The Effects of Spirulina (Arthrospira platensis) Supplementation on Anthropometric Indices, Blood Pressure, Sleep Quality, Mental Health, Fatigue Status, and Quality of Life in Patients with Ulcerative Colitis: A Randomized, Double-blinded, Placebo-controlled Trial

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Running title: The Effects of Spirulina on Ulcerative Colitis Patients

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List of Abbreviations:

BMI: Body mass index

DASS: Depression, Anxiety, Stress Scale

DBP: Diastolic blood pressure

FFS: Fatigue Severity Scale

HC: Hip circumference

IBD: Inflammatory bowel disease

IPAQ: International Physical Activity Questionnaire

NC: neck circumference

PSQI: Pittsburgh Sleep Quality Index

SBP: Systolic blood pressure

SCCA I: Simple Clinical Colitis Activity Index

SIBDQ: Short IBD Questionnaire

WC: Waist circumference

WHR: Waist to hip ratio

ABSTRACT

Background: An emerging body of evidence has highlighted the protective role of spirulina in human health. Thus, we conducted a randomized controlled trial to discern the effects of spirulina supplementation on anthropometric indices, blood pressure, sleep quality, mood, fatigue status, and quality of life among ulcerative colitis patients.

Methods: Eighty participants with ulcerative colitis were randomly allocated to receive, either, 1 g/day (two 500 mg capsules) spirulina (n=40) or placebo (n=40), in a clinical trial for eight

weeks. Dietary intake, physical activity, sleep quality, mental health, fatigue status, and quality of life were assessed for each participant at baseline and trial cessation. Anthropometric indices and blood pressure were also assessed.

Results: Seventy-three participants completed the intervention. Our results revealed that spirulina supplementation significantly reduced sleep disturbances ($p=0.03$), while no significant changes occurred in the sleep quality score or other sleep parameters, vs. the placebo group ($p> 0.05$). Furthermore, a significant reduction in stress score ($p=0.04$) and increase in quality of life ($p=0.03$) was detected; but not anxiety, depression, or fatigue scores ($p> 0.05$). Additionally, anthropometric indices and blood pressure did not significantly change ($p> 0.05$).

Conclusion: An improved quality of life was observed among ulcerative colitis patients following spirulina supplementation, which could be attributed to improved sleep disturbance and stress status. Further clinical studies, with longer duration interventions and suitably powered sample sizes, are necessary to elucidate the veracity of our findings.

Keywords: Spirulina; Ulcerative Colitis; Clinical trial; Sleep quality; Mood

What's already known about this topic?

- An emerging body of evidence has highlighted the protective role of spirulina in human health.
- There have been no studies regarding the effects of spirulina supplementation on ulcerative colitis patients.

What does this article add?

- This study is the first clinical trial to evaluate the effects of spirulina supplementation on anthropometric indices, blood pressure, sleep quality, mood, fatigue status, and quality of life among ulcerative colitis patients.

- An improved quality of life was observed among ulcerative colitis patients following spirulina supplementation, which could be attributed to improved sleep disturbance and stress status.

INTRODUCTION

In recent decades, the prevalence of inflammatory bowel disease (IBD), a chronic immune-mediated disorder, has been rising steadily. [1] Ulcerative colitis is one of the most common forms of IBD and is characterized by clinically intermittent periods of exacerbation and remission .[2] Ulcerative colitis may lead to several additional problems, including, sudden weight loss, abdominal and joint pain, rectal pain and bleeding, cramping, constipation, frequent loose bowels [3,4], severe fatigue [5], poor sleep quality [6], and mental disorders .[7] However, the pathogenesis of this disease is not completely understood; indeed, several studies have documented that the interactions between genetic, environmental factors, gut microbiota, and immunopathologic responses are associated with the triggering of ulcerative colitis.[8-11] Typically, immunosuppressive and anti-inflammatory drugs are used to control the immune-inflammatory reaction in ulcerative colitis patients [12]; however, these drugs tend to cause a number of short-term or long-term side effects,such as incresesed risk of infection, hepatotoxicity, osteoporosis, tremor, eyes problems, gastrointestinal problems, pancreatitis, mental disorders, and antigen-antibody reactions . [13,14] Hence, the use of comparably safer complementary therapies, with fewer side effects and lower toxicities, may be efficacous in ulcerative colitis management.

