The current management of Type 1 and 2 diabetes: essentials for reproductive medicine

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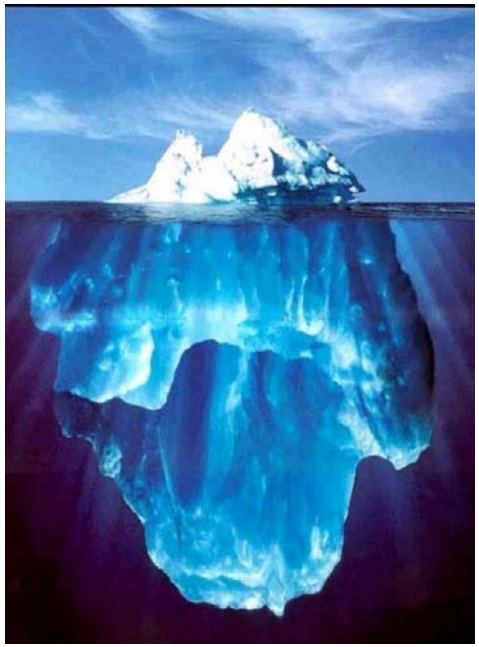
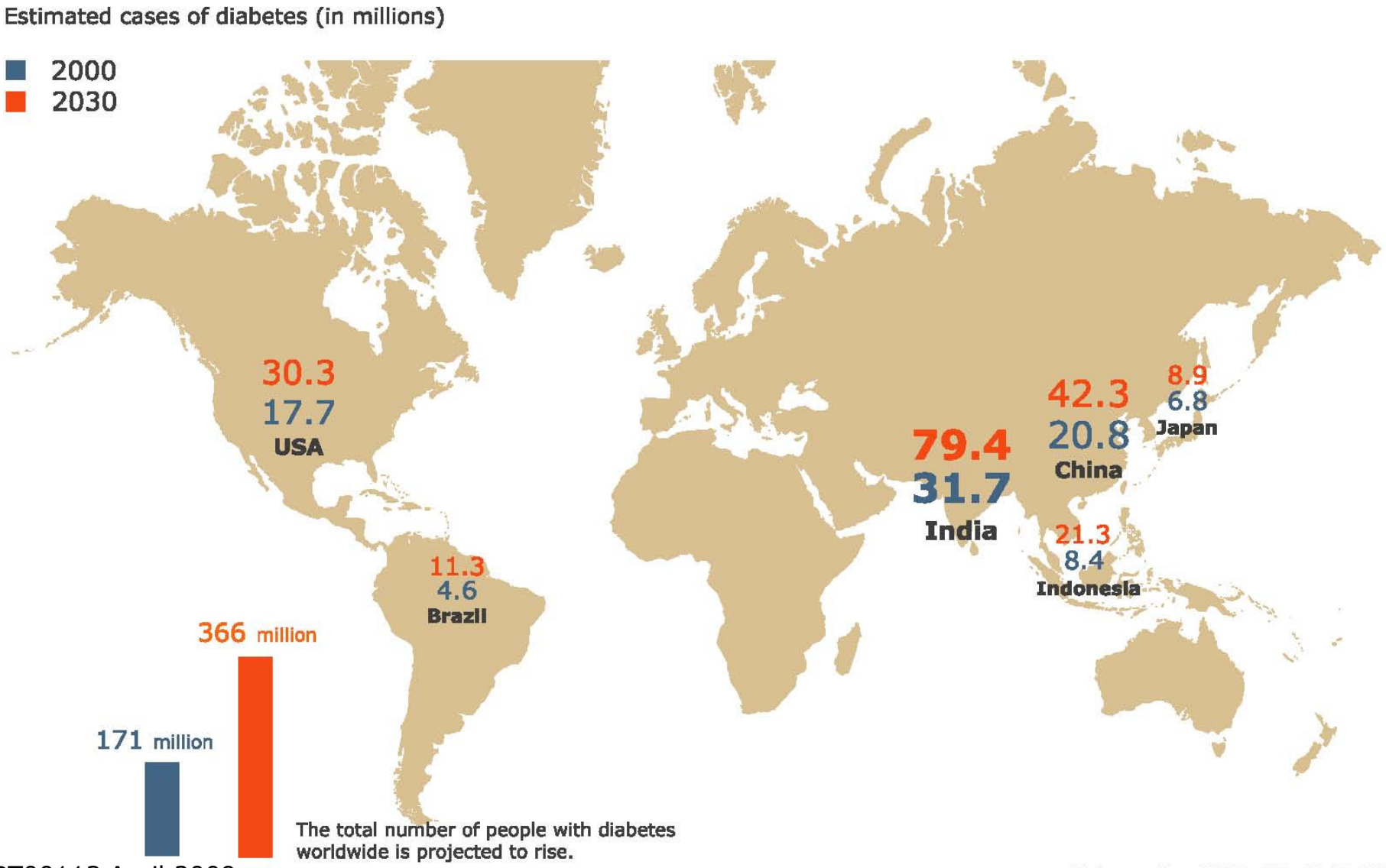
Diabetes: prevalence



In the U.K. 2.3 million people are known to have diabetes with possibly up to a million more undiagnosed

It is projected that by 2025, the number of the worldwide adult population affected by diabetes mellitus will increase by 122%

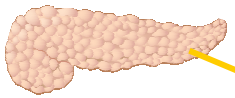
Global prevalence of diabetes: estimates for the year 2000 and projections for 2030

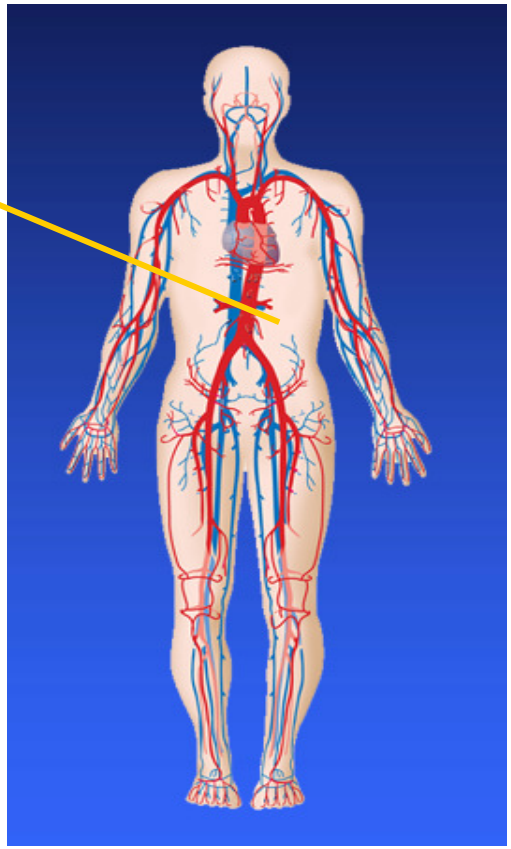


Diabetes Care 2004; 27: 1047-105

Type 1 diabetes

Hyperglycaemia secondary to failure of insulin production

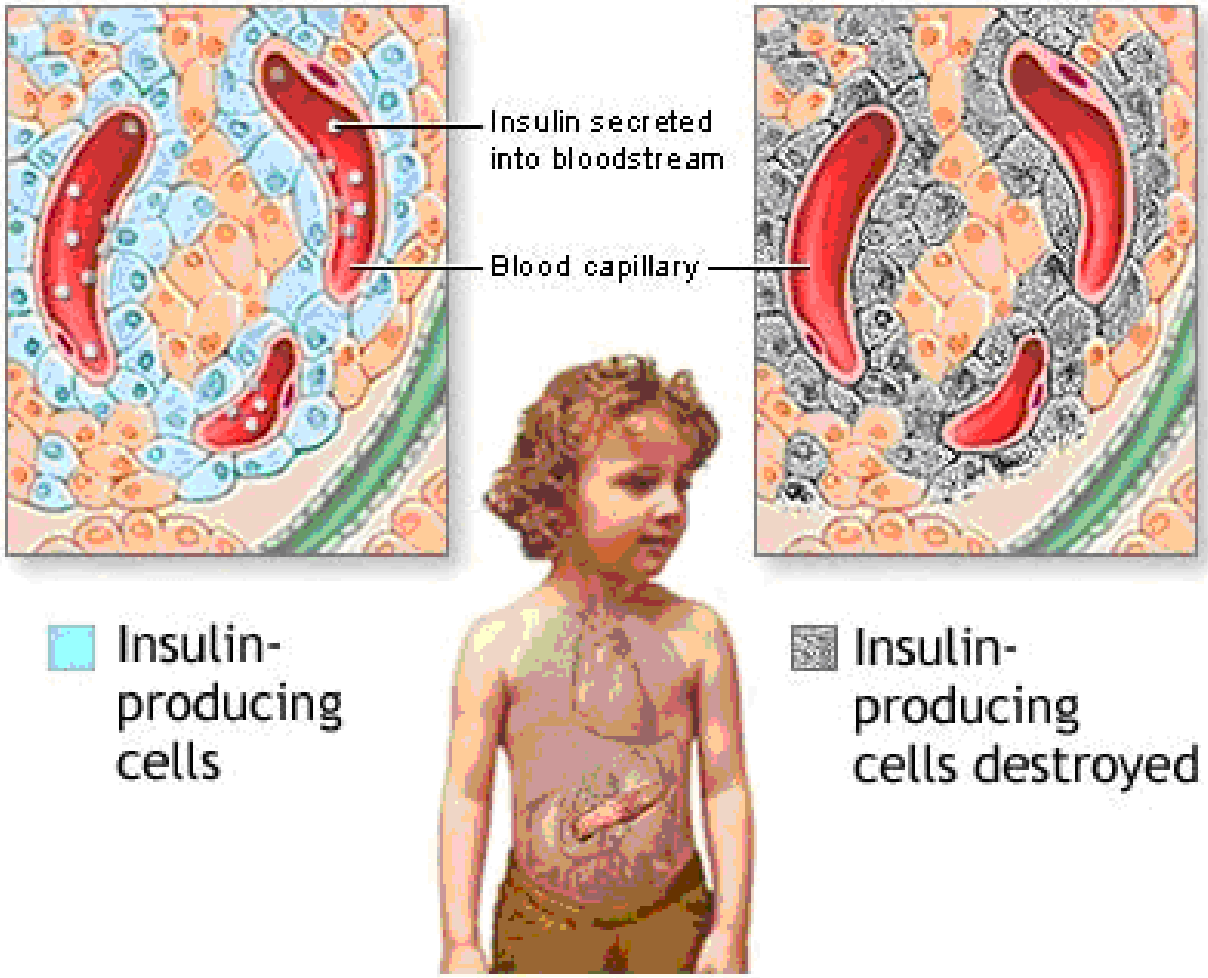




Pancreatic failure
Impaired insulin secretion by pancreatic β-cells

Increased glucagon secretion by α-cells

Type 1 diabetes



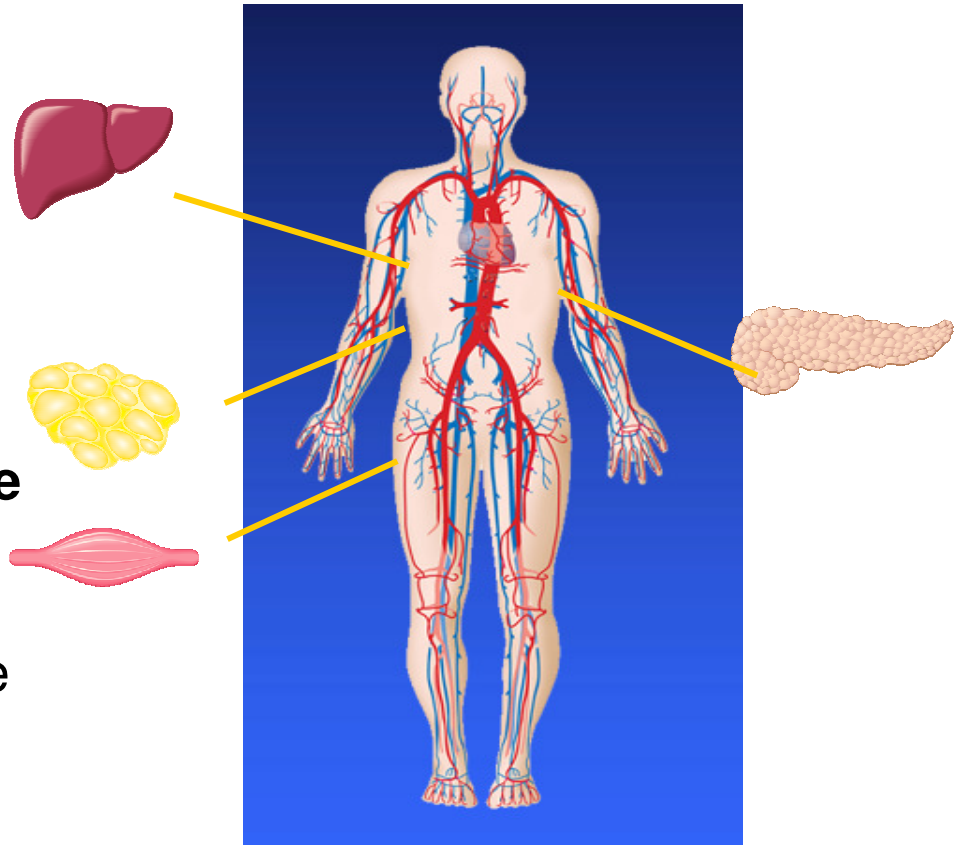
Autoimmune destruction of the pancreatic beta cells

Type 2 diabetes

Hyperglycaemia secondary to peripheral insulin resistance associated with a cluster of cardiovascular risk factors

