

A REVIEW OF RECENT CLINICAL TRIALS OF THE NUTRITIONAL SUPPLEMENT *CHLORELLA PYRENOIDOSA* IN THE TREATMENT OF FIBROMYALGIA, HYPERTENSION, AND ULCERATIVE COLITIS

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fibromyalgia, hypertension, or ulcerative colitis suggests that larger, more comprehensive clinical trials of chlorella are warranted. (Altern Ther Health Med. 2001;7(3):79-91)

Context • It has been suggested that the consumption of natural "whole foods" rich in macronutrients has many healthful benefits for those who otherwise ingest a normal, nonvegetarian diet. One example is dietary supplements derived from *Chlorella pyrenoidosa*, a unicellular fresh water green alga rich in proteins, vitamins, and minerals.

Objective • To find evidence of the potential of chlorella dietary supplements to relieve signs and symptoms, improve quality of life, and normalize body functions in people with chronic illnesses, specifically fibromyalgia, hypertension, and ulcerative colitis.

Design • Double-blind, placebo-controlled, randomized clinical trials.

Setting • Virginia Commonwealth University's Medical College of Virginia.

Patients • Fifty-five subjects with fibromyalgia, 33 with hypertension, and 9 with ulcerative colitis.

Intervention • Subjects consumed 10 g of pure chlorella in tablet form and 100 mL of a liquid containing an extract of chlorella each day for 2 or 3 months.

Main Outcome Measures • For fibromyalgia patients, assessments of pain and overall quality of life. For hypertensive patients, measurements of sitting diastolic blood pressure and serum lipid levels. For patients with ulcerative colitis, determination of state of disease using the Disease Activity Index.

Results • Daily dietary supplementation with chlorella may reduce high blood pressure, lower serum cholesterol levels, accelerate wound healing, and enhance immune functions.

Conclusions • The potential of chlorella to relieve symptoms, improve quality of life, and normalize body functions in patients with

Chlorella pyrenoidosa is a unicellular green alga that grows in fresh water. It has the highest content of chlorophyll of any known plant and also contains high concentrations of certain vitamins, minerals, dietary fiber, nucleic acids, amino acids, enzymes, and other substances. This alga has a strong cell wall that prevents its native form from being adequately digested so that chlorella can be digested by humans only after breaking its cell wall.¹ Chlorella growth factor (CGF) is a water-soluble extract and contains a variety of substances including amino acids, peptides, proteins, vitamins, sugars, and nucleic acids. Estimates of the CGF content in raw *C pyrenoidosa* is approximately 5%. A number of research studies and anecdotal reports from Japan have suggested that broken cell wall preparations and extracts of *C pyrenoidosa* as well as some other *Chlorella* species, when given orally or injected, promote growth and healing, stimulate the immune system and offer protection from infection, and exert significant anticancer activity.²⁻⁶

A number of studies in animals and humans have suggested that adding *C pyrenoidosa* to the diet yields many beneficial effects for the consumer—the most important of which, relative to the present studies, is its capacity to promote healing and nonspecifically enhance the immune system.²⁻⁶ More than a decade ago, the authors conducted a clinical trial with 2 products derived from *C pyrenoidosa*: Sun Chlorella tablets and Wakasa Gold, which contained chlorella extract. These 2 dietary supplements were added to the diets of patients with primary malignant tumors of the brain to determine whether they improved the patients' immune system so antitumor activities might be manifested that, in turn, would lead to some relief of symptoms and/or increase survival.⁷

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The dietary supplements were given to 21 patients as an adjunct to any other treatment they might have been receiving for their brain tumors. Patients consumed 20-g chlorella tablets and 150 mL of the chlorella extract daily for up to 2 years. Although this dietary chlorella supplementation did not significantly affect the patients' survival, immune system parameters including lymphocyte, natural killer cell, and neutrophil counts as well as lymphocyte responses to antigens and natural killer cells' cytotoxic activities were at near-normal levels. These variables were less adversely affected by chemotherapy and the immunosuppressive effects of medications and protein secretions of the tumors than would have been expected in these patients.

No toxic effects have ever been observed in laboratory animals or humans who have consumed *C pyrenoidosa*, regardless of whether the alga's cell walls were intact or broken.²⁷ In clinical studies at other institutions, amounts of chlorella similar to the amount that our group of patients with brain tumors consumed were given without any adverse effects (reviewed by Merchant et al⁷). Temporary changes in the general state of health (loose bowel movements, abdominal cramps, and/or mild nausea), however, have been attributed to the addition of broken cell wall preparations of *C pyrenoidosa* to a diet.

In our study of patients with brain tumors, approximately half reported temporary irregularity of bowel movements and/or mild nausea during the first few days of adding chlorella to their diet. Cramping sensations and flatus also were reported, but any intestinal discomforts the patients experienced resolved spontaneously within a few days to a week after the maintenance daily dosages of chlorella tablets and extract were reached. No disturbances related to long-term use of *C pyrenoidosa* were noted in these patients. Adverse changes in a patient's clinical status usually correlated closely with evidence of tumor recurrence and/or progressive growth seen on computed tomograms or magnetic resonance images and therefore could be not ascribed to any cumulative toxic effects of chlorella in the diet.

Although our findings and those of others have suggested that adding chlorella to the diet of patients with cancer may yield a health benefit, there remains a clear need for more scientific research directed at specific diseases, particularly those of a chronic, protracted nature. Furthermore, such studies must be designed and carried out according to current conventional methods to be recognized as valid by the scientific and medical community. Careful and thorough studies such as those conducted and reviewed in this report involving patients with chronic illnesses will be required to determine which patients may benefit from including chlorella in their diet. Therefore, the principal focus of our recent clinical research was to find evidence of chlorella's potential to relieve signs and symptoms, improve quality of life, and normalize body functions in those with chronic illness. Specifically, the supplements were studied in subjects with fibromyalgia, hypertension, or ulcerative colitis.

