Diabetes Mellitus

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NUTRINED WEBINAR

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HEALTH 121

“There is nothing new under the sun”

Ebers Papyrus 1552 B.C.

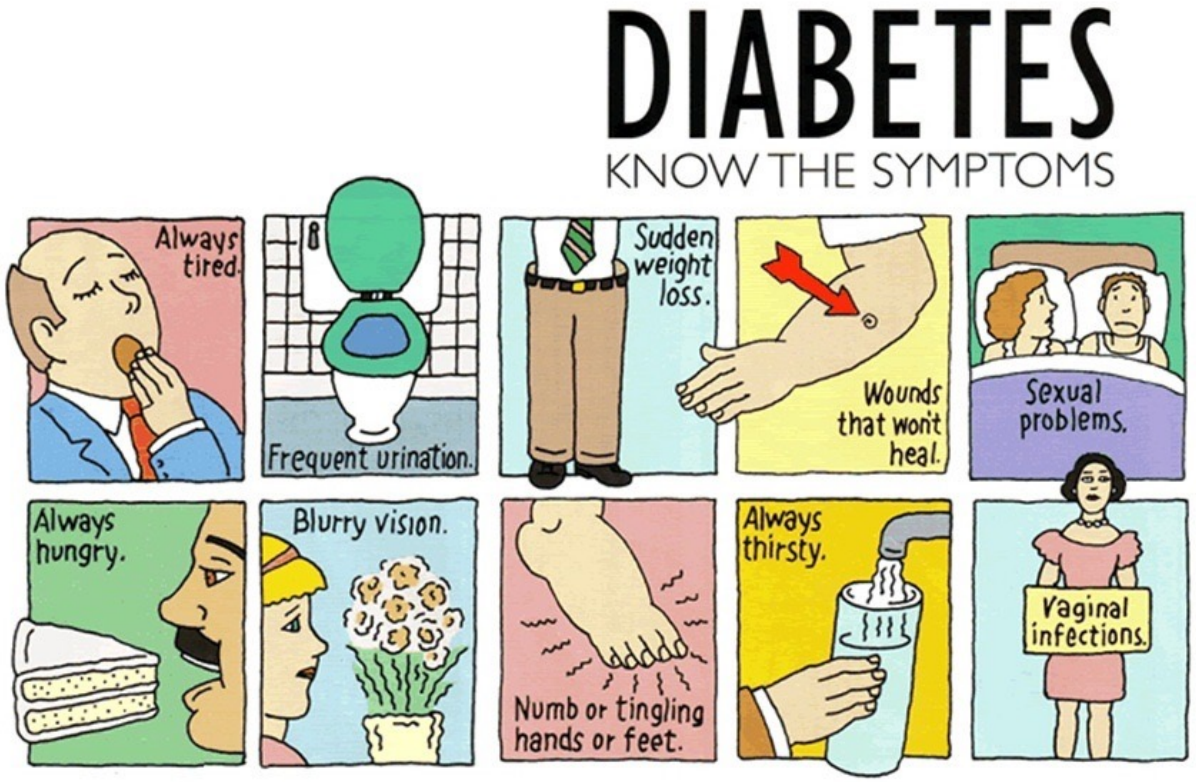
- oldest preserved medical document by Physician
- Translated by Egyptiologist, George Ebers 1875
- Alludes to a mysterious disease
- “…to eliminate urine which is too plentiful”

Aretaeus 100 A.D.

- “Diabetes is a dreadful affliction, not very frequent among men, being a melting down of the flesh and limbs into urine. The patients never stop making water and the flow is incessant…life is short, unpleasant and painful”

By 1000 A.D. – urine “sweet” Used urine wheel diagram

1675 term “mellitus” or “honey” added to diabetes (which means “siphon”)



Diabetes Mellitus

Metabolic condition

Chronically elevated blood glucose

Strict criteria for diagnosis

Symptoms

Osmotic: polyuria, polydipsia, blurred vision

Weight loss

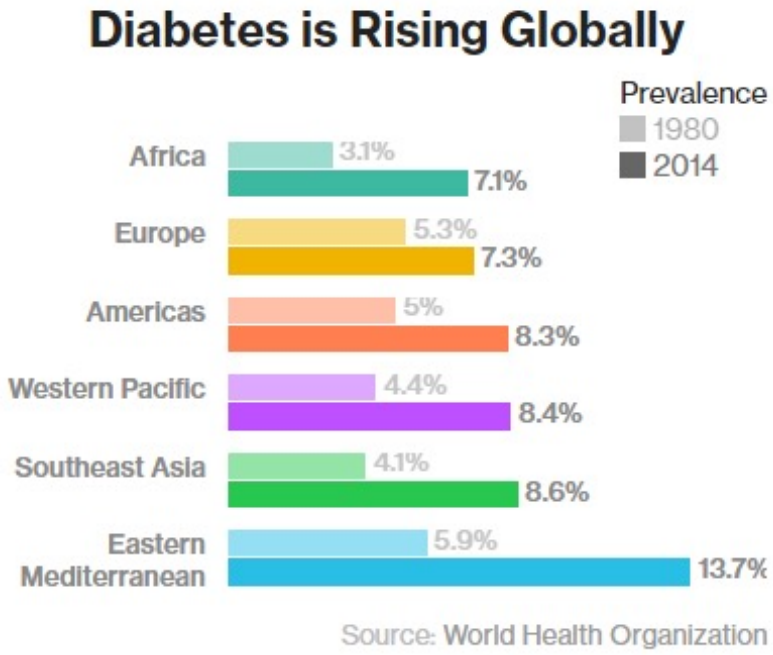
Recurrent skin infections

Diagnosis

Variable	Prediabetes	Diabetes
Hemoglobin A_{1c} level, %	5.7–6.4	≥6.5
Fasting plasma glucose level		
mmol/L	5.6–6.9	7.0
mg/dL	100–125	≥126
Oral glucose tolerance test results*		
mmol/L	7.8–11.0	11.1†
mg/dL	140–199	≥200†
Random plasma glucose level		
mmol/L	–	11.1
mg/dL	–	≥200‡

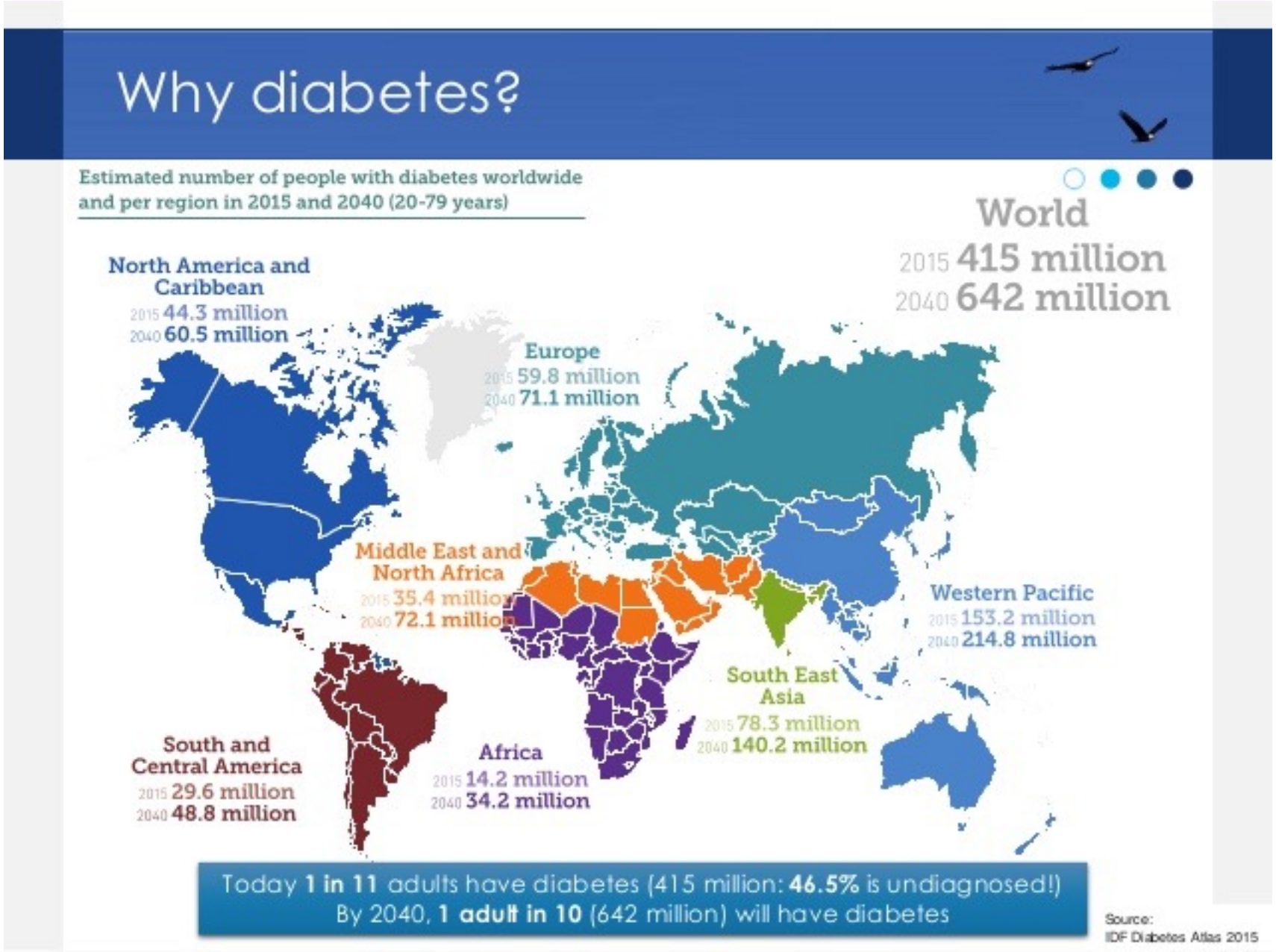
* 2-h plasma glucose level after a 75-g oral glucose tolerance test.
† In the absence of unequivocal hyperglycemia, results should be confirmed by repeated testing.
‡ Only diagnostic in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.

Increase HbA1c	Decrease HbA1c
African heritage	HbS and HbC
HbF and HbG	Haemolytic anaemia
Uraemia	Pregnancy
Alcoholism/Opiate addiction	Acute or chronic blood loss
Iron/B12 deficiency	Chronic Liver disease
Hyperbilirubinaemia	EPO
Chronic aspirin use	Severely elevated TG
Post splenectomy	High dose Vit C/E



2015 Global prevalence 8.8% adults
415 million people

International Diabetes Federation. IDF Diabetes Atlas - 7th edition [Internet], 2015.



Classification of Diabetes Mellitus

Type 1 Diabetes

- Beta cell destruction, Absolute insulin def
- Prone to DKA

Type 2 DM

Type 3

- Exocrine pancreatic diseases (3c): pancreatitis, CF, hemochromatosis
- Endocrine: Cushing's syndrome, acromegaly, pheochromocytoma
- Meds: glucocorticoids, neuroleptics, interferon- alpha
- Infections: Coxsackie, CMV, Mumps, Con Rubella
- Genetic defect
  - Beta cell function e.g. HNF-4alpha (MODY)
  - Genetic defect in insulin action e.g. Alstrom

Type 4: Gestational Diabetes

Diabetes Care 2010 Jan; 33(Supplement 1): S62-S69

Ketosis Prone Diabetes

- Patients who do not fit classical description for Type 1 DM
- Presenting with DKA
- Heterogeneous group
- DKA is due to virtually absent insulin or overwhelming IR
- 103 pts FU 12 months after DKA
- AutoAb (GAD, IA2) measured
- Glucagon Stim test
- Classification according to autoantibody status and beta cell reserve

Ketosis prone DM AB+ and reduced BCR

Antibody + Reduced beta cell reserve

- 17% pts, Age 34+/- 17 years
- Similar to T1DM: Lean BMI 24.5+/- 3.9 (but 39% BMI> 24.9)
- DQB1*02 and DQA*03 (+): type 1 diabetes susceptibility HLA alleles
- All required Insulin at 12 months to prevent DKA
- Predominantly African Americans (72%)!

Antibody -, Reduced beta cell reserve

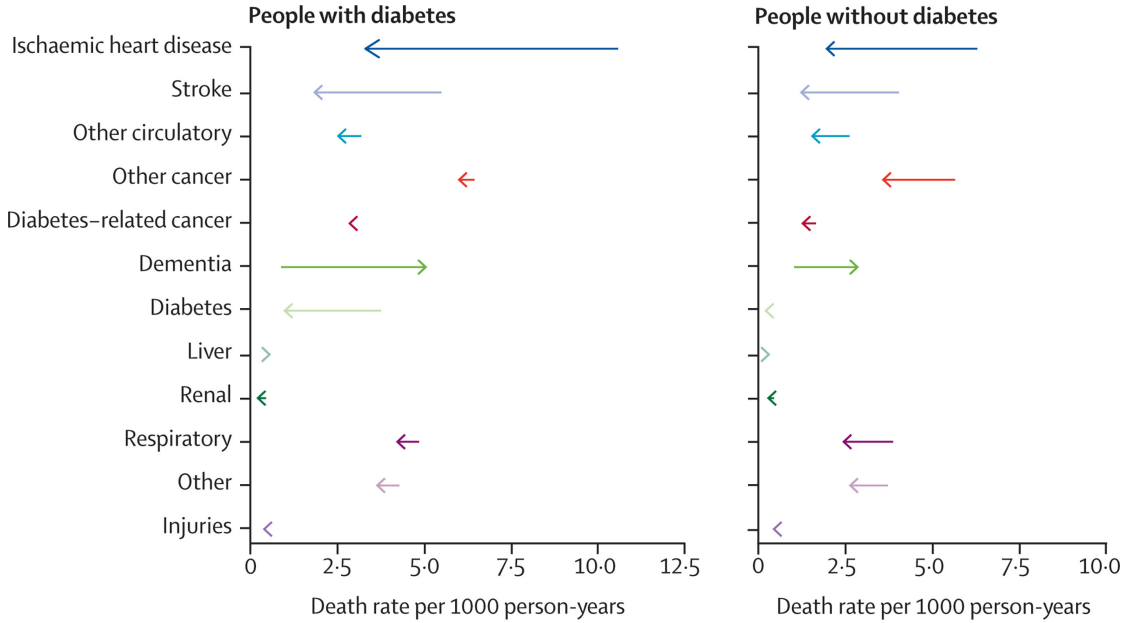
- Thought to be idiopathic T1DM
- ”Likely to have diverse pathological mechanism for ketosis prone DM”
- Age 38+/-15,
- Lean BMI 23 (26% BMI>24.9)
- All of them required insulin at 12 months follow up
- ? Type 3 DM

Ketosis prone DM

Antibody +, normal beta cell reserve
Latent autoimmune diabetes of Adults (LADA)
Age 43 +/- 14 years
BMI 30.6+/-7.6
45% discontinued insulin at 12m
Variable course/aggressiveness:
DQB1*02 (+) required insulin at 12 months to avoid DKA
DQB1*02 (-) were able to discontinue insulin

Antibody negative, normal beta cell reserve

- Largest group
- Majority new onset DM at presentation
- Low susceptibility HLA DQB1*02 and DQA*03
- Very heterogeneous
- 67% overwt/obese, 33% lean
- 88% FHx Diabetes
- 50% good control at 6m
- 61% did not need insulin at 12m



