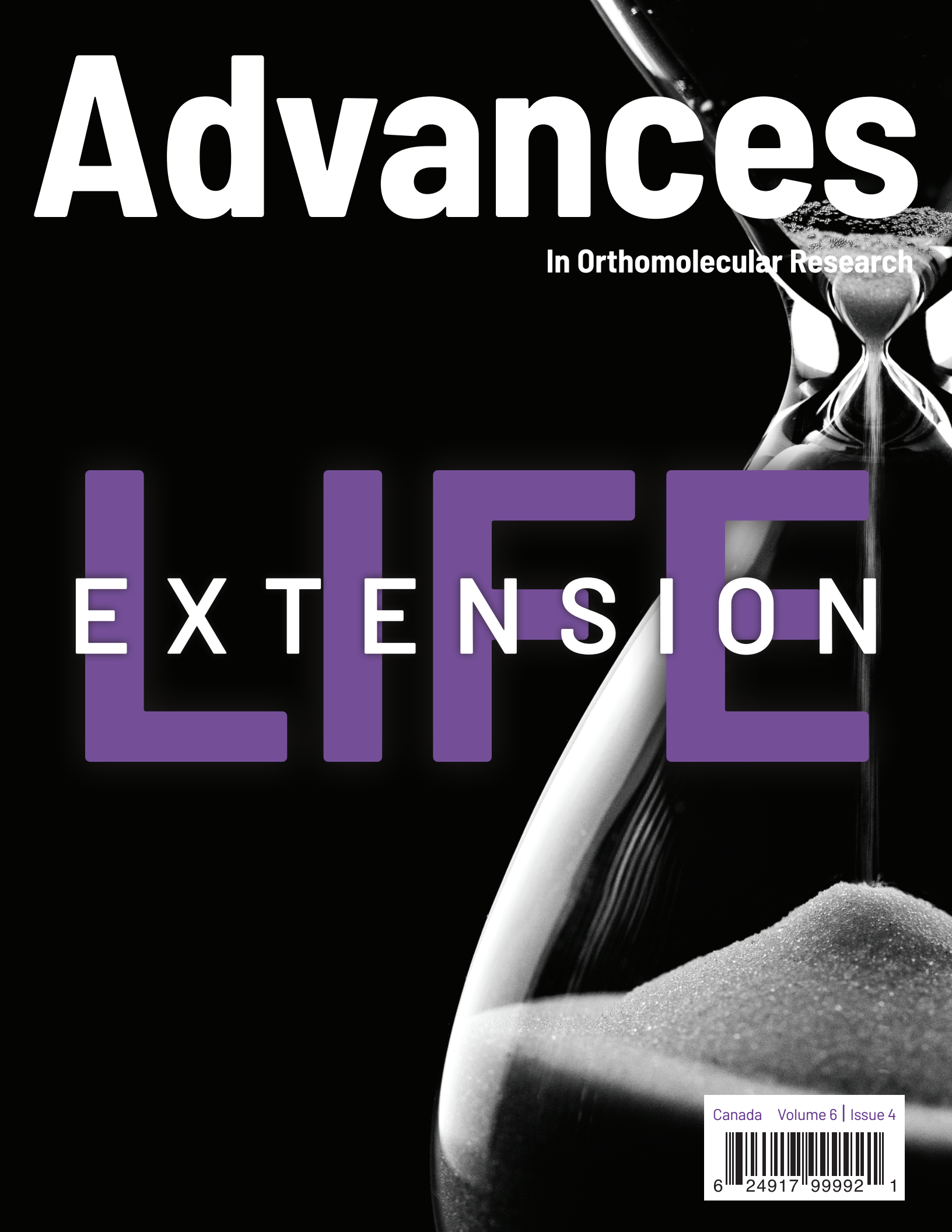
Advances

In Orthomolecular Research

LIFE EXTENSION



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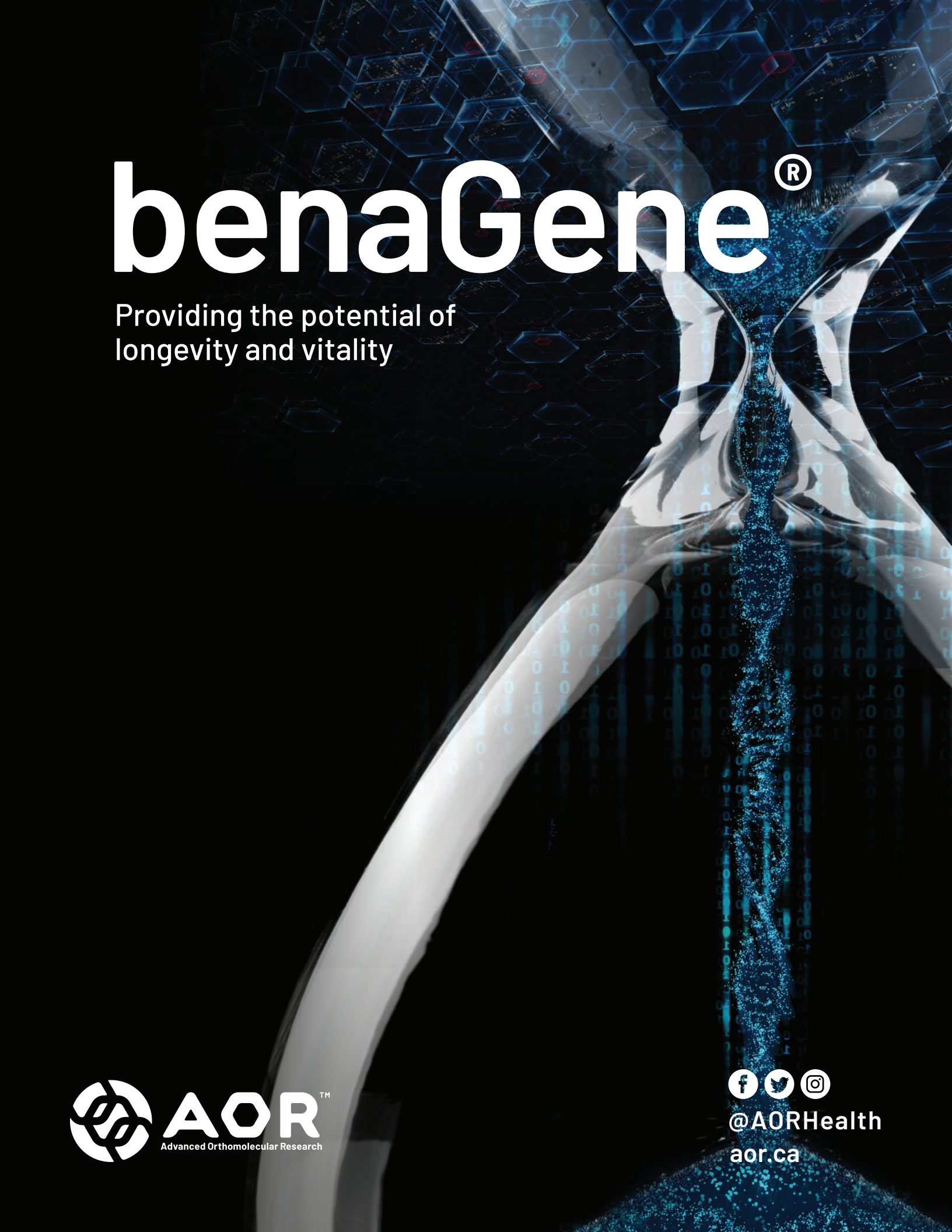
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Editors
Cassy Price, BBA
Krista Powell

Research & Writing
Dr. Aaron Zadek, ND, CISSN
Dr. Sarah Zadek, ND
Cassy Price, BBA
Krista Powell

Graphic Design / Art Production
Leandro Serrano

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How Caloric Restriction can be part of Healthy Aging

By Aaron Zadek, ND

Caloric restriction is a well-studied topic shown to improve overall lifespan as well as the number of healthy years without age-related pathologies. With over 70 years of data caloric restriction of 10-40% has been examined in single-celled organisms as well as a variety of animal models and humans with remarkable success. Human studies continue to show improvements to a variety of metrics including insulin sensitivity and obesity. While caloric restriction might sound difficult, it is manageable with proper preparation.

