Σύγχρονες απόψεις στην ταξινόμηση του ΣΔ

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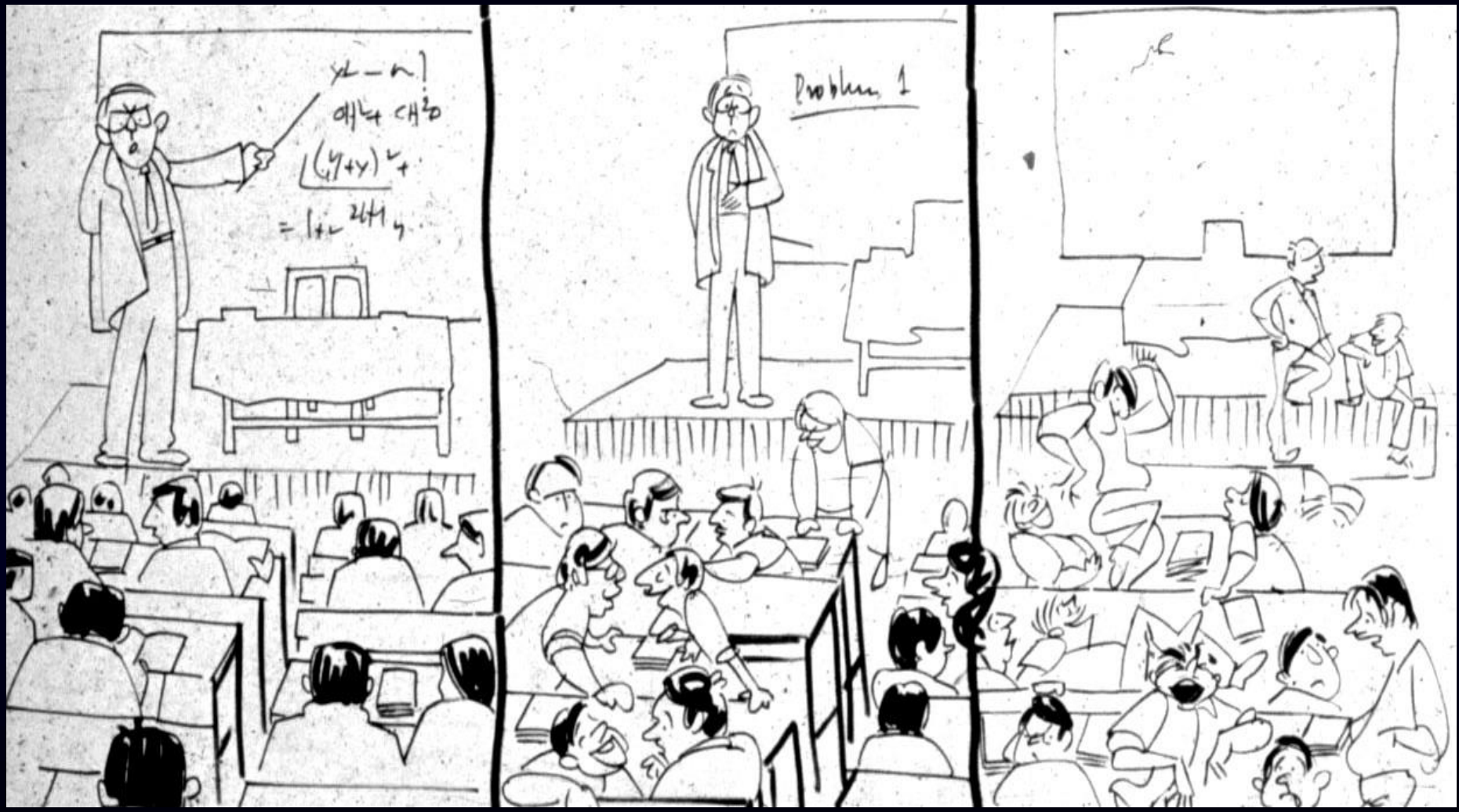
Πανεπιστημιακό Γ.Ν "ΑΤΤΙΚΟΝ"

Ο Σακχαρώδης διαβήτης

- **Ετερογενής**
- **Κληρονομική**
- **Πολυπαραγοντική και**
- **Πολυγονιδιακή νόσος**

Normal **Type 2 DM** **Type 1 DM**



Standards of Care in Diabetes—2024

(*Standards of Care*)

American Diabetes Association.
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Section 2.

Diagnosis and Classification of Diabetes

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Diagnostic Tests for Diabetes

2.1a Diagnose diabetes based on A1C or plasma glucose criteria, either the fasting plasma glucose (FPG) value, 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT), or random glucose value accompanied by classic hyperglycemic symptoms/crises criteria **(Table 2.1).** **A**

2.1b In the absence of unequivocal hyperglycemia (e.g., hyperglycemic crises), diagnosis requires confirmatory testing **(Table 2.1).** **A**

DIAGNOSIS AND CLASSIFICATION of Diabetes

Table 2.1—Criteria for the diagnosis of diabetes in nonpregnant individuals

A1C ≥6.5% (≥48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
FPG ≥126 mg/dL (≥7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (≥11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
In an individual with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (≥11.1 mmol/L). Random is any time of the day without regard to time since previous meal.

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; NGSP, National Glycohemoglobin Standardization Program; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results obtained at the same time (e.g., A1C and FPG) or at two different time points.

Diagnosis and Classification of Diabetes:
***Standards of Care in Diabetes - 2024. Diabetes Care* 2024;47(Suppl. 1):S20-S42**

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Use of A1C for Screening and Diagnosis of Diabetes (continued)

2.3 Marked discordance between A1C and repeat blood glucose values should raise the possibility of a problem or interference with either test. **B**

2.4 In conditions associated with an altered relationship between A1C and glycemia, such as some hemoglobin variants, pregnancy (second and third trimesters and the postpartum period), glucose-6-phosphate dehydrogenase deficiency, HIV, hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, plasma glucose criteria should be used to diagnose diabetes. **B**

Ταξινόμηση Σακχαρώδη Διαβήτη

Ηλικία

ΣΔ σε νέα άτομα

ΣΔ σε ηλικιωμένα άτομα

Ινσουλινοθεραπεία

Ινσουλινοεξαρτώμενος

Μη- Ινσουλινοεξαρτώμενος

Παθογένεια

Τύπου 1

Τύπου 2

LADA

Αυτοανοσία

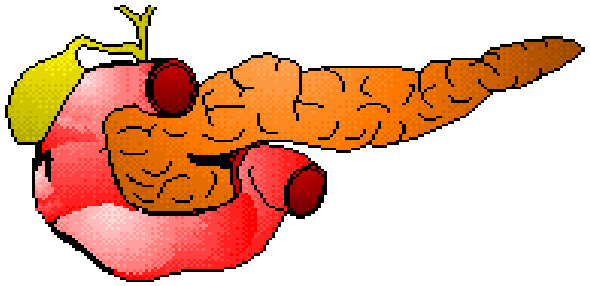
Μεταβολικό Σύνδρομο

Άλλοι τύποι Διαβήτη

Διαβήτης κυήσεως

Σακχαρώδης Διαβήτης τύπου 1

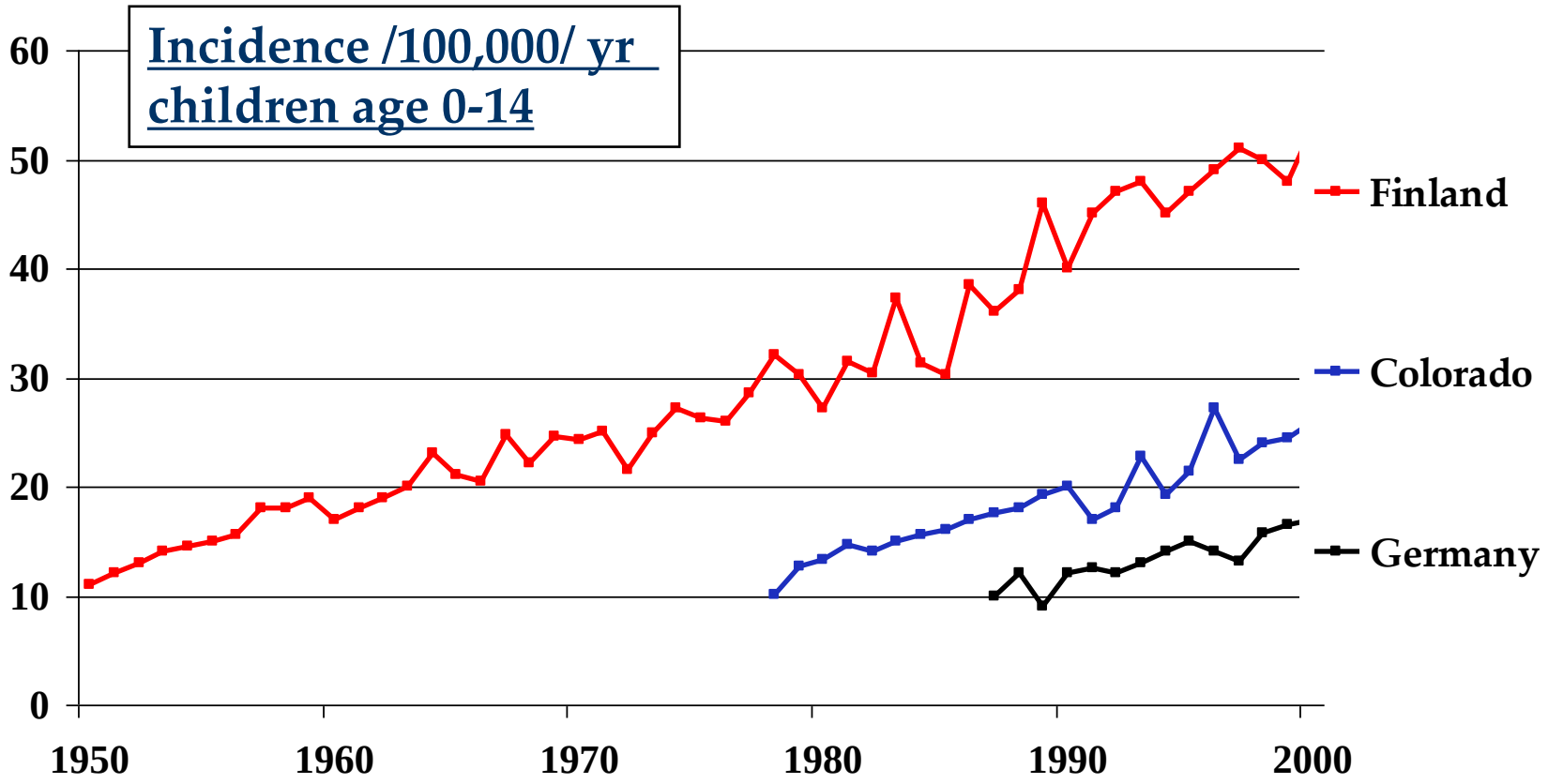
- **Πρωταρχική βλάβη:** απουσία έκκρισης ινσουλίνης



- Κλινική εκδήλωση: 90% καταστροφή των β-κυττάρων.
- Η παθογένεια του ΣΔ 1 αποτελεί ένα εξαιρετικά πολύπλοκο φαινόμενο
  - *Γενετική προδιάθεση*
  - *Περιβαλλοντικοί παράγοντες*
  - *Ανοσολογικοί παράγοντες*

Type 1 DM incidence is rising 3-5% /year

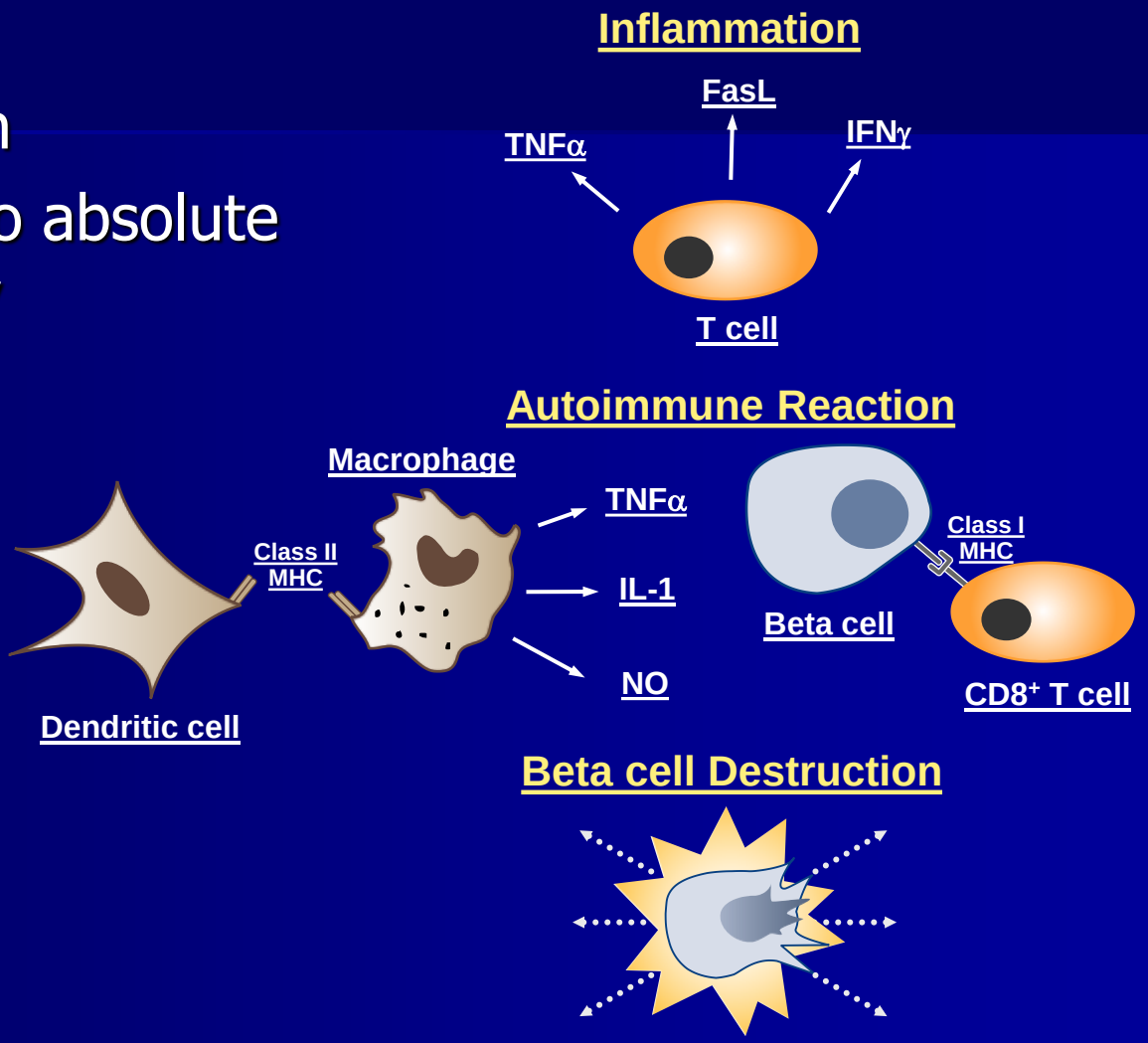
1.4 million patients in the U.S.