Indeed, growing evidence posits that the use of herbal medicines, and their extracted compounds, with protective and antioxidant properties, can also be effective and safe for the management of ulcerative colitis disease .[15-20] For instance, nigella sativa [15], silymarin [16], ginger [17], ferulago[21], curcumin [18], and resveratrol [19] have been shown as potentially effective agents in improving, managing, or ameliorating ulcerative colitis and/or its accomonaying comorbidities. Spirulina *(Arthrospira platensis),* as eco-friendly *cyanobacterium* (*Oscillatoriaceae* family), is a spiral blue-green microalgae [22,23], which is edible and widely consumed as food or nutritional supplement .[24] It is a good source of essential nutrients, especially amino acids, phytochemicals (carotenoids and phycocyanins), vitamins (vitamin B12 and provitamin A), essential fatty acids, minerals (calcium and iron), and fiber .[25-27] Spirulina adminstration has been posited as a

complementary therapy for the management of several diseases, owing to its antioxidant, liver-protecting, anti-inflammatory, anti-hypertension, cancer prevention, anti-viral, and antibacterial activities .[25,26,28] Further, contemporary studies have indicated that spirulina represents a good source of tryptophan, which can viably lead to to improvements in themental health of patients .[29] Moradi-Kor et al.[30] also reported that spirulina supplementation may reduce adolescent stress, anxiety, depression-related neuroanatomical biochemical, and molecular deficits in adult female rats. Concordantly, Madhu et al. [31] showed that spirulina supplementation has dose-dependent antidepressant properties in murine models.

Therefore, we sought to conduct a randomized, double-blinded, placebo-controlled trial to discern the effect of spirulina (Arthrospira platensis) powder on anthropometric indices, blood pressure, sleep quality, anxiety, stress, depression, quality of life, and fatigue status in ulcerative colitis patients.

MATERIALS AND METHODS

Subject characteristics

A total of 426 ulcerative colitis patients, who were referred to the Imam Khomeini Hospital (Kermanshah, Iran), were interviewed during the trial period between 15 May 2020 and 31 December 2020. Among these patients, 80 individuals were eligible and volunteered to participant in the clinical trial. During the two months trial, seven participants dropped out of the study. The inclusion criteria were; having diagnosed ulcerative colitis according to colonoscopy, clinical records, and pathology; being in the age range of 18–65 years; having symptoms of active mild-to-moderate ulcerative colitis disease ($5 \leq$ Simple Clinical Colitis Activity Index (SCCAI)$\leq$ 12 score) . [32] These individuals were excluded: patients with severe ulcerative colitis (SCCAI) < 5 or > 12 scores, individuals in pregnancy or breastfeeding condition; taking antidepressants, anxiety, and stress drugs; taking antioxidant and omega-3 supplements in the last three months; smokers or alcohol consumers; patients with heart disease, liver, kidney, cancer disease, thyroid and parathyroid or other gastrointestinal diseases; participants with poor compliance (using less than 90% of the supplements).

The present clinical trial was conducted according to the Helsinki Declaration, and written informed consent was signed by all patients prior to participation in the study. The protocol of this study was certified by the ethical committee at the Isfahan University of Medical Sciences (code: IR.MUI.RESEARCH.REC.1398.436, approval date Oct. 23 2019) and registered at: http://www.IRCT.ir (code: IRCT20191204045612N1).

Experimental Setting

The current work was a randomized, double-blind, placebo-controlled clinical trial. By simple sampling method, 80 participants, with active mild to moderate ulcerative colitis, were allocated to spirulina (n= 40) or the control (n= 40) groups, randomly. The intervention group supplemented with a 500 mg capsule of Spirulina, two times a day, before lunch and dinner for eight weeks, and the other group received placebo capsules, of inert contents, but of equivalent weight and appearance. Patients visited twice during the trial (at the baseline and end of intervention). All patients were requested to continue their habitual physical activity, dietary intake, and their current drug regimen throughout the follow-up period. Finally, compliance was evaluated through weekly phone calls and monitoring the number of used packages.

Sample size calculation

Sample size was calculated considering type I and statistical power of 5% and 80%, respectively. Minimum detectable effect size (variations in clinical response) was considered to be 0.3, concordant with similar clinical trials in ulcerative colitis patients. [33,34] Sample size was calculated as 33 participants in each intervention/placebo group, and considering ~20% dropout rate, 40 patients were determined as necessary for each group.

Randomization and blinding

In the current study, a simple randomization method, using a random number table, was used, where patients, laboratory staff, researchers, and participants were blinded to the supplement

allocation, until the end of the study. Further, at the start of the supplementation period, capsules were administered in packages labeled with A or B, to blind the researcher and participants.

