

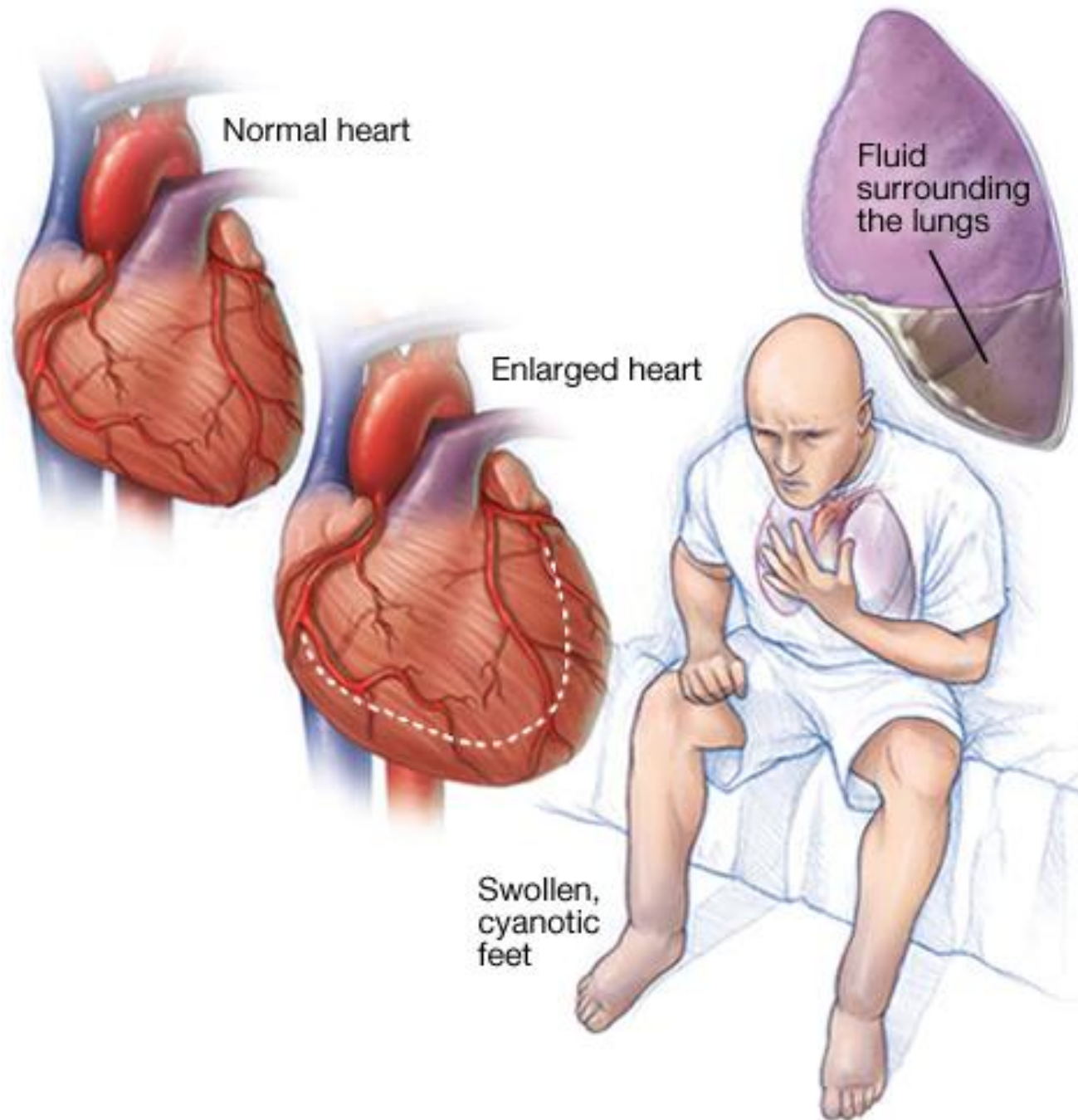
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# Behandlung des Diabetes mellitus: Smarte Medikamente **sind die Zukunft**

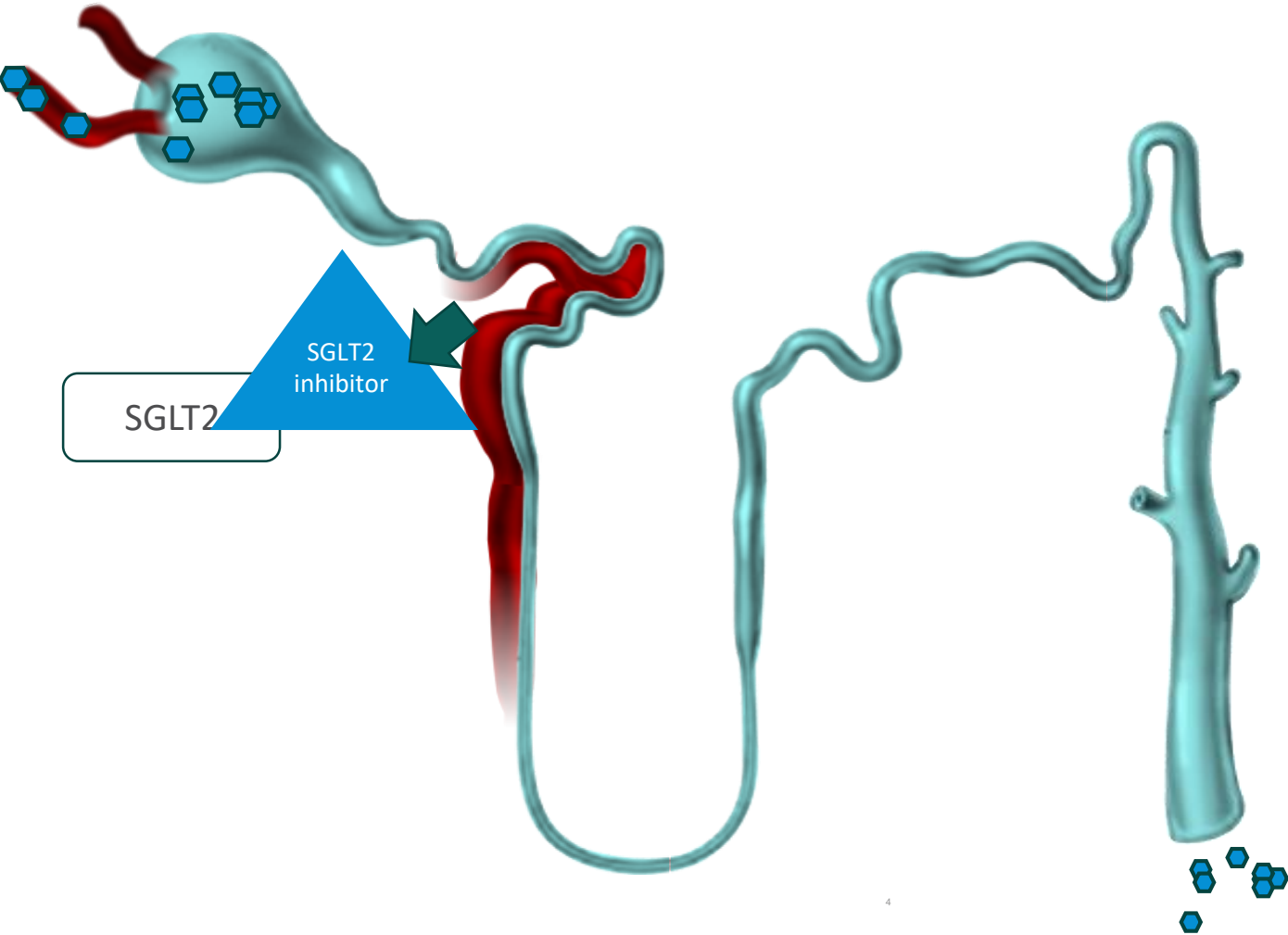
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# Pathogenesis of type 2 diabetes: is insulin resistance the problem?