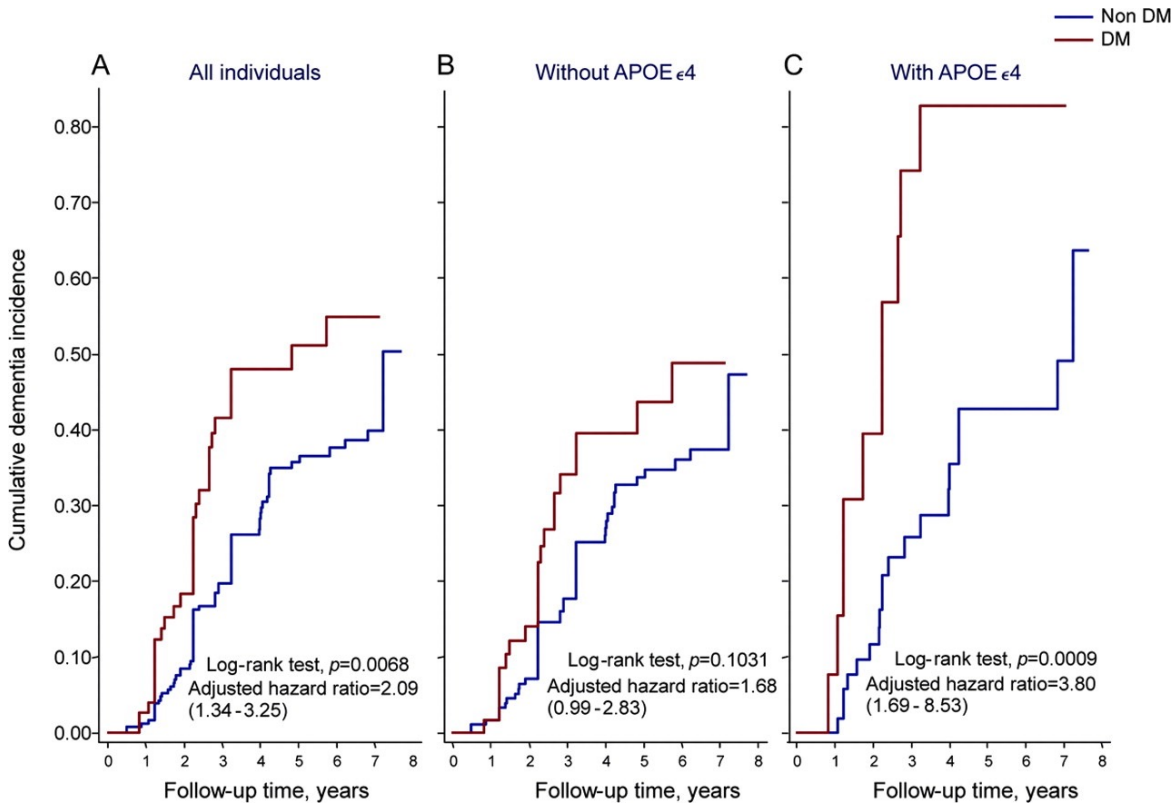
Changes in Mortality 2001-2018 in England

- All cause mortality decreased in all groups
- Cancer leading cause death (but not in US etc)
- People with DM still disadvantaged
- Notice Liver & Dementia related death increasing!!!
- The absolute gap in death rate was maintained!
- Mortality rate was higher in more deprived areas

Lancet Diab & Endo DOI: (10.1016/S2213-8587(20)30431-9)

Alzheimer's dementia

- Both diabetes and Alzheimer’s are age related
- OR for DM patient AD – 2 fold increased!
- Independent of CV risk factors.
- T2DM independent risk factor for conversion of mild cognitive dementia to AD
- AD conversion rate 57.4% in DM patients cf 42.6% in non-DM
- ApoE4 independent risk factor.
- AD: “Type 3 diabetes”



S. Ahtiluoto et al Neurology 2010. Ciudin et al J Diabetes & Complications. 2017

Diabetes and Mortality

- 689,300 participants followed over 13 years (2000-2013)
- Looked at all cause mortality and reduction in life expectancy
- 128,843 deaths
- 60-year old male with no prior history of DM, MI or stroke:
  - Risk of dying 0.7% per year or 6.8/1000 per year
- DM alone doubles the risk!
- HR for any 2 conditions = 4!
- HR for all three = 8!

JAMA. 2015 Jul 7; 314(1): 52–60.

Microvascular complications

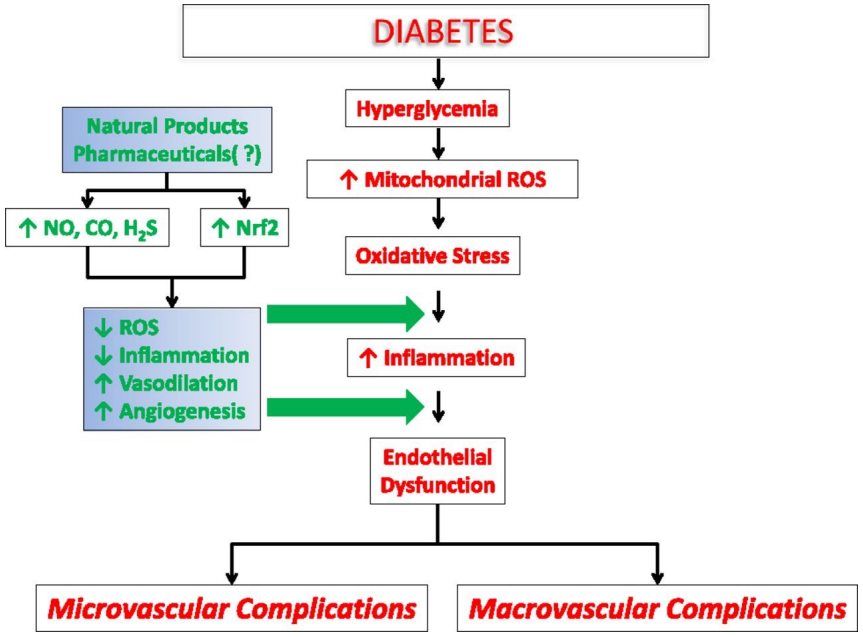
Damage to small blood vessels leads to microvascular complications

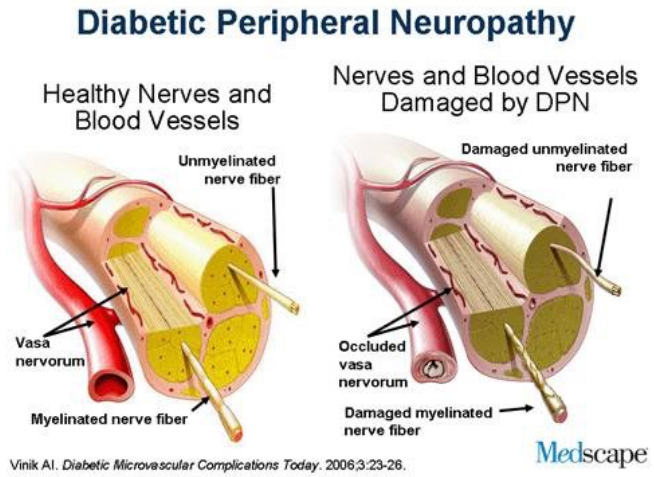
After 5years in T1DM

Might be present at diagnosis in T2DM

- Retinopathy
- Nephropathy
- Neuropathy

DM leading cause of blindness, amputations and kidney failure in Western World





Progress: Microvascular complications

Rate of blindness has been dropping from 1990 to 2012

Two major reasons:

- Annual screening tests – early disease treated quickly with laser/injections
- Tight glucose control

75% of all amputations secondary to diabetes

But Lower extremity amputation (LEA) has also declined

RR LEA Diabetic patient cf control 1990s: 26; dropped to 7.4 in 2005-2007!

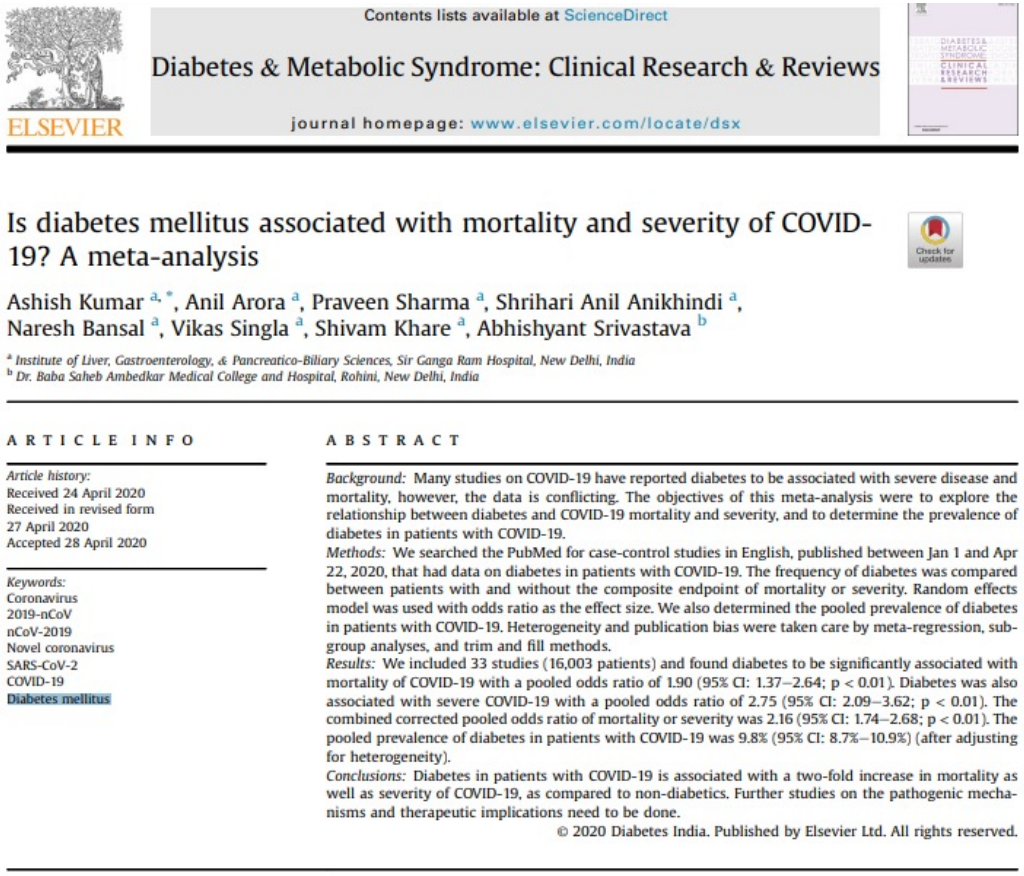
Main reasons similar:

- Daily inspection of feet
- Regular neurological examination of feet
- Tight glucose control

PMID: 29317450, PMID: 28846690

COVID-19 infection and Diabetes

- Meta-analysis 33 studies
- Jan 1 – April 22, 2020
- 16,003 patients
- Composite endpoint: mortality or severity
- DM associated with significantly increased:
  - Pooled OR death 1.9 (1.37-2.64; p<0.01)
  - Pooled OR severe infection 2.75 (95% CI: 2.09–3.62; p < 0.01)



Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis

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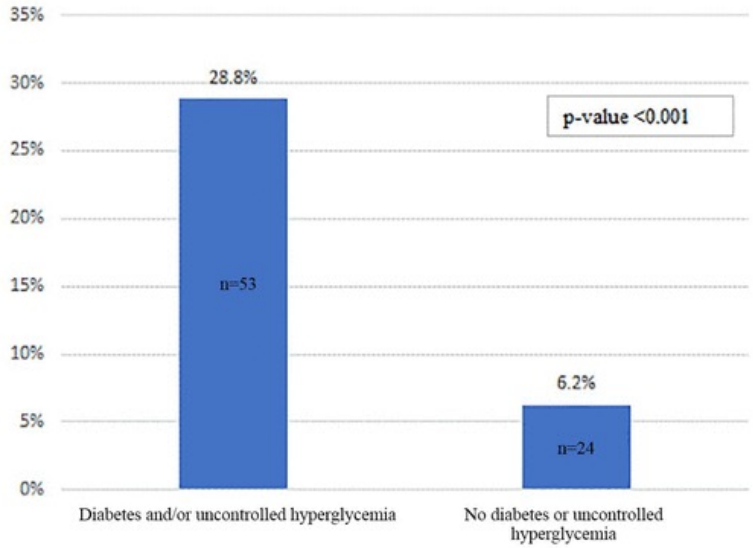
ABSTRACT

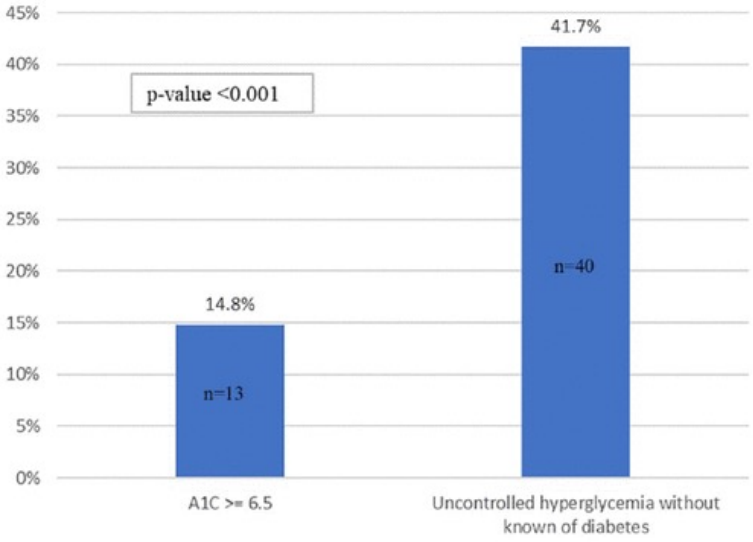
Background: Many studies on COVID-19 have reported diabetes to be associated with severe disease and mortality, however, the data is conflicting. The objectives of this meta-analysis were to explore the relationship between diabetes and COVID-19 mortality and severity, and to determine the prevalence of diabetes in patients with COVID-19.
Methods: We searched the PubMed for case-control studies in English, published between Jan 1 and Apr 22, 2020, that had data on diabetes in patients with COVID-19. The frequency of diabetes was compared between patients with and without the composite endpoint of mortality or severity. Random effects model was used with odds ratio as the effect size. We also determined the pooled prevalence of diabetes in patients with COVID-19. Heterogeneity and publication bias were taken care by meta-regression, subgroup analyses, and trim and fill methods.
Results: We included 33 studies (16,003 patients) and found diabetes to be significantly associated with mortality of COVID-19 with a pooled odds ratio of 1.90 (95% CI: 1.37–2.64; p < 0.01). Diabetes was also associated with severe COVID-19 with a pooled odds ratio of 2.75 (95% CI: 2.09–3.62; p < 0.01). The combined corrected pooled odds ratio of mortality or severity was 2.16 (95% CI: 1.74–2.68; p < 0.01). The pooled prevalence of diabetes in patients with COVID-19 was 9.8% (95% CI: 8.7%–10.9%) (after adjusting for heterogeneity).
Conclusions: Diabetes in patients with COVID-19 is associated with a two-fold increase in mortality as well as severity of COVID-19, as compared to non-diabetics. Further studies on the pathogenic mechanisms and therapeutic implications need to be done.

https://doi.org/10.1016/j.dsx.2020.04.044

Diabetes and COVID

- Risk of hospitalisation 3 times higher
- Risk 4.5 higher if DM and BMI > 40
- Hyperglycaemia on admission correlated with severity
- 29% of hospitalised patients who died were either DM or had uncontrolled hyperglycaemia
  - 41.7% with uncontrolled BG died cf 14.8% with DM but controlled BG
- DM might not increase risk of C-19 but may worsen C-19 outcome





Diabetes Research and Clinical Practice. 2021 (172), 108617. J Diabetes Sci Technol, 14 (2020), pp. 813-821. J Endocrinol Invest, 43 (2020), pp. 867-869

Pathophysiology

TYPE 2 DIABETES

Pathophysiology

Insulin Resistance (diminished response to insulin) PLUS

Decline in beta cell function

IR very important (esp muscle and liver)

Insulin mediated glucose uptake via GLUT-4 impaired in insulin resistance

Reduced cellular uptake – cell “starves”

Effects:

- stimulation of hepatic gluconeogenesis,
- inhibit lipolysis
- Increased hepatic glucose output

Excess carbs converted to TG

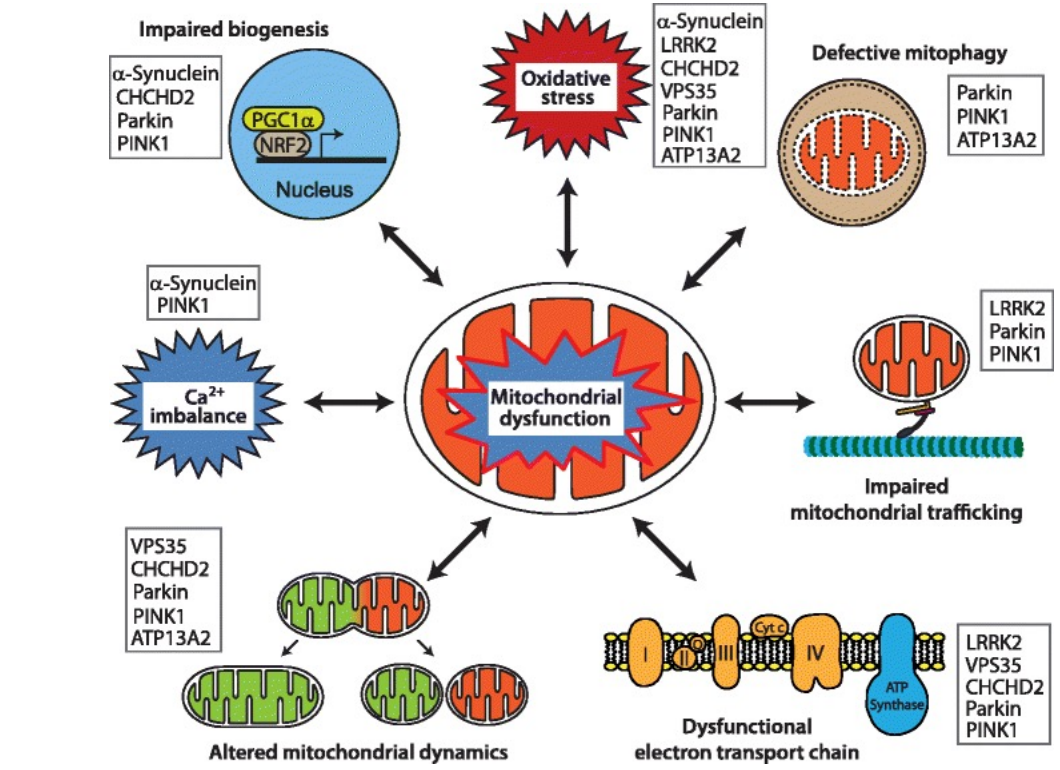
Accumulation of glucose and fats (TG and fat intermediates) in beta cells and liver and muscle drives IR (lipotoxicity)

