

Caloric Restriction, Fasting and Nicotinamide Riboside (/Anti- Aging/Caloric-Restriction-Fasting- and-Nicotinamide-Riboside.html)

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Attempts to extend normal life and to prolong maximum lifespan no doubt are as old as the human race. Many cultures have legends regarding the achievement of greatly extended lives, yet even in the realm of legend, techniques for such accomplishment are generally missing. Nevertheless, there are plenty historical records attesting that aside from deaths due to complications of childbirth, childhood diseases, famine, wars and plagues, a number individuals consuming diets and following habits that we recognize today lived not just the Biblical three score and ten years, but into their 80s and 90s. Many of the famous philosophers, playwrights and poets of Ancient Greece, for instance, still were productive into advanced years. Significantly missing is evidence of two types of longevity. First, average lifespans, which include such data as deaths from infant mortality and childhood diseases and other factors just mentioned, until the mid-Nineteenth Century were short almost everywhere, ranging from between 22 and 35 years in Europe and the US circa 1840. Second, very few individuals reached the age of 100.

Since 1840, life expectancy, taking the world as a whole, has risen to the early 60s. In Japan, which has a population currently exhibiting the longest lifespan, women routinely can expect to reach approximately 85 years of age.¹ Similarly, in an advanced country such as the United Kingdom, the likelihood of reaching 100 years for babies born today is roughly 18.1 percent for boys and 23.5 percent for girls.² These are remarkable improvements in life expectancy. Nevertheless, the maximum human lifespan remains firmly fixed in place. In 2008, one group that tracks the number of individuals who reach 110 years of age or above had confirmed only 74 such individuals as presently alive despite a world population in the billions. The oldest human age known with certainty is 122 years, and for this there is only one case.

The implication of the evidence to date regarding human lifespan arguably is that in the foreseeable future there will be little success in prolonging maximum longevity, yet the consolation prize of **extending normal life** towards a reasonable theoretical limit of 110 years is within reach. In this regard, there are at least three options. **Two are well-attested** in traditional medical systems around the world and the **third, although only recently discovered**, in many ways is an extension of the science of the **first two: caloric restriction, fasting, and the benefits of supplementing with nicotinamide riboside.**

Caloric Restriction To Reduce Insulin And IGF-1

Famine and food scarcity have played a huge role in human history, so one might not imagine that prior to modern times much attention would have been paid to the results of relatively long term reductions in food intake not actually taken to the point of caloric insufficiency. Even today, much of the world suffers from inadequate nutrition during childhood. As a result of two World Wars leading to widespread starvation, in Europe as late as the mid-Twentieth Century there were positive connotations often associated with being a little bit heavy in middle life and later. Nevertheless, it would be a mistake to believe that awareness of the benefits of controlling food intake is restricted to recent times. Indeed, Buddhist medical advice in one or more traditions dating back at least a couple of thousand years hold that one should eat, roughly speaking, only to the point of being perhaps two thirds full, should not eat solid food after the mid-afternoon, and so forth. In Renaissance Europe, the first famous proponent of caloric restriction to enhance health and lifespan was Luigi Cornaro, a 15th century Venetian nobleman who adopted a calorie restricted diet at age 35 and published on the topic his book *Discorsi della vita sobria* (Discourses On the Temperate Life).

Wikipedia has an excellent short review on caloric restriction, some of its history, and early experiments in the last century. The great modern incentive for research in this area was the finding in 1934 that laboratory rats fed a severely reduced calorie diet with otherwise adequate nutrient levels lived almost twice as long as expected. Subsequent tests with mice and many other animals led to similar results. However, although caloric restriction has proven to be useful in extending life towards its upper threshold in life forms ranging from yeast to primates, it does not work in all species. For instance, it does not improve life expectancy in wild mice.

Taken to extremes in humans, which would include a 45 percent reduction in normal food intake for six months, there are a host of negative effects, including "anemia, lower extremity edema, muscle wasting, weakness, neurological deficits, dizziness, irritability, lethargy, and depression."³ **In fact, and contrary to caloric restriction doctrines, many epidemiological studies have found that humans who gain a slight amount of weight in middle age and later in life (meaning trending towards the upper end of the "normal" Body Mass Index range) as a rule**

live longer than those who are thin.