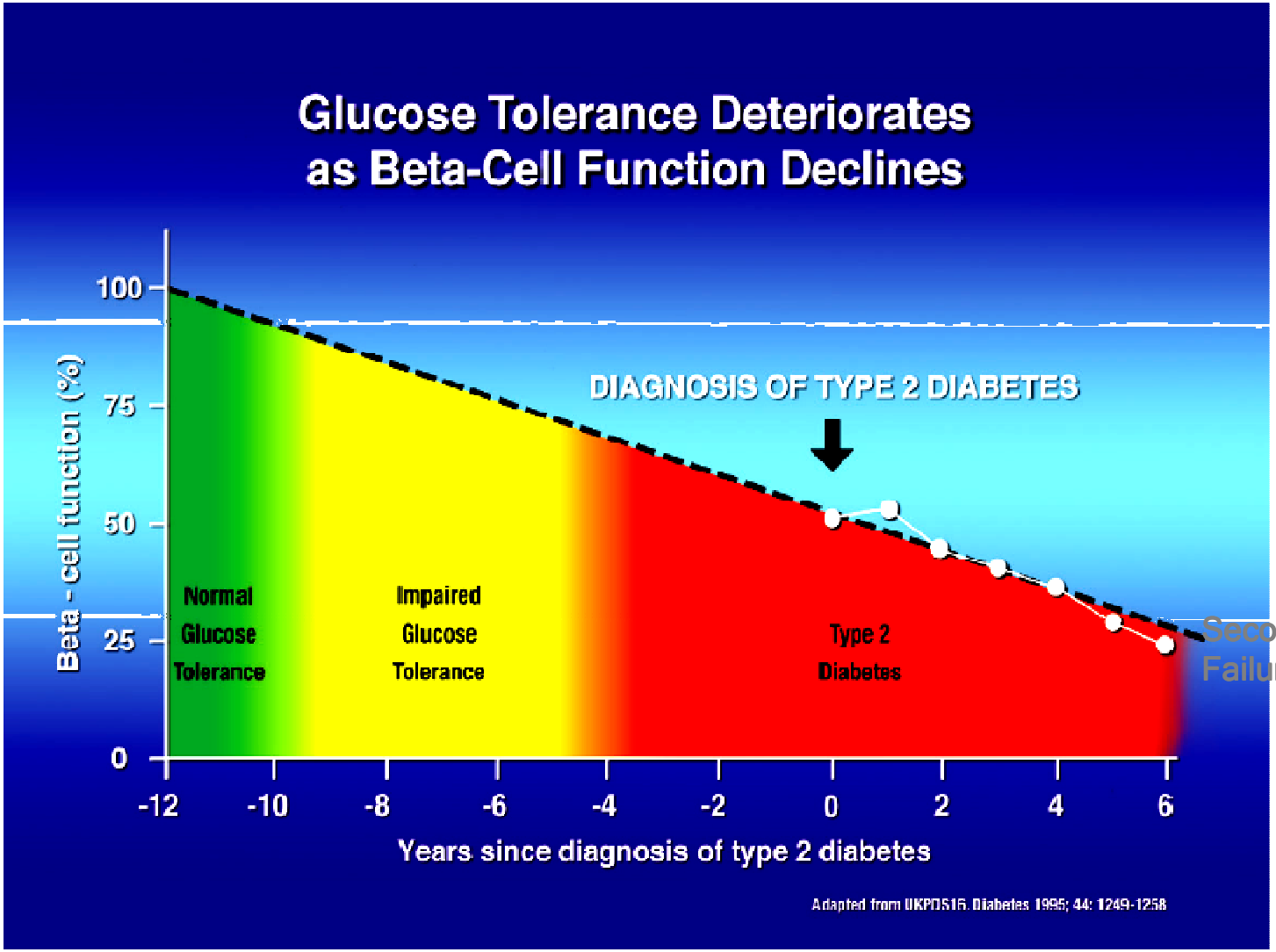
Liver
↑ hepatic glucose production

Muscle and adipose tissue
↓ Insulin-dependent glucose uptake by adipose tissue and muscle



Pancreas
Impaired insulin secretion by pancreatic β-cells
Increased glucagon secretion by α-cells

Decline in β cell function over time



What is the problem?

Insulin resistance

Elevated blood glucose

Pro-thrombotic profile

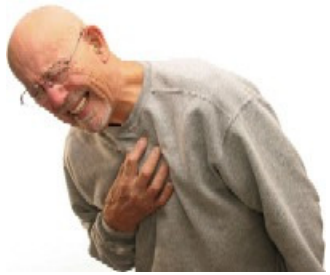
High triglycerides and low 'good Cholesterol'

High blood pressure

Inflammatory profile

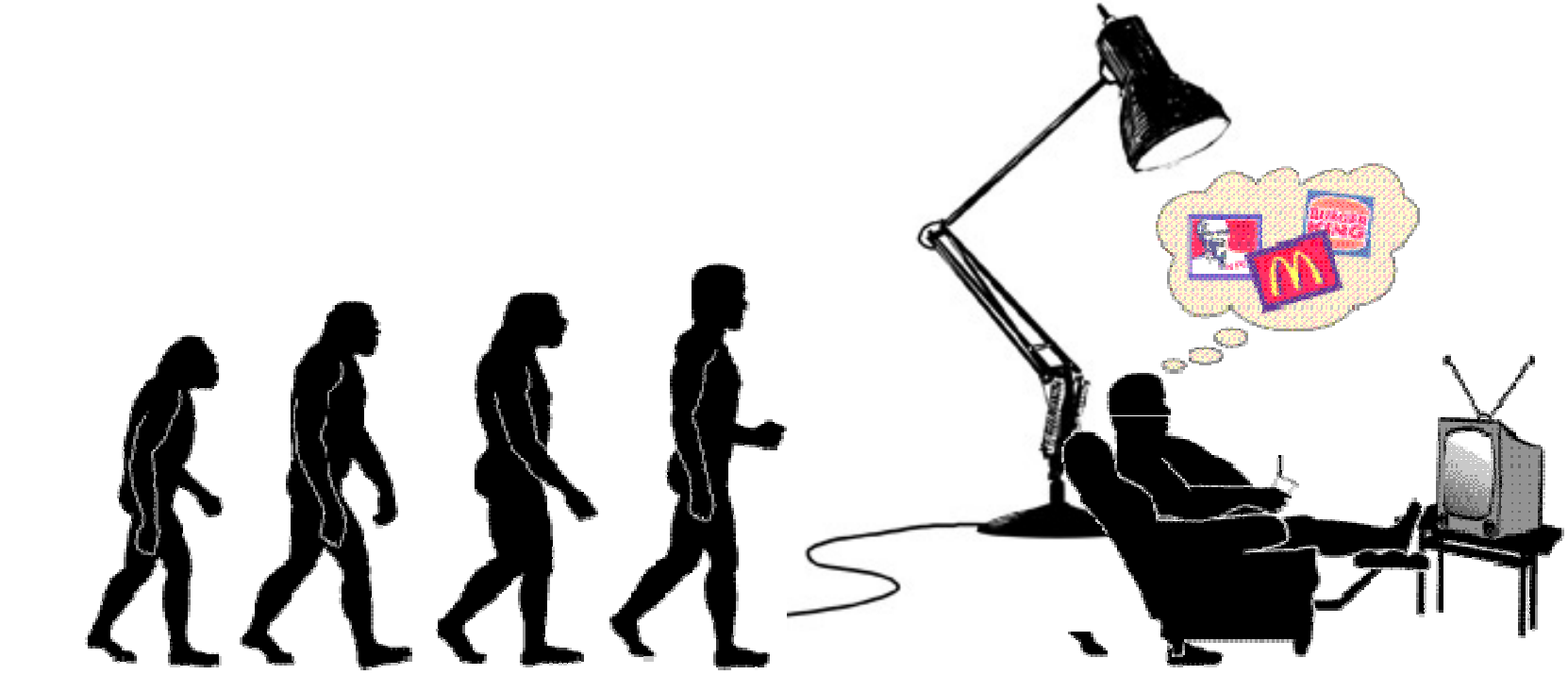
Metabolic syndrome

Type 2 Diabetes



Cardiovascular disease

The evolution of mankind



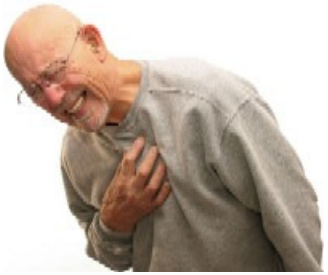
2.5 mn years **50 years**

Understanding the cause of type 2 diabetes

Genetic factors

Environmental / Lifestyle factors

Role of the Adipocyte



Thrombosis

Impaired fibrinolysis

PAI-1

Hypertension

Vasoconstriction

RAS

Cytokines
(IL-6, TNF)

CRP

Pro-inflammatory

Complement

Adiponectin

Insulin sensitivity
glucose tolerance

Diabetes

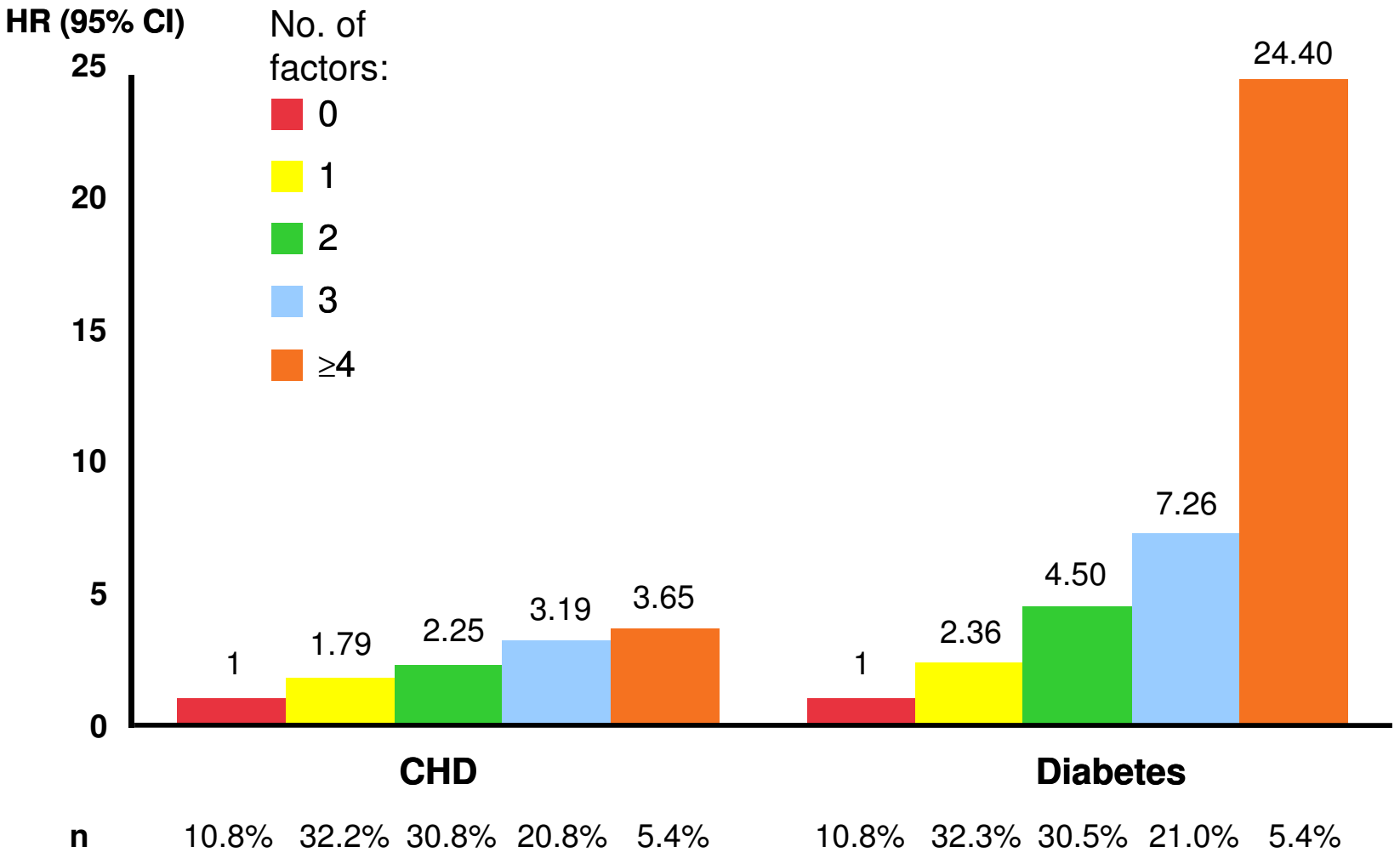
Leptin

Triglycerides
Cholesterol

Feeding behaviour
energy expenditure

Vascular disease

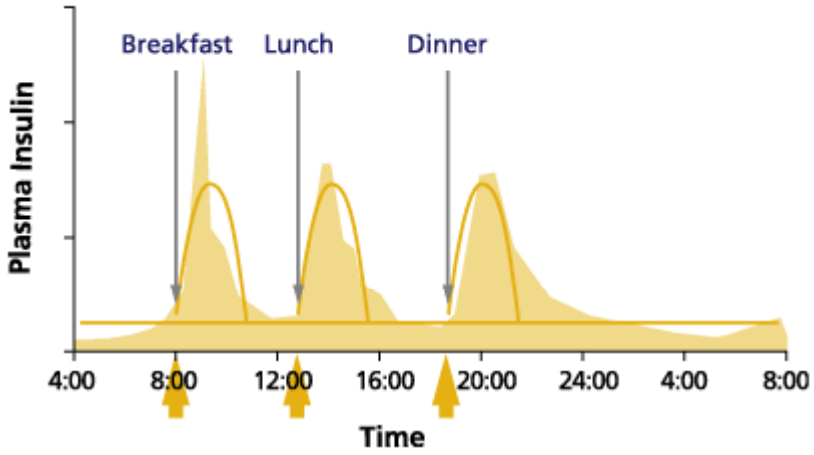
Risk for coronary heart disease and diabetes based on number of metabolic syndrome criteria



Sattar N et al. *Circulation.* 2003;108:414-419.


