

Systematic reviews in the field of clinical nutrition

Ph.D. thesis

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Introduction

The volume of the medical literature has increased spectacularly over recent decades; over 2 million articles published yearly in more than 20,000 journals. On top of this, researchers, therapists, healthcare managers and policy makers often have to deal with unclear or contradictory results. Traditional, narrative reviews have been a part of the medical literature for a long time. Although narrative reviews may be useful to receive a general overview on a topic; they are inadequate to answer specific clinical questions. Systematic reviews can fulfil this need, providing high quality and comprehensive summaries.

The systematic review can be defined as “a review of the evidence on a clearly formulated question that uses systematic and explicit methods to *identify, select* and *critically appraise* relevant primary research, and to *extract and analyse data* from the studies that are included in the review”. The primary goal of the systematic reviews is to summarize the current best evidence on a topic, as well as to determine the gaps and limitations in evidence and identify priorities for future research.

Meta-analysis is the use of statistical techniques in systematic reviews to combine and summarize the results of individual studies; thus to increase the statistical power of studies with small sample size and improve the precision of the estimation of the effect.

Aims

As the importance of nutrition is increasingly recognised, clinical nutrition is now integrated into the mainstream medical treatment. In parallel with this, the use of systematic reviews for nutrition-related topic becomes more widespread. Currently, if the results of a study show no relation between micronutrient status and health outcome, it is not clear if the lack of relation is due to the biomarker being an inadequate measure of status or the absence of any relation between status and the health outcome. Use of biomarkers that reflect changes in status can facilitate the understanding of the relationship between intake and status and it follows from this, the relationship between status and health outcome.

The risk of low dietary zinc intake, consequently zinc deficiency is widespread problem affecting between one-third and one-half of the world's population. In European populations, severe primary zinc deficiency is extremely uncommon, but marginal deficiency is likely to be much more prevalent. The lack of a reliable, responsive, and specific indicator of zinc status means that the diagnosis of marginal zinc deficiency is difficult. Therefore, our aim was to perform a systematic review to assess the usefulness of the biomarkers of zinc status in healthy humans to determine which biomarkers appropriately reflect changes in zinc status in response to supplementation or depletion.

In contrast to various micronutrients, it is not fatty acid deficiency that generates public interest in n-3 long-chain polyunsaturated fatty acid (LCPUFA) supplementation, rather the potential health benefits attributed to enhanced n-3 LCPUFA intake. However, there are no generally accepted, gold standard biomarkers that reflect n-3 LCPUFA status in a specific and sensitive way. Accordingly, our aim was to conduct a systematic review of intervention studies with n-3 LCPUFA in healthy humans to identify the biomarkers of status that reliably reflect change in n-3 LCPUFA intake.

Assessing potential biomarkers of zinc status in humans: a systematic review

Introduction

Zinc is well established as an essential micronutrient for human health because it has numerous structural and biochemical functions at the cellular and subcellular level, which include enzyme function, DNA and RNA metabolism, gene expression, protein synthesis, cell growth and differentiation, and cell-mediated immunity. The ubiquitous nature of zinc in human biological systems indicates the widespread consequences and the complexity of inadequate dietary supply of zinc and zinc depletion.

Unlike other micronutrients such as iron, there is no storage form of zinc in the body that can be readily mobilized when intakes are inadequate, which emphasizes the need for a regular dietary supply. A highly effective homeostatic mechanism responds to alterations in zinc intake, upregulating absorption and conserving losses via the gastrointestinal tract and kidneys when intakes fall. When homeostatic mechanisms fail to ensure that requirements are met, clinical symptoms of zinc deficiency ensue. Severe deficiency is associated with stunted growth, immune dysfunction, and poor wound healing. These symptoms of severe zinc deficiency are most dramatically observed in acrodermatitis enteropathica, a congenital condition in which the infant is born with impaired gastrointestinal zinc transport, which limits the ability to absorb zinc.

