Research Article

Changes in nutrient intake and inflammation following an anti-inflammatory diet in spinal cord injury

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Objective: The objective of the current study was to describe the observed changes in nutrient intakes following a 3-month anti-inflammatory diet, and to explore potential relationships between the change in nutrients and the change in various inflammatory mediators.
Design: A secondary analysis of a prior randomized controlled clinical trial.
Setting: Individuals with SCI within the Niagara region.
Participants: Twenty individuals with various levels and severities of SCI.
Intervention: Three-month anti-inflammatory diet.
Outcome Measures: The change in nutrient intake and corresponding changes to various inflammatory mediators.
Results: The treatment group demonstrated a significant reduction in fat intake ($P = 0.02$), a significant increase in protein intake ($P = 0.02$), and no change in carbohydrates ($P = 0.23$) or energy intake ($P = 0.10$). The treatment group showed a significant increase in some nutrients with established anti-inflammatory properties including vitamins A, C, and E, and omega-3 fatty acids ($P < 0.01$). Significant reductions in proinflammatory nutrients were observed including trans fatty acids ($P = 0.05$), caffeine ($P < 0.01$), and sodium ($P = 0.02$). The treatment group also showed significant reductions in the proinflammatory mediators interferon-γ ($P = 0.01$), interleukin-1β ($P < 0.01$), and interleukin-6 ($P < 0.05$). Further, several proinflammatory mediators were negatively correlated with anti-inflammatory nutrients, including vitamin A, carotenoids, omega-3 fatty acids, and zinc.
Conclusion: This study provides evidence that dietary alterations are effective at reducing chronic inflammation in individuals with SCI and provides a preliminary assessment of the related nutrient changes.

Keywords: Spinal cord injury, Anti-inflammatory, Inflammation, Diet, Cytokines, Nutrient

Introduction

Spinal cord injury (SCI) is associated with drastic changes to various physiological systems which commonly contribute to immune dysfunction and a chronic low-grade inflammatory state.[1] As a state of chronic inflammation has now been shown to influence many conditions which are highly prevalent following SCI (eg. obesity, diabetes, cardiovascular disease, depression, neuropathic pain, edema),[1] it is important to explore the efficacy of safe and sustainable anti-inflammatory treatment options for this population.

Participation in regular exercise is one such option which has been shown to be anti-inflammatory in nature.[2] However, there are certain barriers to exercise participation, such as those related to transportation, immobility, musculoskeletal injuries, and common secondary health complications,[3] that make adherence difficult. Dietary manipulation aimed at reducing systemic inflammation could complement the anti-inflammatory benefits of exercise and help compensate during times whereby barriers related to exercise make participation difficult.

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DOI 10.1080/10790268.2018.1519996

A number of foods and supplements such as omega-3 fatty acids, carotenoids, flavonoids, and tocopherols have been shown to have anti-inflammatory properties when examined in able-bodied individuals.[4,5] The anti-inflammatory nature of such nutrients may be related to the intracellular influence on a protein complex known as nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB). Following its translocation to the nucleus, NFkB plays a role in cytokine production. As free radicals have been shown to increase NFkB activation, the antioxidant nature of tocopherols, flavonoids, carotenoids, and omega-3 fatty acids may help reduce cytokine production.[6–9] Diets rich in foods of plant origin, such as vegetables, fruits, whole grains, and nuts, have been shown to be inversely related to serum levels of inflammatory mediators (pro-inflammatory cytokines interleukin (IL)-1β, IL-6, interferon gamma (IFN-y), tumor necrosis factor alpha (TNF-α), C reactive protein (CRP)) and homocysteine.[4,10] These results have been consistent among both adult[5] and adolescent[10] populations, as well as within ethnically diverse populations.[5] Following SCI, energy expenditure and nutritional requirements typically change drastically[11] resulting in a decline in nutritional status as a result of altered metabolism and changed lifestyle practices.[11–13] Despite the evidence for increased nutritional issues following SCI, and the efficacy of anti-inflammatory foods and supplements in able-bodied individuals, there is a scarcity of research relating to the effects of long-term dietary interventions in this population. Prior research has predominantly included observational studies[14,15] and the assessment of acute dietary alterations.[16]

As such, the primary purpose of this paper was to describe the observed changes in various macronutrients and micronutrients following a 3-month anti-inflammatory diet and explore potential relationships between the change in nutrients and the change in various inflammatory mediators.

