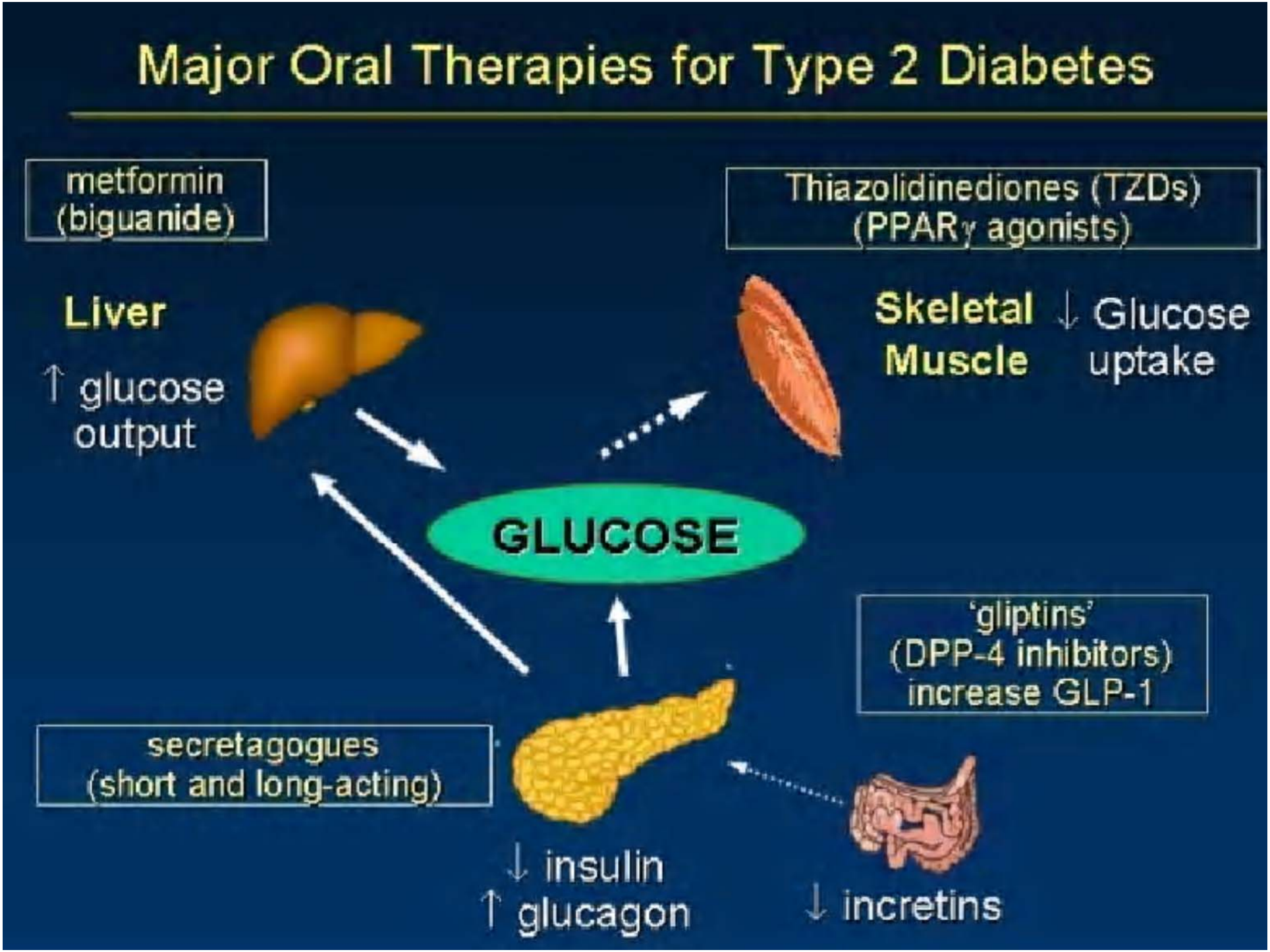
- Large prospective cohort study- PPH an increase risk of pancreatic cancer (*JAMA 2000)*
- Association is stronger in man

Impaired Cognitive Dysfunction

- PPH associated with impaired cognitive function in elderly patient with Type2 Diabetes *(Abbatecola AM, Rizzo, Neurology 2006)*


It's a pleasure to meet you, Mr Dalai Lama

Major Oral Therapies for Type 2 Diabetes



Agents targeting PPG

- Glinides
- Alpha-Glucosidase inhibitors
- Incretins
- Insulin – Rapid-acting analogues