Current recommendations for dietary zinc intake in adults range from 7 mg/day (UK Reference Nutrient Intake) to 11 mg/day (US Recommended Dietary Allowance). This broad range reflects in part the variation in requirements due to differences in the bioavailability of zinc from different national diets and also the difficulties associated with estimating the requirements for optimal health, which depends on a reliable indicator of status.

Methods

Electronic searches were performed with Ovid MEDLINE (www.ovid.com), EMBASE (Ovid) (www.ovid.com), and the Cochrane Library CENTRAL (www.thecochranelibrary.com) database, which were searched from inception to October 2007 for intervention studies by using text terms with appropriate truncation and relevant indexing terms. The search was in the form: [zinc terms] and [intervention study terms] and [human studies]. We did not apply any language restriction.

To be included, a study needed to meet all of the following criteria: 1. be an intervention study in humans (including supplementation and/or depletion studies) without restriction in study design, which could include RCTs, controlled clinical trials, and before-after studies (B/A); 2. report the zinc status at baseline and after supplementation or depletion; 3. minimum duration of supplementation of 2 weeks; 4. report the daily dose of the zinc supplement; 5. use one of the following supplements: zinc sulphate; zinc acetate; zinc gluconate, or zinc methionine; and 6. involve healthy participants who had not recently used mineral or vitamin supplements.

Data for each included study were extracted into a Microsoft Access 2003 database file (Microsoft Corp, Redmond, WA). Meta-analysis was carried out with Cochrane software, Review Manager version 4.2 (Cochrane Collaboration; www.cochrane.org), with random-effects model.

We declare a biomarker effective (statistically significant pooled effect size; $P < 0.05$) or ineffective (statistically insignificant pooled effect size; $P \geq 0.05$) only where the pooling included ≥ 3 studies and ≥ 50 participants overall. Where there were < 3 studies or < 50 participants, it was stated that there were insufficient data to make a decision.

Results

A total of 1334 titles and abstracts were screened after electronic and bibliographic searches or were recommended by experts. Of these, 182 appeared potentially relevant and we attempt to collect them as full-text articles to be assessed for inclusion. Altogether 180 full-text articles were assessed (2 articles could not be traced); 48 studies from 46 publications were found to fulfill the inclusion criteria.

The majority of studies (67%) were carried out in healthy adults, and 19% in elderly people. There were 5 studies in pregnant or lactating women, one study in postmenopausal women, and one study in children and adolescents. In the majority of studies, the reasons for dropping out and the method and outcome of compliance testing were not reported. In studies that claimed to be randomized, only 2 described the methods used.

In the 48 studies included in this review, a total of 32 potential zinc biomarkers, 17 biomarkers of zinc status in zinc supplementation trials, and 25 biomarkers in zinc depletion trials were identified. A summary of all the biomarkers identified, including the number of studies, participants, and the results of the primary analysis where relevant is presented in **Table 1**.

Plasma zinc concentration responded to dietary manipulation in adults, women, men, pregnant and lactating women, the elderly, and those at low and moderate baseline zinc status and in both depletion and supplementation studies. All levels of zinc supplementation resulted in a significant increase in plasma zinc concentration in a dose-dependent manner (**Figure 1**).

Table 1. Primary analyses (the greatest duration and the greatest supplementation dose) for each of the identified biomarkers for supplementation with zinc and zinc depletion

