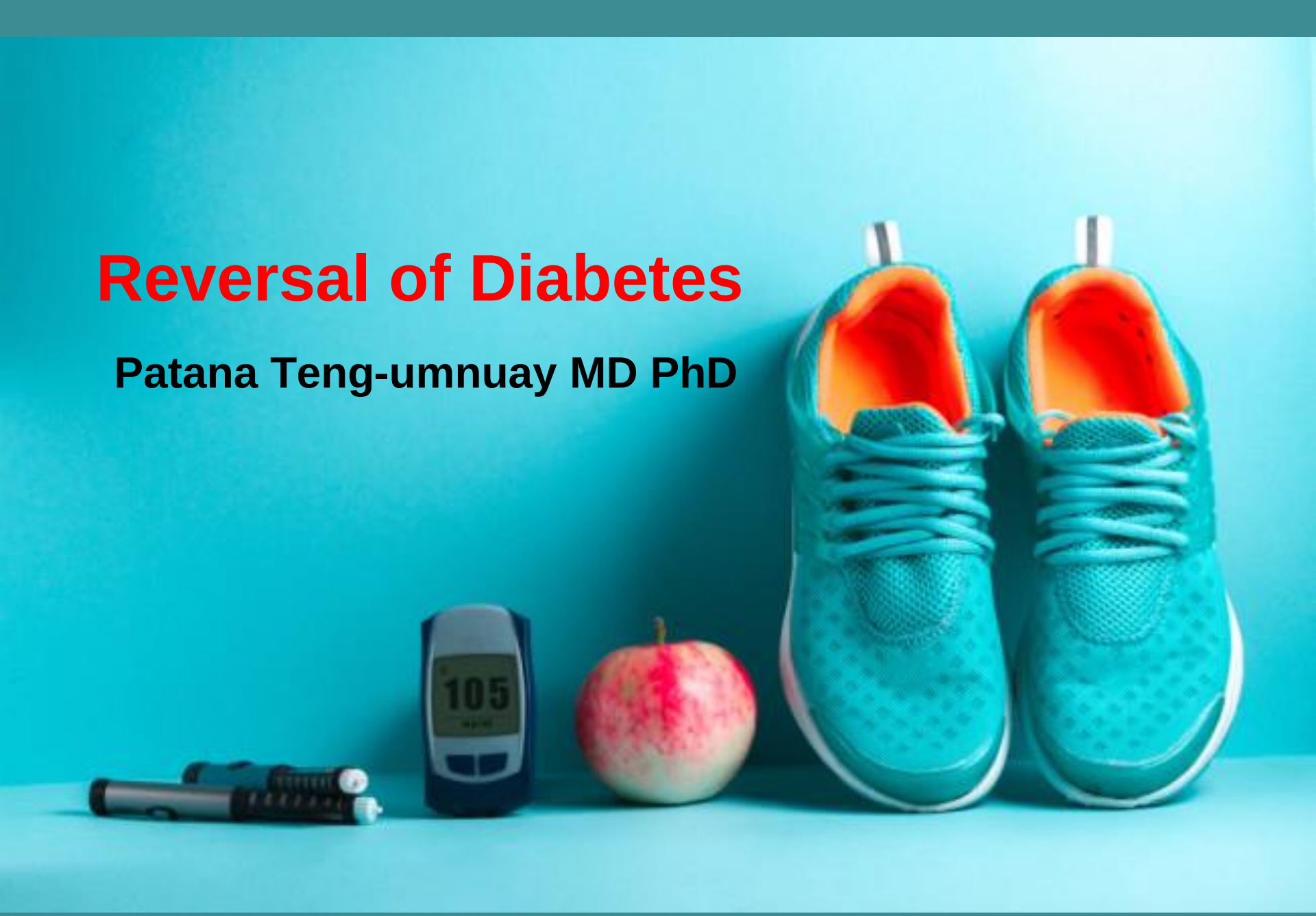
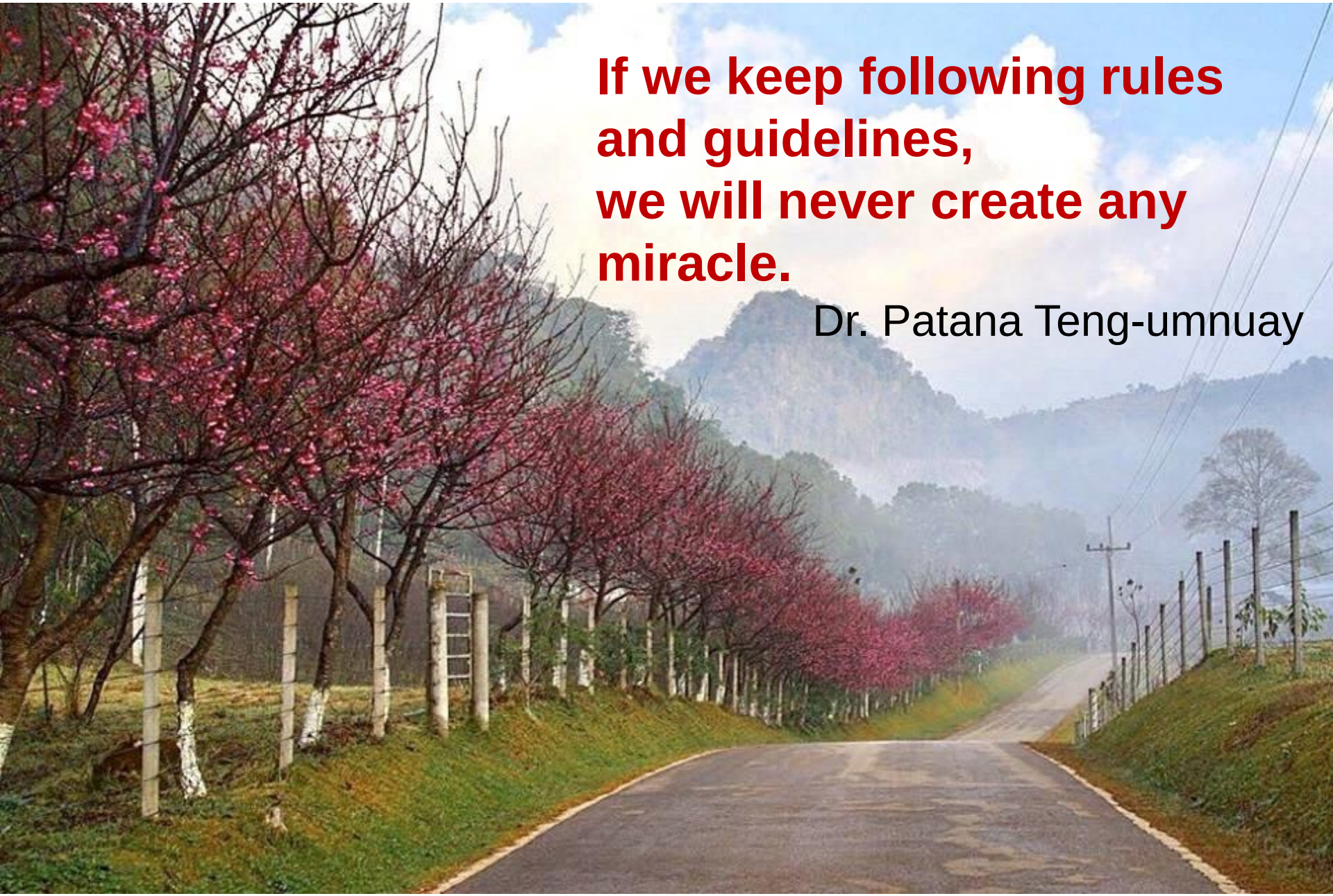
Reversal of Diabetes

Patana Teng-umnuay MD PhD



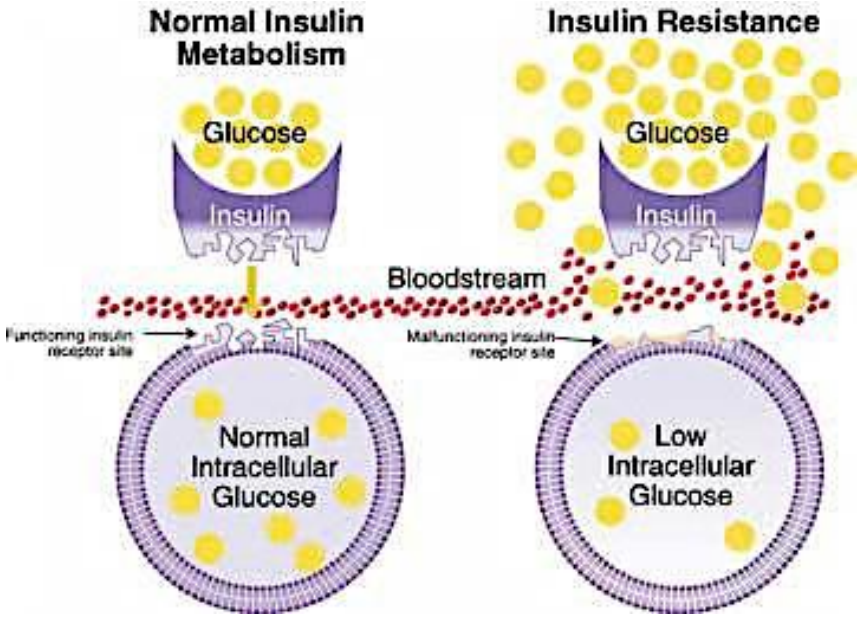

If we keep following rules and guidelines,
we will never create any miracle.
Dr. Patana Teng-umnuay

What is wrong about diabetic care today?

- Doctors only look at blood sugar and ignore the causes of diabetes, such as lifestyle, the lack of good microflora, drugs, and alcohol.
- Diabeticians assume that every adults who have diabetes are type 2 diabetes and forgot about secondary diabetes from pancreatitis.
- When the patients have diabetes, 50% of their beta cells would already be dead. So, why not prevent diabetes by treating pre-diabetes.
- Most patients and doctors misunderstand that the aim of diabetes care is to control blood sugar, but the true reasons that we need to treat diabetes is to prevent complications and sometimes complications come from hypoglycemic drugs.
- The use of sulfonylureas can cause kidney complications, cardiovascular complications, beta cells apoptosis, and increase mortalities despites good control of blood sugar.
- Refuse to prescribe insulin.
- Wrong nutritional advice.
- **Most doctors don’t have time to correct patients’ lifestyle.**

Obesity is the major factor contributed to insulin resistance and diabetes

Obesity decreases ability of insulin to act effectively on peripheral target tissue especially muscle and liver



Why are we gaining weight when we get older?

- Eating too much
- Eat wrong kinds of food (sugar, low fat milk, juice, whole wheat, Fructose)
- Lack of exercise
- Disease (hypothyroid)
- Medicine
  - Insulin and sulfonylurea
  - Steroids
  - Oral contraceptives
  - Anti-depressant and anti-psychotic
- Lack of good bacteria in the bowels

Healthy Food and Lifestyle is for Everyone, NOT just Diabetic Patients!!

- Eat less, live longer
- Sugar is toxin
- Grains over Rice
- Vegetable and fruit in moderation.
- Avoid fried food, cut down animal fat including milk.
- Choose olive oil and rice bran oil.
- Drink more water, filtered water not tap.
- Exercise your muscle, back and leg exercises are best.
- Take supplements (vitamin D, probiotics)
- Try intermittent fasting

Good carbohydrate is GRAINS

Low glycemic index

Reduce sugar absorption

High in vitamin B's and E

High in minerals

Whole grain-rich diet reduces body weight and systemic low-grade inflammation without inducing major changes of the gut microbiome

Roager HM et al. Gut 2017 Nov. 1

- 60 Danish adults at risk of developing metabolic syndrome were included in a randomised cross-over trial with two 8-week dietary intervention periods comprising whole grain diet and refined grain diet, separated by a washout period of ≥6 weeks.
- 50 participants completed both periods with a whole grain intake of 179±50 g/day and 13±10 g/day in the whole grain and refined grain period, respectively. Compliance was confirmed by a difference in plasma alkylresorcinols ($p<0.0001$).
- Compared with refined grain, whole grain did not significantly alter glucose homeostasis and did not induce major changes in the faecal microbiome.
- The whole grain diet did, however, compared with the refined grain diet, **decrease body weight ($p<0.0001$), serum inflammatory markers, interleukin (IL)-6 ($p=0.009$) and C-reactive protein ($p=0.003$)**.

Dietary Fibers and Human Health

Reynolds A et al. Lancet 2018;393:434-445.

