Calorie restriction extends lifespan by lowering iron

Calorie restriction: what it is, what it does

Calorie restriction – cutting back the food of lab animals by 10 to 40%, sometimes more – robustly extends lifespan, in some cases by 50%. It is the most effective anti-aging intervention known. How does it work?

Is it possible that a human could attain most or all of the benefits of calorie restriction without a decreased food intake?

I’m going to make the case here that calorie restriction extends lifespan by lowering iron levels. At least, that’s a major part of its mechanism.

That means that merely by keeping iron accumulation in check, you could counteract aging without any drastic cut in food intake.

How calorie restriction affects physiological pathways to extend lifespan

What does calorie restriction (CR) do that could possibly increase lifespan? Here are a few possibilities.

1. Calorie restriction results in far lower body fat mass. This makes for much better insulin sensitivity and for lower levels of inflammatory cytokines. Since both insulin resistance and inflammation increase with aging, by lessening these, CR decreases aging.

2. CR lowers oxidative stress. Oxygen and molecules like H2O2 can react with macromolecules such as proteins and lipids as well as larger cellular structures, and damage them. When damage exceeds the ability of the body to repair, oxidative stress exists.
3. CR increases autophagy, the cellular self-cleaning process that rids cells of junk, and recycles the components. Autophagy declines with age, and a renewal of it fights aging.

4. CR increases mitochondrial biogenesis. Decline in number and function of mitochondria occurs in aging; increasing mitochondria and improving their function fights aging.

These don’t exhaust all the possibilities, and they aren’t mutually exclusive either. (1)

There’s also another possibility, a main mechanism of action of CR that might account for many of its other effects.

**Calorie restriction decreases iron accumulation**

CR lowers the accumulation of iron, and iron accumulation is associated with higher rates of disease and with aging overall. Let’s look at the evidence.

Iron accumulation in aging: modulation by dietary restriction. (2)

Male Fischer 344 rats fed ad libitum or dietary restricted (maintained on 60% of ad libitum food intake) were sacrificed at 6, 12 and 24 months of age... Total iron content was measured directly and lipid peroxidation (LPO) was assayed as an index of oxidative stress. Tissue total iron content was shown to increase significantly with age in animals fed ad libitum (AL)... This age-related iron accumulation, however, was found to be markedly suppressed by dietary restriction (DR) in all tissues. Similarly, LPO measurements increased in an age-related, tissue-specific fashion... Again, we found DR to markedly suppress age-related LPO in all tissues. Reported here are our findings on the ability of DR to modulate iron status at the tissue level. Consistent with the proposed anti-oxidative mechanism of DR, these findings further suggest that the modulation of tissue total iron content is an important component of that mechanism.

Both iron accumulation and the oxidative damage which it could be expected to do were markedly decreased by CR.

Restriction of a single amino acid, methionine, extends lifespan just about as much as CR, and given this fact some researchers have suggested that the effects of CR may be due to the fact that it results in methionine restriction. (3, 4)

Methionine supplementation results in large increases in iron and oxidative stress in rats. (6) This doesn’t prove that restriction of methionine will lower iron. But if there’s a graded response to methionine, which it appears there is (7), then decreasing methionine both lowers iron accumulation and decreases oxidative damage.
One of the model organisms that scientists use to study aging is the yeast, *Saccharomyces cerevisiae*, the same yeast used to make beer and wine. They can be calorie restricted by growing them in 0.5% glucose (as opposed to 2.0%).

In *Saccharomyces*, normally fed organisms accumulate large amounts of iron, along with large amounts of oxidative damage, and this is almost completely abolished by CR. In rats, CR greatly attenuated the accumulation of iron in muscle as well as the accumulation of oxidative damage. “These findings strongly suggest that the age-related iron accumulation in muscle contributes to increased oxidative damage and sarcopenia, and that CR effectively attenuates these negative effects.”
Iron restriction extends lifespan

So far, we’ve seen that CR results in lower iron accumulation with age, and that this could be a major part of its mechanism of action. But maybe it’s just a coincidence? Maybe CR just happens to lower iron but its life-extension attributes are caused by something else.

Against the notion that it’s just a coincidence, consider that iron restriction alone can extend lifespan of Drosophila.\(^\text{(10)}\)

Iron restriction also extends lifespan in C. elegans \(^\text{(11)}\), and iron supplementation decreases its lifespan.\(^\text{(12)}\)

To my knowledge, there have been no direct studies of iron restriction and lifespan in mammals.

Calorie-restriction mimetics

CR mimetics are chemical agents that mimic the physiological effects of CR without food restriction.\(^\text{(12)}\) One of their characteristics is that they induce autophagy, just as CR does. Among CR mimetics are: hydroxycitrate, EGCG, spermidine, resveratrol, curcumin, metformin, and others.

Many or most of these also chelate iron.\(^\text{(13)}\)

The fact that they increase autophagy also means that they increase iron homeostasis: autophagy also keeps free iron, the damaging kind, under control.\(^\text{(14)}\) Noteworthy here is that this provides a mechanistic link between the decline of autophagy with aging and increased levels of free iron, causing neurodegeneration and other damage.

Furthermore, lipofuscin, “the toxic waste of aging”, is a complex of which iron plays a crucial role, and it inhibits autophagy.

Summing it up

Plenty of evidence points to lower iron accumulation as well as better iron homeostasis as being a major mechanism of the effects of calorie restriction on the retardation of aging. The evidence, while not conclusive, encompasses a number of areas.

- CR both extends lifespan and lowers iron accumulation
- Iron is a reactive metal capable of causing oxidative damage
- Oxidative damage correlates with lifespan across species and is a major correlate of human aging
- Iron restriction also extends lifespan
- Many CR mimetics chelate and remove iron
- Increasing autophagy increases lifespan and allows for better iron homeostasis

If all this is true – and, while not the whole story, I believe it is – then keeping iron levels in low normal range could mimic many of the lifespan-
extending effects of calorie restriction.

Urgently needed are studies of iron restriction and lifespan in mammals, as well as further elucidation of the interactions between CR and iron.