Q J Med 2008; **101**:167–179
doi:10.1093/qjmed/hcm108 Advance Access published on 25 January 2008

Review

QJM

Systematic review of the nutritional supplement *Perna Canaliculus* (green-lipped mussel) in the treatment of osteoarthritis

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Received 17 September 2007 and in revised form 1 January 2008

Summary

Complementary treatments for osteoarthritis (OA) are sought by patients for symptomatic relief and to avoid the iatrogenic effects of non-steroidal anti-inflammatories. This systematic review evaluates the efficacy of the nutritional supplement *Perna Canaliculus* (green-lipped mussel, GLM) in the treatment of OA and substantially adds to previous work by focussing solely on GLM use in OA as well providing a re-analysis of the original trial data. Randomized or quasi-randomized controlled trials (comparative, placebo-controlled or crossover) were considered for inclusion from Cochrane Library, Medline, Embase, Amed, Cinahl, Scopus and NeLH databases where adults with OA of any joint were randomized to receive either GLM vs. placebo, no additional intervention (usual care), or an active intervention. The methodological quality of the trials was assessed using the JADAD scale. Four RCTs were included, three placebo controlled, the fourth a comparative trial of GLM lipid extract vs. stabilized powder extract. No RCTs comparing GLM to conventional treatment were identified. All four studies assessed GLM as an adjunctive treatment to conventional medication for a clinically relevant time in mild to moderate OA. All trials reported clinical benefits in the GLM treatment group but the findings from two studies cannot be included in this review because of possible un-blinding and inappropriate statistical analysis. The data from the two more rigorous trials, in conjunction with our re-analysis of original data suggests that GLM may be superior to placebo for the treatment of mild to moderate OA. As a credible biological mechanism exists for this treatment, further rigorous investigations are required to assess efficacy and optimal dosage.

Introduction

Osteoarthritis (OA) affects over 30 million people in the US and 1 in 10 people aged 35–75 in the UK.[1] Treatment with NSAIDs is effective, but associated with serious gastrointestinal side effects.[2] OA sufferers using NSAIDs are up to 5.5 times more likely to experience side effects which require hospitalization than non-users; 12 000 admissions and approximately 2000 deaths are attributed to NSAIDs in the UK every year.[3] Patients with OA look to complementary and alternative medicine

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(CAM) to gain symptomatic relief and avoid iatrogenic illness with OA being the sixth most common condition treated.[4]

Perna Canaliculus (green-lipped mussel, GLM) may be of benefit in arthritis.[5–12] The observation that Maoris who regularly consumed GLM suffered less arthritis than their inland relatives, led to the development of a marketable, anti-arthritic product, Seatone® in 1974; a freeze–dried, concentrated powder. Subsequently stabilized mussel powder extracts have been shown to have much greater anti-inflammatory effects than[13] un-stabilized extracts (14% and 97%, respectively). Lyprinol® a stabilized GLM lipid extract [containing concentrated omega-3 essential fatty acids (omega-3 EFA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)] has anti-inflammatory activity in rats,[14–17] *in vitro* effects on leucotriene biosynthesis in human ploymorphonuclear leucocytes and on prostaglandin production in human monocytes.[13] Omega-3 EFAs inhibit membrane arachidonic acid metabolism by blocking the lipoxygenase (LOX) and cyclo-oxygenase (COX) pathways, thus decreasing prostaglandin and leukotriene synthesis and down-regulating the inflammatory sequence. Leucotriene modulating effects of omega-3 EFAs compare favourably to NSAIDs.[13] Beneficial effects of GLM have been observed between 2 and 4 weeks of treatment in a number of studies;[18–20] this length of delayed effect is comparable to the time span for the clinical effects of EFAs in arthritis to be apparent.[21]

The objective of this systematic review is to evaluate the existing evidence from randomized controlled trials of GLM in the treatment of OA to determine the efficacy and safety profile of the nutritional supplement *P. Canaliculus* (GLM) in the treatment of OA. A separate review of GLM in OA is pertinent in view of the recent withdrawal of some COX 2 inhibitors.[2,22] A recent systematic review assessing GLM in the treatment of both OA and rheumatoid arthritis (RA)[12] did not allow for the separate evaluation of GLM specifically in OA; in addition a further RCT has subsequently been published. This systematic review therefore provides a new more positive analysis and interpretation of the information available that substantially differentiates it from previous reviews.

