University of Rome “Tor Vergata”

Physical Activity & Health Promotion

2020/2021

Diabetes Mellitus

Dr.ssa Katia Andreadi

Diabetes Mellitus (DM)

DM eventually → microvascular and macrovascular complications

–Microvascular: retinopathy, nephropathy, and peripheral neuropathy
–Macrovascular: coronary heart disease (CHD), stroke, and peripheral vascular disease (PVD)

Glucose Contributions to HbA_{1c}

HbA_{1c} =

Fasting Glucose,
Influenced by:

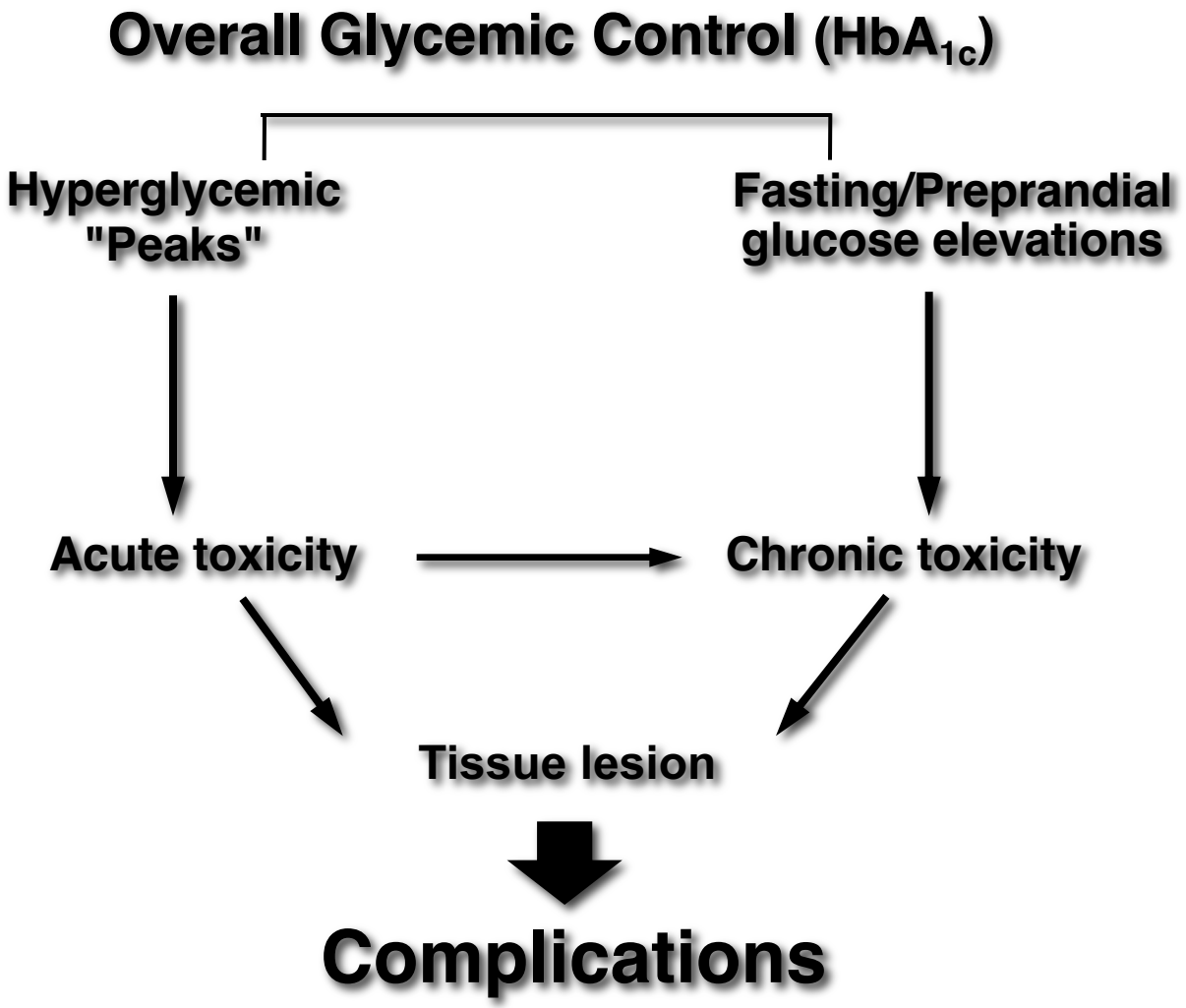
- **Hepatic glucose production**
- **Hepatic sensitivity to insulin**

+

Postprandial Glucose,
Influenced by:

- **Preprandial glucose**
- **Glucose load from meal**
- **Insulin secretion**
- **Insulin sensitivity in peripheral tissues and liver**

Possible Pathogenesis of Diabetic Complications



Type 1 Diabetes

Absolute deficiency in insulin
β-cell destruction

Type 1 Diabetes Mellitus

- Characterized by absolute insulin deficiency
- Pathophysiology and etiology
  - Result of pancreatic beta cell destruction
    - Prone to ketosis
  - Total deficit of circulating insulin
  - Autoimmune
  - Idiopathic

Pathogenesis of Type 1 diabetes.

Autoimmune Type 1 Diabetes

- Beta cells destroyed via autoimmune mechanism.
- Genetically predisposed people:triggering factor = production of islet cell Ab.
- Islet cell Ab destroy Beta cells.
- Insulin production decreases.

Pathogenesis of Type 1 diabetes.

Autoimmune Type 1 Diabetes

- Viruses + other environmental agents have been shown to be **triggering factors**.
- Viruses can damage beta cells by:

  1. Direct invasion.
  2. Triggering an autoimmune response.

Pathogenesis of Type 1 diabetes.

Autoimmune Type 1 Diabetes

- Implicated viruses:

  mumps, intrauterine rubella, coxsackie B virus, echo virus, gytomegalo virus and herpes virus.

- Chemical substances that reduce diabetes:

  alloxan, streptozotosin and dietary nitroamides.

Pathogenesis of Type 1 diabetes.

Idiopathic Type 1 Diabetes

- No known aetiology.
- Permanent insulinopaenia.
- This form is strongly inherited.
- Not HLA associated.

Epidemiology

- **Average onset is in childhood or early adulthood (usually before 30 years of age)**

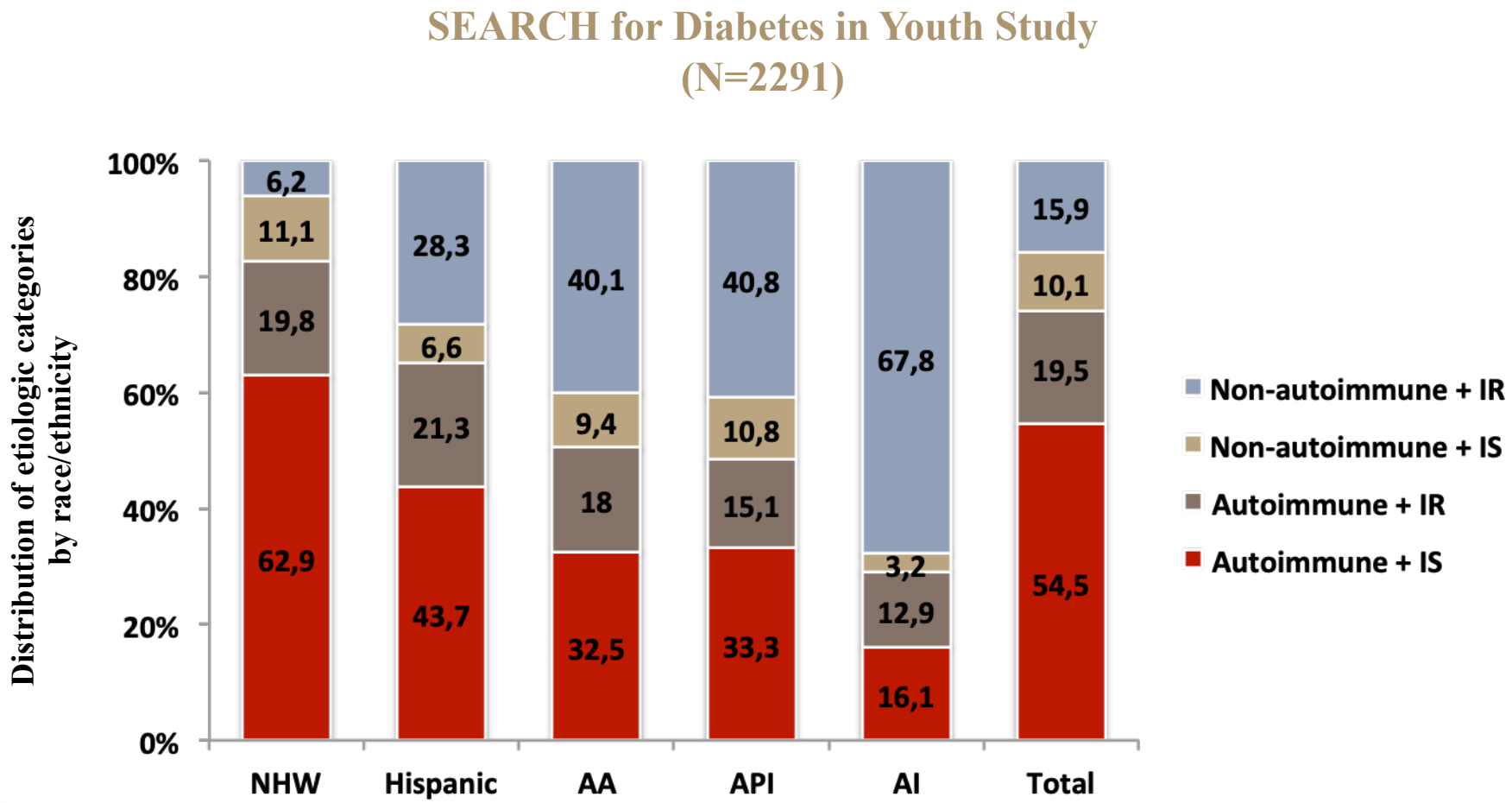
- **Characterized by autoimmune destruction of pancreatic β-cells → absolute insulin deficiency**

- **Patients dependent on exogenous insulin**

Incidence of Type 1 diabetes

- ✓ Incidence peaks at 11-13 years.
- ✓ Seasonal variation: lowest rates in spring and summer.
- ✓ Geographical variation: Japan has a very low incidence.
- ✓ 10% of Type 1 diabetics are over 65 years of age.