CHLORELLA PYRENOIDOSA

For these clinical trials, subjects consumed 2 dietary supple-

ments: solid tablets called "Sun Chlorella" and a liquid called "Wakasa Gold" (provided by the Sun Chlorella Corporation, Kyoto, Japan). The chlorella tablets were formed only of a preparation of *C pyrenoidosa* with broken cell walls and were composed of 60% protein, 20% carbohydrate, and about 11% unsaturated fat. Each chlorella microorganism contains 28.6 g/kg chlorophyll; its proteins contain all the amino acids known to be essential for the nutrition of animals and human beings. Vitamins found in *C pyrenoidosa* include vitamin C, provitamin A (β -carotene), thiamine (B_1), riboflavin (B_2), pyridoxine (B_6), niacin, pantothenic acid, folic acid, vitamin B_{12} , biotin, choline, vitamin K, lipoic acid, and inositol. Minerals in *C pyrenoidosa* include phosphorus, calcium, zinc, iodine, magnesium, iron, and copper. The chlorella extract contains CGF along with malic acid (apple acid), fructose, lemon essence, and water.

When placebo chlorella tablets and placebo liquid chlorella extract were used, they too were provided by the Chlorella Corporation in packaging that was identical to the packaging of the chlorella tablets and extract. The tablets, which were identical in size, shape, and color to the chlorella tablets, were composed mainly of lactose (88.74%), followed by lecithin (3.99%), gardenia yellow (3.55%), sodium iron chlorophyllin (1.77%), sucrose esters (1.77%), and brilliant blue FCF (0.18%). The placebo chlorella extract was mainly water (80.73%), supplemented by 0.1 N sodium hydroxide (11.21%), fructose (5.21%), 5% aqueous caramel coloring (1.68%), malic acid (0.67%), lemon essence (0.42%), and sodium glutamate (0.08%).

For people in good health, the daily maintenance dosage of chlorella recommended by the manufacturer of the tablets and extract used in these studies is 15 tablets (3 g) and 30 mL, respectively. Daily consumption among healthy people who supplement their diet, however, varies from 1 to 30 tablets (0.2-6 g) and up to 45 mL chlorella extract. For the studies described in this review, subjects consumed 50 chlorella tablets (10 g) and 100 mL of chlorella extract daily for 2 months in the hypertension and ulcerative colitis trials, and 3 months in the fibromyalgia crossover study.

COMMON METHODS

All subjects who participated in the clinical trials of chlorella understood their role and responsibilities for the study and granted their informed consent. The treatment protocols were approved by the Virginia Commonwealth University Committee on the Conduct of Human Research and performed in accordance with all appropriate guidelines and regulations. After the subject provided informed consent, his or her eligibility for that particular study was determined and baseline data (described later) specific to each clinical trial were obtained.

For each subject, a brief medical history was taken and a physical examination was performed to establish eligibility. Depending on the study, these examinations were repeated at clinic visits to assess the status of subjects and to determine whether any new medical condition was present that might contraindicate their continuing the dietary supplements. Besides

doing assessments specific to the study in which the subjects participated, the authors collected urine and venous blood samples at baseline and at specific times thereafter for analysis.

In all of these studies, subjects used a log book and recorded the following information each day: (1) total number of chlorella (or placebo) tablets taken; (2) total volume of the chlorella extract (or placebo) consumed; (3) name and total daily dose of any concomitant drugs; (4) any signs or symptoms of their disease that had either improved or worsened and any adverse event; and (5) general level of physical activity, sleep quality, musculoskeletal pain, headache, and any stresses for that day. All participants were asked not to add any new medications or treatments during the course of the study without notifying one of the investigators.

FIBROMYALGIA SYNDROME

In the United States, 2% to 4% of the general population has fibromyalgia syndrome.⁸ The major complaint of patients with fibromyalgia syndrome is a generalized aching, but its definitive diagnosis is based on standards established by the American College of Rheumatology—criteria based on the severity of a patient's tenderness at a minimum of 11 tender points in 18 characteristic locations measured by palpation.^{8,9} A tender point index (TPI) also can be calculated by taking into account the level of pain the subject feels at each site. Besides pain, other symptoms may be present in fibromyalgia syndrome including fatigue, sleep problems, morning stiffness, and headaches.

Most patients with fibromyalgia syndrome can get some relief from symptoms with nonpharmacological methods such as gentle aerobic exercise or by increasing the amount of sleep while maintaining a regular sleep schedule. Tricyclic antidepressants are commonly used in the treatment of fibromyalgia syndrome, and randomized controlled trials of these antidepressants for fibromyalgia have shown improvement in sleep quality and modest benefit for stiffness and tenderness (reviewed by Arnold et al¹¹). Low doses of amitriptyline, for example, improve deep sleep, but the drug may cause some adverse effects such as weight gain, dry mouth, and cognitive impairment when given in doses sufficient to relieve signs and symptoms of fibromyalgia.^{10,12}

Also, because tolerance to its sedative effect can develop, the dose of amitriptyline often must be increased to maintain any benefit. Although several other classes of medications such as cyclobenzaprine (Flexeril) and alprazolam (Xanax) also have been shown in controlled clinical trials to help relieve signs and symptoms of fibromyalgia syndrome,^{10,13} no evidence has been found that selective serotonin reuptake inhibitors such as fluoxetine (Prozac) show a benefit for pain management or relief of other signs and symptoms¹⁴ (reviewed by Smith¹⁵). Serotonin substrate supplementation via L-tryptophan or 5-hydroxytryptophan, however, improves symptoms of depression, anxiety, insomnia, and somatic pains in patients with fibromyalgia syndrome.¹⁶

Relatively few trials of nonpharmacological, "alternative" treatments for fibromyalgia syndrome have been performed.

One of the more interesting trials that used standard data collection instruments for fibromyalgia syndrome was a pilot study using a mind-body approach (cognitive-behavioral therapy) performed at the University of Maryland School of Medicine a few years ago. That study suggested that such an intervention could be an effective adjunctive therapy.¹⁷ In the trial, 28 subjects with fibromyalgia syndrome underwent 8 weekly sessions with 3 components: an educational component focusing on the mind-body connection, a portion focusing on relaxation response mechanisms, and a qigong movement therapy session. The 20 patients who completed the study showed significant reductions in pain, fatigue, and sleeplessness as well as improved function, mood state, and general health. At present, no food, dietary supplement, or herbal preparation has been proven effective for relief of fibromyalgia syndrome in controlled studies.

