Lecture 2b - Annex C

Metabolic disease: additional slides

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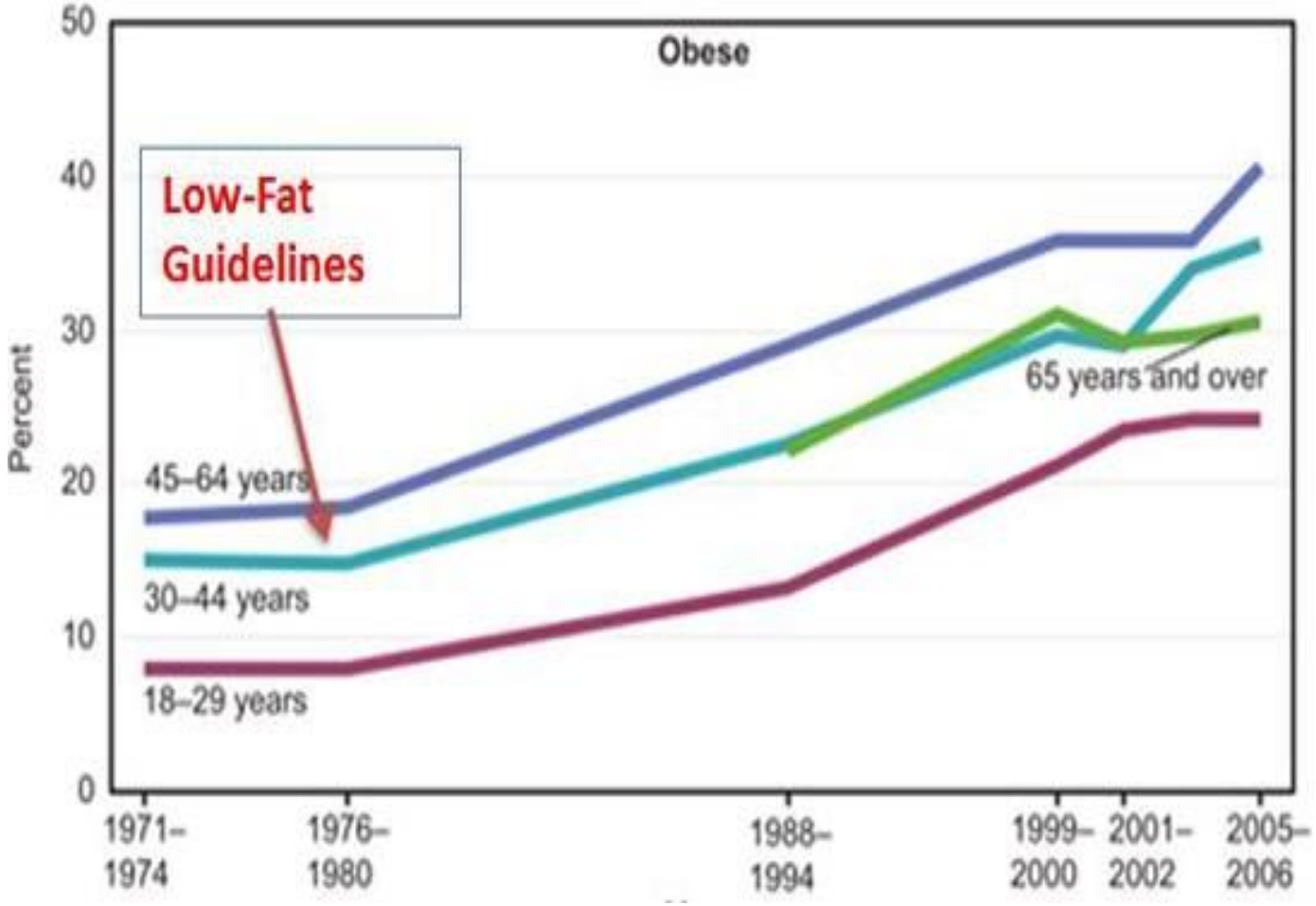
How the obesity epidemic began: The 1995 Food Pyramid designed from the US Dietary Guidelines

- What is on the base? Bread, pasta, cereals, rice
- American Heart Association (AHA) 1995: *An eating plan for Healthy Americans*: Eat 6 or more servings per day of breads, cereals, pasta and starchy vegetables, low in fat and cholesterol. Don't eat cholesterol-rich eggs and red meat. And choose fruit punches and carbonated soft drinks as beverages.
- 2000: the AHA denounce low carb diets as dangerous fads.

