



with omega-3 fish oil and/or copper on disease activity in patients with SLE.

## MATERIALS AND METHODS

**Patients and study design.** Individuals with SLE were recruited via the Northern Ireland Lupus Support Group, rheumatology outpatient clinics, and through a letter sent to all general practitioners in Northern Ireland. The requirements were that all subjects be aged between 18 and 80 years and have stable, active SLE. Patients were excluded where ongoing treatment for potentially life-threatening disease was required. Patients taking steroids > 10 mg daily or immunosuppressive drugs at high doses were excluded. Patients currently taking vitamin or mineral supplements and those who had taken a supplement containing omega-3 or copper in the previous 6 months were also excluded. Subjects with known allergies to fish or copper were ineligible for inclusion in the study.

All patients in the study satisfied 4 or more revised criteria for the classification of SLE as suggested by the American Rheumatology Association (American College of Rheumatology)<sup>29,30</sup>. Ethical approval was granted by the Research Ethics Committee of the University of Ulster, Northern Ireland.

A factorial design was employed in this study as it permits flexibility to explore the effects of 2 independent treatments in the one study instead of conducting a series of independent studies. We are effectively able to combine these studies into one without loss of power. In this study we used a 2 × 2 factorial design, where patients were allocated to one of 4 possible combinations<sup>31</sup>. In this way it was possible to test the independent effect of each treatment on lupus disease activity and the combined effect of the 2 interventions.

Patients were randomly assigned to one of 4 intervention groups in a double blind manner. One group received both the fish oil and copper supplement, one received the fish oil and a placebo copper supplement, one received copper and placebo fish oil, and the fourth group received both the placebo fish oil and placebo copper supplements. They were required to take the supplements daily for 24 weeks and were assessed at baseline, 6, 12, and 24 weeks.

**Supplements.** The dose of MaxEPA was based on a physiological rather than pharmacological dose that is easily achievable by dietary means. Three grams of MaxEPA is roughly equivalent to 2 oily fish-based meals per week. The active fish oil supplement was a 1 g MaxEPA fish oil capsule (Seven Seas Ltd., Hull, UK) containing 18% eicosapentanoic acid (EPA; 180 mg) and 12% docosahexaenoic acid (DHA; 120 mg) with 1 IU vitamin E as the protective antioxidant. Seven Seas Ltd. provided a visually identical placebo capsule containing olive oil that had a peppermint flavor to conceal taste and odor.

The dose of copper used in this study was in accord with the established US safe and adequate dietary intake for copper of 1.5–3.0 mg per day<sup>32</sup>. The active copper supplement provided 3 mg of copper per day in the form of copper di-glycinate amine acid complex (Thomson & Joseph Ltd., Norwich, UK). Thomson & Joseph provided visually identical placebo capsules containing no active ingredient, which were analogous in odor and taste. Subjects were required to take three 1 g MaxEPA capsules and one 3 mg copper capsule per day along with their usual prescribed medication.

**Disease activity assessment.** Disease activity was assessed using the revised Systemic Lupus Activity Measure (SLAM-R)<sup>33</sup>. Items included in this scale represent those manifestations that occur more frequently, those that can be graded, and those that can be operationally defined and reliably rated. This instrument is a valid and reliable measure of activity in SLE<sup>34,35</sup>.

**Dietary assessment.** Dietary intakes were assessed using a 3-day food diary method. Patients were asked to choose 3 days that they felt would represent their typical diet. Published food portion sizes were used to quantify the corresponding food intakes<sup>36</sup>. Analysis of the 3-day diary was performed using WISP version 1.28 for Windows (Tinuviel Software, UK). This allowed an estimate of the habitual intake of polyunsaturated fatty acids and copper in the individual's diet.

**Laboratory measurements.** Peripheral blood samples were taken at each visit to perform routine biochemical, hematological, and immunological examinations. Analysis was carried out under standardized conditions at the Regional Immunology Laboratory, Royal Victoria Hospital, Belfast, and the laboratory at Musgrave Park Hospital, Belfast.