How does caloric restriction slow the aging process?

The magnitude of effect of caloric restriction on lifespan was evident in early experimental animal models in 1935 where lifespan of mice was almost doubled providing the first tangible evidence that aging can in fact be slowed. These mice were kept on restricted caloric intake through their adolescent years and it was noted that they did not grow to be as large as their well-fed counterparts.[8] Research now extends to single-cell organisms such as yeast, and multi-cell organisms including worms, fish, drosophila, and primates showing up to 50% improvements to maximum lifespan.[2,6] The fact that this effect is seen in both simple celled and complex multi-cellular organisms points to the conclusion that the genetic material responsible for improved response to aging has been conserved and passed on through millennia of cellular evolution.

So how does this anti-aging effect occur? It is believed that caloric restriction downregulates insulin and insulin-like signalling as well as reducing rapamycin (TOR)-S6 kinase pathway, and RAS protein Kinase A (PKA) pathway (Lee and Longo 2016).[6]These pathways are influential in growth, protein expression/amino acid signalling and increased metabolism promoting breakdown of glycogen and inhibiting lipid synthesis.

Additionally, cellular resistance to stress appears to improve under calorically restricted conditions. Stressors such as oxidative stress or exogenous toxins are better managed through hormesis to ensure a more positive response.

Is this response the same in all organisms?

Obviously, there are differences in physiology between different organisms i.e. yeast vs primates, but there are a lot of similarities that allow for greater understanding of how caloric restriction impacts organisms at a cellular, genetic, and pathological level. Studies in single cell organisms identify that under caloric restriction, sirtuin (SIR2) is activated and TOR and PKA are downregulated. This represents a major shift in the cell where it acknowledges that access to amino acids and protein are reduced, thus signalling for the conservation of metabolic output. While each organism that has been studied has shown slightly different counter-regulatory response to down regulation of TOR and PKA, including activation of other SIR/SIRTs, reduction in Growth Hormone and IGF-1, it is clear that the resultant cellular changes can improve overall health.

Humans have seven different types of Sir2 homologs aptly named SIRT 1-7. These are expressed predominantly as proteins found throughout the cell including the mitochondria, nucleus and cytoplasm. When activated they are a major part of how the body adapts to provide the benefits observed under caloric restriction.[2] Caloric restriction is believed to increase production of NAD+ which activates Sir2/SIRT1 resulting in adaptation.

The research on primates is unique and most applicable to humans. Interestingly, when juvenile, adolescent and old rhesus monkeys underwent a 30% caloric restriction there was no improvement seen to lifespan but healthy years increased and age related chronic diseases appeared later than expected.[7] Mattison openly discusses how improved husbandry conditions might have played a role in why survivability was not increased as seen in an earlier primate study that showed improvements to both lifespan and disease onset.[9] Other studies have also demonstrated reductions in basal metabolic rate, body temperature, as well as protection from of insulin resistance and type 2 diabetes.[9]

But what about humans?

One of the major studies is the two-year CALERIE experiment (Comprehensive Assessment of the Long-term Effects of Reducing Intake of Energy), sponsored by NIH. 143 overweight but not obese individuals assigned to the caloric restriction group demonstrated that a caloric restriction of at least 11.9% is manageable.[4] Positive outcomes reported were reduced weight, waist circumference, inflammatory markers and risk factors for cardiovascular disease. Negative outcomes included reduced bone mineral density. Not surprisingly, exercise is needed to offset bone mineral density loss.

Does intermittent fasting and nutrient timing contribute to longevity?

Changes to nutrient timing may also improve longevity and intermittent fasting has become quite popular in the last decade and a half. When feeding windows are clearly established and limited to approximately 8-12 hours every day has shown improvements to cardiovascular health, and body weight in animal models.[6] Another fascinating note is that this pattern does not require seven days/week of adherence and it is thought that the benefits might still be maintained if one or two days of ad lib feeding occur per week (i.e., weekend). Intermittent fasting continues to be popular and shows improvements to obesity and insulin sensitivity.[5]

Conclusion

The research on caloric restriction and longevity is compelling and provides many applicable pearls that can be monumental in improving healthy years before age related chronic disease. While compelling, reduced caloric intake must be monitored to ensure that it does not become excessive and result in extreme or rapid weight loss. Additionally, those undergoing caloric restriction are advised to exercise as resistance training will help maintain muscle and bone density mass. For those that are unable to consider caloric restriction but are struggling with type II diabetes or obesity there is research showing that intermittent fasting may provide some of the benefits seen with caloric restriction.

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Alpha -ketoglutarate

By Dr. Sarah Zadek, ND

Intermediates of the Krebs cycle have been gaining more attention in the realm of lifespan extension. These intermediates are a series of compounds that are transformed one after the other, releasing cofactors with each reaction. These cofactors, such as NADH and FADH, are used to create ATP energy, an incredibly important function. But these compounds have many other functions and we're finding new clinical applications. Alpha-ketoglutarate (AKG) in particular is being heralded for its antioxidant functions, its ability to stabilize certain aspects of health post-trauma and surgery, and for its promotion of lifespan extension in certain animal models.

The Krebs cycle, also called the citric acid cycle, takes place in the mitochondria of our cells. This is where cellular energy is produced, and hence why we call mitochondria the "power houses" of the cell.

Glucose sugar is broken down and processed over many steps until we have a compound (Acetyl-CoA) that can enter the chain reactions of the Krebs cycle. Acetyl Co-A is transformed into citrate and the transformation continues through seven other metabolites, including AKG, malate, and oxaloacetate, until we're left with compounds that are then transformed into cellular energy, also called ATP.

Supplementing with certain intermediates has been a strategy of many for improving cellular energy production. Malate in particular, found in magnesium malate preparations, has been used often in cases of chronic fatigue and fibromyalgia for its energy-producing properties. Additionally, most Krebs intermediates have antioxidant functions,[1] and can promote many other metabolic processes in the body.

Antioxidant functions

As part of the natural process of cellular metabolism, these pathways produce reactive oxygen species (ROS) as by-products. ROS are those such as superoxide anion, hydrogen peroxide and hydroxyl radicals. These by-products can act as cellular signals, but in excess can lead to oxidative stress and damage. This damage can cause the oxidation of lipids, breaks in nucleic acids, and can lead to malfunctioning of proteins. Over time, the presence of damage and dysfunctional proteins can lead to the development of many chronic and inflammatory diseases.[2]

The body understands this and manages the presence of ROS using a combination of antioxidants such as vitamin C, vitamin E and glutathione, as well as enzymatic antioxidants such as superoxide dismutase (SOD) and catalase.[2] However, if antioxidants are low in supply, the body is less able to remove excess ROS.

AKG has been shown to react with the ROS hydrogen peroxide. Its specific antioxidant activities have shown it can prevent damage to the DNA in mitochondria.[1] As well, in a model of Drosophila, it has been reported that AKG's antioxidant actions can protect against ethanol toxicity and improve cold tolerance. In humans this may translate into a potential treatment for alcohol poisoning and liver protection.[2]

Collagen synthesis and bone health

AKG is special among the Krebs metabolites in that it acts as a substrate for enzymes called hydroxylases which regulate the production of collagen. In particular AKG has been shown to increase the production of type I collagen in both bone and skin tissue.[1]

The use of AKG has been shown to improve several parameters of bone health. In a rat model of oophorectomy, the development of osteopenia was prevented in rats fed with AKG.[1] In humans, menopausal women given both AKG and calcium had less bone resorption and reduced effects of osteopenia, compared to those given calcium alone.[1]

Researchers are suggesting that AKG not only prevents bone tissue resorption but actually reconstructs the bone tissue to increase density and strength, thereby reducing states of osteopenia and osteoporosis.[1]

AKG's collagen producing effects have also shown benefit when applied onto the skin. In an animal study of UVB radiation, applying AKG to the skin of mice resulted in decreased wrinkles and decreased the amount of collagen degradation within the skin.[1]

Lifespan extension and aging

AKG has well demonstrated its role in cellular metabolism and growth, and cell division. As a compound that exerts epigenetic effects (the ability to affect the expression of certain genes), researchers have identified the role of AKG in several key pathways that affect aging.

