Analysing NAD+ and the Menopause

Dr Nichola Conlon explains possible links between menopausal symptoms, biological ageing and the potential for NAD+ restoration

In the UK, it is estimated that a third of the female population is currently perimenopausal or menopausal – meaning there are around 13 million women currently experiencing the physical symptoms associated with this period of life.[1] Although these symptoms can significantly impact a woman's health and quality of life, menopause is not considered a medical condition, but rather a natural part of the ageing process.

However, recent studies have shown that menopause accelerates a women's rate of ageing, meaning that it can no longer be considered just a consequence of the ageing process, but a driver of it.[2,3] This explains why many women report feeling like they have 'aged rapidly' during the menopause transition. Understanding the link between menopause and accelerated ageing has therefore become an important area of scientific interest.

As nicotinamide adenine dinucleotide (NAD+) can be used to revitalise cellular function and therefore also target the hallmarks of ageing, this article will explore its potential impact on symptoms of the menopause.

Chronological vs. biological age

Whilst chronological age is simply the number of years since birth, biological age is a measure of the rate at which a person is ageing on the inside at the cellular level.[4] Interestingly, it has been found that there is often a discrepancy between a person's chronological and biological age. For example, if a person with a chronological age of 40 has a biological age closer to 50, it indicates that they are ageing at an accelerated rate. Conversely, a person with a biological age younger than their chronological age has a slower rate of ageing.[5,6]

Studies have demonstrated that during menopause, a woman's biological age rapidly increases. One study of 36 women found that biological age increased by an average of nine years in just six months of menopause.[2] Another study of 2,000 women found that their rate of biological ageing doubled during the menopause, with some women experiencing a biological age increase of 20 years during this period, which on average lasts seven years.[3,7] This research highlights the importance of hormones in regulating the cellular ageing process.

Menopause and cellular health

The link between menopause and accelerated biological ageing is due to the critical role that hormones play in maintaining cellular health. Menopause is characterised by a sudden drop in oestrogen, progesterone and testosterone.[8] Although these hormones are traditionally considered as sex hormones, their role extends far beyond the reproductive organs. For example, oestrogen is known to be a critical regulator of cellular health.[9] Oestrogen receptors are found throughout the body; when oestrogen binds to its receptors, many downstream pathways are activated which regulate important cellular functions, resulting in optimal cellular health.[10] In the absence of oestrogen, these pathways remain inactive and cellular damage accumulates.[10]

A higher biological age is indicative of poor cellular health.[4] Scientists have now identified 12 key cellular failures that underpin the ageing process, which are known as the hallmarks of ageing (**Figure 1**).[11] Research suggests that the decline in cellular health during menopause contributes to at least two important hallmarks of ageing – mitochondrial dysfunction and chronic inflammation.[10,12]

Mitochondrial dysfunction and menopause

Mitochondria are the energy powerhouses of the cells. They convert food into adenosine triphosphate (ATP) which is used to power cellular functions.[13]

During ageing, mitochondrial function declines, resulting in reduced ATP production and increased production of damaging reactive oxygen species (ROS).[11] These dysfunctional mitochondria struggle to meet the energy demands of the cell, and produce toxic byproducts that create further cellular damage.[14] This is part of a negative cascade which in turn drives other hallmarks of ageing such as chronic inflammation, cellular senescence and DNA damage, which further increase biological age.[15]

Oestrogen receptors are abundant on the mitochondrial membrane.[14] This hormone is known to influence various aspects of mitochondrial function including energy production, antioxidant defence, mitochondrial biogenesis and mitophagy (recycling of damaged mitochondria).[16,17] This means that alongside the age-related mitochondrial decline experienced by both men and women, menopausal women also experience a drastic impact on their mitochondrial function as oestrogen plummets.[14,15]