Platelet fatty acid methyl esters were analyzed using gas chromatography on the ThermoFinnigan<sup>®</sup> Liquid Autosample AS2000 and a Fawcax column from Restek<sup>®</sup> (25 m column, 0.25 mm diameter). Activity of the cuproenzyme benzylamine oxidase (BAO) was measured using a radiometric benzylamine assay, based on its catalyzed conversion of <sup>14</sup>C-benzylamine to <sup>14</sup>C-benzaldehyde.

**Autoantibodies.** Anti-dsDNA antibodies were measured using a commercial radioimmunoassay technique (Gamma-B <sup>125</sup>I Anti-dsDNA; Immunodiagnostic Systems Ltd.). Anticardiolipin antibodies were measured using a commercially available anticardiolipin ELISA IgG/IgM kit (Sigma-Aldrich).

**Complement assay.** Complement components C3 and C4 were measured by nephelometry using the Behring BNII nephelometer. Normal ranges for C3 and C4 are 0.7–1.7 g/l and 0.13–0.43 g/l, respectively.

**Statistical analysis.** Data were analyzed using the statistical analysis packages Microsoft<sup>®</sup> Excel 2000, SPSS/PC version 9 (SPSS Inc., Chicago, IL, USA) and Minitab<sup>™</sup> V13. Differences in laboratory measurements and disease activity over time in the different supplement intervention groups were examined using general linear model for repeated measures at a significance level of 5%. Analysis of correlation was carried out using the Pearson correlation test at a significance level of 5%. Chi-squared testing was used to examine the frequency in cross-classified categories and to determine whether the criteria were independent. The probability that a clinical trial will have a significant (positive) result is computed under the assumption that the treatment difference equals the minimal detectable difference of clinical importance. Power was calculated based on SLAM-R at a significance of  $\alpha = 0.05$  and was proportional to effect size (ES), sample size (n), variance between experimental units ( $\sigma^2$ ), and the significance level to be used<sup>37</sup>.

## RESULTS

**Clinical features.** Sixty-five Caucasian patients with SLE agreed to participate in the study. Their ages ranged from 22 to 76 (mean 46.6) years, with a female to male ratio of 9:1. Six subjects chose to withdraw from the study after enrolment, a further 3 were admitted to hospital (one patient following a stroke and 2 with chest infections), and 4 subjects completed only 6 weeks of the study owing to personal commitments. Analysis was based on the 52 subjects that completed all 24 weeks of the intervention study. Overall, 27 took a fish oil supplement and 25 took a copper supplement.

The total number of subjects fulfilling each of the ACR criteria is shown in Table 1. No side effects were reported by subjects while taking the supplements. Analysis of the food diary revealed that mean (SD) polyunsaturated fat was 8 (0.39) g per day, which is below the recommended daily intake (RDA) of 11 g/day for women and 17 g/day for men. A mean (SD) daily Cu intake of 0.94 (0.39) mg per day compared favorably with the RDA as published by the US Food and Nutrition Board (FNB 2002). Table 2 reports the clinical and physical characteristics of each treatment group.

**Drug therapy.** Drug treatment in each supplementation group is detailed in Table 2. There was no significant difference between oral steroid or immunosuppressant doses

*Table 1.* Status of American College of Rheumatology (ACR) criteria for the classification of systemic lupus erythematosus (SLE) in patients (n = 52) participating in a placebo controlled randomized intervention study with 3 g MaxEPA and/or 3 mg copper. All patients met at least 4 of the revised criteria for the classification of SLE, which was required for entry to the intervention study. Table represents the breakdown of each component of the criteria for the subjects included in this study (n = 52).