Methods

Literature search strategy and study selection

Trials were included if they were randomized or quasi-randomized assessing GLM for OA in human studies. Case studies, retrospective studies, observational, descriptive articles or studies with historic controls were excluded. Electronic databases [Cochrane Library, Medline, Embase, Amed, Cinahl Scopus and NeLH (CAM Specialist Library)] were used to identify studies between 1950 and February 2007. Free text searches were performed on each database with the following keywords: Osteoarthritis, Degenerative joint disorder, green-lipped mussel, *Perna Canaliculus*, Seatone, Lyprinol®.

Data extraction

Clinical studies in any language were evaluated against the pre-defined criteria for inclusion in the review. RCTs were included if they were; in humans; reported comparison of GLM to placebo, different GLA formulations or conventional treatment; and used relevant, validated outcome measures for OA. The JADAD scale was used to assess the reporting quality and methodological rigour.[23] The trials were assessed by three of the authors independently; any disagreements were discussed and resolved. In addition, the authors also reported on other measures of internal validity (i.e. dosage, treatment period and appropriateness of statistical analysis) and external validity (inclusion and exclusion criteria, baseline characteristics, trial setting and appropriate outcome measures). Additional data such as joint location, age of sample population, outcome measures, compliance, statistical evaluation, results and adverse effects were also extracted and tabulated.

Results

Results of search strategy

The MEDLINE search strategy (1950–2007) resulted in a total of eight citations none of which were human RCTs. The EMBASE search (1980–2007) resulted in a total of eleven citations, of which four RCTs were identified.[18–20,24] The searches on the other databases and citation tracking did not identify any further RCTs [AMED (1985–2007, three citations), CINAHL (1982–2007, two citations), British Nursing Index & BNI Archive (1985–2007; zero citations), SCOPUS (1960–2007; 10 citations) and NeLH (zero citations)]. Three of the RCTs were in English Language[18–20] and one in French.[24] They were published between 1980 and 2004. Three were placebo controlled comparing either a lipid extract of GLM (Seatone®) to placebo,[19,24] or Lyprinol® to placebo.[18] The remaining RCT was a comparator trial[20] comparing two extracts of GLM (a powder form and lipid extract, Lyprinol®).

No studies comparing GLM to conventional treatment were identified. Detailed descriptions of the studies are presented in Tables 1 and 2, and information on adverse events in Table 3.

Placebo controlled trials

The first published study of GLM in OA was in 1980 following an open observational study of GLM in OA and RA[19] (Tables 1 and 2); JADAD 1.5. Patients were randomized to treatment group for 3 months, after which all were placed on 'open' active treatment for 3 months. The dose of GLM in the first 3 months was 1050 mg/day but reduced after 2 months if patients were improving clinically. The hospital pharmacy dispensed the capsules according to a random code without reporting the method of randomization. Outcome measures were appropriate for OA as reported in Table 1. The primary outcome was a 'responder or non responder'. A response (improvement) was judged to have occurred when 'both the patient and the physician agreed and there was objective supporting evidence'. The data for all outcomes were reported after the initial 3 months and for the last three 'open label' months. In the original publication only responder/non-responder data were published but subsequent *post hoc* analysis reported treatment group differences in the primary outcome.[19,25–27] Our subsequent re-analysis of the original data confirms no significant differences between treatment arms were identified ($\chi^2 = 2.92$, $P = 0.09$). However patients receiving Seatone at 3 months did show trends for improvement in pain VAS ($P < 0.10$), and significant improvement in functional index ($P < 0.025$) and time to walk 50 ft ($P < 0.025$) compared to baseline. Five of the 38 patients (13%) dropped out of the trial, and in their subsequent correspondence[25] the authors identified that four drop outs were in the active treatment group, and one in placebo group. Reason for drop out/withdrawal included difficulties with transport, hospital admissions unrelated to the arthritis, capsules aggravating previous dyspepsia and unknown. The findings from our re-analysis of this trial[19] do not support the notion that Seatone is efficacious compared to placebo. However these patients were resistant to conventional medication and the outcomes suggest that further more rigorous investigation of Seatone should be considered.

Audeval and Bouchacourt[24] assessed Seatone® as an adjunctive treatment to NSAIDs for OA; JADAD = 2 (Tables 1 and 2). This trial recruited 53 patients with radiological confirmed mild to moderate OA knee. They received GLM ($n = 27$) or placebo ($n = 26$) for 6 months. The dosage of active medication was not reported and no power calculation was provided. Ten outcome measures were used which included two assessments of function (Tables 1 and 2) but there was no differentiation between primary or secondary outcomes and no Bonferroni correction, thus the interpretation of outcome significance must be cautious. Means for each outcome measure were tabulated by treatment arm for baseline values only and changes over the treatment phase, by treatment arm were reported graphically.