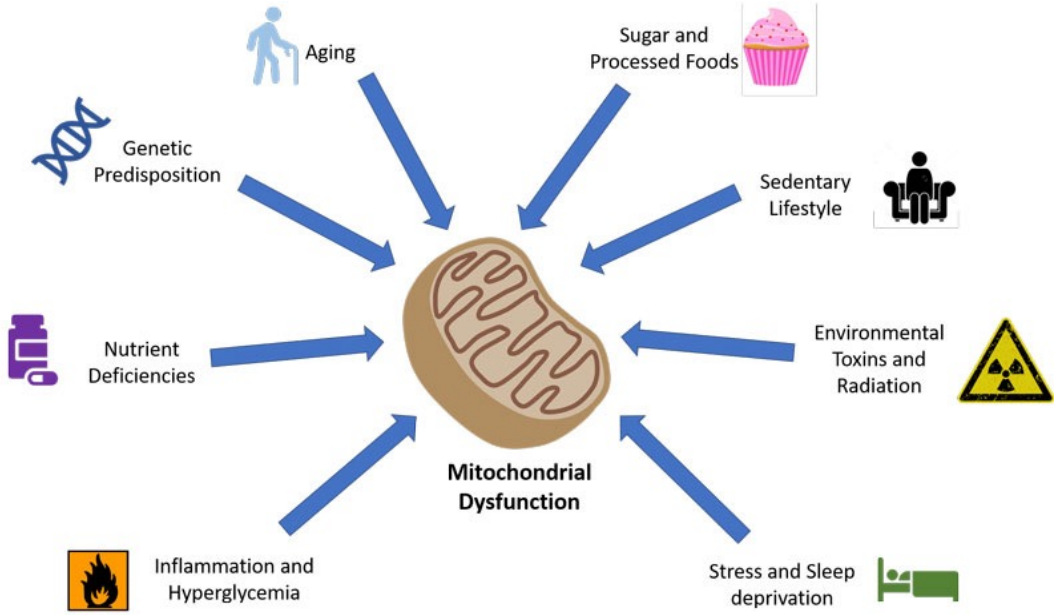
Mito dysfunction thought to be important

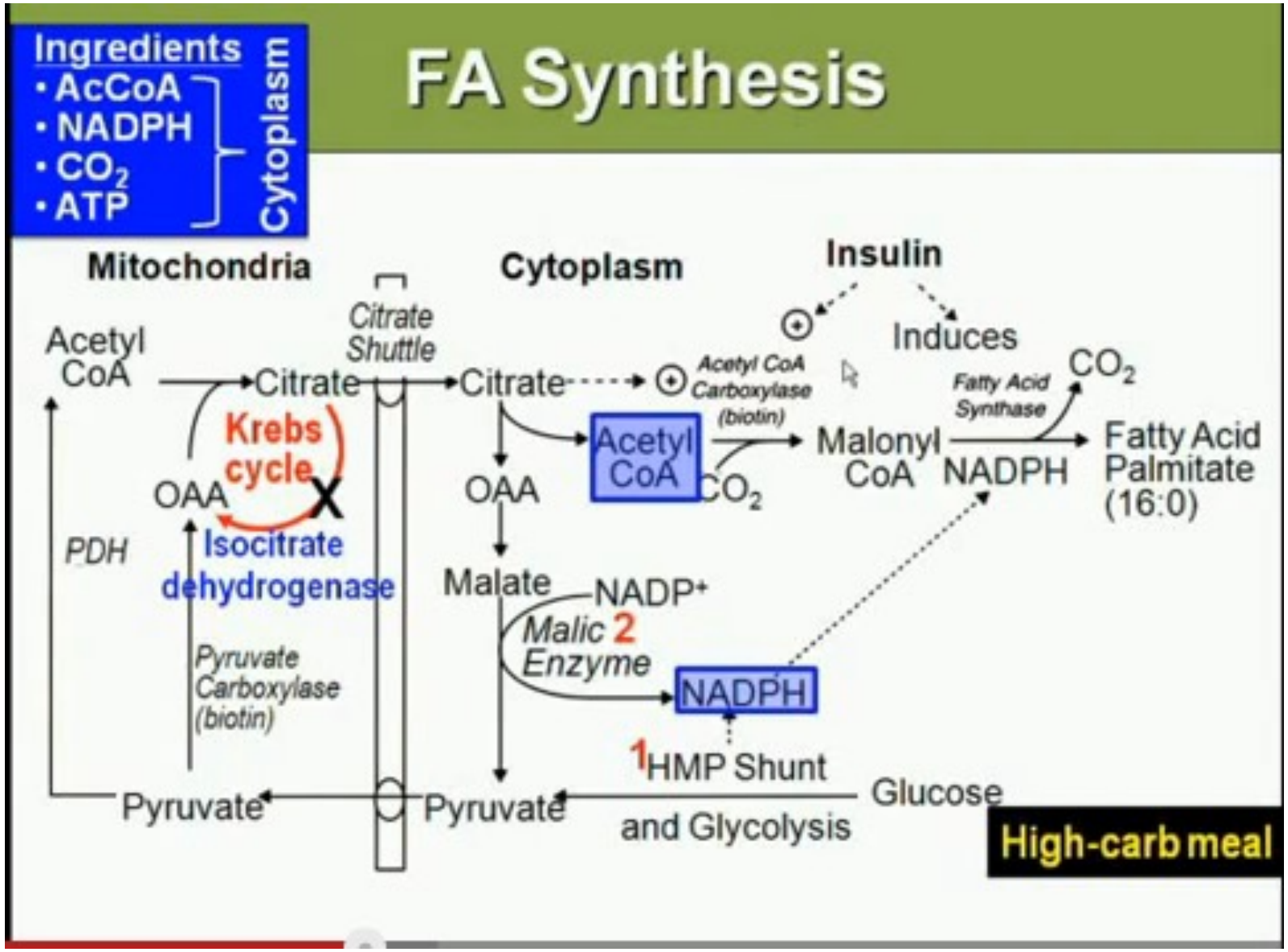
da Silva Rosa et al. Physiological Reports. 2020; 8(19)
Petersen, MC et al. Physiological Reviews 2018; 98: 2133–2223
Mehran AE et al. Cell Metabolism,. 2012;16, 723–737..

Mitochondrial Dysfunction

- Definition not set in stone:
  - Decreased Mito activity or
  - Decreased Mito number or
  - Increased ROS
- Stress response results in:
  - Decreased mitochondria biogenesis
  - Increased mito apoptosis
  - Reduced mito protein content
  - Reduced TCA/ETC activity
- Dysfunction is associated with a number of conditions including Obesity, IR, Pre-DM, T2DM, GDM (reduced placental mito content)

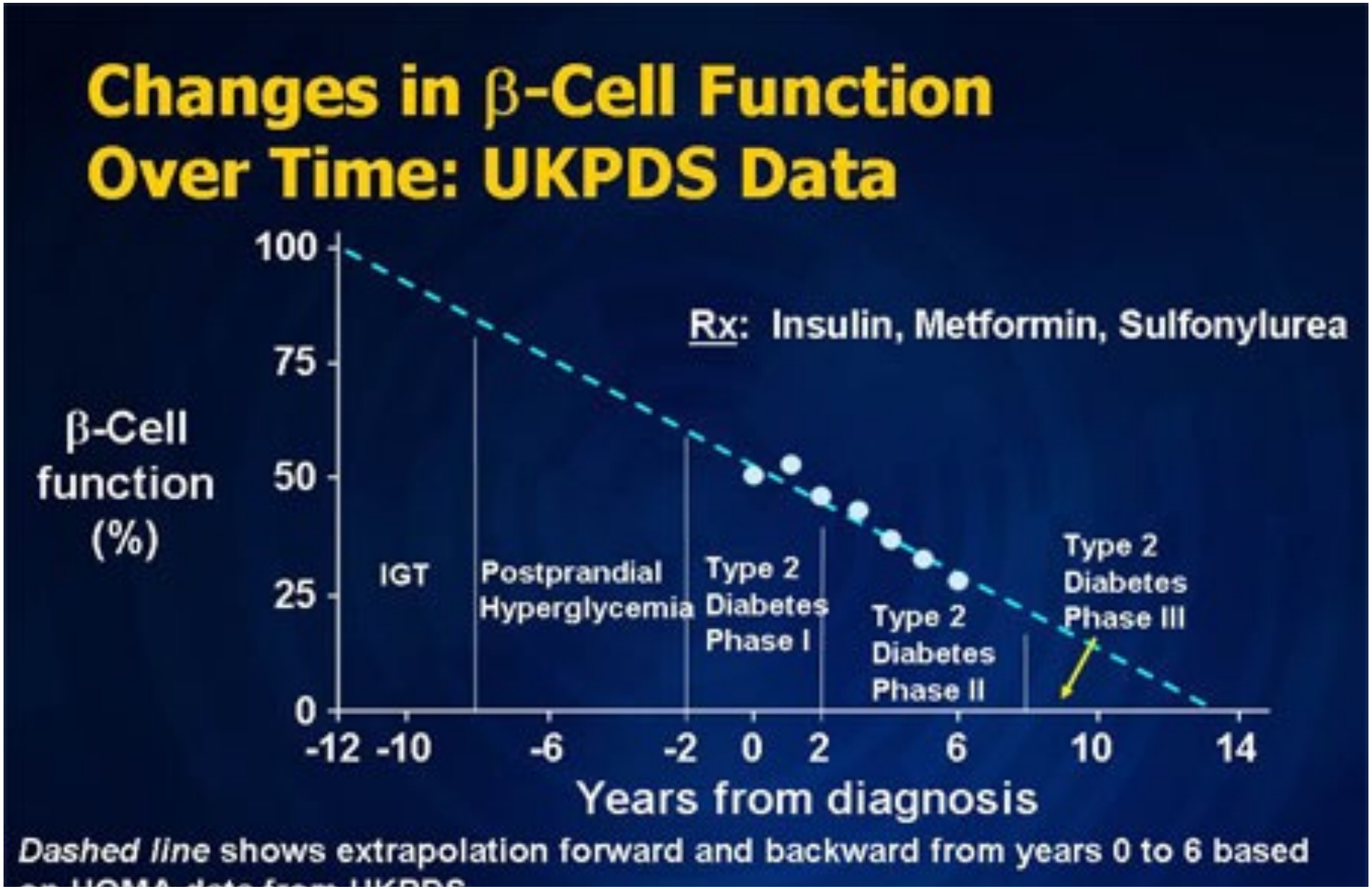






Country/ethnic group	Waist circumference value	
	Male	Female
Europids*	≥94 cm	≥80 cm
South Asians‡	≥90 cm	≥80 cm
Chinese	≥90 cm	≥80 cm
Japanese	≥85 cm	≥90 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available	
Sub-Saharan Africans	Use European data until more specific data are available	
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available	

*In the USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes, ‡Based on Chinese, Malay and Asian-Indians populations



Metabolic Syndrome

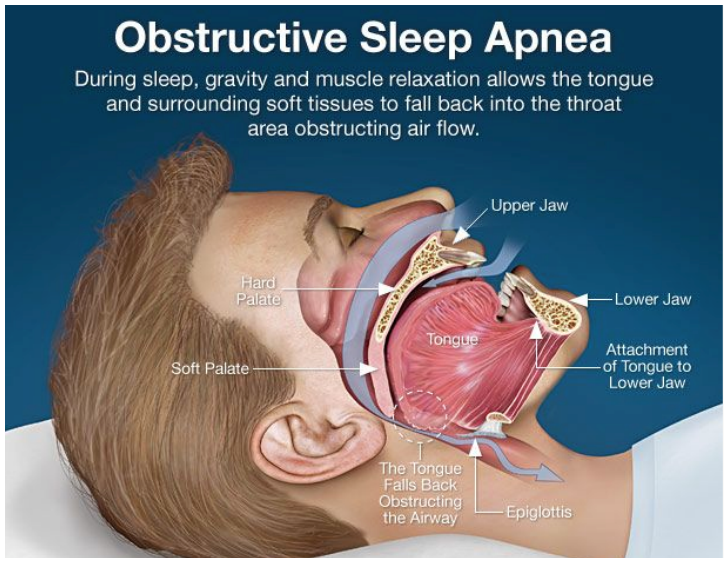
- Observations as early 1920's
- Term first used late 1970's/early 80's
- Constellation of conditions
- Predicts CVD
- Predicts DM risk
- Associations with gout
- Underlying mechanism IR

	TG	HDL	BP	FG	WHR or waist circ	Criteria
IDF	>1.7 or Rx	<1.03 (M), <1.29 (F)	>130/85 or Rx	>5.6 or known T2DM		↑WHR or BMI>30 plus 2
WHO	≥ 1.695	≤ 0.9 (M), ≤ 1.0 (W) in conj with TG	≥ 140/90	Not used but Microalbumin	WHR >0.9 > 0.85 (W) or BMI > 30	T2DM/ IGT/IFG plus 2
EGIR	≥ 2.0	HDL < 1.0 in conj with TG	≥ 140/90 or Rx	≥ 6.1	≥ 94cm	Fasting insulin plus 2

Other Risk Factors

- OSA
- Toxins
- Medications
- Artificial sweeteners

Obstructive Sleep Apnoea



Endocr Pract 13: 355–62
Hypertension. 2011; 58: 811–817

49% Men and 21% women with T2DM have OSA

71% prevalence BMI 35-39.9

80% OSA pts have metabolic syndrome

15% OSA patients have T2DM

80% resistant H/T have OSA

20% risk of Stroke

Increased risk arrhythmias

FATIGUE

Snoring

Nocturia

Night sweats

Early morning headaches

Choking sensation at night

Apnoeic episodes

Neck Collar > 17”

Fructose Metabolism

Glucose → glycogen.