Type of Diabetes in Youth by Race/Ethnicity and Etiology



AA, African American; AI, American Indian; API, Asian/Pacific Islander; IR, insulin resistant; IS, insulin sensitive; NHW, non-Hispanic white.

Dabelea D, et al. *Diabetes Care*. 2011;34:1628-1633.

Pathophysiology

- Immune-mediated destruction of pancreatic β- cells

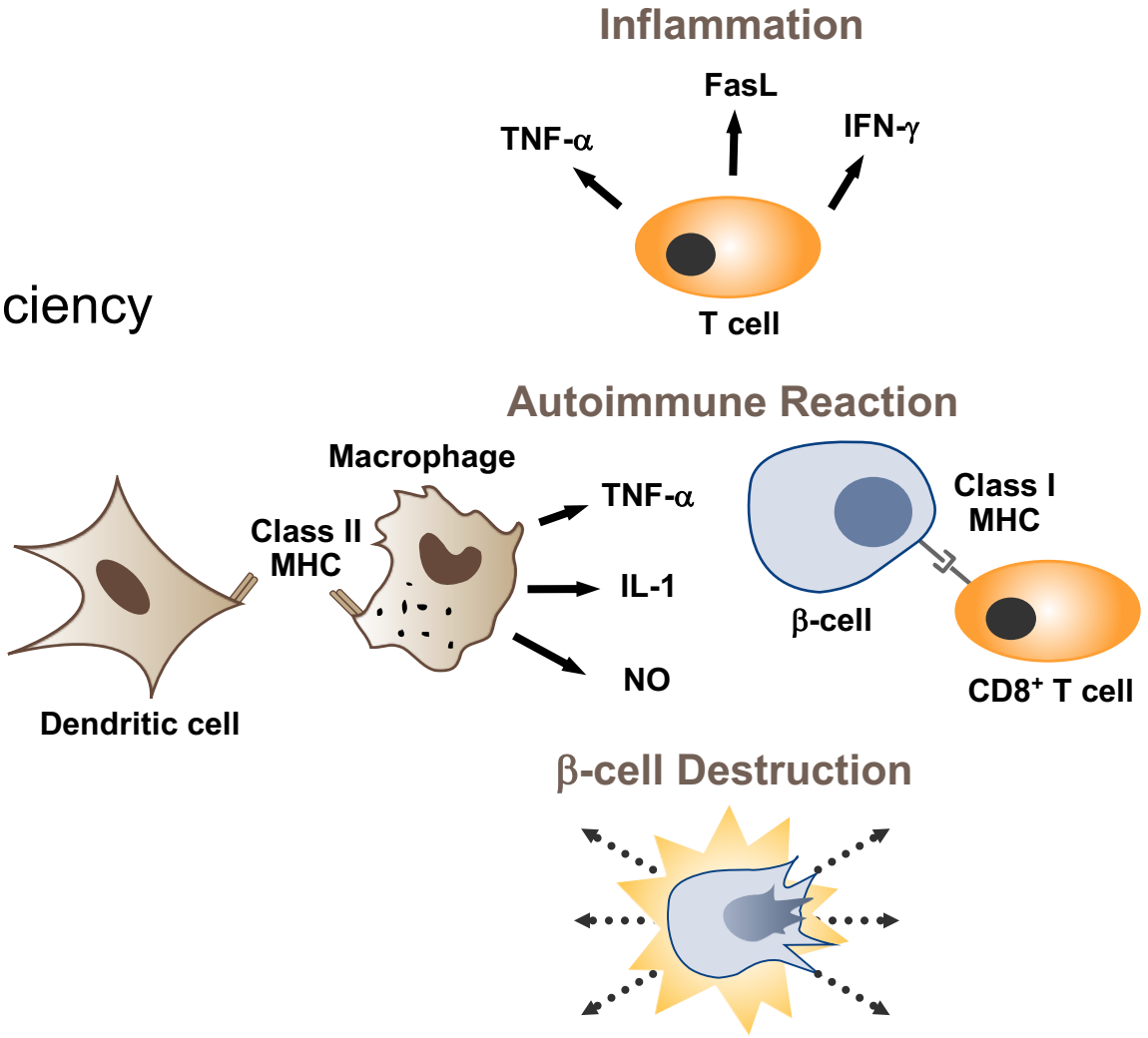
- Certain antibodies detected in blood:
  - Islet cell antibody (ICA)
  - Glutamic acid decarboxylase (GAD65) antibody
  - Insulin autoantibody (IAA)

- HLA-DR3 and HLA-DR4 as well as DQA and DQB genes are strongly associated with type 1 DM

- Strong familial genetic link

Type 1 Diabetes Pathophysiology

- β-cell destruction
  - Usually leading to absolute insulin deficiency
- Immune mediated
- Idiopathic



CD8, cluster of differentiation 8; FasL, Fas ligand; IFN-γ, interferon γ; IL-1, interleukin 1; MHC, major histocompatibility complex; NO, nitric oxide; TNF-α, tumor necrosis factor α.

Maahs DM, et al. *Endocrinol Metab Clin North Am*. 2010;39:481-497.

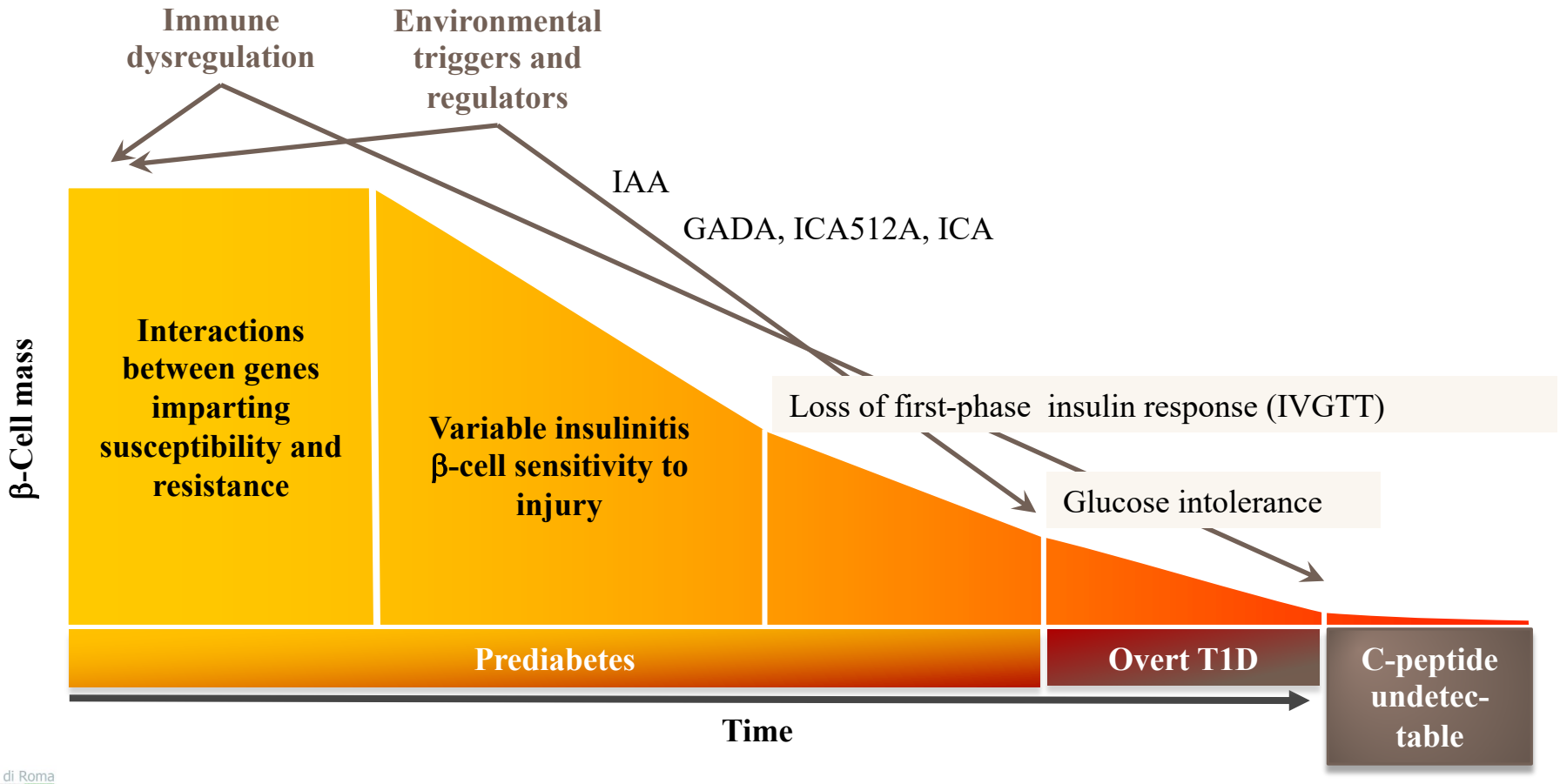
Pathophysiologic Features of Type 1 Diabetes

- Chronic autoimmune disorder
  - Occurs in genetically susceptible individuals
  - May be precipitated by environmental factors
- Autoimmune response against
  - Altered pancreatic β-cell antigens
  - Molecules in β-cells that resemble a viral protein
- Antibodies
  - Approximately 85% of patients: circulating islet cell antibodies
  - Majority: detectable anti-insulin antibodies
  - Most islet cell antibodies directed against GAD within pancreatic β-cells

GAD, glutamic acid decarboxylase.

