Achieving optimal RBC levels of omega-3 fatty acids can help reduce risk for cardiovascular disease.
Objectives

1. Define 5 fatty acid classes in RBC’s
2. Describe how fatty acid status is assessed
3. Explain how RBC fatty acids relate to cardiovascular risk
4. Discuss mechanisms of action
5. Review recommended fatty acid intakes
Take Home Messages

1. The RBC membrane contains >20 individual fatty acids of 5 different classes.

2. The RBC EPA+DHA content (the Omega-3 Index) is a valid and stable biomarker of omega-3 fatty acid status.

3. For cardiovascular health, an Omega-3 Index >8% is optimal and an Index < 4% is deficient. Target trans fat levels are <1%.


5. Omega-3 EPA+DHA intakes should be 400-500 mg/day for most adults and twice that for CHD patients.
Objectives

1. Define 5 fatty acid classes in RBC’s
2. Describe how fatty acid status is assessed
3. Explain how RBC fatty acids relate to cardiovascular risk
4. Discuss mechanisms of action
5. Review recommended fatty acid intakes
A fatty acid is a chain of carbon atoms with an acid group on one end
- Saturated
- Monounsaturated
- Polyunsaturated – Omega-6 and Omega-3 (n-6 or n-3)
- Trans

<table>
<thead>
<tr>
<th>Omega-6 Polyunsaturated Fatty Acids</th>
<th>Non-Essential Fatty Acids</th>
<th>Omega-3 Polyunsaturated Fatty Acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linoleic acid (LA) C18:2n-6</td>
<td>Palmitic acid (PA) C16:0</td>
<td>α-Linolenic acid (ALA) C18:3n-3</td>
</tr>
<tr>
<td>γ-Linolenic acid (GLA) C18:3n-6</td>
<td>Oleic acid (OA) C18:1n-9</td>
<td>Eicosapentaenoic acid, EPA C20:5n-3</td>
</tr>
<tr>
<td>Arachidonic acid (AA) C20:4n-6</td>
<td>Elaidic acid (EA) C18:1n-9 trans; Trans Fatty Acid</td>
<td>Docosahexaenoic acid, DHA C22:6n-3</td>
</tr>
</tbody>
</table>
Types of Fatty Acids
N-6 Polyunsaturates (PUFAs)

• PUFA have >1 double bond; n-6 and n-3 families.
• Major n-6 PUFAs: linoleic acid (LA, C18:2n-6) and arachidonic acid (AA, C20:4n-6).
• All n-6 PUFAs can be synthesized from LA, but LA cannot be made de novo (i.e., essential).
• Linoleic - vegetable oils (corn, safflower, soybean, etc.) with small amounts in canola, olive and flaxseed oils. Arachidonic - only in animal products like meat and eggs (but not in dairy products).
Types of Fatty Acids
N-3 Polyunsaturates

• Major n-3 PUFAs are alpha-linolenic acid (ALA, C18:3n-3), eicosapentaenoic acid (EPA; C20:5n-3), docosapentaenoic acid (DPA; C22:5n-3) and docosahexaenoic acid (DHA; C22:6n-3)

• All n-3 PUFAs can be synthesized from ALA, but ALA cannot be made de novo (i.e., essential).

• ALA is in certain plant oils (canola, olive and flaxseed), whereas EPA and DHA come from seafoods.
Take Home Message

The RBC membrane contains >20 individual fatty acids of 5 different classes
Objectives

1. Define 5 fatty acid classes in RBC’s
2. Describe how fatty acid status is assessed
3. Explain how RBC fatty acids relate to cardiovascular risk
4. Discuss mechanisms of action
5. Review recommended fatty acid intakes
Assessing Fatty Acid Status

RBC fatty acids are hydrolyzed from membranes, derivatized and analyzed by gas chromatography.
Assessing Fatty Acid Status
The Omega-3 Index

A measure of the amount of EPA+DHA in red blood cell membranes expressed as the percent of total fatty acids

There are 64 fatty acids in this model membrane, 3 of which are EPA or DHA

\[
\frac{3}{64} = 4.6\%
\]

Omega-3 Index = 4.6%

Assessing Fatty Acid Status
Low Biological Variability & Long-Term Marker

20 healthy volunteers tested weekly for 6 weeks

Total Coefficients of Variability (CVs)

EPA+DHA in...
- RBC = 4.1%
- Whole Blood = 6.7%
- Plasma = 16%
- Plasma PL = 15%

Take Home Message

The RBC EPA+DHA content (the Omega-3 Index) is a valid and stable biomarker of omega-3 fatty acid status.
Objectives

1. Define 5 fatty acid classes in RBC’s
2. Describe how fatty acid status is assessed
3. Explain how RBC fatty acids relate to cardiovascular risk
4. Discuss mechanisms of action
5. Review recommended fatty acid intakes
RBC Fatty Acids and CVD Risk

Strong evidence
• Omega-3 Index: Low levels = High risk

Intermediate evidence
• Trans fats: High levels = High risk
• Linoleic acid (n-6): Low levels = High risk

Little evidence
• Saturated
• Monounsaturated
• Plant n-3 (α-linolenic acid)
RBC Fatty Acids and CVD Risk

Selecting Omega-3 Index Targets

Greatest Protection
- GISSI-P: ~9–10%
- CHS: 8.8%
- DART: ~8–9%
- SCIMO: 8.3%
- 5 epi studies: ~8%
- PHS: 7.3%
- Seattle: 6.5%

Least Protection
- PHS: 3.9%
- SCIMO: 3.4%
- Seattle: 3.3%

RBC Fatty Acids and CVD Risk

Omega-3 Index Risk Zones

USA/EU  Japan

Undesirable  Intermediate  Desirable

Percent of EPA+DHA in RBC

Risk for cardiac death in the US is 45x higher than in Japan


He et al. Circ 2004;109:2705-2711
Iso et al. Circ 2006;113:195-202
The Omega-3 Index Worldwide

[Graph showing data points from various countries including USA, Germany, Norway, Spain, Japan, Korea, and Alaska. The graph compares EPA+DHA levels between healthy and ill subjects across different regions.]
Multivariable logistic regression model including: age; race; gender; history of diabetes mellitus, hypertension, hyperlipidemia and/or myocardial infarction; a family history of coronary artery disease; and LDL-C, HDL-C, and triglycerides.

