# Diabète et les autoanticorps – quand chercher?

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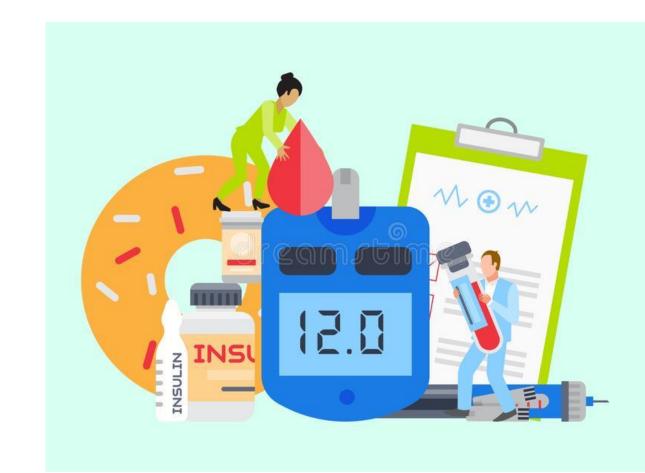
### Diabète sucré: définition

Maladie métabolique chronique

Hyperglycémie permanente

En suite dommage des

- vaisseaux sanguins
- plusieurs organes



### Diabète sucré: symptômes

«débit mielleux»Soif intense, PolydipsieUrines abondantes, Polyurie (>3L/d)Urines douces

Fatigue, somnolence
Perte de poids inexplicable
Vision embrouillée
Troubles de la sensibilité



### Diabète sucré: symptômes

Hyperglycémie chronique:

- sensibilité augmenté aux infections
- retard de croissance chez les enfants

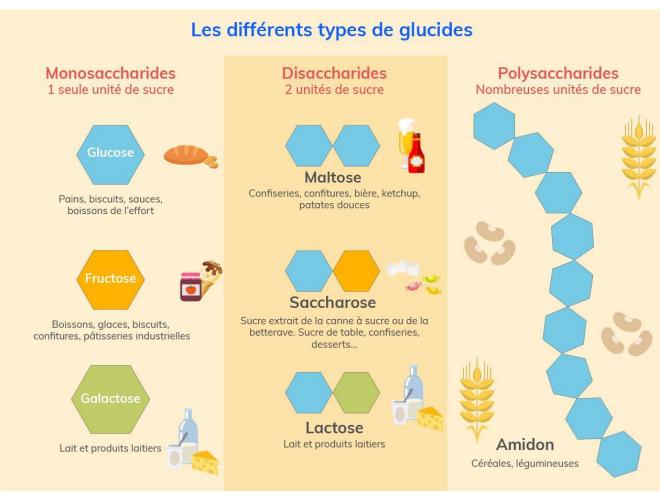
Risques vitaux: Hyperglycémie avec acidocétose et le syndrome hyperosmolaire non cétosique

- → déshydratation, choc circulatoire, coma
- → sans thérapie: mort



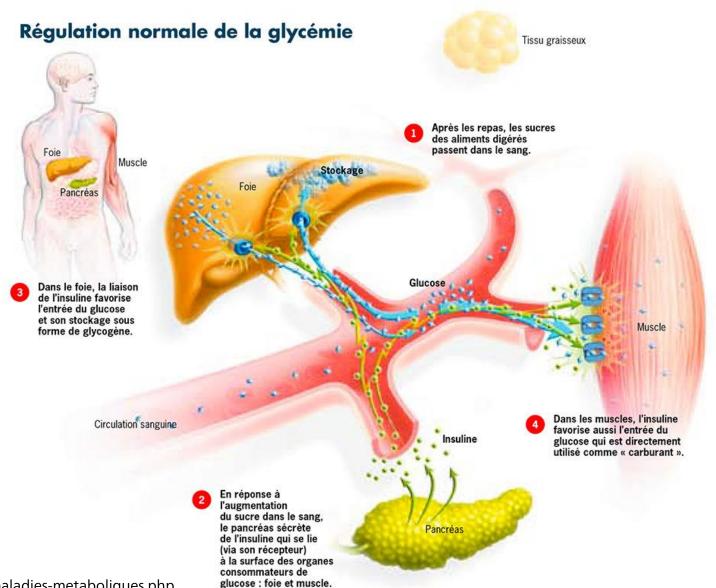
### Métabolisme des glucides



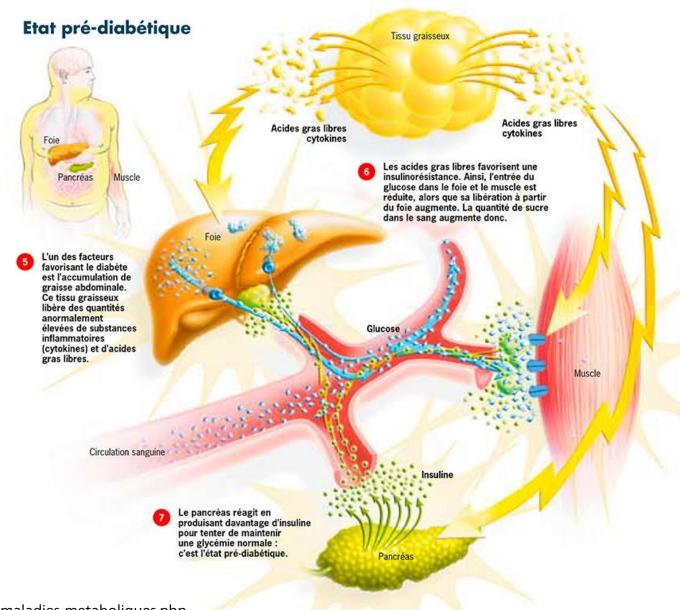




### Métabolisme des glucides



### Métabolisme des glucides



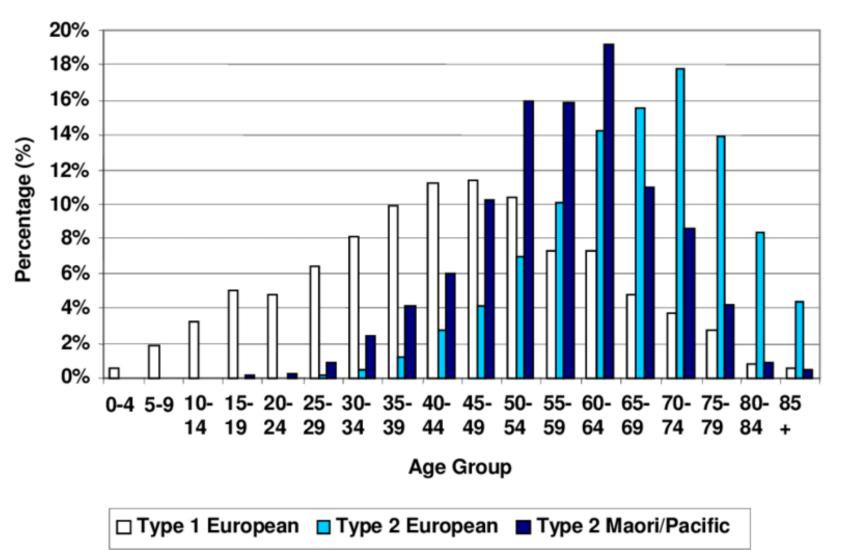


## Classification selon la WHO, 2019

Туре	Cause	Conséquence
Diabète de type 1	Destruction des cellules bêta du pancréas, le plus souvent à médiation immunologique; début souvent dans l'enfance et au début de l'âge adulte	Déficit absolu d'insuline
Diabète de type 2	Forme la plus fréquente, différents degrés de dysfonctionnement des cellules bêta et résistance à l'insuline; souvent associé à l'obésité	Manque d'action de l'insuline dans les organes cibles



### Diabète sucré: répartition par âge au moment du diagnostic





## Classification selon la WHO, 2019: Formes hybrides

Туре	Cause
Diabète de l'adulte à médiation immunitaire et à évolution lente	Comme type 1 à évolution lente chez les adultes présentant des signes de syndrome métabolique, seulement GAD ac et maintient plus de fonction des cellules bêta (avant: Diabète auto-immun latent de l'adulte LADA)
Diabète de type 2 sensible à la cétose	Avec cétose et insuffisance d'insuline, n'a pas besoin d'insuline plus tard Non immuno-médié



## Classification selon la WHO, 2019

Type	Cause
Autres types de diabète spécifiques	<ul> <li>Défauts monogéniques de la fonction des cellules bêta</li> <li>Défauts monogéniques de l'action de l'insuline</li> <li>Maladies du pancréas exocrine</li> <li>Endocrinopathies</li> <li>Induit par des médicaments ou des produits chimiques</li> <li>En fonction des infections</li> <li>Formes rares de diabète à médiation immunitaire</li> <li>autres syndromes génétiques occasionnellement associés au diabète</li> </ul>
Diabète non classifié	Nouveaux types, diagnostic incertain

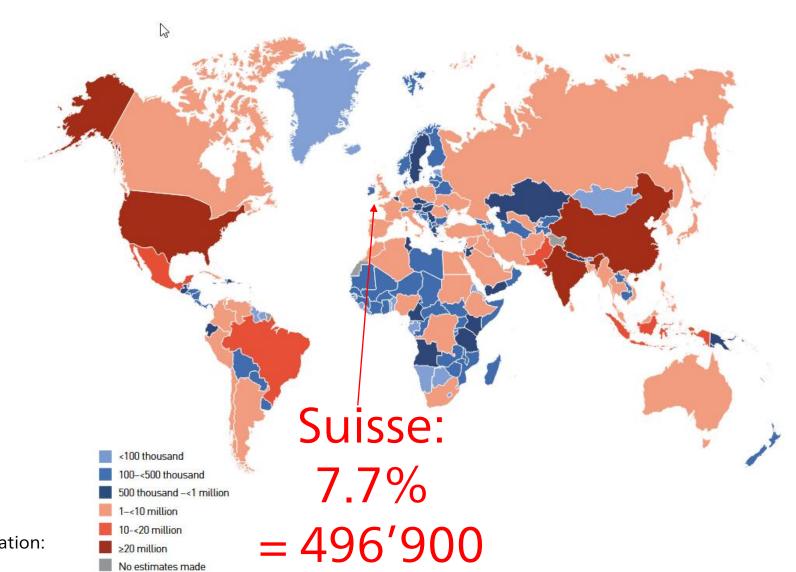
## Classification selon la WHO, 2019

Туре	Cause
Diabète chez la femme enceinte	<ul> <li>Diabète de type 1 ou type 2 détecté pour la première fois pendant la grossesse</li> <li>Hyperglycémie en dessous du seuil de diagnostic du diabète chez la femme enceinte</li> <li>→ Risque de 35-60% dans les 10 années suivantes de développer un diabète sucré</li> </ul>



