Universidade Federal do Rio de Janeiro
Centro de Ciências da Saúde
Instituto de Ciências Biológicas
Programa de Graduação em Farmacologia

Concurso para provimento de cargo de Professor Adjunto A 40h-DE
Pesquisas Translacionais em Doenças Metabólicas

Abordagens terapêuticas do Diabetes *Mellitus* tipo 1: estratégias farmacológicas atuais e potenciais de inovação

Tháyna Sisnande

Rio de Janeiro
2024

Diabetes *mellitus*

Brazil

Diabetes report 2000 — 2045

At a glance	2000	2011	2021	2030	2045
Diabetes estimates (20-79 y)					
People with diabetes, in 1,000s	3,310.4	12,440.0	15,733.6	19,224.1	23,223.6
Age-adjusted comparative prevalence of diabetes, %	-	10.1	8.8	10.2	10.9
People with undiagnosed diabetes, in 1,000s	-	-	5,025.3	-	-
Proportion of people with undiagnosed diabetes, %	-	-	31.9	-	-

Atlas IDF, 2021.

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Diabetes *mellitus*

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At a glance	2000	2011	2021	2030	2045
Diabetes-related health expenditure					
Total diabetes-related health expenditure, USD million	-	-	42,928.5	48,308.7	51,441.2
Total diabetes-related health expenditure, ID million	-	-	77,459.7	87,167.6	92,819.9
Diabetes-related health expenditure per person, USD	-	1,038.0	2,728.5	3,070.4	3,269.5
Diabetes-related health expenditure per person, ID	-	-	4,923.2	5,540.2	5,899.5
Demographics					
Total adult population (20-79 y), in 1,000s	102,431.0	127,994.8	149,916.8	161,892.7	169,190.2
Population of children (0-14 y), in 1,000s	58,042.0	-	43,762.9	-	-
Population of children and adolescents (0-19 y), in 1,000s	-	-	59,701.5	-	-

Atlas IDF, 2021.

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Atlas IDF, 2021.

Diabetes *mellitus*

Brazil

Diabetes report 2000 — 2045

At a glance	2000	2011	2021	2030	2045
Type 1 diabetes estimates in children and adolescents					
New cases of type 1 diabetes (0-14 y), in 1,000s	4.4	0.1	7.1	-	-
New cases of type 1 diabetes (0-19 y), in 1,000s	-	-	8.9	-	-
Type 1 diabetes (0-14 y), in 1,000s	19.9	-	49.9	-	-
Type 1 diabetes (0-19 y), in 1,000s	-	-	92.4	-	-

Atlas IDF, 2021.

Diabetes *mellitus*

Conjunto de doenças crônicas e complexas que requerem cuidados contínuos com estratégias de redução de risco multifatoriais, além do controle glicêmico.

Diabetes *mellitus*

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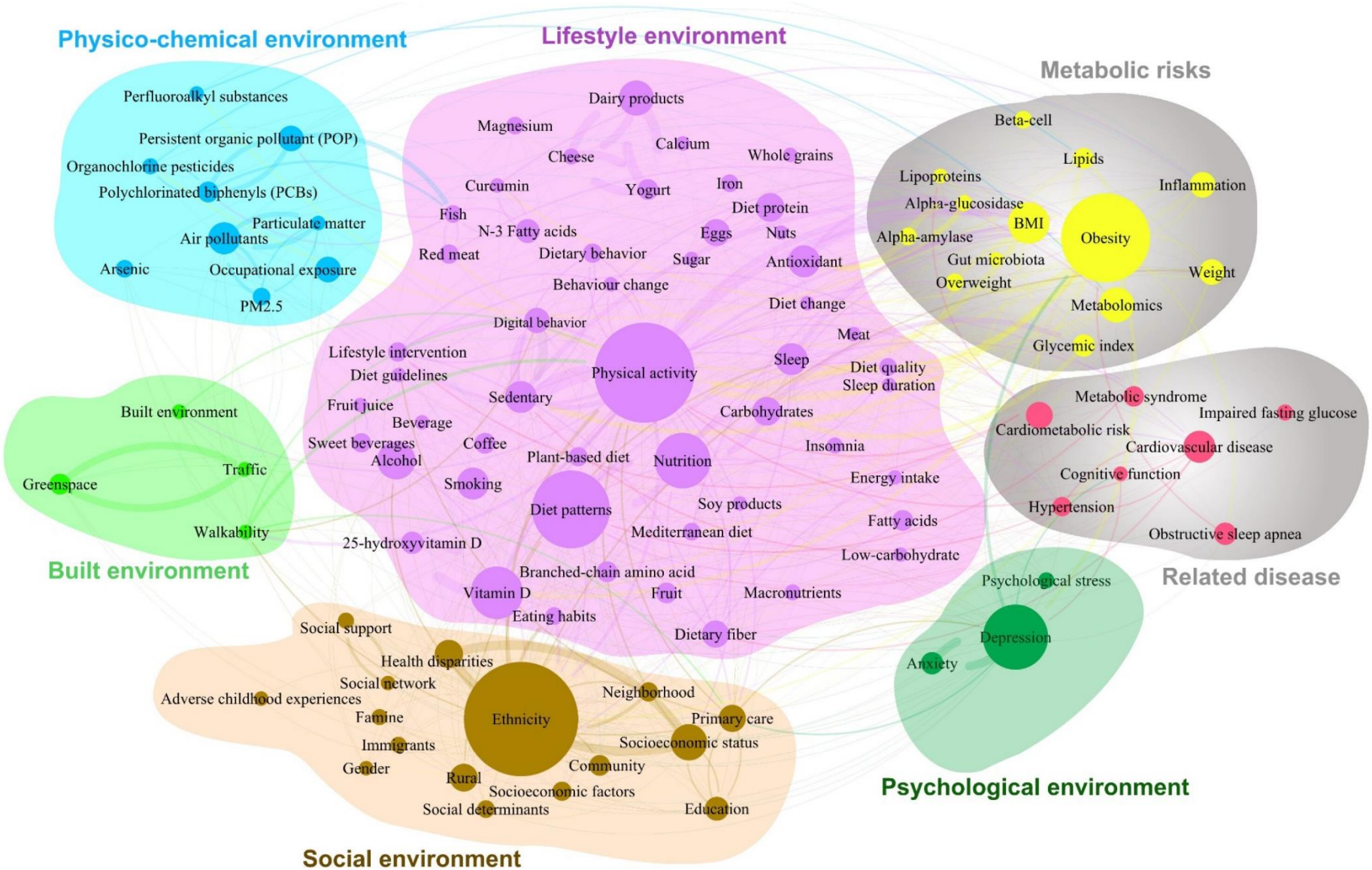
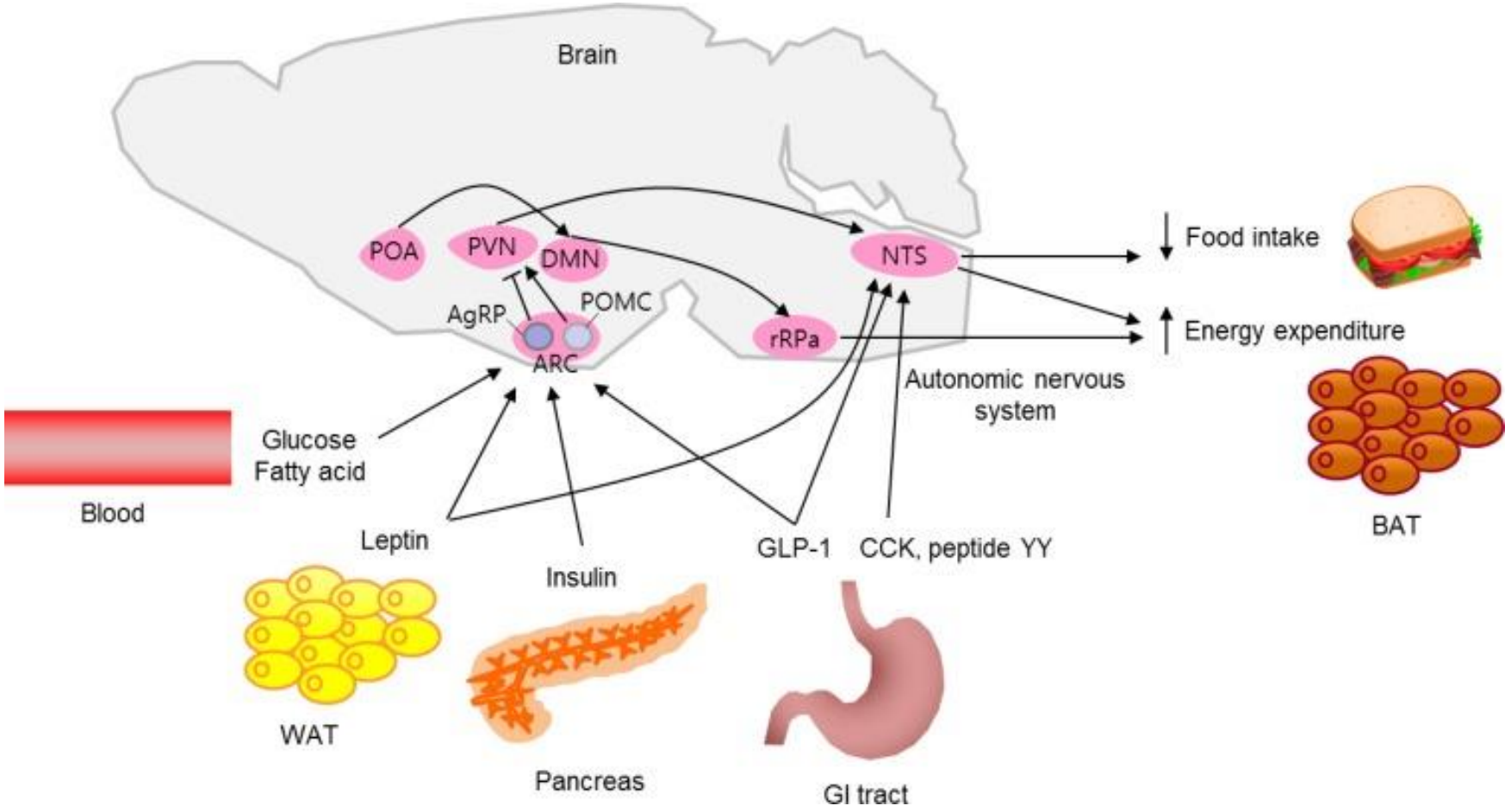
Glicose plasmática de jejum ≥ 126 mg/dL (7 mmol/L);
ou
2 horas após ingestão oral de 75 g de glicose em água, glicemia ≥ 200 mg/dL (11 mmol/L);
ou
Hemoglobina glicada ≥ 6,5% (48 mmol/mol);
ou
Paciente com sintomas de hiperglicemia ou em crise hiperglicêmica, com glicose plasmática aleatória ≥ 200 mg/dL (11 mmol/L).