The two groups were balanced for demographic variables and also for all baseline measures except morning stiffness; the placebo group has significant ($P < 0.01$) reduced duration compared to Seatone group. No data were reported for drop outs or withdrawals. The authors state that GLM was found to be significantly more effective when compared to placebo for four criteria [both before and after adjustment for baseline differences; pain reduction $P < 0.05$; functional index, $P < 0.01$; patient ($P < 0.01$) and physician ($P < 0.01$) assessment of treatment]; with positive trends in favour of Seatone reported for three other outcomes. Disease severity affected outcome with Seatone being reported as efficacious in slight to moderate OA being 'very well tolerated', but with no supporting data presented. Observations in the last treatment month are more variable than previous months suggesting the possibility of drop outs (which may indicate the lack of efficacy or poor tolerance), but no details are provided. It is not possible to confirm or refute the authors conclusions as the statistical methods [two factor analysis of variance (treatment and month)] are inappropriate; summary statistics or repeated measures ANOVA would have been relevant. It is also not possible on the data presented to reanalyse the data with more appropriate methodology.

The most recent study by Lau *et al.*[18] assessed Lyprinol® (Tables 1 and 2) as an adjunctive treatment (to a standardized paracetamol dose), vs. placebo in Chinese patients with a 6-month diagnosis of OA knee (ACR classification); JADAD = 3. Subjects ceased their OA medication 1 week before commencing the trial, replacing it with a standard 2 g/day paracetamol which they took throughout the trial. Additional paracetamol was allowed as rescue medication. However this may have led to possible bias; individual analgesic requirements might have been different and the verum group potentially favoured. Percentage change in paracetamol use compared to baseline over the trial was recorded by treatment arm. Unlike previous trials, patients taking omega-3 EFA supplements were excluded; both groups received the same medication schedule with four capsules per day for the first 2 months then

Table 1 RCTs assessing Green-Lipped Mussel in the treatment of osteoarthritis

Author	Jaded score	Study design	Joint location	Sample size	Intervention/control	Primary outcome measures	Main result
Gibson and Gibson[19]	1.5 Blinding: 0 Blinding inappropriate: −1 Randomization: 1 Withdrawals: 0.5	Single centre Double-blind, placebo-controlled	Hand Hip Knee	$N=38$ Extract $N=16$ Placebo $N=22$	(1) Mussel extract 1050 mg/day (2) Placebo For treatment period: 3 months Then all patients received mussel extract for a further 3 months. However, if patients responded well. dose was reduced after 2 months.	Outcome: assessed monthly (not differentiated between primary and secondary) • Degree of morning stiffness • VAS pain • Functional index • Time taken to walk 50 feet (15.24) • ROM of hip and knee joints • Patient global assessment. Outcome measure = responder or non-responder	At 3 months: In GLM 6 out of 19 (31%) responders vs. 3 out of 22 (14%) responders in the placebo arm. No group difference analysed in this article but re-analysis in subsequent papers (Gibson, 1981[25–27]) confirmed NS group difference in the number of responders.[Subsequent analysis by current authors identified this group difference was not significant ($\chi^2=2.92$, $P=0.09$)]. In terms of individual variables, significant improvement in morning stiffness, pain VAS, functional index and time taken to walk 50 ft at 3 months compared to baseline in Seatone group.
Audeval *et al.*[24]	2 Blinding: 1 Randomization: 1 Withdrawals: 0	Single centre Randomized, double-blind, placebo-controlled	Knee	$N=53$ Seatone $N=27$ Placebo $N=26$	(1) 6 capsules of Seatone/d No dosage details given (2) 6 capsules of placebo/d Treatment period: 6 months	Outcomes: (not differentiated between primary and secondary) • ARA functional classification • VAS pain • Duration of morning stiffness • Likert Pain level (1–4) • Joint mobility • Distance from heel to buttock • Use of walking sticks • Patient assessment • Physician assessment • Tolerance • Side effects • Gastro-protective effects of seatone.	At 6 months: Seatone significant improvement on pain VAS ($P<0.01$), ARA functional stage ($P<0.01$); patient ($P<0.05$) and physician ($P<0.01$) global assessment. NS group differences for other outcomes. Disease severity affected outcome: pain VAS ($P<0.05$), ARA functional stage ($P<0.01$) and patient ($P<0.01$) and physician ($P<0.01$) global assessment. Seatone had significant efficacy in radiological stages 1 and 2 but not 3. Authors conclusion: verum was significantly superior to placebo in four of the criteria assessed and support that GLM could be used as an adjunctive treatment.

