DIABETES MELLITUS

(T1DM, T2DM)

(Definition, Pathogenesis, Clinical presentation , Diagnosis & Management with guidelines)

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AGENDA:

- Epidemiology DM , T1DM & T2DM.
- Molecular mechanisms of Insulin signaling.
- Molicular Mechanism in Diabetes.
- Main pathology of Type 1 DM & Histopathology.
- Main pathology of T2DM.
- Predisposing factors for T1DM & T2DM.
- The course of disease development T1DM & T2DM.
- Clinical Presentation of T1DM & T2DM.
- Diagnosis of Diabetes.

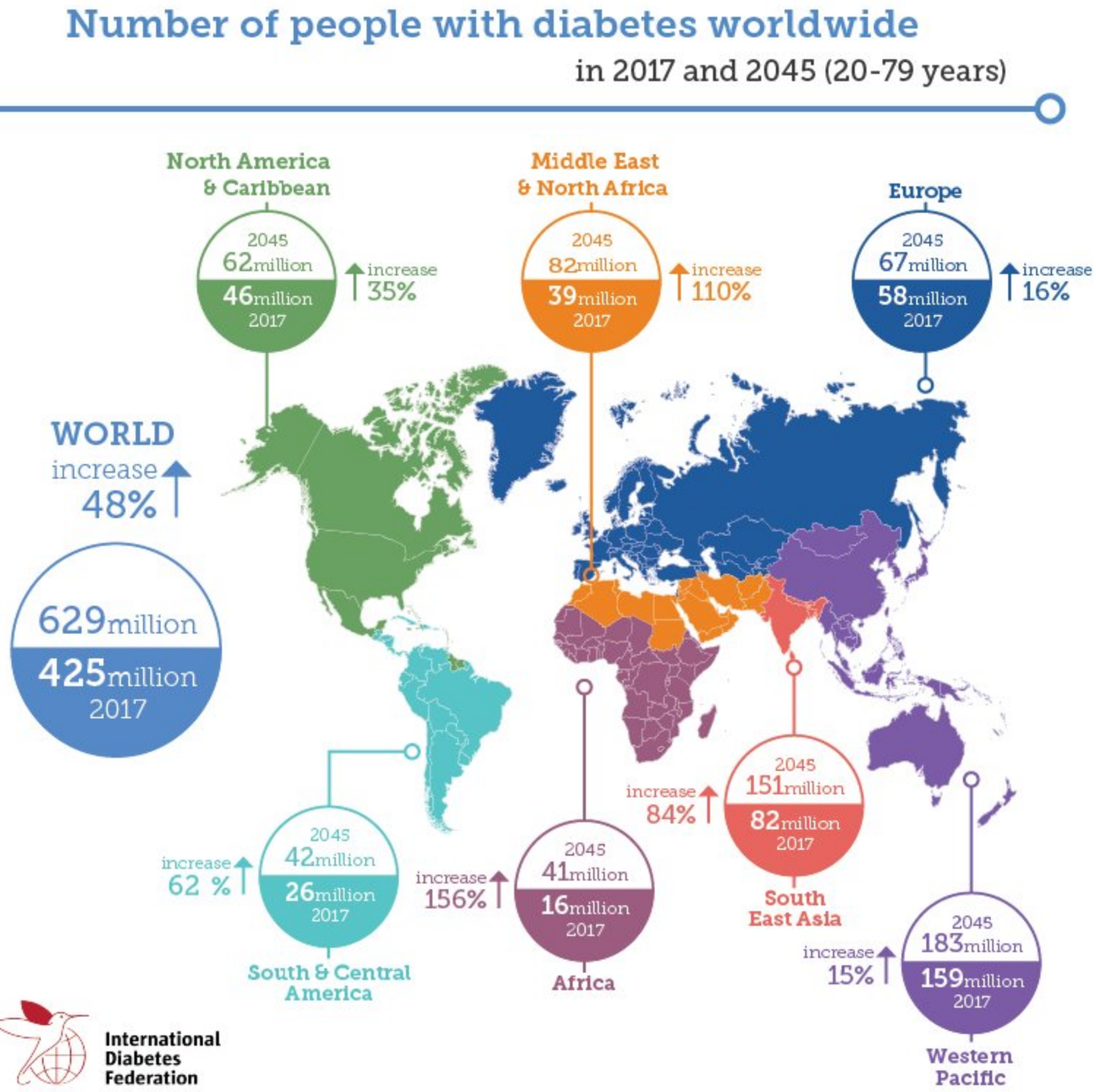
AGENDA:

- EPIDEMIOLOGY DM: T1DM & T2DM.

THE GROWING PROBLEM OF DIABETES GLOBALLY

48%

Figures indicate projected increase in diabetes between 2017 and 2045

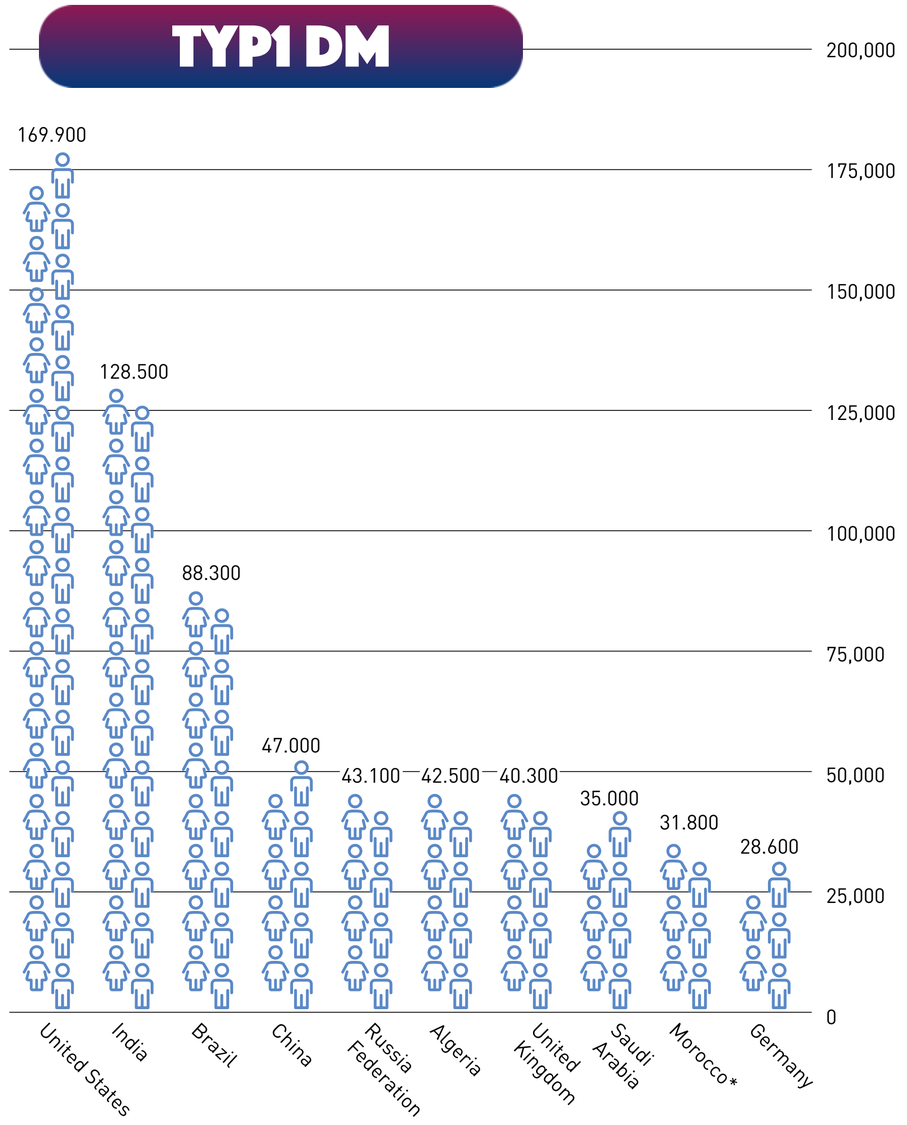


International Diabetes Federation. IDF Diabetes Atlas (Eighth Edition). 2017

Pew Research Center. The Future of World Religions: Population Growth Projections, 2010-2050. Accessed 17 February 2016.

EPIDIMIOLOGY

Top ten countries/ territories for number of children & adolescents with type 1 diabetes (<20 years).



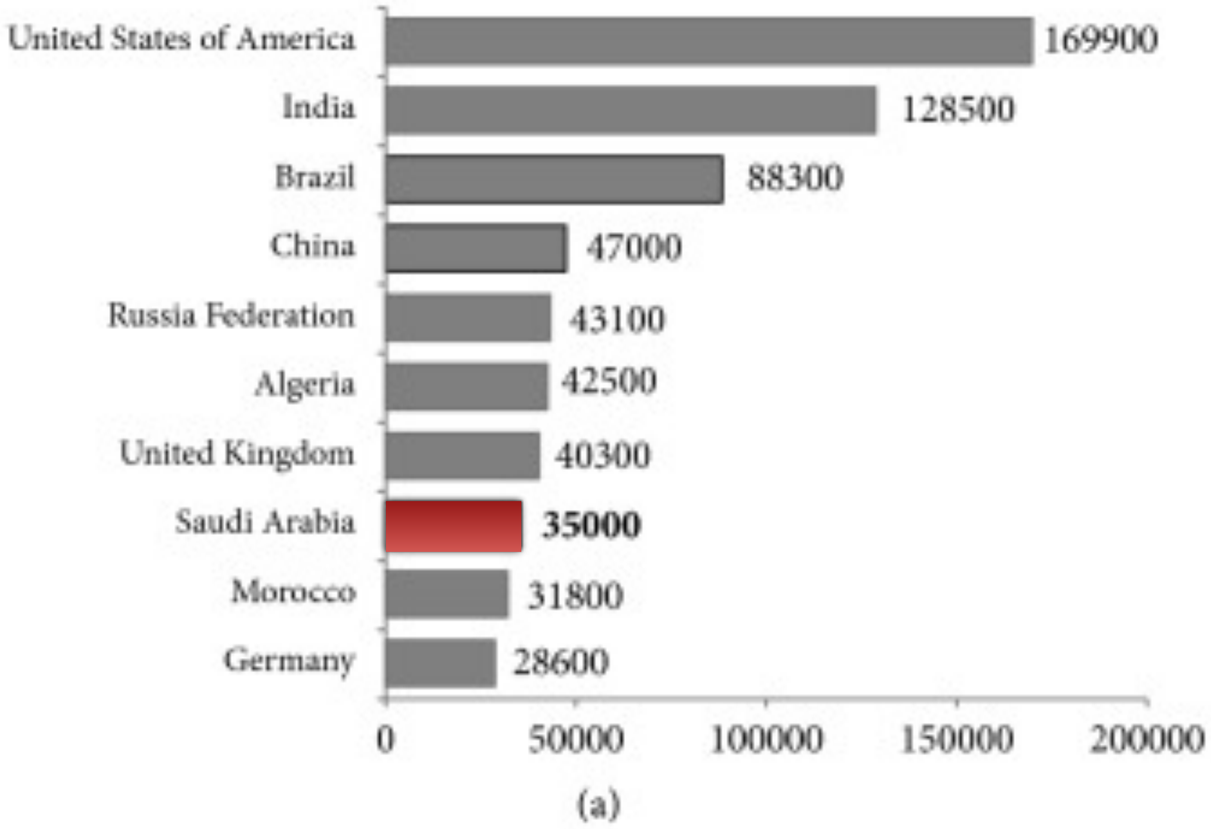
*The data for Morocco is extrapolated from Algeria

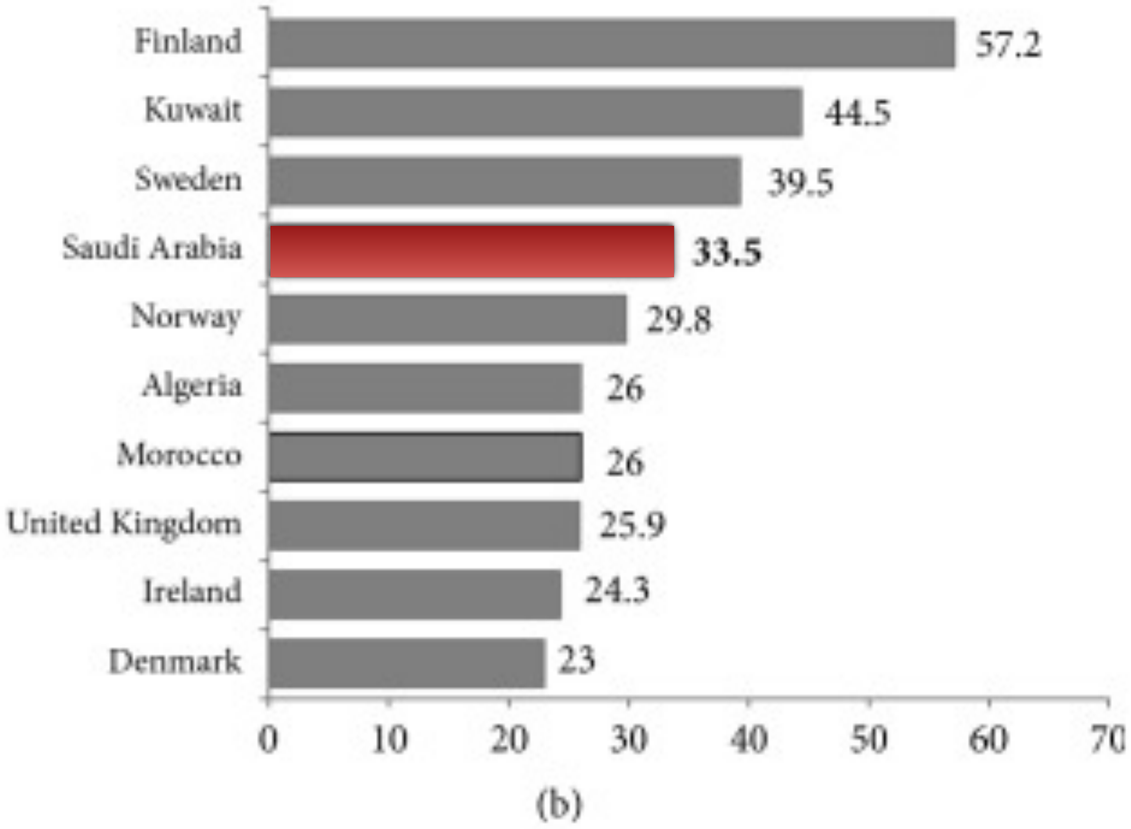
International Diabetes Federation

EPIDIMIOLOGY

TYP1 DM

International Diabetes Federation





(a) Top ten countries/territories for number of children and adolescents with type 1 diabetes (<20 years).
(b) Top ten countries/territories for the incidence rates of type 1 diabetes (<20 years) per 100,000 children per year, 2017

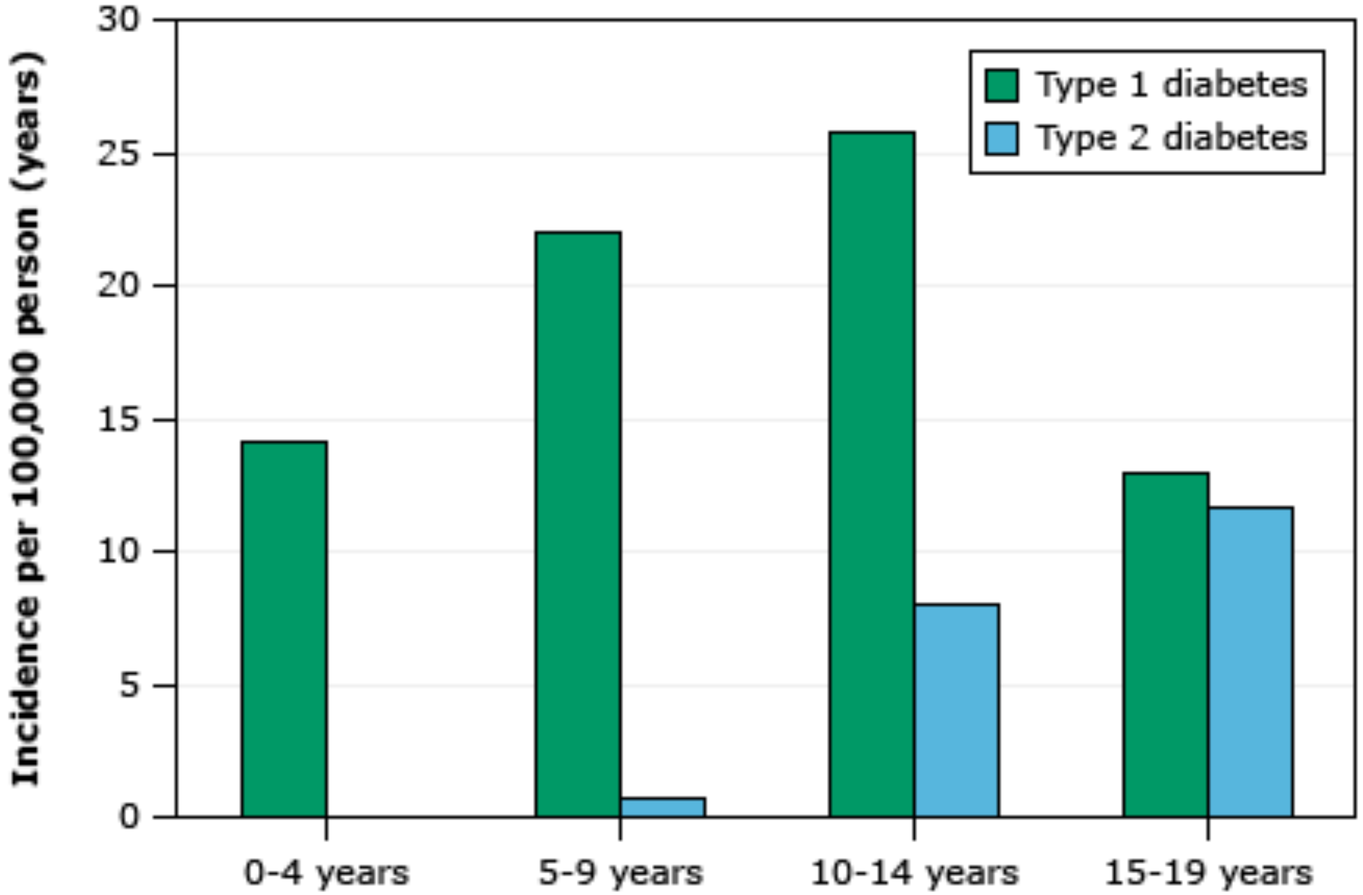
EPIDIMIOLOGY

Incidence of T1DM, T2DM in youth in the USA, from the SEARCH for Diabetes in Youth study group, 2002 to 2003.

45 % of children present < 10 years of age

Males > Females

AGE AND GENDER..TYP1 DM

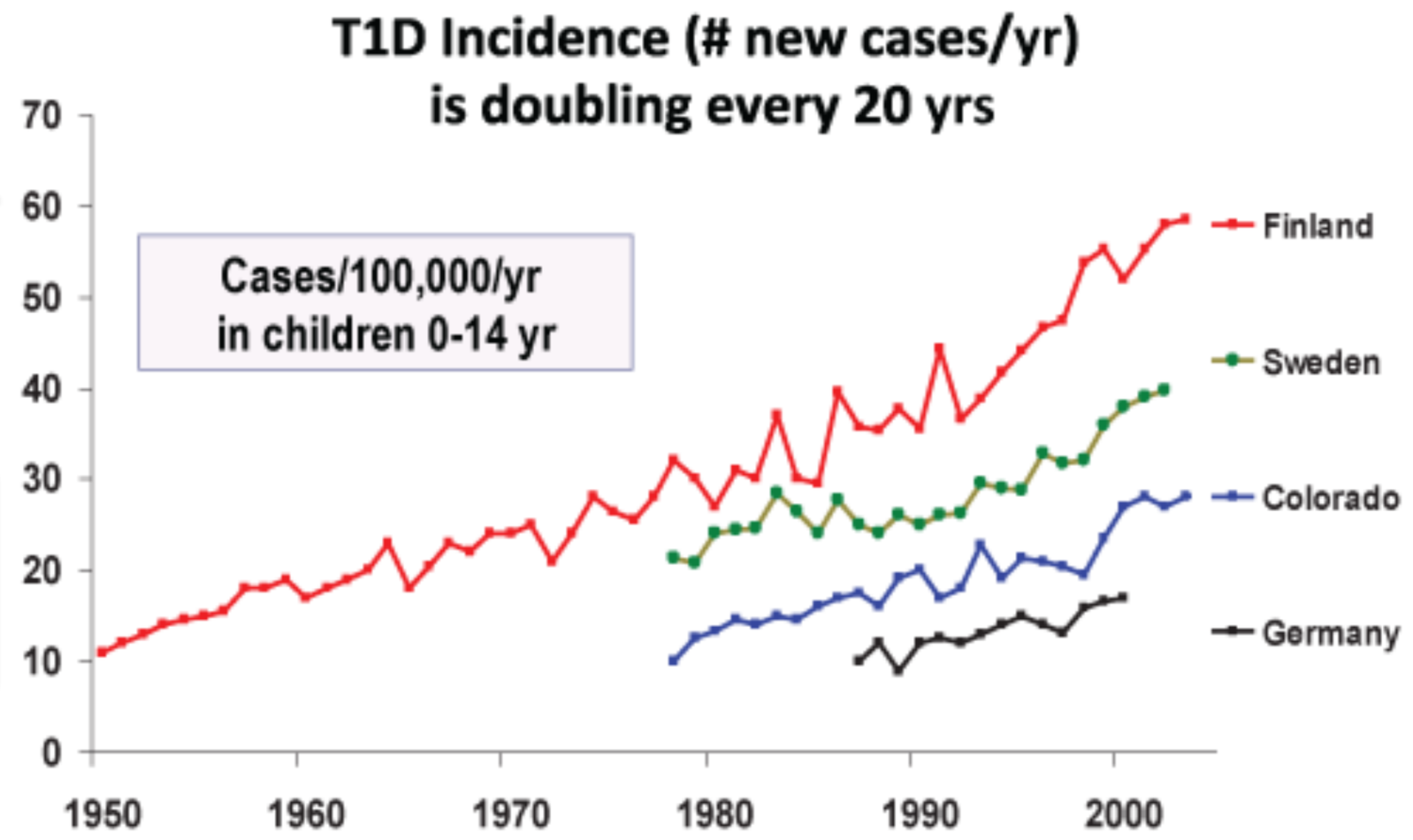


EPIDIMIOLOGY

TIME TRENDS T1 DM

2 - 5 % per year

More rise in younger age group.