Materials and methods

Study design and participants

This study was performed as a component of a larger clinical trial which included the examination of depression,[17] neuropathic pain,[18] cognitive impairment,[19] and somatic nerve function[20] in participants with SCI before and after a strict 12-week dietary intervention specifically designed to decrease systemic inflammation. Data pertaining to the change in inflammatory mediators has been previously published.[18] A detailed description of the study design and participants has been previously reported.[18] Briefly, the study randomized participants with varying levels and severities of SCI to either an anti-inflammatory diet or control group. The intervention included assessments at baseline, 4 weeks, and 12 weeks. Participant characteristics are shown in Table 1.

Anti-inflammatory dietary intervention

The intervention consisted of dietary alterations with the overall intent to decrease inflammation. Participants in the intervention group were instructed to eliminate foods associated with common food intolerances and those which may elevate levels of inflammation, as well as increase their intakes of foods and supplements with established anti-inflammatory properties. For example, foods considered to be inflammation-inducing were those with high glycemic indices,[21] such as refined wheat products and refined sugars. Food which could influence levels of inflammation by negatively influencing cardiovascular health, such as those containing hydrogenated fats[22] were also removed. Finally, as it was not feasible to test all participants for all possible food intolerances, common food intolerances such as cow's milk and peanuts, were removed. Table 2 shows a detailed list of foods that were encouraged and those that were to be avoided to facilitate a reduction in inflammation. Participants also consumed 5 daily

Table 1 Participant characteristics.

Participant	Sex	Age(y)	ISNCSCI score	Level of injury	Time since injury (y)
Treatment					
1	F	44	D	C5	10
2	M	58	B	T10	4
3	F	62	D	L3	4
4	F	37	A	T3	19
5	M	22	A	C7	5
6	M	67	C	C2	4
7	M	66	D	C5	6
8	F	44	A	C7	9
9	F	65	D	T6	4
10	F	64	D	C3	37
11	M	45	A	T6	28
12	M	37	C	C4	23
AVE	–	51.5	–	–	12.8
SD	–	15.3	–	–	11.3
Control					
1	F	30	B	C5	6
2	F	63	D	L4	2
3	M	42	A	C5	6
4	F	58	D	C5	33
5	M	59	D	T4	4
6	F	33	A	T1	17
7	M	41	C	C4	22
8	M	36	A	C5	19
AVE	–	45.3	–	–	13.6
SD	–	12.9	–	–	10.9
P-value		0.38			0.87

*ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury.

Table 2 Foods to eat and foods to avoid.

Foods to consume	Foods to avoid
Sweeteners	
Honey	White/brown sugar
Maple syrup	Aspartame
Protein	
Whole eggs (with yolk)	Shell fish
Chicken	Cold cuts
Turkey	Hot dogs
Fish	Sausages
Lean beef (1x/week)	Bacon
Wild game	Pork
lamb	Frankfurters
Beans	
Lentils	Baked beans
Black beans	White beans
Kidney beans	Broad beans
Chickpeas/hummus	Soy
Grains	
Quinoa	Bread (all kinds)
Brown or wild rice	Muffins
Buckwheat	Pasta (all kinds)
Spelt	White rice
Millet	Processed cereals (all kinds)
	Granola bars
	Crackers (all kinds)
	Oats
	Rice cakes/crackers
Vegetables	
Kale	Corn
Spinach	Eggplant
Squash	Pickles
Romaine	
Green beans	
Cabbage	
Broccoli	
Cauliflower	
Brussels sprouts	
Cucumber	
Asparagus	
Turnips	
Peppers	
Carrots	
Beets	
Sweet potatoes	
Artichokes	
Mushrooms	
Onions	
Garlic	
Fruits	
Bananas	Raspberries
Blueberries	Strawberries
Clementines	Nectarines
Pomegranates	Prunes
Grapes/raisons	Apricots
Plums	Kiwi
Cherries	
Mango	
Papaya	
Pineapples	
Dates	
Figs	
Melon	
Avocado	
Pears	
Apples	
Tomatoes	
Olives	
Cheese	
Cottage cheese	Parmesan
Goat cheese	Cheddar
Feta cheese	Marble
Nuts	
Almonds	Peanuts/butter
Brazil nuts	Walnuts
Chestnuts	Hazelnuts
	Pecans
	Cashews
Seeds	
	Pumpkin
	Sunflower
	Sesame
Oils	
Olive Oil	Canola oil
Flax Seed Oil	Peanut oil
	Sesame oil
	Hydrogenated oils
	Partially hydrogenated oils
	Store bought salad dressings
Condiments	
Butter	Margarine
Vinegar	Mayonnaise
Honey	Mustard
All herbs	Ketchup
Turmeric	Jam
	Relish
	Soy sauce
	BBQ sauce
	MSG
	Artificial flavors
	Artificial colors
Sweets/Snacks	
	Chocolate
	Cakes
	Cookies
	Pastries
	Candy
	Popcorn