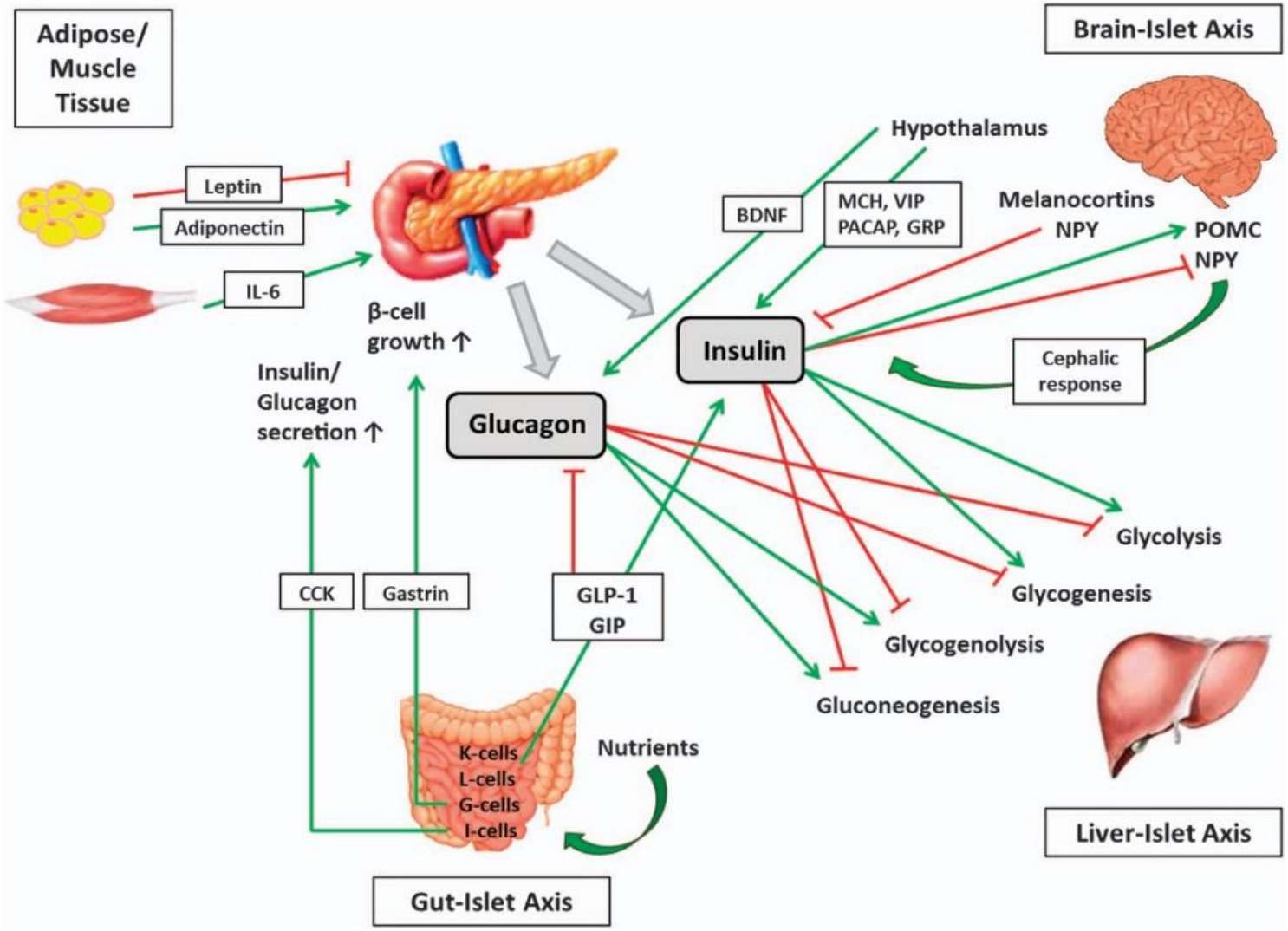
Cal, *et al. 2024*

Fisiologia do controle do metabolismo energético



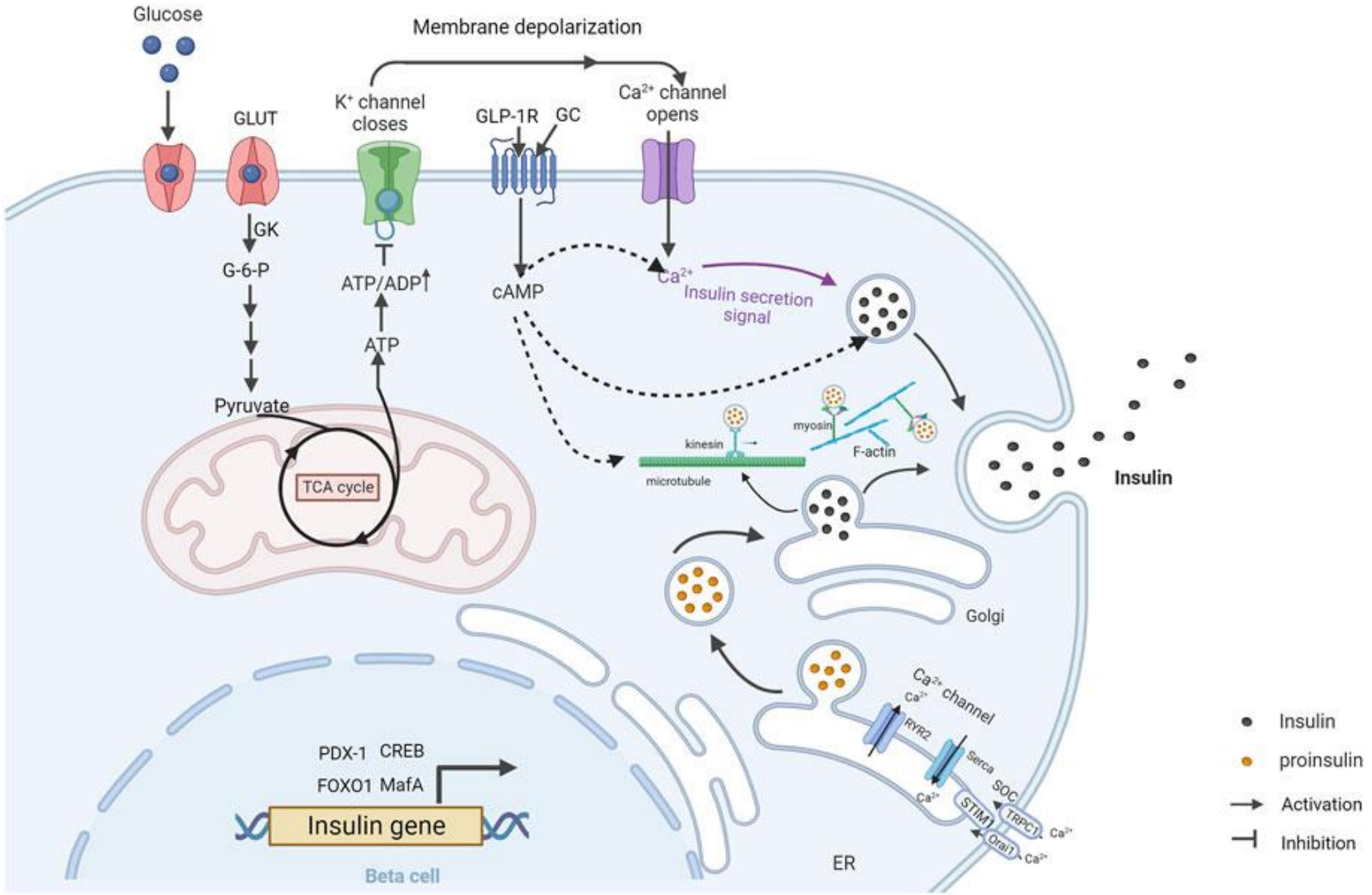
Eun Roh & Min-Seon Kim. 2016

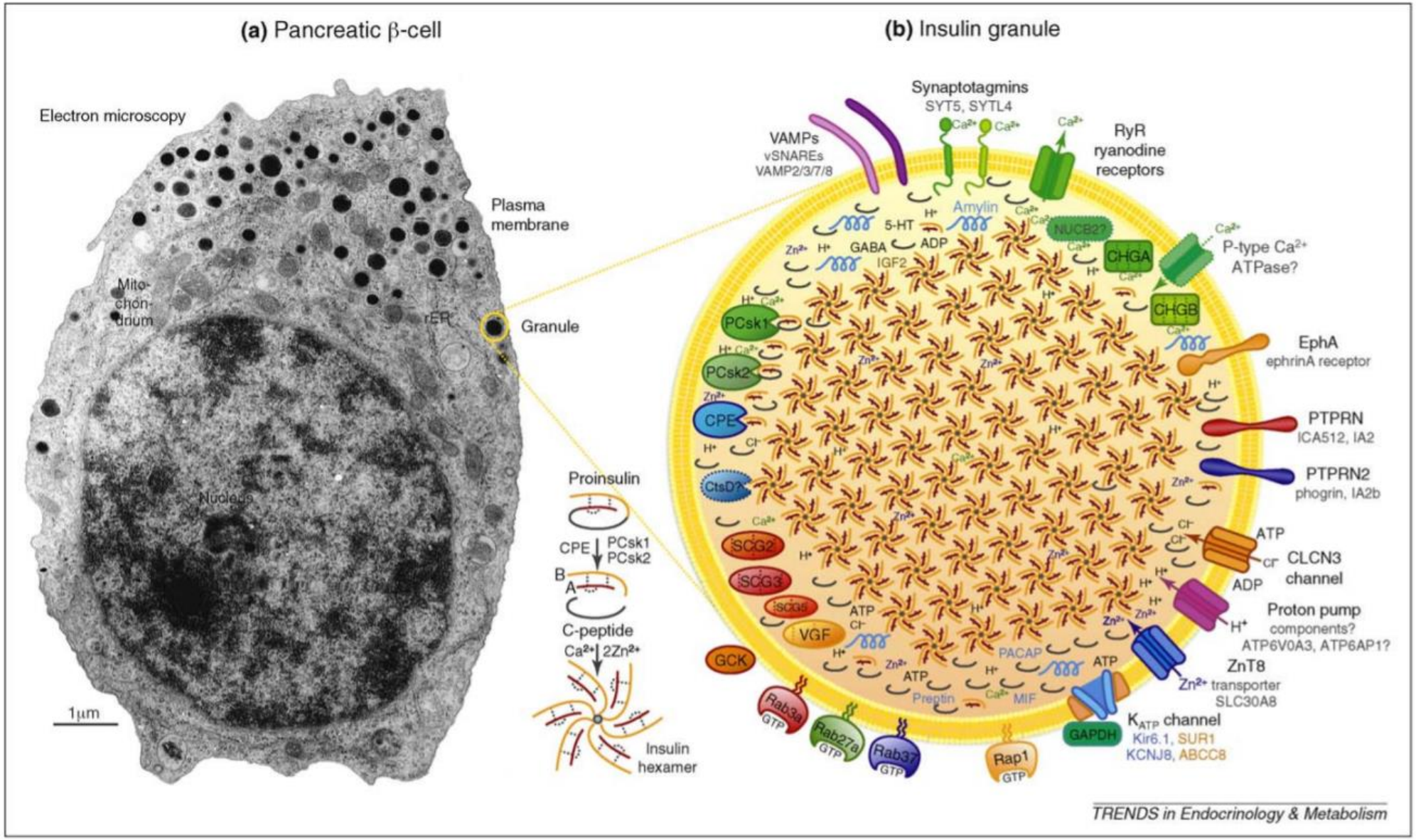
Fisiologia do controle do metabolismo energético



Röder. 2016

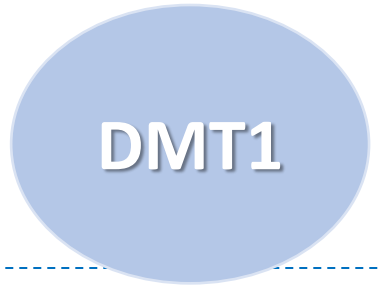
Fisiologia da secreção de insulina e amilina





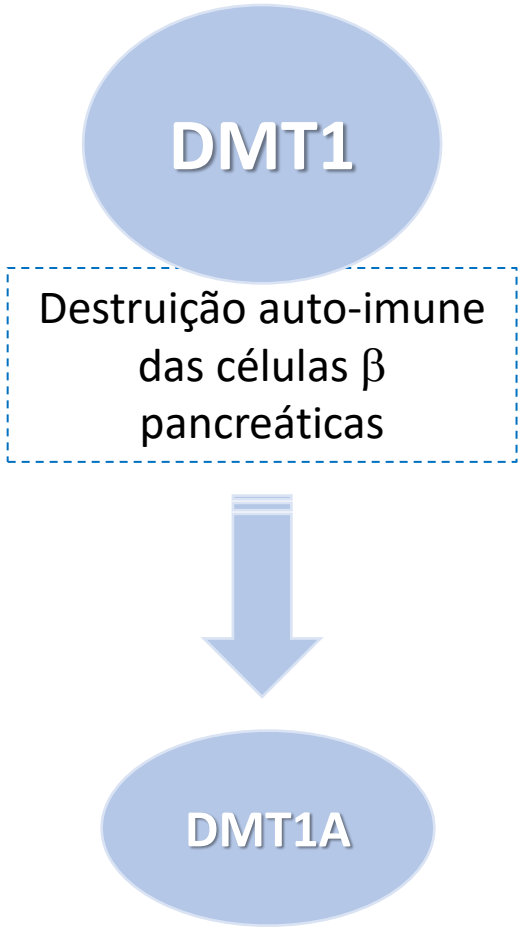
Suckale & Solimena. 2010

Diabetes *mellitus*



Destruição auto-imune das células β pancreáticas

Diabetes *Mellitus*



Autoanticorpos:

Ilhotas;

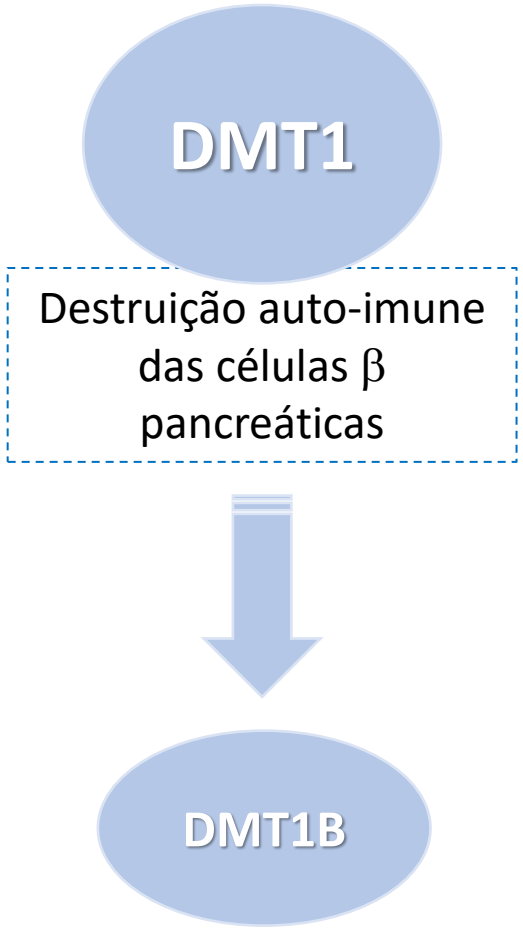
Ácido glutâmico descarboxilase;

Insulina;

Tirosina fosfatase (IA-2) e IA-2β;

ZnT8.

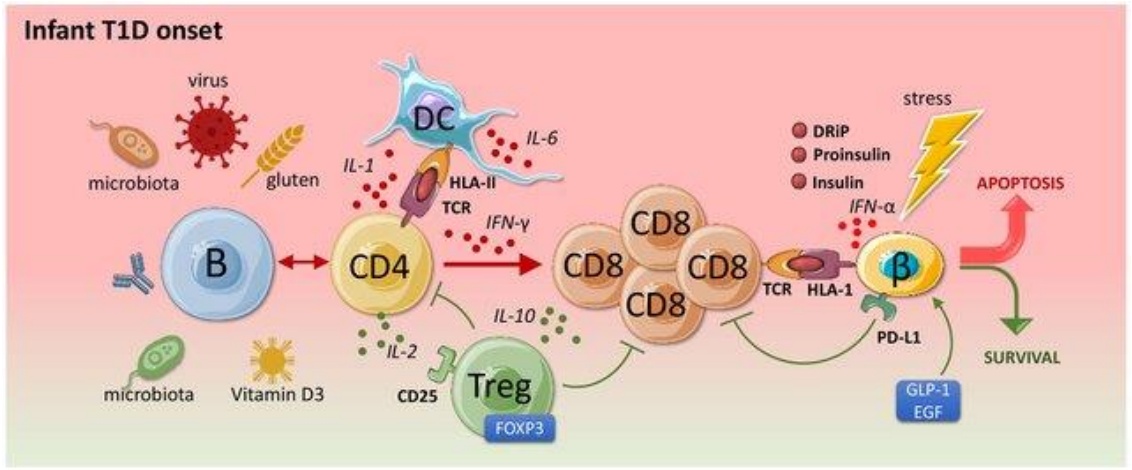
Diabetes *Mellitus*

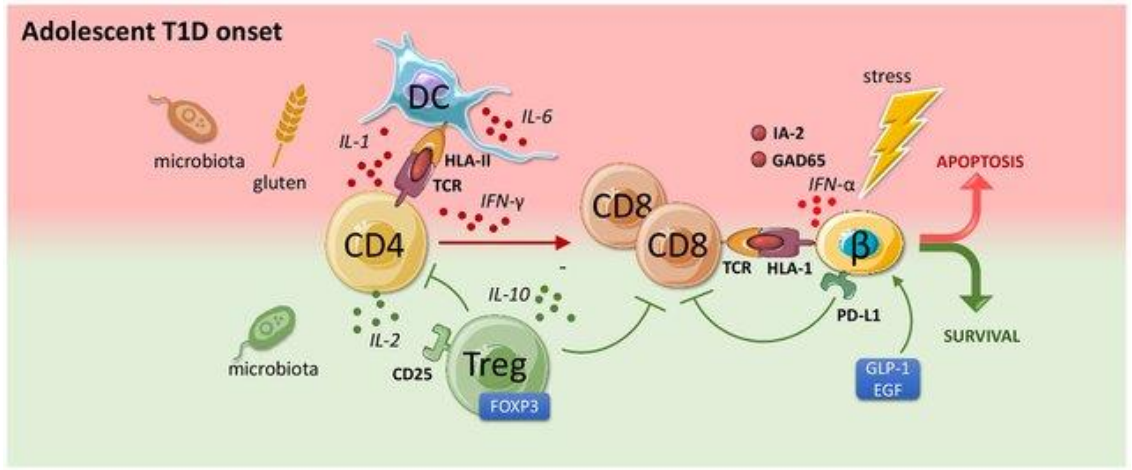


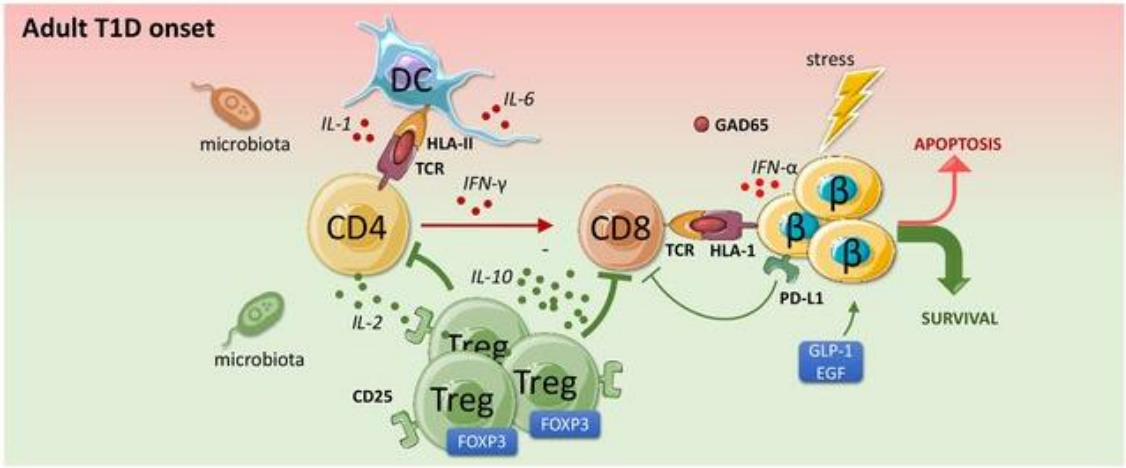
Etiologia desconhecida.

Os indivíduos apresentam insulinopenia e também cetoacidose diabética mas não há evidências de autoimunidade contra células β.

Patogênese Diabetes *Mellitus tipo 1*

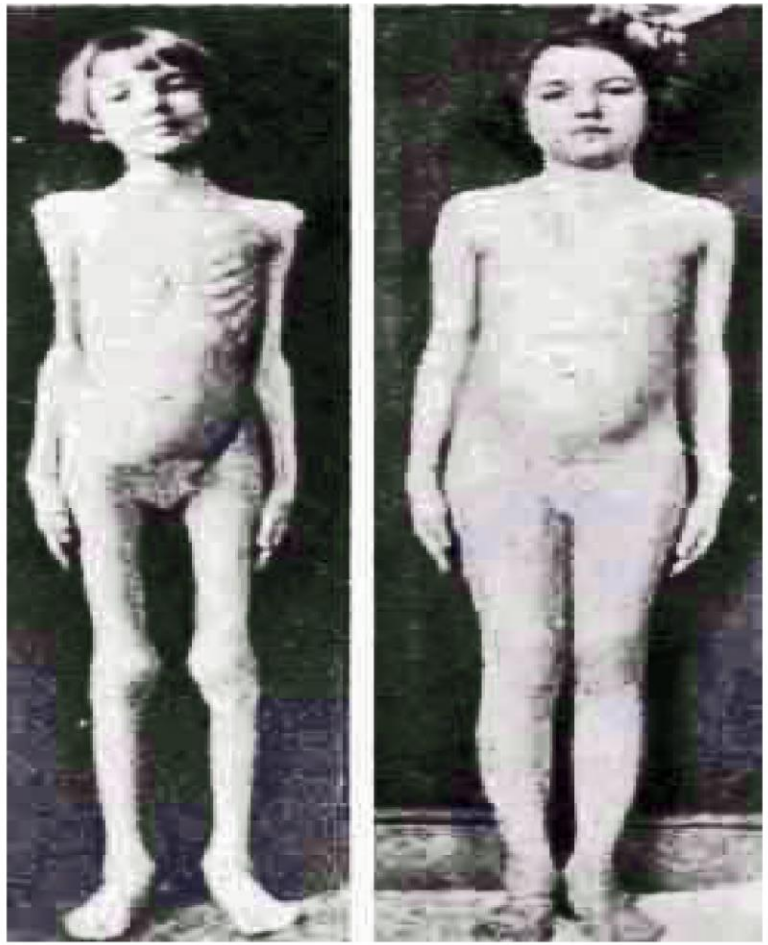






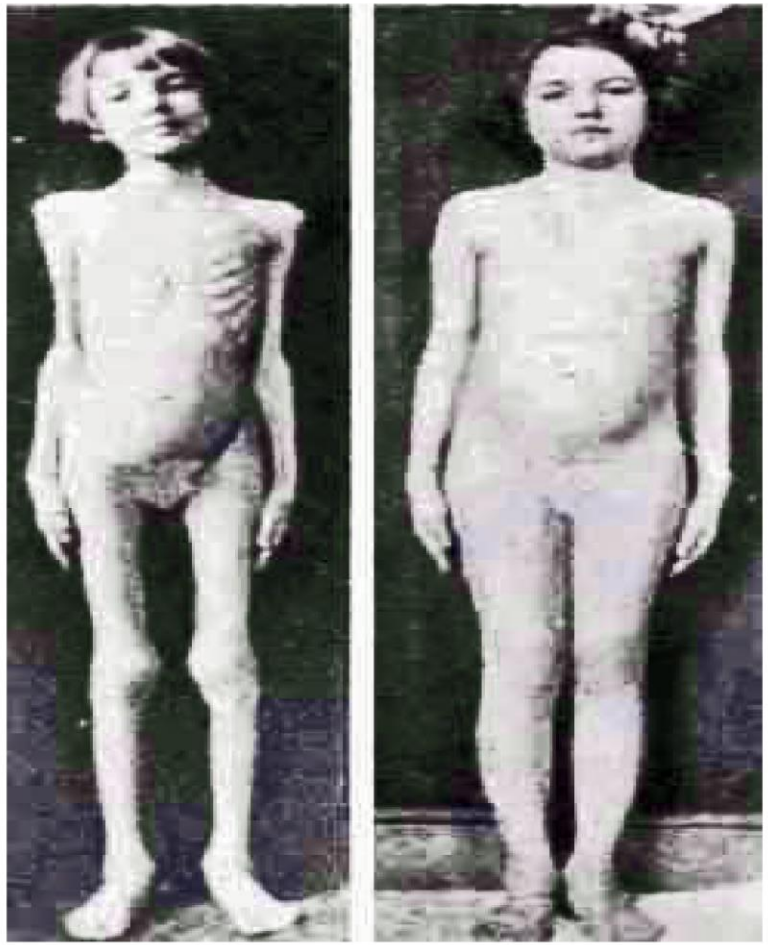
Nicoline H. M. den Hollander & Bart O. Roep. 2022