ACR Criteria	%
Malar rash	58.06
Discoid lupus	4.83
Photosensitivity	70.96
Oral ulcers	61.29
Arthritis	58.06
Serositis	17.74
Renal	16.13
Central nervous system	4.84
Hematological	19.35
Serological	69.35
Antinuclear antibodies	92.31

among the 4 groups. Post-intervention 5 patients had their daily oral steroid dose reduced, 3 of whom were taking copper alone, one fish oil alone, and the other was part of the combined placebo group. The average daily dose at baseline was 8 mg, and this was reduced to 7.1 mg per day at the end of the study period. Treatment with methotrexate was increased in one individual taking the double placebo combination from 10 to 15 mg per week.

*Patient compliance.* To determine that subjects were compliant with supplementation, we asked for any unused capsules to be returned. Eighteen subjects (35%) reported taking all the supplements, the remaining subjects reported

taking greater than 90% of the capsules. Those taking a fish oil supplement demonstrated a significant incorporation of both EPA and DHA into their platelet membranes compared to those not taking a fish oil supplement ( $p < 0.05$ ). Those supplemented with fish oils had mean ( $\pm$  SEM) baseline EPA and DHA levels of  $0.158 \pm 0.06$  mg/ml and  $0.322 \pm 0.17$  mg/ml, respectively. Levels increased significantly to  $1.425 \pm 0.61$  mg/ml EPA and  $1.739 \pm 0.55$  mg/ml DHA following 24 weeks' supplementation with 3 mg omega-3 fish oils. Those taking a copper supplement had a significant increase in activity of the cuproenzyme BAO compared to those not taking a copper supplement ( $p < 0.05$ ). Mean ( $\pm$  SEM) baseline BAO activity for those taking copper was  $340.6 \pm 13.5$  IU/ml and after 24 weeks' supplementation levels of activity increased significantly to  $393.9 \pm 14.4$  IU/ml.

*Disease activity.* Baseline mean SLAM-R scores were 5.69 (0.37) with a range from 1 to 10. There was no significant difference between the supplementation groups for SLAM-R score at baseline ( $p > 0.05$ ). A comparison of subjects taking fish oil with those not taking fish oil revealed a significant fall in SLAM-R score after 24 weeks from 6.12 to 4.69 ( $p < 0.05$ ; Figure 1). The components of SLAM-R most affected by fish oil supplementation were the integument, neuromotor, and laboratory domains. Supplementation with copper showed a rise in SLAM-R score of less than 1 unit after 12 weeks, which returned to baseline value after 24 weeks.

*Effect of supplementation on anthropometrics and laboratory variables.* Diastolic, systolic, and mean arterial blood pressure were not significantly affected by fish oil or copper supplementation. There was no significant change in indi-

*Table 2.* Clinical characteristics for patients participating in study (n = 52) investigating the effect of 3 g MaxEPA and/or 3 mg copper supplementation in SLE. Randomization of supplementation was successful in that the 4 groups compare favorably with each other both in physical characteristics and drug treatments.

Characteristic	Fish Oil + Copper, n = 13	Fish Oil + Placebo Copper, n = 14	Copper + Placebo Fish Oil, n = 13	Placebo Fish Oil + Placebo Copper, n = 12
Mean age, yrs (SD)	46.00 (13.17)	50.66 (15.15)	43.20 (15.80)	43.20 (10.80)
Mean height, m (SD)	1.59 (0.05)	1.62 (0.08)	1.64 (0.08)	1.64 (0.07)
Mean weight, kg (SD)	62.92 (11.35)	68.29 (14.74)	70.73 (16.66)	74.25 (16.61)
Mean body mass index (SD)	24.69 (4.39)	25.94 (5.56)	26.32 (5.80)	27.51 (6.09)
Smokers	1	1	2	2
Nonsmokers	12	13	11	10
Oral contraceptive	0	2	3	2
Hormone replacement therapy	1	0	0	1
Methotrexate, n	0	2	1	0
Mean weekly dose, mg		15	12.5	
Prednisolone, n	5	7	6	4
Mean daily dose, mg (SD)	8.25 (5.15)	8.08 (6.04)	9.00 (6.10)	6.70 (3.17)
Hydroxychloroquine, n	6	5	6	3
NSAID, n	1	4	4	3

NSAID: nonsteroidal antiinflammatory drugs.

