The Use of Ascorbigen in the Treatment of Fibromyalgia Patients: A Preliminary Trial

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Abstract

Twelve female fibromyalgia syndrome (FMS) patients were given 500 mg per day of a blend containing 100 mg ascorbigen and 400 mg broccoli powder in a preliminary, one-month, open-label trial. This group of patients showed a mean 20.1 percent (p=0.044) decrease in their physical impairment score and a mean 17.8 percent (p=0.016) decrease in their total fibromyalgia impact scores as measured by the Fibromyalgia Impact Questionnaire. The mean physical impairment score two weeks post-treatment showed a significant return to near pre-treatment level (p=0.028). Analysis of ten of the patients' mean threshold pain levels at the 18 possible tender points obtained before and at the end of treatment showed a strong trend toward an increase in the mean threshold pain level (p=0.059). The reduced sensitivity to pain and improvement in quality of life measured in this study appear to be clinically relevant and a larger, double-blind study is warranted.

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Introduction

Fibromyalgia is a perplexing and widespread syndrome, afflicting about two percent of the U.S population: 3.4 percent of women and 0.5 percent of men.[1] A rather complex picture of the syndrome has arisen, with patients manifesting a variety of abnormalities, including: increased homocysteine in the cerebrospinal fluid,[2] alterations in several chemical pain mediators (serotonin, substance P, nerve growth factor, and dynorphin A),[3] and in one study, the presence of autoantibodies to serotonin, gangliosides, or phospholipids in more than half the patients.[4] There is also a 25-percent concurrence of FMS with lupus and rheumatoid arthritis and a 50-percent concurrence with Sjogren's syndrome.[5]

Although fibromyalgia may not yet be generally recognized as an autoimmune disorder, based on the recent recognition of autoantibody production and its concurrence with other autoimmune syndromes, it does not seem unreasonable to tentatively accept autoimmunity as one possible etiology. Moreover, considering recent published results showing that estrogen

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selectively induces B-cell hyperactivity in mice,[6] it seems worthwhile to explore whether supplementation with agents that have anti-estrogenic effects might be useful in treating a cluster of autoimmune syndromes, including fibromyalgia. In what may be considered a beginning of this effort, we report on our investigation of ascorbigen in the treatment of female patients with fibromyalgia.

Ascorbigen (AGN) is the most common of a variety of dietary indoles released from homogenized or cooked cruciferous vegetables when the glucosinolate, glucobrassicin, is hydrolyzed by the enzyme myrosinase. Other dietary indoles—such as indole-3-carbinol (AGN without an ascorbic acid moiety) and diindolylmethane (a dimer of indole-3-carbinol)—occur in lesser quantities.[7] Dietary indole research to date has examined the effects of acid-condensation products of indole-3-carbinol (made in the stomach) and their induction of hepatic phase I and phase II detoxification enzymes.[8] Particular interest has focused on the phase I-dependent increase in hydroxylation of estrone at the 2-position (creating a catechol estrogen) and a concomitant decrease in estrone hydroxylation at the 16 position.[9] This action has led to promising research in the possible prevention of estrogen-dependent cancers such as breast cancer, where it is believed an increase in the 2-hydroxyestrone/16∝-hydroxyestrone ratio is beneficial in preventing estrogen-dependent tumor growth.[10] Moreover, although no specific mechanisms of action are suggested for reported increases in overall sense of well-being and reduction in pain, a patent has been issued for the use of dietary indoles, including ascorbigen, in the treatment of fibromyalgia.[11]

In this preliminary, uncontrolled, open-label trial we tested the hypotheses that daily supplementation with 100 mg of ascorbigen and 400 mg of broccoli powder would increase tender point threshold pain levels as measured by an algometer, and decrease fibromyalgia impact and physical impairment scores as measured by the Fibromyalgia Impact Questionnaire (FIQ). We also tested the hypothesis that fibromyalgia impact and physical impairment scores would significantly increase two weeks post treatment.

Materials and Methods

A 20-percent ascorbigen/broccoli powder blend (AGN > 98% pure by HPLC) was encapsulated to contain 500 mg of this blend (100 mg AGN) per capsule. This material was donated by Dave Parish and Merrill Andrus, Designed Nutritional Products, Orem, UT. A blend was used with the intent of approximating the chemistry of *Brassica* plant food, with the understanding that a previous acetonitrile extract of commercially available broccoli powder yielded no dietary indoles.[12] A Commander™ Algometer was provided by Glenn Gustasen of JTECH Medical Industries, Salt Lake City, UT.