The authors of the present study have conducted 2 clinical trials of chlorella in patients with fibromyalgia syndrome. The first was an open-label pilot study that involved 18 subjects with fibromyalgia syndrome who supplemented their diet with 10 g of chlorella tablets and 100 mL of chlorella extract each day for 2 months.¹⁸ Dietary supplementation with these 2 chlorella products led to a mean net decrease of 2 tender points from 17 at baseline to 15 by the end of the study. The average TPI, which was 32 at baseline, decreased to 25, representing a statistically significant decrease in the intensity of pain of 22% ($P=.01$). The results from patients' questionnaires also suggested that they had experienced modest improvements in most of their symptoms of fibromyalgia syndrome.

Although the results of our pilot study suggested that chlorella in the diet improved symptoms of fibromyalgia syndrome, because the subjects were given open-label chlorella, such data were subject to substantial risk of bias on the part of both the subject and the investigator. Nevertheless, the possibility that subjects with fibromyalgia syndrome could have their level of pain (as measured by the TPI) significantly decreased by simply adding chlorella to their diet suggested that a placebo-controlled clinical trial of dietary chlorella supplementation was warranted. Therefore, the objective of this second clinical investigation was to test the hypothesis that subjects with fibromyalgia syndrome benefited from the addition of chlorella to their diet. As we had done in the open-label study, each patient's clinical status was documented at strategic intervals using validated, semiobjective and subjective outcome measures. The magnitude of any resultant change in symptoms of fibromyalgia syndrome—particularly pain—and other outcome variables was determined.

Of the 37 evaluable subjects with fibromyalgia syndrome who met eligibility criteria,¹⁹ there were 36 women and 1 man, with a mean age of 47.1 years (SD, 9.0 years). The average number of tender points was 15.6 (SD, 2.4; range, 11-18), and the mean TPI for the group was 24.4 (SD, 7.4; range, 11-37). To be eligible for the study, subjects also had to indicate a 4 or higher on at least 1 of 2 self-administered 10-cm visual analog scales: one for evaluating pain and the other for evaluating overall

feeling of well-being in light of the signs and symptoms of fibromyalgia syndrome. For these, the mean score for pain was 7.0 (SD, 2.0) and the mean value for well-being was 6.9 (SD, 2.3), indicating that the study population thought that their fibromyalgia syndrome caused them a great deal of pain and was troublesome.

At the beginning of the study, half the participants were randomized to receive chlorella tablets and extract, and the other half were given placebos of the tablets and the extract. The protocol was a double-blind study design, meaning that neither the subject nor the physician doing the tender point assessments knew which of the 2 supplements he or she was consuming. They consumed the supplements (10 g of tablets and 100 mL of liquid) daily for 3 months. After this period, and following a 1-month washout period when no supplement was consumed, subjects crossed over from chlorella to placebo or vice versa.

At the beginning and end of each 3-month period, a physical examination and assessment of tender points were done. Irrespective of the diet supplement the patient was consuming, no new abnormalities were found on physical examination in any of the subjects, and all blood and urine parameters were within normal limits of variation in subjects taking chlorella or placebo.

Measurement of the severity of a patient's pain at each tender point revealed that after 3 months of dietary supplementation with chlorella, a statistically significant ($P=.009$) decrease of 1.1 tender points was detected, whereas in the subjects taking placebo for the same period, a slight increase of 0.3 was found in the mean number of tender points. The difference in the number of tender points between the patients taking chlorella and the patients taking placebo at the end of each diet supplement period was statistically significant ($P=.02$). The mean TPI, which was 23.6 (SD, 6.0) at baseline, decreased to 21.8 (SD, 7.0) after 3 months of taking the chlorella supplements. This decrease of 1.8 points (7.6%) in the intensity of pain approached statistical significance ($P=.07$). After 3 months taking the placebo supplements, the average TPI went from 22.1 (SD, 6.7) at baseline to 21.6 (SD, 6.0), a difference that was not statistically significant. Results for patients who received dietary supplementation with chlorella first were similar to the results for patients who consumed chlorella after taking placebo (data not shown). The same was true when we compared results for patients who received placebo first with results for patients who consumed placebo after taking chlorella.

When we examined the TPI and the percentage change in TPI after subjects consumed the 2 dietary supplements for 3 months, we found that 21 of the 34 subjects (62%) who completed both arms of the crossover showed a better TPI (ie, less pain) after they consumed chlorella than they had shown after taking placebo. Characterization of these responses according to the percentage change in TPI during each of the crossover phases indicated that for the 37 subjects who completed the chlorella arm, 21 (57%) showed a greater than 5% improvement in TPI; 8 of these subjects had a greater than 25% decrease in pain (Table 1). TPI was unchanged in 8 subjects (22%) and worsened in 8

other subjects (22%). When the 34 subjects who completed the placebo arm of the study were subdivided by TPI range, 13 (38%) indicated less pain, 6 (18%) showed no change in TPI, and 15 (44%) indicated that the pain was worse.

Functional abilities or limitations were assessed in subjects by using the Fibromyalgia Impact Questionnaire (FIQ).²⁰ When the subjects were consuming chlorella, there was a steady decrease in the FIQ score, from an average of 58.4 at baseline to 47.0 at the end of the 3-month supplement period (Table 2). This mean decrease of 11.4 (19.5%) in the score indicated a highly statistically significant ($P<.001$) improvement in function. Also, improvements in the FIQ score after 1 month and 2 months with chlorella also were statistically significant ($P=.03$ and $.01$, respectively). For subjects taking the placebo, a statistically significant improvement comparable to the improvement seen when they took chlorella was apparent at 1 month. Unlike the chlorella, however, the improvement resulting from the placebo appeared to plateau, though the slight improvement in FIQ at 2 months remained statistically significant ($P=.04$). At the end of the 3-month period, improvement in the FIQ from visit 1 was only 7.4%, which was not statistically significant.

