With age, NAD+ levels drop up to 50%, which leads to a decrease in mitochondrial health.
It’s no secret that people today are TOO FAT!

Did you know that fat cells secrete cytokines that increase systemic inflammation, disease and aging? (73,74,75).

The double whammy comes from elevated blood glucose levels, that also dramatically increase inflammation (63,65,75)

**AS WE AGE, INFLAMMATION BECOMES THE KEY CONSUMER OF NAD+ AND LEVELS DROP (54,67).**

By age 60, we have 1/2 the NAD+ as in our 20’s (21,57)

Declining NAD+ leads to metabolic dysfunction, age-related diseases and is a key contributor to the aging process(21,22,24,40,41).

**HIGH BLOOD SUGAR -> INFLAMMATION -> LOW NAD+ -> DISEASE AND AGING**

As we age, this become a viscous circle

**LOW NAD+ -> DISEASE & AGING -> LESS EXERCISE -> HIGHER BLOOD SUGAR -> LOWER NAD+**

If you are over 40, and your fasting blood glucose level is >85mg/dl, you are pouring gasoline on the inflammation fire(63).

Understanding the role NAD+ plays in aging can help you REVERSE this circle and combat the effects of aging.

Not just weight and blood sugar levels, but Diabetes, Cardiovascular Disease, Cancer and even aging itself are influenced by lower NAD+ levels (21,22,40,41).

Now researchers are discovering what you can do to elevate your NAD+ levels to fight back.

Here’s some of the topics we cover:

- WHAT IS NAD+
AMPK* – Stimulates NAD+ Production
INFLAMMATION – consumes NAD+
BLOOD GLUCOSE – High Levels Increase Inflammation
EXERCISE – Stimulates AMPK and Lowers Inflammation
KETOSIS *– Stimulates AMPK and Lowers Inflammation
NAD+ Precursor Supplements (NR, NMN)

* AMPK (5’ AMP-activated protein kinase) is an enzyme that plays a key role in energy balance. All creatures from yeast to humans have this enzyme (R). AMPK can detect the level of energy (number of ATP molecules) in a cell and helps regulate responses when it gets too low or high.

* Ketosis is a normal metabolic process. When the body does not have enough glucose for energy, it burns stored fats instead; this results in a build-up of acids called ketones within the body. Ketosis is also commonly observed in patients with diabetes, as the process can occur if the body does not have enough insulin or is not using insulin correctly. Problems associated with extreme levels of ketosis are more likely to develop in patients with type 1 diabetes compared with type 2 diabetes patients.

WHATS THE SECRET
There are several things covered here that seem like a “Secret”, because they aren’t talked about by those just looking to sell pills or get clicks to their overhyped stories.

But I know that truly understanding this article can change people’s lives. I’ll start with this one:

You DON’T have to take some pills to boost your NAD+

Just spend a little time learning about the science, so you can best tailor your nutrition and exercise plan to take advantage of the recent research breakthroughs and boost your NAD+. A little, or a lot – it’s all up to you.

Having a well defined mental image of what increased NAD+ levels do for your health, rather than some vague idea of “it’s good for you”, helps motivate people to stick to their diet and exercise programs.
And that is the goal of this post – to let you know there are many things you can do to raise your NAD+ levels to achieve a more youthful and energetic body.

**WHAT TO DO**

It’s pretty simple once you understand the science behind NAD+ and why it drops as we age. The prescription is:

- Periodic Carbohydrate Restriction – Ketosis
- Exercise

The goal is periodic ketosis, combined with HIIT to maximize AMPK and boost NAD+ levels, restoring the healthy metabolism you had as a teenager. **Weight Loss is just a side effect.**

Even if you have no interest in changing your diet or exercise regimen, and only want to learn more about NAD+ and perhaps take a NAD booster supplement like Nicotinamide Riboside (NR) or Nicotinamide Mononucleotide (NMN), you still need to read this page to better understand how critical it is to get your NAD+ up.

**A LITTLE KETOSIS**

It’s well known that Calorie Restriction (CR) can extend longevity by 30–50% in many mammals (32), but is not a realistic therapy for most humans.

Fortunately, you don’t have to starve yourself.
Researchers have found it is the production of ketone bodies, or Ketosis, that occurs when strict Calorie Restriction is imposed that provides the benefit in lowering inflammation and boosting NAD+ (3,9).

– *Ketone bodies mimic the life span extending properties of caloric restriction (veech,2017)*

Ketosis is a metabolic state in which fat provides most of the fuel for the body.

It occurs when there is limited access to glucose (blood sugar), which is the preferred fuel source for many cells in the body.

