Infiammazione e diabete tipo 2: quali evidenze

Francesca D'Addio MD, PhD

International Center for T1D Romeo ed Enrica Invernizzi,

Università degli Studi di Milano

Endocrinology Division - ASST Fatebenefratelli Sacco Milano

Outline

1. Introduction
2. Inflammation in the pathogenesis of T2D
3. Targeting inflammation in T2D
    i. GLP-1RA
    ii. SGLT2 inhibitors
    iii. Other approaches
4. Conclusions

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Inflammation and type 2 diabetes (T2D)

- Systemic low-grade inflammation is a mild, chronic state of inflammation that involves a subtle, persistent immune system activation.
- Chronic systemic inflammation leads to insulin resistance and beta cell dysfunction
- A chronic low grade inflammatory state favors long-term complications (nephropathy, CVD, NAFLD, retinopathy)
- Low-grade chronic inflammation links T2D to other disease conditions:

  -Alzheimer's disease
  -Polycystic ovarian syndrome
  -Gout
  -Rheumatoid arthritis
  -Autoimmune diseases

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Chronic inflammation and T2D

- Chronic inflammation involves insulin target tissues (adipose tissue, liver, muscle, and islets).
- The recruitment, accumulation, and activation of pro-inflammatory macrophages in metabolic tissues drives chronic low-grade inflammation.
- Other immune cells participate in these inflammatory processes:
  - ✓ CD8 T cells faciliate macrophages polarization into proinflammatory cells
  - ✓ CD4 Th1 cells release proinflammatory cytokines
  - ✓ Tregs modulate monocytes recruitment
  - ✓ Mast cells, innate lymphoid cell type 1 cells, neutrophils, eosinophils, NK cells, B cells modulate monocytes recruitment and phenotype

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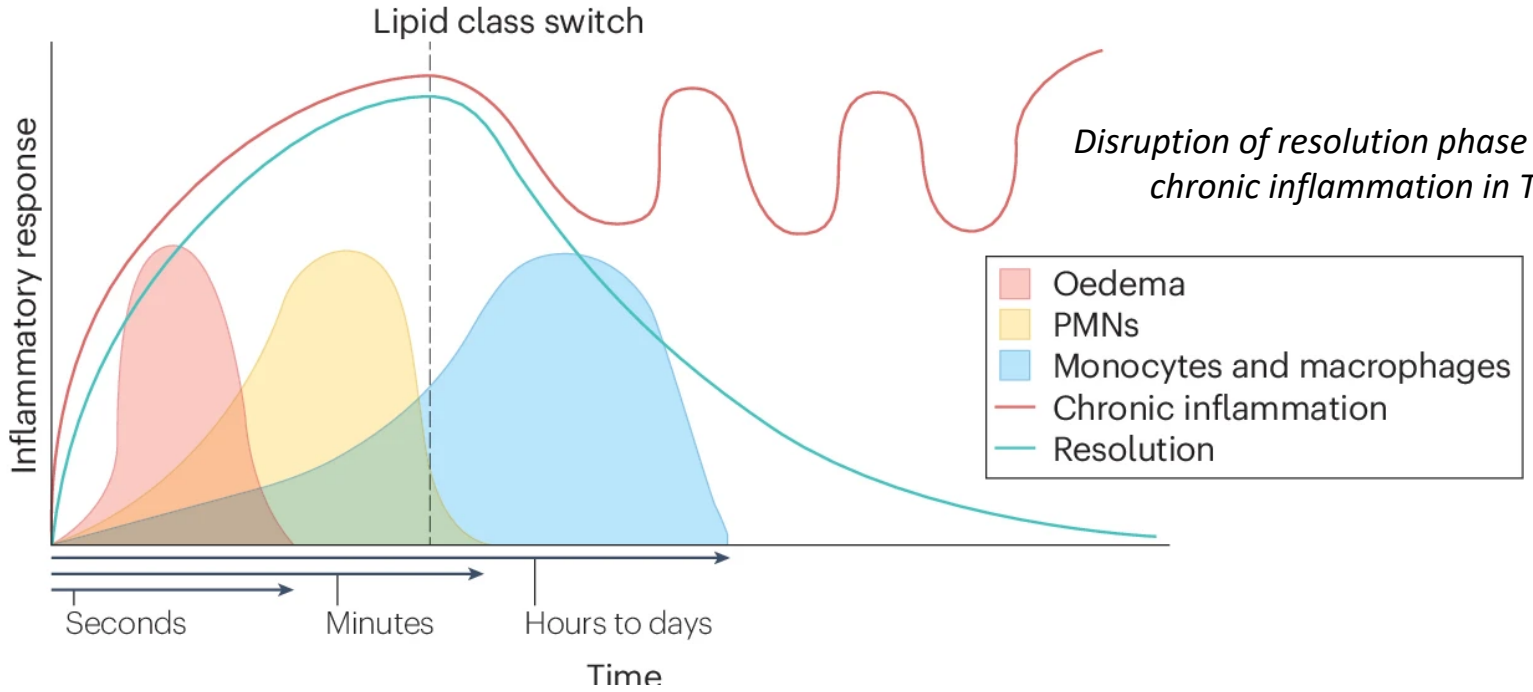
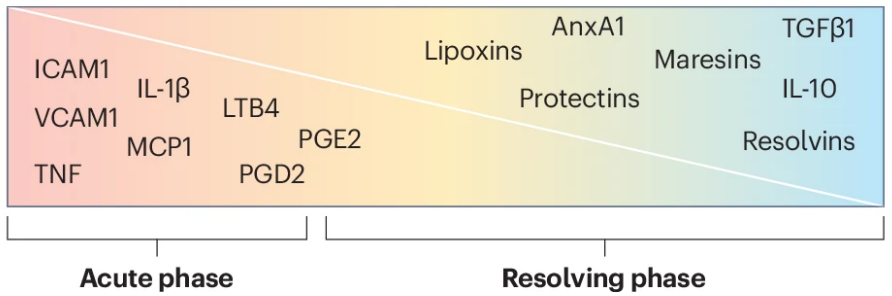
Development of low grade chronic inflammation in T2D