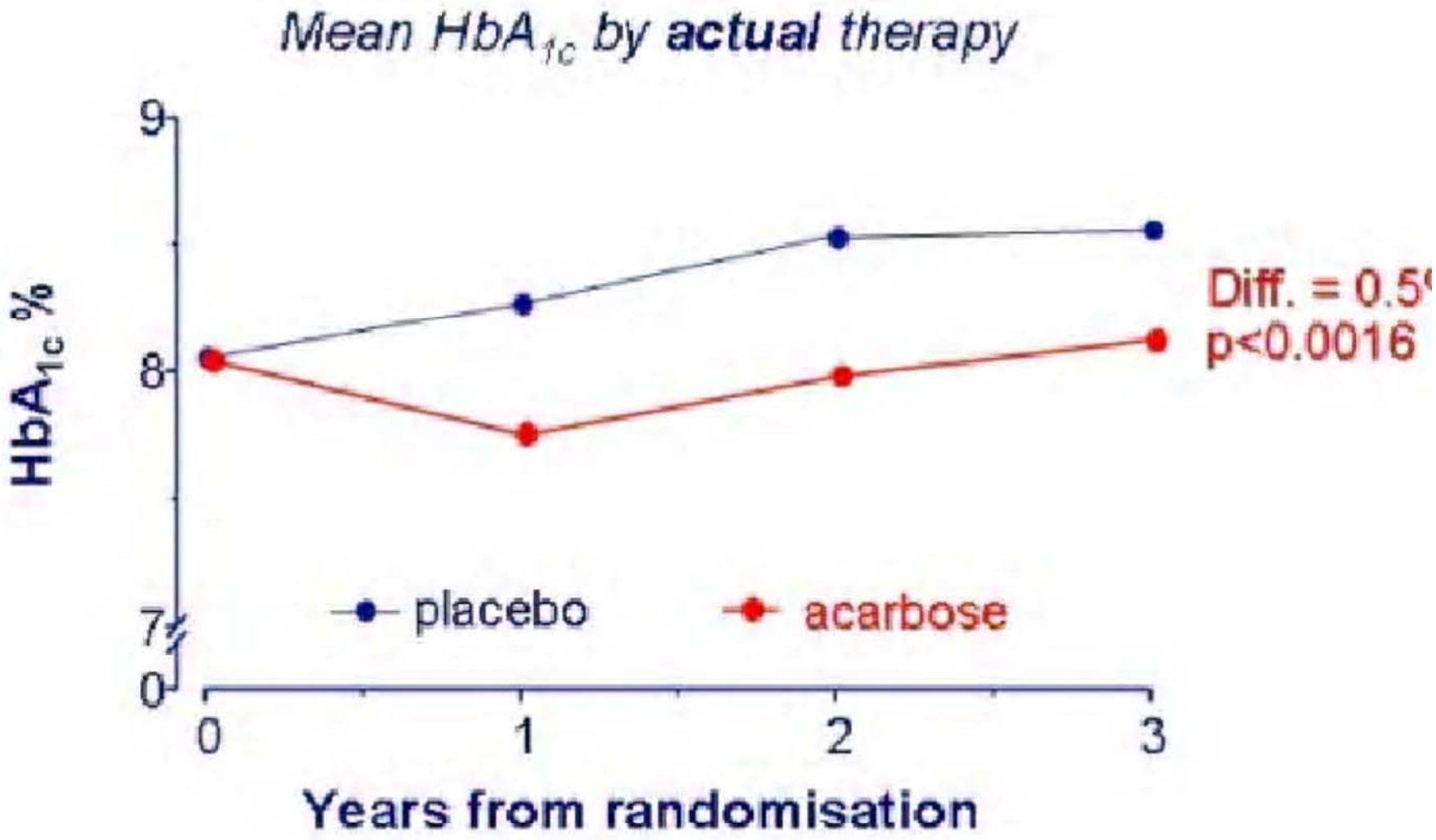
Glitinides
e.g. Novonorm, Prandin

- Stimulate insulin secretion in the presence of glucose
- Reduces peak postprandial glucose and HBA1C
- Other effects: - hypoglycaemia
  - weight gain
  - no effects on lipids

Alpha Glucosidase Inhibitors e.g. Acorbose

- Block enzymes that digest starch in the small intestine
- Decreases peak postpandrial glucose (2.2-2.8 mmol/l)
  Decreases A1C by 0.5-1%
- Other effects -> flatulence & abdominal discomfort
  -> no effects on Bp and lipids
  -> no weight gain
  -> C/I in IBD and cirrhosis
- STOP-NIDDM -> reduces risk of MI and hypertension

Addition of Acarbose to Existing Therapies



UKPDS 44. Diabetes Care 1999; 22: 960-964

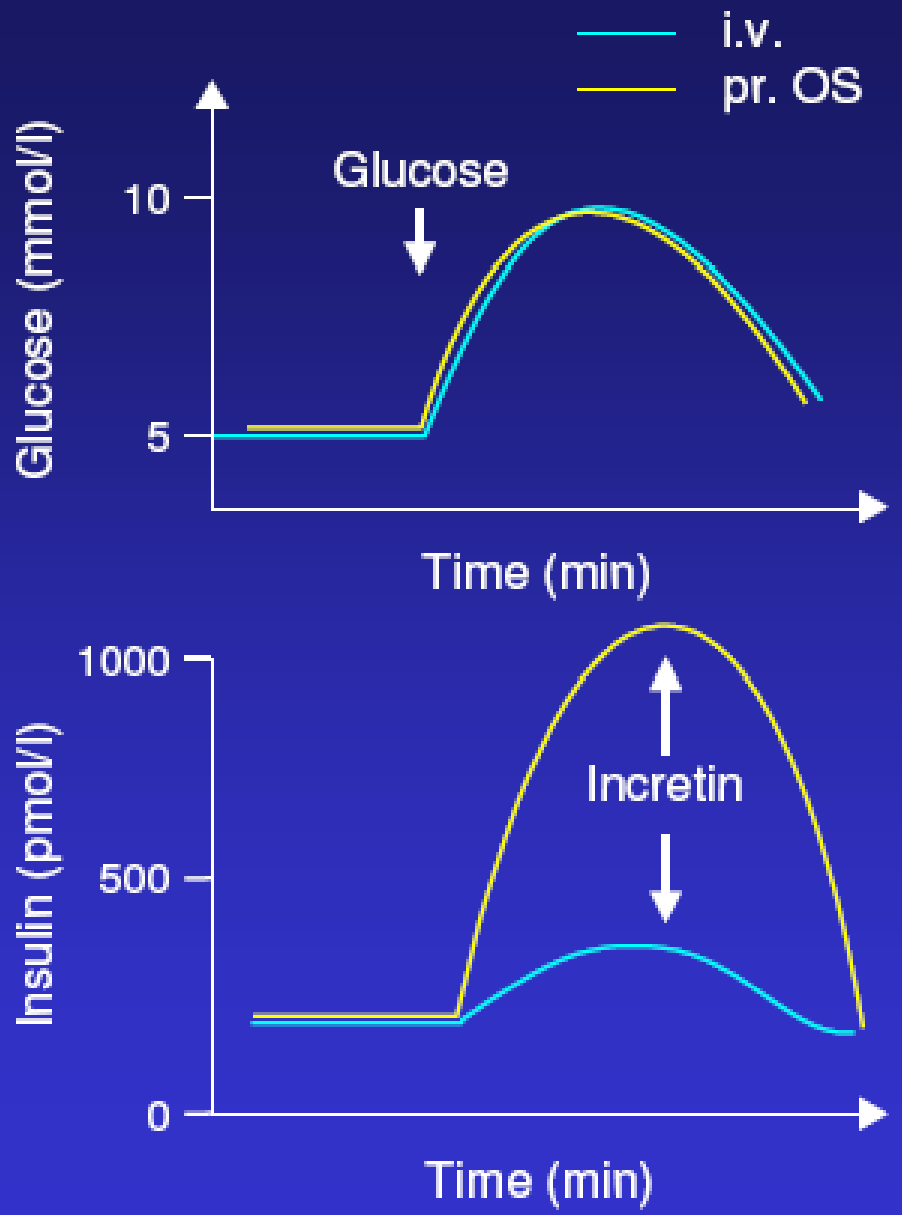
Incretins

The new Darling in the treatment of Type2 Diabetes

- GLP1 analogue, liraglitide, Exenatide, Exenatide LAR
- DPP4 inhibitors : Sitagliptin
  Vildagliptin

The incretin effect

- 70% of post-glucose insulin secretion is due to the effects of incretin
- The incretin effect is due to gut hormones – the incretin hormones