1. Paradox: heavier = more insulin-resistant
  - Active mechanism
2. Insulin resistance = less glucose enters tissue
  - Why should insulin resistance be harmful?
3. Genetic predisposition to insulin resistance affects populations but not sub-groups within a population
  - Possible evolutionary advantage rather than a pathological trait



# Urinary glucose excretion via SGLT2 inhibition



**Glucosuria / day with SGLT2i**

**50-80 g glucose =**

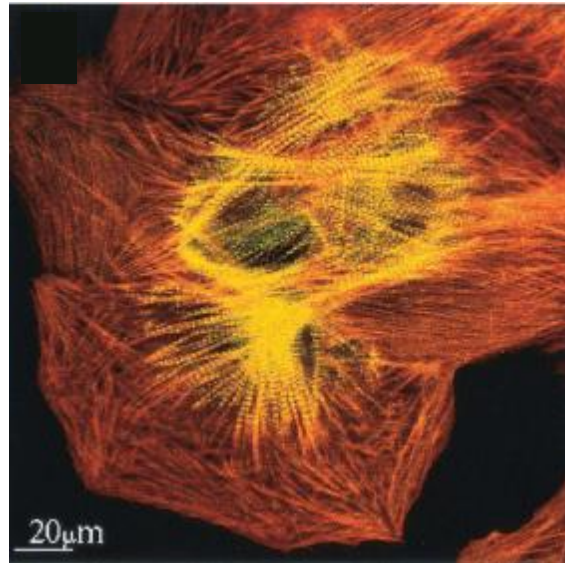