Disruption of resolution phase leads to chronic inflammation in T2D



Polyunsaturated fatty acid (PUFA) produce lipoxins pro-resolving mediators

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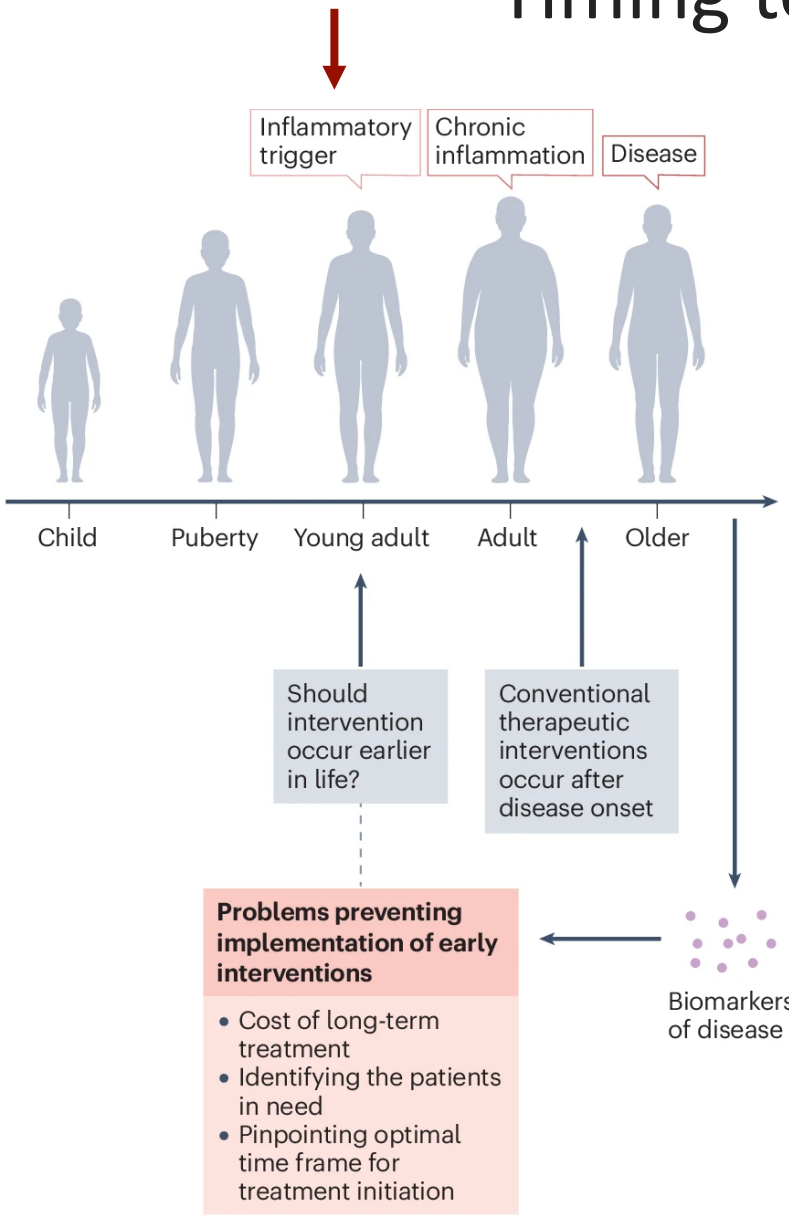
Timing to target inflammation in T2D



- Inflammation precedes CVD and metabolic diseases by years
- Inflammation involves muscle, adipose tissue, liver, islets, gut, brain, connective tissue, immune cells
- Inflammation may favor autoimmune response
- Current therapies are often introduced late
- Introduction before disease onset may be more beneficial
- Identify individuals at risk for CVD/metabolic disease but no biomarkers available
- Financial burden often limits interventions

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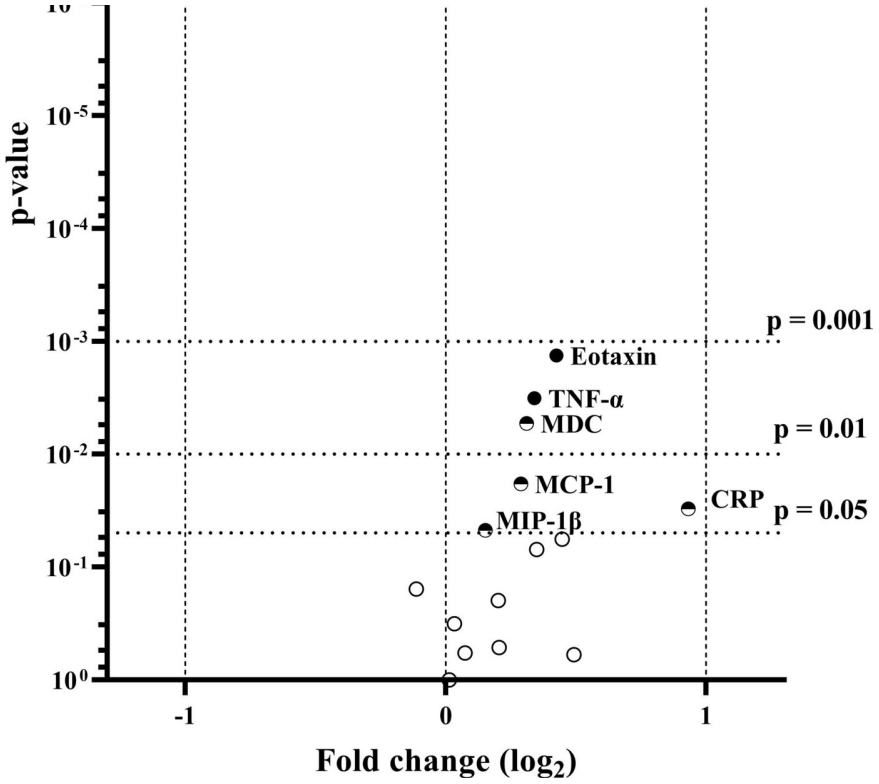
Low-grade inflammatory peripheral profile in T2D