- Insulin stimulated

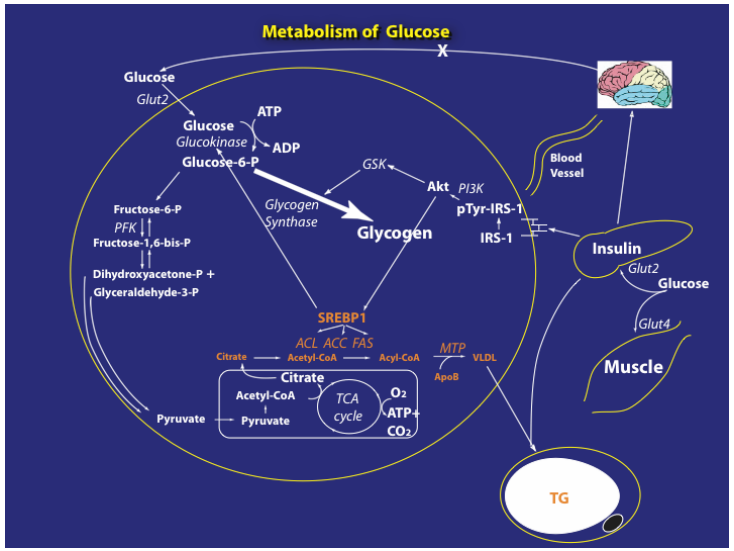
Fructose only metabolised in liver

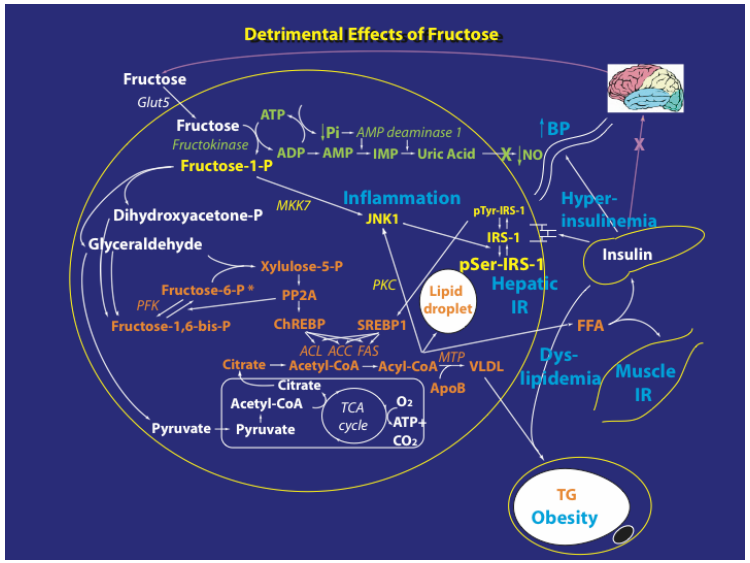
No Insulin

De novo lipogenesis

Inflammation/ROS

Fatty Liver, Hepatic IR





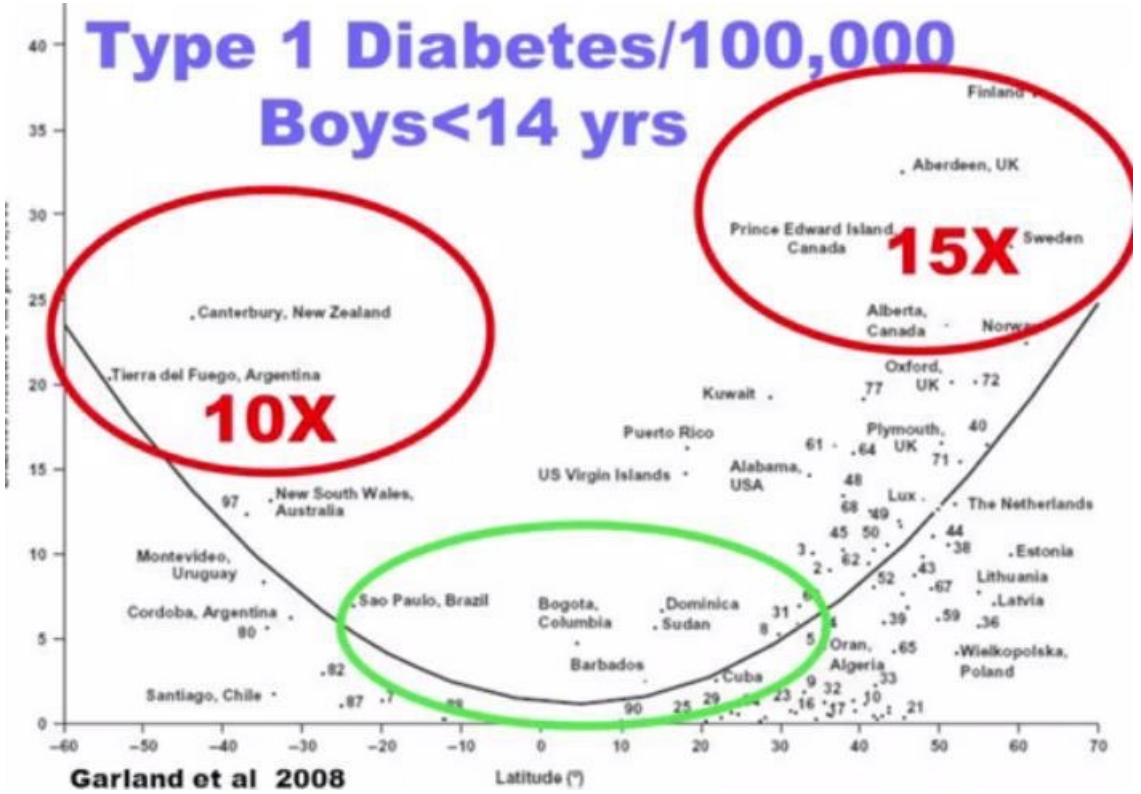
Artificial Sweeteners

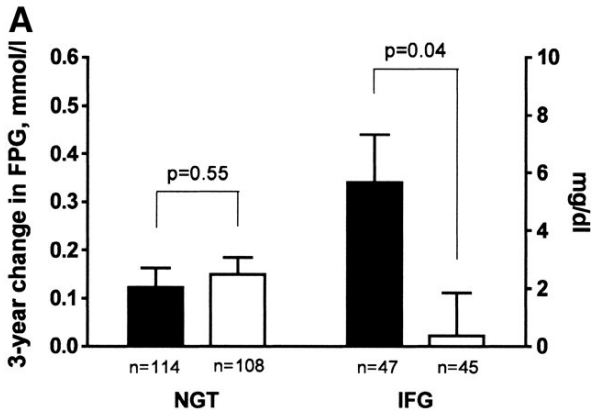
- One study of 27 Healthy volunteers
  - Capsules of sucralose and acesulfame K or placebo
  - Three times a day before meals for 2 weeks
  - Equivalent to 1.5 Liters of diet drink daily
  - Glucose absorption, blood glucose and insulin levels and gut peptides adversely affected by artificial sweeteners in just 2 weeks!
  - Caution – small study
- One Can of diet soda/fizzy drink assoc with:
  - **36% incident MS**
  - **67% incident DM**
- Baseline high waist circum >101cm in males and 87cm in women and FG> 5.4 predicted development of MS
- DM group findings independent of adiposity

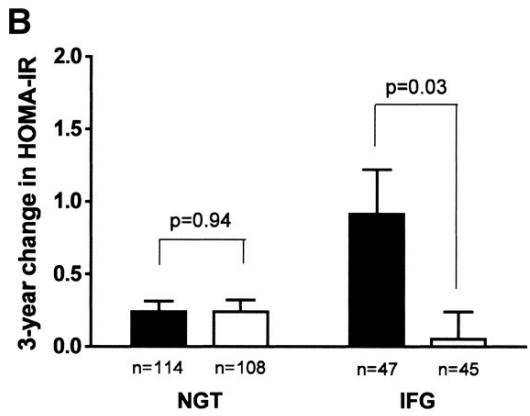
Prof Richard Young Presented EASD 2017
Diet Soda Intake and Risk of Incident Metabolic Syndrome and Type 2 Diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA)

Micronutrients & Vitamin D

- Micronutrient deficiency – paradoxical nutritional deficiency in obese patients.
- Women taking multivitamins reduce hunger,
- Less weight gain with B6, B12 and chromium,
- Men taking multivitamins have lower body fat
- Calcium supplementation accentuates weight loss
- Vitamin D3 in pre-diabetes
- T1DM Study
  - 10,366 Finnish Children
  - Regular Vit D 2000 units/day from 1 year age:
  - Decreased risk of T1DM assessed at age 31 yrs
  - 88% reduction in risk of T1DM!
  - 80% reduction in those with irregular intake
  - 3 fold increased risk T1DM in children who had rickets
- Vitamin D immunomodulatory: reduces cytokine and promotes Treg



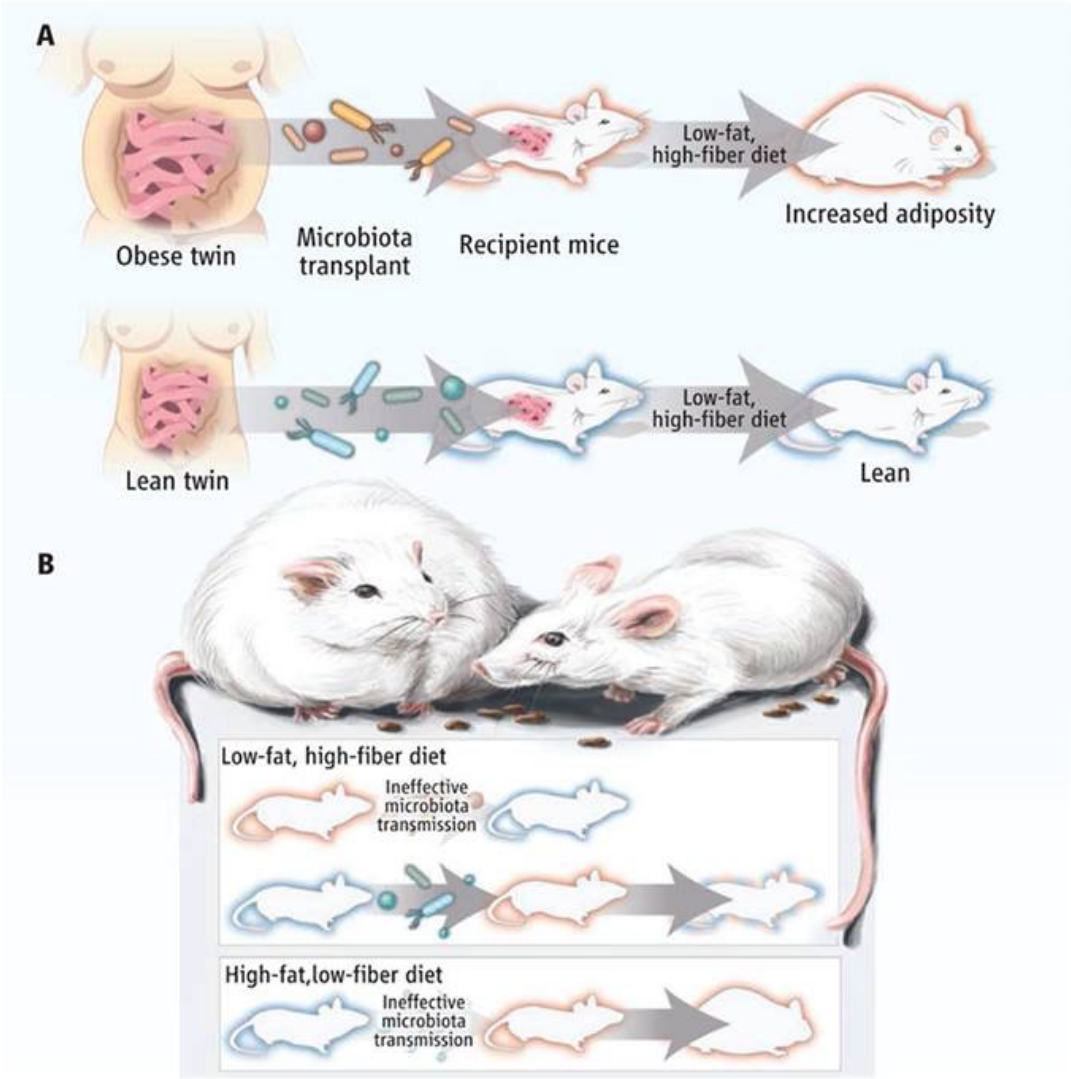




Hypponen et al. Lancet 2001; 358: 1500-03

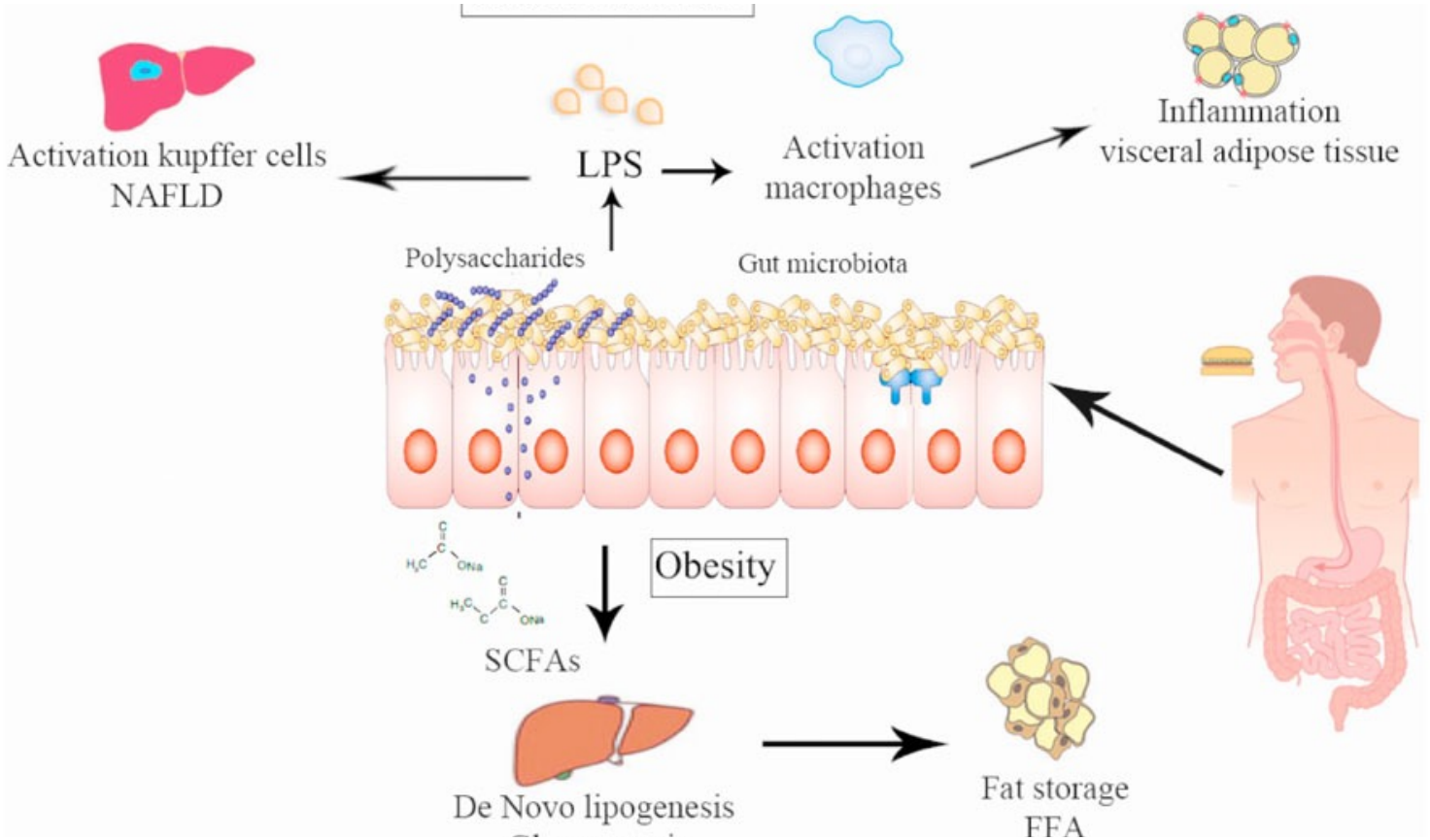
Gut microbiome

- Dietary changes responsible 57% of structural variation in gut microbiota cf 12% genetics
- Diet plays very important role
- Humanized Mice model underwent human fecal transplant and fed low fat plant based foods
  - Then given “Western Diet” or high carb/high fat diet:
  - Microbiota switched to excessive colonization with Firmicutes organisms: Changes in Phyla linked with obesity and diseases
- Another study: Four pairs of human female twins with significantly different BMI
  - Stool transplant into lean germ-free mice and fed low fat diet
  - Mice took on phenotype of host human
  - Mice given “fat stool” were 15 – 17% heavier



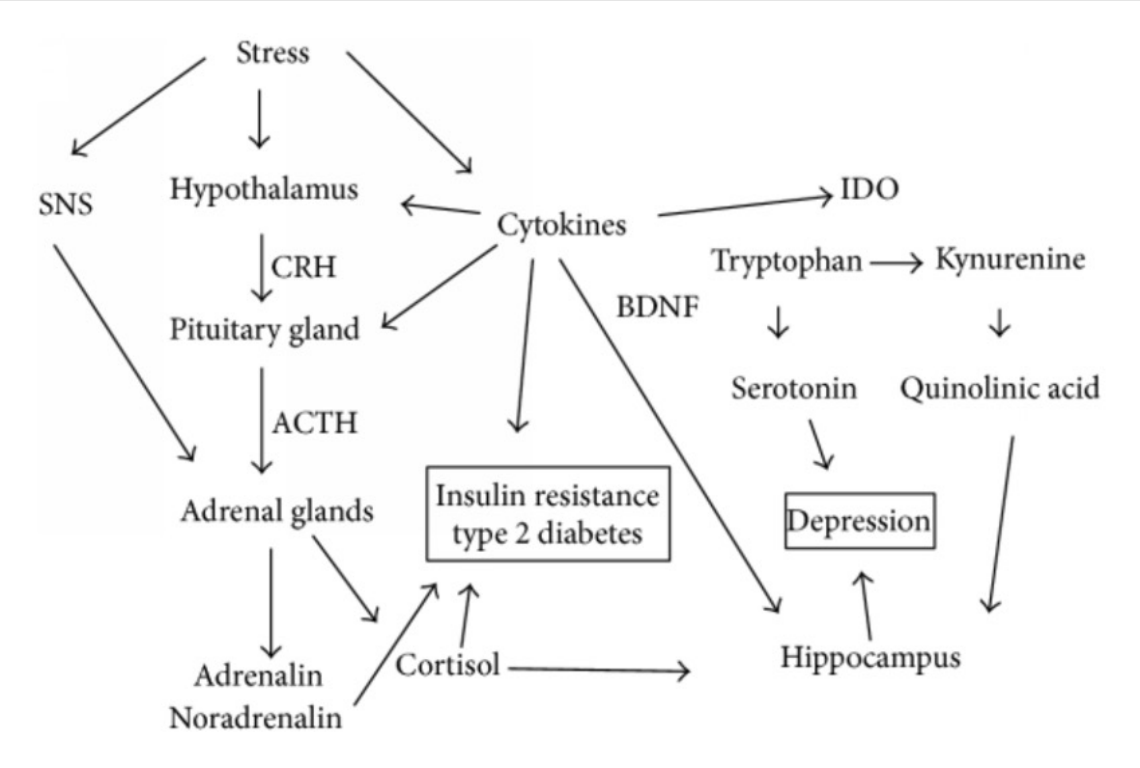
Turnbaugh et al. Sci. Transl. Med. 2009
Ridaura et al Science 2013