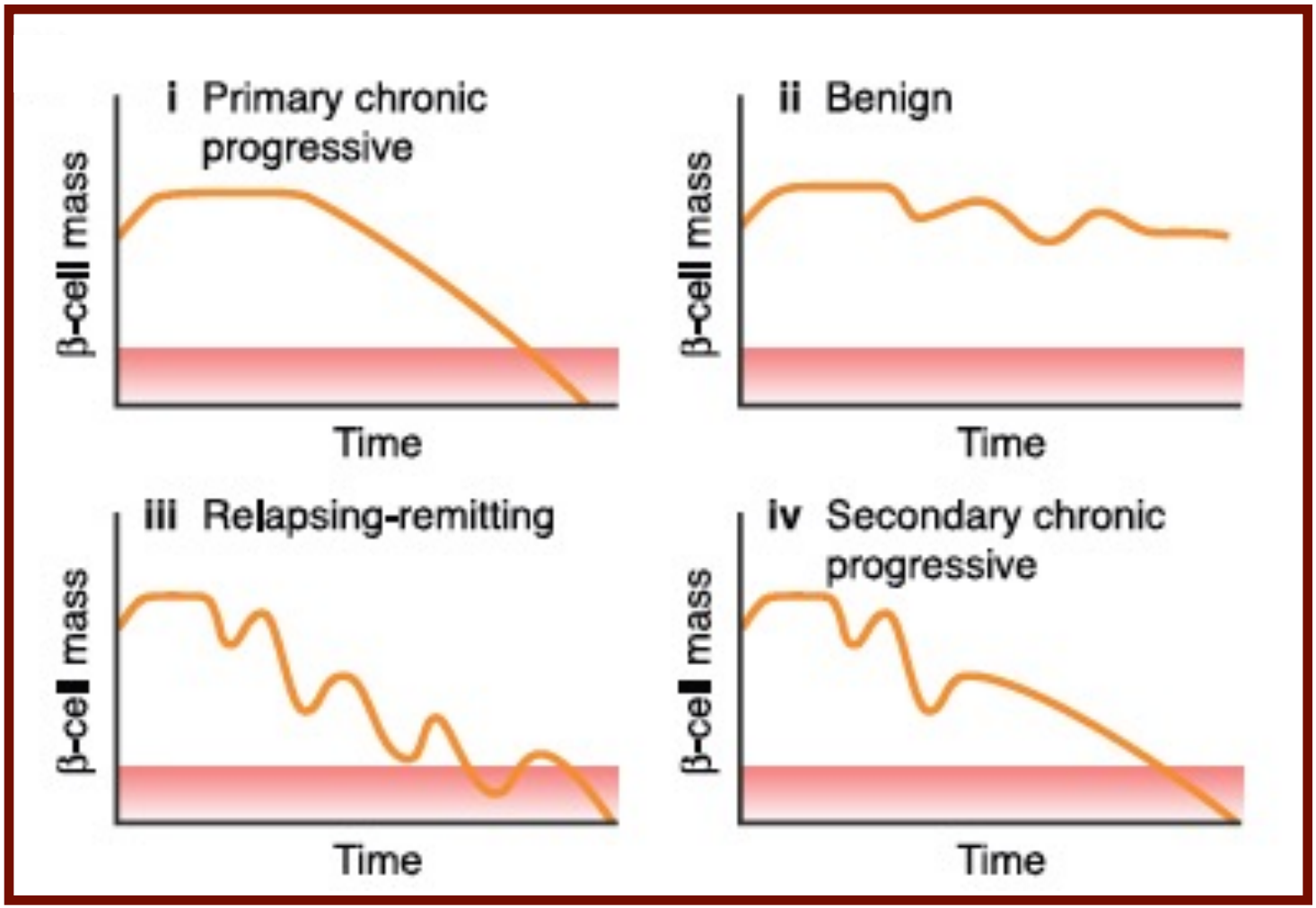
Maahs DM, et al. *Endocrinol Metab Clin North Am*. 2010;39:481-497.

Autoimmune Basis for Type 1 Diabetes



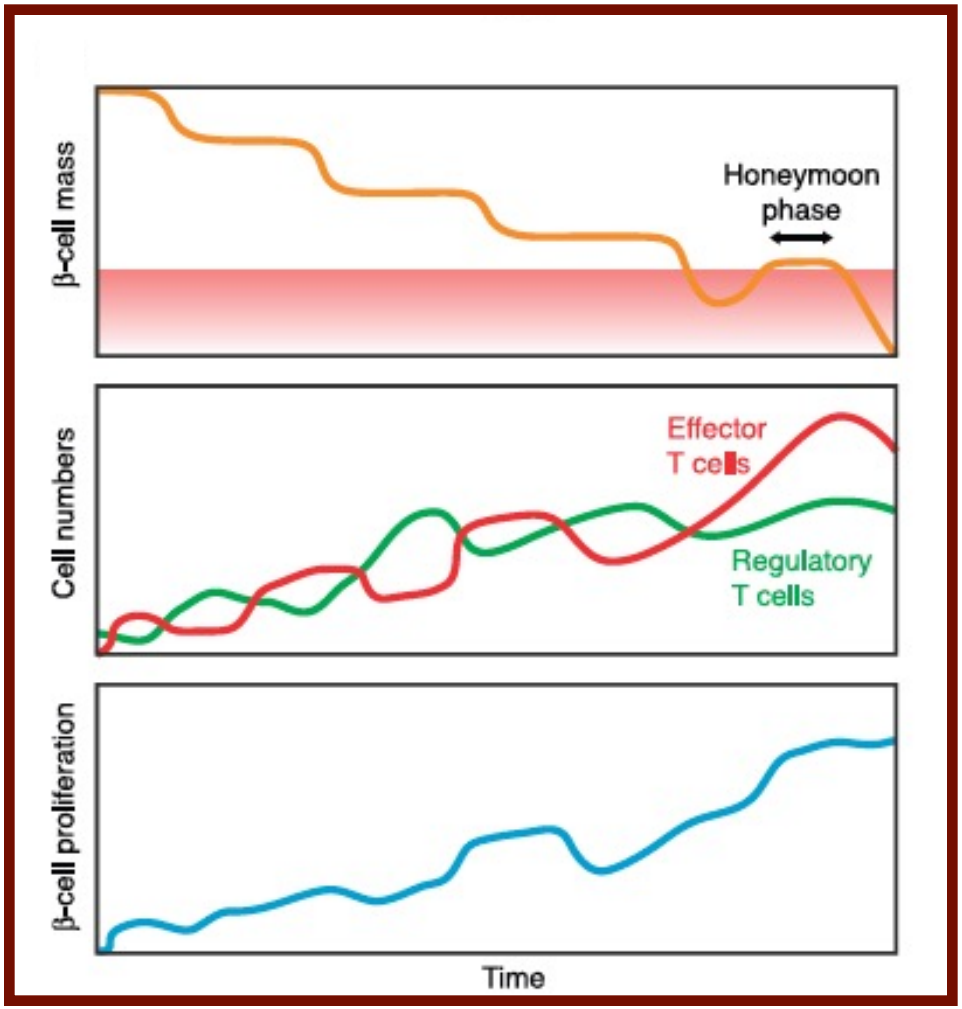
Atkinson MA. *Diabetes*. 2005;54:1253-1263. Adapted from Atkinson MA, Eisenbarth GS. *Lancet*. 2001;358:221-229.

Models for Pathogenesis of T1D



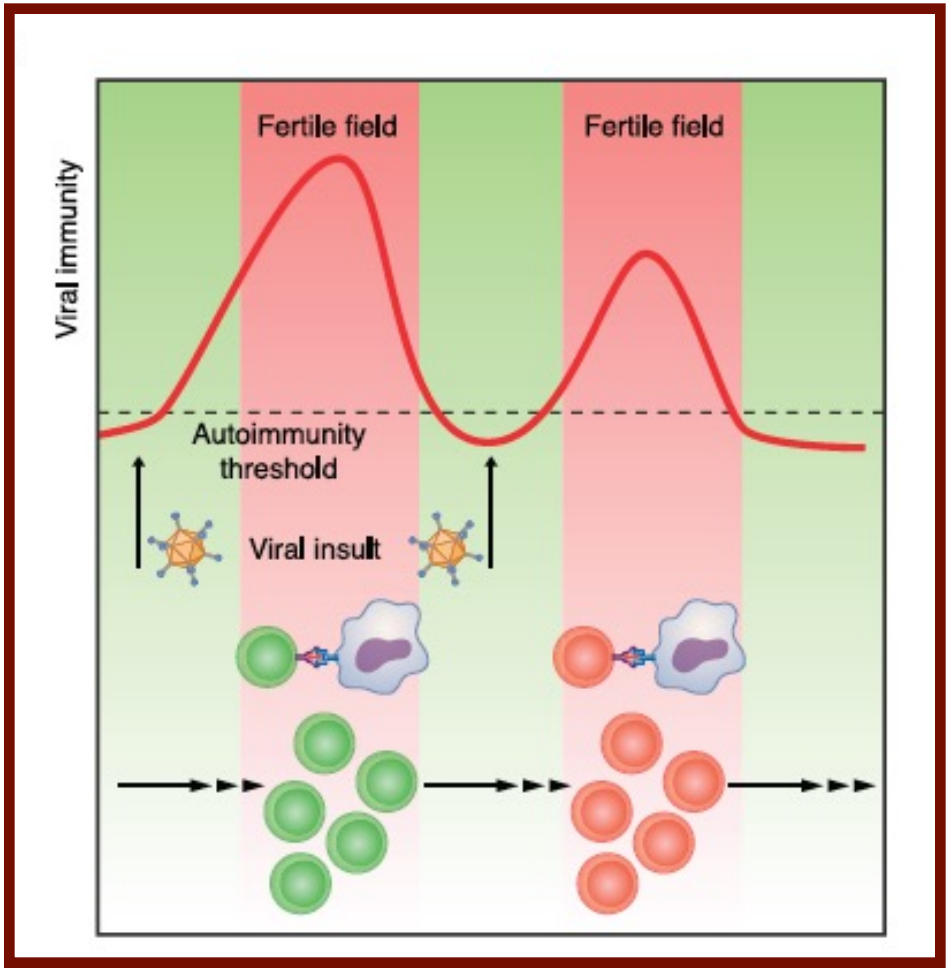
van Belle TL, et al. *Physiol Rev*. 2011;91:79-118.