Healthy vs. T2D



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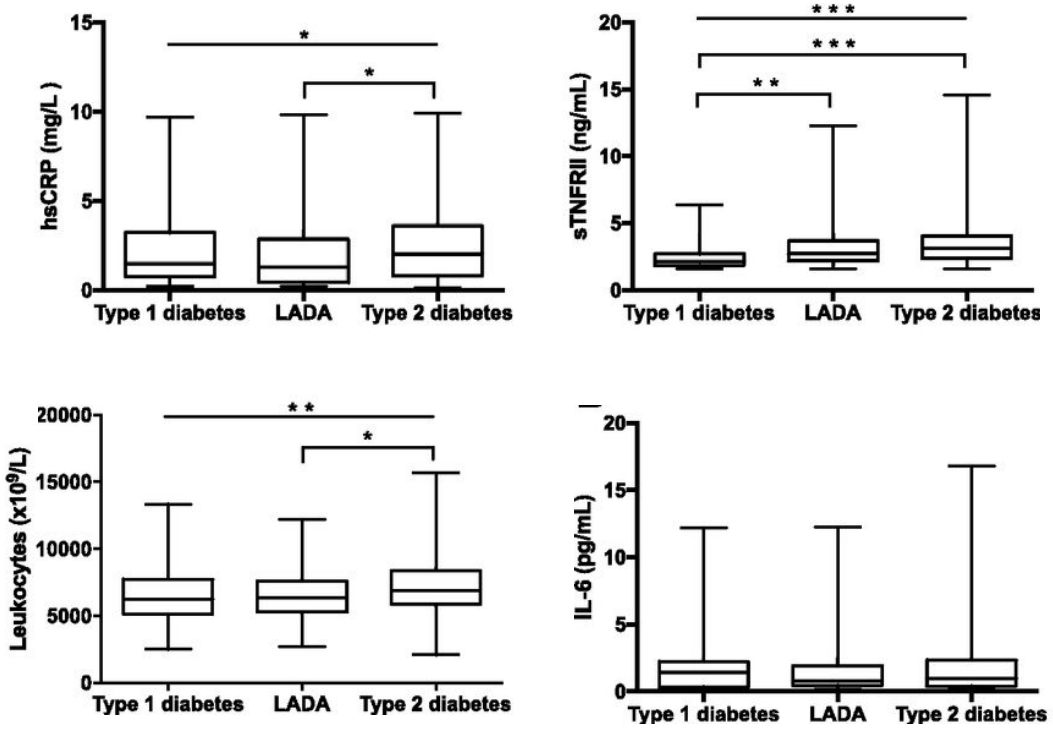
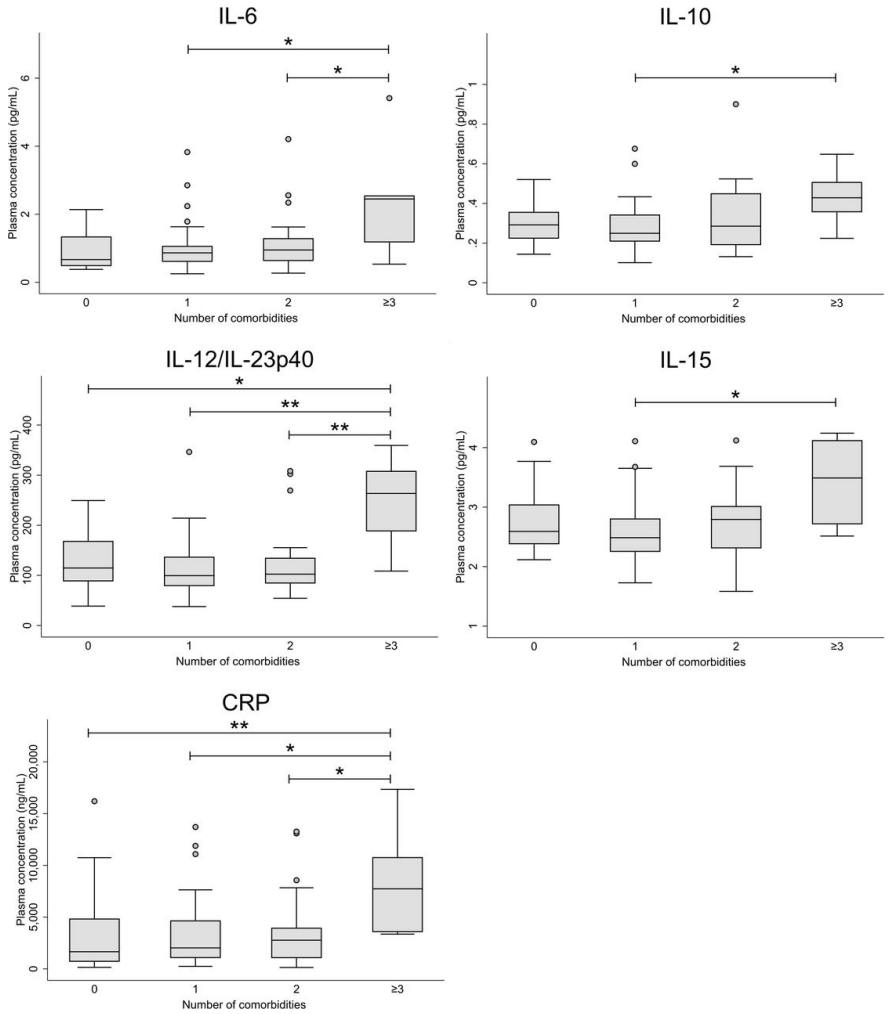
T2D vs LADA vs T1D



Castelblanco E et al Diabetes Care. 2018

Diabetic complications, obesity, glycemic control and therapy affect low grade inflammation profile in T2D

Multiple Diabetic complications



	Adjusted model 2	
	OR (95% CI)	P value
A. Obesity		
IL-12/IL-23p40	1.01 (1.00 to 1.02)	**0.007**
IL-15	2.30 (1.02 to 5.16)	**0.043**
IFN-γ	1.10 (0.99 to 1.22)	0.091
MDC	1.00 (1.00 to 1.00)	**0.049**
CRP	1.00 (1.00 to 1.00)	**0.001**
B. Blood glucose		
IL-8	1.07 (1.00 to 1.15)	0.055
TNF-α	3.09 (1.11 to 8.58)	**0.031**
Eotaxin	1.00 (1.00 to 1.01)	**0.025**
C. Sex		
MDC	1.00 (1.00 to 1.00)	**0.027**
D. DPP-4 inhibitor therapy		
IL-8	0.89 (0.79 to 1.00)	0.051
IP-10	0.99 (0.99 to 1.00)	**0.008**
MDC	1.00 (1.00 to 1.00)	**0.011**
TARC	1.00 (1.00 to 1.01)	**0.005**
E. GLP-1 receptor agonist th		
IL-8	1.08 (1.00 to 1.18)	0.058
IL-15	0.27 (0.08 to 0.92)	**0.036**
IL-16	1.00 (0.98 to 1.00)	0.068
TNF-α	4.70 (1.25 to 17.69)	**0.022**
F. SGLT2 inhibitor therapy		
MDC	1.00 (1.00 to 1.00)	**0.033**