supplements with established anti-inflammatory benefits at doses based on manufacturer recommended intakes. Omega-3 (Now Ultra omega-3) was taken in soft gel form at a dosage of 3 per day. Each soft gel contained 500 mg EPA and 250 mg DHA. Chlorella (Now chlorella) was taken in pill form at a dosage of 6 pills per day (or, 2 servings). One serving (consisting of 3 1000 mg pills) contained 2 g of protein, 60%DV of Vitamin A, 130%DV of Vitamin C, and 35%DV of iron. Antioxidants (CanPrev antioxidant network) were taken in pill form at a dosage of 2 per day. Each pill contained 100 mg coenzyme Q10, 200 mg n-acetyl-cysteine, 150 mg mixed tocopherols, 100 mg DL alpha lipoic acid, 60 mg green tea extract, 5.5 mg zinc, and 100 μg selenium. Curcumin (AOR Inflanox) was taken in pill form at a dosage of 3 per day. Each pill contained 400 mg. A vegetable-based protein powder (Progressive

Vegessential) was taken at a dosage of 1 45 g scoop per day. Each scoop contained 27 g of protein (pea, brown rice, hemp, and cranberry) and other micronutrients.

Assessment of dietary intake

In order to establish baseline eating habits as well as compliance throughout the intervention, participants in the treatment and control groups completed detailed diet records. This included a diet record completed during a 7-day baseline period, as well as during a 3-day period at 1-month, 2-months, and 3-months. Food and nutrient intakes were assessed using ESHA – The Food Processor (ESHA Inc. 2014, version 10.14.2, Salem, OR). Compliance (as a percent of total intake) to the anti-inflammatory diet was also assessed from a detailed analysis of all diet records. Each food item was categorized as either a 'food to consume' a 'food to avoid' or a 'neutral food' based on the parameters of the diet that participants were instructed to follow. Foods were then also categorized into servings in accordance with Canada's Food Guide. A compliance score was based on standard Food Guide servings of foods that participants were instructed to eat vs. foods they were instructed to avoid. To account for differences in total energy intake, compliance scores were expressed as a ratio of the servings of foods to consume over the total servings of food (avoid + consume) multiplied by 100 to generate a compliance percentage.

Prior to beginning the intervention, the treatment group underwent an information seminar in which the diet program was explained to them, followed by a one-on-one consultation with nutritionists who specialize in its implementation. Here, the participants' baseline diet records were reviewed in detail and necessary changes to their nutritional intake to conform to the new diet protocol were discussed. Participants received an information booklet outlining the diet and detailed lists of foods to eat and avoid (see Table 2). The diet was based on guidelines from the book, *Eat well, Live well with spinal cord injury.*[13] They also received a supplement list and intake schedule, and a list of approved recipes. During the study, all the supplements were provided to the participants on a monthly basis. Participants in the treatment group received weekly support via phone calls or in-person meetings from members of the research team (KB and AT). In addition, participants agreed to be members of an online support group where they could share recipes and experiences with each other and have questions answered in a group setting. Participants in the control group were instructed to maintain their habitual diets throughout the duration of the study.

Primary outcome measures

The primary clinical intervention study was designed to assess the effects of an anti-inflammatory diet on depression, neuropathic pain, cognitive impairment, and somatic nerve conduction. We demonstrated that the anti-inflammatory diet, did indeed reduce various inflammatory mediators, which in turn, were associated with significant decreases in depression[17] and neuropathic pain,[18] both of which represent very positive and meaningful changes in this population. As such, this paper aims to describe, in detail, the nutrient changes and dietary compliance of the participants, and explore potential correlations between changes in nutrient intake and changes in various inflammatory mediators in the treatment group. We aim to shed some light on the particular components of the anti-inflammatory diet that seemed to be the most effective at reducing inflammation. The inflammatory mediators of interest in the current study include interleukin (IL)-1 beta, IL-2, IL-6, interferon gamma (IFN-y), as well as the eicosanoid prostaglandin E2 (PGE2), and the kynurenine/tryptophan ratio, as these mediators were shown to be associated with neuropathic pain and depression in our previous investigations.[17,18] Tumor necrosis factor alpha (TNF-α) and C-reactive protein (CRP), were also included as these inflammatory markers have well-established links to metabolic and cardiovascular disease.[23]