Assessments

Anthropometric parameters were assessed at the start of the intervention and at study cessation. The participants' height was evaluated via a nonelastic wall-mounted stadiometer, measured to the nearest 0.5 cm. The individuals' body weight was assessed, with participants dressed in minimal clothes, using a digital scale, with an accuracy of 0.1 kg. Neck circumference (NC), Hip circumference (HC), and The Waist circumference (WC) was measured using a non-stretch tape measure, without any pressure on the body surface. Waist to hip ratio (WHR) was calculated as WC/HC, and body mass index (BMI) was estimated as weight (kg)/square of height (m). Moreover, blood pressure was assessed, with participants in a seated position and after 5 min rest, at the beginning and end of the intervention, based on the European Society of Hypertension [35] guidelines, using a mercury sphygmomanometer (Riester)

All measurements were taken at the beginning and end of the study. To evaluate the dietary intakes of each patient, food diaries for 3 days (including one weekend day) were recorded. Nutrient intakes were computed using Nutritionist IV software (First Databank, San Bruno, CA) modified for Iranian foods. Physical activity levels were assessed via the short form of International Physical Activity Questionnaire (IPAQ)[36], whilst the sleep quality and duration were evaluated using the Pittsburgh Sleep Quality Index (PSQI) questionnaire .[37] Depression, Anxiety, Stress Scale (DASS- 21- items) questionnaire was applied to evaluate mood scores in ulcerative colitis patients, where the reliability and validity of the questionnaire has been demonstrated in Iranian populations .[38] To evaluate the fatigue level of ulcerative colitis patients, the Fatigue Severity Scale (FFS) questionnaire, validated in Iranian populations, was used .[39] The short IBD Questionnaire (SIBDQ) score was used to assess the quality of life of patients, where its' validity and reliability have been confirmed, first, by Jowett et al. for patients with ulcerative colitis ($r = 0.83$)[40], and second, in an Iranian population .[41]

Statistical Methods

Data analyses were conducted using SPSS Version 22 (Inc., Chicago IL., USA.) Q–Q plots, skewness, and normality tests were used to evaluate the distribution of the data. All variables were reported as mean ± standard deviation (SD). Participants' characteristics and micro-nutrients and macro-nutrients intake were evaluated between spirulina and the placebo groups, using independent t-tests for quantitative and Chi-square for qualitative variables. The within-group analysis was carried out using paired t-tests. Multiple linear regression (adjusted for baseline value of age, disease length, and beginning BMI) was applied to find any differences between the spirulina and the placebo groups at the end of the intervention. Bonferroni correction was used for multiple testing adjustments. We considered a p value < 0.05 to represent statistical significance, *a priori*, for all the efficacy measures.

RESULTS

Subjects' Baseline Characteristics

A total of 80 participants, with mild or moderate levels of ulcerative colitis, were registered in our study and randomly dichotomized into a spirulina and a placebo group. Among the 80 patients who were included in the study, seven participants withdrew, for personal reasons (n = 3) and alteration of supplementation (n = 4) (Figure 1). Ultimately, analyses were conducted on 73 patients (36 in the Spirulina group and 37 in the control group), with a compliance of >90%.

Table 1 details the participants' characteristics at the beginning of the study. No significant differences in baseline characteristics of ulcerative colitis patients between intervention and control groups, for age, sex, height, weight, BMI, WC, HC, NC, SBP, DBP, disease duration, the dose of mesalazine, family history, sleep quality, anxiety, stress, depression, fatigue scores, and current medication (all p> 0.05), (Table 2). Further, the differences in macronutrient and micronutrient intake and physical activity were not significantly different between group (p> 0.05), (**Table 2**).

Effects of Spirulina Supplementation on Anthropometric Parameters and Blood pressure

The efficacy of spirulina administration on anthropometric parameters are shown in **Table 3.** Within-group comparison revealed a significant increase in body weight (p= 0.02) and BMI (p= 0.02) among participants who supplemented with spirulina. However, after correcting for multiple testing, no significant effects were detected in the body weight, BMI, WC, HC, NC, WHR, systolic blood pressure (SBP), diastolic blood pressure (DBP), in comparison with the placebo group (all p> 0.05).

Effects of Spirulina Administration on Sleep quality

The results of spirulina supplementation on sleep quality score and its parameters are reported in **Table 3.** Within-group comparison demonstrated a significant decrease in sleep quality score (p=0.01 for spirulina group and p=0.01 for the placebo group) and sleep disturbances (p=0.004) for the spirulina group. After correcting for multiple comparisons, there was a significant reduction in sleep disturbances (p= 0.03) in the spirulina group, while no significant changes occurred in the sleep quality score, sleep duration, subjective sleep quality, sleep latency, sleep efficiency, use of sleep medication, and daytime dysfunction parameters, in comparison with the control group (p> 0.05).

Effects of Spirulina Supplementation on Mood and Fatigue status and Quality of life

Within-group comparison indicated a significant decrease in stress score (p<0.001 for spirulina group and p= 0.04 for placebo group) and depression score (p= 0.01 for spirulina group and p= 0.02 for placebo group) among tow group (**Table 3**). Further, within-group comparison demonstrated a significant increase in quality of life (p<0.001 for spirulina group and p= 0.01 for the placebo group) in both groups. After correcting for multiple testing, the stress score (p= 0.04) remained statistically significant in comparison with the control group. Furthermore, a significant increase in quality of life remained after correcting for multiple comparisons (p=0.03)

vs. the placebo group (**Table 3**). However, there were no significant changes regarding anxiety, depression, and fatigue scores in comparison with the control group ($p > 0.05$).

