

Adjourning Alzheimer's

Dietary Modification (Day 71)

Interest rapidly grows in the use of **dietary modification** to combat Alzheimer's. For many people, sticking to a modified diet is more difficult than taking a medication or embarking on a regular exercise program. However, compared to medications and even exercise, there are reasons to believe that the right dietary modification could substantially impact not only the symptoms of Alzheimer's, but also the pathological process itself.

There is a movie called *The Shawshank Redemption* in which a prisoner named Andy is desperate to escape the confines of his cell, yet is unable to overcome the thick stone walls that surround him; he is trapped. His friend, a fellow prisoner named Red, mentions that even an "impossible" wall can be breached if a person applies **enough pressure, for enough time**. Red states matter-of-factly, "That's all it takes really - pressure and time." We will apply Red's statement to the "impossible" disorder of Alzheimer's. In order to treat it, perhaps we need a therapy that focuses not so much on finding a medical magic bullet but on these two principles - pressure, and time.



Andy and Red.

First, **pressure**. Many medications treat disorders by targeting a single weak point, often a critical enzyme or receptor, resulting in a therapeutic effect. That's ok for some disorders - for example, the bacteria *Streptococcus pneumoniae* often triggers pneumonia (an acute lung infection). The antibiotic, penicillin, targets an enzyme in the bacteria's cell wall, which kills the bacteria and resolves the pneumonia. However, **Alzheimer's probably has no single weak point**; it is complex and involves tau accumulation, mitochondria dysfunction, microtubule disassembly, and of course, impaired brain insulin signalling. A single-target therapy won't work; we need a **multi-target therapy** that can alter the Alzheimer's by exerting pressure on many levels.

Second, **time**. Many of our most effective medications are given over a short time course, usually a few days or weeks. That's ok for some disorders - for example, asthma (a chronic inflammatory disease of the airways) is partially alleviated by the corticosteroid, prednisone, which suppresses both the

inflammation and the immune cells involved in an asthma attack. When given for a few days or weeks, prednisone can be a powerful short-term fix for asthma (although it does not cure the asthma in the long-term). Since **Alzheimer's is an insidious, decades-long pathological process**, a blitzkrieg attack from even the most powerful medication probably won't work. We need a **sustained therapy**, one that slowly alters the Alzheimer's over time.

Dietary modification is **not a magic bullet**; many positive changes take weeks or months to appear, and the short-term adverse effects can be challenging to deal with until the person adapts to a new diet. However, in the long-term, dietary modification has the right tools to combat a complex, longstanding disorder like Alzheimer's. The right dietary modification can attack Alzheimer's from hundreds of different angles, altering the epigenetic expression of genes that have been silenced for decades through enzymes such as AMPK, a master regulatory enzyme that reawakens genes involved in cell energy conservation, survival, and autophagy (a process by which cells recycle "junky" proteins so they can be used for energy). Moreover, the right dietary modification can sustain this attack on the core pathological process of Alzheimer's for months or even years, as long as the person sticks to the diet and is free of long-term adverse effects. But what is the "right" diet for Alzheimer's?

To answer this crucial question, let's focus on **impaired brain insulin signalling**, since it is close to the origin of Alzheimer's and influences all the other major events. In Alzheimer's (or if you prefer, type 3 diabetes) brain insulin and insulin receptors are both reduced 80-90%, resulting in a significant 20-40% shortfall in neuron glucose metabolism. There's an "impenetrable" wall separating neurons from their major fuel, glucose - or is it really impenetrable?



Andy stares at the wall of his cell; for a person with Alzheimer's, a big part of that wall is impaired brain insulin signalling, blocking neurons from their main fuel, glucose.

Generally, when there is a big wall in the way, your two options are to either go through the wall, or circumvent the wall. If there is a right diet in Alzheimer's, then in addition to altering epigenetic gene expression it probably needs to do one of two things - either produce a sustained increase in brain insulin levels, **pushing through** the impaired insulin signalling pathway, or provide a sustained level of an alternative fuel, **circumventing** the impaired insulin signalling pathway.

If we want to **push through** the impaired brain insulin signalling pathway, then **diets high in natural carbohydrates and low in fats** make sense. Carbohydrates increase insulin levels more than proteins or fats. Large observational studies show that three high-carbohydrate, low-fat diets are associated with cognitive improvements - the Japanese diet, a “healthy” diet, and the Mediterranean diet.

The **Japanese diet** is roughly 20% fat, 20% protein, 60% carbohydrate by energy intake (10% fat, 20-25% protein, 65-70% carbohydrate by weight) and is supported by the 2013 Hisayama Study, a large observational study in which 1006 elderly Japanese people were followed over 15 years. People who ate more vegetables, soybean products, dairy, algae, and fruits developed less dementia.

A **“healthy” diet** is roughly 30-40% fat, 20% protein, 40-50% carbohydrate by energy intake (20-25% fat, 25% protein, 50-60% carbohydrate by weight) and is supported by a 2012 French observational study in which 3054 patients were followed over 13 years. People who ate more fruits, vegetables, fish, fresh dairy, whole grains, cereals, vegetable fats, nuts, and tea retained better cognition.