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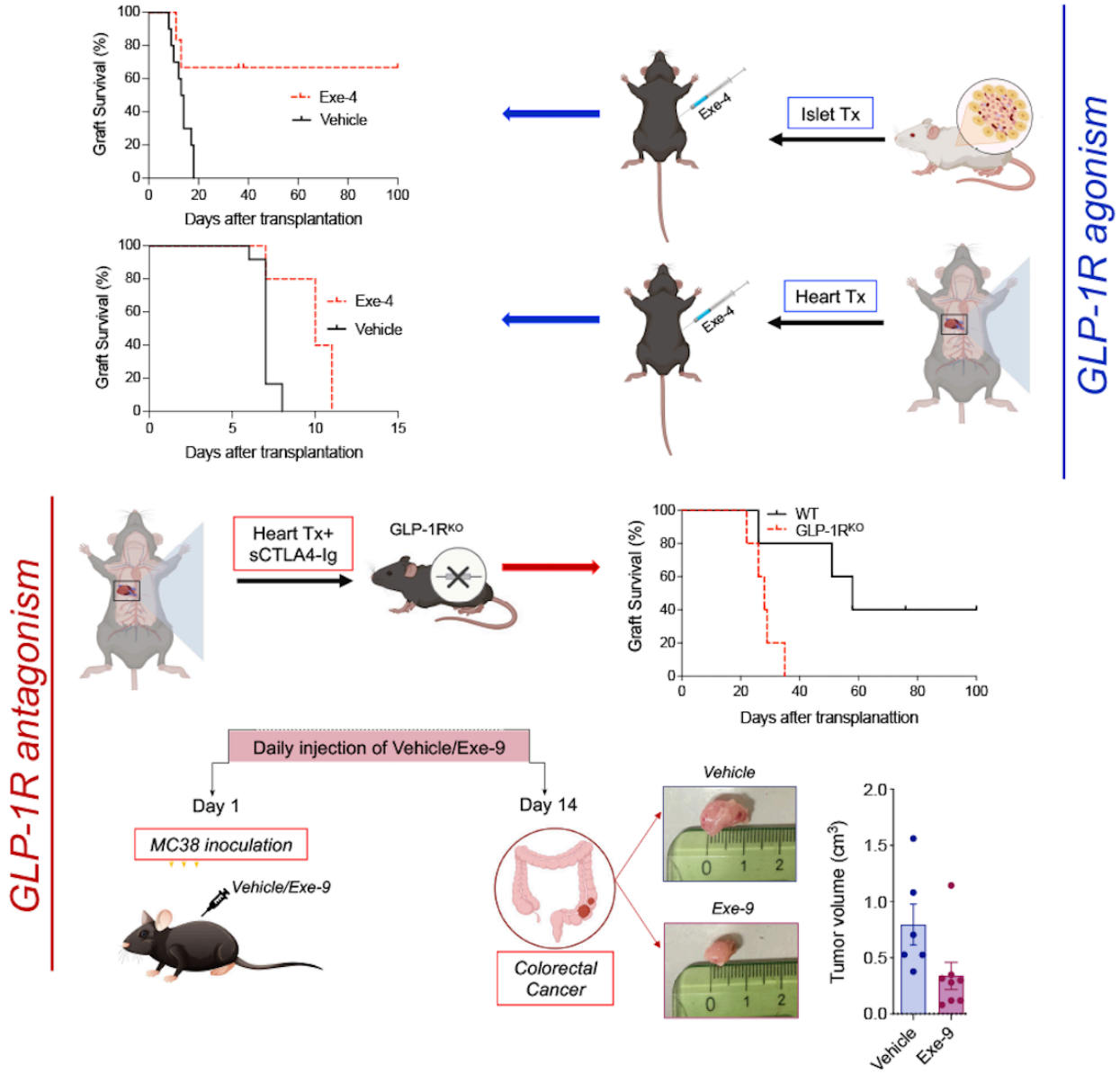
GLP-1R are immunoregulatory and anti-inflammatory



Fiorina P et al., Cell Met 2024

GLP-1RA anti-inflammatory effects *in vitro*

GLP-1RAs	Type of cells	Sample/model	Effects	Reference
In vitro				
Exendin-4	Macrophages	Cells from Mice	↓TNF-α; ↓IL-1β; ↓IL-6	[25]
	Macrophages	Cells from healthy human blood	↓CD36	[19]
	Lymphocytes	Cells from healthy human	↓$CD4^+$	[16]
Exenatide	Monocytes/macrophages	Cells from healthy human blood	↑IL-10; ↓TNF-α; ↓IL-1β	[24]
Liraglutide	Mononuclear cells	Cells from COPD human blood	↓PD-1 expression in $CD4^+$ and $CD8^+$ T cells	[78]
	Mononuclear cells	Cells from healthy human blood	↓TNF-α, ↓MCP-1, ↑IL-10	[27]
	Kupffer cells	Cells from murine liver	↑$CD206^+$, ↓$CD16^+$	[29]
	Lymphocytes	Cells from murine spleen	↓Th1 and Th7 cells	[63]

Fiorina P et al., Pharmacol Res. 2022

GLP-1RA anti-inflammatory effects in preclinical studies

GLP-1RAs	Type of cells	Sample/model	Effects	Reference
In vivo				
Exendin-4	Macrophages	ApoE$^{-/-}$ mice	↓TNF-α, ↓MCP-1	[44]
	Macrophages	Normoglycemic post-myocardial infarction mice	↓CD11b^{+}, ↓CXCL10, ↓CXCL1, ↓CCL2	[35]
	Macrophages	T1D mice	↓TGF-β1, ↓CD14^{+}	[45]
Exenatide	Macrophages	Chronic stressed-induced mice	↓CXCL4, ↓TLR2, ↓TLR4	[39]
Liraglutide	iNTK cells	Obese mice	↑CD69, ↑IL-10	[57]
	Lymphocytes from lymph nodes and thymus	Nonobese diabetic mice	↑CD4^{+} and CD8^{+} T cells; ↓CD4^{+}CD25^{+}Foxp3^{+} regulatory T cells	[58]
	Splenic and visceral lymphocytes	Obese mice	↑CD4^{+} IL-4 T cells (Th2) and CD4^{+} CD25 + T cells (Treg); ↓CD4^{+} IFN-γ^{+} T cells (Th1) and CD4^{+} IL-17a^{+} T cell (Th17); ↓IL-17a, IFN-γ, ↓IL-22	[34]
	Macrophages	High-cholesterol diet-induced mice	↓CCR7, ↓IL-6, ↓TNF-α; ↑IL-10, ↑CD163^{+}	[27]
	Intestinal intraepithelial lymphocytes	GLP-1R$^{+/+}$mice	↓IL-1β, ↓IL-6, ↓IL-22, ↓IL-12β, ↓TNF-α, ↓CCL2, ↓CXCL1, ↓CXCL2	[18]
	Intestinal leucocytes	Diet-induced dysmetabolic mice	↓CD4^{+} T cells; ↑ CD4-Treg cells and Th17 cells; ↓dendritic cells	[60]
	Splenic lymphocytes	NAFLD mice	↓CD4^{+} T cells; ↓IFN-γ, ↓IL-4	[62]
Dulaglutide	Encephalitogenic lymphocytes	Autoimmune encephalomyelitis mice	↓Th1 GM-CSF	[55]
	Intrahepatic leucocytes and monocytes	Nondiabetic NASH mice	↓CD8^{+}IL17^{+} cells, ↓CD4^{+}IFN-γ cells, ↑Foxp3^{+} regulatory T cells; ↓CCL2, ↓CD11c^{+}, ↓TNF-α, ↓IL-1β	[50]