Side effects

The participants did not report any allergic or serious adverse events during the clinical trial. Some of the patients reported mild bloating at the beginning of supplementation during the study; however, all bloating events resolved during the supplementation period. Although not observed in this study, possible adverse consequences for Spirulina have been observed in some case reports, including acute rhabdomyolysis and anaphylaxis.[42] Indeed, it would be advisable to consider an allergy risk evaluation before supplementation.[24]

DISCUSSION

An emerging body of evidence has highlighted the beneficial effects of spirulina in human health. Indeed, this spiral blue-green microalgae is a good source of important nutrients [25-27], and could be used as a complementary therapy for health improvement in several non-communicable diseases. [25,26,28] To the best of our knowledge, the current work is the first randomized, double-blinded, placebo-controlled trial to comprehensively assess the efficacy of spirulina (Arthrospira platensis) supplementation on anthropometric indices, blood pressure, sleep quality, anxiety, stress, depression, and fatigue status in ulcerative colitis patients. Accordingly, our results revealed that no significant effects were detected in the anthropometric indices or blood pressure, after spirulina supplementation, among patients with ulcerative colitis, in comparison with the placebo group. However, spirulina supplementation significantly reduced sleep disturbances at the end of eight weeks, although no significant changes occurred in the sleep quality score or other sleep parameters, in comparison with the control group. In addition, a significant reduction in stress score and an increase in quality of life was observed following eight weeks of administration with spirulina in comparison with the placebo group, but not for depression, anxiety, or fatigue scores.

The present study indicated that 1 g/day spirulina supplementation did not affect anthropometric indices in ulcerative colitis patients. A previous systematic review and meta-analysis of randomized clinical trials [24], incongruent to our results, posited that >2 g/day spirulina

administration can significantly decrease anthropometric indices among overweight or obese subjects. The authors reported that spirulina supplementation may lead to decreases weight or other anthropometric indices through reduction of oxidative stress and free radicals, anti-inflammatory effects, decreasing liver-lipid accumulation, and a mediatory effect on appetite. [24] Although, a more recent meta-analysis [43], concordant with our results, suggested that relatively low doses of spirulina supplementation did not affect weight or BMI, respectively. Although, in quantities >2g/day, some anthropometric changes were observed[43]. Nevertheless, given that loss of appetite and weight loss are the common symptoms in patients with ulcerative colitis [44,45], more than 2 g/day of spirulina supplementation may exacerbate the symptoms and complications of ulcerative colitis.

We observed that eight weeks of 1 g/day Spirulina administration did not significantly change blood pressure in ulcerative colitis patients. Previous clinical studies have reported conflicting outcomes regarding the efficacy of spirulina on blood pressure. [46,47] Driessche et al [46] indicated that a daily intake of 4.8 g spirulina did not affect SBP or DBP among non‐hypercholesterolemic adults. In contrast, several studies revealed that 2 to 4.5 g/day spirulina supplementation significantly reduced the SBP or DBP .[48-52] However, Huang et al.[47], in their meta-analysis, observed that spirulina administration has a beneficial effect on DBP improvement, but not SBP. Indeed, the extant literature posits that spirulina contains phycocyanin and peptides with antihypertensive properties which may be able to decrease the SBP or DBP via increases nitric oxide synthase, inhibition of angiotensin I-converting enzymes, and consequently inhibiting renin–angiotensin–aldosterone system. [48-52] However, the effective spirulina dosage and its' mechanism of action on blood pressure are still controversial, and therefore, more clinical trials with a longer length of intervention and suitably powered sample sizes are essential.

Several studies have shown that sleep and its parameters may be related to some symptoms and severe exacerbations of ulcerative colitis. [6,53,54] Hood et al.[6] reported that poor sleep quality is prevalent in ulcerative colitis patients, whilst Ananthakrishnan et al.[53] also, in their prospective cohort study, indicated that less than six hours/day or higher than nine hours/day sleep were each related with an enhanced risk of ulcerative colitis. Moreover, Sobolewska-Wlodarczyk et al. [54] revealed that sleep disturbance was prevalent among ulcerative colitis patients. Therefore, the