Table 3. SLE patient self-reported treatment effects during intervention with 3 g MaxEPA fish oil and/or 3 mg copper over 24 weeks.

Supplementation Group	Improvement	No Change	Worse
Fish oil and copper <sup>a</sup> , n = 13			
After 6 weeks	4	7	2
After 12 weeks	3	9	1
After 24 weeks	6	7	0
Fish oil and placebo <sup>b</sup> , n = 27			
After 6 weeks	9	15	3
After 12 weeks	9	16	2
After 24 weeks	12	14	1
Copper and placebo <sup>c</sup> , n = 25			
After 6 weeks	10	10	5
After 12 weeks	7	15	3
After 24 weeks	13	12	0
Placebo, n = 13			
After 6 weeks	1	9	3
After 12 weeks	2	9	2
After 24 weeks	1	9	3

Chi-square analysis between reported improvement and the combined no-change and worse groups revealed significantly better outcomes, after 24 weeks, in those taking fish oil and/or copper compared to those not taking any supplement (<sup>a</sup> p = 0.027; <sup>b</sup> p = 0.020; <sup>c</sup> p = 0.007).

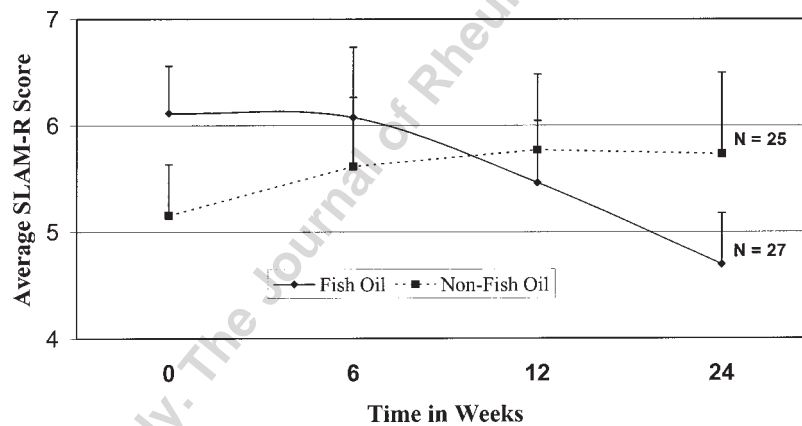


Figure 1. Effect of supplementation with 3 g MaxEPA fish oil, compared to those taking placebo fish oil, on SLAM-R score after a 24 week randomized double-blind intervention in patients with SLE. Patients taking 3 g per day fish oil (n = 27) had a significant reduction in SLAM-R score after 24 weeks (p < 0.05) compared to those not taking fish oil (n = 25). Values are mean (SEM) SLAM-R score at each assessment point.

vidual body mass index following the intervention study. Analysis of dsDNA showed a reduction in levels over time in all treatment groups, but there was no significant difference between treatment groups. Antibodies to dsDNA did not correlate with SLAM-R score. Anticardiolipin IgG and IgM and complement factors 3 and 4 showed no significant change over time or with treatment.

Dietary supplementation had no significant effect upon hematological indices including hemoglobin, white cell and differential white cell count, platelets, and erythrocyte sedimentation rate. Fish oil and copper supplementation again had no significant effects on blood biochemistry including

sodium, potassium, chloride, total protein, urea, and creatinine.

*Patient self-reported improvement.* All patients taking an active supplement reported feeling better than those in the placebo group. Patients receiving fish oil and/or copper had a better outcome than those taking both placebo capsules (Table 3).