Type 1
basics

Management of Type 1 diabetes



Condition of insulin deficiency

Insulin normally produced in response to carbohydrate in food

Some background insulin produced

Treatment aims to replace with exogenous insulin to mimic normal insulin secretion

Management of Type 1 diabetes

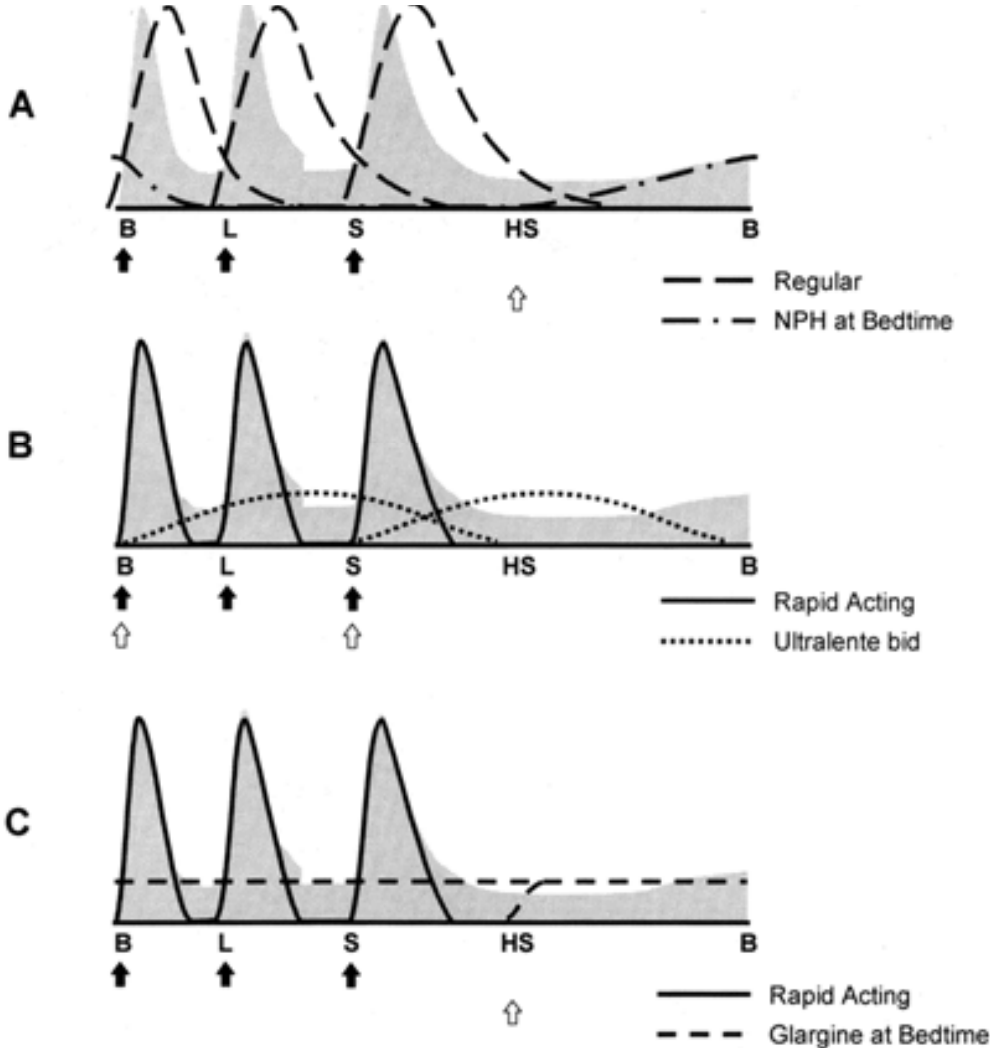
There are four main types of insulin:

Rapid-acting modern (analogue) insulins

Short-acting (human) insulin (also known as soluble insulin)

Long-acting modern (analogue) insulins

Long-acting (human) insulin (also known as intermediate-acting insulin)



Insulin

There are three types of injection devices:

Pre-filled insulin pens (disposable)

Durable insulin pens (re-usable)

Bottle of insulin (vial), syringe and needle

Continuous subcutaneous insulin infusion (CSII)

An open loop insulin delivery system

A rate adjustable portable pump infuses insulin into subcutaneous tissue

Basal insulin is constantly infused

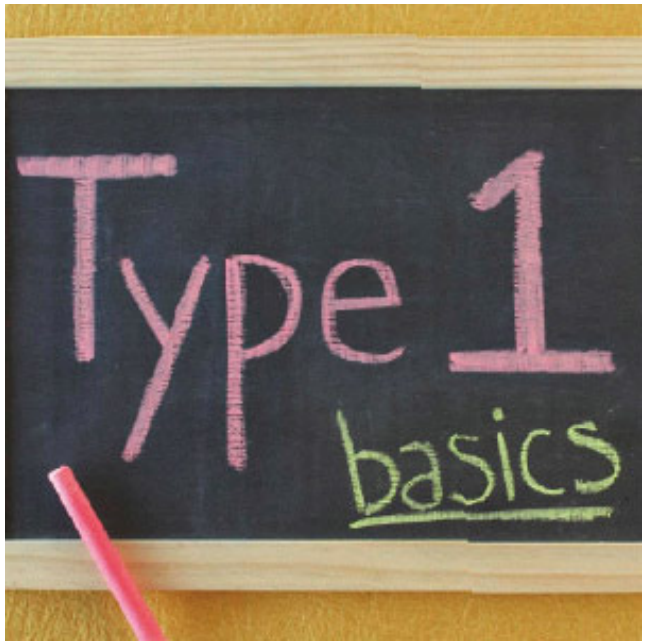
Boluses given with meals

More closely mimics normal insulin secretory patterns

Associated with fewer hypoglycaemic events

Inhaled insulin

What is type 1 diabetes? a summary



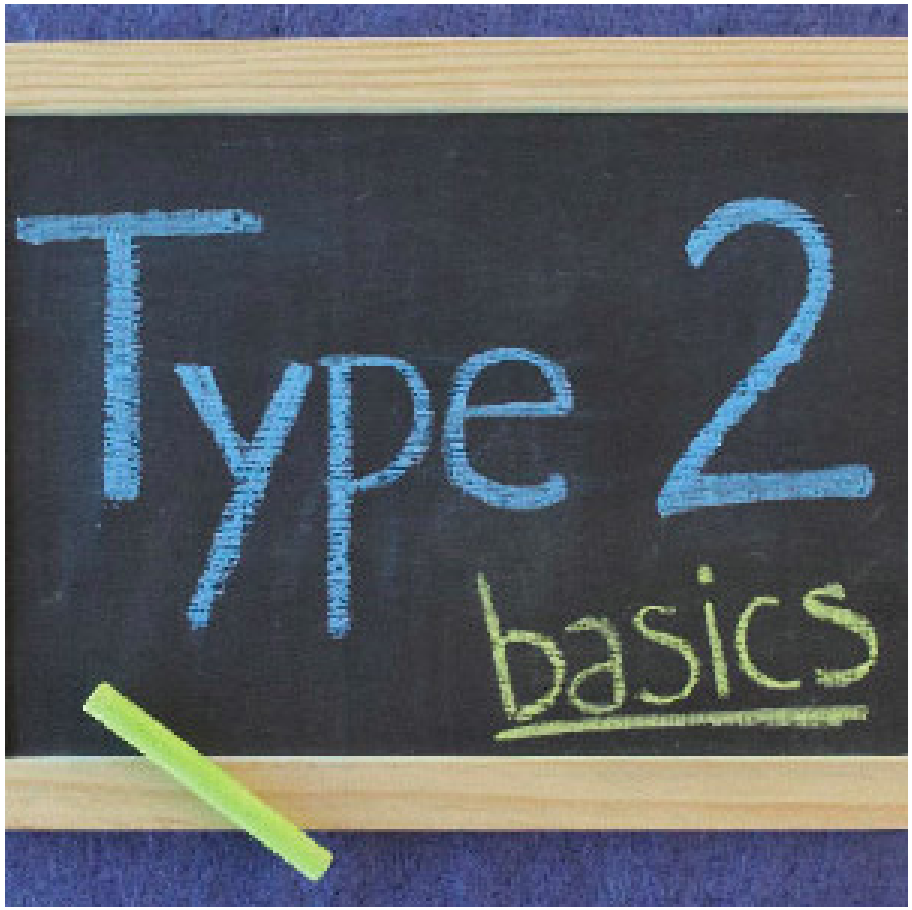
It's caused by a lack of insulin in the body
Which prevents transport of sugar to the body's cells and leads to build-up of sugar in the blood

Untreated diabetes can make you feel tired, thirsty and urinate more frequently

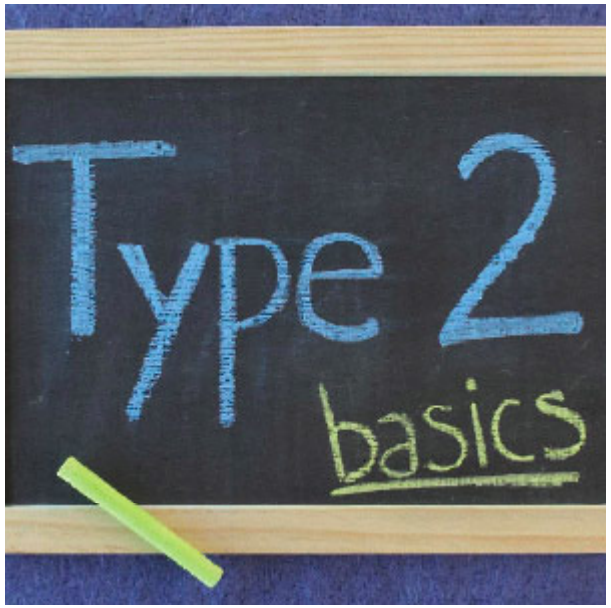
Untreated diabetes can lead to ketoacidosis

Treatment for diabetes means insulin injections to keep blood sugar levels close to normal

Keeping blood sugar levels low helps prevent long term health complications.


Type 2
basics

What is type 2 diabetes? a summary



It is caused by the body making too little or no insulin and reduced sensitivity to the effect of insulin

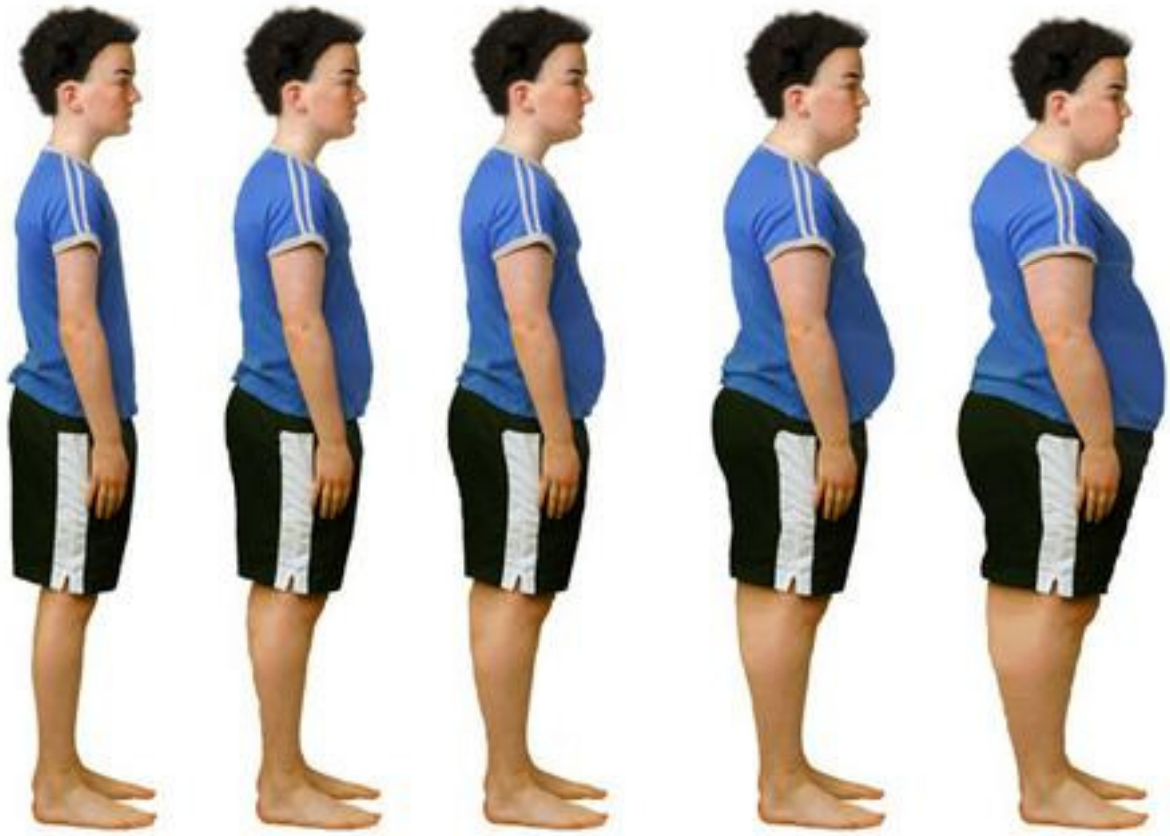
Lack of insulin leads to build-up of sugar in the blood

Treatment for diabetes can be:

- Diet and exercise
- Medication to increase insulin production or insulin sensitivity
- Insulin or GLP-1 injections

Keeping blood sugar levels low helps prevent long term health complications

Predominantly caused by obesity therefore key aim of treatment is weight loss



Making the right food choices and losing weight

Dietary advice given to encourage weight loss

Low fat, low sugar, high fibre diet.