monitoring and management of sleep abnormalities can help colitis patients to improve their health status. The results of the current trial, for the first time, suggested that spirulina administration for eight weeks could significantly diminish sleep disturbances in ulcerative colitis patients, albeit no significant differences were detected in the sleep quality score or other sleep parameters in comparison with the control group. Spirulina can putatively improve sleep disturbances via various proposed mechanisms. First, spirulina manufactures extracellular products with microbial-modulating properties [42], where it has been reported that non-normal microbial diversity was observed among participants who had poor sleep quality. [55] The microbial-modulating properties of spirulina via inhibit the growth of some Gram-negative or Gram-positive bacteria [42], which may help achieve normal intestinal bacterial distribution in poor sleep quality individuals. Second, spirulina as functional food has several bioactive contents with anti-inflammatory or antioxidant functions. [56-58] According to previous literature, a higher oxidative or inflammatory condition in patients is strongly associated with poor sleep quality and sleep disturbance problems. [59,60] Spirulina bioactive components, including phycobiliprotein, β-carotene, and phycocyanin, can elicit decreases in lipid peroxidation or attenuate expression of inflammatory genes, which can ameliorate oxidative or inflammatory status [56-58], and consequently enhance sleep quality. Third, spirulina can increase leptin secretion from adipose tissue [61]; indeed, Hirota et al suggested that plasma leptin concentrations were positively related to higher sleep quality. [62] It is possible that the increased leptin levels may lead to a higher sleep quality. Notwithstanding the posited mechanisms, further clinical trials are necessary to confirm the precise mechanism of action.

The main therapeutic strategies in ulcerative colitis patients are to sustain a good quality of life by preventing relapse, and treating symptomatic periods when they happen. [63] Langhorst et al. [64] reported that short-term stress was positively related to higher risk of relapse among ulcerative colitis patients, whilst Levenstein et al.[65] also demonstrated that life stress was related with both subjective and objective aspects of relapse in ulcerative colitis. Therefore, stress management methods may help to decrease disease relapse risk in ulcerative colitis patients and increase the quality of life. [64,66] Indeed, a novel finding in our study was that a significant reduction in stress score and increase in quality of life was observed following supplementation with spirulina in comparison with the control group. Spirulina supplementation, via potential mechanisms, may conceivably affect stress status of ulcerative colitis patients through anti-oxidative or anti-

inflammatory features. [67,68] In addition, spirulina can help to maintain normal intestinal bacterial distribution and decrease potential disorders from opportunistic pathogens, like E.coli and Candida albicans, and subsequently lower leakage into the bloodstream [22], which, in turn, can reduce inflammatory load and stress risk. [69] C-phycocyanin, a bioactive component of spirulina, selectively inhibits cyclooxygenase-2 [70], which is involved stress-related psychiatric disorders [71], in addition to possessing bio-absorptive attributes against environmental heavy metals exposure, such lead or cadmium [72,73], and may reduce risk of heavy metals-induced neurotoxicity. [74] Furthermore, spirulina supplementation, through an inhibitory effect on pancreatic lipase enzymes and jejunal cholesterol absorption [24], may lead to improvements in cholesterol-induced mood disorders. [75] Despite the apparent effect of spirulina supplementation on reducing stress, it did not yield on changes in depressive and anxiety symptoms or fatigue score of ulcerative colitis patients in our study. Considering the potential effects of spirulina on mental health [29,31,76,77], a longer course of intervention or a higher dose ma improve the efficacy of spirulina supplementation on other aspects of mental health, however further trials are warranted accordingly.

Overall, improvements in quality of life observed after spirulina supplementation in the present study could be due to improved sleep disturbance [78] and stress [63] status in patients with ulcerative colitis. Indeed, the enhanced quality of life among individuals with ulcerative colitis might potentially decrease disease activity and risk of symptomatic periods. [63,78]

STRENGTHS AND LIMITATIONS

We, for the first time, conducted a parallel randomized, placebo-controlled, and double-blind clinical trial that comprehensively examined the efficacy of spirulina supplementation on health status among free-living participants with ulcerative colitis disease. Further, the high number of participants that completed the clinical trial indicated good compliance of patients with their therapy. Additional strengths of this work include the homogeneous population of ulcerative colitis patients, and also the assessment of physical activity and dietary intake as important confounding factors during the intervention.

However, notwithstanding the strengths outlined above, our study, like other clinical trials, had some limitations. Due to the participants declining post-intervention colonoscopy, because of its invasive nature, we were not able to apply colonoscopy or tissue biopsy results to evaluate the severity of ulcerative colitis disease. Although, we applied a valid and reliable SCCAI questionnaire as an effective tool to counteract this issue. The dose-dependent efficacy of spirulina supplementation was not evaluated in the study, meaning that we cannot infer such a relationship. Finally, the time of intervention in the current trail was potentially not long-enough to elicit anthropometric changes, so a longer duration for spirulina supplementation in ulcerative colitis patients is recommended.

CONCLUSION

In summary, the present study was conducted to assess the efficacy of spirulina (Arthrospira platensis) supplementation on anthropometric indices, blood pressure, sleep quality, mood, and fatigue status among patients with ulcerative colitis. Our results revealed that no significant effects were detected in the anthropometric indices or blood pressure, after spirulina supplementation in comparison with the placebo group. However, spirulina supplementation significantly reduced sleep disturbances, in comparison with the control group. Furthermore, a significant reduction in stress score and increase in quality of life was observed following spirulina supplementation vs. the placebo group, but not for depression, anxiety, or fatigue scores. Further clinical trials, with a longer duration of intervention, higher doses and suitably powered sample sizes in different groups, are necessary to confirm the veracity of our results.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

SM, MZ and ME designed this study. SM, MZ and ME contributed in trail operation. SM and AF performed the statistical analysis, and interpretation of data. SM wrote the manuscript. ME and CC critically revised the manuscript. All authors approved the final version of the manuscript.