Biomarker	No. of studies (no. of participants)	Pooled effect size, MD (95% CI)	Heterogeneity I ² (%)	Appears effective as a biomarker?
Plasma Zn (μmol/L)	50 (1454)	2.88 [2.24 – 3.51]	93.6	yes
Urine Zn (mmol/mol creatinine) supplementation	5 (373)	0.31 [0.20 – 0.43]	0	yes
Urine Zn (μmol/day) depletion	4 (30)	3.89 [1.01 – 6.76]	92.9	unclear
Erythrocyte Zn (μmol/L)	7 (537)	2.20 [-4.58 – 8.98]	0	no
Platelet Zn (nmol/10 ⁶ cells)	5 (105)	0.09 [-1.12 – 1.30]	76.0	no
Plasma alkaline phosphatase (IU/L)	6 (410)	4.14 [-2.38 – 10.65]	56.6	no
Mononuclear cell Zn (μmol/10 ¹⁰ cells)	5 (95)	-0.05 [-0.21 – 0.11]	37.7	no
Polymorphonuclear cell Zn (μmol/10 ¹⁰ cells)	6 (101)	0.05 [-0.13 – 0.22]	83.3	no
Aminolevulinic acid dehydratase (IU/L RBC)	2 (19)	7.88 [-7.90 – 23.66]	89.4	unclear
Erythrocyte metallothionein (μg MT/g protein) supplementation	2 (25)	121.82 [-22.65 – 266.29]	90.7	unclear
Erythrocyte metallothionein (nmol/g protein) depletion	1 (5)	0.30 [-0.43 – 1.03]	n.a.	unclear
Monocyte metallothionein cDNA (pg cDNA/ng RNA)	2 (40)	1.02 [0.48 – 1.56]	0	unclear
Salivary-sediment Zn (μmol/g dry wt)	2 (14)	0.27 [-0.07 – 0.60]	n.a.	unclear
Saliva Zn (mg/dL)	1 (50)	2.82 [-2.67 – 8.31]	n.a.	unclear
Mixed saliva Zn (μmol/L)	1 (7)	-0.73 [-2.49 – 1.03]	n.a.	unclear
Plasma extracellular superoxide dismutase (IU/mL)	1 (52)	0.50 [-1.46 – 2.46]	n.a.	unclear
Plasma 5'-nucleotidase (Shinowara Units)	1 (15)	1.75 [0.54 – 2.96]	n.a.	unclear
Lymphocyte ecto-5'-nucleotidase (nmol/hr/10 ⁶ cells)	1 (6)	-0.60 [-3.91 – 2.71]	n.a.	unclear
T lymphocyte metallothionein-2A mRNA (fg MT-2A mRNA/pg β-actin mRNA)	1 (7)	6.60 [-1.77 – 14.97]	n.a.	unclear
Hair Zn (ppm)	3 (93)	13.24 [11.91 – 14.56]	0	yes
Nail Zn (ppm)	1 (60)	24.10 [4.69 – 43.51]	n.a.	unclear
Plasma Zn flux (mmol/day)	1 (5)	3.74 [2.42 – 5.06]	n.a.	unclear
Endogenous Zn excretion (μmol/day)	1 (5)	36.70 [33.96 – 39.44]	n.a.	unclear
Exchangeable Zn pool (mmol)	1 (5)	0.92 [0.27 – 1.57]	n.a.	unclear
Feces Zn (μmol/day)	1 (5)	60.39 [57.00 – 63.78]	n.a.	unclear
Neutrophil Zn (μg/10 ¹⁰ cells)	3 (26)	7.44 [-15.71 – 30.58]	95.0	unclear
Lymphocyte Zn (μmol/10 ¹⁰ cells)	3 (18)	-0.36 [-1.61 – 0.90]	99.7	unclear
Plasma angiotensin-converting enzyme (IU/L)	1 (5)	-19.40 [-38.34 – -0.46]	n.a.	unclear
Carbonic anhydrase (IU/g Hgb)	1 (5)	-0.10 [-0.89 – 0.69]	n.a.	unclear
Neutrophil alkaline phosphatase (nmol product/h/mg protein)	1 (15)	-122.80 [-294.85 – 49.25]	n.a.	unclear
Neutrophil α-D-mannosidase (nmol product/h/mg protein)	1 (15)	-5.30 [-58.75 – 48.15]	n.a.	unclear
Erythrocyte membrane Zn (μmol/g protein)	1 (15)	0.05 [-0.11 – 0.21]	n.a.	unclear
Erythrocyte membrane alkaline phosphatase (nmol product/min/mg protein)	1 (15)	0.15 [-0.04 – 0.34]	n.a.	unclear
Erythrocyte membrane neutral phosphatase (nmol product/min/mg protein)	1 (15)	0.00 [-0.15 – 0.15]	n.a.	unclear

Abbreviations: n.a., no available data; MD, mean difference; CI, confidence interval.