In particular, AKG can affect the expression of genes in the AMPK, mTOR and JNK pathways, which accompany its lifespan enhancing effects.[3] In promoting AMPK activity, AKG supports the process of cellular autophagy: the process of cleaning out and eliminating old or dysfunctional cells. This is a critical function in our body, and in genetic animal models such as the fruit fly (Drosophila), nematode (C. elegans) and mice, a regular induction of autophagy can lead to lifespan extension.[4]

The mTOR signaling pathway, also known as the "mammalian target of rapamycin," affects cell metabolism, growth, and survival. It functions to support the balance between cell growth and proliferation and cell autophagy, depending on surrounding signals such as nutrient availability and environmental stressors.[3] AKG, by inhibiting mTOR, suppresses protein synthesis and cell proliferation, and increases autophagy.[3] In one study, AKG administration also led to an increase in the gene expression of heat shock proteins (HSP22 and HSP70), increasing the tolerance to heat stress.[3]

These studies have shown that administering AKG can increase the average lifespan of a fruit fly by 8%, and the maximum lifespan by 15%, with no toxicity issues.[3] On top of its effect on longevity, AKG-fed flies displayed enhanced climbing ability and physical activity compared to non-AKG-fed flies.[3]

These effects may be specific to AKG compared to its precursors in the Krebs cycle: AKG seems to be better than its precursor intermediates citrate and isocitrate at delaying aging. When fed to the genetic animal model C. elegans, the nematode, AKG, but not citrate or isocitrate, extended the lifespan of these animals by about 50%.[5]

These studies, though conducted in genetic animal models, are opening the doors for the use of AKG in settings of human trauma and surgery. Abnormal protein metabolism is part of the aging process but is also affected by trauma, surgery, and infections. Currently, AKG is being used to stabilize blood pressure during cardiac surgeries, as well as for preventing muscle breakdown post-surgery and trauma.[1] Considering its role in autophagy and heat resistance, AKG continues to show therapeutic potential in aging and tissue protection.

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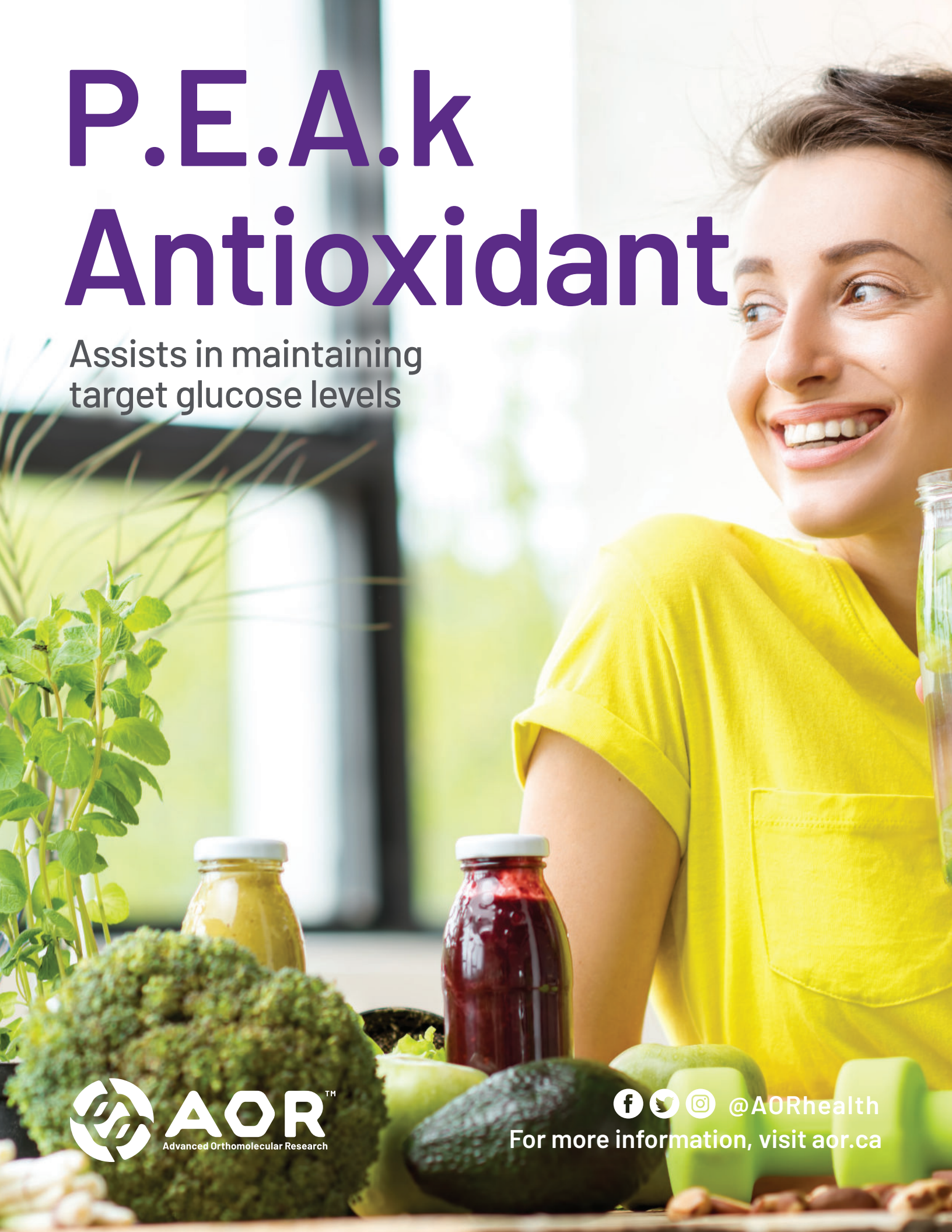
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Polyamines

By Aaron Zadek, ND

What are polyamines, why are they important?

Polyamines are present in all tissues and are an important part of cellular function and division. Most recently they have been discussed as one of the new potential interventions in anti-aging. Composed of multiple amino acids, polyamines are protective against oxidative stress and help stabilize the cell, its organelles, and membrane. Additionally, they have been found to help regulate ion channel activity and promote cellular growth, differentiation and even apoptosis.[8] Polyamine concentration is tightly regulated and can be increased in response to hormonal stimulation as well as disease.

The main polyamines present in humans, as well as plants, are putescine (Put), Spermidine (Spd), and Spermine (SpM).[3] In times of rapid growth or high cellular turnover, polyamine content can become reduced and need to be replenished through decarboxylation of arginine, ornithine and S-adenosylmethionine (SAMe). Polyamines are present in both plant and mammalian physiology, as aging occurs, polyamine concentration declines. This decline is present not only with aging but with other health disorders including Alzheimer's and Parkinson's diseases.[3] Homeostasis is crucial, while polyamines may increase longevity and reduce cardiovascular disease risk; there are a number of conditions, such as cancer, where higher polyamine intake would have negative health implications.

Polyamines

Animal models first confirmed that there might be a relationship between polyamines and memory, with age dependent memory impairment linked to reduction in polyamine levels.[3] Studies on mice and drosophila have showed that this might be reversible, with improvements to memory loss seen when these animals with induced age-related memory decline are fed diets rich in the polyamine spermidine. It was not just memory that benefited from polyamine supplementation. In fact, survivability also improved in the groups that were fed diets high in polyamines compared to control groups that were not.[9] There appears to be an increase in removal of

damaged cellular components through autophagy when these animals are supplemented with spermidine. Autophagy acts as a recycling process, destroying the damaged components and reusing contents such as cellular proteins, organelles and genetic material.