Between June and November 1999, 16 non-smoking, non-pregnant,lactating female participants previously diagnosed with FMS were recruited by advertisements posted at National College of Naturopathic Medicine (NCNM) clinics, advertisements in a local newspaper, and by distribution of flyers at a local FMS support group. Ages of participants ranged from 29 to 52 (mean 44.2 years). All but one participant had attended some level of college, with four having completed bachelor's degrees and three having completed master's degrees. Participants read and signed a consent form approved by NCNM's IRB prior to inclusion in the study. For inclusion in the study participants needed to have baseline tender point threshold pain of the equivalent of approximately 4 kg/cm^2, in our case 4.4 lbs/0.5 cm^2, at a minimum of 11 of the 18 tender points given by the American College of Rheumatology as diagnostic criteria for FMS.[13] Participant visits were conducted at one of three NCNM clinics in the greater Portland area by two clinical investigators (Scarlett and

Table 1: Past and Present FMS Treatment Approaches.

Physical, Mental/Emotional	Medications and Diet
Acupuncture	Tylenol III/PM/other
Chiropractic Adjustments	Ibuprofen
Hydrotherapy Walking Massage	Prescription anti-depressants (Doxepin, Trazodone,others unspecified)
Moderation of strenuous activities	Prescription sleep medications (unspecified)
Stretching Yoga Stress Reduction	Kava, Multivitamins, Malic acid, MSM, 5HTP, low sodium diet, avoidance of food sensitivities.
	Medications listed by participants and not found in 1998 PDR: SRelax and Minerol (injection)

Ferguson). When asked what approaches to dealing with FMS alleviated their symptoms and if they employed any of these approaches currently, participants reported using a variety of the modalities summarized in Table 1. No attempt was made to alter any of the modalities being used by participants during the course of this study.

Threshold pain values—the pressure at which the patient first they felt pain—were measured as gradually increasing pressure was applied with the algometer at each of the 18 tender points. Measurements were taken at baseline and after 28-30 days of supplementation with one capsule per day of the ascorbigen/broccoli powder blend (100 mg ascorbigen and 400 mg of broccoli powder per day). One participant was allowed to undergo her initial exam and begin her supplementation 30 days thereafter, with a follow-up exam 28-30 days from the beginning of her supplementation. All other participants started supplementation immediately after their initial exam, with a follow-up exam in 28-30 days. The algometer's data collection threshold was set at 0.2 pounds and for this experiment a 0.5 cm^2 palpation pad was used.

Additional insight into the impact of therapy on each patient's physical functioning, work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety, and depression was gained by utilizing the Fibromyalgia Impact Questionnaire (FIQ). The FIQ is a simple, self-administered questionnaire constructed and described by Bennett et al.[14] FIQs were filled out at both clinic visits and an additional FIQ was given to each patient at their second visit with instructions that they fill it out two weeks after cessation of supplementation (which took place immediately following the second visit).

Statistical Analysis

We tested two hypotheses: 1) threshold pain levels would increase and physical impairment (PI) and total impact (TI) scores

Table 2: Individual Mean Threshold Scores Before and at Conclusion of Treatment (Standard Deviation in parentheses)

Patient ID#	Baseline Mean Threshold Pain of 18 possible tender points (lbs/0.5cm^2)	Post Tx Mean Threshold Pain of 18 possible tender points (lbs/0.5cm^2)
1	1.72 (0.912)	2.68 (1.449)
2	2.34 (1.325)	2.14 (0.741)
3	1.41 (0.406)	1.80 (0.660)
6	2.22 (0.961)	2.65 (1.148)
7	3.32 (2.506)	3.57 (2.513)
8	2.23 (0.826)	2.50 (1.142)
9	1.77 (0.582)	1.77 (0.782)
10	3.23 (1.180)	3.51 (1.283)
11	2.34 (0.831)	2.37 (0.635)
12	1.66 (0.851)	1.28 (0.797)
Mean of means	2.22 (0.640)	2.43 (0.732)

would decrease by the conclusion of treatment; and, 2) PI and TI scores would significantly increase two weeks after cessation of treatment. Two approaches were employed in the analysis of pain threshold levels. The first approach was to compare the mean threshold score of all 18 possible tender points in each patient before and at the conclusion of treatment, thus assuring a normal distribution of the data and minimizing variance. This was accomplished using one sided, paired T-tests. The second approach was to compare the scores of each tender point across participants before and after treatment. The data from this second approach contains greater variance and because it is prone to non-normalcy the one-sided Mann-Whitney test, which compares a population median instead of mean, was used. We felt this second approach might yield interesting indications as to localizations of treatment impact that may be amplified in further, larger studies. Scoring from the FIQ was completed as directed by its authors, yielding summed total PI and TI scores. Lower PI and TI scores indicate improvement of the fibromyalgia patient. All tests were performed using Minitab7 version 12.