**200-320 calories**



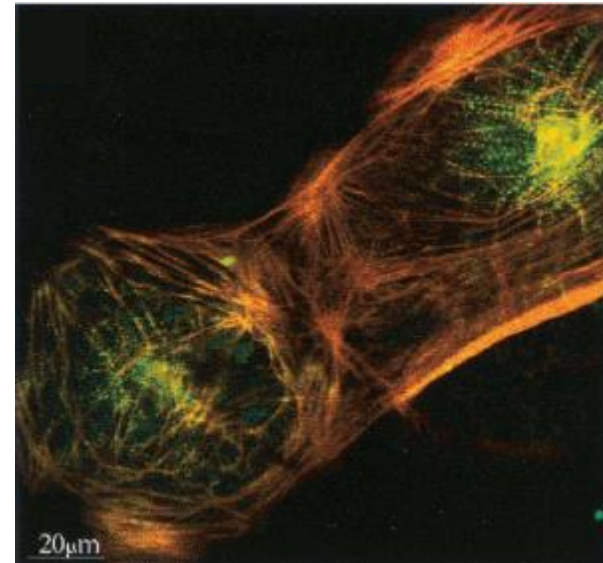


# Cardiomyocytes

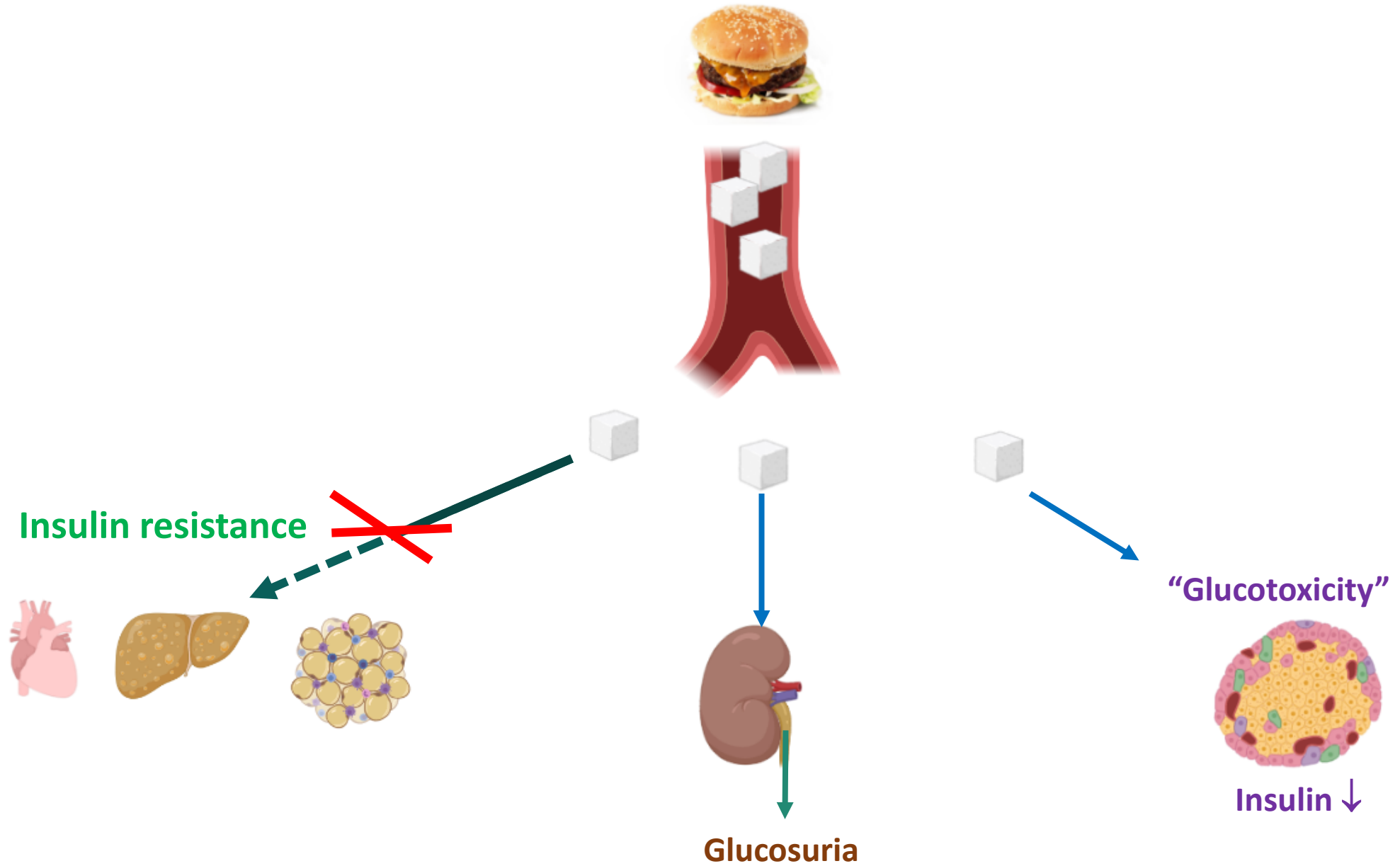
Control



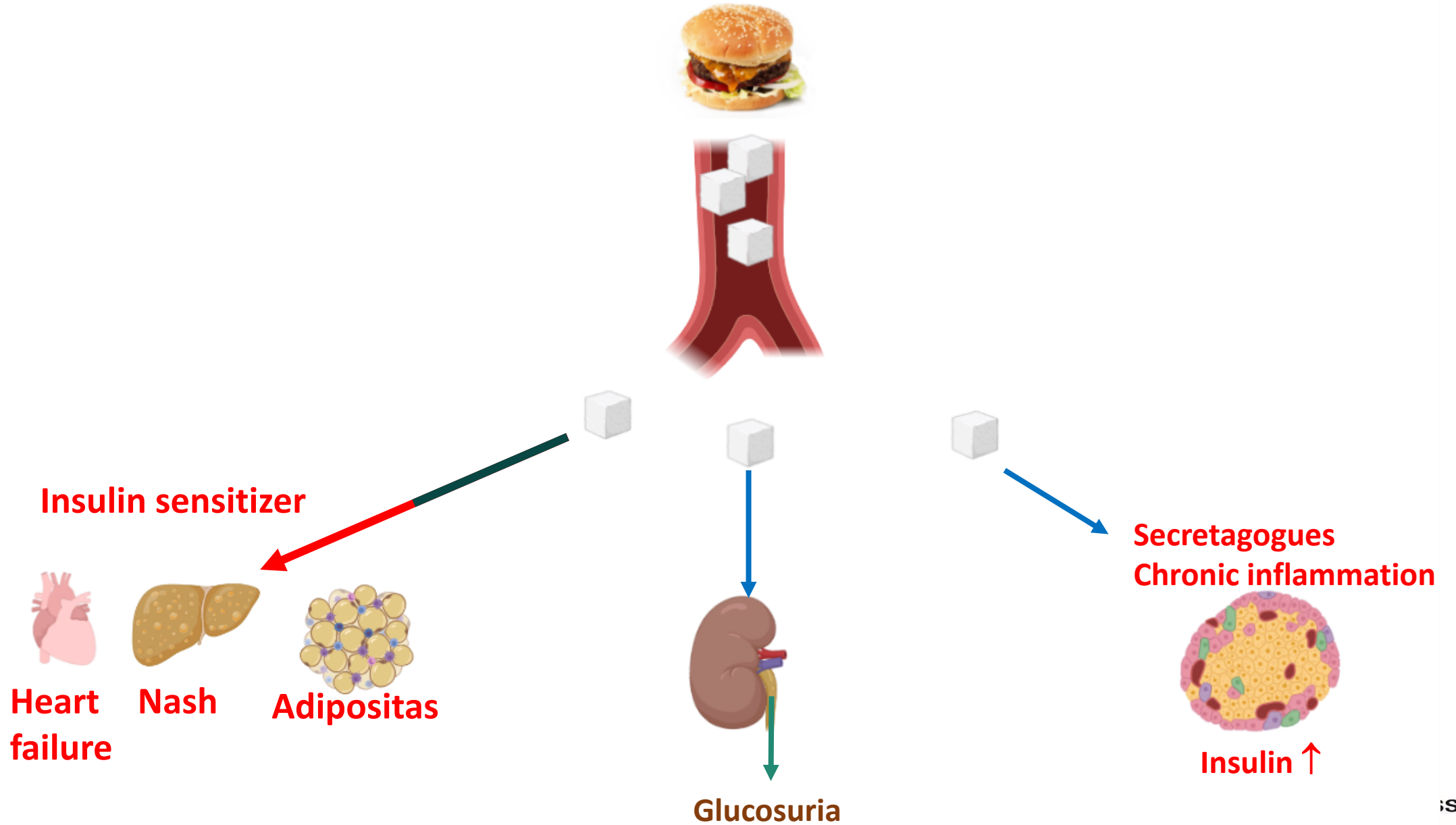
Glucose



# Protection against Over-nutrition



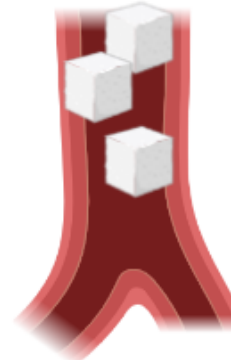
# Protection against Over-nutrition





# Protection against Over-nutrition

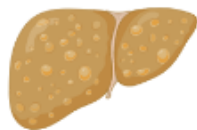
GLP-1