Gut Inflammation



- Lipopolysaccharides (LPS)
- Endotoxin from outer membrane of Gram (-) bacteria
- Initiate inflammation associated with obesity and IR
- Much higher conc LPS in obesity cf healthy controls
- Unfavorable diet (high fat/high carb) alters gut microbiome = gut dysbiosis
- Increased gut permeability
- Increased systemic LPS
- Activation of inflammation in Liver and adipose tissue

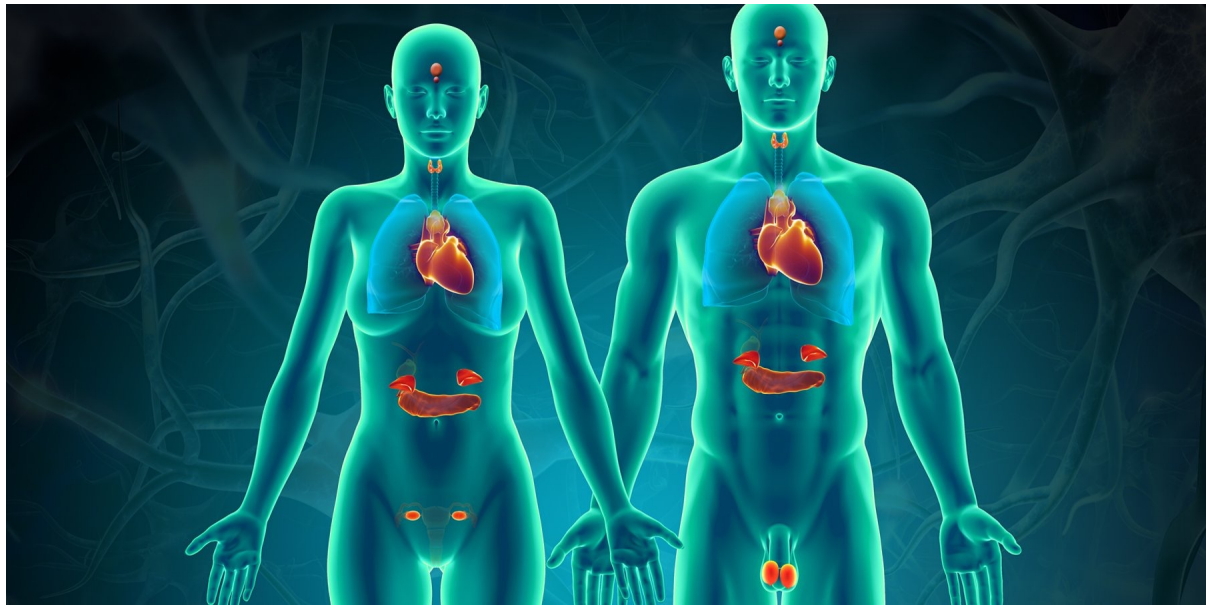
Stress



- 7,956 Elderly individuals
- Cumulative stressful life events and recent stress associated with incident diabetes
- Human studies shown increased association of stress with
  - T1DM,
  - T2DM,
  - Obesity and
  - poor control in patients with DM
- Animal models show association with T1DM

Endocrinopathies

- Sex hormone
- Males: Hypogonadism
- Women Child bearing age: PCOS
- Menopausal women: HRT?
- Peri-menopause: progesterone
- Thyroid dysfunction
- Cushing's – rare
- High blood pressure in young individuals



Medications

Weight Gain

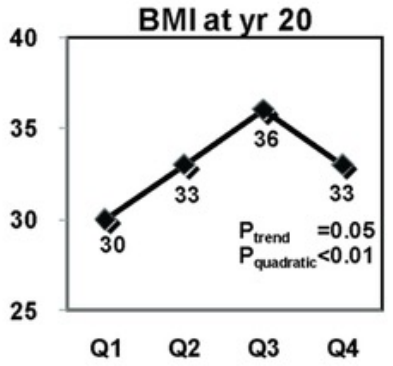
- Atypical antipsychotics
- Antidepressants
- Valproate
- Insulin, SU
- Beta blockers
- Steroids
- Synthetic progesterone

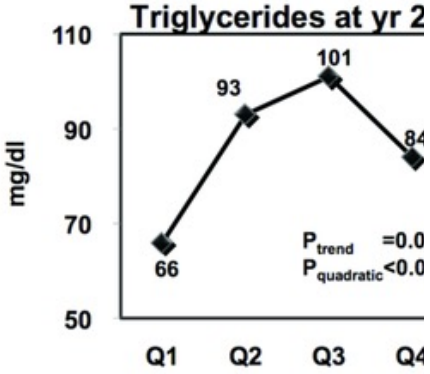
Weight loss/neutral

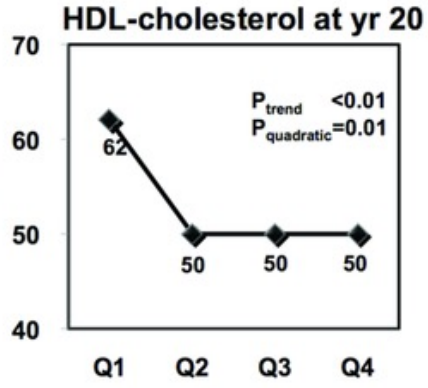
- Aripiprazole
- Fluoxetine, rTMS
- Topiramate
- Metformin, GLP-1 agonists, SGLT-2i
- ACEI, ARB

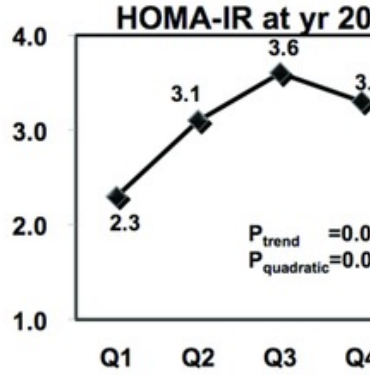
OC Pesticides and PCB predict Obesity, Dyslipidemia and DM

- Non diabetic population
- Serum levels of POP at 2 years and 20 years
- Organochlorine pesticides and Polychlorinated biphenyls predicted:
  - Higher TG
  - Higher BMI
  - Lower HDL
  - Increased IR
- Simultaneous exposure to POP contributed to MS



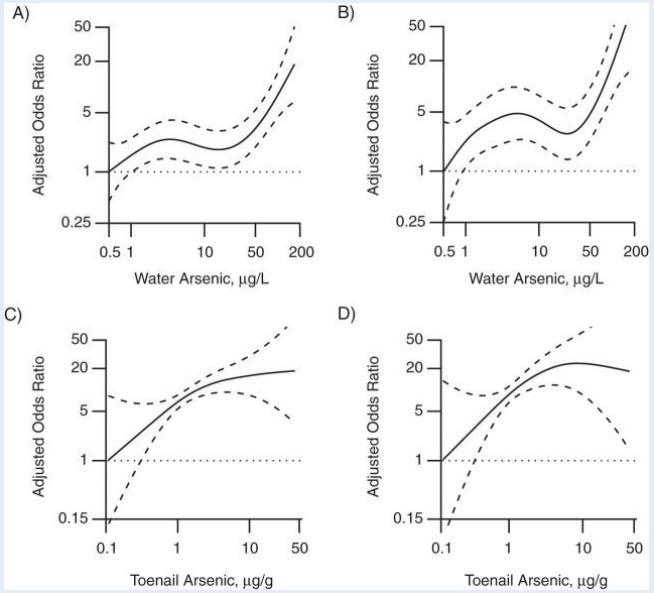






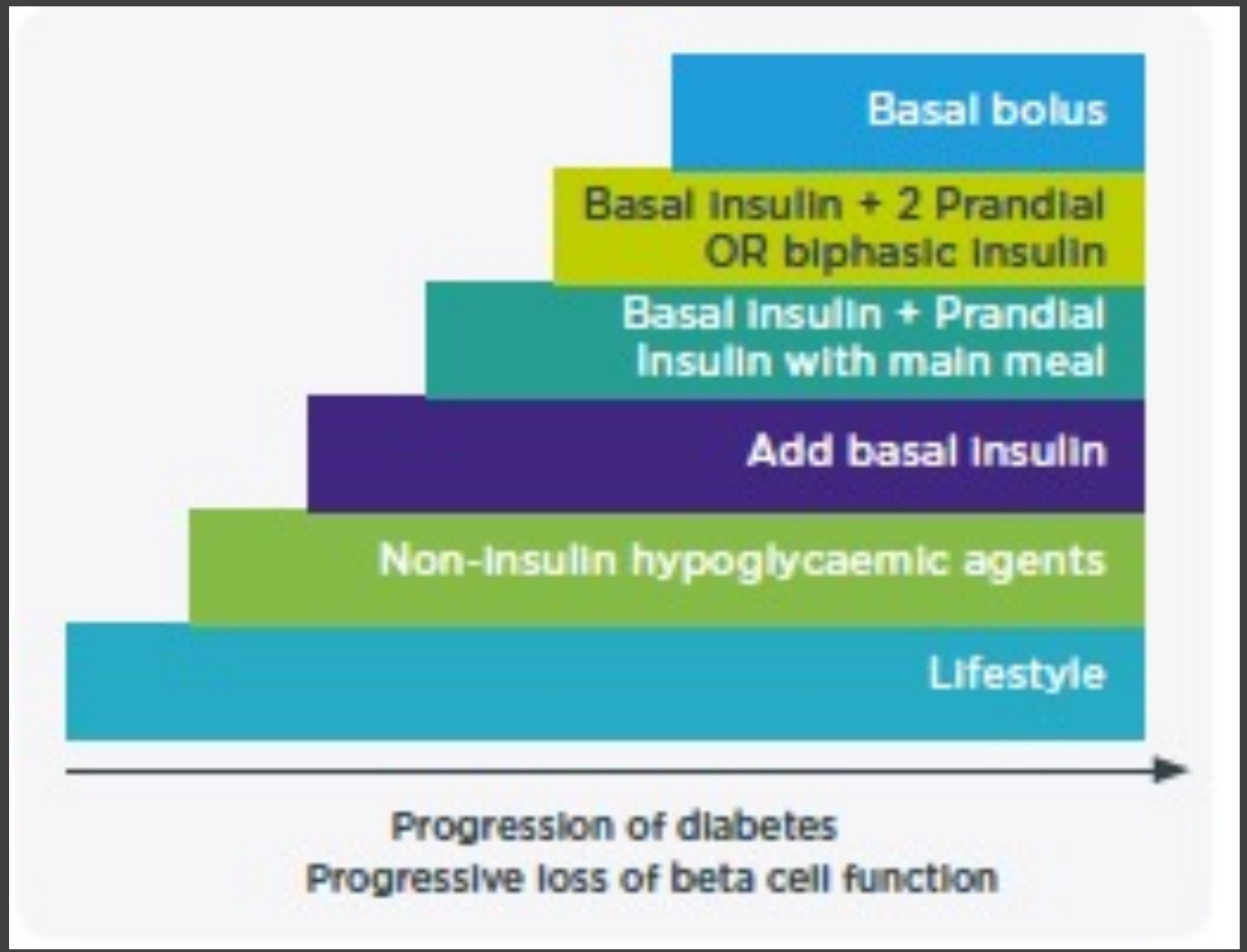
Lee DH et al. PLoS 2011; 6(1):e15977

Arsenic



- 1004 Individuals
- 9% discovered to have Type 2 DM on FG
- But glucometer!
- Dose dependent association contaminated water
- O.R. 1.9 with highest quartile
- Arsenic removed from chicken feed present in manure

Pan W-C et al. American Journal of Epidemiology. 2013;178(10):1563-70



Conventional Management

Metformin

Biguanide

Mechanism unclear:

- Decreases HBP
- Insulin dependent increased skeletal muscle Glucose uptake
- Decreases glucose absorption
- increased secretion of serotonin
- Increased GLP-1
- Altered gut microbiome
- Changes to bile acid circulation

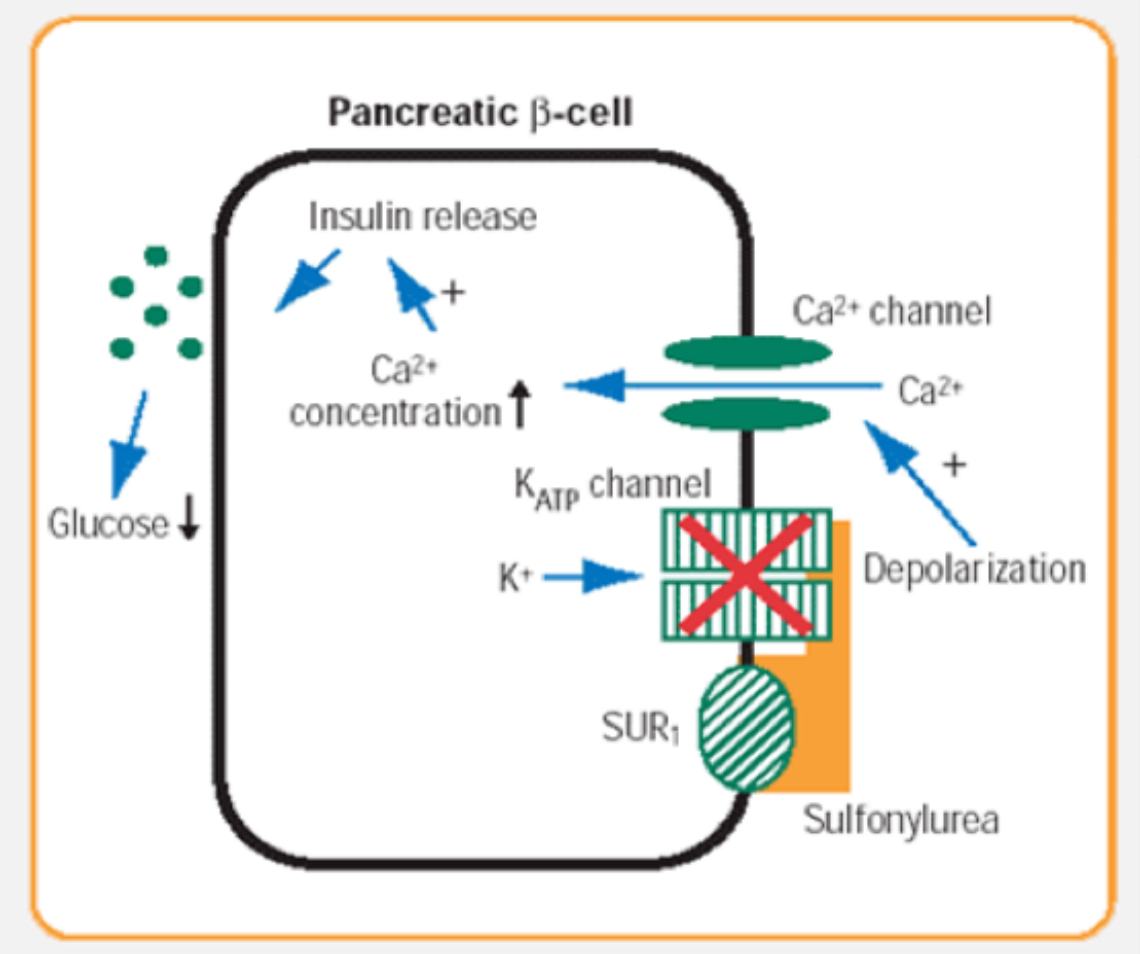
Cheap, GI Side effects limit use

Extended release, liquid version, creams

- Lowers HbA1c by ~ 1.7% or ~19mmol/mol
- TG lowered by 10 – 30%
- LDL-C lowered by 5 – 10%

Used in PCOS, Pre-DM, DM

Viollet et al. Clinical Science Mar 01, 2012



Sulphonylureas

"Secretagogues"