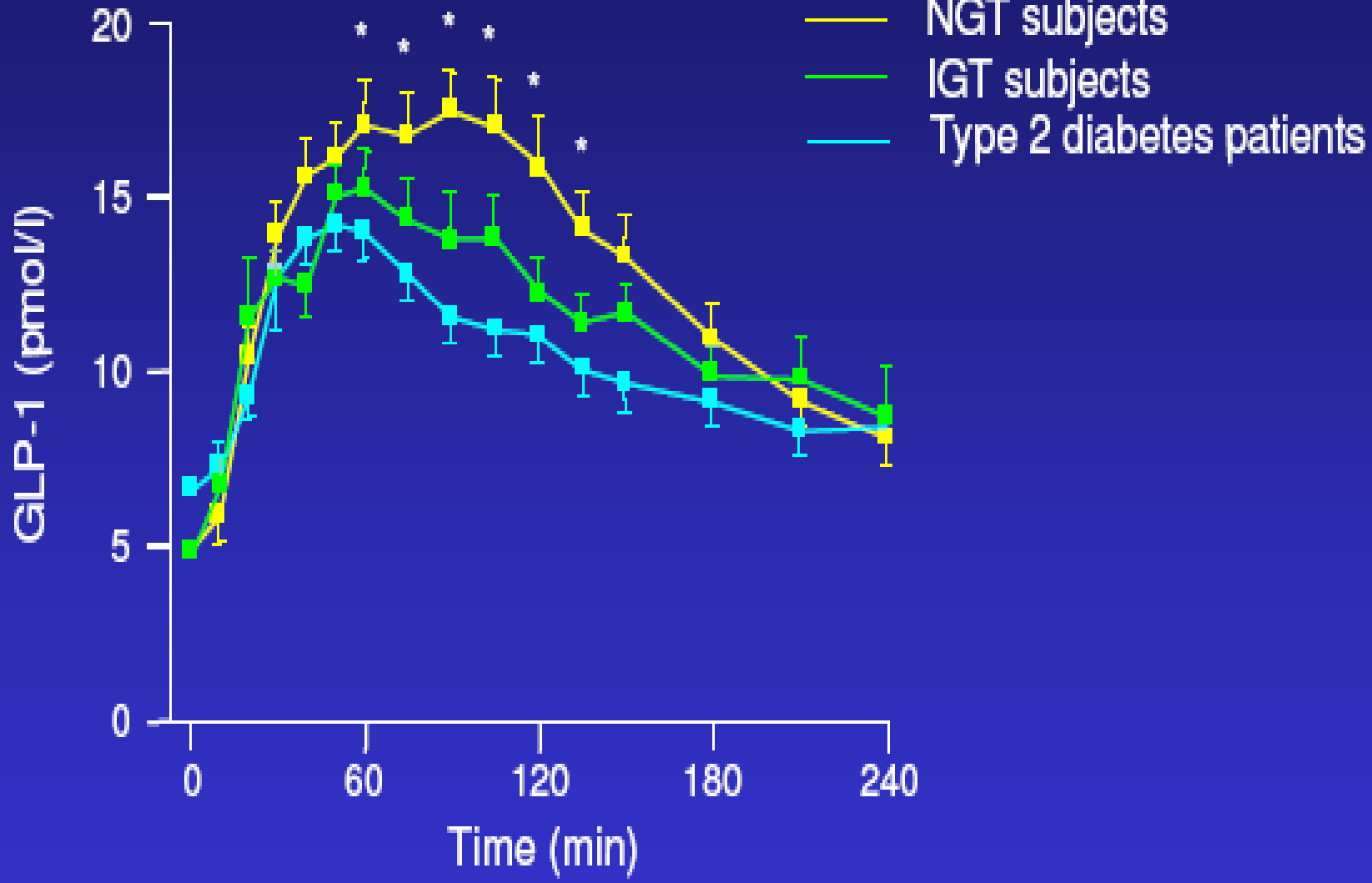
Incretin & Glucose Metabolism

- Intestinal hormones stimulate post prandial secretion of insulin, e.g,:

GIP (glucose dependant insulin polypeptide)

GLP1 (glucagon-like peptide 1)

- Low levels of GIP & GLP1 during fasting
- Raise level within minutes of eating -> specific receptors in islet Bcells -> stimulates insulin secretion
- GIP & GLP1 rapidly degraded by enzyme dipeptidyl peptidase (DPP4)



*$p < 0.05$ between the type 2 diabetes and NGT group
The meal was started at time zero and finished in the 10- to 15-minute period

Toft-Nielsen et al. J Clin Endocrinol Metab 2001;86:3717–23

Incretin & Glucose Metabolism

- Incretin response is impaired in Type2 Diabetes
- Hence drugs enhancing Incretin activity:

- Mimicking GLP1
- Inhibiting DPP4

- Exedin 4 – longer half life

Actions of GLP1

1. Effects on 1st phase insulin secretion
2. Slows gastric emptying
3. Suppresses appetite
4. Decrease glucagon secretion

Exenatide

- GLP1 analogue
- License for use with metformin and/or sulphonylurea
- Dosage 5mcg and 10 mcg (before meals)
- AMIGO studies: exenatide significantly reduce HBA1C (0.8-1%) in association with weight loss in patients not at goal
- 2 blinded non-inferiority studies

  Exenatide v/s Glargine

  Exenatide v/s Bi-phasic insulin

Both studies showed non-inferiority to insulin (HBA1C↓ 0.9-1.1%)

Weight reduction 4.1kg (in Glargine 5.4kg in bi-phasic insulin)

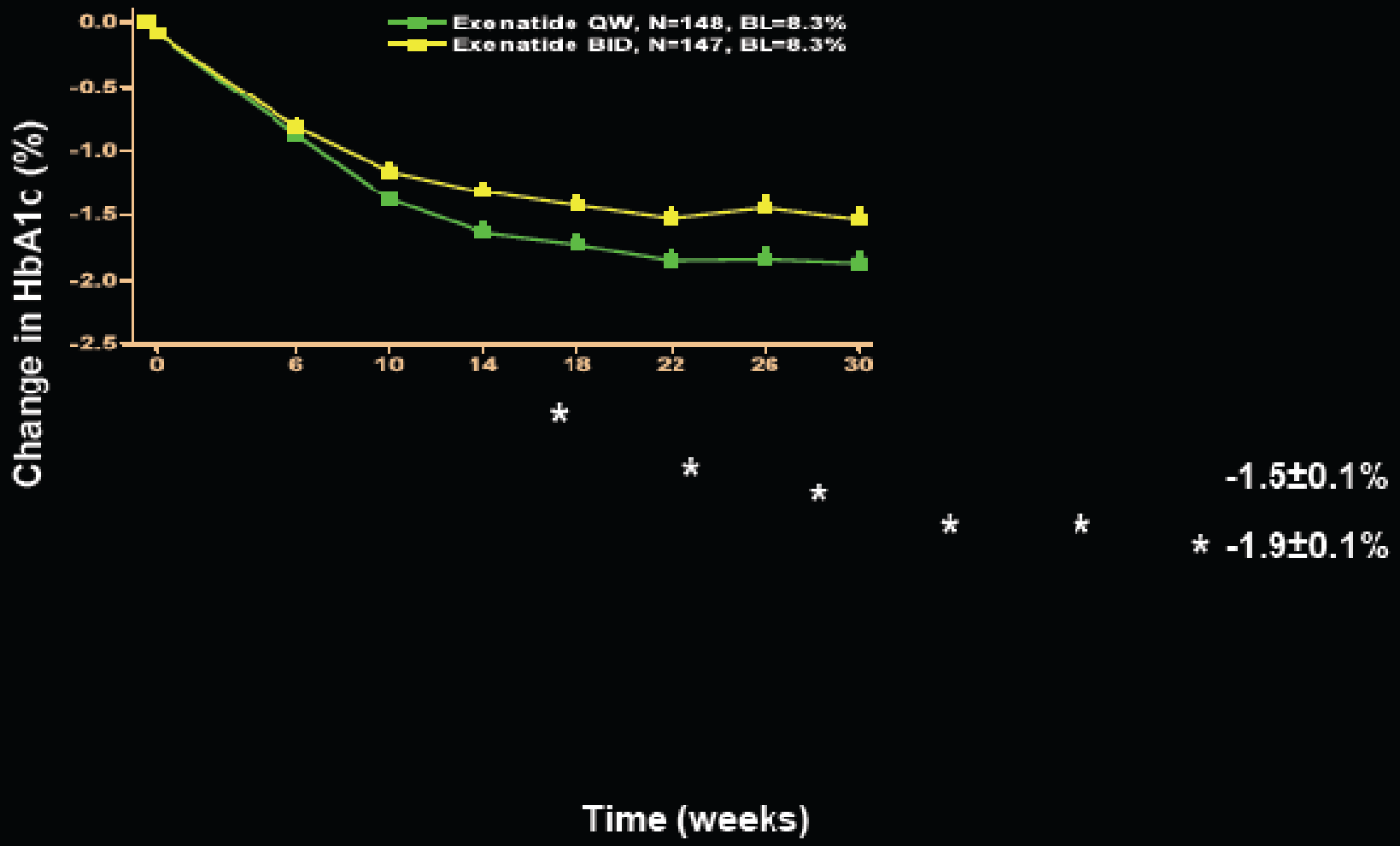
Exenatide

- Unwanted effect of nausea and vomiting
- Mild hypo glycaemia
- Reports of acute pancreatitis with exenatide -> FDA WARNING