Models for Pathogenesis of T1D



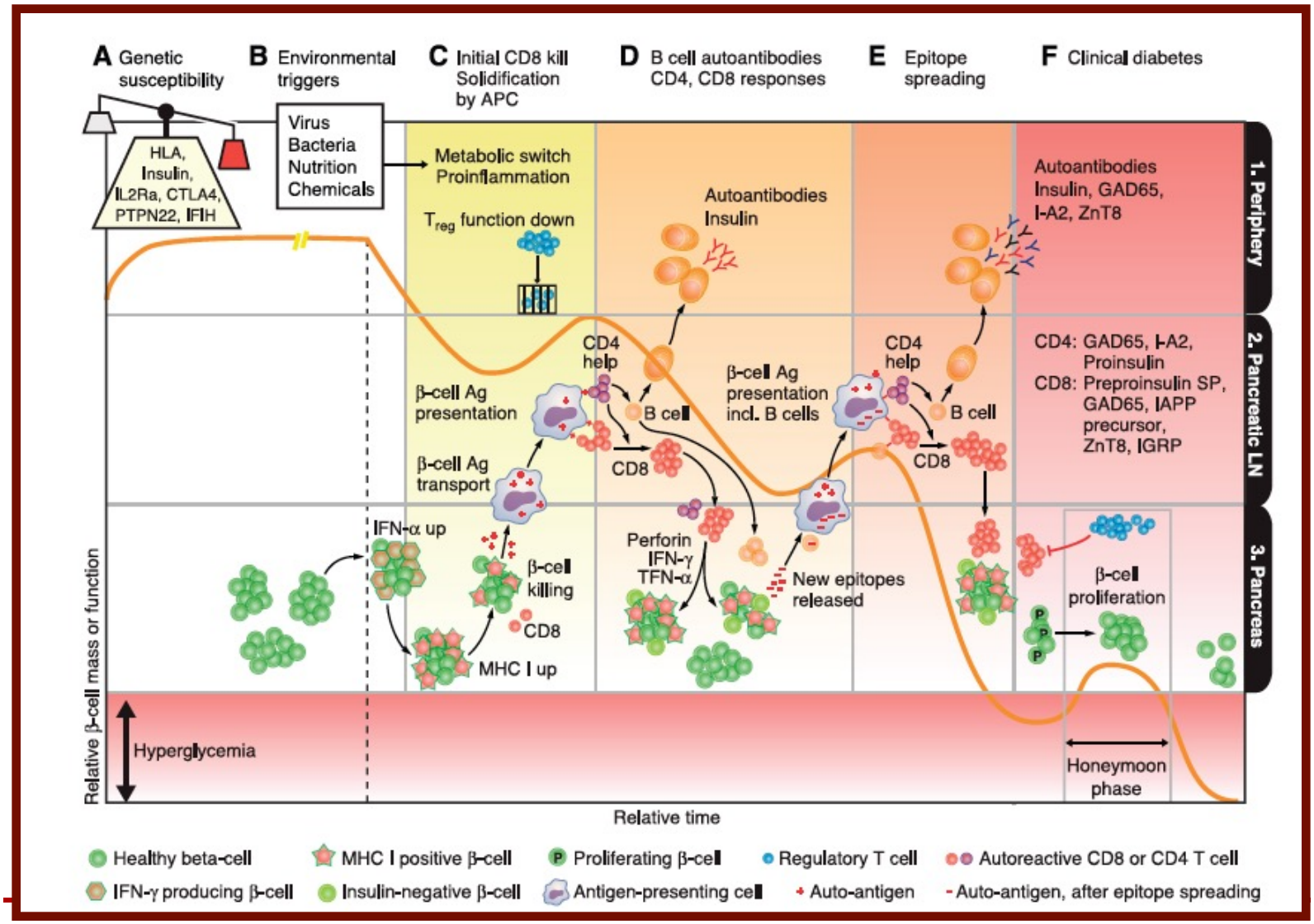
van Belle TL, et al. *Physiol Rev*. 2011;91:79-118.

Models for Pathogenesis of T1D: Fertile Field Hypothesis



van Belle TL, et al. *Physiol Rev*. 2011;91:79-118.

How Type 1 Diabetes Might Arise



van Belle TL, et al. *Physiol Rev*. 2011;91:79-118.

Insulin and Glucose Metabolism

Major Metabolic Effects of Insulin

- Stimulates glucose uptake into muscle and adipose cells
- Inhibits hepatic glucose production

Consequences of Insulin Deficiency

- Hyperglycemia → osmotic diuresis and dehydration

Diagnostic Elements

- ✓ DKA
- ✓ Symptoms of diabetes and a casual plasma glucose ≥ 200 mg/dl

- ✓ Fasting Plasma Glucose (FPG) ≥ 126 mg/dl

- ✓ Impaired Fasting Glucose (IFG)
- 2-h plasma glucose ≥ 200 mg/dl after an OGTT
- These criteria should be confirmed by repeat testing on a different day

Clinical features of Type 1 diabetes.

- Presents acutely. Symptoms due to hyperglycaemia (thirst, polyuria, tiredness,weight loss).
- Ketone production - abdominal pain, nausea and vomiting.
- Other symptoms: blurred vision, repeated infections.
- No chronic complications at diagnosis, may only be apparent 5-10 years post diagnosis.

Pharmacotherapeutic Goals

Glycemic Controls	
HbA1c	<7 – 6.5%
Pre-prandial capillary plasma	90 – 130 mg/dL
Post prandial capillary plasma	<180 mg/dL

Desired Outcomes

- ✓ Reduce risk for microvascular and macrovascular complications
- ✓ Reduce mortality
- ✓ Achieve glycemic control
- ✓ Improved quality of life

Medical Nutrition Therapy

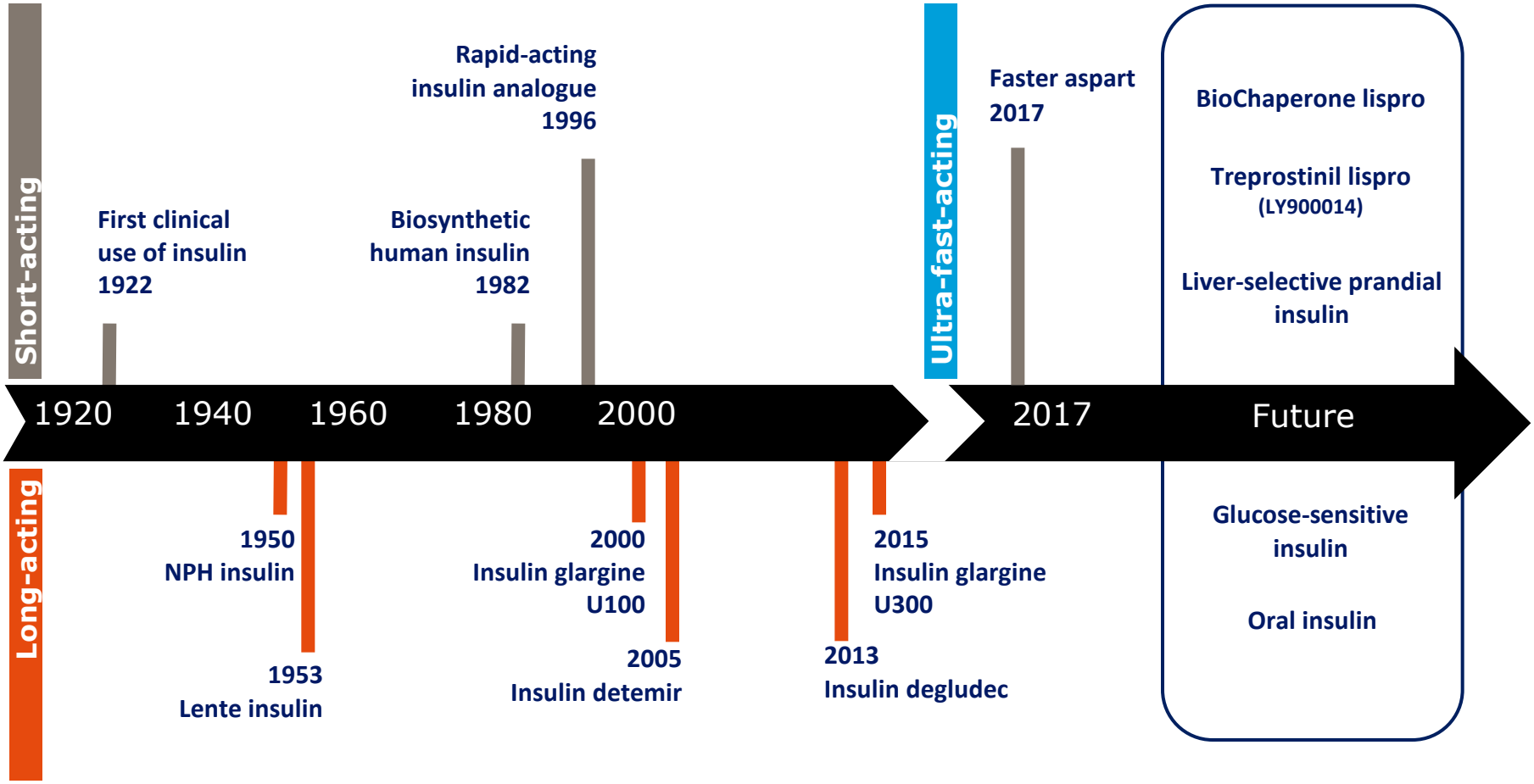
Nutrient	Recommended Intake
Carbohydrate	50-60% of total calories
Protein	15-20%
Totale fat	25-35%
Saturated fat	< 10 (<7 % in dyslipidemia)
Polyunsaturated fat	10 %
Mono unsaturrated fat	up to 20%
Cholesterol	< 300 mg/dL (<200 mg/dl in dyslipidemia)
Total calories	Asjust based on age, weight and height