Rewers

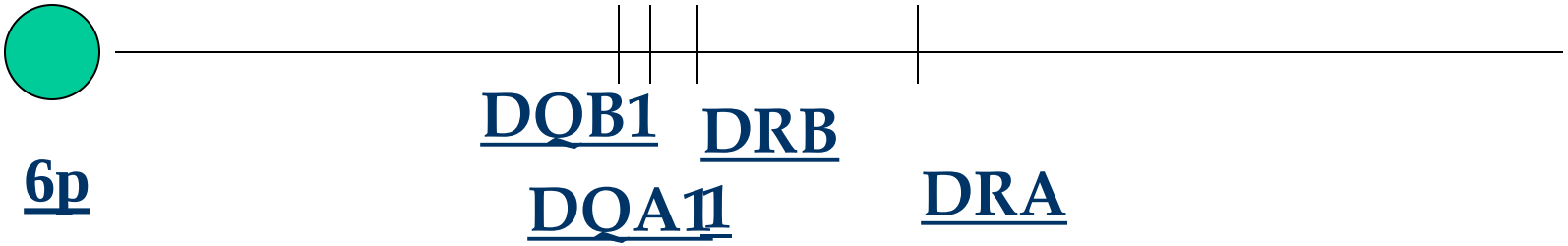
Type 1 Diabetes

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



American Diabetes Association. *Diabetes Care.* 2003;26:S33–S50.

Common HLA Haplotypes

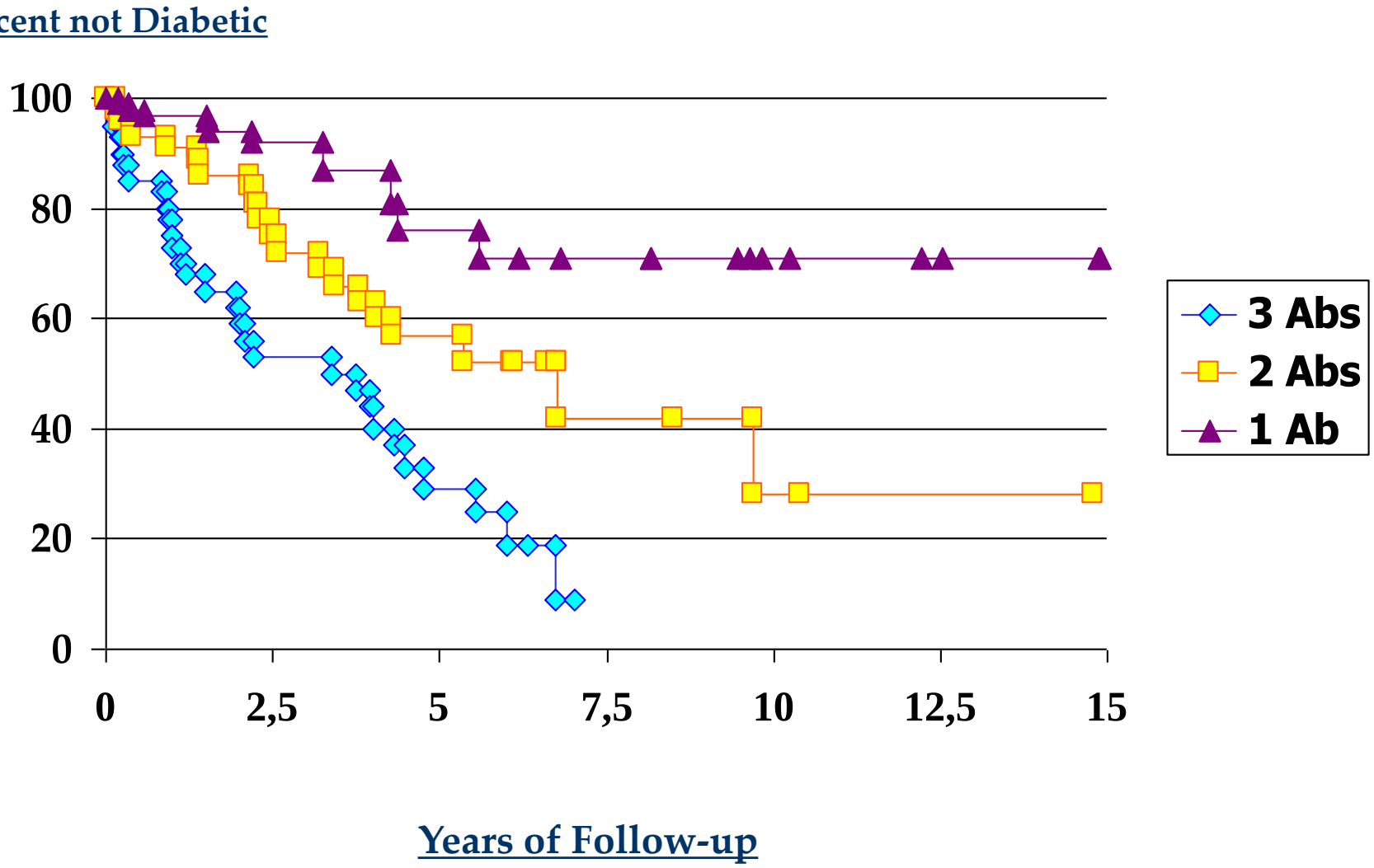


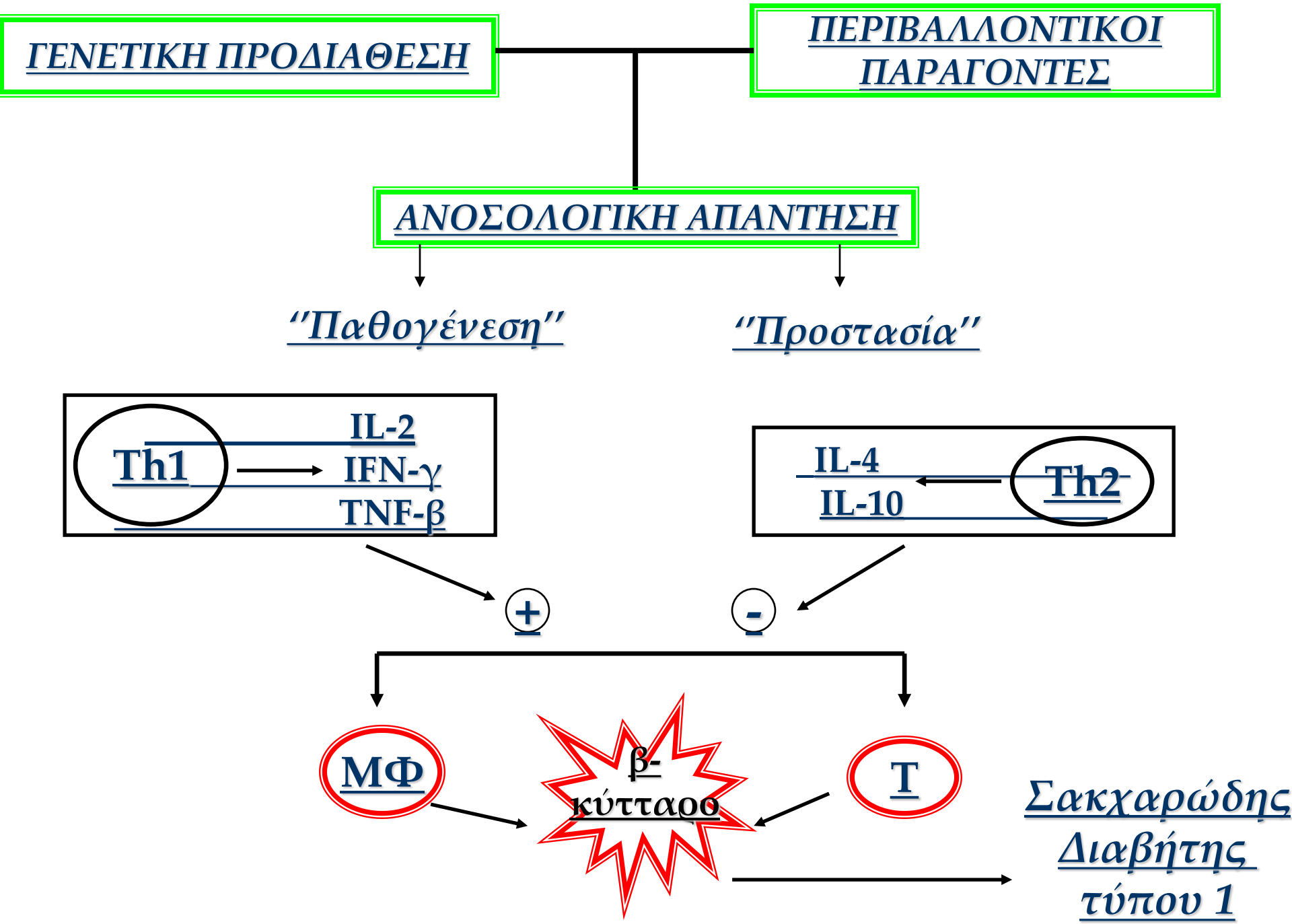
- **High Risk**
  DR3: DQB1*0201, DQA1*0501, DRB1*0301
  DR4: DQA1*0301, DQB1*0302, DRB1*0401
- **Protective**
  DR2: DQB1*0602, DQA1*0102,, DRB1*1501

ΑΥΤΟΑΝΤΙΣΩΜΑΤΑ

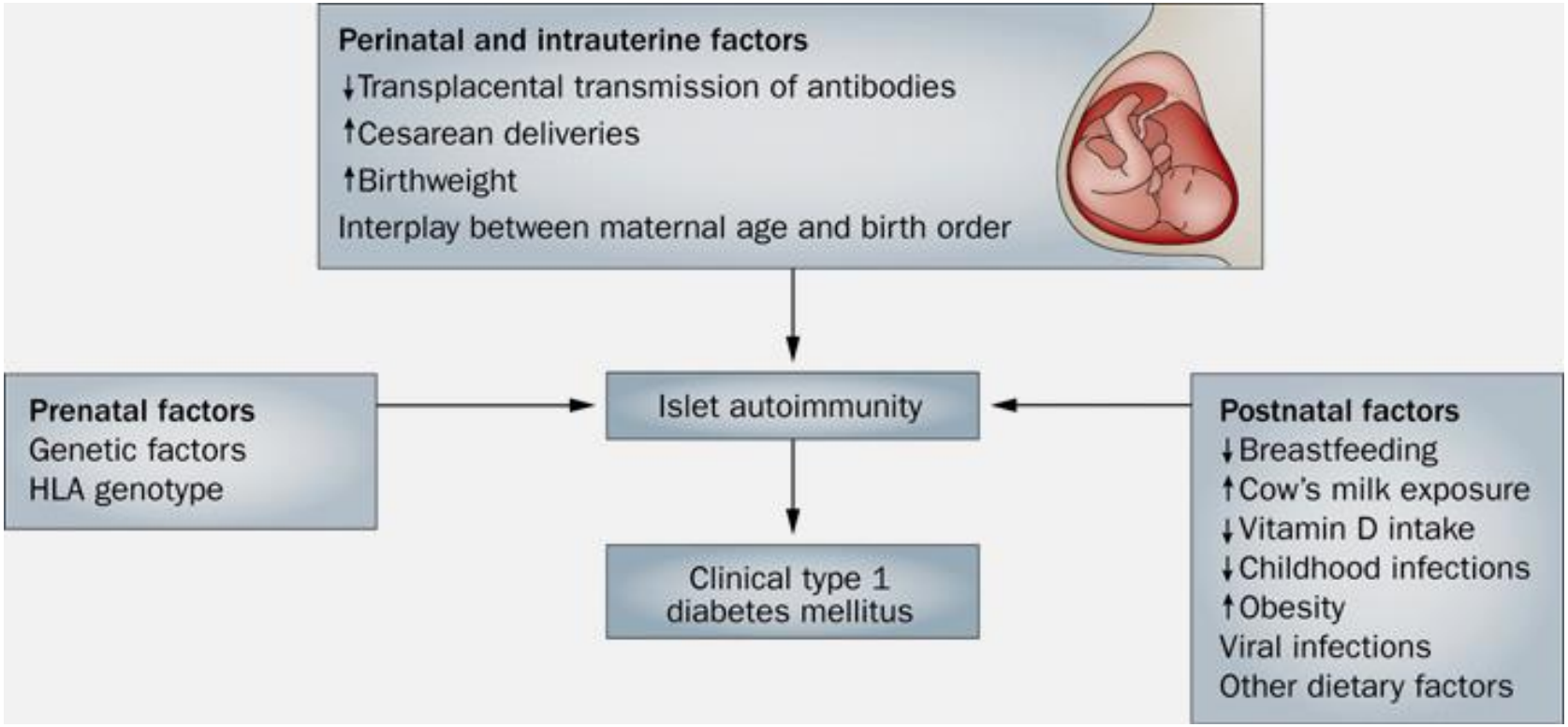
- **Αντι-ινσουλινικά αντισώματα (IAA)**
  - ✓ ΣΔ 1 16-69%
  - ✓ Συγγενείς 1ου βαθμού 2-4%
  - ✓ Γενικός πληθυσμός 1.5-3.9%
- **Αντι-νησιδιακά αντισώματα (ICA)**
  - ✓ ΣΔ 1 60-90%
  - ✓ Συγγενείς 1ου βαθμού 1-9%
  - ✓ Γενικός πληθυσμός 1.4-5.3%
- **Αντισώματα έναντι της αποκαρβοξυλάσης του γλουταμινικού οξέος (GAD)**
  - ✓ ΣΔ 1 22-81%
  - ✓ Συγγενείς 1ου βαθμού 5-13%
  - ✓ Γενικός πληθυσμός 1.4-5.3%
- **Αντισώματα έναντι της φωσφατάσης της τυροσίνης (IA-2ic)**
  - ✓ ΣΔ 1 48-80%
  - ✓ Συγγενείς 1ου βαθμού 2-5%
  - ✓ Γενικός πληθυσμός 1.5-2.4%
- **zinc transporter 8 (ZnT-8).**

Progression to Diabetes vs Number of Autoantibodies (GAD, ICA512, Insulin)




ΓΕΝΕΤΙΚΗ ΠΡΟΔΙΑΘΕΣΗ
ΠΕΡΙΒΑΛΛΟΝΤΙΚΟΙ ΠΑΡΑΓΟΝΤΕΣ
ΑΝΟΣΟΛΟΓΙΚΗ ΑΠΑΝΤΗΣΗ
''Παθογένεση''
''Προστασία''
Th1
IL-2
IFN-γ
TNF-β
IL-4
IL-10
Th2
+
-
ΜΦ
β-κύτταρο
Τ
Σακχαρώδης Διαβήτης τύπου 1

