DIET

Changing the recipe

Dietary changes may be able to alleviate the symptoms of multiple sclerosis, but testing the effects of diet will need a different protocol to the one used for drugs.

CATHY CLARKE/MOUNT SINAI HOSPITAL

Ilana Katz Sand (right) is trying to see whether dietary changes can benefit her patients.

BY SUJATA GUPTA

Ilana Katz Sand's grocery shopping list for people with multiple sclerosis (MS) includes fish, whole grains, nuts, almond milk, blueberries and carrots. It excludes milk, cheese, meat, crisps and foods containing refined flour or sugar.

Katz Sand, a neurologist and MS specialist at the Mount Sinai Hospital in New York City, says she came up with this diet after scouring the literature for studies, often in animal models, that found a correlation between a given food, supplement or dietary restriction and positive outcomes in MS.

But rather than looking at a single ingredient, or providing patients with ready-made, standardized meals, Katz Sand wants to let patients buy their own ingredients and prepare their food at home. "People are not mice," she says. "We can't put them in a cage and feed them exactly what we want to feed them."

And that's the problem. Hints have begun to emerge that dietary (and lifestyle) changes that reduce inflammation may help people to control their MS, but it is simply not possible to study diet in the same way as drugs. When researchers test a new drug, they divide people randomly into a treatment or a control group, blind all participants and investigators to that selection, and then provide a standardized amount of the drug or placebo for a set length of time. This highly regimented set-up, known as a double-blind, randomized, controlled trial, is the gold standard for drug research.

But it is almost impossible to standardize diets in this way, and participants always know which group they are in. Those in the control group have little incentive to wait around for months or years, leading to high dropout rates. Efforts are underway to establish a methodology for dietary studies, but it will take time to yield results. Meanwhile, in an environment that effectively favours pharmaceuticals over wellness initiatives, people with MS do not want to wait and are making dietary changes on their own — and it does not always help.

LOW FAT

The idea that people can treat MS by changing their diet has been around for more than half a century. One of the pioneers was neurologist Roy Swank, who, in the 1940s, studied the disease at the University of Montreal in Canada. He observed that MS was prevalent in the meat-eating countries of Europe and the United States, but was nearly absent in most of Asia, Africa and South America, where meat consumption was much lower. He found the perfect test case in Norway, where people living inland, who ate lots of meat and potatoes, had higher rates of MS than coastal residents, whose diet was based on fish. He sent a questionnaire to neurologists and hospital administrators in both regions and discovered that inland Norwegians were eight times more likely to develop MS than those on the coast.

In 1949, Swank put Norwegians with MS on a diet that involved eating less meat and milk products, but more fish. Other approved foods included a small amount of lean meat, eggs, nuts, cereal and skimmed milk. Swank studied 144 of the participants for several decades. In a 1990 analysis[1], he reported that when patients adhered to a diet of less than 20 grams of saturated fat per day, 95% of them were able to maintain normal activities for the next 30 years. When they deviated from the

diet, even after years of compliance, the disease invariably got worse.

But Swank's research was flawed by today's standards. When investigators for Cochrane Reviews, systematic reviews of primary research, looked at the purported link between diet and MS in 2012, they determined[2] that Swank's studies did not meet the inclusion criteria, says lead reviewer Mariangela Farinotti, a lab technician at the Carlo Besta Neurological Institute in Milan, Italy. Swank's studies lacked a control group and stringent screening criteria — and because imaging technologies were not available at the time, it is possible that some of Swank's patients did not have the disease at all. And crucially, during the fourth year of Swank's study, a large number of patients dropped out.

Even worse, Farinotti's team found that none of the studies included in the review showed an alleviation of MS symptoms. "We have no evidence about any kind of dietary treatment being effective on MS," Farinotti says.

VITAL VITAMINS

Despite this lack of evidence, many people with MS have latched onto the idea that lifestyle and dietary changes can help. Studies from Europe, Australia and the United States show that 50–75% of people with MS couple their pharmaceutical treatments with some form of complementary or alternative medicine.

Inflammation in MS occurs when the immune cells attack the nervous system, so any dietary and lifestyle changes known to reduce inflammation do make sense, at least in theory.

And the Cochrane review does not disprove the idea of dietary benefits for people with MS. Farinotti and her team excluded studies of vitamin D, for example, which has been linked to MS, as they were covered under a different review that showed some benefit of vitamin D, but in a study too small to justify making any recommendations. Moreover, because Farinotti's team limited their review to randomized, controlled trials, they examined only six studies, all investigating polyunsaturated fatty acids (PUFAs), which are found mainly in fish. No vitamin, antioxidant or holistic dietary studies made the cut.

This constraint makes some advocates of dietary therapy view the Cochrane review with suspicion. "We don't eat supplements, we eat food," says Terry Wahls, director of the Therapeutic Lifestyle Clinic at the Iowa City VA Hospital. Wahls, who has MS, has created an enormously popular diet for MS that is a variation on the low-grain, meat-heavy Palaeolithic diet, but is higher in vegetables and lower in meat.

