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REVIEW ARTICLE

ALSUntangled #76: Wahls protocol

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Abstract

The Wahls diet is a modified Paleolithic diet that emphasizes dark green leafy vegetables, colorful fruits, high-quality animal proteins, and omega-3 polyunsaturated fatty acids, while limiting grains, legumes, dairy products, sugar, and processed foods containing proinflammatory omega-6 fatty acids. The Wahls diet may reduce inflammation, oxidative stress, and mitochondrial dysfunction and has plausible mechanisms for slowing amyotrophic lateral sclerosis (ALS) progression. However, research on its dietary components in the ALS animal models has yielded conflicting results. Though multiple cohort studies suggest high carotenoids, omega-3 fatty acids and fruit intake are associated with reduced ALS risks, neither the diet nor its components has been demonstrated to slow down ALS progression in case studies or clinical trials. On the contrary, the Wahls diet, a restrictive, low-carbohydrate and low glycemic index diet, caused an average weight loss of 7.2% BMI in multiple sclerosis clinical trials, which is a significant concern for people living with amyotrophic lateral sclerosis (PALS) as weight loss is associated with faster ALS progression and shorter survival. Considering the above, we cannot endorse the Wahls diet for slowing ALS progression.

Keywords: ALS, Wahls protocol, neuroinflammation, oxidative stress

ALSUntangled reviews alternative and off-label ALS treatments on behalf of people living with amyotrophic lateral sclerosis (PALS). Here, we review Wahls protocol for which we have received 245 requests.

Overview

The Wahls protocol was developed and experimented by Dr. Terry Wahls after she was diagnosed with multiple sclerosis (MS). In her book

“The Wahls Protocol: a radical new way to treat all chronic autoimmune conditions using paleo principles”, Dr. Wahls recounts her recovery from MS after implementing the Wahls diet, detoxification, neuromuscular electrical stimulation, and an exercise program. In this review, we will focus on the utility of the Wahls diet as a possible treatment for amyotrophic lateral sclerosis (ALS).

The basic principle of the Wahls diet is to create a modern resemblance of the Paleolithic (also known as hunter-gatherer) diet that humans ate for 500,000 years based on the geographic availability of food in the form of green leaves, fruits, roots, and meat before the development of agriculture and production of grains, legumes, and dairy. Wahls diet consists of multiple levels of dietary modifications and starts with nine cups of vegetables and fruits and 6–12 ounces of protein daily, preferably animal proteins. The nine cups are divided into three cups of cooked or six cups of raw dark green leafy vegetables, three cups of sulfur-rich vegetables and three cups of brightly colored vegetables and fruits. Wahls Paleo and Paleo Plus further limit or eliminate gluten-free grains and legumes, increase protein and specific fats intake and add seaweed and fermented foods. Wahls elimination is the most restricted version by further eliminating lectin-rich nightshade vegetables (e.g. tomatoes and eggplants) from the Paleo Plus diet.

Notably, the Wahls diet prohibits all gluten-containing foods, dairy products, eggs, processed meats, any foods sweetened with sugar, high-fructose corn syrup or artificial sweeteners, and vegetable oils high in omega-6 fatty acids. When compared to the average US diet, the Wahls diet is more nutrient-dense and contains higher levels of vitamins, minerals, essential fatty acids, and carotenoids (1).

Dr. Wahls has occasionally mentioned adding creatine to the Wahls protocol (Minding your mitochondria | Dr. Terry Wahls | TEDxIowaCity). After reviewing the literature, we found three randomized, double-blinded, placebo-controlled trials on creatine monohydrate in a total of 386 ALS patients, and 5–10 g creatine daily treatment did not show benefit in preserving motor function, slowing disease progression, or prolonging survival compared to placebo (2–4). The clinical trial data were well summarized in the previous Cochrane Review 2012 (5). Another small trial did not show benefit of creatine on respiratory muscle function in ALS (6). Given the consensus on its lack of efficacy in ALS, we will not discuss creatine further in this review.

Mechanistic plausibility

The ALS-relevant mechanisms possibly addressed by the Wahls diet include neuroinflammation, oxidative stress, and mitochondrial dysfunction.

Neuroinflammation plays a critical role in ALS progression. Studies have shown increased proinflammatory T lymphocytes and serum biomarkers called cytokines and a reduction of their anti-inflammatory counterparts in ALS patients' peripheral blood, and this shift correlates with disease severity (7, 8). Microglia, the innate immune cells in the central nervous system, are anti-inflammatory and neuroprotective in early ALS but convert to a proinflammatory state and contribute to neurotoxicity as ALS advances (8, 9). Since the Wahls diet restricts the intake of proinflammatory omega-6 fatty acids (10) and processed foods, it has the potential to reduce inflammation. However, inflammatory biomarkers have not been directly studied in Wahls diet-related clinical trials. A systematic review and meta-analysis of randomized controlled trials in MS on the effects of dietary interventions on inflammatory biomarkers is currently underway (11).