Statistical analysis

Paired Student t tests were performed to assess the change in dietary compliance and changes in macronutrients and micronutrients among participants from the beginning to the end of the dietary intervention. Two-way repeated measures ANOVA were performed for the pro-inflammatory cytokine TNF-α, the eicosanoid PGE2, and the KYN/TRP ratio. As the remaining inflammatory mediators were not normally distributed, non-parametric analyses were performed. A Friedman's test of differences among repeated measures (baseline, 1 month, and 3 month) for the treatment group and control was performed. If the Friedman's test resulted in a significant value, a Wilcoxon signed-rank test was then performed to provide specific information regarding which time points were significantly different from one another. Finally, A Mann–Whitney test was performed on change scores (3-month – baseline) between groups to establish if the change experienced significantly differed between groups. These data are expressed as means ± standard deviations. Exploratory post-hoc analyses were also performed to assess potential relationships between changes in inflammatory

mediators and changes in nutrient intake ($n = 20$). Correlations were assessed by means of Pearson's r correlation. Statistical significance was set at $p \leq 0.05$ for all tests.

Results

Among the 24 potentially eligible participants, 20 agreed to participate in the study. Of these individuals, 2 agreed to participate only as members of the control group meaning a total of 18 (75%) were willing to participate in the dietary intervention. Twelve of these participants were randomly allocated to the treatment group. Examples of reasons for not participating included unwillingness to take daily supplements (1 participant), fears about how a change in diet may affect bowel management (1 participant), and concerns about the time and effort required to substantially alter eating habits (2 participants). Participant characteristics are presented in Table 1. All 12 participants allocated to the treatment group completed the 3-month dietary intervention. Compliance to the diet significantly improved from a baseline score of 30% to an average compliance score of 87.5% at 3-months, with scores ranging from 61% to 100% ($P < 0.01$). Compliance to each of the daily supplements was 100% as assessed from the diet records, by personal communication and the return of empty pill bottles.

Nutrient intake / overall diet composition

A summary of nutrient intakes (from both supplements and dietary sources) from the intervention group is shown in Table 3. The change in total energy intake from baseline (1815 ± 743 Kcal per day) to the end of the intervention (1400 ± 367 Kcal per day) did not reach statistical significance ($P = 0.10$). Alterations in macronutrient intake included a significant reduction in total fat intake ($P = 0.02$) and a significant increase in protein intake ($P = 0.02$). Carbohydrate intake was not significantly altered ($P = 0.23$). Of note, nutrients with established anti-inflammatory properties including vitamin A, carotenoids, vitamin C, vitamin E, and omega-3 fatty acids demonstrated significant increases ($P < 0.01$ for each), while nutrients with inflammation-inducing properties including trans fatty acids, caffeine and sodium demonstrated significant reductions ($P = 0.05$; $P < 0.01$ and $P = 0.02$, respectively). No significant changes were observed in the control group for total energy intake, macronutrients, or nutrients with anti-inflammatory or inflammation-inducing properties.

Change in serum biomarkers

Data pertaining to the change in inflammatory mediators has been previously published.[18] Changes in serum levels of inflammatory mediators are shown in Table 4. The Mann–Whitney test indicated that the change scores (3-month – baseline) were significantly different between the treatment group and the control group for IFN-y ($U = 13.0$, $P = 0.01$.), IL-1β ($U = 14.0$, $P = 0.01$), and IL-2 ($U = 12.0$, $P = 0.01$) and showed a trend for CRP ($U = 27.0$, $P = 0.10$). The Friedman test showed that in the treatment group there was a statistically significant reduction in IFN-y ($x2 = 8.67$, $P = 0.01$), IL-1β ($x2 = 17.78$, $p < 0.01$), IL-6 ($x2 = 6.17$, $P < 0.05$), and a trend for CRP ($x2 = 4.5$, $P = 0.10$). The Friedman test showed no statistically significant reductions for any inflammatory mediator in the control group. Post-hoc analysis performed with the Wilcoxon signed-rank test showed significant reductions in the treatment group for IFN-y from baseline to 1 month and baseline to 3 months ($z = –2.275$, $P = 0.02$; $z = –2.510$, $P = 0.01$ respectively), as well as significant reductions in the treatment group for IL-1β from baseline to 1 month and baseline to 3 months ($z = –3.059$, $P < 0.01$; $z = –2.934$, $P < 0.01$ respectively), and a significant reduction in the treatment group for IL-6 from baseline to 1 month, and a trend from baseline to 3 months ($z = –2.275$, $P = 0.02$; $z = –1.726$, $P = 0.08$ respectively). Two-way repeated measures ANOVA were performed for the normally distributed biomarker's TNF-α, PGE2 and KYN/TRP. TNF-α and PGE2 showed trends towards group x time interactions ($P = 0.10$; $P = 0.07$ respectively) while KYN/TRP did not ($P = 0.32$).