## DISCUSSION

This study demonstrates that supplementation with doses of omega-3 fish oils, which are easily achievable by dietary modification, reduces symptomatic disease activity in



patients with SLE. We have been able to confirm this using the validated SLAM-R scoring system. Previous human intervention studies with omega-3 fish oils in SLE were performed in smaller cohorts of patients using less practical doses for everyday use and in the era prior to the introduction of such validated and reliable indices. The supplements were well tolerated, with no reports of drug interactions. Patient compliance was acceptable in that EPA and DHA were significantly incorporated into the platelet membranes, and copper supplementation significantly increased activity of the copper dependent enzyme BAO.

We were unable to detect any significant reduction in dsDNA or other laboratory modalities with fish oil supplementation, as was the experience in other human studies<sup>20,25</sup>. Similarly, copper supplementation did not produce significant changes to the serological picture. The usefulness of laboratory indices in predicting a flare in activity has been questioned<sup>38,39</sup>, as individuals with identical serological pictures can present with different severity of SLE<sup>40,41</sup>.

Fish oil significantly reduced SLAM-R score compared to those not taking a fish oil supplement ( $p < 0.05$ ; Figure 1). The integument, neuromotor, and laboratory domains of SLAM-R were most affected by fish oil supplementation. Assessment of disease activity in the majority of previous dietary intervention studies used nonvalidated indices for determining lupus activity. An unconfirmed method used by a leading British SLE research group found that fish oil significantly reduced disease activity in individuals with SLE<sup>19</sup>. Dietary factors have been implicated in the development and progression of SLE<sup>1-5</sup>. Recent work suggests there is a valuable role for omega-3 polyunsaturated fatty acids as antiinflammatory agents<sup>42</sup>. These fatty acids may also have anti-autoimmune properties<sup>43</sup>. Investigations with murine models of SLE suggest that the type of fat consumed will determine the severity of disease<sup>6-18</sup>. Application of the findings from murine models to human studies has led to speculation that fish oil supplementation may be beneficial, but the precise dosage required and the time for effect remain unknown. In patients with SLE, low levels of omega-3 polyunsaturated fatty acids such as alpha-linolenic acids, gamma-linolenic, EPA, and DHA have been observed in blood<sup>44</sup>.

The majority of studies suggest a protective effect of fish oils, with a decrease in inflammatory cytokines together with enhanced levels of antiinflammatory cytokines, increased activity of antioxidant enzymes, and improvement in disease activity. Incorporation of omega-3 fatty acids into the phospholipid fractions of cell membranes is believed to alter the prostaglandin pathway to favor antiinflammatory cell reactions<sup>42</sup>. The antiinflammatory effect of fish oil in SLE has been demonstrated by its modulation of prostaglandin synthesis, altered cell chemical and biological properties, and decreased inflammatory mediators<sup>19,22-24</sup>.

Although it is possible that confounding effects of

prescribed drugs or the variability of SLE has contributed to the beneficial effect of omega-3 fish oil supplementation observed here, randomization in terms of medication and clinical variables was successful in minimizing these limiting factors.

Our study did not show any significant therapeutic benefit from supplementation with copper. The effect of copper in SLE has not been widely investigated. Exogenous copper decreased the formation of LE cells in rats with a hydralazine induced collagen disease similar to SLE<sup>28</sup>. This was believed to be related to higher levels of superoxide dismutase activity in the copper supplemented rats. Copper is also proposed to have antiinflammatory properties through modulation of eicosanoid synthesis<sup>45</sup>.

Fish oil supplementation in patients with SLE having mild to moderately active disease would appear to be beneficial; and since the US Food and Drug Association have deemed fish oil supplementation safe<sup>43</sup>, further investigation of the effect of fish oils in SLE is warranted. Longer-term, dose-ranging studies with larger numbers of patients with SLE will be required to conclude exactly what role fish oil supplementation has in the management of SLE.

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