

Dementia: Is Gluten the Culprit?

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Editor's Note:

In his new book [Grain Brain: The Surprising Truth About Wheat, Carbs, and Sugar -- Your Brain's Silent Killers](#), Dr. David Perlmutter, Associate Professor at the University of Miami School of Medicine, advocates that lifestyle modifications, starting with a high-fat, nearly carbohydrate-free diet, can prevent or greatly lower dementia risk and progression -- and he's armed with plenty of data to back up the claim. But detractors say the evidence isn't quite there. With Grain Brain about to hit its 15th straight week on the New York Times best-seller list (including a stint at the top spot) Medscape spoke with Dr. Perlmutter about his thoughts on the impact of carbohydrates and gluten on the brain.

Medscape: For those unfamiliar with your ideas, can you summarize the thesis behind your new book and how you arrived at it?

Dr. Perlmutter: Certainly. I'm a board-certified neurologist and a fellow of the American College of Nutrition. I've been very frustrated with neurology over the past 20 years, because we're trained in residency and practice to basically treat symptoms of neurologic disorders. I found that not to be satisfying and thought it was important to delve into causality as opposed to just focus on treating the smoke and ignoring the fire.

That said, with time we began seeing wonderful research citations that were drawing a link between risk for dementia, for example, and blood sugar levels appearing in our most well-respected journals. For example, a study published in *Neurology* in 2005^[1] pointed a finger squarely at the most powerful metric being glycated hemoglobin. Even back then, it was becoming clearer that there was something going on with blood sugar correlating with rate of brain atrophy, specifically hippocampal atrophy, and cognitive decline. When you now retrospectively evaluate that study, you begin to appreciate that glycated hemoglobin is more than just a metric of average blood sugar, which is typically how it's looked upon even today.

Glycated hemoglobin is a glycated protein. This is a marker not just of average blood sugar, but more important, it's a marker of the degree of glycation that's going on in human physiology -- a process that increases inflammation and dramatically increases the production of free radicals and oxidative stress. So the idea that even subtle elevations of sugar, which is a dietary lifestyle choice, are related to risk for brain degeneration really began to crystallize.

This notion has gained traction and, I think, is profoundly supported by a couple of more recent studies. A study published in August 2013 in the *New England Journal of Medicine* (NEJM)^[2] was very supportive, indicating that even subtle elevations of fasting blood sugar translates to dramatically increased risk for dementia. This was a prospective analysis that measured fasting blood sugar and followed 839 men and 1228 women for a mean of 6.8 years. I'll quote the conclusion: "Our results suggest that higher glucose levels may be a risk factor for dementia, even among persons without diabetes."

Why? These are levels of 105 and 110 mg/dL -- levels that most doctors are going to be satisfied with. However, according to the study, these numbers translated into a significantly increased risk for dementia in individuals who were not demented.

Medscape: That is striking. However, I think it's important to point out that many of the studies you cite report associations between glucose and risk for dementia and don't necessarily prove causality, correct?

Dr. Perlmutter: You are 100% correct. I'll stand and take my lumps from those individuals who want to make the argument that there's no smoking gun here. But when a prestigious journal like NEJM calls our attention to this relationship effect in glucose and cognitive decline, we've got to take notice, especially at a time when we have no other choice. It's the best thing that we have going.

We know that a lower-carbohydrate diet is the right choice for the heart and the immune system. There's no downside to it. I offer it up as being supported by the current peer-reviewed literature. If that's as good as it gets, that's the best we have right now.

You can wage criticism that the NEJM study was not interventional. It wasn't a double-blind study testing some sort of pharmaceutical intervention. It was a prospective study that basically asked who's going to get dementia on the basis of fasting blood sugar levels.

Some people criticize prospective or even retrospective studies because they're not interventional. I tend to think that they can provide very, very valuable information. There's never been an interventional trial that's demonstrated that seatbelts are effective in reducing injuries in a car accident.