- Data from 185 prospective studies and 58 clinical trials with 4635 adult participants were included in the analyses.
- Observational data suggest a 15–30% decrease in all-cause and cardiovascular related mortality, and incidence of coronary heart disease, stroke incidence and mortality, type 2 diabetes, and colorectal cancer when comparing the highest dietary fibers consumers with the lowest consumers.
- Clinical trials show significantly lower bodyweight, systolic blood pressure, and total cholesterol when comparing higher with lower intakes of dietary fibers.
- Dose-response curves suggested that higher intakes of dietary fibers could confer even greater benefit to protect against cardiovascular diseases, type 2 diabetes, and colorectal and breast cancer. Similar findings for whole grain intake were observed.

Association Between Plant-Based Dietary Patterns and Risk of Type 2 Diabetes

JAMA Intern Med. 2019 Jul 22. doi: 10.1001

- Data analysis was conducted between December 2018 and February 2019 on all prospective observational studies that examined the association between adherence to plant-based dietary patterns and incidence of type 2 diabetes among adults 18 years or older were identified.
- A total of 9 studies were identified, totaling 307,099 participants with 23,544 cases of incident type 2 diabetes.
- A significant inverse association was observed between higher adherence to a plant-based dietary pattern and risk of type 2 diabetes in comparison with poorer adherence.
- This association was strengthened when healthy plant-based foods, such as fruits, vegetables, whole grains, legumes, and nuts, were included in the definition of plant-based patterns

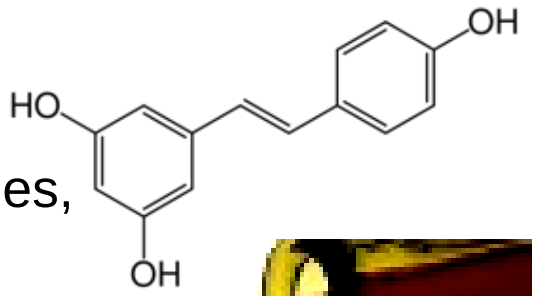
Herbs and Diabetes

Plant Chemicals	Mechanism of Action
Pterocarpus Marsupium Heart Wood (Epicatechin/Pterostilbene)	Protect and promote beta cell regeneration Increase adiponectin and reduce insulin resistance
Salatia Reticulata Root	Liver protection and PPAR gamma activation
Withania Somnifera Root	Enhances glucose uptake in skeletal muscle
Gymnema Sylvestere Extract	Beta Cell Regeneretion
Curcumin Longa-Rhizome Powder	Anti-oxidant Anti-inflammatory Improves endothelial function
Resveratrol	Enhances Mitochondria Biogenesis Sirtuin Activation

www.cresvin.com

Resveratrol

Caloric Restriction Mimetic



- Polyphenolic compound found in red wine, grapes, blueberries, peanuts.
- Phytoestrogenic and anti-oxidants.
- Increased SIRT1 actvities.
- Cancer chemopreventive activities.
  (Science 1997;275:218)
- Increased lifespan in yeast, worms, and flies.
- Enhanced mitochondria activities.
- Increased aerobic capacity in mice.
  (Nature 2004;430:686)
- Protected mice against diet-induced obesity and insulin resistance.
  (Cell 2006;127:1109)
- Prevent the development of fatty liver in high-fat-diet mice.
  (Nature 2006;444:337)

French Paradox

Resveratrol

Up-regulates

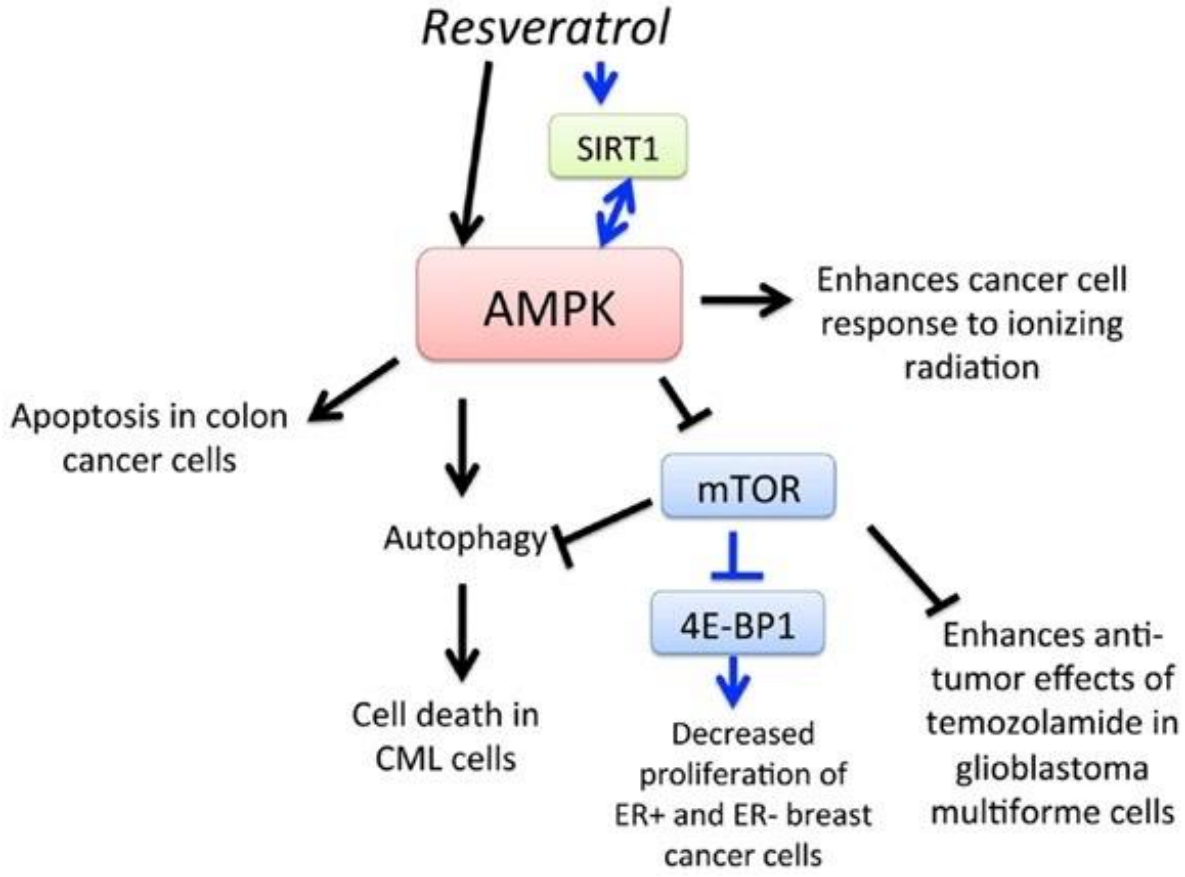
- SIRTIUN-1
- SOD
- Catalase
- Glutathione reductase/peroxidase
- NRF2
- AMPK
- G6PD
- PPAR gamma co-activator
- Nitric oxide

Down-regulates

- COX-1
- iNOS
- Lipid peroxides
- Myeloperoxidase
- NADPH oxidase
- Poly ADP-ribose

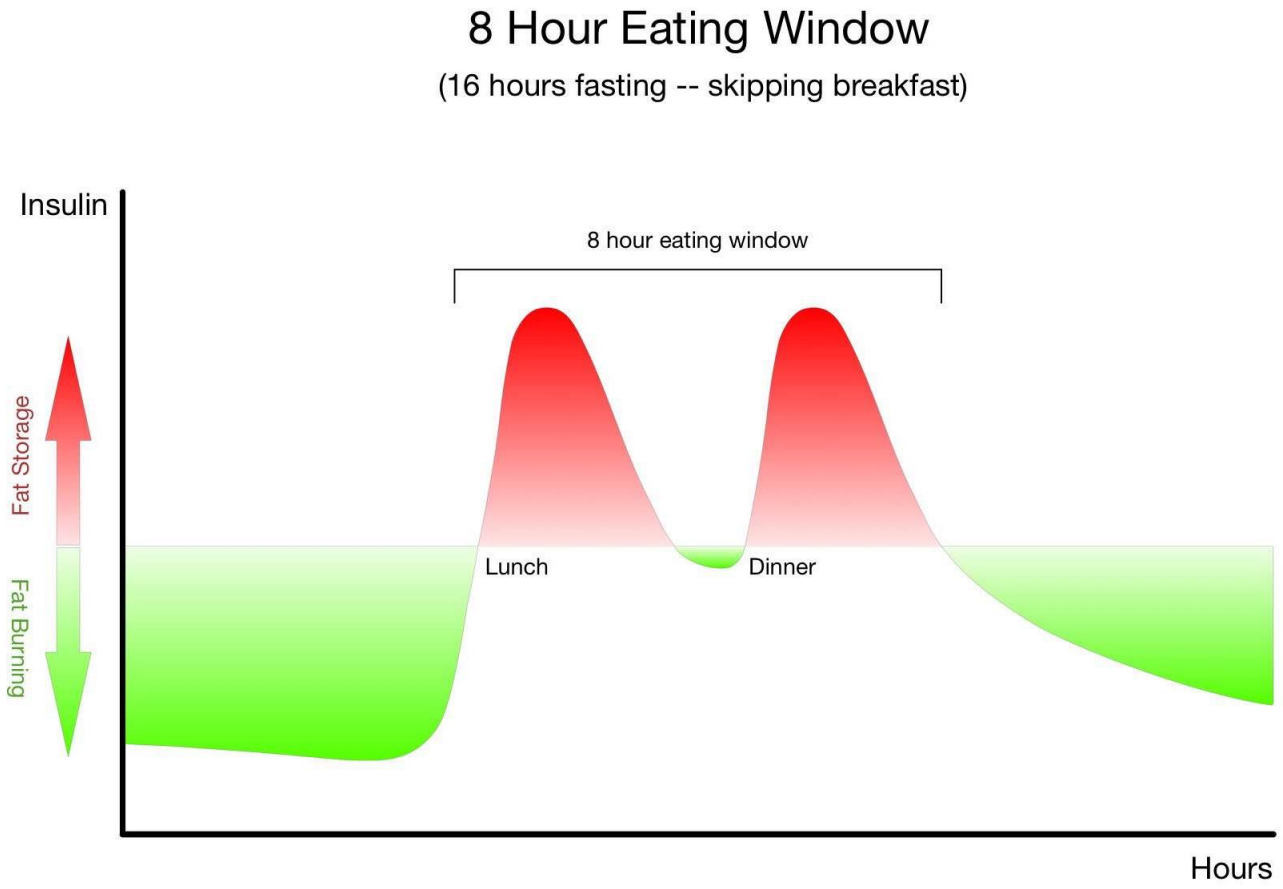
Front Aging Neurosci. 2014;6:218

Resveratrol stimulate AMP activated protein kinase (AMPK)