#### Diabète sucré: Prévalence

Map 3.1 Estimated total number of adults (20-79 years) with diabetes in 2019



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### Diabète sucré: Prévalence

At a glance	2019	2030	2045
	•	•	•
Total world population	7.7 billion	8.6 billion	9.5 billion
Adult population (20-79 years)	5.0 billion	5.7 billion	6.4 billion
Diabetes (20-79 years)			
Global Prevalence	9.3%	10.2%	10.9%
Number of people with diabetes	463.0 million	578.4 million	700.2 million
Number of deaths due to diabetes	4.2 million	-	-
Total health expenditures for diabetes <sup>i</sup>	USD 760.3 billion	USD 824.7 billion	USD 845.0 billion
Hyperglycaemia in pregnancy (20-49	years)		
Proportion of live births affected	15.8%	14.0% <sup>ii</sup>	13.3% <sup>ii</sup>
Number of live births affected	20.4 million	18.3 million	18.0 million
Impaired glucose tolerance (20-79 ye	ars)		
Global prevalence	7.5%	8.0%	8.6%
Number of people with impaired glucose tolerance	373.9 million	453.8 million	548.4 million
Type 1 diabetes (0-19 years)			
Number of children and adolescents with type 1 diabetes	1,110,100	-	-
Number of newly diagnosed cases each year	128,900	-	-

i Health expenditures for people with diabetes are assumed to be on average two-fold higher than people without diabetes.

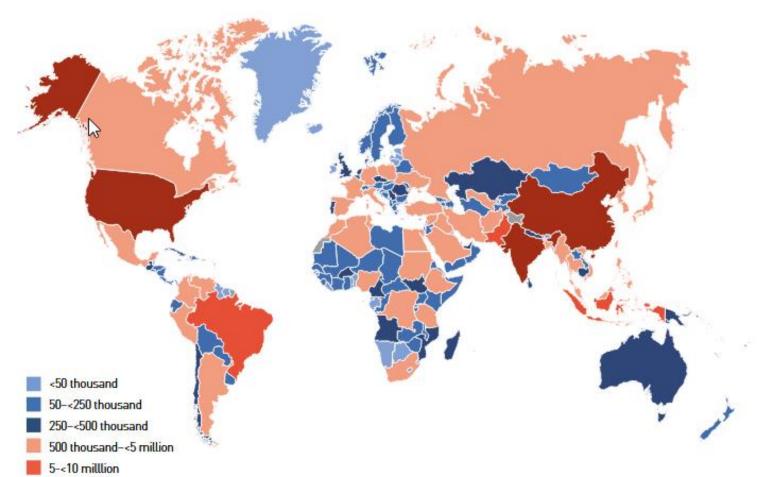
ii Age-adjusted prevalence.

## Diabète sucré: non diagnostiqué

≥10 million

No estimates made

Map 3.4 Number of adults (20-79 years) with undiagnosed diabetes in 2019



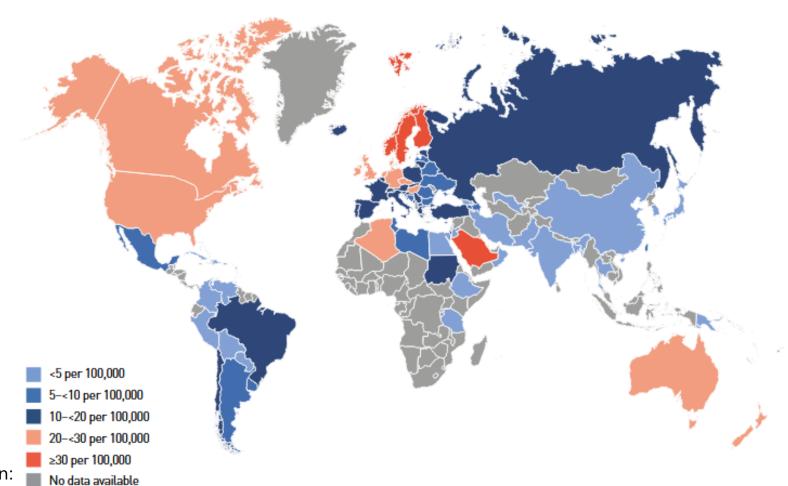
World Bank income classification	Proportion undiagnosed (%)
High-income countries	38.3
Middle-income countries	52.6
Low-income countries	66.8

i 95% confidence intervals are reported in brackets.



### Diabète de type 1: Incidence

Map 3.5 Age-sex standardised incidence rates (per 100,000 population per annum) of type 1 diabetes in children and adolescents aged 0-14 years





International Diabetes Federation: Diabetes Atlas 2019

### Diabète de type 1: Incidence Europe 1989-2013

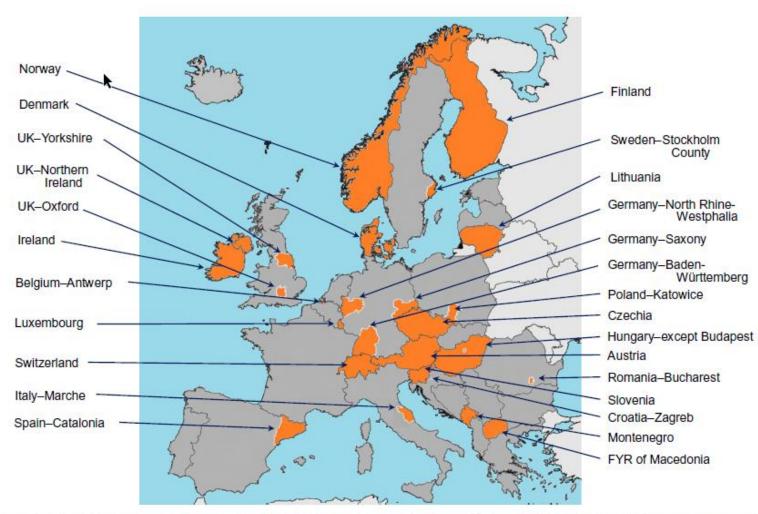


Fig. 1 Map of 26 participating EURODIAB centres (whole nations unless a region is specified). Administrative boundaries: ©EuroGeographics 2018; adapted with permission. FYR, Former Yugoslav Republic



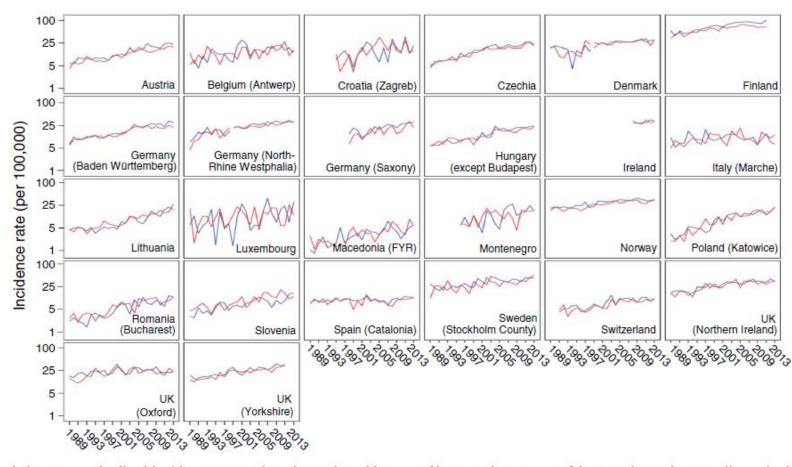


Fig. 2 Trends in age-standardised incidence rates, plotted on a logarithmic scale, by sex for type 1 diabetes in 26 European centres during 1989–2013. Blue lines, boys; red lines, girls. Breaks are shown for Denmark and Germany (North Rhine-Westphalia) between 1998 and 1999 because

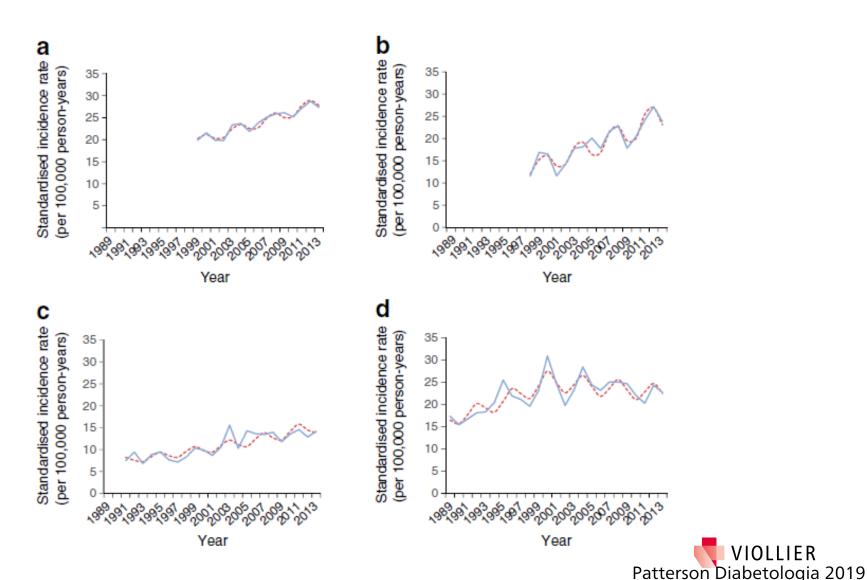
of increased coverage of these registers, but any discontinuities appear to be very minor. Macedonia (FYR), Former Yugoslav Republic of Macedonia