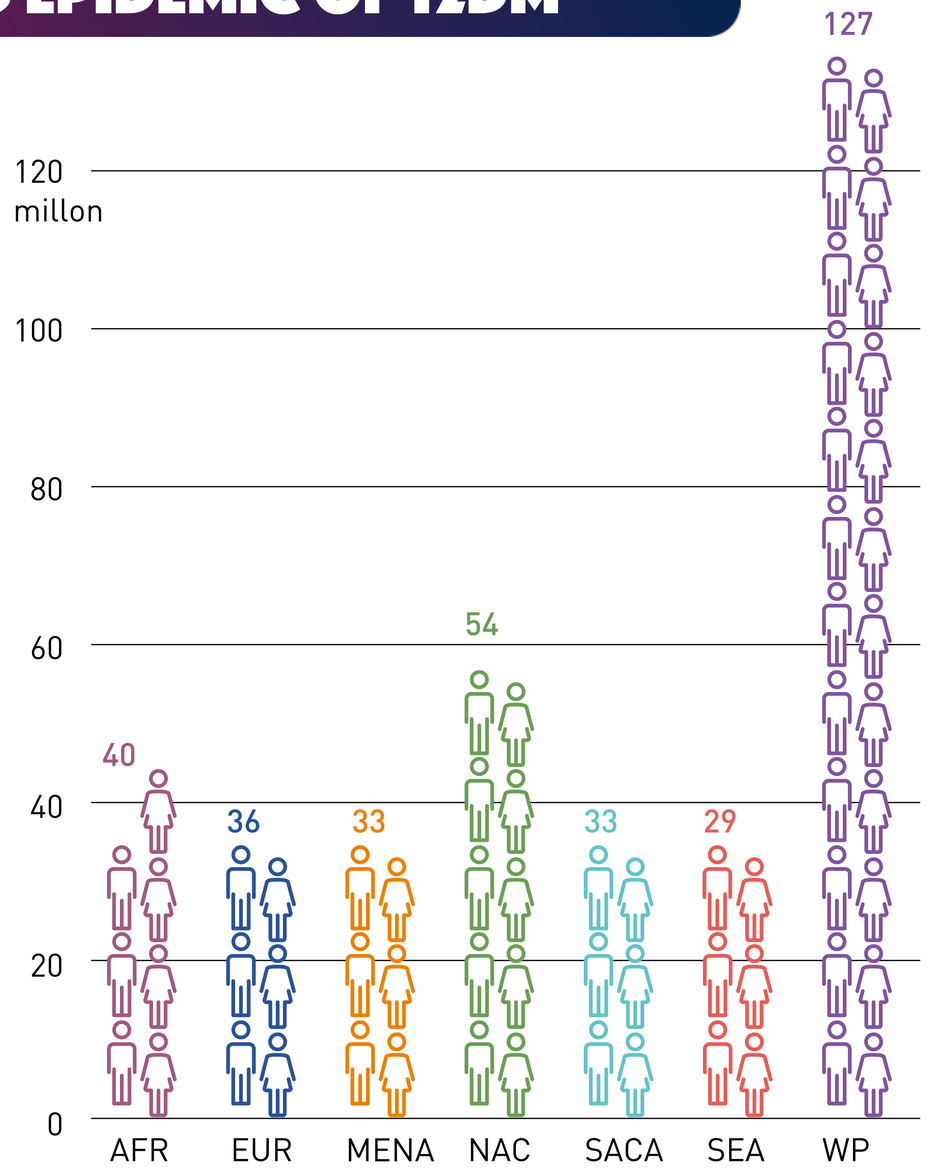


After 3003, T1DM appears to have plateaued USA, Australia

AGENDA:

- EPIDEMIOLOGY DM , T2DM.

THE GROWING EPIDEMIC OF T2DM



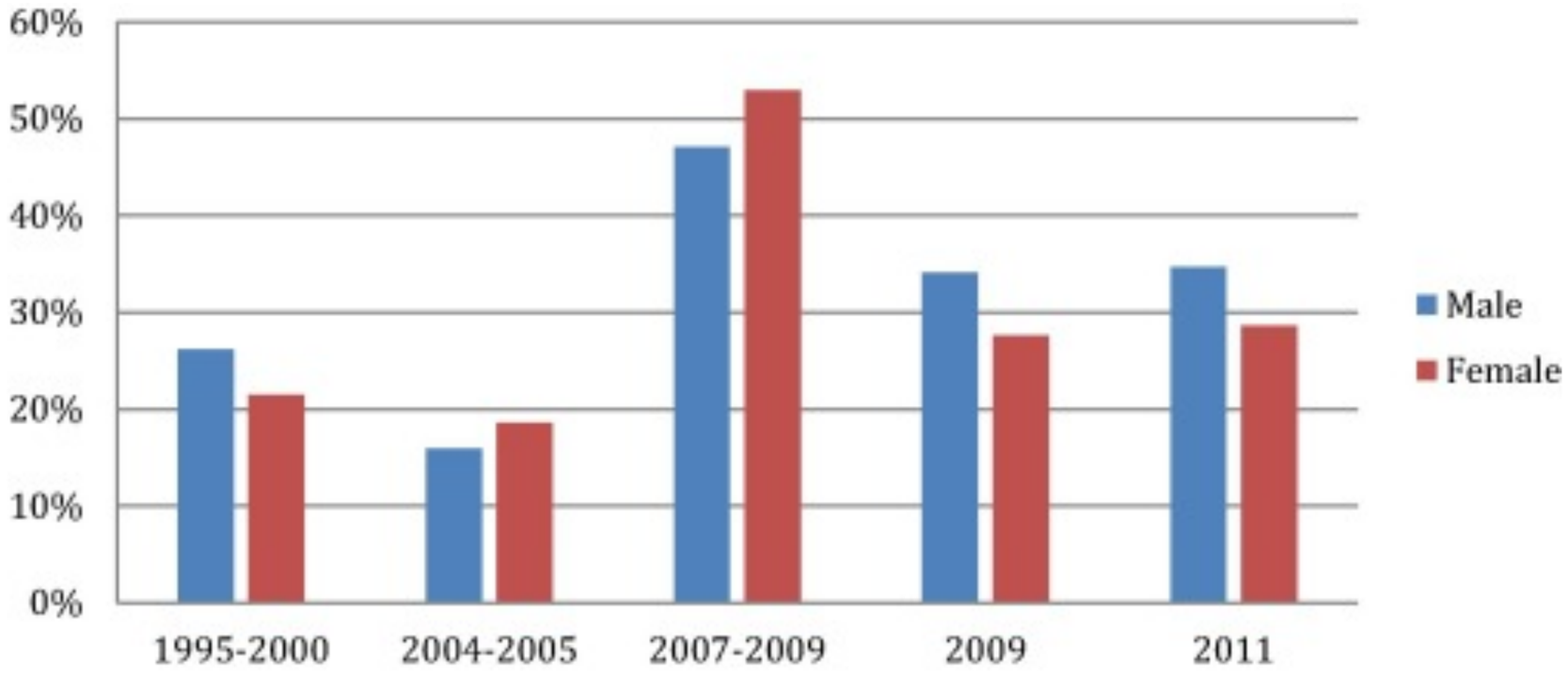
International
Diabetes
Federation

EPIDIMIOLOGY

T2DM

International Diabetes Federation

Incidence & prevalence rates of diabetes mellitus in Saudi Arabia: An overview



Note: Adapted from Al-Daghri et al. [19]; Alqurashi et al. [22]; Al-Baghli et al. [23]; Al-Nozha et al. [24]; Al-Rubeaan [21]

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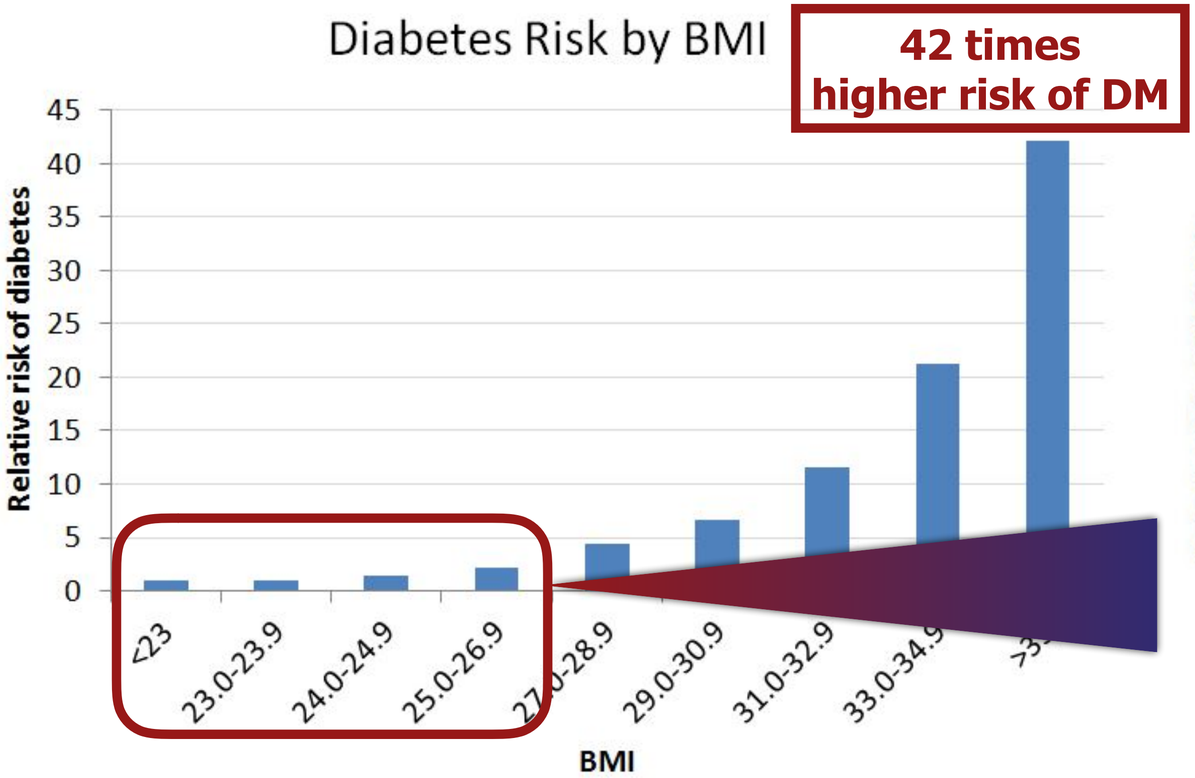
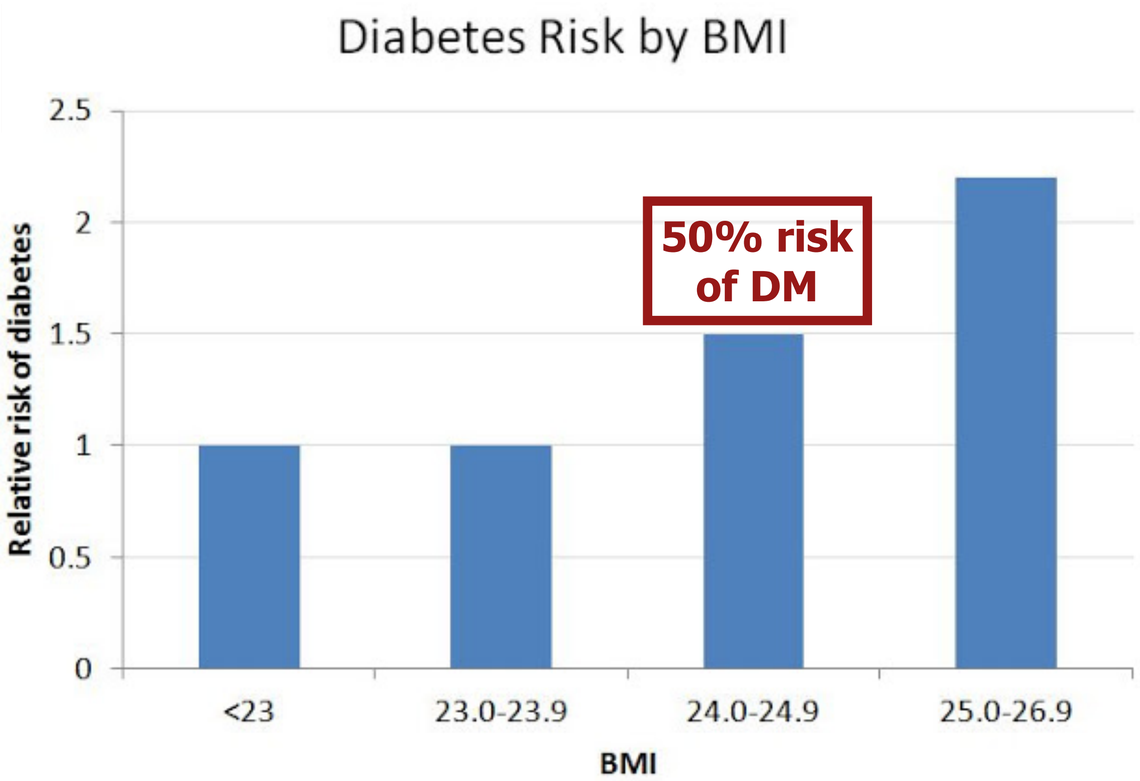
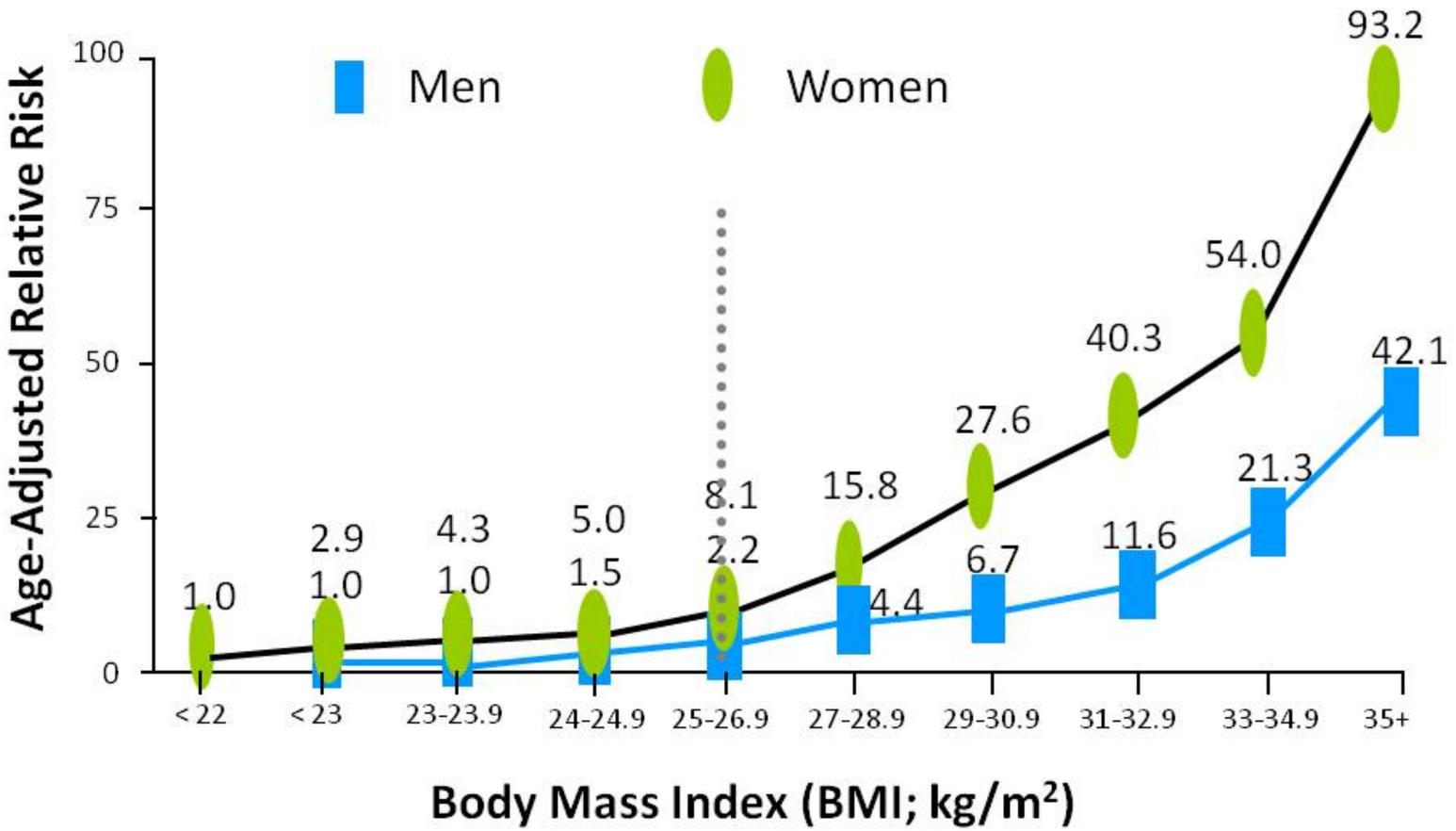
BODY MASS INDEX & RISK OF T2DM





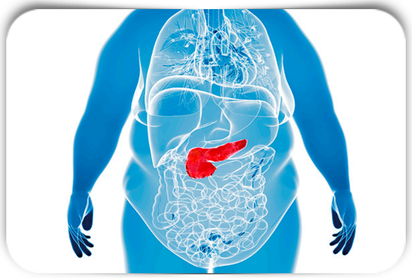
Colditz GA et al. Annals of Internal Medicine 1995; 122: 481-86

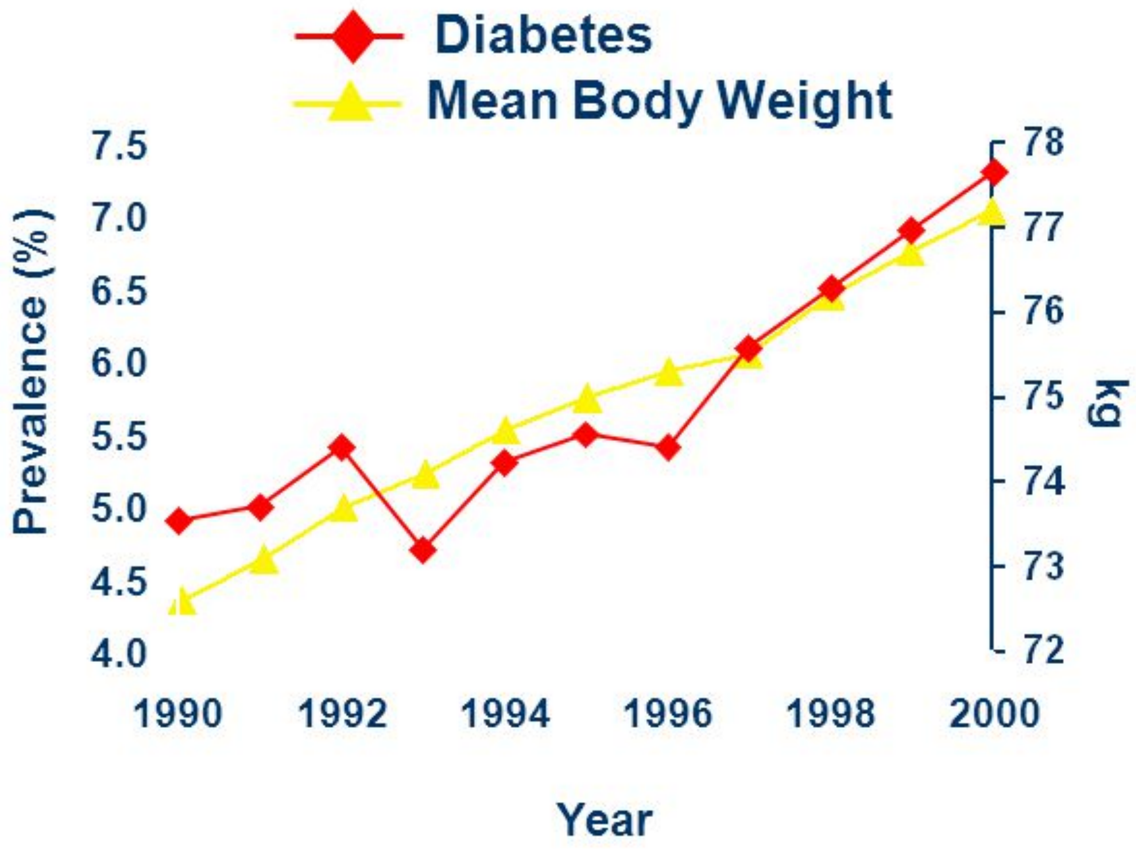
RELATIONSHIP BETWEEN BMI & RISK FOR T2DM



Chan J, et al. *Diabetes Care*. 1994;17:961-969.
Colditz G, et al. *Ann Intern Med*. 1995;122:481-486.

THE GROWING EPIDEMIC OF T2DM IN RELATION TO OBESITY

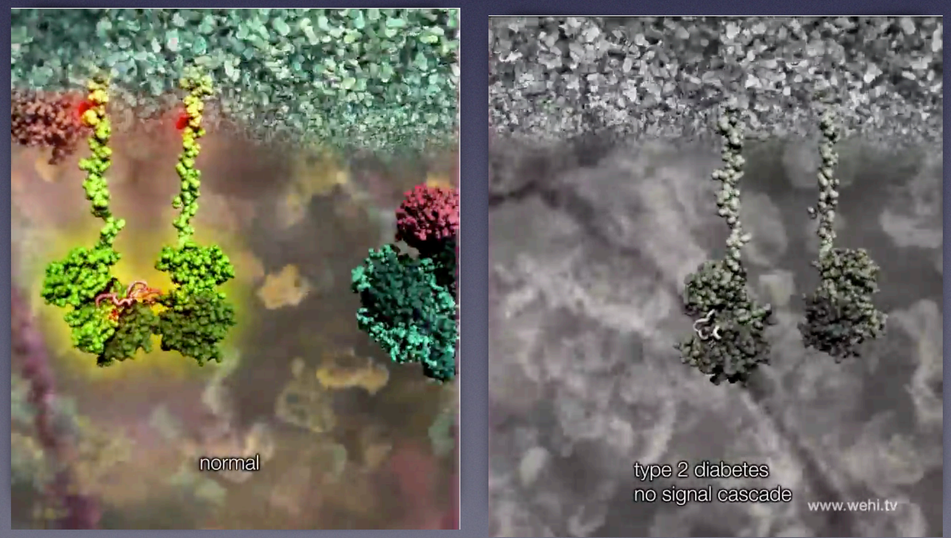




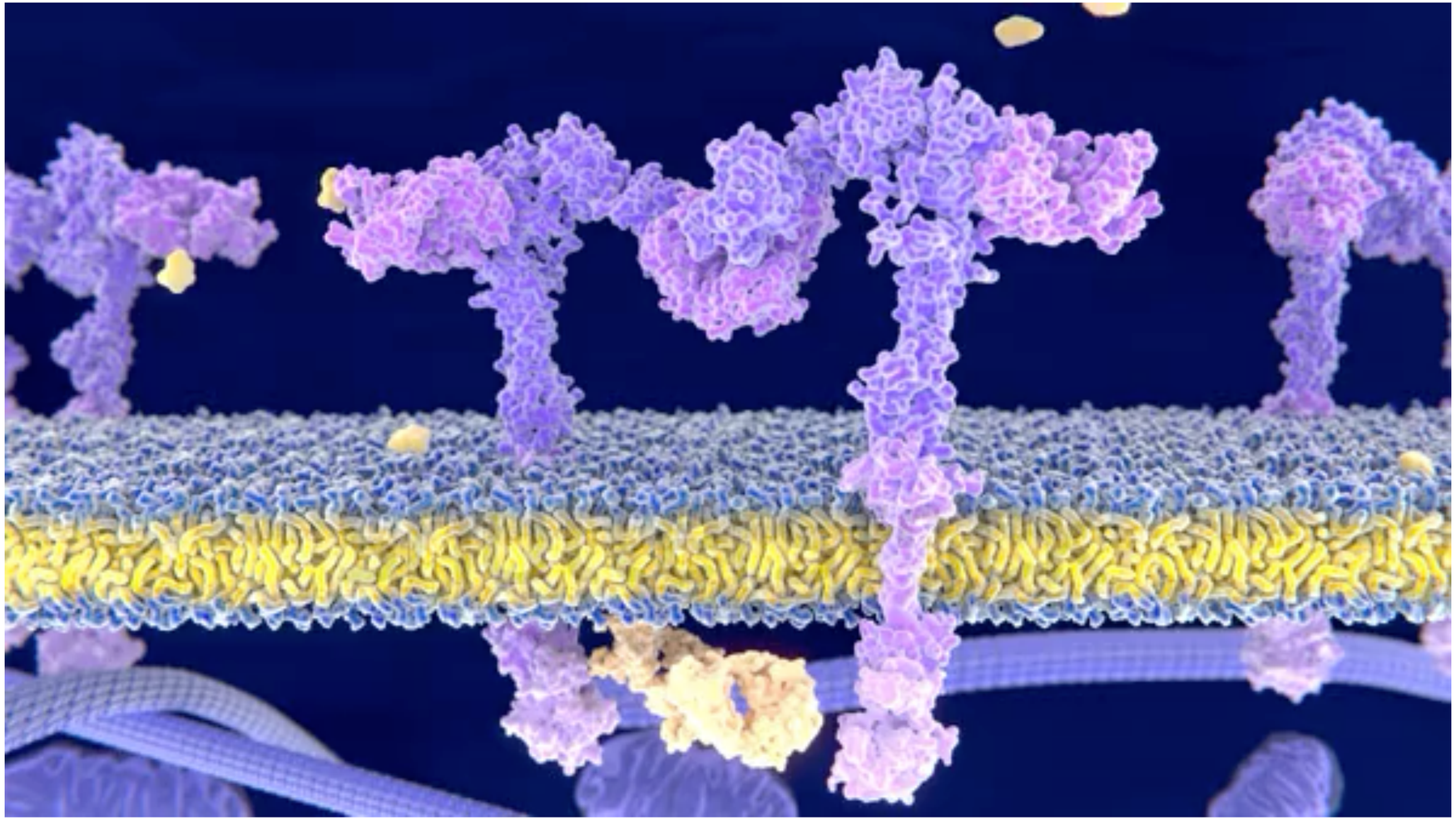
Diabetes Care 2000;23:1278-83.
JAMA 1990;282:1519-22
JAMA 2001;286:1195-200