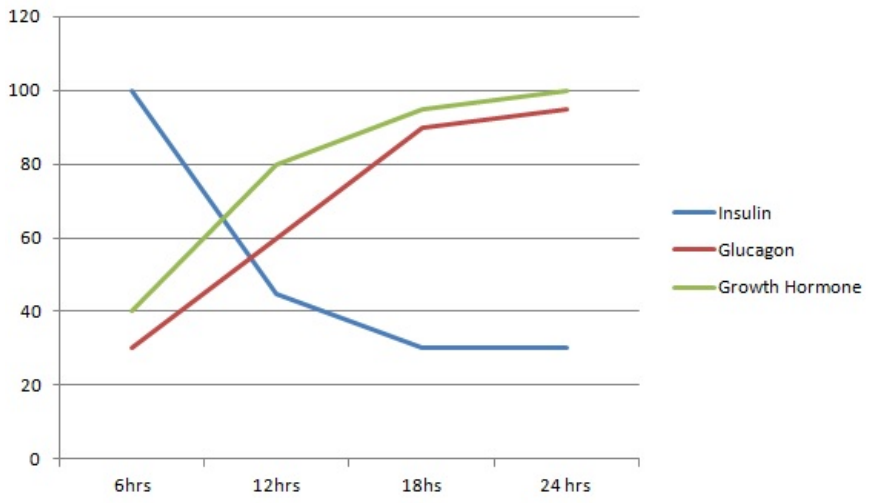


Intermittent Fasting

More practical approach to caloric restriction



Physiological effects of fasting



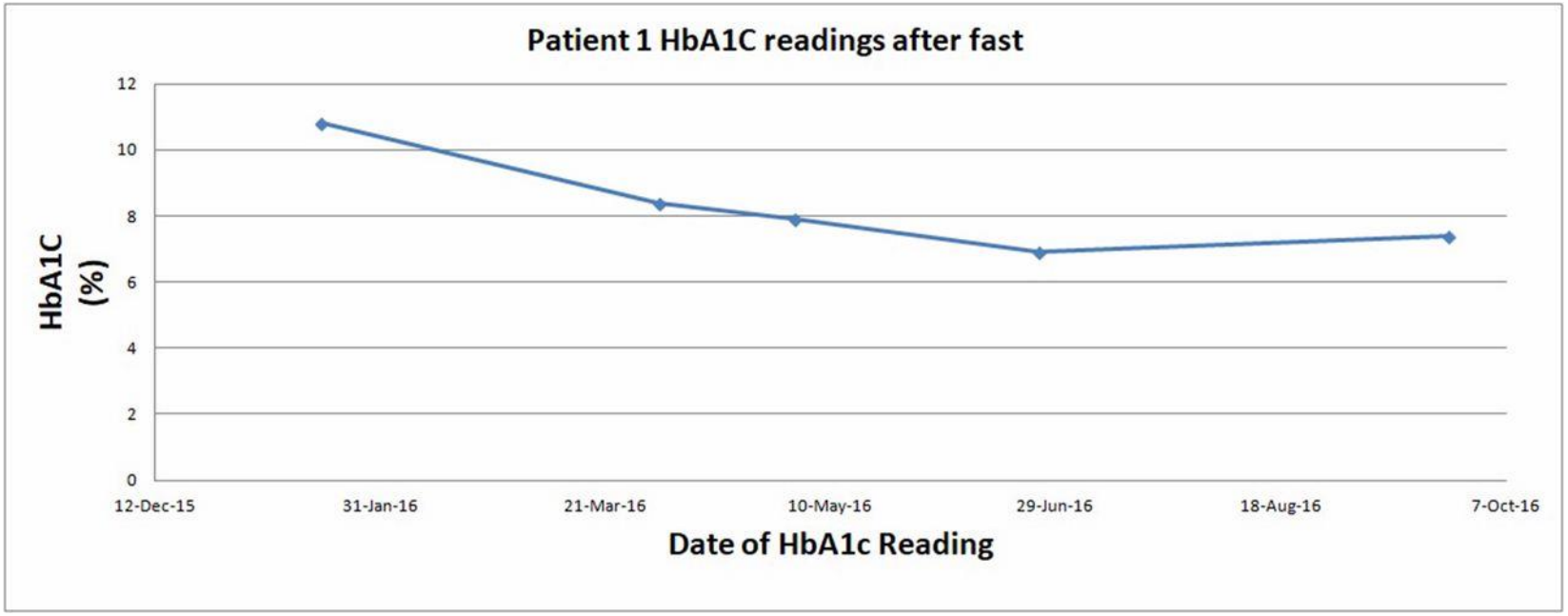
- Fasting increases hepatic glycogenolysis, hepatic gluconeogenesis, fatty acid oxidation and ketogenesis, glucogon and epinephrine. During fasting state, the tissue will use fatty acids or ketones for energy.
- The levels of insulin will drop and lipolysis increases.
- Oxidation rates decrease.
- Mild acidosis with increased ammonia excretion due to ketogenesis (sodium bicarbonate supplement is recommended).

Therapeutic use of intermittent fasting for people with type 2 diabetes as an alternative to insulin

BMJ Case Reports 2018; doi:10.1136/bcr-2017-221854

- Three men who'd had type 2 diabetes for 10 to 25 years — and who were taking various pharmacotherapies, including insulin — underwent nutritional training and were instructed to fast for 24 hours three times a week for several months.
- On fasting days, they ate just dinner. On non-fasting days, they ate lunch and dinner. Low-carbohydrate meals were advised, and participants were seen twice a month for lab testing.
- All three patients were able to discontinue insulin within 5 to 18 days. Two ultimately stopped all diabetes medications.
- All participants saw reductions in hemoglobin A1c, and none experienced symptoms of hypoglycemia.
- All three lost weight (10%–18% of body weight) and reduced their waist circumference.
- Patients described feeling "terrific" and "excellent" on fasting days.

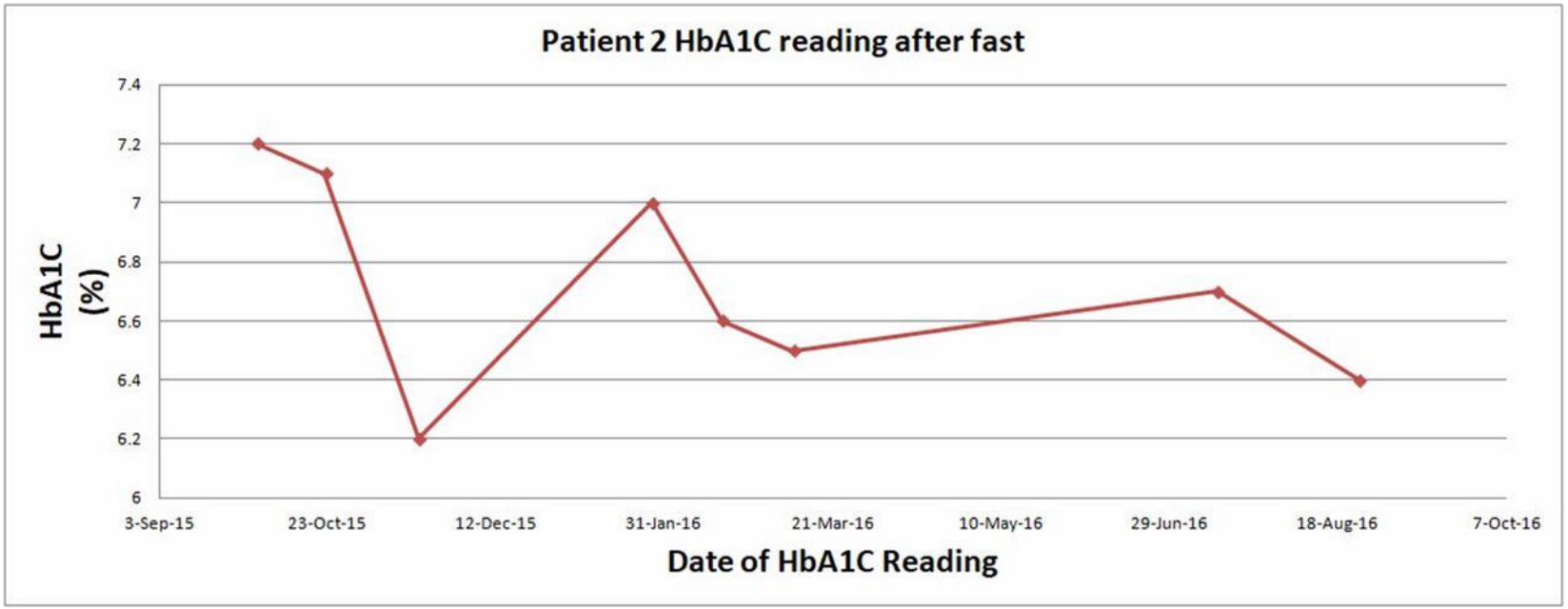
Change in glycosylated haemoglobin while on fast for patient 1.



Suleiman Furmli et al. BMJ Case Reports 2018;2018:bcr-2017-221854

BMJ Case Reports

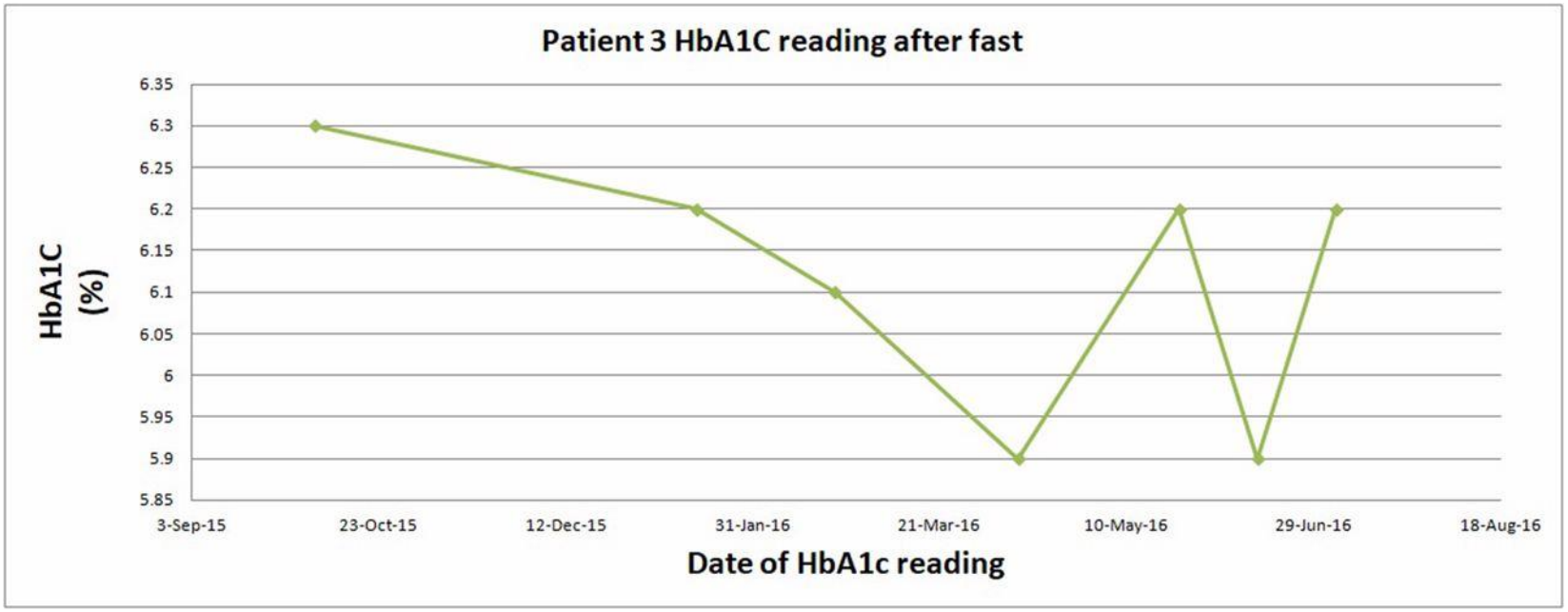
Change in glycosylated haemoglobin while on fast for patient 2.



Suleiman Furmli et al. BMJ Case Reports 2018;2018:bcr-2017-221854

BMJ Case Reports

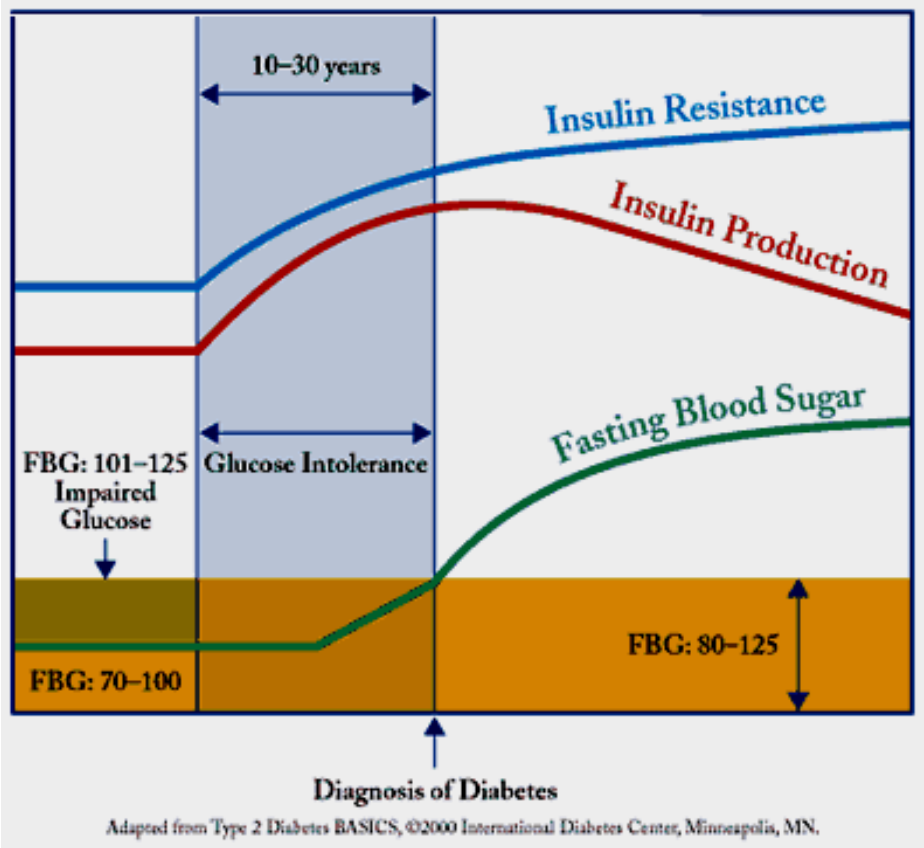
Change in glycosylated haemoglobin while on fast for patient 3.



Suleiman Furmli et al. BMJ Case Reports 2018;2018:bcr-2017-221854

BMJ Case Reports

By the time the patients are diagnosed with diabetes, 50% of their beta cells are already dysfunction or dead. We need to start treatment sooner!