Relationship between change in inflammatory mediators and change in nutrient intakes

Pearson's r correlation coefficients for the change in inflammatory mediators and the change in various nutrient intakes are shown in Table 5. The change in total calories as well as individual macronutrients were not shown to be significantly correlated with any inflammatory mediator. The change in vitamin A was negatively correlated with the change in CRP ($r = –.518$, $P = 0.02$), IL-1B ($r = –.502$, $P = 0.02$), IFNy ($r = –.459$, $P = 0.04$), and KYN/TRP ($r = –.607$, $P < 0.01$). The change in carotenoids was negatively correlated with the change in CRP ($r = –.721$, $P < 0.01$), IL-1B ($r = –.632$, $P < 0.01$), PGE2 ($r = –.446$, $P = 0.05$) and KYN/TRP ($r = –704$, $P < 0.01$). The change in omega-3 was negatively correlated with the change in IL-1B ($r = –.496$, $P = 0.03$) and KYN/TRP

Table 3 Treatment group nutrient intake (pre-and post-intervention).*

Nutrient	Baseline (*n* = 12)	3-month (*n* = 12)	% Change	P-value
Energy (kcal)	1815 ± 743	1400 ± 367	–22.8	0.10
Protein (g)¥	73 ± 24 (16%)	95 ± 22 (27%)	31.0	0.024
Carbohydrates (g)¥	228 ± 117 (50%)	180 ± 63 (51%)	–21.0	0.23
Dietary Fiber (g)	21 ± 13	29 ± 12	37.5	0.13
Soluble Fiber (g)	1.3 ± 0.9	5.2 ± 3.5	316.6	0.001
Total Sugars (g)	104 ± 102	68 ± 29	–34.4	0.25
Sucrose (g)	8 ± 7	11 ± 6	39.1	0.26
Fat (g)¥	71 ± 35 (35%)	42 ± 17 (27%)	–41.1	0.016
Saturated Fat (g)	27 ± 19	10 ± 3	–61.4	0.008
Monounsaturated Fat (g)	11 ± 6	11 ± 6	3.8	0.86
Omega 3 FA (g)	0.8 ± 0.6	4.9 ± 0.2	534.9	<0.001
Omega 6 FA (g)	4.9 ± 3.6	4.4 ± 2.8	–11.2	0.68
Trans fatty acid (g)	0.8 ± 1.2	0.1 ± 0.1	–84.3	0.049
Cholesterol (mg)	228 ± 122	215 ± 112	–5.6	0.79
Vitamin A (RAE)	387 ± 209	2030 ± 445	424.1	<0.001
Carotenoid (RAE)	410 ± 371	1739 ± 899	324.3	<0.001
Vitamin B1 (mg)	0.8 ± 0.5	0.6 ± 0.3	–24.0	0.26
Vitamin B2 (mg)	1.1 ± 0.5	1.0 ± 0.5	–8.9	0.64
Vitamin B3 (mg)	12.4 ± 8	12.0 ± 6	–3.1	0.89
Vitamin B5 (mg)	2.5 ± 1.4	3.3 ± 1.3	32.0	0.20
Vitamin B6 (mg)	1.1 ± 0.6	1.5 ± 0.6	34.6	0.14
Vitamin B12 (mg)	2.3 ± 1.7	2.1 ± 1.5	–9.4	0.74
Biotin (µg)	11.1 ± 13	14.5 ± 7	30.2	0.44
Vitamin C (mg)	78 ± 64	469 ± 96	500.7	<0.001
Vitamin D (IU)	78.7 ± 53	107.6 ± 78	36.7	0.30
Vitamin E (mg)†	2.6 ± 2	612 ± 9	23072.1	<0.001
Folate (µg)	206.1 ± 144	322.9 ± 344	56.7	0.29
Vitamin K (µg)	38.4 ± 58	256.3 ± 414	567.3	0.084
Calcium (mg)	645.9 ± 280	615.7 ± 200	–4.7	0.76
Chromium (µg)	1.7 ± 1.2	3.3 ± 2.3	93.5	0.047
Copper (mg)	0.7 ± 0.5	1.1 ± 0.8	73.5	0.10
Fluoride (mg)	967 ± 1212	328 ± 522	–66.1	0.11
Iodine (µg)	24.3 ± 16.2	25.3 ± 15.6	3.9	0.89
Iron (mg)	11.6 ± 4	27.4 ± 2	136.4	<0.001
Magnesium (mg)	167 ± 117	242 ± 90	44.9	0.092
Manganese (mg)	2.8 ± 2.5	2.9 ± 1	5.7	0.84
Molybdenum (mg)	10.0 ± 13.7	19.0 ± 20.5	90.6	0.22
Phosphorus (mg)	754 ± 696	772 ± 253	2.5	0.93
Potassium (mg)	1697 ± 963	2515 ± 1270	48.2	0.089
Selenium (mg)	44.4 ± 29	75.5 ± 76	70.1	0.20
Sodium (mg)	2502 ± 1137	1564 ± 606	–37.5	0.019
Zinc (mg)	6.1 ± 4.2	27.7 ± 1.9	355.3	<0.001
Alcohol (g)	3.6 ± 11	0.3 ± 1.1	–91.2	0.30
Caffeine (mg)	133 ± 103	57 ± 53	–74.5	0.005

