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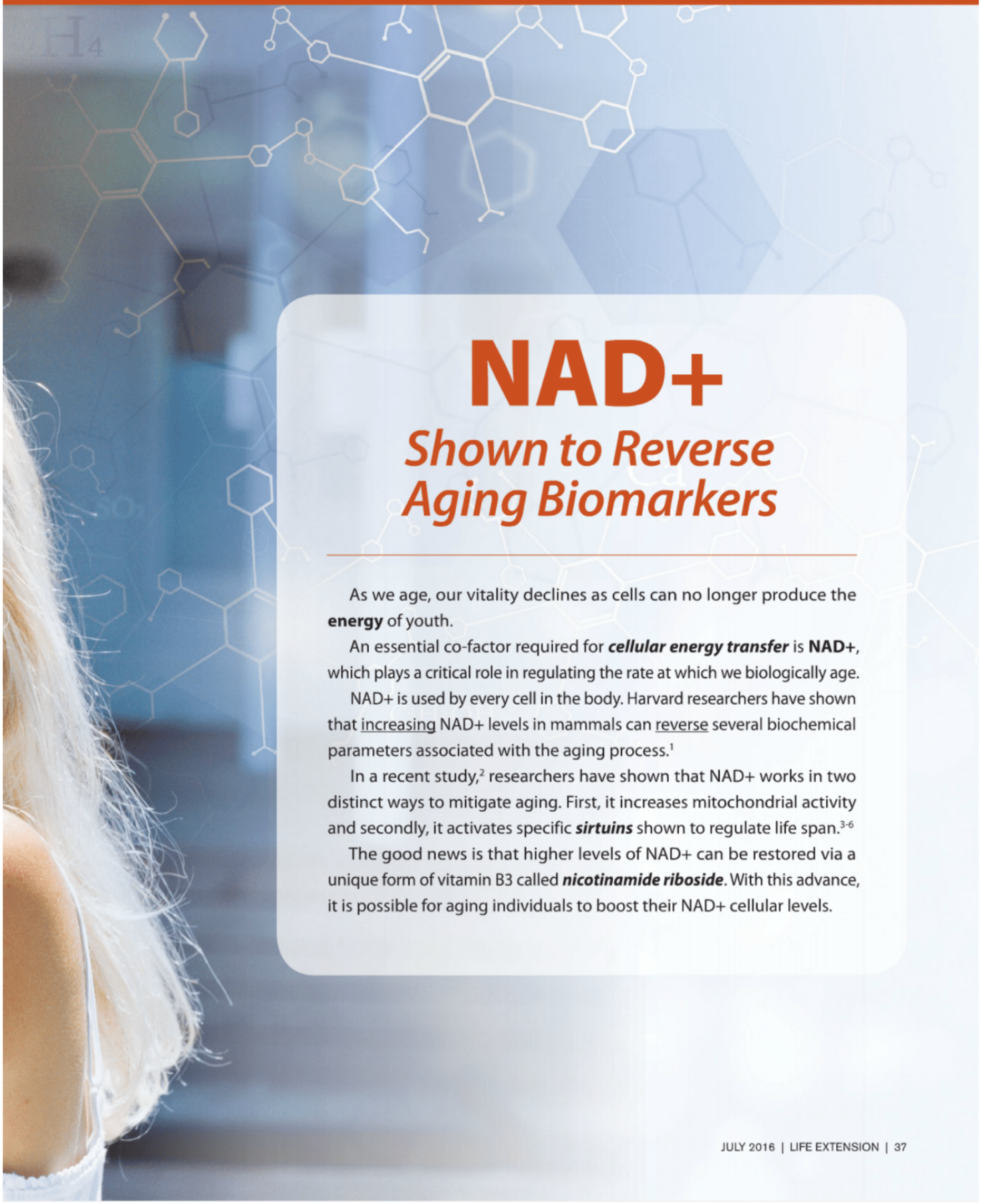

NAD+

Shown to Reverse Aging Biomarkers

As we age, our vitality declines as cells can no longer produce the **energy** of youth.

An essential co-factor required for ***cellular energy transfer*** is **NAD+**, which plays a critical role in regulating the rate at which we biologically age.

NAD+ is used by every cell in the body. Harvard researchers have shown that increasing NAD+ levels in mammals can reverse several biochemical parameters associated with the aging process.[1]

In a recent study,[2] researchers have shown that NAD+ works in two distinct ways to mitigate aging. First, it increases mitochondrial activity and secondly, it activates specific ***sirtuins*** shown to regulate life span.[3-6]

The good news is that higher levels of NAD+ can be restored via a unique form of vitamin B3 called ***nicotinamide riboside***. With this advance, it is possible for aging individuals to boost their NAD+ cellular levels.