Pharmacotherapy in Type 1 DM

The primary therapy for type 1 DM is insulin therapy

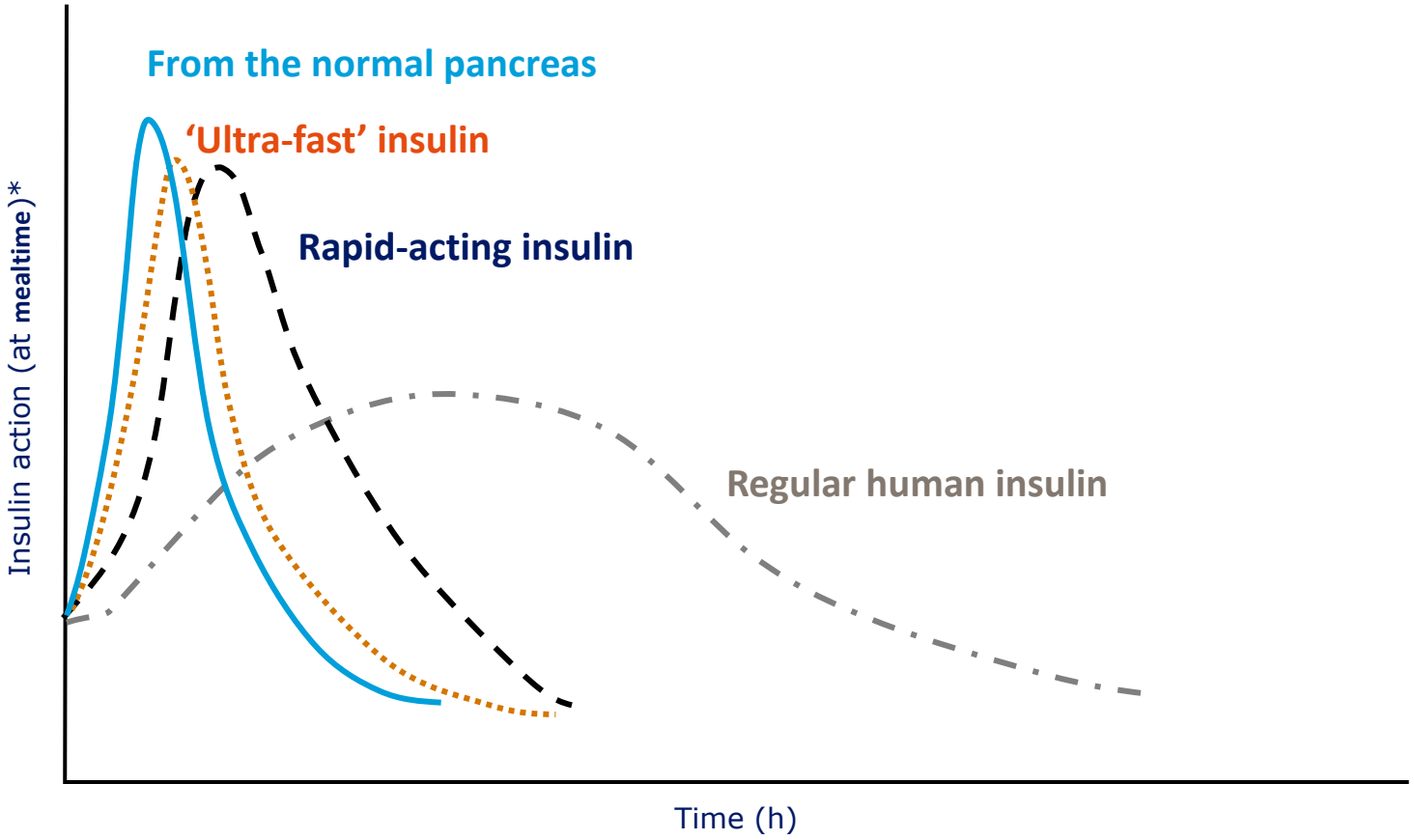
Four basic forms of insulin:

- **Rapid-acting**
- **Short-acting**
- **Intermediate-acting**
- **Long-acting**