### Diabète de type 1: Incidence Europe 1989-2013

Fig. 4 Observed (continuous blue line) and fitted (red dashed line) standardised incidence rates (per 100,000 person-years) obtained by Poisson regression in four centres that showed significant (p < 0.01) 4 year periodicity when superimposed on long-term Joinpoint segmented regression trends: (a) Germany-North Rhine-Westphalia; (b) Germany-Saxony; (c) Switzerland; (d) UK-Oxford

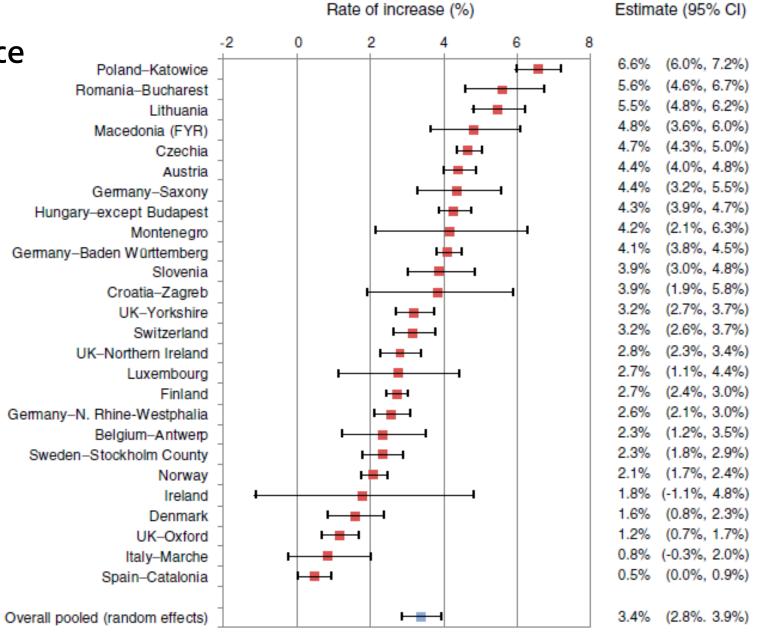
# Infections virales?



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Diabète de type 1: Incidence Europe 1989-2013

Style de vie moderne Prise de poids Augmentation de la taille Réduction des nombres des infections Césarienne?



### Complications à long terme

#### Lésions micro vasculaires:

- Rétinopathie avec perte de la vue
- Néphropathie avec insuffisance rénale
- Neuropathie périphérique avec ulcères du pied
- Neuropathie autonome
- Symptômes gastro-intestinales, urogénitales et cardiovasculaire ainsi que les troubles sexuels



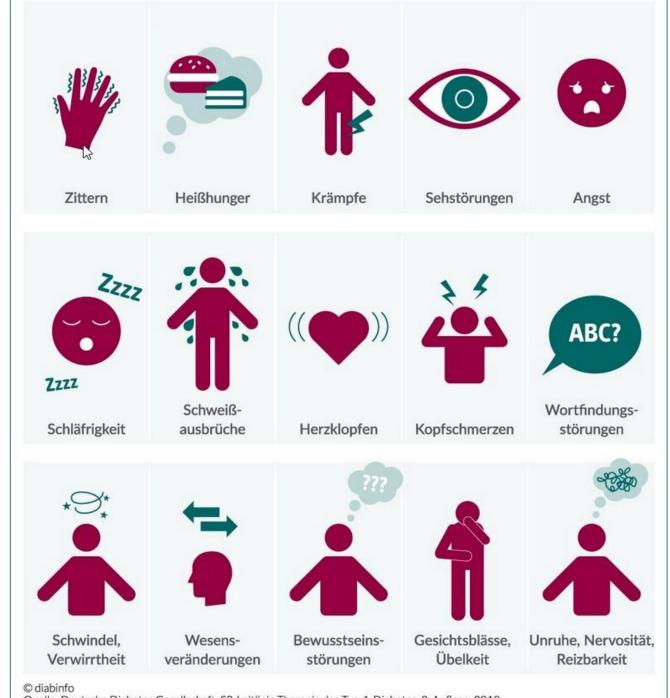
### Complications à long terme

### Complications macro vasculaires:

- Maladies cardiovasculaires (infarctus du myocarde), cause de décès chez 75% des patients
- Maladies vasculaires périphériques:
   troubles de la circulation sanguine, par ex. artères des jambes
- Maladies cérébrovasculaires (attaque cérébrale 4x plus fréquent);
   accélérée par l'hypertension et l'hyperlipidémie
- Démence: risque 3x plus élevé, 11x si en plus hypertension
- Dépression et M. Parkinson 2x plus fréquentes



## Hypoglycémie





Quelle: Deutsche Diabetes Gesellschaft: S3-Leitlinie Therapie des Typ-1-Diabetes. 2. Auflage. 2018

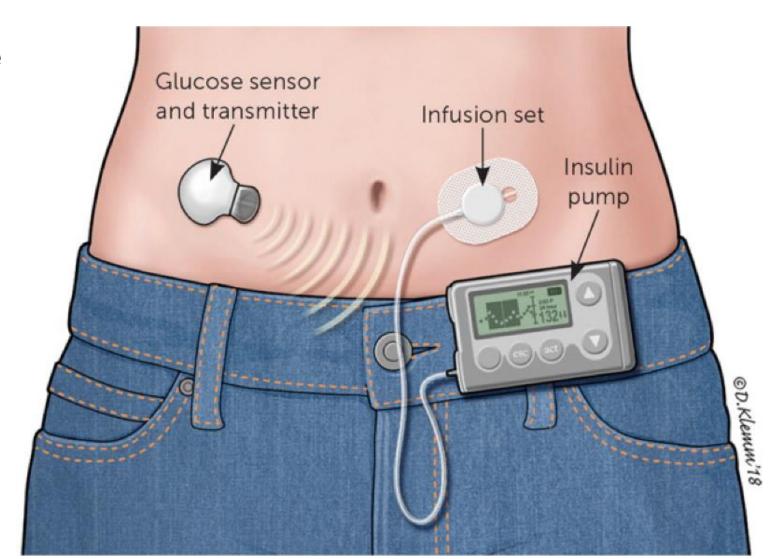


### Diabète de type 1: thérapie

Remplacement de l'insuline manquante

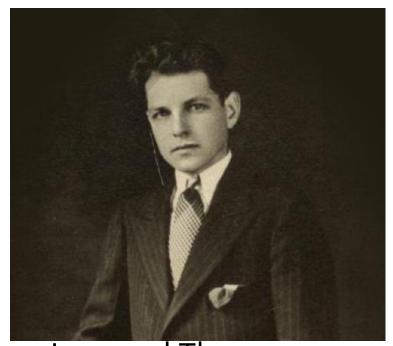
## Dépend de:

- Glycémie actuelle
- Quantité de glucides consommés
- Activité physique



### Insulinothérapie

Janvier 1922: Première dose d'insuline



Leonard Thompson

(1908-1935)



Frederick G. Banting, 1891–1941



J. J. R. MacLeod, 1876-1935



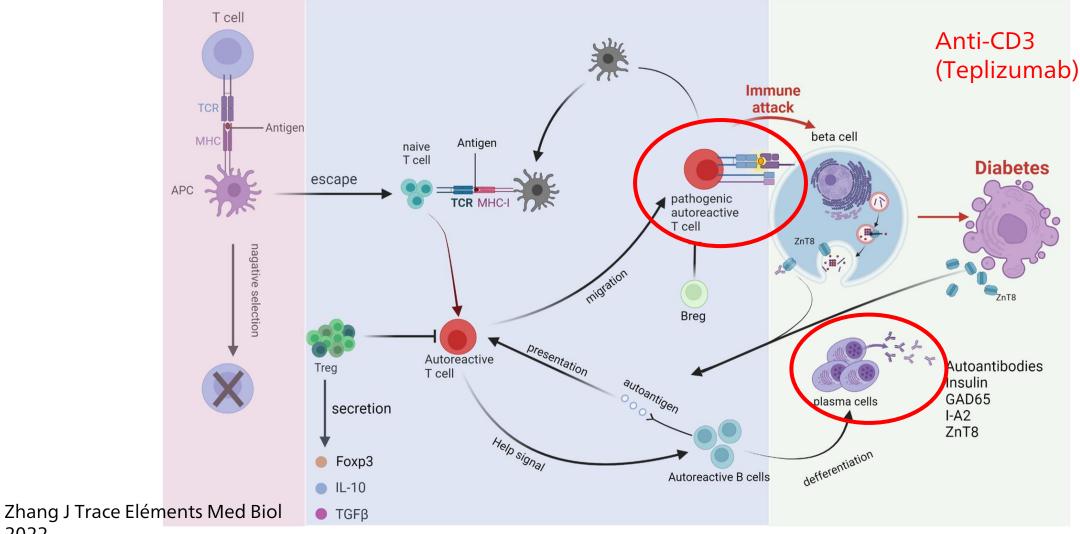
Charles Best, 1899–1978



J. B. Collip, 1892-1965

The Nobel Prize in Physiology or Medicine 1923 was awarded jointly to Frederick Grant Banting and John James Rickard Macleod "for the discovery of insulin."

### Diabète de type 1: thérapie immunomodulatoire?



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### Qui tester?