Less ‘supersizing’ of portions

Consider weight loss therapies

- Orlisat
- Bariatric surgery

Exercise

Strongly encouraged

To aid weight loss

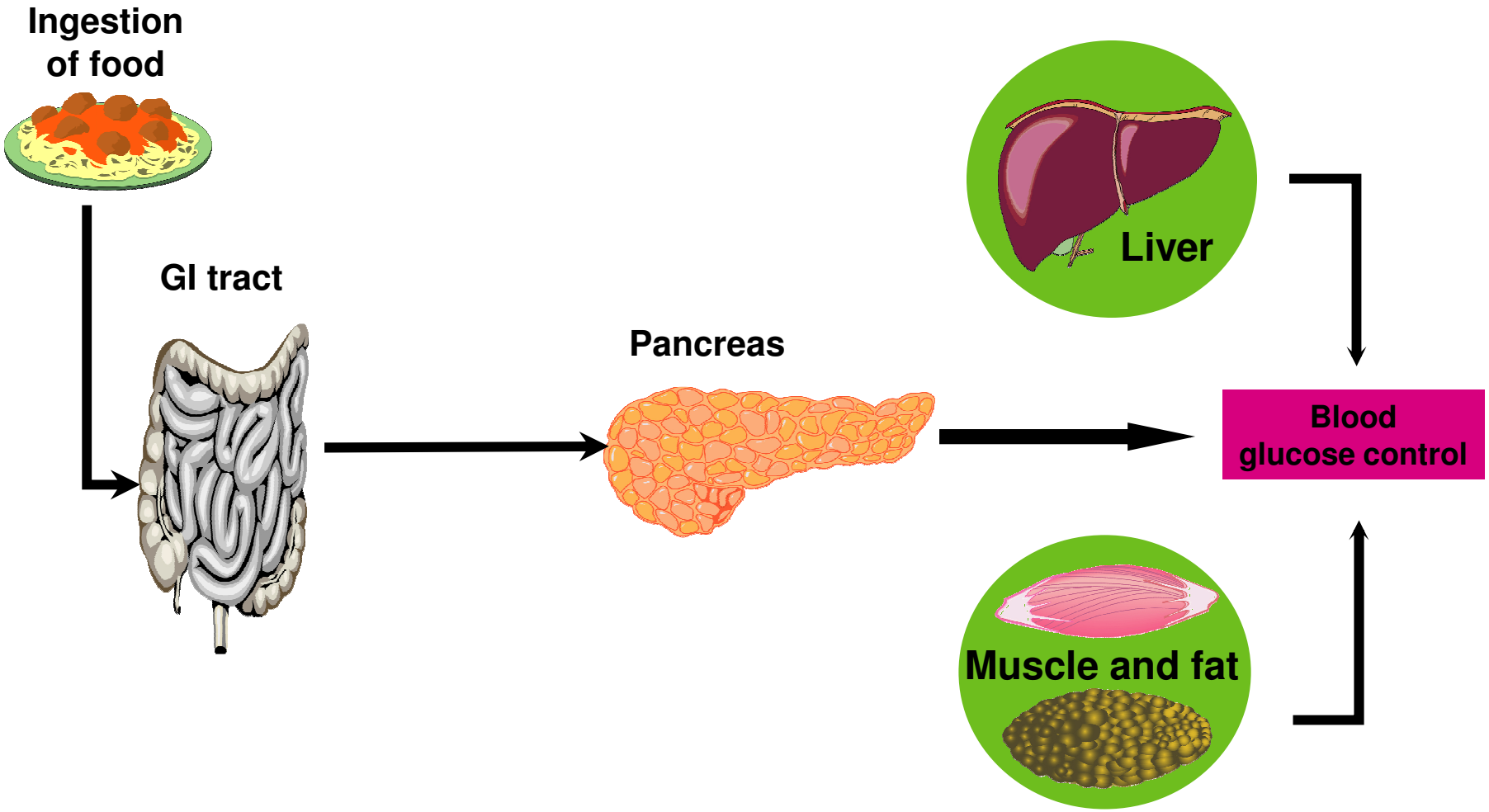
To improve glycaemic control

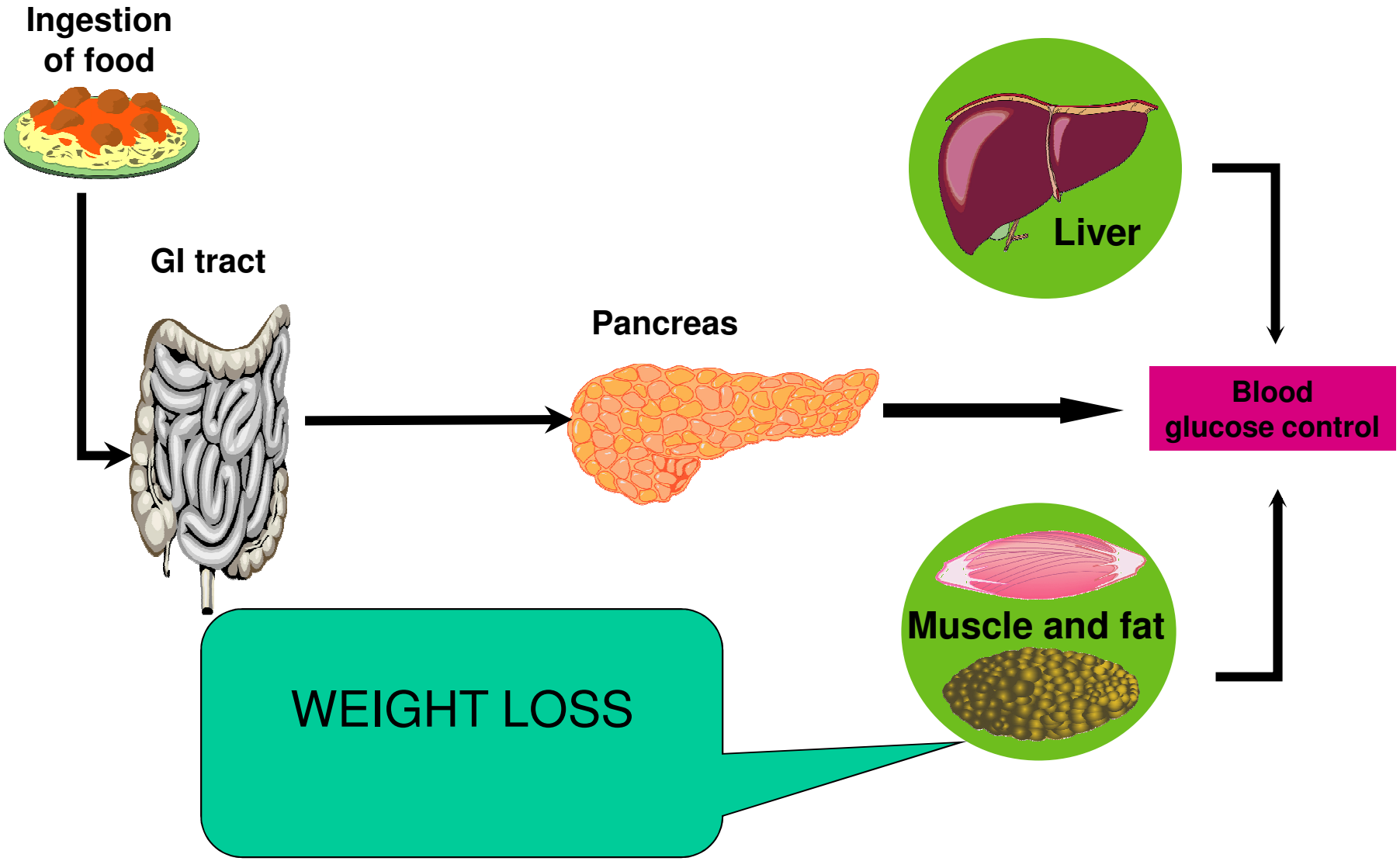
To improve cardiovascular fitness

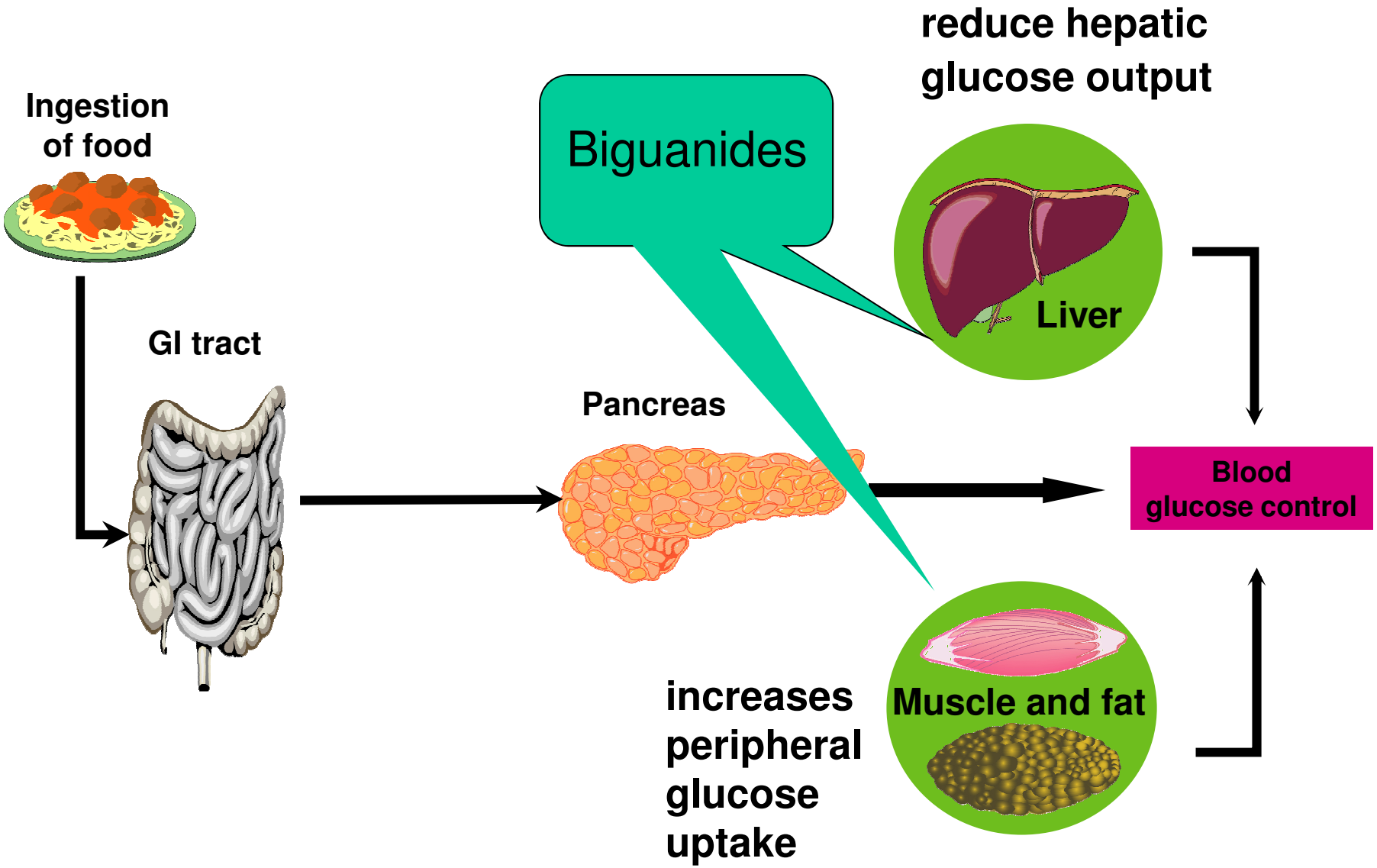
Oral medications

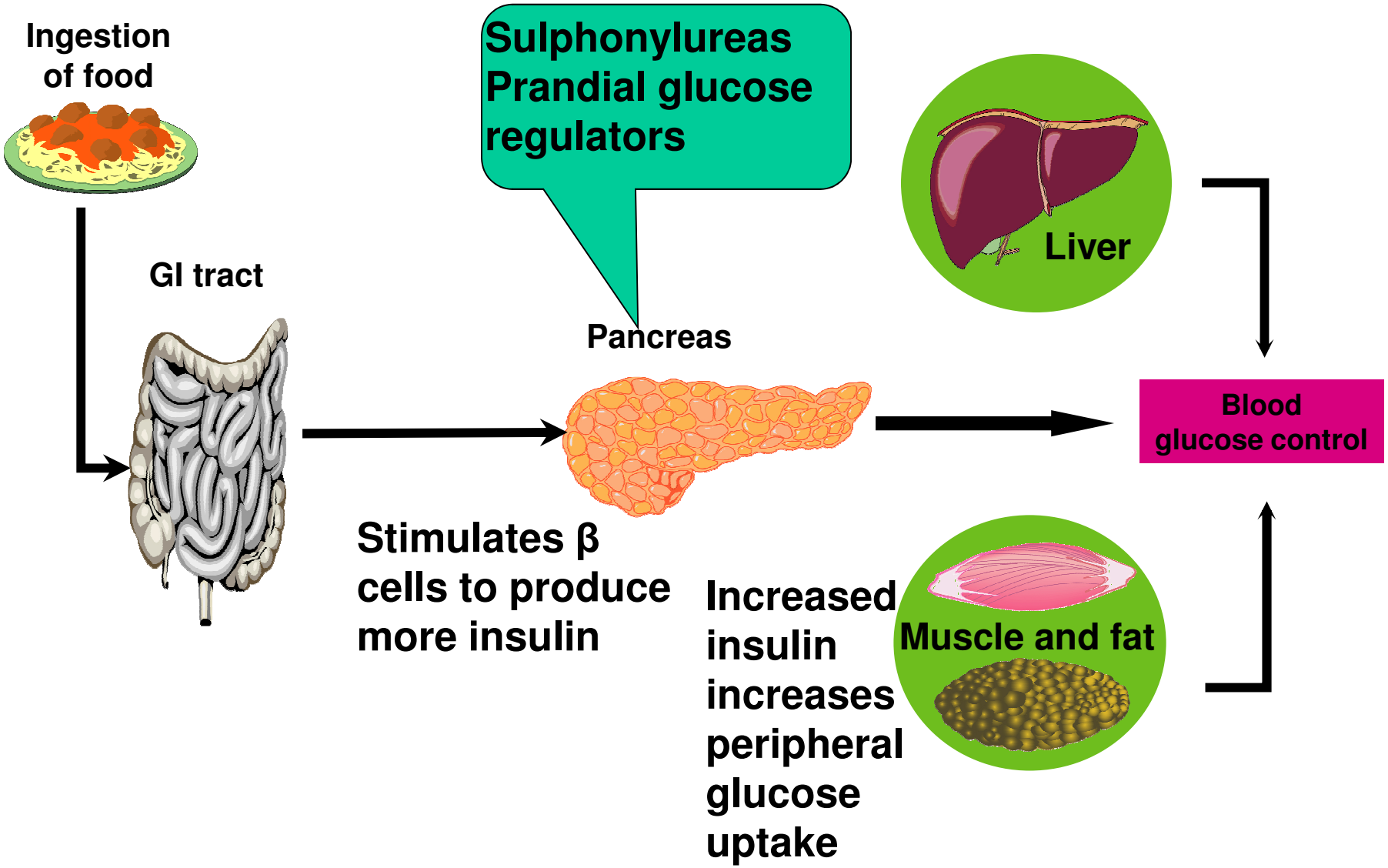
Types of oral medications:

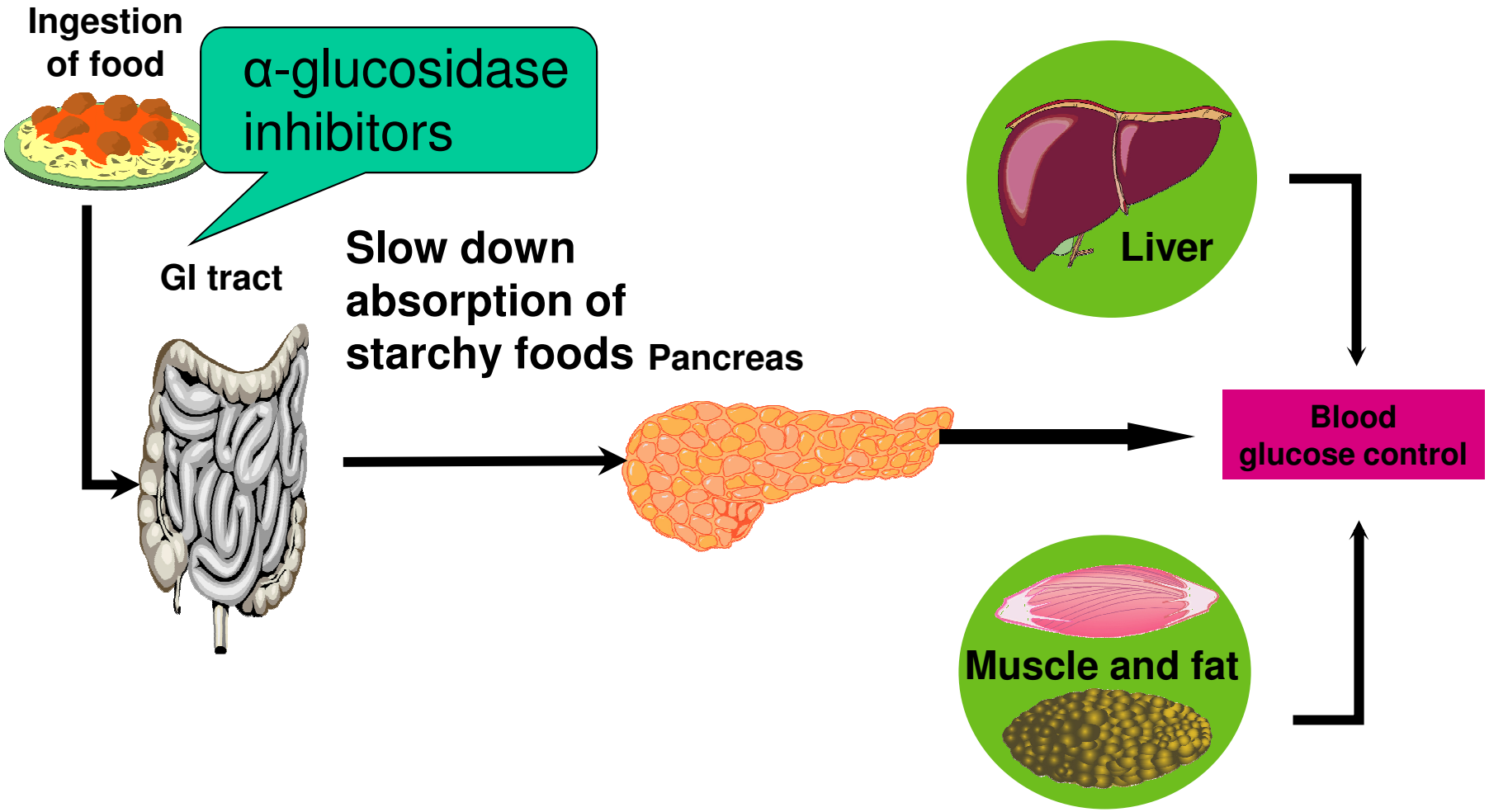
biguanides
sulphonylureas (SUs)
insulin sensitisers (or thiazolidinediones)
meglitinide analogues
alpha-glucosidase inhibitors
prandial glucose regulators
DPP4 inhibitors (gliptins)

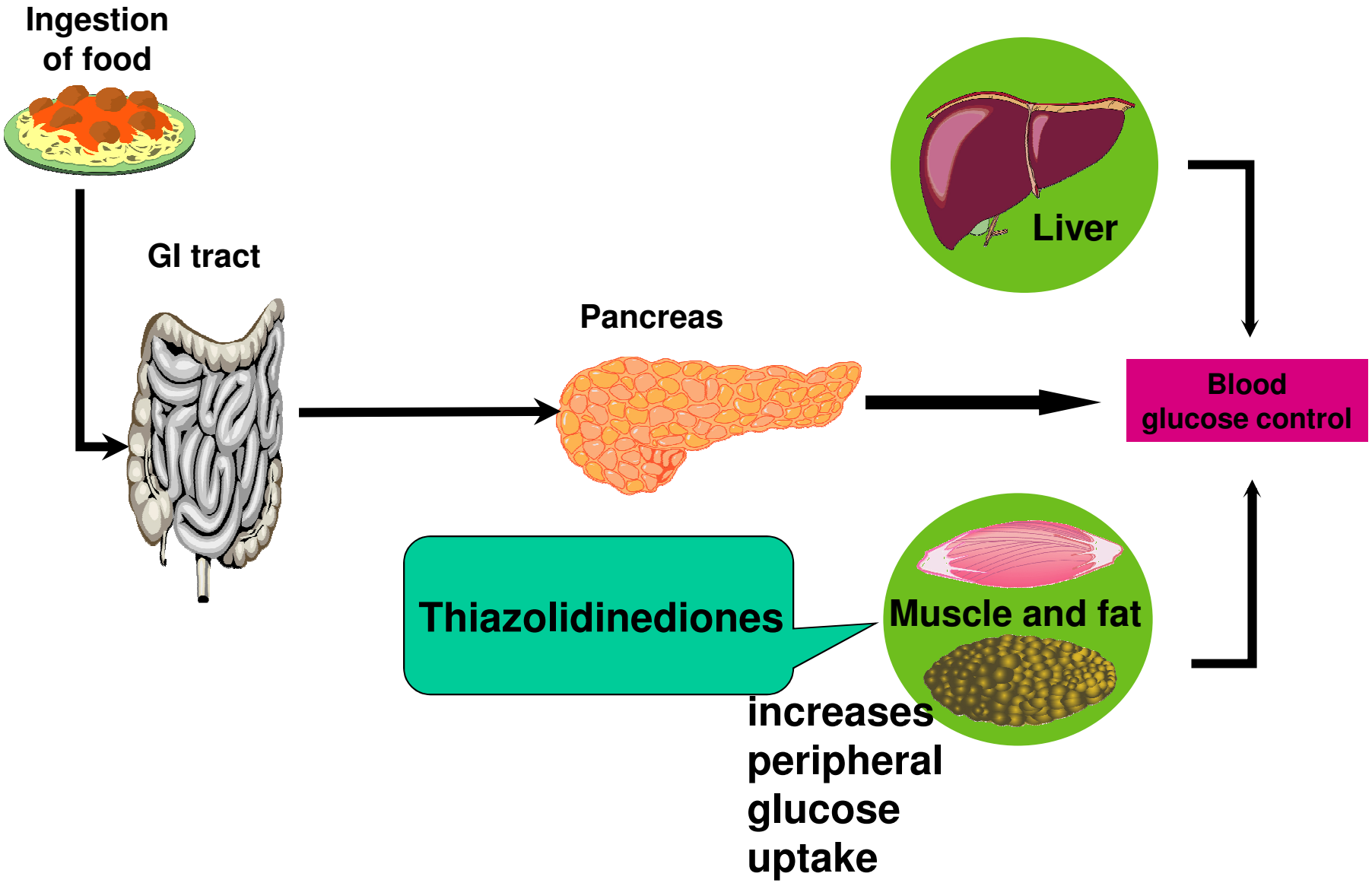

Ingestion of food
GI tract
Pancreas
Liver
Blood glucose control
Muscle and fat

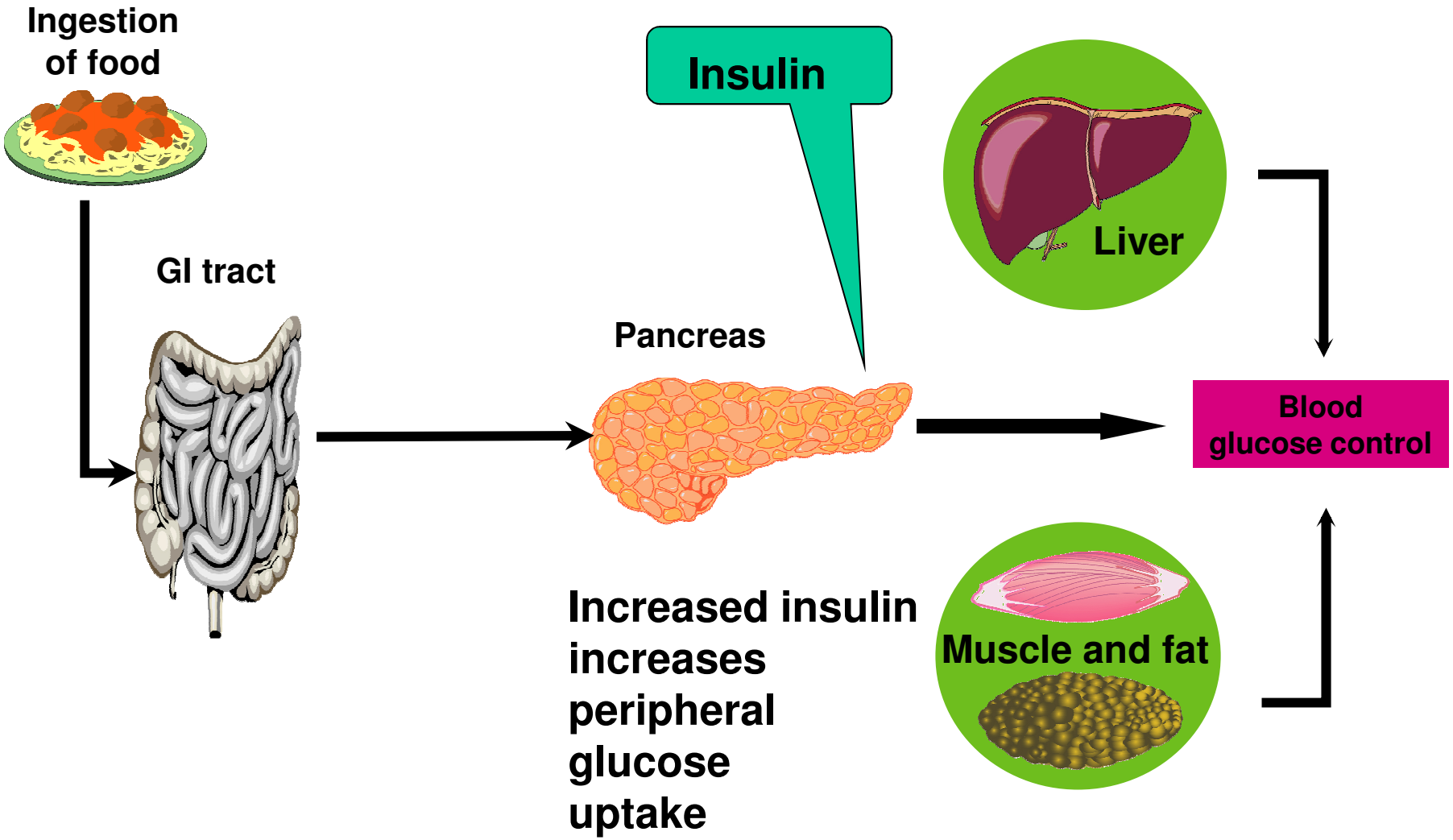

Ingestion of food
GI tract
Pancreas
Liver
Blood glucose control
Muscle and fat
WEIGHT LOSS


Ingestion of food
GI tract
Pancreas
Biguanides
reduce hepatic glucose output
Liver
Blood glucose control
Muscle and fat
increases peripheral glucose uptake


Ingestion of food
Sulphonylureas
Prandial glucose regulators
Liver
GI tract
Pancreas
Blood glucose control
Stimulates β cells to produce more insulin
Increased insulin increases peripheral glucose uptake
Muscle and fat


Ingestion of food
α-glucosidase inhibitors
GI tract
Slow down absorption of starchy foods
Pancreas
Liver
Blood glucose control
Muscle and fat


Ingestion of food
GI tract
Pancreas
Liver
Blood glucose control
Thiazolidinediones
Muscle and fat
increases peripheral glucose uptake


Ingestion of food
GI tract
Insulin
Pancreas
Liver
Blood glucose control
Muscle and fat
Increased insulin increases peripheral glucose uptake

Current treatment options for type 2 diabetes & their effect on β-cells, and weight

Increased β-cell workload (Insulin Resistance)

Biguanides: ↓ hepatic glucose output ↔ weight

TZDs: ↑ insulin sensitivity ↑ weight

Diminished β-cell response (Insulin Deficiency)