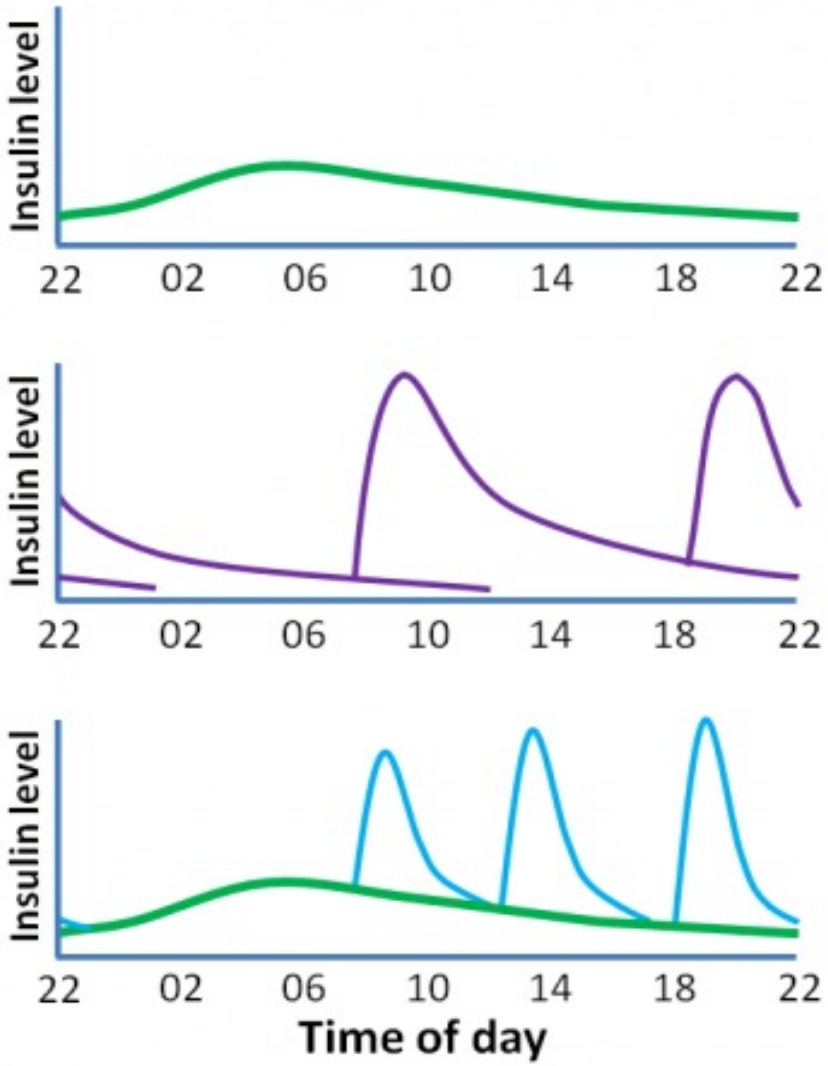


Faster aspart, fast-acting insulin aspart; NPH, neutral protamine Hagedorn

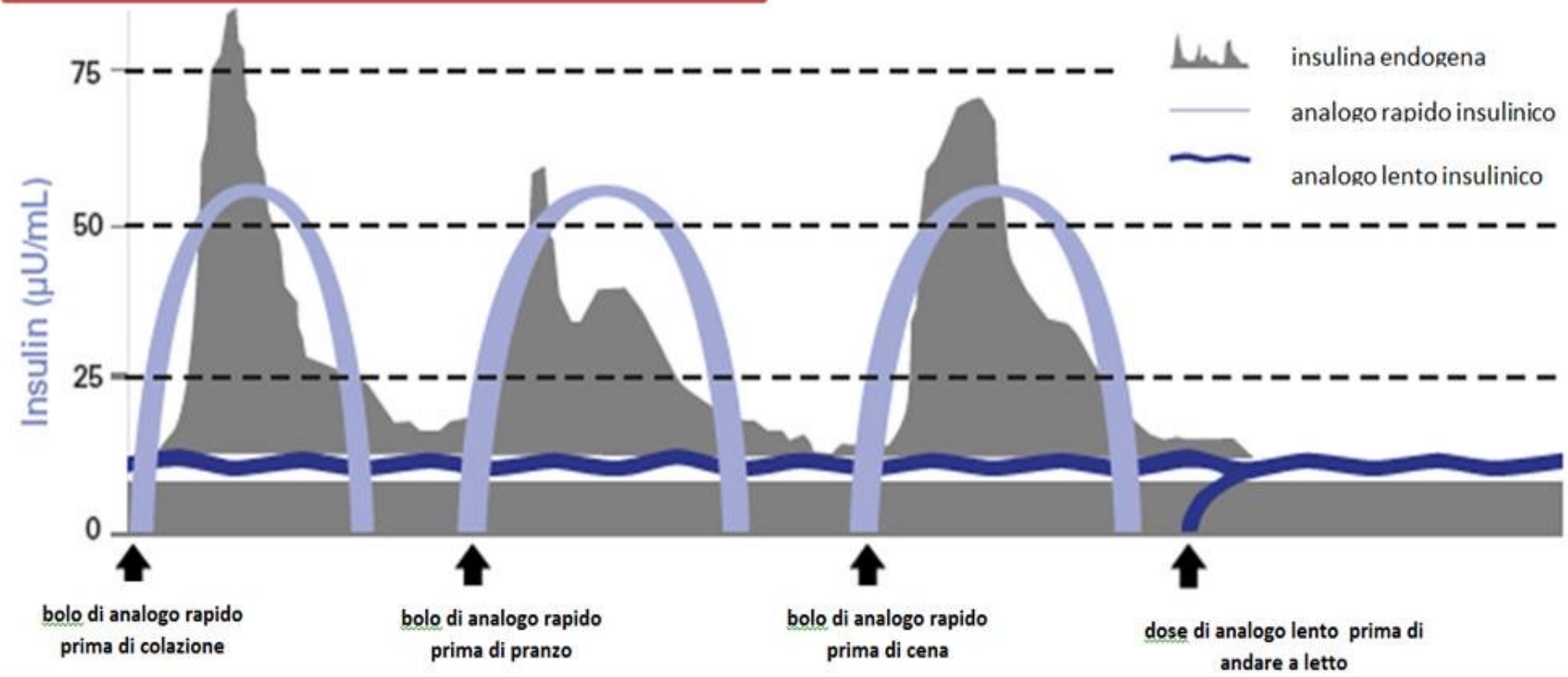
Adapted from Cahn *et al. Lancet Diabetes Endocrinol* 2015;3:638–52; Kazda *et al*. ADA 2017 (poster, P-959); Kim & Plosker. *Drugs* 2015;75:1679–86; Novo Nordisk. Capital Markets Day R&D update, 19 November 2015



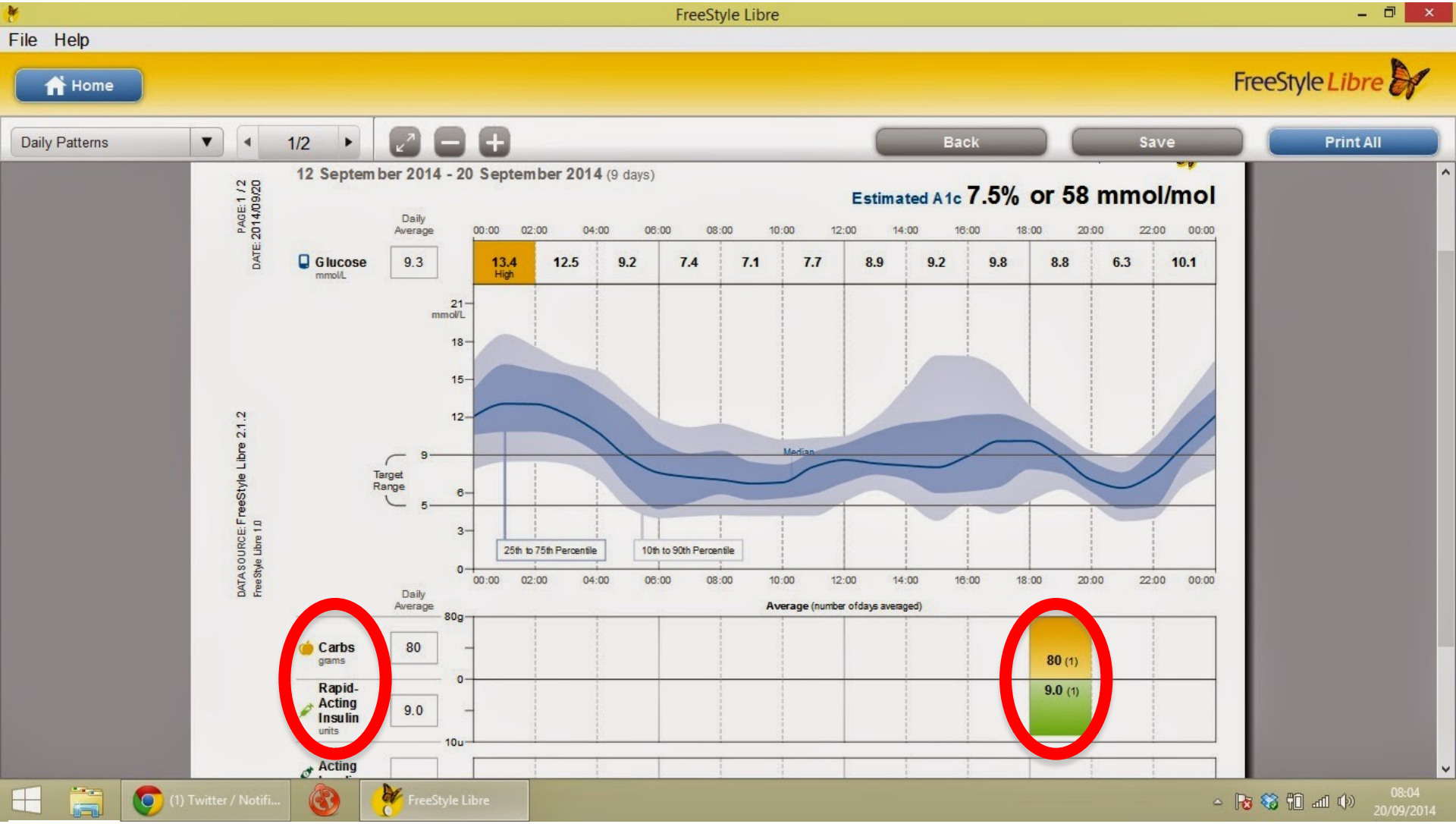
*Schematic representation
T1D, type 1 diabetes; T2D, type 2 diabetes
Adapted from Home. *Diabetes Obes Metab* 2015;17:1011–20