Diabetes *Mellitus*



Brink. 2022

Diabetes *Mellitus*



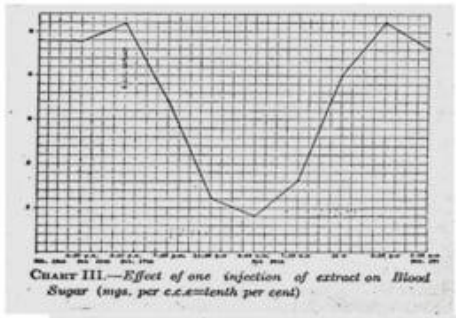


CHART III.—*Effect of one injection of extract on Blood Sugar* (mgs. per c.c.=tenth per cent)

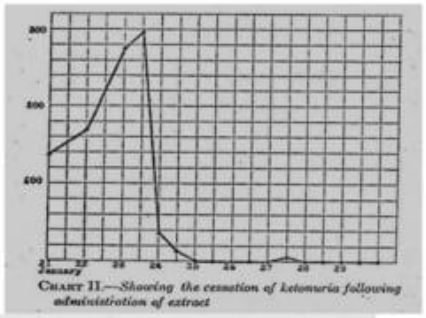


CHART II.—*Showing the cessation of ketonuria following administration of extract*

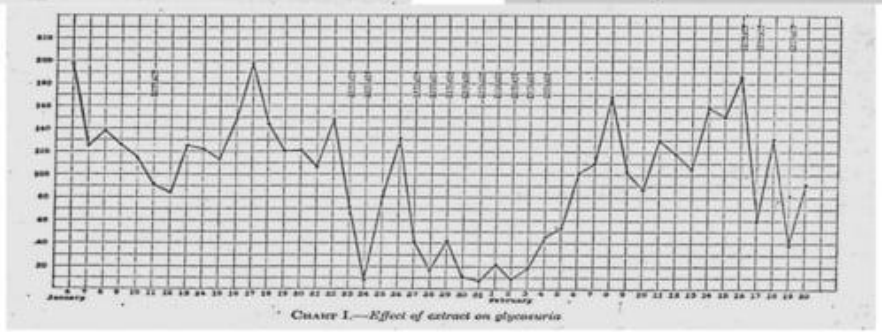
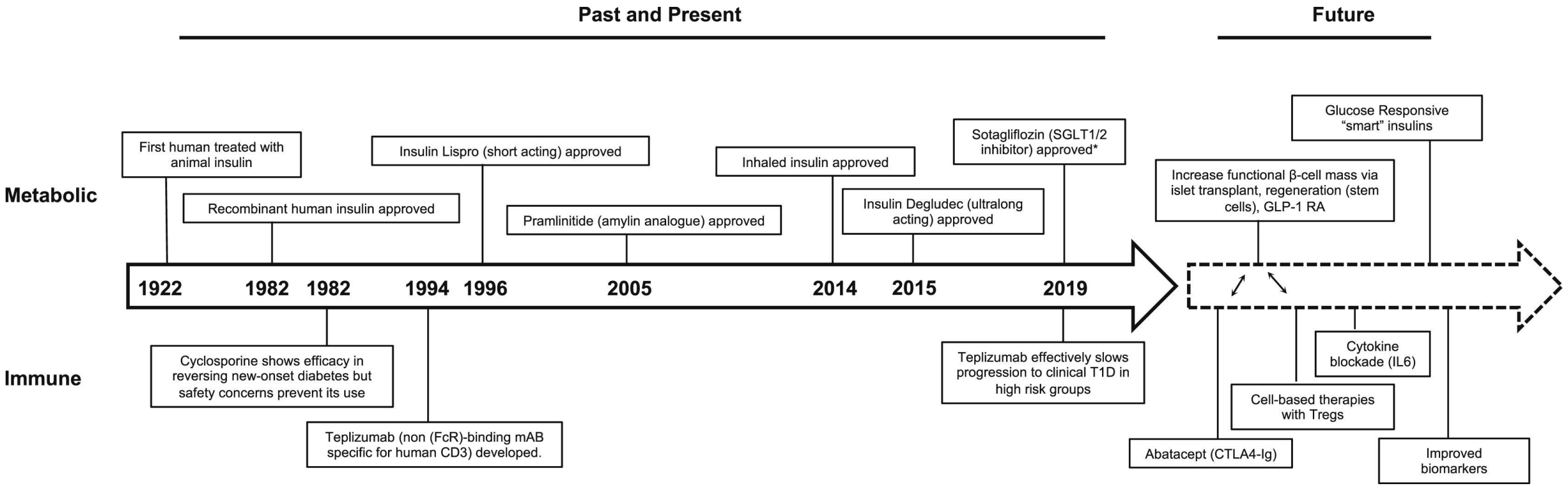


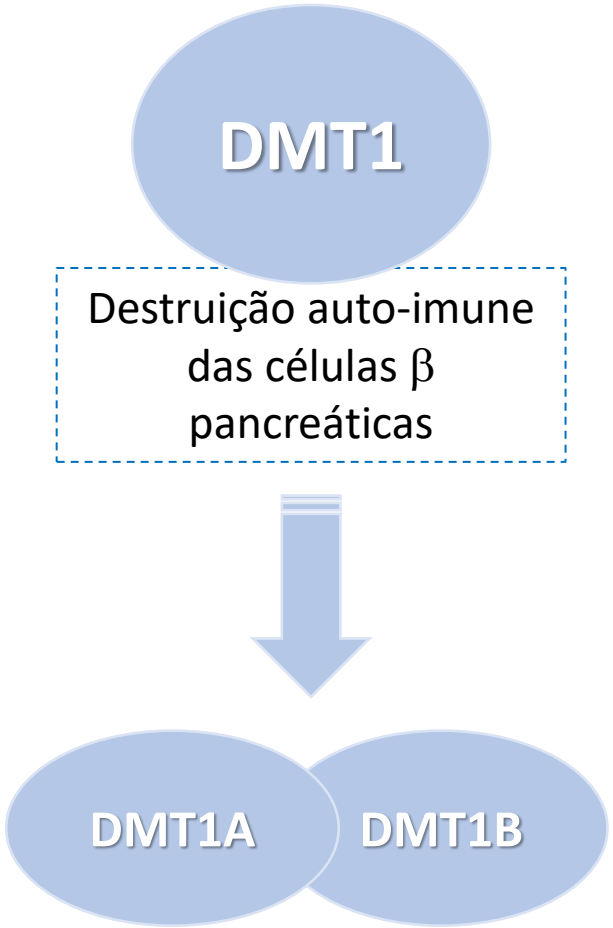
CHART I.—*Effect of extract on glycosuria*

Brink. 2022



Warshauer, 2020

Diabetes *mellitus*



Diabetes *mellitus*

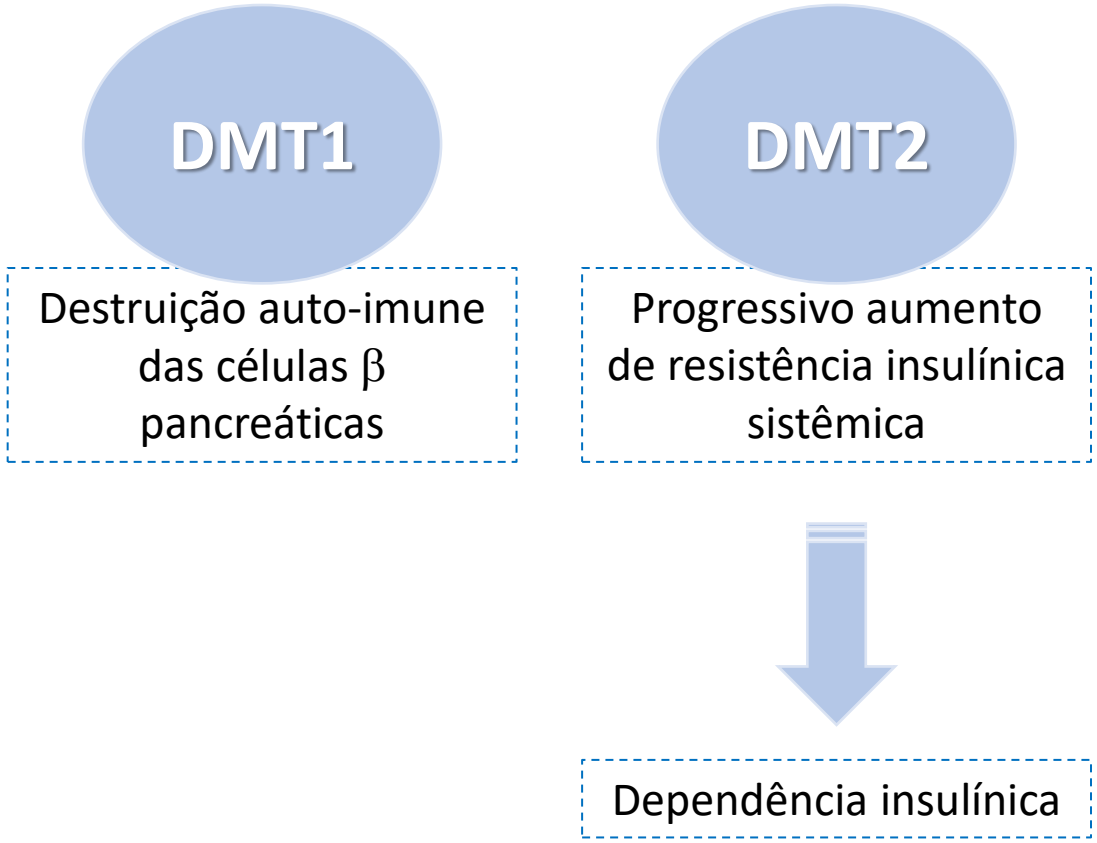
DMT1

Destruição auto-imune das células β pancreáticas

DMT2

Progressivo aumento de resistência insulínica sistêmica

Diabetes *mellitus*



Diabetes *mellitus*

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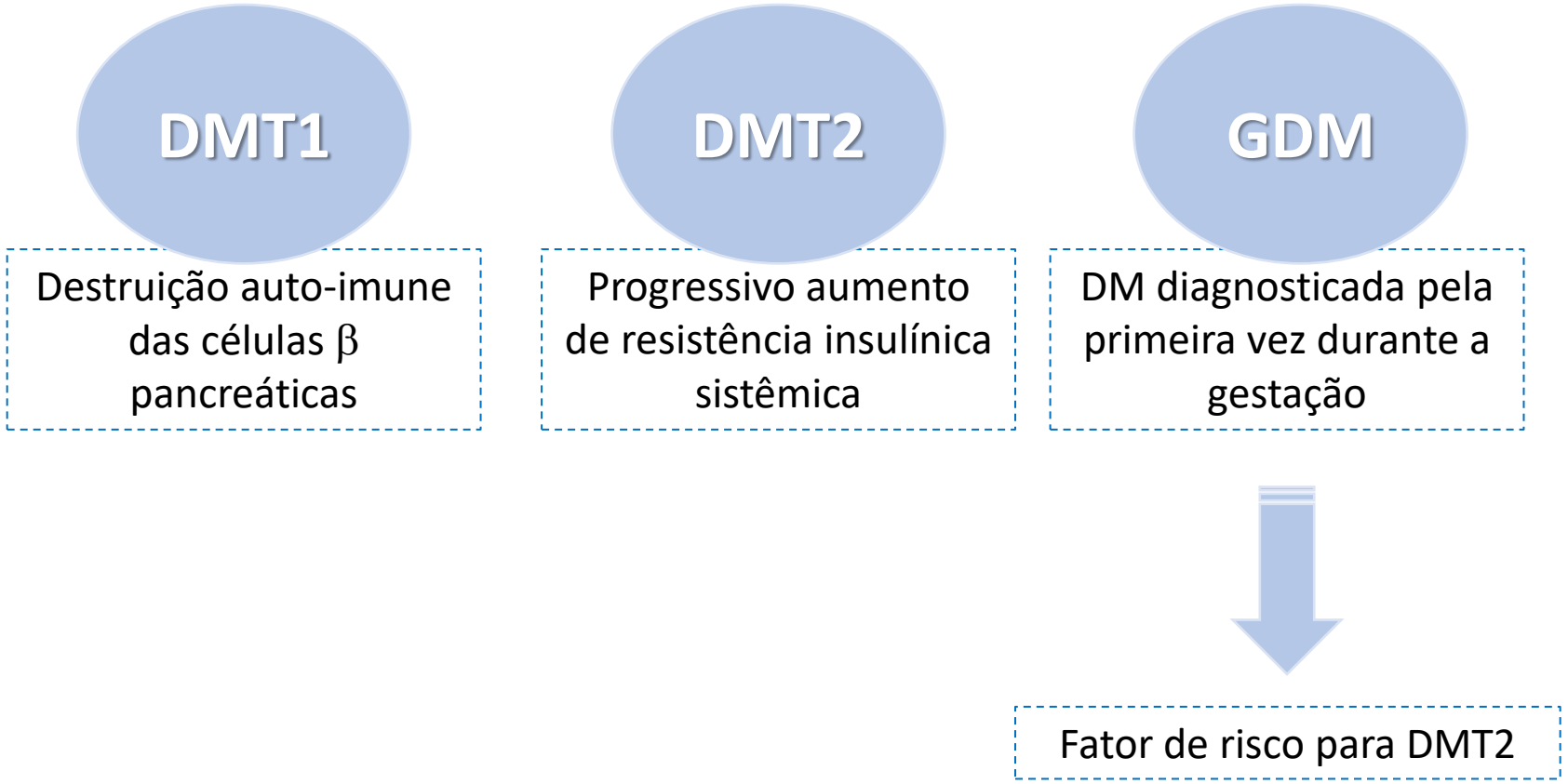
GDM

DM diagnosticada pela primeira vez durante a gestação

Diabetes *mellitus*



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Progressivo aumento de resistência insulínica sistêmica

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DM diagnosticada pela primeira vez durante a gestação

Outros

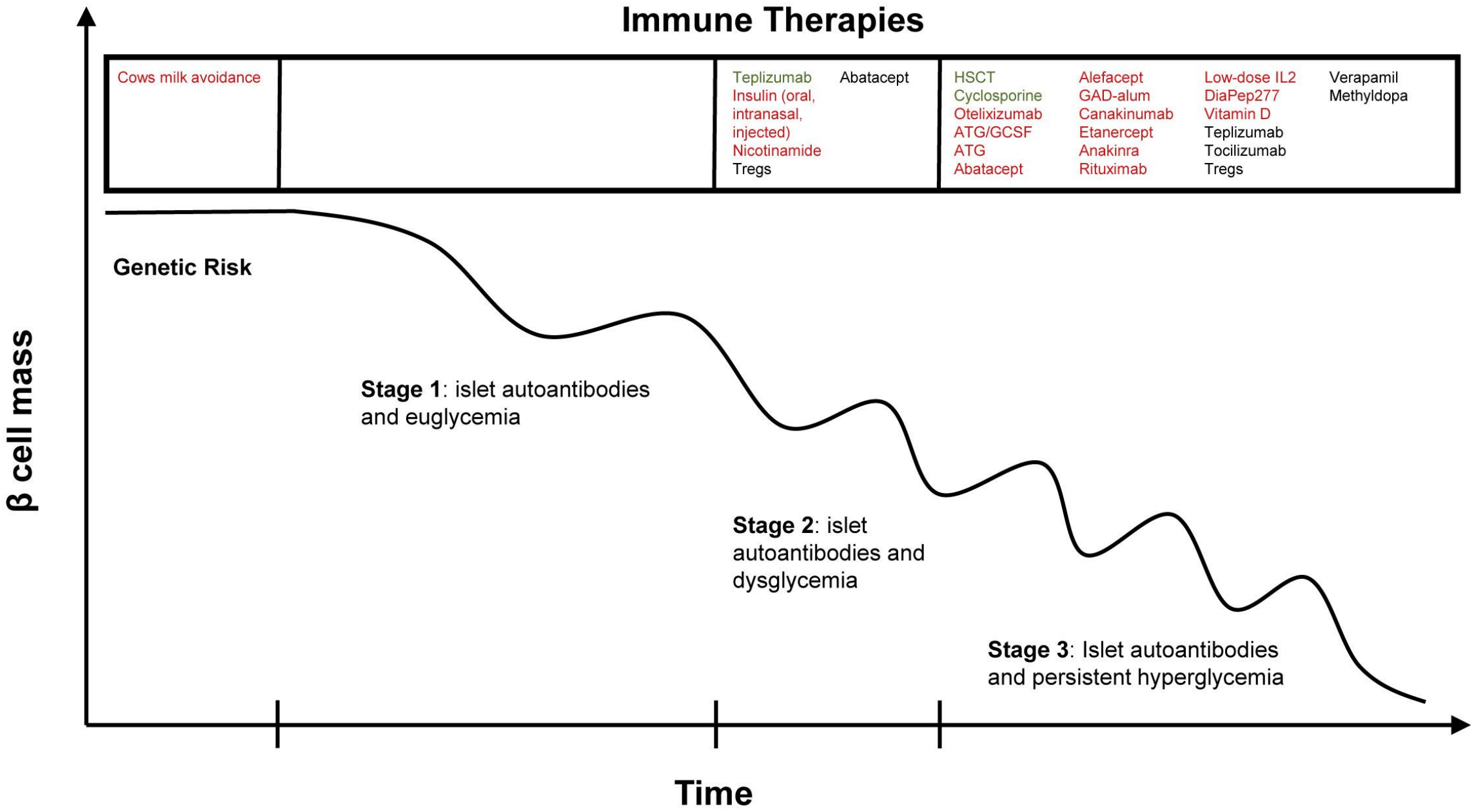
MODY, doenças do pâncreas exócrino, induzido por drogas/produtos químicos, ...