To claim that a biomarker was effective (reflected change in status) within a review, 3 conditions needed to be met: 1) statistical significance within a forest plot (95% CI did not include 0 or P < 0.05), 2) ≥3 trials contributing data, and 3) ≥50 participants contributing data in the intervention and control arm. To claim that a biomarker was ineffective, 3 conditions had to be met: 1) lack of statistical significance within a forest plot (95% CI included 0 or P ≥ 0.05); 2) ≥3 trials contributing data; 3) ≥50 participants contributing data in the intervention and control arm.

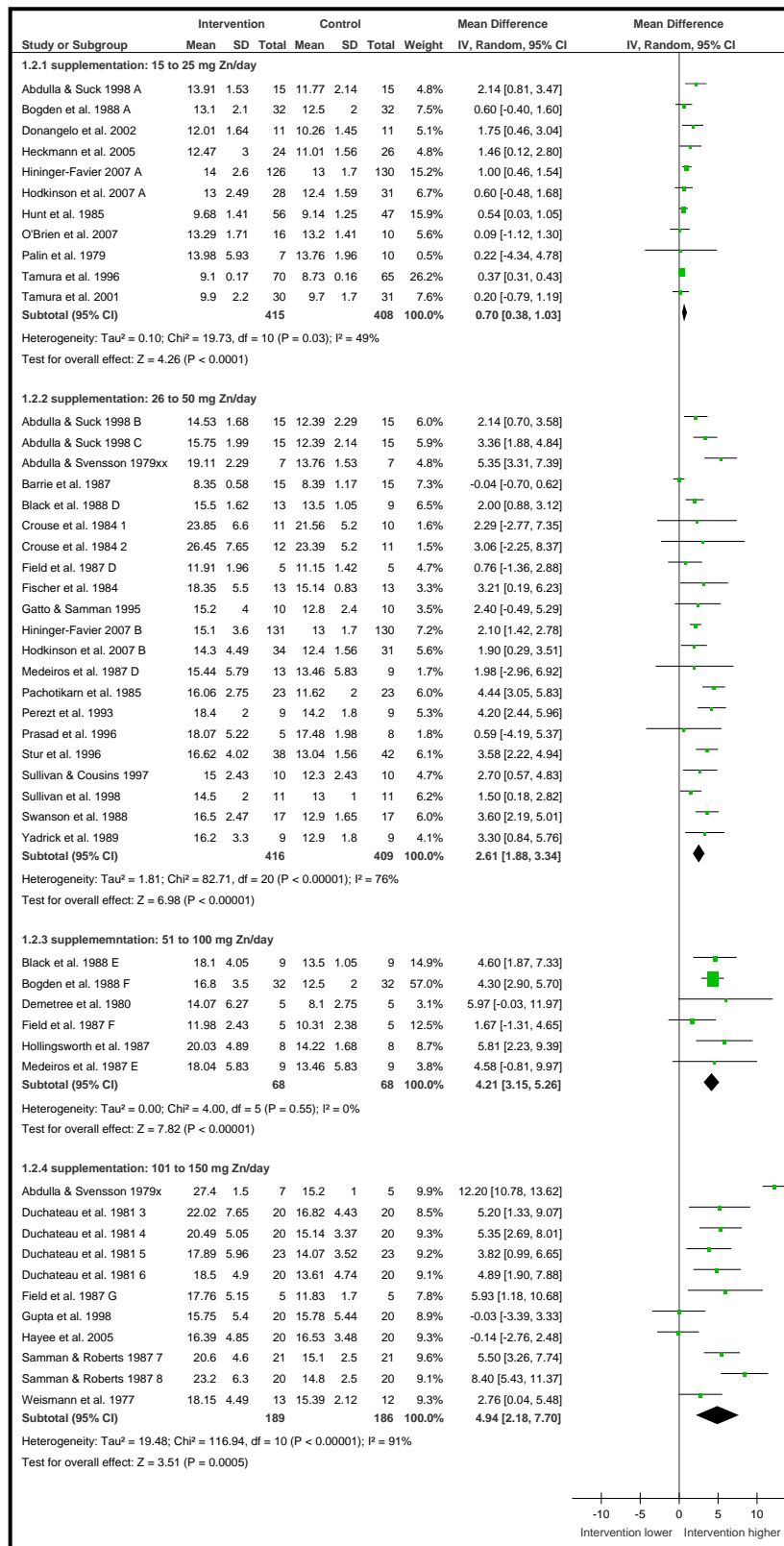


Figure 1: Secondary analysis of the response of plasma zinc concentration ($\mu\text{mol/L}$) to zinc supplementation with subgrouping by dose (mg/day)