Reported as mean ± standard deviation.
P-value from paired-*T*-test. Significance at $P < 0.05$.
*nutrient intakes derived from the dietary analysis plus the nutrients in the added study supplements.
†includes 'mixed tocopherols' from the supplements.

($r = –.540$, $P = 0.01$). The change in zinc was negatively correlated with the change in IL-2 ($r = –.457$, $P = 0.04$), IL-6 ($r = –.450$, $P = 0.05$), IL-1B ($r = –.569$, $P < 0.01$), TNF-α ($r = –.503$, $P = 0.02$), IFNy ($r = –.478$, $P = 0.03$), and KYN/TRP ($r = –.593$, $P < 0.01$). The change in both vitamin C and iron were shown to be negatively correlated with the KYN/TRP ratio ($r = –.447$, $P = 0.05$; $r = –.586$, $P < 0.01$, respectively). The change in iodine was shown to be positively correlated with the change in IL-2 ($r = .496$, $P = 0.03$), the change in IL-6 ($r = .564$, $P = 0.01$) and the change in IFNy ($r = .529$, $P = 0.02$).

Discussion

The anti-inflammatory diet intervention was shown to be effective at reducing inflammation in individuals with SCI as indicated by the significant reduction in pro-inflammatory cytokines in the treatment group. Prior research related to diet following SCI is scarce, and has typically focused on observational nutrient intake,[14,15] or acute inflammatory responses following a single meal.[16] To the authors knowledge, the current study provides the first insight regarding the effects of longer-term dietary alterations on inflammation in SCI via a randomized-controlled trial.

Table 4 Changes in serum biomarkers.

	Treatment (n = 12)			Control (n = 8)			2-Way ANOVA (p-value)	Mann-Whitney (p-value)	Friedman [Treat.] (p-value)
	Baseline	1 Month	3 Month	Baseline	1 Month	3 Month			
CRP (ng/ml)	4474.7 ± 3578.9	3822.6 ± 3749.4	2865.0 ± 2684.9	2388.1 ± 2928.1	3074.0 ± 3026.4	2458.8 ± 3678.9	–	0.10	0.10
IL-2 (pg/ml)	21.3 ± 51.2	15.1 ± 41.7	17.2 ± 42.1	1.7 ± 3.4	2.9 ± 3.6	2.3 ± 3.3	–	<0.01	0.23
IL-6 (pg/ml)	13.9 ± 28.2	9.2 ± 21.3*	9.5 ± 19.3	9.0 ± 10.5	13.8 ± 21.2	13.5 ± 21.9	–	0.13	<0.05
IL-1B (pg/ml)	0.9 ± 1.1	0.3 ± 0.3**	0.3 ± 0.2**	0.3 ± 0.3	0.4 ± 0.5	0.3 ± 0.2	–	<0.01	<0.01
TNF-α (pg/ml)	12.5 ± 3.6	11.8 ± 5.5	11.2 ± 4.1	9.8 ± 3.9	11.3 ± 6.7	12.9 ± 10.3	0.10	–	–
IFN-y (pg/ml)	52.9 ± 94.0	31.9 ± 57.5*	35.0 ± 68.4*	28.1 ± 46.8	48.8 ± 84.6	49.6 ± 95.3	–	<0.01	0.01
PGE2 (pg/ml)	496.5 ± 452.7	636.4 ± 544.9	353.0 ± 357.5	605.1 ± 491.2	605.6 ± 504.6	661.7 ± 503.7	0.07	–	–
KYN/TRP	27.0 ± 11.6	28.5 ± 10.9	24.0 ± 6.6	16.8 ± 4.9	20.3 ± 4.7	20.6 ± 6.0	0.32	–	–