Glucose is usually the brain’s main fuel. However, unlike fatty acids, ketones can cross the blood-brain barrier and provide up to 70% of the brain’s energy needs when glucose levels are low (3).
Ketosis is most often associated with ketogenic and very low-carb diets, but can also occur under Calorie Restriction, or any of the diet plan where carbohydrate intake is insufficient to supply blood glucose requirements. (3, 4, 5, 6).

When carb intake falls below 50 grams per day, the lower blood glucose levels cause the Pancreas to signal the liver to process fatty acids, from the blood stream and from body fat, where they are processed into ketones to provide energy.

A Ketogenic Diet is an easier alternative for putting the body into Ketosis than severe CR, and is great for boosting NAD+, but many people still find it difficult to adhere to.

Better yet, Intermittent or Periodic Ketosis is effective at extending lifespan and likely achieves much of the benefit(36,37).

– A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan.
– Diet mimicking fasting promotes regeneration and reduces autoimmunity and multiple sclerosis symptoms
In fact, this recent study found more benefit from cyclical than from full time ketogenic diet (71).

**Ketogenic Diet Reduces Midlife Mortality and Improves Memory in Aging Mice** (Newman, 2017)

This chart shows production of the ketone body BHB. Note the huge increase in those subjects on the cyclic Keto diet (red). Read about the importance of BHB below.

**Conclusion:** *Ketones become the main source of energy for the body and brain when carb intake and insulin levels are low, and are likely the reason CR extends health span.*

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**A LITTLE EXERCISE**

Fortunately, it’s really just 1-2 hours a week. Researchers are finding that 2-3 short bouts of High Intensity Interval Training (HIIT) is far more effective at lowering inflammation (and increasing NAD+), especially among older adults (55)

Exercise is not actually required, but it is very effective at boosting NAD+, especially when performed at the right time – when blood glucose is low (see HIIT below, or [here](#)).

Hours a day of grinding endurance training does not boost NAD+ and can even be counter-productive (55). You’re not trying to “burn fat”, but activate AMPK, which drives creation of NAD+.
HIGH BLOOD SUGAR INCREASES INFLAMMATION, LOWERS NAD+, AND SHORTENS LIFESPAN

Elevated blood glucose levels increase inflammation, contributing to disease and aging. You can predict death more reliably by blood sugar level than you can by age.

Studies have found blood glucose levels even at the normal range can have a significant impact on brain atrophy in aging. ([Neuro Science News])

Incidence of disease starts to increase when fasting blood sugar rises above 85 mg/dl (63)

A study of 46,000 middle-age individuals and found more than 80% had fasting blood sugar of 85 mg/dL or greater. (64)

This means the vast majority of aging humans today endure chronic cellular damage associated with elevated blood sugar(65).

The link between Blood Glucose levels and inflammation is well known and explored more here and here.
More than 80% of the population have high blood glucose levels and are slowly poisoning their body!

INFLAMMATION DRIVES DISEASE AND AGING

Chronic, low-grade inflammation is recognized as a major characteristic of aging.

This phenomenon is so pervasive that the term inflammation has been coined to emphasize that many major age-related disabilities, including cancers, susceptibility to infections, and dementia have immunopathogenic components (31).

When we are injured, inflammation is the body’s first line of defense against invading microbes; but in old age inflammation attacks healthy tissues.

Chronic inflammation is a direct cause or major contributor to almost all aging-related diseases (4, 5, 6).

Arthritis. The old view of arthritis was that the cartilage that cushions and lubricates our joints wears away with years of use. Now it is recognized that osteo-arthritis has the same roots as rheumatoid arthritis. It is an auto-immune disorder, the body’s immune system turned traitor against our bones and cartilage.

Atherosclerosis. The old view of coronary heart disease was that over many years, cholesterol deposits on the artery walls in the same way that mineral deposits build up inside a water pipe and gradually come to clog the pipe completely. Now it is recognized that inflammation plays an essential role.

Cancer. The old view was that there are random mutations that cause the cells to disregard regulating signals from the body and just continue replicating and growing out of control. Now we realize that cancer is a failure of the body’s immune defense system. Cancer mutations
themselves are not steady and random, but are ramped up as we get older by chronic, systemic inflammation.

**Alzheimer’s Disease.** This is the latest paradigm to shift, highlighted in an [this article](#) in the MIT Technology Review about the work of Harvard Med School Professor Beth Stevens. Now we are beginning to see that glial cells “go rogue” and begin—unexplainably—to destroy nerve connections that are healthy, even essential for the brain’s function.

read more about [inflammation and aging here](#)

**WHAT IS NAD+**

NAD+ stands for nicotinamide adenine dinucleotide. From simple bacteria to mammal including humans, Life as we know it cannot exist without NAD+.