Various environmental toxins and ALS causal genes such as C9ORF72, SOD1, TARDBP, and FUS mutations affect motor neuron mitochondrial function and lead to oxidative stress (12–15). Therefore, oxidative stress and mitochondrial dysregulation are central to ALS pathogenesis. Edaravone, an antioxidant, has been used for ALS and modestly slows disease progression in a subset of ALS population (16). The Wahls diet is enriched (relative to the typical American diet) with carotenoids and other antioxidants. One such carotenoid, astaxanthin, acts as reactive oxygen species scavenger (17). Studies have shown that astaxanthin, beta-carotene, and lutein have antioxidant effects in a mouse cell model of bacterial infection. Recently, astaxanthin was also found to enhance mitochondrial function (18).

Given its anti-inflammatory and anti-oxidative effects and the potential relevance to ALS pathogenesis, ALSUntangled assigns TOE “Mechanism” grade of C (Table 1).

Preclinical

We did not find studies investigating the Wahls diet in its entirety in ALS animal models but did find research data on various dietary components enriched in the Wahls diet; the results were conflicting.

One study using the G93A SOD1 ALS mouse model found that increased extra virgin olive oil (EVOO) intake was associated with a prolonged lifespan (142.87 ± 2.92 days) compared to a control diet (127.5 ± 4.47 days) and better motor functions (19). On the contrary, another study using the same mouse model showed the mice started on a high omega-3 polyunsaturated fatty acid diet at the pre-symptomatic stage had faster ALS progression and shorter life spans. Histology

Table 1. Evidence for Wahls protocol.

	Grade	Explanation
Mechanism	C	The Wahls dietary components have anti-inflammatory and anti-oxidative effects which are potentially relevant to ALS pathogenesis.
Pre-clinical	U	No pre-clinical study on the Wahls diet has been conducted. One dietary component, extra virgin olive oil, is associated with prolonged survival; the other component, omega-3 polyunsaturated fatty acid, leads to faster progression and shorter life span. Carotenoids containing tomato-enriched foods shows no benefit.
Cases	U	No published case study on the Wahls diet; no PALS in the PLM community has tried the diet.
Trials	U	No clinical trials has been done in PALS
Risks	C	At least 10% of patients exposed to the Wahls diet in MS clinical trials experienced significant weight loss. This is especially problematic for PALS as weight loss is associated with accelerated disease progression.

in these mice showed widespread vacuole formation (indicating tissue injury) in their spinal cord compared to the typical confined vacuolization in the ventral horns of SOD1 mice fed with a regular diet (20).

Carotenoids containing tomato-enriched food did not show survival benefit in the G93A SOD1 ALS model (21). The mice were randomly assigned to have a tomato-enriched or control diet at the age of day 29. The mean survival time did not show difference between these two groups (179.4 vs. 185.3 days). Notably, the measurement of serum carotenoids in the tomato-based diet group showed undetectable level of beta-carotene and lutein, two key carotenoids associated with better motor function and lower ALS risk in human studies (see section “Cases”), which may explain its lack of survival benefit.

We advise our readers to exercise caution when attempting to apply the data from the EVVO study directly to the Wahls diet; the diet as a whole contains many more components that may interact and offset each other, and how it may affect the motor function and survival in the ALS animal models is unknown. Therefore, ALSUntangled assigns TOE “Preclinical” grade of U.

Data in PALS

Cases

We did not find published ALS case studies or PALS online who reported trying the Wahls diet. Based on this lack of information, ALSUntangled assigns a TOE “Cases” grade of U.

Interestingly, several groups studied the association between macro- and micronutrients enriched in the Wahls diet and ALS progression and the risks of developing ALS. In the longitudinal ALS Multicenter Cohort Study of Oxidative Stress (ALSCOSMOS study), cross-sectional data indicated participants (302 PALS) who had a high intake of antioxidants and carotenoids had better function on ALSFRS-R at baseline (i.e. at the time of the study entry) after controlling for age, sex, disease duration, calorie intake, and BMI. Further analysis using the weighted quantile sum regression method identified lutein, zeaxanthin (both carotenoids), and omega-3 fatty acids to be associated with high baseline ALSFRS-R scores (22).