Exenatide LAR

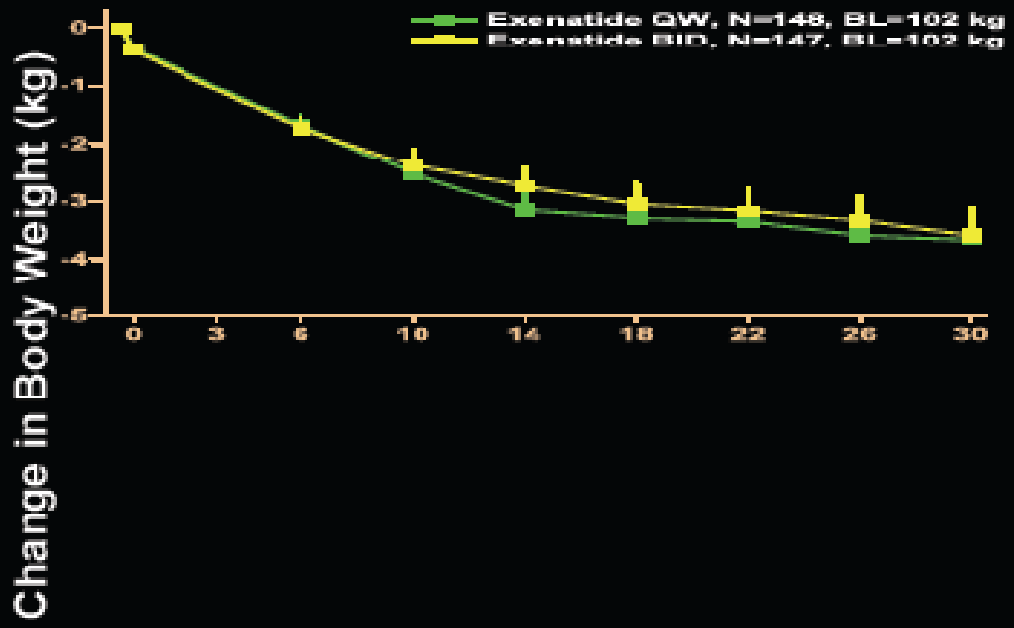
- Phase 3 clinical trial 50% had A1C < 6.5% and 75% had A1C < 7.0%
- LANCET -> non inferiority study showed showed greater reduction in A1C and fewer side effects

Type 2 Diabetes – Exenatide once weekly - Change in HbA1c



ITT population N=295; Data are LS mean (SE); *p<.01, once weekly vs BID
Drucker DJ, et al. Lancet. 2008;372:1240-1250.

Type 2 Diabetes – Exenatide once weekly - Change in Body Weight



-3.6 kg
-3.7 kg

ITT population N=295; Data are LS mean (SE)
Drucker DJ. et al. Lancet. 2008:372:1240-1250.

LIRAGLUTIDE

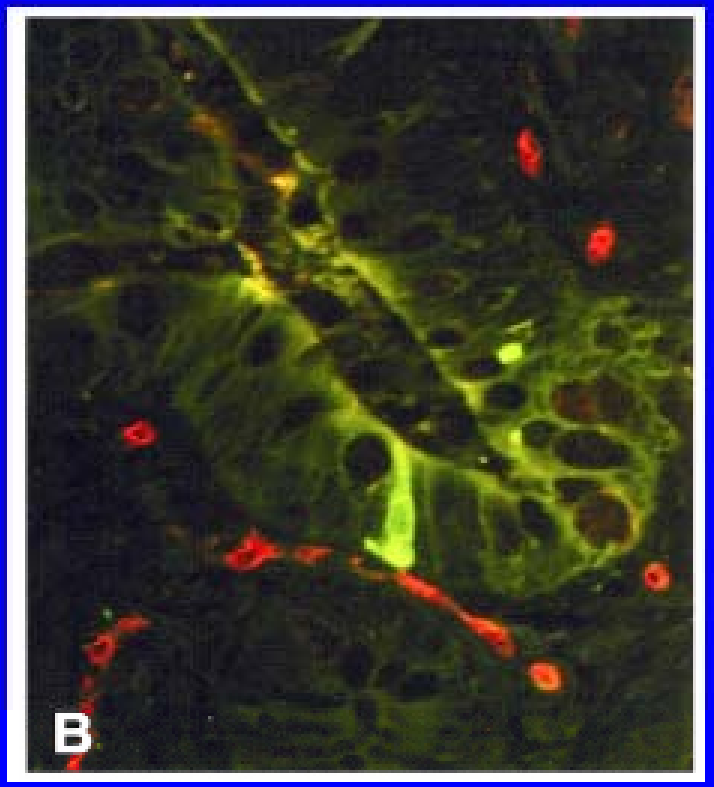
- Long acting GLP1 analogue
- Derivative of human GLP1 (97% homology)
- Once daily preparation: 0.6mg, 1.2mg, 1.8mg
- (LEAD IV) – lower TG & systolic blood pressure, more weight loss
- Care! Medullary Ca of thyroid in animal subject

Native GLP-1 is Rapidly Degraded by DPP IV

Plasma $T_{½}$ = 1-2 minutes (i.v.)
MCR = 5-10 l/min

MCR=metabolic clearance rate.

Vilsbøll T et al. *J Clin Endocrinol Metab*. 2003;88:220–224.



DPP IV (red) and GLP-1 (green) in human small intestine

DPP IV=dipeptidyl peptidase IV

Hansen et al, *Endocrinology* 1999; 140:5356-5363

DPP4 inhibitors

- Sitagliptin – license in dual or triple therapy
- 100mg once daily dose
- Meta analysis: as monotherapy reduce HBA1C (0.77% v/s placebo)
- Less effective as monotherapy v/s other oral agents
- Weight neutral