NAD+ is required for our mitochondria to burn glucose to power the basic functions of all our cells, and also plays a key role in signaling with our cells.

It has now been demonstrated that [cellular NAD levels decline with age and disease](#).
This decline impairs mitochondrial function, playing a crucial role in the development of metabolic dysfunction, age-related diseases and that this decline is both a consequence of and contributor to the aging process. (24,53).

A vicious cycle exists in which molecular mechanisms involved in the aging process, such as oxidative stress, DNA damage, senescence, and inflammation, lead to tissue NAD decline which subsequently exacerbates the processes that caused its decline in the first place. (24,53,54)

- NAD levels decline precipitously with aging in mammals and humans, and are strongly negatively affected by multiple disease and stress processes including obesity. At advanced ages these levels are a tiny fraction of what they are in young people.
- Maintaining a high level of constitutive NAD+ in the body is critical for maintaining health and functionality, for averting or reversing a number of deleterious disease phenomena, for energy and vitality, and possibly for extending life spans in humans.
- The rate of DNA damage increases significantly with aging, increasing demand for NAD+ for DNA repair. However in general, the reasons for age-related decline in NAD are not well understood.
- It has long been known that many deleterious disease phenomena can be prevented or reversed by promoting higher levels of NAD in animal models. There appears to be ample evidence that this approach is generally safe.

**Conclusion:** As we age, declining NAD+ is a key contributor to illness, disease and deteriorating health

See more about NAD+ Benefits and research
WHAT DEPLETES NAD AS WE AGE?

Our bodies do create NAD+ from Tryptophan in a 7 step process termed “de novo”. But this is a very small quantity and not thought to fluctuate much depending on demand.
By far, the greatest source of NAD+ is thru the salvage pathway. That is, recycled from NAM, NA, NR, or NMN. The entire NAD+ pool is recycled nearly 3 times every day (21)

When we are young and have high levels of NAD+, it is mostly consumed as part of normal cellular respiration process – that is, oxidation of ATP for energy.

So where does all this NAD+ go when we age?

Does the salvage, or de novo creation pathways break down? Not really.

The problem is, as we age there are more demands for NAD+ from 2 sources:

- PARPs
- CD38 and related Enzymes

**PARPs** repair damaged DNA strands, which increase as we age. A popular aging theory holds that DNA damage is the cause of aging.

DNA damage is repairable, but PARPS consume up to 80% of available NAD+ in older humans, meaning it is a major cause of NAD+ shortage, leaving less NAD+ for cellular respiration, fighting inflammation, and disease (21)

*PARP activity is reported to be a major consumption pathway for NAD+ (29)*

**CD38** is an enzyme that responds to inflammation. As NAD+ levels drop while aging, CD38 levels rise in response to inflammation. Its main function is metabolizing NAD+ (25)

As we age, demand for NAD+ from PARPs and CD38 greatly increases, leaving less and less NAD+ for our mitochondria to perform the basic task of energy production.

No wonder we have less and less energy as we age, and look at our grandchildren with such envy!

*AS WE AGE, INFLAMMATION BECOMES THE KEY CONSUMER OF NAD+ (54).*
NAMPT

NAD+ is constantly being created and consumed, with the entire NAD+ pool being recycled every day, primarily through the salvage pathway (21,54).

NAMPT is the rate-limiting enzyme in mammalian NAD+ salvage pathway, converting Nam into NMN as the first step for maintaining NAD+ (54).
Both, aging and obesity impairs NAMPT-mediated NAD+ biosynthesis.(54)

Chronic inflammation induced by prolonged oxidative stress and inflammatory cytokines also reduce NAMPT and NAD+ levels in multiple tissues (54)

NAMPT is down-regulated by over-eating and sedentary lifestyle. Obesity, high blood sugar levels, and aging decrease NAMPT-mediated NAD^+ biosynthesis (20,54).

Fasting and exercise up-regulate AMPK, which stimulates NAMPT to metabolize more NAD^+ (20,54)

**Conclusion:** *NAMPT is the rate limiting enzyme necessary to continuously renew NAD*+

**AMPK CONTROLS THE AGING PROCESS**

AMPK is both a sensing and signaling enzyme. It senses ATP activity in the mitochondria – basically, energy levels. When blood glucose levels are low, such as with CR or Keto diet, ATP activity is low and AMPK signals NAMPT to create more NAD^+ (19)

The December 2011 e-publication AMP-activated protein kinase (AMPK) controls the aging process via an integrated signaling network makes the point that control of Nrf2 along with control of other key pathways by AMPK drives aging.