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Table 1. Participants' properties at baseline

Variables	Spirulina group (n = 36)	Placebo group (n = 37)	p^a
Age(years)	37.77 ± 11.67	39.48 ± 11.03	0.52
Sex (female/male)	18/18	20/17	0.72
Height (cm)	166.73 ± 8.38	165.37 ± 8.82	0.50
Weight (kg)	75.33 ± 13.59	69.72 ± 14.54	0.43
BMI (kg/m2)	26.01 ± 4.41	25.61 ± 5.05	0.73
WC (cm)	89.83 ± 11.46	87.56 ± 11.06	0.39
HC (cm)	9418 ± 18.83	96.81 ± 11.80	0.47
NC (cm)	36.72 ± 3.99	35.30 ± 3.97	0.30
SBP (mmHg)	11.87 ± 0.90	11.78 ± 1.66	0.77
DBP (mmHg)	7.97 ± 1.16	7.97 ± 1.16	0.74
Disease duration (year)	7.16 ± 5.59	5.21 ± 5.02	0.12
Dose of Mesalazine (mg/day)	2277.77 ± 1614.41	1959.45 ± 1180.73	0.41
Sleep quality score	11.11 ± 6.55	11.45 ± 6.02	0.81
Anxiety score	15.83 ± 12.57	16.45 ± 10.50	0.81
Stress score	22.00 ± 10.48	20.43 ± 9.54	0.51
Depression score	16.72 ± 12.74	16.91 ± 11.28	0.94
Fatigue score	33.55 ± 13.53	35.02 ± 11.57	0.61
Family history n (%)	8 (22.2)	7 (18.9)	0.72
Current medication n (%)			
Mesalazine (oral)	30 (83.3)	32 (86.4)	0.23
Mesalazine (rectal)	11 (30.5	12 (32.4)	0.32
Sulfasalazine	6 (16.6)	3 (81)	0.69
Prednisolone	3 (8.3)	3 (8.1)	0.35
Azathioprine	6 (16.6)	5 (13.5)	0.62

Note: Variables are expressed as mean ± SD. Abbreviations: BMI, Body mass index; WC, Waist circumference; HC, Hip circumference; NC, Neck circumference; SBP, Systolic Blood Pressure; DBP, diastolic blood pressure . [a] p values resulted from independent t tests for quantitative and Chi-square for qualitative variables between the two groups.

Table 2. Dietary intake and physical activity of the participants throughout the study subjects

Variables	Spirulina group (n = 36)	Placebo group (n = 37)	p^a
Energy (kcal/day)	2138.92 ± 540.58	2408.41 ± 2314.80	0.49
Carbohydrate (g/day)	311.60 ± 105.13	405.12 ± 495.94	0.26
Protein (g/day)	91.39 ± 31.84	100.5 ± 69.1	0.47
Fat (g/day)	60.97 ± 19.57	59.69 ± 20.26	0.78
Cholesterol (mg/day)	406.12 ± 295.03	365.78 ± 188.8	0.49
Linolenic fat (g/day)	29.60 ± 94.43	12.99 ± 46.01	0.34
Omega 3 (g/day)	186.44 ± 0.49.57	106.57 ± 684.86	0.32
Linoleic fat (g/day)	54.08 ± 139.51	36.32 ± 86.63	0.51
Poly fat (g/day)	15.16 ± 10.97	12.30 ± 8.14	0.21
Dietary fibre (g/day)	15.64 ± 7.06	17.98 ± 17.55	0.45
Arginine(mg/day)	491.01 ± 679.35	401.12 ± 391.46	0.49
Alanine(mg/day)	458.45 ± 660.60	400.02 ± 390.28	0.65
Glutamic Acid(mg/day)	2264.44 ± 2119.63	1890.66 ± 1541.69	0.39
Leucine (mg/day)	5776.92 ± 2208.18	5388 ± 1407.34	0.37
Methionine (mg/day)	1820.36 ± 809.611	1759.28 ± 1407.34	0.72
Calcium (mg/day)	814.46 ± 269.71	891.71 ± 415.17	0.35
Phosphorus (mg/day)	1160.54 ± 416.85	1202.33 ± 367.22	0.65
Iron (mg/day)	16.48 ± 5.58	22.1 ± 19.88	0.10
Magnesium (mg/day)	208.60 ± 83.16	238.96 ± 64.90	0.08
Zinc (mg/day)	8.77 ± 2.74	9.82 ± 2.53	0.09
B6 (mg/day)	1.37 ± 0.59	1.63 ± 0.922	0.15
B9 (Ug/day)	301.03 ± 150.05	311.56 ± 128.90	0.74
B12 (Ug/day)	4.57 ± 2.33	4.82 ± 2.37	0.65
Physical activity (MET/h/day)	24.65 ± 1.69	2397 ± 1.93	0.87

Note: Note: Variables are expressed as mean ± SD.