### Adultes asymptomatiques avec:

- IMC  $\geq$  25 kg/m<sup>2</sup>
- Manque d'activité physique (<5h/semaine)</li>
- Parents au 1er degré souffrant de diabète sucré
- Hypertension artérielle, hypertonie
- Cholestérol HDL ≤35 mg/dL (0.90 mmol/L)
- Triglycérides ≥250 mg/dL (2.82 mmol/L)
- Troubles cardiaques



American Diabetes Association

### Qui tester?

- Femmes atteintes de diabète gestationne
  - → tous les 3 ans à vie



- Patients atteints de prédiabète (HbA1c ≥5.7%, 39 mmol/mol)
  - → annuel

- Tous avec 45 ans et plus
  - → tous les 3 ans à vie





### Qui tester?

Enfants à partir de 10 ans tous les 3 ans, si:

- Obésité (>120% poids idéal)
- Parents au 1er ou 2e degré souffrant de diabète sucré
- Symptômes de résistance à l'insuline
- Antécédents maternels de diabète gestationnel

En cas de symptômes!



### Diabète sucré: Diagnostic

#### **TABLE 1** Criteria for the diagnosis of diabetes mellitus

1. Classic symptoms of diabetes or hyperglycemic crisis, with plasma glucose concentration ≥11.1 mmol/L (200 mg/dL).

or

2. Fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL). Fasting is defined as no caloric intake for at least 8 h.a

or

Two-hour postload glucose ≥11.1 mmol/L (≥200 mg/dL) during an OGTT.<sup>a</sup>

The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g.

or

4. HbA1c ≥6.5%<sup>b</sup>

The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.

<sup>&</sup>lt;sup>b</sup> A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests. The role of HbA1c alone in diagnosing type 1 diabetes in children is unclear.



<sup>&</sup>lt;sup>a</sup> In the absence of unequivocal hyperglycemia, the diagnosis of diabetes based on these criteria should be confirmed by repeat testing.

### Diabète sucré: valeurs de laboratoire

	Sain	Prédiabète	Diabète sucrés
Glucose à jeun 8h	<100 mg/dL <5.6 mmol/L	100-125 mg/dL 5.6-6.9 mmol/L	> 125 mg/dL ≥ 7.0 mmol/L
Test de tolérance au glucose	<140 mg/dL <7.8 mmol/L	140-199 mg/dL 7.8-11.0 mmol/L	≥ 200 mg/dL ≥ 11.1 mmol/L
HbA1c	<5.7%	5.7-6.3%	≥ 6.4% ≥ 48 mmol/mL
Réduit par	Drépanocytose, thalassémies, carence de fer?		
Faussement élevé par	Carence de fer, carence en vitamine B12, carence de acide folique		

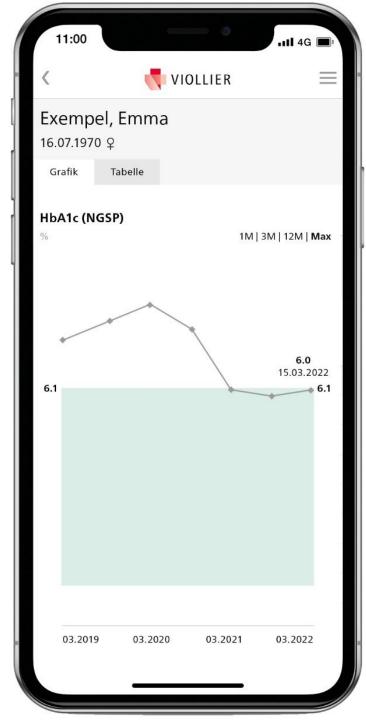
#### Diabète sucré: contrôle

Tabelle 1: Empfohlene Orientierungswerte zur Blutglukosekontrolle

nach [Rewers et al. 2007 EK IV]

BZ-Kontrolle – Klinisch-chemische Bewer- tung	Gesund	Gut	Mäßig (Maßnahmen empfohlen)	Schlecht (Maßnahmen erforderlich)
Präprandiale oder nüchtern BG	3.6-5.6	5-8 <sup>2</sup>	> 8	> 9
(mmol/l mg/dl)	65-100	90-145	> 145	> 162
Postprandiale BG	4.5-7.0	5-10	10-14	> 14
	80-126	90-180	180-250	> 250
Nächtliche BG <sup>3</sup>	3.6-5.6	4.5-9	< 4.2 oder > 9	< 4.0 oder > 11
	65-100	80-162	< 75 oder > 162	< 70 oder > 200
HbA1c-Wert (standardisierte Messung nach Vorgaben des DCC-Trials)	< 6.05	< 7.5	7.5-9.0	> 9.0

Diese allgemeinen Orientierungswerte müssen den individuellen Umständen eines Patienten angepasst werden. Abweichende Werte gelten insbesondere für Kleinkinder, Patienten mit schweren Hypoglykämien oder Patienten, die nicht in der Lage sind, Hypoglykämien zu erkennen [Cranston et al. 1994 EK III].



<sup>&</sup>lt;sup>2</sup> Ist die morgendliche Nüchtern-Blutglukose unter 72 mg/dl (unter 4 mmol/l), sollte die Möglichkeit einer vorangegangenen nächtlichen Hypoglykämie in Erwägung gezogen werden [Holl et al. 1992 EK III].

<sup>&</sup>lt;sup>3</sup> Diese Zahlen basieren auf klinischen Studien, es liegen aber keine strikten, evidenzbasierten Empfehlungen vor.

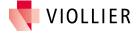
## Diabète de type 1: facteurs de risque

Risk and Protective Factors	Reported Effects and Associations
HLA class II DR3-DQ2 and DR4-DQ8 haplotypes [	Increased risk of rapid progression; expansion of autoimmunity in children with both IAA- and GADA-initiated autoimmunity
HLA class I -A and -B alleles	Modified age of onset of T1D; increased risk of T1D; modulated the $\beta$ -cell destruction
INS, PTPN22, SLC30A8, and BACH2 gene SNPs; alterations in the VNTR region within the INS gene	Increased progression from islet autoimmunity to clinical T1D; $\beta$ -cell destruction early after the initial seroconversion
High Genetic Risk Score	Prediction of T1D; increased progression from islet autoimmunity to clinical T1D; increased disease progression pace
Young age at autoantibody appearance	Increased risk of T1D
Positivity to multiple autoantibodies	Increased risk of T1D; association with the extremely high-risk of T1D
Seroconversion to IAA	Increased risk of T1D; association with young age at seroconversion and increased risk of T1D; reverse correlation between IAA levels and age at primary seroconversion; association with HLA class II DR4-DQ8 risk haplotypes



## Diabète de type 1: facteurs de risque

Risk and Protective Factors	Reported Effects and Associations
First-degree relatives	Increased risk of T1D; more severe disease progression; more frequent severe diabetic ketoacidosis and weight loss in children with affected father
C-section delivery	Increased risk of T1D; reduced taxonomic and functional diversity of gut microbiome
Complicated vaginal delivery	Increased risk of T1D
Breastfeeding while introduction of the new food	Decreased risk of T1D
Short breastfeeding time	Increased risk of T1D
Early introduction of gluten-containing solid foods; introduction of solid foods early in life	Increased risk of islet autoimmunity
Fluctuations in the gut microbiome; high Bacteroidetes/Firmicutes ratio; decreased microflora diversity	Increased risk of T1D; rapid development of islet cell autoantibodies
Increased vitamin D consumption and higher serum 25-hydroxyvitamin D levels	Decreased risk of T1D



# Diabète de type 1: facteurs de risque

Risk and Protective Factors	Reported Effects and Associations
Coxsackie B virus, enteroviruses, and rotaviruses	Increased risk of T1D; rapid progression to T1D; activation of the immune system; destruction of pancreatic β-cells
Measles, and influenza vaccinations	Decreased risk of T1D
SARS-CoV-2 infection	Destruction of pancreatic β-cells
Early exposure to cow's milk, and high consumption of cow's milk	Increased risk of T1D; rapid progression to T1D
Higher consumption of sugars and carbohydrates	Increased risk of T1D; rapid progression to T1D
Higher birth weight and weight gain during the first year of life	Increased risk of T1D
Overweight, and obesity	Increased risk of T1D; association with high-risk HLA genotypes; increased risk of progression from islet autoimmunity to type 1 diabetes and with development of type 1 diabetes, but not with development of autoantibodies

#### Diabète de type 1: pathogenèse

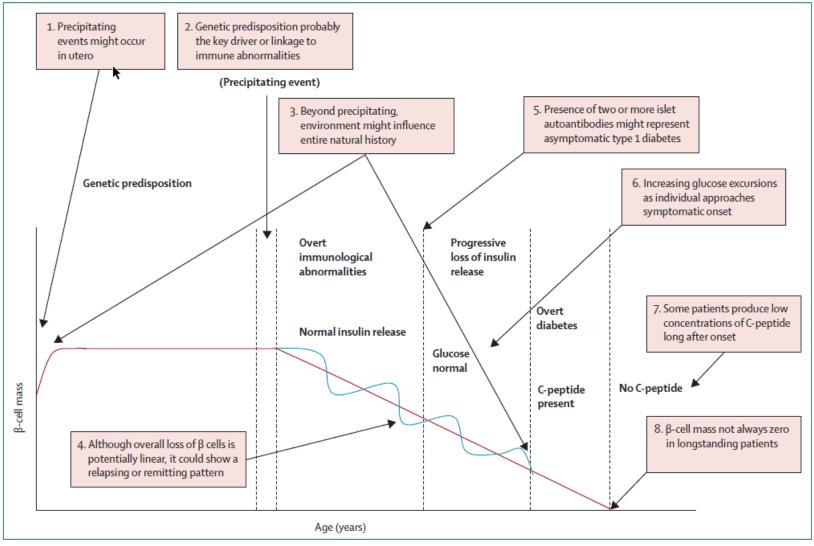
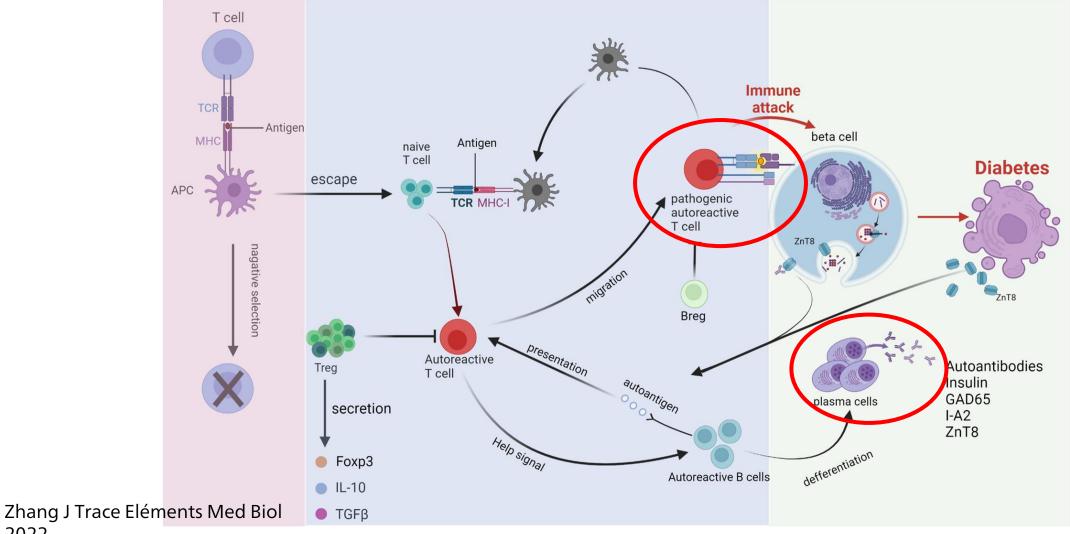


