Mitochondria and metabolic diseases

- Obesity
- Insulin resistance
- Type 2 diabetes (T2D)
- [Slides for T1D on website]
- [Lecture on mitochondrial function in weight loss from Professor Eija Pirinen]

- Because there are relatively more studies for metabolic disease than other conditions, it is possible to investigate whether mitochondrial dysfunction causes metabolic disease or vice versa.

How is conventional medicine coping with the epidemic of obesity?

- According to the WHO in 2016, globally, more than 1.9 billion adults (39%) were overweight. Of these, over 650 million (13%) were obese. These figures are double those from the 1980s and three times those from 1975.
- In 2017-18, over 40% of adults were obese. The US 2014 obesity healthcare cost of over $1.4 trillion is more than twice what the US spends on defence and is equivalent to 8.2% of US GDP. And this is for obesity alone! This sum exceeds the economies of all but three U.S. states and all but 10 countries globally.
- In the UK, around 67% of adults are overweight, of whom 29% are obese (London does best at only 24%!). 21% of British children are obese by the time they finish primary school.
- There were four times as many hospital admissions with a primary or secondary diagnosis of obesity in 2016/17 compared with 2009/10. Obesity incidence is now occurring at considerably younger ages. 2017 data showed that 1 in 10 children aged 5-10 in the UK is obese.
- Public Health England blames it on the "increasingly obesogenic environment".
- In the UK, around 67% of adults are overweight, of whom 29% are obese (London does best at only 24%!). 21% of British children are obese by the time they finish primary school.
- There were four times as many hospital admissions with a primary or secondary diagnosis of obesity in 2016/17 compared with 2009/10. Obesity incidence is now occurring at considerably younger ages. 2017 data showed that 1 in 10 children aged 5-10 in the UK is obese.

Millken Institute, Weighing Down America, 2016; World Health Organization. Obesity and Overweight: http://www.who.int/mediacentre/factsheets/fs311/en/)

Obesity: conventional medicine still focused on low fat, calorie-controlled diets – more on this at Annex C

- Conventional doctors and dieticians continue to say that obesity is a result of caloric imbalance and recommend a low-fat, calorie-controlled diet as the treatment of choice for obesity. But it's this approach that has failed so miserably.
- Apparently calories make us fat. But calories are not a food or even a food group. They are a unit of energy.
- At the end of WW2, a period of real austerity and food rationing, Britons consumed 2,900 kcal/day, considered barely enough to keep the population alive and healthy. Yet we have never been healthier!
- Recent reports from DEFRA show that we are now consuming only 2,200 kcal/day, yet we are far more obese than in 1945.
- Virtually everyone who has tried caloric reduction as a route to weight loss may have succeeded in the short term but ultimately failed because the weight returns and sometimes exceeds baseline.
- Furthermore, the real problem is not losing weight but keeping the weight off once it is lost.

More on obesity, insulin resistance and T2D studies at Annex C

Annex C shows slides of studies demonstrating:

- How and why the low fat diet, calorie counting, pharmaceuticals and exercise failed to prevent or cure obesity;
- How obesity is in fact linked to intake of sugar and refined carbohydrates raising blood glucose and hence insulin.
- The obesity epidemic began with the issue of low fat guidelines.
- Excess blood glucose not stored in cells is firstly stored as glycogen in the liver, with further excess being transported to fat cells where it is stored as triglycerides, thereby increasing fat mass.
- How insulin resistance develops.
- Involvement of hormones in obesity.
- Eating patterns and the dangers of snacking.
- How studies of intensive glucose control failed to impact diabetes co-morbidities.

Mitochondrial dysfunction is routinely found in obesity

- Lower ATP synthesis in skeletal muscle from obese humans (Tran L, Exp Physiol, 2019).
- Downregulated adipose tissue OXPHOS with reduced mtDNA amount in obese humans (Heinonen S, Diabetes, 2015).
- Decreased activity of elements of the TCA cycle in obese humans (Christe M, ISRN Obes, 2013; Maples JM, Am J Physiol Endocrinol Metab, 2015).
- Animal models of obesity: fragmented mitochondria in skeletal muscle, upregulated mitochondrial fission proteins and downregulated fusion proteins (Holmstrom MH, Am J Physiol Endocrinol Metab, 2012; Jheng HF, Mol Cell Biol, 2012; Molina AJ, Diabetes, 2009; Bach D, J Biol Chem, 2003; Greene NP, Physiol Rep, 2015).
- In obese rats, apoptosis pathways activated in cardiac, but not skeletal, muscle (Peterson JM, J Appl Physiol, 2008).
- But…Mitochondrial and/or ETC dysfunction is not reported in all instances of obesity (Sergi D, Front Physiol, 2019).

Does obesity cause mitochondrial dysfunction?

Possibly

- A typical statement in a paper: ‘Obesity is the primary driver of impaired adipocyte mitochondrial respiration’ (Wessels B, Obesity, 2019).
- In visceral fat from mice fed an obesogenic diet for 12 months, impairment of glucose tolerance and increased fat mass developed after 1 month. Increased mitochondrial oxygen consumption rate and mitochondrial ROS were seen after 2 months but up until 6 months there was markedly increased mitochondrial DNA content and biogenesis and expression of PGC-1α, TFAM and MnSOD. At 12 months there was a decrease in mitochondrial biogenesis and mitochondrial function. (Wang PW, Antioxid Redox Signal, 2014)
- Adipocytes from visceral adipose tissue of obese subjects release reduced amounts of adiponectin, which leads to reduced activation of the AMPK/PGC-1α pathway in skeletal muscle (Wu Z, Cell, 1999; Semple RK, Int J Obes Relat Metab Disord, 2004; Roden M, Int J Obes, 2005; Hoeks J, Diabetologia, 2006).

Does mitochondrial dysfunction cause obesity?

Possibly

- There is a growing body of research demonstrating that altered mitochondrial energy production, particularly in skeletal muscles, is capable of setting off a chain of metabolic events leading to obesity. (Rogge MM, Biol Res Nurs, 2009)
- Mice lacking the mitophagy receptor develop more severe obesity and insulin resistance, with impaired mitochondrial quality control in WAT. Hence dysregulated mitochondrial quality control due to defective mitophagy receptor is associated with metabolic disorders. (Wu H, Autophagy, 2019)
- A shift towards mitochondrial fission promotes obesity and insulin resistance, as demonstrated in mice following ablation of the fusion protein (Sebastian D, Proc. Natl. Acad. Sci. USA, 2012).

