FROM NAD+ SUPPLEMENTATION TO REVERSING CELL SENESCENCE...

Dr Steven Land and Dr Nichola Conlon ask, are we getting closer to the 'Elixir of Youth'?

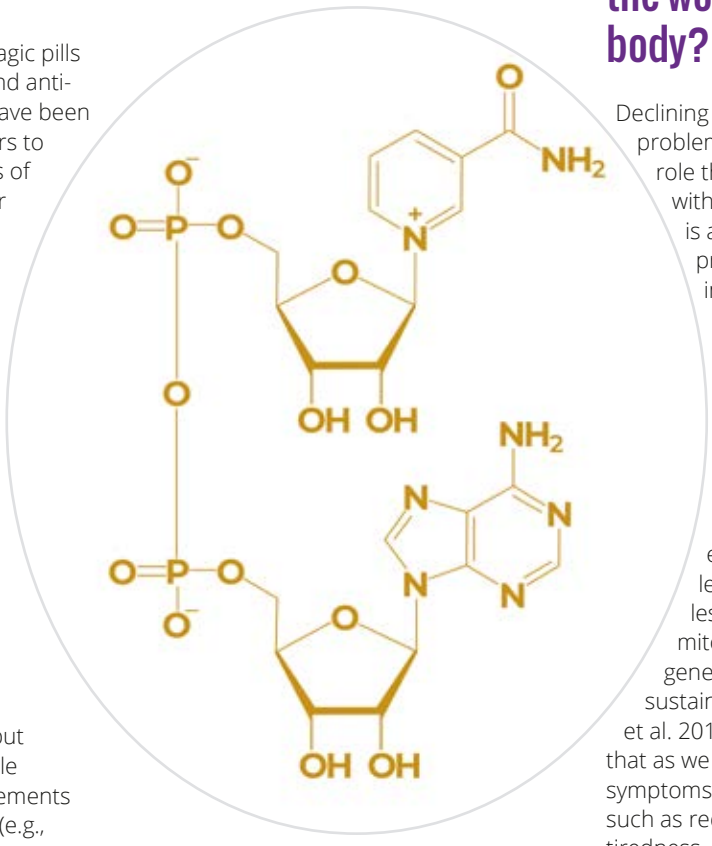
Cutting edge understanding of ageing looks at mitochondrial changes, cellular senescence, epigenetics, DNA repair, inflammation, energy metabolism and how all of these are locked together in a complex and accelerating spiral of decline (López-Otín et al. 2013). Taken individually, each one of these processes involves hundreds of different enzymatic pathways – whilst looking at the whole, shows that age-related decline is a colossal cascade of complexity, spinning ever faster towards inexorable system failure.

Dietary supplements and magic pills for regenerative medicine and anti-ageing are not new. There have been many attempts over the years to reverse ageing and the signs of ageing. The myth of the Elixir of Youth can be traced back to The Epic of Gilgamesh, a poem from ancient Mesopotamia c.1800BC.

In more recent years, a significant amount of research has gone into finding supplements and medicines that will help cellular regeneration, renewal and reversing the signs of ageing. Some of this research is accurate, and some is questionable - as with all subjects - which has led to a great deal of 'snake oil' - with big claims, but little in the way of measurable benefits. Despite this, supplements with demonstrable benefits (e.g., probiotics, polyphenols, collagen, vitamins A, C, E, amongst others) are well recognised by the aesthetics community for how they can help support our patients anti-ageing and wellness journeys from the inside, alongside the treatments we perform on the outside. Now, research has revealed newer chemicals involved in many of the pathways of ageing, that could be 'magic-bullets' for supplements or medication. One of the most promising of these is NAD+ (Nicotinamide Adenine Dinucleotide) (Katsyuba et al. 2020).

What is NAD+?

It is a cofactor central to metabolism found in every cell in the body. It is estimated to be involved in more than 500 different reactions that allow cells to sustain vital processes and maintain good health.



However, cellular NAD+ levels are now known to decline with age (Zhu et al. 2015, Massudi et al. 2012), and this decline has been found to correlate with an accumulation of damage that leads to many of the symptoms, and negative health consequences, associated with ageing (McReynolds et al. 2020).