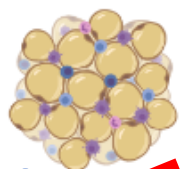
~~Insulin sensitizer~~



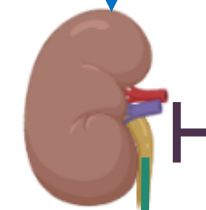
~~Heart failure~~



~~NASH~~



~~Adipositas~~

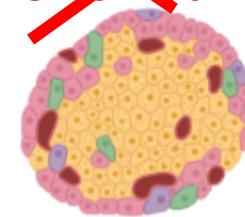


SGLT-i

Glucosuria ↑↑



~~Secretagogues~~  
~~Chronic inflammation~~

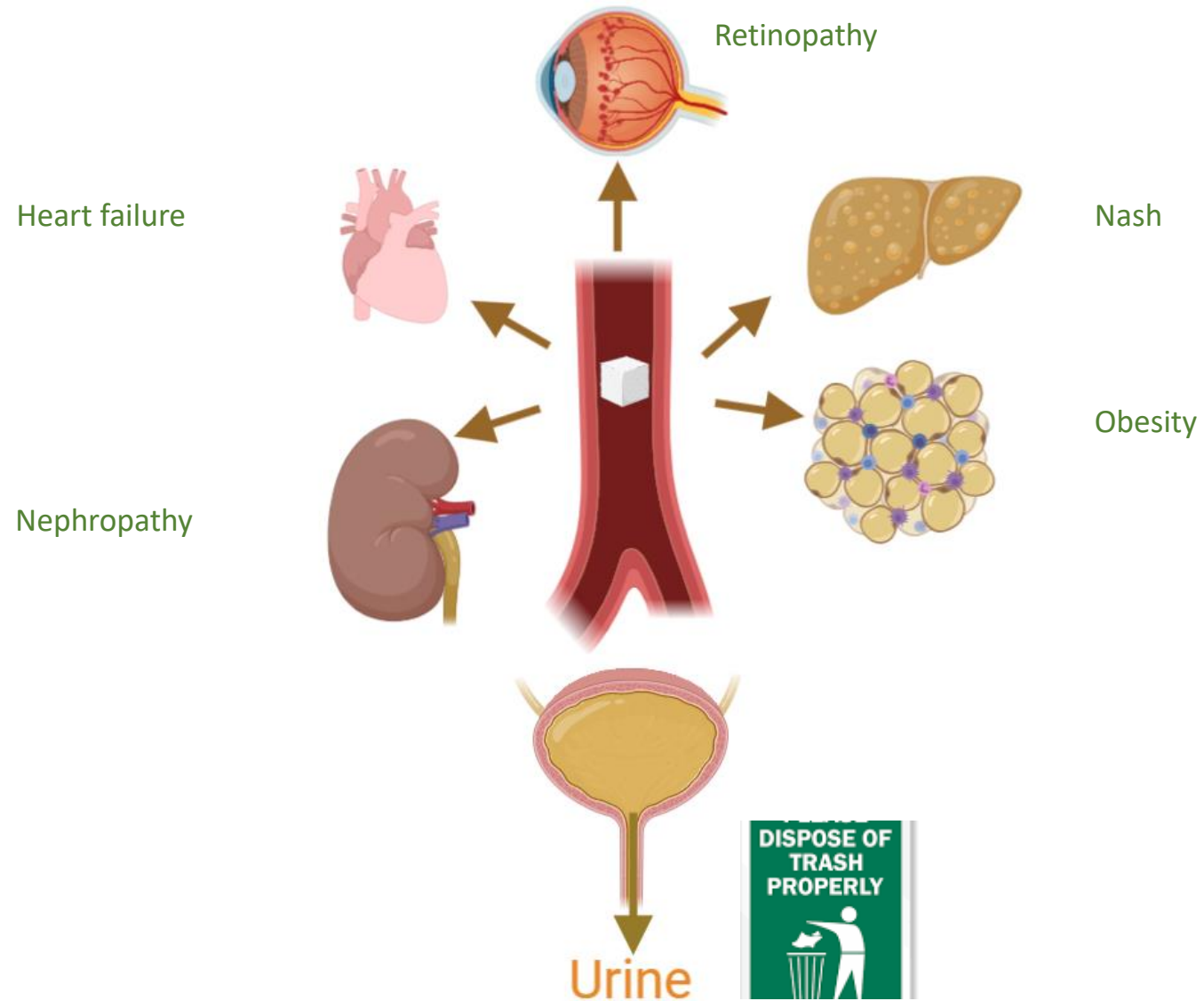


Insulin ↓

Anti-IL-1

hospital

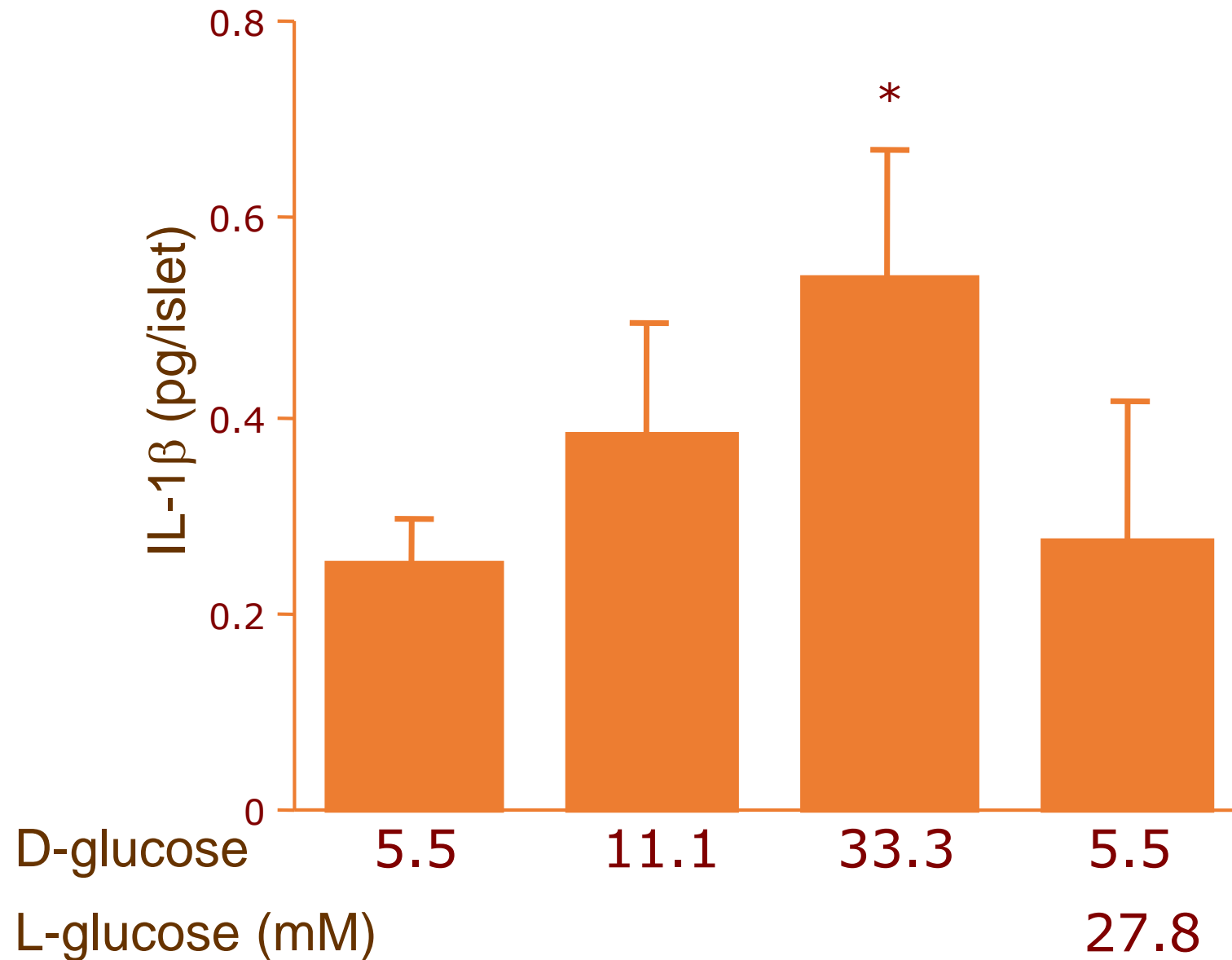
# Glucose disposal: HbA1c reflects only glycemia