AGENDA:

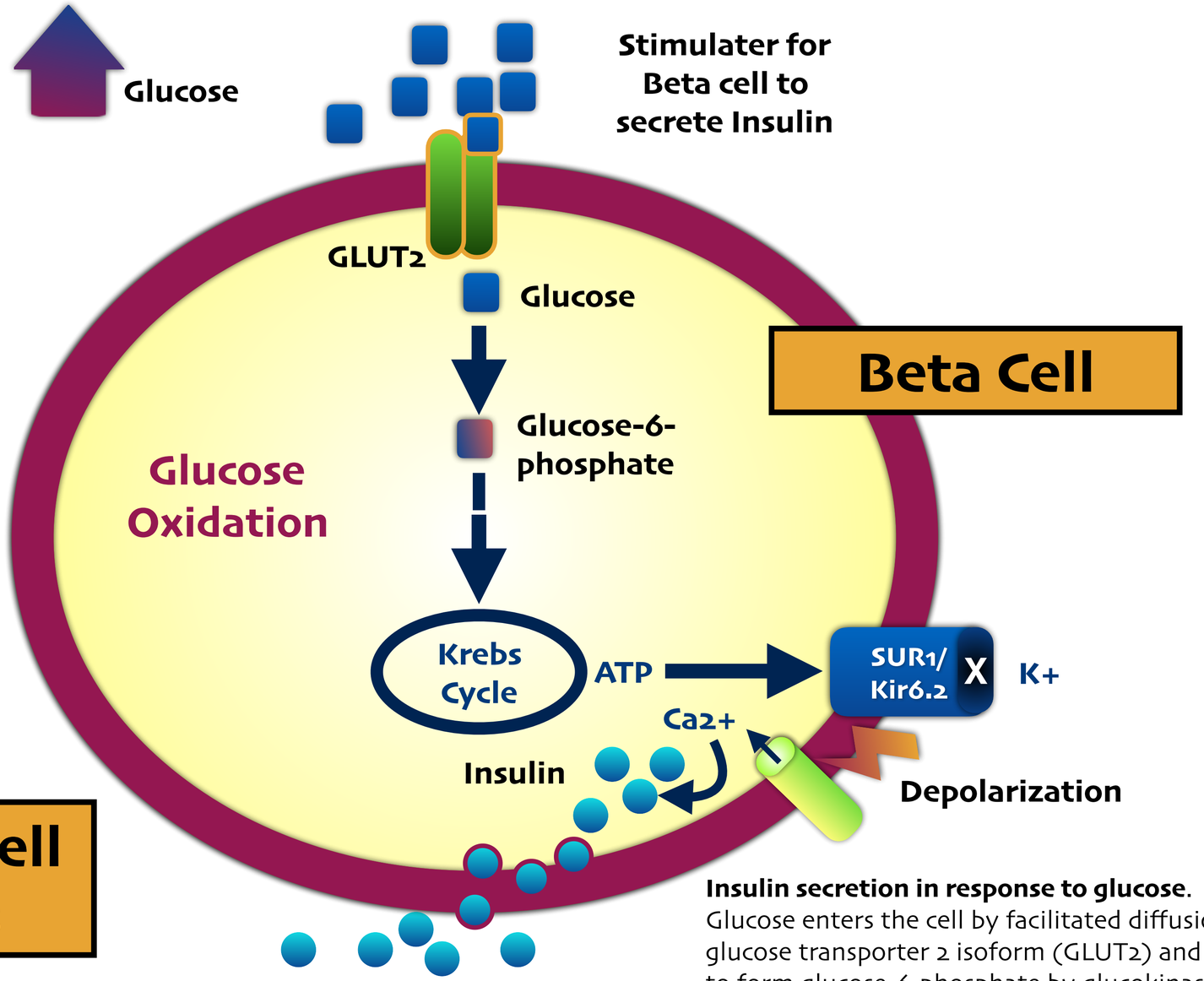
- MOLECULAR MECHANISMS OF INSULIN SIGNALING



INSULIN RECEPTORS



INSULIN SECRETION IN RESPONSE TO GLUCOSE

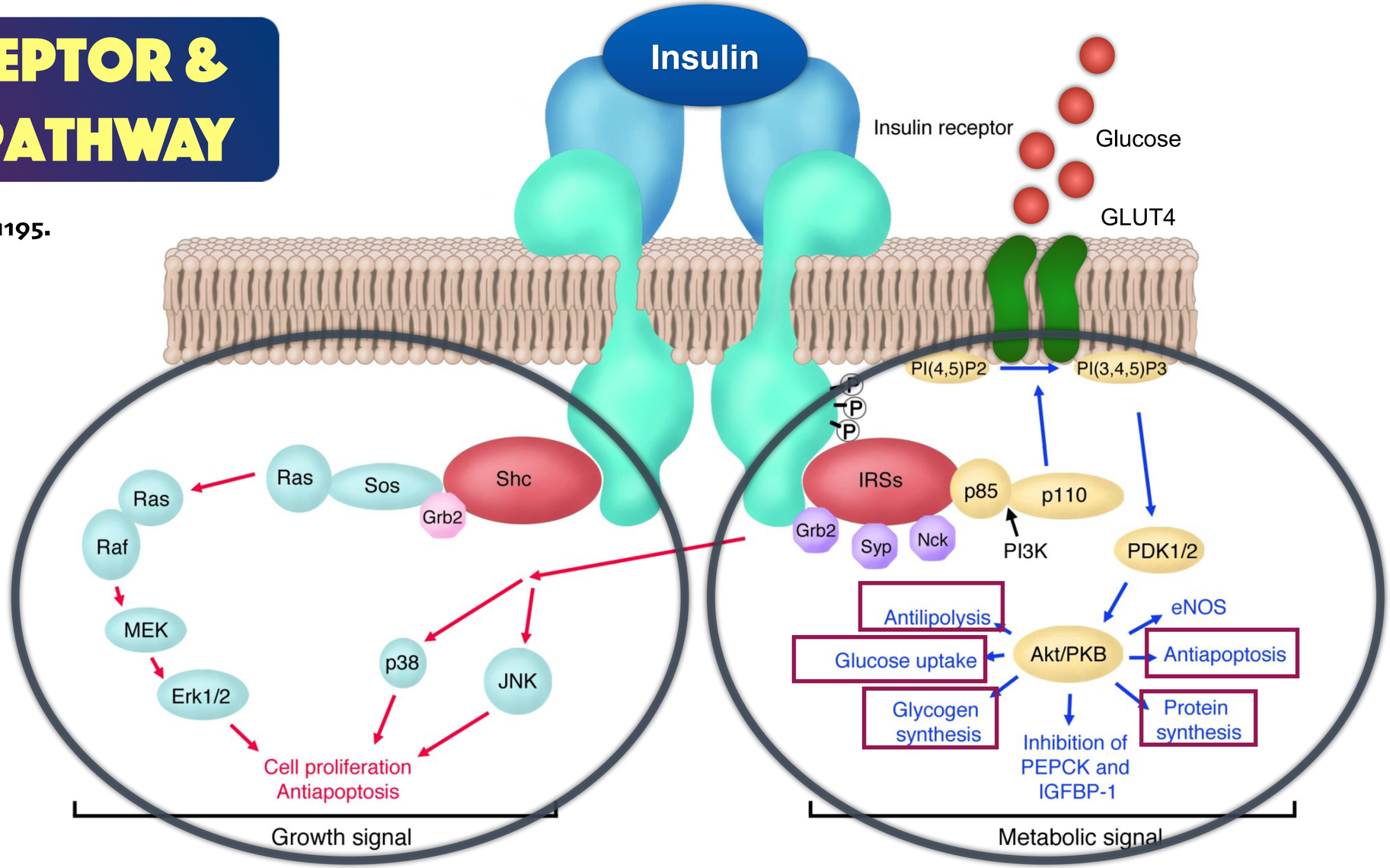


Insulin secretion in response to glucose.
Glucose enters the cell by facilitated diffusion mediated the glucose transporter 2 isoform (GLUT2) and it is phosphorylated to form glucose-6-phosphate by glucokinase.

INSULIN RECEPTOR & SIGNALING PATHWAY

J Clin Invest. 2004;114(9):1187-1195.

Insulin & insulin-like growth factors



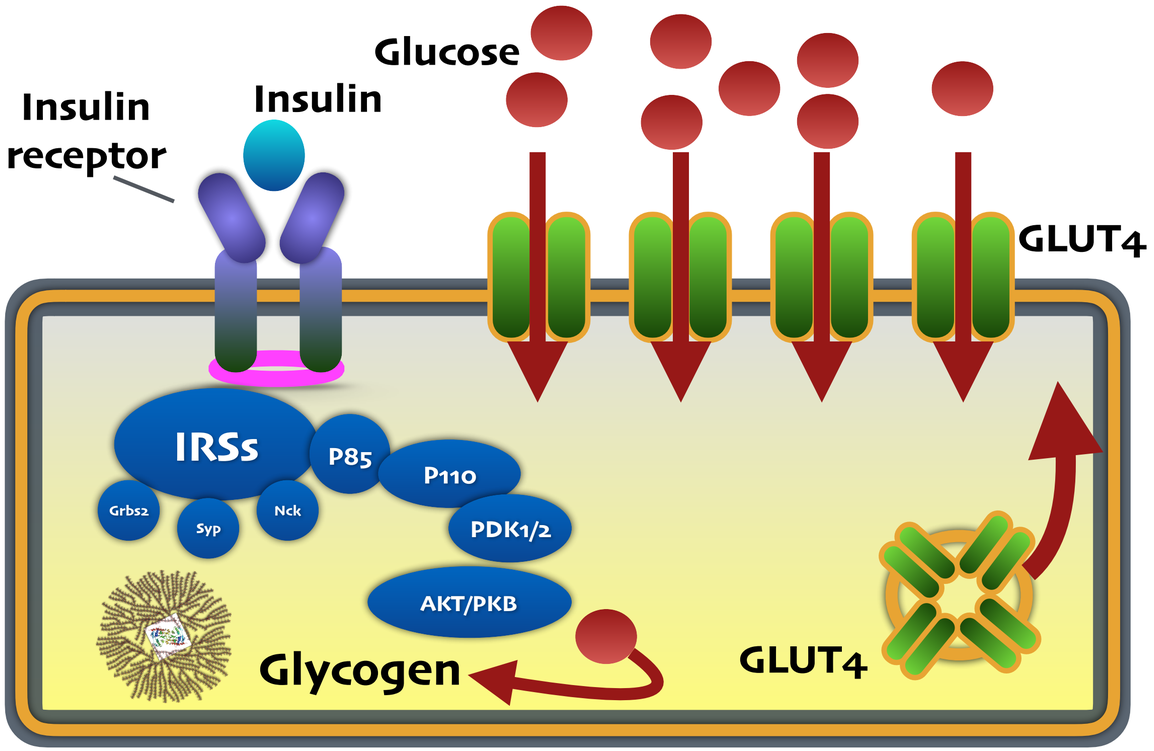
Cell proliferation
Tissue development & differentiation.

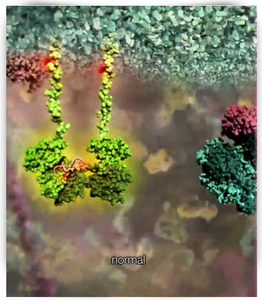
The regulation of energy metabolism.

AGENDA:

- MOLICULAR MECHANISM IN DIABETES

NORMAL INSULIN SIGNALING

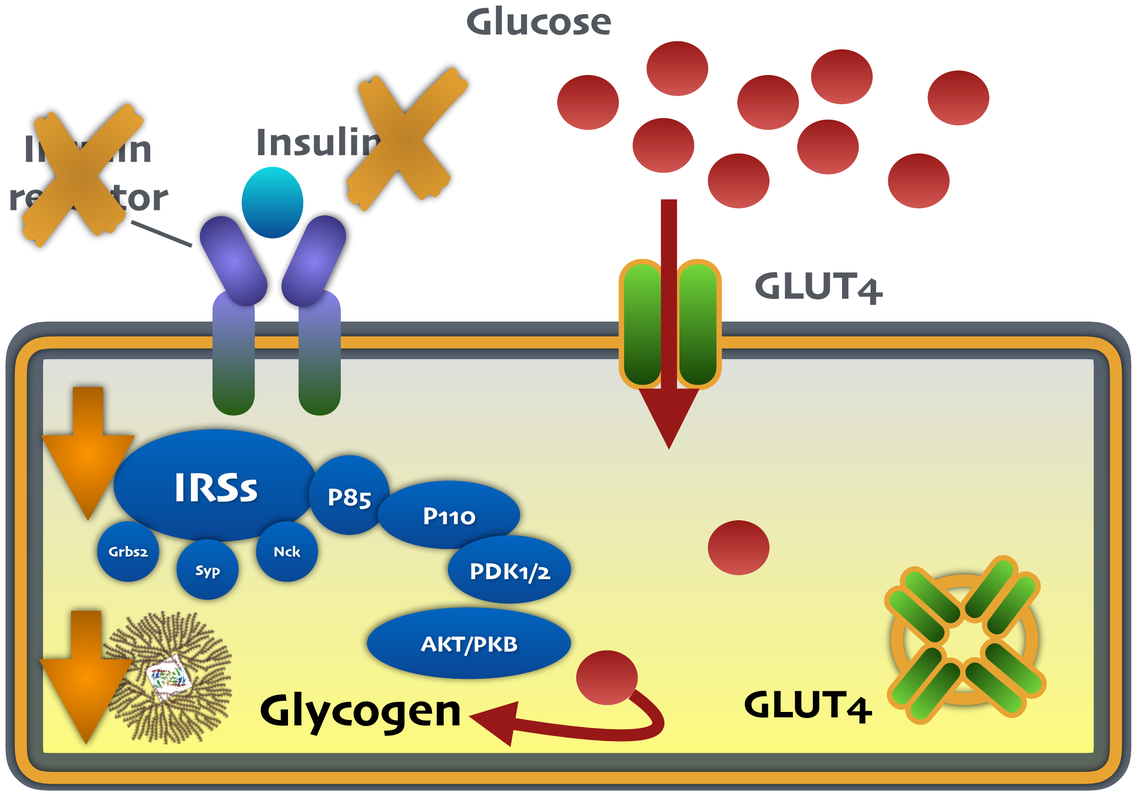


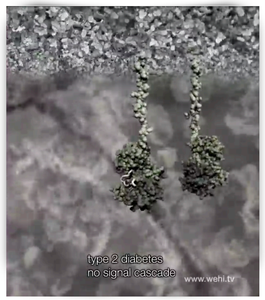


Peripheral Tissue
(Liver, Muscle)

Normal

PATHOGENESIS OF DM

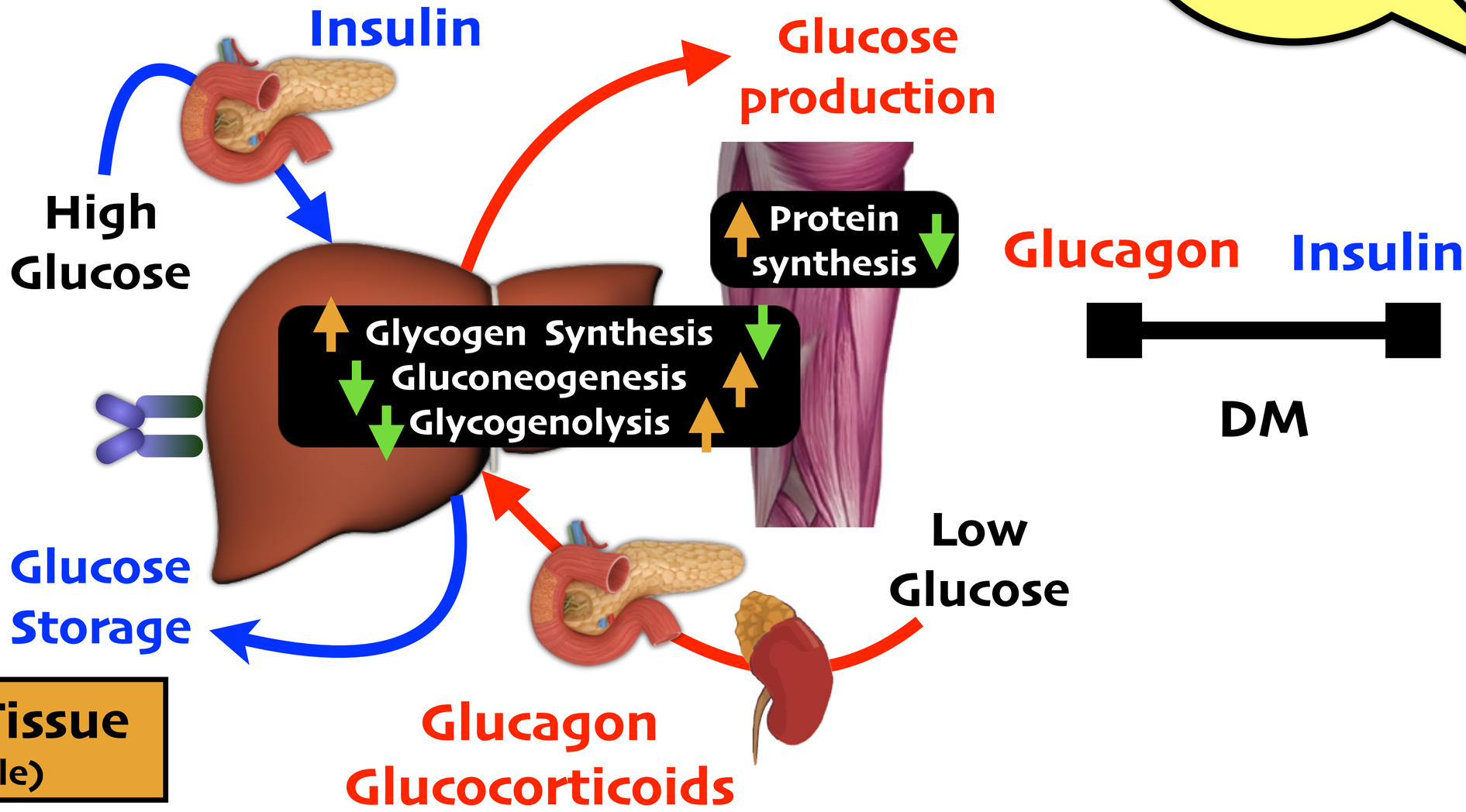




Diabetes

INSULIN-MEDIATED GLYCOGEN SYNTHESIS
INSULIN REPRESSION OF GLUCOSE OUTPUT

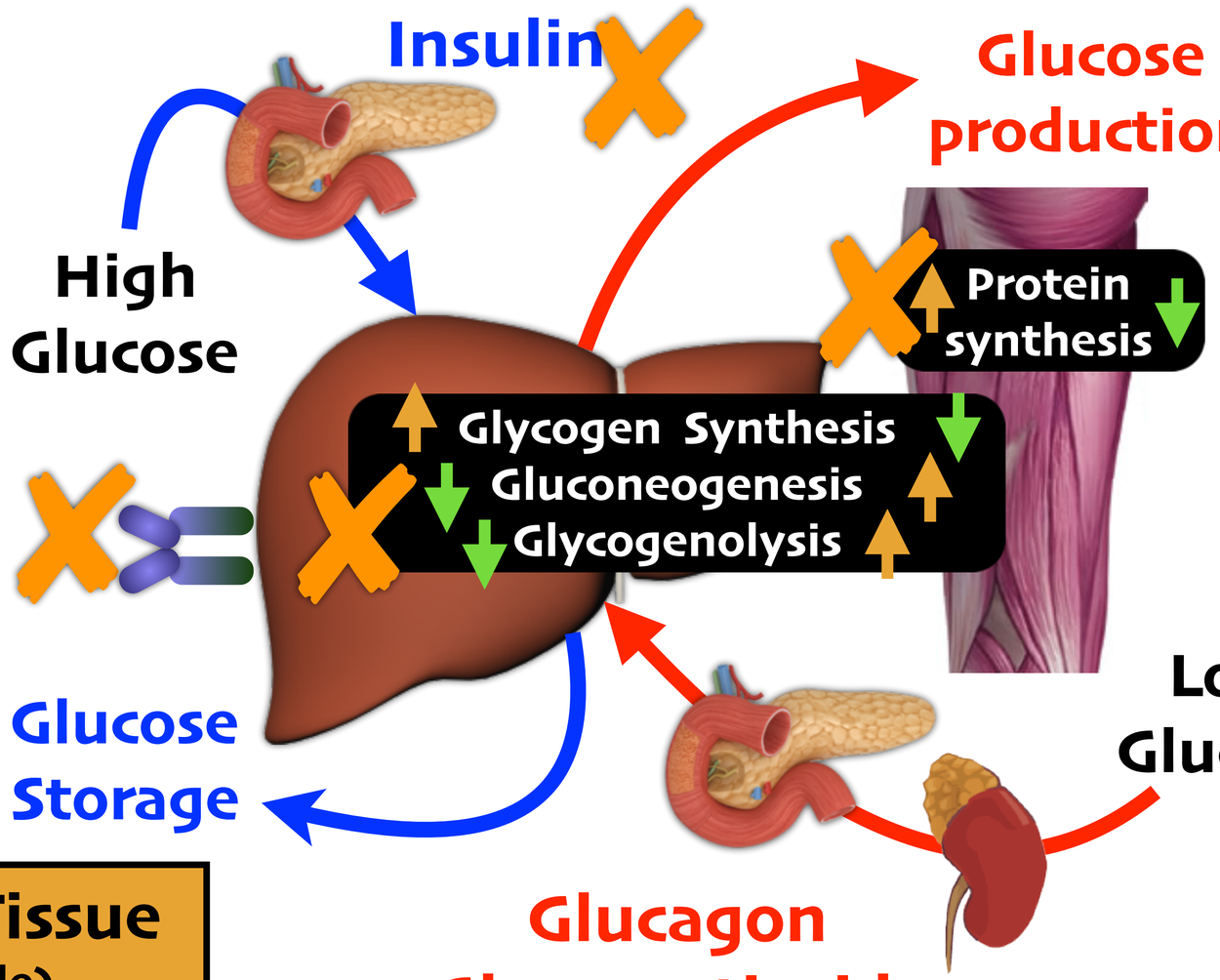
Glucose uptake
Glycogenesis
Protein synthesis



Peripheral Tissue
(Liver, Muscle)

MOLECULAR MECHANISM IN DIABETES

Glucose
uptake
Glycogenesis
Protein synthesis



Glucagon Insulin

DM

Peripheral Tissue
(Liver, Muscle)