Consequences of compliance with the US Dietary Guidelines

- Fat intake decreased from 45% of calories to 35%, animal protein decreased 18%, egg consumption decreased 18%, grains and sugar consumption increased exponentially. America had complied!
- How much rigorous testing of the low fat diet had been carried out prior to these recommendations? None.
- Were our genes adapted to low fat, high sugar and high carbs? No.
- Did rates of heart disease decrease? Yes, but not by as much as expected and this may be due to earlier detection and medication.
- Instead, obesity and T2D increased dramatically.
- Coincidence?

The Obesity Epidemic in the US started at almost the same time as the low-fat Dietary Guidelines were published



National Center for Health Statistics (US). Hyattsville (MD):

2009 Mar Chartbook.

The 2006 Women's Health Initiative Dietary Modification Trial

- Intervention group were told to reduce dietary fat to 20% of daily calories, and increase F&V to 5 a day and grains to 6 portions a day and were encouraged to increase exercise. They received education, group activities, message campaigns and personalised feedback, all highly labour- and therefore cost-intensive.
- The control group was told to eat their normal higher calorie, higher fat diet but were given dietary guidelines.

<u>Results at Year 3</u>:

- The intervention group reduced calories by around 20% and reduced fat to 30% of calories (not 20%).
- Intervention group difference in mean weight from baseline: 2.4 lbs (1.1kg).
- Difference between intervention and control groups: mean 2.2lbs (1kg).

Actual weight loss is not mentioned once in the Abstract – the failure to lose much weight is buried in the body of the paper.

Howard BV, JAMA, 2006

And other studies?

- Virtually all the studies in recent years have shown that this approach does not work. In the words of one:

  [There was] no association between caloric intake or dietary fat intake and obesity.

  In fact caloric intake decreased while obesity increased.

(Griffith R et al, UK Institute of Fiscal Studies, 2013 http://www.ifs.org.uk/publications/6918 accessed 25/11/2016)

What about pharmaceutically-induced caloric reduction?

- The fake fat Olestra, which is not absorbed by the body, was supposed to induce weight loss. But in fact it induced no weight loss at all. Time Magazine included it as one of the 50 worst inventions of all time, just behind asbestos.
- Orlistat was designed to block the absorption of dietary fat, and is the drug equivalent of the low fat, low calorie diet. It works in the short term but weight regain begins after only 4 months (Douglas IJ. Br J Clin Pharmacol. 2015).
- Many side effects, including 'faecal leakage' and 'oily staining of underwear'. As a result, in 2007 Orlistat won the 'Bitter Pill Award' for the worst drug.
- Other Orlistat adverse effects: it blocks a major detoxification enzyme, causes vitamin deficiency and can cause gallstones and permanent liver and kidney damage.
- But Orlistat is available for sale in the UK without prescription, despite the health risks.

The Exercise Myth

- Exercise has become fashionable in western countries, and governments have poured a great deal of money into promoting exercise for weight loss. In the UK, between 1997 and 2008, regular exercise increased from 32% - 39% in men and 21% - 29% in women. Weight loss was the main motivation in all countries.
- But obesity prevalence just kept on increasing.
- An international survey found that Americans exercised the most but the Dutch and Italians exercised the least. Yet country statistics show that Dutch and Italian obesity prevalence is relatively low, whereas the US have the highest rates of obesity in the world.
- An NHANES study showed that from 2001 to 2009, there was a general increase in adult physical activity, with some considerable variation between states. Yet regardless of whether the state was a 'high exerciser' or a 'low exerciser', the rate of increase in obesity was the same.
- Surely there must be an association in children? A 2013 paper showed there was no association between physical activity in children aged 3-5 and their BMI.