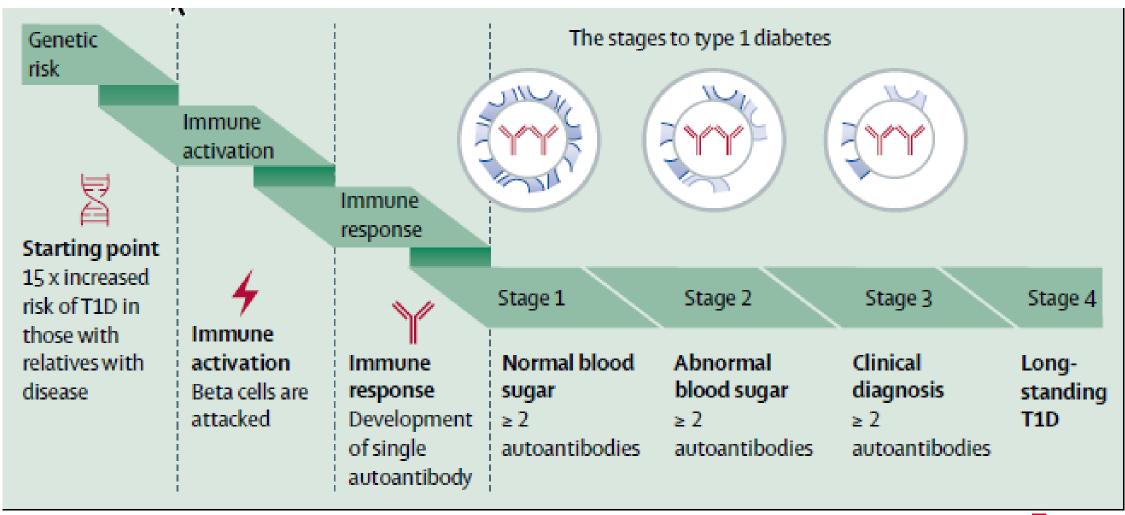
Figure 4: The natural history of type 1 diabetes—a 25-year-old concept revisited

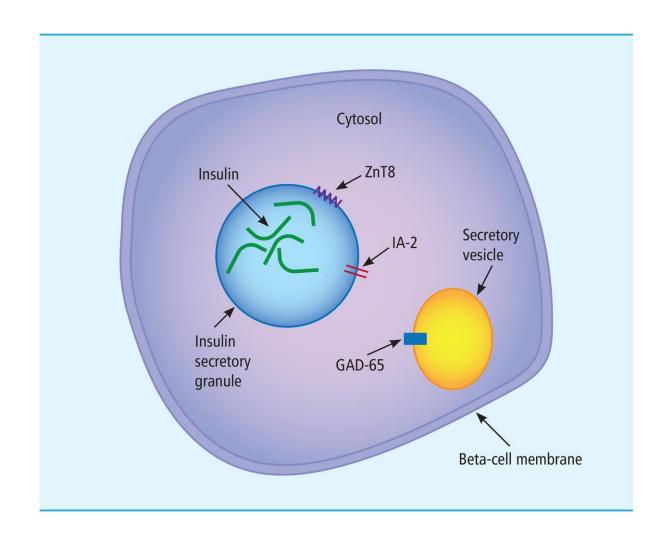
### Diabète de type 1: pathogenèse



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#### Diabète de type 1: pathogenèse







	Antigène	Association HLA	À quel âge
IAA	Insuline / Proinsuline > Attention: ne pas tester en cas d'insulinothérapie	HLA DR4-DQ8	<10 ans, pas dans les adults Souvent 1. AA
GADA	Glutamat décarboxylase 65kDa	HLA DR3-DQ2	>10 ans, le plus souvent femmes, persistant
IA-2	Antigène associé à l'insulinome 2 (tyrosine phosphatase)	HLA DR4-DQ8	>10 ans
ZnT8A	Transporteur de zinc protéine 8	Pas connu	<10 ans
ICA	Céllules d'îlots IIF		

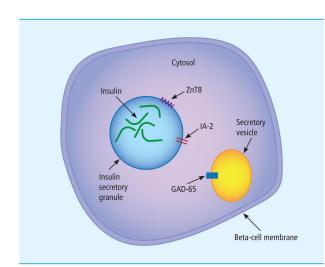
<b>Table 1.</b> Autoantibodies associated with autoimmune diabetes (T1DM).
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Autoantibody	Antigen	Diagnostic sensitivity for diagnosis of T1DM, %	Diagnostic specificity for diagnosis of T1DM, %	Reference(s)
IAA	Insulin/proinsulin	50–60 (children); ≅40 (adults)	99	24, 31
GADA	Glutamic acid decarboxylase 65	70-80	90	24
IA-2A	IA-2 protein tyrosine phosphatase	55-75	100	24, 26
ICA	eta cell cytoplasmic proteins	44–100	64-100	24
ZnT8A	Zinc transporter on secretory granules	61–72	97-99	29, 30



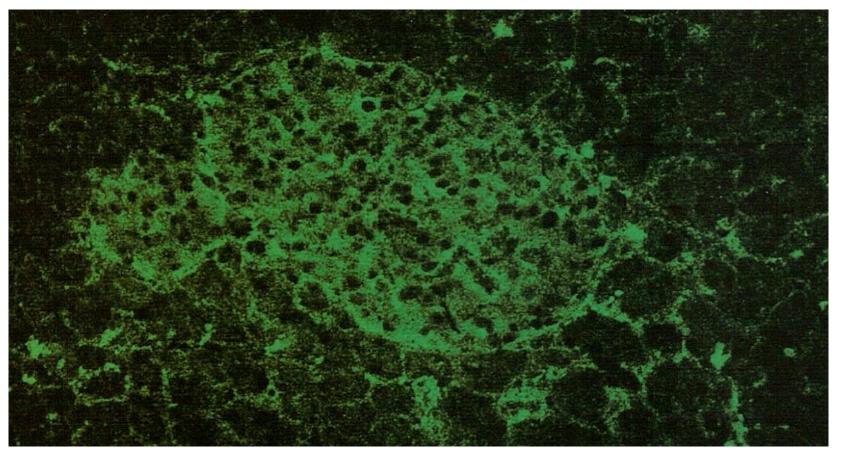
#### ICA IIF: auto-anticorps cellules d'îlots

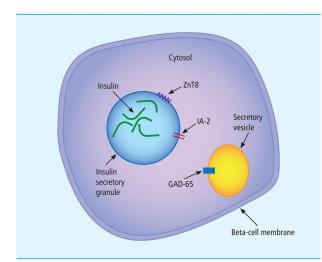
- Immunofluorescence indirecte sur des coupes cryostates non fixées de pancréas humain (group sanguin 0)
- Détecte différents auto-antigène
- Sensibilité:
  - 89-90% enfants
  - 70-80% adultes
- Sensibilité maximale au moment du diagnostic



#### ICA IIF: auto-anticorps cellules d'îlots

Coupe de pancréas de primate: cytoplasme des îlots de Langerhans

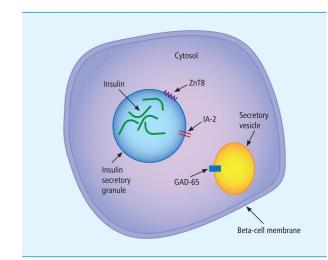




AR Bradwell Atlas of autoantibody patterns on tissues 1997

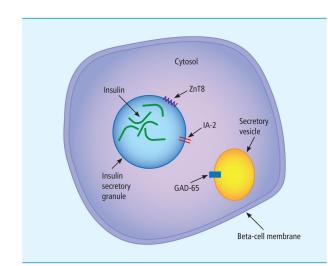
#### GAD (Glutamat décarboxylase) 65kDa

- Enzyme pour la catalyse de la synthèse de l'acid gamma-aminobutyrique
- Concentration la plus élevée dans le cerveau, y compris dans les cellules de Langerhans
- Détection par RIA ou dosage immunoenzymatique plus sensible que l'IIF
- Chez les personnes en bonne santé: 1-4%
- Plus jeune et plus le titre est élevé,
   plus il y a le risque de diabète type 1