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

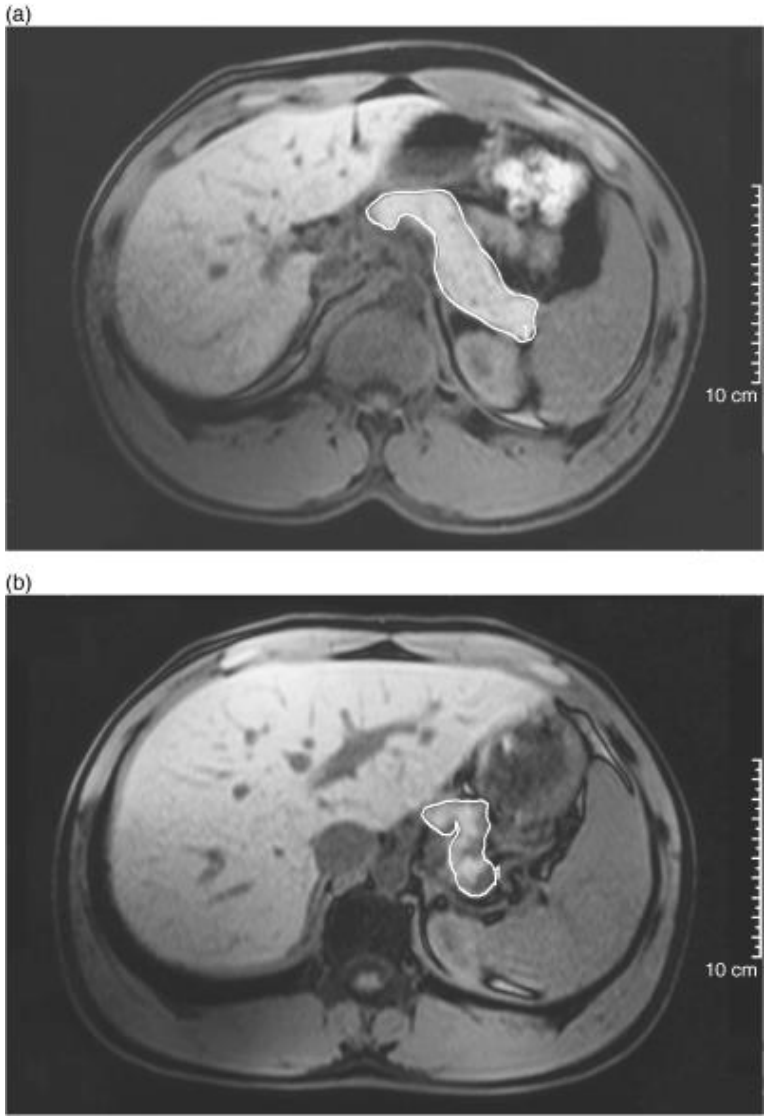
Adapted from Skyler et al. (40). FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose. Alternative additional stage 2 diagnostic criteria of 30-, 60-, or 90-min plasma glucose on oral glucose tolerance test ≥200 mg/dL (≥11.1 mmol/L) and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

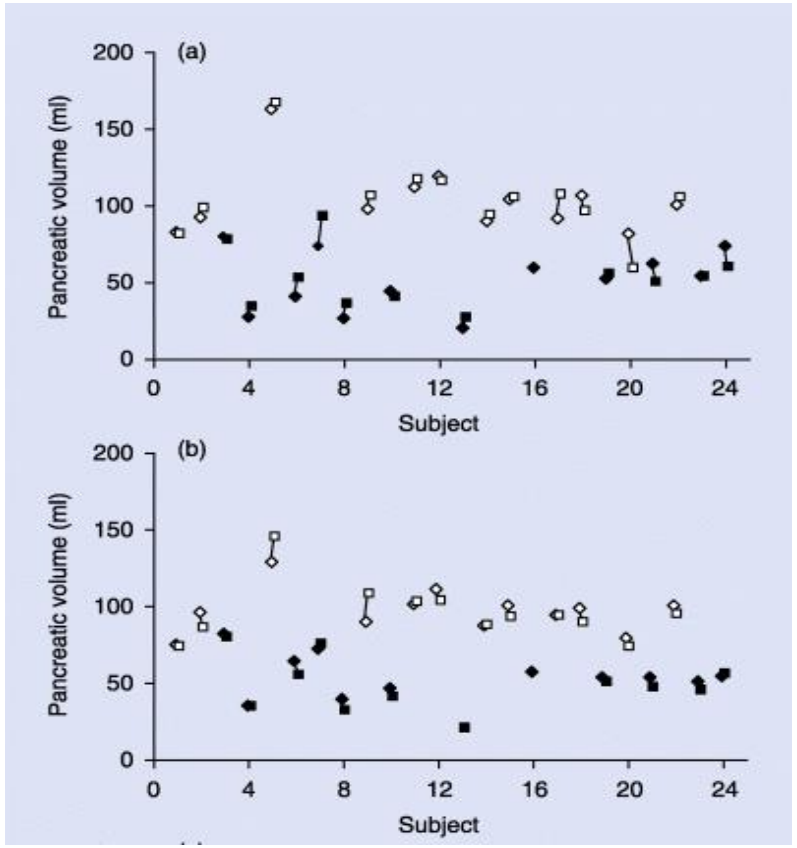
ADA, 2024

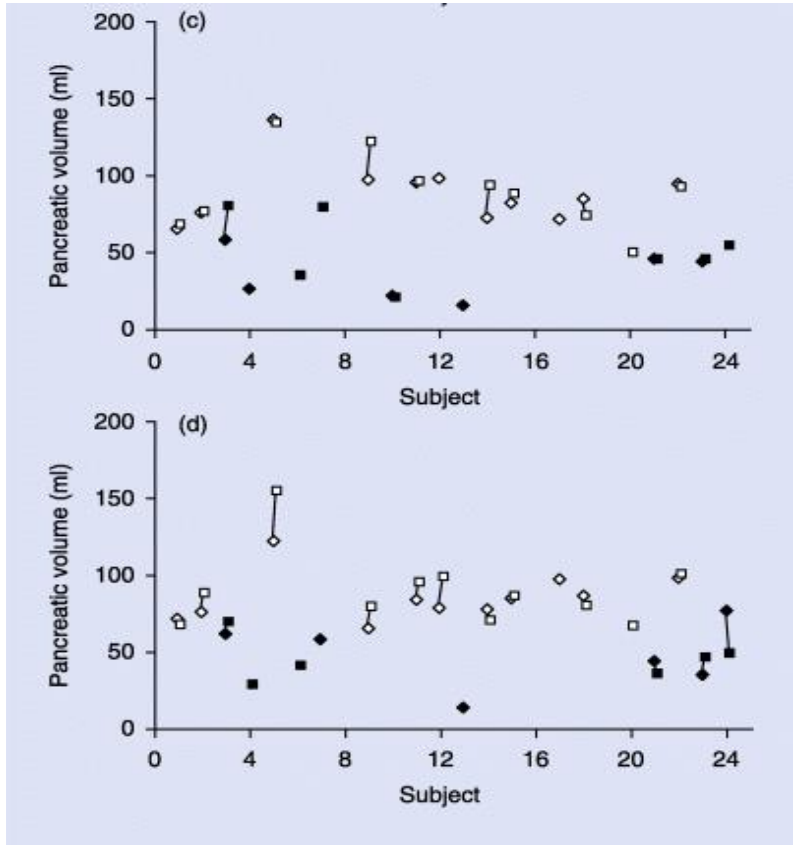


Warshauer, 2020

Atrofia pancreática após diagnóstico de DMT1







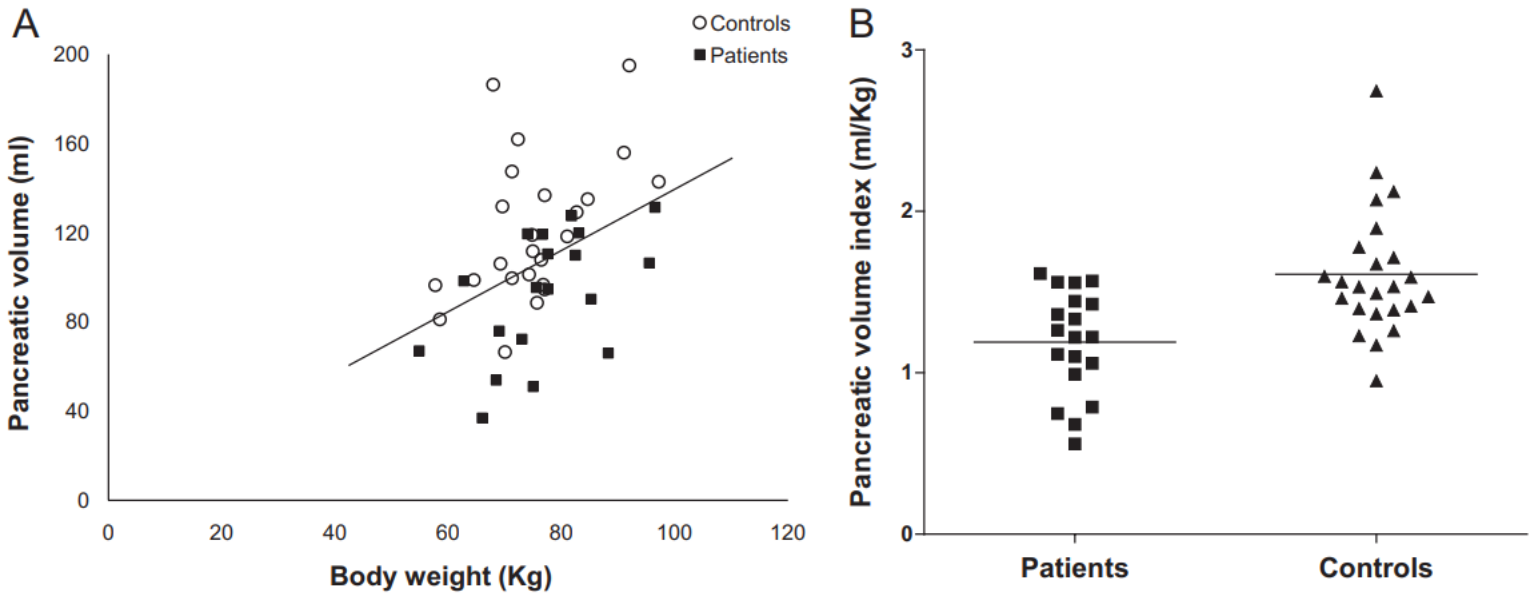
Legenda

Pacientes: ●
Controles: ○
1° varredura: ◊
2° varredura: ■

a – VIBE
b – T1BHFS
c – Padrão T1
d – Padrão T2

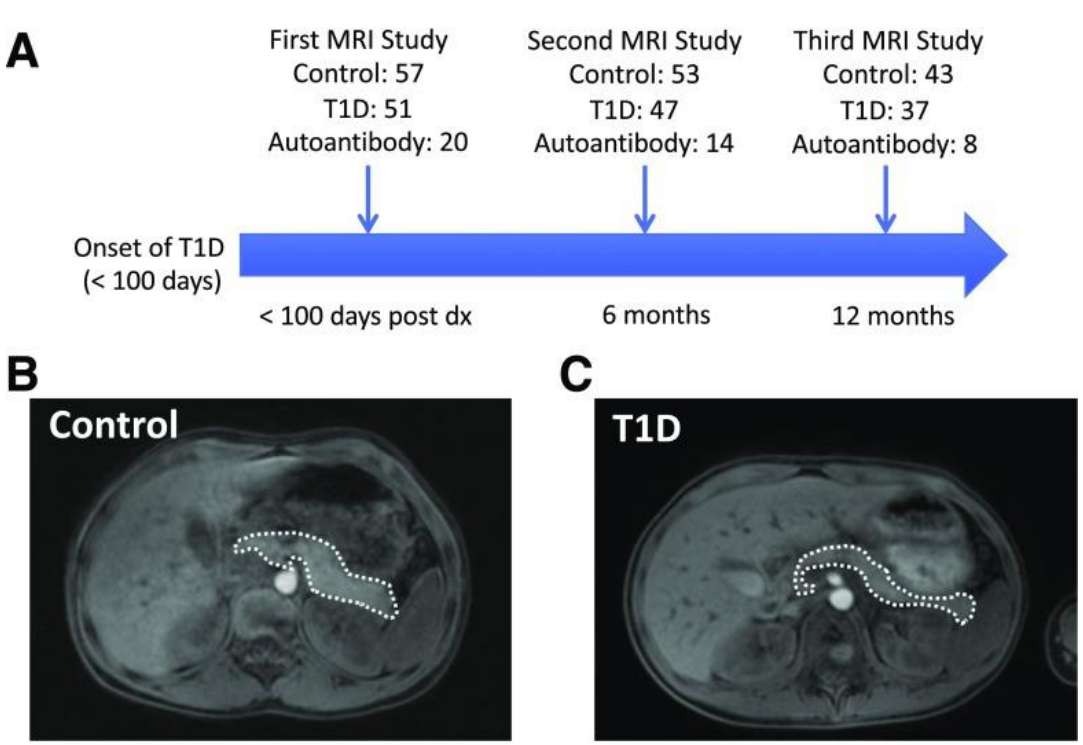
Williams *et al* 2007

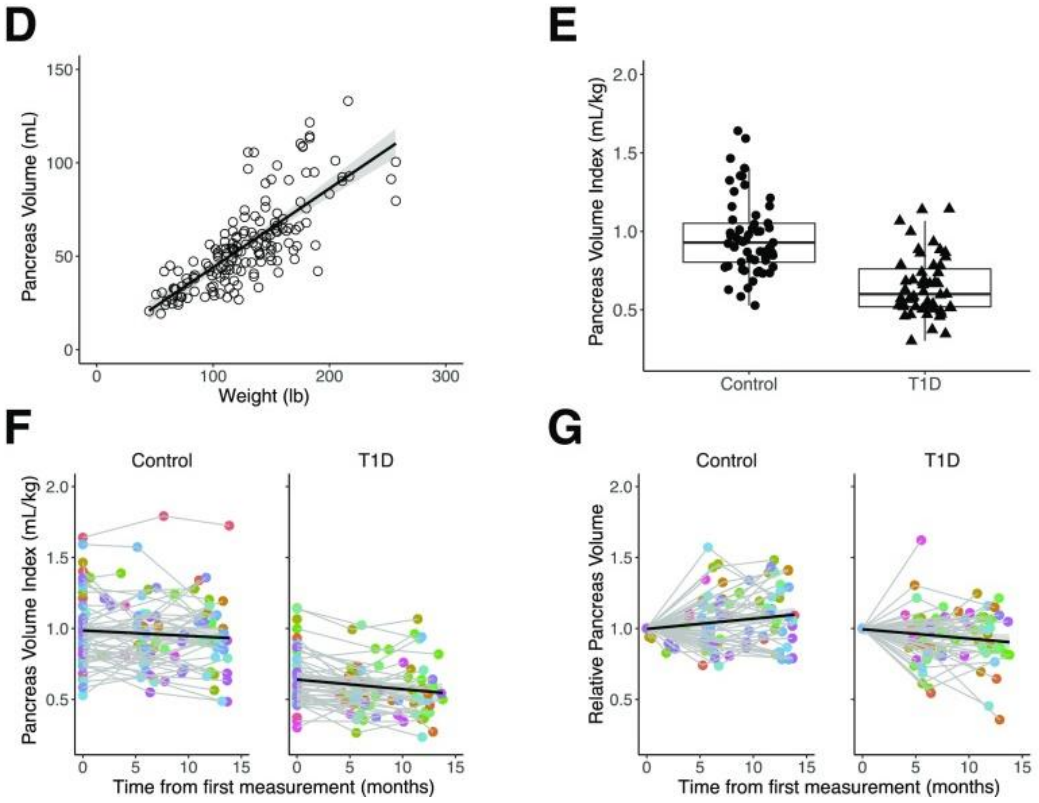
Atrofia pancreática após diagnóstico de DMT1



Williams *et al* 2012

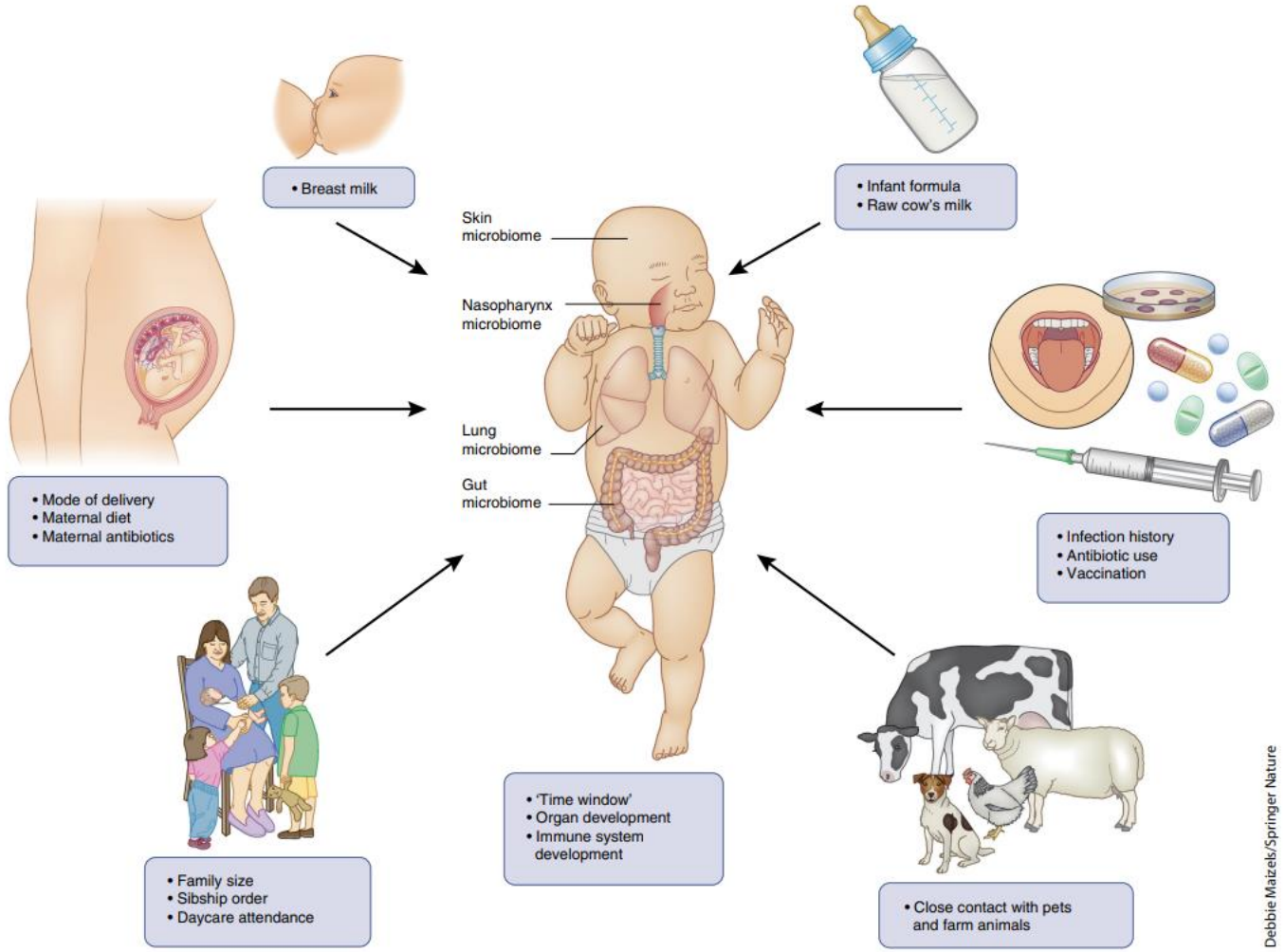
Atrofia pancreática após diagnóstico de DMT1