RBC Fatty Acids and CVD Risk

The Omega-3 Index and Cellular Aging

Chromosome

Telomeres
end caps that protect the chromosomes

As cells divide

over time ...

... telomeres shorten, and eventually cell division stops.
RBC Fatty Acids and CVD Risk

Blood Omega-3 is Inversely Associated with the Rate of Telomere Attrition

Adapted from Farzanah-Far, et al. *JAMA* 2010;303:250-257
RBC Fatty Acids and CVD Risk
Omega-3 Index and Time to Death in 982 CHD Patients

It took 1.2 years longer for 20% of the population to die in the higher vs. the lower omega-3 group.
Why is the Omega-3 Index Target 8%?

• The average Omega-3 Index estimated from 11 studies was 8.1%

• An Omega-3 Index of >8% was associated with reduced probability for acute coronary syndrome compared to an Index of <4%

• The Omega-3 Index associated with the slowest rate of cellular aging was 8.7%

• The average Index in Japan (where CHD is rare) is 9-10%
Clinical Evidence – Cross Sectional
Primary Cardiac Arrest and the Omega-3 Index
Seattle PCA Study

Odds Ratio

90% reduction in risk
*p<0.05 vs Q1

Midrange RBC EPA+DHA by Quartile

3.3% 4.3% 5.0% 6.5%

Adapted from Siscovick DS et al. JAMA 1995;274:1363-1367.
Clinical Evidence – Prospective
Sudden Cardiac Death and the Omega-3 Index
Physicians' Health Study


Mean Blood Omega-3 FA (%) by Quartile

3.6% 4.8% 5.6% 6.9%

90% reduction in risk

p for trend = 0.001
The Omega-3 Index, Brain Volume and Cognitive Function in Framingham Quartile 1 vs 2-4 (<4.4% vs above)

<table>
<thead>
<tr>
<th>Model</th>
<th>Covariates</th>
<th>Total Cerebral Brain Volume (%)</th>
<th>Visual Memory</th>
<th>Executive Function</th>
<th>Abstract Thinking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

“The MRI finding of lower brain volume [in those with an Omega-3 Index <4.4%] represents a change equivalent to approximately 2 years of structural brain aging.”

n=1575; age=67

Executive Functioning and Cognitive Flexibility by Quartile of the HS-Omega-3 Index in Army Members Deployed in Iraq

P<0.01 for trend

N=78, mean age 31 yrs
Take Home Message

For cardiovascular (and possibly neurocognitive) health, an Omega-3 Index >8% is optimal and an Index < 4% is deficient.
Objectives

1. Define 5 fatty acid classes in RBC’s
2. Describe how fatty acid status is assessed
3. Explain how RBC fatty acids relate to cardiovascular risk
4. Discuss mechanisms of action
5. Review recommended fatty acid intakes
Effects of Omega-3...
- Reduced heart rate
- Reduced inflammation
- Improved vascular function
- Reduced susceptibility to cardiac arrhythmias

* Primarily from nutritionally-achievable intakes: 500-1,000 mg/d

Mediated by....
- Altered cell membrane physiochemical properties
- Shifts in eicosanoid production
- Altered gene expression

Mozaffarian and Wu. JACC 2011; 58:2047–67
Take Home Message

Dietary doses of EPA+DHA reduce risk for CHD via non-traditional pathways by changing membrane physiochemical properties and improving the eicosanoid profile. Pharmacologic doses lower triglycerides.
Objectives

1. Define 5 fatty acid classes in RBC’s
2. Describe how fatty acid status is assessed
3. Explain how RBC fatty acids relate to cardiovascular risk
4. Discuss mechanisms of action
5. Review recommended fatty acid intakes
# AHA Scientific Statement on Omega-3s

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients without documented CHD</td>
<td>Eat a variety of fish (preferably oily) at least twice a week*, include oils and foods rich in ALA</td>
</tr>
<tr>
<td>Patients with documented CHD</td>
<td>Consume ~1 gm of EPA+DHA per day, preferably from fish, supplements could be used in consultation with a physician</td>
</tr>
<tr>
<td>Patients needing TG lowering</td>
<td>2 – 4 gm of EPA+DHA per day provided as capsule under a physician’s care</td>
</tr>
</tbody>
</table>

*Equal to about 400-500 mg EPA+DHA/day

## AHA Recommendations for Women

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women with high blood cholesterol or triglycerides; for primary or secondary prevention</td>
<td>Consumption of omega-3 fatty acids in the form of fish or capsules (e.g., EPA 1800 mg/d)</td>
</tr>
</tbody>
</table>

Our tests of 16 leading pill brands found that all contained roughly as much omega-3s as their labels claimed, and none were contaminated or spoiled. So choose them based mainly on price.
Take Home Messages

1. The RBC membrane contains >20 individual fatty acids of 5 different classes

2. The RBC EPA+DHA content (the Omega-3 Index) is a valid and stable biomarker of omega-3 fatty acid status

3. For cardiovascular health, an Omega-3 Index >8% is optimal and an Index < 4% is deficient. Target *trans* fat levels are <1%.


5. Omega-3 EPA+DHA intakes should be 400-500 mg/day for most adults and twice that for CHD patients.