*Efficient control of energy metabolic homeostasis, enhanced stress resistance, and qualified cellular housekeeping are the hallmarks of improved healthspan and extended lifespan. AMPK signaling is involved in the regulation of all these characteristics via an integrated signaling network.*

Many studies with lower organisms have revealed that increased AMPK activity can extend the lifespan.

Furthermore, inhibition of NF-κB signaling by AMPK suppresses inflammatory responses.

Emerging studies indicate that the responsiveness of AMPK signaling clearly declines with aging. An increase of NAD+ levels followed by sirtuin activation is observed in situations of energy deficit, such as fasting (47), calorie restriction (CR) (47) or low glucose feeding (Fulco et al, 2008), and exercise (47,48).
On the contrary, multiple studies reported that high-fat high-sucrose (HFHS) feeding diminishes NAD+ content in liver (46,51), skeletal muscle (49), BAT (49), and white adipose tissue (WAT).

**Conclusion:** AMPK senses low energy levels and responds by signaling NAMPT to increase intracellular NAD+ concentrations (18)

**CALORIE RESTRICTION DECREASES INFLAMMATION AND EXTENDS LIFESPAN**

Calorie Restriction (CR) can extend longevity by 30–50% and remains the surest path to increased longevity and resilience to diseases of aging across many organisms, from yeast to monkeys and perhaps humans (32).

CR can lower the prevalence of age-related loss of function and multiple diseases, including tumors, cardiovascular disease, neurodegeneration, and protects against diabetes, cancer, cardiovascular disease, sarcopenia, and neurodegeneration of certain brain regions in rhesus monkeys (31).

Human aging is characterized by a chronic, low-grade inflammation, and this phenomenon has been termed as “inflammaging.” Inflammaging is a highly significant risk factor for both morbidity and mortality in the elderly people, as most if not all age-related diseases share an inflammatory pathogenesis [r]

CR decreases inflammation, which is believed to be the reason it protect against multiple diseases and extends lifespan.
In non-obese, healthy adults, 25% CR decreases inflammation with no significant adverse effect.

These CR-induced changes suggest a shift toward a healthy phenotype, given the established role of these pro-inflammatory molecules as risk markers in the development of metabolic syndrome and age-related chronic diseases, in particular CVD, T2D and cancer(1).

**Conclusion:** Calorie Restriction of 25% or more has significant effect at combating disease and aging – But, is difficult to follow for humans

* Older mice and humans (70+) have not shown benefits from Calorie Restriction that younger people do
DIETARY RESTRICTION

The definition of dietary restriction has been expanded from an alternative description of caloric restriction to also encompass a broader scope of interventions, including:

- Periodic fasting
- Fast Mimicking diet
- Intermittent Fasting
- Time-Restricted Feeding

These relatively novel interventions are reported to have beneficial effects on overall health and in some cases longevity (34).

Both intermittent and periodic fasting can increase lifespan, even when there is little or no overall decrease in calorie intake (34).

When mice were given access to food for only 8–9 hours during the active phase of the day, metabolic diseases induced by a high-fat, high-fructose, and high-sucrose diet, were reduced without lowering caloric intake(34).

Ad lib feeding during the weekend did not interfere with the protective effects of time-restricted feeding(34).

**Conclusion:** *Constant Calorie Restriction is not necessary. Short periods of deprivation provide the same benefits for health and life extension*

GLUCONEOGENESIS

Although most of the brain can use ketones, there are portions that require glucose to function.

On a very-low-carb diet, the liver can also switch on gluconeogenesis, which means “making new glucose” from amino acids in protein, or from glycerol in triglycerides.

Gluconeogenesis increases metabolism to burn more calories (26, r).

**Conclusion:** *On a very low-carb diet, up to 70% of the brain can be fueled by ketones. The rest can be fueled by glucose produced in the liver.*
KETOGENIC DIET

The pie charts below show the typical nutrient breakdown of a low-fat Western diet, a low-carb diet and a typical ketogenic diet:

The ketogenic diet is a popular weight loss diet that is well-supported by science (1).

In fact, research shows that the ketogenic diet is far superior to the recommended low-fat diets for weight loss. (2, 14, 15, 16).

What’s more, you can lose weight without counting calories or tracking your food (16).
One study found that people on a ketogenic diet lost 2.2 times more weight than those on a calorie-restricted low-fat diet. Triglyceride and HDL cholesterol levels also improved (17).