Gibson and Gibson[20]	2.5 Blinding: 1 Blinding inappropriate: −1 Randomization: 1 Randomization process: 0 Withdrawals: ½	Single-centre Randomized, double-blind, comparison of lipid extract v mussel powder, parallel arm, with follow-up treatment of lipid extract for 3 months for both arms	Not specified	*N* = 30 Lipid extract *N* = 15 Powder *N* = 15	Group A: mussel lipid extract, 3 capsules 210 mg/day. Group B: biomax stabilized mussel powder, 5 capsules 1150 mg/day. Treatment period: 3 months Another 3 month all were given lipid extract.	Outcome: (not differentiated between primary and secondary) • AI • Morning stiffness • Grip strength • VAS pain • FI • Night pain • Patient and physician global assessment.	At 3 month, significant improvements for both preparations of GLM for: AI: mean change, CI, *P*-values Group A −5.2, CI 2.0–8.3, $P<0.05$ Group B −8.2, CI 4.8–11.7, $P<0.05$ VAS pain: mean change, CI, *P*-value Group A −1.3. CI 0.1–2.6, $P<0.05$ Group B −1.1, CI 0.02–2.1, $P<0.05$ FI: mean change, CI, *P*-values Group A −5.6, CI 4.1–7.9, $P<0.05$ Group B −5.4, CI 3.8–7.0, $P<0.05$ Patient and physician global assessment: Group A 11/15 (73%) and Group B 13/15 (87%) improved at 3 months. The authors reported no significant differences between treatment groups for measures assessed.
Lau *et al.*[18]	3 Blinding = 1 Randomization = 1 Withdrawals = 1	Single centre Randomized Double-blind, placebo-controlled	Knee	*N* = 80 Lyprinol® *N* = 40 Placebo *N* = 40	(1) Lyprinol® (2) Placebo Treatment period: 6 months Dose not reported Dosing schedule: 4 capsules/day for 2 months then 2 capsules per day for 4 months.	Primary outcomes • VAS pain • COKS • CAIMS2-SF physical assessment • Patient global assessment • ESR, CRP. Secondary outcomes • Consumption of paracetamol • Psychological status.	Significant improvement Lyprinol® compared to placebo for:- Pain VAS (week 8, $P=0.035$; week 12, $P=0.032$ and week 24, $P=0.045$) Patient global assessment: weeks 12 ($P=0.035$) and 18 ($P=0.04$) No significant difference in% change of paracetamol use from baseline to the end within groups; no between group analysis reported. No GI adverse events reported in either group.

GLM: green-lipped mussel; VAS: visual analogue scale; COKS: Validated Chinese version of the Oxford knee Score; ROM: range of movement; ARA: functional classification; NS: non-significant; CAIMS2-SF: Validated Chinese version of the Arthritis Impact Measurement Scale 2-short form; AI: articular index; FI: functional index; CI: confidence interval; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table 2 Further methodological details of RCTs for green-lipped mussel in osteoarthritis

Author	Sex ratio (M:F)	Mean age of sample group (year)	Inclusion criteria stated	Exclusion criteria stated	Concomitant medications recorded	Consort statement	Compliance assessed	Power calculation performed? Statistical analysis	Dropouts	Comments
Gibson and Gibson[19]	1:37 GLM: 0:16 Placebo: 1:21	Total group 68.8	No specific • Radiological evidence of OA • clinical evidence of OA • on waiting list for surgery	Not specific but exclude those with fish or shell fish allergies	Previous therapy (all NSAIDs) continued through study	No	No	No Primary outcome Analysed by non-parametric test Wilcoxon	5 out of 38 i.e. 13% drop out rates per treatment arms were not reported.	• Patients recruited had been using NSAIDs for up to several years without clinical improvement. • Both RA ($N=28$) and OA ($N=38$) patients treated in this study; analysis completed on each group of patients. • Difference between treatment groups were not analysed at 3 months in this article but subsequently in later papers (Gibson and Gibson, 1980, 28–30) and confirmed no group differences in responders/ non-responders. • No statistical evaluation of baseline characteristics. • Issue of multiple testing not addressed. • Dose was not standardized throughout the study for all patients. Where patients were maintained on their dose for 2 month or more, the dose was reduced. • The patients treated in this study were patients with severe OA and resistant to conventional medication.