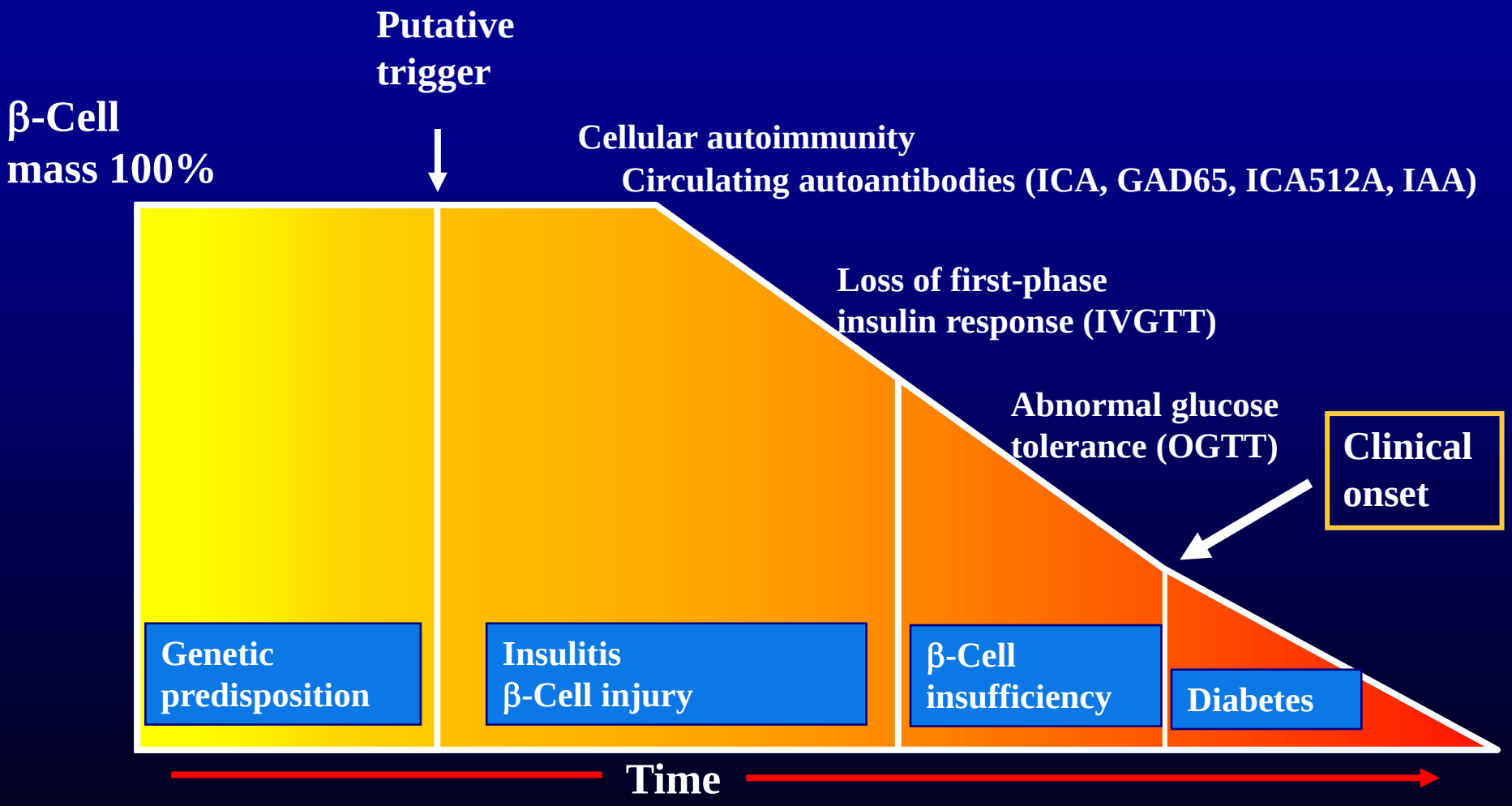
Prenatal, perinatal and postnatal factors implicated in the development of autoimmune type 1 diabetes mellitus



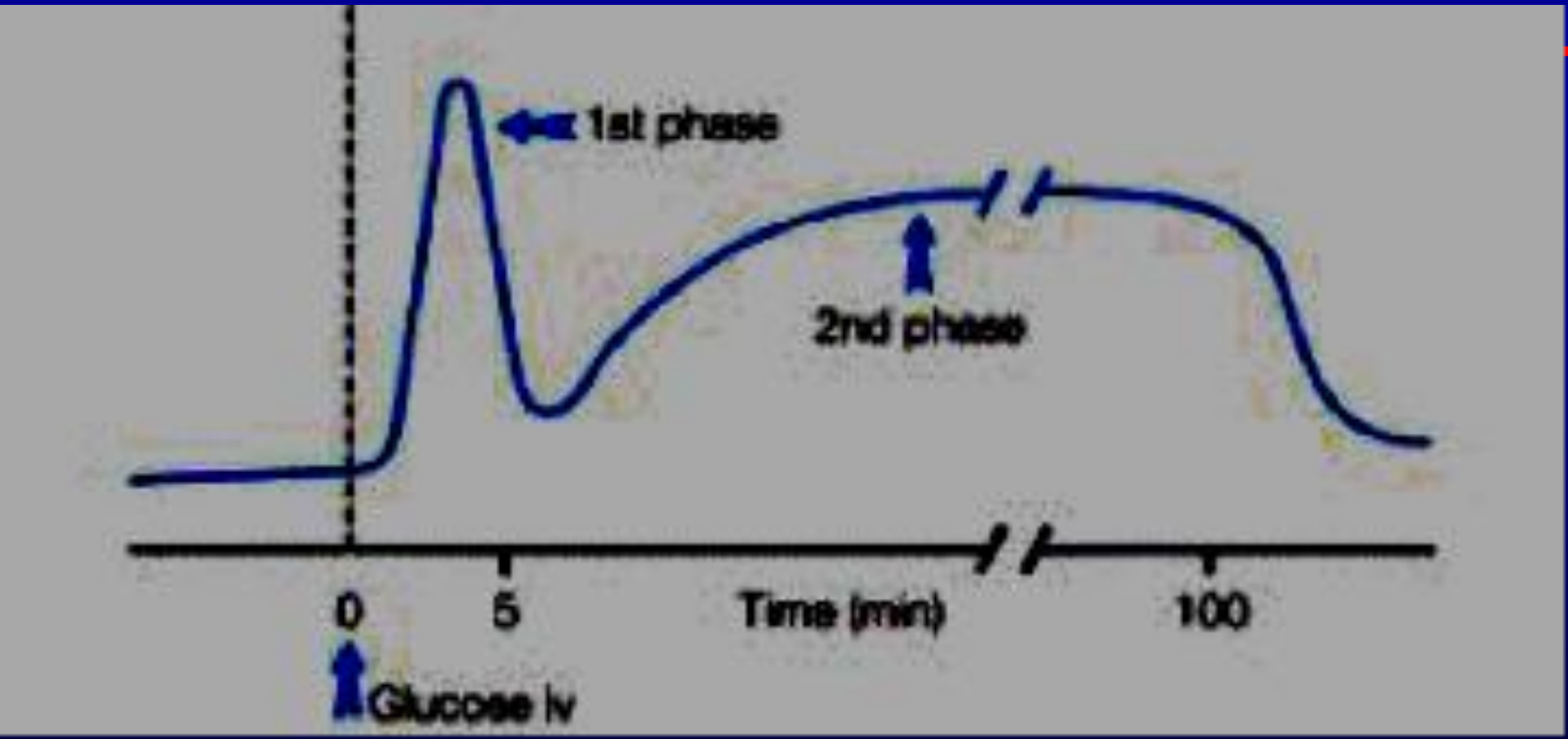
Ma, R. C. W. and Chan, J. C. N. (2009) Incidence of childhood type 1 diabetes: a worrying trend
***Nat. Rev. Endocrinol.* doi:10.1038/nrendo.2009.180**

nature REVIEWS ENDOCRINOLOGY

Natural History of "Pre"–Type 1 Diabetes



Eisenbarth GS. *N Engl J Med*. 1986;314:1360-1368


1st phase
2nd phase
0
5
Time (min)
100
Glucose iv

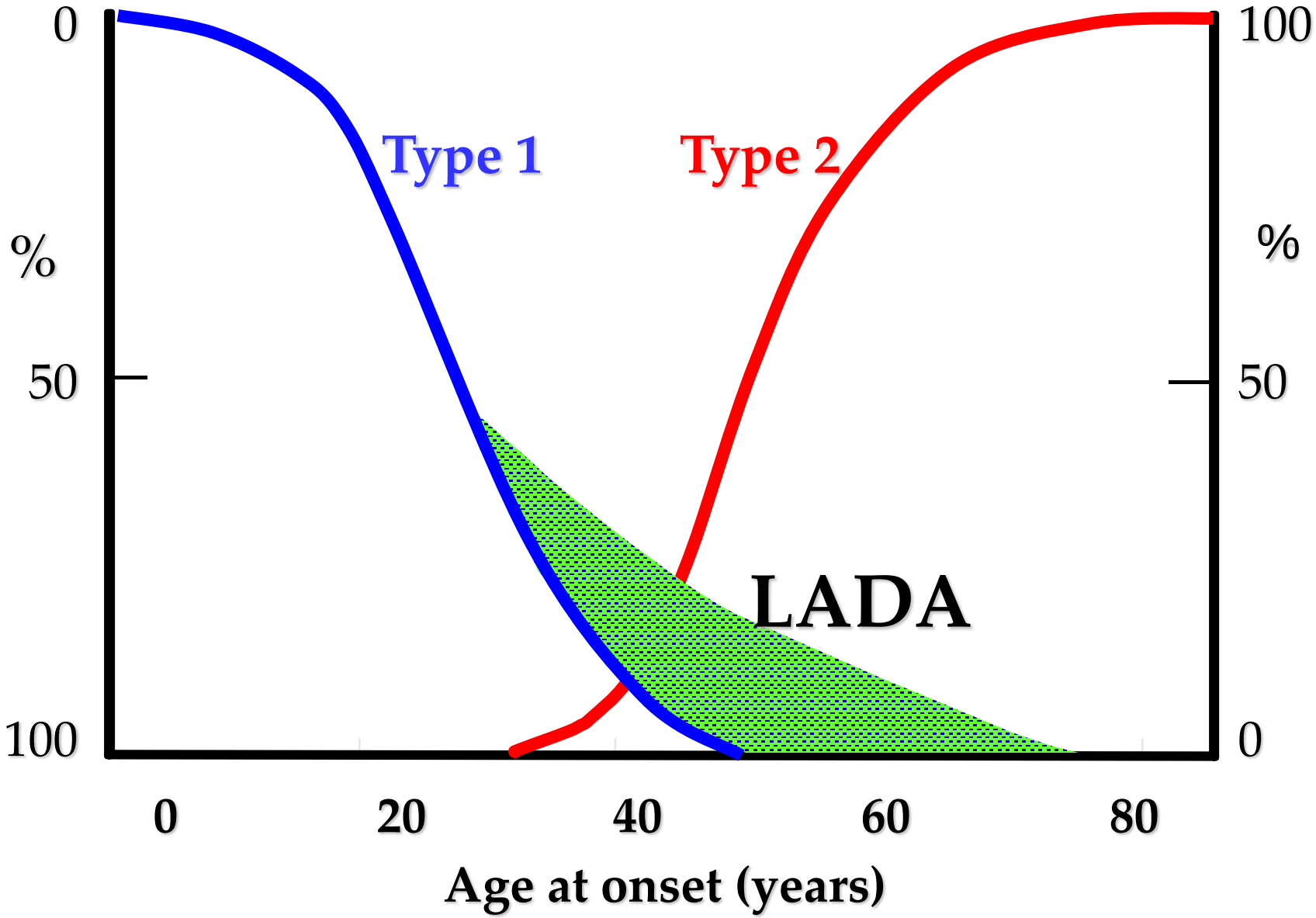
LADA

(Latent Autoimmune Diabetes in Adults)

- 1986: Ετερογενής ομάδα ο ΣΔ τύπου 2
  Αυτοαντισώματα και HLA συνδέονται
  με μειωμένη έκκριση ινσουλίνης
  (Kobaayshi et al., 1986, Bottazo et al., 1988, Lernmark et al., 1993)

- 1994: LADA (Zimmet et al.): Κριτήρια
  - *Διάγνωση σε ηλικία > 30 ετών*
  - *Γρήγορη έναρξη ινσουλινοθεραπείας*
  - *θετικά GAD 65 Abs.*
- 1996: Scherbaum et al., Hatziagelaki et al.,
  - *Συχνότης ασθενών με διαβήτη τύπου LADA 10-20%*

Cumulative prevalence of diabetes



Incidence of Type 1 Diabetes

- Incidence increasing by 3.4% per year
- 50% of patients diagnosed before age 20 years
- 50% of patients diagnosed *after* age 20 years
  - ***Often mistaken for type 2 diabetes—may make up 10% to 30% of individuals diagnosed with type 2 diabetes***
  - Oral agents ineffective; insulin therapy required
  - Autoimmune process slower and possibly different
  - Can usually be confirmed by beta cell antibodies
  - Loss of c-peptide

EURODIAB ACE Study Group. *Lancet.* 2000;355:873-876;
Naik RG, Palmer JP. *Curr Opin Endocrinol Diabetes.* 1997;4:308-315

DM Type I → *LADA*

DM Type I (WHO)

Ταχεία Εξέλιξη

Αργή → LADA

LADA

- Θετικά αυτοαντισώματα
- 30-50 ετών
- ↓ BMI
- διαιτα → OHD → ινσουλίνη

Δοκιμασία c-πεπτιδίου (normal)
(iv χορήγηση 1 mg γλυκαγόνης)

Χρόνος (min)	Γλυκόζη (mg/dl)	C-Πεπτίδιο (ng/ml)
-30	83	1.93
0	85	1.82
2	133	5.74
4	126	9.35
6	110	10.75
10	94	8.27
15	95	8.5

Δοκιμασία c-πεπτιδίου (type 1)

(iv χορήγηση 1 mg γλυκαγόνης)

Χρόνος (min)	Γλυκόζη (mg/dl)	C-Πεπτίδιο (ng/ml)
-30	201	0.3
0	208	0.2
2	240	0.2
4	270	0.3
6	330	0.4
10	320	0.4
15	278	0.3

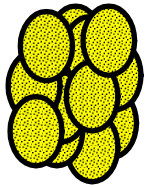
Δοκιμασία c-πεπτιδίου (LADA)

(iv χορήγηση 1 mg γλυκαγόνης)

Χρόνος (min)	Γλυκόζη (mg/dl)	C-Πεπτίδιο (ng/ml)
-30	160	1.1
0	175	1.1
2	190	1.6
4	206	1.9
6	210	2.6
10	200	1.9
15	160	1.8