Dwyer-Lindgren L, Popul Health Metr, 2013; Byun W, In J Obes, 2013

Surely obesity must be due to lack of energy expenditure?

- Exercise is inherent in the ‘Eat less, move more’ mantra. And it makes intuitive sense: we used to walk, now we drive; we used to do manual labour, now there are labour-saving devices, mechanisation and computers; children used to play outside, now they play video games.
- A study of the modern day hunter gatherers, the Hadza tribe of Tanzania, showed that they often run 15-20 miles per day to gather food. Yet the number of calories they burned per day was indistinguishable from that of typical European or US adults.
- And a study showed that even compared to 1980, around the start of the obesity epidemic, the rate of burning calories has barely declined at all and in a Northern European population, physical energy expenditure actually increased since the 1980s.
- The authors then compared the energy expenditure of vigorous wild animals and *homo obesus* and found little difference.

Pontzer H, PLoS One, 2012; Werterterp KR, Int J Obes, 2008

So why doesn't exercise help?

- I said earlier that total energy expenditure comprises many factors, and here they are:

  Total energy expenditure = basal metabolic rate + thermogenic effect of food + non-exercise activity thermogenesis + excess post-exercise oxygen consumption + exercise

- So total energy expenditure is not the same as exercise and in fact the majority of total energy expenditure is down to basal metabolic rate: breathing, maintaining body temperature, keeping the heart pumping, maintaining the vital organs, etc.
- Let's take an example.
- Basal metabolic rate for a lightly active average male is roughly 2500 kcal/day. Walking at a moderate pace for 45 minutes every day would burn roughly 104 calories, i.e. not even 5% of total energy expenditure.
- Because total energy expenditure, with the exception of exercise, is so difficult to calculate, we make the mistake of assuming that it remains constant and the only variable is exercise. But basal metabolic rate, in particular, is highly variable.

So what determines basal metabolic rate (BMR)?

- Genetics
- Gender (BMR is normally higher in males)
- Age (BMR normally declines with age)
- Weight (BMR normally increases with muscle mass)
- Height (BMR generally increases with height)
- Diet (caloric restriction decreases BMR by up to 40%)
- Body temperature
- External temperature
- Organ function

Surely diet and exercise are equally important?

- Certainly the mantra ‘Eat less, move more’ make it appear that the two measures are equally important.
- But they are not. Diet is 95% of the effort. Exercise has many benefits, but weight loss is not one of them.
- A 2007 RCT of sedentary adults given aerobic exercise for weight loss, 1 hour/day, 6 days/week over 1 year, found a significant difference in weight and BMI loss between exercisers and controls.
- But this represented a 3lb (1.4 kg) loss in women and a 4lb (1.8 kg) loss in men.
- A Danish team trained a previously sedentary group over 18 months to run a marathon. Men lost around 5lbs (2.4kg) of body fat. But for the women, the body fat loss was….
- Zero……And in both genders, intake of energy as carbs had increased significantly.

Church TS, PLoS One, 2009; McTiernan A, Obesity, 2007; Janssen GM, Int J Sports Med, 1989

Preventing childhood obesity (1)

- Several large long term studies on the prevention of childhood obesity were begun in the late 1990s.
- Pathways Study: Children at risk for obesity and T2D received a special low fat breakfast and lunch in the school cafeteria, 'healthy' (low fat) eating lessons and special exercise breaks.
- 3 years later, the children had successfully reduced dietary fat and calories (1892 calories/day compared to the control group with 2157 calories). But there was no difference in weight between the 2 groups.
- The study was buried because no-one wanted to accept the results. But other studies had exactly the same results….

Caballero B, Am J Clin Nutr, 2003;

Preventing childhood obesity (2)

- The 1999 RCT objective was to reduce CV risk factors in 5,106 multi-ethnic elementary school children over 3 years through education, food selection (low fat), encouraging exercising and continual monitoring. The children's compliance was excellent.

  Abstract extract: 'No significant differences were noted among indicators of body mass index, blood pressure or serum lipid and cholesterol levels.' After 3 years! In 5,106 children!