The Dementia Diet

Medscape: What type of diet or interventions do you recommend to prevent or slow dementia?

Dr. Perlmutter: The data show that individuals with lower blood sugar levels have a lower risk for dementia. Therefore, we've got to keep blood sugar low. We do so by using the time-honored dietary intervention of a lower-carbohydrate, higher-fat diet.

This is what the scientists have told us for years is the best way to lower blood sugar. If you look at the A TO Z trial, which was published in *JAMA* in 2007,^[3] dramatic reductions in blood sugar were seen in participants on a lower-carb, higher-fat diet.

A similar article was published in NEJM in 2008.^[4] This was an interventional trial demonstrating both weight loss and reduction of fasting blood sugar in individuals eating a higher-fat, lower-carbohydrate diet.

The Mayo Clinic published a study^[5] in the *Journal of Alzheimer's Disease* in 2012 demonstrating that in individuals favoring a high-carb diet, risk for mild cognitive impairment was increased by 89%, contrasted to those who ate a high-fat diet, whose risk was decreased by 44%. Drs. Barnes and Yaffe from the University of California, San Francisco, published a study in *Lancet Neurology* in 2011^[6] indicating that about 54% of cases of Alzheimer disease in the United States could have been prevented with attention to lifestyle changes, such as exercise, weight loss, and controlling hypertension.

This province of lifestyle modification in neurologic diseases has not been one of comfort for neurology in general. We neurologists are acting in an essentially reactionary manner. In other words, we are responding to illnesses by hoping that there are medications to treat symptoms,

whereas we really ought to embrace the notion of preventive medicine, because the science is staring us in the face.

Medscape: One of the points in your book I found interesting is that you're not just talking about processed carbohydrates or sugars here, right? You believe that whole grains -- typically presumed healthy -- also increase dementia risk?

Dr. Perlmutter: Yes, they do. There's a lot of very good information provided on the glycemic index of these foods. That is a metric of not only just the elevation of blood sugar and the consequence of consuming a particular food, but actually it's also a measurement of how long the blood sugar remains elevated.

The glycemic index measures what the blood sugar is between 90 and 120 minutes after consuming a particular food. When you look at the glycemic index of whole-grain bread, for example, it's extremely high: 72-74. It's higher than that of white bread. It's much higher than that of many candy bars. It becomes a huge issue in terms of how long your blood sugar remains elevated -- that is, how long you have increased risk for glycation of proteins. It becomes a big issue that we have to reconsider these recommendations about whole grains in terms of the simple fact of looking just at the glycemic index.

Medscape: Does the same go for other grains common in health foods these days, such as flax and quinoa?

Dr. Perlmutter: Flax and quinoa (which by definition is actually not a grain) are gluten-free foods rich in fiber and healthful fat. However, they do contain modest amounts of carbohydrate, and assessing these foods by evaluating their glycemic indices will help decide how healthful they really are.

Giving Up Gluten, and the Paleo Diet Fad

Medscape: Why do you feel that gluten is particularly detrimental to our brain health?

Dr. Perlmutter: Gluten-containing foods stimulate inflammatory reactions in a significant number of individuals, well beyond the 1.8% of the population that has celiac disease. This may lead to increased bowel permeability and even increased blood/brain barrier permeability, as described by Dr. Alessio Fasano (formerly at the University of Maryland, now at Harvard).^[7] The mechanism deals with the expression of the protein zonulin brought on by gluten exposure. What is so compelling about this newer research is the fact that this reaction to gluten may occur in *all* humans.

This may explain to some degree the array of neurologic issues now correlated with gluten sensitivity in nonceliac patients, as described by Dr. Anna Sapone and colleagues.^[8] So we have to look at gluten sensitivity in a new light, recognizing that its manifestations may extend well beyond the gut. Writing in the *Journal of Neurology, Neurosurgery & Psychiatry*,^[9] Dr. Marios Hadjivassilou stated, "That gluten sensitivity is regarded as principally a disease of the small bowel is a historical misconception. Gluten sensitivity can be primarily and at times exclusively a neurological disease."