Type 2 Diabetes: Major Metabolic Defects

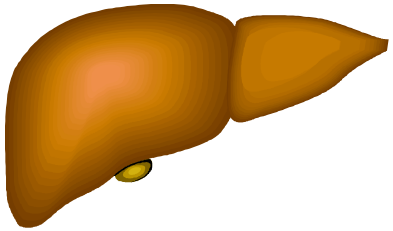
- Peripheral insulin resistance in muscle and fat



↑ *Lipolysis*
↓ clearance of TG
↓ glucose uptake
↓ glucose utilisation
↑ *FFA*

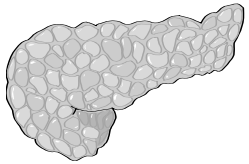
↓ clearance of TG
↓ *Glucose uptake*
↓ *Glucose utilisation*

- Hepatic insulin resistance



↑ *VLDL production*
↑ *Glucose output*
↓ glucose uptake
↓ glucose utilisation

- Relative insulin deficiency



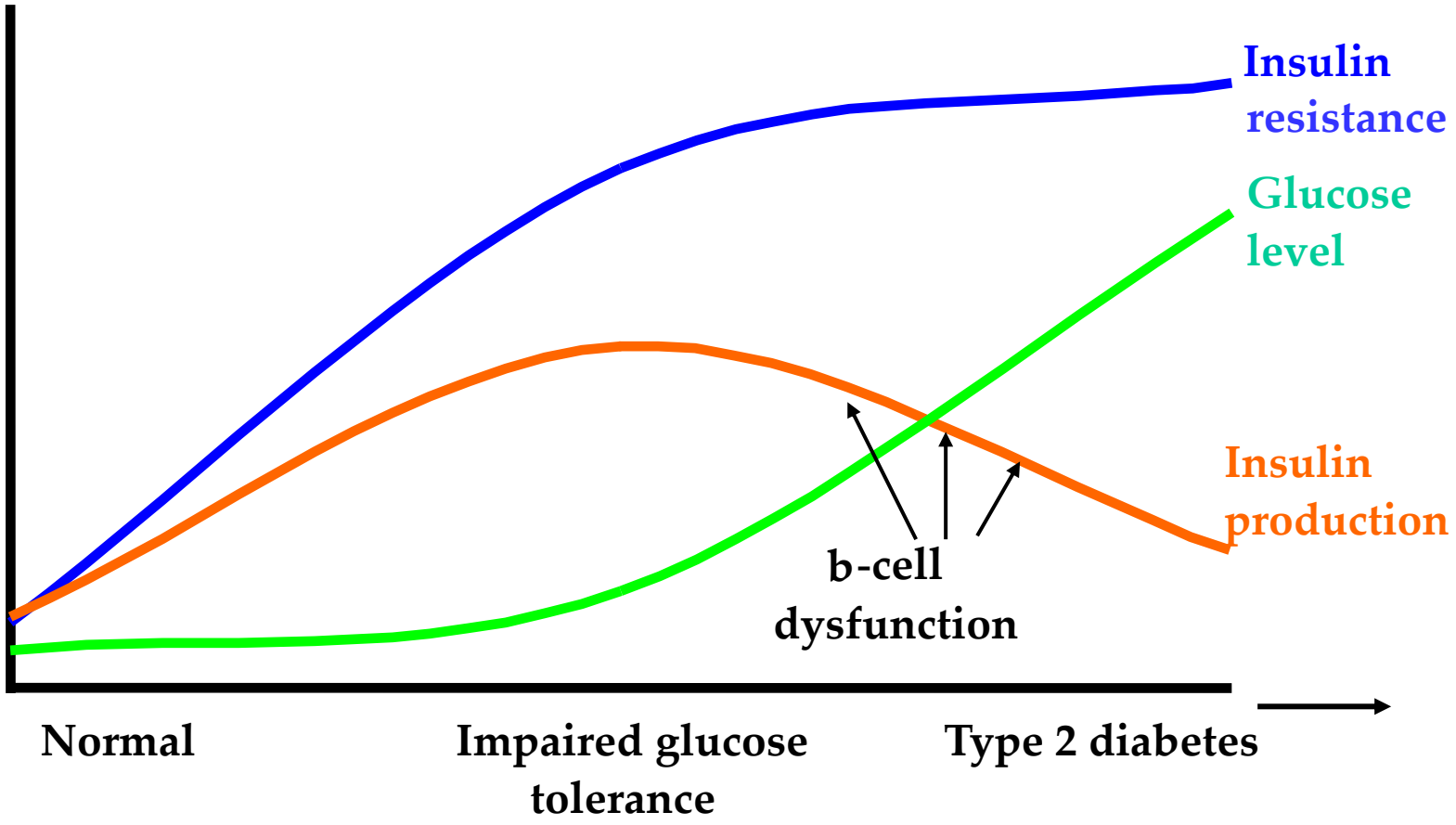
Insulin secretion not sufficient to overcome insulin resistance

Η μάζα του β-κυττάρου στον ΣΔ2

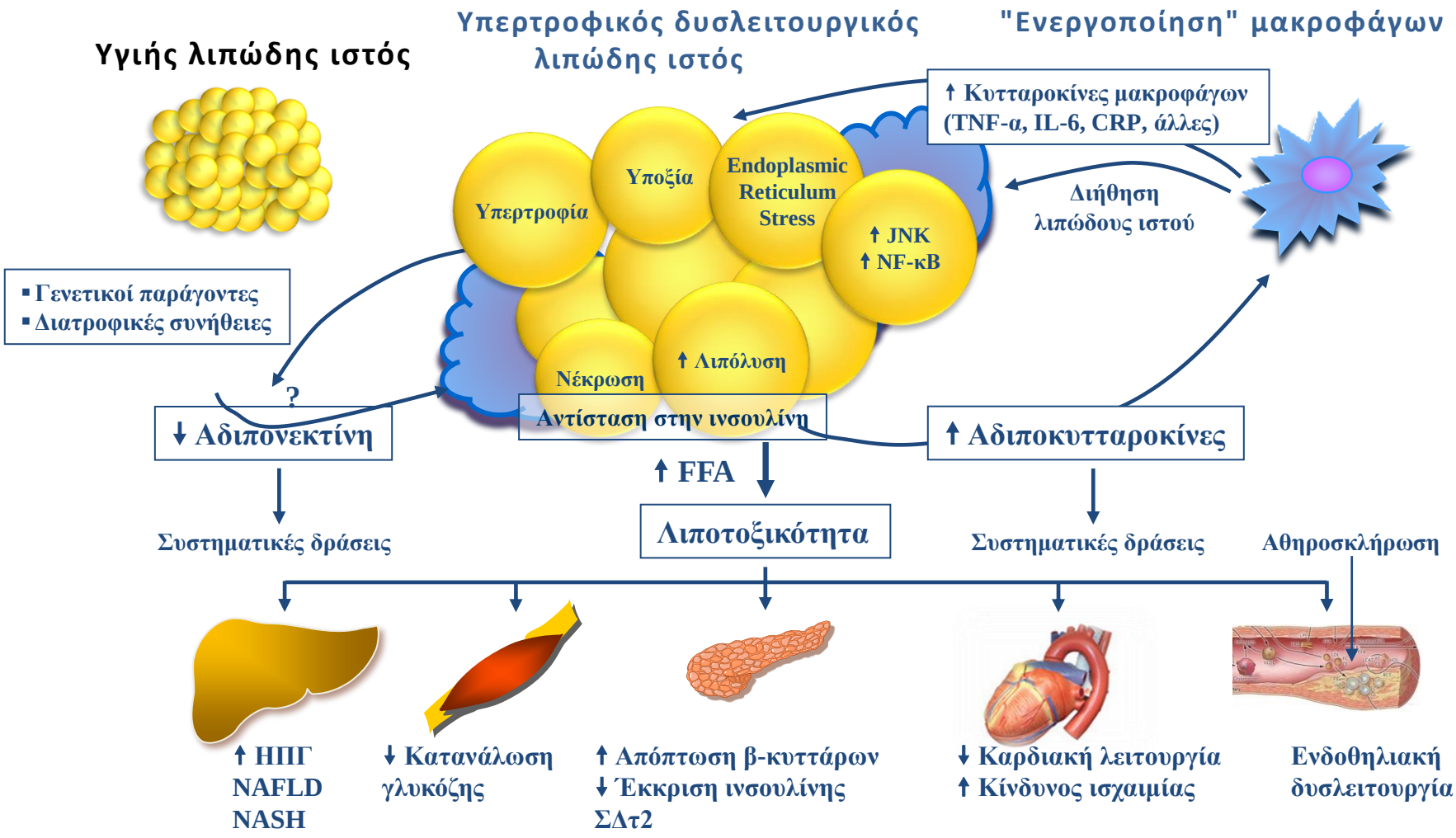
ND=non-diabetic; IFG=impaired fasting glucose; T2DM=Type 2 diabetes mellitus

Butler et al. *Diabetes.* 2003

Natural History of Type 2 Diabetes

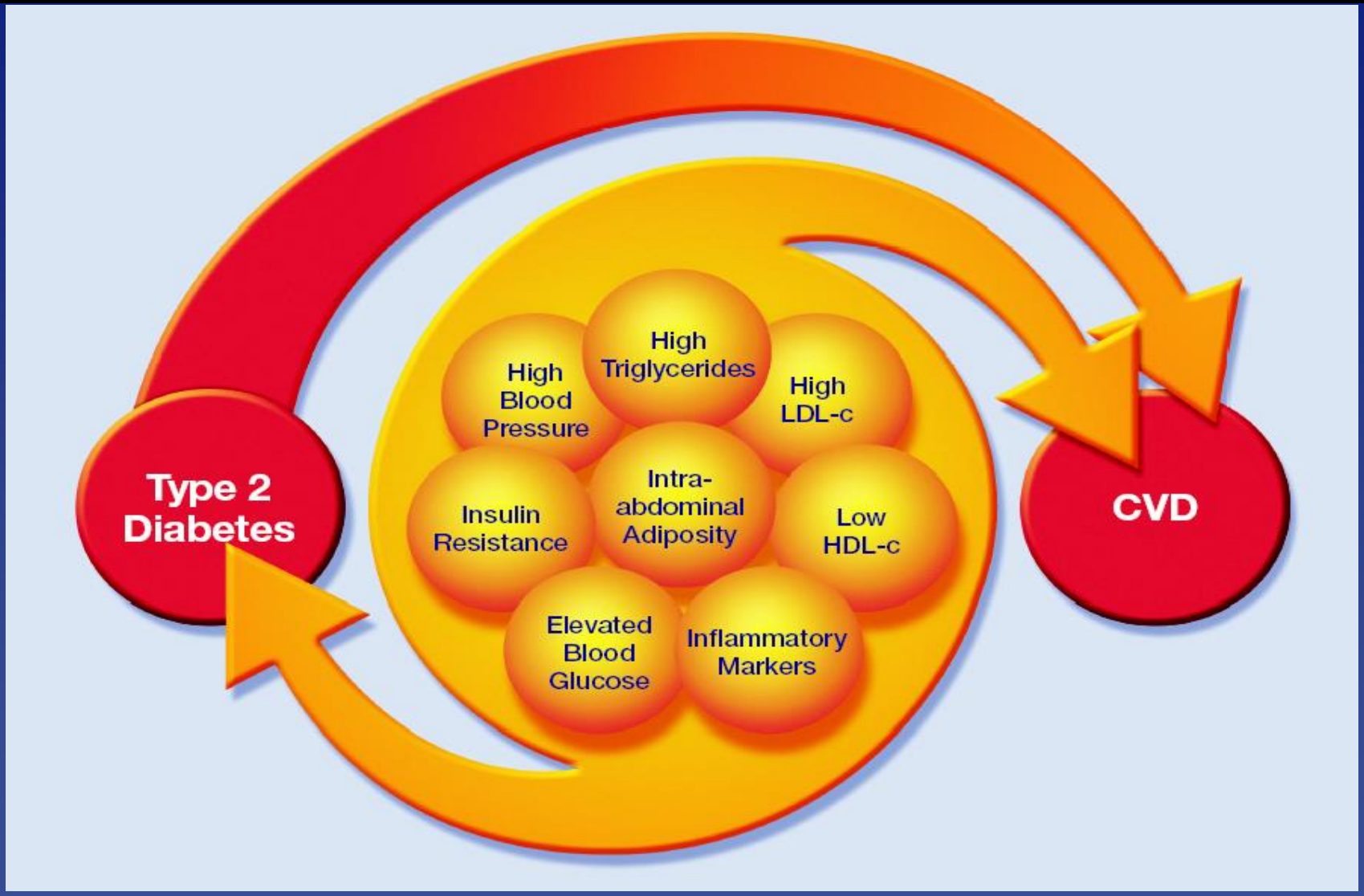


Ο ρόλος του λιπώδους ιστού



Cusi K. Curr Diab Rep 2010; 10:306-315

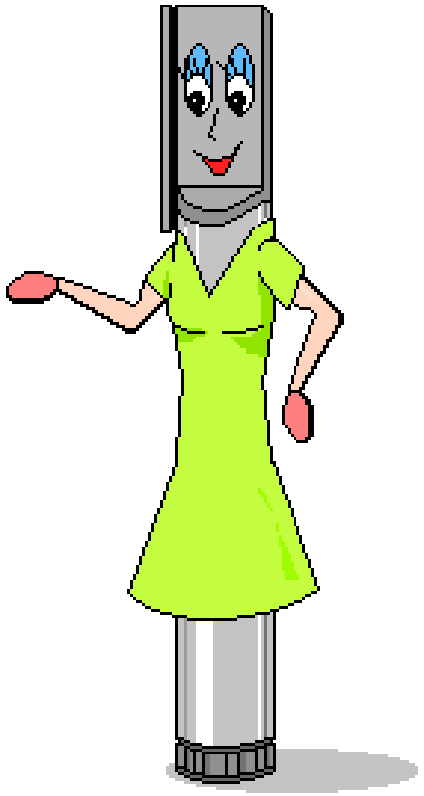
Global Cardiometabolic Risk*



Gelfand EV *et al*, 2006; Vasudevan AR *et al*, 2005

Διαταραγμένη Ανοχή στη Γλυκόζη (IGT)

- Αυτά τα άτομα δεν έχουν διαβήτη
- Έχουν υψηλότερη γλυκόζη αίματος από το φυσιολογικό αλλά χωρίς σαφή διαγνωστική αξία
- Περίπου το 25% αυτών θα αναπτύξουν κατά πάσα πιθανότητα διαβήτη