Audeval *et al.*[24]	Extract: 8:18 Placebo: 8:19	Extract: 65 Placebo 66 (55–78)	Yes • Radiological evidence of OA of knee Stable pain for several weeks	Yes (1) Severe OA of the knee (ARA4) (2) Recently had surgery	Previous therapy continued through study (analgesics, NSAID, physiotherapy rehab)	No	No	No 1 factor ANOVA (treatment) at one month; two factor ANOVA (treatment and month) at 6 months	No information	• Baseline characteristics: verum group had significant longer ($P<0.01$) duration of morning stiffness. Analysis of data did not adjust for this. • Unclear reporting of analysis. Two factor ANOVA is inappropriate; repeated measures ANOVA would be correct method. • Issue of multiple testing not addressed. • Not possible to complete a sensitivity analysis since standard errors are not reported. • No reporting of drop outs nor adverse events. ? efficacy ? tolerance.
Gibson and Gibson[20]	Group A 5:10 Group B 3:12	57.3 52.8	Yes • Radiological evidence of OA • Signs and symptoms of OA	Yes (1) Concomitant chronic disorder (2) Pregnancy (3) Too far to travel to trial centre.	Previous medication continued through study ($N=27$ on NSAIDs $N=3$ not on NSAIDs)	No	No	Yes $N=7$–15 per group based on 50% reduction of symptoms with 95% CI Primary outcome: non-parametric Wilcoxon Mann Whitney test.	Total:13% Group A: 2 (13%) Group B: 2 (13%)	• Comparative trial of two types of lipped mussel treatment. • Both RA ($N=30$) and OA ($N=30$) patients treated in this study; analysis completed on each separate disease group of patients. • The groups may not have been homogenous as the site of osteoarthritis per group was not reported. Clinical improvement between joints may vary. • No statistical evaluation of baseline characteristics. • Issue of multiple testing not addressed. • Not all patients were on standard NSAIDS throughout the trial. • Unclear what outcome measure the sample size was based on. • The two preparations were distinguishable and blinding of medication therefore not adequate. • Authors report both treatment arms equally efficacious but no data presented. In addition, subsequent sensitivity analysis confirmed the study was underpowered for group comparisons.

(continued)

Table 2 Continued

Author	Sex ratio (M:F)	Mean age of sample group (year)	Inclusion criteria stated	Exclusion criteria stated	Concomitant medications recorded	Consort statement	Compliance assessed	Power calculation performed? Statistical analysis	Dropouts	Comments
Lau *et al.*[18]	Lyprinol® 5:35 Placebo 6:34	Lyprinol® 62.1 Placebo 62.9	Yes • OA of knee according to ACR criteria i.e. • Radiological evidence • Knee pain and ⩾1 of the following • Age >50 years • Morning stiffness • Crepitus	Yes (1) Current inflammatory arthritis (2) Uncontrolled comorbidity (3) Oral steroids in previous 4/52 (4) Use of intra- auricular hyaluronic acid in prev 4/52 (5) Beef allergies (6) Dietary suppl of omega-3 essential fatty acids	Previous medication ceased 1/52 before commenced trial. Replaced with 2 g/day paracetamol with up to 2 g/day of paracetamol as rescue medication. Daily use of paracetamol recorded by diary during active treatment. Paracetamol use was an outcome measure.	Yes	Yes Capsule count	No power calculation Repeated measures ANOVA adjusted for baseline paracetomol use	Lyprinol®: 5 (12.5%) Placebo: 8 (12.5%) Fully described	• The largest RCT on GLM conducted to date. • No baseline comparison of outcome measures reported (potential bias issue) only demographics reported. • Only study to assess current medication as outcome measure. • Only study to exclude use of omega-3 essential fatty acids. • Query washout period for subject's medication. Is one week adequate? Also issue of bias—individual requirements may differ and verum group may have been favoured. • Bias concerns are the use of standardized medication (no between-group analysis of analgesic use) and also baseline characteristics. • No results reported for compliance • Statistical methods used appropriate but issue of multiple testing not addressed.