Another study found that participants on the ketogenic diet lost 3 times more weight than those on the Diabetes UK’s recommended diet (r).

A ketogenic diet also lowers risk for many diseases (8, r, r, 11, r, 13).

They are now being studied as a treatment for a wide variety of conditions (r):

- **Heart disease.** Reducing carbs to achieve ketosis may improve heart disease risk factors like blood triglycerides, total cholesterol and HDL cholesterol (r, r).
- **Type 2 diabetes.** The diet may improve insulin sensitivity by up to 75%, and some diabetics are able to reduce or even stop diabetes medication (r, r).
- **Metabolic syndrome.** Ketogenic diets can improve all major symptoms of metabolic syndrome, including high triglycerides, excess belly fat and elevated blood pressure (r).
- **Alzheimer’s disease.** A ketogenic diet may have benefits for patients with Alzheimer’s disease (r).
- **Cancer.** Some studies suggest that ketogenic diets may aid in cancer therapy, possibly by helping to “starve” cancer cells of glucose (r, r).
- **Parkinson’s disease.** A small study found that symptoms of Parkinson’s disease improved after 28 days on a ketogenic diet (r).
- **Acne.** There is some evidence that this diet may reduce the severity and progression of acne (r).

**Conclusion:** *Studies show that ketogenic diets lead to more weight loss than low-fat diets, and help with a number of chronic diseases, including metabolic syndrome, type 2 diabetes and Alzheimer’s.*

**FAT FASTING**

A report by the US Institute of Medicine’s Food and Nutrition Board states: “*The lower limit of dietary carbohydrates compatible with life apparently is zero, provided that adequate amounts of protein and fat are consumed.*”
In one study, a group of volunteers fasted for 84 hours (3.5 days), or received a lipid infusion such that they got all the calories they needed.

The researchers found that there were no differences in “plasma glucose, free fatty acids, ketone bodies, insulin, and epinephrine concentrations” between fasting and non-fasting conditions (30).

The authors conclude, “These results demonstrate that restriction of dietary carbohydrate, not the general absence of energy intake itself, is responsible for initiating the metabolic response to short-term fasting.” (30)

**Conclusion:** Calorie Restriction is NOT NECESSARY – Carbohydrate restriction provides the benefits

**DON’T BE AFRAID OF “GOOD FAT”**
For those that have a fat phobia, here’s 3 recent studies that may open your eyes a little.

1: Compared three different diets for weight loss: Weight Loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet. (New England Journal of Medicine.)

The low-fat diet was calorigically restricted, with a target 1800 calories a day for men, 1500 for women. It was 30% of calories from fat, and “participants were counseled to consume low-fat grains, vegetables, fruits, and legumes and to limit their consumption of additional fats, sweets, and high-fat snacks”.

The Mediterranean diet’s target calorie intake was the same as for the low-fat, but with a goal of 35% calories from fat, “the main sources of added fat were 30 to 45 g of olive oil and a handful of nuts (five to seven nuts, that’s it).
The low-carbohydrate diet was not restricted in calories; it was all you can eat. It provided “20 g of carbohydrates per day for the 2-month induction phase…, with a gradual increase to a maximum of 120 g per day to maintain the weight loss. The intakes of total calories, protein, and fat were not limited.

The study lasted for 2 years; all participants were either overweight (BMI ≥27), or with diabetes or coronary heart disease.

**Study 2:** More proof that high fat, low carb diets are healthy found in this paper: A high-fat, ketogenic diet induces a unique metabolic state in mice.

This was a high-fat diet, with 95% fat, 5% protein, and 0% carbohydrate. When animals were switched to this diet they lost weight, lower glucose and insulin, and higher AMPK activity.

**Study 3:** Heres’ an interesting new study on the effects of keto diet on human muscles. The effects of ketogenic dieting on skeletal muscle and fat mass. One reason why it’s interesting is that the men in the study were already resistance-trained.

Twenty-six college aged resistance trained men volunteered to participate in this study and were divided into either:

- VLCKD (5 % CHO, 75 % Fat, 20 % Protein)
- traditional western diet (55 % CHO, 25 % fat, 20 % protein)

All subjects participated in a periodized resistance-training program three times per week

The ketogenic diet group gained 4.3 kg lean mass (muscle) compared to only 2.2 kg for the traditional diet group

The ketogenic group lost 2.2 kg of fat, compared to 1.5 kg in the traditional group.

Here’s some more articles that dispel the myths about Carbohydrates vs Fats in the human diet.