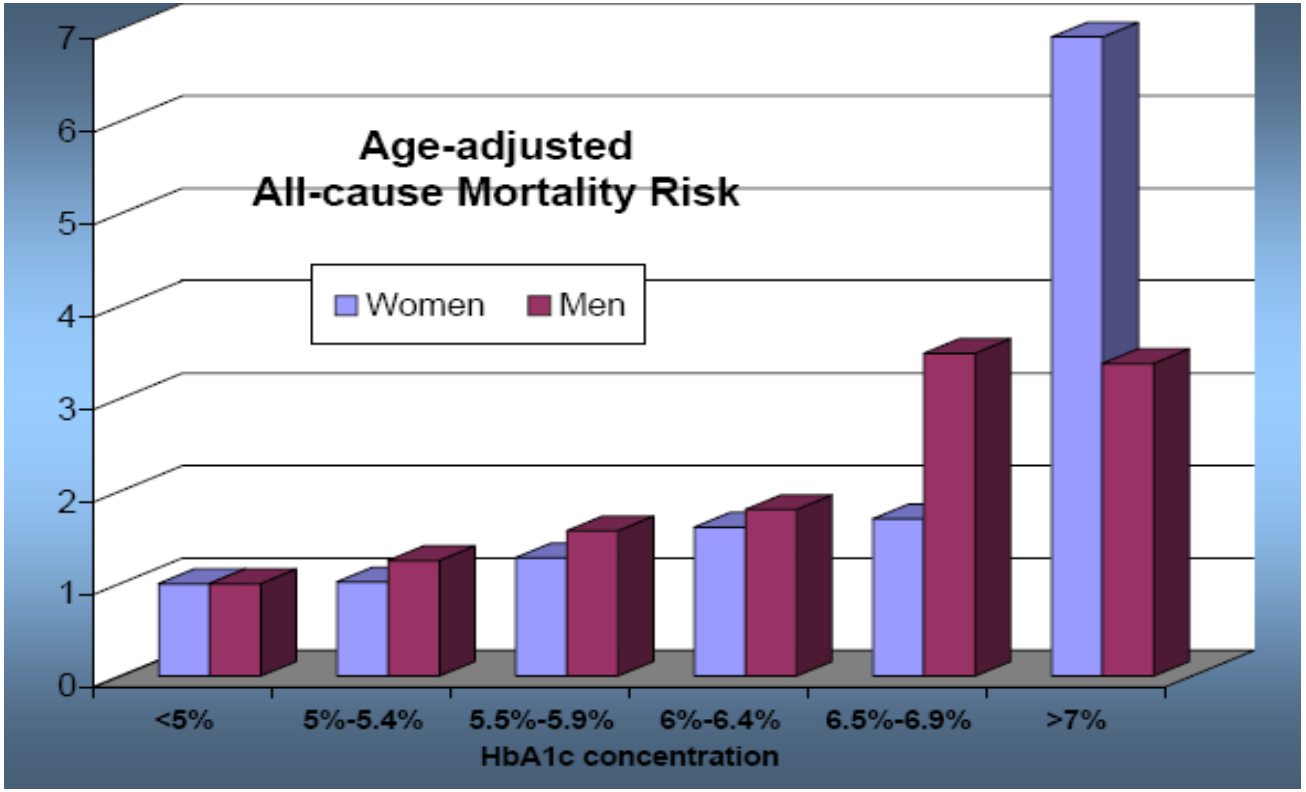


Insulin Resistance and Fasting Plasma Glucose

Glycated Hemoglobin
Not just a risk factor for a diabetic!

EPIC-Norfolk Study (Ann Intern Med 2004;141:413)

HbA_{1C} concentrations predict mortality continuously across the whole population distribution in people with or without diabetes.

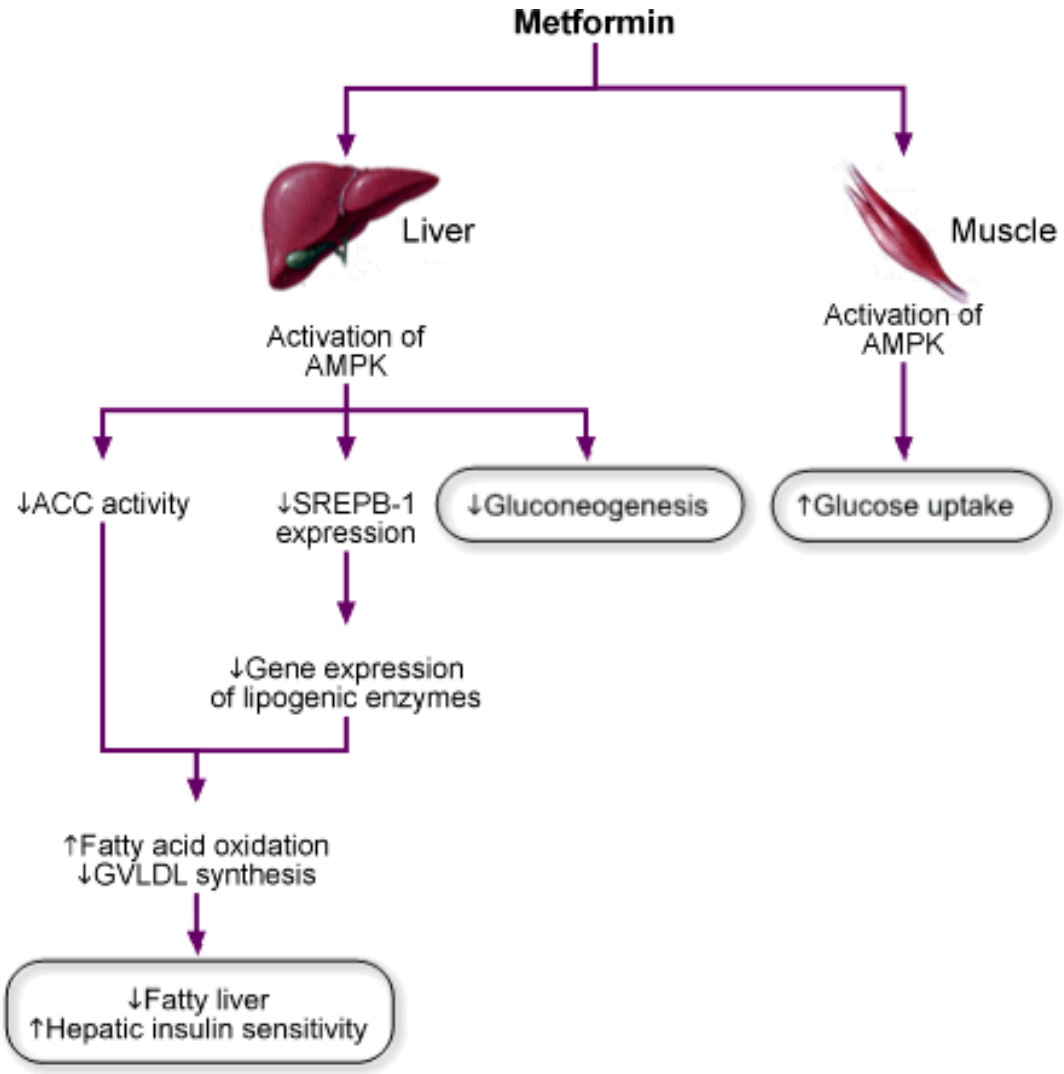


To cure diabetes, we need to detect PRE-DIABETES

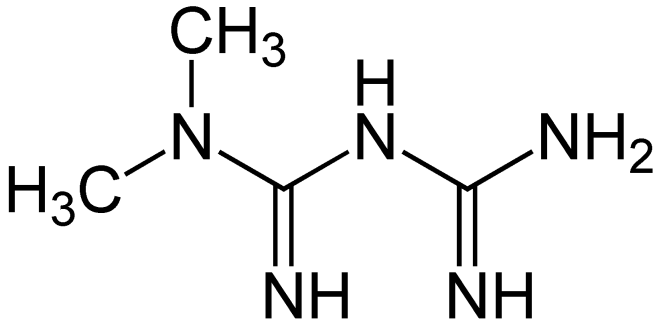
- To detect pre-diabetes, we need to know **HbA1c**
- **Lifestyle changes** and treatment with **Metformin** both reduced the incidence of diabetes in persons at high risk.
- The lifestyle intervention was more effective than **Metformin** (N Engl J Med 2002;346:393-403).
- **The problems about using metformin to prevent diabetes:**
  - No insurance coverage
  - The patients will be labeled as diabetes for life
  - Most experts consider prescribing metformin in pre-diabetes is dangerous and rather wait until the patient develop diabetes (when at least 50% of beta cells has already been dead!)

Metformin

First Drug of Choice for Diabetes and **Pre-diabetes**



Metformin (Glucophage®)



- Anti-diabetic biguanide derived from the herb, Goat's rue (Galega Officinalis)
- First-line drug of choice for overweight diabetes with normal kidney and liver functions.
- Treatment of polycystic ovary syndrome
- Prevent type 2 diabetes in high risk group
- Most common side effects are gastrointestinal upset.
- Lactic acidosis is uncommon found in overdosage and in people with kidney and liver failure.
- Long term use can cause vitamin B12 deficiency
- Can be used in gestational diabetes

Practical Metformin

- Glucophage is the common trade name for metformin.
- Some company will add metformin with other medicine to reduce cost (Janumet, Actosmet, Jardiance Duo).
- Common Dosage is 500 mg bid or 850 mg bid, higher dosage will not give better results.
- Glucophage XR (750 mg or 1000 mg) is once daily form of metformin.
- Low dose, interval dosage metformin can be used as anti-aging medicine.
- Vitamin B12 supplementation is recommended.
- Lactic acidosis is rare unless the dosage is too high.

Aim of diabetes care in NOT about blood sugar control

- Aim of diabetes treatment is to prevent complications
- Complications of diabetes is related to blood sugar control.
- However, good blood sugar control may not prevent its complications
- Some doctors don’t even recognize that many complications may come from diabetic drugs! (sulfonylurea, statins)

Experts say good glycemic controls (HbA_{1C} < 7%) reduce diabetic complications.

But, if the true reason is patients who have good diabetic control using less drugs

It may be drugs not blood glucose that cause complications!

Complication	DCCT N=1441	Kumamoto N=110	UKPDS N=5102
Retinopathy	**↓76%**	**↓69%**	**↓21%**
Nephropathy	**↓54%**	**↓70%**	**↓34%**
Neuropathy	**↓60%**		

DCCT (Diabetes Control and Complications Trial) N Engl J Med 1993;329:977

Kumamoto Diabetes Res Clin Prac 1995;28:103

UKPDS (UK Prospective Diabetes Study) Lancet 1998;352:837

Treat patients, not blood sugar…PLEASE

- A female patient 55 year old with underlying diabetes for 6 years and was taking 6 tablets of 5 mg glipizide per day. Her brother told me diabetic nurse advised her to eat sugar anytime she had hypoglycemic symptoms. So, she always eat sugar and when her endocrinologist saw her blood sugar, she would increase the drug dosage. (After all, most endocrinologist prefer lowering blood sugar with drug and more drug).
- Two year ago, she developed seizure. A neurologist who was not aware that seizure could be due to hypoglycemia, gave her anti-epileptic drug. Her seizure stop, but her hypoglycemia symptoms went unnoticed.
- One year ago, she had deafness and mild dementia. CT brain scan showed that she had frontal lobe atrophy.
- Eventually, her husband and her children left her in a psychiatric hospital since they can no longer take care of her.
- All this time, she continue to take glipizide and her blood sugar control is…perfect.

Numerous studies have shown that intensive glucose lowering provide no benefits and can be dangerous

BMJ

BMJ 2011;343:d4169 doi: 10.1136/bmj.d4169

RESEARCH

Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials

Less Intensive Blood Glucose Control in Diabetes?

Ann Intern Med March 6, 2018

- The American College of Physicians now recommends that most patients with type 2 diabetes **aim for a hemoglobin A1c level between 7% and 8%.**

- In a guideline update published in the *Annals of Internal Medicine*, the ACP cites evidence that treating to targets of 7% or lower rather than 8% does not reduce the risk for death or macrovascular events over 5–10 years — but does result in "substantial harms," such as hypoglycemia.

Can diabetic nephropathy comes from diabetic drug?

- A 49 year old women came to see me with the problem of rising creatinine. She was taking glipizide 5 mg per day and her creatinine was 1.8 mg%. Her HbA1c was 6.8%
- I asked to stop glipizide and start insulin treatment but she refused and disappeared.
- One year later, she came back with her creatinine 2.3 mg%. She was so afraid of receiving dialysis and agree to start insulin treatment.
- She has been with me for the past ten year and saw her creatinine levels slowly reduced.
- From the last visit, her creatinine is 1.3 mg%

Sulfonylurea: Friends of Foes?