Impaired glucose tolerance (IGT) – usual development

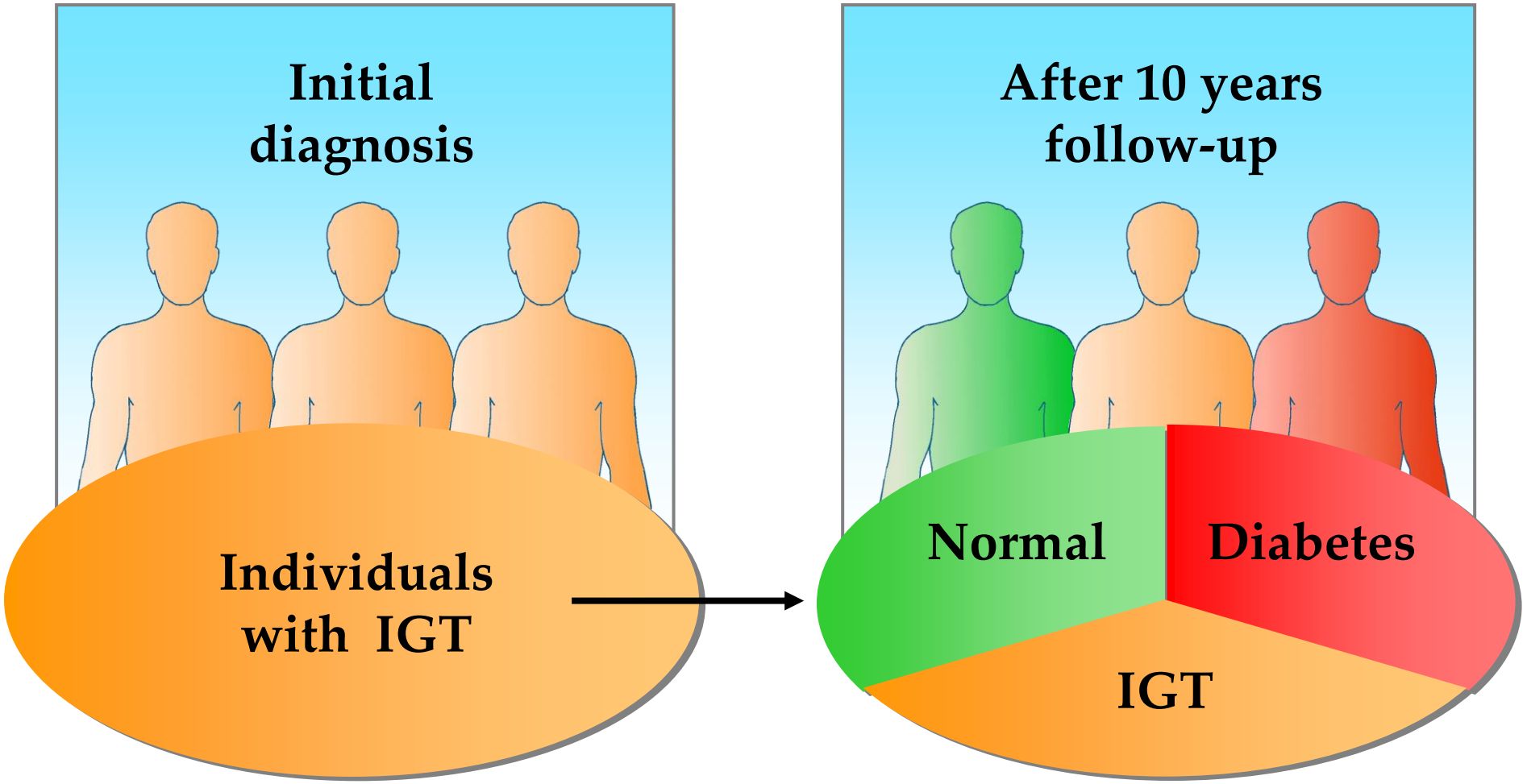


Table 2.2—Criteria defining prediabetes in nonpregnant individuals

A1C 5.7–6.4% (39–47 mmol/mol)
OR
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)

For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range. FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose.

Diagnosis and Classification of Diabetes:
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Classification (continued)

Diabetes can be classified into the following general categories:

1. **Type 1 diabetes** (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes of adulthood)
2. **Type 2 diabetes** (due to a non-autoimmune progressive loss of adequate β-cell insulin secretion, frequently on the background of insulin resistance and metabolic syndrome)
3. Specific types of diabetes due to other causes, e.g., **monogenic diabetes** syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), **diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV, or after organ transplantation)**
4. **Gestational diabetes mellitus** (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation or other types of diabetes occurring throughout pregnancy, such as type 1 diabetes).

Type 1 Diabetes

2.6 Screening for presymptomatic type 1 diabetes may be done by detection of autoantibodies to insulin, glutamic acid decarboxylase (GAD), islet antigen 2 (IA-2), or zinc transporter 8 (ZnT8). **B**

2.7 Having multiple confirmed islet autoantibodies is a risk factor for clinical diabetes. Testing for dysglycemia may be used to further forecast near-term risk. When multiple islet autoantibodies are identified, referral to a specialized center for further evaluation and/or consideration of a clinical trial or approved therapy to potentially delay development of clinical diabetes should be considered. **B**

2.8 Standardized islet autoantibody tests are recommended for classification of diabetes in adults who have phenotypic risk factors that overlap with those for type 1 diabetes (e.g., younger age at diagnosis, unintentional weight loss, ketoacidosis, or short time to insulin treatment). **E**

Table 2.3—Staging of type 1 diabetes

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• Autoimmunity • Overt hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple islet autoantibodies • No IGT or IFG	• Islet autoantibodies (usually multiple) • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Autoantibodies may become absent • Diabetes by standard criteria

Adapted from Skyler et al. (40). FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose. Alternative additional stage 2 diagnostic criteria of 30-, 60-, or 90-min plasma glucose on oral glucose tolerance test ≥200 mg/dL (≥11.1 mmol/L) and confirmatory testing in those aged ≥18 years have been used in clinical trials (79).

Diagnosis and Classification of Diabetes:
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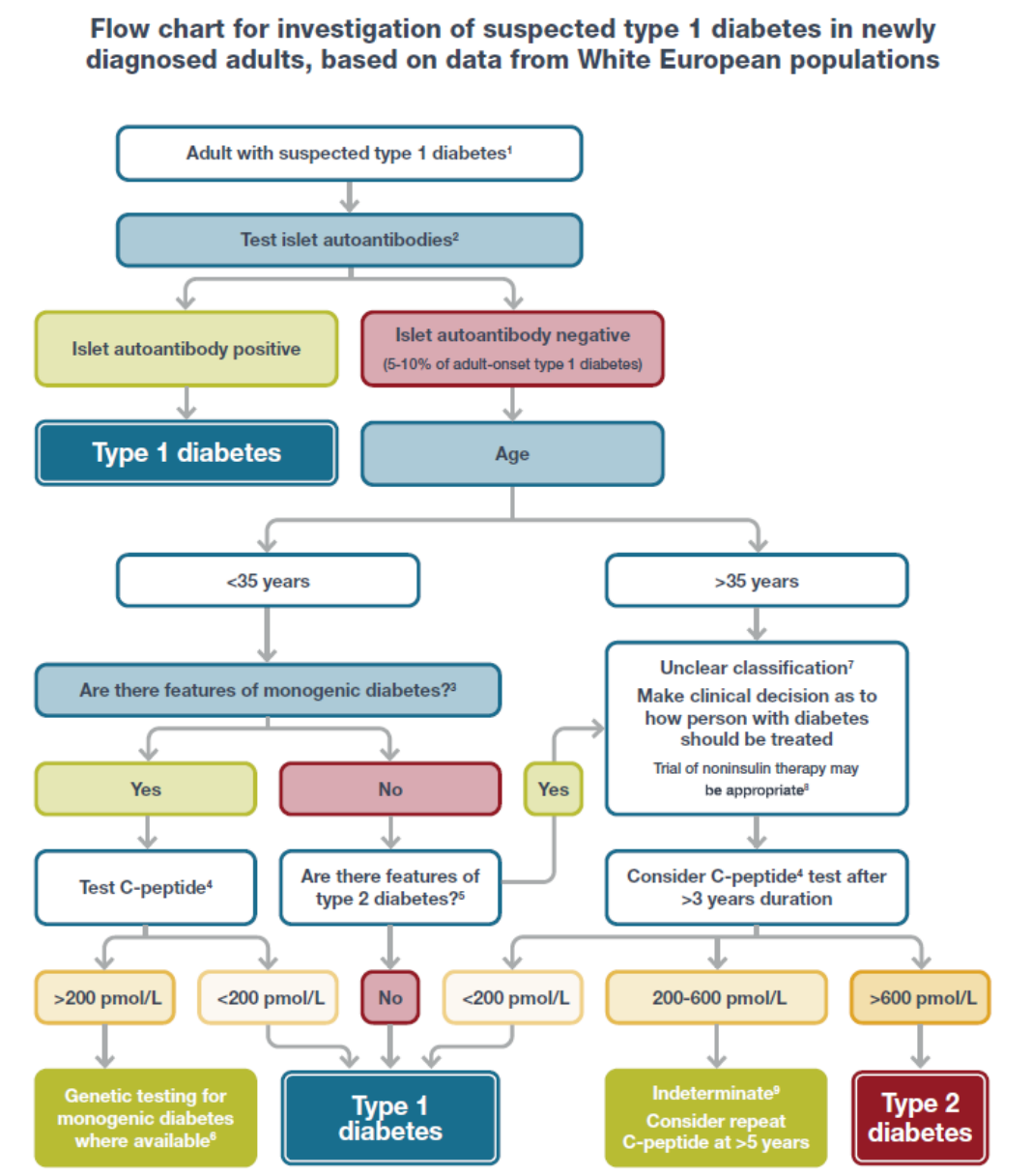
DIAGNOSIS AND CLASSIFICATION OF DIABETES



Diagnosis and Classification of Diabetes:
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Prediabetes and Type 2 Diabetes

2.9 Screening for prediabetes and type 2 diabetes with an assessment of risk factors or validated risk calculator should be done in asymptomatic adults. **B**

2.10a Testing for prediabetes or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity who have one or more risk factors **(Table 2.4).** **B** Testing for prediabetes or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity who have one or more risk factors **(Table 2.4)**. **B**

2.10b For all other people, screening should begin at age 35 years. **B**

Prediabetes and Type 2 Diabetes (continued)

2.11 If tests are normal, repeat screening recommended at a minimum of 3-year intervals is reasonable, sooner with symptoms or change in risk (e.g., weight gain). **C**

2.12 To screen for prediabetes and type 2 diabetes, FPG, 2-h PG during 75-g OGTT, and A1C are each appropriate **(Table 2.1 and Table 2.2).** **B**

2.13 When using OGTT as a screen for prediabetes or diabetes, adequate carbohydrate intake (at least 150 g/day) should be assured for 3 days prior to testing. **A**

Prediabetes and Type 2 Diabetes (continued)

2.14 Risk-based screening for prediabetes or type 2 diabetes should be considered after the onset of puberty or after 10 years of age, whichever occurs earlier, in children and adolescents with overweight (BMI ≥ 85th percentile) or obesity (BMI ≥ 95th percentile) and who have one or more risk factors for diabetes. (See **Table 2.5** for evidence grading of risk factors.) **B**

2.15a Consider screening people for prediabetes or diabetes if on certain medications, such as glucocorticoids, statins, thiazide diuretics, some HIV medications, and second-generation antipsychotic medications, as these agents are known to increase the risk of these conditions. **E**

Table 2.4—Criteria for screening for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in adults with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian American individuals) who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race and ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of cardiovascular disease
   - Hypertension (≥130/80 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (<0.9 mmol/L) and/or a triglyceride level >250 mg/dL (>2.8 mmol/L)
   - Individuals with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. People with prediabetes (A1C ≥5.7% [≥39 mmol/mol], IGT, or IFG) should be tested yearly.
3. People who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other people, testing should begin at age 35 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.
6. People with HIV, exposure to high-risk medicines, history of pancreatitis

GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Diagnosis and Classification of Diabetes:
***Standards of Care in Diabetes - 2024. Diabetes Care* 2024;47(Suppl. 1):S20-S42**

American Diabetes Association.
Connected for Life.

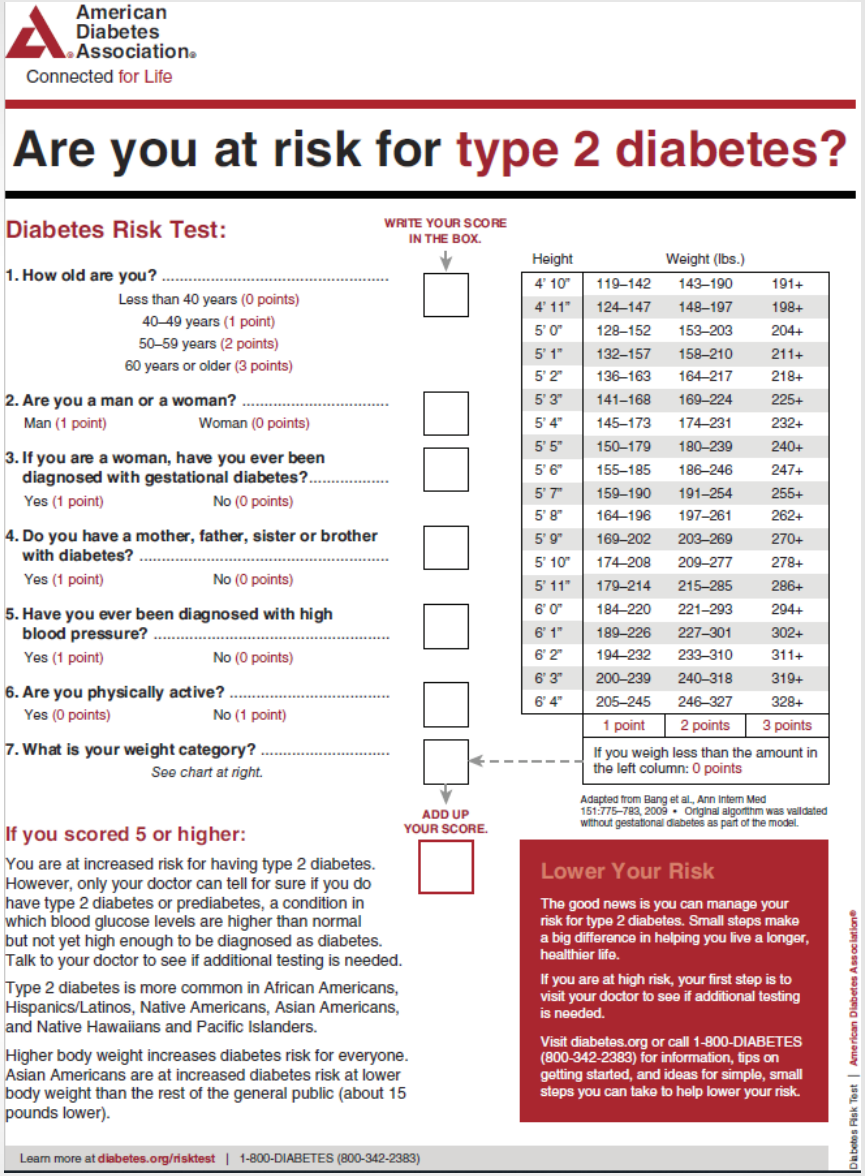
Table 2.5—Risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting

Screening should be considered in youth* who have overweight (≥85th percentile) or obesity (≥95th percentile) A and who have one or more additional risk factors based on the strength of their association with diabetes:

- Maternal history of diabetes or GDM during the child's gestation A
- Family history of type 2 diabetes in first- or second-degree relative A
- Race and ethnicity (e.g., Native American, African American, Latino, Asian American, Pacific Islander) A
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight) B

GDM, gestational diabetes mellitus. *After the onset of puberty or after 10 years of age, whichever occurs earlier. If tests are normal, repeat testing at a minimum of 3-year intervals (or more frequently if BMI is increasing or risk factor profile is deteriorating) is recommended. Reports of type 2 diabetes before age 10 years exist, and this can be considered with numerous risk factors.

diabetes.org/socrisktest



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Are you at risk for type 2 diabetes?