NAD+ has recently gained a lot of attention in anti-ageing medicine since it was demonstrated that boosting NAD+ back to youthful levels has the potential to rejuvenate old cells back to a state of youth. As a result, many scientists now agree that maintaining high levels of NAD+ as you age is one of the most promising ways to combat the ageing process (Mills et al. 2016, Rajman et al. 2018).

How does NAD+ affect the workings of the body?

Declining NAD+ levels are problematic due to the important role that this molecule plays within the body. Firstly, NAD+ is an essential part of the process that converts food into the energy that cells need to function.

This happens in the mitochondria, the 'energy powerhouses' of the cell. Here NAD+ helps to make ATP which is the main source of cellular energy. Hence, as NAD+ levels go down with age, less NAD+ is available to the mitochondria, so cells cannot generate enough energy to sustain normal function (Gomes et al. 2013). Ultimately, this means that as we get older, we experience symptoms of low cellular energy such as reduced cell turnover, tiredness, muscle weakness, and poor concentration.

The second major role that NAD+ plays is as a signalling molecule, working to switch other cellular processes on and off. High levels of NAD+ signal the activation of protective cellular maintenance and repair processes.

NAD+ molecule image courtesy of Nuchido

For example, the activation of DNA repair enzymes that fix damaged DNA and other processes which make sure that damaged proteins in the cell are recycled and renewed (Hou et al. 2018). During youth, when we have high levels of NAD+, maintenance and repair processes are fully switched on; this keeps our cells in good health. But as we age and NAD+ levels decline, these maintenance and repair processes start to get turned down, leading to cellular damage and ultimately ageing.

Notably, NAD+ is also essential to activate 'longevity proteins', a family of seven proteins called 'Sirtuins' found in every cell (Bonkowski & Sinclair 2016). These proteins are nicknamed the 'guardians of the genome' because they play a key role in maintaining cellular health and switching off genes that are associated with ageing. These proteins do not work without NAD+, so when NAD+ levels become low, their protective capabilities are lost.

Do we know why NAD+ declines as we age?

There are two main reasons known to cause cellular NAD+ decline. The first is that old cells use up more NAD+ (mostly via CD38, PARP and SARM1). They have more damage and inflammation than younger cells, and repairing this damage uses up large amounts of NAD+ (Camacho-Pereira et al. 2016). The second reason is that as we age, the cell factory does too. Production becomes less efficient at making NAD+ because the enzymes in our cells that produce NAD+ decline with age. Thus, right at the time in our lives when our cells could do with more NAD+, they become less efficient at producing it - resulting in a deficit. Therefore, critical cellular processes have to fight over a short supply of NAD+ (Frederick et al. 2016).

As we age, the cell factory does too. Production becomes less efficient and NAD+ declines...

Does NAD+ decline at the same rate in everyone?

It is estimated that NAD+ levels decline by 50 per cent every 20 years (Massudi et al., 2012). But the effects of low NAD+ generally become noticeable around age 30 to 40, which by no coincidence correlates with the age bracket when people start to notice the first signs of ageing, such as loss of skin elasticity, or longer recovery times after exercise.

While NAD+ decline is inevitable, the rate at which NAD+ levels decline is influenced heavily by lifestyle. A poor diet and lack of exercise are both known to decrease the natural production of NAD+, whilst exposure to DNA damaging agents such as UV rays and cigarette smoke require large amounts of NAD+ to repair the damage they cause. Certain tissues in the body also appear to be more sensitive to NAD+ decline, most notably the skin and nervous system, as evidenced by the disease pellagra which is caused by NAD+ deficiency and characterised by extreme dermatitis and dementia.