Comparisons of the percentage changes in the score on the FIQ from visit 1 to visit 4 for the chlorella and placebo arms of the study indicated a better response from participants in the chlorella arm of the crossover, and this difference approached statistical significance ($P=.06$). The results of the FIQ also indicated that after consuming chlorella, 32 subjects' fibromyalgia symptoms were improved, whereas only 9 subjects had worsening of symptoms and 4 had no change in symptoms. This differs from the results after consuming placebo, which indicated that 14 subjects' symptoms were better, but 16 subjects had worsening of symptoms and 4 had no change. Taken together, the results of this randomized, placebo-controlled, double-blind crossover study lead the authors to conclude that for most subjects with fibromyalgia syndrome, dietary chlorella supplementation helped to relieve symptoms.

HYPERTENSION

Hypertension is a serious public health problem that affects an estimated 50 million Americans.²¹ High blood pressure is defined as a mean sitting systolic blood pressure (SiSBP) of 140 mm Hg or higher or a mean sitting diastolic blood pressure (SiDBP) of 90 mm Hg or higher. Hypertension carries the risk for stroke, heart attack, and other vascular diseases. Pharmacological treatment of hypertension has been shown to decrease the risk of these diseases and their complications. Several classes of antihypertensive agents are available to treat high blood pressure.²² Thiazide diuretics and β -blockers are used as first-line agents to treat hypertension, because these drugs reduce morbidity and death from cardiovascular disease. Other classes of drugs also in use for hypertension include angiotensin-converting enzyme inhibitors, α_1 -antagonists, and calcium antagonists.

Nonpharmacological intervention also can be effective in lowering blood pressure and increasingly has been emphasized

TABLE 1 Changes in Tender Point index (TPI) after chlorella and placebo from visits 1 to 4

Status based on change from baseline TPI	No. (%) of subjects	
	Chlorella (n=37)	Placebo (n=34)
Very significantly improved (>50% decrease in TPI)	1 (3)	0 (0)
Significantly improved (>25-50% decrease in TPI)	7 (19)	5 (15)
Moderately improved (>10-25% decrease in TPI)	9 (24)	5 (15)
Mildly improved (>5-10% decrease in TPI)	4 (11)	3 (9)
No change (\pm 5% decrease in TPI)	8 (22)	6 (18)
Mildly worse (>5-10% increase in TPI)	0 (0)	2 (6)
Moderately worse (>10-25% increase in TPI)	4 (11)	10 (29)
Significantly worse (>25-50% increase in TPI)	3 (8)	3 (9)
Very significantly worse (>50% increase in TPI)	1 (3)	0 (0)

as a useful method for prevention and treatment of hypertension.²³⁻²⁵ The 4 principal nonpharmacological methods are weight control (or weight loss), diet modification, exercise, and reduced alcohol consumption. Dietary modifications have focused on reductions in sodium and dietary fat or supplementation with calcium, magnesium, potassium, and dietary fiber. Randomized controlled trials have examined such diet modifications, but failed to demonstrate that a decrease or increase in any one component lowers blood pressure.^{26,27} This result has led to the hypothesis that cations and fiber, which are found together in "whole foods" such as fruits, nuts, vegetables, and cereals, and whose intake is therefore highly correlated, act in synergy to produce a hypotensive effect. Vegetarians with diets rich in fruits and vegetables have substantially lower blood pressure levels on average than do nonvegetarians.²⁷⁻³⁰ The extensive Dietary Approaches to Stop Hypertension (DASH) clinical trial also has demonstrated that a diet that emphasizes fruits, vegetables, and low-fat dairy products; includes whole grains, nuts, fish, and poultry; and reduces fats, red meat, sweets, and sugar-containing beverages can be highly effective in lowering blood pressure.³¹ More clinical trials of specific foods, food groups, and dietary patterns are clearly warranted. Therefore, the objective of this clinical trial of chlorella was to uncover any evidence of chlorella's potential to lower diastolic blood pressure, improve quality of life, and normalize dyslipidemia in subjects with mild to moderate hypertension.

Our study was open to people of either sex, aged 21 years or older with mild (mean SiDBP, 90-104 mm Hg) to moderate (mean SiDBP, 105-115 mm Hg) hypertension who met all other entry criteria for enrollment. All subjects had to be willing to discontinue all medications given specifically for hypertension, including diuretics, though chronic therapies such as aspirin for prevention of myocardial infarction, premarin, and thyroxine were allowed.

A complete physical examination and 12-lead electrocardiography were performed at the screening visit (visit 1) and the final visit (visit 5, or whenever the subject left the study).

Laboratory evaluations (ie, serum chemistry, lipid profile, hematology, and urinalysis) were done at the screening, initiation, and final visits (visits 1, 3, and 5). If the subject's mean SiDBP was between 90 and 115 mm Hg, inclusive, and the subject met all other eligibility criteria, he or she received a month's supply of placebo tablets and placebo liquid and began taking 50 tablets and 100 mL of the liquid every day. None of the subjects were aware that the tablets and liquid were placebos; most importantly, all subjects were instructed to discontinue any medications they were taking for hypertension and to return to the clinic after 4 weeks.

Following this placebo period, subjects had to have a mean SiDBP of between 90 and 115 mm Hg confirmed on 2 occasions at least 24 hours apart (ie, visits 2 and 3) to remain in the study. On visit 2 (approximately 4 weeks after visit 1), subjects completed the quality-of-life questionnaire and had their vital measurements taken. One to 7 days later, during visit 3, subjects completed the quality-of-life questionnaire, had their vital measurements taken, and had laboratory assessments of blood cytology, serum (chemistry and lipids), and urine. At this visit, subjects who still met eligibility criteria began daily dietary supplementation with chlorella.