Diabetes Risk Test:

WRITE YOUR SCORE IN THE BOX.

1. How old are you?
Less than 40 years (0 points)
40–49 years (1 point)
50–59 years (2 points)
60 years or older (3 points)

2. Are you a man or a woman?
Man (1 point) Woman (0 points)

3. If you are a woman, have you ever been diagnosed with gestational diabetes?
Yes (1 point) No (0 points)

4. Do you have a mother, father, sister or brother with diabetes?
Yes (1 point) No (0 points)

5. Have you ever been diagnosed with high blood pressure?
Yes (1 point) No (0 points)

6. Are you physically active?
Yes (0 points) No (1 point)

7. What is your weight category?
See chart at right.

Height	Weight (lbs.)		
4' 10"	119–142	143–190	191+
4' 11"	124–147	148–197	198+
5' 0"	128–152	153–203	204+
5' 1"	132–157	158–210	211+
5' 2"	136–163	164–217	218+
5' 3"	141–168	169–224	225+
5' 4"	145–173	174–231	232+
5' 5"	150–179	180–239	240+
5' 6"	155–185	186–246	247+
5' 7"	159–190	191–254	255+
5' 8"	164–196	197–261	262+
5' 9"	169–202	203–269	270+
5' 10"	174–208	209–277	278+
5' 11"	179–214	215–285	286+
6' 0"	184–220	221–293	294+
6' 1"	189–226	227–301	302+
6' 2"	194–232	233–310	311+
6' 3"	200–239	240–318	319+
6' 4"	205–245	246–327	328+
	1 point	2 points	3 points

If you weigh less than the amount in the left column: 0 points

Adapted from Bang et al., Ann Intern Med 151:775–783, 2009 • Original algorithm was validated without gestational diabetes as part of the model.

ADD UP YOUR SCORE.

If you scored 5 or higher:

You are at increased risk for having type 2 diabetes. However, only your doctor can tell for sure if you do have type 2 diabetes or prediabetes, a condition in which blood glucose levels are higher than normal but not yet high enough to be diagnosed as diabetes. Talk to your doctor to see if additional testing is needed.

Type 2 diabetes is more common in African Americans, Hispanics/Latinos, Native Americans, Asian Americans, and Native Hawaiians and Pacific Islanders.

Higher body weight increases diabetes risk for everyone. Asian Americans are at increased diabetes risk at lower body weight than the rest of the general public (about 15 pounds lower).

Lower Your Risk

The good news is you can manage your risk for type 2 diabetes. Small steps make a big difference in helping you live a longer, healthier life.

If you are at high risk, your first step is to visit your doctor to see if additional testing is needed.

Visit diabetes.org or call 1-800-DIABETES (800-342-2383) for information, tips on getting started, and ideas for simple, small steps you can take to help lower your risk.

Learn more at diabetes.org/risktest | 1-800-DIABETES (800-342-2383)

Diabetes Risk Test | American Diabetes Association®

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American Diabetes Association.
Connected for Life.

Pancreatic Diabetes or Diabetes in the Context of the Exocrine Pancreas

2.17 Screen people for diabetes within 3–6 months following an episode of acute pancreatitis and annually thereafter. Screening for diabetes is recommended annually for people with chronic pancreatitis. **E**

Cystic Fibrosis-Related Diabetes

2.18 Annual screening for cystic fibrosis-related diabetes (CFRD) with an OGTT should begin by age 10 years in all people with cystic fibrosis not previously diagnosed with CFRD. **B**

2.19 A1C is not recommended as a screening test for CFRD due to low sensitivity. However, a value of ≥ 6.5% (≥48 mmol/mol) is consistent with a diagnosis of CFRD. **B**

2.20 Beginning 5 years after the diagnosis of CFRD, annual monitoring for complications of diabetes is recommended. **E**

Posttransplantation Diabetes Mellitus

2.21 After organ transplantation, screening for hyperglycemia should be done. A formal diagnosis of posttransplantation diabetes mellitus (PTDM) is best made once the individual is stable on an immunosuppressive plan and in the absence of an acute infection. **B**

2.22 The OGTT is the preferred test to make a diagnosis of PTDM. **B**

2.23 Immunosuppressive plans shown to provide the best outcomes for individuals and graft survival should be used, irrespective of PTDM risk. **E**

Monogenic Diabetes Syndromes

2.24a Regardless of current age, all people diagnosed with diabetes in the first 6 months of life should have immediate genetic testing for neonatal diabetes. **A**

2.24b Children and young adults who do not have typical characteristics of type 1 or type 2 diabetes and who often have a family history of diabetes in successive generations (suggestive of an autosomal dominant pattern of inheritance) should have genetic testing for maturity-onset diabetes of the young (MODY). **A**

2.24c In both instances, consultation with a center specializing in diabetes genetics is recommended to understand the significance of genetic mutations and how best to approach further evaluation, treatment, and genetic counseling. **E**

Table 2.6—Most common causes of monogenic diabetes

	Gene	Inheritance	Clinical features
MODY	*HNF1A*	AD	HNF1A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2-h PG level on OGTT (>90 mg/dL [>5 mmol/L]); sensitive to sulfonylureas
	HNF4A	AD	HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight and transient neonatal hypoglycemia; sensitive to sulfonylureas
	HNF1B	AD	HNF1B-MODY: developmental renal disease (typically cystic); genitourinary abnormalities; atrophy of the pancreas; hyperuricemia; gout
	GCK	AD	GCK-MODY: higher glucose threshold (set point) for glucose-stimulated insulin secretion, causing stable, nonprogressive elevated fasting blood glucose; typically does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (<54 mg/dL [<3 mmol/L])
Neonatal diabetes	*KCNJ11*	AD	Permanent or transient: IUGR; possible developmental delay and seizures; responsive to sulfonylureas
	INS	AD	Permanent: IUGR; insulin requiring
	ABCC8	AD	Permanent or transient: IUGR; rarely developmental delay; responsive to sulfonylureas
	6q24 (*PLAGL1*, *HYMA1*)	AD for paternal duplications	Transient: IUGR; macroglossia; umbilical hernia; mechanisms include UPD6, paternal duplication, or maternal methylation defect; may be treatable with medications other than insulin
	GATA6	AD	Permanent: pancreatic hypoplasia; cardiac malformations; pancreatic exocrine insufficiency; insulin requiring
	EIF2AK3	AR	Permanent: Wolcott-Rallison syndrome: epiphyseal dysplasia; pancreatic exocrine insufficiency; insulin requiring
	EIF2B1	AD	Permanent diabetes: can be associated with fluctuating liver function (157)
	FOXP3	X-linked	Permanent: immunodysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome: autoimmune diabetes, autoimmune thyroid disease, exfoliative dermatitis; insulin requiring

Adapted from Carmody et al. (156). AD, autosomal dominant; AR, autosomal recessive; IUGR, intrauterine growth restriction; OGTT, oral glucose tolerance test; UPD6, uniparental disomy of chromosome 6; 2-h PG, 2-h plasma glucose.

Maturity-Onset Diabetes of the Young (MODY)

1975 Ορισμός

- **ΣΔ 2 σε νεαρά άτομα**

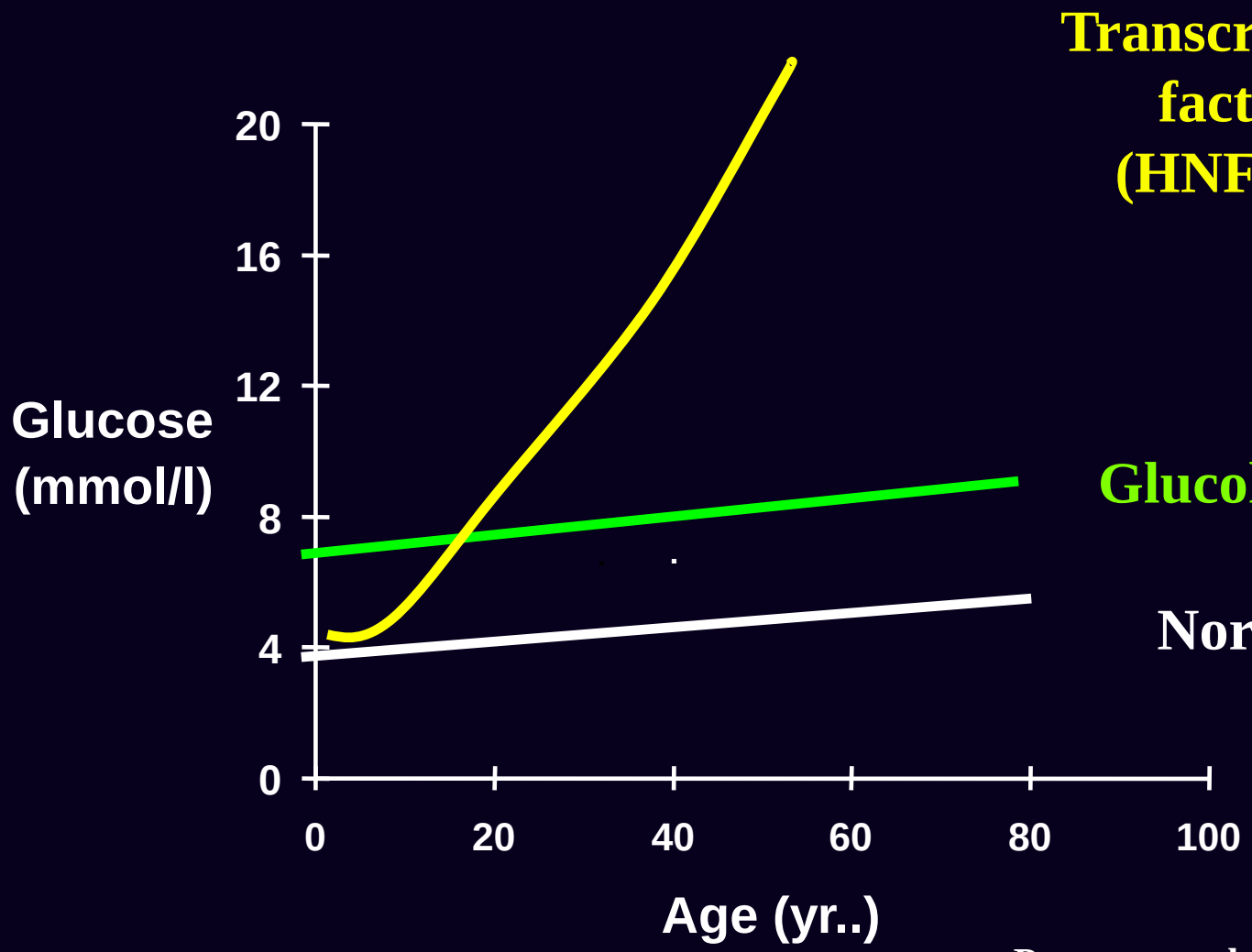
και

- **Αυτοσωμικός επικρατούν τύπος κληρονομικότητας**

Σύγχρονος ορισμός του MODY

- Ετερογενής διαταραχή οφειλόμενη σε ετερόζυγο μονογονιδιακή μετάλλαξη σε ένα από τουλάχιστον 6 γονίδια
- Εμφάνιση του διαβήτη σε νεαρή ηλικία: παιδιά, έφηβοι, νέοι ενήλικες
- Αυτοσωμικός επικρατούν τύπος κληρονομικότητας
- Πρωτοπαθές ελάττωμα στην έκκριση ινσουλίνης

Two subtypes of MODY
Glucokinase and Transcription factor



Pearson, et al Diabetes 2001

Glucokinase and Transcription factor diabetes rather than "MODY"

MODY

Glucokinase mutations

- έναρξη μετά τη γέννηση
- Σταθερή υπεργλυκαιμία
- Θεραπεία κυρίως με δίαιτα
- Επιπλοκές σπάνιες

Transcription factor mutations

(HNF-1α, HNF-1β, HNF-4α)

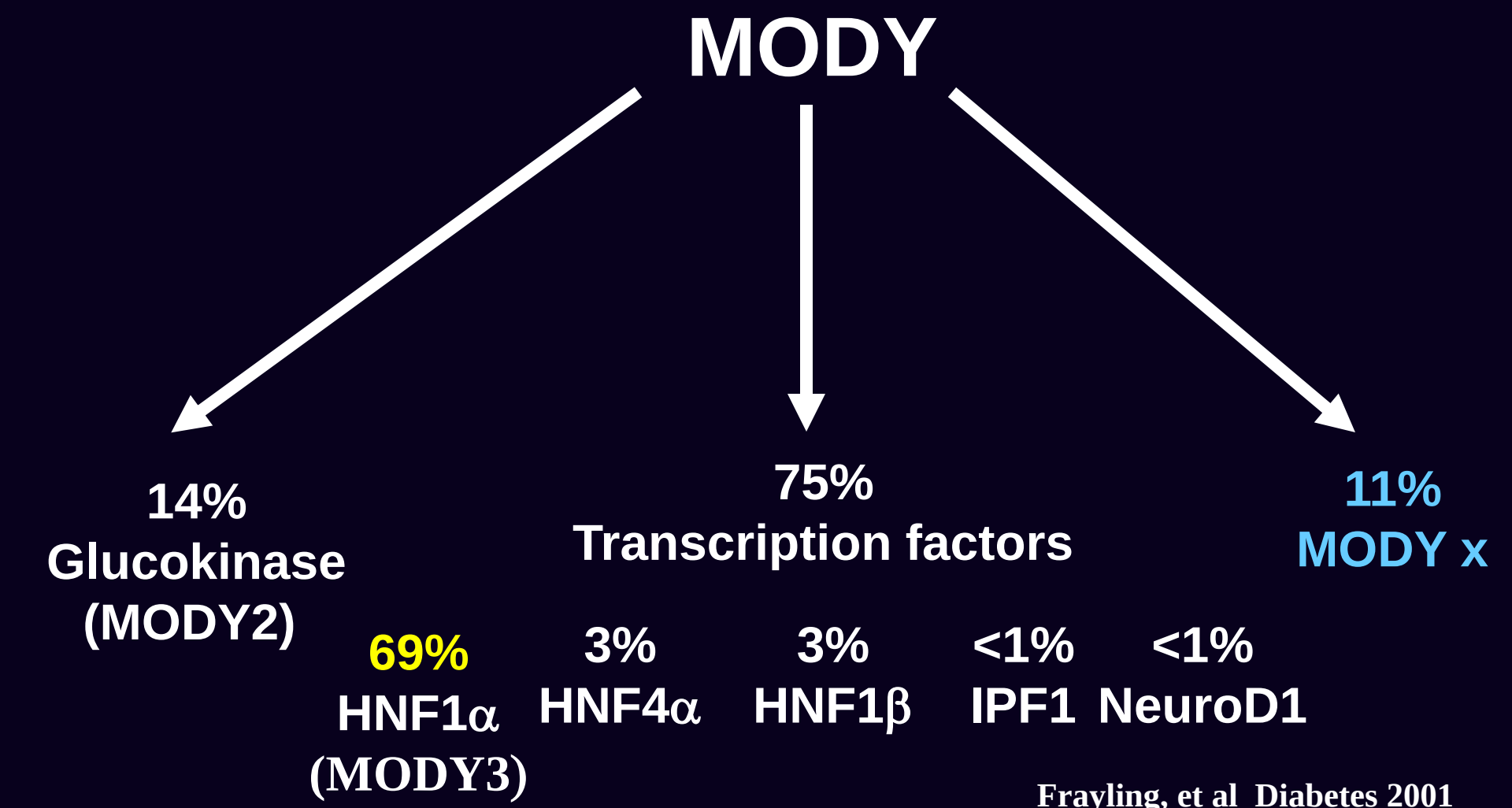
- Εμφάνιση στην εφηβεία/νεανική ηλικία
- Προοδευτικά επιδεινούμενη υπεργλυκαιμία
- 1/3 δίαιτα, 1/3 ΟΗΑ, 1/3 ινσουλίνη
- Επιπλοκές συχνές