Aging occurs due to a litany of variables that occur throughout an organism's lifespan. Factors that influence aging include chronic inflammation, cellular stress, and abnormal lipid metabolism.[5] Human spermidine levels are observed to be a potential predictor of aging; those 60-80 years old show lower spermidine levels than those who are younger than 50. Interestingly enough, those who live to be older than 90 demonstrate spermidine levels similar to that seen in the under 50 category. This shows that perhaps, one of the secrets to longevity is the importance to maintaining levels of spermidine and other polyamines. This concept has been tested in mouse models by examining age-related pathological changes in the kidney, DNA methylation and tumorigeneses in groups fed a "high polyamine" diet vs "normal" and "low polyamine" diet. Mice in the high-polyamine group had three times the normal amount of dietary polyamines compared to the normal group and showed significant improvements to glomerular atrophy, DNA specific changes, as well as observed improvements to physical activity and thicker coats.[10]

Unfortunately, the data on cancer in these mice showed that, while incidents of colon tumours decreased from 60% in the low group to 25% in the high polyamine diet group, it was noted that the increased polyamine intake group had significantly faster growth in established tumours. Soda and his team concluded that polyamines seem to suppress pro-inflammation and decrease damage caused by oxidative stress which might decrease incidence of neoplastic events but if tumours are already present there is potential for unwanted growth.


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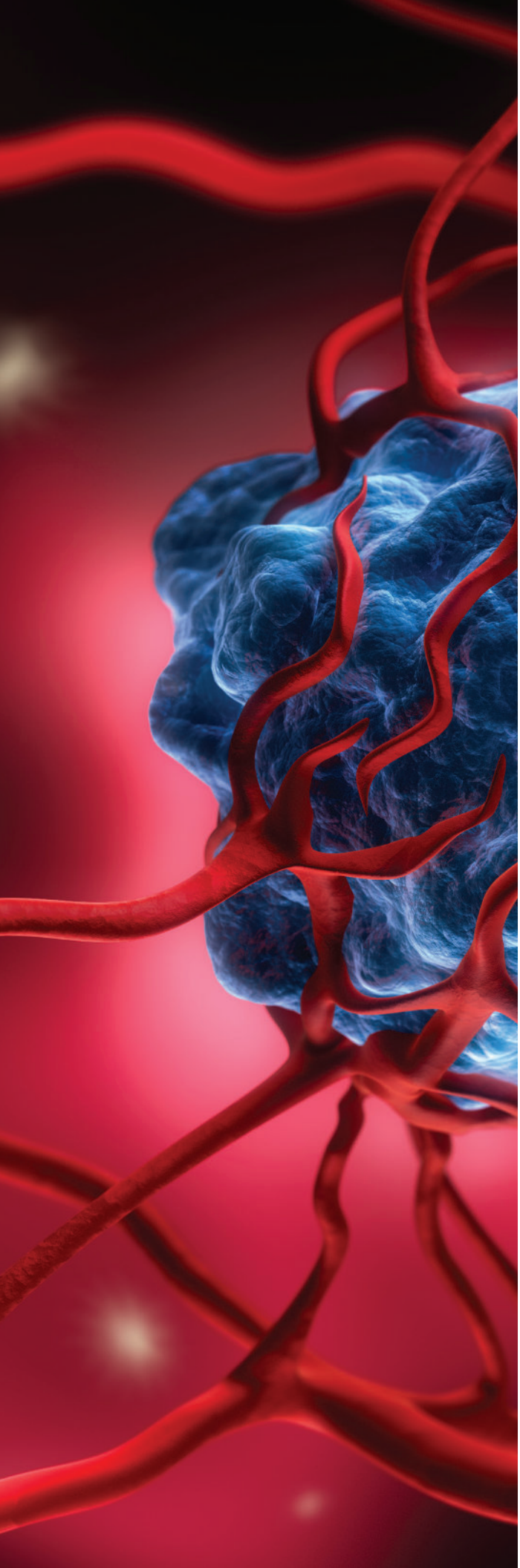

Polyamines in Cancer

As polyamines are essential for cellular proliferation, hypertrophy and tissue growth there is substantial concern about the risk of increased polyamine levels in individuals with cancer. Elevated levels of polyamines were first observed in tumours in 1968. High levels of ornithine decarboxylase (ODC), the first enzyme involved in the synthesis of polyamines has since been found to be active in several human cancers including breast, colon, prostate, lung, and skin cancers.[2] Follow-up studies have shown that urinary polyamine levels are increased in patients with some cancers though this is not established as diagnostic. Still, there is data showing that hormones that stimulate growth such as androgens, as well as carcinogenic substances like asbestos, can induce local ODC. When polyamines are increased in cancer cells, there is greater cellular division, decreased apoptosis and greater expression of the genes that code for tumour metastasis.

Research is ongoing to reveal if targeting ODC, other enzymes or substrates in polyamine production holds value for those undergoing treatment for cancer.[6] Polyamine pathway inhibitors such as DENPSM and DMFO have been investigated and results have been mixed. In animal models, while tumour growth was shown to be delayed, significant weight loss and toxicity were seen at higher doses.[1] While it is becoming more apparent that polyamines are unlikely to cause cancer, research is still ongoing to determine how to best target the polyamine pathway using chemotherapeutic strategies representing a new frontier in cancer treatments.[7] It might be plausible to be cautious with foods rich in polyamines in those with an active cancer diagnosis.

Cognitive decline

Decline of polyamine levels with aging is also a hot topic within Alzheimer's and Parkinson's disease research. Similar to what was found in cancer studies, Alzheimer's patients appear to also exhibit higher levels of ODC activity and polyamine concentrations in the brain.[3] It is known that toxic accumulation of amyloid-beta is a culprit in the physiological development of AD, and there appears to be a relationship between polyamine levels and plaque accumulation.[11] It has been observed that when cultured neurons are exposed to spermine and amyloid-beta the result is significantly more neurotoxic than when neurons are exposed to only amyloid-beta. When neurons were exposed to polyamine synthesis promoting compound S-adenosyl-1,8-diamino-thiooctane (AdoDATO) amyloid-beta induced toxicity was enhanced. Blocking polyamine synthesis has now been shown to improve memory loss in some but not all animal Alzheimer's models. What is of note is that this appears to oppose research showing polyamines improve learning and memory in healthy animals.[3,11] Polyamine research in Parkinson's disease has identified a connection between aggregation of alpha-synuclein and production of polyamines via the NMDAr pathway but the magnitude of effect and pathogenesis is yet to be fully understood.[4] There is still much to learn about why polyamines have such stark contrast in healthy memory compared to pathological cognitive decline.

Conclusion

Polyamines are essential to cellular health, growth and maintenance. Research continues to show that their involvement in processes from ion transport to proper aging is essential and when maintained in healthy individuals, might extend healthy aging process and memory. It is also clear that when cellular abnormalities such as cancer or deposition of amyloid-beta plaques occur, as seen in Alzheimer's disease, that production of polyamines might be detrimental. Polyamine regulation might hold the key to helping better understand these conditions and provide guidelines on healthy supplementation and food selection to ensure we are optimizing this system in times of health and limiting it in times of disease.

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Honey Lavender

Face Wash

Honey has preservative and anti-aging properties and is naturally antibacterial. It has a slightly astringent quality and helps to regulate oil production in the skin.

Lavender is full of antioxidants, which help to reduce the damage of free radicals. It reduces inflammation and helps restore moisture to dry, mature skin.

Adding rose hip powder gives it a little bit of a gritty feel, which is gently exfoliating. The vitamin C from the rose hips adds brightness to the skin and calms any redness, leaving the skin tone even.

Ingredients

1/2 cup raw, unfiltered honey

24 drops of lavender essential oil

1/4 teaspoon rose hip powder

Directions

Combine all the ingredients until smooth. Gently massage into the skin for one to two minutes. Rinse thoroughly with warm water and pat dry with a towel.

Anti-Aging

Cocoa Mask

This cocoa mask provides antioxidants, replenishes moisture and restores youthful vitality to the skin. Sour cream is a form of lactic acid that hydrates and exfoliates. Honey is a humectant that boosts moisture while the protein in the egg white helps to tighten and firm skin.