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GLP-1RA anti-inflammatory effects in clinical trials

GLP-1RAs	Dose	Median Follow up	N of patients	Population	Comparison	Effects	Reference
Exenatide	10 μg twice daily	12 weeks	24	T2D with BMI $\geq$ 30 kg/m^2	Placebo	↓TNF-α, ↓TLR-2, ↓TLR-4, ↓IL-1β, ↓MCP-1, ↓IL-6	[74]
Dulaglutide	1.5 mg/week	24 weeks	44	T2D with BMI $\geq$ 25 kg/m^2	Add-on treatment	↓IL-6	[71]
Liraglutide	0.6 mg/day for the first 2 weeks, 1.2 mg/day for the next 4 weeks and then 1.8 mg/day	24 weeks	41	T2D with BMI $\geq$ 25 kg/m^2	Add-on treatment	↓IL-6	[71]
	1.8 mg	12 weeks	27	T2D with UACR > 30 mg/g	Placebo	↓TNF-α	[75]
	0.6 mg /day for 2 weeks followed by 1.2 mg/day	8 weeks	10	T2D with BMI $\geq$ 30 kg/m^2	/	↓sCD163, ↓TNF-α, ↓IL-1β, ↓IL-6	[65]
Semaglutide	Subcutaneous 0.05, 0.1, 0.2, 0.3 or 0.4 mg/day	52 weeks	957	Patients with BMI $\geq$ 30 kg/m^2	Placebo	↓hsCRP	[72]
	Oral 3 mg /day for the first 4 weeks, 7 mg for the next 4 weeks and then 14 mg/day	52 weeks	3183	T2D	Empaglifozin	↓hsCRP	[73]

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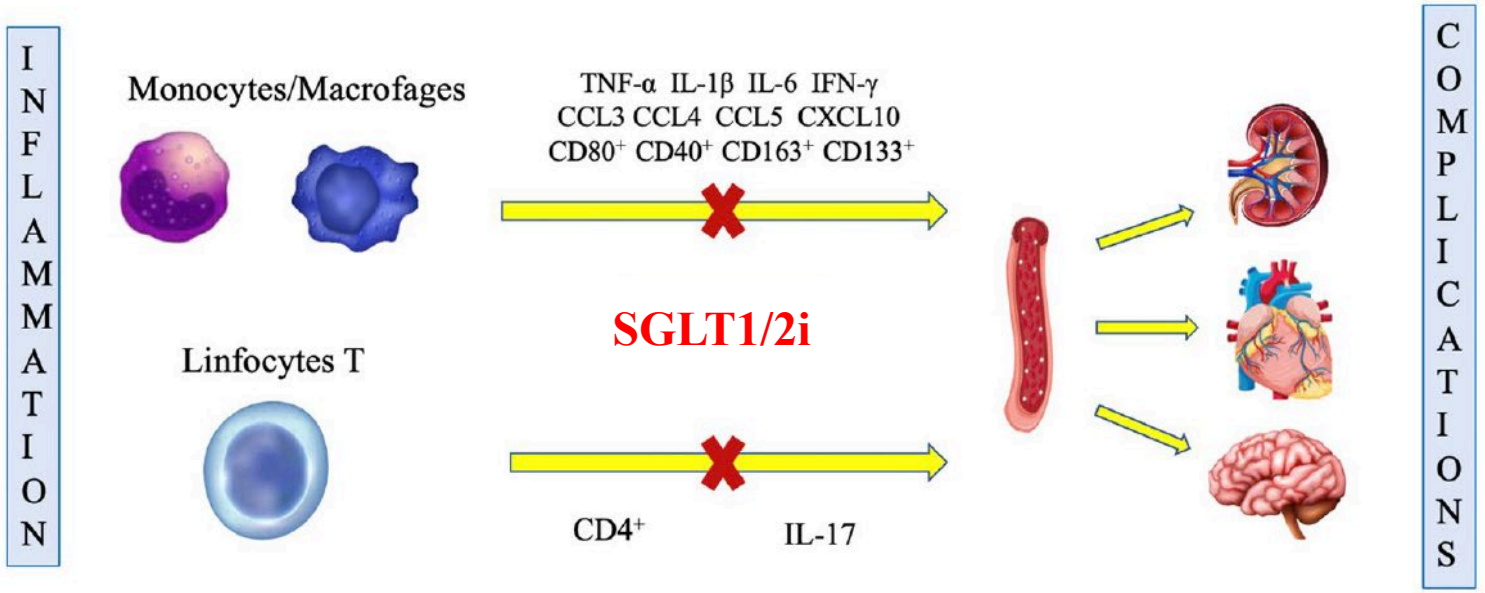
Anti-inflammatory effects of SGLT1/2i



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SGLT1/2i anti-inflammatiry effects *in vitro*

SGLT1/2i	Type of cells	Effects	References
Canagliflozin	Monocytes (RAW 264.7 and THP-1 cells)	↓IL-1α, ↓IL-6	Xu et al. [74]
	Alveolar macrophages	↓TNF-α, ↓IL-1β, ↑$CD206^+$, ↑M2 phenotype	Lin et al. [56]
Empagliflozin	Macrophages	↓$CD-40^+$, ↑$CD206^+$	Koyani et al. [76]
	RAW 264.7 macrophages	↓$CD80^+$, ↓TNF-α, ↓IL-1β, ↓IL-6, ↓IFN-γ, ↓CCL3, ↓CCL4, ↓CCL5, ↓CXCL10	Lee et al. [77]

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SGLT1/2i anti-inflammatory effects in preclinical models