Heterozygous Gene Mutations Identified in MODY

Name (Year)	Gene	Chromosome
MODY1 (1991)	HNF-4α	20q
MODY2 (1993)	Glucokinase	7p
MODY3 (1996)	HNF-1α	12q
MODY4 (1997)	IPF-1 (PDX-1)	13q
MODY5 (1997)	HNF-1β	17q
MODY6 (1999)	Neuro-D1 / BETA-2	2q

HNF = Hepatocyte nuclear factor
IPF = Insulin promoter factor
PDX-1 = Pancreatic duodenal homeobox-1

The Genetic Causes of MODY



Frayling, et al Diabetes 2001

Homozygous Mutations of MODY-Related Genes

- **Μόνιμος νεογνικός διαβήτης (PND) που προκύπτει από ομόζυγη μετάλλαξη στα γονίδια:**
  - **Glucokinase gene**
  - **Insulin promoter factor (IPF-1) gene**

MODY (2)-Related Proteins

- **Γλυκοκινάση**
  - **Εκφράζεται στα β-κύτταρα και στο ήπαρ**
  - **Καταλύει τη μεταφορά του φωσφόρου από το ATP στη γλυκόζη, δημιουργώντας τη G-6-P, ένα μόριο κλειδί στο μεταβολισμό της γλυκόζης**
  - **“Glucose sensor” στα β-κύτταρα**
  - **Ευοδώνει τη γλυκογονοσύνθεση στο ήπαρ**

Glucokinase (MODY2)

1. Σπάνια αναγνωρίζεται σε νοσηλευόμενους.

   Περιστασιακή υπεργλυκαιμία σε παιδιά

   Συχνά εμφανίζεται ως διαβήτης κύησης

2. Εμμένουσα υπεργλυκαιμία νηστείας (5.5-9 mmol/l)

   από την γέννηση. Μικρή αύξηση στην OGTT (< 3mmol/l)

3. Χωρίς εξωπαγκρεατικές εκδηλώσεις.

   Απουσία παχυσαρκίας συνήθως

3. Συχνά ασυμπτωματικός

4. Απαραίτητος ο έλεγχος των γονιών

MODY (1,3,5)-Related Proteins

[2/4]

- **Μεταγραφικοί παράγοντες στο ήπαρ**

  HNF-4a, HNF-1a and HNF-1b

  - **Εκφράζονται στο ήπαρ αλλά και στα νησίδια, τους νεφρούς και τις γονάδες.**
  - **Τροποποιούν την έκφραση του γονιδίου της ινσουλίνης και πρωτεϊνών που ενέχονται στη μεταφορά και το μεταβολισμό της γλυκόζης, αλλά και στο μεταβολισμό των μιτοχονδρίων.**

HNF1α (MODY3)

1. Η συχνότερη μορφή MODY. Συχνά διαγιγνώσκεται ως τύπος 1
2. Τυπικά αναπτύσσεται 12-30 yr
3. FPG μπορεί να είναι φυσιολογική αρχικά.

   Μεγάλη αύξηση (>5mmol/l) στην OGTT
2. Επιδείνωση στης υπεργλυκαιμίας με το χρόνο.
3. Χαμηλός νεφρικός ουδός (γλυκοζουρία).
4. Απουσία παχυσαρκίας συνήθως
5. Γονείς και παππούδες συνήθως διαβητικοί
6. *Ιδιαίτερα χαμηλή τιμή CRP*

MODY (4)-Related Proteins [3/4]

- **Μεταγραφικός παράγων IPF-1**
  - **Εκφράζεται στα παγκρεατικά κύτταρα**
  - **Ρυθμίζει τη μεταγραφή πολλών γονιδίων, όπως αυτά της ινσουλίνης, σωματοστατίνης, του αμυλοειδούς πολυπεπτιδίου του παγκρέατος, της γλυκοκινάσης και του GLUT-2**
  - **Τροποποιεί τη γλυκοζοεξαρτώμενη ενεργοποίηση του γονιδίου της ινσουλίνης**

MODY (6)-Related Proteins [4/4]

- **Μεταγραφικός παράγων Neuro-D1 (BETA2)**
  - **Εκφράζεται στα νησίδια**
  - **Ενεγοποιεί τη μεταγραφή του γονιδίου της ινσουλίνης**
  - **Χρειάζεται για την ομαλή ανάπτυξη των νησιδίων**

Φαινοτυπική έκφραση και φυσική ιστορία του MODY

- **Αναγνώριση σε νεαρή ηλικία**
  - **Κάτω από 25 ετών**
  - **7-13 ετών ή νεότερα άτομα, αν γίνει γλυκαιμικός έλεγχος στις νεότερες γενιές**
- **Μη-προοδευτική ή ελάχιστα προοδευτική νόσος**
  - **Απάντηση στη δίαιτα και/ή στα αντιυπεργλυκαιμικά δισκία για χρόνια/ δεκαετίες**
  - **Δύναται να εξελιχθεί σε ινσουλινοθεραπευόμενο ΣΔ (μη-ινσουλινοεξαρτώμενο, χωρίς κέτωση)**
  - **Δύναται σπανιότερα να έχει ταχεία εξέλιξη από τη νεαρή ηλικία**

The diagnosis of monogenic diabetes should be considered in children and adults diagnosed with diabetes in early adulthood with the following findings:

- Diabetes diagnosed within the first 6 months of life (with occasional cases presenting later, mostly *INS* and *ABCC8* mutations)
- Diabetes without typical features of type 1 or type 2 diabetes (negative diabetes-associated autoantibodies, no obesity, and lacking other metabolic features, especially with strong family history of diabetes)
- Stable, mild fasting hyperglycemia (100–150 mg/dL [5.6–8.5 mmol/L]), stable A1C between 5.6% and 7.6% (between 38 and 60 mmol/mol), especially if no obesity

Gestational Diabetes Mellitus

2.25 In individuals who are planning pregnancy, screen those with risk factors **(Table 2.4)** **B** and consider testing all individuals of childbearing potential for undiagnosed prediabetes or diabetes. **E**

2.26a Before 15 weeks of gestation, test individuals with risk factors **(Table 2.4)** **B** and consider testing all individuals **E** for undiagnosed diabetes at the first prenatal visit using standard diagnostic criteria if not screened preconception.

2.26b Before 15 weeks of gestation, screen for abnormal glucose metabolism to identify individuals who are at higher risk of adverse pregnancy and neonatal outcomes, are more likely to need insulin, and are at high risk of a later gestational diabetes mellitus (GDM) diagnosis. **B** Early treatment for individuals with abnormal glucose metabolism may provide some benefit. **E**

Gestational Diabetes Mellitus (continued)

2.26c Screen for early abnormal glucose metabolism with dysglycemia using FPG of 110–125 mg/dL (6.1–6.9 mmol/L) or A1C 5.9–6.4% (41–47 mmol/mol). **B**

2.27 Screen for GDM at 24–28 weeks of gestation in pregnant individuals not previously found to have diabetes or high-risk abnormal glucose metabolism detected earlier in the current pregnancy. **A**

2.28 Screen individuals with GDM for prediabetes or diabetes at 4–12 weeks postpartum, using the 75-g OGTT and clinically appropriate nonpregnancy diagnostic criteria. **A**

2.29 Individuals with a history of GDM should have lifelong screening for the development of prediabetes or diabetes at least every 3 years. **B**

ΚΡΙΤΗΡΙΑ ΔΙΑΓΝΩΣΗΣ ΣΑΚΧΑΡΩΔΗ ΔΙΑΒΗΤΗ ΣΕ ΕΓΚΥΜΟΣΥΝΗ

Έλεγχος σε 24-28 εβδομάδες

75gr glu, 2h OGGT

Σάκχαρο νηστείας (mg/dl)	92
Σάκχαρο 1 ώρα mg/dl	180
Σάκχαρο 2ώρες mg/dl	153

Diagnosis and Classification of Diabetes:
***Standards of Care in Diabetes - 2024. Diabetes Care* 2024;47(Suppl. 1):S20-S42**

Φαινοτυπική έκφραση ΣΔ2 στους νέους

The risk is changing in children due to: a) less physical activity, b) increased food intake, c) obesity

Hormone Research 2003; 59 (Suppl 1): 77-84.

SEARCH Findings

In young people with type 2 diabetes:

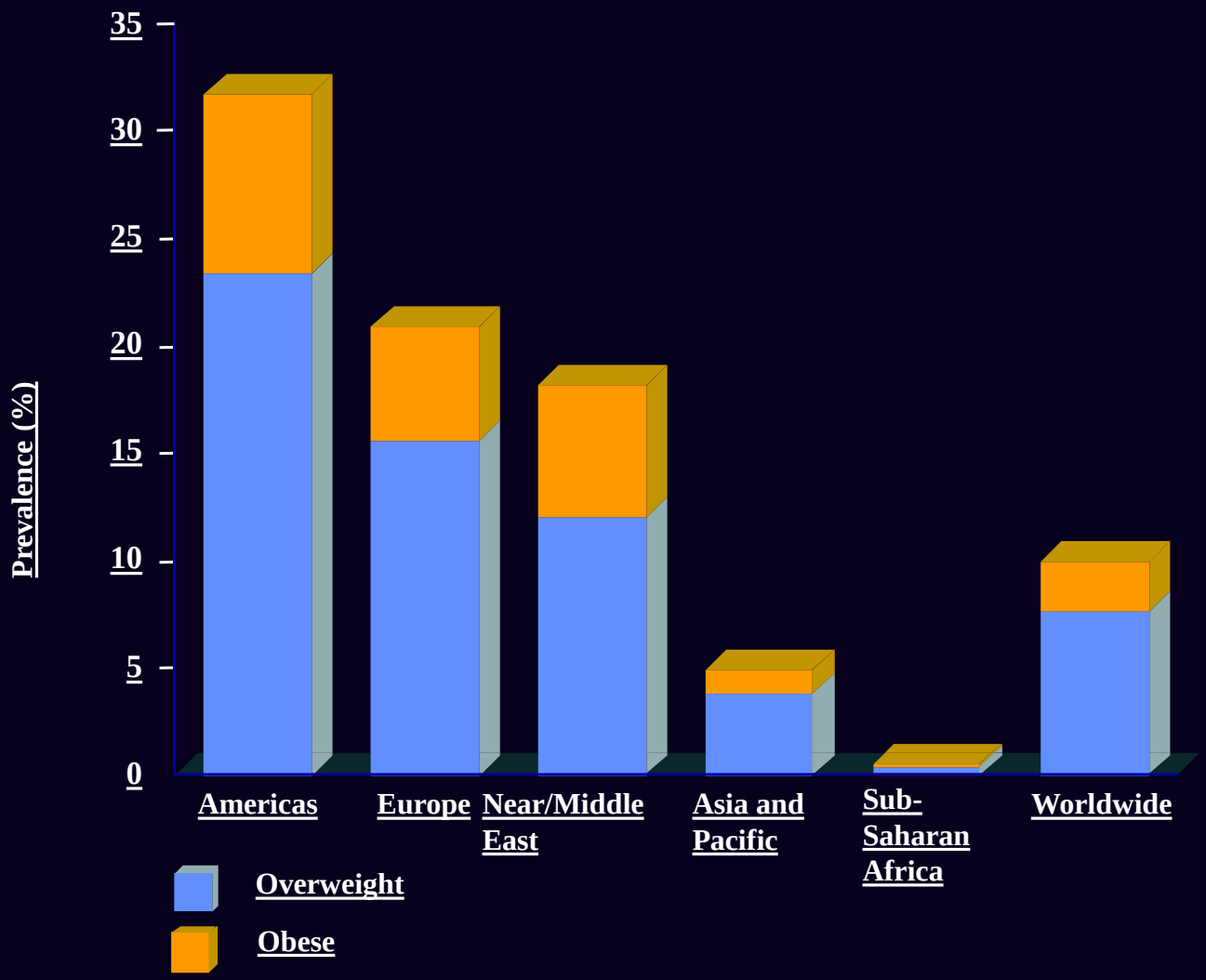
- 92% had at least two CVD risk factors

In young people with type 1 diabetes:

- 14% had at least two CVD risk factors

***(SEARCH)*. Diabetes Care 2006 29(8): 1891-6.**

Overweight and obesity among school age children (5–17 Years)