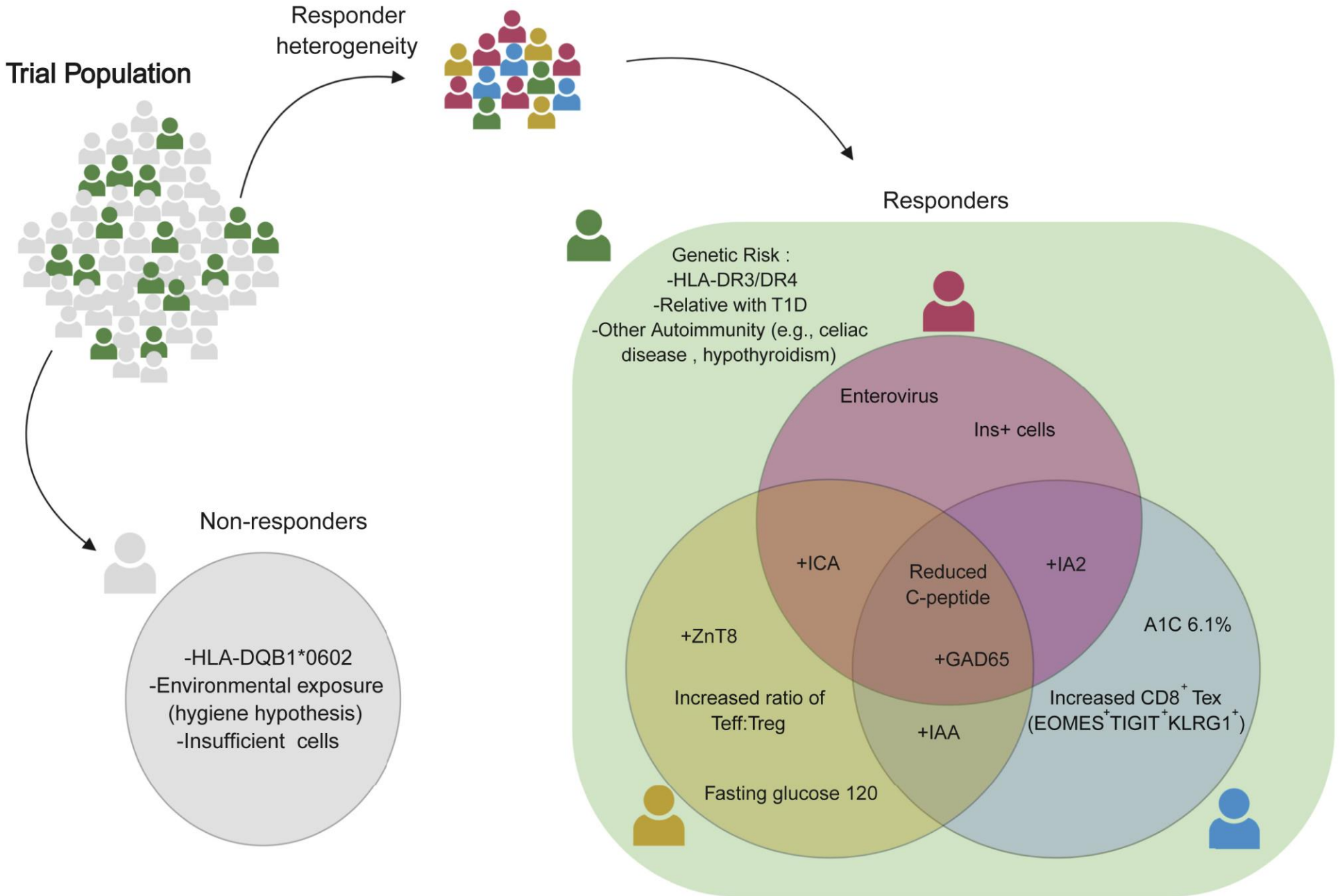


Virostko *et al* 2018

Hipótese da higiene



Bart N Lambrecht & Hamida Hammad. 2017



Warshauer, 2020

Diabetes *mellitus* tipo 1 – Farmacologia atual

Diabetes *mellitus* tipo 1 - Farmacologia atual

- Insulina basal, pós-prandial e correção
- Pré-mix
- sistema contínuo de insulina de ação rápida

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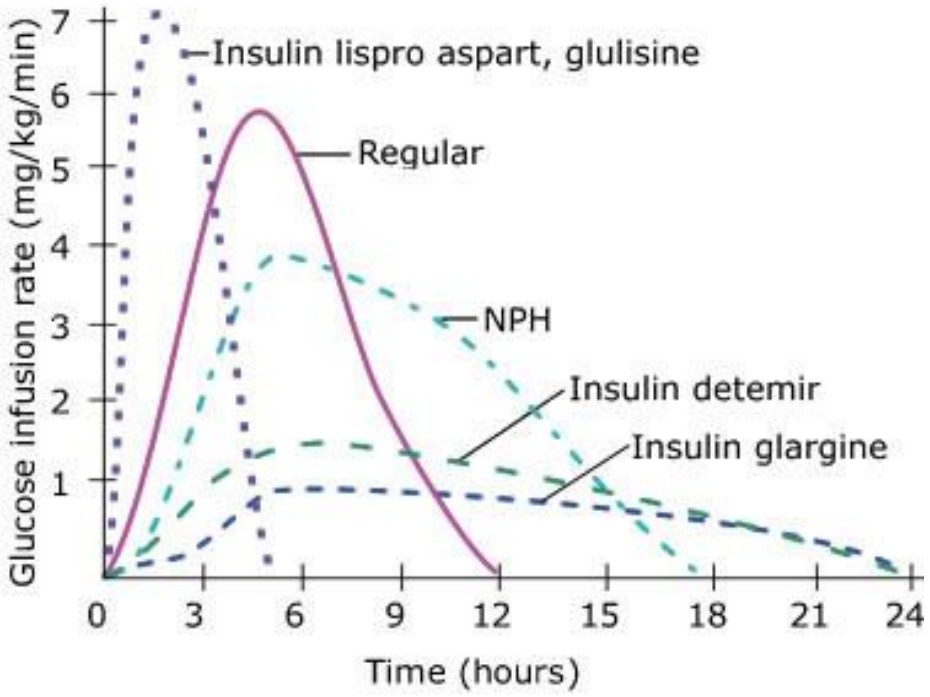

Type of Insulin	Onset	Peak	Duration
Regular	½-1 hr.	2-4 hr.	6-8 hr.
Lyspro/ Aspart/ Glulisine	<15 min.	1-2 hr.	4-6 hr.
NPH	1-2 hr.	6-10 hr.	12+ hr.
Long-acting			
Detemir	1 hr.	Flat, Max effect in 5 hrs.	12-24 hr.
Glargine	1.5 hr.	Flat, Max effect in 5 hrs.	24 hr.

Grey, 2022

Diabetes *mellitus* tipo 1 - Farmacologia atual

- Insulina basal, pós-prandial e correção
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Diabetes *mellitus* tipo 1 - Farmacologia atual

Manufacturer	Commercial name	Composition
Eli Lilly and Company	Humulin® 70/30	70% human insulin isophane suspension, 30% regular human insulin
	Humalog® Mix25™	25% insulin lispro, 75% insulin lispro protamine suspension
	Humalog® Mix50™	50% insulin lispro, 50% insulin lispro protamine suspension
Novo Nordisk	Novolin® 70/30*	70% human insulin isophane suspension, 30% regular human insulin
	NovoMix® 30	70% protamine-crystallized insulin aspart and 30% insulin aspart
	NovoMix® 50*	50% protamine-crystallized insulin aspart and 50% insulin aspart

Diabetes *mellitus* tipo 1 - Farmacologia atual

- Insulina basal, pós-prandial e correção
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Diabetes *mellitus* tipo 1 - Farmacologia atual

- Análogos de amilina
- Agonistas de GLP-1
- Inibidores do transportador de sódio e glicose

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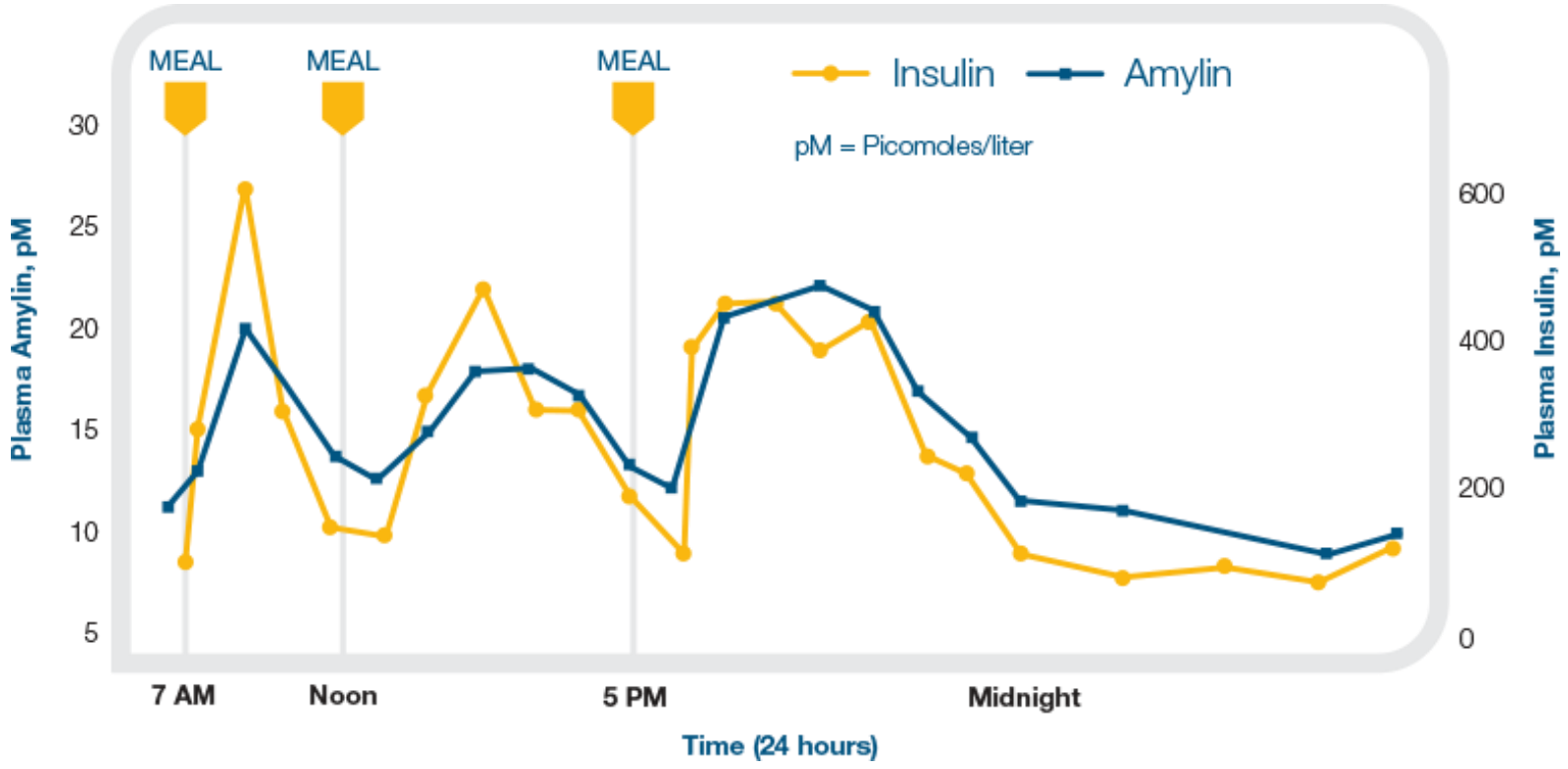
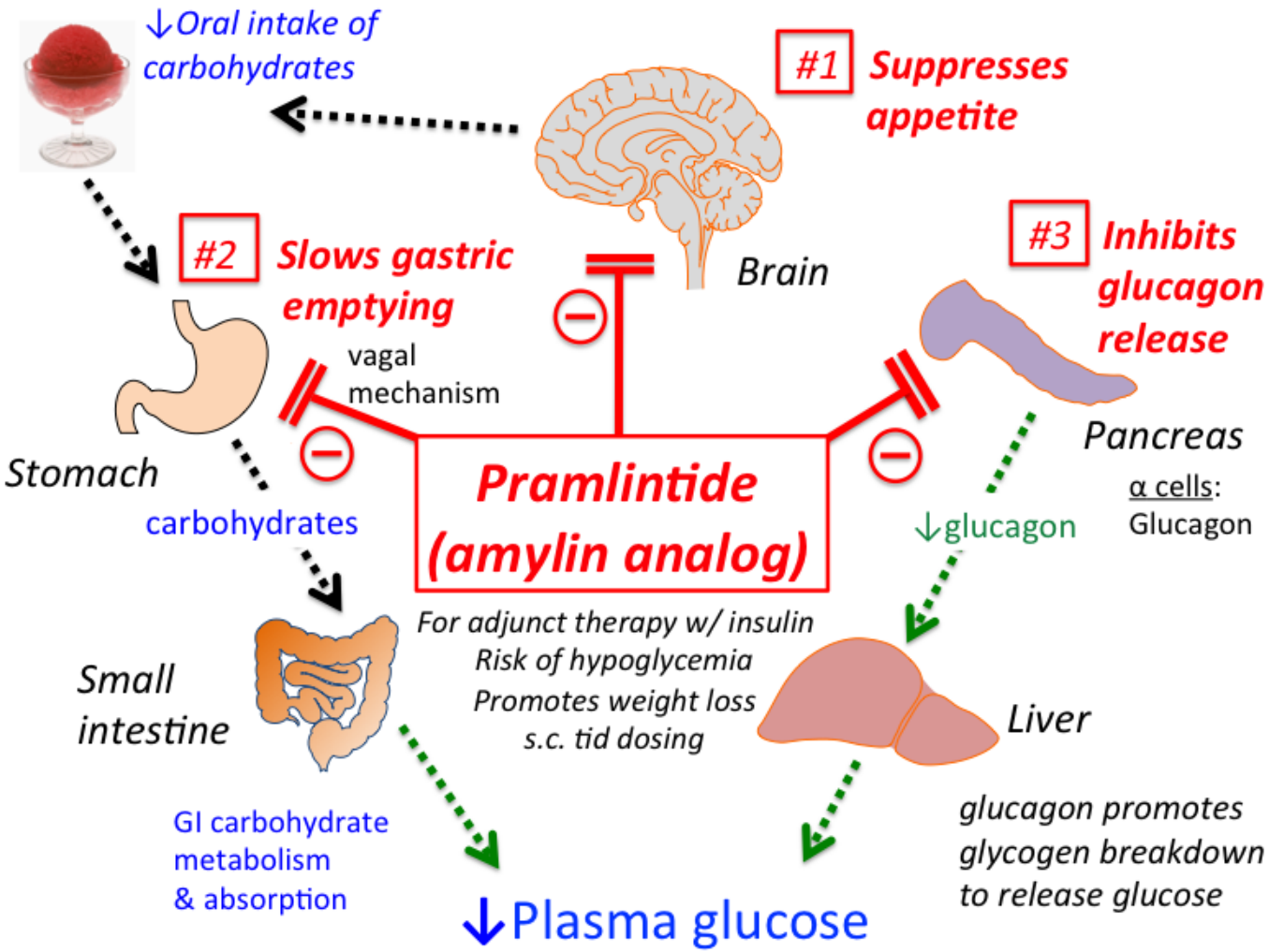
Diabetes *mellitus* tipo 1 - Farmacologia atual