NAD+: An Essential Component of Life

Nicotinamide adenine dinucleotide (NAD+) is found in every cell in the body and is critical for regulating genes that accelerate aging.[7]

NAD+ also plays an important part in the transfer of energy released from fatty acids and glucose to the mitochondria to be converted into cellular energy.[8,9]

When NAD+ levels decline, energy transfer in cells breaks down, leading to ***mitochondrial dysfunction*** that results in many of the physical symptoms of aging.[1,10,11] Fortunately, by increasing intracellular levels of NAD+, age-related mitochondrial dysfunction can be reversed.[1]

NAD+ battles aging by activating key anti-aging enzymes called ***sirtuins***, specifically **SIRT1** and **SIRT3**. Sirtuins contribute to longevity by favorably controlling gene expression.[8,11-15]

SIRT1 and **SIRT3** modulate multiple biological processes summarized in the table at the end of this article.[3]

Sirtuins can be activated at any age through **caloric restriction**. In response to undereating, cellular levels of **NAD+** increase.[8]

Studies in yeast have shown that increasing NAD+ levels positively affects the function of sirtuins and significantly extends yeast life span.[18] A study done in worms (*C. elegans*) showed that older worms had lower levels of NAD+ when compared to younger worms. When NAD+ levels were decreased even further, the worms aged faster. When worms had their NAD+ levels restored, it prevented metabolic changes of aging and increased their life span.[5]

Of course, it is a large step—evolutionarily and biologically—from yeast and worms to mammals. However, studies done in mammals have also shown that NAD+ levels are critical for not only healthy cellular and mitochondrial functioning, but aging itself.

A study done at Harvard has shown that increasing NAD+ levels in mammals can reverse the aging process.[1] This study was done on mice that were bred to have a defect in SIRT1. These mice exhibited multiple signs of accelerated aging, including mitochondrial dysfunction. However, when the levels of NAD+ were increased in these 22-month-old mice, the results were nothing short of amazing: Key markers of aging, including insulin resistance, inflammation, and muscle wasting—all processes commonly associated as a "normal" part of aging—were lowered to that of mice aged 6 months.

Knowing that NAD+ is vital to cellular functioning and that NAD+ levels decrease as we age, many scientists believe a key process in slowing, stopping, or even reversing the aging process is to maintain healthy, youthful NAD+ levels. The interest in finding ways to maintain youthful NAD+ levels has given rise to a form of vitamin B3, **nicotinamide riboside**, which converts to NAD+ in the body.[19,20]

By increasing NAD+ levels, nicotinamide riboside has been shown in multiple studies to positively affect mitochondria. In addition, a recently released study[2] has shown that nicotinamide riboside can both increase healthy mitochondrial activity and activate specific sirtuins shown to regulate life span.[3-6]

What You Need to Know

The Importance of Optimal NAD+

- **Nicotinamide adenine dinucleotide, or NAD+, is a co-factor that plays a crucial role in many biochemical reactions.**
- **Optimal levels of NAD+ are essential for the proper functioning of mitochondria, the producer of energy for the body, and sirtuins, which are enzymes known to be an integral part of the aging process.**
- **While NAD+ levels decrease with age, the use of the natural compound nicotinamide riboside can restore NAD+ to healthy, youthful levels.**
- **Raising levels of NAD+ has been shown to reverse key indicators of aging.**

Let's now examine some of the well-studied mammalian sirtuins to better understand the importance of maintaining healthy NAD+ levels in preventing premature aging.

SIRT1 and Longevity

SIRT1 is the most extensively studied mammalian sirtuin. It plays an important part in multiple biological functions, including tumor suppression, apoptosis, metabolic regulation, and the aging process. Several mouse studies have demonstrated the influence of SIRT1 activity on extending life span.[34,35] Delayed bone loss, reductions in the incidence of sarcomas and carcinomas, and improved glucose control and wound healing have been shown in a model of SIRT1 transgenic mice.[34] In another transgenic mouse model, increased activity of brain-specific SIRT1 resulted in an approximate **11%** increase in median life span.[35]

An array of research has shown the connection of SIRT1 with premature cellular senescence, a process that contributes to accelerated aging.[36,37] By interacting with biological molecules like p53, SIRT1 regulates cellular senescence, apoptosis, metabolism, and cell cycle.[36] A study examining the effects of SIRT1 inhibition in human umbilical vein endothelial cells suggested the role of this enzyme in protecting against ***endothelial dysfunction***, one of the consequences of cellular senescence.[36]