Results

Twelve of the 16 patients completed both of the required visits and filled out at least the first and second FIQs, before and at the end of supplementation. Of these 12, two patients each reported two points as being non-tender at their baseline visit and tender at the follow-up exam. Because it could not be determined whether the points had actually been non-tender at baseline or if they were missed due to the use of the rather small palpation pad on the algometer, these patients' results were dropped from the comparison of mean threshold pain. Mean threshold pain scores

Table 3: Point-by-Point Analysis of Threshold Scores

Tender Point	Pretreatment Median (lbs/0.5cm2)	Concluding Median (lbs/0.5cm2)	P-Value
L. Occipital	1.40 (1.006)	2.00 (0.872)	0.1785 (n=11)
R. Occipital	1.90 (0.580)	2.40 (0.727)	0.2988 (n=11)
L. Cervical	1.15 (0.841)	1.00 (0.505)	--------- (n=12)
R. Cervical	0.80 (0.490)	0.95 (0.280)	0.0889 (n=12)
L. Trapezius	1.70 (0.584)	2.20 (0.824)	0.1121 (n=12)
R. Trapezius	2.00 (0.691)	2.00 (0.749)	0.3628 (n=12)
L. Supraspinatus	2.10 (0.905)	2.75 (1.153)	0.1012 (n=12)
R. Supraspinatus	2.15 (0.952)	2.60 (0.836)	0.1358 (n=12)
L. 2nd Rib	1.65 (0.744)	1.60 (0.863)	--------- (n=12)
R. 2nd Rib	1.50 (0.691)	1.55 (0.897)	0.4424 (n=12)
L. Lateral Epicondyle	1.40 (1.191)	1.40 (1.371)	--------- (n=11)
R. Lateral Epicondyle	1.50 (1.197)	1.70 (1.308)	0.3224 (n=11)
L. Gluteal	2.75 (1.725)	3.40 (1.572)	0.1125 (n=12)
R. Gluteal	2.50 (2.110)	3.40 (1.801)	0.1425 (n=12)
L. Greater Trochanter	3.65 (1.449)	3.60 (1.299)	0.3973 (n=12)
R. Greater Trochanter	3.20 (1.622)	3.25 (1.731)	0.2172 (n=12)
L. Knee	2.20 (1.165)	2.00 (1.265)	--------- (n=12)
R. Knee	2.35 (0.893)	1.90 (1.133)	--------- (n=12)

Standard Deviation in parentheses

from each of the remaining 10 participants' 18 points before and at the conclusion of treatment are presented in Table 2. Threshold score comparisons of each point across the group, before and at the conclusion of treatment, are presented in Table 3.

The difference in mean threshold pain scores shows a strong trend toward statistical significance (p=0.059) and would represent a 9.1-percent increase in the group's mean tender point threshold level.

An interesting trend was noticed when this data was tabulated: median threshold scores tended to be lower in the upper body and higher at the gluteal, greater trochanter, and knee points. Comparison of pretreatment

Table 4: Physical Impairment and Total Impact Scores Before, Concluding, and 2 Weeks Post-Treatment

Patient ID #	FIQ1 PI (before)	FIQ2 PI (concluding)	FIQ3 PI (2 week post)	FIQ1 TI (before)	FIQ2 TI (concluding)	FIQ3 TI (2 week post)
1	2.36	1.91	2.64	44.37	41.22	45.28
2	0.00	0.00	0.09	32.15	30.29	25.45
3	1.64	1.20	1.30	57.67	27.29	38.62
4	2.11	1.11	0.78	46.32	22.29	30.17
5	0.73	0.22	1.20	37.57	22.90	46.72
6	1.22	0.30	1.00	48.93	37.15	45.05
7	2.30	1.80	1.80	50.09	44.28	45.85
8	1.09	1.27		34.35	31.39	
9	1.36	0.73	1.09	38.54	34.71	41.56
10	2.09	1.73	1.82	43.25	37.47	39.77
11	1.55	2.18	2.18	54.15	64.27	51.27
12	0.60	1.18	1.27	36.86	37.80	40.10
Mean	1.42	1.14[a]	1.38[b]	43.69	35.92[c]	40.89[d]
	(0.74)	(0.71)	(0.74)	(8.04)	(11.25)	(7.87)
N=	12	12	11	12	12	11

[a]p=0.044; [b]p=0.028 with score from participant 8 removed and compared to the adjusted mean FIQ2 PI of 1.124[c]p=0.016; [d]p=0.067 with score from participant 8 removed and compared to an adjusted mean FIQ2 TI of 36.33. Standard Deviation in parentheses.

median scores of the upper 12 to lower six points from Table 3 (again using the one-sided Mann-Whitney) yielded a p-value of 0.0004. The same comparison at the conclusion of treatment was also significant, although the p-value was over 25 times higher (0.0109).