- Asked to account for the programme failure, the authors suggested that the study was not long enough, didn't reduce fat enough, the children were cheating when they got out of school or the parents were sabotaging the study so they wouldn't be blamed for their child's obesity.
- Anything except examine the basic premise that 'Eat less, move more' doesn't work and that the low fat diet is not the way to lose weight.

Nader PR, Arch Pediatr Adolesc Med 1999

Finally, some success!

- The Australian 'Romp and Chomp' trial targeted around 12,000 children aged 0-5 years with specific targets:
  - To decrease consumption of high sugar drinks and promote consumption of milk and water.
  - To decrease consumption of energy-dense snacks and increase consumption of F&V.
- So finally, no mention of calories, low fat or exercise.
- Results showed a significant difference between the control and intervention groups, which showed a 2-3% drop in obesity prevalence.
- In the UK, 6 schools launched a 'Ditch the Fizz' programme. The sole goal was to reduce consumption of sugar-rich fizzy drinks in children aged 7-11.
- While the intervention group reduced obesity by 0.2% over a school year, the control group increased by 7.5%.

De Silva-Sanigorski AM, Am J Clin Nutr, 2010; James J, BMJ, 2004

Why do exercise studies show that actual fat loss is so much less than predicted?

Answer: Compensation - explained by 2 major mechanisms:

1. Contrary to expectations, caloric intake increases in response to exercise. An hour of exercise vs watching television is associated with a 3-fold increase in caloric intake.

The authors stated: 'although physical activity is thought of as an energy deficit activity, our results do not support this hypothesis'.

2. With increased exercise, non-exercise activity is reduced.

The Hadza, who walked 15-20 miles per day, reduced their other physical activity where possible.

A study of boys aged 8-10 compared total exercise between those who had PE lessons in schools (mean 9.2 hours of exercise per week) with those who did not. There was no difference in activity between the groups. Those who had PE at school took no exercise at home, while those with no PE lessons had more physical activity at home.

- So increasing calories out is not going to help.

Sonneville KR, Int J Obes, 2008; Pontzer H, PLoS One, 2012; Fremeaux AE, Int J Obes, 2011

The hormonal theory of obesity

- We've talked about ghrelin (the hunger hormone) and the satiety hormones PYY, amylin and CCK. Might injecting the satiety hormones lead to less hunger and more weight loss?
- No. Studies showed that this had no impact on weight.
- Could it be leptin?
- Leptin is produced by WAT but it is controlled by the hypothalamus. It is known that hypothalamic damage can result in intractable weight gain. The more adipose tissue, the higher the serum leptin concentrations.
- Although leptin is available in i/v and supplement form, other than in certain medical conditions, it has been found to have no effect on overweight or obesity.
- This is because continued elevated leptin generates a state of leptin resistance. Because the brain is leptin-resistant due to constant exposure, it does not alter its output of the satiety hormones. (Lustig RH, Pediatr Endocrinol Rev, 2008)

Several hormones impact obesity (thyroid, pregnenolone, other sex hormones) but we are focusing on cortisol and insulin.

Cortisol and weight (1)

- Cortisol, a glucocorticoid, is the stress hormone which mediates the fight or flight response. It raises blood glucose to provide energy for the muscles so that we can run from the sabre-toothed tiger, burning off the raised glucose. Once the threat is over, blood cortisol, glucose and insulin levels return to normal.
- In healthy subjects, cortisol levels correlate with fasting insulin and measures of adiposity.
- In the short-term, cortisol and insulin have opposite effects: cortisol mobilises glucose from storage into the blood, while insulin returns glucose to storage in cells.
- But if stress is chronic, as it often is with modern life, blood glucose is not burned off and can remain elevated for months. This inevitably triggers fairly permanent insulin production, weight gain and increased BMI.
- Glucocorticoids also cause muscle breakdown, releasing proteins for gluconeogenesis, so increasing blood glucose.