schema basal-bolus

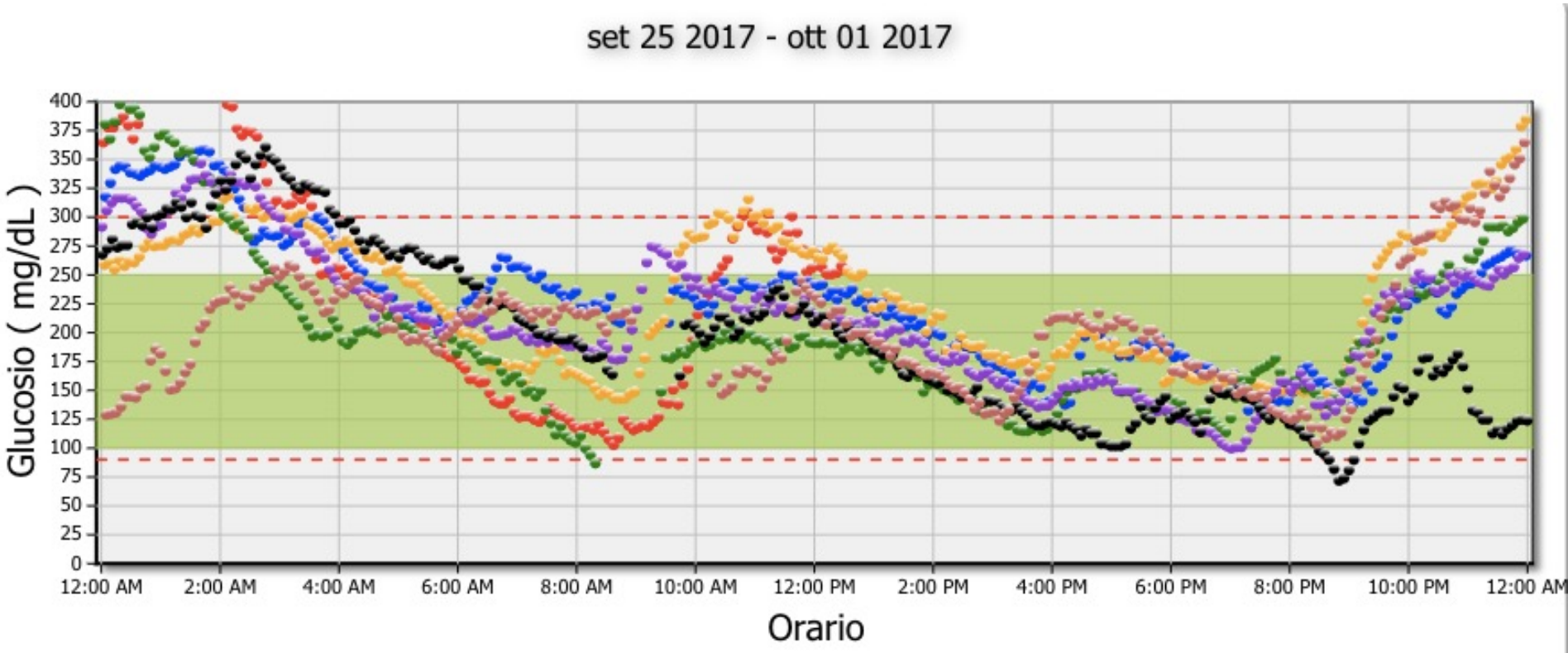


Sensor Smart Transmitter Mobile App

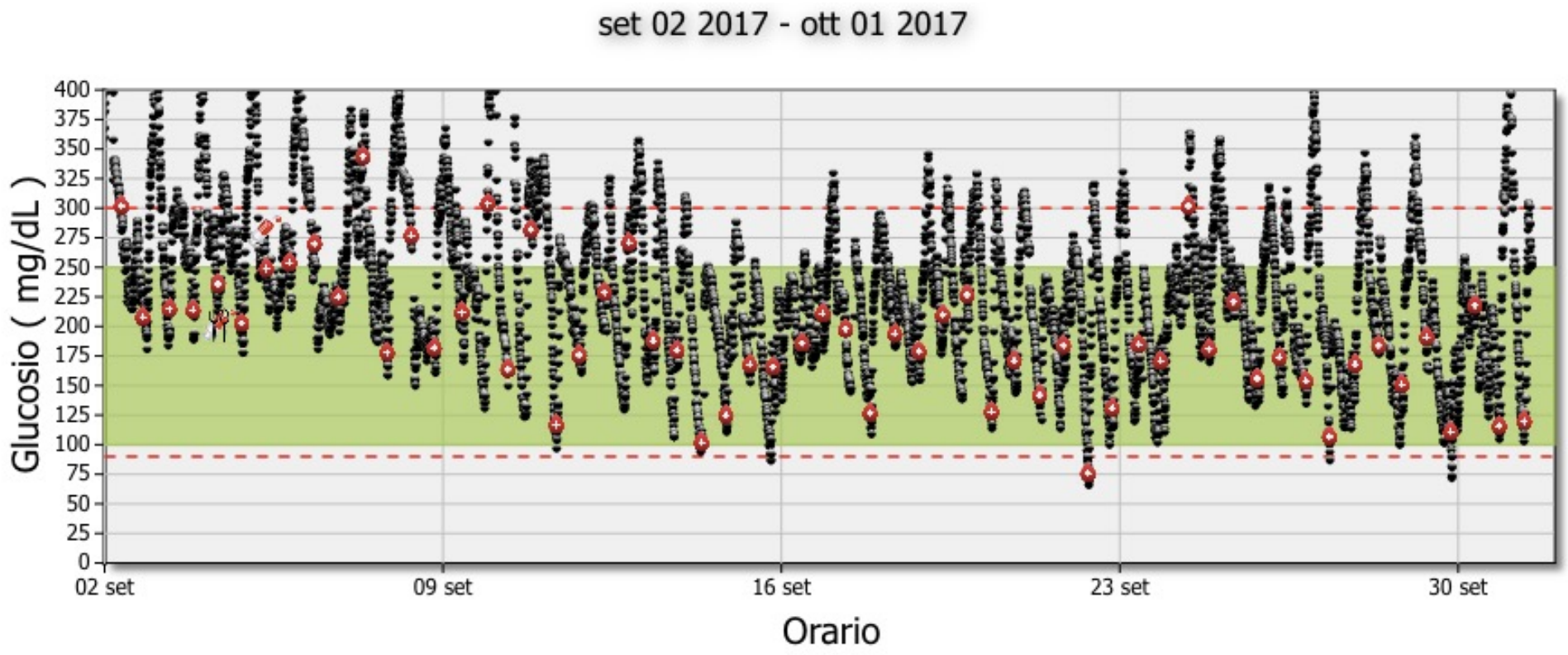


eversense™

Tendenza glucosio



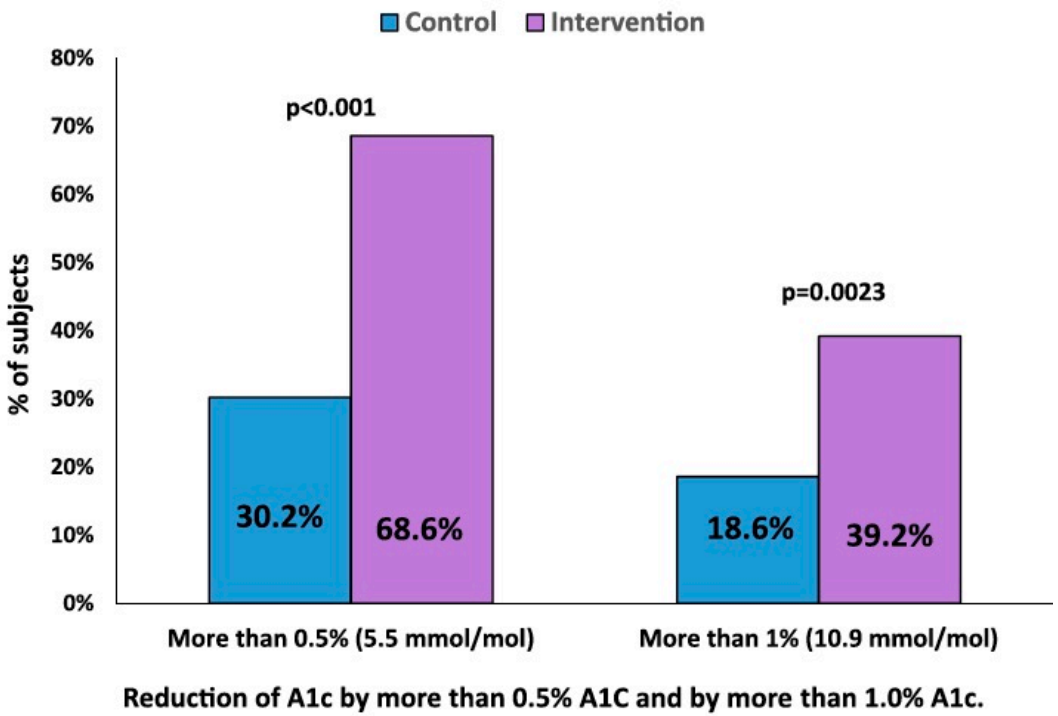
eversense™



Effect of Flash Glucose Monitoring Technology on Glycemic Control and Treatment Satisfaction in Patients With Type 2 Diabetes

https://doi.org/10.2337/dc18-0166

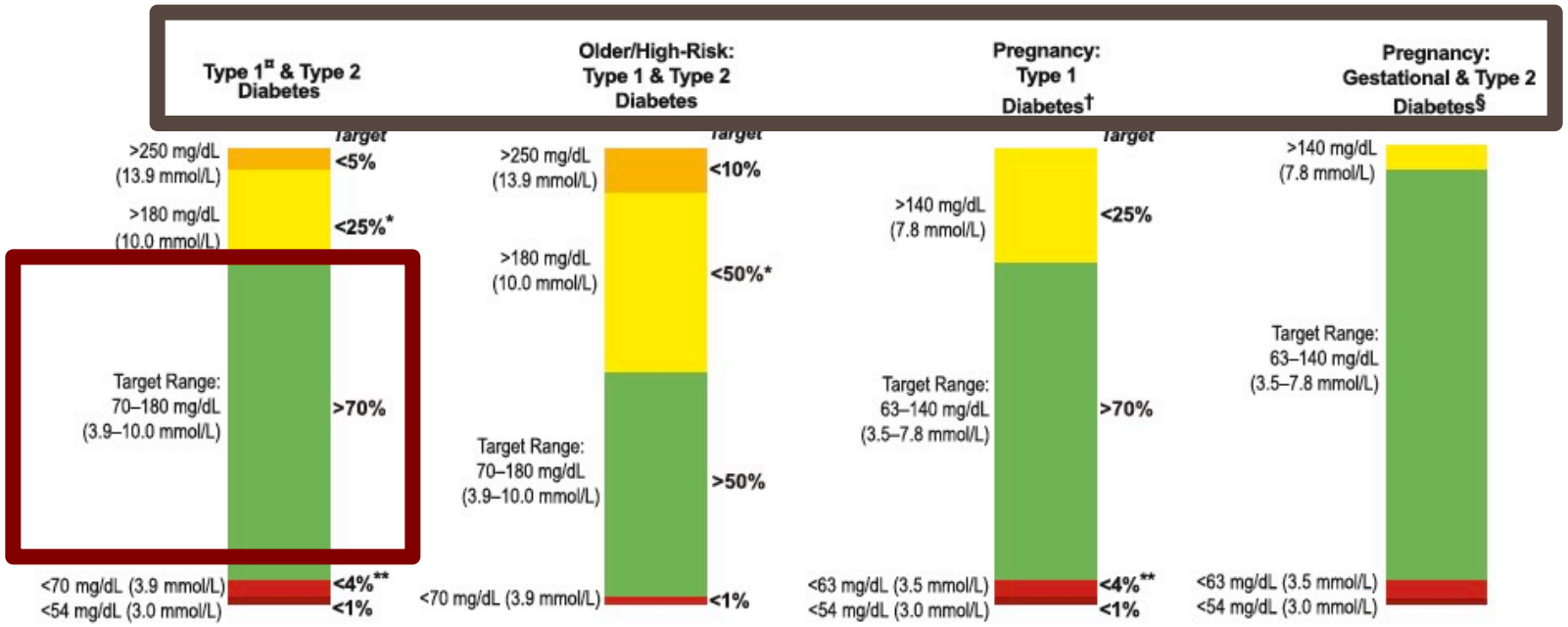
Marianna Yaron,[1,2] Eytan Roitman,[1] Genya Aharon-Hananel,[1] Zohar Landau,[1,2,3] Tali Ganz,[3] Ilan Yanuv,[4] Aliza Rozenberg,[4] Moshe Karp,[1] Maya Ish-Shalom,[1,2] Joelle Singer,[1,2] Julio Wainstein,[1,2,3] and Itamar Raz[1,4]



Reduction of A1c by more than 0.5% A1C and by more than 1.0% A1c.

Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range

https://doi.org/10.2337/dci19-0028



¤ For age <25 yr., if the A1C goal is 7.5%, then set TIR target to approximately 60%. (See *Clinical Applications of Time in Ranges* section in the text for additional information regarding target goal setting in pediatric management.)