Data from physical impairment and total impact scores from the 12 participants completing the first two FIQs and 11 participants completing all three FIQs are summarized in Table 4.

The differences between PI and TI scores before and at the conclusion of treatment are more striking than that of threshold pain. Statistically significant decreases are seen in both PI (p=0.044) and TI (p=0.016) scores. The downward shift in PI and TI represented decreases in the group's mean scores of 20.1 and 17.8 percent, respectively. Moreover, comparison of PI at the end of treatment and two weeks after cessation of supplementation in the 11 patients completing the third FIQ show a statistically significant return to near pre-treatment levels. When the same comparison is done for the 11 patients' TI scores from the second and third FIQs, the results are not significant (p=0.067) but show a strong trend toward pre-treatment levels.

Reported adverse effects in this trial were minimal. One patient complained of increased flatulence and abdominal distension. There was also one complaint of distasteful

aftertaste and one complaint that the smell of the capsule was undesirable. Other participants either reported no adverse effects or stated explicitly that there were none.

Discussion

The results of this study suggest at least one interesting insight—our participants feel pain more acutely in the upper head and neck area than they do in the region of the gluteus, trochanter, and knees. The lowest median score in the pretreatment group was at the right cervical (0.80 lbs per 0.5 cm^2), the highest median score was at the left greater trochanter (3.65 lbs per 0.5 cm^2). Although this distribution of pain sensitivity might not be totally unexpected, neither may its occurrence be totally academic. It may be that some of the presenting symptoms of fibromyalgia are caused by anatomical aberrations in the cervical vertebrae, prolonged tension of the upper musculature, and or long-term occupational assaults of repetitive tasks; e.g., sitting nearly motionless for hours at a computer work station. Future work to explore these possible contributing factors of etiology seems justified.

It may also be the case that a greater understanding of dietary indole biochemistry might be of value in understanding the pathophysiology of FMS. Oral supplementation with dietary indoles can decrease urinary levels of 16 μ-hydroxyestrone, estradiol, and estriol.[15] It would be interesting to explore whether these decreases are associated with decreases in the levels of autoantibodies present in those fibromyalgia patients who exhibit autoantibodies to serotonin, gangliosides, or phospholipids. Alternatively, there is evidence that catechol estrogens do bind to and inhibit catechol-o-methyl transferase and that catechol estrogens are manufactured not only in rat liver but in the brain and pituitary as well.[16,17] It would be valuable to see if moderate supplementation with dietary indoles can increase 2-hydroxyestrone levels enough to significantly inhibit catechol-o-methyl transferase in humans. Such an action might lead to an increase in catecholamine neurotransmitter levels otherwise decreased in FMS patients. However, this hypothetical scenario would stand in contrast to catechol estrogen-induced inhibition of tyrosine hydroxylase, the enzyme catalyzing the rate limiting step in the production of dopamine and norepinephrine.[18]

Our study lacks the size and structure necessary to determine whether or not ascorbigen is more useful than placebo in the treatment of FMS. However, the results do provide preliminary support for anecdotal claims that dietary indole supplementation in FMS patients might help alleviate pain and improve quality of life. If our results can be reproduced in a double-blind trial of sufficient size, physicians will gain a somewhat valuable tool in the treatment of a majority of female patients with FMS. A future trial could also explore the possible association between estrogen levels and the presence and change in autoantibody levels in fibromyalgia patients during dietary indole therapy.

Conclusion

Our results demonstrate that participants in this open-label trial experienced significant decreases in physical impairment and total fibromyalgia impact scores as measured by the Fibromyalgia Impact Questionnaire, while a strong trend was seen toward an increase in mean threshold tender point scores. Due to the small number of participants and the open-label design of this study, we cannot rule out a placebo effect as a mechanism of the positive changes seen. Given the large number of people suffering from FMS and the current lack of effective treatments, a larger, randomized, double-blind study is warranted.

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