Carbohydrates, Not Saturated Fat, Are Correlated with Cardiovascular Disease
How Coconut Oil and other MCT’s aid weight loss
KETONE BODY β-hydroxybutyrate (BHB) THE KEY TO LIFE EXTENSION PROPERTIES OF CALORIC RESTRICTION

When the blood-glucose level drops the liver generates glucose by breaking down glycogen. If glucose levels drop too much, the liver synthesizes ketone bodies as a sort of back up fuel source for use by other organs (4).

So, levels of ketone bodies are elevated by starvation, caloric restriction, high-intensity exercise, or the low-carbohydrate ketogenic diet (5).

Studies in cells (r), animals (r), and patients (r, r) suggest that it may be useful in common neurodegenerative diseases, such as Parkinson’s and Alzheimer’s diseases, as well as in insulin-resistant states, such as trauma, heart failure, and diabetes (r).

Many aging-induced changes, such as the incidence of malignancies in mice (10), the increases in blood glucose and insulin caused by insulin resistance (11), and the muscular weakness have been shown to be decreased by the metabolism of ketone bodies (12).

BHB INHIBITS INFLAMMATION
β-hydroxybutyrate (BHB) is one such ketone body of particular interest as it has unique properties in reducing inflammation (5).

BHB is not used solely as a energy source, but also acts as a signal to regulate metabolism when energy sources are low (5).

Due to this special role, only BHB suppresses activation of the NLRP3 inflammasome, a key driver of systemic inflammation.

Other ketone bodies such asAcAc, butyrate and acetate do not have a similar effect on inflammation (5).

*The ketone metabolite BHB blocks NLRP3 inflammasome-mediated inflammatory disease and mimics the life span extending properties of caloric restriction*
**BHB AND NAD+**

keto diet creates bhb to extend lifespan

A 2016 study found β-hydroxybutyrate significantly increased the phosphorylation of AMPK (16).

AMPK activation is the key signal that drives increased NAMPT, which is the rate limiting factor in the bodies constant recycling of NAD+ (r).

Metabolism of one BHB molecule require 2 molecules of NAD+ instead of the 4 molecules required in normal glucose metabolism, thereby preserving the cytoplasmic NAD+ pool (7).

- Inhibits inflammation which is a key consumer of NAD+ as we age
- Activates AMPK which drives endogenous production of NAMPT and NAD+
- Uses 50% less NAD+ in the production of ATP for basic cellular energy

In humans, serum levels of BHB are usually in the low micromolar range but begin to rise to a few hundred micromolar after 12–16 h of fasting, reaching 1–2 mM after 2 days of fasting (r) and 6–8 mM with prolonged starvation (r).

Similarly, serum levels of BHB can reach 1–2 mM after 90 min of intense exercise (r). Consistent levels above 2 mM are also reached with a ketogenic diet that is almost devoid of carbohydrates (r).

**BHB, NAD+, INFLAMMATION, DISEASE, AGING – PUTTING IT ALL TOGETHER**

Three new independently conducted studies show that the increased BHB produced in a ketogenic diet improved the NAD+/NADH ratio which decreases expression of the pro-inflammatory NF-κB gene, resulting in:

- weight loss
- improved memory
- improved physical strength
- 13-percent increase in median life span
One study – led by Drs. Eric Verdin and John Newman, looked at the effect of the keto diet on aging mice.

Remarkably, the older mice on the ketogenic diet had a better memory than the younger mice – months after they had gone off a ketogenic diet.

Dr. Verdin, says this is the first study to demonstrate how BHB improves memory and lifespan. “This opens up a new field in aging research. We think the health benefits of BHB may go beyond memory and could affect tissues and organ systems”

The second study – led by Dr. Jon Ramsey, looked at adult mice and had similar findings about the impact of the keto diet, with the addition that it may also improve strength and coordination.

The second study not only showed the improvement from a cyclical keto diet, but were able to prove that BHB was the mechanism behind it.

The third study by Yiguo Shen and Raymond Swanson found the BHB produced in a keto diet improved the NAD+/NADH ratio to block brain inflammation following stroke and brain trauma.

The researchers used a small molecule called 2-deoxyglucose, or 2DG, to block glucose metabolism and produce a ketogenic state in rats. They found 2DG could mimic a keto diet, increasing BHB and NAD+ production, and bring inflammation levels down to normal levels.
NMN GREATLY INCREASES FAT METABOLISM
Administration of NMN improves mitochondrial fatty acid oxidation (33)
NMN-administered mice switched their main energy source from glucose to fatty acids (23)

EXERCISE INCREASES LIFESPAN

The best way to stay young really might be to keep moving. Research has shown physical activity can reduce inflammation in your body and improve heart health—both important for staying young beyond your years.