After 4 weeks, subjects returned to clinic for a brief consultation (visit 4). At this time, they completed the quality-of-life questionnaire, had their vital measurements taken, and were given enough chlorella tablets and liquid extract for another 4 weeks. On visit 5 (ie, the end of the study), subjects again completed the questionnaires, had their vital measurements and an electrocardiogram taken, and had blood and urine samples taken for laboratory assessments.

A total of 33 subjects were enrolled in the trial (range, 22-73 years; mean age, 50 years). Hypertension had been diagnosed a mean of 11 years before the subjects joined the trial (range, 0-47 years), and all but 6 were taking some type of daily medical treatment for hypertension. Mean heart rate was 73.7/min (SD, 10.2/min), mean SiSBP was 136.8 mm Hg (SD, 11.5 mm Hg), and mean SiDBP was 90.8 mm Hg (SD, 6.2 mm Hg).

TABLE 2 Mean overall changes in scores on the Fibromyalgia Impact Questionnaire (FIQ)

Dietary supplement	FIQ score, mean (SD)		% change from visit 1	FIQ score, mean (SD) Visit 3	% change from visit 1	FIQ score, mean (SD) Visit 4	% change from visit 1
	Visit 1	Visit 2					
Chlorella	58.4 (14.9)	52.1 (16.9)	10.7*	49.5 (20.9)	15.1*	47.0 (18.7)	19.5*
Placebo	54.9 (18.6)	49.6 (17.3)	9.7	48.6 (16.5)	11.5*	50.9 (20.0)	7.4

* Statistically significant improvement from visit 1.

Following the 1-month washout of drug and daily consumption of placebo, 24 subjects remained in the trial. Seven were dropped from the study because they no longer met eligibility criteria for mild to moderate hypertension; 2 withdrew due to adverse effects possibly related to their not taking the antihypertensive drug treatment. The mean age of the 24 subjects who finished the protocol was 49 years (range, 22-73 years), and the average duration of hypertension was 10 years (range, 1-40 years). All but 5 of these subjects were taking some type of daily medical treatment for hypertension while enrolled in the trial.

The primary objective of the study was to determine whether adding chlorella to the daily diet of subjects with mild to moderate hypertension would lead to a reduction in mean SiDBP after 2 months. At the first visit (baseline), the mean heart rate for the 24 subjects who finished was 73.4/min (SD, 9.1/min), mean SiSBP was 137.3 mm Hg (SD, 12.3 mm Hg), and mean SiDBP was 92.3 mm Hg (SD, 5.5 mm Hg). After a month off the hypertension medicine and dietary supplementation with placebo, the subjects' mean heart rate increased to 76.5/min (SD, 9.9/min), their mean SiSBP increased to an average of 141.6 mm Hg (SD, 14.4 mm Hg), and their mean SiDBP increased by 4.3 mm Hg to 96.5 mm Hg (SD, 6.6 mm Hg). Although the increase in mean SiSBP was not statistically significant, the increase in mean SiDBP was significant ($P=.004$).

These levels were used to assess blood pressure changes in the subjects. After 1 or 2 months of dietary chlorella supplementation with 10 g of chlorella tablets and 100 mL of chlorella extract, subjects' heart rates, SiSBP, and SiDBP changed only slightly from the values at visit 3 (end of the placebo/washout period). SiDBP was 96.5 mm Hg (SD, 6.6 mm Hg) at visit 3 and 96.3 mm Hg (SD, 9.5 mm Hg) at visit 5. Discontinuation of the antihypertensive medications for a month may have been responsible for the patients' increase in SiDBP; during dietary chlorella supplementation essentially no increase (ie, worsening) was found in the mean SiDBP.

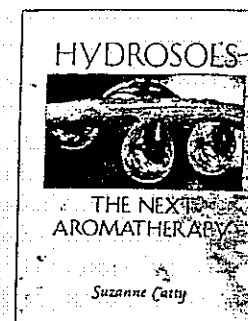
Because working with only mean changes in SiDBP might mask individual responses (ie, decreases in SiDBP) among subjects, each subject's response also was characterized on the basis of 3 different criteria (Table 3). These results indicate that one fourth of the subjects enrolled (6/24) had an excellent response to the dietary supplement (ie, after 2 months of taking chlorella,

their SiDBP was less than 90 mm Hg). Another 3 subjects with an SiDBP greater than 90 mm Hg still showed between a 4 and 9 mm Hg decrease in SiDBP. The remaining 15 subjects, however, were considered inadequately treated by stopping their antihypertensive medication and adding chlorella to their diet; SiDBP either increased during this period or decreased by less than 4 mm Hg. Therefore, if we use the conventional pharmacological criteria for assessing response, slightly more than one third (38%) of the subjects showed some improvement in their hypertension after adding chlorella to their diet.

This improvement with chlorella supplementation, however, was amplified when only a 4 mm Hg change in SiDBP was used as an indicator of response. When the first SiDBP of subjects (measured when most were taking an antihypertensive medication) was compared with the SiDBP measured on their last visit (after 3 months off medication and 2 months taking chlorella), 5 subjects (21%) showed improvement, 6 subjects (25%) showed an essentially unchanged SiDBP, and 13 (54%) had a worsening of their hypertension (Table 3). According to these criteria, almost half of the subjects (11/24) achieved as good or better control of their SiDBP by taking the dietary supplement as they did by taking an antihypertensive drug.

The effects of the dietary supplement were even more dramatic when these same criteria were used to compare the SiDBP of visit 3 (after 1 month off medication and placebo) and after 2 months of dietary chlorella (visit 5; Table 3). Here 9 subjects (38%) showed improved SiDBP, 7 (29%) showed a stable SiDBP, and only one third (8/24) showed a worsening of their hypertension. This finding that the SiDBP of two thirds of the study population either improved or was stable, with the subjects taking no antihypertensive medications, suggested that, for most subjects, dietary supplementation with chlorella either improved the hypertension or kept it under control.