SUs: ↑ insulin secretion ↑ weight

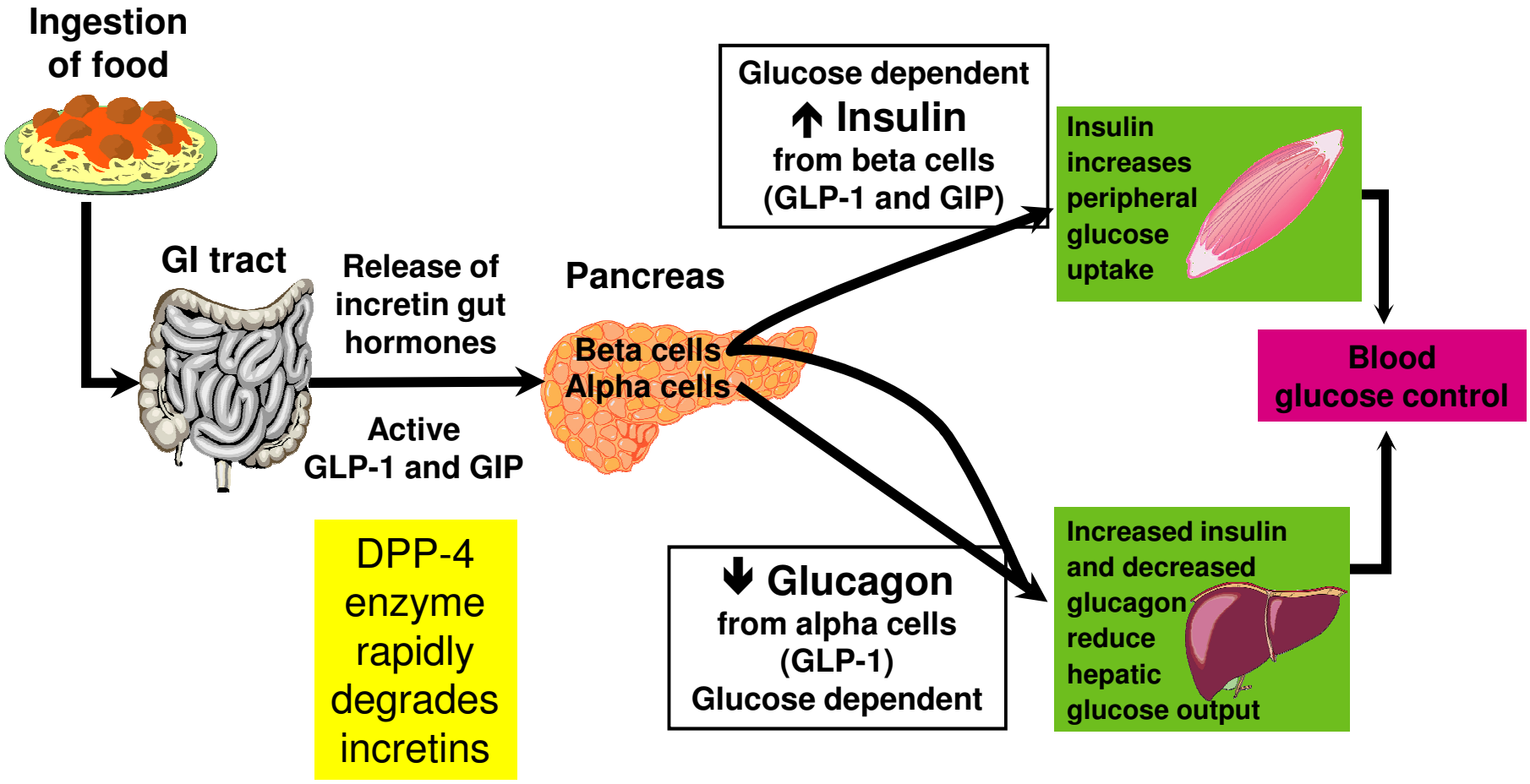
Meglitinides: ↑ insulin secretion ↔ weight

Insulin: exogenous replacement ↑ weight

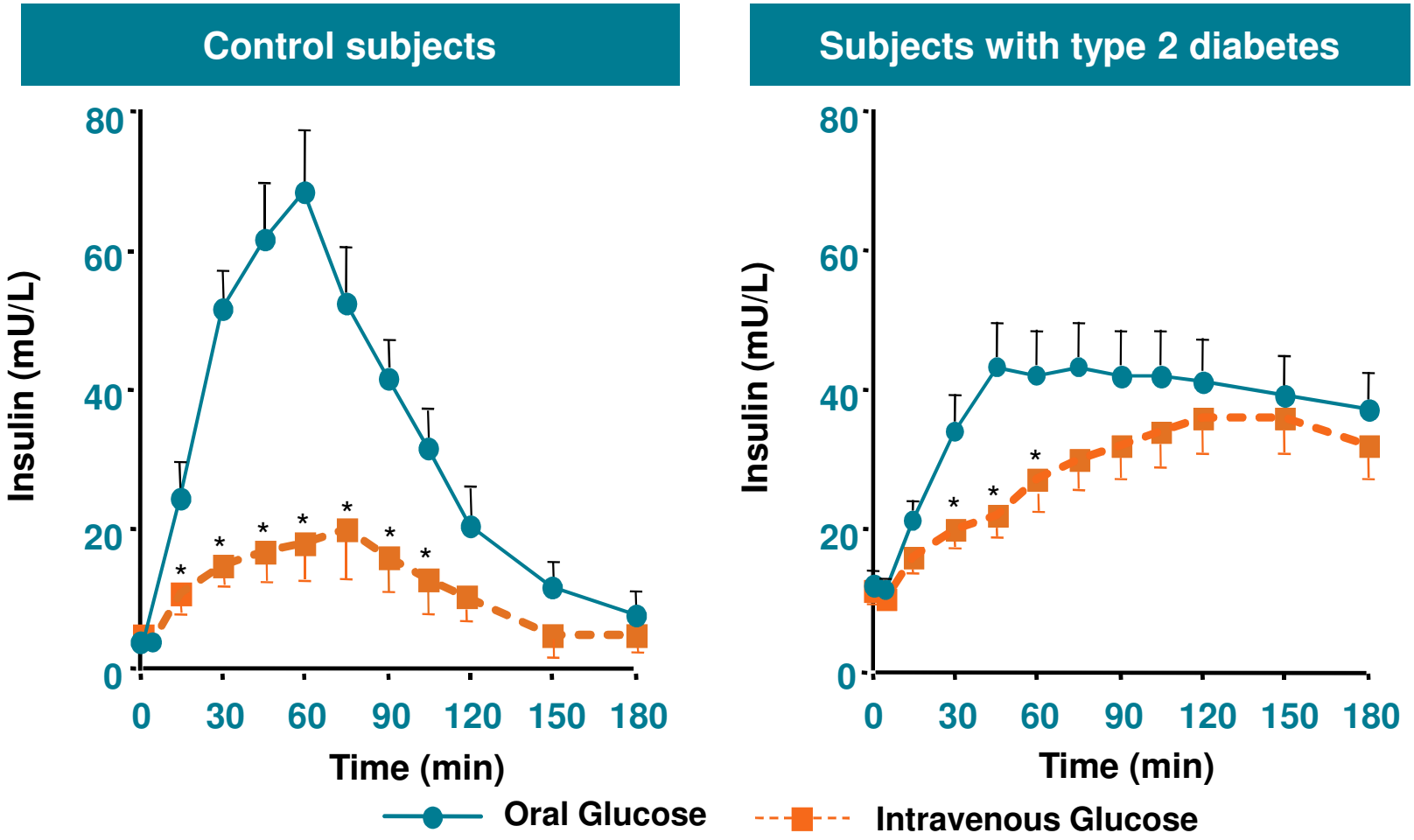
Acarbose: Slow the absorption of dietary starches ↔ weight

Newer agents

Incretin pathway



The Incretin effect is reduced in subjects with type 2 diabetes

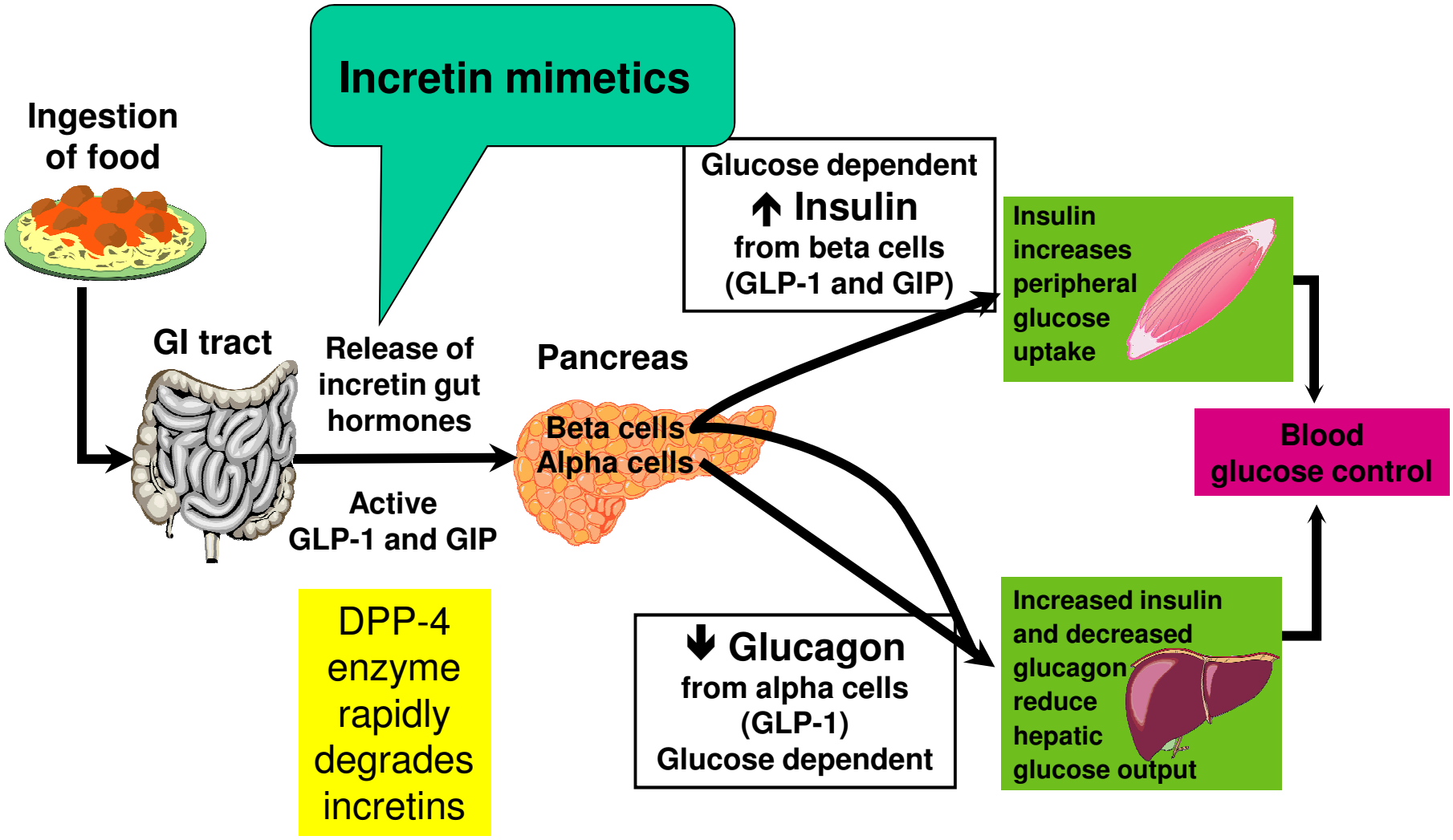


The Incretin Effect accounts for ~ 60% of total Insulin release following a meal

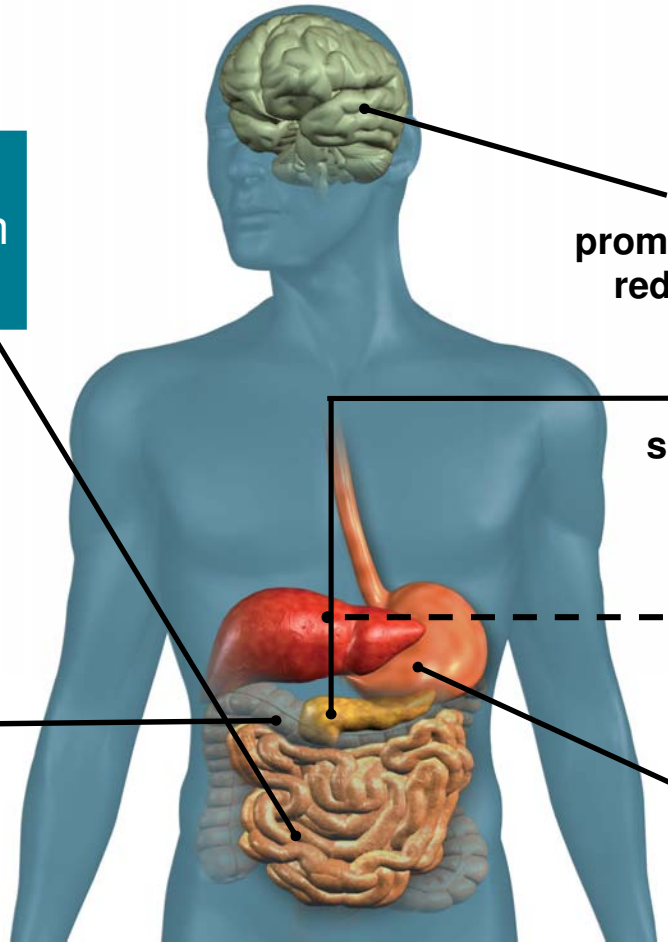
GLP-1 analogues

Exenatide

Liraglutide


Incretin mimetics
Ingestion of food
GI tract
Release of incretin gut hormones
Active GLP-1 and GIP
Pancreas
Beta cells
Alpha cells
Glucose dependent
↑ Insulin
from beta cells
(GLP-1 and GIP)
Insulin increases peripheral glucose uptake
Blood glucose control
↓ Glucagon
from alpha cells
(GLP-1)
Glucose dependent
Increased insulin and decreased glucagon reduce hepatic glucose output
DPP-4 enzyme rapidly degrades incretins