Aging results in chronic low grade inflammation that is associated with increased risk for disease, poor physical functioning and mortality. Strategies that reduce age-related inflammation improve the quality of life in older adults (1).

Regular exercise is recommended for older people for a variety of reasons including increasing muscle mass and reducing risk for chronic diseases of the heart and metabolic systems (2).

This recent study found that 4 hours of running per week increased average lifespan by 3 years. Surprisingly, time spent running added more time that it took to run, with each hour running adding 7 hours on average.

More about exercise and inflammation
HIIT IS BETTER

HIIT involves short bursts of intense exercise alternated with low-intensity recovery periods. Interestingly, it is perhaps the most time-efficient way to exercise (4, 5).

Typically, a HIIT workout will range from 10 to 30 minutes in duration (4).

Despite how short the workout is, it can produce health benefits similar to twice as much moderate-intensity exercise (6, 7).

This would be considered one “round” or “repetition” of HIIT, and you would typically complete 4 to 6 repetitions in one workout (4).

Regardless of how it is implemented, high-intensity intervals should involve short periods of vigorous exercise that make your heart rate speed up (4, 8).

This recently published study compares HIIT with resistance training and combined weights/cardio training. It found HIIT to be far more effective, particularly for older humans.

HIIT continues to burn calories long after you finish exercising because your muscles need to use more energy to recover after exercise (68, 69).

In fact, research has shown that HIIT can burn up to 190 calories over 14 hours after exercising (69).

Research also shows that HIIT can help your body build and preserve muscle mass with age (70).

In some cases, the high-intensity regimen actually seemed to reverse the age-related decline in both mitochondrial function and muscle-building proteins.

- High intensity interval training (HIIT), in particular sprint interval training (SIT), has been shown to promote mitochondrial biogenesis
- SIT is usually performed as very short sprints (20-30 s) at maximal intensity (“all out” effort) repeated 4-8 times.
- As few as 4-6 sprints have been shown to increase mitochondrial biogenesis to a similar extent as long duration cycling (90-120 min at 65% of VO2max)
- research shows that it is more beneficial to undertake most training in a “low”
glycogen state (Hansen et al., 2005).

More about the Benefits of HIIT
Read more about HIIT and Aging

EXERCISE AND CR INCREASE NAD+ PRODUCTION

It’s clear that the same things that help fight inflammation also increase NAD+.

AMPK is the reason why. CR and exercise active AMPK, which stimulates NAMPT to metabolize more NAD⁺ (20, 54)

Exercise, especially HIIT, activates the enzyme AMPK to increase your NAD+ levels, stimulate glucose uptake ad mitochondrial biogenesis (31, 55)

Exercise while fasting is even more effective at cranking up AMPK to elevate your NAD+ levels (r). Exercise while fasting, or continue to exercise after you “hit your wall” (55)

“Athletes have a 2-fold higher levels of NAMPT in their skeletal muscle compared with sedentary adults” (38)

Exercise, especially HIIT, activates the enzyme AMPK to increase your NAD+ levels, stimulate glucose uptake and mitochondrial biogenesis (31)

Exercise while fasting is even more effective at cranking up AMPK to elevate your NAD+ levels (r).

Conclusion: HIIT 2-3 times per week while in low blood glucose state is ideal for Activating AMPK and boosting NAD+

SUPPLEMENTS TO INCREASE NAD+
Studies show that high levels of NAD+ result in stronger, healthier cells and mitochondrial function. (r)

More importantly, their analysis revealed that mitochondrial dysfunction is reversible with NAD+ supplementation, enabling the life and health of cells to be prolonged at the molecular level. (r)

NAD+ cannot be taken as oral supplements because it does not survive the digestive system long enough to enter your cells (25).

However, researchers have found that the molecules our bodies use to make NAD+ can be taken as supplements and DO make their way through the digestive system where they are processed (mostly) by the liver and DO raise NAD+ levels in the blood and organs.

These NAD+ precursors have been tested in mice and humans to evaluate their effectiveness at elevating NAD+ levels and treating various disease conditions. The NAD+ precursors are (25):

- **NMN** – Nicotinamide Mononucleotide
NAM, Niacin, and Tryptophan have been shown to alleviate symptoms in a wide variety of disease, but have some drawbacks such as intense flushing (niacin).