Mitochondrial dysfunction is found in insulin resistance

- Reduced mitochondrial DNA content in lymphocytes in patients with hyperglycaemia and insulin resistance (Abu Bakar MH, Clin Exp Med, 2018).
- Impaired mitochondrial oxidative capacity is associated with greater insulin resistance and a higher likelihood of prediabetes in insulin resistant subjects without T2D (Fabbri E, Diabetes, 2017).
- Markers of mitochondrial biogenesis and metabolism are lower in insulin-resistant subjects (Heilbronn LK, J Clin Endocrinol Metab, 2007).
- Increased ROS production and reduced elements of the TCA cycle in insulin-resistant human skeletal muscle (Lefort N, Diabetes, 2010).
- Increased mitochondrial calcium uptake and upregulation of several mitochondrial calcium uniporter (MCU) components in insulin-resistant adipocytes and human visceral adipose tissue (Wright LE, Am J Physiol Endocrinol Metab, 2017).
- In patients with T2D, skeletal muscle oxidative capacity was a better predictor of insulin sensitivity than lipid status (Bruce CR, J Clin Endocrinol Metab, 2003).
- Decreased intracellular ATP and mitochondrial membrane potential, increased ROS and mtDNA damage in insulin resistant adipocytes, with decreased PGC-1, Nrf1, and TFAM and dysregulated fission and fusion proteins and increased mitochondrial mass with no change to mtDNA copy number. In insulin resistant hepatocytes: increased DNA damage and formation of the mtPTP. (Luan G, Molecules, 2019)
- Lower mitochondrial mass and reduced oxidative phosphorylation in insulin resistant skeletal muscle (Civitarese AE, Curr Opin Clin Nutr Metab Care, 2007).

Does mitochondrial dysfunction cause insulin resistance?

YES, at least in animals

- Diet-induced modifications in mitochondrial membrane proteins precede the development of hepatic insulin resistance in male mice (Kahle M, Mol Metab, 2014).
- Diet-induced mitochondrial dysfunction is a key event in the pathophysiological development of insulin resistance. The accumulation of ROS, lipotoxicity and alterations of mitochondrial gene expression leads to aberrant intracellular insulin signalling, thereby leading to insulin resistance. (Hafizi Abu Bakar M, Diabetes Metab Res Rev, 2015)
- Mitochondrial dysfunction caused by saturated fatty acid loading induces myocardial insulin-resistance in differentiated myocytes (Nobuhara M, Exp Cell Res, 2013).
- Aberrant mitochondrial fission causes insulin resistance in skeletal muscle (Jheng HF, Mol Cell Biol, 2012).
- Young obese rats displayed hepatic mitochondrial dysfunction which later led to increased triglyceride levels and insulin resistance. (Rector RS, J Hepatol, 2010)
- The depletion of cellular mtDNA causes insulin resistance in rat myocytes (Park SY, Diabetes Res Clin Pract, 2007).
- Disruption of MAM integrity contributes to insulin resistance in muscle (Tubbs R, Diabetes, 2018) and hepatocytes (Shinjo S, Exp Cell Res, 2017; Sergi D, Front Physiol, 2019).
- A shift towards mitochondrial fission promotes obesity and insulin resistance (Sebastian D, Proc. Natl. Acad. Sci. USA, 2012).
- But…evidence of compensation/adaptation again: An increase in mitochondrial efficiency precedes and therefore can contribute to the development of high-fat-induced insulin resistance in skeletal muscle (Crescenzo R, Front Physiol, 2015; Sergi D, Front Physiol, 2019).

Does insulin resistance cause mitochondrial dysfunction?

Maybe

- '…even 39 years after the first publication describing a relationship between IR and diminished mitochondrial function, it is still unclear whether a direct relationship exists, and more importantly if changes in mitochondrial capacity are a cause or consequence of IR.' (Montgomery MK, Endocr Connect, 2015)
- The interaction between mitochondria and insulin sensitivity is bidirectional and varies depending on tissue, experimental model, methodological approach, and features of mitochondrial function tested (Koliaki C, Annu Rev Nutr, 2016).

How is conventional medicine coping with the epidemic of T2D?

- In 2016, an estimated 1.6 million global deaths were directly caused by diabetes, and between 2000 and 2016 there was a 5% increase in premature mortality from diabetes, which is also a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation. Diabetes was the seventh leading cause of death in 2016. (WHO)
- The number of people with diabetes rose from 108 million in 1980 to 422 million in 2014. The global prevalence of diabetes among adults over 18 years of age rose from 4.7% in 1980 to 8.5% in 2014.
- In the UK, 10% of all people aged over 40 in the UK are now living with a diagnosis of T2D. This amounts of 4.7 million of us, expected to reach 5.5 million by 2030; in addition there is estimated to be around 1 million who do not know they have diabetes. This compares to 1.4 million in 1996. (https://www.diabetes.org.uk/about_us/news/new-stats-people-living-with-diabetes).
- Diabetes UK forecasts that diabetes prevalence is estimated to rise to 5 million by 2025, a rise of 43% in 16 years.
- The NHS spends £9bn a year on treating Type 2 diabetes - nearly 10% of its total budget; this equates to £173 million a week. In the US, diabetes is the costliest chronic disease for the healthcare profession. The next 4 costliest conditions are diabetes co-morbidities.

The Randle cycle: still influencing conventional medicine, despite being completely wrong!

- The Randle cycle is a metabolic process involving the competition of glucose and fatty acids for oxidation and uptake in tissues in the fed and fasted state in muscle and adipose tissue.
- Basically, in 1963, Randle decided to study how metabolism works at a cellular level. He took some muscle tissue and dropped some fat onto it. The muscle cells stopped metabolising glucose and used the fat for fuel instead, so Randle theorized that the presence of fat halts metabolism of glucose and leads to the production of fat. In other words, Randle thought that eating fat makes you fat.
- Many large organizations, including the American Diabetic Association, still use Randle's study to outline treatment plans for diabetics: high amounts of glucose and low amounts of fat.

Insulin resistance and the PDC

- With age and development of insulin resistance, we reduce our ability to activate the PDC. The PDC is dependent on insulin signalling to facilitate the conversion of glucose-derived pyruvate to acetyl CoA.
- Unless the PDC is activated, pyruvate has nowhere to go and so is converted in the cell to lactic acid. But eventually the drop in cellular pH from the lactic acidosis means that the cell will become dysfunctional and will operate anaerobically, even though oxygen may be plentiful. This increases the risk of cancer and AD.
- We see this production of lactic acid particularly in muscle, leading to pain and muscle fatigue. Chronic fatigue syndrome patients who suffer lactic acid build-up in muscles and the central nervous system, also have poor PDC function.
- Acetyl CoA and NADH build up in skeletal and cardiac muscle. But this makes it very difficult for the Randle cycle to shift back to pyruvate utilisation because a requirement is that acetyl CoA and NADH be low. This positive feedback loop contributes to increased insulin resistance.