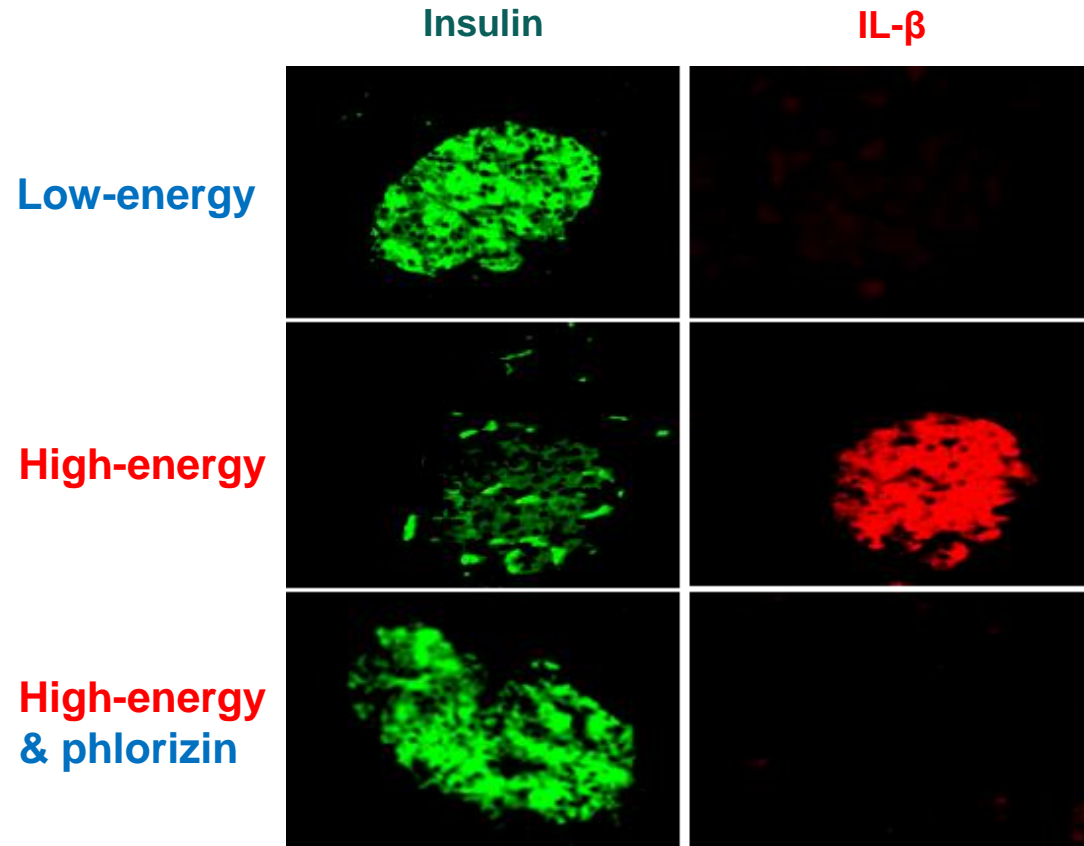
# Pathogenesis of type 2 diabetes: insulin resistance is protective

1. Paradox: heavier = more insulin-resistant
  - Active mechanism
2. Insulin resistance = less glucose enters tissue
  - Why should insulin resistance be harmful?
3. Genetic predisposition to insulin resistance affects populations but not sub-groups within a population
  - Possible evolutionary advantage rather than a pathological trait