[a] Obtained from independent t test.

Table 3. The effects of Spirulina administration on anthropometric measurements, blood pressure, sleep quality, mood, fatigue status and quality of life

Variables	Spirulina group (n = 36)				Placebo group (n = 37)				
	Baseline	End of trial	Change	p^a	Baseline	End of trial	Change	p^a	p^b
Weight(kg)	72.33 ± 13.59	72.89 ± 13.98	0.56 ± 1.48	0.02	69.72 ± 14.54	70.0 ± 14.42	0.32 ± 1.34	0.15	0.29
BMI(kg/m2)	26.01 ± 4.41	26.22 ± 4.59	0.20 ± 0.51	0.02	25.61 ± 5.50	25.73 ± 5.52	0.26 ± 0.51	0.14	0.33
WC (cm)	89.83 ± 11.46	90.43 ± 11.10	0.59 ± 3.03	0.24	87.56 ± 11.69	87.70 ± 11.68	0.13 ± 2.50	0.74	0.34
HC (cm)	94.18 ± 18.83	97.14 ± 11.76	2.96 ± 15.47	0.25	96.81 ± 11.80	96.37 ± 11.44	- 0.43 ± 2.12	0.25	0.51
NC (cm)	36.27 ± 3.99	36.10 ± 3.98	0.16 ± 1.02	0.34	35.30 ± 3.93	35.32 ± 3.86	0.02 ± 0.37	0.66	0.32
WHR	0.91 ± 0.07	0.91 ± 0.07	0.003 ± 0.02	0.42	0.91 ± 0.09	0.91 ± 0.09	0.003 ± 0.01	0.41	0.92
SBP (mmHg)	11.87 ± 0.90	11.83 ± 0.66	- 0.49 ± 0.04	0.73	11.78 ± 1.66	11.86 ± 0.48	0.08 ± 1.29	0.37	0.39
DBP (mmHg)	8.04 ± 0.56	8.06 ± 0.53	0.02 ± 0.31	0.54	7.97 ± 1.16	8.00 ± 0.47	0.02 ± 1.04	0.59	0.44
Sleep quality score	11.11 ± 6.55	9.00 ± 6.00	- 2.11 ± 3.61	0.01	11.45 ± 6.02	10.18 ± 6.31	-1.27 ± 3.15	0.01	0.69
Sleep duration (hours)	7.13 ± 1.61	7.09 ± 1.89	-0 .03 ± 1.69	0.90	6.78 ± 1.68	6.91 ± 1.59	0.13 ± 0.72	0.24	0.45
Subjective sleep quality score	1.30 ± 1.70	1.02 ± 0.73	-0.27 ± 1.25	0.06	1.35 ± 0.75	1.40 ± 0.64	0.05 ± 0.57	0.57	0.16
Sleep latency (minutes)	17.22 ± 17.54	15.33 ± 14.57	-1.89 ± 7.93	0.16	17.51 ± 16.40	16.16 ± 14.11	-1.35 ± 0.74	0.33	0.91
Sleep efficiency (%)	85.7 ± 0.10	86.2 ± 0.09	0.5 ± 0.04	0.47	85.6 ± 0.10	85.4 ± 0.09	-0.2 ± 0.46	0.78	0.49
Sleep disturbances score	5.19 ± 4.10	4.16 ± 3.78	-1.02 ± 2.31	0.004	7.45 ± 4.23	7.97 ± 5.09	0.51 ± 2.76	0.26	0.03
Use of sleep medication score	0.40 ± 0.83	0.37 ± 0.75	-0.02 ± 0.55	0.35	0.19 ± 0.62	0.27 ± 0.65	0.08 ± 0.28	0.08	0.67
Day-time dysfunction score	0 .61 ± 0.90	0.75 ± 0.87	0.13 ± 0.89	0.74	0.91 ± 1.18	1.05 ± 1.15	0.13 ± 0.91	0.09	0.57
Anxiety score	15.83 ± 12.57	14.02 ± 10.54	-1.80 ± 5.90	0.07	16.45 ± 10.50	14.81 ± 8.75	-1.64 ± 5.20	0.06	0.60
Stress score	22.00 ± 10.84	16.88±10.05	- 5.11 ± 7.50	<0.001	20.43± 9.54	18.40 ± 8.79	-2.03 ± 5.83	0.04	0.04
Depression score	16.72 ± 12.74	13.61 ± 10.71	-3.11 ± 7.34	0.01	16.91 ± 11.28	14.70 ± 10.62	-2.21 ± 5.76	0.02	0.50
Fatigue score	33.55 ± 13.53	31.86 ± 11.39	-1.69 ± 11.71	0.39	35.02 ± 11.57	33.16 ± 10.98	-1.86 ± 5.58	0.05	0.63
Quality of life score	41.61 ± 10.95	48.30 ± 8.95	6.69 ± 7.69	<0.001	42.08 ± 9.72	44.97 ± 9.02	2.89 ± 6.66	0.01	0.03