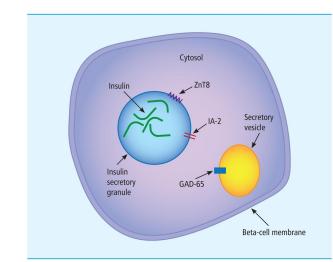
# GAD (Glutamat décarboxylase) 65kDa

_				
	ELISAª	RIA Medipan <sup>a</sup>	RIA DIA-source <sup>b</sup>	BDR RIAC
Sensitivity, % (n=76/70)	97.4 (90.9-99.3)	86.8 (77.4-92.7)	67.1 (55.5–77.0)	85.5 (75.9–91.7)
Sensitivity, %, ≤18 years of age	87.5	68.8	60.0	68.8
Sensitivity, %, >18 years of age	100	91.7	69.1	90.0
Specificity, %, (n = 131)	96.9 (92.4-98.8)	98.5 (94.6-99.6)	96.8 <sup>b</sup> (92.1-98.7)	
Specificity, % (n = 42)	100 (91.6–100)	95.2 (84.2-98.7)	92.3 <sup>b</sup> (79.7-97.3)	100 (91.6–100)



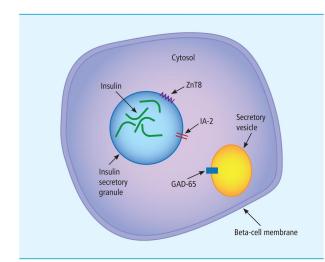
#### GAD (Glutamat décarboxylase) 65kDa

- GAD 67kDa: concentration 200x plus basse que GAD 65kDa
- Marquer pour Stiff-Person-Syndrome: GAD 67kDA et GAD 65kDa autoanticorps ensemble
- Titre plus haut en cas de Stiff-Person-Syndrome
- Également possible en cas d'encéphalite limbique ataxie cérébelleuse épilepsie résistante aux traitements



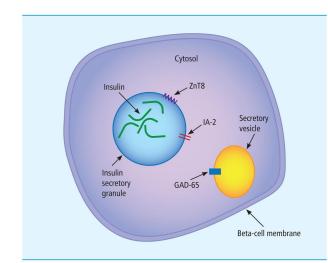
#### IA-2 Antigène associé à l'insulinome 2

- Protéine tyrosine phosphatase spécifique du pancreas, pour la transduction du signal intracellulaire
- Protéine transmembranaire dans les granules de sécrétion des cellules endocrines sécrétant des peptides, comme les cellules bêta, et les granules neurosécrétoires des neurones du SNc
- Sensibilité:
  - 50-70% enfants
  - 30-50% adults



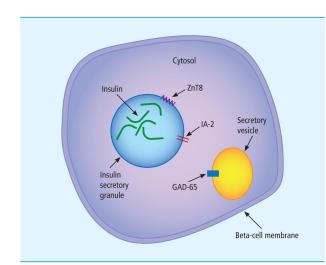
# IA-2 Antigène associé à l'insulinome 2

_	IA-2A		
	ELISA	BDR RIA <sup>c</sup>	
Sensitivity, % (n=76/70)	60.5 (49.3-70.8)	63.2 (51.9–73.1)	
Sensitivity, %, ≤18 years of age	68.8	81.3	
Sensitivity, %, >18 years of age	58.3	58.3	
Specificity, %, (n = 131)	98.5 (94.6-99.6)		
Specificity, % (n = 42)	97.6 (87.7–99.6)	97.6 (87.7–99.6)	



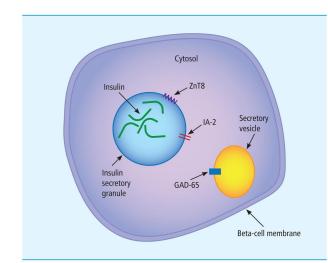
#### **IAA** Insuline auto-anticorps

- Souvent premier auto-anticorps dans l'enfance
- Spécifique aux cellules des îlots de Langerhans du pancréas (sans insulinothérapie)
- Sensibilité: >90% <5 ans, 40% 12-18 ans, <30% adults
- Seulement tester pour des enfants < 10 ans
- Pour le diagnostic différentiel T1 vs T2 en cas d'obésité



# **IAA** Insuline auto-anticorps

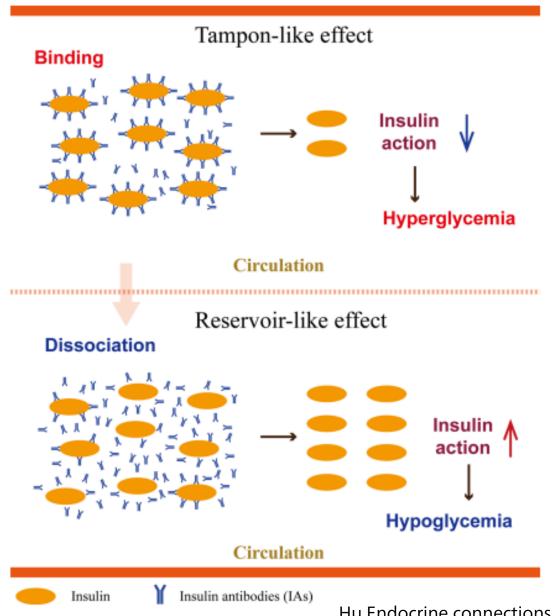
_	IAA		
	ELISAª	BDR RIA <sup>c</sup>	
Sensitivity, % (n=76/70)	1.3 (0.2–7.1)	30.3 (21.1–41.3)	
Sensitivity, %, ≤18 years of age	0	31.3	
Sensitivity, %, >18 years of age	1.7	30.0	
Specificity, %, (n = 131)	96.2 (91.4-98.4)		
Specificity, % (n = 42)	97.6 (87.7-99.6)	90.5 (77.9-96.2)	



# Anticorps insuliniques exogènes en cas de traitement

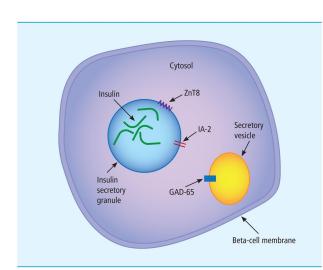
Surtout pour l'insuline des cellules animales

- Réactions d'hypersensibilité
- Résistance à l'insuline



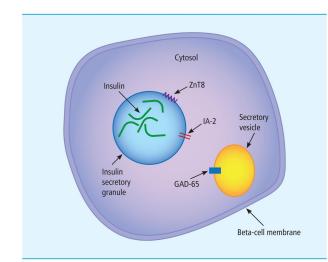
#### Transporteur de zinc protéine 8 auto-anticorps

- Transporteur de zinc spécifique aux vésicules
- Dernier auto-anticorps contre le diabète de type 1 découvert (2007)
- Marqueur le plus spécifique du diabète de type 1, en partie le seul autoanticorps
- 60-80% des patients diabète de type 1



# Transporteur de zinc protéine 8 auto-anticorps

	ZnT8A		
	ELISAª	BDR RIA <sup>c</sup>	
Sensitivity, % (n=76/70)	69.7 (58.7-78.9)	57.9 (46.7–68.4)	
Sensitivity, %, ≤18 years of age	75.0	62.5	
Sensitivity, %, >18 years of age	68.3	56.7	
Specificity, %, (n = 131)	97.7 (93.5-99.2)		
Specificity, % (n = 42)	95.5 (84.2-98.7)	100 (91.6–100)	



#### Récepteur de l'insuline auto-anticorps

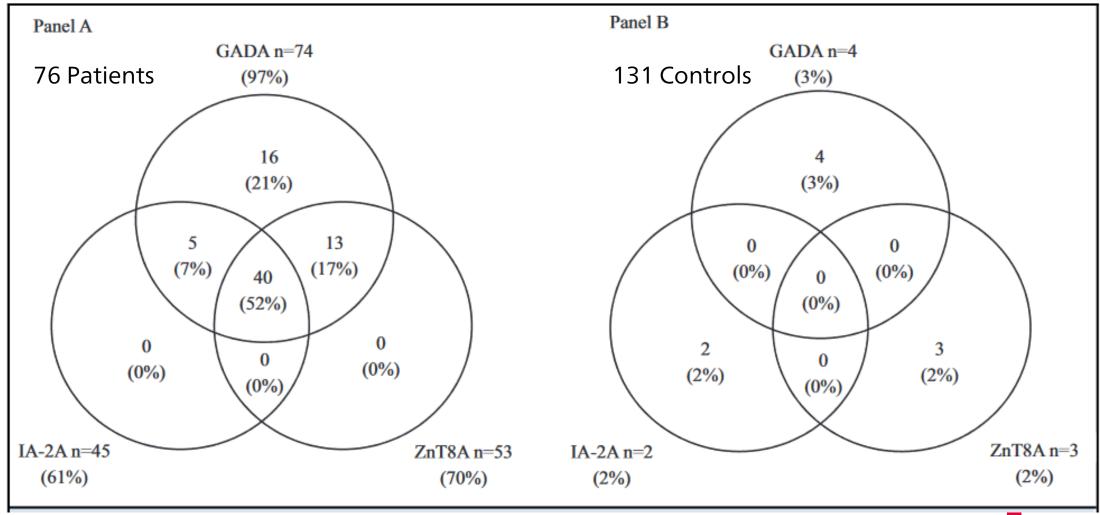
- Non spécifiques des cellules bêta
- Peuvent être inhibitrices ou stimulantes
- Dans d'autres maladies auto-immunes (LED)
- Stimulant dans les syndromes paranéoplasiques (lymphomes Hodgkin) -
- > hypoglycémie
- Non caractéristique du diabète sucré de type 1
- Signification diagnostique incertaine



Table 1. Autoantibodies associated with autoimmune diabetes (T1DM).					
Autoantibody	Antigen	Diagnostic sensitivity for diagnosis of T1DM, %	Diagnostic specificity for diagnosis of T1DM, %	Reference(s)	
IAA	Insulin/proinsulin	50–60 (children); ≅40 (adults)	99	24, 31	
GADA	Glutamic acid decarboxylase 65	70-80	90	24	
IA-2A	IA-2 protein tyrosine phosphatase	55-75	100	24, 26	
ICA	eta cell cytoplasmic proteins	44–100	64-100	24	
ZnT8A	Zinc transporter on secretory granules	61–72	97–99	29, 30	