Ingredients

1 tablespoon cocoa powder

1 tablespoon sour cream

1 tablespoon honey

1 egg white

Directions

Combine all ingredients into a smooth paste. Apply to face and let dry for 15-20 minutes. Rinse thoroughly with warm water.

Lemon-Agave Exfoliating

Hand Scrub

Age spots will always make your skin look older but this scrub can help skin look and feel youthful again. Exfoliating your hands lifts off the top layer of dead skin cells and removes some of the pigment. The rice exfoliates, the agave hydrates, and the lemon helps lighten skin and remove dead cells.

Ingredients

1/2 cup cooked rice

1 tablespoon agave nectar

1 tablespoon lemon juice

Directions

Mix together the above ingredients and blend thoroughly. Apply the mixture to dry hands, moving the scrub around your hands in circular motions with firm but gentle pressure for one to two minutes.

For extra soft hands, soak them in a bowl of warmed whole milk for 10 minutes after exfoliating. The fat from the milk will hydrate skin, and vitamins A and E will increase elasticity.

Ultra Moisturizing

Face and Body Lotion

Skin that is well hydrated will look younger and healthier. Shea butter provides anti-aging antioxidants and almond oil nourishes skin, making it soft and supple. The essential oils help to calm inflammation and rejuvenate aging skin.

Ingredients

½ cup shea butter

2 tablespoons almond oil

5 drops rosemary essential oil

3 drops carrot seed essential oil

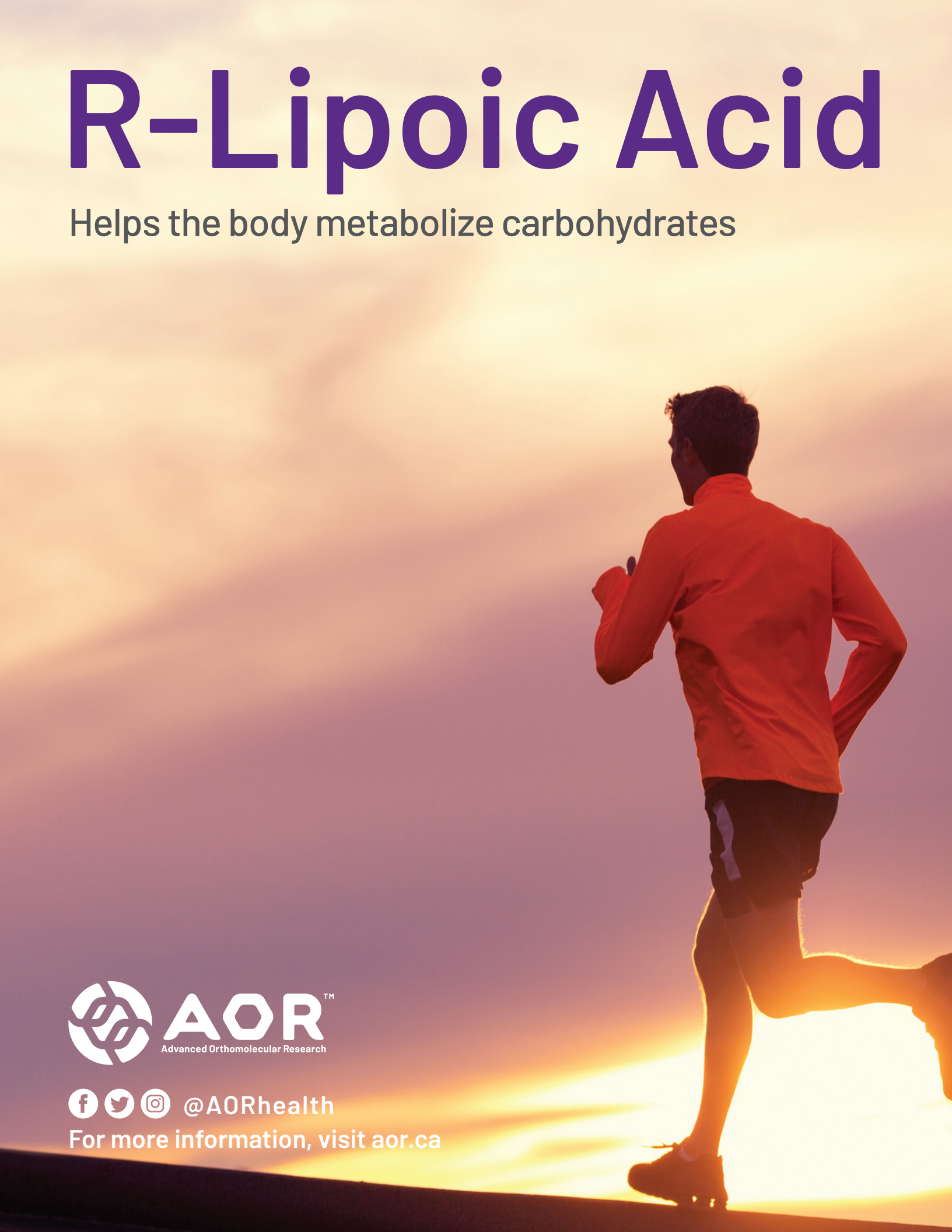
3 drops tea tree essential oil

Directions

1. In a double boiler over medium-low heat, melt the shea butter. Add in the almond oil. Turn off the heat.
2. Pour into a bowl and place in the fridge or freezer and allow to cool for about 15-20 minutes.
3. Once opaque and slightly firm, remove the bowl from the freezer. Add in the essential oils and mix with a whisk or fork to combine. Scoop into a jar and store at room temperature. Apply to both body and face as desired.

