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ISSFAL Official Statement Number 6: The importance of measuring blood omega-3 long chain polyunsaturated fatty acid levels in research

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Abstract

A statement on measuring blood omega-3 long chain polyunsaturated fatty acid levels was developed and edited based on input from ISSFAL members and accepted by vote of the ISSFAL Board of Directors. Summary of Statement: Omega-3 long chain polyunsaturated fatty acid (n-3 LCPUFA) levels at baseline and post-intervention should be assessed and reported in future research to evaluate the efficacy of n-3 LCPUFA supplementation: b ecause; 1. there are numerous factors that affect n-3 LCPUFA levels in humans as described in the systematic literature review [1]; 2. assessing intake of n-3 LCPUFA from the diet and/or supplements is not sufficient to accurately determine n-3 LCPUFA levels in humans; 3. some studies do not provide sufficient doses of n-3 LCPUFA to produce a significant impact on bloodstream/organ content and there is substantial variability in the uptake of n-3 LPCUFA into tissues between individuals. In secondary analyses, clinical trials should consider the influence of fatty acid status (baseline, endpoint and change from baseline to endpoint) on the outcome variables.

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The importance of measuring blood omega-3 long chain polyunsaturated fatty acid levels in research

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A statement on measuring blood omega-3 long chain polyunsaturated fatty acid levels developed and edited based on input from ISSFAL members and accepted by vote of the ISSFAL Board of Directors.

Summary of Statement

Omega-3 long chain polyunsaturated fatty acid (n-3 LCPUFA) levels at baseline and post-intervention should be assessed and reported in future research to evaluate the efficacy of n-3 LCPUFA supplementation

Because:

1. There are numerous factors that affect n-3 LCPUFA levels in humans as described in the systematic literature review [1].
2. Assessing intake of n-3 LCPUFA from the diet and/or supplements is not sufficient to accurately determine n-3 LCPUFA levels in humans.
3. Some studies do not provide sufficient doses of n-3 LCPUFA to produce a significant impact on bloodstream/organ content and there is substantial variability in the uptake of n-3 LPCUFA into tissues between individuals. In secondary analyses, clinical trials should consider the influence of fatty acid status (baseline, endpoint and change from baseline to endpoint) on the outcome variables.

Introduction

It is becoming increasingly clear that n-3 LCPUFA play an important role in human health [2]. N-3 LCPUFA have been shown to be important for neurological development [3, 4], cardiovascular health [5, 6] and there is emerging evidence of their beneficial role in other disease states, including mental health conditions [7].

Several mechanisms have been suggested for these potential health benefits [8], including effects on cell membranes which can influence signal transduction, promotion of neuronal growth, altering neurotransmitter release, and facilitating glucose uptake from the endothelial cells into the brain. N-3 LCPUFA are also important precursors of the eicosanoids and docosanoids, which have anti-thrombotic and vasodilatory effects [8].

The evidence for the above-mentioned potential health benefits are derived from a large number of studies, including both epidemiological/observational studies and baseline data from randomised, controlled trials (RCT). However, many of these studies have failed to include measurements of n-3 LCPUFA levels. This may have serious implications for their ability to draw correct conclusions about the effects of omega-3 on the measured outcome/s.

The recently published systematic literature review [1] highlights that there are many factors associated with the n-3 LCPUFA levels of an individual. Therefore, the aims of the current statement paper are to: 1. Recommend that researchers should measure n-3 LCPUFA levels at baseline and post-intervention, 2. report on the full fatty acid results in future research and 3. analyse the results as intention to treat, but also to analyse by the effect of the change of n-3 LCPUFA levels and the change in the outcome variable(s) where possible.

Methods

Professors Barbara Meyer and Renate de Groot proposed to the ISSFAL executive board to write a statement about the importance of measuring n-3 LCPUFA levels in research. After receiving a positive reply from the executive board and support from the ISSFAL board, the procedure for writing ISSFAL statements, as described on the ISSFAL website (http://www.issfal.org/statements/procedures-for-policy-statements), was followed. After a review by the ISSFAL Board, it became clear that a systematic review of factors associated with n-3 LCPUFA was necessary and has since been published [1]. This statement contains the summarised outcomes from the systematic literature review which focused on adults.

Results of the evaluation

Terminology

Various terminologies exist in the literature when describing n-3 LCPUFA levels (defined as n-3 PUFA not containing alpha-linolenic acid (ALA, 18:3n-3)) in an individual; including the Holman index; the Lands Highly Unsaturated Fatty Acids (HUFA) [9]; long chain omega-3 PUFA [10] and the HS-Omega-3 Index [11]. The n-3 LCPUFA levels are similar to the afore-mentioned terminologies, and hence n-3 LCPUFA levels are used in the current statement.

Factors affecting n-3 LCPUFA levels

The n-3 LCPUFA levels in an individual are associated with many factors including diet. It is well-documented that dietary intake of n-3 LCPUFA is associated with n-3 LCPUFA levels [12, 13]. However, dietary intake assessment is less reliable than measuring n-3 LCPUFA levels [14, 15]. The non-dietary factors that are associated with n-3 LCPUFA levels are identified in the systematic literature review [1] and these are listed in **Table 1**. The following factors have been found to be associated with n-3 LCPUFA levels through assessment of correlation studies and baseline data from RCT.