INSULIN-MEDIATED LIPID SYNTHESIS
INSULIN REPRESSION OF LIPOLYSIS

Lipogenesis
Antilypolysis

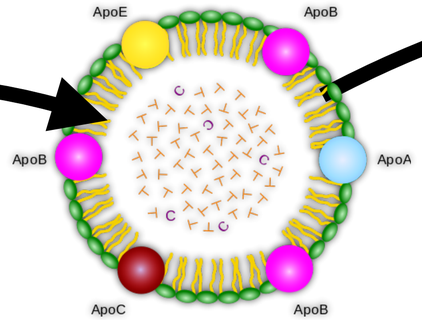
Insulin

High Glucose

Lipogenesis (FA synthesis)

Glucose Storage

Peripheral Tissue
(Fat Tissue)



Lipoprotein

Free Fatty Acids (FFA)

High Glucose

Glycerol

GLUT4

Triglyceride (TG)

Insulin

Intracellular Lipase

Glucose Storage

Breakdown inhibition of fat in adipose tissue

(inhibition of intracellular lipase that hydrolyzes TG to release FFA)

No Lipolysis

MOLECULAR MECHANISM IN DIABETES

Lipogenesis
Antilypolysis

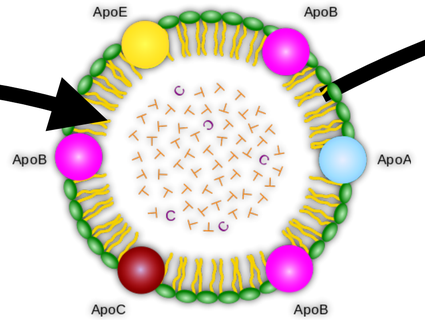
Insulin

High Glucose

Lipogenesis (FA synthesis)

Glucose Storage

Peripheral Tissue
(Fat Tissue)



Lipoprotein

Free Fatty Acids (FFA)

High Glucose

Glycerol

GLUT4

Triglyceride (TG)

Insuli

Intracellular Lipase

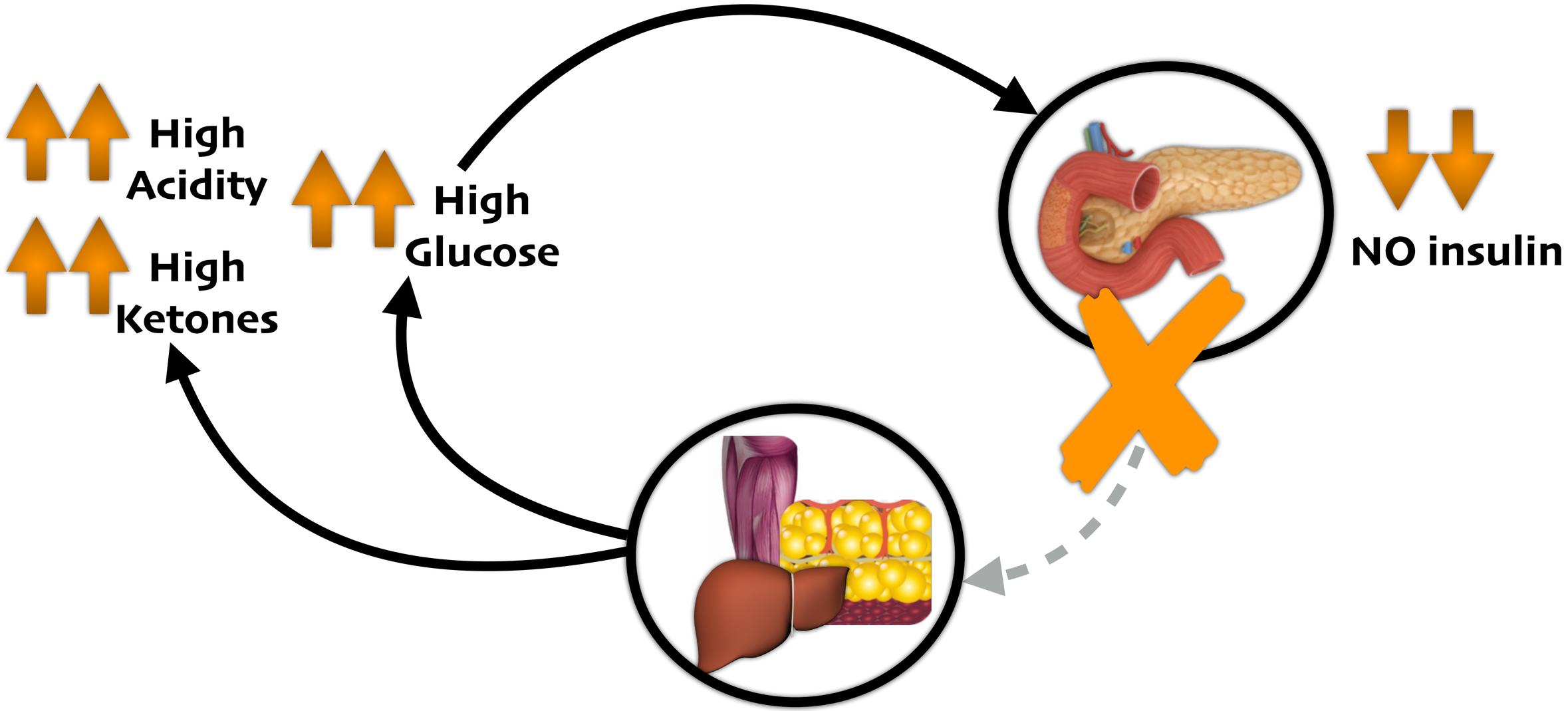
Glucose Storage

Breakdown inhibition of fat in adipose tissue

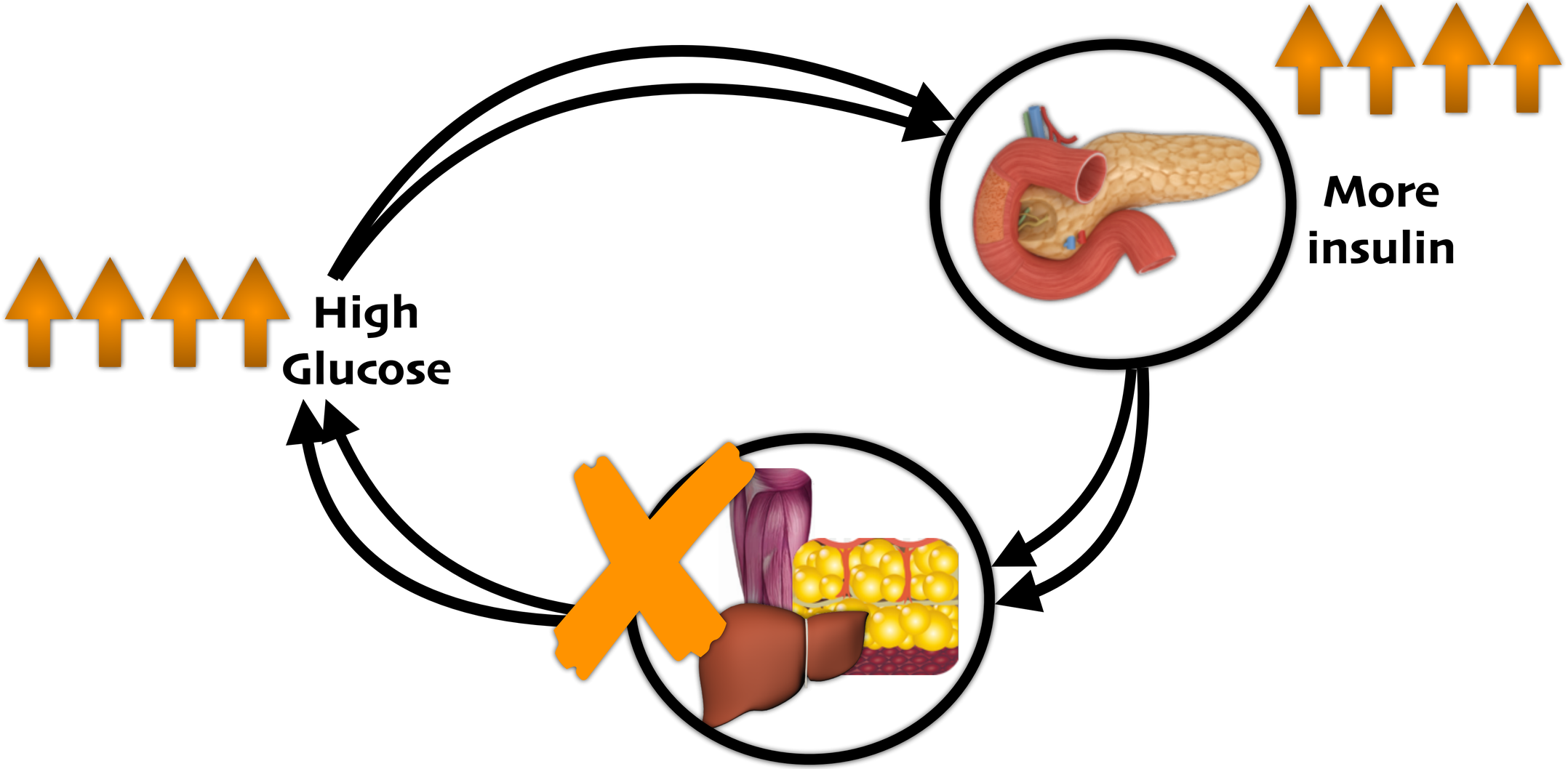
(inhibition of intracellular lipase that hydrolyzes TG to release FFA)

More Lipolysis

T1DM TRUNCATED (CUT OFF) CYCLE



T2DM VICIOUS CYCLE - GLUCOTOXICITY



AGENDA:

- MAIN PATHOLOGY OF TYPE 1 DM & HISTOPATHOLOGY.

ABSOLUTE INSULIN DEFICIENCY

Type 1 diabetes mellitus: results from

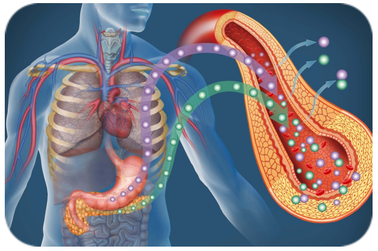
Destruction of the insulin-producing beta cells in the islets of Langerhans

Types:

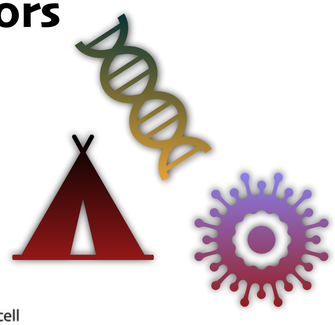
Type1 A: Autoimmune destruction 95%

Type 1B: Non-autoimmune islet destruction 5%

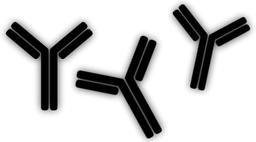
PATHOGENESIS OF T1DM

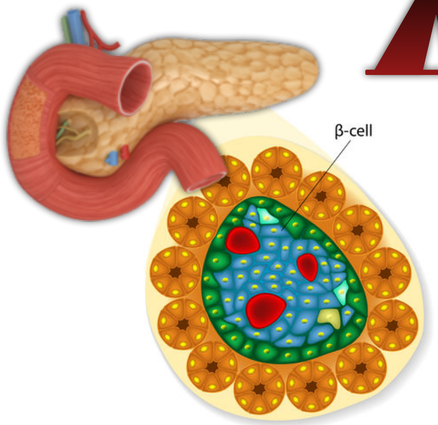


Environmental, Viral, Genetic … factors



TYPE 1 DIABETES

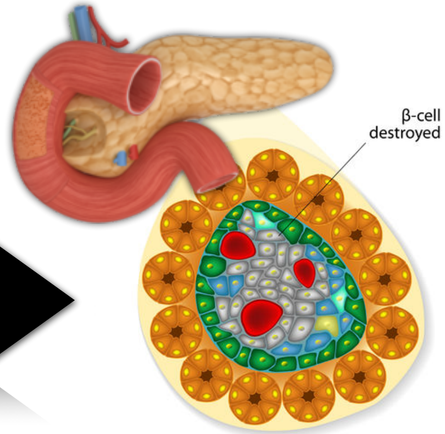




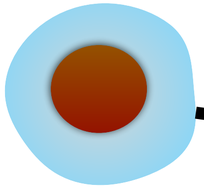
GADA
Glutamic acid decarpoxylase antibodies

IA2A
Insulinoma-2 antigen antibodies

ZnT8A
Zinc transporter-8 antibodies



T cell mediated



Abnormal insulin secretion.

	Sensitivity	Specificity	AUC	SE	95% CI
GADA	64.77	96.6	0.807	0.034	0.74-0.86
IA2A	19.32	100.00	0.597	0.043	0.52-0.67
ZnT8A	31.82	97.73	0.648	0.041	0.57-0.71

ASSOCIATION WITH OTHER AUTOIMMUNE DISEASES

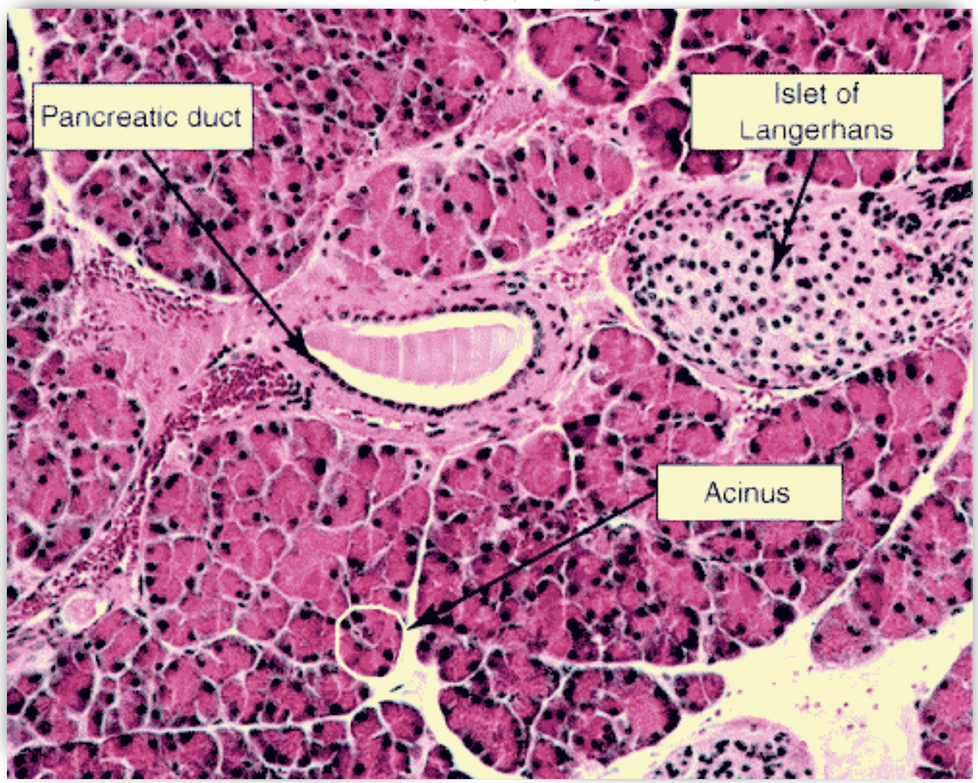
The autoimmune response in type 1 diabetes may be accompanied by antibodies directed against other organs including the following:

- **Thyroid autoimmunity:**
  Affecting more than **25%** of individuals.
  Recommend annual testing of TSH in children to detect early thyroid metabolic abnormalities. If anti-thyroid autoantibodies are present (eg, anti-thyroid peroxidase), risk of hypothyroidism is greatly increased.

- **Antiadrenal antibodies & adrenal insufficiency:**
  1.7% with type 1 diabetes have antibodies against 21-hydroxylase a common autoantigen in primary adrenal insufficiency. 3 of 8 patients **37%** with anti-21-hydroxylase antibodies had adrenal insufficiency.

- **Polyglandular autoimmune disease, especially type II:**
  which adrenal insufficiency, autoimmune thyroid disease, & gonadal insufficiency are the other major components.

Normal histology of pancreas



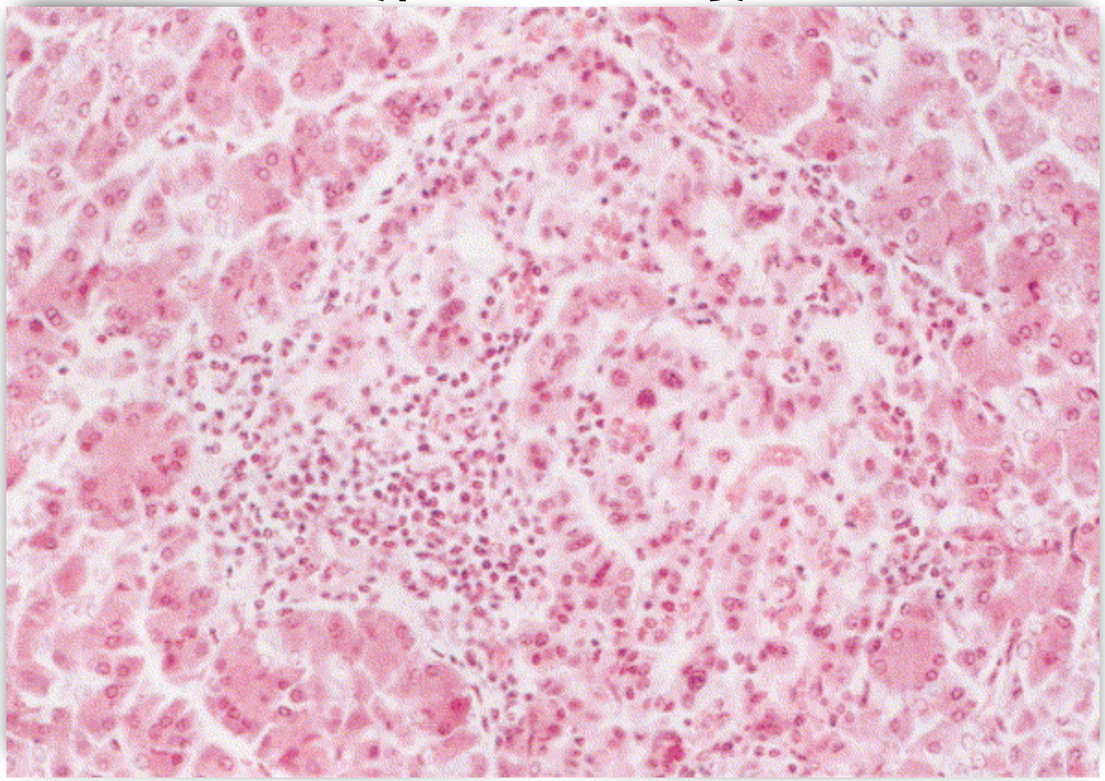
Exocrine Cells:
It secretes a digestive enzyme rich alkaline fluid into the duodenum via the pancreatic duct.

Endocrine Cells:

- **alpha** - secrete glucagon
- **beta** - secrete insulin
- **delta** - secrete somatostatin

Normal

Type 1 DM histology



Chronic, atrophic, lymphocytic insulitis where mononuclear cells infiltrate the islets & selectively destroy pancreatic β-cells.

T1DM

AUTOIMMUNITY

One of the best predictors of progression to T1A DM:

is expression of 2 or 3 autoantibodies: GAD, IA-2 or insulin autoantibodies

What are the confirmed targets (Auto antigenes) of autoantibodies in T1DM of man?

Insulin

Studies on the NOD (non-obese diabetic) mouse model indicate that proinsulin/insulin itself is the likely primary target for the autoantibodies

Insulin autoantibodies are often the first to appear in children followed from birth & progressing to diabetes, & are **the highest in young children developing diabetes.**

Of note, **once insulin is administered subcutaneously, essentially all individuals develop insulin antibodies**, & thus insulin autoantibody measurements after approximately **two weeks of insulin injections** cannot be used as a marker of immune mediated diabetes (type 1A)

Glutamic acid decarboxylase GAD

which is present in the islets as well as in the central nervous system & testes.

Antibodies to GAD (a 65-kD protein) are found in about **70 %** of patients with type 1 diabetes at the time of diagnosis.

ZnT8 (zinc transporter)

60-80 % of patients with newly diagnosed type 1 diabetes

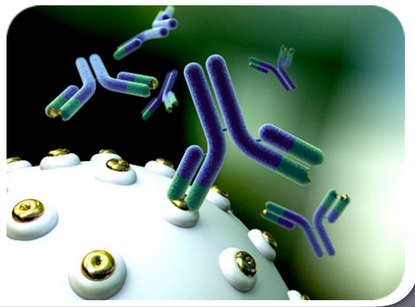
26 % of subjects with antibody negative (insulin, GAD, IA-2 and ICA) type 1 diabetes have ZnT8 autoantibodies

ZnT8 autoantibodies appear later than insulin autoantibodies, & the antibody is typically lost very early after the onset of diabetes

Insulinoma associated antigens 2 {IA-2 alpha & IA-2 beta}

Antibodies to this antigen were found in the serum of **58 %** of patients with type 1 diabetes at the time of diagnosis .

Appear later than autoantibodies to insulin & GAD, & are highly associated with expression of multiple anti-islet autoantibodies & progression to diabetes.

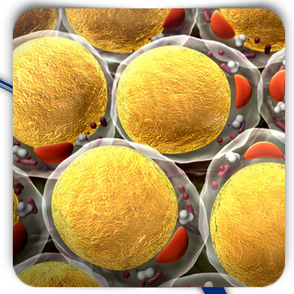


AGENDA:

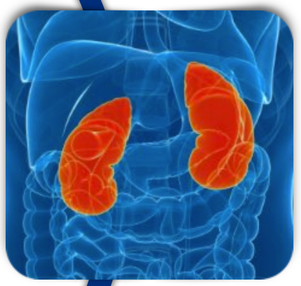
- PATHOGENESIS OF TYPE 2 DM.

PATHOGENESIS OF T2DM

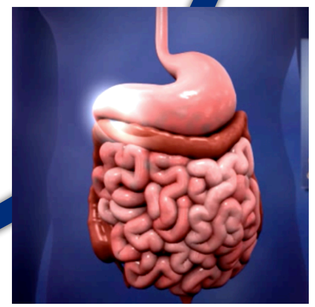
Neurotransmitter dysfunction



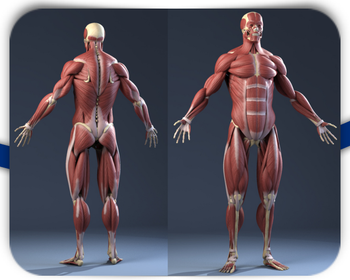
Increased Lipolysis inflammation



Increased Glucose reabsorption



Decreased Incretin effect



Decreased Glucose Uptake

Increased Glucose hepatic production

Increased Glucagon secretion

Decreased Insulin secretion

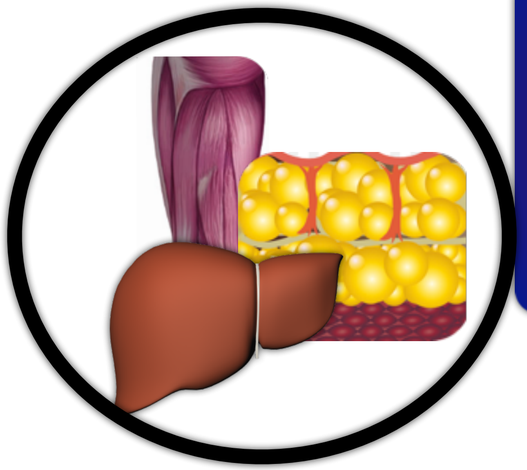
TYPE 2 DIABETES

DeFronzo RA. Diabetes 2009

PATHOGENESIS OF T2DM

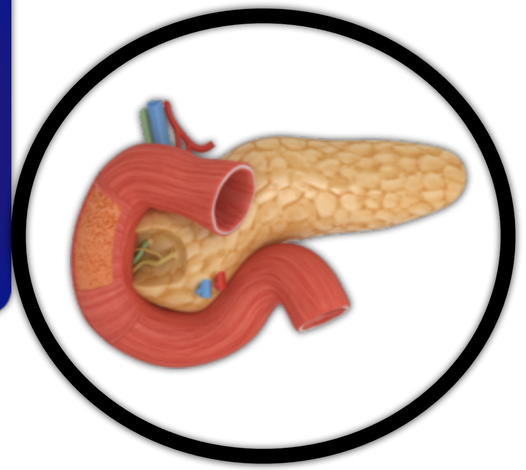
TYPE 2 DIABETES

is characterized



Impaired insulin action

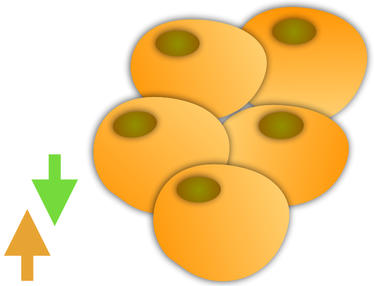
Abnormal insulin secretion.