Rosmond R, J Clin Endocrinol Metab, 1998; Rizza RA, J Clin Endocrinol Metab, 1982; Stolk RP, J Endocrinol, 1996; Kauh EA, Diabetes Obes Metab, 2011; Pagano G, J Clin Invest, 1983

Cortisol and weight (2)

- Patients with Cushing's syndrome (long-term excessive cortisol production) are characterised by weight gain and many develop high blood glucose and T2D.
- The opposite situation occurs in Addison's disease (adrenal insufficiency, resulting in low cortisol production), which is characterised by weight loss.
- So stress causes weight gain. But stress is not a calorie and nor is it a food or a food group.
- Reducing stress is very important: mindfulness meditation and yoga have been shown to reduce cortisol concentrations and abdominal fat.

Fraser R, Hypertension, 1999; Marin P, Metabolism, 1992; Wallerius S, J Endocrinol Invest, 2003; Wester VL, Obesity, 2014

Cortisol, stress, sleep and weight

- One of the worst causes of stress is sleep deprivation; there are now many studies linking poor sleep with T2D and weight gain, particularly among shift workers.
- A study of healthy volunteers showed that a single night of sleep deprivation raised cortisol levels by >100%, with a 40% decrease in insulin sensitivity.
- Even short-term sleep deprivation results in increased hunger and appetite as ghrelin is elevated and leptin depressed.
- Prednisone (synthetic cortisol) is well known for inducing insulin resistance and weight gain.
- A study which weaned transplant patients off prednisone found that plasma insulin dropped by 25%, weight dropped by 6% and waist circumference decreased by 7.7%.

Joo EY, J Clin Neurol, 2012; Spiegel K, J Appl Physiol, 2005; Copinschi G, Front Horm Res, 2014; Lemieux I, Kidney Int, 2002

Insulin and obesity

First of all, a refresher on the mechanics of blood glucose and insulin secretion:

- In the fed state, all foods, but particularly sugars and refined carbohydrates, raise blood sugar levels sufficiently to trigger insulin secretion. Proteins and fats also raise blood sugar and insulin levels, but to a lesser extent.
- Insulin then binds to receptors on the cell surface, triggering uptake of glucose into the cell to provide energy.
- But with a high carbohydrate/sugar diet, there is often more circulating glucose than is needed in cells. So insulin takes the excess to the liver for storage as glycogen (*glycogenesis*).
- But the liver has only limited storage space for glycogen, so insulin converts any excess glucose to fats (VLDL containing triglycerides) which is stored in adipose tissue (*de novo lipogenesis*).
- Adipose tissue has unlimited space for fat storage: either adipocytes increase in size or new adipocytes are formed as needed.
- Adipocyte increase is the major cause of weight gain but insulin also stimulates the kidneys to reabsorb water, as a secondary cause.

Insulin's relationship with obesity (1)

- Studies show that the insulin response is different in lean and obese subjects, with the obese having 20% higher fasting insulin as well as an exaggerated insulin response to food. In the obese, insulin levels remain elevated for longer.
- Elevated fasting insulin is a consistent predictor of metabolic syndrome.
- In the obese, insulin levels correlate with measures of obesity, such as waist circumference and waist/hip ratio, and with weight gain.

Polonsky KS, J Clin Invest, 1988; Ferrannini E, J Clin Invest, 1997; Han TS, Obes Res, 2002

Insulin's relationship with obesity (2)

- Studies show time and again that both type 1 and type 2 diabetics given insulin gain weight and over time become obese. The extent of weight gain is proportional to the insulin dose.
- But reducing caloric intake in these patients had no impact; patients on insulin still gained the same amount of weight.
- However, in the untreated Type 1 diabetic (no insulin): severe weight loss
- A study of non-diabetic insulinoma patients showed that the high insulin levels caused severe weight gain. Removal of the tumour lowered insulin levels and led to rapid and sustained weight loss.
- The authors noted: 'Loss of body weight after removal of the tumour correlated with a dramatic reduction of insulin resistance, to such a degree that diet alone proved sufficient for satisfactory glycaemic control'.

Russell-Jones D, Diabetes Obes Metab, 2007; Diabetes Care, 2001; Lancet, 1998; Henry RR, Diabetes Care, 1993; Ravnik-Oblak M, Wien Klin Wochenschr, 2001;

How do pharmaceuticals affect insulin and weight?