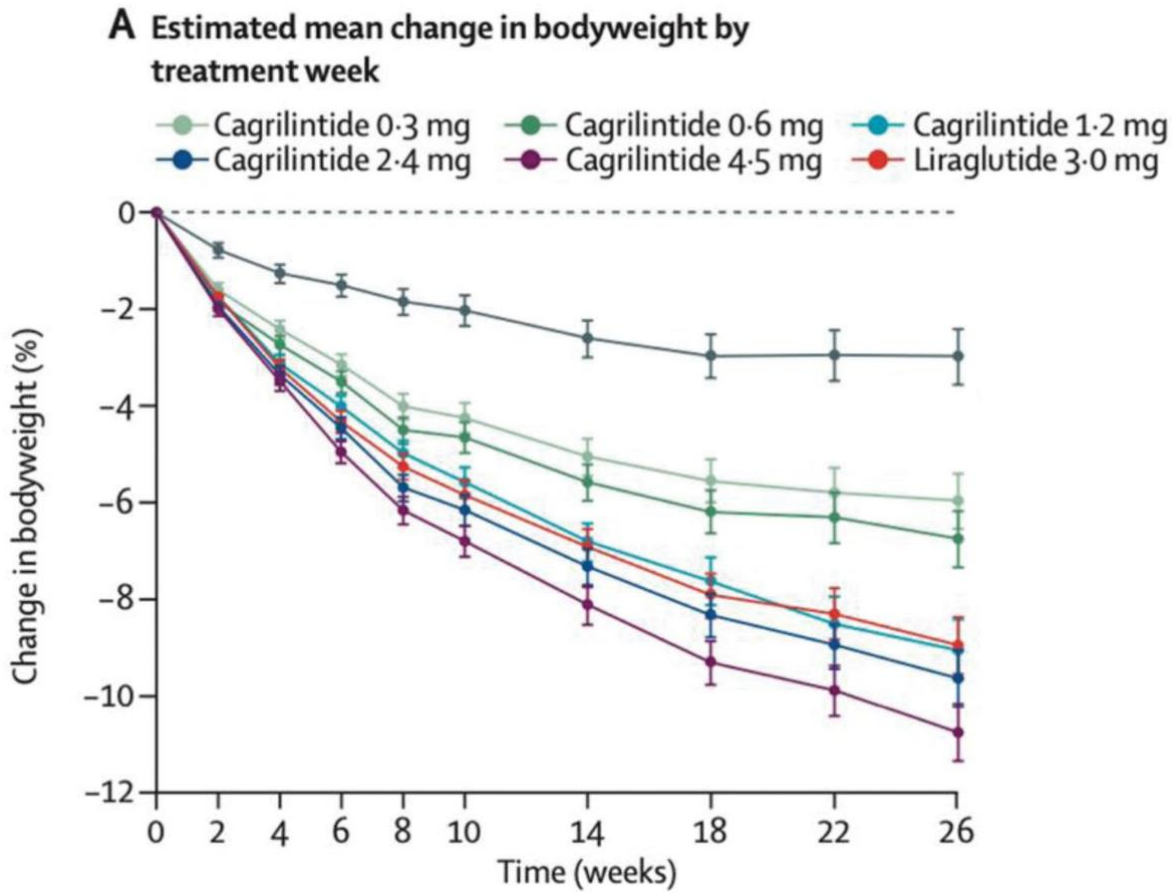
<https://www.symlinhcp.com/science-of-symlin.html>

Diabetes *mellitus* tipo 1 - Farmacologia atual



Dungan, 2015

Diabetes *mellitus* tipo 1 - Farmacologia atual



D'Ascanio *et al* 2024

Diabetes *mellitus* tipo 1 - Farmacologia atual

- Análogos de amilina
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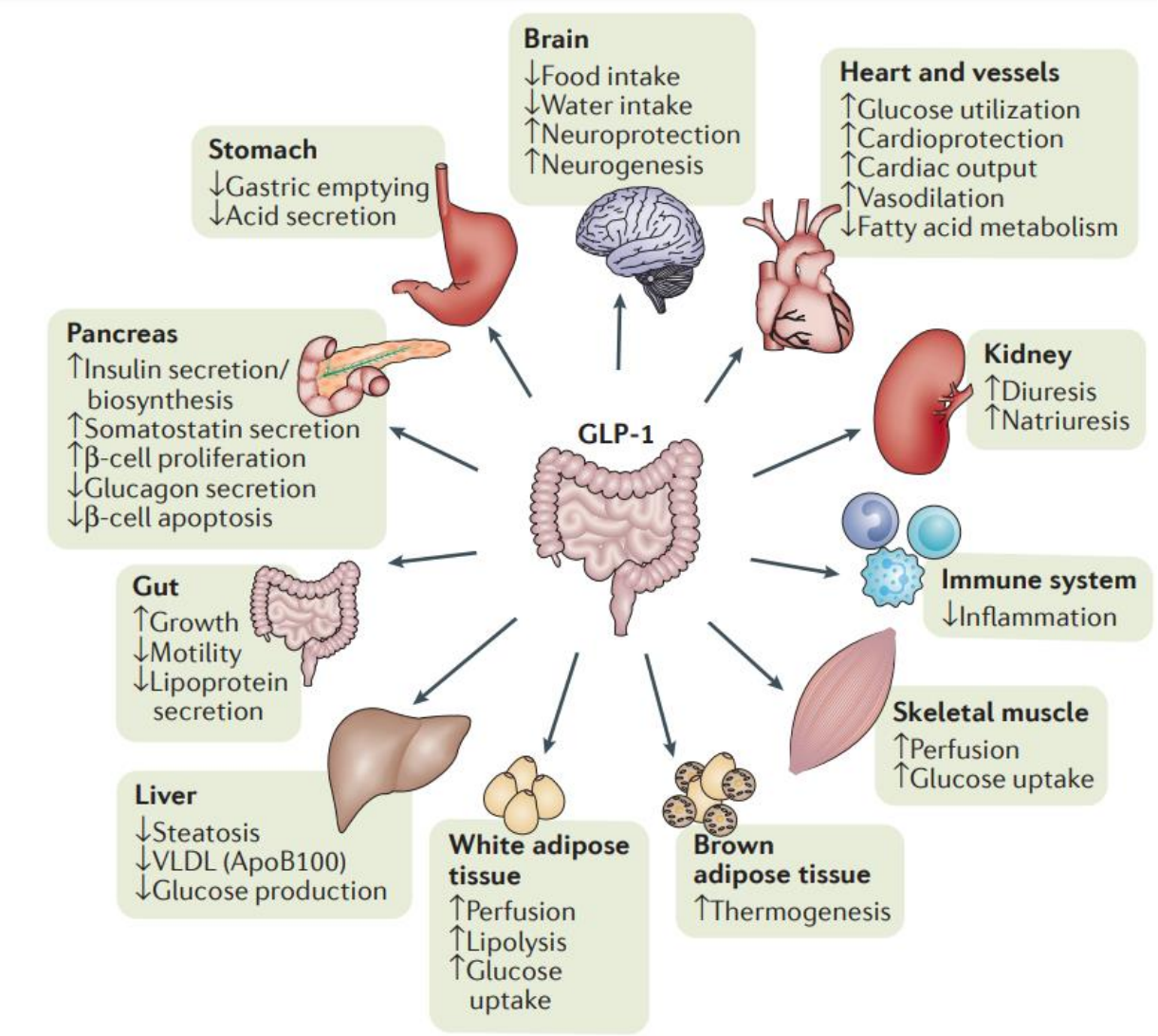
- Inibidores do transportador de sódio e glicose

Diabetes *mellitus* tipo 1 - Farmacologia atual

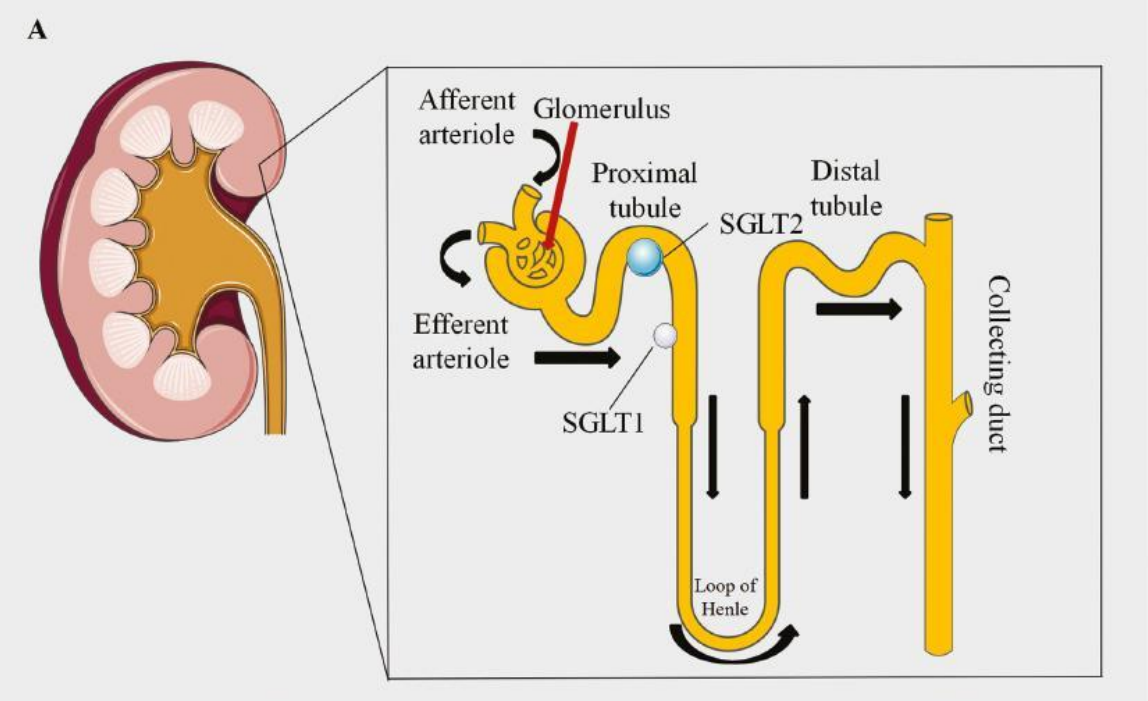


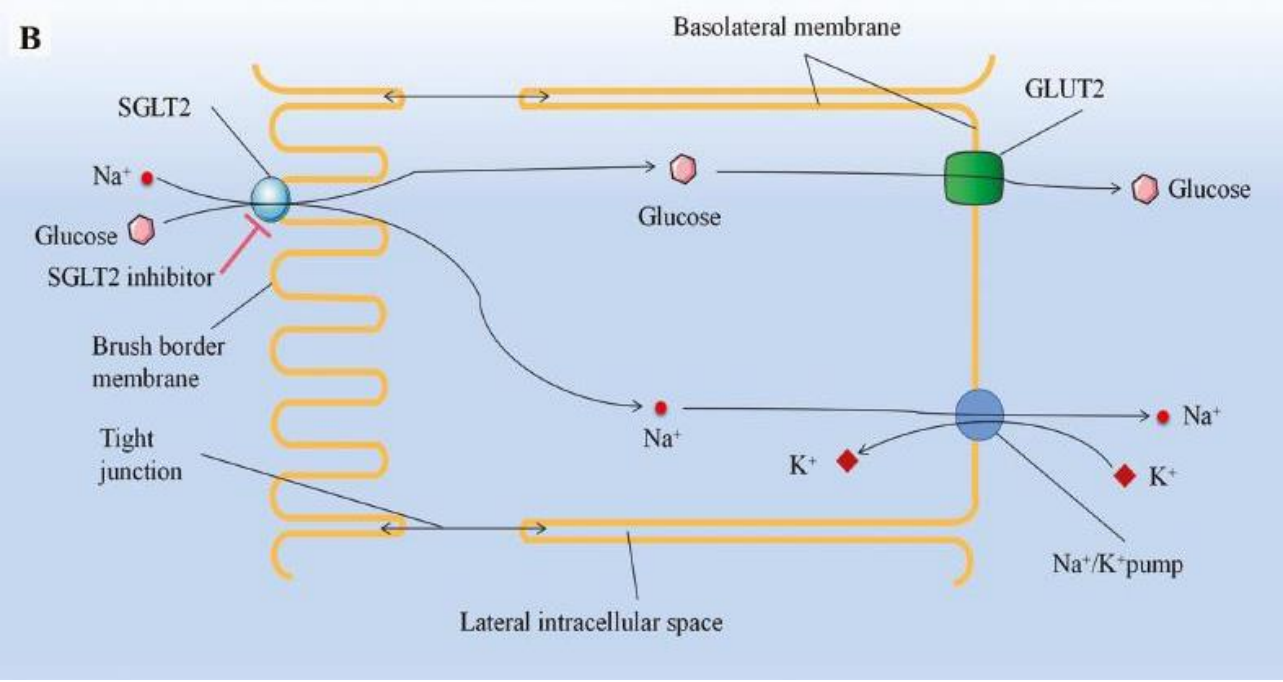
Muskiet *et al* 2017

Diabetes *mellitus* tipo 1 - Farmacologia atual

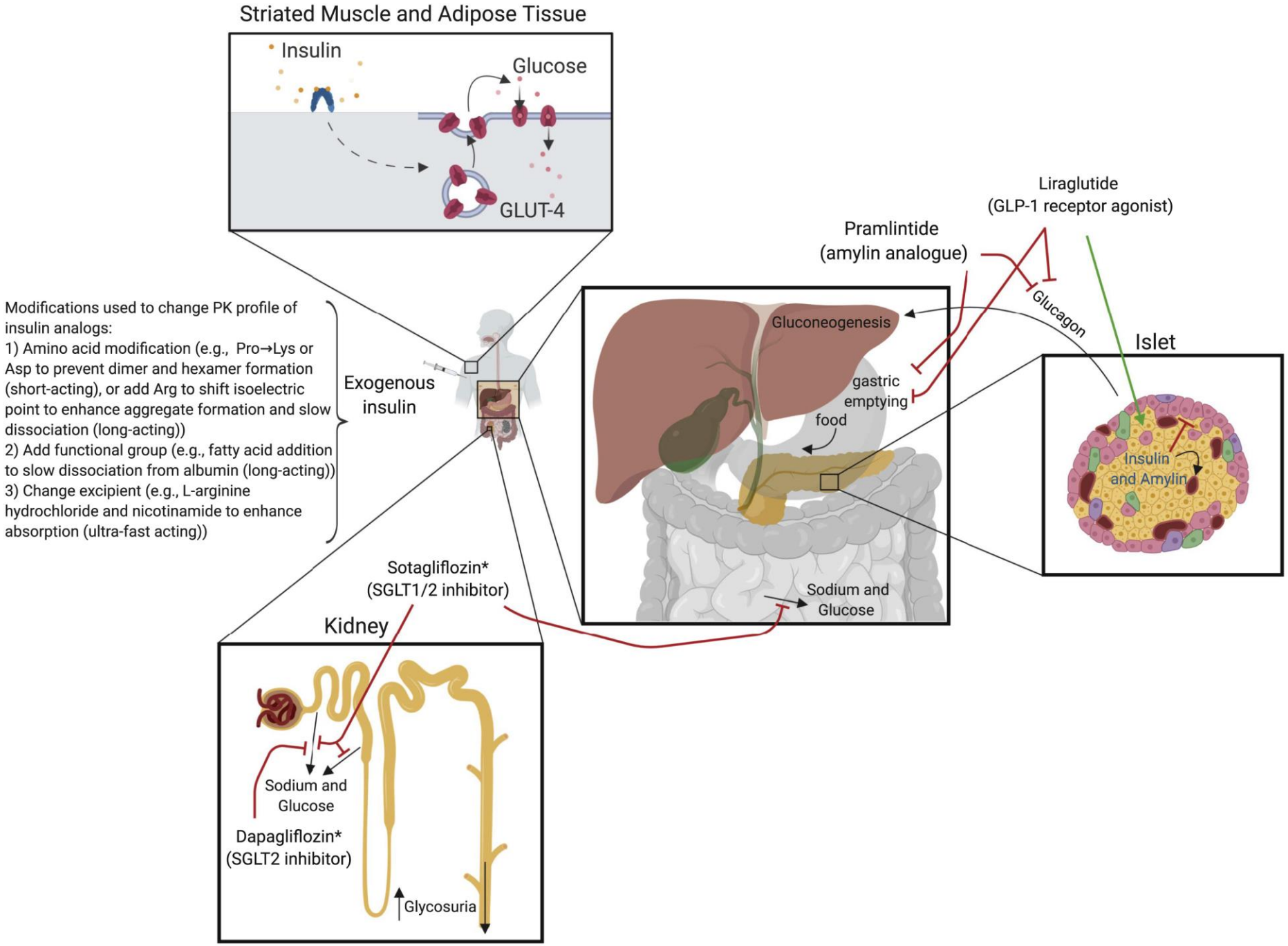
- Análogos de amilina
- Agonistas de GLP-1
- Inibidores do transportador de sódio e glicose

