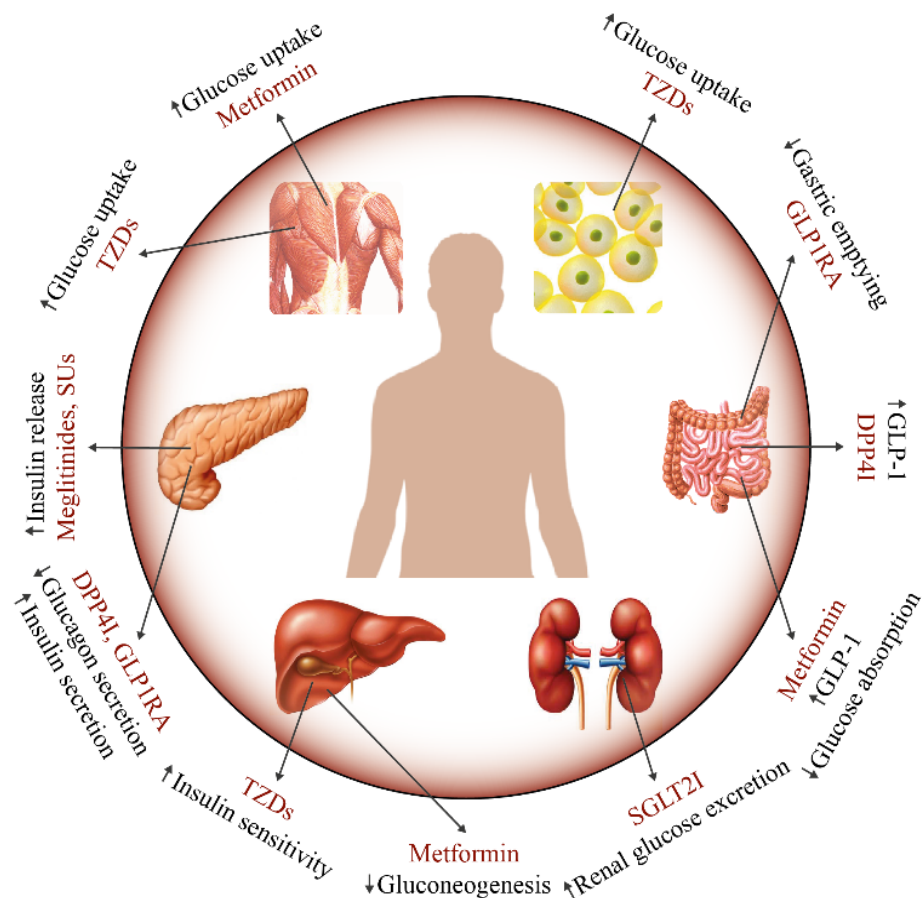


OVERVIEW

- What we think we know about Metformin
- Diabetes UK funded project on Metformin
action-progress update

A spectrum of drugs available for T2DM



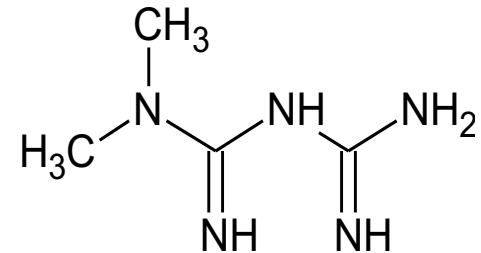
**Each drug is only effective in some patients
Some patients get side effects**

Metformin

- Metformin is a member of a class of drugs termed Biguanides.
- They were developed from a traditional medicinal plant French lilac or goat's rue (*Galega officinalis*). This contains the chemical guanidine which is probably the 'active' ingredient in the plant.



Metformin



- Mechanism(s) of action complex
- Main clinically relevant actions:
 - Mimics INSULIN by turning off glucose production in liver
 - Also increases glucose uptake into muscle
 - May have other actions on brain, pancreas, gut.....

Metformin: Background

- Anti-diabetes effect discovered by Karl Slotta in 1929
- Initially this action of metformin was dismissed:
 - Discovery of insulin in 1922 meant that all diabetics were being tried on insulin
 - No clinical differentiation between type 1 and type 2 at this time
- **Over time it became clear however that not all patients responded to insulin, spurring the search for non-insulin agents**

The improved distinction between Type 1 and 2 diabetes improved treatment protocols.



Fig. 1. Karl Heinrich Slotta in his laboratory at the Instituto Butantan (reproduced by kind permission of the Instituto Butantan, São Paulo, Brazil).