That being acknowledged, it remains the case that long running caloric restriction experiments, one concluded only just recently, demonstrated that the primates involved were “only 36.4% as likely to die from age-related causes ... and had only 56.2% the rate of death from any cause” as compared with control animals.⁴ The Wikipedia article provides a long list of proposed mechanisms, including “reduced cellular divisions, lower metabolic rates, reduced production of free radicals, reduced DNA damage and hormesis.” Other articles describe the life extending benefits in higher animals of autophagy achieved by reducing not calories, but instead protein components, such as methionine and tryptophan. (Autophagy involves a type of cellular house cleaning in which cells degrade and remove unnecessary and worn out components, thus renewing the cells from the inside.) Readers who desire an elaborate academic discussion should start with “Caloric restriction: From soup to nuts,” by Stephen R. Spindler.⁵

A look at human groups noted for extremely long lives even without any obvious attention to diet points towards a more manageable set of factors focusing on insulin and insulin-like growth factor signaling, such as IGF-1, in those who are insulin sensitive (as opposed to low insulin in diabetics). For instance, impaired IGF-1 receptor activity has been linked to extreme longevity in Ashkenazi Jews. These two related factors, in turn, it can be argued, play large roles in regulating sirtuins (recently popularized in conjunction with resveratrol), mTOR (mechanistic target of rapamycin), the ratio of NAD⁺/NADH in cells, and AMPK (5' adenosine monophosphate-activated protein kinase), four other factors often cited by researchers as important to longevity.⁸

Inhibiting insulin/IGF-1 signaling extends lifespan and delays age-related disease in species throughout the animal kingdom.⁶ In fact, this complex is at the regulator center of many or even most of the components thought to be important to longevity.⁷ This is an important reason that a number of researchers are looking at the anti-diabetes drug metformin and other compounds that accomplish similar results as potential longevity boosters. The actions of metformin to reduce hyperglycemia and hyperinsulinemia by decreasing insulin resistance already have been demonstrated to extend lifespan and inhibit carcinogenesis in rodents.⁸

CR » ↓ insulin/IGF-1 » ↑ NAD⁺ concentration/ratio » ↑ Sirt-1 »
↑ autophagy » ↑ longevity

CR » ↓ glucose (and ↓ insulin/IGF-1) » ↑ AMPK » ↓ mTOR »
↑ longevity

Presently, there is little agreement on what constitutes the proper level of caloric restriction in humans. As already observed, restriction in the range of 40 percent and above appears to be too high. In the two long running primate studies, calories were restricted by 30 percent. Such factors as age, natural body weight, activity levels (such as the greater calorie needs of the actively growing and athletes) and the like complicate matters. Similarly, shifts in protein consumption to above the Daily Reference Intake may negate some of the most important aspects of caloric restriction, including the reduction in IGF-1.⁹ (Many protein sources, for instance, beef, are gluconeogenic; the amino acid leucine can increase insulin release as much as 40 percent when eaten with carbohydrates and may be related to the development of insulin resistance^{10,11}; and so forth.)

A number of groups exist that help to supply guidance on the practice of caloric restriction, including the Methuselah Foundation and the CR Society International.

What About Fasting?

Getting caloric restriction right and practicing it over the long term can present a challenge. How much is enough, how much is too much, for whom and under what conditions? Should total calories be restricted, total carbohydrates, fats, protein, which aspects of protein, and so on? Clearly, a workable alternative to caloric restriction is needed, albeit even without practicing such restrictions it always is an option to reduce consumption of sugars and refined carbohydrates. Fortunately, yet another age-old practice, fasting, apparently can be employed to deliver at least some of the benefits of caloric restriction. Significantly, the proposed mechanism of action is...a reduction in IGF-1, just as in caloric restriction!

In fact, fasting in 2014 received very important scientific backing as a means to improve some key factors that typically decline with age. The headline on June 5, 2014 at ScienceDaily ran, "Fasting triggers stem cell regeneration of damaged, old immune system." On June 6, Medical News Today headlined, "Prolonged fasting 're-boots' immune system." Similar headlines were still appearing in December. Clearly, this research is considered to be important.

Indeed it is. The scientists involved described their own findings in the following terms: "prolonged fasting reduces circulating IGF-1 levels and PKA [protein kinase A] activity in various cell populations...Multiple cycles of fasting abated the immunosuppression and mortality caused by chemotherapy and reversed age-dependent myeloid-bias in mice, in agreement with preliminary data on the protection of lymphocytes from chemotoxicity in fasting patients." Importantly, these benefits could be blunted by giving endogenous IGF-1.¹² Another set of researchers came to the same conclusions, i.e., "the loss of HSC [hematopoietic stem cells] function in the elderly ("immunosenescence") is a major source of morbidity and

mortality... These effects are at least partially mediated by lowered insulin-like growth factor-1 levels in the blood and stem cell microenvironment..."¹³ Prolonged fasting for both sets of authors means 72 hours in mice, although perhaps four to five days may be more beneficial in humans. Nevertheless, 72 hours in a clinical trial was sufficient to deliver key benefits: "the results from a phase I clinical trial indicate that 72 but not 24 hr of PF in combination with chemotherapy were associated with normal lymphocyte counts and maintenance of a normal lineage balance in WBCs [white blood cells]." ¹⁴ The chief caveats are that those who are quite old or in weakened health would need to exercise caution and perhaps medical supervision.