Evidence from NAD+ anti-ageing research

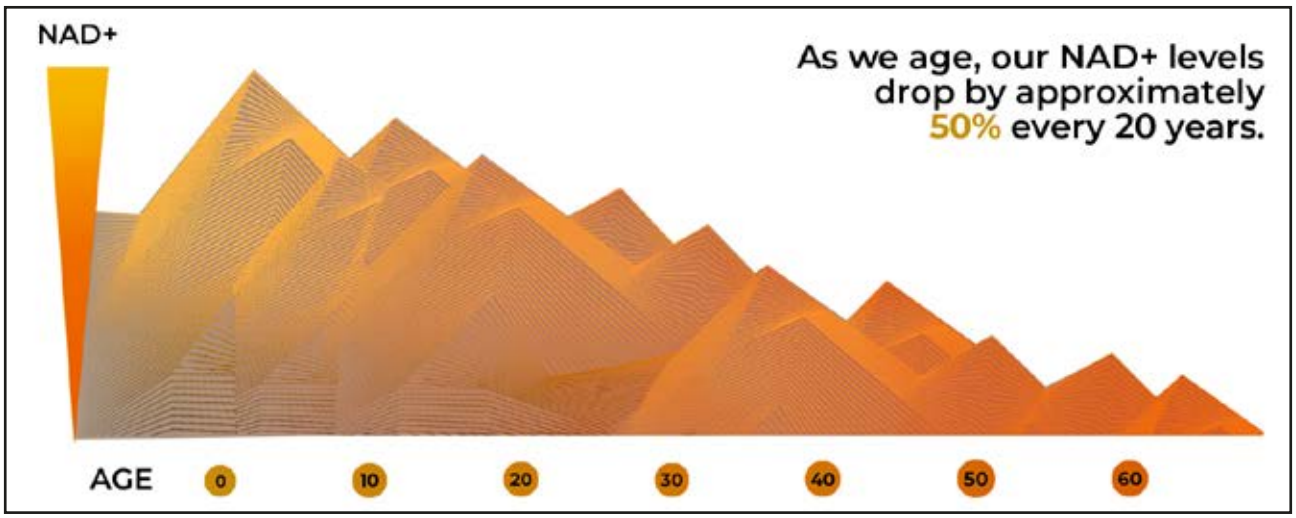
Multiple scientific studies have shown that if you prevent cellular NAD+ levels from declining, or indeed restore them to youthful levels, you can prevent the negative impact of low NAD+ levels on ageing (Rajman et al. 2018). At a cellular level, this means better mitochondrial function, increased DNA damage repair, increased energy metabolism and activation of genes that are associated with healthy ageing. At a whole body level, boosting NAD+ levels has been scientifically shown to:

- restore age-associated muscle loss,
- increase endurance and strength,
- increase neurogenesis, improve cognition and memory,
- decrease amyloid-beta production (associated with Alzheimer's),
- and improve markers of metabolic health such as increased insulin sensitivity.

Notably, the highest level of evidence for NAD+ restoration therapy in humans is for skin diseases.

How can we maintain or improve levels of NAD+?

The good news is that there are scientifically proven ways to boost NAD+ levels. One increasingly popular way is to use an NAD+ -boosting supplement (Radenkovic et al. 2020). This type of supplement is a fairly new addition to the supplement market but has the credibility of strong scientific research supporting the benefits of boosting cellular NAD+.



NAD+ decline graph courtesy of Nuchido

GLOSSARY		
CHEMICAL	**NAME**	**FUNCTION**
NAD+	Nicotinamide adenine dinucleotide	Co-factor central to metabolism - involved in over 500 metabolic reactions
ATP	Adenosine tri-phosphate	Main molecule of intracellular energy transfer
CD38	Cyclic ADP ribose hydrolase	Enzyme utilising NAD+ to help regulate intracellular Ca. Increasingly expressed in senescence and inflammation
PARP	Poly ADP-ribose polymerase	
SARM1	Sterile alpha & TIR motif containing 1	Enzyme involved in initiating cell death due to injury
Sirtuins		Class of proteins implicated in cellular ageing, apoptosis inflammation, stress resistance and energy efficiency
NR	Nicotinamide riboside	NAD+ precursor
NMN	Nicotinamide mono nucleotide	NAD+ precursor
NAMPT	Nicotinamide phosphoribosyltransferase	Enzyme in the NAD+ salvage pathway - converts nicotinamide to NMN
NAD(P)H	NAD(P)H dehydrogenase	Enzyme that helps in the salvage of NAD+
AMPK	Adenosine monophosphate-activated protein kinase	Enzyme that helps cellular energy homeostasis, activating fatty acid and glucose uptake and oxidation. Helps with salvage of NAD+
Senescent cells		Cells in a permanent state of cell-cycle arrest. They do not divide or support the tissues of which they are part and secrete a range of proinflammatory factor that's damage neighboring cells. They are known to accumulate in tissues with age and contribute to agerelated tissue dysfunction and disease.
Epigenetic		Whilst DNA is inherited and does not change throughout life, epigenetics is how different genes are turned off and on and can be influenced by external factors.