(Stacpoole PW, Aging Cell, 2012)

T2D: conventional medicine still focused on lowering fasting glucose and improving glucose tolerance

- The current treatment paradigm focuses on lowering fasting blood glucose and improving glucose tolerance. This is because excess glucose was found to be highly toxic.
- But this ignores the cause of the problem, which is a continual supply of excess blood glucose unless eating patterns are improved.
- Conventional medicine provides glucose-lowering pharmaceuticals and has advocated low fat, high carbohydrate diets. It's not even logical!
- When treatment with insulin was found to lower risk of glucotoxicity in patients with T1D, it was assumed that it would be equally beneficial in T2D. In the US, 1/3 of diabetic patients now use some form of insulin treatment, a rise of 50% in a decade.
- Insulin treatment leads to worsening of insulin resistance and weight gain, analogous to quenching a fire by pouring on petrol!
- This was all, until….

Until….Professor Roy Taylor of Newcastle University

- Initiated by Professor Roy Taylor of Newcastle University, the trial included patients diagnosed with T2D within the past 6 years who over overweight or obese but not treated with insulin.
- In the intervention group, he took diabetics **off all glucose-lowering medication and gave them commercial liquid diet replacement formula** of 825-853 kcal/day for 3-5 months. The control group were given normal care (i.e. anti-diabetic medication).
- **After 12 months there was mean weight loss of 10kg (22lbs), while 24% lost more than 15kg (33lbs) and diabetes remission was seen in 46%** (Lean ME, Lancet, 2018).
- **The NHS is so excited about this study that it is now running its own!**
- This was an expensive study, requiring all meals provided and plenty of support from health professionals. Yet it was found to be below the annual cost of diabetes (including complications) of the control group (Xin Y, Diabet Med, 2019).

Mitochondrial dysfunction is routinely found in T2D

- Plasma mtDNA fragments and skeletal muscle mtDNA damage were elevated in T2D patients and correlated positively with insulin resistance (Yuzefovych LV, PLoS One, 2019).
- The rate of lymphocyte apoptosis was significantly higher in T2D patients, there were fewer mitochondria and lower mitochondrial membrane potential (Xu H, Chin Med J, 2014).
- Pre-diabetic subjects exhibited increased mitophagy markers, whereas those with T2D there was decreased expression of mitophagy markers which was time from diagnosis-dependent. A progressive rise in oxidative stress was seen in individuals with pre-diabetes, newly diagnosed T2D and long-term T2D. (Bhansali S, Front Endocrinol, 2017)
- In skeletal muscle of males with T2D, mitochondrial function was decreased by 12.5% and metabolic flexibility was lower (Van der Weijer T, PLoS One, 2013). In addition, mitochondria were smaller, more spherical and more polarised and mitochondrial mass was lower, with higher superoxide production (Widlansky ME, Transl Med, 2010).
- Skeletal muscle of T2D patients shows reduced mitochondrial respiration and lower expression of PGC-1α and Mfn2 (Antoun G, Diabetologia, 2015; Zorzano A, Biochim Biophys Acta, 2010 ; Minet AD, Biochem Biophys Res Commun, 2011).
- In leukocytes from T2D patients there was decreased mitochondrial O2 consumption and membrane potential, impaired Complex 1 activity, increased mitochondrial fission with decreased fusion, increased ROS production, increased calcium levels and decreased glutathione levels (Hernandez-Mijares A, Free Radic Biol Med, 2011; Escribano-López I, J Clin Med, 2019; Diaz-Morales N, Antioxid Redox Signal 2016).
- Decreased mitochondrial respiration was found in non-diabetic 1st degree relatives of individuals with T2D (Phielix E, Diabetes, 2008).
- A 35% decrease in mitochondrial respiration was found in T2D patients after normalisation for mitochondrial content (Phielix E, Diabetes, 2008).
- Mitochondrial dysfunction is not reported in all cases of T2D (Sergi D, Front Physiol, 2019).

Pancreatic function and mitochondria in T2D development

- In the pancreas, the β-cell rapidly reacts to fluctuations in blood glucose concentrations by adjusting ATP production and the rate of insulin secretion to maintain glycaemia and nutrient homeostasis.
- In the short-term: In response to a rise in blood glucose, β-cell mitochondria stimulate the synthesis of nucleotides and metabolites and increase ATP production. The increased ATP triggers membrane depolarisation, which opens voltage-gated calcium channels to increase intracellular calcium, which triggers insulin secretion, facilitated by the additional energy from ATP production. (Maechler P, Mol Cell Endocrinol, 2013; Maechler P Best Pract Res Clin Endocrinol Metab, 2012; Jitrapakdee S, Diabetologia, 2010; Fex M, J Endocrinol, 2018)
- In the long-term: The upregulated mitochondrial activity also triggers additional mitochondrial ROS production. The persistent ROS increase activates β-cell UCP2, which results in proton leak across the mitochondrial inner membrane, leading to reduced ATP synthesis, leading to reduced glucose-stimulated insulin secretion. The ROS also oxidise PUFAs in mitochondrial cardiolipin and other phospholipids, which impairs membrane integrity and leads to cytochrome c release into the cytosol, followed by apoptosis of the β-cell. (Ma ZA, Exp Diabetes Res, 2012; Supale S, Trends Endocrinol Metab, 2012)

Does mitochondrial dysfunction cause T2D?

Possibly

- 'Mitochondrial dysfunction is a central contributor to β-cell failure in the evolution of T2D' (Ma ZA, Exp Diabetes Res, 2012).
- ‘There is a growing body of evidence showing that mitochondrial dysfunction plays an important role in the pathogenesis of T2D’. Variation in mtDNA quantity and quality are associated with the risk of developing diabetes. (Kwak SH, Front Biosci, 2016)
- 'Mitochondrial ROS production may be a key factor...in the development of insulin resistance and type 2 diabetes (Nishikawa T, Diabetes Res Clin Pract, 2007).
- Decreased pancreatic mtDNA copy number is linked to the pathogenesis of T2D. Low mtDNA levels in pre-diabetic patients predict T2D development, while mitochondrial dysfunction leads to pancreatic beta cell malfunction (Lamson DW, Altern Med Rev, 2002).
- Increased activity of UCP2, found in pancreatic β-cells, is associated with cell degeneration, decreased insulin secretion and T2D. β-cell UCP2 expression is upregulated by glucolipotoxic conditions, regulated by mitochondrial superoxide. (Chan CB, Diabetes, 2004; Sreedhar A, Mitochondrion, 2017).
- Dysregulation of intracellular Ca2+ homeostasis due to mitochondrial dysfunction or defects in the function of MAMs are involved in the pathogenesis of insulin insensitivity and T2D (Wang CH, J Biomed Sci, 2017).
- Whereas the association between impaired mitochondrial function and T2D is strong, a causal pathogenic relationship remains uncertain (Patti M. Endocr Rev. 2010).