GLM: green-lipped mussel; OA: osteoarthritis; RA: rheumatoid arthritis; Group A: mussel-lipid extract; Group B: powder extract; ARA: functional classification; NSAID: non-steroidal anti-inflammatory drug; ANOVA: analysis of variances; 95% CI: 95% confidence interval.

Table 3 Adverse effects recorded RCTs assessing green-lipped mussel in osteoarthritis

Author	Nutritional supplement	Adverse events noted	How noted and by whom	Total number of adverse events	Total number of patient experiencing adverse effect	Observed adverse effects
Gibson and Gibson[19]	Green-lipped mussel	Yes 'any previous un-noted side effects'	At 3 month and 6 month	Total reported = 6 GLM: 5 Placebo: 1	GLM: 8 (12%) Placebo: 1 (2%) In addition, six patients [treatment arm or disease (OA or RA) not identified] experienced a flare up between weeks 2 to 4.	Authors do not state which disease group the adverse effects occurred in. The following AE were experienced by all OA and RA patients: Green-lipped mussel: • Increased stiffness (2 patients) • Epigastric discomfort (1 patient) • Flatulence (1 patient) • Nausea (3 patients), • Fluid retention (1 patient). Placebo: • Nausea (1 patient) In addition, six patients [treatment arm or disease (OA or RA) no reported] experienced a flare up between weeks 2 to 4.
Audeval *et al.*[24]	Seatone	Yes	Monthly	No information	No information	No information
Gibson and Gibson[20]	Green-lipped mussel	Yes	No information	Total reported = 2 Lipid extract: 1 Stabilized mussel: 1	Lipid extract: 1 (7%) Stabilized mussel: 1 (7%)	Authors do not state which treatment group (OA or RA) the adverse effects occurred in: Lipid extract: • Fluid retention (1 patient). Stabilized mussel extract: • Nausea (1 patient)
Lau *et al.*[18]	Lyprinol®	Yes	No information	Total reported = 4 Lyprinol®: 3 Placebo: 1	No clearly stated – at least $N = 4$ Lyprinol®: 3 (7.5%) Placebo: 1 (2.5%)	Lyprinol®: • Nausea (1 patient) • Elevated serum liver aminotransferase (1 patient)[a] • Heart failure (1 patient)[a] Placebo: • Elevated serum liver aminotransferase (1 patient)

RA: rheumatoid arthritis; GLM: green-lipped mussel; OA: osteoarthritis.

two capsules per day till completion. The placebo capsules were prepared with olive oil, and as no further details were reported, active and placebo capsules may have smelt differently. No details of randomization process or method were reported. Outcome measures were recorded at baseline, weeks 2, 4, 8, 12, 18 and 24. Tolerability was assessed (i.e. adverse event reporting, liver and renal function, full blood counts) as well as compliance (capsule count). The study was conducted to GCP and the data were monitored on a regular basis. There was no differentiation between primary or secondary outcomes, therefore the results must be interpreted with caution. Demographic, screening, baseline and treatment data were all reported using descriptive statistics by treatment arm and between-group comparisons over time was reported for treatment phase; no between-group analysis for baseline characteristics appeared to be conducted. Disease severity and radiological stage were not considered in the analysis. Univariate analysis of variance for repeated measures (adjusted for change in paracetamol use over time) was employed to assess efficacy and safety.

Thirty-five patients completed the study in the Lyprinol® arm, 32 in placebo arm. Drop outs were due to a variety of reasons [did not want to continue ($N=2$ placebo); lack of efficacy ($N=1$ Lyprinol®; $N=3$ placebo); development of exclusion criteria ($N=1$ Lyprinol® (diagnosed with RA); $N=1$ placebo (joint steroid injection)); adverse events ($N=3$ Lyprinol®—nausea, abnormal liver function test, heart failure; $N=1$, placebo—abnormal liver function) and poor compliance ($N=1$, placebo)]. Pain VAS was significantly reduced in both treatment groups from baseline to end of treatment (Lyprinol® $=-9.0$ mm; placebo $=+6.7$ mm). Adjustment for paracetamol use (to take into account changes in individual needs for rescue medication), resulted in a greater significant reduction in VAS pain score in the active treatment arm compared to placebo (week 8, $P=0.035$; week 12, $P=0.032$ and week 24, $P=0.045$). Patient global assessment improved in both arms during the study period (mean score reduction from baseline to end of treatment of 0.75 for Lyprinol®; but an increase of 0.4 for placebo). Improvements in the other efficacy assessments were reported but no significant group differences noted. No results were presented for compliance assessment. Although no data were presented, the authors report that there were no significant group differences in adverse event or withdrawal rates. The authors conclude that Lyprinol® was well tolerated and was associated with decrease pain perception and patient's global assessment of his/her arthritis state after at least 2 months of treatment when compared with placebo. The main methodological concern with this trial, which could bias the findings, relates to group differences in analgesic requirements. Although the authors adjusted outcomes for percentage change in analgesic use, individual requirements might have been different from the standardized dose and the verum group may have been favoured; no screening data on subjects' standardized analgesic use was reported. Data reporting was also inadequate; for instance the lack of group comparison of baseline characteristics.