Introducing NAD+ to your practice

When choosing an NAD+ -boosting supplement for your clinic, there are some important things to consider.

The first to note is that you cannot supplement with 'pure NAD+'. Some companies sell tablets or powders containing 'pure NAD+' and advertise them as a method for directly boosting NAD+ levels. Unfortunately, these products do not work as advertised because NAD+ is a large and unstable molecule that is broken down in the digestive system before it can reach the bloodstream, let alone the cells where it is needed.

Other NAD+ boosting supplements work by supplying the body with the raw materials that cells use to make NAD+. These are referred to as 'precursor supplements' and tend to contain only a single ingredient such as Nicotinamide Riboside (NR) or Nicotinamide Mononucleotide (NMN) (Yoshino et al. 2018).

But this approach is also problematic as it ignores the fact that the enzymes that convert these precursors into NAD+ decline with age.

Using this approach to boost NAD+ can be compared to the idea of shipping more raw materials into a factory, and hoping to see an increase in production, whilst ignoring the fact that the machines on the production line are broken.

Therefore, when looking for an NAD+ -boosting supplement, it is vital to look for one that helps to fix the underlying reasons why cellular NAD+ declines with age.

The best NAD+ -boosting supplements are those that take a whole system approach. They contain not only a precursor, i.e. the raw material, but also other ingredients designed to boost levels of the enzymes which make and recycle NAD+, i.e. NAMPT, NAD(P)H, AMPK, (in other words, fix the machines too).

These products help to restore the cells natural ability to produce and recycle their NAD+ and have been proven to be a far more efficient way of boosting cellular NAD+.

The future of regenerative medicine

As scientists deepen their understanding of the pathways involved in cellular ageing, it is clear that we have reached a tipping point with true cellular rejuvenation now being proven possible.

For example, therapies designed to destroy troublesome senescent cells in old tissues have resulted in the attenuation of age-related tissue dysfunction and chronic inflammation (Kirkland & Tchkonia, 2020). Whilst a process called epigenetic reprogramming has shown that older cells can be literally 'reprogrammed' back to a state of youth using a fairly simple set of epigenetic modifications (Zhang et al. 2020). These emerging scientific fields have shown that what was once thought of as pure science fiction, is now undoubtedly scientific fact with the anti-ageing market about to experience an explosive growth in products that really do turn back the clock.

What does this all mean for our patients?

Introducing NAD+ -boosting supplements into your clinic can have many positive benefits for your patients. Increasing their years of wellness, increasing their endurance, strength, mental and physical energy, and potential improving the condition of their skin. We can treat their whole body, not just the visible signs of ageing.

Several NAD+ supplements are already available on the market, some just providing precursors, some looking at the whole system of NAD+ salvage and production.

Ongoing research is looking at the effect of increasing intracellular NAD+ on cell longevity, acne, kidney disease, Alzheimer's, obesity, skin health and many others with over 500 studies registered as ongoing/upcoming on *clinicaltrials.gov* and improving NAD+ seems to have the potential to be the elixir for anti-ageing - a huge leap forward in the science of ageing. It represents a huge opportunity for aesthetic medicine to further improve the lives of their patients.

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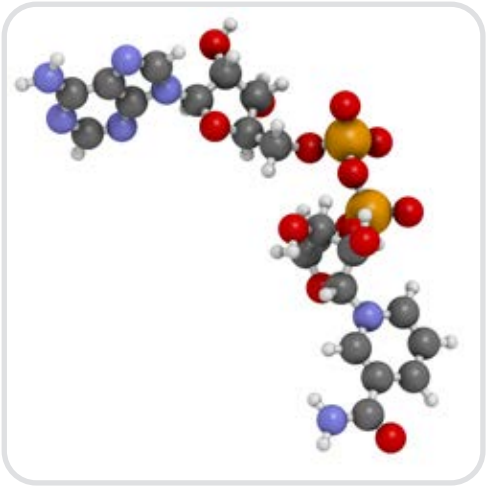

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