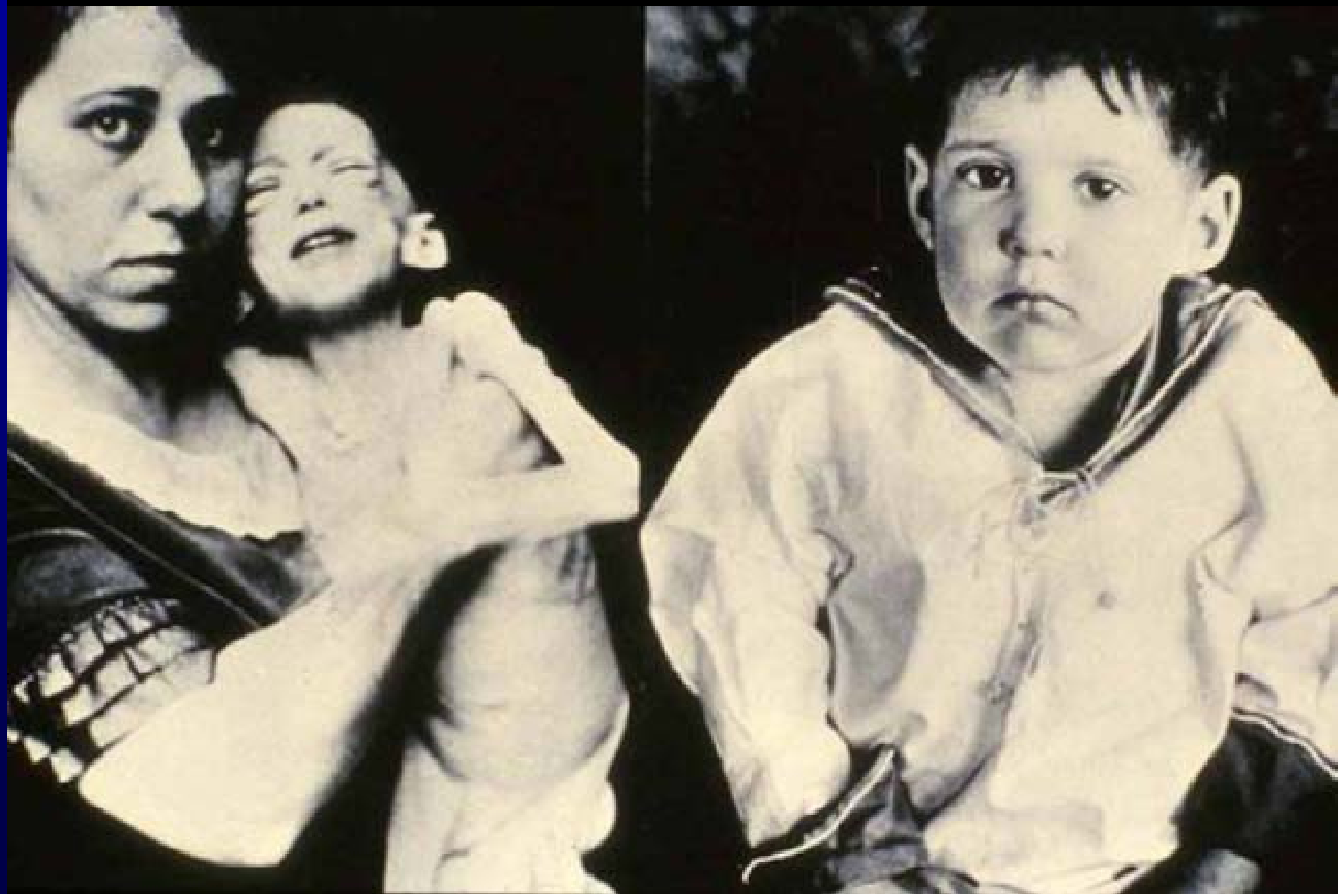
DPP4 inhibitors

- Vildagliptin – dose 50mg bd with metformin
  - dose 50mg od with sulphonylurea
- Further reduction in A1C

Role of GLP1
in the life and death of pancreatic cells

- Stimulates insulin secretion
- Induces replication of islet cells
- Promotes islet cells neogenesis of pancreatic ductal cells
- Inhibits apoptosis

The Miracle of Insulin.

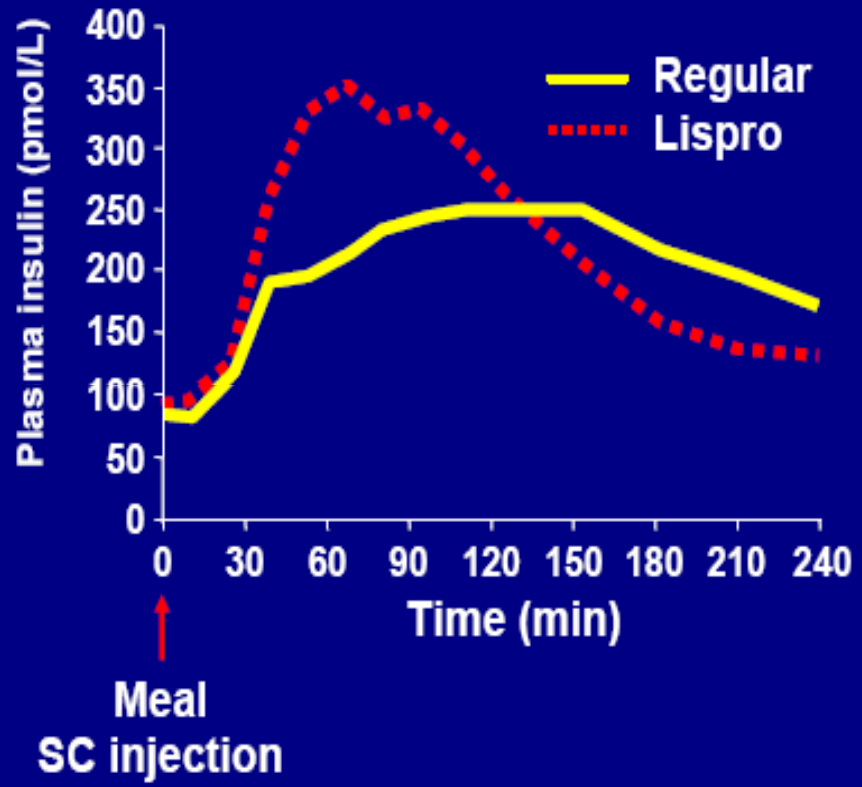


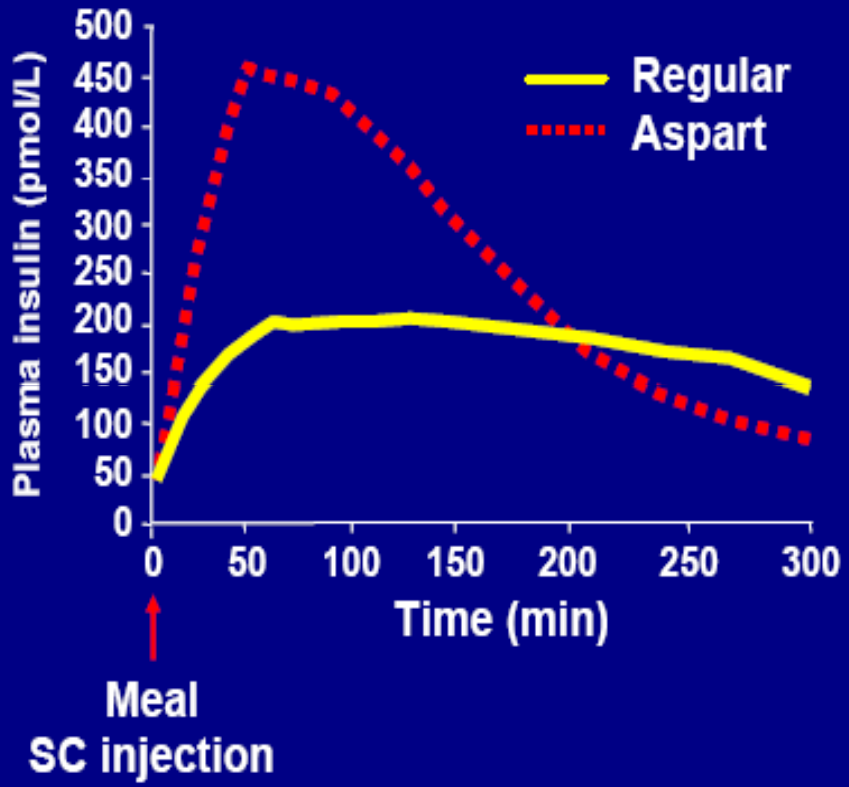
Short-Acting Analogs

Aspart-Glulisine-Lispro

- Convenient administration immediately prior to meals
- Faster onset of action
- Limit postprandial hyperglycemic peaks
- Shorter duration of activity
  - Reduce late postprandial *hypoglycemia*
  - Frequent late postprandial *hyperglycemia*
- Need for basal insulin replacement revealed