That said, many people shop the gluten-free aisle of the grocery store, thinking that those gluten-free breads, pastas, pizza doughs, crackers, and so on are much better because they're gluten-free. The bottom line is these are still powerful sources of carbohydrates.

Even fruit is a source of aggressive carbohydrate in the human diet. Take a simple 12-ounce glass of freshly squeezed orange juice -- what could be better, right? As a matter of fact, that's about 34-36 grams of pure carbohydrates. That's 9 teaspoons of pure sugar with breakfast before your breakfast cereal has even arrived.

My recommendation is to try to keep the total carbohydrates per day to 60-80 grams. If you have 2 glasses of orange juice, you've already consumed 72 grams of pure carbohydrate.

It's really fundamentally important that we address this mechanism of glycation of proteins as being a cornerstone of brain degeneration pathology, and recognize that beta-amyloid itself is a protein that can become glycated and as such can become a powerful nexus for the production of free radicals in inflammation.

We have watched with dismay over the past several years the failure of the drugs designed to rid the brain of beta-amyloid. Most recently, as published in NEJM,^[10] a higher dosage of the experimental drug semagacestat was associated with increased cognitive decline of individuals compared with placebo.

Medscape: How does your diet compare with the paleo diet -- the idea that we should be following the presumed diet of Paleolithic humans?

Dr. Perlmutter: They are very similar. It's basically focused on very low carbohydrates and the aggressive addition of good fats: by all means, avoiding modified fats, trans fats, and hydrogenated modified fats, but welcoming back to the table such things as extra virgin olive oil, nuts, seeds, and grass-fed beef (not typical beef).

My diet is not a big beef, go out and eat a lot of meat, kind of diet. When Drs. Campbell and Campbell published *The China Study*^[11] about the possible health consequences of eating meat, their report was valid because by and large, the type of meat that people are eating is derived from animals that have been fed genetically modified corn and soy and high levels of omega-6 fatty acids, which are proinflammatory. Therefore, clearly the idea that there's a relationship between that type of meat consumption and cardiovascular disease, and even cancer, is valid.

We're talking about specifically small amounts of grass-fed beef and wild fish. We're moving the meat, chicken, and fish away from being the centerpiece of the meal to being the side dish, the garnish. Lots of above-ground leafy green vegetables, colorful vegetables, and welcoming back good fats, because that's what the brain is desperate for.

Medscape: So, it's in line with a review published by the American Society for Nutrition^[12] last year, as well as other recent data^[13] suggesting that a little saturated fat, particularly from free-range red meat, might not be so bad for our brain health and may protect against anxiety and depression?

Dr. Perlmutter: Absolutely. And not just from grass-fed beef, but from the dreaded egg as well. There is no relationship in the current peer-reviewed literature between egg consumption and cardiovascular risk -- none whatsoever. Yet, there is still the ubiquitous egg-white omelet on every restaurant menu that you can find.

Diet Isn't Everything

Medscape: There are a lot of data on other lifestyle factors with benefits in dementia -- physical activity and mental and social stimulation in particular. How much weight do you give these nondietary factors?

Dr. Perlmutter: We were all over exercise in *Grain Brain*. One of the notions that I think is very, very empowering and compelling is the idea of neurogenesis -- that humans retain the ability to grow new neurons in the hippocampus throughout our entire lifetime. We can enhance our ability for this activity through the process of epigenetics.

A study published in *Proceedings of the National Academy of Sciences* in 2011 showed that we can actively modify the gene for the production of brain-derived neurotrophic factor (BDNF) with simple exercise.^[14] The investigators looked at 120 elderly nondemented individuals over a 1-year period who either stretched or did aerobics. They measured 3 variables: serum BDNF levels, memory function, and morphometric analysis of hippocampal size on MRI before and after the intervention period. After 1 year, the group that did the aerobic exercise had an increase in hippocampus size by about 1%, improvement of memory function, and higher levels of serum BDNF.