Mitochondrial dysfunction particularly impacts cells and tissues with high metabolic demands such as the brain.[18] This helps to explain another common symptom of menopause – brain fog.[17] Mitochondrial oestrogen receptors are abundant in key regions of the brain which regulate memory and cognition,[9] and studies have shown that the metabolic function of a woman's brain declines by around 15-25% after menopause.[18,19] This leads to neurons being unable to form new connections, inability to store memories correctly, forgetfulness and ultimately brain fog.[20]

Chronic inflammation and menopause

Oestrogen is also a key regulator of immune function where it helps to balance pro-inflammatory and anti-inflammatory signals.[21]

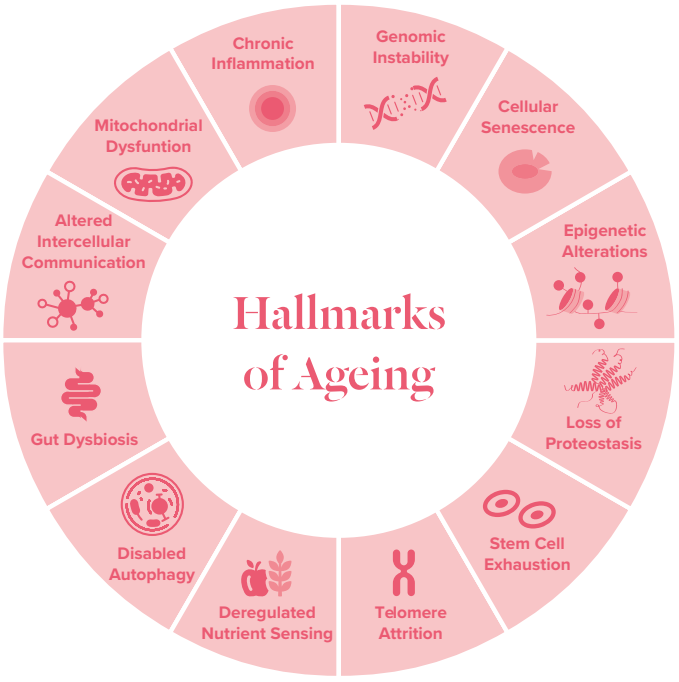

Figure 1: The hallmarks of ageing[11]

Declining oestrogen shifts the body towards a pro-inflammatory state.[12] This rise in low-grade chronic inflammation is an established hallmark of ageing and is often referred to as 'inflammaging', characterised by persistent expression of inflammatory cytokines such as IL-1, IL-6, CRP and TNF-a.[22] This overactivation of the immune system during menopause accelerates cellular ageing and increases biological age.[20]

Additionally, chronic inflammation is also linked with multiple age-related diseases such as neurodegenerative decline, cardiovascular disease, metabolic dysfunction and osteoporosis, all of which have an increased incidence in post-menopausal women.[23-25]

NAD+ and cellular health

This deeper understanding of the link between menopause and the hallmarks of ageing has highlighted the need for strategies that target the impact of menopause at the cellular level.

One molecule that has been the focus of scientific research is NAD+, which is a natural molecule found in every cell that powers vital reactions that govern cellular health.[26] NAD+ is required for optimal mitochondrial function, and also serves to activate multiple cellular repair pathways.[27,28] The role of NAD+ in regulating cellular health means that it is one of few molecules known to impact all of the hallmarks of ageing.[29]

Unfortunately, cellular NAD+ levels have been found to decline with age, driving the hallmarks of ageing and the cellular ageing process.[30] NAD+ declines by approximately 50% every 20 years, meaning that cellular NAD+ levels are severely depleted by the time a woman enters menopause.[31] Combined with the rapid decline in oestrogen, low NAD+ during menopause is detrimental in accelerating the ageing process (**Figure 2**).