Does mitochondrial dysfunction contribute to diabetes complications? Probably

- Mitochondrial dysfunction contributes to the development and progression of diabetic kidney disease through ROS overproduction, activation of apoptosis and defective mitophagy (Wei PZ, Clin Chim Acta, 2019) as well as reduced mtDNA copy number (Al-Kafaji G, Exp Ther Med, 2018).
- Development of diabetic peripheral neuropathy is mediated through inhibition of the AMPK/PGC-1 α pathway leading to mitochondrial dysfunction which contributes to neuron apoptosis, distal axonopathy and nerve demyelination (Zhang Q, Chin J Integr Med, 2019).
- Excessive mitochondrial ROS from dysfunctional mitochondria play a key cell-signalling role in the development of diabetic vascular endothelial dysfunction (Widlansky ME, Transl Res, 2018; Chandrasekaran K, Int Rev Neurobiol, 2019).
- Many studies demonstrate that mitochondrial defects occur in the heart in individuals with insulin resistance or T2D, while diabetic cardiomyopathy is associated with dysregulated oxidative substrate selection (Montgomery M, Biology, 2018).
- Mitochondrial fission induced by Drp1 plays a critical role in the pathogenesis of several diabetes complications (Williams M, Front Endocrinol, 2018).

Does T2D cause mitochondrial dysfunction?

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Mitochondrial dysfunction is routinely found in T1D

- T-cells from patients with T1D exhibited mitochondrial inner membrane hyperpolarisation, increased mtROS production and lower intracellular ATP levels; excess mtROS can signal antigen-specific T cell activation (Chen J, Sci Rep, 2017; Chen J, Antioxid Redox Signal, 2018).
- In young adults with T1D, skeletal muscle mitochondrial oxidative capacity was significantly lower, and specifically at Complex II of the ETC, with increased mitochondrial H2O2 emission at Complex III (Monaco CMF, Diabetologia, 2018).
- Leukocyte mitochondrial membrane potential was elevated in T1D patients, which correlated with fasting plasma glucose (Matteucci E, Cell Biochem Biophys, 2011).
- In T1D patients deprived of their insulin, muscle expression of OXPHOS genes and mitochondrial ATP production were decreased (Karakelides H, Diabetes, 2007).
- In the cortex of type 1 diabetic rodents, depressed mitochondrial respiration rate, Mfn2, DRP1, AMPK, SIRT2 and PGC-1α expression, antioxidant production and membrane polarisation were seen (Roy Chowdhury S, Mol Cell Neurosci, 2018).
- Coronary endothelial cells from diabetic mice showed fragmented mitochondria, reduced mitochondrial fusion proteins and elevated fission proteins, with raised mitochondrial superoxide (Makino A, Diabetologia, 2010).
- Cardiac mitochondria from T1D rodents displayed severe metabolic inflexibility, with reduced respiration in the presence of non-fatty acid substrates and lowered pyruvate dehydrogenase and Complex II activity (Vadvalkar SS, Biochem J, 2013).
- In mice with T1D, renal superoxide production was reduced, with decreased mitochondrial biogenesis, pyruvate dehydrogenase and AMPK (Dugan LL, J Clin Invest, 2013).

Does mitochondrial dysfunction cause T1D? Too few studies

- Human studies are limited but a specific SIRT1 mutation was found to be associated with type 1 diabetes (Kane AE, Circ Res, 2018).
- Mitochondrial dysfunction in β-cells sensitises these cells to immune-mediated destruction via direct or indirect mechanisms.
- Excess mtROS can signal antigen-specific T cell activation; mitochondrial dysfunction in T cells has been noted as a feature of some human autoimmune diseases. Under immune attack, mtROS participate in β-cell damage. Sensitivity of β-cells to mtROS is associated with genetic T1D risk. Mitochondrial dysfunction and altered metabolism have also been observed in immune cells of patients with T1D. (Chen J, Antioxid Redox Signal, 2018)

Does T1D cause mitochondrial dysfunction? Too few studies

- Hyperglycaemia in T1D caused cytosolic Ca2+ influx and activation of cyclophilin D, which increased opening of the mitochondrial permeability transition pore (MPTP), causing an oxidative outburst and cell death (Papu John AS, Am J Physiol Endocrinol Metab, 2019).

Similarity of T1D and T2D?

- It has often been remarked that both T1D and T2D are associated with the same long term complications because they arise from the same pathogenic processes at mitochondrial level.
- Furthermore, the drug streptozotocin, which generates beta-cell toxicity, is used to induce T1D in animals and is sometimes used to induce T2D as an alternative to a high fat diet.
- Can these results for T2D induction really be extrapolated to humans?

So what is going on?

It looks as if metabolic disease may cause mitochondrial dysfunction and mitochondrial dysfunction may cause metabolic disease.

I came up with 5 possible reasons why this might be so:

- There have not yet been enough studies carried out to demonstrate a reliable direction of causality.
- There is a confounding factor: some other factor which has not yet been identified is the mediating factor between both relationships.
- The direction of causality varies by tissue type.
- There is an element of adaptation that masks the direction of causality.
- Both are true: positive feedback loop.

Examples of adaptation and compensation

- Despite an impairment in mitochondrial function, mitochondrial elements are initially upregulated to compensate but if the impairment is not corrected, a disease state ensues. This may explain the lack of clarity of study results.
- Despite lower mitochondrial content, skeletal muscle showed no differences in OXPHOS or ETC capacity between patients with T2D and healthy controls, suggesting that OXPHOS is upregulated to compensate for fewer mitochondria (Boushel R, Diabetologia, 2007).
- An increase in mitochondrial efficiency precedes the development of insulin resistance in skeletal muscle (Crescenzo R, Front Physiol, 2015; Sergi D, Front Physiol, 2019).
- Insulin resistant β-cells exposed to increased lipids respond by increasing mitochondrial volume, which is associated with enhanced mitochondrial metabolism as a means of β-cell compensation (Fex M, Diabetologia, 2007).
- In the pancreas, the β-cell rapidly reacts to fluctuations in blood glucose concentrations by adjusting ATP production and the rate of insulin secretion to maintain glycaemia and nutrient homeostasis. In the longer term, because the upregulated mitochondrial activity also triggers additional ROS production, this activates β-cell UCP2, which results in proton leak across the mitochondrial inner membrane, leading to reduced ATP synthesis, leading to reduced glucose-stimulated insulin secretion and apoptosis of the β-cell. (Maechler P, Mol Cell Endocrinol, 2013; Maechler P Best Pract Res Clin Endocrinol Metab, 2012; Jitrapakdee S, Diabetologia, 2010; Fex M, J Endocrinol, 2018; Ma ZA, Exp Diabetes Res, 2012; Supale S, Trends Endocrinol Metab, 2012)