Comparator study

The aim of Gibson and Gibson study[20] was to compare two different preparations of GLM over 6 months: a lipid extract (Lyprinol®) 210 mg/day vs. the stabilized mussel powder form 1150 mg/day (Biomax, Australia). On the basis of their previous study,[19] the authors considered a placebo arm was not necessary. They utilized their previous study protocol,[19] with GLM as an adjunctive treatment. An equal number of patients with RA were included but their results were analysed and presented as a separate data set.

Sample size calculation, based on their previous study, identified that 15 patients were required in each treatment group. Thirty patients with confirmed radiological evidence of OA (hands, hips and knee joints), were randomized to lipid fraction ($N=15$, Group A) or stabilized mussel powder ($N=15$, Group B). Patients in Group A took five capsules per day (1150 mg/day mussel powder) and Group B, three capsules per day (210 mg/day lipid extract) for 3 months. All patients took lipid extract for a further 3 months, and the randomization code was broken at the end of 6 months treatment. The main outcome measures were the articular index of joint tenderness (AI), morning stiffness (LuT), visual analogue scale of pain (VAS), handgrip strength and functional index. In addition, patient and physician global assessment after 3 and 6 months and adverse events were recorded. Differences between baseline and 3 months treatment were analysed using Wilcoxon matched pair test; comparisons between treatment groups were conducted but no data were presented. Randomization codes were hand prepared by placing equal numbers of slips for Groups A and B in envelopes. Envelopes were randomly drawn by pharmacy staff for each patient; the authors report that both patients and physicians were blinded to treatment allocation. Although described as a double-blinded study, the number of tablets

taken differed for the two treatment groups, and although pharmacy and subjects did not know which preparation had how many tablets, both the change in tablet numbers and symptom reporting after 3 months may possibly have violated blinding. In addition, subjects reported differences in appearance, smell and taste between the two preparations (lipid extract vs. powder).

The two treatment arms were balanced for demographic variables. Two patients dropped out from each treatment arm (due to transport difficulties), leaving $N=13$ in Group A and $N=13$ in Group B. Both interventions showed significant improvements at 3 months in articular index (Group A, mean change $=-5.2$, CI 2.0–8.3, $P<0.05$, Group B, mean change $=-8.2$, CI 4.8–11.7, $P<0.05$), pain VAS (Group A, mean change $=-1.3$ cm, CI 0.1–2.6, $P<0.05$, Group B, mean change $=-1.1$ cm, CI 0.02–2.1, $P<0.05$) and functional index (Group A, mean change $=-5.6$, CI 4.1–7.9, $P<0.05$, Group B, mean change $=-5.4$, CI 3.8–7.0, $P<0.05$). Significant improvement in morning stiffness was observed in both groups (Group A, mean change $=-28.2$ min, $P<0.01$, Group B, mean change $=-29.0$ min, $P<0.01$). Patient and physician global assessment identified improvement of 85% in Group A and 69% in Group B. Although the data were not presented, comparison between treatment arms was conducted using non-parametric tests, and no significant group differences were observed in any measure. In addition, the populations compared may not have been homogenous; the numbers of patients with OA in different joints per group was not stated; and response to treatment may vary between different joints. The authors reported no difference in the speed of efficacy in either preparation with both being efficacious. Adverse effects were minimal; two side effects were reported (lipid extract; and nausea, stabilized mussel powder), but there was no indication whether these occurred in RA or OA patients. Subsequent sensitivity analysis for this article identified that although sample size for individual variables was adequate, the power for comparison between treatment groups was insufficient. Consequently the lack of a statistically significant group difference may be due to inadequate power rather than ineffective treatment. Other methodological issues as indicated in Tables 2 and 3 also suggest caution.