NAD+ restoration to mitigate menopause symptoms

Ensuring optimal NAD+ levels during menopause may help counteract some of the negative effects of oestrogen decline on cellular health, and positively impact menopausal symptoms (**Figure 2**).[8,10,12,31,32]

NAD+ is particularly important for optimal mitochondrial function and energy production.[27] It functions as an electron donor in redox reactions during ATP production; without NAD+, energy production cannot occur.[33] Increasing NAD+ has been found to improve mitochondrial function and drive efficient cellular energy production.[32,34] NAD+ also activates mitochondrial repair pathways which promote the recycling of damaged mitochondria and the production of new mitochondria.[35] Enhancing NAD+ can therefore help to relieve physical symptoms of poor cellular energy production such as tiredness and fatigue.[36]

NAD+ is also critical for energy production in neurons.[37] NAD+ dependent enzymes have been found to be involved in synaptic plasticity and neuronal stress resistance, and declining NAD+ has been found to contribute to brain ageing.[38] A study of 30 people has shown that increasing NAD+ levels has a positive impact on brain health,[39] and may help to reduce symptoms of brain fog during menopause.[40]

NAD+ is also known to regulate appropriate inflammation (such as in response to injury) and help prevent the chronic inflammation that is known to accelerate ageing.[41] In combination with sirtuins, NAD+ regulates the activation of NF-κB – the master regulator of pro-inflammatory pathways – to reduce the persistent inflammation that can be associated with oestrogen decline.[42]

Given the positive influence of NAD+ on diverse aspects of cellular health and the hallmarks of ageing, it is no surprise that interventions designed to boost cellular NAD+ levels were found to reverse biological age in a human clinical study on 26 subjects.[43] Although this sample size is small and more research is needed in this area, the research to date demonstrates that NAD+ has the potential to be used as a tool to help protect cellular health and slow the biological ageing observed during the menopause.

Methods to restore NAD+

Given the benefits associated with NAD+, several methods to restore NAD+ levels have emerged. The use of intravenous infusions of pure NAD+ and subcutaneous NAD+ injections have gained popularity; however, these methods should be approached with caution.[39] This is because of the absence of clinical data surrounding the ability of the large and unstable NAD+ molecule to cross from the systemic circulation into cells where it performs its function.[44] Further studies are needed in this area to enhance understanding and safety.

To date, oral supplements designed to fix the root cause of NAD+ decline have emerged as the gold standard for NAD+ restoration.[45] This category of supplement works by restoring levels of the NAD+ producing enzyme NAMPT to reactive natural cellular NAD+ production, and is supported by human clinical data demonstrating safety and efficacy for boosting NAD+, reducing inflammation and lowering biological age.[43]

Lifestyle factors also play an important role in NAD+ levels. In general, a poor lifestyle consisting of lack of exercise, an inflammatory diet and factors like smoking deplete NAD+, while healthier practices like intermittent fasting and exercise are known to promote NAD+ production in the body.[46]

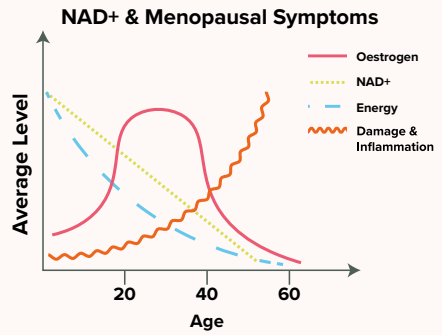

Figure 2: Correlation between NAD+, oestrogen and symptoms of ageing[8,10,12,31,32]

Aiding menopausal women through ageing

As evidence continues to emerge highlighting menopause as a key driver of the cellular ageing process in women, it is important to look at therapies that restore cellular health as a means to alleviate the symptoms of menopause. Whilst NAD+ restoration is known to be important in both men and women, evidence suggests that restoring NAD+ in perimenopausal and menopausal women may be of particular importance to protect cellular health during this life transition.

Disclosure: Dr Nichola Conlon is the chief executive officer and shareholder of Nuchido Ltd. and has filed patents on NAD+ boosting therapies.

Dr Nichola Conlon is a molecular biologist specialising in the study of cellular ageing. She is passionate about translating the latest science into products that slow biological ageing. After a career in drug development, she founded Nuchido Laboratories to translate longevity science into consumer products.
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