ADIPOSE TISSUE & INFLAMMATION

In the lean state

- Lipolysis FFA
- Adiponectin



Eosinophil

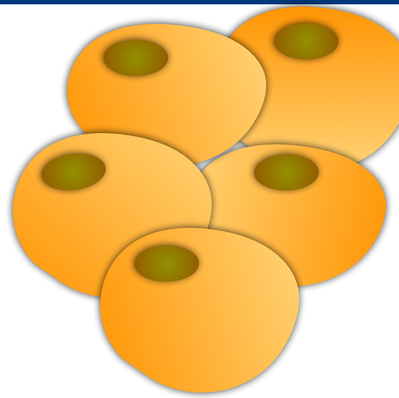
T regulatory (Treg)

M2

IL-10
IL-4
IL-13

Anti-inflammatory
Insulin Sensitive

In the Obesity



- Hypertrophic Adipocytes
- Lipolysis FFA
- Adiponectin
- Liptin

Neutrophil

IFN-gama+Th1

Mast Cell

B-2

CD8+

M1

TNF-alfa
IL-6
IFN
IL1 beta

Adipose Inflammation
Insulin Resistance

Osborn O, Olefsky JM. The cellular and signaling networks linking the immune system and metabolism in disease. Nat Med 2012;18(3):363-374.

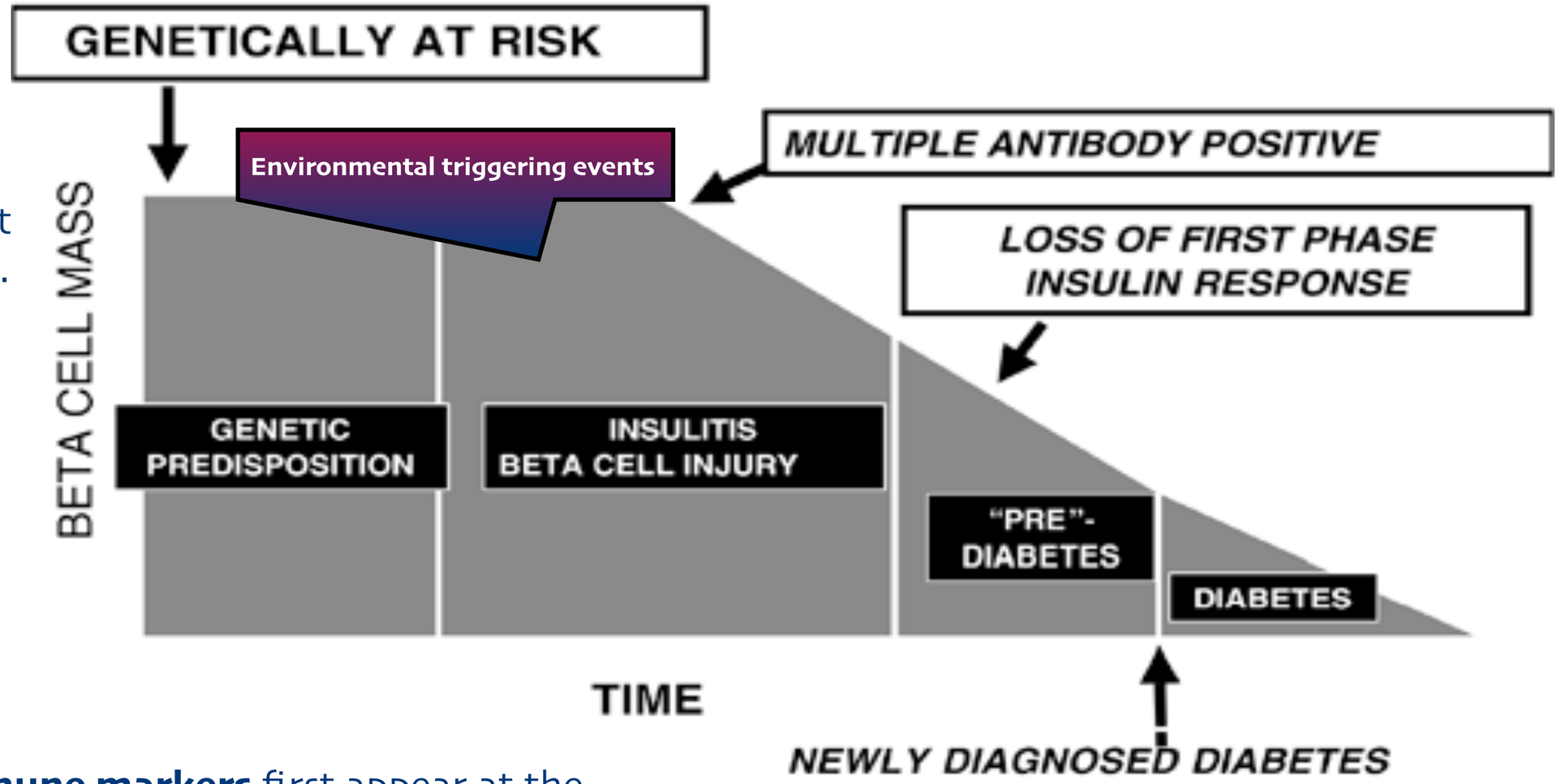
Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. Annu Rev Physiol 2010;72:219-246.

AGENDA:

- TIME COURSE OF T1DM & T2DM DEVELOPMENT

TIME COURSE OF THE DEVELOPMENT OF TYPE 1 DIABETES

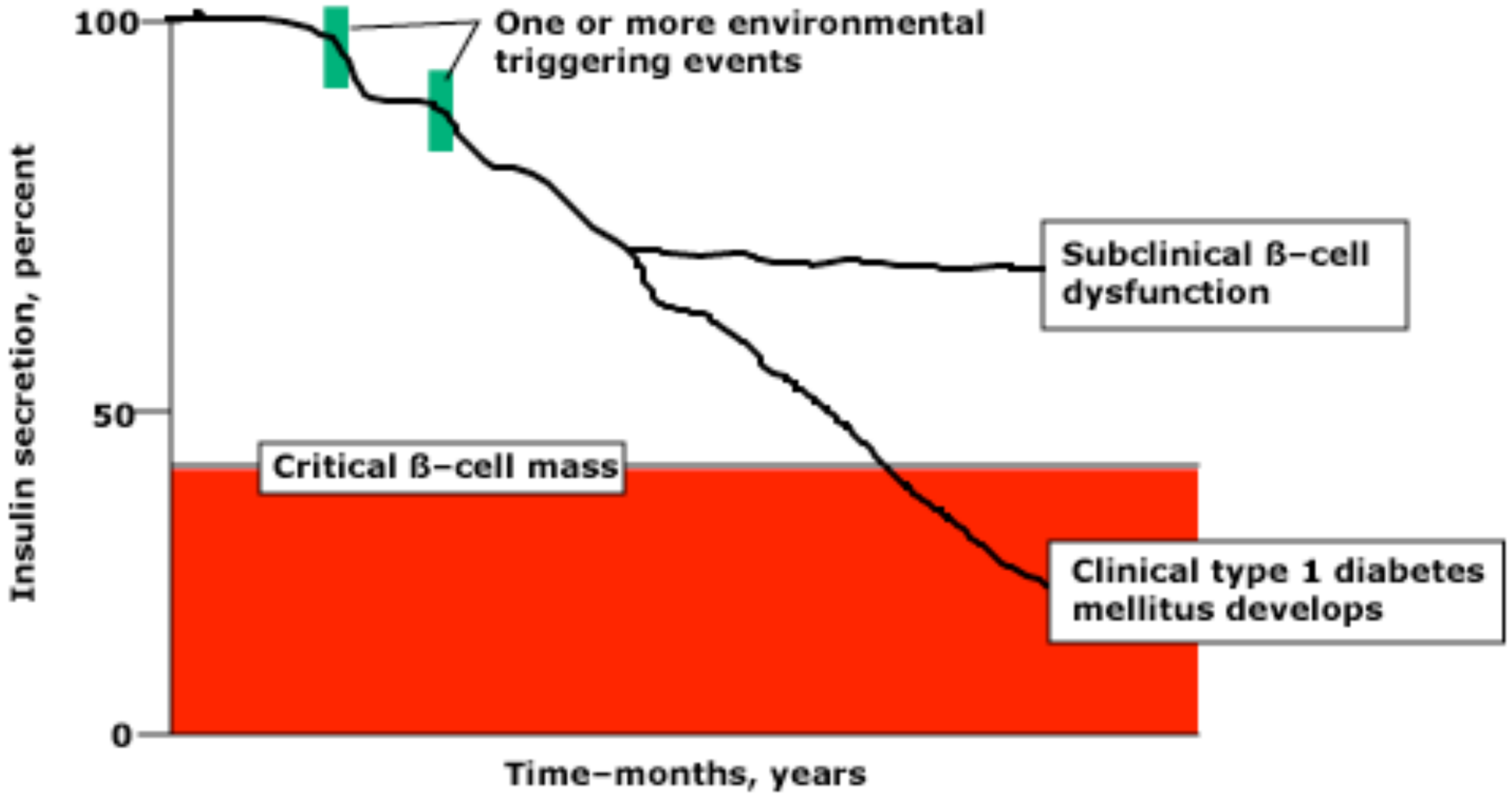
Genetic markers are present from birth.



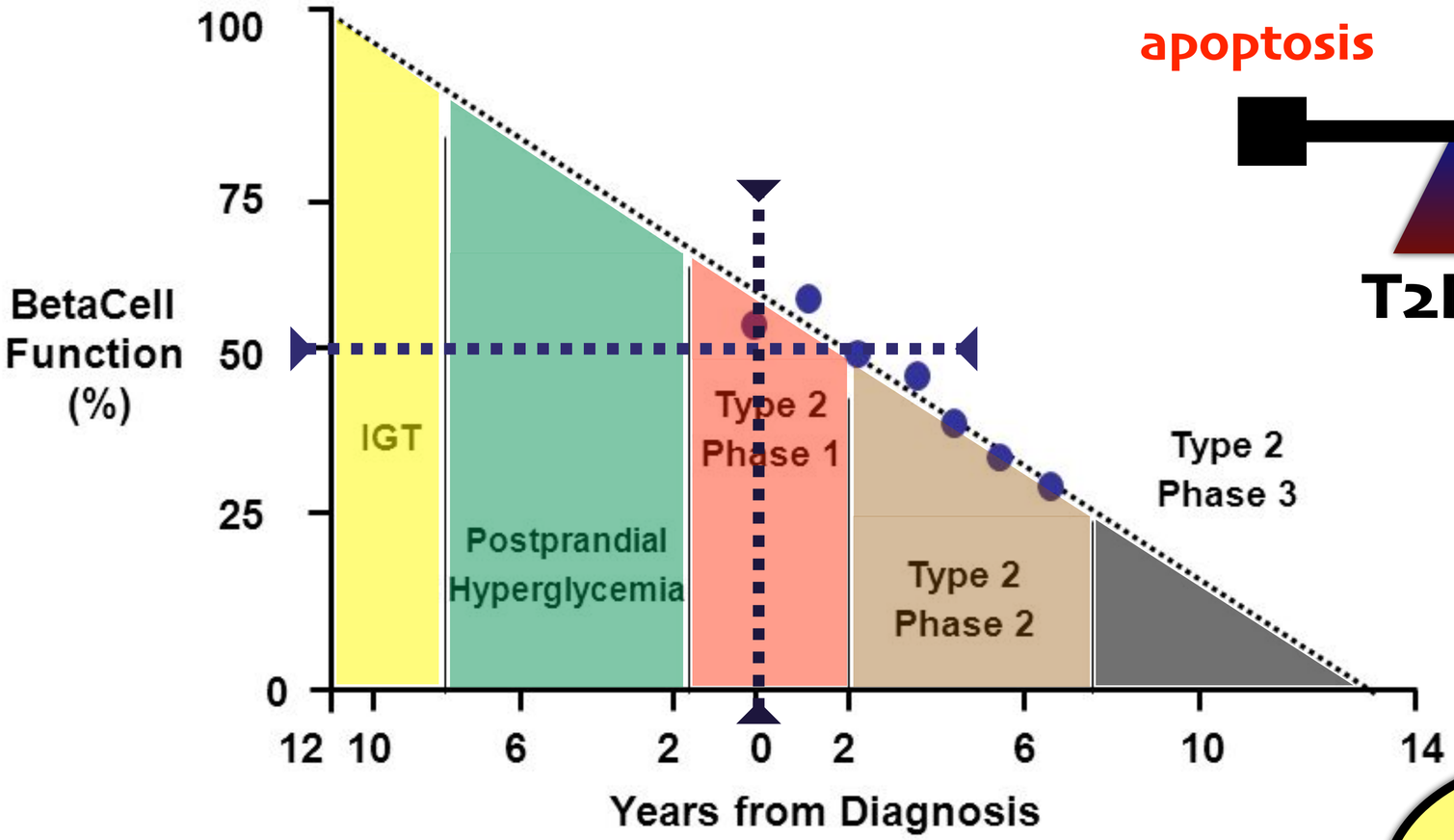
Immune markers first appear at the time of the environmental triggering events.

Sensitive metabolic markers of deficient insulin secretion begin to appear.

TIME COURSE OF THE DEVELOPMENT OF TYPE 1 DIABETES



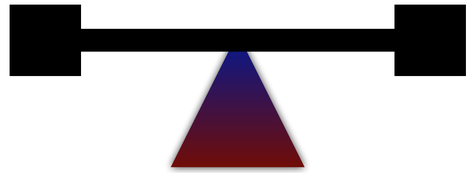
NATURAL HISTORY OF T2DM
STAGES OF T2DM RELATED TO BETA CELL FUNCTION



Adapted from Lebovitz HE. *Diabetes Reviews*. 1999;7(3).

Beta cell apoptosis

Beta cell replication & neogenesis



T2DM

Insulin has antiaboptosis activity

AGENDA:

- PREDISPOSING FACTORS T1DM.

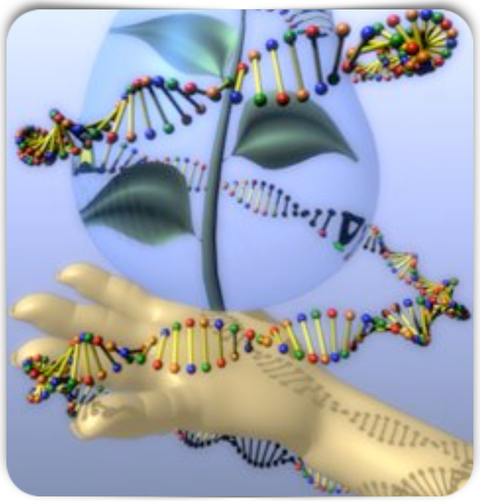
WHAT ARE THE FACTORSFOR T1DM??

Genetically susceptible subjects

Triggered by

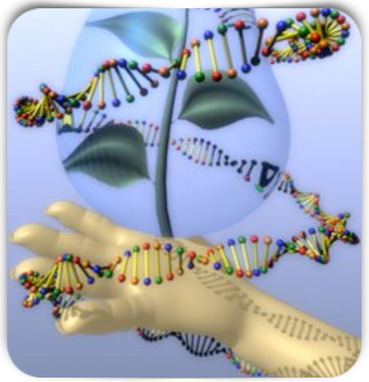
one or more
environmental factors

Progresses over many months or years during which the subject is asymptomatic & euglycemic.



GENETIC SUSCEPTIBILITY

- **The lifetime risk of developing T1DM is significantly increased in close relatives of a patient with T1DM**
  - **No family history – 0.4 %**
  - **Offspring of an affected mother – 1-4 %**
  - **Offspring of an affected father – 3-8 %**
  - **Offspring with both parents affected – Reported as high as 30 %**
  - **Non-twin sibling of affected patient – 3-6 % by age 20 years, & 10 % by 60 years**
  - **Dizygotic twin – 8 %**
  - **Monozygotic twin – 30 % within 10 years of diagnosis of the first twin & 65 % concordance by age 60 years.**
- **Polymorphisms of multiple genes are reported to influence the risk of T1A DM**



- ISPAD Clinical Practice Consensus Guidelines 2018: Definition, epidemiology, and classification of diabetes in children and adolescents. Mayer-Davis EJ, Kahkoska AR, Jefferies C, Dabelea D, Balde N, Gong CX, Aschner P, Craig ME Pediatr Diabetes. 2018;19 Suppl 27:7.
- Age-corrected empirical genetic risk estimates for first-degree relatives of IDDM patients. Tillil H, Köbberling J. Diabetes. 1987;36(1):93.
- Secondary attack rate of type 1 diabetes in Colorado families. Steck AK, Barriga KJ, Emery LM, Fiallo-Scharer RV, Gottlieb PA, Rewers MJ . Diabetes Care. 2005 Feb;28(2):296-300.

ENVIRONMENTAL FACTORS

- **Perinatal factors** such as maternal age >25 years, history of preeclampsia, Neonatal respiratory distress & jaundice.
- **Viral infections**, particularly respiratory or enterovirus infections.
- **Immunizations.**
- **Diet** (Vitamin D & Omega-3 supplements, Nitrates).
- **Vitamin D deficiency.**
- **Higher socioeconomic status.**
- **Obesity.**
- **Low birth weight (Protective)** decreases the risk of developing T1DM, while high birth weight for gestational age & lower gestational age at birth may increase the risk for T1DM.
- **Seasonal variation.**

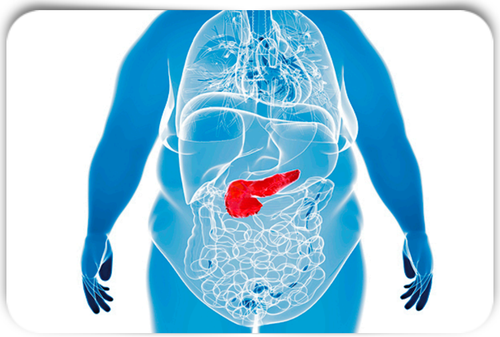
AGENDA:

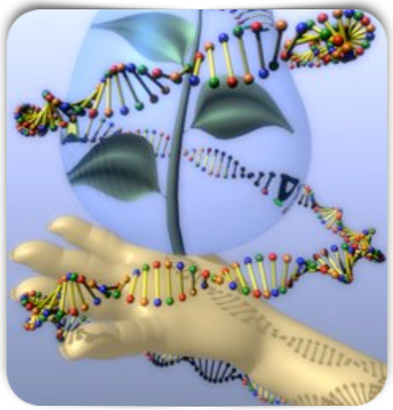
- PREDISPOSING FACTORS T2DM.

WHAT ARE THE FACTORS FOR T2DM??

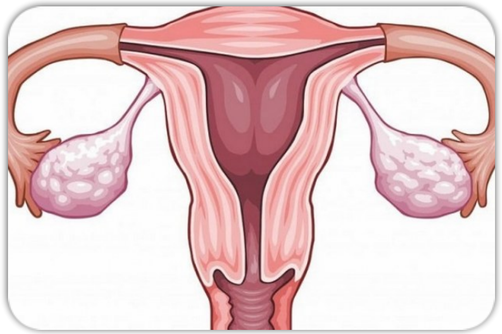
- Age ≥45 years
- Overweight (body mass index [BMI] ≥25 kg/m2); the risk with increased weight is also a continuum, with significantly increased risk for obese individuals (eg, BMI ≥30 kg/m2)
- Diabetes mellitus in a first-degree relative
- Sedentary lifestyle
- High-risk ethnic or racial group (eg, African American, Hispanic, Native American, Asian American, and Pacific Islanders)
- History of gestational diabetes mellitus
- Hypertension (blood pressure ≥140/90 mmHg)
- Dyslipidemia (serum high-density lipoprotein cholesterol concentration ≤35 mg/dL [0.9 mmol/L] and/or serum triglyceride concentration ≥250 mg/dL [2.8 mmol/L])
- A1C ≥5.7 %, impaired glucose tolerance (IGT) or impaired fasting glucose (IFG)
- Polycystic ovary syndrome (PCOS)
- History of vascular disease

WHAT ARE THE FACTORS CHILDHOOD-ONSET T2DM??





- Obesity
- Positive family history
- Specific racial and ethnic groups
- Female gender
- Conditions associated with insulin resistance



AGENDA:

- CLINICAL PRESENTATION OF T1DM

CLINICAL PRESENTATION:

Childhood type 1 diabetes mellitus (T1DM) can present in several different ways:

- **Classic new onset of chronic polydipsia, polyuria, & weight loss with hyperglycemia & ketonemia (or ketonuria)… most common**
- **Diabetic ketoacidosis (DKA)**
- **Silent (asymptomatic) incidental discovery**

Other presentations include:

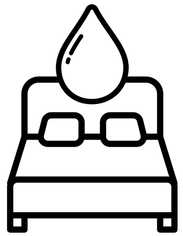
- **perineal candidiasis.**
- **Visual disturbances/cataracts.**

SYMPTOMS OF T1DM

Abnormal thirst and dry mouth

Sudden weight loss

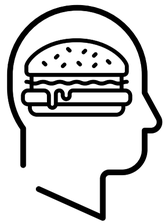
Frequent urination



Bedwetting

Lack of energy, fatigue

Blurred vision



Constant hunger

CLINICAL PRESENTATION:

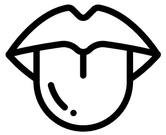
Type 2 diabetes mellitus (T2DM) can present in several different ways & Childhood T2DM can present in several ways:

- **Asymptomatic – Approximately 40 %**
- **Symptomatic (eg, polydipsia & polyuria) without ketonuria or acidosis – 57 -70%**
- **Diabetic ketoacidosis (DKA) – 5-12 %**
- **Hyperosmolar hyperglycemic state (HHS) – Uncommon but serious**

Other presentations include:

- **perineal candidiasis.**
- **Visual disturbances/cataracts.**

SYMPTOMS OF T2DM



Excessive thirst and dry mouth

Frequent and abundant urination

Lack of energy, extreme tiredness

Tingling or numbness
in hands and feet

Recurrent fungal infections
in the skin

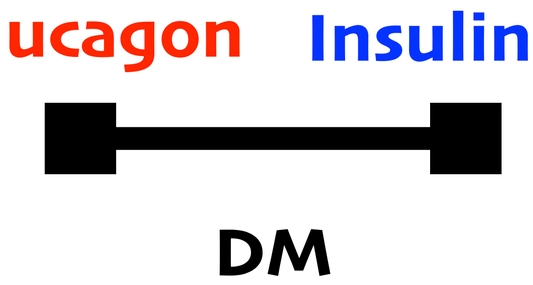
Slow healing wounds

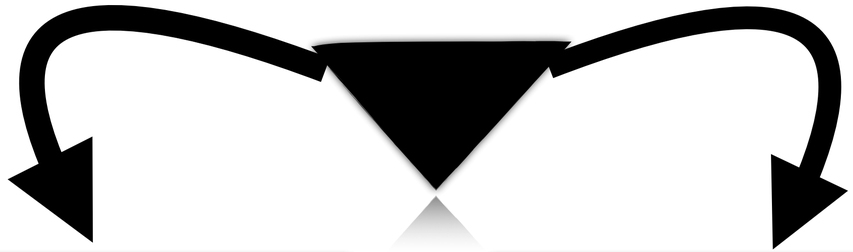
Blurred vision

PATHOGENESIS OF DKA & HONK

Spectrum of metabolic abnormalities:

1-Two hormonal abnormalities are largely responsible for the development of (DKA) & (HONK/HHS) in patients with uncontrolled diabetes:





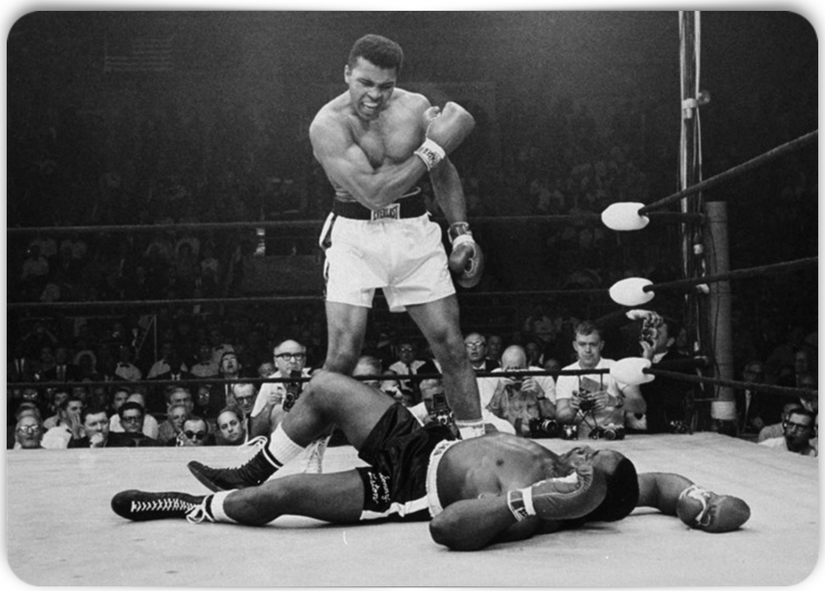
Insulin deficiency &/or resistance.