- Binds to SUR receptor
- Closes K+ channel
- Cell depolarization
- Calcium influx and insulin release
- Increased insulin production and secretion

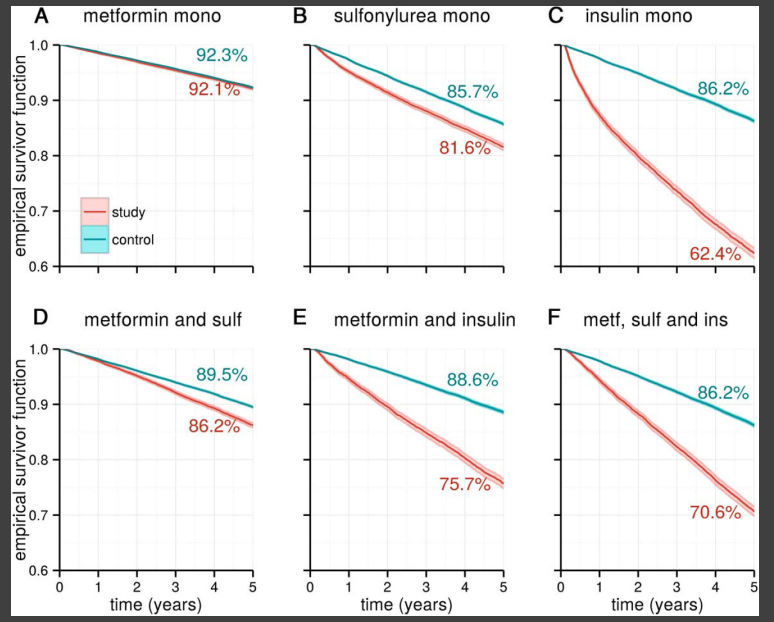
Lowers HbA1c ~ 1.7%

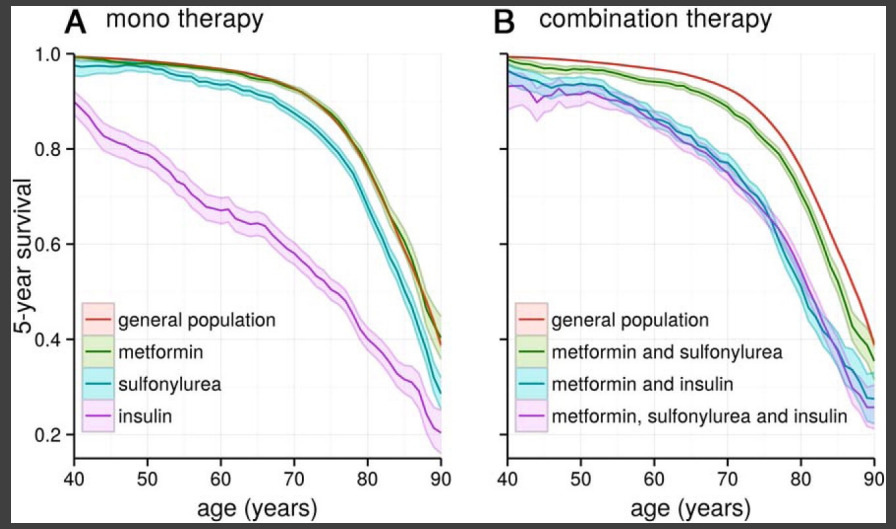
Main side effect hypoglycaemia

Elderly patients and renal impairment risk factors

Mortality in Individuals Treated With Glucose-Lowering Agents

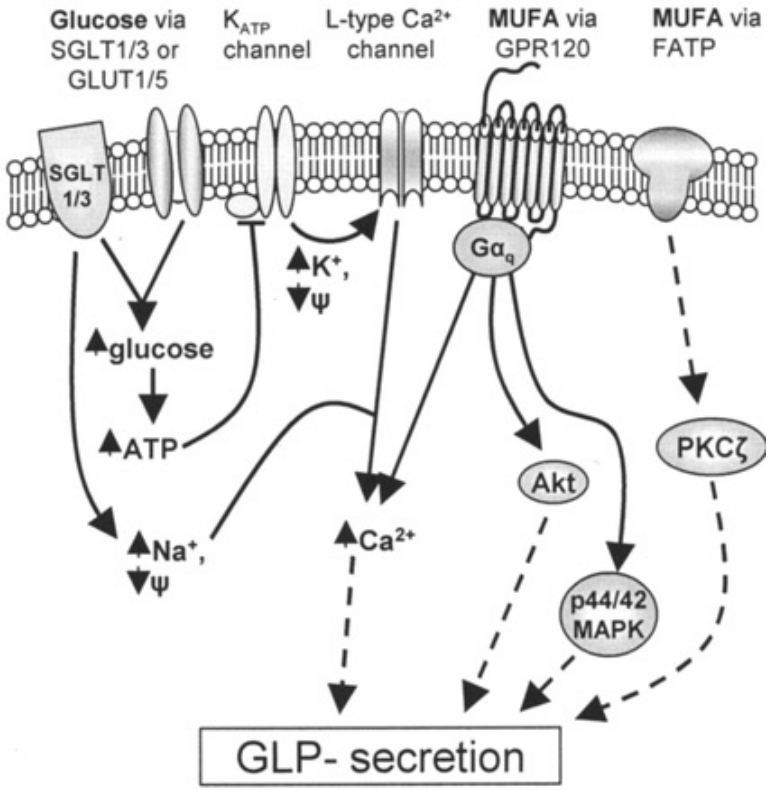
- 115 896 patients starting metformin, SU, or insulin (alone or in combination)
- Jan 2003 - Dec 2007
- Outcome: Five-year survival after the start of GLA
- Controls: not taking GLA
- Metformin lowest mortality risk
- Excess mortality with SU and insulin.
- Even combined with metformin!
- "…this might reflect the progressive nature of type 2 diabetes"





GLP-1

- Produced by L cells in ileum and colon
- Glucose and fat potent releasers
- Initial rapid rise 15-30mins after meal, second peak 90-120mins.
- Slows gastric emptying
- Promotes satiety
- Glucose stimulated insulin release
- Short half life
- Post-meal GLP-1 levels reduced in diabetes



Diabetes 2006 Dec; 55(Supplement 2): S70-S77

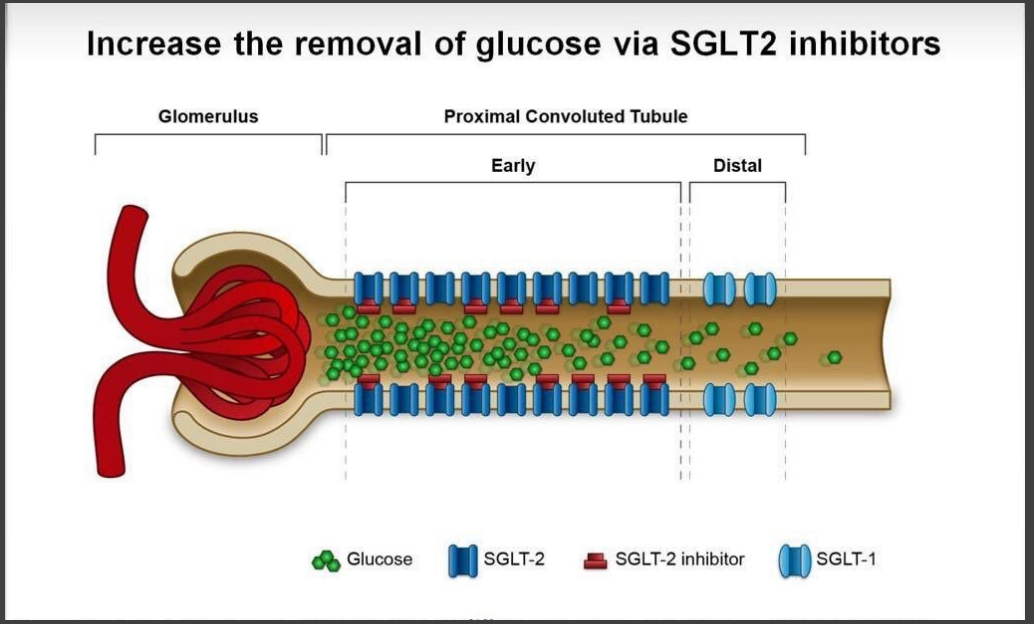
GLP-1 receptor agonists

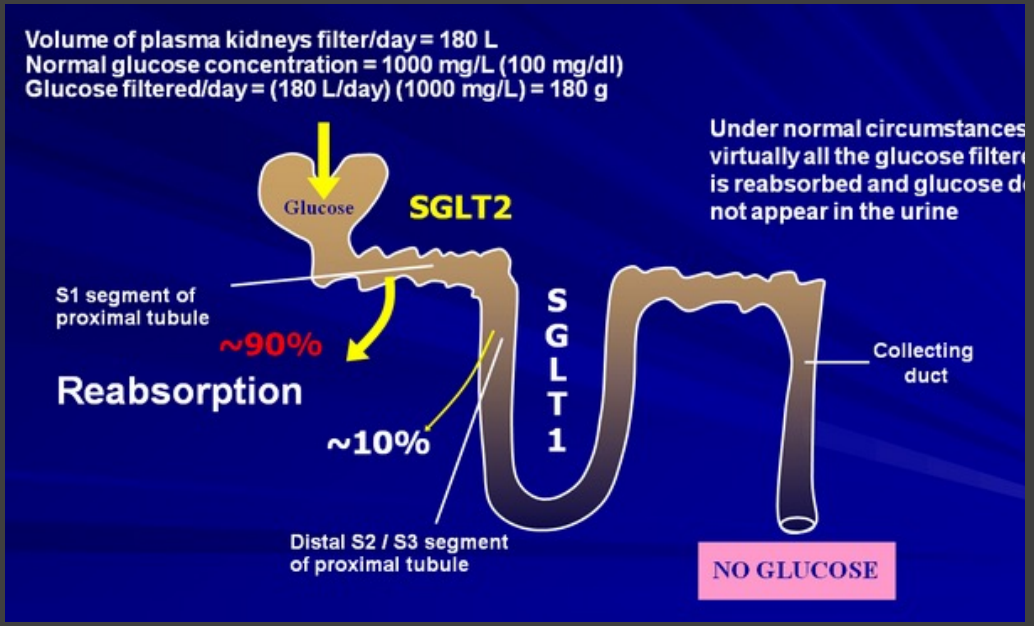
- Synthetic version peptide
- Has to be injected: daily or weekly
- Oral version available
- Reduce blood glucose
- Lower systolic blood pressure
- Does not cause weight gain, modest weight loss.
- Side effects nausea, diarrhoea, can resolve within 2 months
- Pancreatitis, Thyroid Ca
- Meta-analysis: significant reduction of MI, stroke and CV death

DOI:https://doi.org/10.1016/S2213-8587(19)30249-9

SGLT-2

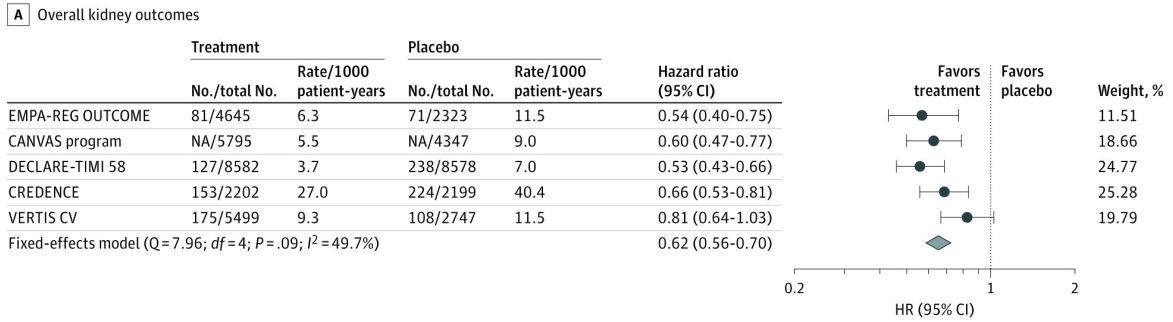
- SGLT2 located proximal tubule of nephron
- Normally 100% of filtered glucose reabsorbed by kidneys; 90% by proximal tubules via SGLT2
- If glucose very high, then SGLT2 is saturated and glycosuria results
- SGLT2 inhibitors exploit this
- Less glucose is reabsorbed; Independent of insulin levels
- Weight loss, reduces HbA1c 0.43 – 0.67%
- NICE: 2nd line option after Metformin
- Side effects - UTI, increases glucagon, Diabetic Ketoacidosis, leg amputations

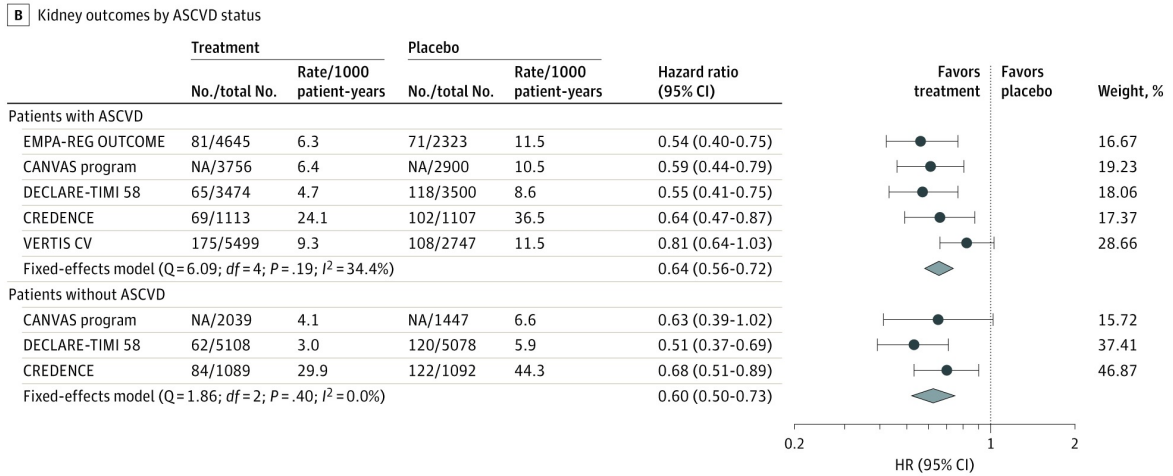


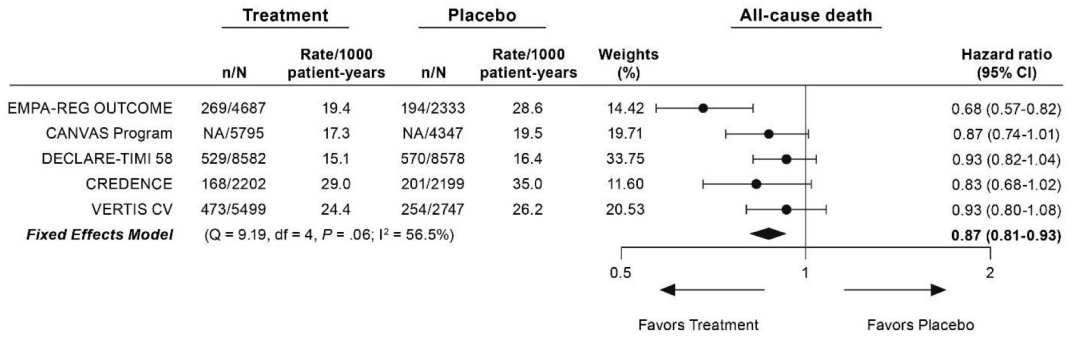


SGLT2 inhibitors

- Drop eGFR by 4% initially
- This is good thing (reduces pressure in glomerulus and prevent renal failure in future)
- Not much glucose lowering if eGFR< 50
- Meta-analysis
  - 10% reduction in MACE (Time to First Event of CV Death, MI, or Stroke)
  - 15% reduction CV death
  - 13% reduction in all cause death
  - 38% reduction in renal composite
  - 32% reduction in hospitalisation for heart failure
- These results were seen in both DM and non-DM patients