SIRT1 is emerging as an outstanding housekeeper for the maintenance of stem cells by fighting *cellular senescence*. This was seen in a study involving human mesenchymal stem cells in which the reduction of SIRT1 activity resulted in accelerated cellular senescence. However when SIRT1 activity was increased in bone marrow-derived **stem cells**, it showed that senescence was delayed, leading the authors to conclude that SIRT1 may contribute to the prevention of human mesenchymal stem cell senescence.[38]

A more recent study discussed the importance of SIRT1 in the maintenance of hematopoietic stem cells' homeostasis and that loss of SIRT1 in hematopoietic stem cells resulted in DNA damage.[39]

It is well established that genomic instability and impaired DNA damage repair are some of the contributing factors that result in accelerated aging and cellular senescence.[40] Exciting findings show that SIRT1 fosters DNA damage repair[41] and that it protects vascular smooth muscle cells against DNA damage and atherosclerosis.[42] Neurodegenerative disorders and age-related cognitive decline have been linked with defects in DNA repair.

Researchers at MIT determined that SIRT1 activation reduces DNA damage and provides an important therapeutic path in neurodegenerative diseases.[43] Together, these findings confirm the protective roles that SIRT1 has not only in maintaining genomic integrity but also against neurodegeneration.

A study in mice found that an increase of SIRT1 activity in the brain increased longevity by an approximate **11%**, while at the same time reducing the incidence of cancer.[45] Yet a more recent study on age-related muscle loss or sarcopenia determined that activation of SIRT1 can improve muscle performance, one of the hallmarks of sarcopenia.[44] This is clear evidence that SIRT1 can fight premature aging and promote longevity.

SIRT3: A Key Mitochondrial Sirtuin

Primarily located in the mitochondria, SIRT3 plays an important role in the regulation of several mitochondrial processes.[45] It has been associated with fatty liver, obesity, hyperlipidemia, and insulin resistance in mice lacking SIRT3 and fed high-fat diets.[46]

Impacts of Age-Related Decline on NAD+

The defects in both gene- and energy-related functions caused by the age-related decrease in NAD+ characterize the disorders that we identify as aging.[11] The consequences of a decline in NAD+ levels and subsequent reduction in sirtuins are:

- **Neurodegeneration** in the brain,[11,21,22]
- **Vascular inflammation**, producing damage to blood vessels that can result in stroke or heart attack,[21,23,24]
- **Increased fat storage in the liver**, which can lead to non-alcoholic fatty liver disease (NAFLD),[25-27]
- **Increased fat production and deposition** in white adipose tissue, the primary fat storage form found in dangerous belly fat,[28,29]
- **Insulin resistance**, preventing cells from appropriately removing glucose from blood, producing higher blood sugar levels and leading directly to metabolic syndrome,[23,30,31]
- **Fatigue**, **loss of muscle strength**, **and fatty infiltration of muscles**, resulting in reduced fatty acid oxidation ("burning"), thereby depriving muscles of their normal sources of energy.[32,33]

A recent report found that increased SIRT3 activity improved the regenerative capacity of hematopoietic stem cells.[47] It is also recognized that this sirtuin is important in neurodegenerative disorders like Huntington's disease.[48] Clearly, the impact that SIRT3 has on metabolic regulation, neurodegenerative disorders, and stem cell regeneration plays a crucial role in premature aging when impaired.

Summary

Nicotinamide adenine dinucleotide, or NAD+, is a critically important molecule for multiple biochemical processes in the body.

Numerous studies show that maintaining optimal levels of NAD+ through the use of natural compounds such as **nicotinamide riboside** are necessary for the health of mitochondria.

Sirtuins, which are enzymes that play a crucial role in the aging process, are dependent upon NAD+ to perform their life-giving functions.

New and groundbreaking studies are showing that maintaining optimal NAD+ levels can positively impact indicators of aging such as insulin resistance, muscle wasting, and inflammation. This gives credence to the hypothesis that aging itself is not only preventable, but reversible. ●

If you have any questions on the scientific content of this article, please call a **Life Extension**® Wellness Specialist at 1-866-864-3027.

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Sirtuins and Their Impact on Pathways That Contribute to Premature Aging When Dysregulated[3,16,17]

Pathways that contribute to premature aging	SIRT1	SIRT3
Cellular senescence	✓	?
Genomic integrity maintenance	✓	✓
Inflammation	✓	?
Metabolic regulation	✓	✓
Neurodegeneration	✓	✓
Stem cells maintenance	✓	✓
Tumor regulation	✓	✓

✓: Confirmed roles ?: Possible roles

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