All results are shown as mean ± SD. P-values correspond to group × time interactions, Mann-Whitney change scores, and Friedman scores for treatment group respectively.
*Significantly different from baseline with P value < 0.05.
**Significantly different from baseline with P value < 0.01.
Note: Adapted from 'Targeting inflammation as a treatment modality for neuropathic pain in spinal cord injury: A randomized clinical trial' by David J. Allison, Aysha Thomas, Kayleigh Beaudry and David S. Ditor, 2016, Journal of Neuroinflammation.

Table 5 Correlation matrix.

	ΔKCal	ΔCHO	ΔProtein	ΔFat	ΔN3	ΔN6	ΔTFA	ΔVitRAE	ΔCAR	ΔVitC	Δ*Zinc*	ΔIodine	ΔCaffeine	ΔNa+
ΔCRP	0.073	0.103	–0.105	0.029	–0.292	–0.124	0.002	–0.518*	–0.721**	–0.301	–0.401	0.403	–0.082	0.365
ΔIL-2	–0.237	–0.181	–0.303	–0.099	–0.356	–0.191	–0.130	–0.381	–0.417	–0.268	–0.457*	0.496*	–0.062	0.114
ΔIL-6	–0.177	–0.134	–0.177	–0.069	–0.331	0.060	0.168	–0.357	–0.243	–0.285	–0.450*	0.564**	–0.130	0.101
ΔIL-1B	–0.226	–0.207	–0.151	–0.165	–0.496*	–0.251	–0.207	–0.502*	–0.632**	–0.393	–0.569**	0.123	-0.213	0.123
ΔTNF-α	–0.323	–0.284	–0.319	–0.113	–0.292	–0.008	–0.002	–0.403	–0.331	–0.295	–0.503*	0.288	–0.305	–0.105
ΔIFN-y	–0.163	0.088	–0.380	–0.058	–0.392	–0.009	0.115	–0.459*	–0.408	–0.366	–0.478*	0.529*	–0.113	0.071
ΔPGE2	0.073	–0.008	0.047	0.213	–0.413	–0.328	–0.266	–0.432	–0.446*	–0.197	–0.379	–0.066	–0.064	–0.041
ΔKYN/TRP	0.011	–0.091	–0.251	0.272	–0.540*	–0.083	–0.106	–0.607**	–0.704*	–0.447*	–0.593**	–0.182	–0.025	0.083

R values derived from Pearson's correlations.
*P ≤ 0.05; **P ≤ 0.01.
CHO, carbohydrates; N3, omega-3; N6, omega-6; TFA, trans fatty acids; VitA, vitamin A; CAR, carotenoids; VitC, vitamin C; Na+, sodium.

The main findings concerning the dietary alterations in the current study included a trend towards a reduction in calories, a significant reduction in fat intake, a significant increase in protein intake, and no significant change in carbohydrate intake. Also of interest, nutrients with anti-inflammatory properties including vitamins A, C, E and omega-3 fatty acids were significantly increased, while the intake of certain proinflammatory aspects of the diet, including trans fatty acids, caffeine, and sodium, were significantly reduced.