SGLT1/2i	Organ/tissue murine model	Effects	References
Canagliflozin	Heart of high-fat diet-fed ApoE$^{-/-}$ mice	↓MCP-1, ↓CD68^{+}	Nasiri-Ansari et al. [57]
	LPS-induced lung injury	↓TNF-α, ↓IL-6, ↓IL-1β, ↑CD206^{+}	Lin et al. [56]
Empagliflozin	T2D	↓F4/80^{+}, ↓IL-6, ↓CCL2, ↓CCR2, ↑IL-10	Radlinger et al. [47]
	Liver of mice fed with carbohydrate–high-fat diet	↓F4/80^{+}, ↓IL-6, ↓MCP-1, ↓TNF-α	Nasiri-Ansari et al. [19]
	C57BL/6 J mice fed with high-fat diet	↓F4/80^{+}, ↓CD3^{+}, ↓CD4^{+}, ↓CD8^{+}	Xu et al. [50]
	Mice fed with high-fat diet	↓Th1 and Th7 cells	Park et al. [54]
Dapagliflozin	Aortic vessel of C57BL/6 J mice	↓CD4^{+}, ↓CD8^{+}	Liu et al. [44]
	Diabetic cardiomyopathy	↓TNF-α, ↓IL-6, ↓IL-1β	El-Shafey et al. [40]
	Diabetic kidney disease	↓Th7/Treg cells	Wang et al. [43]
	Mice with acute infarction	↓IL-6, ↓IL-1β, ↑CD68^{+}	Lee et al. [77]

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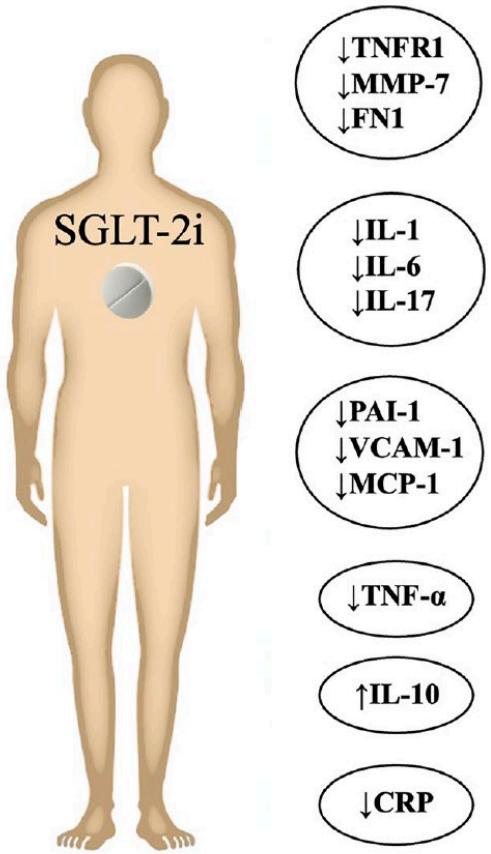
SGLT1/2i effects in clinical trials



References	Drugs	Median follow-up	No. of patients	Population	Comparison	Effects
Heerspink et al. [72]	Canaglifozin	2 years	3316	T2D	Glimepiride	↓TNFR1, IL-6 ↓MMP7, FNI
Hess et al. [79]	Empagliflozin	24 weeks	23	T2D	Placebo	↓$CD163^+$, ↓$CD133^+$, ↑$CD80^+$
Kim et al. [80]	Empagliflozin	30 days	61	T2D	Glimepiride	↓IL-1β
Borzouei et al. [78]	Empagliflozin	24 weeks	56	T2D	Add-on treatment to metformin and gliclazide	↓$CD4^+$ T cells, ↓IL-17, ↑IL-10, ↑FOXP3, ↑STAT5
Bonora et al. [75]	Dapagliflozin	74 weeks	31	T2D	Placebo	↑$CD34^+KDR^+$

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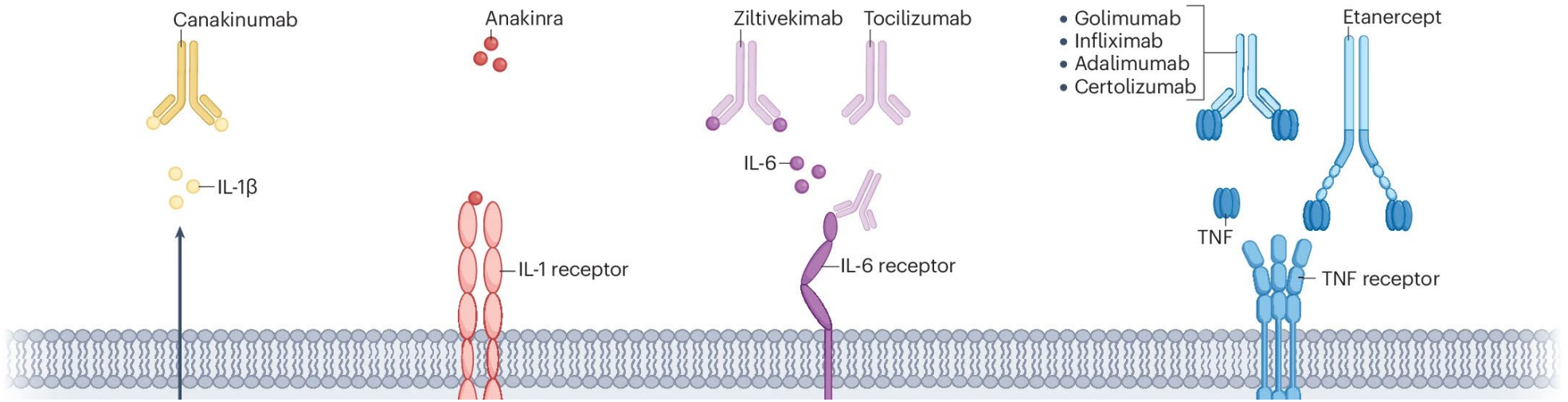
Targeting surface receptors and circulating cytokines

Action	Effects	Adverse effects
IL-1β inhibitor	↓ CRP	↑ Fatal infections

Action	Effects
IL-1 receptor antagonist	↓ CRP

Action	Effects
• IL-6 inhibitor (ziltivekimab) • IL-6 receptor antagonist (tocilizumab)	• ↓ CRP • ↓HbA_{1c} • ↓ Neutrophils

Action	Effects	Adverse effects
TNF inhibitor	• ↓ CRP or ⇆CRP • ↓HbA_{1c} • ↓ Fasting levels of glucose • ↓ IL-6 or ⇆IL-6 • ⇆TNF • ⇆Lipids	Weight gain