Findings on physical examinations and electrocardiograms did not change between the beginning and end of the study period. Blood cell counts, routine serum chemistries, and urinalysis of the study population at visits 1, 3, and 5 were within normal limits of variation, and no single variable significantly changed during the 3-month course of the investigation. However, when serum lipid levels (ie, total cholesterol, triglycerides, high- and low-density cholesterol) were measured, the averages and standard deviations

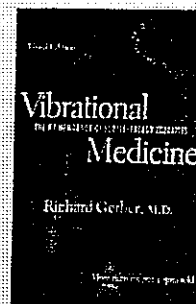


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were within normal limits of variation, and there were numerous statistically significant changes during the course of the investigation (Table 4).

First, a significant decrease in serum cholesterol level was apparent, both from the beginning and from visit 3 to the end of the study ($P=.003$ and $P<.001$, respectively). A significant decrease in triglyceride levels was found from visit 1 to visit 3 ($P=.04$), though this decrease was not maintained and therefore the levels did not differ significantly between visits 1 and 5. High-density cholesterol level decreased after 2 months of dietary chlorella. Between visits 1 and 5, the difference approximated significance ($P=.06$), but between visits 3 and 5, the difference was significant ($P=.03$). Low-density cholesterol showed a similar pattern, decreasing significantly between visits 1 and 5 ($P=.05$) and visits 3 and 5 ($P=.003$).

We also sought to determine whether dietary supplementation with chlorella improved the quality of life of these hypertensive subjects. The Psychological General Well-Being Index²² was used for this assessment, with responses summed to create 6 subscales that measured anxiety, depressed mood, positive well-being, self-control, general health, and vitality. An overall score also was calculated. The subjects' perceived level of anxiety between visit 1 and visit 3 was slightly less and not statistically significant. The decrease in anxiety between visits 3 and 5 also was not significant. However, a comparison of visits 1 and 5 indicated a significant ($P=.02$) decrease in anxiety. Compared with visit 1, depressed mood was significantly improved at visit 3 ($P=.01$) and—even more—at visit 5 ($P=.02$). The improvement in mood between visits 3 and 5 was not statistically significant. The subjects' sense of well-being was significantly better at visit 3 ($P=.002$) and at the end of the study ($P=.007$), but the difference in well-being between visits 3 and 5 was not significant.

Although all values indicated a trend for improvement over the course of the trial, none of the subjects' perceived changes in self-control and general health were statistically significant. The overall scores for the General Well-Being Index showed improvements at every time point. The differences between visits 1 and 3 and visits 1 and 5 were statistically significant ($P=.04$ and $.01$, respectively). These results indicate that subjects were feeling better overall. Anxiety and depression improved significantly for the subjects because of the combined effects of their no longer having to take their regimen of antihypertensive drug(s) and supplementing their diets with chlorella.

ULCERATIVE COLITIS

Inflammatory bowel disease (IBD) is not a single disease, but a group of chronic disorders of the small and large intestines that cause inflammation or ulceration. In the United States, approximately 2 million people have some form of IBD. One of the most common types of IBD is ulcerative colitis. This disease causes ulceration and inflammation of the inner lining of the rectum and large intestine and is considered incurable.

Ulcerative colitis usually begins in the rectum and sigmoid colon and spreads upward through the entire large intestine. It

TABLE 3 Characterization of changes in sitting diastolic blood pressure (SiDBP) after chlorella supplementation

Summary of results by standard end points used in pharmacological studies of hypertension		
Result	Description	No. (%) of patients
Excellent	SiDBP <90 mm Hg	6 (25)
Good	SiDBP >90 mm Hg and reduction from baseline of at least 10 mm Hg	0 (0)
Fair	SiDBP >90 mm Hg and reduction from baseline from 4 to 9 mm Hg	3 (13)
Inadequate	SiDBP >90 mm Hg and reduction from baseline of < 4 mm Hg or an increase	15 (62)
Summary of results based on change of 4 mm Hg or more in SiDBP from visit 1		
Result	Description	No. (%) of patients
Improved	Final SiDBP reduced by 4 mm Hg or more from screening (visit 1)	5 (21)
Stable	Final SiDBP less than 4 mm Hg change from screening (visit 1)	6 (25)
Worse	Final SiDBP increased by 4 mm Hg or more from screening (visit 1)	13 (54)
Summary of results based on change of 4 mm Hg or more in SiDBP from visit 3		
Result	Description	No. (%) of patients
Improved	Final SiDBP reduced by 4 mm Hg or more from initiation (visit 3)	9 (38)
Stable	Final SiDBP less than 4 mm Hg change from initiation (visit 3)	7 (29)
Worse	Final SiDBP increased by 4 mm Hg or more from initiation (visit 3)	8 (33)

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rarely affects the small intestine. The inflammatory process, which is limited to the mucosa and submucosa, causes the mucosal layer of the colon to die and slough off, causing ulcers to form. The inflammation causes the colon to empty frequently, resulting in diarrhea. The most common symptoms of ulcerative colitis are abdominal pain and bloody diarrhea, but patients may have anemia, fatigue, weight loss, loss of appetite, rectal bleeding, dehydration, and malnutrition as well.

The cause of ulcerative colitis is unknown, and the disease currently has no cure except surgical excision of the colon and rectum. However, drugs are commonly used to help control symptoms and slow progression of the disease; examples include sulfasalazine, mesalamine, and prednisone. Because no special diet or dietary supplement has proven effective for preventing or treating ulcerative colitis, the purpose of this study was to determine whether patients with this form of IBD would benefit from the inclusion of chlorella in their diet. This objective was specifically addressed by documenting the clinical status at monthly intervals using validated, semiobjective, and subjective outcome measures administered before, during, and at the end of the diet therapy, and by determining the magnitude of any change in clinical symptoms, signs, and outcome variables over time that could be attributed to the dietary supplement.