Diabète de type 1: 98% avec ≥1 auto-anticorps





Enfants à risque génétique de diabète du type 1: Recherche des auto-anticorps

• 8597 enfants

1994-2009

Finlande



2818 enfants

1989-2006

Allemagne



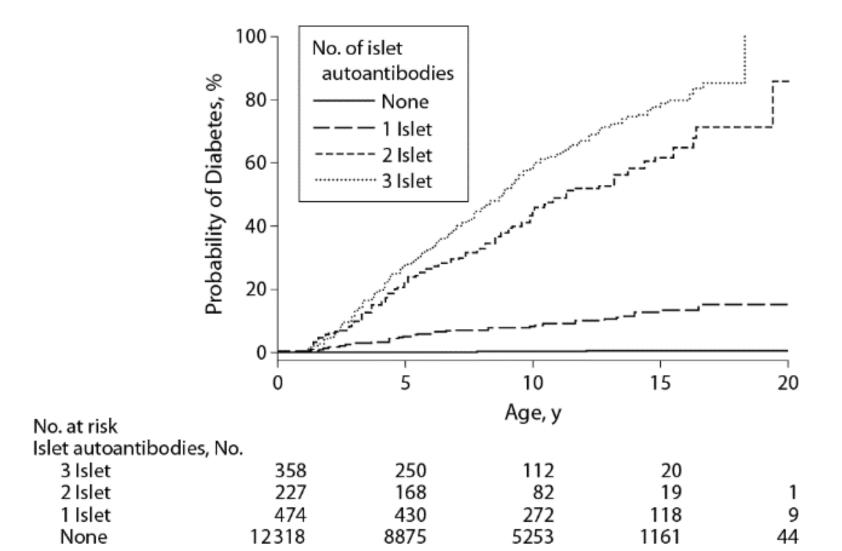
1962 enfants

1993-2006

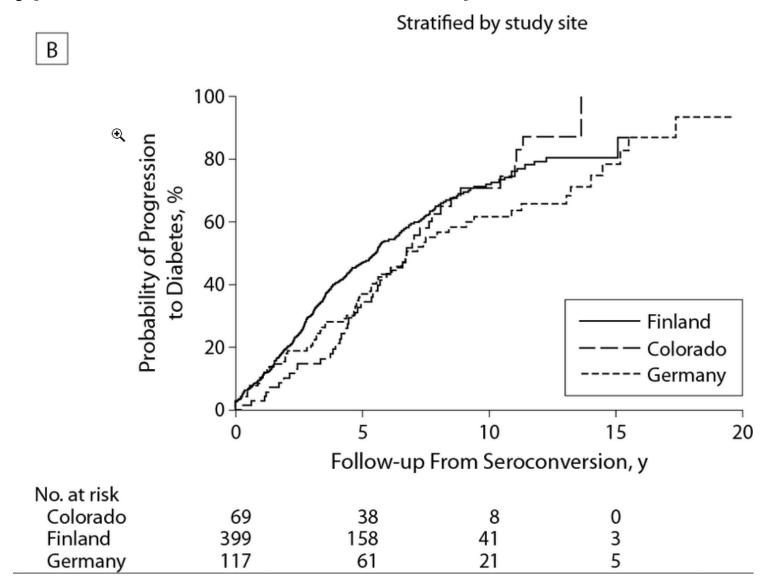
Colorado



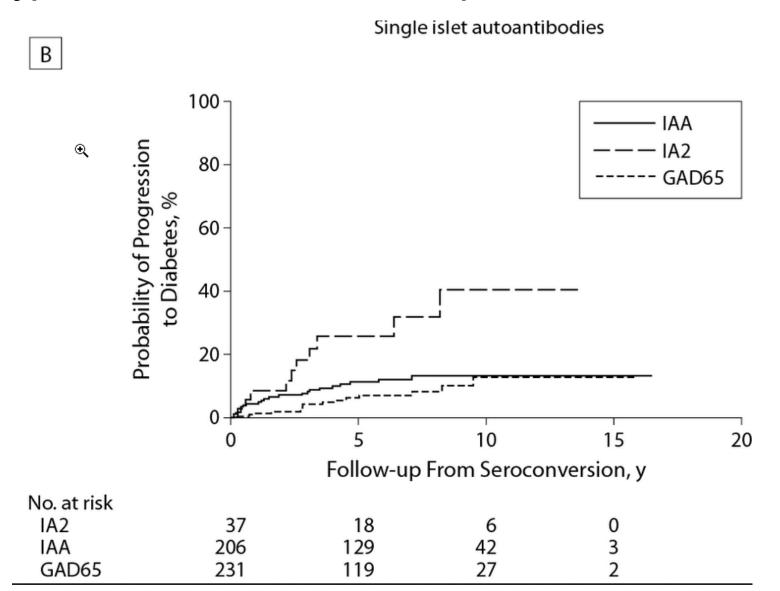




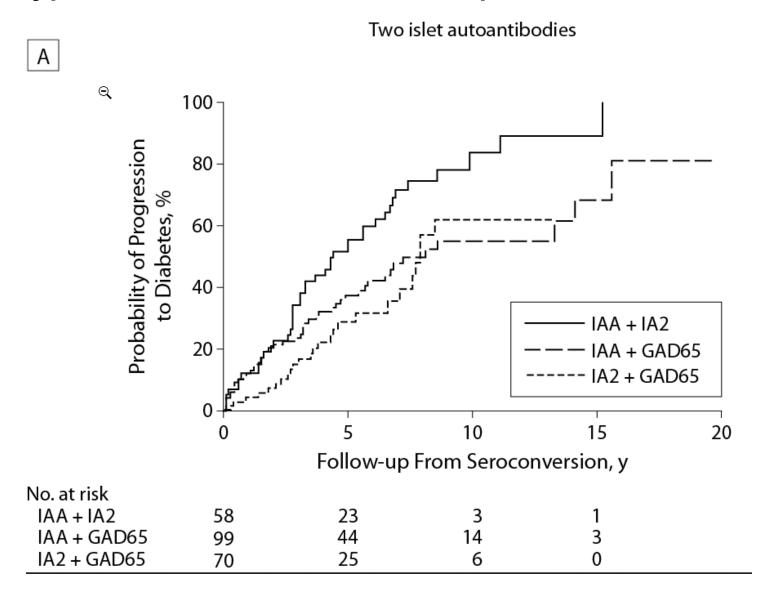














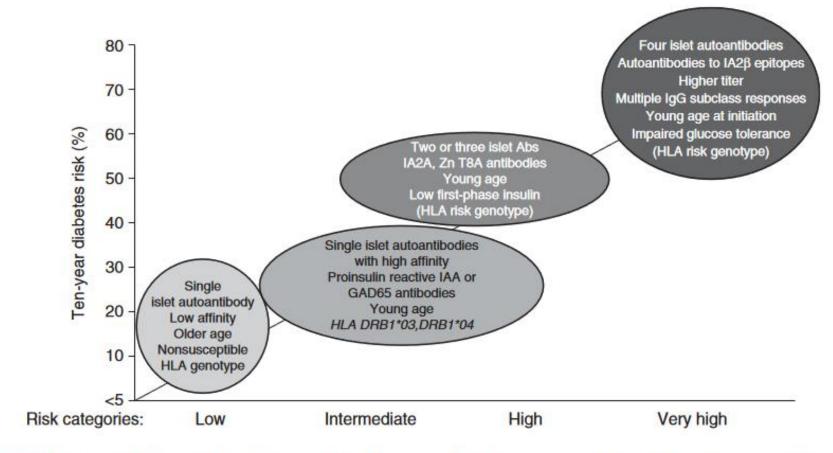


Figure 4. Type 1 diabetes risk stratification by islet autoantibody properties. (Adapted from Ziegler and Nepom 2010; with permission.)



<b>Table 3.</b> Likelihood ratios for the GADA, IA-2A, and ZnT8 ELISA.			
Cutoff value	LR	95% CI	
GADA ELISA			
<5 IU/mL	0.027	0.01-0.11	
5-10 IU/mL	1.72	0.25-11.99	
>10 IU/mL	60.05	15.67-245.74	
IA-2A ELISA			
<10 IU/mL	0.41	0.32-0.54	
10-30 IU/mL	10.34	1.27-84.29	
>30 IU/mL	67.22	18.21–1031.15	
ZnT8A ELISA			
<1.5 U/mL	0.061	0.020-0.19	
1.5-15 U/mL	0.80	0.51-1.26	
15-50 U/mL	7.76	1.72-34.97	
>50 U/mL	75.84	10.66-539.43	



# Diabète de type 1: concentration auto-anticorps au moment du diagnostic

The Journal of Clinical Endocrinology & Metabolism, 2022, Vol. 107, No. 12

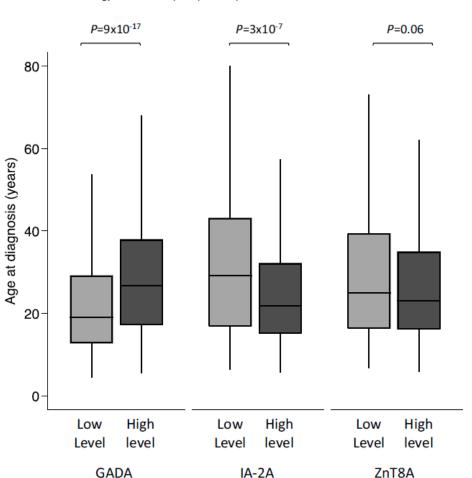


Figure 2. Box plot showing age of diagnosis of type 1 diabetes (T1D) in high- and low-level groups for glutamate decarboxylase (GADA), islet antigen-2 (IA-2A), and zinc transporter 8 (ZnT8A). The nadir value between the 2 modes of GADA level (450 DK U/mL) and IA-2A level (125 DK U/mL) distribution at diagnosis of T1D patients who were positive for respective autoantibodies was used to define high- and low-level categories. There were 604 of 1364 and 760 of 1364 cases in low- and high-level GADA groups and 803 of 1099 and 296 of 1099 cases in high- and low-level IA-2A groups. The median value of ZnT8A level (35.6 AU/mL) was used for defining low- and high-level groups (n = 477 each). Median age of diagnosis was higher for the high-level GADA group (P = 9 x 10<sup>-17</sup>), lower for the higher-level IA-2A (P = 3 x 10<sup>-7</sup>), and similar between ZnT8A level categories (P = .06).