Glipizide, Gliclazide, Glibenclamide, Glimepiride

- Bind to ATP-dependent K^+ (K_{ATP}) channel on the cell membrane of pancreatic beta cells
- Most common medicine used in diabetes.
- Promote insulin release by binding to sulfonylurea receptor can result in hypoglycemia, weight gain, and beta cell apoptosis.
- The binding to the same receptor at myocardial cell impairs ischemic preconditioning and has arrhythmogenic effects.
  (Leibowitz Diabetologia 1996;39:503-514)
- Increase overall mortality.
  (Simpson et al. CMAJ 2006;174:169-174)
- Compared to metformin, sulfonylurea users had an increased risk for persistent declined in GFR, end stage renal disease, and death
  (Kidney Int 2012;81:698-706)

Aim of Diabetes Care is to Prevent Complications

Diabetic complications

Microvascular

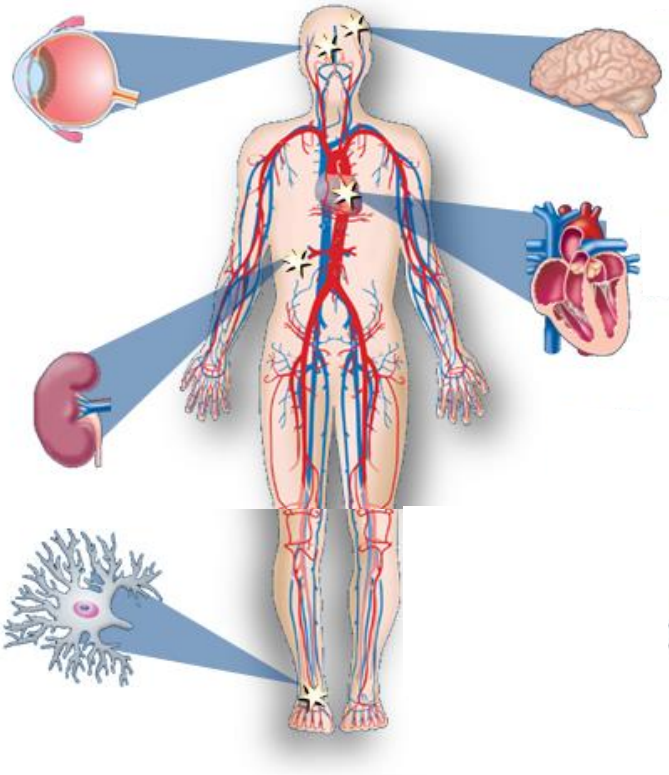
Damage to smaller blood vessels

- Diabetic **Retinopathy**
- Diabetic **Nephropathy**
- Diabetic **Neuropathy**

Macrovascular

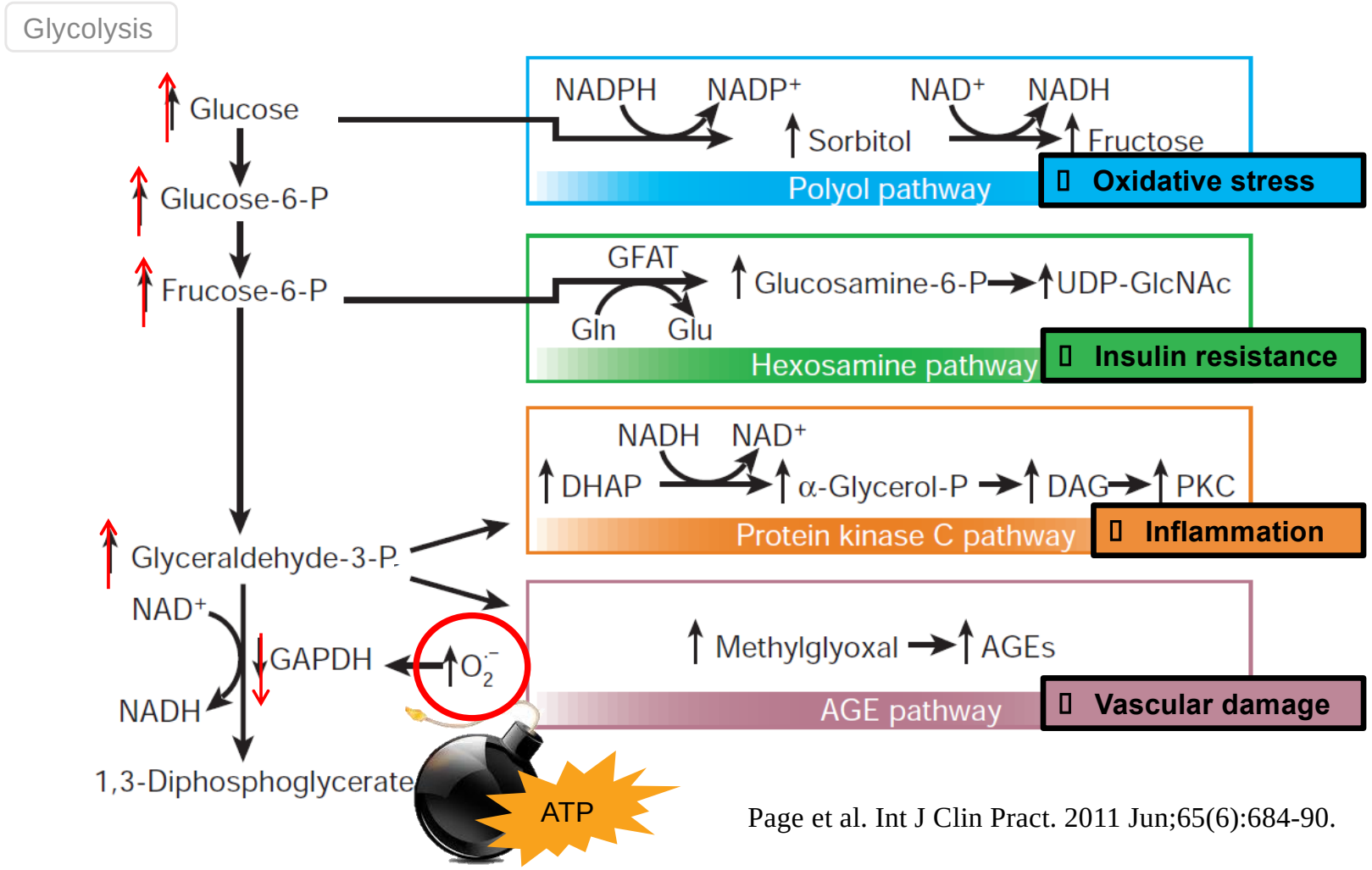
Damage to larger blood vessels

- Stroke
- Ischemic heart disease
- Peripheral arterial disease (PAD)



Pathogenesis of diabetic complications

Activation of alternative, pathological pathways



Page et al. Int J Clin Pract. 2011 Jun;65(6):684-90.

Preventing AGE with Special B's

- **Benfotiamine (active B1)**
  - Thiamine derivative with better bioavailability. Blocks three major pathways of hyperglycemic damage (hexosamine, advanced glycation end product, and diacylglycerol-protein kinase pathway) and prevents experimental diabetic complications.

- **Pyridoxamine (active B6)**
  - Natural intermediate of vitamin B6 metabolism. Reduce AGE accumulation in association with Improvemnets in renal and vascular funtion in experimental diabetes. (Kidney Int 2002;61:939-50)

Vitamin B1 / Thiamine

The “problem” with water-soluble thiamine salt is it requires active transport to move across cellular membrane.

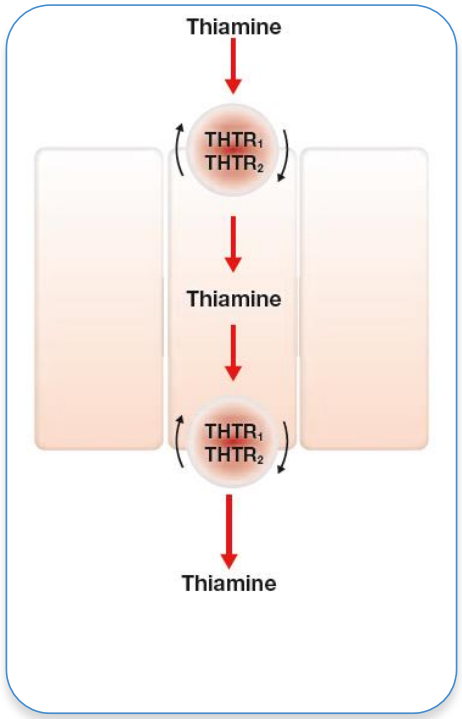
Lower expression of thiamine transporters (THTR-1, THTR-2) in renal tubular cells

Lower re-absorption of thiamine in proximal renal tubulus

Higher thiamine losses with urine

The rate of absorption declines with increasing oral dosage:

1 mg	**:**	**50% - 100%**
20 mg	**:**	**25%**
50 mg	**:**	**2% - 5.3%**



Singleton et al. Curr Mol Med (2001);1:197-207. Tallaksen et al. Eur J Clin Pharmacol 1993; 44:73-78. Weber et al. Eur J Clin Pharmacol 1985, 28:213-219.

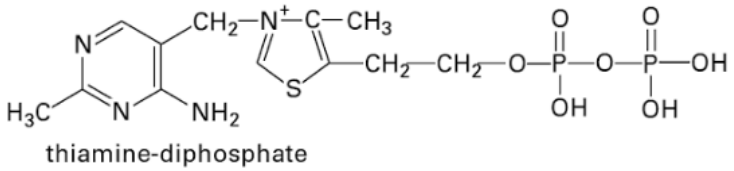
Hahn et al. Ernährung Physiologische Grundlagen. Prävention, Therapie (2016),

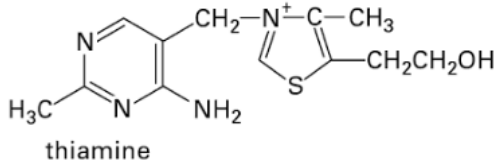
Hoyumpa et al. J Lab Clin Med 1982, 99:701-708.

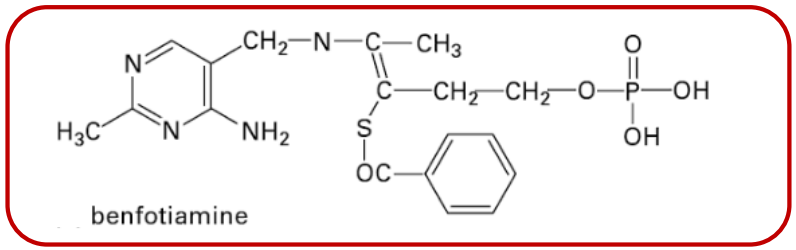
Benfotiamine

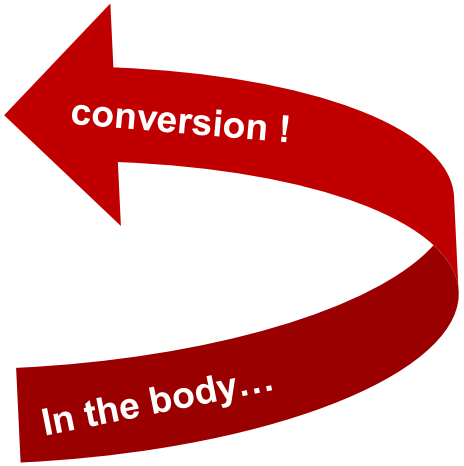
A vitamin B1 prodrug

- Benfotiamine = S-benzoylthiamine-O-monophosphate
- A prodrug, which is converted into thiamine (vitamine B1) and the active coenzyme form thiamine diphosphate (TDP) within the body
- Higher bioavailability than thiamine









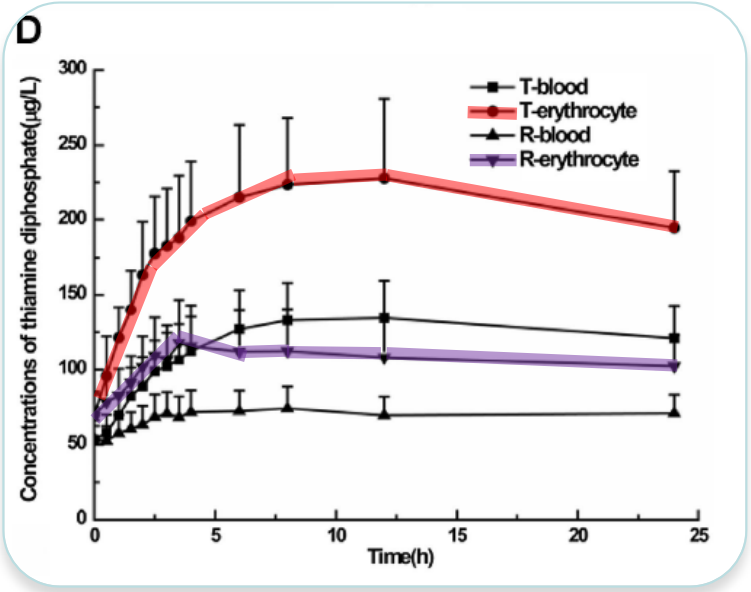
Beltramo, Vitamins in the Prevention of Human Diseases.