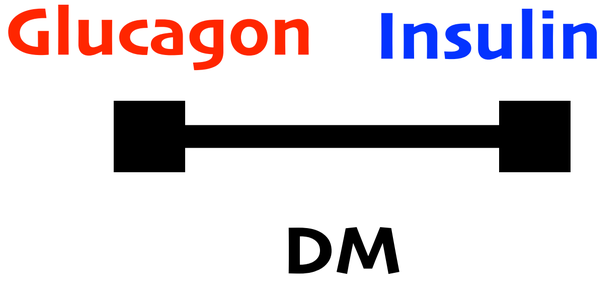
Glucagon excess, which may result from removal of the normal suppressive effect of insulin.

PATHOGENESIS OF DKA & HONK

Spectrum of metabolic abnormalities:

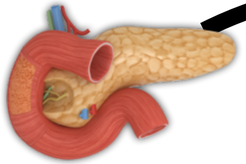
2-Increased secretion of **catecholamines, cortisol, & growth hormone**, which oppose the actions of insulin, also contribute to the increases in glucose & ketoacid production





DKA

Absolute or relative insulin deficiency



Hyperglycemia

Glucoseuria, urinary loss of water & electrolytes

DEHYDRATION & HYPOVOLEMIA → Increased Lactate

counter regulatory hormone, & epinephrine → Acidosis

Glucose uptake

Free Acyl CoA

Acetyl-CoA

Acetoacetyl-CoA

Acetoacetate A

Gluconeogenesis Glycogenolysis

Beta Hydroxybuterate

Acetone

Lipolysis

Triglyceride (TG)

FFA

Glycerol

Proteolysis

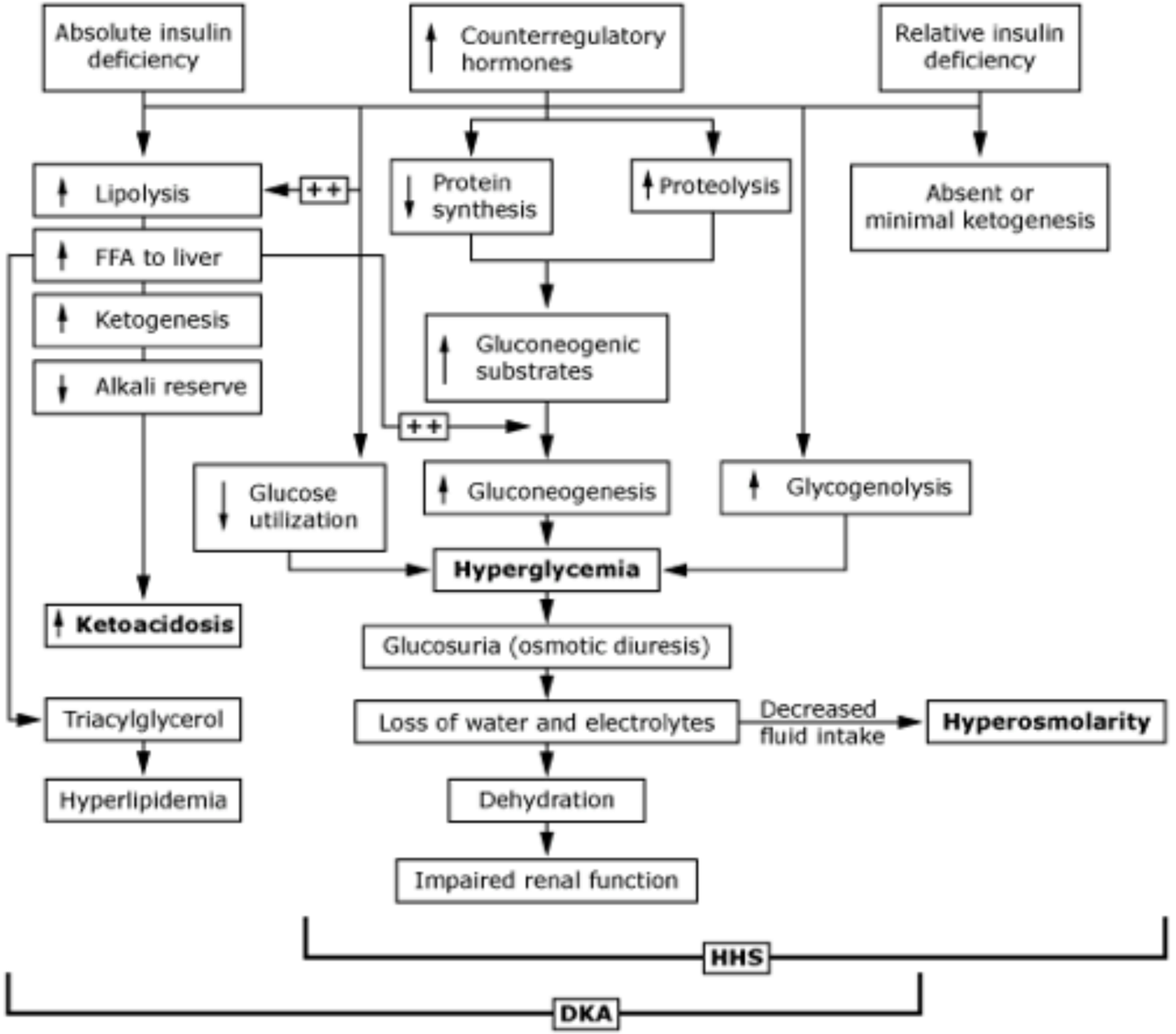
AminoAcids

HYPERGLYCEMIA

ACEDEMIA

KTONEMIA

Pathogenesis of diabetic ketoacidosis and hyperosmolar hyperglycemic state



AGENDA:

- DIAGNOSIS OF DIABETES

DIAGNOSTIC CRITERIA OF DIABETES & PRE-DIABETES

Diagnostic criteria for Diabetes (ADA)	
Fasting (8hours)	>/= 7 mmol/L (126 mg/dl)
OR 2 hours (75 gm OGTT)	>/= 11.1 mmol/L (200 mg/dl)
OR HbA1c	>/= 6.5 %
OR	Clinical symptoms with random glucose of 200 mg/dl

Diagnostic criteria for Pre-Diabetes (ADA)	
IFG: Fasting (8hours)	5.5-6.9 mmol/L (100-125 mg/dl)
IGT: 2 hours (75 gm OGTT)	8-11 mmol/L (144-199 mg/dl)
HbA1c	5.7-6.4 %

COMPARISONST1DM & T2DM

	T1DM	T2DM
Age	45% <10 yrs	>30 yrs, can present in younger
Pathogenesis	Autoimmunity Absolute Insulin reduction, no receptor defect, association with other autoimmune disease	Obesity Insulin resistance (receptor defect), relative insulin reduction
Genetic Susibtability	5-10%	85-90%
Predisposing factors	Genetic, environmental factors	Age, genetic, obesity, metabolic syndrome, smoking, HTN, PCOS..
Body hapitus & Clinical presentation	Thin, rapid progression symptoms, DKA, over weeks to month	Obese, asymptomatic, or gradual symptoms of hyperglycemia over years, Neuropathy can be first presentation
Treatment	Insulin	Insulin, Non Insulin therapy

DIABETES MELLITUS

(T1DM, T2DM)

(Management of DM & guidelines)

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Clinical Assistant Professor of Medicine

Consultant Endocrinologist & Diabetes

Endocrine & Diabetes Division - IM Department at KKUH, KSUMC

PHARMACOTHERAPY IN DIABETES MANAGEMENT

- INSULIN
- NON-INSULIN

WHEN & WHICH PATIENTS NEED INSULIN?

Type 1 DM	**Autoimmune islet-cell injury that eventually leads to virtually complete insulin deficiency**
Type 2 DM	**Both insulin resistance & relative insulin deficiency, consider in severe persistent hyperglycemia, patient with symptoms of weight loss as initial therapy.**
Atypical presentation	**Occasionally difficult to distinguish between type 1 & atypical presentations of type 2 diabetes (LADA)**
Pancreatic Insufficiency	**Secondary diabetes due to pancreatic insufficiency, including from cystic fibrosis, chronic pancreatitis, or after pancreatectomy.**

MANAGEMENT IN T1DM

- **THE MAINSTAY OF TREATMENT FOR T1DM** is Insulin.

- **THE GOAL OF INSULIN THERAPY** is to replace the deficient hormone & to attain normoglycemia.

- The acute & chronic complications of diabetes are attributable to the failure of exogenous insulin to completely mimic physiologic insulin secretion.

- There are many different insulin preparations & delivery systems available. The selected regimen is individualized for the child & family to fit their lifestyle & optimize compliance while providing glycemic control.

HISTORY OF INSULIN DEVELOPMENT OVER THE LAST 100 YEARS

First clinical use of insulin 1922

Short acting

Biosynthetic human insulin 1982

Rapid-acting insulin analogue 1996

2006 Exubera inhaled insulin (withdrawn 2007)

Afrezza inhaled insulin 2015

Rapid acting

Fast-acting insulin aspart

Recombinant insulin plus hyaluronidase

Recombinant insulin plus EDTA

BioChaperone lispro

1920 1940 1960 1980 2000 2014 2015 Future

1950 NPH insulin

1953 Lente insulin

2000 Long-acting insulin analogue

2013 Degludec

2014 Biosimilar glargine insulin

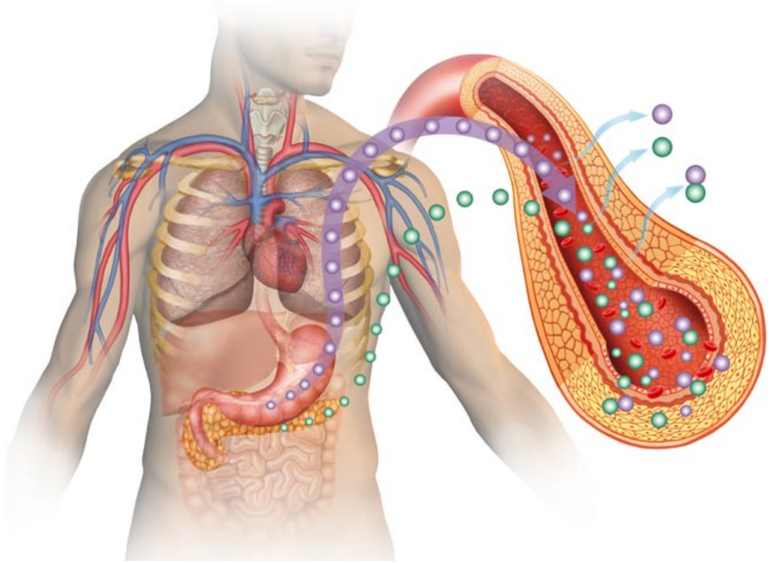
Glargine U300

PEGylated insulin

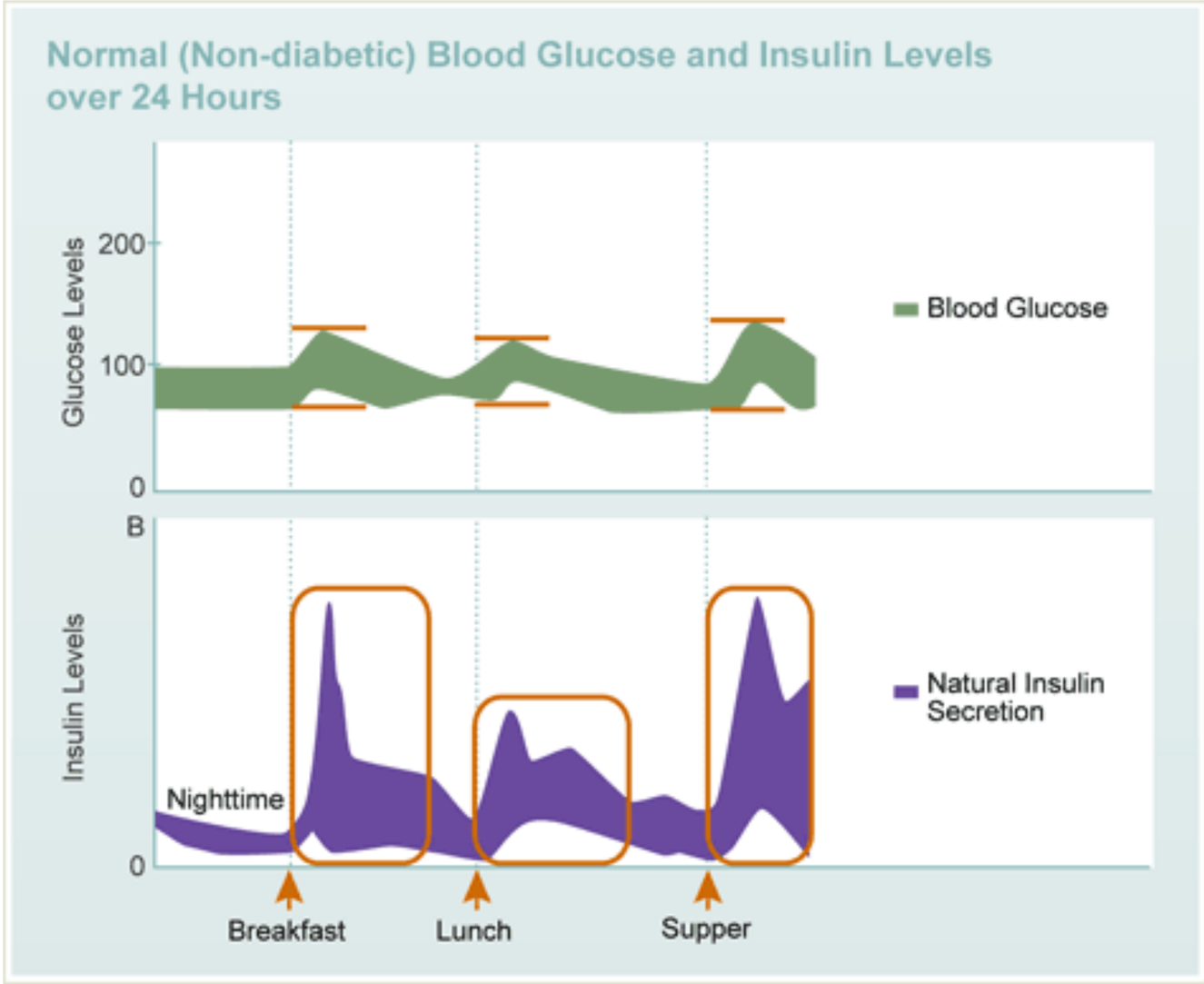
Smart insulin

Long acting

NATURAL INSULIN & BLOOD GLUCOSE LEVELS OVER 24 HOURS

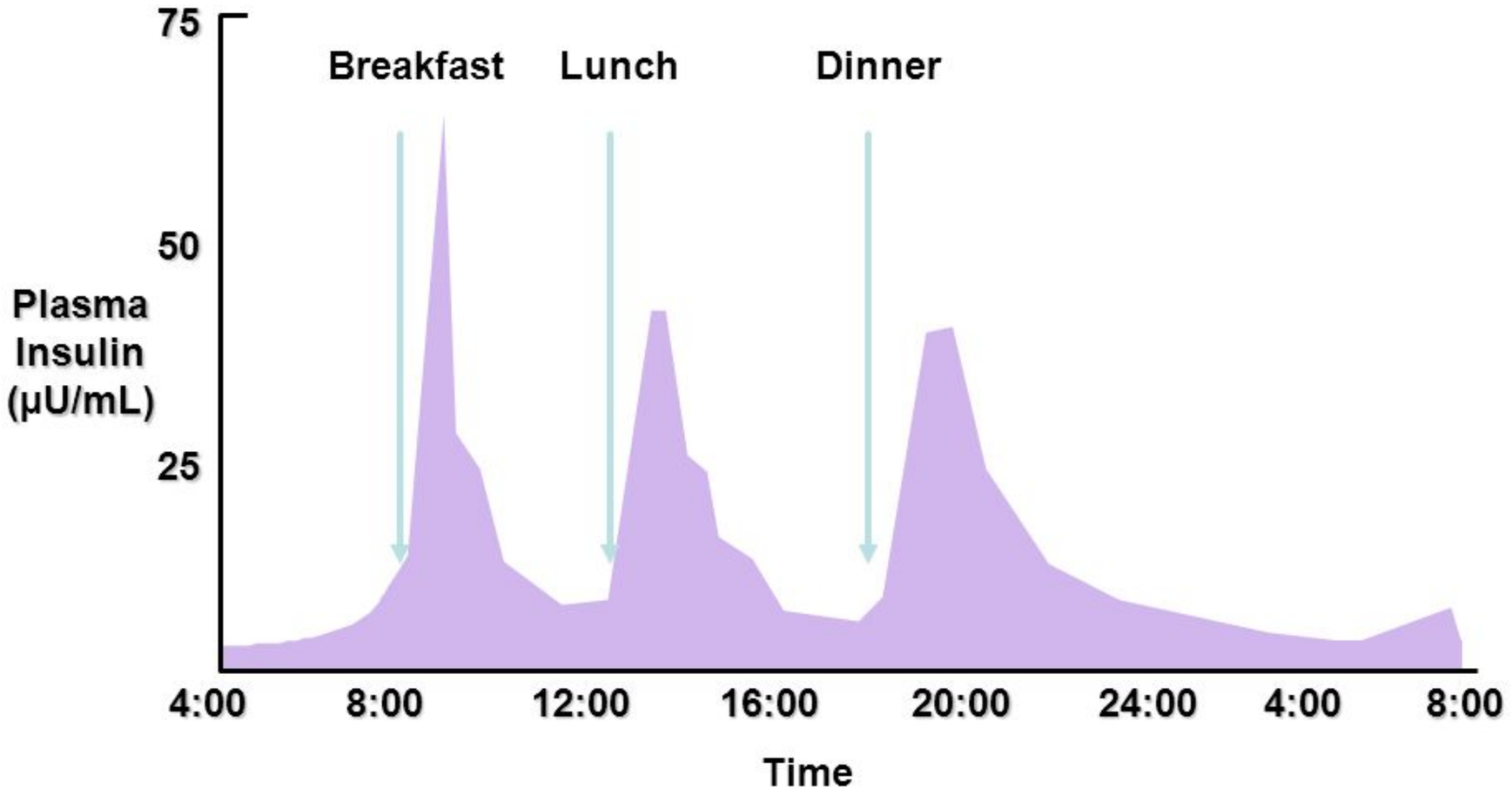


To keep the blood glucose in a narrow range throughout the day, there is a low steady secretion of insulin overnight, fasting & between meals with spikes of insulin at mealtimes.



Adapted: Jacobs DM Care 20:1279, 1997

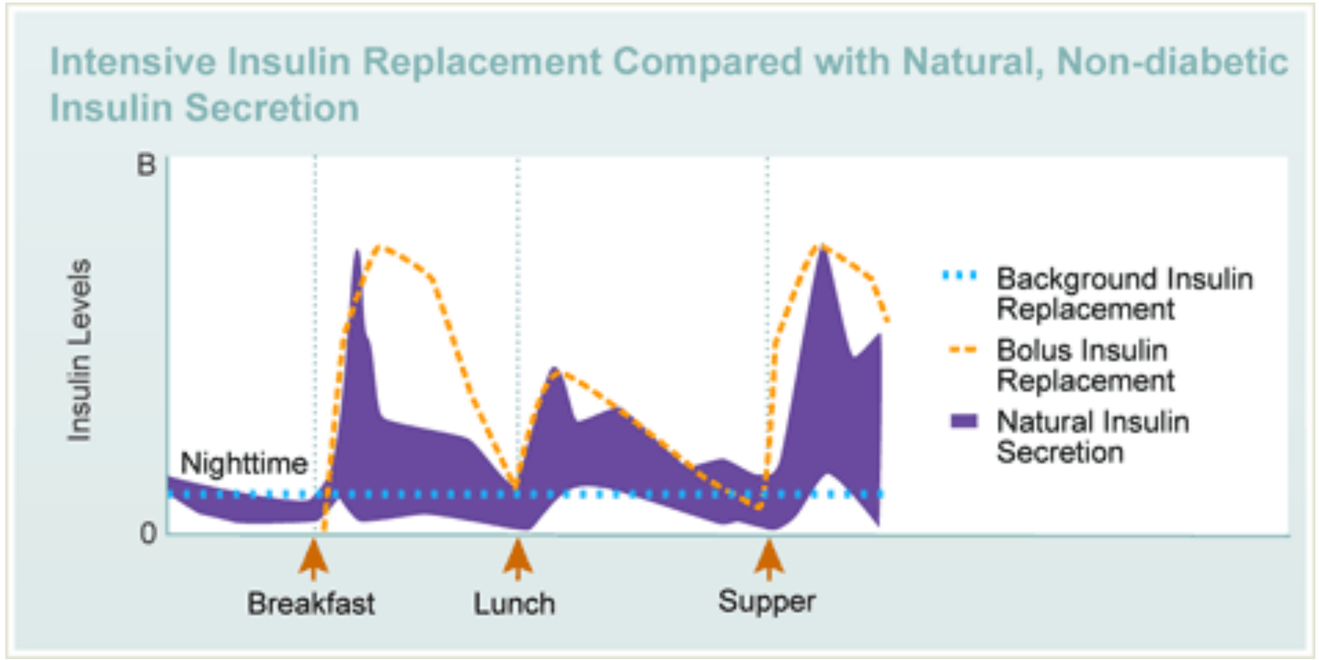
PHYSIOLOGIC BLOOD INSULIN SECRETION PROFILE



Adapted from White JR, Campbell RK, Hirsch I. Postgraduate Medicine. June 2003;113(6):30-36.