† Percentages of time in ranges are based on limited evidence. More research is needed.

§ Percentages of time in ranges have not been included because there is very limited evidence in this area. More research is needed. Please see *Pregnancy* section in text for more considerations on targets for these groups.

* Includes percentage of values >250 mg/dL (13.9 mmol/L).

** Includes percentage of values <54 mg/dL (3.0 mmol/L).

Insulin Adverse Reactions

- **Lipoatrophy: loss of fat at injection site due to antibody formation leading to breakdown of fat in the area of injection (need to rotate sites!)**
- **Hypertrophy: increase in fat mass at the site, the area is anesthetized, however leads to erratic insulin absorption**
- **Resistance: require large amounts of insulin to get desired effect, due to antibody formation**

Insulin Adverse Reactions

- Foods that will provide 10g of carbs:

– . cup of orange juice or soda
– Sugar: 2 teaspoons or 2 cubes
– Glucose tablets: 2-4 tablets
– Apple juice: 1/3 cup

- Foods to avoid
– Ice cream, candy bars, cookies, cakes
– Complex carbs slowly absorbed

- If unconscious: Glucagon 1mg SQ, IM, or IV and Dextrose 50% 50ml infusion

Hormonal Responses to Exercise (non-diabetic)

Insulin Secretion
↓↓

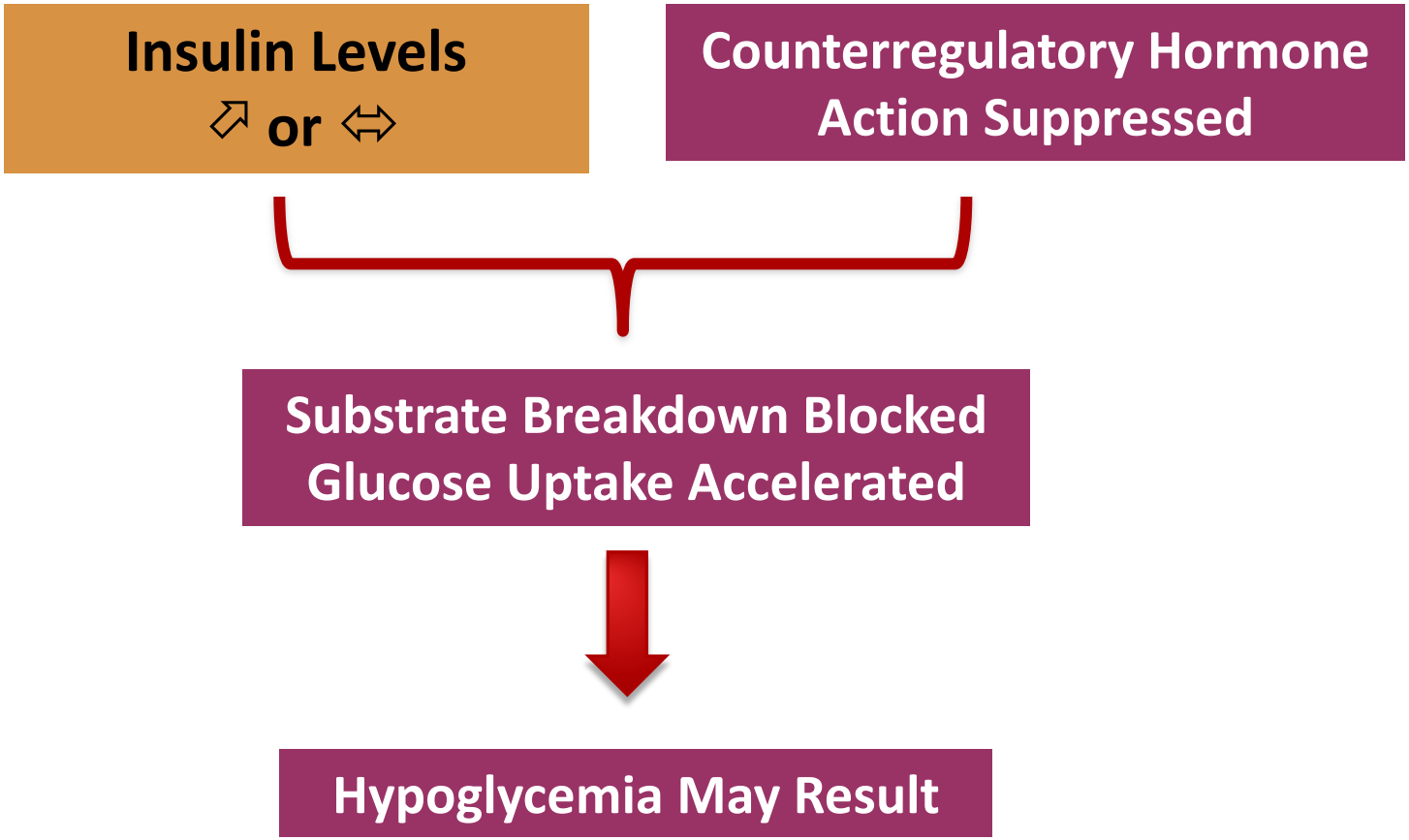
Counterregulatory Hormone Secretion
↑ (Epi/Nepi • Glucagon • GH, Cortisol)

Substrate Breakdown
- Glycogenolysis
- Lipolysis

↓

BG Holds *Steady* Despite
↑ Glucose Utilization by Muscle

Hormonal Responses to Exercise (diabetic using insulin)



Insulin Adjustment Based on Timing and Duration

	Activity Within 2 Hours After Meal	Activity Before or Between Meals
Short Duration (<90 Minutes)	↓ Mealtime Bolus	Snack Prior to Activity

Diabetes Care, vol. 24, no. 4, 4/2001, 625-630.

Insulin Adjustment Based on Timing and Duration

	Activity Within 2 Hrs After Meal	Activity Before or Between Meals
Long Duration (>90 Minutes)	↓ Mealtime Bolus ↓ Basal Rate Snack at regular intervals Watch for delayed-onset hypoglycemia	Snack Prior to Activity ↓ Basal Rate (if using pump) Snack at regular intervals Watch for delayed-onset hypoglycemia

Insulin Adjustments

Meal Bolus Adjustment

(for post-meal activity)

- Low Intensity Cardio ↓ 25%
- Mod. Intensity Cardio ↓ 33%
- High Intensity Cardio ↓ 50%
- Competitive/Anaerobic ???

Diabetes Care, vol. 24, no. 4, 4/2001, 625-630.

Insulin Adjustments

Basal Adjustment

(for > 90 min. activity)

- CSII: ↓ Basal rate 50% starting 1 hr pre-activity, *or:*
- CSII: Disconnect 1-hr prior, but reconnect hourly and bolus 50% of usual basal rate

(for day-long activity)

- CSII: ↓ basal 50% daytime, 25% nighttime
- Shots: ↓ basal insulin 25%

Diabetes Care, vol. 24, no. 4, 4/2001, 625-630.

Original Article

Artificial Pancreas Device Systems for the Closed-Loop Control of Type 1 Diabetes: What Systems Are in Development?

Journal of Diabetes Science and Technology
2016, Vol. 10(3) 714–723

DOI: 10.1177/1932296815617968
dst.sagepub.com
SAGE

Sara Trevitt, BSc, PhD[1], Sue Simpson, BSc, PhD[1], and Annette Wood, MB, BCh, FFPH[1]

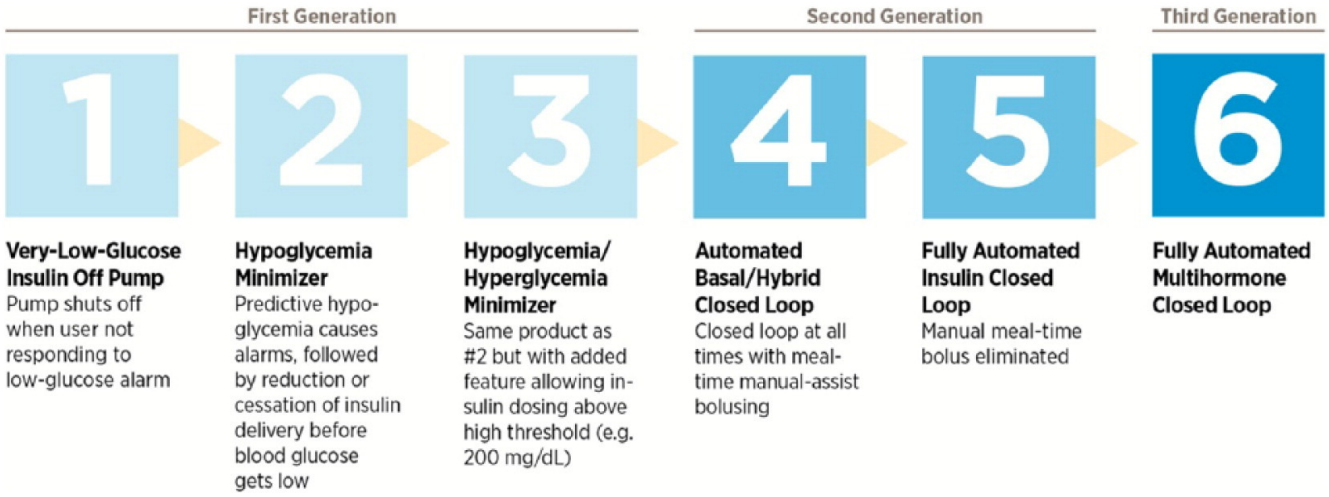


Figure 1. The 6 developmental stages of artificial pancreas device systems (copyright JDRF).5

Published in: Sara Trevitt; Sue Simpson; Annette Wood; *J Diabetes Sci Technol* 10, 714-723.
DOI: 10.1177/1932296815617968