1957: Metformin widely implemented in treatment of diabetes

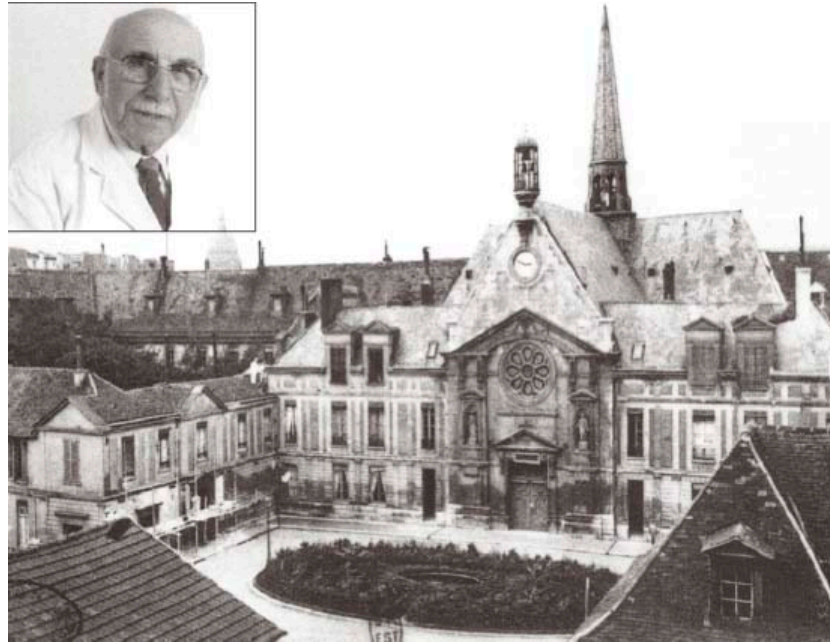
USA, FRANCE 1950s

France: First clinical use of metformin reported in 1957 by Jean Sterne (1909–1997) (inset, above the Hôpital Laennec)

USA: A screen of 200 biguanides was carried out in the USA.

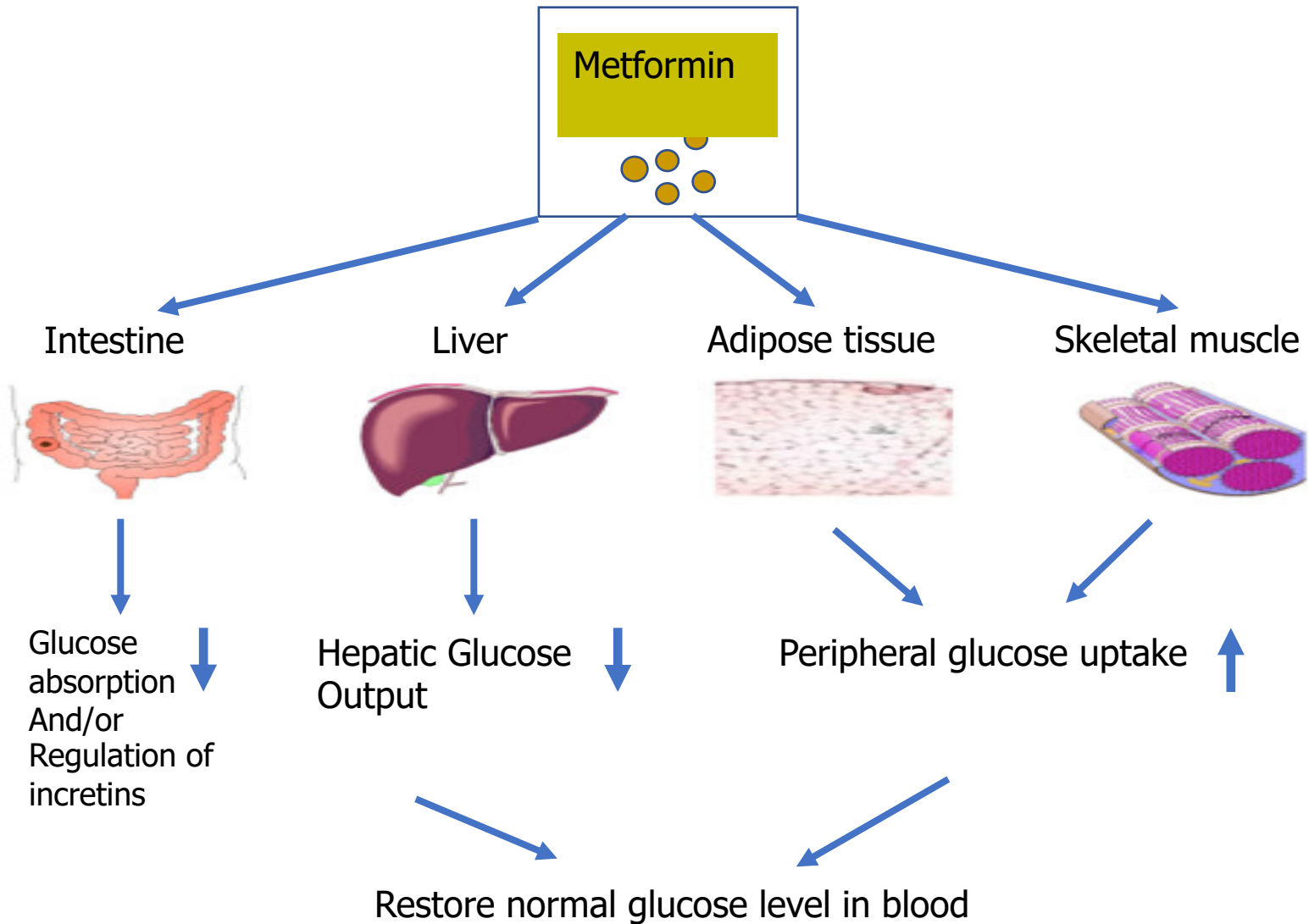
Originally, metformin and two analogues phenformin, and buformin were used