Benfotiamine drug concentration is higher than Thiamine

Bioavailability study:

Oral dosage with relative bioavailability of thiamine (300 mg benfotiamine, 220 mg thiamine HCl)

T: After oral benfotiamine
R: After oral thiamine-HCl



Benfotiamine:

- Higher concentrations of thiamine diphosphate (TDP, active metabolite of thiamine) in erythrocytes and blood than Thiamine-HCl
- Pharmacokinetic of thiamine in plasma and blood have main effected to increase form Benfotiamine.

Xie et al. J Clin Pharmacol. 2014;54(6):688-95

Diabetes Mellitus Classification

All of them indicate insulin production defects!

Type 1

- **Absolute insulin deficiency from pancreatic beta cell destruction**

Type 2

- **Progressive insulin secretory defect on the background of insulin resistance.**

- However, there are other types of diabetes that most doctors don't recognize such as alcoholic pancreatitis, post pancreatitis, malnutrition diabetes, and aging diabetes. I call it secondary diabetes.
- Without understanding the nature of disease, all the treatment guidelines went wrong and it is the patients who pay the price.

Secondary diabetes needs insulin

- A 65 years old male, who had diabetes for five years and was taking a lot of oral hypoglycemic drugs but couldn’t control his blood sugar with his HbA1c = 10.1% and creatinine 1.4 mg%
- He is a skinny man with history of heavy alcohol drinking.
- I asked him to stop oral hypoglycemia agents and start insulin injection. He also followed my dietary advice and taking supplements.
- One year after, his HbA1c was 7,1% with only insulin 12 units per day.
- His creatinine is now 1.1 mg% and he has no other diabetic complications.

Most doctors will avoid using insulin until it is late, way too late causing beta cells to die because of working overload!

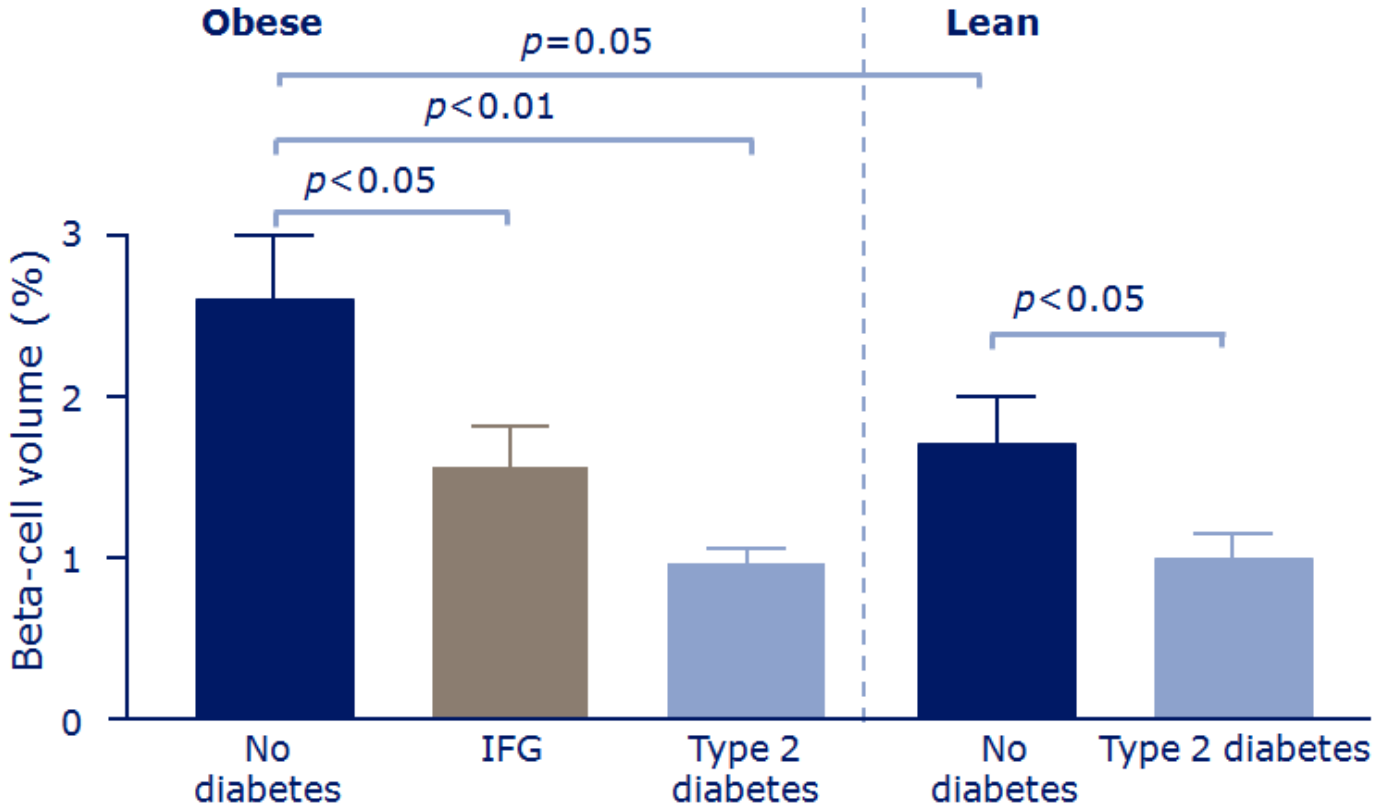
Insulin is not a bad thing because it will allow beta cell to rest and recover.

These diabetes patients will need insulin injection

- Diabetes with kidney and liver failure
- Skinny, malnourished diabetes
- Skinny, alcoholic with diabetes
- Post pancreatitis diabetes
- Long standing diabetes who begins to lose weight and loss appatite
- Older people with sarcopenia (frailty)

The pathophysiology underlying T2DM is progressive pancreatic beta-cell failure with consequently reduced insulin secretion plus insulin resistance in peripheral tissues.

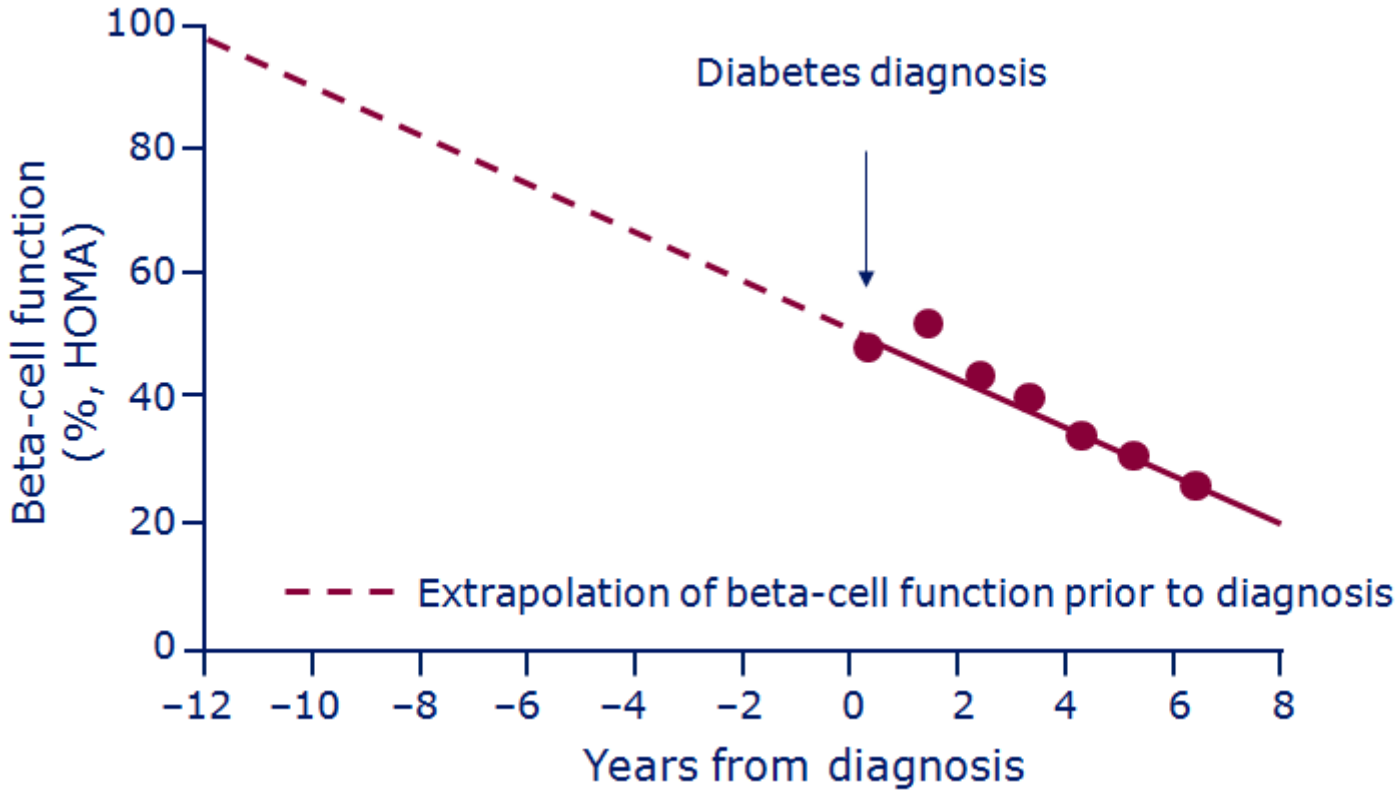
It has been suggested that, at diagnosis, only 20-50% of original beta-cell function remains.



IFG, impaired fasting glucose. Data are mean±SE
Obese: BMI >27 kg/m^2
Lean: BMI <25 kg/m^2

Adapted from Butler *et al. Diabetes* 2003;52:102–10

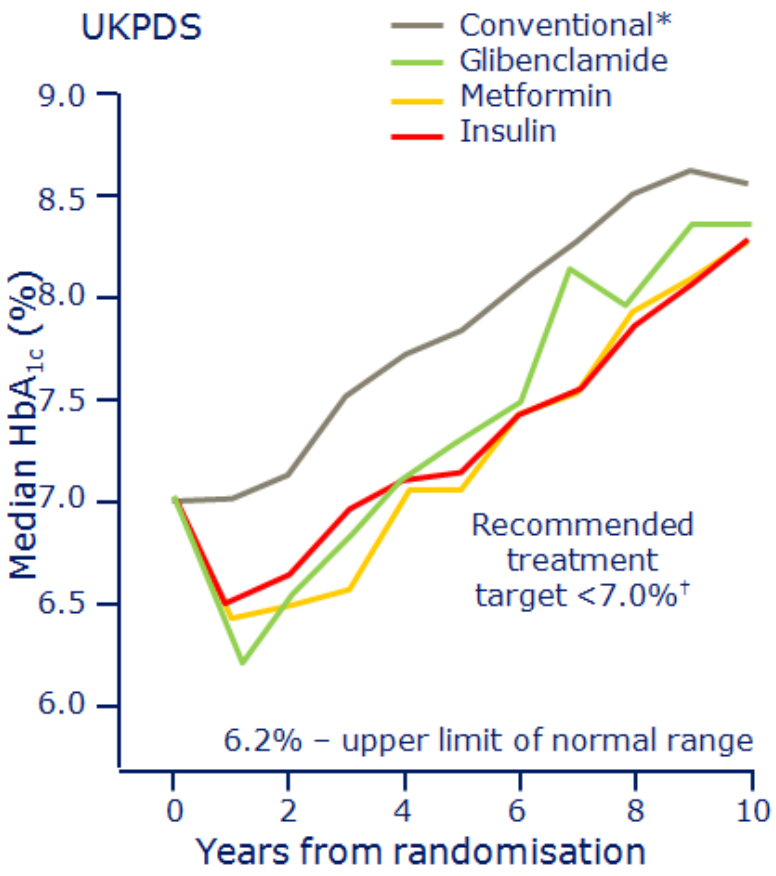
In T2DM, beta-cell function progressively declines despites treatment