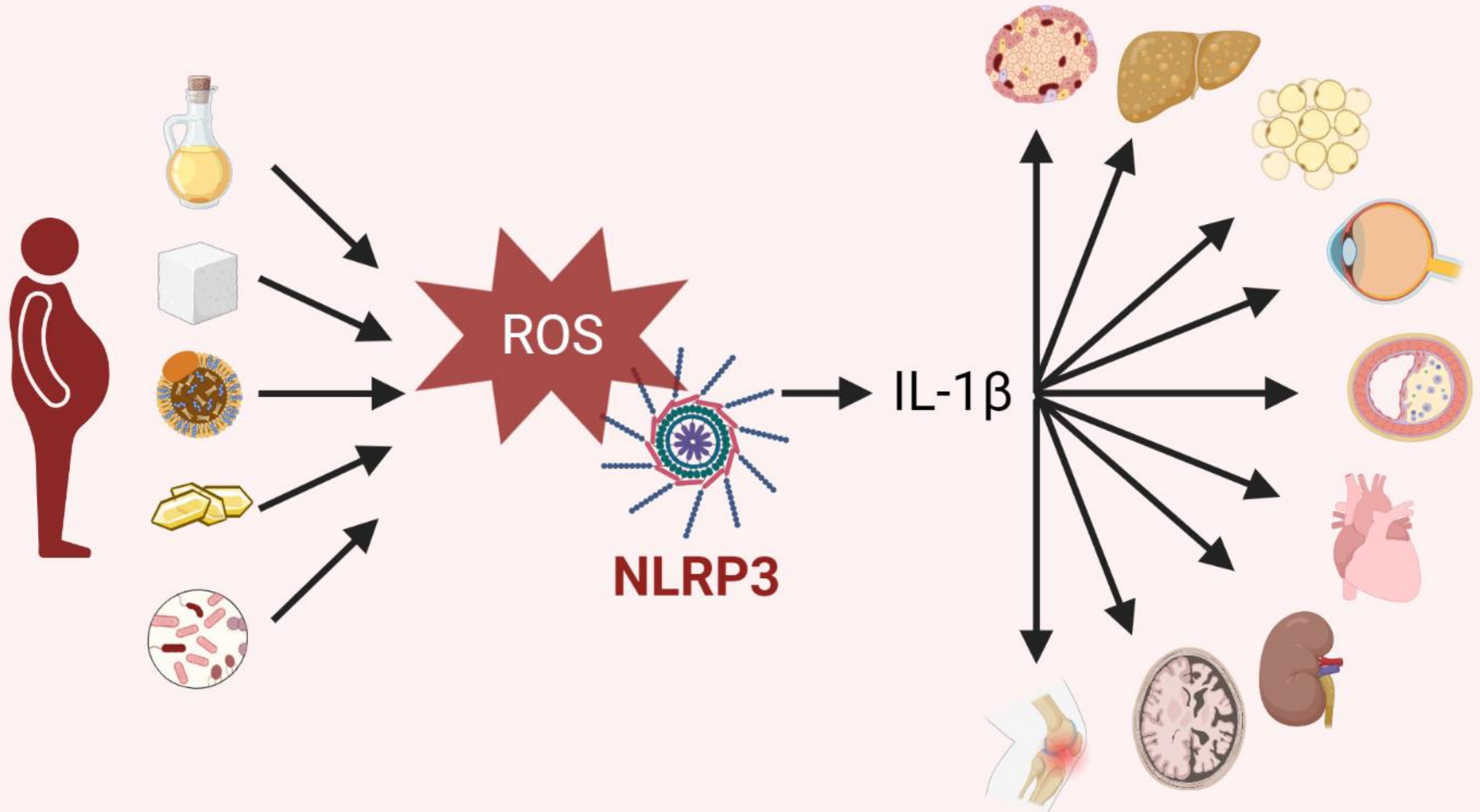
# Glucose induces IL-1 $\beta$



# Glucose induces IL-1 $\beta$



└ SGLT-inhibition



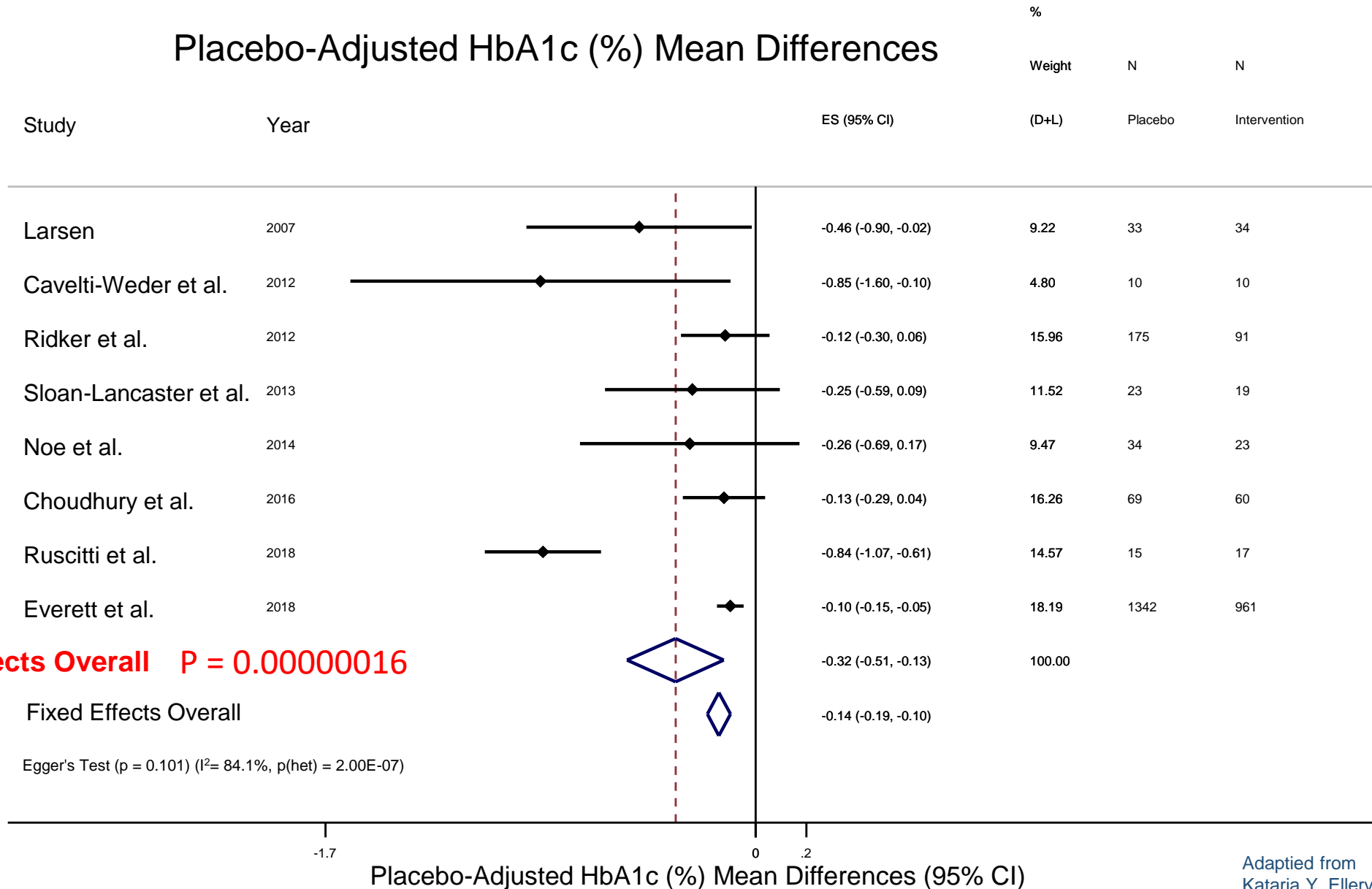
**Metabolic stress**

**Metabolic syndrome**



# Treatment of type 2 diabetes by targeting IL-1:a meta analysis of 2921 patients

## Placebo-Adjusted HbA1c (%) Mean Differences



**Random Effects Overall P = 0.00000016**

# Anti-IL-1 $\beta$ or NLRP3 inhibition in patient with a metabolic syndrome

## BENEFITS:

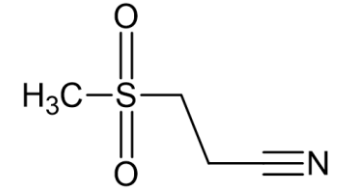
- Cardiovascular complications ↓
- Heart failure ↓
- Glycaemia ↓
- $\beta$ -cell function ↑
- Gout ↓
- Arthritis ↓
- Lung cancer mortality ↓
- No hypoglycaemia
- Possible effects: renal & eye protection, NASH prevention, treatment of neuropathy & periodontitis

## Limitations:

- Severe infections (for antibodies)

# Dapansutrine (OLT1177): oral inhibitor of the NLRP3

Patients with type 2 Diabetes in phase 1B heart failure trial:  
Fasting Glucose



	Dapansutrine 500 mg	Dapansutrine 1000 mg	Dapansutrine 2000 mg	Dapansutrine All	Placebo
Day 14 –change from Baseline (mmol/L)	<b>-1.1</b>	<b>-0.9</b>	<b>- 2.4</b>	<b>- 1.4</b>	<b>-0.5</b>
P-value	0.3	0.6	0.12	<b>0.029</b>	0.4