Type 2 diabetes,

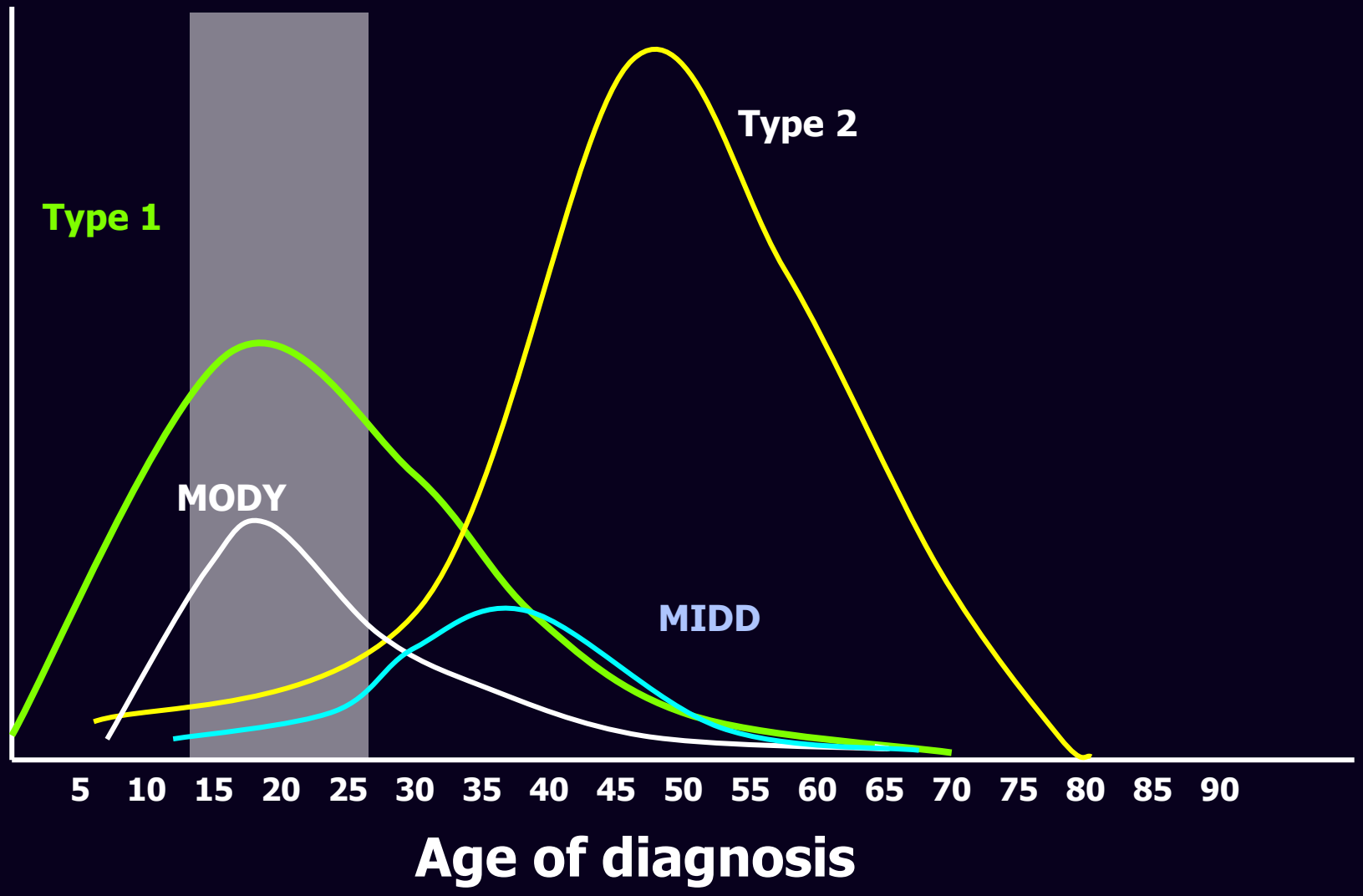
the metabolic syndrome and cardiovascular disease in Europe

Αυτοάνοσος τύπου 2, υβριδικός ΣΔ, double diabetes, LADA

- 17,4% των νέων με ΣΔ2 που αναγνωρίζεται κλινικά έχουν αυτοαντισώματα GAD, IA2
- Στην πραγματικότητα είναι υπέρβαροι, ινσουλινοάντοχοι (κληρονομικά) τύπου 1
- Κλινικά πρακτικά δύσκολη η διαφοροδιάγνωση
- Οι Ab+ συχνότερη κετοναιμία/κετονουρία, οι Ab+ υψηλοτερη ΑΠ και AST
- Επιθετικότερη ινσουλινοθεραπεία και νωρίτερα στους Ab+

Klinkgensmith et al, Diabetes 2006

Diabetes in Young Adults (15-30 years)



Διαφορική διάγνωση MODY και ΣΔ2 [1/2]

- **Τύπος κληρονομικότητας**
  - **MODY: Μονογονιδιακός, αυτοσωμικός επικρατών**
  - **DM2: Πολυγονιδιακός**
- **Ηλικία έναρξης**
  - **MODY: παιδική-εφηβική ηλικία, συνήθως<25 years**
  - **DM2: Συνήθως 40-60 years; περιστασιακά σε παχύσαρκους έφηβους**
- **Γενεαλογία**
  - **MODY: Εμφάνιση σε πολλές γενιές**
  - **DM2: σπάνια σε πολλές γενιές**

Διαφορική διάγνωση MODY και ΣΔ2 [2/2]

- Διεισδυτικότητα
  - MODY: 80-95 %
  - DM2: ποικίλλη (10-40 %)
- Φαινότυπος-σώμα
  - MODY: μη παχύσαρκοι
  - DM2: συνήθως παχύσαρκοι/υπέρβαροι
- Δυσμεταβολικό σύνδρομο
  - MODY: απόν
  - DM2: συνήθως παρόν

MODY diagnostic criteria separate well from Type 1 but do not separate well from early-onset Type 2

	MODY	Type 2	Type1
Non insulin dependent	Yes	Yes	No
Parents affected	1	1-2	0-1
Age of onset < 25yr	Yes	unusual	Yes
Obesity	+/-	+ + +	+/-
Acanthosis Nigricans	-	+ +	-
Racial groups (Type 2 prevalence)	low	high	low

HNF-1β mutations: a new genetic syndrome
Renal Cysts And Diabetes (RCAD) –MODY5

Renal cysts

- Often seen on anti-natal scanning - variable
- Renal function variable - mild impairment - endstage renal failure 50% require dialysis
- Different renal histology

Diabetes

- Diagnosis 22 (10 - 47) yr., often on insulin

Other extra-pancreatic features

uterine abnormalities, insulin resistance and gout

Nishigori et al Diabetes 1998, Lindner et al 1999 Hum Mol Gen
Bingham et al 2000 Kidney Int, Bingham et al 2001 AmJ Hum Gen, Bingham et al 2002 Kidney Int,

Διαγνωστικό γενετικό τεστ: Γιατί να γίνει?

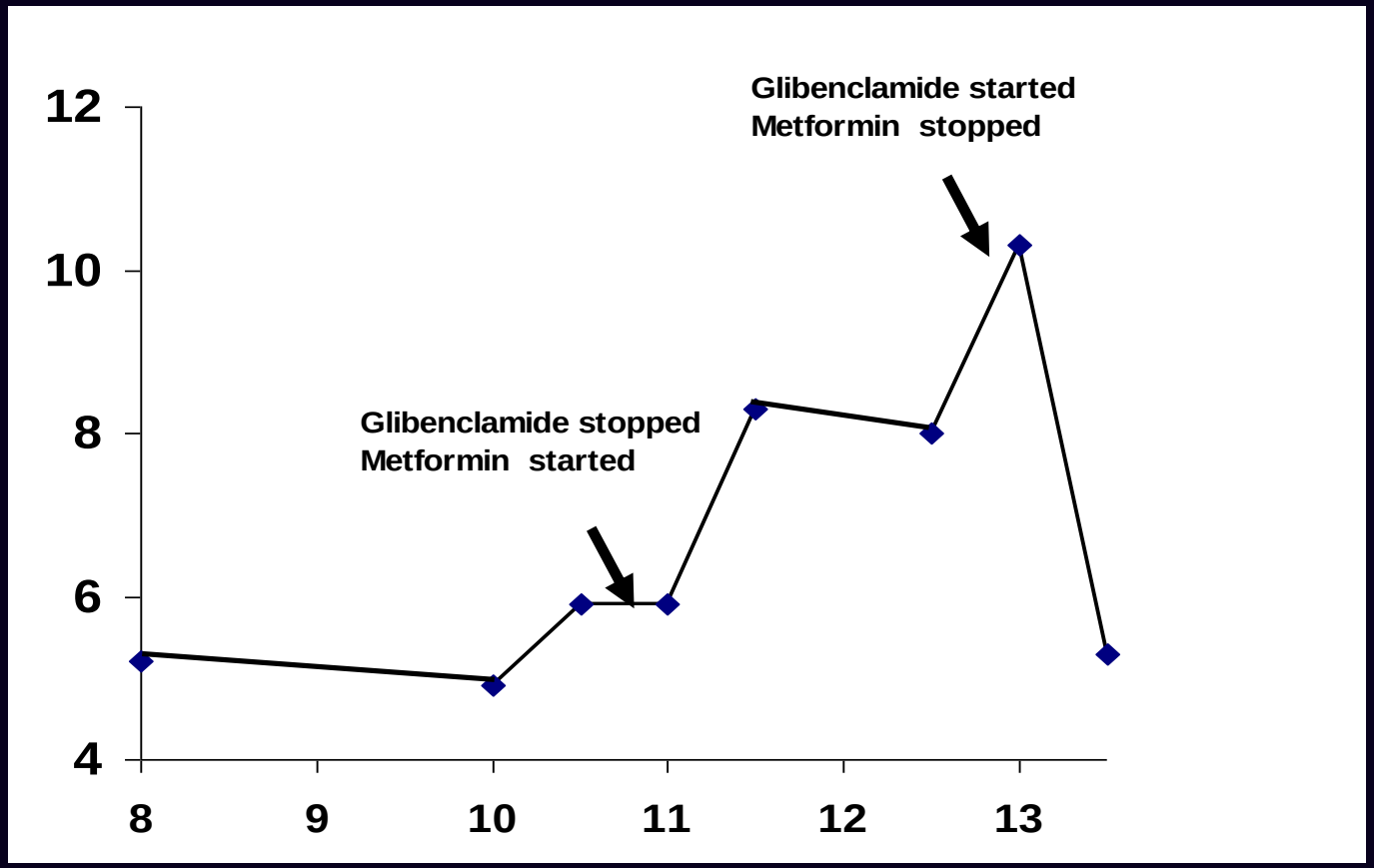
- Θέτει τη διάγνωση : αναγνωρίζει τους μονογονιδιακούς διαβήτες και τον υπότυπο
- Διαφοροδιαγνώσκει από type 1
- Βοηθά στον καθορισμό της πρόγνωσης
- Βοηθά στη συμβουλευτική της οικογένειας
- Καθοδηγεί τη θεραπεία

Διαγνωστικό γενετικό τεστ: Γιατί να γίνει?

Glucokinase:
Safely leave children off treatment

www.diabetesgenes.org

Diagnostic Testing : why do it?
HNF1α:very sensitive to sulphonylureas



(Pearson et al Diab Med 2000)

Classifying types of diabetes

•The differentiation between type 1, type 2 and monogenic diabetes has important implications for both therapeutic decisions and educational approaches.

•***The possibility of other types of diabetes should be considered in the child who has: An autosomal dominant family history of diabetes.***

• Associated conditions such as ***deafness, optic atrophy or syndromic features.*** Marked insulin resistance or requiring little insulin outside the partial remission phase.

•***A history of exposure to drugs known to be toxic to beta cells or cause insulin resistance.***

• Genetic testing for neonatal diabetes (onset < 6 months of age) should be performed as transition from insulin to sulphonylurea treatment may be possible.

Stress hyperglycaemia

Stress hyperglycaemia has been reported in up to ***5% of children presenting to an emergency department.*** Acute illness or injury; traumatic injuries, febrile seizures and elevated body temperature (> 39oC) were identified as the most common associated features .

The reported incidence of progression to overt diabetes varies from 0% to 32%.
Islet cell antibodies and insulin autoantibody testing ha high positive and negative predictive value for type 1 diabetes in children with stress hyperglycaemia

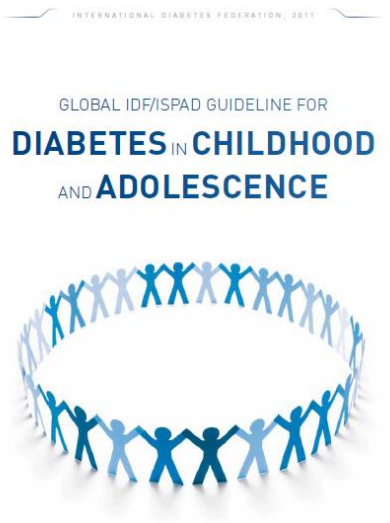


Table 2. Clinical characteristics of type 1 diabetes, type 2 diabetes and monogenic diabetes in children and adolescents

Characteristic	Type 1	Type 2	Monogenic
Genetics	Polygenic	Polygenic	Monogenic
Age of onset	6 months to young adulthood	Usually pubertal (or later)	Often post pubertal except glucokinase and neonatal diabetes
Clinical presentation	Most often acute, rapid	Variable; from slow (often insidious) to severe	Variable (may be incidental in glucokinase)
Autoimmunity	Yes	No	No
Ketosis	Common	Uncommon	Common in neonatal diabetes, rare in other forms
Glycemia	High	Variable	Variable
Obesity	Population frequency	Increased frequency	Population frequency
Acanthosis nigricans	No	Yes	No
Frequency (% of all diabetes in young people)	Usually 90%+	Most countries < 10% (Japan 60-80%)	1-2%
Parent with diabetes	2-4%	80%	90%

Table 3. Aetiological Classification of Disorders of Glycaemia (modified ADA and WHO)

I. Type 1

β -cell destruction, usually leading to absolute insulin deficiency

a. Autoimmune

b. Idiopathic

II. Type 2

May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance

III. Other specific types

A. Mongenic defects of β -cell function

1. HNF-1α MODY (MODY 3),
2. Glucokinase MODY (MODY 2)
3. HNF-4 α MODY (MODY 1),
4. HNF-1β MODY (MODY 4)
5. WFS1 Wolfram syndrome
6. Neonatal diabetes
7. Other MODY

B. Mitochondrial diabetes

C. Genetic defects in insulin action

1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipoatrophic diabetes
5. Others

F. Drug- or chemical-induced

1. Glucocorticoids
2. Vacor
3. Pentamidine
4. Nicotinic acid
5. Thyroid hormone
6. Diazoxide
7. β-adrenergic agonists
8. Thiazides
9. Dilantin
10. α -Interferon
11. Others

G. Infections

1. Congenital rubella
2. Cytomegalovirus
3. Others

D. Diseases of the exocrine pancreas

1. Fibrocalculous pancreatopathy
2. Pancreatitis
3. Trauma / pancreatectomy
4. Neoplasia
5. Cystic fibrosis
6. Haemochromatosis
7. Others

H. Uncommon forms of immune-mediated diabetes

1. Insulin autoimmune syndrome (antibodies not insulin)
2. Anti-insulin receptor antibodies
3. "Stiff-man" syndrome
4. Others

E. Endocrinopathies

1. Acromegaly
2. Cushing syndrome
3. Glucagonoma
4. Phaeochromocytoma
5. Hyperthyroidism
6. Somatostatinoma
7. Others

I. Other genetic syndromes sometimes associated with diabetes

1. Down syndrome
2. Klinefelter's syndrome
3. Turner syndrome
4. Friedreich's ataxia
5. Huntington's chorea
6. Laurence-Moon-Biedl syndrome
7. Myotonic dystrophy
8. Porphyria
9. Prader-Willi syndrome
10. Others

IV. Gestational diabetes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