What is so incredible about that is there is no pharmaceutical that can do that. Believe me, you would have probably the world's most valuable pharmaceutical if you could develop a drug that would do that. Plain old physical exercise, nonproprietary. No one owns it. That's why you don't hear about this on the evening news. It's not advertised in our medical journals. Just aerobic exercise improved memory, grew the hippocampus, and raised BDNF levels -- which beyond neurogenesis also stimulates neuroplasticity, which is fundamental for learning. How incredible that you can modify the growth of your brain today by engaging in aerobic exercise! All you need to go out and buy is a pair of sneakers.

The Obama administration just dedicated \$33 million to help pharmaceutical companies develop an Alzheimer disease prevention pill, and yet this article has already been published showing preservation of hippocampal size and function -- in fact, regeneration of hippocampal size and function.

A Whole-Grain Gripe

Medscape: What do you say to the fact that many global diets proven to be healthy -- particularly the Mediterranean diet, which is continually shown to be beneficial in numerous medical and mental conditions -- include whole grains? And that many of the world's so-called "blue zones" -- regions in which residents have notably long lifespans -- also include grains in their diets?

Dr. Perlmutter: I think people do tolerate some amount of grains, and that the classic Mediterranean diet is one that has added fat and lower carbs. Of note, an April 2013 article in *NEJM*^[15] compared a standard US diet with a Mediterranean diet supplemented with extra-virgin olive oil and a Mediterranean diet supplemented with mixed nuts. The investigators looked at 3 endpoints: myocardial infarction, stroke, and death. They had to stop the study halfway through it, at 4.6 years, because the individuals with the highest fat consumption had a 30% lower risk for the endpoints. It was unfair to the rest of the participants.

Can people get away with having some whole grain products? I suspect so. But you have to understand that wheat products represent 20% of our caloric intake in the United States. That's not

the way it is around the rest of the world. The Mediterranean diet, for example, does not pound people over the head with soda.

Medscape: How would you respond to your detractors that there just isn't enough evidence to support would could be considered a somewhat extreme change in our country's dietary habits?

Dr. Perlmutter: My response is that the "extreme change in dietary habits," to quote you, is actually what has happened to human nutrition in only the past several centuries. In the early 19th century, Americans consumed just over 6 pounds of sugar each year. That figure now exceeds 100 pounds. And there has been a dramatic reduction in the consumption of healthful fat. Beyond the mechanism of protein glycation, as well as the powerfully detrimental downstream effects of uncontrolled insulin signaling, we haven't even begun to understand the epigenetic consequences related to the effects of these new dietary challenges in terms of maladaptive genetic expression.

So in reality, I am not suggesting a change. I am recommending that we end this grand experiment and return to a diet that isn't evolutionarily discordant.

Medscape: Do you have any final comments for Medscape's audience of clinicians? How do you feel your ideas should be incorporated into patient care?

Dr. Perlmutter: Again, look at A1c in a different way. Rather than simply representing a metric of average blood sugar over a 3- to 4-month period, look at it as a way of modifying your pharmaceutical intervention; look upon it as a marker of what it really is, glycation of protein. That glycation of protein dramatically relates to inflammation and oxidative stress. That's number one.

Second, begin to incorporate a fasting insulin metric as a way of anticipating who's going to then develop elevations of fasting blood sugar and glycation of hemoglobin moving forward. The earliest sign of pancreatic stress is elevation of fasting insulin -- which ideally should be less than 8, not up to 24, which is what is in the so-called normal range.

Third, recognize that vitamin D is a powerful player in terms of brain health. Beyond strong and healthy bones, vitamin D activates more than 900 genes in human physiology, most of which are important for brain health. Low levels of vitamin D correlate with increased risk for multiple sclerosis, dementia, and Parkinson disease. Those are my 3 take-home messages.

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