Since the Cochrane review was completed, many studies, including some that would have met the reviewers' stringent criteria for inclusion, have shown promise in treating MS with dietary changes. Perhaps most striking is a series of studies that support the Cochrane review in debunking the belief that PUFAs found in fish oil pills can benefit people with MS, instead attributing those benefits to vitamin D. In 2012, a two-year Norwegian trial[3] involving 92 patients, in which half received fish-oil capsules and half were given a placebo, found no difference between the groups in terms of lesion number observed by magnetic resonance imaging (MRI), disease progression, fatigue levels or other measures of quality of life.

Earlier this year, researchers reported results of a study[4] in which 30 people with relapsing–remitting MS, a form that affects 85% of those initially diagnosed with the disease, received high doses of vitamin D. They were slightly less likely to experience relapses, and had fewer lesions visible on MRI scans, than the 23 control subjects.

Both vitamin D and PUFAs are high in certain species of fish, says Øivind Torkildsen, a neurologist at the University of Bergen in Norway, who was involved with both studies. "We were looking at the wrong compound."

"We don't eat supplements, we eat food."

Another study published this year[5] — a randomized, controlled trial of 61 patients — found that those who ate no animal products or took no supplements for a year (the McDougall diet, named after John McDougall, a doctor inspired by Swank) had lower levels of fatigue than those in the control group.

SMART DESIGN

These studies are starting to show that dietary changes can benefit patients with MS, but designing trials to test diets remains enormously challenging. Wahls had to make some difficult choices as she designed a trial to compare her high-fat, modified Palaeolithic diet with Swank's low-fat diet. The study, which is funded by a US$1 million grant from the US National Multiple Sclerosis Society, could shed light on the rift in the MS community over whether fat is good or bad for people with MS.

Wahls will observe 100 people with relapsing–remitting MS for 12 weeks before splitting them randomly into the Swank or the Wahls treatment. For 12 weeks, participants will receive dietary guidance for their allotted diet, followed by 12 weeks for them to follow the diet on their own. Wahls and her team will then use a questionnaire to measure fatigue levels. Because fatigue changes faster than mental clarity and gait, Wahls says, it is easier to study in the short term than other measures. To minimize drop-out, she opted against using a control group and will instead compare fatigue levels between the observation and treatment periods.

But George Jelinek, a neuroepidemiologist at the University of Melbourne in Australia, who like Wahls began studying the link between diet and MS after being diagnosed with the disease, thinks that the lack of a control group is a problem. "What if the diets are equivalent?" he asks. "It could be a placebo effect for both of them."

Even if the treatments both work equally well, the 12 week observation period serves as a proxy for a control group, Wahls says. "The best outcome," she says, "is that both diets are relatively equivalent, and they both do a greater job of reducing fatigue than during the observation period."

Meanwhile, at Mount Sinai, Katz Sand was grappling with the same issues as her colleagues as she sought to set up her own study. How was she going to measure participants' adherence to the diet, for instance? Should she jump on the high-fat or low-fat bandwagon? How could she stop people dropping out?

To sort out her methodology, Katz Sand designed a 30 person, 6 month pilot study that launched at the start of October. After some preliminary research, she opted to test a modified Mediterranean diet that is rich in whole grains, fruits, vegetables and healthy fats, such as those found in fish, nuts and avocados. She excluded foods that contain saturated fat, such as meat and cheese. She allowed vitamin D supplements, but only if participants fell below the established normal range.

People in the treatment group also receive intensive education about the diet and have regular meetings with a nutritionist. To measure adherence, participants must complete dietary questionnaires and have routine blood tests to measure their levels of salt, fatty acids and other nutrients. To discourage participants from dropping out, those in the control group will meet every month to discuss health and wellness issues in MS. Katz Sand has also implemented a modified waiting list control group, so that people assigned to the control group will be offered the same treatment (apart from the regular meetings and monitoring) as the test group at the end of the study.

The difficulties of studying wellness initiatives, such as changes to diet and lifestyle, affect the assessment of treatments for a wide range of conditions. But MS provides a measurable way to study the effect of diet on long-term health. Nicholas LaRocca, vice-president of health-care delivery and policy research at the National Multiple Sclerosis Society, hopes investigators will one day be able to show quantitatively how dietary changes alleviate the symptoms of MS.

In the meantime, if Katz Sand's methodology works, she will have helped to contribute to the development of a new gold standard for clinical trials that will let wellness-based treatments stand on an equal footing with their pharmaceutical counterparts. ■

Sujata Gupta *is a freelance science writer based in Burlington, Vermont, USA.*

1. Swank, R. L. & Dugan, B. B. *Lancet* **336,** 37–39 (1990).
2. Farinotti, M. *et al. Cochrane Database Syst. Rev.* **12,** CD004192 (2012).
3. Torkildsen, Ø. *et al. Arch. Neurol.* **69,** 1044–1051 (2012).
4. Muris, A.-H. *ECTRIMS Online Library* 146467 (2016).
5. Yadav, V, *et al. Mult. Scler. Relat. Disord.* **9,** 80–90 (2016).