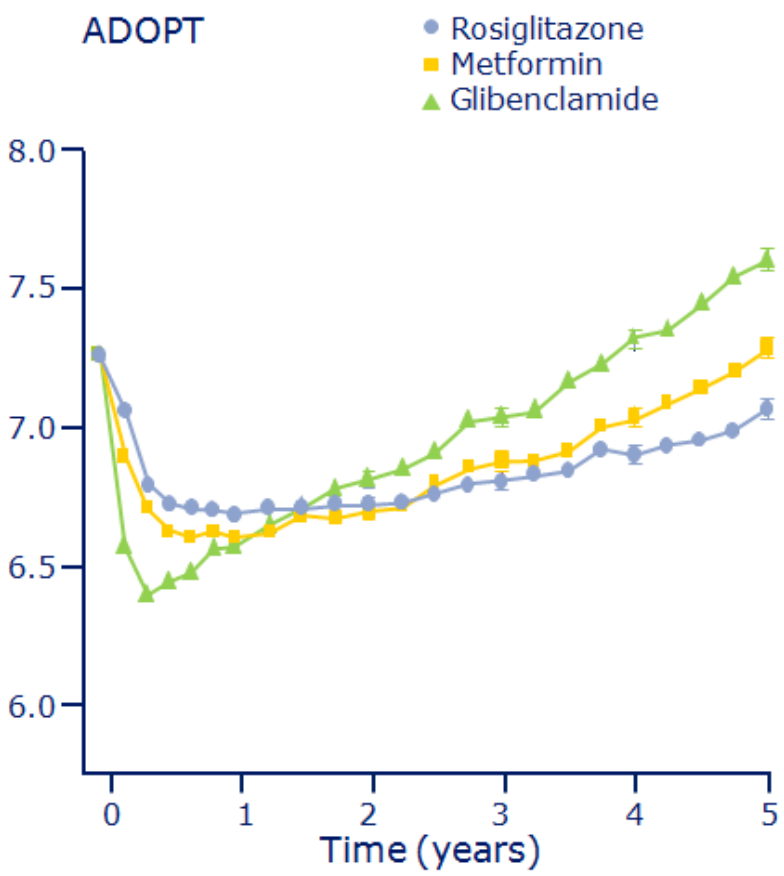


HOMA: homeostasis model assessment

Lebovitz. *Diabetes Reviews* 1999;7:139–53
(data are from the UKPDS population: UKPDS 16. *Diabetes* 1995;44:1249–58)

Continuous loss of beta-cells results in worsening glucose control over time



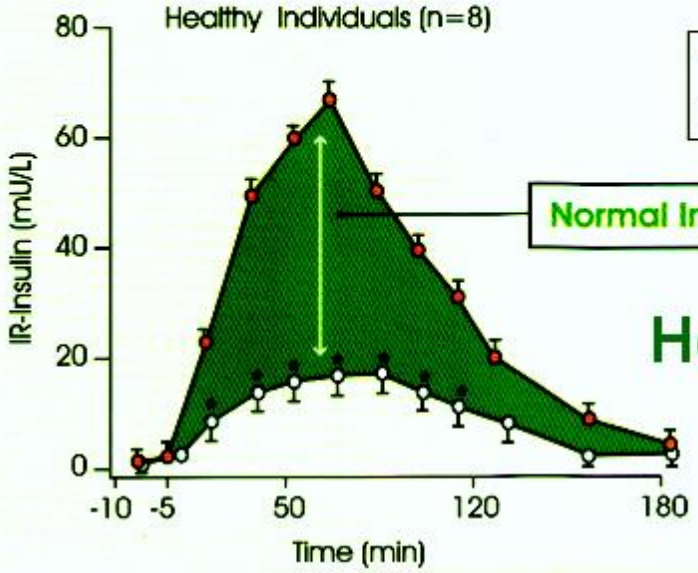


***Diet initially then sulphonylureas, insulin and/or metformin if FPG >15 mmol/L**

†ADA clinical practice recommendations. UKPDS 34, n=1704

UKPDS 34. *Lancet* 1998:352:854–65; Kahn *et al* (ADOPT). *N Engl J Med* 2006;355:2427–43

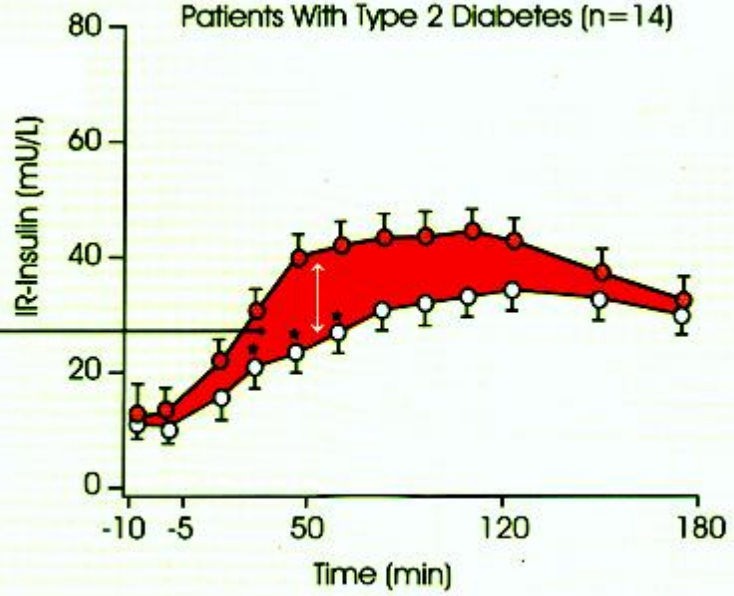
Oral administration of glucose increases pancreatic insulin secretion greater than an equivalent intravenous glucose.



Healthy Individuals

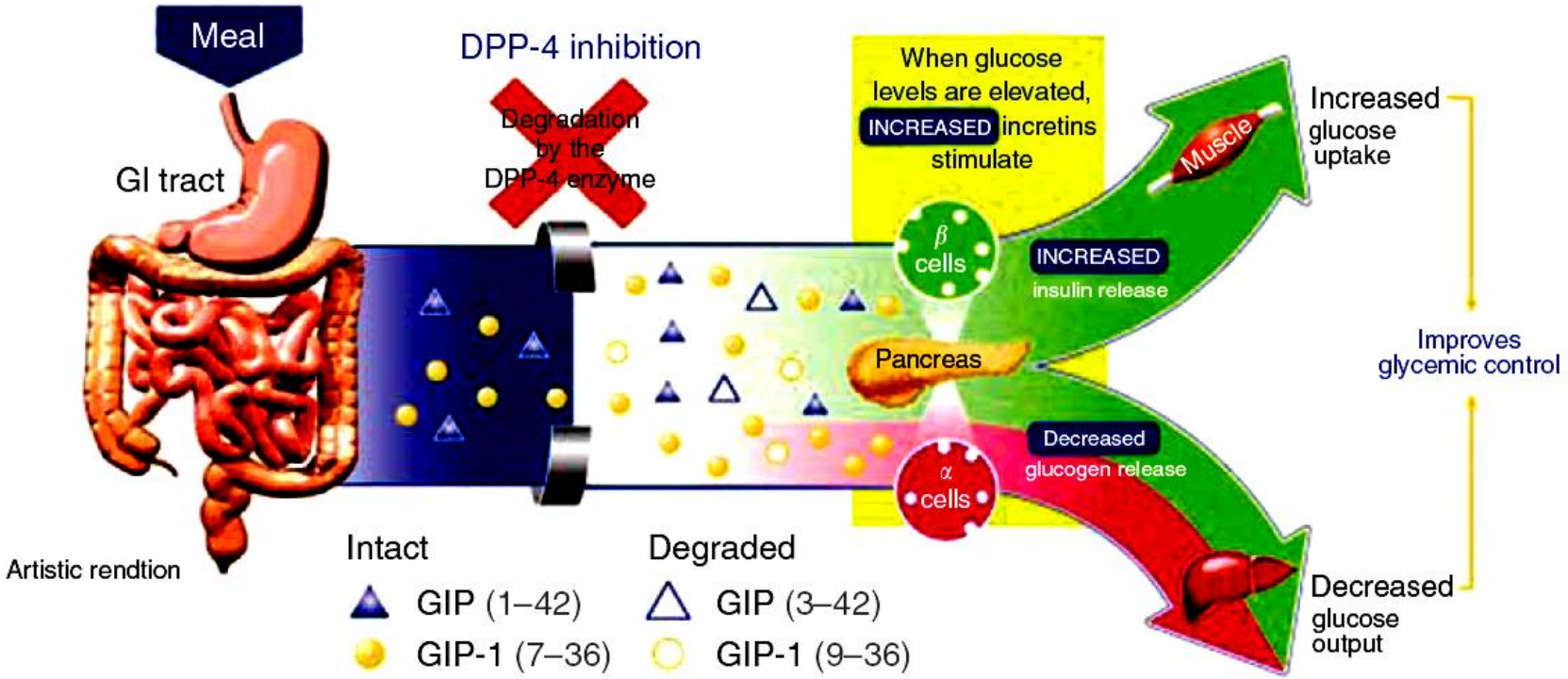
Type 2 Diabetes

Reduced Incretin Effect

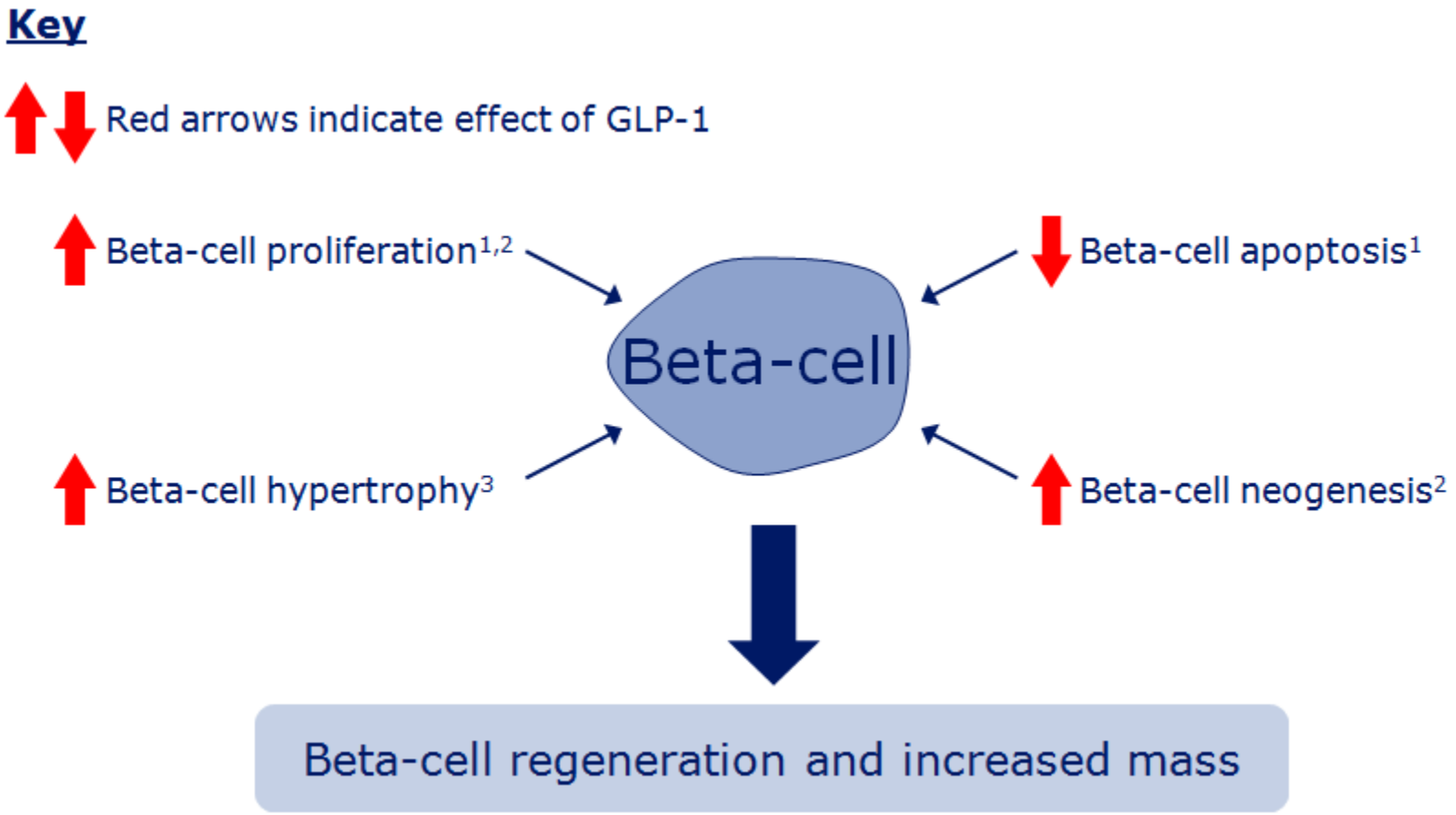


Meal stimulates the release of incretin hormones from intestinal mucosa resulting in insulin secretion

- **Glucagon-like peptide-1 (GLP-1)**
- **Glucose-dependent insulinotropic polypeptide (GIP)**