GLP-1 analogues



GLP-1 secreted upon the ingestion of food

Brain:
promotes satiety and reduces appetite

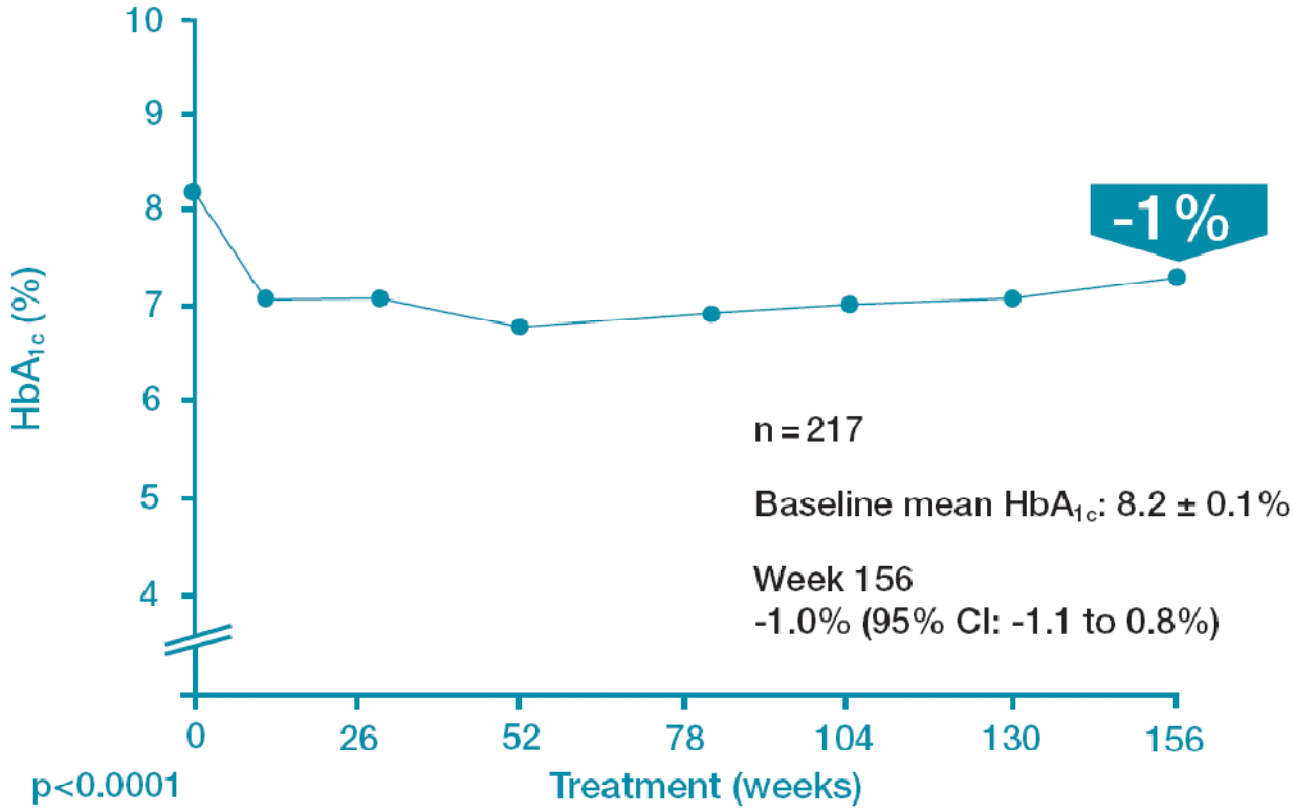
α-cell:
suppresses postprandial glucagon secretion

Liver:
reduces hepatic glucose output

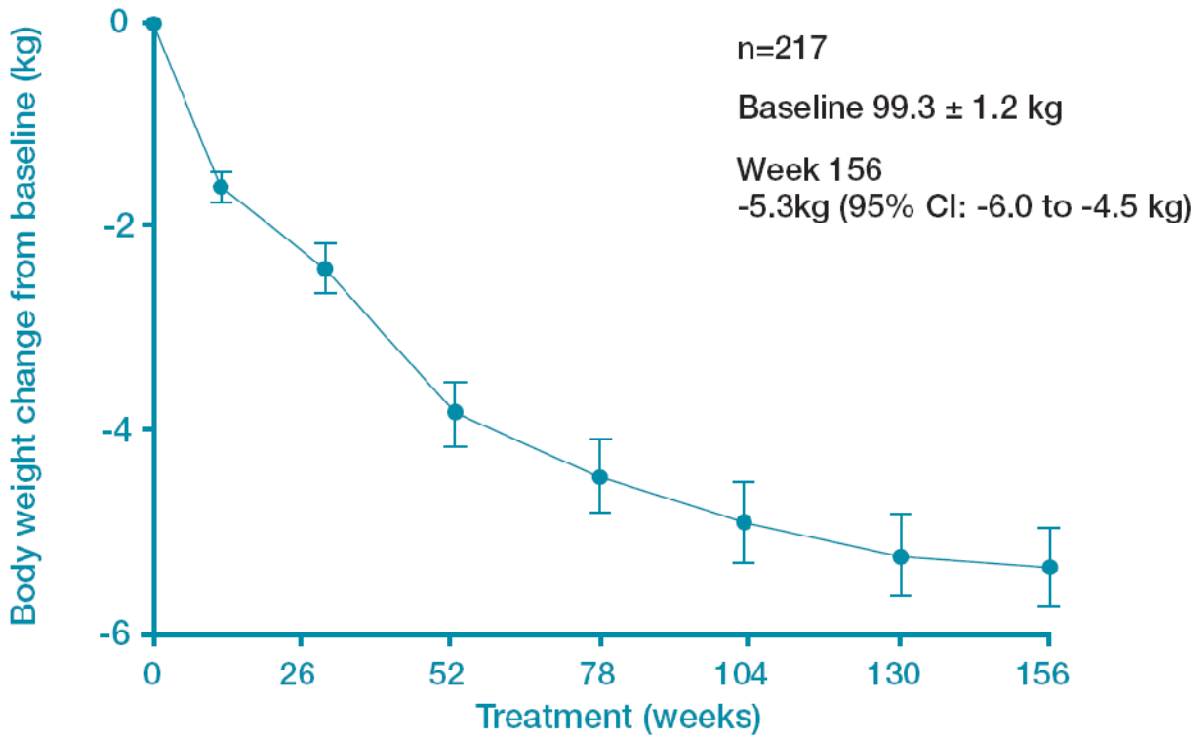
β-cell:
enhances glucose-dependent insulin secretion in the pancreas

Stomach:
slows the rate of gastric emptying

At 3 years exenatide 10µg BD provided sustained reductions in HbA_{1c} in the completer population



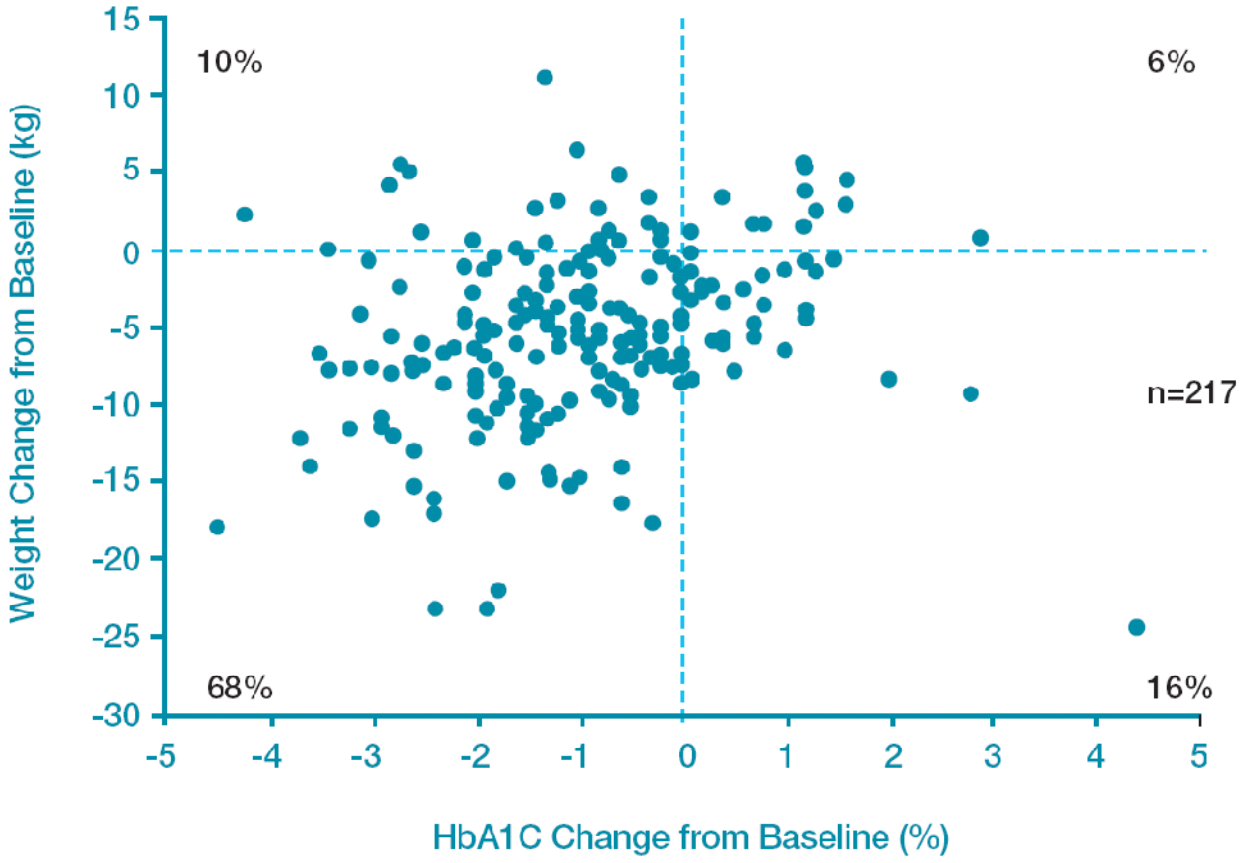
…and progressive weight loss

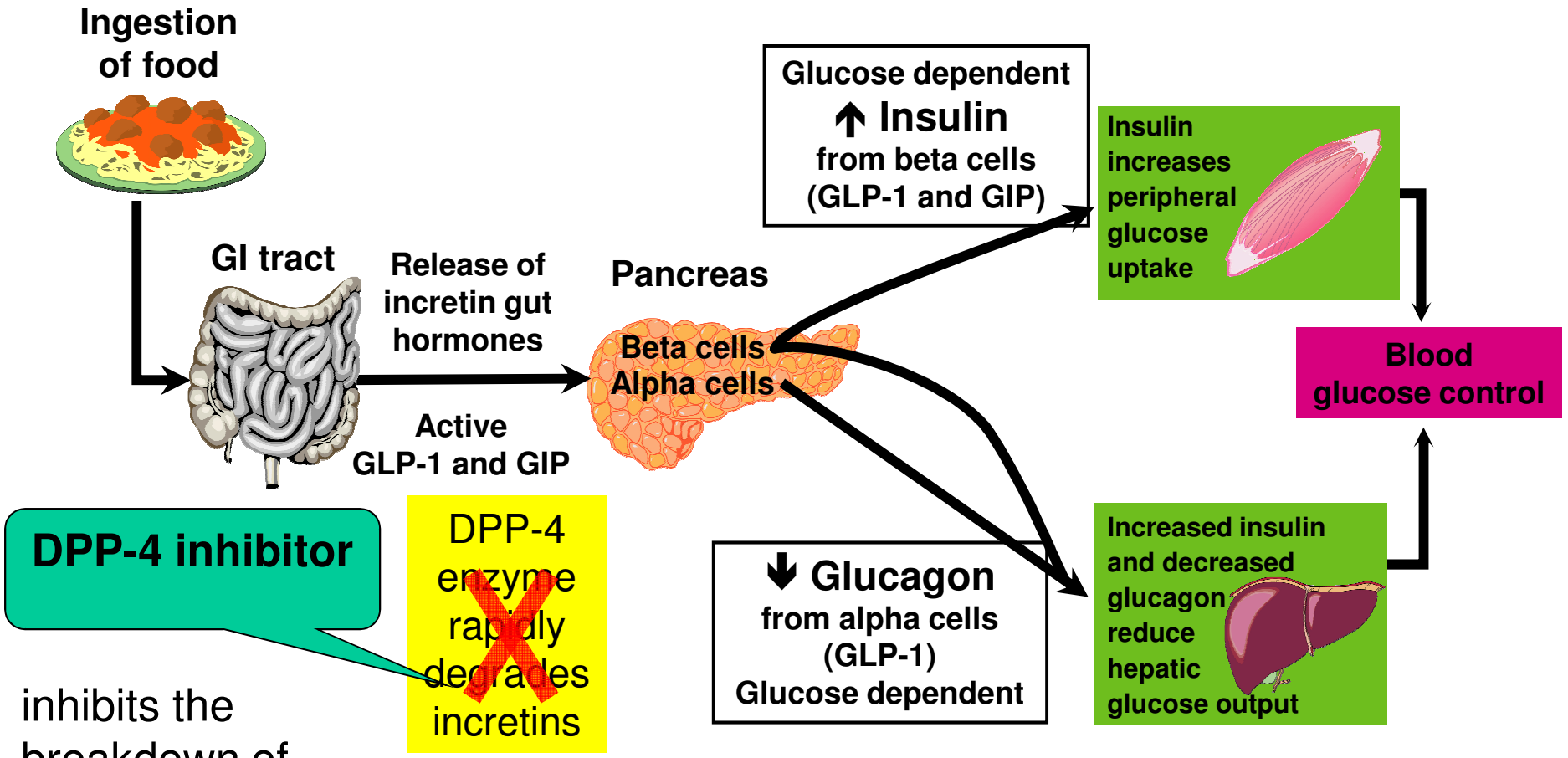


84% of exenatide patients lost weight over 3 years of treatment

50% of patients lost at least 5% of baseline body weight

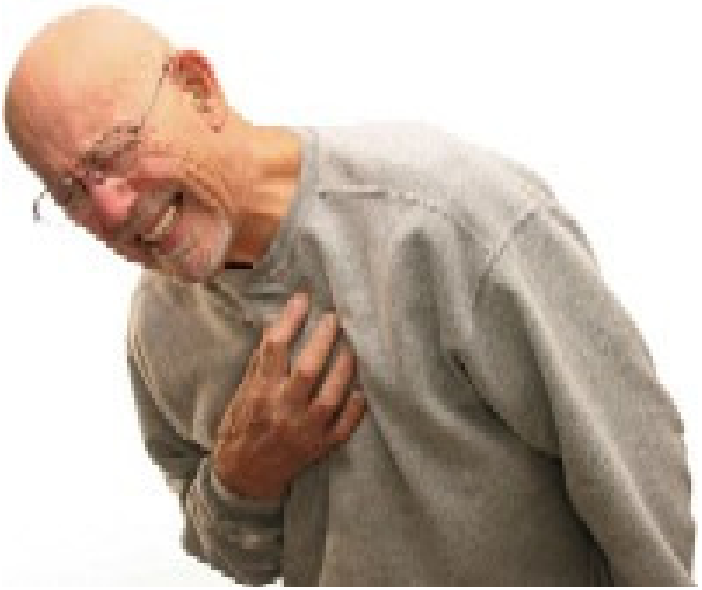
The majority of exenatide patients had reduced HbA_{1c} and weight





inhibits the breakdown of incretins and thereby increases active incretin levels

Main cause of death in Type 2 diabetes is cardiovascular disease



Drugs to reduce cardiovascular risk are a major priority for diabetes management

Dyslipidaemia – statins

Hypertension – ACE inhibitors and all antihypertensive agents

Aspirin

Why we need better preparation for pregnancy in diabetic women

Diabetes in pregnancy is associated with risks to the woman and developing fetus

Miscarriage, pre-eclampsia and pre term labour are more common in women with diabetes