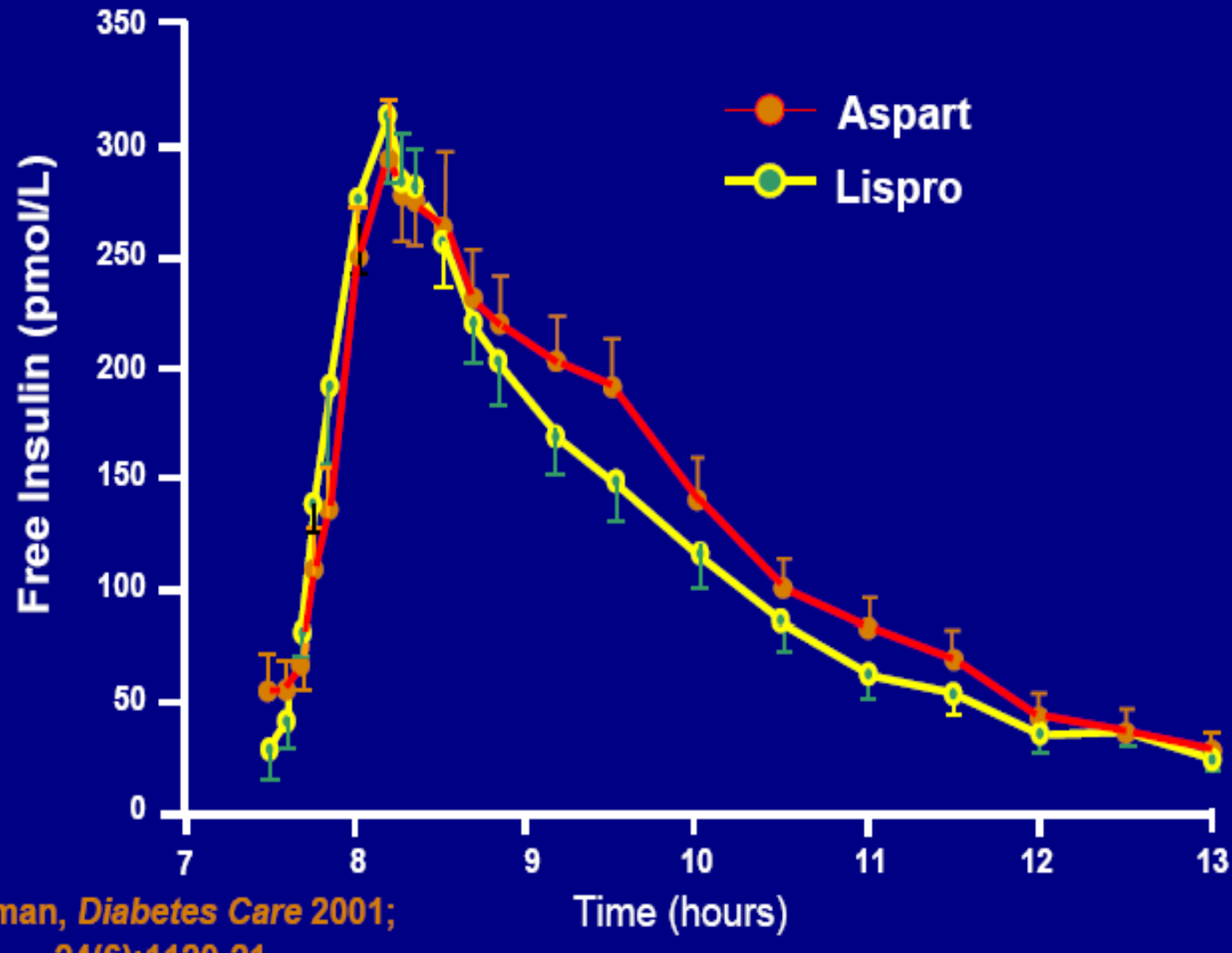
Short-Acting Insulin Analogs





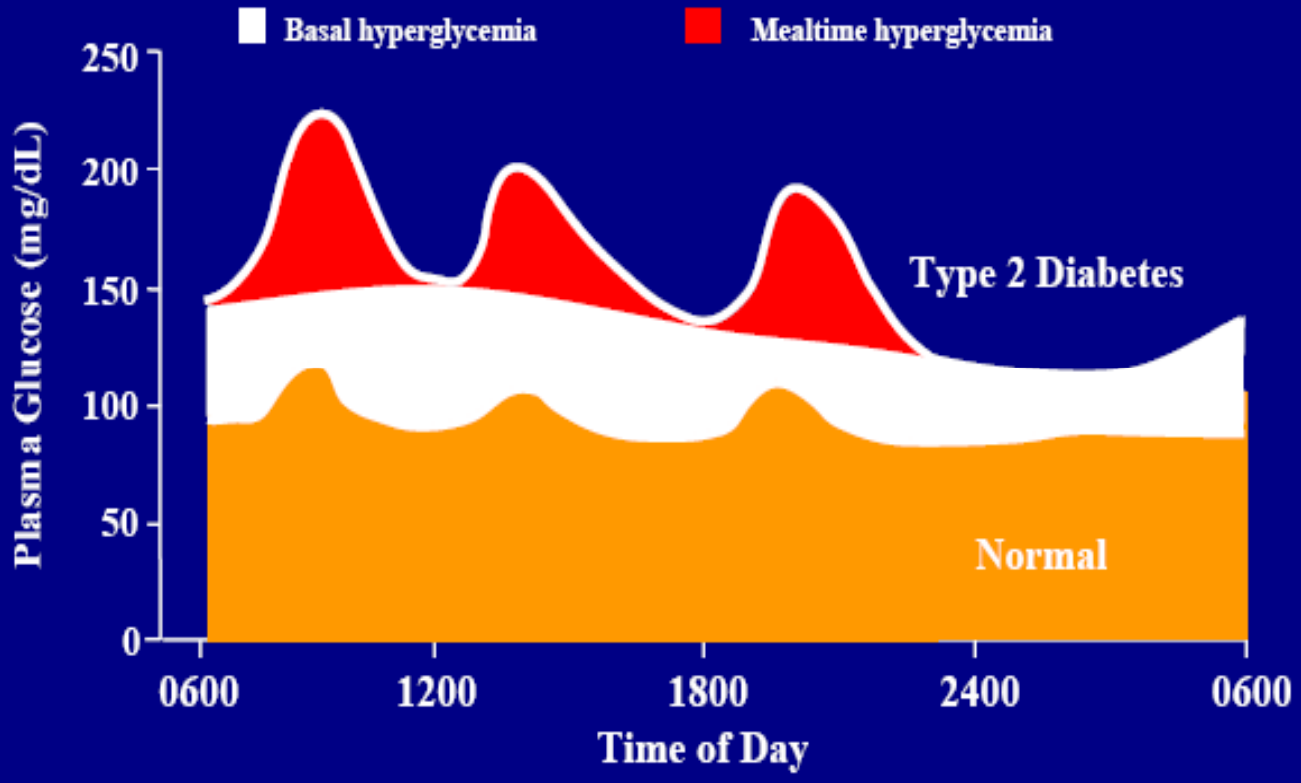
Heinemann, et al. *Diabet Med.* 1996;13:625–629; Mudaliar, et al. *Diabetes Care*. 1999;22:1501–1506.