-4

# Diabète de type 1: concentration auto-anticorps au moment du diagnostic Diabetologia (2015) 58:980–987

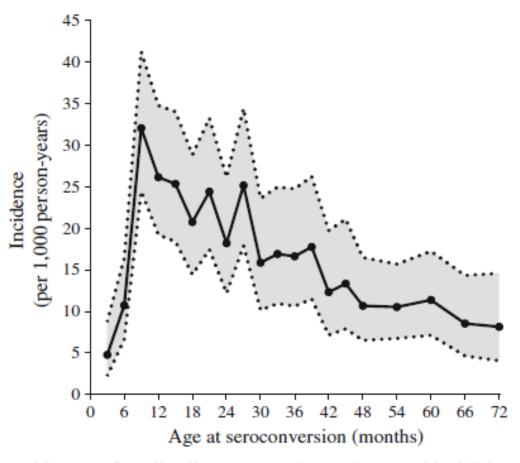


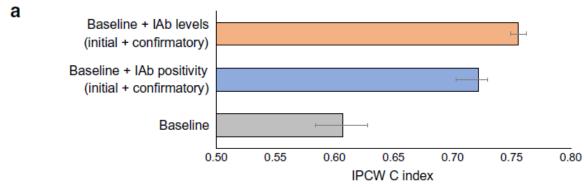
Fig. 1 Incidence of antibodies among 0- to 6-year-old children in the TEDDY study by age of seroconversion (incidence and 95% piecewise confidence bands). Autoantibodies appeared in 549/8,503 children

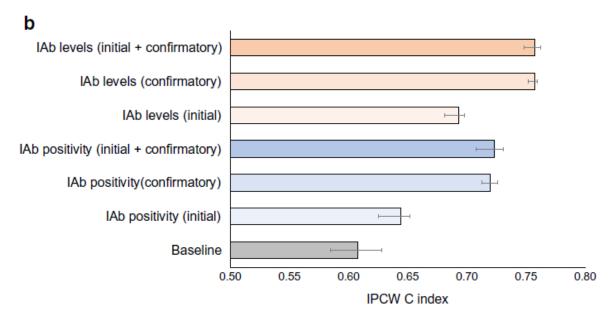


# Diabète de type 1: concentration auto-anticorps au moment du diagnostic

Diabetologia (2023) 66:93–104

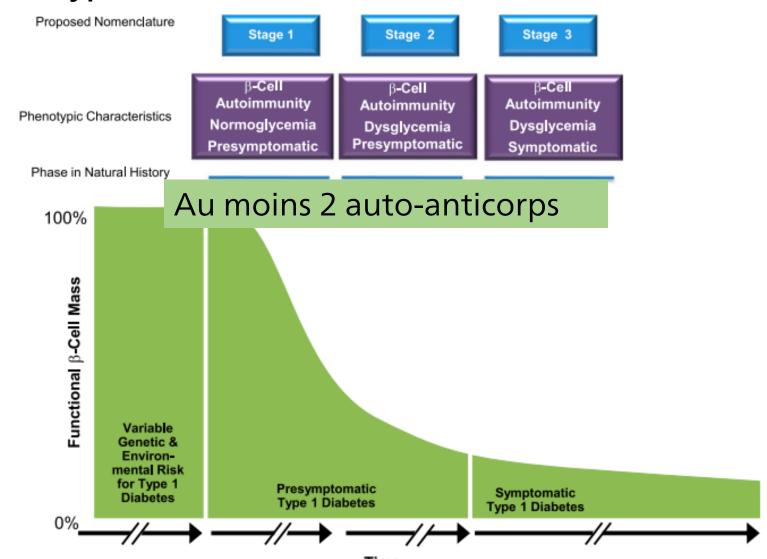
Fig. 1 Type 1 diabetes prediction performance (IPCW concordance index [C index] with 95% CI) for various covariate sets. (a) Performance for a model using baseline covariates; a model using baseline covariates and IAb positivity indicators from both initial and confirmatory visits; and a model using baseline covariates and IAb levels from both initial and confirmatory visits. (b) Performance for a model using baseline covariates, models using IAb positivity indicators from the initial visit, the confirmatory visit and both visits, and models using IAb levels from the initial visit, the confirmatory visit and both visits. The prediction start time ('time 0') was the seroconversion confirmatory visit. The duration of the follow-up period was 10 years. IAbs include GADA, IA-2A and IAA







#### Diabète de type 1: Stades





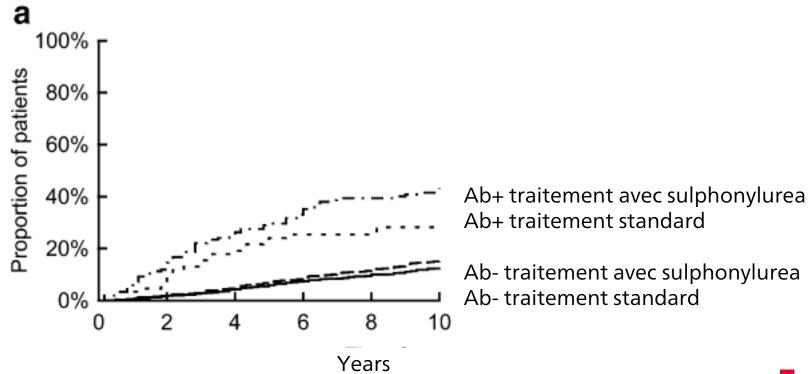
• UK: 4545 patients atteints de diabète de type 2 ont été testés pour les auto-anticorps au moment du diagnostic

**Table 1** Demographic and clinical characteristics after dietary runin of 4,545 patients classified according to autoantibody status

	Ab+ve	Ab-ve	p Value
Number (% of total)	526 (11.6%)	4,019 (88.4%)	
Male $[n \ (\% \ \text{of total})]$	293 (56%)	2,437 (61%)	0.030



• Risque plus élevé d'avoir besoin d'insuline si des auto-anticorps ont été détectés



# Diabète de type 1: Screening?

#### RESEARCH DESIGN AND METHODS

#### **Study Participants**

The Fr1da study offered screening for islet autoantibodies to children aged 1.75–5.99 years in Bavaria, Germany. Families of children who were positive for multiple islet autoantibodies (i.e., presymptomatic type 1 diabetes) were invited to participate in a program of diabetes education, metabolic staging, assessment of psychological stress associated with diagnosis, and prospective follow-up for progression to clinical diabetes. Details on the Fr1da study protocol have previously been published (24,25). The study was approved by the institutional review board at Technical University Munich. This analysis includes data from 90,632 children (median age 3.1 years; interquartile range 2.1–4.2; 47% girls) who participated in the Fr1da study between February 2015 and May 2019, of whom 280 (0.31%) were diagnosed with presymptomatic type 1 diabetes (25).



#### Diabète de type 1: Screening?

Costs of Screening for Type 1 Diabetes

Diabetes Care Volume 45, April 2022

Table 2—Cost of screening for presymptomatic type 1 diabetes as estimated for standard care in Germany
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Simulated standard care scenarios	Total costs	Pediatric practice	Coordination center and laboratory
Cost per child screened (model A)*	€21.73 (16.76; 28.19)	€12.25 (7.24; 18.52)	€9.34 (8.29; 10.42)
Cost per case diagnosed†	€7,035 (5,426; 9,124)	€3,967 (2,344; 5,996)	€3,024 (2,684; 3,373)
Model A plus 100% pediatrician time costs	€33.80 (23.72; 47.43)	€24.21 (14.61; 37.28)	€9.45 (8.41; 10.53)
Model A minus 50% pediatrician time costs	€15.70 (13.28; 18.51)	€6.27 (4.07; 8.87)	€9.29 (8.26; 10.38)
Model A with lower 3-Screen ELISA costs (€1.4 per test)	€21.93 (19.96; 28.39)	€12.25 (7.24; 18.52)	€9.54 (8.49; 10.62)
Model A with higher 3-Screen ELISA costs (€3.6 per test)	€24.13 (19.16; 30.59)	€12.25 (7.24; 18.52)	€11.74 (10.69; 12.82)

Data are means (95% CI). 3-Screen ELISA, 3 Screen Islet Cell Antibody ELISA measuring GADA, IA-2A, and ZnT8A. \*Probabilistic costs for metabolic staging and education were €0.14 (95% CI 0.12; 0.15) in the simulated standard care scenario and completely accounted for as costs for the local diabetes clinics. †The costs per case diagnosed for the local diabetes clinic were €44.02 (95% CI 38.19; 49.80).



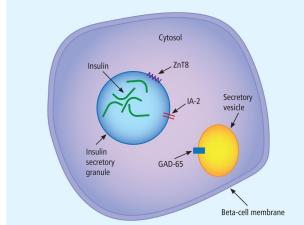
#### Screening des auto-anticorps

Tester en priorité les auto-anticorps suivants:

Enfants <10 ans: IAA + GAD65</li>

• Enfants > 10 ans: IA-2 + GAD65

→ En plus tester les auto-anticorps contre le transporteur de zinc protéine 8 pour une sensitivité optimale



#### Diabète et autre maladies auto-immunes

- Hyperthyroïdie auto-immune (Morbus Basedow, Hashimotothyroïdite)
- Maladie coeliaque
- Maladie d'Addison
- Syndromes auto-immuns polyglandulaires



#### Diabète de type 1: résumé

- Y penser et tester!
- Symptômes aigus chez les enfants
- Possible aussi chez les adultes, transition douce
- Diagnostic: déterminer les auto-anticorps
- Combinaison de tous les auto-anticorps permet de détecter un diabète de type 1 même dans les phases précoces



#### Merci de votre attention!