Ulcerative colitis involves documented symptoms of hematochezia and diarrhea, negative stool cultures, and typical sigmoidoscopic findings such as superficial ulcerations, distorted mucosal vascular patterns, granularity, and exudate. From these data, a Disease Activity Index (DAI) can be calculated.³³ The DAI is computed from 4 subscales: stool frequency, rectal bleeding, mucosal appearance, and physician's overall assessment. To be eligible for the study, patients had to have mild to moderate ulcerative disease for at least 1 year and a total DAI score between 4 and 10, inclusive. All examinations and interviews for determination of the DAI were performed by the same physician. Nine subjects aged 25 to 56 years met the DAI criteria for ulcerative colitis such that, at baseline, the mean DAI for the group was 7.2 (SD, 2.4). Patients supplemented their diets with 10 g of chlorella and 100 mL of chlorella extract daily for 2 months.

A brief history was gathered and a physical examination and blood analyses were performed at every clinic visit to assess the status of the patient's disease. A flexible sigmoidoscopic examination was again performed to determine the DAI after 2 months of dietary supplementation. Eight subjects completed the entire 2-month study.

Findings on the patients' basic physical examinations did not change significantly from the beginning to the end of the study period. Laboratory values at the 2 visits during the study period remained within the normal limits of variation. For the 8 subjects who completed the trial, the average score decreased (ie, symptoms improved) in every subclass of the DAI between baseline and month 2 (Table 5). The decrease in stool frequency was statistically significant ($P=.02$). The physician's sigmoidoscopic examination of rectal mucosa showed significantly less inflammation ($P=.02$); his overall assessment was that the patients' ulcerative colitis was

significantly better ($P=.008$). Although the occurrence of rectal bleeding was less frequent for most patients, the change was not significant ($P=.18$). The total DAI of every subject declined during the 2-month study, from an average of 7.2 (SD, 2.4) to 2.8 (SD, 2.5)—a 61% drop that was highly significant ($P=.008$).

The effects of dietary chlorella supplementation on patients' quality of life were quantified with the IBD Questionnaire,³⁴ which contains 32 questions about 4 aspects of the patient's life: (1) symptoms related to the primary bowel disturbance, (2) systemic symptoms, (3) emotional aspects, and (4) social functions. The response options for each question were framed as a 7-point scale, with 7 indicating the best function and 1 the worst. Patients' responses on the questionnaire indicated improvements in all 4 categories during the course of the study (Table 6). The greatest improvement was in symptoms related to the primary bowel disturbance. After 1 month, the scores in this category increased by 33% and remained 30% above baseline (visit 1) after 2 months; both scores were highly statistically significant ($P=.001$ and $.003$, respectively).

Scores for emotional aspects of the disease also were significantly improved both at the interim visit ($P=.01$) and the end of the study ($P=.001$). There was a trend for improvement in social functions at 1 month ($P=.07$); improvement was statistically significant by the end of the second month ($P=.02$). Strong trends were observed for improvements in scores for systemic functions, but these improvements were not statistically significant at the interim ($P=.11$) and final ($P=.08$) visits.

The total score of 156 (SD, 26) at baseline increased by 16% by the end of the first month and was 18% higher than baseline at the end of the second month. The improvements observed at both of these times were highly statistically significant ($P=.007$ and $.003$, respectively). Taken together, the DAI results indicating that every participant's objective symptoms of ulcerative colitis improved, combined with the positive assessment each patient gave in his or her questionnaires, strongly suggested that all 8 subjects benefited from adding chlorella to their diet.

DISCUSSION

Treatment of chronic diseases with drugs may relieve symptoms and slow progression, or, as in the case of hypertension, reduce the risk of cardiovascular disease. Unfortunately, drug treatment could entail the lifelong use of an agent that may have adverse effects. For this reason, there is a great deal of interest in nonpharmacological interventions that might reduce or eliminate the need for drugs to treat various illnesses. The principal focus of the research reviewed here was to provide solid evidence from small clinical trials that dietary supplementation with chlorella could relieve symptoms and improve quality of life for those suffering from fibromyalgia, hypertension, or ulcerative colitis.

Fibromyalgia Syndrome

People with fibromyalgia syndrome are typically treated with the tricyclic antidepressant amitriptyline to improve their

TABLE 4 Serum lipid levels during chlorella supplementation*

Parameter	Visit 1, screening	Visit 3, initiation	Visit 5, final	Normal values
Total cholesterol, mmol/L (mg/dL)	5.22±1.11 (202±42.9)	5.15±1.01 (199±38.9)	4.86±1.04 (188±40.1)	0.00 - 5.17 (0-200)
Triglycerides, mmol/L (mg/dL)	1.43±0.92 (127±81.8)	1.23±0.73 (109±65.1)	1.39±0.88 (123±77.6)	0.34 - 2.26 (30-200)
High-density cholesterol, mmol/L (mg/dL)	1.25±0.33 (48.5±12.9)	1.26±0.32 (48.7±12.3)	1.19±0.30 (46.2±11.5)	1.01 - 2.48 (39-96)
Low-density cholesterol, mmol/L (mg/dL)	3.31±1.05 (128±40.7)	3.34±0.93 (129±35.9)	3.05±0.96 (118±37.2)	1.91 - 4.91 (74-190)

* All values are mean ± SD.

sleep and relieve other symptoms. Other classes of psychotropic drugs are less efficacious, including selective serotonin reuptake inhibitors like fluoxetine and paroxetine, benzodiazepines such as alprazolam (Xanax), and muscle relaxants (eg, cyclobenzaprine). Nonpharmacological approaches that are sometimes used include light exercise and psychological support. Nutritional approaches, however, have received little attention. The results of the study with fibromyalgia syndrome indicate that, for some subjects, taking chlorella daily can improve sleep and reduce anxiety levels. These 2 factors might in turn lead to a reduction in perceived pain and the number of tender points in the same way that medications that improve sleep or reduce anxiety produce relief of fibromyalgia symptoms.

Another interesting avenue of speculation for chlorella's action comes from the observation that some of the clinical features of fibromyalgia syndrome resemble those seen in adults with growth hormone deficiency syndrome. Several investigations have suggested that fibromyalgia syndrome is

associated with growth hormone deficiency and that this may be responsible for some of its symptoms.³⁵⁻³⁸ Levels of insulin-like growth factor I (IGF-I), a surrogate marker for growth hormone activity, also are frequently reduced in those with fibromyalgia syndrome.