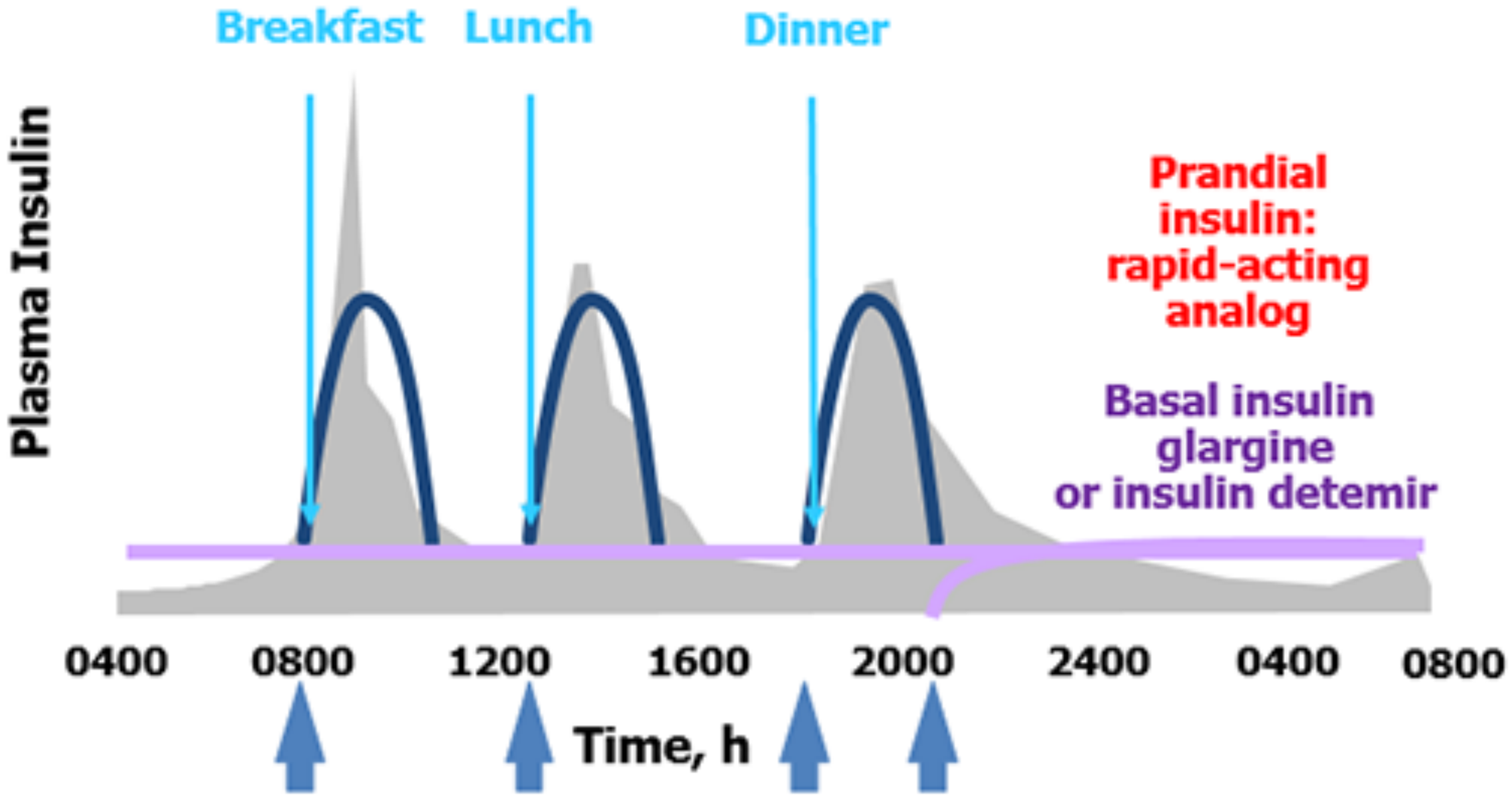
(MDI) INTENSIVE INSULIN REPLACEMENT COMPARED TO NATURAL INSULIN SECRETION

Intensive insulin therapy tries to duplicate the body's natural pattern of insulin secretion. With intensive insulin therapy, a low steady level of insulin overnight, fasting, between meals, & a rapid surge of insulin at mealtime are needed.



Adapted: Jacobs DM Care 20:1279, 1997

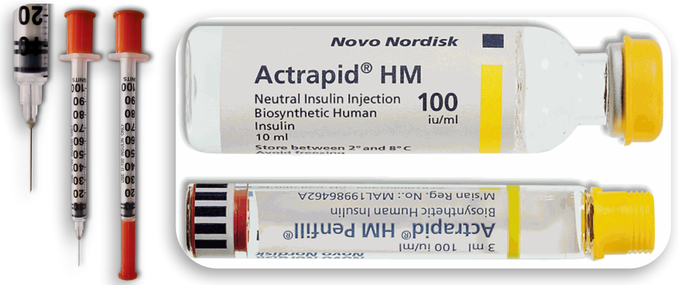
MIMICKING NORMAL PHYSIOLOGY WITH BASAL-BOLUS INSULIN



INSULIN PREPARATIONS

OLD CLASSES HUMAN INSULIN

Short acting Insulin 4-6 hours



Intermediate acting Insulin 10-18 hours

Mixed Insulin

(GLP-1) Non-Insulin Injection (GLP1)

Exinatide

Liraglutide

Dulaglutide

Lixisenatide

Semagutide

Oral Semagutide

COMBINATION OF INSULIN & (GLP-1)

Insulin Deludec

TRESIBA®
insulin degludec injection 100 U/mL, 200 U/mL

VICTOZA®
liraglutide injection 1.2 mg | 1.8 mg

Liraglutide

Insulin therapy

Non-Insulin therapy (GLP1)

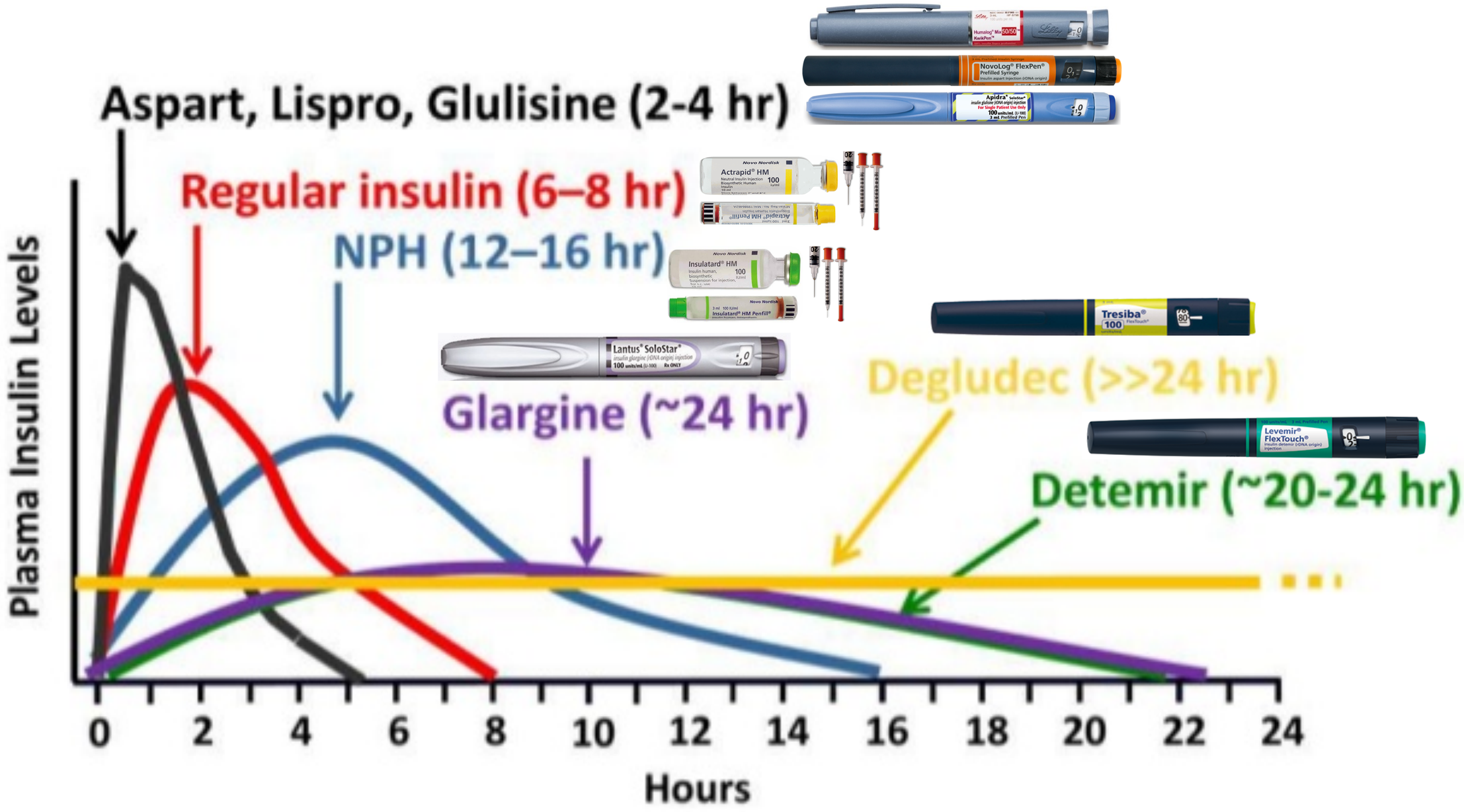

Aspart, Lispro, Glulisine (2-4 hr)
Regular insulin (6–8 hr)
NPH (12–16 hr)
Glargine (~24 hr)
Degludec (>>24 hr)
Detemir (~20-24 hr)
Plasma Insulin Levels
0
2
4
6
8
10
12
14
16
18
20
22
24
Hours
Humalog® Mix 50/50 KwikPen™
NovoLog® FlexPen® Prefilled Syringe
Apidra® SoloStar®
Actrapid® HM
Insulatard® HM
Insulatard® HM Penfill®
Lantus® SoloStar®
Tresiba® 100 FlexTouch®
Levemir® FlexTouch®

TABLE OF INSULIN ACTION

Type of Insulin	Onset	Peak	Duration of action	Appearance
Fast-acting				
Regular U-100 (Novolin R, Humulin R)	30-60 min.	2-4 hr.	6-10 hr.	clear
Regular U-500	30-60 min.	2-4 hr.	Up to 24 hr.	clear
Lispro (Humalog)/ Aspart (Novolog)/ Glulisine (Apidra)	<15 min.	1-2 hr.	4-6 hr.	clear
Intermediate-acting				
NPH	1-2 hr.	6-10 hr.	10-18 hr.	cloudy
Long-acting				
Detemir (Levemir)	1 hr.	Flat, Max effect in 5 hrs.	12-24 hr.	clear
Glargine 1U-100 (Lantus)	1.5 hr.	Flat, Max effect in 5 hrs.	24 hr.	clear
Glargin U-300 (Togueo)	6 hr.	No significant peak	24 hr.	clear
Degludec U-100 U-200 (Trisiba)	1-4 hr.	No significant peak	24 hr.	clear
Afrezza	<15 min	Approx. 50 min.	2-3 hr.	—-

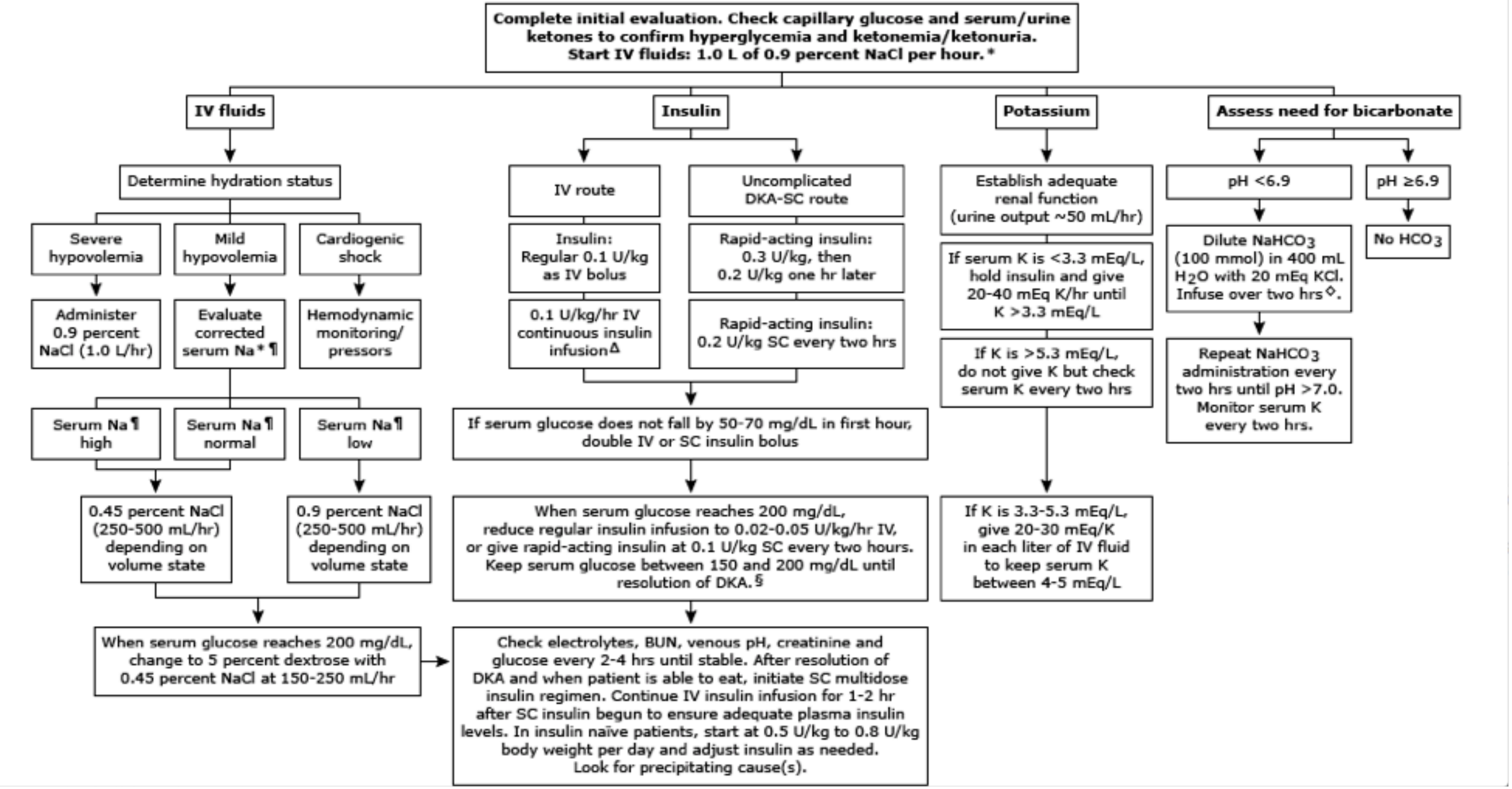
INSULIN ADMINISTRATION

Emergent diabetic ketoacidosis (DKA) management in adults: Rapid overview

Clinical features
DKA usually evolves rapidly over a 24-hour period.
Common, early signs of ketoacidosis include nausea, vomiting, abdominal pain, and hyperventilation. The earliest symptoms of marked hyperglycemia are polyuria, polydipsia, and weight loss.
As hyperglycemia worsens, neurologic symptoms appear and may progress to include lethargy, focal deficits, obtundation, seizure, and coma.
Common causes of DKA include: infection; noncompliance, inappropriate adjustment, or cessation of insulin; new-onset diabetes mellitus; and myocardial ischemia.

TREATMENT OF DKA

Protocol for the management of adult patients with DKA



T1DM POST DKA

Patient young presented with DKA, or hyperglycemia with symptoms

Treat DKA & hyperglycemia with IV insulin

Overlap Insulin Infusion with Subcutaneous Insulin 30-60 min

TDD: 0.4-1 Unit/Kg/day for newly diagnosed patients, & previous dose for well controlled T1DM
& dose adjustment for uncontrolled previously

Basal Insulin: (40-50%)
- Degludec once
- (Glargine, Detemir, NPH) once or twice

Bolus Insulin:
- Rapid acting (Aspart, Lisipro, Glulisine) pre-meals
- Short acting (HRI) pre-meals

- Fasting hyperglycemia consider adjustment of evening dose
- Prandial hyperglycemia through Carbs counting or prandial adjustment

- Target FBG: 80-140 mg/dl (4.7-7.2 mmol/L)
- HbA1c <7%

DESIGNING INSULIN REGIMEN

Safety

Humen Insulin **OR** Insulin Analogues

Efficacy

Cost effectiveness

MDI (Multidoses Insulin) **OR** CSII (Continues Subcutaneous Insulin Infusion)

Patient needs & Type of DM

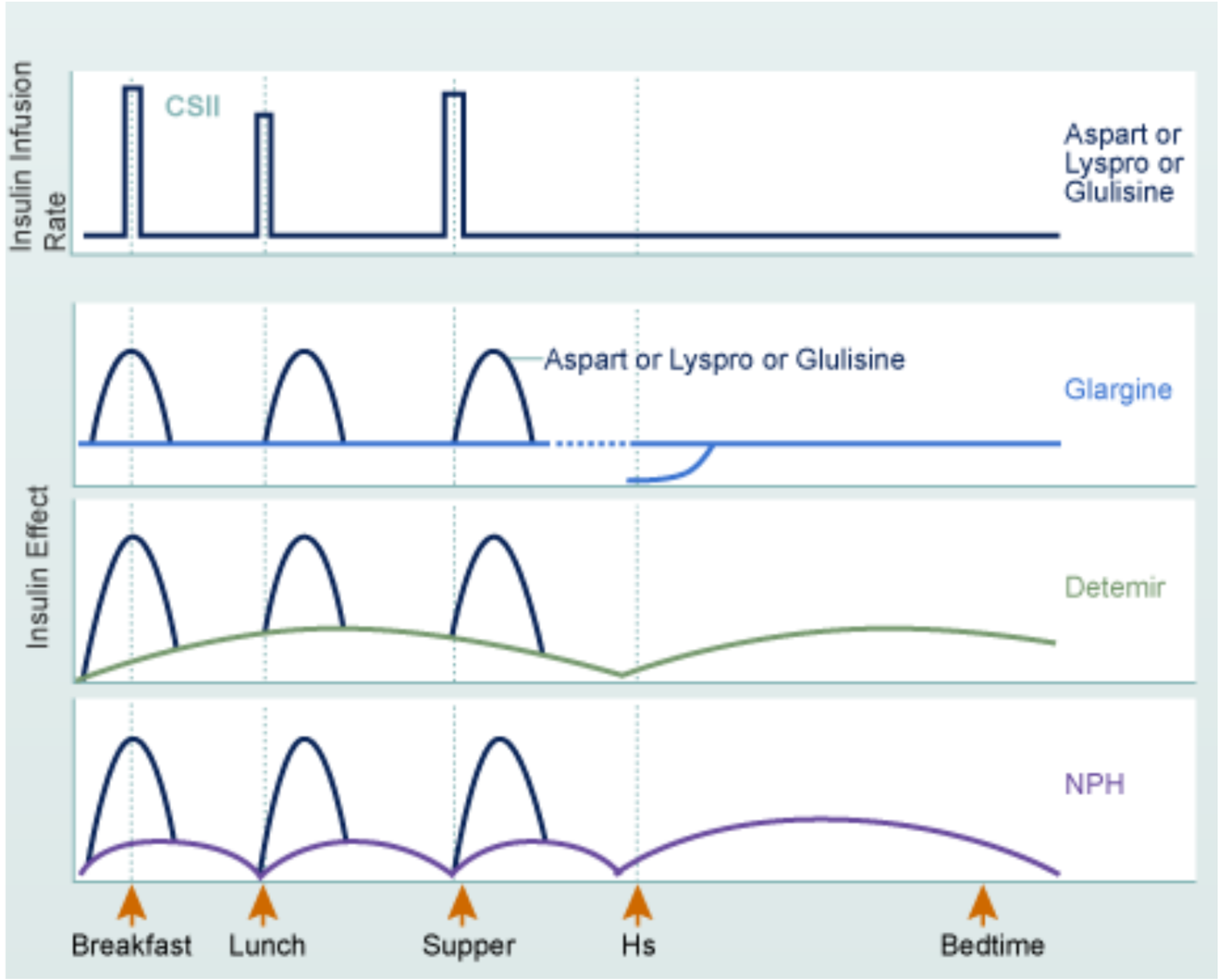
SE: Servere hypoglycemia

SE: weight gain

COMMON INTENSIVE REGIMENS FOR TYPE 1 DIABETES

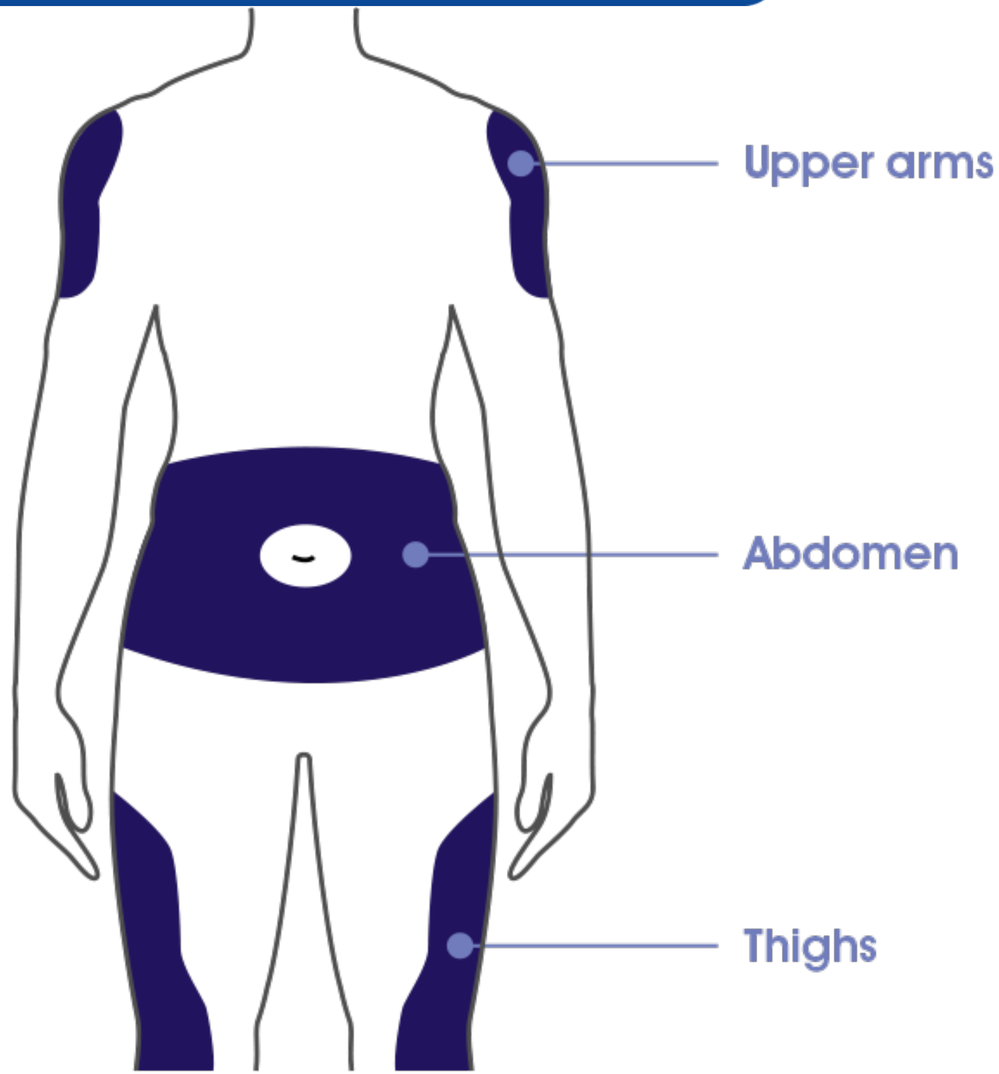
Intensive insulin therapy requires:

- Multiple daily injections of insulin (MDI)
- Insulin pump therapy (CSII)



Adapted: Jacobs DM Care 20:1279, 1997

SITE OF INJECTIONS



INSULIN SIDE EFFECTS

SIDE EFFECTS OF INSULIN

- Weight gain
- Hypoglycemia

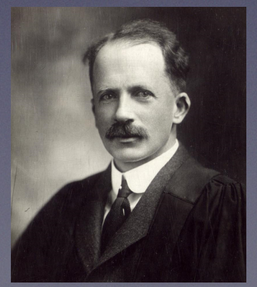
MANAGEMENT IN T2DM

HISTORY OF ANTI-HYPERGLYCEMIC MEDICATIONS OVER THE LAST 100 YEARS

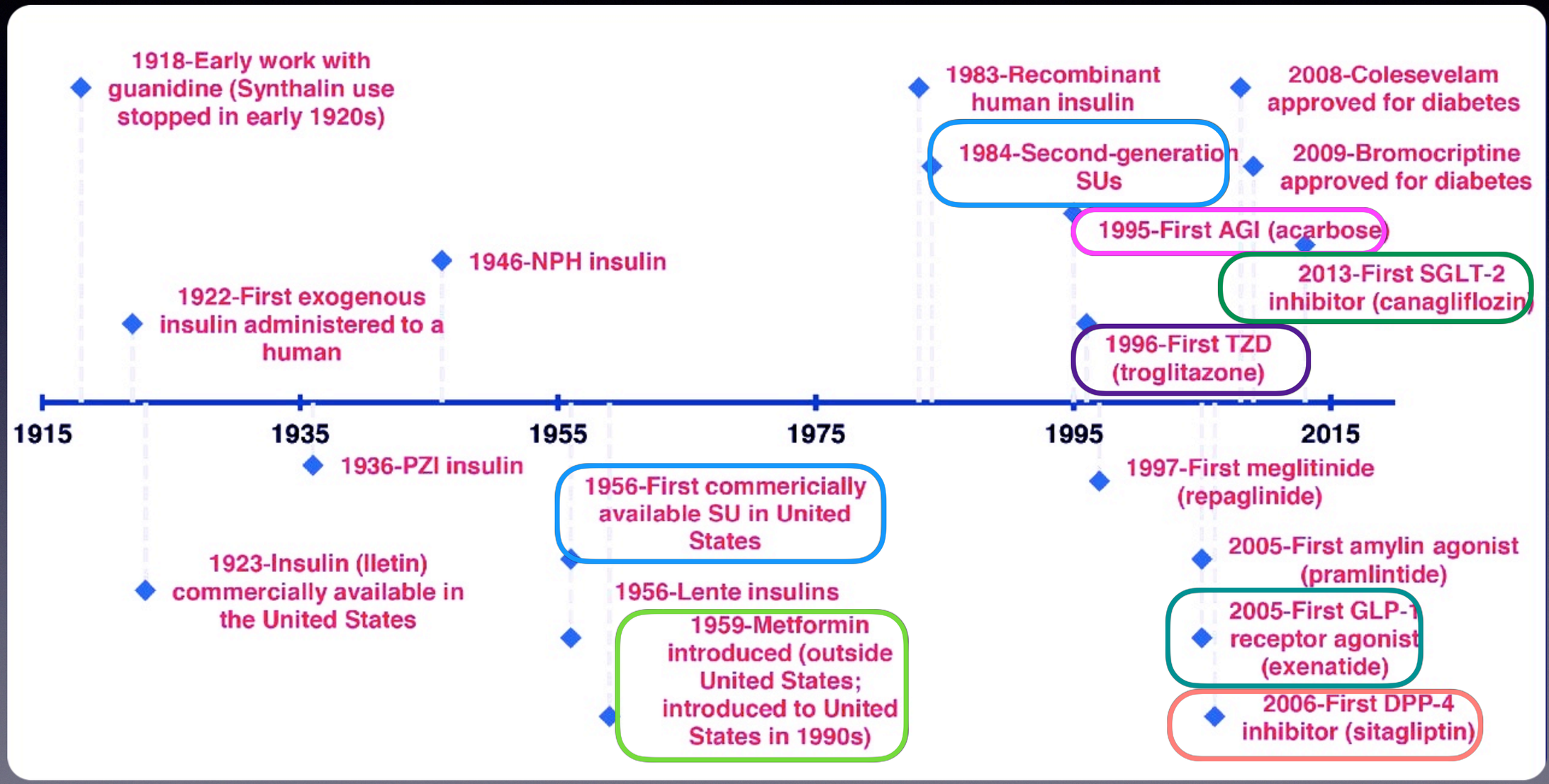
1774, Mathew Dobson

1988, Joseph von Mering

1922, Sir Frederick Grant Banting



1923, John Macleod



- **THE TREATMENT FOR T2DM** is Non Insulin or Insulin.

- **THE GOAL OF THERAPY** is to attain normoglycemia & Cardiovascular risk factor management.

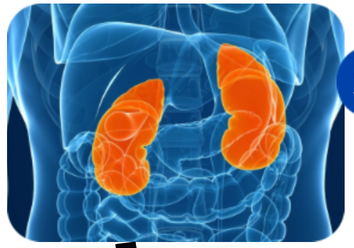
NON-INSULIN PHARMACOTHERAPY FOR T2DM

AHA

MECHANISM OF ACTION OF OHA CLASSES

NEW CLASSES

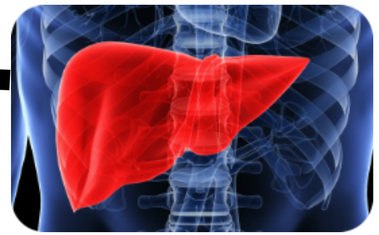
OLD CLASSES



Empagliflozin
Canagliflozin
Dapagliflozin
Sotagliflusine

SGLT2 inh.

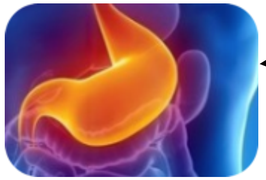
Decrease glucose reabsorption



Bigunide
TZDs

Metformin

dec hepatic production for glucose



Incritin Hormones

DDP-4 Inh.
GLP-1

Dec. Glucose

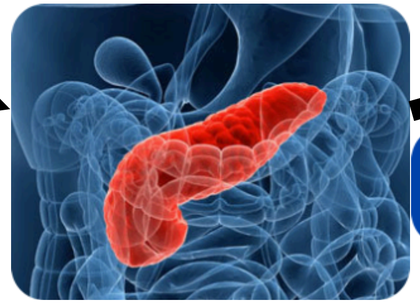
Alpha Gucosidase Inh.

Glucobay

dec glucose absorption

Sitagliptin
Linagliptin
Vildagliptin
Saxagliptin

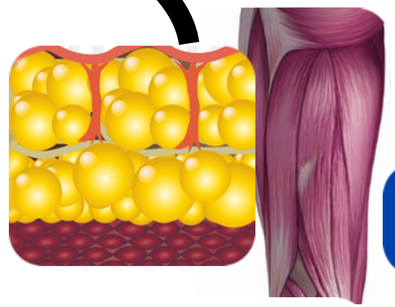
Exenetide
Liraglutide
Dulaglutide
Semaglutide



inc insulin secretion
dec glucagone secretion

SUs
Metaglinides

Gliclazide
Glyburide(glibenclamide)
Repaglinide



inc peripheral glucose uptake

TZDs
Bigunide

Bioglitazone
Rosiglitazone

EFFICACY OF HYPOGLYCEMIC AGENTS (OLD & NEW)

Clinical Efficacy of Oral Hypoglycemic Agents

Class of hypoglycemic agents	*Reduction in HbA_{1c} (%)*	*Reduction in FPG (mg per dl)*
Sulfonylureas	0.8 to 2.0	60 to 70
Meglitinides	0.5 to 2.0	65 to 75
Biguanides	1.5 to 2.0	50 to 70
Thiazolidinediones	0.5 to 1.5	25 to 50
Alpha-glucosidase inhibitors	0.7 to 1.0	35 to 40
DPP-4 inhibitor	0.5 to 0.9	20 to 30
SGLT-2 Inhibitor	0.4 to 0.67	15 to 20
GLP-1 Agonist	0.7-1.8	35 to 65

SIDE EFFECTS OF AHA CLASSES

GI upset

- Bigunide
- Alpha Gucosidase Inh.
- ~~DDP-4 Inh.~~ GLP-1

Weight Gain

- TZDs
- SUs Metaglinides

Fluid retention

- TZDs

UTI, Gentalian infection Risk of DKA

- SGLT2 inh.

Risk of Heart Failure

- DDP-4 Inh. (Sexagliptin)

Risk of re-ambutation

- SGLT2 inh. (Canagliflosin)

Risk of Sinusitis

- DDP-4 Inh. ~~GLP-1~~

Risk of fracture

- TZDs
- SGLT2 inh. (Canagliflosin)

Hypoglycemia

- SUs Metaglinides

Risk of MI

- TZDs (Rosiglitazon)

BEYOND GLYCEMIC BENEFIT OF AHA CLASSES

Weight Reduction

Cardiovascular benefit

~~DDP-4 Inh.~~
GLP-1

SGLT2 inh.

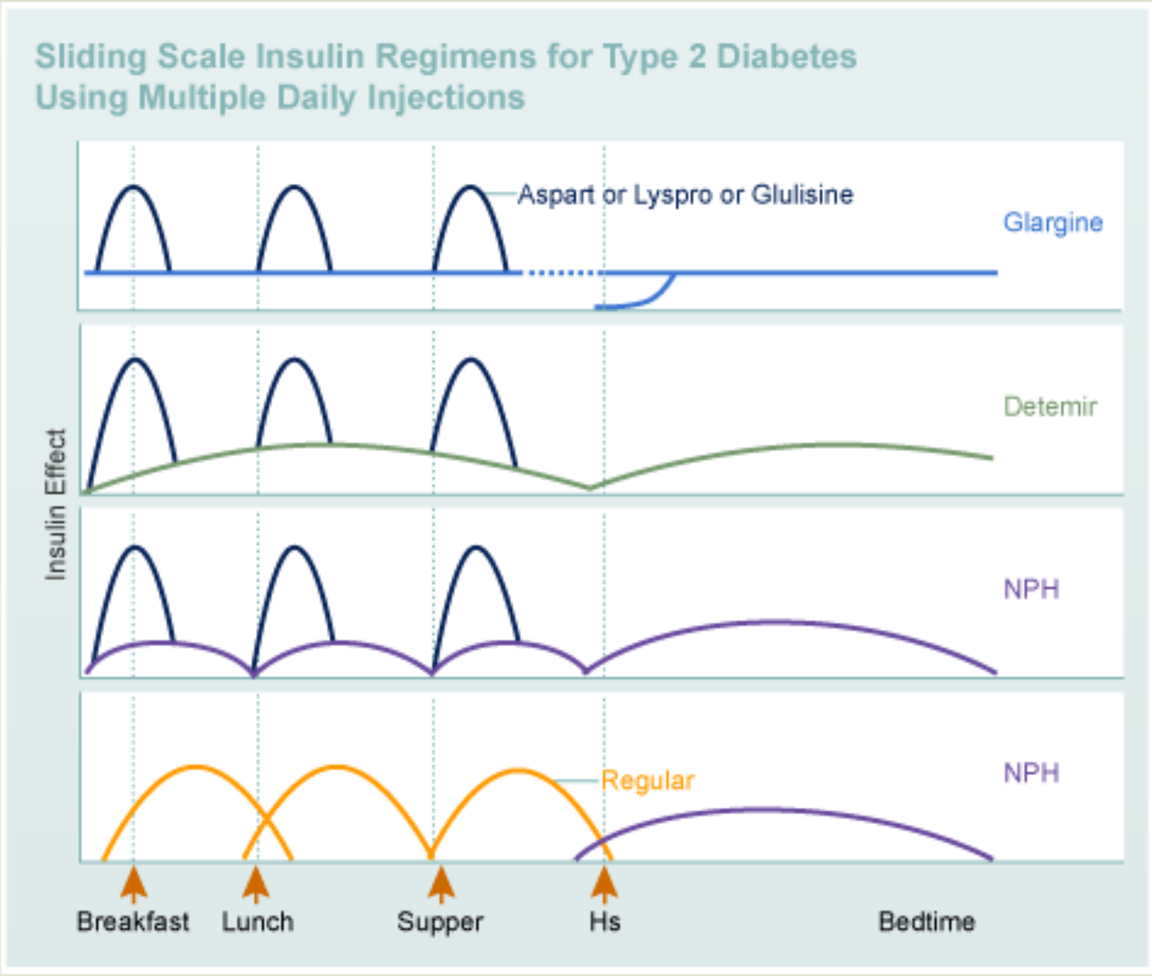
INSULIN PHARMACOTHERAPY FOR T2DM

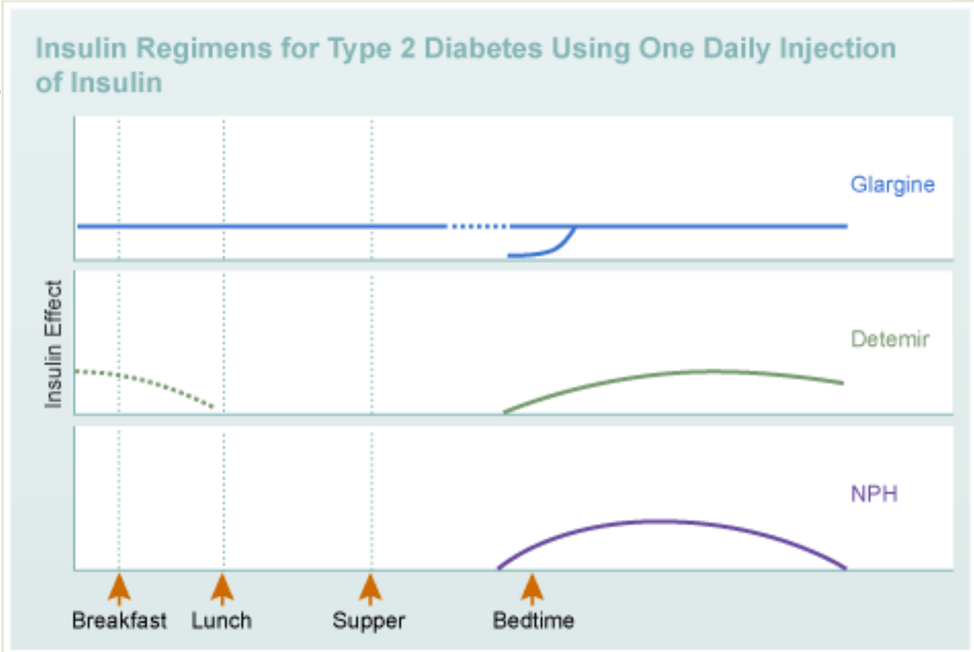
COMMON INTENSIVE REGIMENS FOR TYPE 2 DIABETES

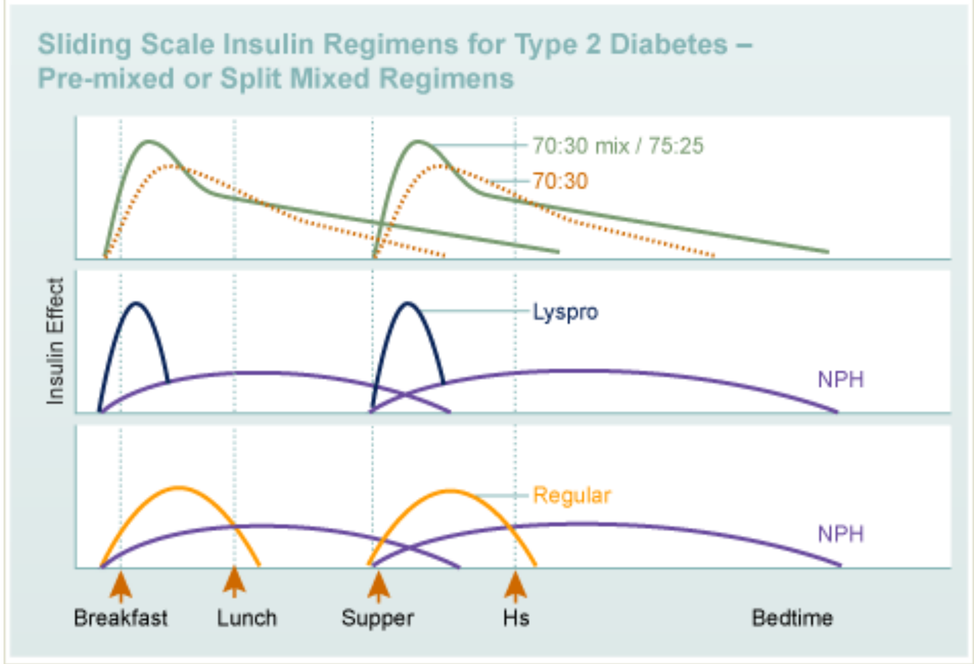
Intensive insulin therapy:

- Multiple daily injections of insulin (MDI)

Adapted: Jacobs DM Care 20:1279, 1997



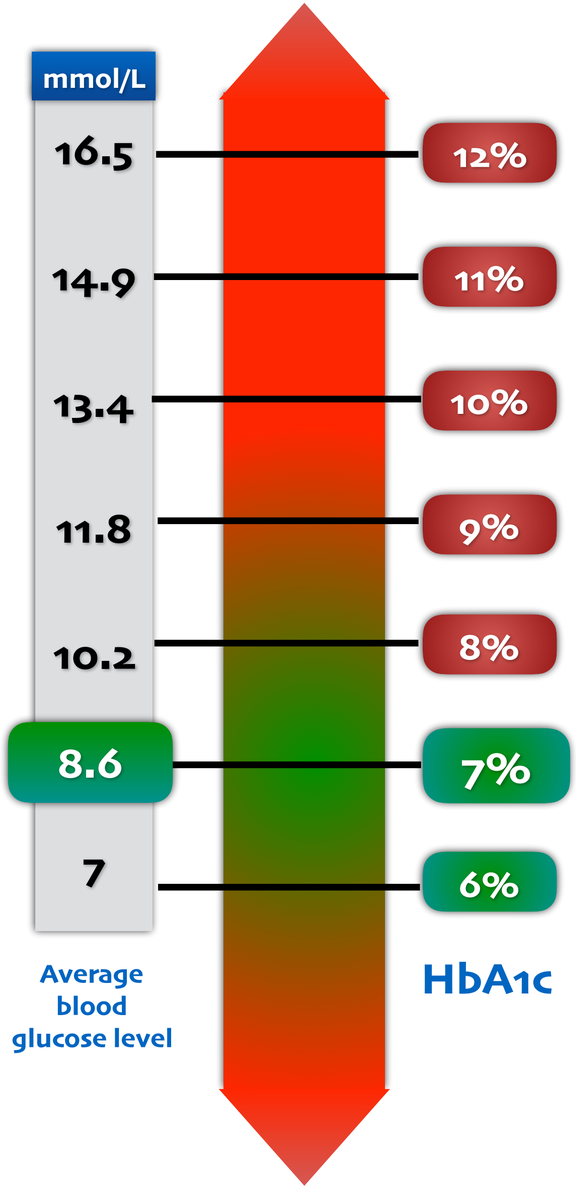




NON-PHARMACOTHERAPY FOR DIABETES MANAGEMENT

GLUCOSE MONITOR

CORRELATION OF HBA1C WITH AVERAGE GLUCOSE



LIFE STYLE MODIFICATIONS

Healthy Diet

Exercise

Blood Pressure control

Smoking cessation

Lipids control

PATIENT EDUCATION

GUIDELINES FOR DM MANAGEMENT

T2DM

American Diabetes Association® 2018

Antihyperglycemic Therapy in Adults with Type 2 Diabetes

At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:

- A1C is less than 9%, **consider Monotherapy.**
- A1C is greater than or equal to 9%, **consider Dual Therapy.**
- A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Lifestyle Management + Metformin

Initiate metformin therapy if no contraindications* (See Table 8.1)

A1C at target after 3 months of monotherapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Dual Therapy

Dual Therapy — Lifestyle Management + Metformin + Additional Agent

ASCVD?

Yes: - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**)

No: - Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

A1C at target after 3 months of dual therapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Triple Therapy

Triple Therapy — Lifestyle Management + Metformin + Two Additional Agents

Add third agent based on drug-specific effects and patient factors# (See Table 8.1)

A1C at target after 3 months of triple therapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Combination Injectable Therapy (See Figure 8.2)

Combination Injectable Therapy (See Figure 8.2)

T2DM

American Diabetes Association® 2018

Initiate Basal Insulin

Usually with metformin +/- other noninsulin agent

Start: 10 U/day or 0.1–0.2 U/kg/day

Adjust: 10–15% or 2–4 units once or twice weekly to reach FBG target

For hypo: Determine & address cause; if no clear reason for hypo, ↓ dose by 4 units or 10–20%

If A1C not controlled, **consider combination injectable therapy**

Combination injectable therapy for type 2 diabetes.
FBG, fasting blood glucose; hypo, hypoglycemia.

Add 1 rapid-acting insulin injection before largest meal

Start: 4 units, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ↓ basal by same amount

Adjust: ↑ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached

For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

If A1C not controlled, **advance to basal-bolus**

Add ≥2 rapid-acting insulin injections before meals ('basal-bolus')

Start: 4 units, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider ↓ basal by same amount

Adjust: ↑ dose(s) by 1–2 units or 10–15% once or twice weekly to achieve SMBG target

For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

Add GLP-1 RA

If not tolerated or A1C target not reached, change to 2 injection insulin regimen

If goals not met, **consider changing to alternative insulin regimen**

If goals not met, **consider changing to alternative insulin regimen**

Change to premixed insulin twice daily (before breakfast and supper)

Start: Divide current basal dose into ⅔ AM, ⅓ PM or ½ AM, ½ PM

Adjust: ↑ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached

For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

If A1C not controlled, **advance to 3rd injection**

Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)

Start: Add additional injection before lunch

Adjust: ↑ doses by 1–2 units or 10–15% once or twice weekly to achieve SMBG target

For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

FIRST-LINE therapy is metformin and comprehensive lifestyle (including weight management and physical activity) if HbA_{1c} above target proceed as below

American Diabetes Association® 2018

NO

ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

EITHER/ OR

- GLP-1 RA with proven CVD benefit[1]
- SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

If HbA_{1c} above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin[4]
- TZD[5]
- SU[6]

HF OR CKD PREDOMINATES

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]

If HbA_{1c} above target

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[4]
- SU[6]

WITHOUT ESTABLISHED ASCVD OR CKD

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i	GLP-1 RA	SGLT2i[2]	TZD
If HbA_{1c} above target			
SGLT2i[2] **OR** TZD	SGLT2i[2] **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i[2] **OR** DPP-4i **OR** GLP-1 RA

If HbA_{1c} above target

Continue with addition of other agents as outlined above

If HbA_{1c} above target

Consider the addition of SU[6] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia[7]

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

EITHER/ OR

- GLP-1 RA with good efficacy for weight loss[8]
- SGLT2i[2]

If HbA_{1c} above target

- SGLT2i[2]
- GLP-1 RA with good efficacy for weight loss[8]

If HbA_{1c} above target

If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

• SU[6] • TZD[5] • Basal insulin

COST IS A MAJOR ISSUE[9-10]

- SU[6]
- TZD[10]

If HbA_{1c} above target

- TZD[10]
- SU[6]

If HbA_{1c} above target

- **Insulin therapy** basal insulin with lowest acquisition cost

OR

- Consider DPP-4i **OR** SGLT2i with lowest acquisition cost[10]

THANK YOU

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