Examples of adaptation in obesity, insulin resistance and T2D *

- Despite lower mitochondrial content, skeletal muscle showed no differences in OXPHOS or ETC capacity between patients with T2D and healthy controls, suggesting that OXPHOS is upregulated to compensate for fewer mitchondria (Boushel R, Diabetologia, 2007).
- Skeletal muscle from insulin resistant rats showed reduced mitochondrial fatty acid oxidative capacity at week 6, which was compensated for by an adaptive increase in mitochondrial function at week 12, which could not be sustained by week 19, at which point hyperglycaemia developed (Lenaers E, Obesity, 2010).
- An increase in mitochondrial efficiency precedes the development of insulin resistance in skeletal muscle (Crescenzo R, Front Physiol, 2015; Sergi D, Front Physiol, 2019).
- Insulin resistant β-cells exposed to increased lipids respond by increasing mitochondrial volume, which is associated with enhanced mitochondrial metabolism as a means of β-cell compensation (Fex M, Diabetologia, 2007).
- In visceral fat from mice fed an obesogenic diet, increased mitochondrial oxygen consumption rate and mitochondrial ROS were seen after 2 months but up until 6 months there was markedly increased mitochondrial DNA content and biogenesis and expression of PGC-1α, TFAM and MnSOD (Wang PW, Antioxid Redox Signal, 2014).

Elements of mitochondrial dysfunction seen in developed metabolic disease

- Decreased elements of the TCA cycle, downregulation of OXPHOS, impaired Complex 1 activity, decreased supercomplexes, decreased O2 consumption and reduced ATP synthesis.
- Decreased metabolic flexibility.
- Reduced quantity of mtDNA, mtDNA damage.
- Mitochondria are smaller and more spherical. Fewer and fragmented mitochondria due to downregulated fusion and mitochondrial biogenesis (decreased PGC-1, Nrf1 and TFAM) and upregulated fission. Mitophagy is often downregulated in T2D development.
- Excess ROS production and decreased mitochondrial antioxidants.
- Increased mitochondrial calcium uptake and upregulation of the MCU.
- Decreased mitochondrial membrane potential and modification of membrane proteins. In T2D, high blood glucose concentrations can be the cause of the misfolding of the pancreatic protein amylin (aka islet amyloid polypeptide). (Pillay K, Biomed Res Int, 2013)
- Formation of the mtPTP, leading to apoptosis (in hepatocytes and pancreatic β-cells).
- Disruption of MAM integrity.
- In the pancreas: β-cells-cells are swollen, with disordered cristae and in islet cells, NADPH oxidase was elevated.

Most conventional treatments for obesity and diabetes utilise mitochondrial pathways

- One of the earliest successful weight loss drugs (DNP: 2,4,-dinitrophenol) was an 'uncoupler', preventing the manufacture of ATP. It had some rather serious side effects: cataracts, toxicity symptoms similar to pesticides and vehicle exhaust a,nd death. It was removed from the market in 1938.
- Metformin: inhibits Complex I and mitochondrial fission but also improves mitochondrial respiratory function and membrane potential, upregulating expression of SIRT3 and activity of PGC-1α. It also works by activating AMPK, which inhibits glucose production in the liver (gluconeogenesis).
- Insulin: upregulates OXPHOS. Standard treatment in T1D and treatment of last resort in T2D.
- GLP-1 receptor agonists: upregulate mitochondrial biogenesis in BAT and induce browning of WAT.
- Thiazolidinediones (Glitazones): increase mitochondrial biogenesis and OXPHOS but can also inhibit Complex I to reduce ATP production.

Insulin *

- In obese subjects, visceral adipose tissue exhibited decreased Complex II activity. Insulin treatment stimulated complex II activity in subcutaneous fat but in visceral fat it led to a decrease in complex II activity (Ngo DTM, Am J Physiol Endocrinol Metab, 2019).
- In humans, insulin infusions led to increased expression of skeletal muscle mitochondrial proteins, higher oxidative enzyme activity and greater ATP production (Asmann YW, Diabetes, 2006; Stump CS, PNAS, 2003).
- Insulin increases ATP synthesis, OXPHOS coupling efficiency and glucose sensitivity. The improvement in mitochondrial function is explained by an insulin-induced decrease of mitochondrial proton leak. (Nisr RB, Biochim Biophys Acta, 2014)
- In rats with T1D, insulin increased mitochondrial ETC proteins, increasing spare respiratory capacity by up to 3-fold in sensory neurons, which enhanced neurite outgrowth and protected against neuropathy (Aghanoori MR, Exp Neurol, 2017). It also downregulated SIRT1 and AMPK in the diabetic rat, probably contributing to hepatic lipid accumulation (Barazzoni R, Clin Nutr, 2011).

Liraglutide (GLP-1 receptor agonist) *

- In obese mice, liraglutide attenuated weight gain and fat mass and upregulated the BAT AMPK-SIRT-1-PGC1-α pathway, suggesting that the anti-obesity effect of liraglutide occurs through adaptive thermogenesis by inducing beige fat development (Zhou J, Endocrine, 2019).
- Liraglutide reduces cerebral ischaemic injury in diabetic rats by reducing inflammation and oxidative stress and hence upregulating mitochondrial ATP-sensitive potassium channels (Shi N, Neuroreport, 2019).

Thiazolidinediones (Glitazones)*

- Rosiglitazones and pioglitazones inhibited Complex I in skeletal muscle, reducing ATP production and inducing a switch to aerobic glycolysis (Brunmair B, Diabetes, 2004).
- Pioglitazone increased mitochondrial biogenesis, mtDNA content and levels, nuclear-encoded ETC proteins, oxygen consumption and Complex I and IV activities and lowered mitochondrial peroxide levels in neurons (Ghosh S, Mol Pharmacol, 2007).
- Pioglitazone also improved insulin response and exercise capacity in diabetic rodent skeletal muscle by improving mitochondrial respiration and reducing oxidative stress (Takada S, Eur J Pharmacol, 2014).
- In skeletal muscle from obese diabetic subjects, rosiglitazone increased insulin sensitivity and metabolic flexibility and upregulatged genes for PGC-1α, independently of mitochondrial protein content (Mensink M, Int J Obes, 2007).
- In adipocytes from diabetic subjects, rosiglitazone restored the expression level of genes in the mitochondrial respiratory complexes I - IV and increased the number of mitochondria (Hakansson J, Diabetol Metab Syndr, 2011).
- In general, glitazones increase PGC-1α expression and mitochondrial DNA copy number, and enhance the oxidative capacity of adipocytes, leading to insulin sensitisation (Wilson-Fritch L, J Clin Invest, 2004; ; Bogacka I, Diabetes, 2005; Wilson-Fritch L, Mol Cell Biol, 2003).