Results from the systematic literature review [1] showed that in general women had higher levels of DHA than men [16, 17]. Studies regarding the genetic factors revealed that mutations in FADS1, FADS2 [18-23] and ELOVL2 [22, 23] resulted in lower levels of gamma-linolenic acid (GLA, 18:3n-6), arachidonic acid (AA, 20:4n-6), EPA, and DHA due to constraint(s) in the fatty acid metabolism pathway, however these constraint(s) may be overcome by supplementation with preformed EPA and DHA [24]. N-3 LCPUFA levels are positively associated with increased age [17, 25-47]. There is a negative association between participants' BMI and n-3 LCPUFA levels (erythrocyte EPA and DHA < 6%) [25, 36, 48-50], but not in individuals with a higher (> 6%) erythrocyte EPA and DHA [34, 46, 51-53]. Limited data suggests that waist girth [25, 43-45, 49, 50] and also the amount of physical activity [46, 51, 52, 54-58] is not associated with n-3 LCPUFA levels. There is a negative association with alcohol consumption and n-3 LCPUFA levels, especially when the beverage type is beer or spirit [43-45, 59, 60-64]. Lower n-3 LCPUFA levels are found in smokers [25, 39, 43, 44, 51, 65-67]. Regarding bioavailability, there is no convincing evidence that krill oil is more bioavailable than fish oil [68, 69]. There is no convincing evidence suggesting that the chemical form of n-3 LCPUFA supplements matters in terms of bioavailability [70, 71]. With respect to the conversion of plant-derived n-3 fatty acids to n-3 LCPUFA there is some evidence that supplementation with ALA increases EPA but not DHA and high intakes of linoleic acid reduces the conversion of ALA to EPA (http://www.issfal.org/statement-5). Limited evidence suggests that stearidonic acid (SDA, 18:4n-3) supplementation increases EPA to a greater extent than supplementation with ALA, but SDA supplementation does not increase DHA levels [72].

The above findings support the statement that n-3 LCPUFA levels at baseline and post-intervention should be assessed and reported in future research to evaluate the effectiveness of n-3 LCPUFA supplementation.

Full fatty acids profiles are encouraged to be reported for the following reasons: (1) invariably people are looking at published data from a different perspective and with different goals in mind and the full composition is useful in many such ways; (2) it may also offer some quality control to see if the fatty acid profiles are consistent with other reports, especially since such data is often reported as a percentage so other fatty acid levels can affect the values in question; and (3) inspection can determine how extensive and complete was the identification of the fatty acids in a given tissue.

In summary, the factors that need to be taken into account when assessing the effect of n-3 LCPUFA include sex, age, BMI, alcohol consumption (and type of alcohol) and smoking.

[INSERT TABLE 1]

Conclusions

1. Factors positively associated with the n-3 LCPUFA levels are: age, sex (women less than 50 years of age).
2. Factors negatively associated with the n-3 LCPUFA levels are: genetics, BMI (if erythrocyte EPA and DHA is less than 6%), smoking and alcohol.
3. There is inconclusive evidence for the association of waist girth and physical activity with n-3 LCPUFA levels.
4. There is no convincing evidence that krill oil versus fish oil, or the chemical form of n-3 LCPUFA matters in terms of bioavailability.
5. It is unreliable to predict the n-3 LCPUFA levels in an individual according to food intake measured with food frequency questionnaires or comparable instruments.

Recommendations

The recommendations below are for people of all ages, however the systematic literature review [1] focussed on adults.

1. ***It is essential that in all types of research, including cross-sectional, cohort and clinical research, the n-3 LCPUFA levels are measured in biological samples, and this should be done according to appropriate study protocol. So, for cross-sectional studies the biological samples must be measured at one time point and for cohort and clinical intervention studies the biological samples must be measured at baseline and follow-up.*** Whether the biological samples should be, whole blood, plasma, or tissue, that is not the focus of this statement, however, there are algorithms available for data conversion [16]. Note that there are other publications for best practices for research in this field [17, 18].
2. In secondary analyses, researchers conducting clinical trials should consider the influence of fatty acid status on the outcome variables.
3. Lastly, publishing full fatty acid profiles (expressed both as percent of total fatty acids and as concentrations), rather than just n-3 LCPUFA, is highly recommended.

Table 1: Various factors affecting n-3 LCPUFA levels. For further details, please refer to the systematic literature review [1].

Factors		Direction of association or comments	Should take factor into account Yes or No
Unmodifiable factors			
Sex		In general women have higher DHA levels than men.	Yes
Genetics	FADS1 & FADS2	Negative association with GLA, AA, EPA, and DHA levels.	No in supplementation trials
	ELOVL2	Negative association with DHA levels	
Age		n-3 LCPUFA levels are positively associated with age	Yes
Modifiable factors			
Body size	BMI	Negative association between n-3 LCPUFA levels and BMI in participants with erythrocyte EPA and DHA < 6%, but not in individuals with erythrocyte EPA and DHA >7%.	Yes
	Waist girth	Inconclusive evidence.	No
Physical activity		Inconclusive evidence.	No
Alcohol		Negative association between alcohol consumption and n-3 LCPUFA levels.	Yes, Specification of type and amount of alcohol is highly recommended
Smoking		Negative association between smoking and n-3 LCPUFA levels resulting in 6-17% lower n-3 LCPUFA erythrocyte EPA and DHA in smokers.	Yes
Bioavailability factors			
Different forms of supplements		There is no convincing evidence.	No
Krill oil versus fish oil bioavailability		No convincing evidence.	No

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