Diabetic retinopathy can worsen rapidly in pregnancy

Stillbirth, congenital malformations, macrosomia, birth injury, perinatal mortality and postnatal adaptation problems are more common in babies born to women with diabetes

Baby at increased risk of developing obesity and diabetes

Most of the damage is done very early
(first 6-7 weeks of pregnancy)

CEMACH - Diabetes
Confidential Enquiry into Maternal and Child Health

CEMACH 2005

Audit between 2002-2003 of 3,808 diabetic pregnancies across UK

CEMACH 2007

National Enquiry into 521 diabetic pregnancies across UK

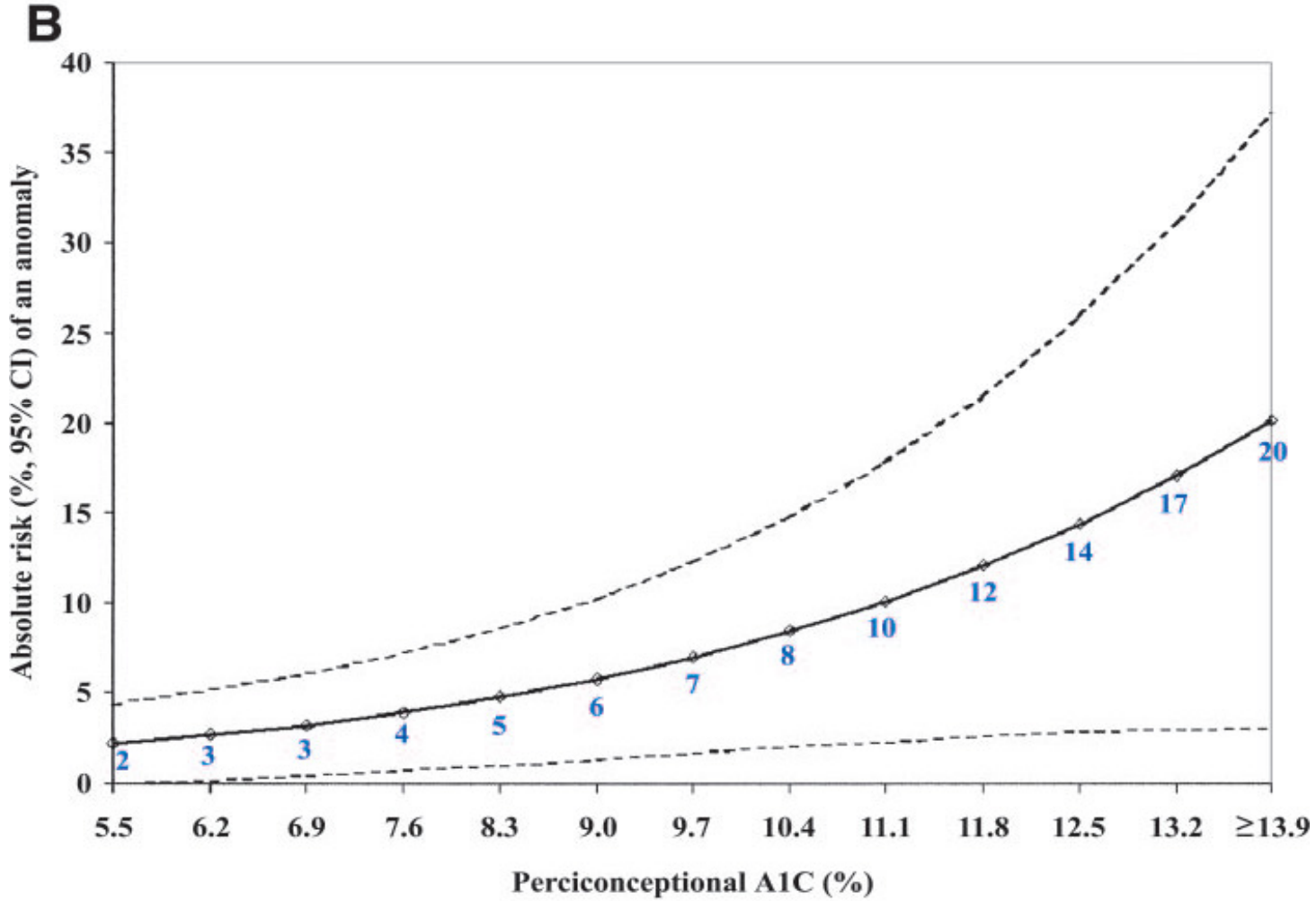
CEMACH – Diabetes Key Findings

- Major congenital malformations increased 2 fold
- Stillbirth increased 4 fold
- Perinatal mortality rates increased 4 fold

Pregnancy outcomes were similarly poor in women with Type 2 DM as those with Type 1DM

Poor glycaemic control (HbA1c) at the start of pregnancy was the most significant risk factor for both congenital malformations, and stillbirth

Risk of congenital anomalies depending on peri-conception HbA1c



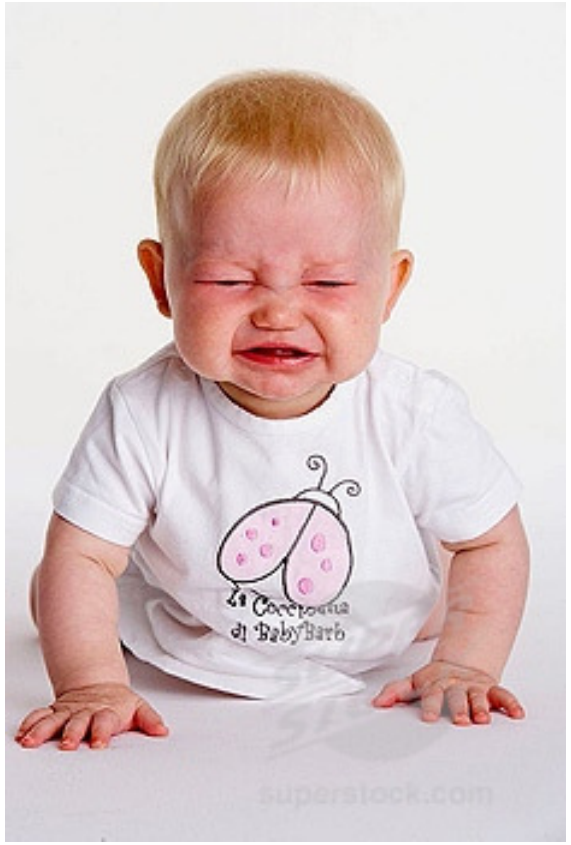
Guerin 2007 Diabetes Care

Periconceptional HbA1c and risk of serious adverse pregnancy outcome in 933 women with Type 1 diabetes

Jensen DM Diabetes Care June 2009

HbA1c	Congenital malformations%	Perinatal mortality %	Serious adverse outcome %
>10.4	10.9	5.5	16.3
8.9-10.3	3.9	6.3	7.8
7.9-8.8	5.0	3.3	7.7
6.9-7.8	4.9	2.6	7.7
<6.9	3.9	2.1	5.6
Background population	2.8	0.75	3.5

CEMACH – Diabetes Key Findings

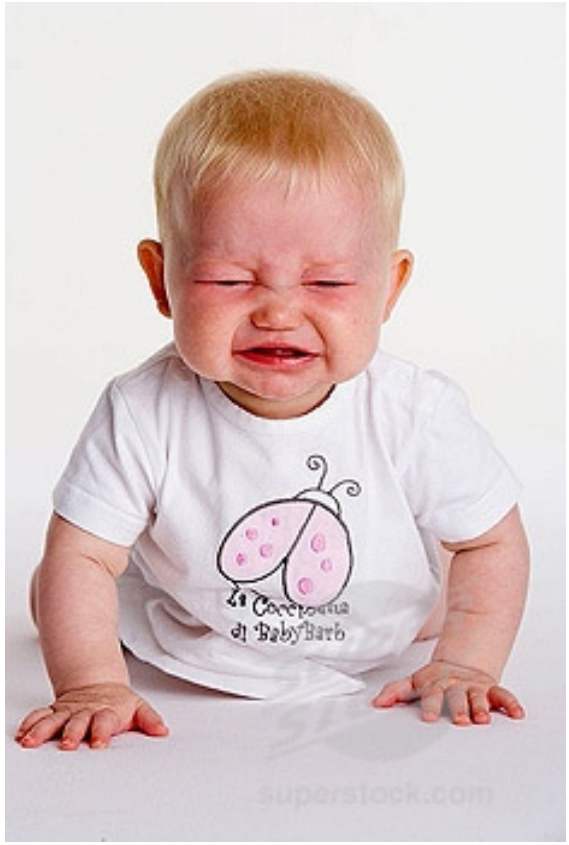


Women with diabetes were inadequately prepared for pregnancy
(73% suboptimal preconception care!)

Poor evidence, if any, of

- prepregnancy counselling
- preconception use of folic acid
- safe glycaemic targets being achieved
  - 79% had suboptimal glycaemic control before pregnancy!
  - only 54% had documentation of HbA1c in the 12 months prior to pregnancy!

CEMACH – Diabetes Key Findings



Only a minority had been using contraception in the preceding 12 months despite known poor glycaemic control

Lack of pre-pregnancy care was especially true for women with Type 2 diabetes

Preconception awareness

Starting from adolescence

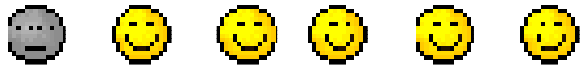
'*Health care professionals should give information (and document this) on the benefits of preconception glycaemic control at each contact*'

HbA1c <6.1% (Where safely achievable)

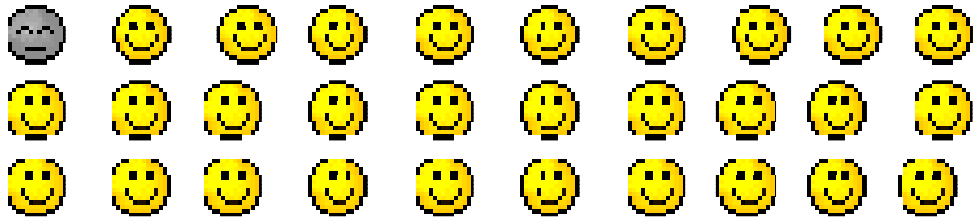
Explain that establishing good glycaemic control before conception and continuing throughout pregnancy **will reduce** the risk of miscarriage, congenital malformation, stillbirth and neonatal death

Diabetes in pregnancy is associated with risks to the woman and developing fetus

For women with diabetes, who do not plan their pregnancy, the risk of a serious complication is about 1 in 6. That is, they have a stillbirth or an infant with a malformation.



For women without diabetes about 1 in 30 have a serious complication when they get pregnant



Planning the pregnancy reduces the risk almost to the background population

Preconception awareness

Starting from adolescence

'*Should record pregnancy intentions and contraceptive use at each contact*'

Explain the importance of avoiding unplanned pregnancy

Advise to avoid pregnancy altogether whilst HbA1c >10% (risk of congenital malformation ~ 10%)

Preconception care

'Offer women seeking pregnancy specialist preconception advice'

To include structured preconception education

Advice on diet, body weight and exercise, including weight loss for women with a BMI>27kg/m^2

Preconception care

Glycaemic targets (HbA1c <6.1%)

Self monitoring of blood glucose

Monthly HbA1c

Close follow up and active advice (dietary, exercise, insulin adjustment) to achieve these targets

Preconception care

How to manage pregnancy related nausea and vomiting, maintain glycaemic control, and avoid hyperglycaemia (and ketoacidosis) at all costs

How to manage hypoglycaemia and hypo unawareness

Preconception care

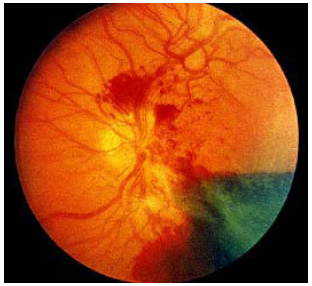
Review medication and change those contraindicated in pregnancy

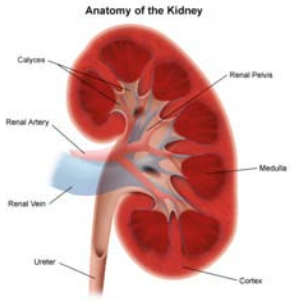
Insulin and Metformin may be used before and during pregnancy, but be extremely careful of other drugs (especially cardiovascular risk prevention)

Avoid all other oral hypoglycaemics and GLP-1 analogues

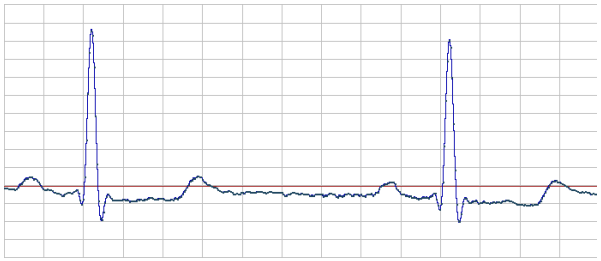
Preconception care

Assessment of long term complications prior to stopping contraception:



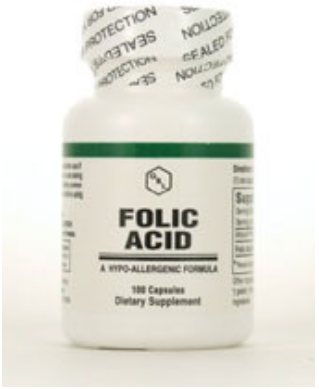


- BP control
- Microalbuminuria/ nephropathy
- Retinopathy
- Hypoglycaemia unawareness
- Autonomic neuropathy



Preconception care

Smoking and alcohol cessation advice



Folic acid supplement (5mg/day)

Contemporary challenges

Obesity

Type 2 Diabetes