In 2 recent clinical studies,^{35,38} subjects who had fibromyalgia syndrome and low IGF-I levels showed improvements in overall symptoms and pain as well as reduction in the number of tender points following several months of daily growth hormone therapy. Bennett³⁷ hypothesized that dysfunctional secretion of growth hormone in patients with fibromyalgia syndrome was due to intermittent hypercortisolemia from stress, which in turn up-regulated the density of β-adrenergic receptors in the hypothalamus. The augmentation of β-adrenergic receptors stimulated the release of somatostatin, which impaired secretion of growth hormone. It remains to be seen whether consumption of chlorella works in some way to increase production of growth hormone and whether, by doing so, it reduces symptoms of fibromyalgia syndrome.

TABLE 5 Changes in symptoms during the course of the trial as determined by the Disease Activity Index

Patient No.	Stool frequency		Rectal bleeding		Mucosal appearance		Overall assessment		Total	
	Visit 1	Visit 3	Visit 1	Visit 3	Visit 1	Visit 3	Visit 1	Visit 3	Visit 1	Visit 3
01	1	0	1	0	1	1	1	0	4	1
03	0	0	1	0	2	1	2	1	5	2
04	2	0	0	0	1	0	1	0	4	0
06	3	2	1	2	3	3	3	2	10	8
07	2	0	2	2	2	1	2	1	8	4
09	2	0	1	1	1	1	2	1	6	3
10	2	0	3	0	3	1	2	0	10	1
11	1	0	2	1	2	1	2	1	7	3
Mean	1.8	0.3	1.6	0.8	1.9	1.1	1.9	0.8	7.2	2.8
SD	0.9	0.7	1.0	0.9	0.6	0.8	0.6	0.7	2.4	2.5

TABLE 6 Results of the Inflammatory Bowel Disease Questionnaire

Patient No.	Primary bowel disturbance			Systemic symptoms			Emotional functions			Social functions			Total		
	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3
01	51	59	64	15	17	22	57	56	69	30	31	35	153	163	190
03	44	65	63	20	29	21	62	68	72	34	35	35	178	197	191
04	35	58	59	13	25	25	49	63	67	28	35	35	125	181	186
06	49	57	53	30	32	28	63	67	73	32	32	31	174	188	185
07	35	44	43	30	23	30	50	54	57	26	32	29	141	153	159
09	47	63	66	21	27	25	67	78	74	22	35	35	157	203	200
10	41	61	59	27	29	28	69	80	80	30	33	34	167	203	201
11	43	46	44	21	24	23	60	62	66	29	27	30	153	159	163
Mean	43	57	56	22	26	25	60	66	70	29	33	33	156	181	184
SD	6.0	7.7	8.9	6.4	4.6	3.2	7.3	9.4	6.8	3.7	2.7	2.6	26	24	21

Hypertension

Randomized, controlled, clinical trials and population studies have shown that the blood pressure of hypertensive subjects could be lowered with a vegetarian diet. Such diets are characterized by relatively low saturated fats, a high polyunsaturated/saturated fat ratio, and a high intake of fruit, vegetables, and other fiber-containing and vitamin-rich products. Comprehensive studies, however, have failed to uncover which specific nutrients in the vegetarian diet account for its blood-pressure-lowering effect and instead have suggested that "whole foods," with their complex combination of nutrients acting synergistically, are responsible.

The study with chlorella sought to determine whether daily intake for 2 months could lead to a reduction in diastolic blood pressure. Based on standard criteria of the pharmaceutical industry, the results indicated that one quarter of the subjects who completed the trial (6/24) had an excellent response to the dietary supplement (ie, their SiDBP was less than 90 mm Hg), and that 3 subjects whose SiDBP was greater than 90 mm Hg still showed between a 4 and 9 mm Hg decrease in SiDBP. When a 4 mm Hg change in SiDBP was used as an indicator of response and the SiDBP at visit 3 (after 1 month off medication and placebo) was compared to the SiDBP after 2 months of dietary chlorella (visit 5), 9 subjects showed improved SiDBP, 7 showed a stable SiDBP, and one third showed a worsening of hypertension. Questionnaires administered to subjects at each clinic visit indicated that during the course of the study, overall perception of health was significantly improved. The results of the study therefore indicated that some subjects could have mild or moderate hypertension reduced or kept stable with daily dietary supplementation of chlorella alone, eliminating the need for an antihypertensive medication. A daily supplement of chlorella could have direct and indirect effects on blood pressure and on the regulatory functions of endothelial cells, or could cause noradrenaline-induced vasoconstriction of arterioles, as other dietary supplements have been shown to do.^{39,40}

Ulcerative Colitis

Because studies with animals and humans have suggested that *C pyrenoidosa* in the diet has many beneficial effects on wound healing and immunologic reactions, the authors hypothesized that the supplement could be effective for relief of symptoms of ulcerative colitis. This was indeed the observation; all subjects showed a statistically significant decline in DAI, from an average of 7.2 (SD, 2.4) to 2.8 (SD, 2.5) after 2 months. Furthermore, the subjects' own assessments of their symptoms, as indicated in their responses to the IBD Questionnaire, indicated that they believed the severity of their ulcerative colitis lessened soon after beginning the trial, continuing to decrease or remain stable throughout the course of the study.

CONCLUSION

Additional comprehensive studies are clearly needed to identify the macronutrients and micronutrients in chlorella as well as how such nutrients might act together to exert beneficial effects for the chronic diseases studied here. Further laboratory and dietary clinical studies will uncover the mechanisms by which chlorella improves conditions and symptoms of these and other chronic diseases.

Acknowledgments

These studies were supported in part by a contract and grant from Sun Chlorella Corporation of Kyoto, Japan. The authors thank Christopher M. Wise, MD, Domenic A. Sica, MD, Cynthia B. Bettinger, MD, and Donald F. Kirby, MD, for their collaboration on these clinical trials.

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