**NMN is the precursor used by Dr David Sinclair** in all his experiments with NAD+ repletion.

The landmark 2013 study by Dr. Sinclair demonstrated that supplementation with NMN increased levels of NAD+ and reversed age related degeneration in mice, giving older mice the muscle capacity, endurance and metabolism of much younger mice – the “equivalent of a human 60 year old becoming more like a 20 year old” (24).

That study really lit a fire to research in the role NAD+ plays in regulating our metabolism and aging, with dozens of studies already completed and even more underway.

A later study by Dr Sinclair published in 2016 looked at the effects on health of long term (12 months) administration of NMN on mice (23). The following quotes are from that study:

**NMN effectively mitigates age-associated physiological decline in mice**

**NMN suppressed age-associated body weight gain, enhanced energy metabolism, promoted physical activity, improved insulin sensitivity and plasma lipid profile, and ameliorated eye function and other pathophysiologies**

**These effects of NMN highlight the preventive and therapeutic potential of NAD⁺intermediates as effective anti-aging interventions in humans**
NR was discovered in 2004 by Dr Charles Brenner, and is used in his experiments. Although NR is unstable by itself, Dartmouth University has patented production methods that combine it with Chloride which makes it stable.

Chromadex has licensed this technology and has been selling NR commercially since 2014 under the brand name “Niagen”.

They controlled the market for NR until just recently, when Elysium Health has begun to market their own version of NR in their Basis product.

Dr. Brenner has been instrumental in leading research into the health benefits of NAD+ supplementation using NR, and led the first human studies of NR published in 2016. He is the chief science officer for Chromadex, and founder of the company that markets Tru Niagen, the official brand favored by Chromadex.

According to Dr Brenner:

“Not every cell is capable of converting each NAD+ precursor to NAD+ at all times...the precursors are differentially utilized in the gut, brain, blood, and organs” (R).

Conclusion: Although NMN and NR show the most potential for slowing physiological decline due to aging, NAD+ levels can also be increased by administration of NAD+ precursor molecules NA, NAM, and Tryptophan(25).

AMPK and NAMPT activators

With the realization of the profound impact that boosting NAD+ levels has on health and lifespan, researchers are now testing thousands of natural products that may stimulate AMPK (60).

You might notice that many the SAME supplements that have the greatest positive impact on health ALSO ACTIVATE AMPK.
This is further confirmation that the AMPK-NAD+ pathway is a key determinant of healthy aging (60)

- **Berberine** has been shown to lower blood sugar levels as much as the leading prescription drug Metformin. They may be equally effective at lowering inflammation thru their effect on blood sugar levels, but Metformin has been shown to lower NAD+ levels (r), so I would definitly recommend Berberine.

- Chlorogenic Acid (CGA), one of the active ingredients in Green Coffee beans, has prove to be a strong activator of AMPK (58). CGA was also show to increase metabolism, lower blood sugar levels, and decrease risk of diabetes (59).

- EGCG – EGCG activates AMPK, enhancing insulin signaling pathway by membrane translocation and phosphorylation of IRS-1, improving insulin sensitivity and secretion (60)

- Curcumin

- Leucine – “Addition of leucine to HFD restored NAMPT expression. In addition, dietary leucine stimulates SIRT1 signaling through activation of AMPK and increased NAD+/NADH ratio was observed”(52)

- **Sulforaphane** – strongly activates AMPK, and has been shown to have numerous disease fighting and anti-aging potential(R). Here is a short list of studies showing Sulforaphane activating AMPK to fight Cancer(R),Diabetes(R),Obesity(R),Neurological disease (R),Heart disease (R),HIV (R),Colitis(R).

**NAD BOOSTING PROTOCOL**

-coming soon-

**CONCLUSION – IT FEELS SO GOOD FEELING GOOD AGAIN**

YES, YOU CAN HAVE THE HEALTH AND ENERGY YOU HAD 10 or 20 YEARS AGO!
A bold statement, but I truly believe it is possible for most people, if you:

**Activate AMPK to boost NAD+**

- **CKD** (Cyclical Keto Diet) – At least 48 hours prior to HIIT sessions
- **HIIT** (High Intensity Interval Training) – 2-3 short sessions a week, when blood glucose levels are at their lowest
- **MCT oil** (More BHB production)

**Decrease Inflammation to spare NAD+**

- **Omega 3 Fats** (Fish oil, Flax oil, Chia seeds)
- **Sufficient Sleep**
- **Heat/Cold Therapy**
- **Don’t overtrain** – 5 or 6 days a week is ok, but only 2-3 days HIIT – the rest should be light

Niagen and NMN clearly boost NAD+ levels, but you can do a lot yourself.

*All Information on this page is generic and not intended to replace guidance from your doctor*

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