- Oral hypoglycaemic drugs:
  - Metformin (does not cause the body to produce more insulin): no weight gain
  - Glitazone drugs (increase insulin sensitivity, so magnify the effect of insulin): weight gain
  - Incretin agents (do not affect insulin): no weight gain
  - Alpha glucosidase inhibitors (block enzymes that digest carbs, so less insulin secreted): some weight loss
  - SGLT-2 inhibitors (lowers blood sugar resulting in less insulin secretion): some weight loss
  - Sulphonylureas (cause the body to produce more insulin): some weight gain
- Many other drugs, including:
  - Olanzapine (for psychiatric disorders, raises insulin levels and insulin resistance): weight gain
  - Gabapentin (for nerve pain, increases insulin production): weight gain

UK Prospective Diabetes Study Group, Lancet, 1998; Ebenbichler CF, J Clin Psychiatry, 2003; Scholl JH, Br J Clin Pharmacol, 2015; Penumalee S, Am J Kidney Dis, 2003;

The interaction of insulin and leptin

- Robert Lustig: 'Obesity is characterized by hyperinsulinaemia……(but) obesity is also a state of leptin resistance, in which defective leptin signal transduction promotes excess energy intake, to maintain normal energy expenditure. Insulin and leptin share a common central signalling pathway, and it seems that insulin functions as an endogenous leptin antagonist. Suppressing insulin ameliorates leptin resistance, with ensuing reduction of caloric intake.'

- So insulin and leptin are opposites: insulin promotes fat storage, leptin reduces fat storage. But both insulin and leptin are higher in the obese, indicating both insulin and leptin resistance.

Lustig RH, Nat Clin Pract Endocrinol Metab, 2006;

What determines the insulin response?

- The blood sugar response is identical whether glucose is given orally or intravenously. But the insulin response to oral glucose is much more powerful and is independent of blood sugar level.
- This is contrary to common sense; intravenous doses are 100% bioavailable, whereas oral doses may be incompletely absorbed or partially deactivated by the liver before reaching the bloodstream.
- The insulin response to oral sugars is so much more powerful because the stomach and small intestine produce incretins in response to all foods. Incretins are hormones which increase insulin secretion by the pancreas. Since i/v glucose bypasses the GIT, incretins are not activated. The incretin effect accounts for 50-70% of insulin secretion following oral glucose.
- The incretin hormones are GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide). They are secreted within minutes of food entering the stomach and peak secretion occurs at around 1 hour.
- The cephalic phase is another glucose-independent insulin secretion pathway. This acts by anticipation of food as soon as it enters the mouth. Merely placing food in the mouth and spitting it out will increase insulin secretion.

All foods cause an insulin response: implications

- All foods trigger incretin stimulation and food anticipation responses and raise blood glucose to some extent. Hence all foods contribute to insulin secretion and weight gain.
- But our relentless drive to eat 3 meals a day, not to mention 'grazing', means that insulin is kept fairly constantly triggered. So if we are not hungry, we should not eat.
- This is why, although some diets are more effective and healthier than others, ultimately all diets fail because we are continuing to eat, and therefore to secrete insulin.

Pal S, Br J Nutr, 2010

The time factor is often ignored

- Conventional caloric theories of obesity state that losing weight is the same experience whether one has been obese for a year or 20 years (a calorie is a calorie). But it's not true. Long-standing obesity is much more difficult to treat than recent obesity.
- The reason for this is insulin resistance. And insulin resistance is at the root not just of obesity, but T2D, fatty liver, HBP, dyslipidaemia, heart disease, cancer.
- Kong et al: The degree of weight loss during caloric restriction is inversely associated with baseline insulin resistance, i.e more insulin resistance = less weight loss. The degree of weight regain thereafter is positively associated with baseline insulin resistance, i.e, more insulin resistance = more weight regain.

Kong LC, Am J Clin Nutr, 2013;

Eating patterns

- There are 2 requirements for development of insulin resistance. High insulin levels and a constant blood glucose stimulus to secrete insulin.
- It is no coincidence that obesity did not develop all the time we ate 3 strict meals a day, when periods of increased insulin secretion were balanced by periods of fasting.
- A US survey showed that in 1977 most people ate 3 times per day but by 2006 most people were eating 5-6 times per day. The average time between eating dropped 30% from 271 minutes to 208 minutes. To counter the proponents of grazing, those surveyed had a higher energy intake as a result of continual snacking.
- Do we think the situation might have improved in 2021?