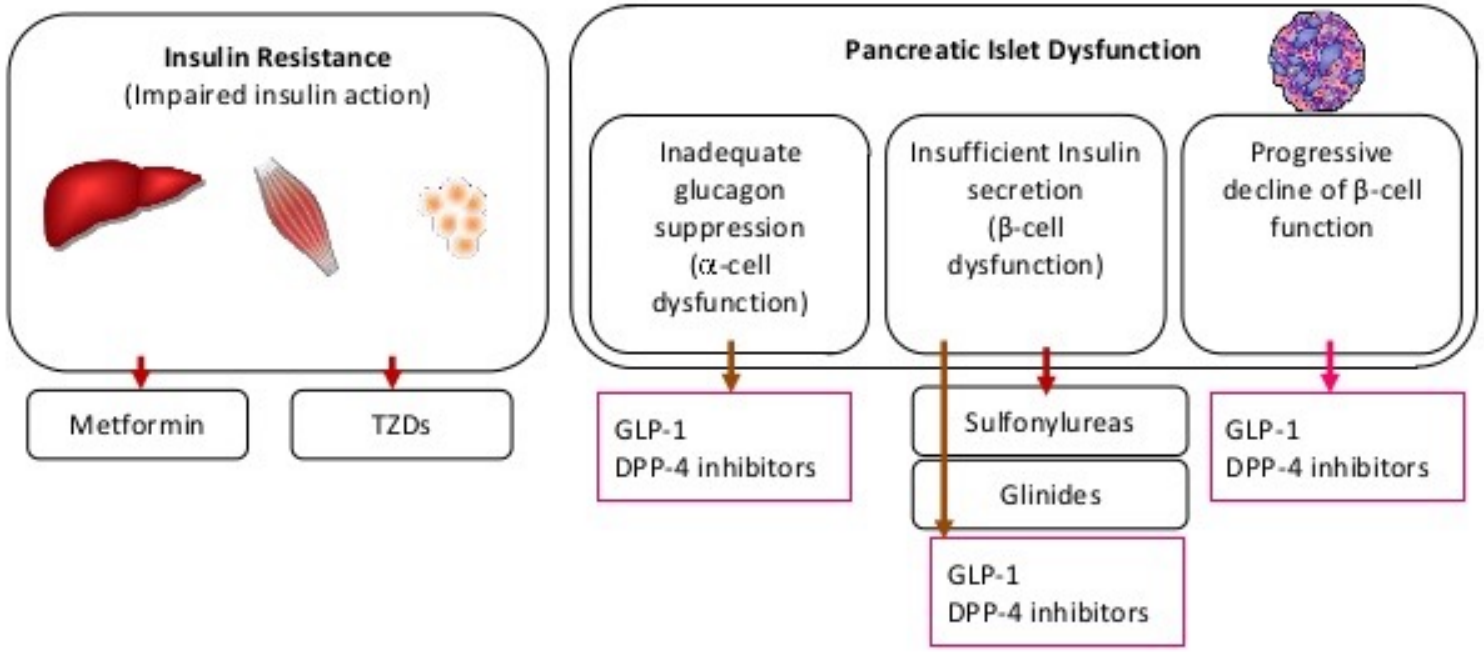






JAMA Cardiol. 2021;6(2):148-158. doi:10.1001/jamacardio.2020.4511

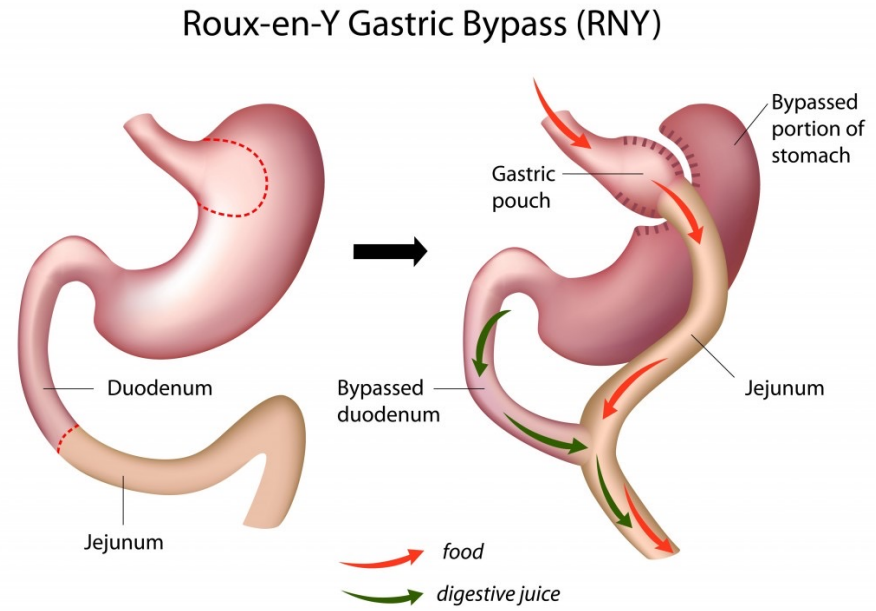
Traditional current *oral* therapies do not address all islet cell dysfunction

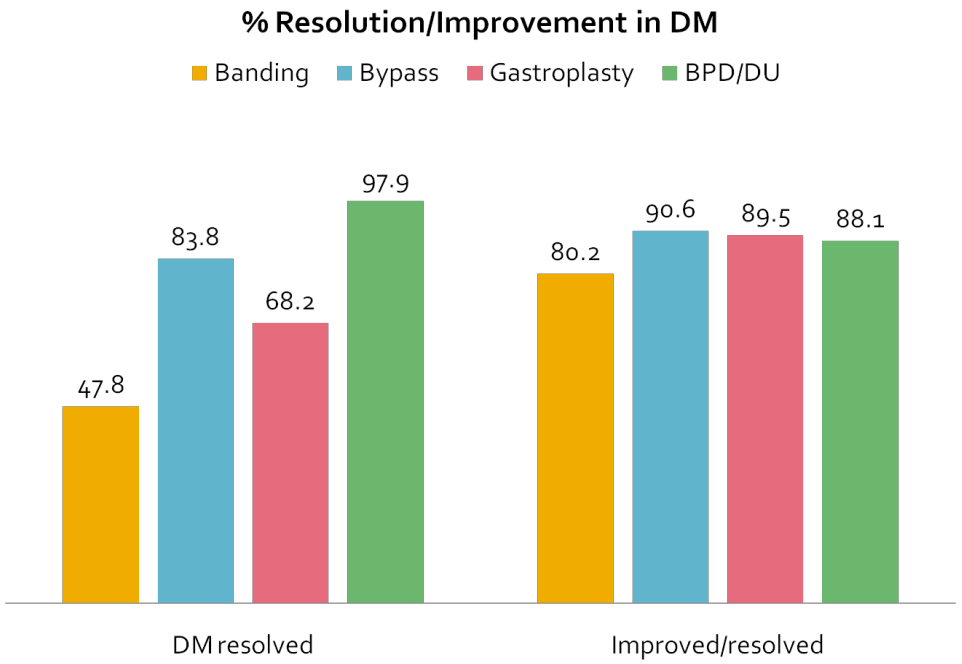


TZD=thiazolidinedione; T2DM=type 2 diabetes mellitus
Adapted from DeFronzo RA. *Br J Diabetes Vasc Dis.* 2003; 3 (Suppl 1): S24–S40.

Bariatric Surgery

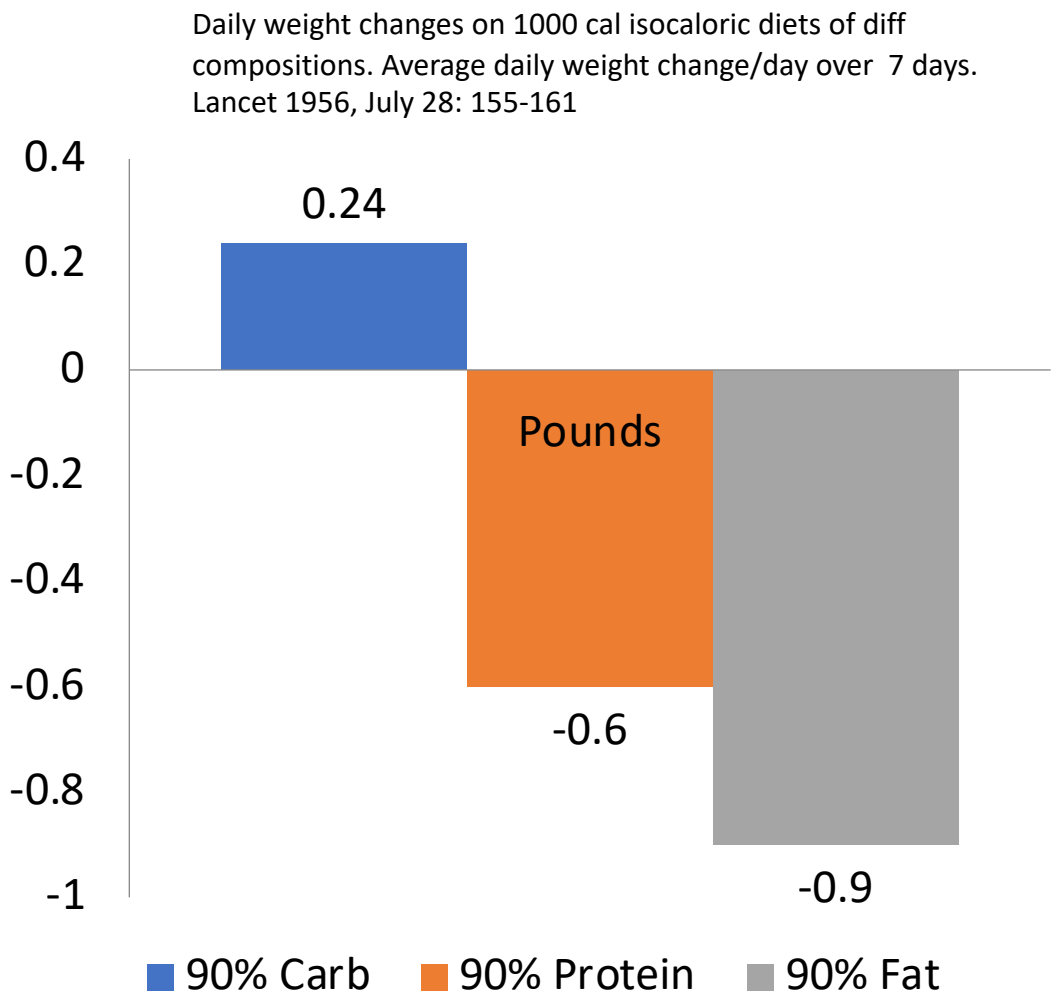
- Longest surgical study for weight loss
- 2010 patients BMI > 34 men and > 38 women, 2037 controls
- 23.4% body weight loss in surgical group cf 0.1% at 2 years
- All mortality ↓ 31%, MI ↓ by 43%
- Mortality better for those BMI > 45
- Benefit exclusively DM patients





Sjöströsm et al. NEJM 2004, 2007
Buchwald H et al. JAMA 2004; 292: 1724-37

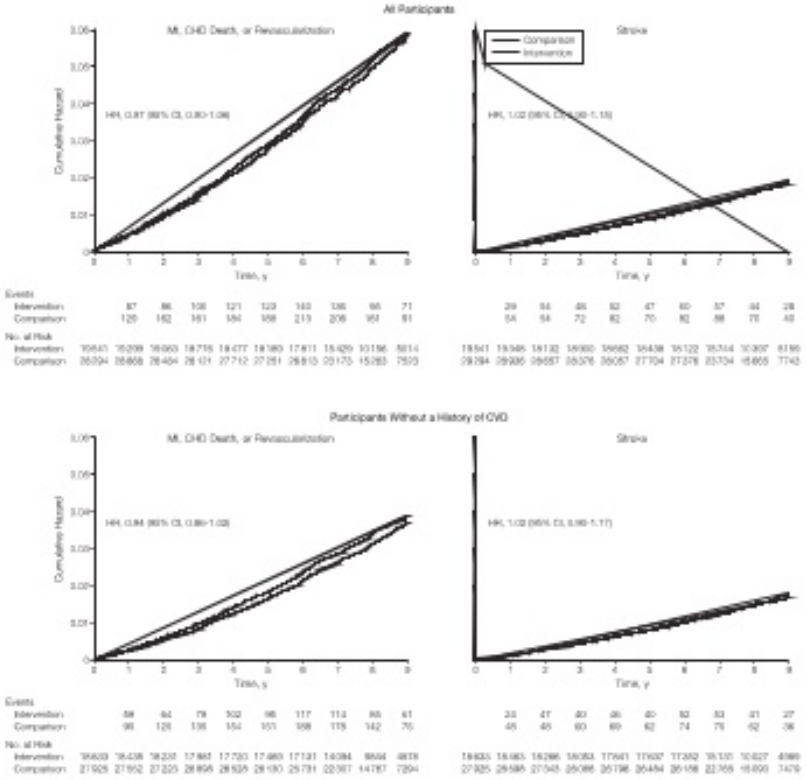
Low Carb Diets



- 3 groups of people given 1000 calories
- 90% as CHO
- 90% as protein
- 90% as fats
- Group that had carbs gained weight!
- Group that had fats lost the most weight.
- Remember carbs promote insulin production = visceral fat = diabetes

The Women's Health Initiative Randomized Controlled Dietary Modification Trial

48835 post-menopausal women randomized to a low-fat* diet or usual diet for 8.1 years



- A dietary intervention that reduced total fat intake and increased intakes of vegetables, fruits, and grains
- Low fat diet did not significantly reduce the risk of CHD, stroke, or CVD in postmenopausal women

* Less then 20% of energy intake

Howard, B.V. et al. (2006). JAMA, 295, 655–6

Low Fat Diets

Low Fat Heart Hypothesis: Fat and cholesterol cause heart disease

WHI most expensive and ultimate test of hypothesis

- Aggressive lowering of fat to 20% of dietary intake (suggests at least 65% of energy from carbs) cf usual group 37% fat intake
- At 8years F/U, low fat group:
- No reduction in IHD, stroke, breast/colon cancer

Massive increase in Heart procedures despite reduction in fat

Intermittent Fasting

IF studies
- Reduces oxidative stress
- Improves cognition
- Delays ageing

One study in Overweight women
- Fasted 2 days a week
- Reduction in insulin levels

Alternate day fasting cf 800cal VLCD:
- 3.31kg more fat mass loss with Alternate day fasting
- Greater preservation of fat-free mass

16/8 INTERMITTENT FASTING - LEANGAINS

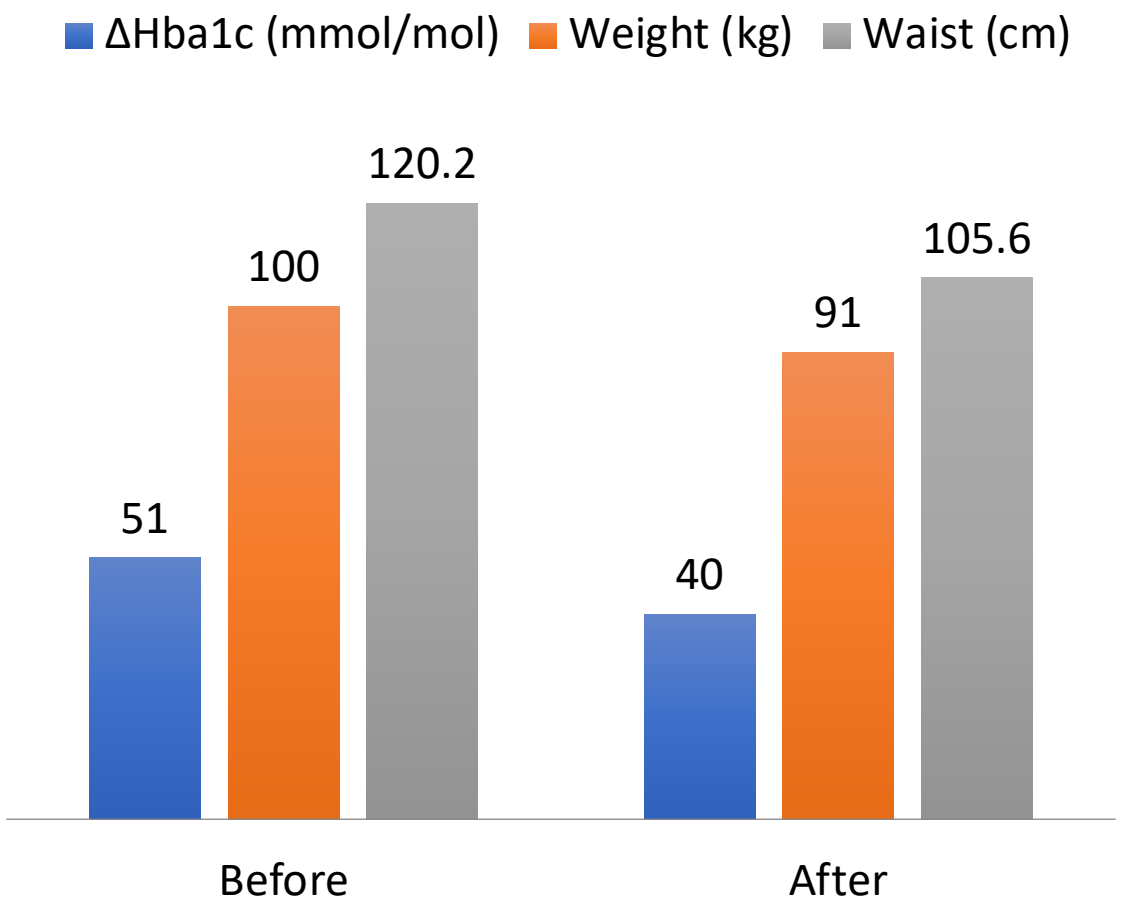
TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
MIDNIGHT - 8 AM	SLEEPING	SLEEPING	SLEEPING	SLEEPING	SLEEPING	SLEEPING	SLEEPING
8 AM - NOON	FASTING 4 HOURS	FASTING 4 HOURS	FASTING 4 HOURS	FASTING 4 HOURS	FASTING 4 HOURS	FASTING 4 HOURS	FASTING 4 HOURS
NOON - 8 PM	8 HOUR EATING WINDOW	8 HOUR EATING WINDOW	8 HOUR EATING WINDOW	8 HOUR EATING WINDOW	8 HOUR EATING WINDOW	8 HOUR EATING WINDOW	8 HOUR EATING WINDOW
8 PM - MIDNIGHT	FASTING 4 HOURS	FASTING 4 HOURS	FASTING 4 HOURS	FASTING 4 HOURS	FASTING 4 HOURS	FASTING 4 HOURS	FASTING 4 HOURS