Pharmacokinetic Comparison Aspart and Lispro



Hedman, *Diabetes Care* 2001; 24(6):1120-21

Basal vs Mealtime Hyperglycemia in Diabetes

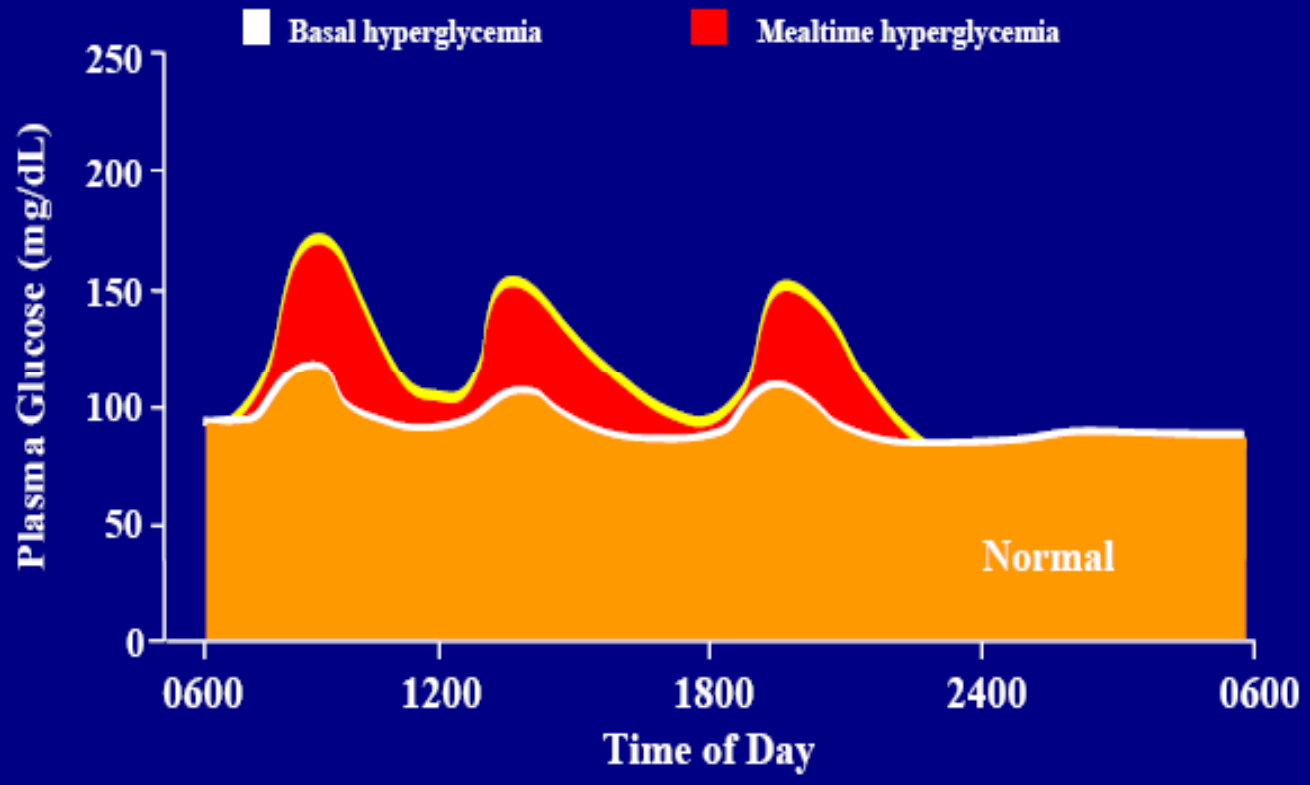


Δ AUC from normal basal >1875 mgm/dL·hr; Est $HbA1_c$ >8.7%

Riddle. *Diabetes Care.* 1990;13:676-686.