Popkin BM, Am J Clin Nutr, 2010

How do we develop insulin resistance?

- ‘Resistance’ or ‘tolerance’ is not a new phenomenon, c.f. antibiotic resistance, drug resistance. When there is a prolonged and excessive exposure to any substance, the body reacts by downregulating the receptors in an attempt to return the body to its original state (homeostasis).
- So when there is prolonged exposure to insulin, the insulin receptors downregulate, letting a little glucose into the cell but not a sufficient amount. The body detects that it has too little glucose in the cell and too much in the blood, so it signals the pancreatic β-cells to produce more insulin.
- So prolonged high insulin causes insulin resistance. But it also causes higher insulin levels – a positive feedback loop, aka a vicious cycle! The longer the cycle continues, the worse it becomes. This is why obesity is more difficult to reverse the longer the patient has been obese.
- Once insulin resistance has developed, it is completely independent of diet and exercise; it is dependent only on insulin secretion.
- Not willpower. Not caloric intake. Not exercise. Insulin resistance.

We can see this in the studies:

- A study simulating the effect of an insulinoma showed that 40 hour insulin infusions in normal healthy volunteers increased insulin resistance by 15%.
- Similarly, a 96 hour insulin infusion reduced insulin sensitivity by up to 40%. The authors commented: ‘These findings indicate that hyperinsulinaemia should be considered, not only as a compensatory response to insulin resistance, but also as a self-perpetuating cause of the defect in insulin action’.
- And what about T2D patients? Patients started on insulin treatment for 6 months showed very well-controlled blood glucose but there was a measurable correlation between insulin dose and degree of insulin resistance. The patients also gained a mean 19lbs (8.7kg) from baseline in 6 months!
- The authors commented: ‘This degree of metabolic improvement, however, requires large doses of exogenous insulin to overcome peripheral insulin resistance and results in greater hyperinsulinemia with progressive weight gain.’

Rizza RA, Diabetologia, 1985; Del Prato S, Diabetologia, 1994; Henry RR, Diabetes Care, 1993

So how did the insulin receptor's prolonged exposure to insulin start?

- There are many possible causes.
- The first, and most obvious, is a continual intake of sugar and/or refined carbs, which keep blood glucose elevated, causing continual secretion of insulin.
- But there are other possibilities….

The microbiome

This research is still in its infancy but nevertheless studies have shown that:

- The balance of *bacteroidetes* and *firmicutes* changes with BMI through release of lipopolysaccharides. In obese mice, the *firmicutes phylum* dominates the microbiome, which is notably different from that of lean mice, and diversity is greatly reduced.
- Several Lactobacillus and Lactococcus species are particularly associated with obesity and metabolic disorders.
- Imbalanced microbiota (from *E. coli* or *H. pylori* infection) induce increased BMI and desire for sugary foods through metabolic endotoxaemia. Dysbiosis is thought to affect metabolism through activating inflammatory pathways, impacting gut hormone secretion and altering SCFA production and the bile acid profile.
- A change in diet can shift the composition of the microbiome in as little as 24 hours.
- Cyclical changes in the microbiome from feeding/fasting rhythms contribute to the diversity of gut microflora, generally acknowledged to be beneficial, but are dampened in diet-induced obesity.
- Probiotics can help reduce insulin resistance and improve carbohydrate metabolism.

Udayappan SD, Clin Exp Immunol, 2014; Shen J, Mol Aspects Med, 2013; Zarrinpar A, Cell Metab, 2014; Zarrinpar A, Trends Endocrinol Metab, 2016; Saez-Lara MJ, Int J Mol Sci, 2016

Environmental toxins

- It is not ethical to carry out RCTs of environmental toxins in humans so we must rely on observational studies and animal experiments.
- Observational studies show an association between insulin resistance and serum concentrations of persistent organic pollutants (POPs): polychlorinated dibenzodioxins, dibenzofurans, phthalates, dioxins, mercury and manganese.
- Animals trials have shown that insulin resistance can be caused by POPs, including pesticides and particulate matter (air pollution).
- Environmental toxins causing insulin resistance are mostly EDCs, which bind to insulin receptors through molecular mimicry.