Metformin *

- Metformin has long been in use as a treatment for obesity and T2D.
- It is an anti-hyperglycaemic agent and works by decreasing gluconeogenesis in the liver through activation of AMPK and/or inhibition of mitochondrial glycerophosphate dehydrogenase (Madiraju AK, Nature, 2014; Zhou G, J Clin Invest, 2001). The average T2D patient has three times the normal rate of gluconeogenesis; metformin treatment reduces this by over a third.
- It can also inhibit Complex I in hepatocytes and skeletal muscle (Owen MR, Biochem J, 2000; Brunmair B, Diabetes, 2004), inducing a switch to anaerobic glycolysis.
- In a rodent model of diabetic heart failure, metformin significantly improved the mitochondrial respiratory function and mitochondrial membrane potential, upregulating expression of SIRT3 and activity of PGC-1α in myocardial tissue (Sun D, Biochem Biophys Res Commun, 2017).
- Metformin slowed the progression of diabetes-induced atherosclerosis in mice by inhibiting mitochondrial fission in endothelial cells and reducing mitochondrial fragmentation and ROS production (Wang Q, Diabetes, 2017).
- Metformin also increases the insulin sensitivity of other body tissues, enhancing peripheral glucose uptake by upregulating GLUT-4 and may antagonise the action of glucagon, thus reducing fasting glucose levels, possibly through inhibition of ROS-associated mitochondrial fission (Li A, Mol Cell Endocrinol, 2016).
- However, although separately metformin and exercise improve insulin sensitivity, together the two negate the beneficial effect. Metformin abolished the improvement in insulin sensitivity and cardiorespiratory fitness after aerobic exercise by inhibiting skeletal muscle mitochondrial respiration and protein synthesis in older adults (Konopka AR, Aging Cell, 2019).

Metabolic inflexibility

- **In metabolic flexibility, the mitochondria switch freely between fuel choices: glucose and fatty acids.** Flexibility is mediated by the opposing actions of insulin and glucagon, which influence, principally, adipose tissue lipolysis (insulin promotes fat storage, glucagon promotes fat breakdown). (Muoio DM. Cell. 2014)
- **Metabolic inflexibility**, thought to afflict 88% of Americans, **occurs where over-consumption and excess carbohydrates results in the mitochondria becoming stuck in metabolising glucose.** Metabolic inflexibility has now been seen in obesity, T2D, heart disease, NASH and PCOS.
- **So could excessive ketogenic diet adherence similarly promote metabolic inflexibility?**
- **Probably. Several practitioners (including Dr Mercola) are now advocating a cyclical ketogenic diet.**
- As excess fuel increases, the NADH/NAD+ ratio increases and inhibits several enzymes of the TCA cycle, leading to accumulation of acetyl co-A at bottlenecks, which further inhibits the TCA cycle.
- To restore flexibility: there is evidence for success with intermittent fasting, a ketogenic diet with L-carnitine supplementation and exercise.

Mitochondrial therapies for metabolic disease

- **Caloric restriction/intermittent fasting**: improves weight, BMI, insulin resistance and glucose disposal (in diabetics). **More effective for weight loss than exercise**. Intermittent fasting as effective as continuous.
- **Ketogenic diet**: improves weight, markers for obesity, blood glucose, HbA1c and triglycerides. **More effective for weight loss than a low calorie diet or conventional anti-diabetic diet.**
- **Exercise**: Little effect on weight but improves insulin sensitivity. A combination of aerobic and resistance training is most effective but aerobic is more effective than resistance exercise.
- **Oxygen therapy** (supplemental and hyperbaric): lowers glucose and HbA1c and improves insulin sensitivity and glucose tolerance in diabetics.
- **Extreme temperature therapy** (both heat and cold exposure): heat improves visceral adiposity, weight, HbA1c, insulin resistance, fasting plasma glucose and glycaemic control in subjects with T2D, while cold can increase glucose uptake and insulin sensitivity, decrease insulin secretion, upregulate BAT.
- **Pulsed EMFs**: improves diabetic foot ulcers and reduces pain.
- **Infrared radiation**: enhances fat layer reduction, reduces body circumference and improves diabetic foot ulcers, reduces ulcer area and decreases neuropathy.

Cold exposure and brown adipose tissue (BAT)

- **BAT is brown because of the high concentration of mitochondria, with their high iron content.**
- **We saw in Lecture 1 that brown adipose tissue (BAT) converts energy from food into heat via the mitochondrial uncoupling protein UCP1, whereas white adipose tissue (WAT) stores energy as triglycerides.**
- Scientists used to think that it was impossible to increase BAT, but now we know that **BAT can be grown and this improves metabolic function, improves the ability to use insulin and increases mitochondrial biogenesis**.
- **WAT can take on the characteristics of brown adipose tissue by a process known as 'browning', creating 'beige' or 'brite' adipose tissue. This can be induced by cold exposure** and certain supplements. WAT can acquire BAT characteristics with up-regulation of UCP1 after cold exposure or adrenergic stimulation. When we avoid the cold, we never build up sufficient brown fat.
- These beige/brite adipocytes have characteristics similar to classical brown adipocytes and thus can burn lipids to produce heat. They normally have low thermogenesis activity and low mitochondrial number but once activated (such as by repeated exposure to cold or alternating between hot and cold), they behave in a similar manner to BAT, with increased mitochondrial biogenesis and upregulated UCP1.
- Babies have very high levels of BAT but deposits decline with age. It is mixed in with WAT and is located around the spinal cord, kidneys, neck and between the shoulder blades.

(Peirce V, Nature, 2014; Wang S, Biochem Biophys Res Commun, 2015; Rossato M, Mol Cell Endocrinol, 2014)

Uncoupling proteins in metabolic disease: different effects depending upon type and location

- Cold exposure activates UCP1-mediated thermogenesis to maintain normal body temperature. This is known as adaptive thermogenesis (i.e., the recruitment of thermogenic capacity in BAT). UCP1 synthesis is increased proportionally to temperature and duration of cold exposure.
- It has been suggested that UCP1-mediated thermogenesis is naturally employed for metabolic thermogenesis to prevent the development of obesity. However, it seems to have failed in many cases!
- UCP2, however, is found in pancreatic β-cells, where increased UCP2 activity is associated with cell degeneration, decreased insulin secretion and T2D. Upregulated UCP2 can lead to mitochondria-associated metabolic disease (Sreedhar A, Mitochondrion, 2017).
- β-cell UCP2 expression is upregulated by glucolipotoxic conditions, regulated by mitochondrial superoxide (Chan CB, Diabetes, 2004).
- In health, a protective mechanism exists: uncoupling protein 3 (UCP3) located on the mitochondrial membrane acts as an overflow valve, so that the excessive proton gradient does not slow down the ETC. Dysfunctional UCP3 leads to free radical damage in cells, which is associated with insulin resistance and T2D.