R-Lipoic Acid

Helps the body metabolize carbohydrates



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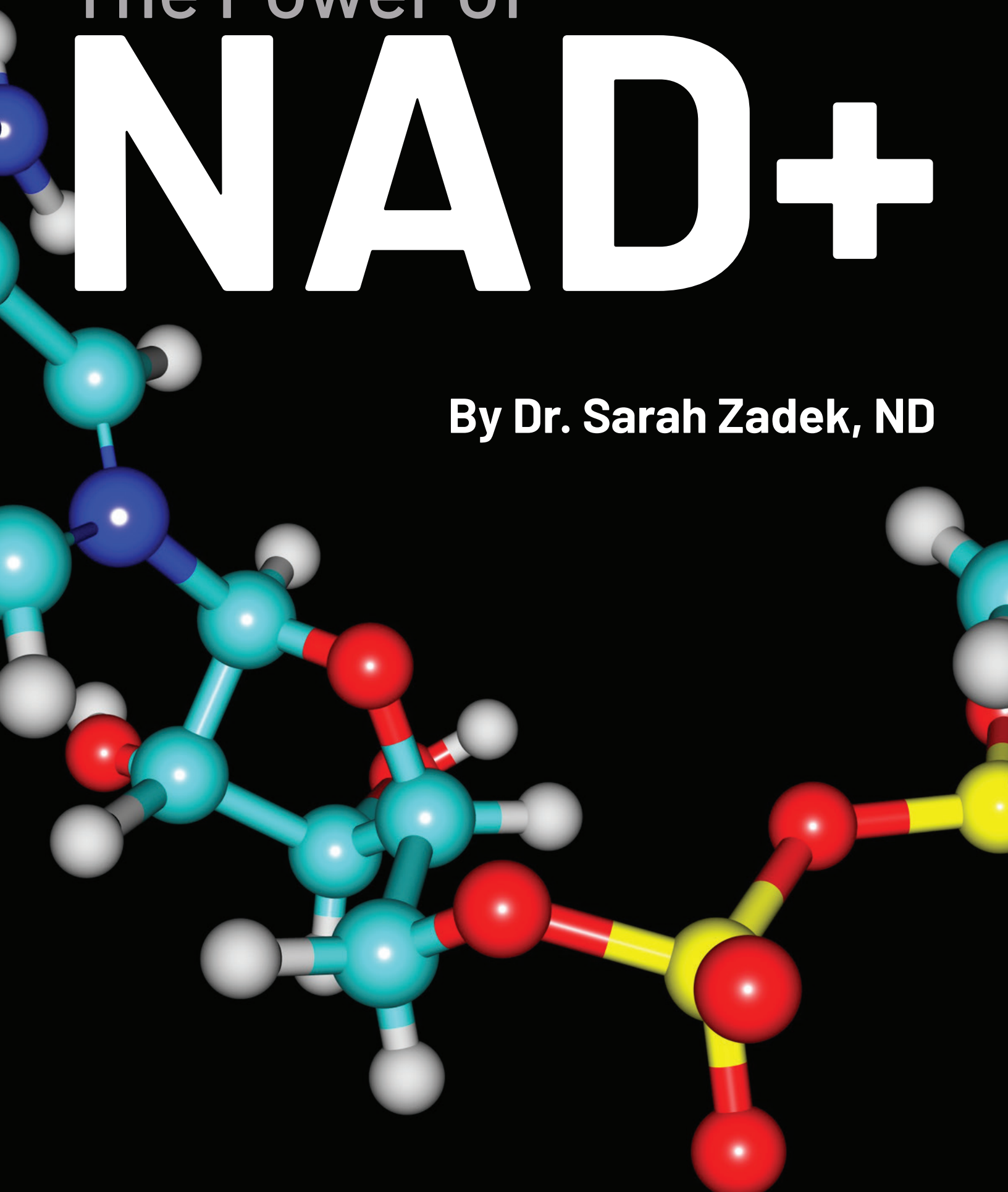
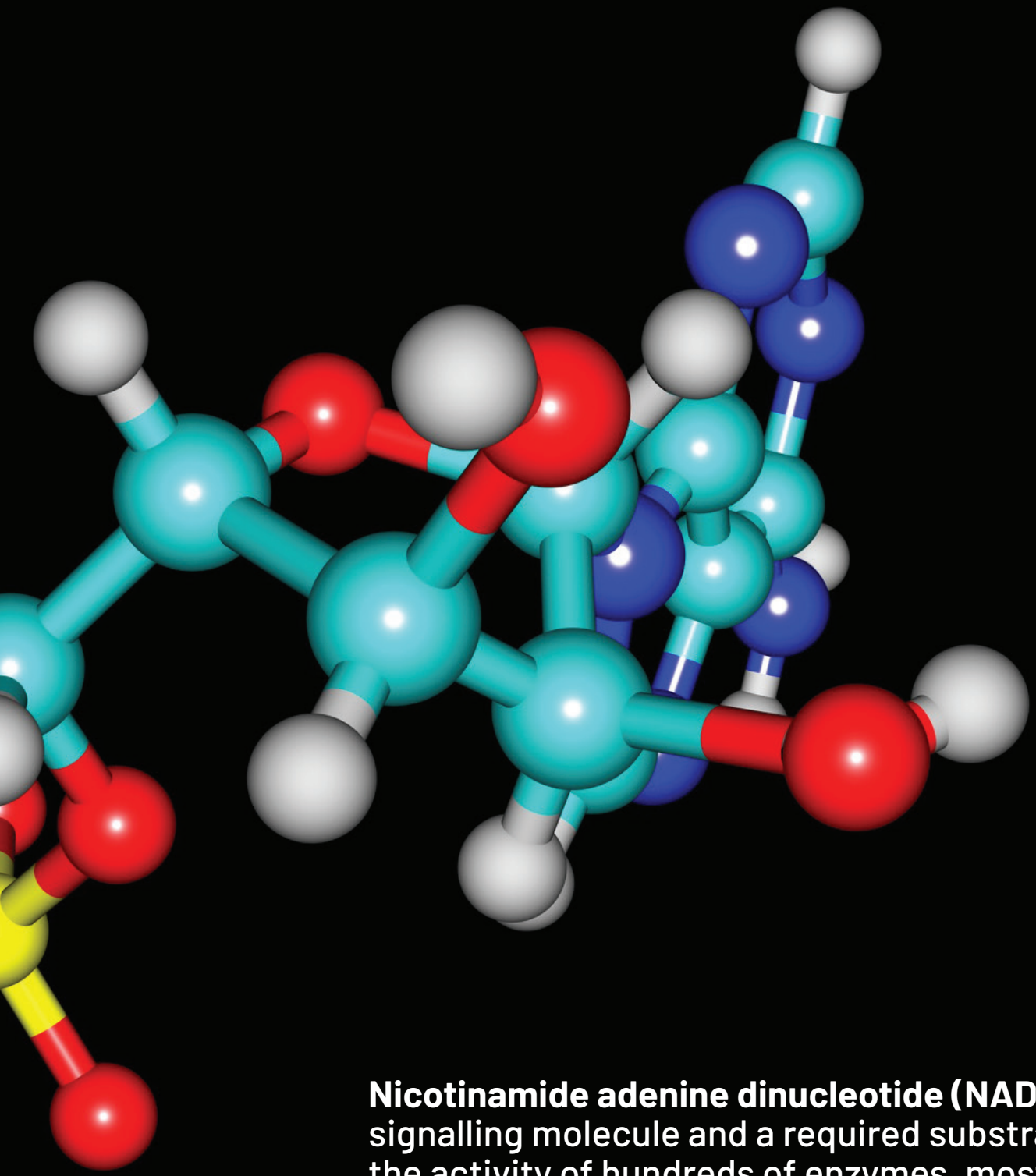
The Power of NAD+

By Dr. Sarah Zadek, ND





Nicotinamide adenine dinucleotide (NAD+) is a signalling molecule and a required substrate for the activity of hundreds of enzymes, most notably the sirtuin family of enzymes. It also plays a key role in the production of cellular energy from the breakdown of sugars, fatty acids and proteins.[1]

When the body is under conditions of chronic stress, or as a result of aging, NAD+ levels decrease which leads to a decrease in sirtuin activity. We are now finding that NAD+ levels can be enhanced by supplementing with NAD+ precursors and that this can boost sirtuin activity.[2,3]

This is so important because sirtuins are an integral part in DNA protection and repair in addition to cell cycle regulation and overall longevity.[3] Dysfunction in these areas leads to cell and tissue senescence and the start of age-related disorders including cardiovascular disease (CVD), fatty liver, neurodegeneration, insulin resistance and an increase in oxidative stress and inflammation.[3] Therefore, the use of NAD+ precursors could potentially be used therapeutically for increasing health span (the number of healthy lived years).

Producing and boosting NAD+

NAD+ can be made from the amino acid tryptophan, but not all tissues in the body can support this reaction, so the body relies on other methods for generating NAD+, specifically by using dietary vitamin B3. However, there are multiple forms of vitamin B3 and their effects can differ slightly. B3 vitamins and B3 metabolites include niacinamide, nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN), and each of these can boost NAD+ levels. Niacinamide (a.k.a. nicotinamide), however, has not been able to reliably induce sirtuin function.[1]

The recommended daily allowance of vitamin B3 from the diet is about 15 mg, which will provide enough B3, and thus NAD+, to prevent the effects of a deficiency. A deficiency in vitamin B3 can cause a disorder known as pellagra, a condition characterized by dermatitis, diarrhea, dementia and death.[1] However, the doses needed to reach therapeutic levels are substantially higher than what we can obtain from the diet. For example, the dose used to increase NAD+ levels in a recent human trial was 1000mg of NR daily[1]

As a supplement taken in therapeutic doses, certain forms of niacin can cause skin flushing and are therefore less tolerated.[1] Instead, compounds NR and NMN are showing promise as supplements with a low adverse effect profile.