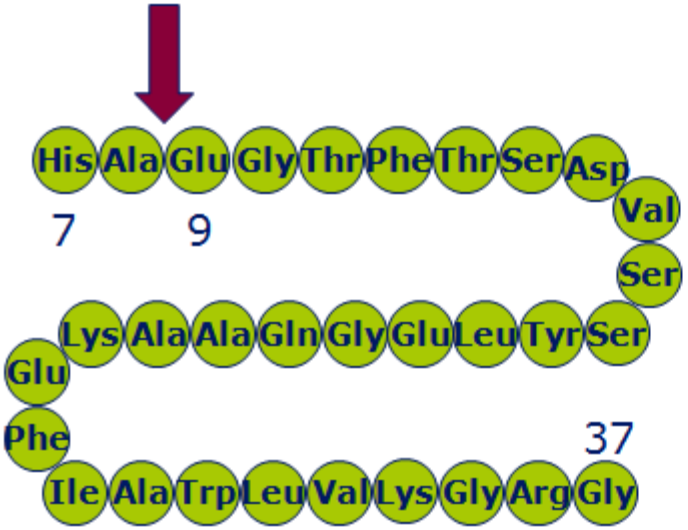
GLP-1 stimulates beta-cell regeneration and mass in animal models



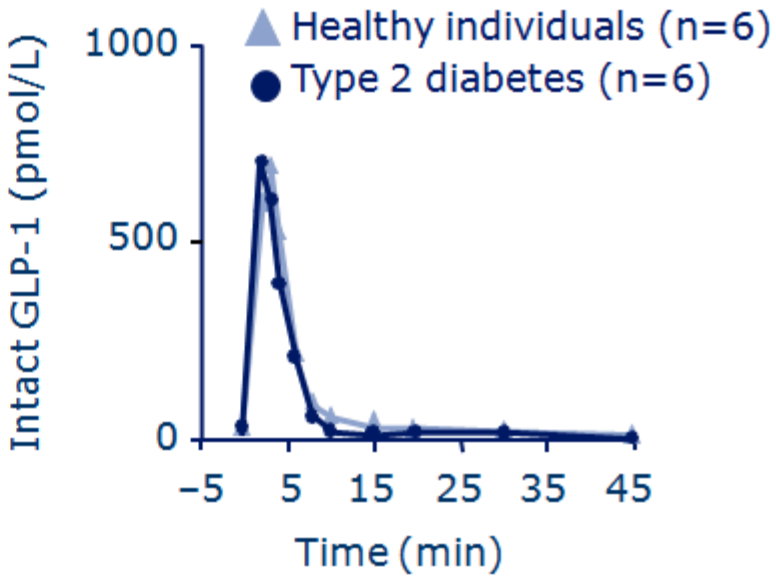
1. Farilla et al. Endocrinology 2003;144:5149–58; 2. Bulotta et al. J Mol Endocrinol 2002;29:347–60;
3. Klinger et al. Diabetes 2007;57:584–93

Native GLP-1 has limited clinical value because of its short half-life

Proteolytic inactivation by DPP-4



IV bolus GLP-1 (15 nmol/L)



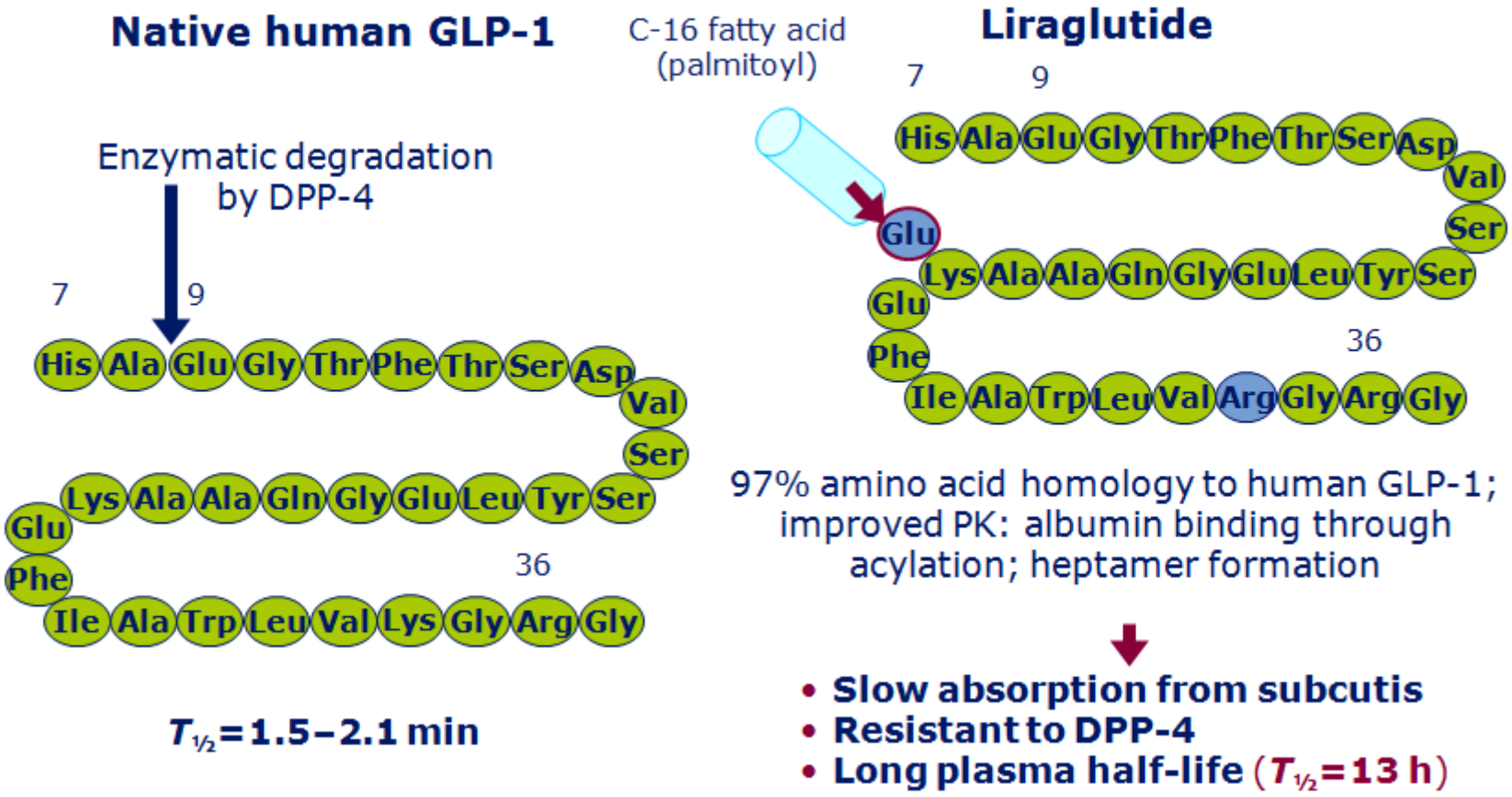
Enzymatic cleavage

High clearance (4–9 L/min)

→ $T_{½}$=1.5–2.1 min (IV bolus 2.5–25.0 nmol/L)

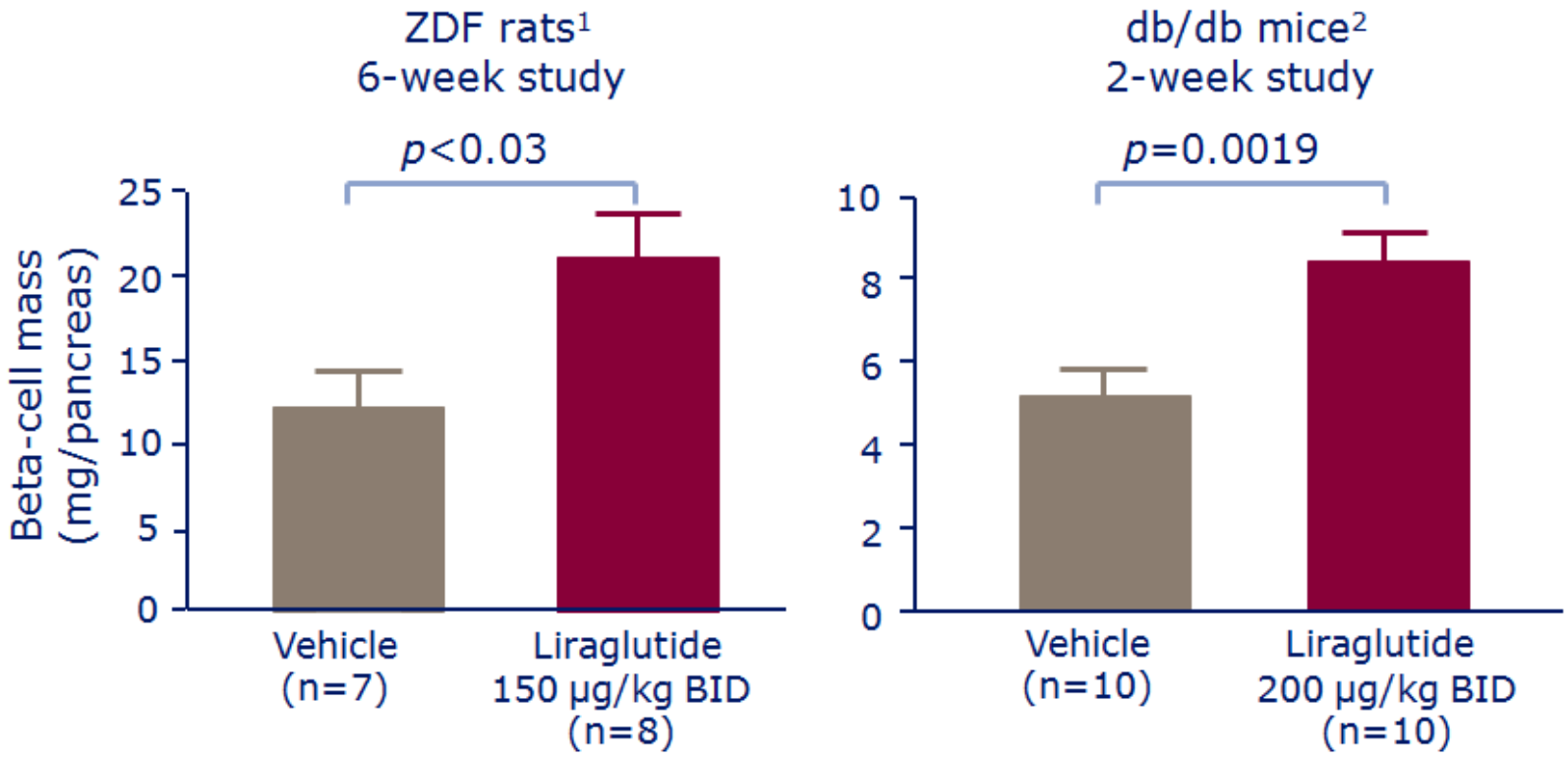
Adapted from: Knudsen. J Med Chem 2004;47:4128–34; Vilsbøll. J Clin Endocrinol Metab 2003;88:220–4

Liraglutide is a once-daily, human GLP-1 analogue



Knudsen *et al. J Med Chem* 2000;43:1664–9; Degn *et al. Diabetes* 2004;53:1187–94

Liraglutide increases beta-cell mass in animal models of diabetes



BID, twice daily; db, diabetic; ZDF, Zucker diabetic fatty (rats)

Adapted from 1. Sturis *et al. Br J Pharmacol* 2003;140:123–32; 2. Rolin *et al. Am J Physiol Endocrinol Metab* 2002;283:E745–52

Liraglutide Benefits
(LEADER Trial)

- Liraglutide is now approved for
  - 1. obesity
  - 2. blood sugar control in diabetes
  - 3, reduce the risk for heart attack, stroke, and cardiovascular death in those with type 2 diabetes and established cardiovascular disease.
-
- A trial of 9300 high-risk patients found that the composite **endpoint of myocardial infarction, stroke, and cardiovascular death was less common in patients assigned to liraglutide than those assigned to placebo** (13.0% vs. 14.9%) after 4 years' follow-up. Specifically, liraglutide was associated with lower rates of cardiovascular death (4.7% for liraglutide vs. 6.0% for placebo) and all-cause mortality (8.2% vs. 9.6%).

Practical Points of GLP-1 Application

- Start with 0.6 mg and increase the dosage every 2-3 days.
- Once patients don't feel too well stop injection for one day, and continue at lower dose.
- Continue injection for 3-6 months, then break for 3-6 month.
- Side effects are:
  - Dizziness, nausea, vomiting.
  - Brain fog
  - Hypoglycemia due to sugar dependent insulin secretion
  - Paradoxical Over-eating.
- To avoid side effects
  - Start injection at night, but you can switch to the morning time later.
  - Avoid eating simple sugar or high carbohydrate diets, it only makes things worse
  - Add intermittent fasting into program

When you are acutely ill, you may want to see a doctor, but when you have a chronic illness, the best doctor could be "YOURSELF".

Dr. Patana Teng-umnuay