Harvie et al Int J Obes (Lond). 2011. Curr Obes Rep. 2018 Jun;7(2):172-185 accessed 23rd May 2018. Alhamdan et al Obes Sci Pract 2016

Low carbohydrate Diet: Study from Primary Care

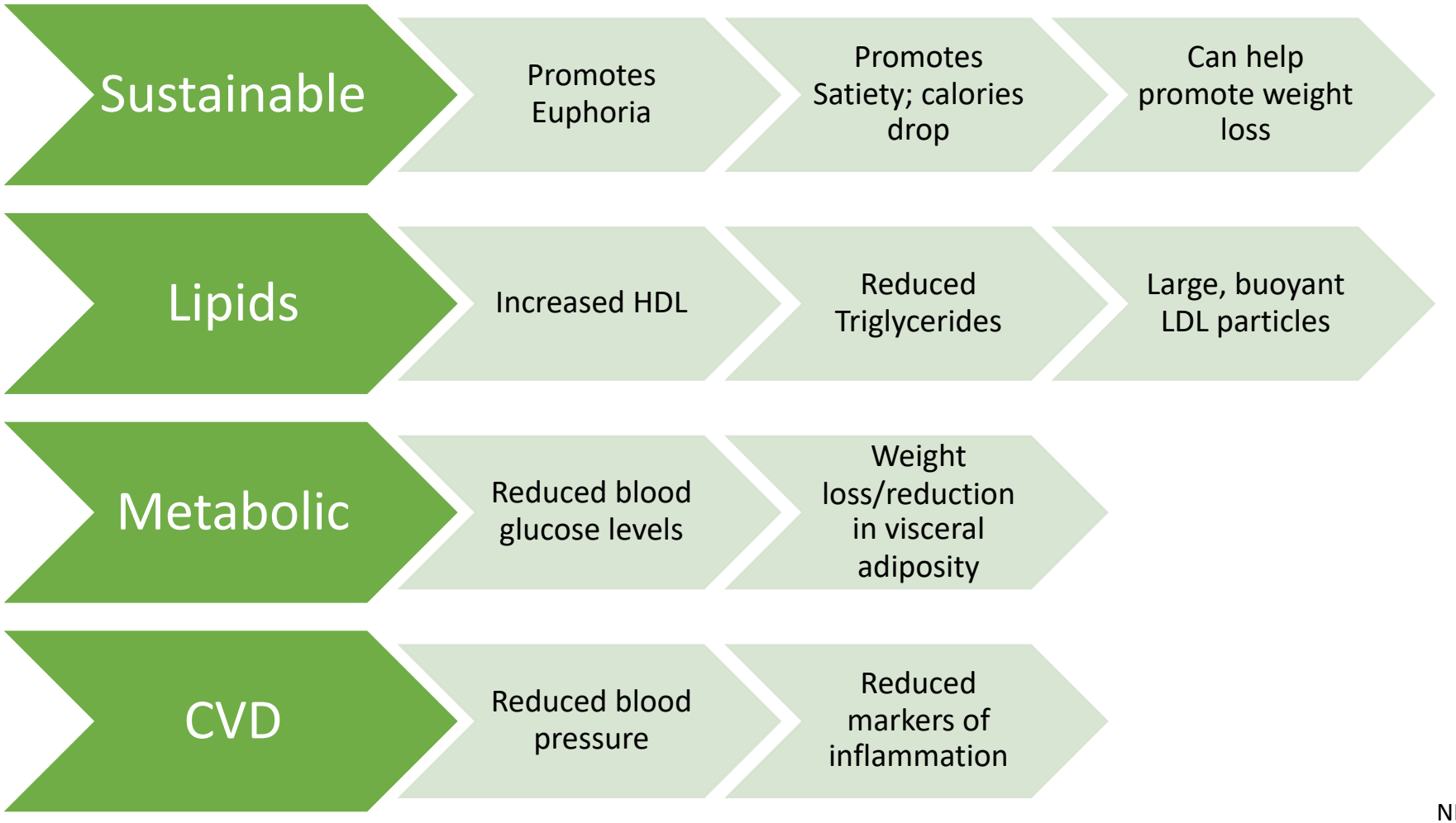
- GP Study
- 19 patients with T2DM/pre-DM
- 8-month study
- Further 18-month study
- MS, T2DM, Obesity, H/T
- Low CHO Diet

- Significant reduction in
  - HbA1c
  - Weight
  - Waist circumference
  - Blood pressure

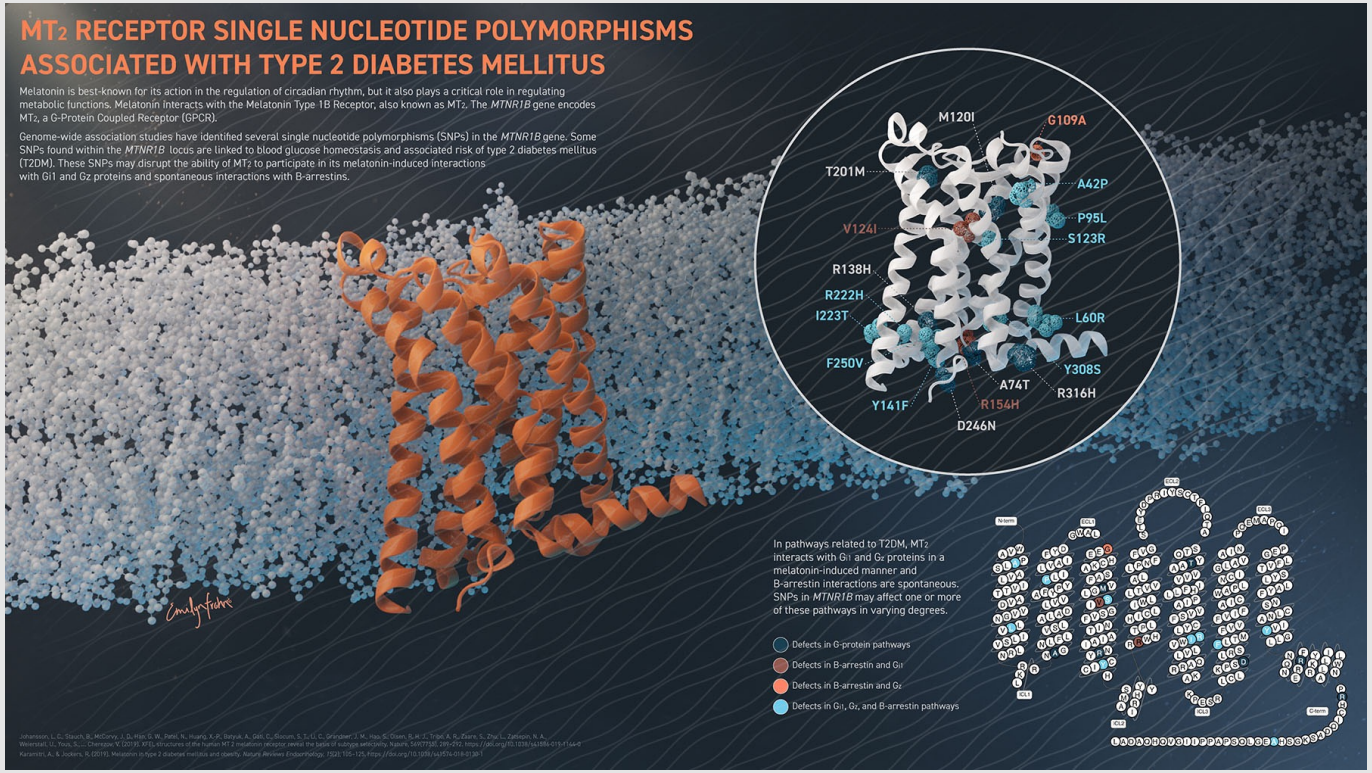


Unwin et al. Practical Diabetes March 2014

Benefits of a low carbohydrate diet



NEJM 2008; 359 (3): 229-41
Lipids 2008; 43(1):65-77.
JAMA 2007; 297(9):969-77



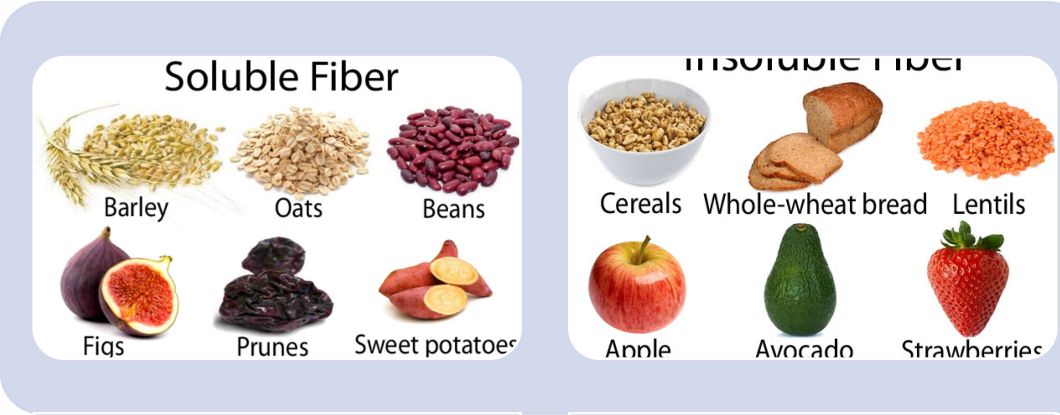
Melatonin receptor type 1B

- rs10830963 SNP of Melatonin receptor type 1B (MTNR1B) assoc with
  - Early waking
  - Increased fasting glucose
  - Reduced insulin secretion
  - Increased risk T2DM and GDM
  - Avoid carbs before and after sleep
- MELATONIN assoc with:
- Significant antioxidant function (in higher concentrations)
- Prevents Oxidative damage
  - Stimulates antioxidant enzymes
  - Inhibits lipoxygenase
  - Increases GSH and GSH S-transferase & activity of GPx
- Inhibits oxidation of LDL-C
- Heavy Metal detoxification:
- Binds aluminium, cadmium, copper, iron, lead, and zinc

J Pineal Res 2004;36:1-9. J Pineal Res. 1998;24:15–21.
Toxicol Pathol 2003;31:589-603

Fiber

- Meta-analysis :
- Moderate carbohydrate, high fiber diets compared to low fiber diets associated with:
  - Lower postprandial plasma glucose,
  - Lower total and low-density lipoprotein cholesterol, and triglycerides.
- High carbohydrate, high fiber diets compared to moderate carbohydrate, low fiber diets are associated with lower fasting, postprandial and average plasma glucose



SOLUBLE dissolves in water – feeds good bacteria, reduces cholesterol, stabilises blood sugar, promotes satiety, forms a gel protecting GI tract

INSOLUBLE – increases bulk and prevents constipation.

J Am Coll Nutr. 2004 Feb;23(1):5-17.

Botanicals

- Milk Thistle 200g daily for 120 days reduced HbA1c and body weight.
- Coccinia cordifolia – lowered glucose, HbA1c in one study
- Fenugreek – thought to increase insulin secretion. Reduced BG and HbA1c in conjunction with GLA cf placebo.
  - Caution GI side effects including diarrhoea

Phytother Res 2009; 20:1036-1039
Diabetes Care 2008; 31:216-220
Chin J Integr Med 2008; 14: 56-60

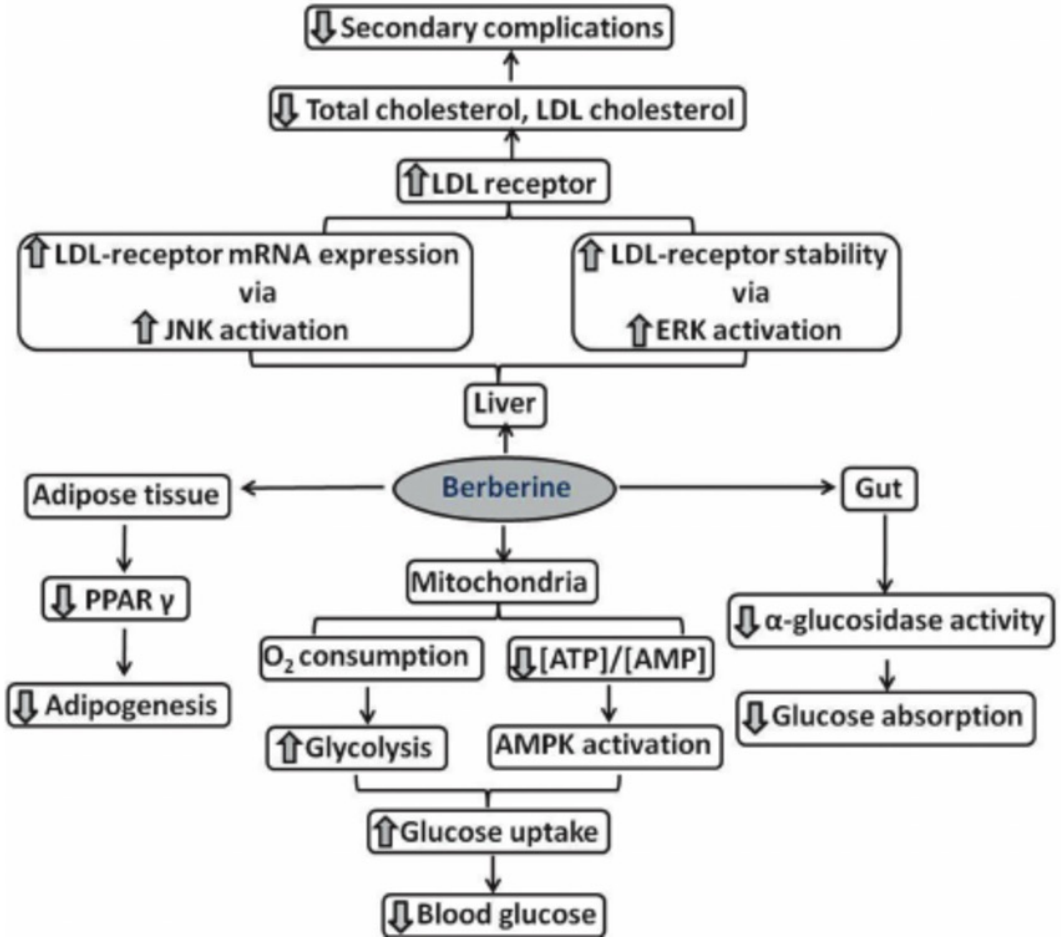
Cinnamon

- Majority of preparations are cassia and Ceylon cinnamon (C)
- Aqueous extract improves insulin sensitivity
  - Improved insulin receptor function
  - Increased glycogen synthase activity
- Studies variable results including meta-analysis
- One meta-analysis showed C lowered fasting glucose
- Optimal dose not clear but 3 - 6g might be helpful
- Prediabetes study: C 500mg three times a day associated with:
- Stable fasting glucose at 12 weeks (rose with placebo grp)
- Reduced area under curve for plasma glucose

PMC6425402, PMID 21480806
Romeo et al. J Endo Soc 2020
Elsevier Integrative Med

Berberine

- Increases expression of Insulin receptor
- Modulates AMPK
- Reduces pro-inflammatory cytokines
- Clinical studies:
  - Lowers blood glucose
  - Lowered HbA1c
  - Lowered TG
  - Lowered insulin levels
- Doses range 0.9 – 1.5g a day



Zhang et al Metabolism. 2010 Feb;59(2):285-92.
Wei wt al Meta-analysis