Note: Variables are expressed as mean ± SD. Abbreviations: BMI, Body mass index; WC, Waist circumference; HC, Hip circumference; NC, Neck circumference; WHR, Waist to hip ratio; SBP, Systolic Blood Pressure; DBP, diastolic blood pressure

[a] Obtained from paired t test.

[b] Obtained from multiple linear regression test, adjusted for baseline value of age, disease length and baseline BMI

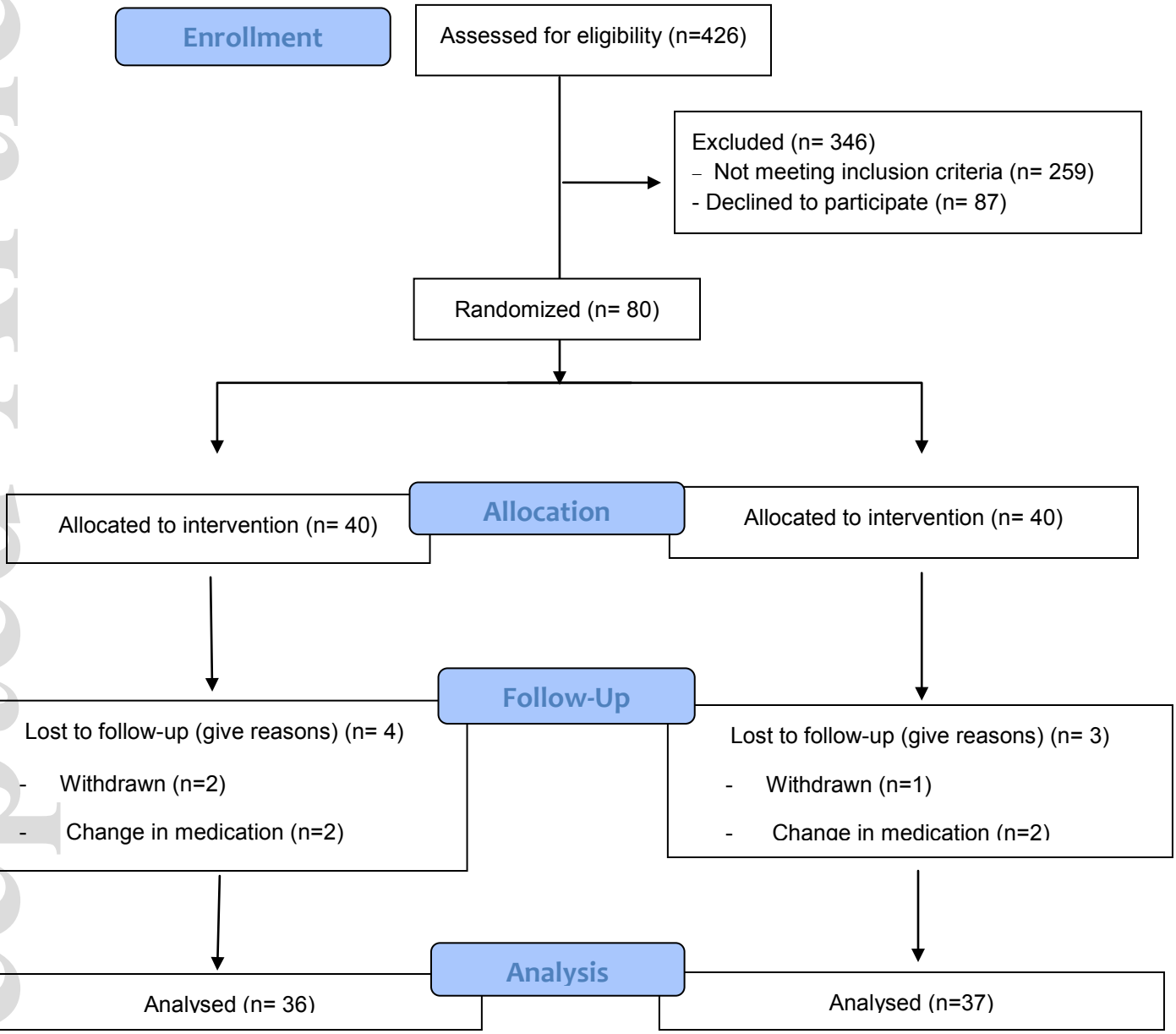

Figure 1: Patient's flow diagram