Diabetes *mellitus* tipo 1 - Farmacologia atual





Jiangjun Wei & Jianlin Du 2023

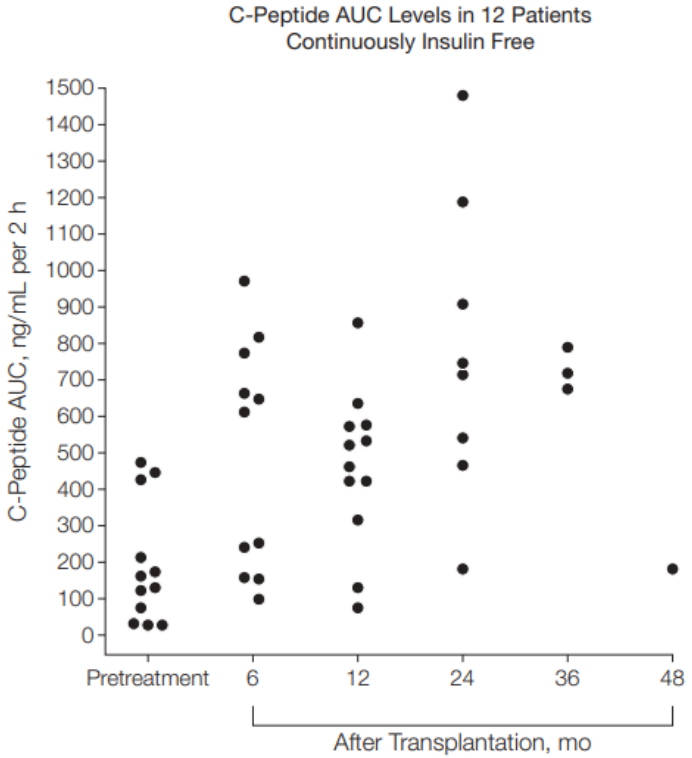


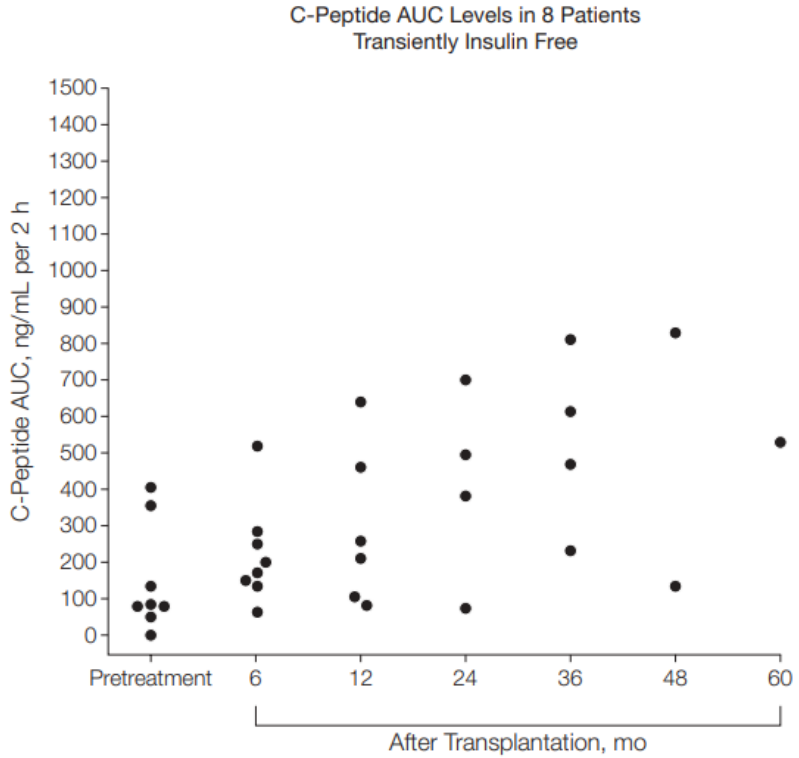
Warshauer, 2020

Diabetes *mellitus* tipo 1 – potenciais de inovação

Diabetes *mellitus* tipo 1 – potenciais de inovação

- Transplante autólogo de células-tronco hematopoiéticas não mieloablativas

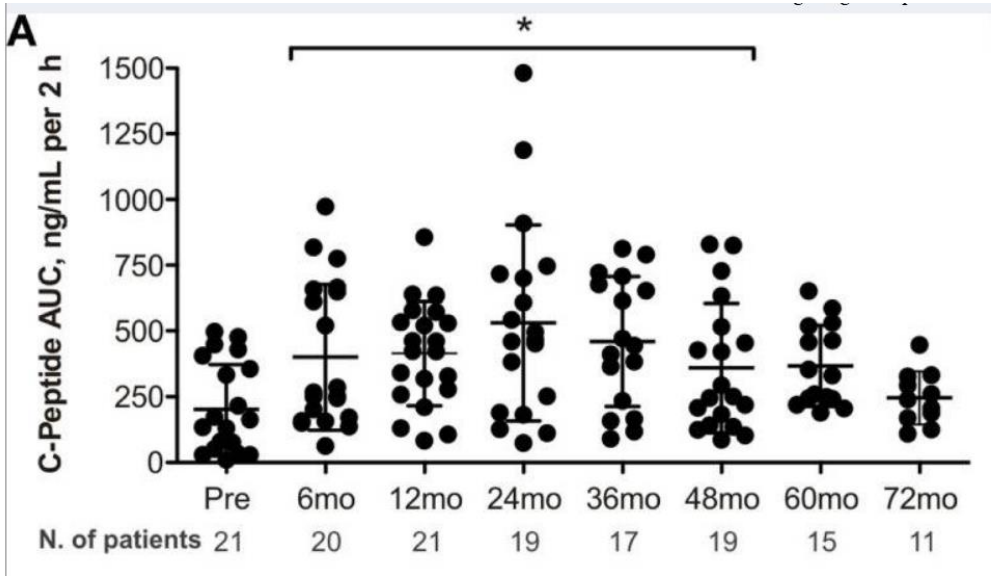


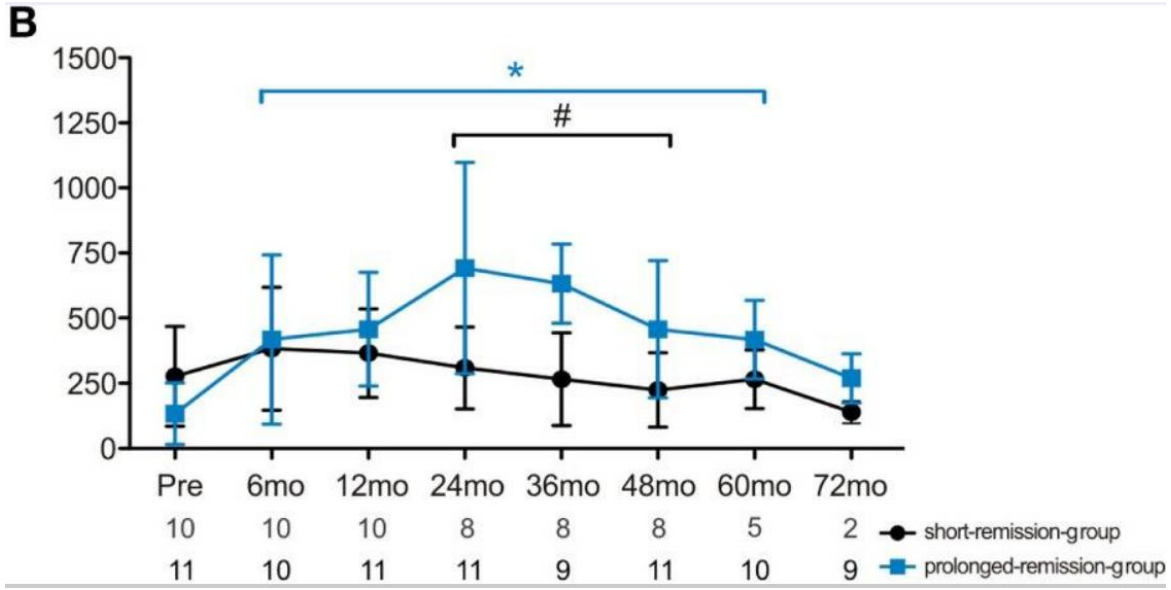


Couri *et al* 2009

Diabetes *mellitus* tipo 1 – potenciais de inovação

- Transplante autólogo de células-tronco hematopoiéticas não mieloablativas





Malmegrim *et al* 2017

Diabetes *mellitus* tipo 1 – potenciais de inovação

- Transplante de pâncreas

Points to differentiate	Pancreas transplantation	Islet transplantation
Type	Whole organ transplant	Islet cell transplant alone
Indication in diabetes	Complications of type 1 diabetes	Used instead of pancreas transplant in some patients
Indication in chronic pancreatitis	No specific indication	As part of total pancreatectomy and autologous islet transplantation
Pediatric indication	No routine indication	Part of total pancreatectomy and autologous islet transplant
Insulin independence rates	70% at 5 yr	25%–50% at 5 yr
Surgical risk	More	Less
Complications	More	Less

Inderpal Singh Kochar & Rakhi Jain. 2021

Diabetes *mellitus* tipo 1 – potenciais de inovação

- Transplante de pâncreas

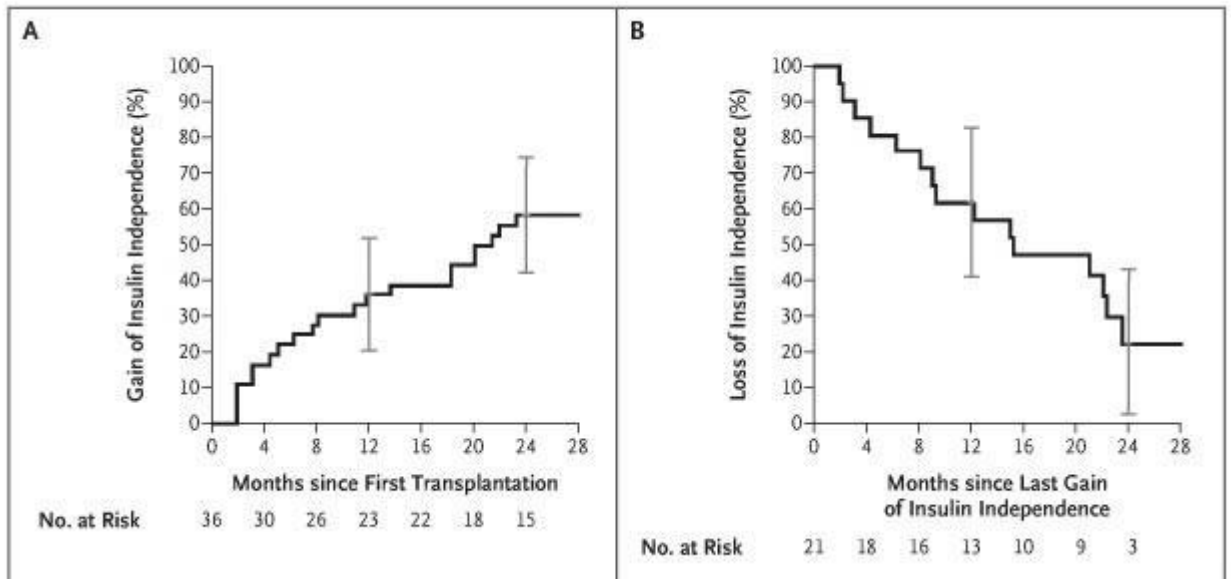
		Survival (%)	Year of transplant					
			1998	1999	2000	2001	2002	2003
SPK	Patient	One year	93.9	94.8	95.1	94.1	94.8	95.5
		Three years	89.6	90.6	90.2	89.6	+	+
PAK	Patient	One year	94.5	94.4	96.0	95.2	95.7	95.5
		Three years	90.8	88.1	91.2	89.1	+	+
PTA	Patient	One year	96.8	97.3	99.1	97.5	97.6	94.5
		Three years	90.5	90.9	95.5	90.8	+	+
SPK	Pancreas	One year	82.7	83.1	84.0	85.0	85.4	85.8
		Three years	75.8	76.0	77.0	78.9	+	+
	Kidney	One year	91.2	91.5	92.5	91.5	91.2	91.7
		Three years	83.9	83.0	83.5	83.7	+	+
PAK	Pancreas	One year	72.0	80.3	74.0	81.8	77.3	77.9
		Three years	63.4	66.8	62.3	71.5	+	+
PTA	Pancreas	One year	79.2	83.3	75.3	78.3	79.3	74.4
		Three years	60.3	69.3	60.5	64.4	+	+

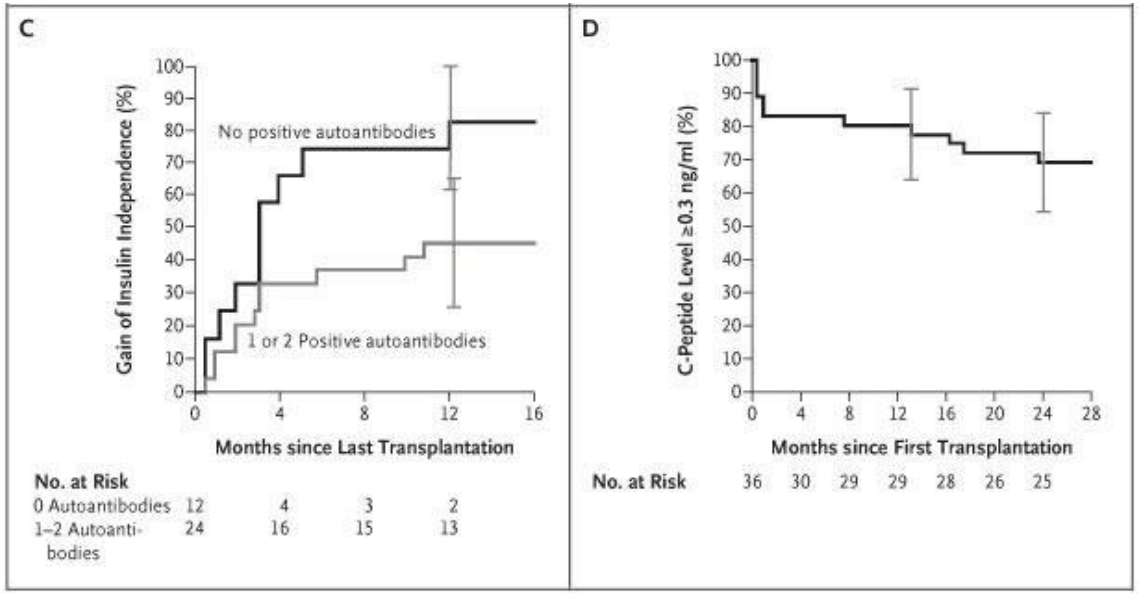
SPK : pancreas and kidney transplant
PAK: pancreas after kidney transplant
PTA: pancreas transplant alone

Meloche. 2007

Diabetes *mellitus* tipo 1 – potenciais de inovação

- Transplante de ilhotas pancreáticas

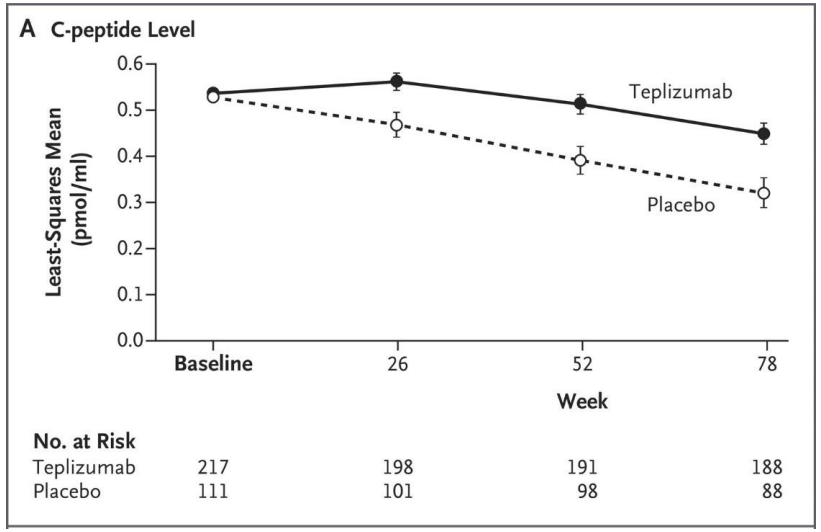


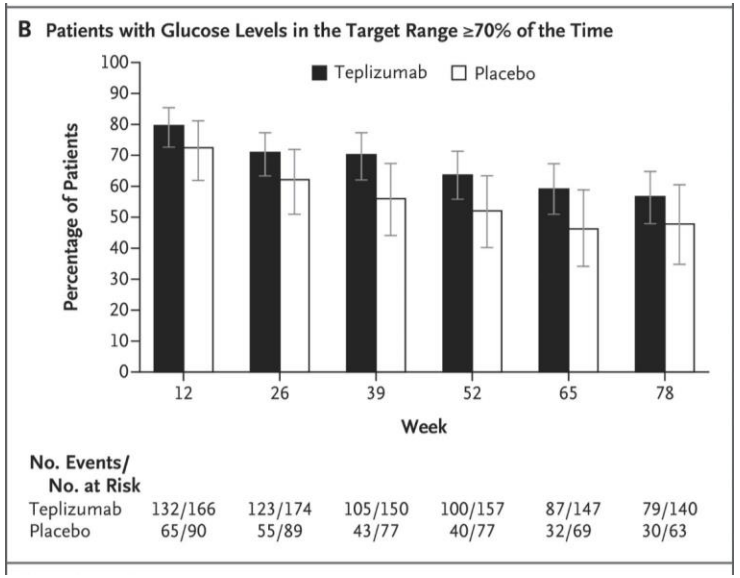


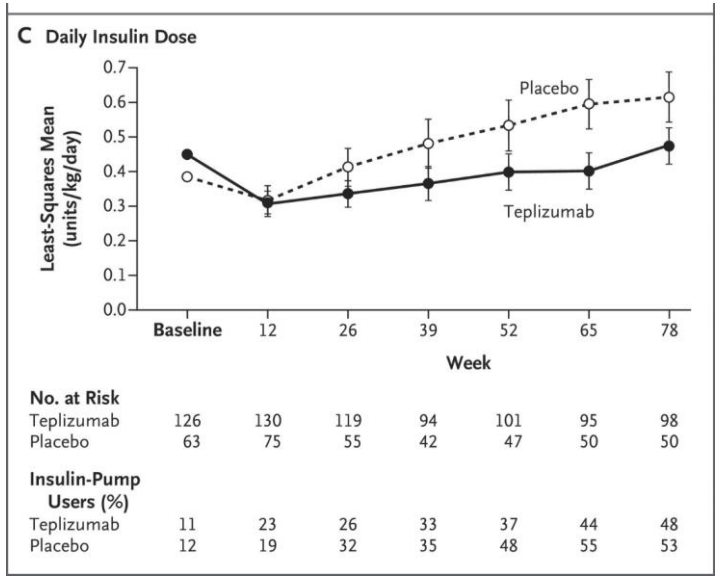
Malmegrim *et al* 2017

Diabetes *mellitus* tipo 1 – potenciais de inovação

- Teplizumab: mAb humanizado para CD3 em células T







Ramos *et al* 2023

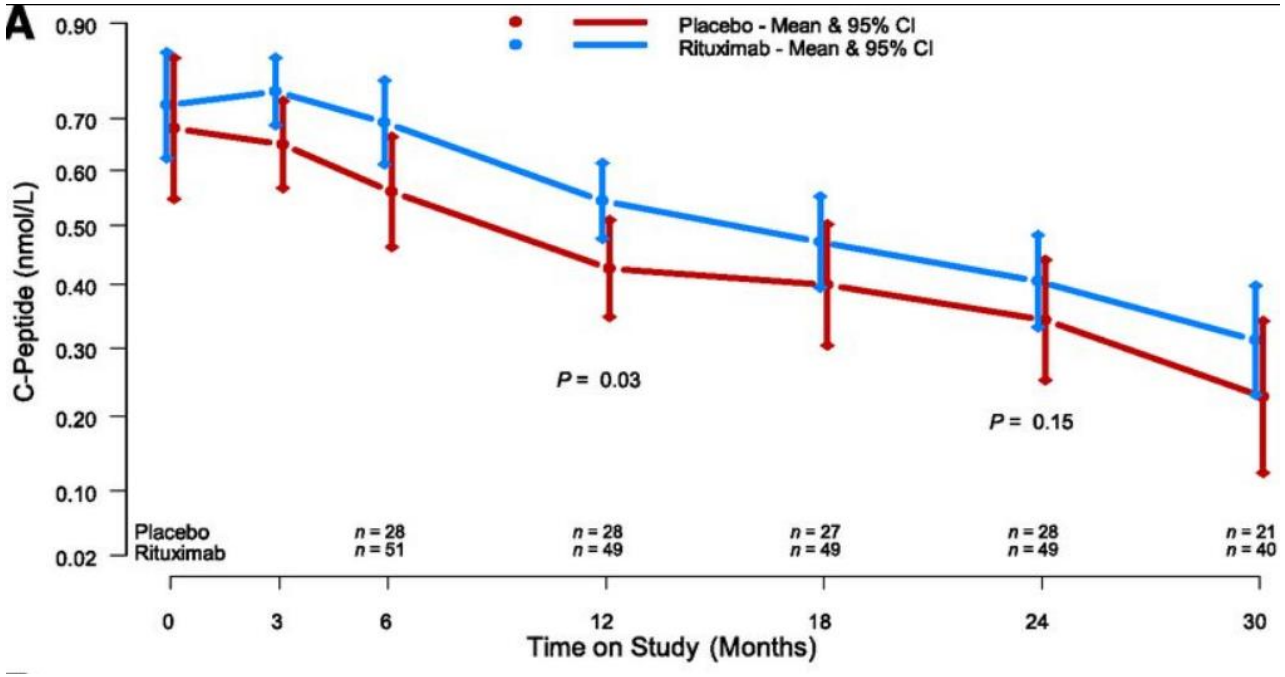
Diabetes *mellitus* tipo 1 – potenciais de inovação