In the 1970s Phenformin and buformin were withdrawn from use due to side effects.



Practical Diabetes International (2004) 21 115-117

Metformin (Glucophage) as a first-line treatment for type 2 diabetes



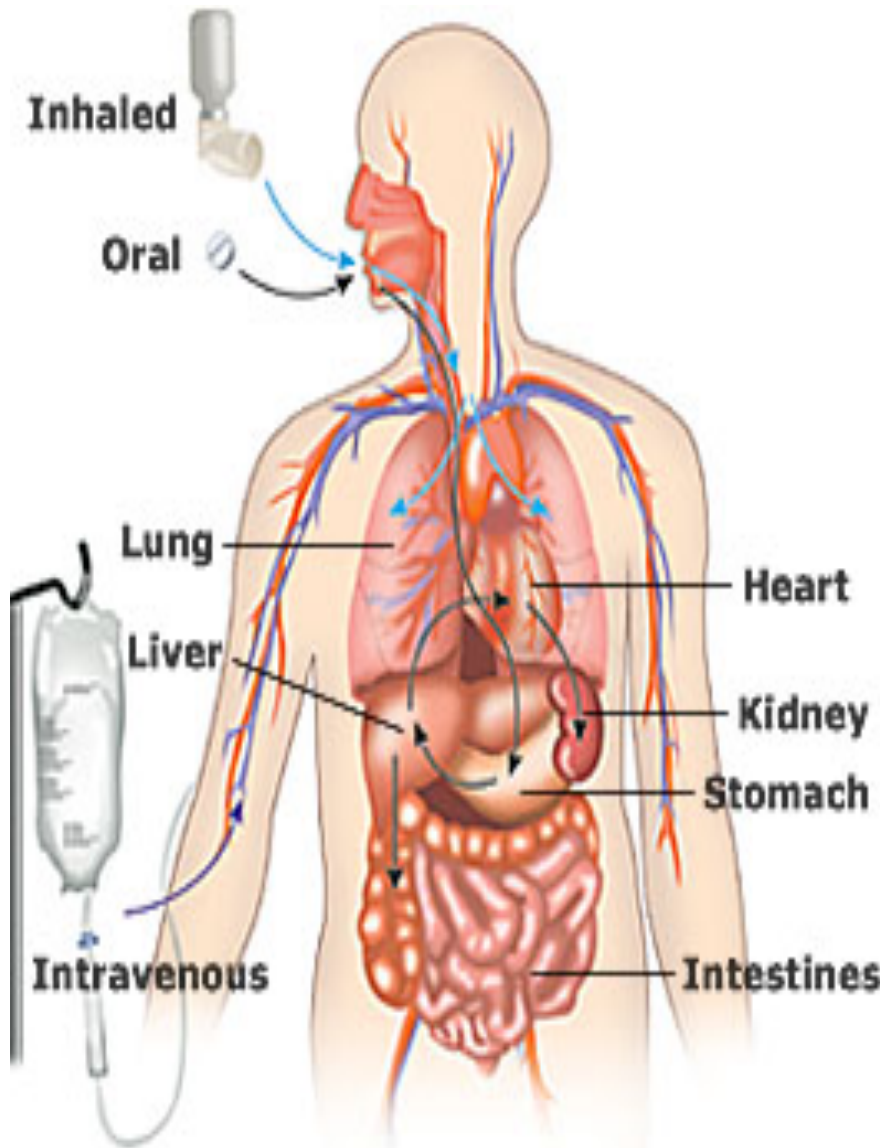
Metformin-problems

- Only works in around 50% of patients -----WHY?????
- Can't use in patients with kidney damage
- Not pleasant to take, intestinal problems.
- Resistance to metformin often occurs after a few years (keep increasing the dose)

Pharmacogenetics of type 2 diabetes

Genetics can affect drug response!

GENES can affect **how a drug works**
But also the life of a drug in the body



ADME

- Absorption
- Distribution
- Metabolism
- Excretion

Inter-individual variation in metformin response

Response to metformin varies considerably, with possibly only half of patients getting significant clinical benefits:

Can we use genetics to identify poor-responders?

To avoid giving patients useless treatment and stop wasting NHS funds.

Professor Ewan Pearson, Ninewells Medical School



Studies compared the DNA sequence in:

**People with Type 2 diabetes who had good control of their glucose using metformin
with**

People with Type 2 diabetes who could not control their glucose using metformin

Genes with possible biological actions identified from these genetic studies

1. Ataxia Telangiectasia Mutated (ATM)