Many components of the diet utilized in this study are similar to that of the Mediterranean diet, which has been extensively studied in able-bodied individuals. Similarities include an emphasis on increased intake of fruits and vegetables, olive oil, fish, whole grains, and tree nuts (e.g. almonds, brazil nuts, and chestnuts) while reducing the intake of red meats, processed foods, and refined sugars. The PREDIMED (primary prevention of cardiovascular disease with a Mediterranean Diet) trial is among the largest studies to assess the effects of the Mediterranean diet in an able-bodied population.[24] This trial was designed to assess the long-term effects of a Mediterranean diet on cardiovascular disease prevention in 7477 high risk individuals. In addition to reducing the incidence of major cardiovascular events by 30%, members of the treatment group also demonstrated significant reductions in inflammation as shown by reductions in CRP, IL-6, endothelial and monocyte adhesion molecules and chemokines.[25] Similar to our study, the PREDMID trial was designed to overcome the limitations associated with the single-nutrient approach by evaluating overall dietary patterns. This approach is now considered superior as dietary patterns represent a broader evaluation of food and nutrient consumption and may therefore be more predictive of disease risk than individual food or nutrient intake.[26]

In contrast, a recent systematic review and meta-analysis evaluating the efficacy of the Mediterranean diet to reduce inflammation in individuals with coronary heart disease found no significant effect.[27] Despite previous promising findings from observational studies, this systematic review of 11 intervention studies demonstrated mostly non-significant reductions in inflammation (assessed by CRP concentrations), and no difference to that of low-fat diets. Such discrepancies in findings related to the anti-inflammatory benefits of dietary alterations may however, relate to variability in study populations, variable markers used to assess inflammation, poor compliance scores, and differences in the diet itself.

Several significant relationships between changes in nutrient intake and changes in inflammatory mediators were also found. The change in vitamin A, carotenoids, omega-3, and zinc were shown to be negatively correlated with several pro-inflammatory mediators (Table 5). The relationships between vitamin A and carotenoids with these mediators may be explained by the antioxidant properties of these nutrients.[28] Omega-3 fatty acids act both intracellularly and extracellularly to produce a number of anti-inflammatory effects resulting in the altered production of various eicosanoids, resolvins, and proinflammatory cytokines.[6] Zinc also possesses antioxidant properties and has previously been shown to reduce reactive oxygen species as well as the production of proinflammatory cytokines.[29] The above relationships between certain nutrients and inflammatory mediators may be clinically significant as previous work from our lab has shown increased levels of IL-1B and KYN/TRP to be associated with depression,[17] and increased levels of IFNy and IL-2 to be associated with neuropathic pain,[18] in those with SCI. Future research is needed to further examine what nutrients are most responsible for changes in inflammation and changes in secondary health complications in the SCI-population.

Several study limitations should be mentioned. The sample size in this study was small, and may have represented a more motivated sub-population of individuals with SCI as participants were recruited from a voluntary out-patient rehabilitation clinic. As well, dietary intake data were collected from self-reported food records. Although this is common practice in clinical intervention trials, the potential for bias in reporting can be a limitation[30] It is also important to note that in the current study, all supplements were provided to participants at no additional cost. If future studies were to require participants to purchase their own supplements it may negatively influence recruitment as well as compliance and retention. Finally, as the dietary intervention was not intended to be calorie restrictive, weight loss was not an expected outcome and therefore body weight was not assessed. However, as many participants did anecdotally report weight loss, this outcome measure should be included in future trials.

Major strengths of the current study were the use of inflamed subjects and very strong compliance scores. Together, this may have contributed to the successful reduction in inflammation. Our study had a recruitment rate of 75%, and dietary compliance scores ranging from 61% to 100%, with an average score of 87.5%. Further, participants had no issue maintaining the supplement schedule as indicated by supplement compliance scores

of 100%. These strong compliance scores and high participant retention suggest it is at least feasible to perform such longer-term dietary interventions in this population. The support provided in our study via weekly phone calls and/or in-person meetings as well as the online support group (utilized by 11 of the 12 anti-inflammatory diet participants), also likely positively impacted compliance scores and should be considered in future studies.

Conclusion

In conclusion, the current study showed that longer-term dietary alterations can be used as an effective means of reducing inflammation in individuals with SCI. This study also provides a preliminary exploration regarding the nutrient changes that may be most influential in this effect. Future larger scales studies are warranted in this population.

Acknowledgements

This study was supported by the Ontario Neurotrauma Foundation. We wish to thank Now, CanPrev, AOR, and Progressive for providing the supplements utilized in the dietary intervention.

Disclaimer statements

Contributors None.

Funding This study was funded by the Ontario Neurotrauma Foundation. We wish to thank Now, CanPrev, AOR, and Progressive for providing the supplements utilized in the dietary intervention.

Conflict of interest None of the authors has any potential conflict of interest.

Disclosure of interest The authors declare no conflicts of interest

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