NR and NMN have both been shown to boost NAD+ levels with a corresponding improvement in different models of health in animal studies. For example, when aged mice were supplemented with NMN, their cardiovascular function improved.[1] This isn't surprising when we consider that aging is strongly correlated with endothelial dysfunction.[4] Dysfunctional changes within blood vessels can lead to an increased risk of clotting, and decreased tissue perfusion (less oxygen delivery) as we age.[4] They can also cause the microvascular barrier to breakdown leading to a leakage of microbial by-products into the main circulation.[4]

The result of age-related vascular changes is an increased risk of developing cardiovascular and cerebrovascular diseases such as heart attack, coronary heart disease, stroke, cognitive impairment, stroke, dementia and Alzheimer's disease (AD), hypertension, peripheral artery disease, and sarcopenia, as well as kidney and eye diseases.[4]

Animal models of aging have shown that treatment with these NAD+ precursors have anti-aging effects including improving brain and eye function, skeletal muscle function, and endothelial function within the aorta.[4]

Nicotinamide riboside (NR) and Nicotinamide mononucleotide (NMN)

Researchers have reported that NR is readily taken up by cells and is effective at producing NAD+.[1] It is newly available as a human supplement though long-term studies are still needed.

In one small clinical trial, healthy middle-aged or older adults were randomized to receive 1000mg of NR daily or placebo for six weeks.[1] NR supplementation was reported to be well-tolerated and effectively increased NAD+ levels by about 60% compared to placebo.[1] In a follow-up analysis, patients in the NR group who had started the study with stage 1 hypertension (defined as a systolic blood pressure between 120-139mmHg and a diastolic blood pressure of 80-89mmHg) had an average decrease in systolic blood pressure by 9mmHg.[1]

NMN is another NAD+ precursor and human supplement available on the market, though it can be found in small amounts in edamame, avocado and broccoli.[4] The ability of NMN to boost NAD+ levels has been directly measured in mice: in one study, oral supplementation led to quick absorption in the gut and increases in NAD+ concentration were observed within minutes.[4]

NAD+ supplementation on memory and neuroinflammation

In the brains of patients with AD, DNA repair mechanisms seem to be deficient or compromised.[5] In a mouse model of AD, a decreased ratio of NAD+: NADH was been measured in the cerebral cortex of the brain, compared to wild type mice. AD mice also had lower levels of SIRT3 and SIRT6 expression compared to wild type mice.[5] Researchers noted that after treatment with NR, SIRT3 activity increased and there was a decrease in DNA damage.[5]

Many studies have been conducted on NAD+ supplementation in models of AD and decreased cognition. In one study, AD mice were shown to have deficits in spatial learning and working memory. These mice were given a daily oral supplement of NR or placebo for six months, and in an array of behavioural tests that followed, treatment with NR appeared to reverse the effects of AD by improving memory deficits.[5]

Immune pathways also seem to be altered after NR treatment, indicating that NR may reduce inflammatory pathways in the brain, particularly the hippocampus, responsible for spatial learning and memory, and the cerebral cortex.[5]

From our current knowledge, the pathology of AD is associated with neuroinflammation, neurofibrillary tangles of Tau protein, and the development and presence of amyloid-beta plaques.[5] Treatment of AD mice with NR was shown to suppress inflammatory pathways and normalize cytokine levels to those of wild type mice, as well as decrease the buildup of Tau protein in the brain.[5] Though it did not have an effect on amyloid-beta production. In other animal studies, supplementation with NMN has been shown to improve memory and learning in animal models of AD as well as mitochondrial function and lifespan in AD and Parkinson's disease.[5]

NAD+ supplementation in obesity and metabolism

It has been suggested that the sirtuin enzyme SIRT1 may be an important cellular clock regulator and that NAD+ supplementation could affect diurnal feeding patterns in mice in addition to their glucose metabolism.[6]

Increased feeding frequencies throughout the day and night have been observed in obese mice. This behaviour leads to increased caloric consumption, but also interferes with their sleep periods and normal diurnal feeding patterns.[6] In one study, when obese mice were injected with NAD+ it supressed their weight gain, decreasing their appetite and food intake.[6] It also increased their locomotor activity and energy expenditure in addition to modestly improving glucose tolerance.[6] Improvements in glucose metabolism were also documented in a study where diabetic mice were supplemented with NMN for one week.[6] This highlights the potential for NAD+ supplements in obesity-related day-night eating patterns and glucose metabolism.

Conclusions

In general, we are protected against short-term decreases in NAD+ levels as a result of stress, but with chronic stress, or as a result of the aging process, NAD+ levels fall and sirtuin activity decreases. This can lead to increased DNA damage accumulation and tissue dysfunction. Although our daily requirements for NAD+ precursors in the form of vitamin B3 are often easily met via dietary sources, this only provides protection against deficient states that can lead to pellagra. Whereas currently, researchers are still early in the process of using therapeutic doses in humans to reduce the risk and effects of age-related diseases such as hypertension, CVD, diabetes, neurodegeneration, and chronic low-grade inflammation. There seems to be a lot of promise in using precursors NR and NMN to boost NAD+ levels and increase sirtuin activity, both of which are available as human supplements, though more long-term studies should be conducted to find out the magnitude at which NR and NMN affect longevity in humans.

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Sirtuins

By Sarah Zadek, ND

Sirtuins became a popular topic of study in the late 1990's when it was found that overexpression of the SIR protein SIRT2 extended the lifespan of yeast by up to 70%.[1] Sirtuins are proteins that regulate processes of gene expression, cellular metabolism, cell death, DNA repair, cell division, and immune responses. They are most studied for their role in the aging process and the prevention of age-related diseases as they provide protection to DNA and major organ system tissues such as blood vessels, heart muscle, brain and nervous system tissue. Furthermore, we are starting to discover dietary compounds that can stimulate sirtuin activity, such as resveratrol and curcumin. Sirtuins, or SIR proteins, are termed, "silent information regulators", for their ability to keep specific parts of the DNA strand silent. By doing this, they prevent reactions that lead to accumulation of extrachromosomal ribosomal DNA circles, which can be toxic.[1] The increase in these DNA circles are a leading cause of aging in yeast. Mutations in the SIRT2 gene can cause of buildup of the DNA circles, while increasing expression of SIRT2 inhibits the formation of these circles and extends the lifespan of species such as yeast (Saccharomyces cerevisiae), the nematode (C. elegans), and the fruit fly (Drosophila melanogaster).[1]

Aging and Cell Senescence

Diseases of aging are the result of the accumulation of senescent (deteriorating) cells in tissues, which can impair the function of these tissues. The main cause of cellular senescence is DNA damage from short telomeres (breaks in the DNA strand) and oxidative stress from the presence of reactive oxygen species (ROS).[1] As the ability to repair DNA decreases as we age, damage accumulates. These cells can also secrete cellar signals involved in the inflammatory cascade causing neighbouring cells to become senescent as well. These reactions can lead to an overall low-grade inflammatory state that is common in aged individuals.[1]

As cells become senescent they are more likely to have supressed cell cycles (reduced or inhibited cell division), and contain more granularity and DNA damage.[1] By activating sirtuins, DNA is protected by keeping the structure of chromatin, DNA's compact packaging, in its condensation state to prevent it from changing into a form more susceptible to damage.[1]

Sirtuins could potentially function as protein markers of frailty in older individuals. Lower SIRT1 and SIRT3 levels are associated with frailty as it relates to sarcopenia, reduced cognitive function, poor or abnormal functioning of immune and hormone systems and reduced energy regulation. Low levels of these sirtuins are also associated with oxidative stress, neurodegeneration, cardiac hypertrophy, adiposity and the presence of fatty liver.[1]

Sirtuin function

There are seven known enzymes of the sirtuin family: SIRT1-7. The presence and action of these enzymes has been evolutionarily conserved from yeast and bacteria all the way to humans; however, the complexity of their functions has also increased as species evolved.[1]

These proteins belong to a class of enzyme called histone deacetylases (HDAC). They regulate genes and pathways involved in aging but also on many other signalling pathways.