The **Mediterranean diet** varies depending on who you speak with, but it is roughly 30-40% fat, 20% protein, 40-50% carbohydrate by energy intake (20-25% fat, 25% protein, 50-60% carbohydrate by weight) and is supported by many observational studies, including a 2010 meta-analysis of 17 major observational studies of over 2 million people. People who ate more fruits, vegetables, potatoes, beans, fish, poultry, cereal, bread, olive oil, and nuts had less neurodegenerative disease.

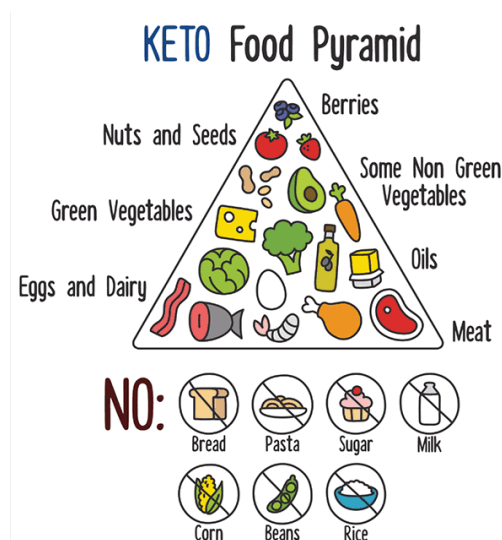


High-carbohydrate, low-fat diets for people with cognitive impairment are supported by plenty of observational evidence, but this can only prove correlation - not causation.

Alternatively, if we want to **circumvent** the impaired brain insulin signalling pathway, **ketogenic diets high in fats and low in carbohydrates** might be the way to go. The reason for this is that if a person’s fat intake is high enough and their carbohydrate intake low enough for several days or longer, their liver takes all the extra fat and convert much of it into ketones, energy molecules that the brain and most of the rest of the body can utilize for energy as an alternative to glucose. Interestingly, Alzheimer’s neurons **utilize ketones just as efficiently** as those of a cognitively normal person; thus, ketones could provide the extra energy that Alzheimer’s neurons need. Two small interventional studies suggest that ketogenic diets may improve cognition in people with cognitive impairment and Alzheimer’s.

A 2012 randomized controlled study by Robert Krikorian and colleagues compared a **high-fat, low-carbohydrate diet against a low-fat, high-carbohydrate diet** in 23 people with mild cognitive impairment (MCI) for 6 weeks. The high-fat, low-carbohydrate diet was 60% fat, 25% protein, 15% carbohydrate by energy intake (40% fat, 40% protein, 20% carbohydrate by weight). The low-fat, high-carbohydrate diet was 35% fat, 15% protein, 50% carbohydrate by energy intake (19% fat, 18% protein, 63% carbohydrate by weight). By the end of 6 weeks, the high-fat, low-carbohydrate group has a slight improvement in verbal memory. Unfortunately, the diet in this study was high-fat but only borderline ketogenic, and the high-fat, low-carbohydrate group ate less calories and lost more weight than the other group, so the improvement *may* have been partly due to reduced calorie intake.

In 2018, a single-group study by **Matthew Taylor** and colleagues examined the effects of a **ketogenic diet** in 15 people with mild to moderate Alzheimer's for 12 weeks. The diet was 70% fat, 20% protein, 10% carbohydrate by energy intake (50% fat, 30% protein 15% carbohydrate by weight). Ten people completed the 12-week study and had a small but clinically significant improvement in cognition. Notably, the ketogenic diet used was rather weak, and - crucially - there was no control group.



Ketogenic diets for people with cognitive impairment are thinly supported, by two small interventional studies (figure sourced from www.keystokeketosis.com).

So, what is the **right diet** for Alzheimer's? Tough to say with current evidence. The high-carbohydrate, low-fat Japanese, "healthy," and Mediterranean diets are supported by observational studies, but remember - observational studies can tell us that a particular diet is **associated** with less cognitive impairment and Alzheimer's, but they cannot tell us whether that diet **caused** the decrease in cognitive impairment and Alzheimer's. In contrast, although ketogenic diets are supported by two interventional studies - which can discover causation - both studies were small in numbers, contained methodological flaws, and employed relatively weak ketogenic diets.

Let's sum up. Dietary modification may play a crucial role in determining whether a person develops Alzheimer's, and certain diets may be able to improve the cognitive symptoms of the disorder, but **the**

evidence is weak as to which diet might be best at doing so. However, given that a dietary modification can theoretically impact a complex, longstanding disorder like Alzheimer's by applying multi-targeted metabolic and epigenetic pressure over a sustained period of time, the right diet **may significantly impact the Alzheimer's pathological process**. To discover whether that right diet exists, we must conduct properly-designed randomized controlled studies.

Sticking to a modified may be difficult for some people, but success at doing so can **take you right to the edge**, the place where you challenge yourself. Dietary modification bears the potential to reclaim a substantial amount of your epigenetic power, reawakening many of the anti-Alzheimer's genes that we must unleash against the pathological process. Given the tantalizing promise that dietary modification holds in treating Alzheimer's, I sincerely hope you will join us for the **Alzheimer's Dietary Study** over the next several months, where we will try to reawaken your epigenetic power. Let's look at one last important class of potential therapies before we do.

Matt (Neurologist, Waikato Hospital).

References

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