Caloric restriction (CR)/fasting in metabolic disease

- CR and intermittent fasting (IF) improved weight, insulin resistance and T2D development, but the results are not consistent across studies or between tissues (Sergi D, Front Physiol, 2019).
- In obese adults, zero calorie alternate day fasting lowered weight, insulin resistance, BMI and lipids (Catenacci VA, Obesity, 2016). In older obese adults, CR induced weight loss, lowered blood glucose, waist circumference and triglycerides and improved insulin sensitivity (Yassine HN, J Gerontol A Biol Sci Med Sci, 2009). Intermittent CR was as effective for weight loss as continuous CR (Schubel R, Am J Clin Nutr, 2018).
- Among overweight females undergoing a programme of CR, weight loss was 43% greater, in diet-responsive than in diet-resistant subjects. Diet resistant females displayed decreased mitochondrial proton leak and reduced expression of UCP3 in skeletal muscle. (Harper ME, Diabetes, 2002)
- In obese type 2 diabetics, CR lowered BMI, waist circumference, HbA1c and blood glucose and increased glucose disposal rate; it also lowered insulin dose (Ruggenenti P, Diabetes, 2017; Meehan CA, Medicine, 2015).
- In obese, older subjects, CR promotes weight loss and increased lean mass and glucose disposal and was more effective for weight loss than exercise (Coker RH, J Clin Endocrinol Metab, 2009).

Ketogenic diet in metabolic disease

- A low calorie ketogenic diet significantly reduced obesity and performed better than a standard low calorie diet (which also significantly reduced obesity). Similar results, including lower fat mass and waist circumference, were seen with a very low calorie ketogenic diet. (Moreno B, Endocrine, 2014; Moreno B, Endocrine, 2016).
- In overweight subjects, a ketogenic diet lowered weight, fat mass and triglycerides to a greater extent than a low calorie diet (Yancy WS, Ann Intern Med, 2004).
- A ketogenic diet lowered weight, HbA1c and triglycerides compared to a conventional anti-diabetic diet (Saslow LR, J Med Internet Res, 2017).
- In type 2 diabetics, a ketogenic diet lowered weight, BMI, waist circumference, blood glucose, HbA1c and triglycerides to a greater extent compared to a low calorie diet (Hussain TA, Nutrition, 2012).
- A low calorie ketogenic diet in subjects with T2D was more successful than a low calorie diet alone in achieving weight and waist circumference reduction, lowering of HbA1c and achieving glycaemic control (Goday A, Nutr Diabetes, 2016).

Exercise in metabolic disease

- Several trials have shown that exercise improves both insulin sensitivity, maximal oxygen consumption and skeletal muscle mitochondrial respiration in subjects with and without T2D (Montgomery M, Endocrinol Connect, 2015; Hey-Mogensen M, Diabetologia, 2010), although some have shown no effect.
- Both forms of exercise also promote mitochondrial biogenesis through upregulation of AMPK, which activates PGC-1α and Nrfs to activate the mitochondrial transcription factor TFAM (Tonkonogi M, Exerc Sport Sci Rev, 2002; Kjøbsted R, Diabetes, 2016).
- In subjects with T2D, mitochondrial content increased after 9 months of resistance training but not after aerobic training, although both forms of exercise induced clinical improvements and significantly improved most aspects of skeletal muscle mitochondrial content and substrate oxidation, whereas the combination of resistance and aerobic training improved all aspects (Sparks LM, J Clin Endocrinol Metab, 2013).
- Among males with T2D, exercise restored mitochondrial function and metabolic flexibility and improved insulin sensitivity (Meex RC, Diabetes, 2010).
- In obese insulin-resistant adults, aerobic exercise increased insulin sensitivity and fat oxidation in skeletal muscle, decreasing mitochondrial fission (Fealy CE, J Appl Physiol, 2014).
- In adults with longstanding T2D, 1 year of training raised skeletal muscle ATP production capacity and increased expression levels of genes for β-oxidation, TCA cycle and OXPHOS (Van Tienen FH, J Clin Endocrinol Metab).

Exercise in metabolic disease
(mostly meta-analyses)

- Several trials have shown that exercise improves both insulin sensitivity, maximal oxygen consumption and skeletal muscle mitochondrial respiration in subjects with and without T2D (Montgomery M, Endocrinol Connect, 2015; Hey-Mogensen M, Diabetologia, 2010), although some have shown no effect.
- In adults, exercise alone resulted in only little weight loss (Shaw K, Cochrane Database Syst Rev, 2006; Cheng CC, Menopause, 2018).
- In overweight/obese children or adolescents, exercise had no effect on fasting blood glucose but aerobic exercise lowered fasting insulin and insulin resistance (Corrêa Marson E, Prev Med, 2016).
- In obese insulin-resistant adults, aerobic exercise increased insulin sensitivity in skeletal muscle (Fealy CE, J Appl Physiol, 2014).
- In subjects with T2D, resistance exercise did not significantly lower blood glucose but lowered insulin and HbA1c; the longer the intensity and during, the greater the result (Liu Y, Int J Environ Res Public Health, 2019; Grace A, Cardiovasc Diabetol, 2017).
- In subjects with T2D, the combination of resistance and aerobic exercise improved all aspects of the condition; only aerobic exercise lowered blood glucose and visceral fat (Sparks LM, J Clin Endocrinol Metab, 2013; Pan B, Int J Behav Nutr Phys Act, 2018; Sabag A, Diabetes Metab, 2017).
- Among males with T2D, exercise improved insulin sensitivity (Meex RC, Diabetes, 2010).
- In children with T1D, regular vigorous activity improved glycaemic control, insulin dose, waist circumference and trigycerides but not HbA1c or blood glucose; in adults with T1D it also lowered BMI (Aljawarneh YM, J Nurs Scholarsh, 2019; Ostman C, 2018).

Oxygen therapy in metabolic disease

- Supplemental oxygen while exercising improved skeletal muscle mitochondrial OXPHOS and lowered HbA1c in sedentary obese adults with T2D (Cree-Green M, Diabetes, 2018).
- Hyperbaric oxygen therapy improved fasting blood glucose and glucose tolerance in subjects with T2D (Vera-Cruz B, Adv Exp Med Biol, 2015). It also improved peripheral insulin sensitivity in overweight and obese adults, with and without T2D (Wilkinson D, Diving Hyperb Med, 2015).
- A meta-analysis of 9 RCTs also found that hyperbaric oxygen improved the healing of diabetes-related lower limb ulcers and reduced the requirement for amputation (Golledge J, Diabet Med, 2019).