2. Nuclear Protein, Ataxia-Telangiectasia Locus (NPAT)
3. Glucose Transporter isoform 2 (GLUT2)

Important Question-

Why would changes in any of these proteins alter the response to metformin?

Need to understand the biology.

Diabetes UK funded study

We have further evidence that people with LESS GLUT2 respond to metformin better



We have mice that have reduced levels of GLUT2 in their cells
(experimental model for the patients)



We investigated

1) Does less GLUT2 lead to problems with glucose levels

And

2) Does less GLUT2 speed up the development of Type 2 diabetes or complications

And

3) Does less GLUT2 change the response to metformin as a treatment of diabetes

And if so, why? Can we find a new way to treat people- for example reduce GLUT2!

Roles of GLUT2 in the body

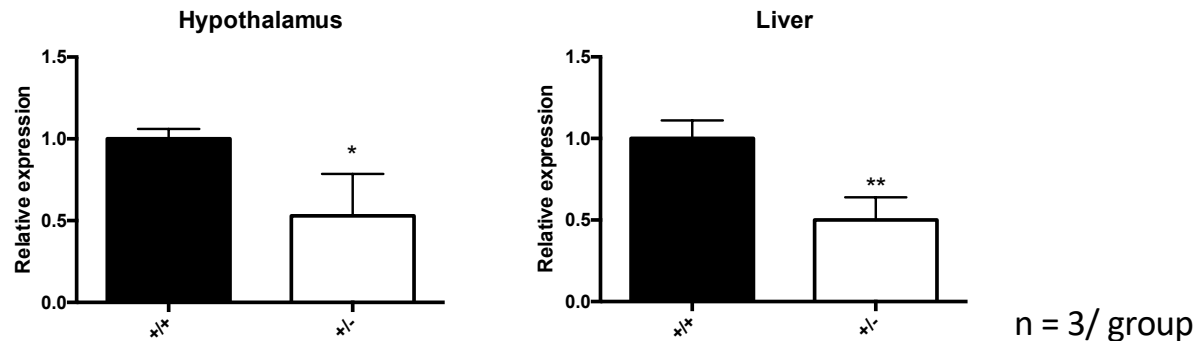
- Major glucose transporter in pancreatic beta cells (Thorens et al, *Cell*, 1988)
 - Required for glucose-stimulated insulin secretion (GSIS)
- Major glucose transporter of liver (Fukumoto et al, *PNAS*, 1988)
 - Absence reduces glucose uptake (Seyer et al, *J Clin. Invest.*, 2013)
- Important for nutrient balance and feeding control
 - GLUT2 deficiency in glutamatergic neurons of paraventricular nucleus linked to increase sugar consumption in mice (Labouebe et al, *Nat Neuro*, 2016)

So why would this influence how metformin works?