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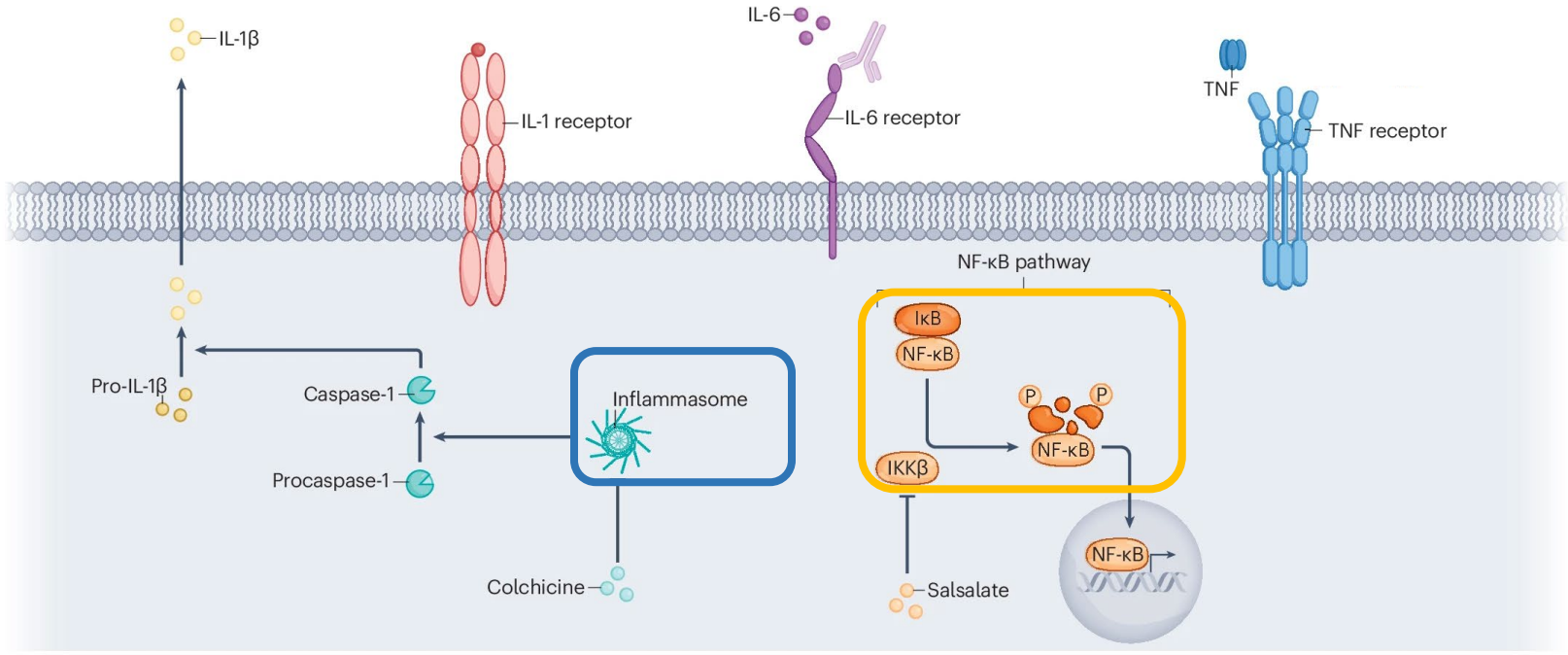
New intracellular targets: inflammasome and NF-kB



Action	Effects
Inhibits the inflammasome and prevents the release of active IL-1β	• ↓ CRP • ↓ Resistin • ↓ Monocytes • ↓ Neutrophils • ↓ Rate of lipolysis

Action	Effects
Inhibits the NF-κB pathway via inhibiton of IKKβ Inhibits COX enzymes and modulates AMPK activation	• ↓ CRP • ↓ Free fatty acids • ↓ Fasting levels of glucose • ↑ Insulin sensitivity • ↑ Adiponectin • ⇆ Insulin

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Direct targeting of inflammation in T2D

	Targets	Drugs	References
Glycaemia	NF-κB	Salsalate	(Faghihimani et al., 2013; Fleischman et al., 2008; Goldfine et al., 2013a; Goldfine et al., 2013b; Goldfine et al., 2010; Goldfine et al., 2008; Koska et al., 2009)
	TNF-α	Etanercept, remicade (mixed results)	(Bernstein et al., 2006; Dominguez et al., 2005; Gonzalez-Gay et al., 2006; Huvers et al., 2007; Kiortsis et al., 2005; Marra et al., 2007; Ofei et al., 1996; Paquot et al., 2000; Ruscitti et al., 2019; Stanley et al., 2011; Timper et al., 2013; Yazdani-Biuki et al., 2006; Yazdani-Biuki et al., 2004)
	IL-1β NLRP3	Anakinra, canakinumab, gevokizumab, LY2189102, diacerein, dapansutrile	(Cavelti-Weder et al., 2012; Everett et al., 2018; Kataria et al., 2019; Larsen et al., 2007; Ramos-Zavala et al., 2011; Rissanen et al., 2012; Ruscitti et al., 2019; Sloan-Lancaster et al., 2013; van Asseldonk et al., 2011; van Poppel et al., 2014; Wohlford et al., 2020)
β-cell function	IL-1β	Anakinra, diacerein	(Larsen et al., 2007; Ramos-Zavala et al., 2011; van Asseldonk et al., 2011; van Poppel et al., 2014)
Insulin resistance	NF-κB	Salsalate	(Faghihimani et al., 2013; Fleischman et al., 2008; Goldfine et al., 2013a; Goldfine et al., 2013b; Goldfine et al., 2010; Goldfine et al., 2008; Koska et al., 2009)
	TNF-α	Etanercept, remicade (mixed results)	(Bernstein et al., 2006; Dominguez et al., 2005; Gonzalez-Gay et al., 2006; Huvers et al., 2007; Kiortsis et al., 2005; Marra et al., 2007; Ofei et al., 1996; Paquot et al., 2000; Ruscitti et al., 2019; Stanley et al., 2011; Timper et al., 2013; Yazdani-Biuki et al., 2006; Yazdani-Biuki et al., 2004)
	IL-1β	Anakinra	(Ruscitti et al., 2019; van Asseldonk et al., 2015)

and in other diseases and T2D complications

Cardiovascular complications	IL-1β	Canakinumab	(Ridker et al., 2017)
Heart failure	IL-1β NLRP3	Anakinra, canakinumab, dapansutrile	(Abbate et al., 2015; Abbate et al., 2010; Everett et al., 2019; Van Tassell et al., 2017; Van Tassell et al., 2018; Wohlford et al., 2020)
Gout	IL-1β NLRP3	Anakinra, canakinumab, dapansutrile	(Klück et al., 2020; Martinon et al., 2006; So et al., 2007; Vitale et al., 2015)
Rheumatoid arthritis	IL-1β	Anakinra	(Ruscitti et al., 2019)
Retinopathy	IL-1β	Canakinumab	(Stahel et al., 2018)

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Repurposing of antidiabetic drugs in neuroinflammation