Extreme temperature therapy in metabolic disease

- T2D is associated with protein misfolding but induction of heat shock proteins can protect cells from injury by preventing protein damage and aggregation. Pancreatic β-cells exposed to acute heat shock activate defence mechanisms which include HSP synthesis and are less sensitive to the effects of cytotoxic agents. (Miova B, Curr Pharm Des, 2016)
- There is evidence that the heat shock response is defective in diabetes, with diminished thermoregulatory sweating, which makes the tissues vulnerable to stress-induced pathological changes. Heat exposure may therefore present a risk for T2D patients, although careful activation of HSPs improves insulin resistance and glucose homeostasis. (Padmalayam I, Discovery Med, 2014; Yardley JE, Diabetes Technol Ther, 2013; Kondo T, Curr Diabetes Rev, 2011)
- Obese subjects also have a blunted metabolic response to cold stimulation in BAT, with lower glucose uptake and blood flow (Orava J, Obesity, 2013).
- Human studies of heat therapy show a significant reduction in HbA1c, fasting plasma glucose, body weight and adiposity (Krause M, Curr Opin Clin Nutr Metab Care, 2015).
- In obese subjects with T2D, activation of the heat shock response improved visceral adiposity, HbA1c, insulin resistance and glycaemic control (Kondo T, Sci Rep, 2016).
- A study found that cold water swimming at least twice a week for 6 months in overweight subjects increased insulin sensitivity and decreased insulin secretion in females but not males, whereas another found that 10 days of cold acclimation increased insulin sensitivity in all subjects with T2D by upregulating skeletal muscle GLUT-4. Similar results were seen in normal weight females. (Gibas-Dorna M, J Aging Phys Act, 2016; Hanssen MJ, Nat Med, 2015; Gibas-Dorna M, Scand J Clin Lab Invest; 2016).
- In obese males, short-term cold acclimation has been shown to enhance the presence and activity of BAT in lean humans, increasing glucose uptake, but also to improve the skeletal muscle metabolic profile in subjects with T2D (Hanssen MJ, Diabetes, 2016).

Extreme temperature therapy in metabolic disease

- Induction of heat shock proteins (HSPs) can protect cells from injury by preventing protein misfolding and aggregation. The HSP response to both heat and cold is often defective in obesity and diabetes but careful activation of HSPs improves insulin resistance and glucose homeostasis.
- In obese subjects with T2D, activation of HSPs improved visceral adiposity, weight, HbA1c, insulin resistance, fasting plasma glucose and glycaemic control.
- A study found that cold water swimming at least twice a week for 6 months increased insulin sensitivity and decreased insulin secretion in overweight females, whereas others found that 10 days of cold acclimation enhanced the presence and activity of BAT, increased glucose uptake and improved skeletal muscle metabolic profile in subjects with T2D.
- Similarly, cold exposure for diabetes improved how the body metabolised glucose and almost reversed the symptoms of diabetes.
- Cold exposure dose- and time-dependently activates UCP1-mediated thermogenesis in BAT to maintain normal body temperature (adaptive thermogenesis).

(Miova B, Curr Pharm Des, 2016; Padmalayam I, Discovery Med, 2014; Yardley JE, Diabetes Technol Ther, 2013; Kondo T, Curr Diabetes Rev, 2011; Orava J, Obesity, 2013; Krause M, Curr Opin Clin Nutr Metab Care, 2015; Kondo T, Sci Rep, 2016; Gibas-Dorna M, J Aging Phys Act, 2016; Hanssen MJ, Nat Med, 2015; Gibas-Dorna M, Scand J Clin Lab Invest; 2016; Hanssen MJ, Diabetes, 2016; van Marken Lichtenbelt W, 2015)

Pulsed EMFs in metabolic disease – diabetic foot ulcers and peripheral neuropathy

- In subjects with diabetic foot ulcers, PEMFs decreased wound size and increased blood flow velocity and capillary diameter (Kwan RL, Adv Skin Wound Care, 2015).
- In the feet of subjects with and without diabetes, PEMFs improved cutaneous circulation (Sun J, Bioelectromagnetics, 2016).
- In feet, PEMFs reduced diabetic peripheral neuropathy and increased epidermal nerve fibre density (Weintraub MI, Arch Phys Med Rehabil, 2009).

Infrared radiation in metabolic disease – diabetic foot ulcers and peripheral neuropathy

- Low level laser therapy reduced body circumference in humans (Jackson RF, 2009, Lasers Surg Med; Jackson RF, 2012, Lasers Surg Med; McRae E, 2013, Lasers Surg Med; Caruso-Davis MK, Obes Surg, 2011)
- A review showed that llow level laser therapy was efficacious in fat layer reduction and in humans (Avci P, Lasers Surg Med. 2013)
- Infrared radiation improves body composition in conjunction with exercise (Mockel F, Ger Med Sci, 2006).
- Pulsed infrared light therapy improved peripheral protective sensation in subjects with T1D and T2D (Arnall DA, Acta Diabetol, 2006).
- In patients with a diabetic foot ulcer, infrared therapy induced an improvement in wound area (Tantawi SA, Lasers Med Sci, 2018).
- In patients with diabetic peripheral neuropathy, infrared therapy improved sensation and decreased neuropathic symptoms (Leonard DR, Diabetes Care, 2004).
- In diabetic mice, infrared therapy prevented the decline in β-cell mass and function via the mitochondria-mediated SIRT1 pathway (Hsu YH, Metabolism, 2020).

Mitochondrial remedies for which there is evidence for benefit in metabolic disease (Annex B)

- Astaxanthin
- B vitamins
- β-lapachone
- Berberine
- Butyrate
- Capsaicin
- L-carnitine
- Carnosine
- Coenzyme Q10
- Copper *
- Creatine
- Ginkgo biloba
- Ginseng
- Supplementary ketones and MCTs
- Lipoic acid
- Magnesium
- Melatonin
- Molecular hydrogen
- N-acetyl cysteine
- NAD+ and precursors
- Omega 3 fatty acids
- Pyrroloquinoline quinone
- Selenium *
- Sulphoraphane
- Taurine
- Tauroursodeoxycholic acid (TUDCA)
- Vitamin D
- Zinc *

Flavonoids and isoflavones

- Apigenin
- Baicalin/Baicalein
- Curcumin
- Epicatechin
- Epigallocatechin-3-gallate (EGCG)
- Grape seed extract
- Icariin
- Kaempferol
- Luteolin
- Milk thistle
- Myricetin
- Naringin/Naringenin
- Nobiletin
- Quercetin
- Resveratrol
- Rutin

- Genistein
- Daidzein
- Puerarin

Vitamins and minerals with *

All essential for mitochondrial function but in excess can be highly toxic and is implicated in metabolic disease.

Both mitochondrial deficiency and excess induce mitochondrial damage.

Flavonoids

A combination works best, as this is how they arise in nature. Their individual effects complement each other.

Top 10 remedies for metabolic disease in humans

- Berberine: 1500-2000mg/day
- Folate
- L-carnitine: 2-4g/day
- CoQ10: 100-200mg/day
- Creatine: 5-10g/day
- Panax ginseng: 3g/day
- α-lipoic acid: 300-600mg/day
- Inorganic zinc
- Curcumin: ≥1000 mg/day
- Milk thistle

*