A Japanese epidemiology study of 102 PALS and 306 gender- and age-matched controls found that higher consumption of fruits and vegetables was associated with a lower risk of ALS after adjustment for age, sex, BMI, total energy and smoking and drinking habits. Additionally, the study found a significant inverse relationship between beta-carotene and ALS risk (23). A study in the Korean ALS population showed a similar negative association between fruits and beta-carotene intake and ALS risks (24).

Further, a pooled analysis of five large prospective cohorts of over 1 million people (the National Institutes of Health AARP diet and Health Study, the Cancer Prevention Study II Nutrition Cohort, the Multiethnic Cohort, the Health Professionals Follow-up Study, and the Nurses’ Health Study) found high intake of carotenoid (beta-carotene and lutein) enriched foods and omega-3 fatty acid were associated with reduced ALS risk (25, 26).

In summary, although greater intake of foods enriched with carotenoids and omega-3 fatty acid nutrients appears to correlate with low ALS risks and better motor function at the time of ALS diagnosis, its association with ALS progression is yet to be demonstrated.

It is also important to note that these observational studies do not establish a causal relationship between specific nutrient intake and ALS risks and function, as the results may be confounded by various uncontrolled factors such as participants’ socioeconomic status and environmental exposures.

Trials

We found one registered clinical trial (NCT 03659422) titled: a dietary approach to improve quality of life in ALS. However, the trial was withdrawn due to lack of funding, and no data are available.

Since there have been no completed trials of the Wahls diet on PALS, ALSUntangled assigns a TOE “Trials” grade of U.

Risks

In an open-label multimodal intervention study (27) involving patients with secondary progressive multiple sclerosis, 10 patients were placed on the Wahls diet for 12 months. Four participants showed $\geq 10\%$ weight loss from baseline, and among them, one lost 23.9%, which was attributed to leukemia. The average weight loss over 12 months was 7.7% of BMI. This is a worrisome side effect for PALS as two-thirds of the population already experience weight loss at the time of the diagnosis, and it is well-established that weight loss and low BMI are associated with fast ALS progression (28–30). One study found that every 10% increase in weight loss increased the risk of death by 23% (28).

In addition, mild to moderate gastrointestinal symptoms were reported in some participants and were attributed to concomitant dietary supplements. These adverse effects resolved after supplement discontinuation.

In the WAVES trial, no serious adverse events were reported in the 43 relapsing remitting MS patients who were on the Wahls diet for 24 weeks (31). Notably, the study excluded patients with BMI $< 19 \text{ kg/m}^2$.

The nutritional adequacy study showed that the Wahls elimination diet met or exceeded the recommended dietary allowance (RDA) for most nutrients except vitamin D and calcium (32). MS patients on the Wahls diet for 12 weeks exhibited inadequate calcium, thiamin, and vitamin B12 intake and required dietary supplements (33). The potential consequences of these vitamin deficiencies are particularly troublesome for PALS, who are already at higher risks of falls, bone fractures and cognitive decline. Among the aforementioned risks, we are most concerned about its low-carbohydrate and low-glycemic index nature, which may be the main reason for weight loss. The dietary research in PALS demonstrated that a high-carbohydrate high-caloric diet was better tolerated than high-fat high-caloric diet and associated with less adverse events including fewer death in a small randomized controlled trial (34). A new study found that a high glycemic index and glycemic load diet was associated with slow ALS progression (35).

In addition to the identified risks above, there are likely additional unmeasured risks that vary for the individual. These additional risks may include limiting the social capacity of diet flexibility, leading to potential isolation or anxiety when deviation from the restricted protocol happens, demanding time and mental energy, and taking these away from activities that may be preferable to an individual.

Based on the risks identified in MS studies, ALSUntangled assigns TOE “Risks” grade of C. However, the risks in PALS are anticipated to be more severe.

Conclusions

Because components of the Wahls diet may affect inflammation, oxidative stress and mitochondrial dysfunction, it has plausible mechanisms for slowing ALS. Although a cross-sectional study suggests the intake of certain macro- and micronutrients enriched in the Wahls diet was associated with better baseline motor function and lower risk for getting ALS, no case reports or clinical trials are showing the Wahls diet affects disease progression or survival in PALS. On the contrary, the clinical trial in MS patients showing significant weight loss and essential vitamin and mineral deficiencies raises serious concerns; two thirds of PALS already experience weight loss at the time of diagnosis, and weight loss is a strong predictive factor for fast disease progression and shorter survival. Therefore, we cannot endorse the Wahls protocol for slowing ALS progression.

Declaration of interest

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