Jaacks LM, Environ Int, 2015; Batista TM, PLoS One, 2012; James-Todd T, Environ Health Perspect, 2012; Ruzzin J, Environ Health Perspect, 2010; Bolton JL, Brain Behav Immun, 2014; Lasram MM, Environ Toxicol Pharmacol, 2014; Schumacher L, J Appl Toxicol, 2017; Ibrahim MM, PLoS One, 2011; Batista TM, PLoS One, 2012

Diabetes: studies of intensive glucose control

- The Accord Study
- The VADT Study
- The ORIGIN Study

The ACCORD Study

- Action to Control Cardiac Risk in Diabetes (ACCORD) was an RCT of 10,000 patients funded by the US NIH to study the effects of intensive glucose control.
- It was highly successful in lowering HbA1c from 7.5% to 6.5%.
- But the trial was ended prematurely in 2008 when it became clear that the mortality rate in the intervention group was 22% higher than in the untreated control group. This represents 1 unnecessary death for every 95 patients treated.

Other RCTs

- Veterans' Affairs Diabetes Trial (VADT): RCT of 1700 adults on intensive glucose-lowering medication vs placebo to determine the effect on CHD events and renal or eye disease.
- No significant effect on any outcome.
- Outcome Reduction with Initial Glargine Intervention (ORIGIN): RCT of >12,000 pre-diabetics treated with early insulin vs placebo to determine the effect on CVD, CV mortality, stroke, peripheral vascular disease and eye disease.
- No significant effect on any outcome.

Finally the T2D medications shifted away from targeting blood glucose

- A new type of drug (Empaglifozin) works by inhibiting the sodium-glucose transporter (SGLT2) and forcing patients to urinate out the glucose.
- This was tested in an RCT called EMPA-REG to test for CVD and renal outcomes and showed significant reductions of 14% for all-cause mortality, MI or stroke and 38% for CVD mortality. Similar results for kidney disease. But it has its adverse effects…..
- Yeast infections and carb cravings – likely to make patients top up the depleted glucose levels!

When in doubt, study the Pima Indians

- The Pima Indians have the highest rates of diabetes and obesity in North America. An estimated 50% of adults are obese and of these, 95% have T2D. The Pima Indians also live in abject poverty.
- Evidence suggests that the ancestral way of life kept them extremely lean and healthy. But then refined sugar and white flour appeared in the diet because they could be kept at room temperature without spoilage.
- By the 1950s, obesity was widespread among all native American populations, decades before the current epidemic among non-native Americans began.
- Was this due to driving instead of walking, playing computer games instead of football?
- No, Pima Indians did not have vehicles or computer games in the 1950s.
- Was it down to the arrival of fast food and burger bars? No, Pima Indians did not have access to fast food and burger bars in the 1950s.
- They only had access to refined sugar and white flour.

But if all else fails (which it does!), we can always try…..

- Bariatric surgery: the ultimate cure for obesity and T2D
- Highly successful in reversing obesity and T2D…..at least in the short term. The stomach reduction causes nausea and vomiting with over-eating, effectively preventing a return to old eating habits.
- But….over the long term, the stomach slowly expands again if larger portion sizes are consumed and patients can then resume their old eating habits.
- This alone demonstrates that T2D is reversible, it is not inevitably progressive.
- Bariatric surgery is thought to work by altering the gut hormones. This may be a factor but….
- Comparison studies of bariatric surgery vs the CR imposed immediately after surgery (but without the surgery) show that weight loss and T2D reversal is identical, i.e. don’t bother with the surgery!

So what is all this telling us?

- Focusing on reducing blood glucose has no impact on diabetes comorbidities and can increase weight.
- Reducing glucose and carbohydrate absorption can improve CVD and renal outcomes. And lower weight in many cases.
- But we don’t need drugs for this…..