Discussion

The four RCTs reviewed all assessed GLM as an adjunctive treatment in OA and not as a cure or as a replacement therapy. All four single centred studies reported positive clinical improvement for GLM over a clinically relevant period of at least 2 months in mild to moderate OA. The studies were generally well designed. All patients entered had established (5–14 years) radiological evidence of OA; and the populations in all the studies were generally representative of this condition i.e. elderly with appropriate comorbidity. In addition, the trials employed standard disease specific outcome measures assessing pain and functional status. Where reported, drop out rates were also acceptable. However, poor methodological reporting was an issue in all the studies, making a definitive conclusion difficult, and lowering the JADAD score. For example, acceptable inclusion and exclusion criteria (according to ACR) were presented in only one study;[18] adequate baseline characteristics, to allow for the evaluation of possible confounding factors, was also reported in only one of the studies,[24] and there was poor reporting of both randomization[18,19,24] and withdrawal data.[24] More serious methodological limitations were identified in three of the four studies i.e. inadequate blinding;[20] inappropriate statistical methodology;[19,24] and the incorrect re-analysis of the Gibson[19] data.[25–27] Our re-analysis of the Gibson[19] paper in addition to the study by Lau *et al*. now indicates that GLM may have positive effects in the treatment of OA. The Gibson study involved OA knee, hip and hand and identified a positive but non-significant benefit for GLM over placebo. This was conducted in treatment resistant patients, which may account for the lack of significant difference between the treatment groups. Lau *et al*. recruited OA knee conducting the largest GLM trial to date. They identified significant group differences in two key outcomes; pain and patient global assessment. We therefore suggest that the evidence from both studies now indicates that GLM may be superior to placebo in OA. Further multicentred trials are needed to confirm this.

Biological mechanisms of action for GLM have been investigated and have contributed to the evidence base for its supposed anti-inflammatory activity. The history, pharmacology and pre-clinical studies of GLM have been reviewed comprehensively elsewhere, and much of the evidence for the pharmacological activity of GLM comes from the work of Whitehouse *et al*.[13] and Halpern[28] who have demonstrated that freeze–dried GLM powder has an anti-inflammatory activity associated with the omega-3 EFA contained within its lipid fraction.

The lack of consistency in the type and dosage of extracts used in these studies must be addressed in further trials. Comparison between trial findings

is hampered by variation in the potency of nutritional supplements (the use of different preparations, manufacturers and dosing schedules) differing nutritional status of patients, and the presence of omega-3 fatty acids in the placebo.[19] These factors may all contribute to variability in trial outcomes. Only one of the studies addressed the issue of subject's dietary consumption of omega-3 fatty acids.[18] This issue is not confined solely to GLM; supplementation trials of omega-3 EFA in arthritis patients have also reported these problems as a possible explanation for variable study findings.[29]

No serious AE were reported in any of the trials reviewed and there are no reports in other literature of any severe or serious adverse effects to GLM. In all four studies, adverse effects were acceptable (<10%of the study population), minor and transient and included increased stiffness,[19] flatulence,[19] epigastric discomfort,[19] nausea,[19,20] exacerbation of symptoms[19] and fluid retention.[20] This may have been caused by the concomitant NSAID prescriptions; GLM is not considered gastrotoxic, with some animal studies[17,30] suggesting that GLM could help reduce gastrointestinal irritation. No definitive conclusions can be drawn from these four trials regarding the tolerability and safety of GLM because of both the small population entered (a total of $N=113$ patients received GLM in these trials) and inadequate reporting.

This systematic review provides new analysis and re-interpretation of studies assessing the role of GLM in the treatment of OA. We have highlighted the necessity for improved design, analysis and reporting in future studies. Despite GLM having a plausible biological mechanism for its purported action, further rigorous investigations are needed to provide further evidence for the efficacy of GLM as an adjunctive treatment in OA. A phase II dosing study to identify the optimal dose is initially required followed by a definitive trial in patients with mild to moderate OA to determine the effectiveness of this supplement.

Acknowledgements

Funding sources had no involvement in this review. S.B. is funded by a Personal Award Scheme Postdoctoral Researcher Development Award, for Complementary and Alternative Medicine, from the National Institute of Health Research (Department of Health) (ref. no. PDA04/CAMs2/02). G.L's post is funded by the Rufford Maurice Laing Foundation. P.P., B.C. and N.B. received no source of funding for this article.

Conflict of interest: None declared.

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