# Dapansutrile in Diabetes and Complications

A Multicentre Randomized, Double-Blind, Placebo-Controlled Trial of  
Dapansutrile, an Oral NLRP3 inhibitor  
in Subjects with Type 2 Diabetes Mellitus



**Funded by  
the European Union**



Schweizerische Eidgenossenschaft  
Confédération suisse  
Confederazione Svizzera  
Confederaziun svizra

State Secretariat for Education,  
Research and Innovation SERI

**OLATEC**

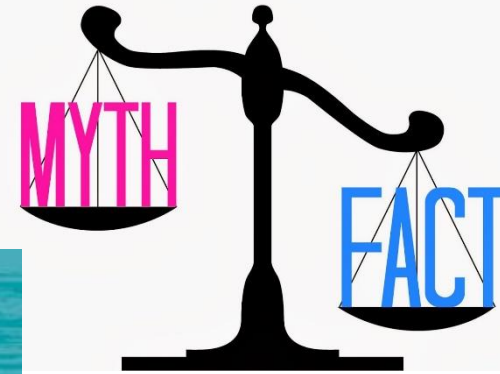
Type 2 diabetes is part of the  
metabolic syndrome

# Overweight = major risk of many diseases

1. **Diabetes**
2. **Cardiovascular diseases (heart attack, stroke...)**
3. **Cancer**
4. **Joint pain and diseases (Osteoarthritis, Gout...)**
5. **Neuroinflammation (depression, Alzheimer's...)**



Healthy overweight is a myth,  
like a healthy smoker



ROXANE GAY

# HUNGER

btb

«Ein brillantes, bewegendes Buch, das weit über  
Roxane Gays persönliche Geschichte hinaus Leser  
und Leserinnen im Innersten berühren wird.»  
NEW YORK TIMES

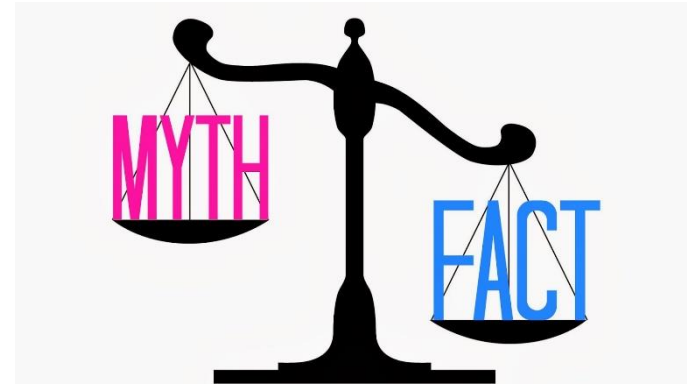
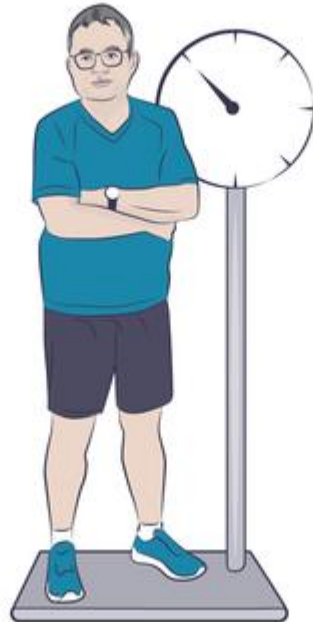
Die Geschichte meines Körpers



Dass Lifestyle-Interventionen nicht funktionieren,  
ist ein Mythos

*Neue Zürcher Zeitung*

Serie: «Ich nehme ab»





