Joint health and omega-3s: pain and inflammation

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Effects of fish oil on mediators of inflammation

Eicosanoids
Reduced PGE$_2$
✓ PGE$_2$ is nociceptive, ∴ ↓ PGE$_2$ → analgesia
✓ Inhibition of 5-lipoxygenase
✓ ↓ LTB$_4$ → ↓ chemotaxis & leucocyte activation

Resolvins
✓ Complex oxy-lipids formed from EPA & DHA by the action of multiple lipoxygenases
✓ Actively resolve inflammation (Serhan CH et al. 2000)

Inflammatory proteins
✓ Reduce synthesis of inflammatory cytokines
✓ TNF$_{α}$, IL-1$β$, IL-6
✓ Down regulate NF$κ$B
✓ Reduced adhesion molecule expression
✓ G-protein coupled receptor GPR120 on macrophages
✓ Engaged by EPA & DHA → anti-inflammatory effects
Clinical Trials with Fish Oil in Rheumatoid Arthritis

>14 double-blind, placebo-controlled studies

Meta-analyses

10 studies in 1995
(Fortin et al)

Fish oil decreased:
- tender joint count
- duration of morning stiffness

13 studies in 2007
(Goldberg et al)

Fish oil decreased:
- tender or swollen joint count
- duration of morning stiffness
- pain intensity
- NSAID use

Defining the place of fish in early intensive management of RA

✔ Need for data within context of early intensive treatment of RA
  ✔ In studies to date, trial subjects have had established disease with the average disease duration of 10.2 ± 5.2 years across all studies.

✔ DMARD use needs to be ‘real life’
  ✔ not held constant with a need for change being a withdrawal criterion
  ✔ drug variation needs to occur according to pre-defined rules

*DMARD = disease modifying anti-rheumatic drug*
Minimisation of Cumulative Damage – Contemporary Management of RA

✓ Early treatment (“window of opportunity”)
  ✓ Combination DMARD therapy
  ✓ Goal of remission can be achieved without initial biologics or steroids\(^1\)

✓ Tight control of inflammation
  ✓ Frequent assessments (3-6 weekly until target reached)
  ✓ Treat to agreed target
    ✓ Low Disease Activity or remission
  ✓ Adherence to treatment protocol

Aim

To assess the effects of high vs. low dose fish oil (FO) on disease outcomes in RA patients receiving a “treat-to-target” protocol of combination DMARDs over three years.

Data from the first 12 months are presented.
Methods

Consecutive patients attending Early Arthritis Clinics at RAH, 2001-2008

Active, DMARD-naïve, ACR criteria RA, < 6 mths’ duration

- at least 3 swollen and 3 tender joints, AND
- ESR ≥ 28 mm/hour and/or CRP ≥ 10 mg/dL

Rules-based “triple therapy” DMARDs

Randomised 2:1 to receive 10ml/day of study oil

- High dose (FO) : 5.5 g/d EPA+DHA*
- Low dose (control) : 400mg/d EPA+DHA#

*Incromega TG3525 contains 35% EPA and 25% DHA.

#sunola oil: capelin oil (2:1): sunola oil is a monounsaturated oil. Capelin oil contains 6.6% EPA and 5.7% DHA and was added to match for smell and taste.
Methods

✓ Primary end-point:
  ✓ Extent of DMARD use (permitted by rules-based DMARD use)

✓ Secondary end-points:
  ✓ DAS28-ESR
  ✓ DAS28-ESR and ACR remission
  ✓ mHAQ
  ✓ plasma phospholipid fatty acids (EPA+DHA)

Assessments every 3 months
Rules for changes in dose/agent

**Triple Therapy:**
Methotrexate 10mg/w (+ folic acid 0.5mg/d)
Sulphasalazine 0.5g/d, increase by 0.5g/d every week to 1g bd
Hydroxychloroquine 200mg bd
(MTX parenteral if GI side effects)

- Increase SSA to 1.5g bd
- Increase MTX to 15mg/wk (MAX DOSE if creat.cl.<30)
  (MTX parenteral if GI side effects)
- Increase MTX to 20mg/wk
  (MTX parenteral if GI side effects)

If weight<50kg and/or creat. cl. >30 but <60, MTX 20mg/wk oral –>parenteral,

- MTX 25mg/wk parenteral
- Leflunomide 10mg/day added
  (can be increased to 20mg/day if tolerant)

If weight >50kg and creat. cl. > 60,
Increase MTX to 25mg/wk (oral)
(MTX parenteral if GI side effects)

- Biologic DMARD, if criteria is fulfilled

NSAID use discouraged
Parenteral (i.m.) glucorticoids used as clinically indicated

gold thiomalate
cyclosporin
azathioprine

- Leflunomide 10mg/day added
  (can be increased to 20mg/day if tolerant)

- Biologic DMARD, if criteria is fulfilled

Rules for changes in dose/agent
Conclusion

Despite less compliance, FO was associated with additional benefits over and above those achieved by combination “treat-to-target” DMARDs with similar MTX use:

✔ Reduced likelihood of progressing to leflunomide
✔ Lower disease activity at 12 months
✔ Shorter time to achieving ACR remission

✔ High plasma fatty acids were associated with higher OR of achieving remission.

✔ Compliance was a factor limiting efficacy
Therapeutic choices

✓ Fish oil v. non-steroidal anti-inflammatory drugs
✓ Fish oil v. krill oil
## A guide to the decision: an NSAID or Fish Oil

<table>
<thead>
<tr>
<th></th>
<th>NSAIDs</th>
<th>Fish Oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID sparing</td>
<td>no</td>
<td>Yes ($\downarrow$PGE$_2$)</td>
</tr>
<tr>
<td>Other desirable anti-inflammatory actions</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Serious CV Events</td>
<td>increased</td>
<td>reduced</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>increased</td>
<td>reduced</td>
</tr>
<tr>
<td>Upper GI Bleeding</td>
<td>increased</td>
<td>not increased</td>
</tr>
<tr>
<td>Renal failure</td>
<td>may aggravate</td>
<td>can delay</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>may aggravate</td>
<td>can improve</td>
</tr>
<tr>
<td>Mortality</td>
<td>increased</td>
<td>reduced</td>
</tr>
<tr>
<td>Contraindications</td>
<td>numerous</td>
<td>few</td>
</tr>
<tr>
<td>Time to effect</td>
<td>prompt</td>
<td>delayed</td>
</tr>
</tbody>
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Cleland, James, Proudman - Fish oil: what the prescriber needs to know
http://arthritis-research.com/content/8/1/202
## Comparisons between krill oil & fish oil

<table>
<thead>
<tr>
<th></th>
<th>Fish oil</th>
<th>Krill oil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPA &amp; DHA</strong></td>
<td>as triglycerides</td>
<td>as phospholipids &amp; free fatty acids</td>
</tr>
<tr>
<td></td>
<td>EPA 18%, DHA 12%</td>
<td>EPA 15%, DHA 9%</td>
</tr>
<tr>
<td></td>
<td>slightly less well absorbed</td>
<td>slightly better absorbed</td>
</tr>
</tbody>
</table>

Differences in absorption offset by differences in concentration

- Schuchardt JP et al. *Lipids in Health and Disease* 2011, 10:145

### Discounted Retail Price

|                | Fish oil: 5 cents per gram                    | Krill oil: $1.67 per gram                   |

### Krill oil contains astaxanthin

Marketing claim of 10 fold greater potency v. fish oil alludes to unspecified tests of anti-oxidant activity of dubious clinical relevance
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