In mice with half as much GLUT2.....

- Humans with reduced GLUT2 expression respond better to metformin

- Aim is to model this *in vivo* to understand the mechanisms behind this finding



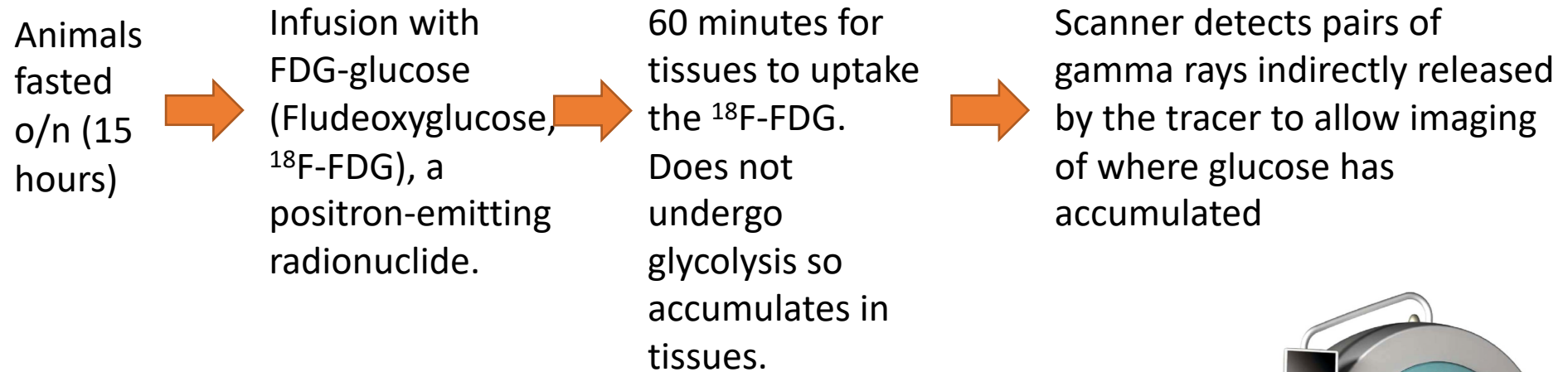
- What are the effects of Metformin in animals with reduced *Glut2* expression fed a high-fat diet?