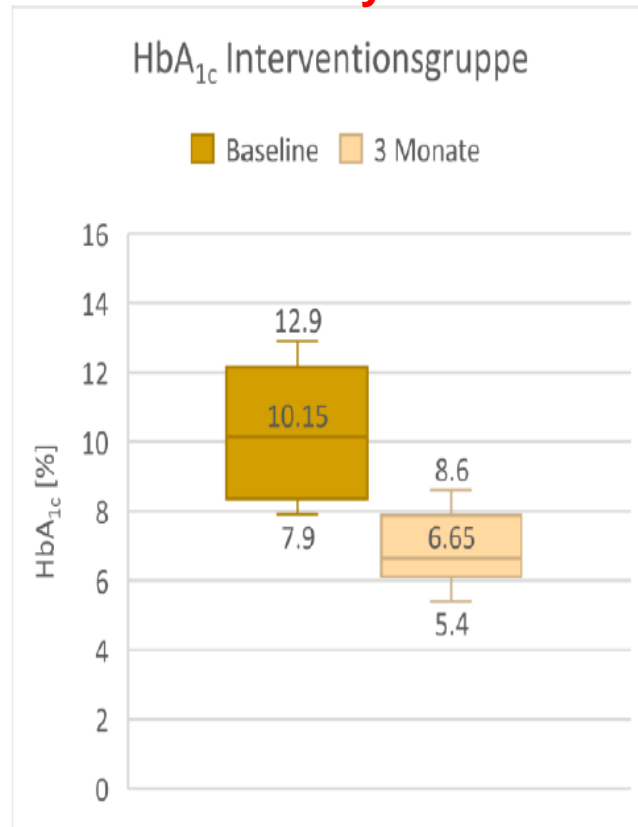
# THE BELIFE STUDY

## Bicycle Exercise & Lifestyle Intervention in Newly Diagnosed Diabetes

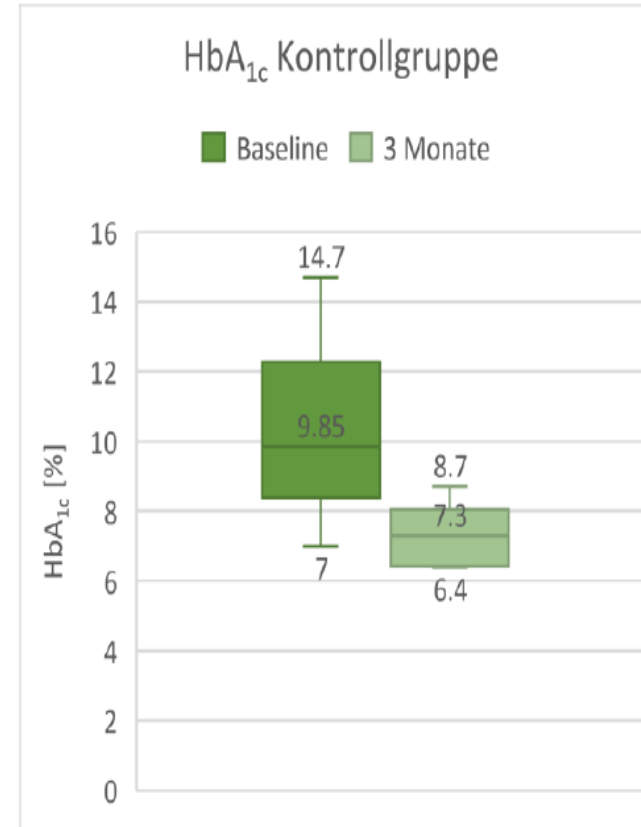


# Lifestyle only versus standard care in patients with new onset diabetes

## Lifestyle

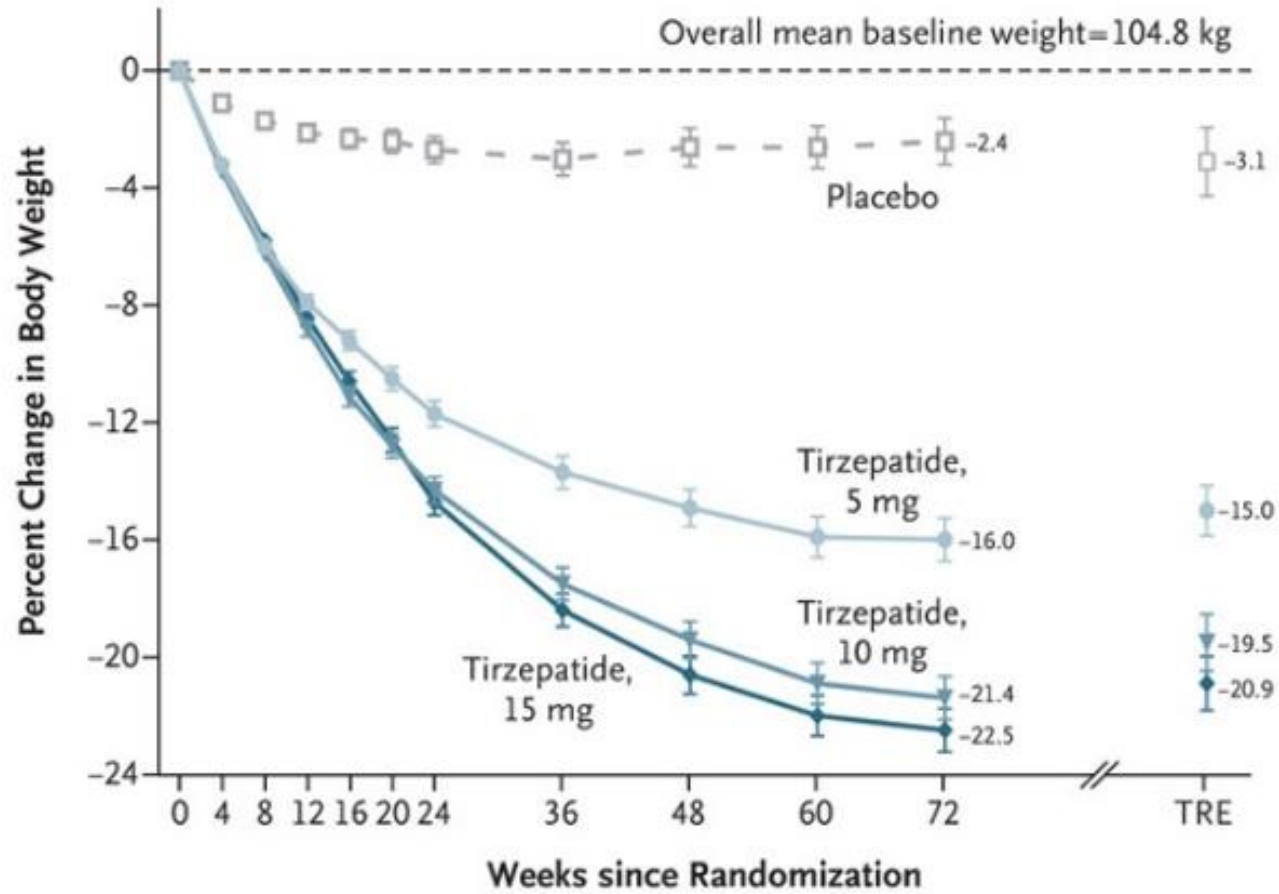


## Standard care





# Outlook



Nur im Rahmen einer Lebensstilintervention wirksam!