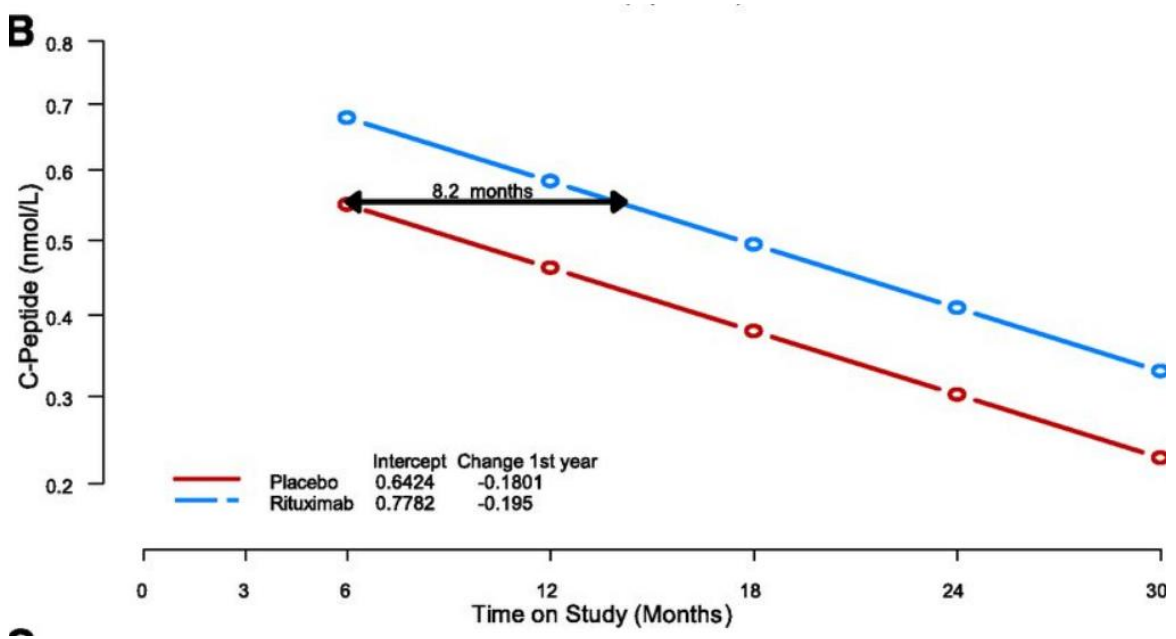
- Globulina Antitimócito (ATG)

Foster *et al* 2024

Diabetes *mellitus* tipo 1 – potenciais de inovação

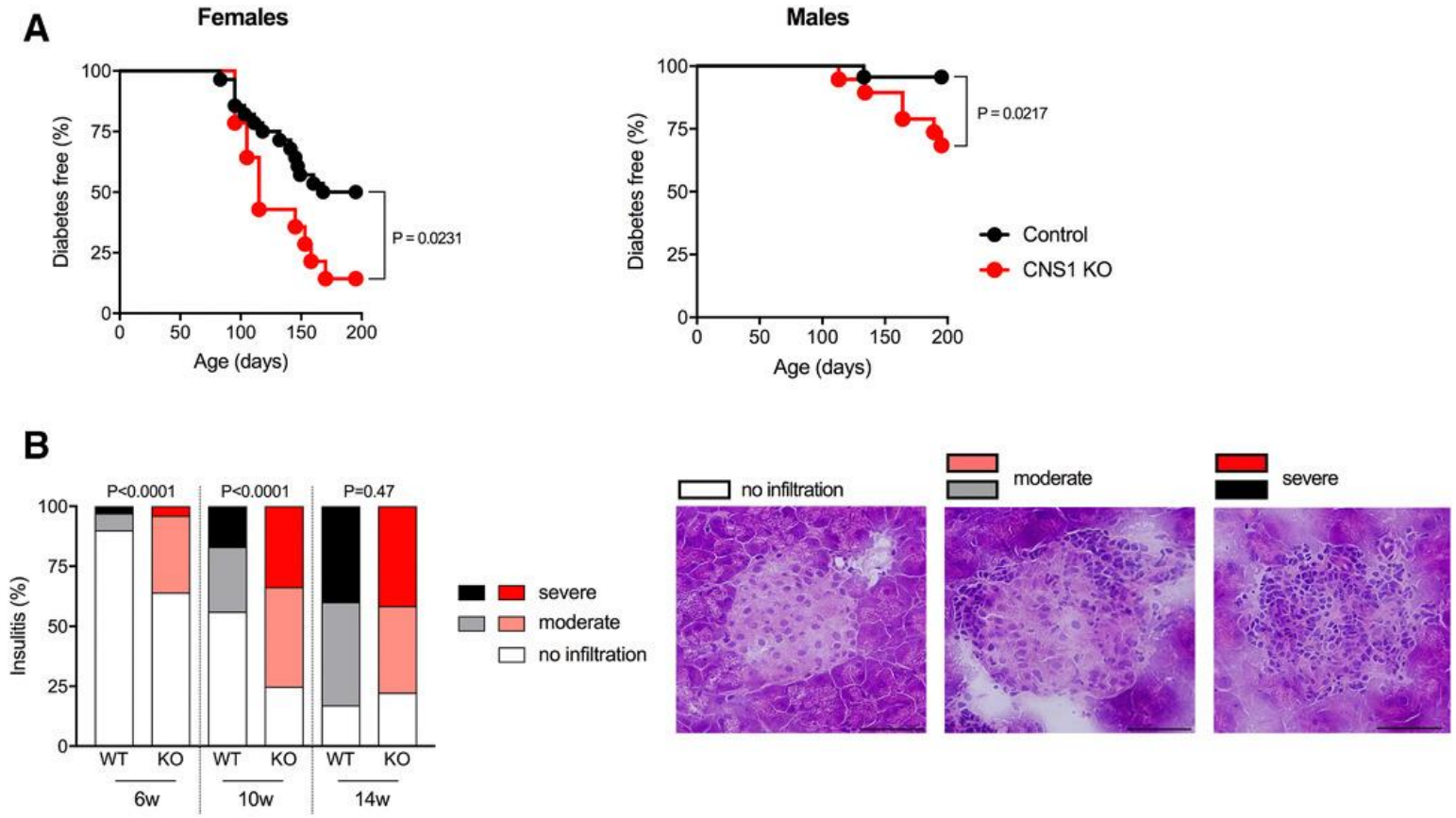
- Rituximab: mAb anti CD20 em células B





Diabetes *mellitus* tipo 1 – potenciais de inovação

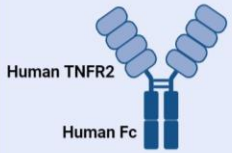
- Células T regulatórias - pTreg



Cornelia Schuster *et al.* 2018

Diabetes *mellitus* tipo 1 – potenciais de inovação

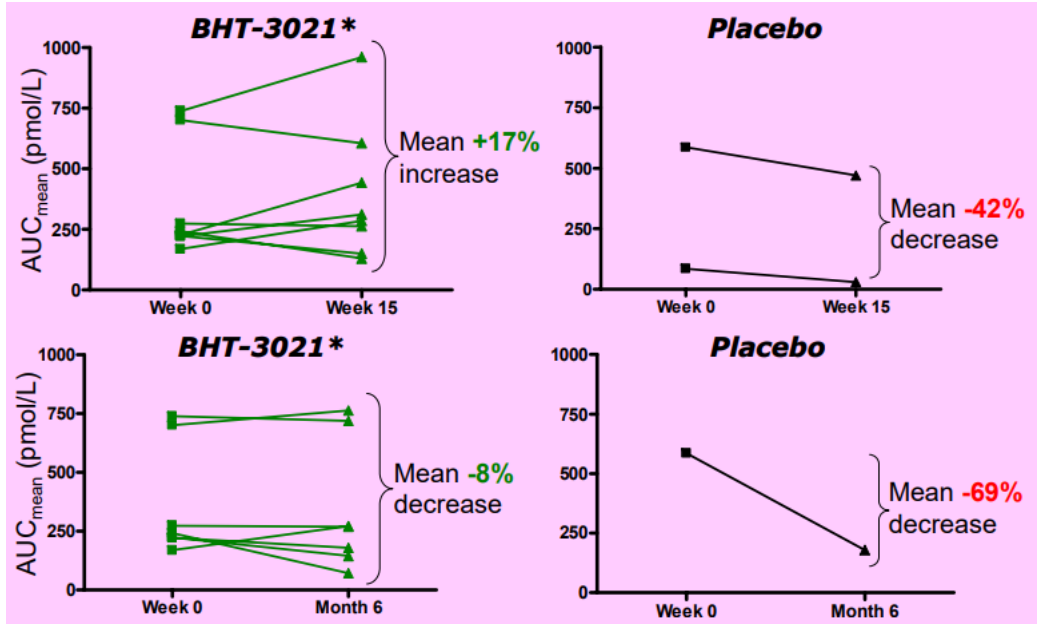
- Inibidores de TNF-α

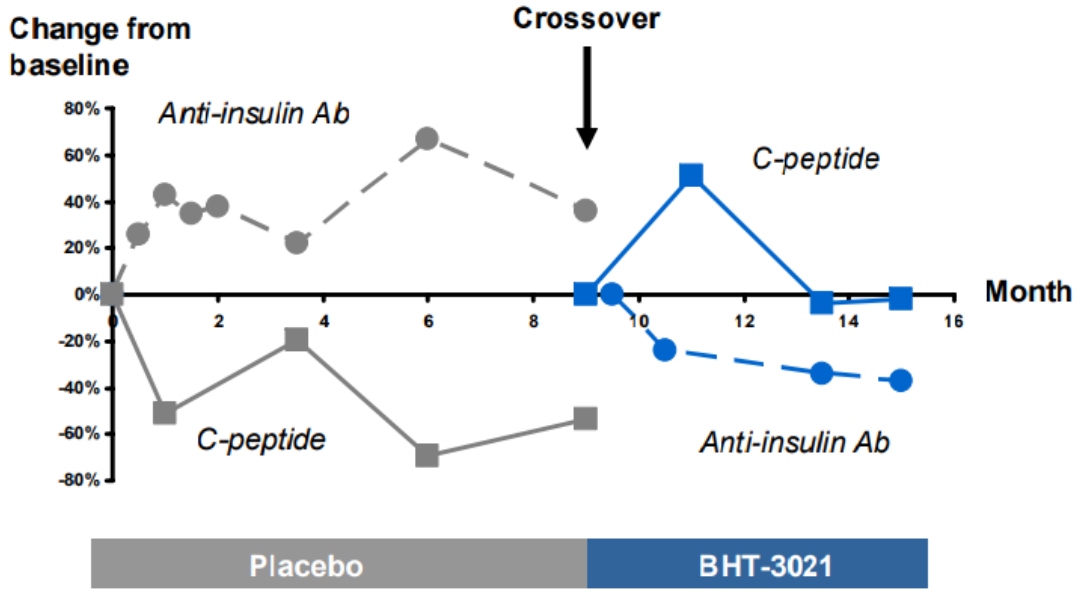
	Adalimumab (Humira)	Certolizumab Pegol (Cizma)	Etanercept (Enbrel)	Golimumab (Simponi)	Infliximab (Remicade)
					
Molecule Type	Monoclonal Antibody	Monoclonal Antibody and Fusion Protein	Fusion Protein	Monoclonal Antibody	Monoclonal Antibody
Description	Fully Human mAb IgG1 against TNFα	Humanized Fab fragment conjugated to a polyethylene glycol	Fusion Protein containing Soluble TNFR fused to IgG1 Fc	Fully Human mAb IgG1 against TNFα	Chimeric (murine and human) mAb IgG1 against TNFα
Assessment in T1D	Observational study in patient with JIA and T1D	Not assessed	Phase I clinical trial	Phase II clinical trial	Observational study in patient with CD and T1D

Bazile *et al.* 2024

Diabetes *mellitus* tipo 1 – potenciais de inovação

- Vacinas

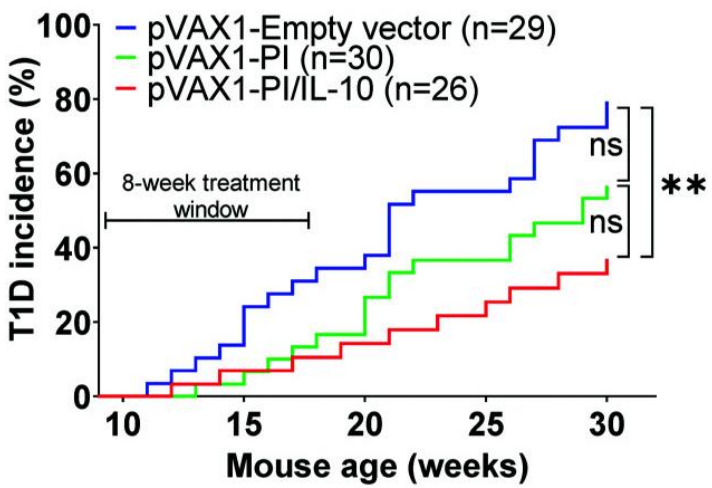


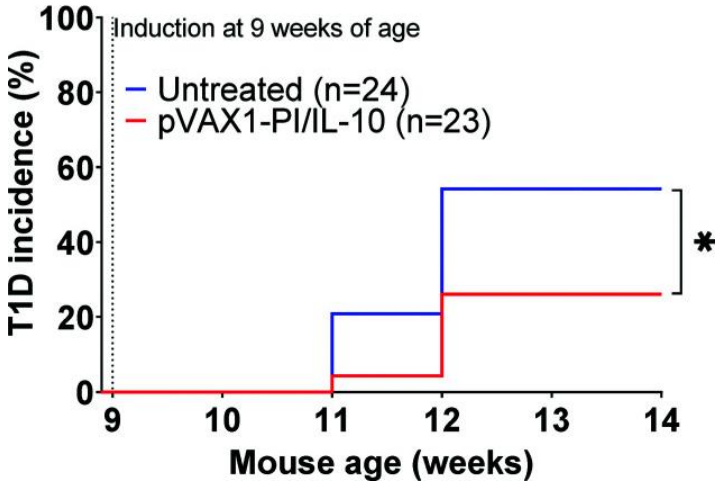


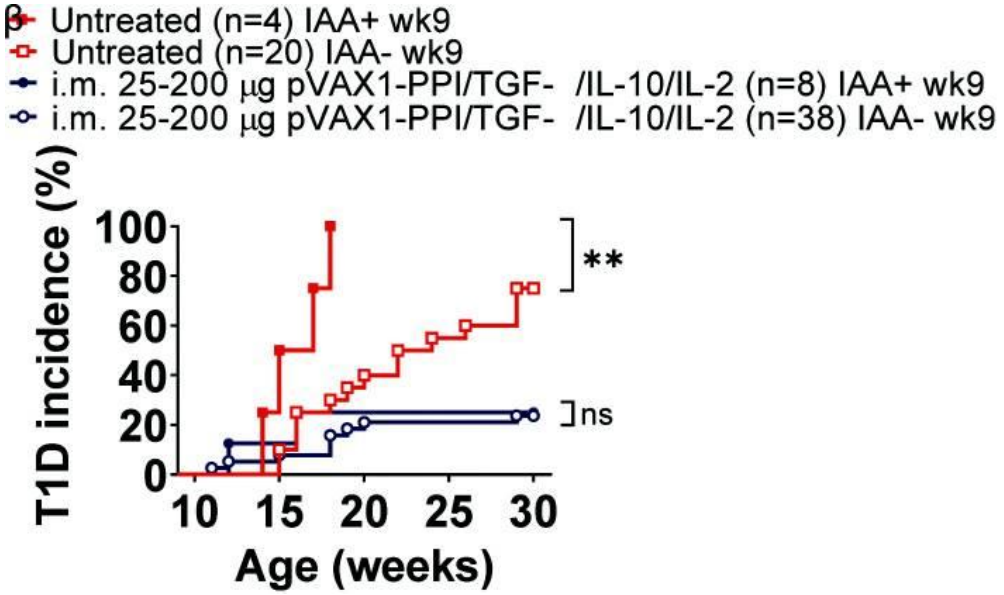
Glottrieb *et al.* 2008; Eisenbarth *et al* 2009

Diabetes *mellitus* tipo 1 – potenciais de inovação

- Vacinas







Pagni *et al.* 2021

Obrigada!