Animal study outline

**Having half as much GLUT2 has very little effect
on diet induced obesity and diabetes**

FDG-PET (Positron emission tomography) scanning

- **Performed in collaboration with University of Turku, Finland**



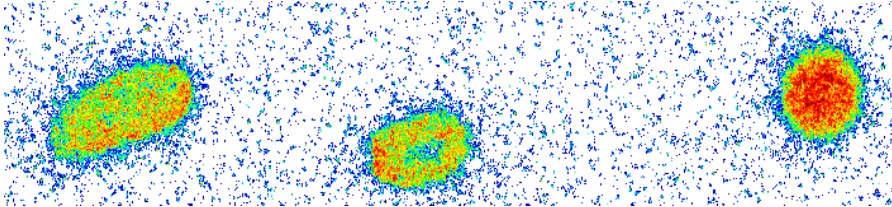
Example autoradiography

control

jejunum

ileum

colon

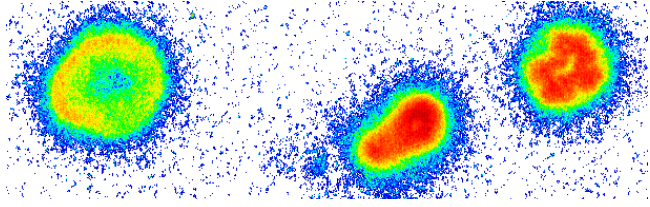


Control & metformin

jejunum

ileum

colon

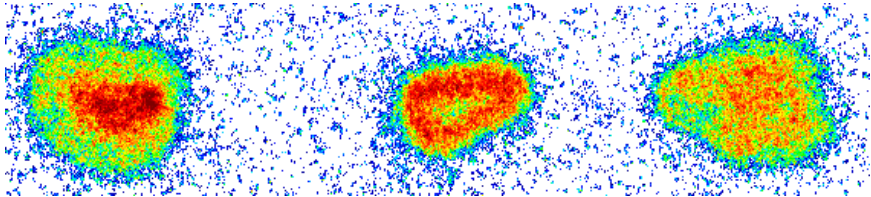


Less GLUT2

jejunum

ileum

colon

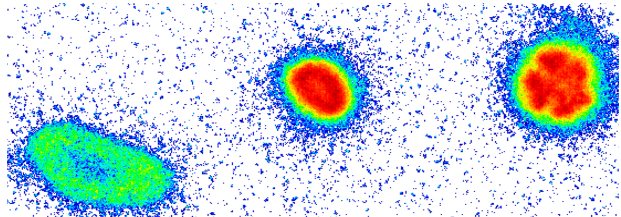


Less glut2 & metformin

jejunum

ileum

colon



GLUT2 influences glucose uptake in the gut in response to METFORMIN

This emphasises that the gut is a major site of action of metformin

It explains why people with less GLUT2 respond better to metformin

We hypothesise that people with more GLUT2 could benefit from combination of metformin with new SGLT inhibitors or just replace metformin with SGLT inhibitor– needs testing

Next- confirm using different approach

New mouse model: Mice with NO GLUT2 protein in their intestine are available

In vitro work in Caco2 cells (intestinal model) to investigate the mechanism in more detail

Gut organoid generation (in collaboration with Gribble lab, University of Cambridge)

Then clinical trial to test benefit of different drug.

We propose to establish if having less GLUT2 means that

1) You need more metformin than normal to treat diabetes

or

2) You don't respond to metformin at all

or

3) You could be treated with another approach rather than metformin

Ultimately we want a simple genetic test to decide

What dose of metformin you should start on

Whether it is worth even trying metformin at all

If we can develop a new treatment for those who can't take metformin

The best biomarker for T2DM risk is Body Fat!

BMI>30 (obese) ----- 7 fold greater risk of developing T2DM (cf BMI <25)

BMI 25-30 (overweight)----- 3 fold greater risk of developing T2DM (cf BMI <25)

**90% of adults with type 2 diabetes aged 16-54
years are overweight or obese**

**(although 62% of whole adult
population is overweight or obese!)**

So T2DM prevention is simple!



BUT half of people who are overweight won't get diabetes in next 10 years.

Diabetes Prevention Programmes

- Focus is on weight management
- Get people who are overweight to join programme (Not SIMPLE!)- expand to other risk groups- HOW?
- Lifestyle advice, 12 month programme of diet education and exercise.
- Many people really struggle to lose weight- WHY?
- Recent evidence show that weight loss can reverse diabetes- so including newly diagnosed diabetes in Scottish programme

What would make YOU join the programme?

- Fear
- Hope
- Money
- ????? Personal interaction ??????

Type 2 Diabetes Prevention Programmes

- England started in 2016, trying to ‘treat’ 100,000 people every year. If you have diabetes you can’t join!
- Other programmes in USA, Germany, Finland, Australia, Arabia.... Over last 20 years Limited impact- WHY?
- Scotland- only national programme that includes newly diagnosed T2 diabetes.

Scottish Type 2 Diabetes Prevention Programme

<https://www.gov.scot/publications/healthier-future-framework-prevention-early-detection-early-intervention-type-2/pages/10/>

- Initially only 3 sites
- Tayside, Ayrshire and Arran, Lothian.
- Started this year. Will expand across Scotland next year.
- If you know people who are at risk of Type 2 diabetes, tell them to look it up and talk with their GP!
- For details- search for NHS diabetes prevention scotland

What is your risk of Type 2 diabetes?

<https://riskscore.diabetes.org.uk/>

Combination of family history, weight, lifestyle- pretty accurate

A mention for Type 1 diabetes prevention

- Used to think it would never be possible to prevent T1D
- Things have CHANGED!!!
- We can identify people at risk (Autoantibodies, genetics and insulin)
- Need a treatment! As we learn about the immune system better treatments are becoming available. Some are simple!

POInT study

The aim of POInT (Primary Oral Insulin Trial) is to prevent the onset of type 1 diabetes in children with a high risk of type 1 diabetes through the daily administration of oral insulin powder.

The daily administration of insulin powder along with a meal should tell the immune system that insulin is NOT something it must fight.

Only really works before the immune system attacks the beta cells

Your child may take part in this study if they were involved in the INGR1D screening study and were found to be at high risk of developing type 1 diabetes, and if your child is aged between 4 – 7 months.

SUMMARY

We are making progress on understanding how metformin works

We hope this will improve the use of metformin in the NHS

There is a real effort to PREVENT both of the main types of diabetes.

And

To use the prevention programme in Scotland to reverse T2 Diabetes