Will fasting three to five days once a year to perhaps a few times a year lead to many of the same benefits as caloric restriction? The effects on insulin and IGF-1 are dramatic, yet the experiments have not been performed over a period of years as is true with the CR primate trials, hence the final impact on longevity is not proven. A good bet would be "yes," but not if one returns to a bad diet built around excessive and/or empty calories between fasts.

Nicotinamide Riboside/Niagen™— CR In A Bottle?

The new kid on the block for attempting to do with a nutrient what otherwise takes either caloric restriction or fasting is nicotinamide mononucleotide and its precursor that can be taken orally rather than injected, nicotinamide riboside. The two nutrients are related to CR and fasting for several reasons, not the least of these being that they are linked to nicotinamide adenine dinucleotide (NAD⁺), which acts in the regulation of NAD⁺ consuming enzymes, including sirtuins, such as Sirt1, which are important to longevity. As two of the leading researchers in this area recently wrote, "NAD⁺ levels decline during the aging process and may be an Achilles' heel, causing defects in nuclear and mitochondrial functions and resulting in many age-associated pathologies. Restoring NAD⁺ by supplementing NAD⁺ intermediates can dramatically ameliorate these age-associated functional defects, counteracting many diseases of aging..."¹⁵ Proof of concept came not long ago in a mouse model in which "treatment of moderately old mice ... with nicotinamide adenine dinucleotide (NAD⁺) precursor nicotinamide mononucleotide (NMN) for 1 week [restored] oxidative phosphorylation activity and other markers of mitochondrial function in skeletal muscle."¹⁶

Reverse aging with a nutrient? This is pretty heady stuff. Other researchers have provided a nice explanation for how reduced NAD⁺ during later life plays a central role in increasing dysfunction of the mitochondria with age, noting that declining NAD(+) induces a pseudohypoxic state disrupting nuclearmitochondrial communication during aging. As they explain, "Mitochondrial dysfunction is a hallmark of aging ... raising NAD(+) levels in old mice restores mitochondrial function to that of a young mouse in a SIRT1-dependent manner."¹⁷ Thus it might be said that the primary focus of aging is the mitochondria of the cell, not the

nuclear components, such as DNA. Renewing the mitochondria might turn back aspects of the clock the equivalent of decades in humans.

In less technical language, the overall argument is that during aging a type of communication breakdown takes place between the mitochondria, the chief sources of cellular energy, and other components of the cell. Until now, the only practical solutions to slowing this process were caloric restriction and intense exercise. Inactivity and poor dietary habits, to the contrary, speed up the development of this miscommunication. The new finding is that nicotinamide mononucleotide mimics some of the effects of diet and exercise. Injected at sufficient quantity, the compound in mice leads to extremely rapid improvements, seemingly in as little as a week.

So, now we are back with one of the main benefits of caloric restriction, which is an increase in available NAD+ leading to activation of SIRT-1 and longevity. Insulin and IGF-1 clearly are implicated once again. The question is this: when will this magic nutrient become available and how soon will it be proven in human trials?

Nicotinamide mononucleotide requires injection. For quite a number of reasons, B3 vitamin precursors to nicotinamide mononucleotide, such as niacin and niacinamide, cannot be taken to accomplish the same end. Fortunately, there is a precursor to nicotinamide mononucleotide that can be taken orally and has been shown to be active, again in rodents, albeit at a dosage level that translates into two or three grams per day as a human equivalent dose. This precursor compound is nicotinamide riboside, which is produced via a special manufacturing process protected by four issued and pending US patents and sold under the name Niagen™. Still at issue is whether far smaller dosages ingested chronically will provide some of the same benefits to human beings. Niagen™ only now is becoming available as a dietary supplement as a next generation form of vitamin B3 (niacin). The usual amount available is 100 to 300 mg per capsule or tablet. The same range is being tested clinically to determine the efficacy of chronic ingestion of Niagen™ at this level of intake.

Conclusion

Caloric restriction and fasting have demonstrated that they are practical approaches to “turning back the clock” on aging. Benefits range from cardiovascular protection to reducing immune senescence and cellular malfunctioning to providing protection against neurologic decline. Common to both practices is a positive effect upon many aspects of metabolism, especially those that involve insulin and insulinlike growth factors. Also common are issues such as how intense, how often, how long, under what conditions, for which groups of individuals, etc., plus the obvious drawback of sheer inconvenience. Recently, it was discovered that it may be possible to accomplish at least some of the anti-aging goals of caloric restriction

and fasting by supplementing with a special form of vitamin B3, nicotinamide riboside, which is becoming available under the trade name Niagen™. If this supplement lives up to the early research findings and can be taken at relatively low amounts chronically to achieve significant benefits, the phrase “exercise in a bottle” at long last may be more than merely an optimistic phrase.

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