SIRT1 is the most well studied of all the sirtuin proteins. In addition to its important role in fetal development, it provides neuroprotection, vascular protection and assists in the function of glucose metabolism and insulin secretion.[1]

In a reproductive mouse study, researchers found that mouse zygotes lacking SIRT1 genes were less likely to develop. Of those lacking SIRT1, only half were born and only 20% of those reached maturity. These SIRT1 knockout mice were also sterile, smaller in size, and had an increase in abnormal eye and heart development.[1]

When mice were given an extra copy of the SIRT1 gene, researchers noticed less DNA damage and a decrease in age-related diseases such as bone loss, inflammation, diabetes and neurodegeneration.[2] In another study, when SIRT1 was overexpressed in cardiac muscle cells, it provided protection of the tissue from a myocardial infarction (MI) and assisted in post-MI recovery.[1]

SIRT3 is particularly known for its antioxidant actions. The balance of ROS is crucial for tissue function. ROS are those that include superoxide anion, hydrogen peroxide and hydroxyl radicle. These molecules when in controlled levels act as important signalling molecules. However, when levels are excessive, they can cause oxidative damage to lipids, proteins and DNA. Sirtuins support both aspects of ROS regulation: they modulate ROS-involved signalling, as well as the elimination of and protection against excessive levels of ROS.[3]

SIRT3 acts by inducing the enzyme SOD2 - which reduces the accumulation of the ROS superoxide anion - as well as induces function of the electron transport chain (ETC) resulting in more efficient cellular energy production and reduced production of ROS. In SIRT3 knockout mice, researchers reported an increase in ROS levels with a corresponding increase of oxidative stress in muscle tissue.[1]

In general, sirtuins are involved in the regulation of cellular metabolism, the welfare of DNA and processes of cellular and tissue aging. In the case of SIRT6 and SIRT7, they are also critical for reaching a normal lifespan. In one animal study, SIRT6 knockout mice showed symptoms of degeneration and premature aging at just three weeks of age. Most were smaller in size than wild type mice and only survived a total of four weeks.[1] Meanwhile SIRT7 knockout mice have been reported to age prematurely; likely due to SIRT7's role in regulating the cell cycle and rRNA transcription.[1]

Supplementing with sirtuin-activating compounds

With such dramatic and influential effects, it's no wonder why researchers are pouring over sirtuins and trying to find dietary compounds that activate them. This could lead to potential therapies for the prevention and treatment of age-related diseases and degeneration.

Several polyphenol constituents found in plants have demonstrated the ability to activate sirtuins. These sirtuin-activating compounds (STACs) include flavones, anthocyanidins, catechins and stilbenes, and can be found in quercetin, curcumin and resveratrol. Preclinical studies are showing that these may be effective for age-related disorders such as type 2 diabetes mellitus, cardiovascular disease, stroke, fatty liver, cancer and inflammation in general, while animal studies are suggesting STACs have potential in the prevention and treatment of Alzheimer's and Parkinson's diseases.[1]

Resveratrol

Resveratrol has been shown to activate SIRT1 and increase lifespan, as well as improving health span, in animal models.[1] Treating mice with STACs such as resveratrol has been shown to stimulate sirtuin activity and produce a corresponding improvement in organ function, physical endurance, resistance to disease and longevity.[1]

Curcumin

Pre-treatment with curcumin has shown to significantly increase SIRT1 activity and protect against oxidative stress in animal models. This was shown in a study of myocardial ischemia reperfusion injury where curcumin acted as a cardioprotectant in rats.[1] More so, when curcumin supplementation is combined with physical activity, it more efficiently up regulates SIRT1 compared to supplementation alone.[1]

Other polyphenols and supplements

Melatonin is a hormone that declines in concentration as we age. It has been documented that melatonin induces SIRT1 and prevents certain processes associated with neurodegeneration in the brain.[1]

Other polyphenols such as oligopoly found in the lychee fruit also modulate the SIRT1 pathway, but in addition to other aging regulators such as the AMPK pathway and the process of autophagy.[1]

Conclusions

There are multiple factors associated with the aging process but researchers agree that DNA damage and telomere shortening both correspond with cell senescence and overall aging of an organism. Sirtuins are an evolutionarily conserved family of NAD-dependent enzymes that have an integral role in aging and longevity. Levels of sirtuins influence the cell cycle (cell division), DNA damage and repair, regulate ROS balance, and is involved in insulin secretion and glucose metabolism.

Substances that activate sirtuins, and/or the upregulation of SIR genes show potential in preventing age-related disorders such as diabetes, cardiovascular diseases, neurodegenerative diseases, and fatty liver. Research continues to look at the use and potential therapeutic value of supplementing with curcumin and resveratrol; and additionally into substances that increase NAD+ itself - the molecule that sirtuins rely on to function.

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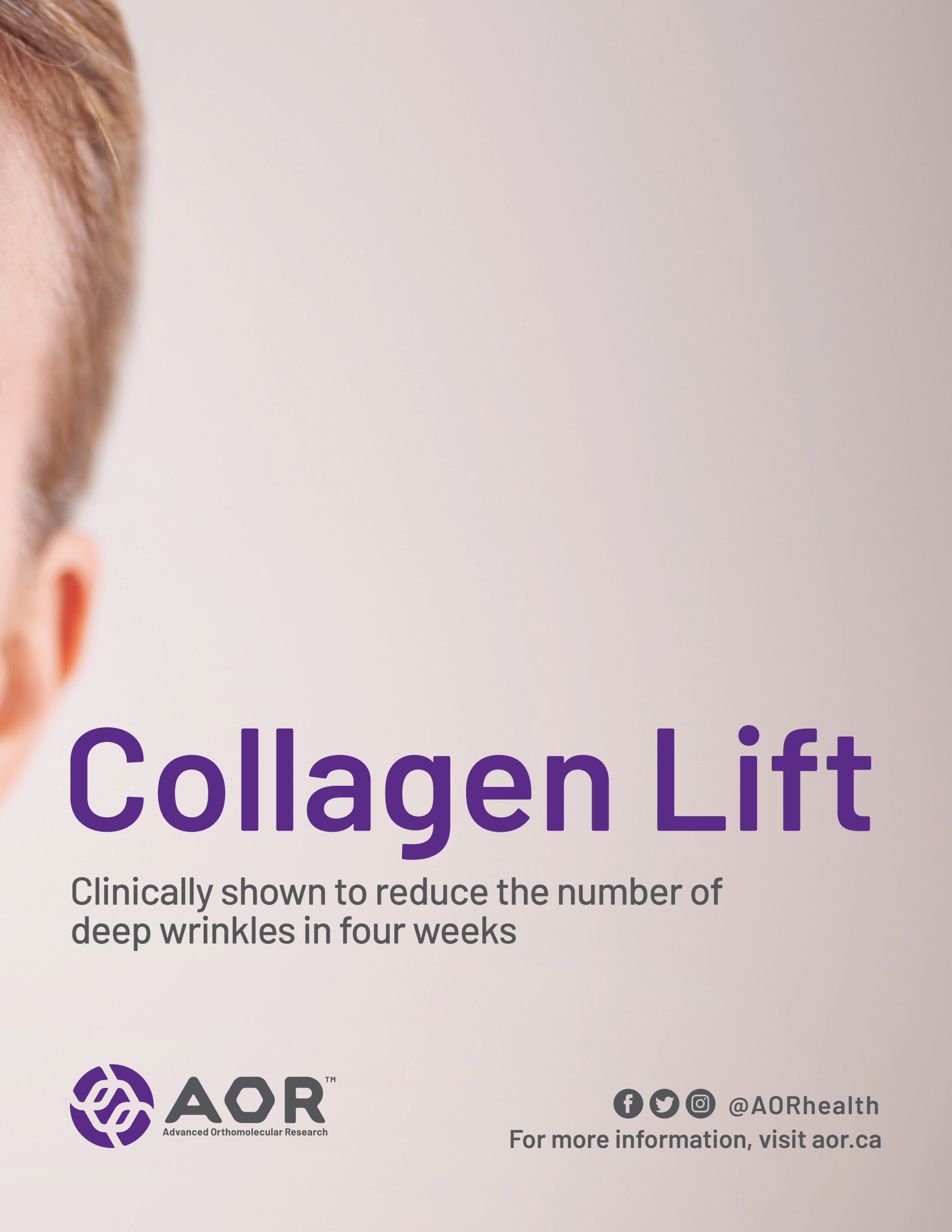

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