Basal vs Mealtime Hyperglycemia in Diabetes

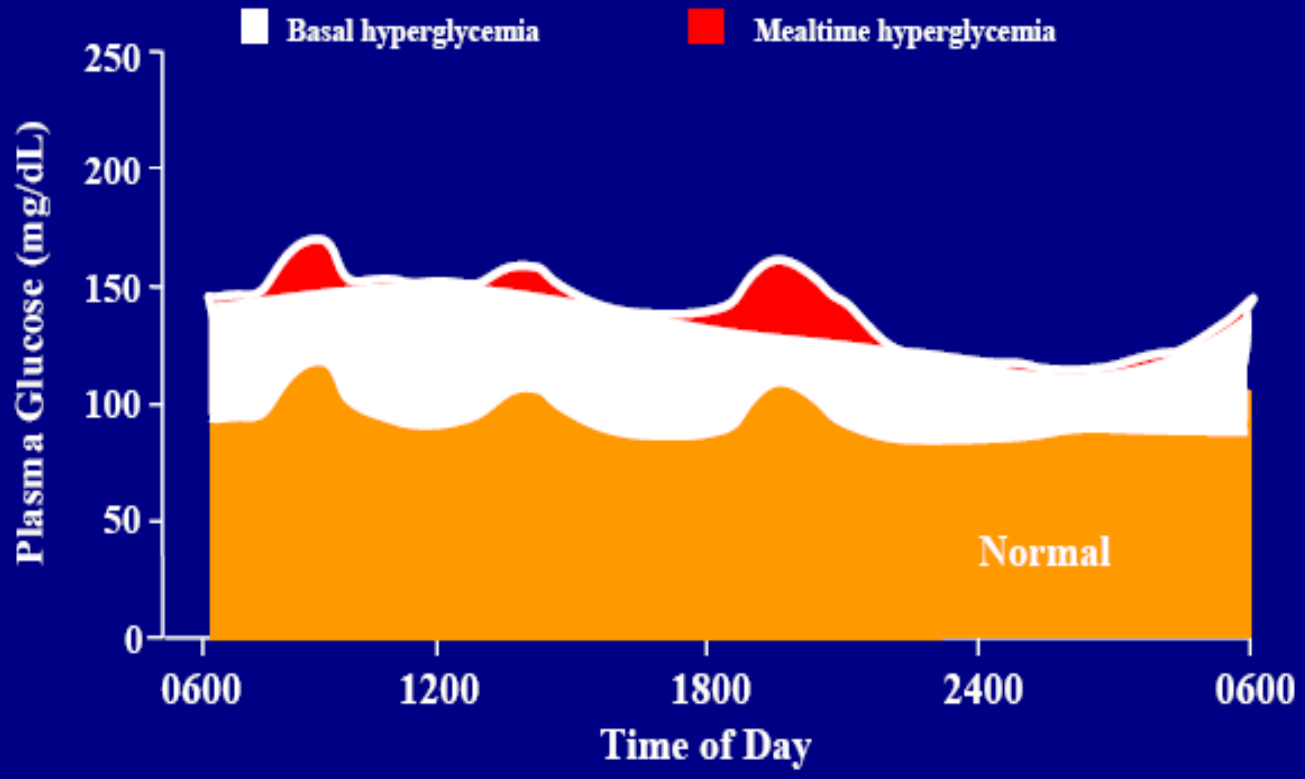
When Basal Corrected



Δ AUC from normal basal 900 mgm/dL·hr; Est $HbA1_c$ 7.2%

Basal vs Mealtime Hyperglycemia in Diabetes

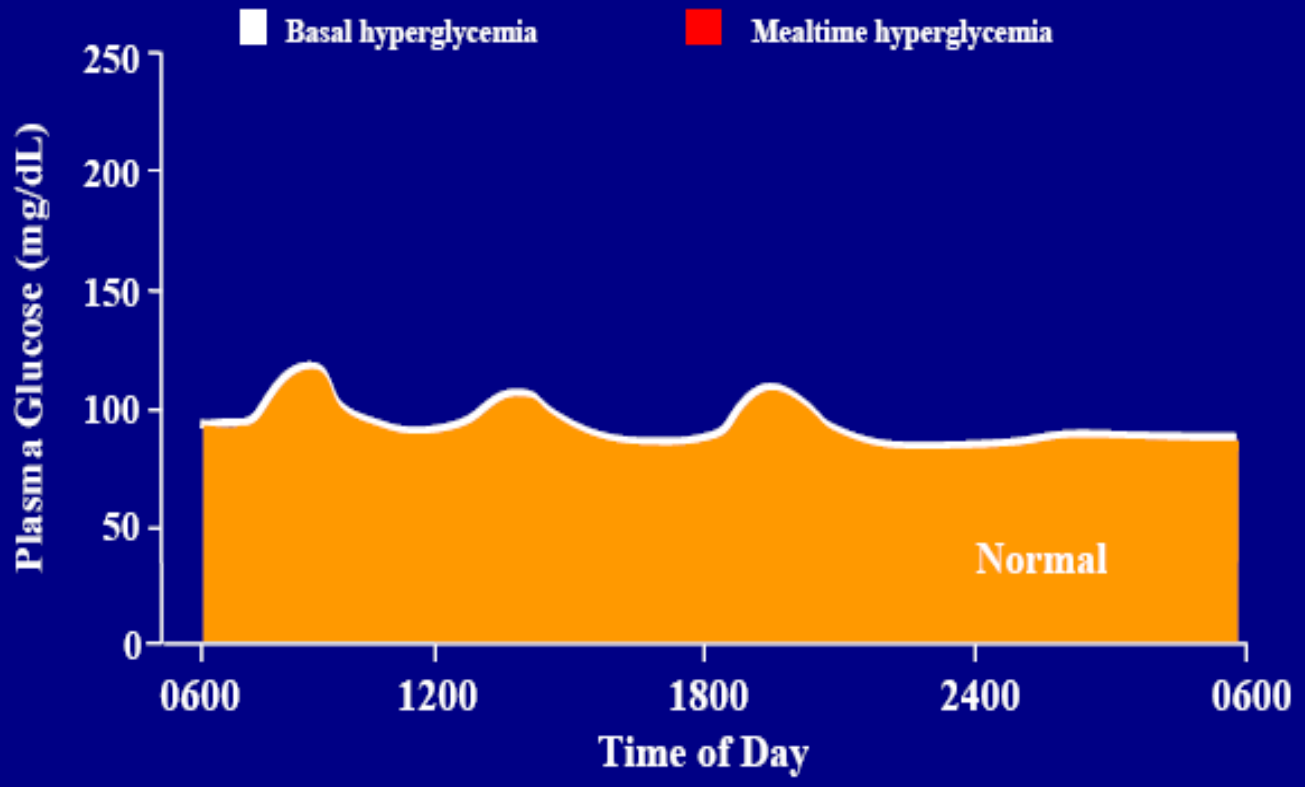
When Mealtime Hyperglycemia Corrected



Δ AUC from normal basal 1425 mgm/dL·hr; Est $HbA1_c$ 7.9

Basal vs Mealtime Hyperglycemia in Diabetes

When Both Basal & Mealtime Hyperglycemia Corrected



Δ AUC from normal basal 25 mg/dL·hr; Est $HbA1_c$ 6.4%

Case Presentations

Case 1

- Mrs X:
  - 53 yrs old. Type 2 DM 17yrs
  - BMI 31 kg/m^2
  - Lifestyle OK, sees dietician
  - Medication: Lantus
    - 90 units bedtime
    - Pioglitazone 30mg OD
    - Medformin 1g BD
    - Glimepiride 6mg OD

- HBA1C 8.5%
- Fasting glucose 6.5 mmol/l
- Premeal glucose 9-13 mmol/l
- Postmeal glucose greater than 16mmol/l

WHAT WOULD YOU DO NEXT ?

- Started on Basal bolus regime
- Dose titration
- 60 units lantus, 20-25 units of postprandial insulin

3 Months later

- HBA1C 7.2%
- No increase in weight

Clinical Pearls

- A pattern of rising blood glucose during the day, with partial or complete correction overnight, suggests insufficient prandial insulin effect.
- Basal bolus regime allows greater freedom for patients to eat as they would like while making healthy food choices.
- This was also clearly a case of β-cells failure

Case #2

- 45 yr old man with Type2 Diabetes
- Referred with 6 weeks history of osmotic symptoms
- Was started on metformin 500mg bd by GP, 3 months ago, HBA1C 9.4%, BMI=32.4
- Now HBA1C 8.4% but now BMI=31.8
- Has made big efforts re diet & exercise

What is the most appropriate treatment?

1. Insulin
2. Pioglitazone
3. Increase metformin
4. Add sulphonyrea
5. GLP1
6. DDP4 inhibitors

CONCLUSION

- Earliest abnormality of Type2 diabetes is postpandial hyperglycaemia

- Good evidence to support beneficial effect of targeting PPG excursions

- Emerging therapies -> aiming at PPG
  -> will benefit people with Type2 Diabetes

Clinical description of diabetes by Aretaeus of Cappadocia (2nd century AD)

"Diabetes is a dreadful affection, not very frequent among men, being a melting down of the flesh and limbs to urine. The patients never stop making water and the flow is incessant, like the opening of aqueducts. Life is short, unpleasant and painful, thirst unquenchable, drinking excessive, and disproportionate to the large quantity of urine, for yet more urine is passed. One cannot stop them either from drinking or making water. If for a while they abstain from drinking their mouths become parched and their bodies dry; the viscera seem scorched up; the patients are affected by nausea, restlessness and a burning thirst, and within a short time, they expire."

(Adapted from Papaspyros, NS. The history of diabetes mellitus. George Thieme Verlag, Stuttgart, 2nd Edition, 1964.)

THANK YOU !!!