Company	Drug Name		Use	Clinical Trial	Phase	Status	Outcomes
AstraZeneca	Exenatide	Bydureon®	PD	#NCT03456687	1	Ongoing	N/A
				#NCT01971242	2	Completed (2020)	Treatment improved off-medication motor scores. See (a.) *Athauda et al., 2017.*
				#NCT04305002	2	Recruiting	N/A
				*EUCTR2019-000732-26-SE	2	Ongoing	N/A
				#NCT04232969	3	Ongoing	N/A
				*ISRCTN14552789	3	Ongoing	N/A
				*ACTRN12620000627954	4	Recruiting	N/A
		Byetta®	AD	#NCT01255163	2	Completed (2016)	Treatment reduced amyloid-β-42 concentration in extracellular vesicles. See (b.) *Mullins et al., 2019.*
			PD	#NCT01174810	2	Completed (2013)	Treatment improved motor abilities and cognition. See (c.) *Aviles-Olmos et al., 2013.*
			FRDA	*EUCTR2014-003598-41-BE	Pilot	Completed (2019)	Treatment improved frataxin levels in FRDA patients. See (d.) *Igoillo-Esteve et al., 2020.*
Novo Nordisk	Liraglutide	Victoza®	AD	#NCT01469351	2	Completed (2013)	Treatment maintained healthy brain glucose metabolism. See (e.) *Gejl et al., 2016.*
				#NCT01843075	2	Ongoing	N/A
			PD	#NCT02953665	2	Completed (2022)	Treatment improved non-motor symptoms, quality of life, and mobility. See (f.) *Hogg et al., 2022.*
	Semaglutide	Ozempic®	PD	#NCT03659682	2	Not yet recruiting	N/A
		Rybelsus®	AD	*ISRCTN71283871	2	Recruiting	N/A
				#NCT04777409	3	Recruiting	N/A
				#NCT04777396	3	Recruiting	N/A
Neuraly Inc.	Exenatide	NLY01	PD	#NCT03672604	1	Ongoing	N/A
				#NCT04154072	2	Ongoing	N/A
Peptron	Exenatide	PT320	PD	#NCT04269642	2	Ongoing	N/A
Sanofi-Aventis	Lixisenatide	Adlyxin® / Lyxumia®	PD	#NCT03439943	2	Ongoing	N/A
Various	Any GLP-1R agonist approved for metabolic disease treatment	Various	Glaucoma	N/A	N/A	Completed (2021)	GLP-1R agonist treatment cohort had reduced risk of developing glaucoma. See (g.) *Sterling et al., 2021.*

Kopp KO et al Pharmacol Res 2022

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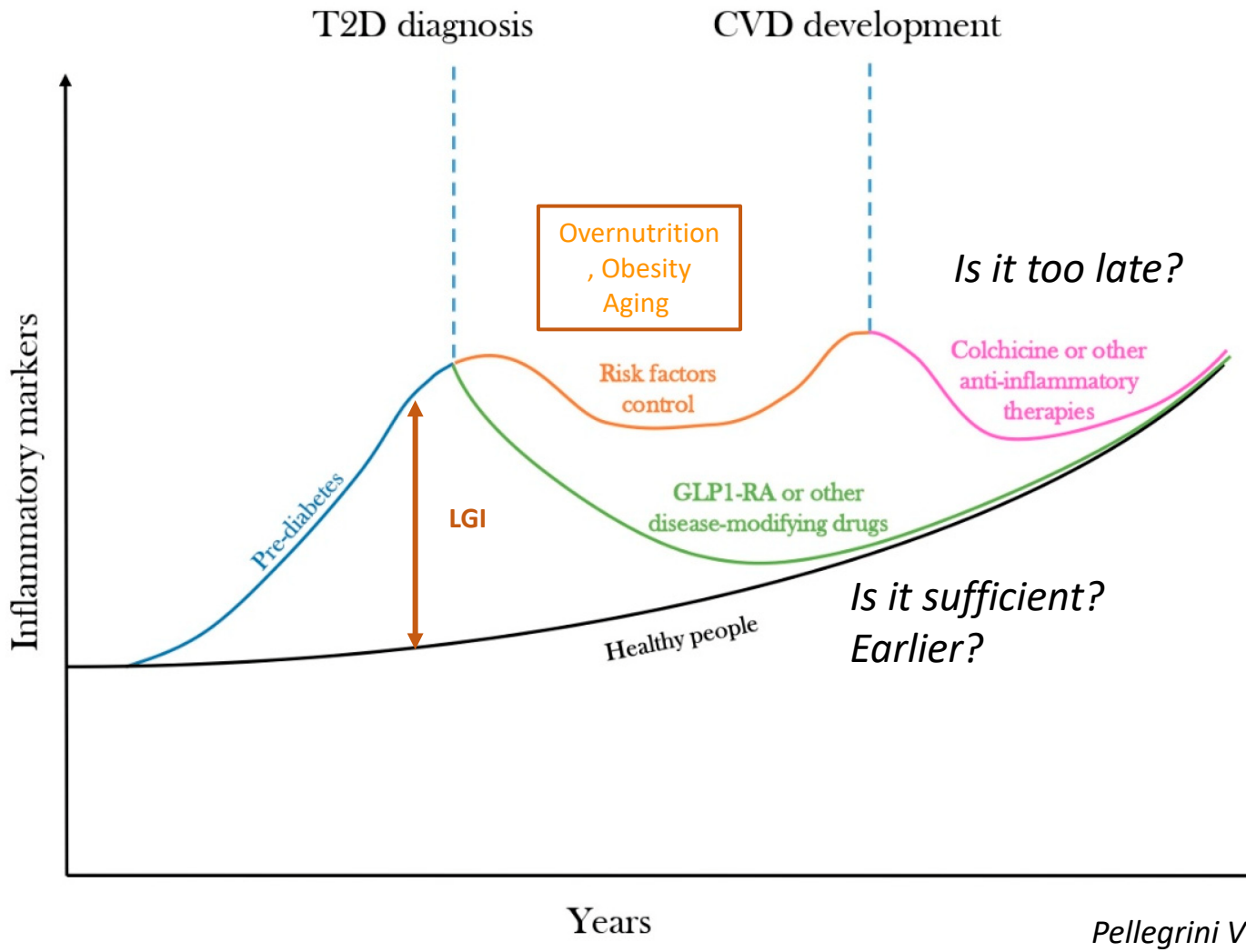
Conclusions

Low grade inflammation in T2D



Pellegrini V et al Cells 2024

Conclusions

- Chronic unresolved systemic inflammation drives T2D and related cardiometabolic disease.
- Anti-inflammatory drugs are approved but have adverse effects (weight gain, infections)
- Specialized pro-resolving mediators (lipoxins) are of therapeutic interest.
- Specific biomarkers for low grade chronic inflammation to identify at risk patients are lacking.
- Studies evaluating effects of antidiabetic drugs on low grade chronic inflammation are lacking.

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