Specification of the groups as represented in the original articles: x, study 1; xx, study 2; A, 15-mg Zn/day group; B, 30-mg Zn/day group; C, 45-mg Zn/day group; D, 50-mg Zn/day group; E, 75-mg Zn/day group; F, 100-mg Zn/day group; G, 150-mg Zn/day group; 1, endurance-trained male group; 2, sedentary male group; 3, male group (20–40 yrs); 4, female group (20–40 yrs); 5, female group (20–40 yrs + oral contraceptive); 6, female group (40–50 yrs); 7, male group; 8, female group.

Urinary zinc excretion also appeared to respond to change in zinc status for all groups for which we had data, but with fewer studies there were fewer subgroupings with enough studies to make a clear decision about urinary zinc response. Hair zinc concentration also responded to zinc supplementation, but there were insufficient studies to assess in which subgroups these may be effective markers. For platelet, polymorphonuclear cell, mononuclear cell, and erythrocyte zinc concentration and alkaline phosphatase activity, there were sufficient data to judge them as likely to be ineffective as biomarkers of zinc status (**Table 1**).

We found at least one study each to assess the effects of zinc supplementation or depletion on the following potential zinc biomarkers: aminolevulinic acid dehydratase, erythrocyte metallothionein, monocyte metallothionein cDNA, salivary-sediment zinc, salivary zinc, mixed-saliva zinc, plasma extracellular superoxide dismutase, plasma 5'-nucleotidase, lymphocyte ecto-5'-nucleotidase, T lymphocyte metallothionein -2A mRNA, nail zinc, plasma zinc flux, endogenous zinc excretion, exchangeable zinc pool, fecal zinc, neutrophil zinc, lymphocyte zinc, plasma angiotensin-converting enzyme, carbonic anhydrase, neutrophil alkaline phosphatase, neutrophil α -D-mannosidase, erythrocyte membrane zinc, erythrocyte membrane alkaline phosphatase, and erythrocyte membrane neutral phosphatase. However, there were not enough eligible studies of these markers to allow us to decide whether they were effective markers of zinc status (**Table 1**).

This review highlights a number of gaps in the field of zinc research. More high-quality studies are required to assess the effects of most potential zinc biomarkers and in a variety of populations. There were some notable gaps in the availability of data from certain population groups; in particular, there was a complete absence of data regarding infants and immigrant population groups and a paucity of studies of zinc status in adolescents.

Assessing potential biomarkers of n-3 long-chain polyunsaturated fatty acid status in humans: a systematic review

Introduction

Long-chain polyunsaturated fatty acids (LCPUFAs) are important components of membrane lipids in all tissues. The most important of them are the n-6 (omega-6) essential fatty acid, linoleic acid (C18:2n-6, LA), and the n-3 (omega-3) essential fatty acid, α -linolenic acid (C18:3n-3, ALA), as well as their longer-chain metabolites, arachidonic acid (C20:4n-6, AA), eicosapentaenoic acid (C20:5n-3, EPA) and docosahexaenoic acid (C22:6n-3, DHA). N-6 fatty acids, mainly AA and dihomo- γ -linolenic acid (C20:3n-6), are predominantly precursors of proinflammatory prostaglandins, thromboxans and leucotriens, while n-3 fatty acids, mainly EPA, are precursors of antiinflammatory eicosanoids. AA and DHA are concentrated in the central nervous system, as well as in the retina, heart and skeletal muscle, and play an important role in the maintenance of normal development and normal neural functions.

Vegetables are good sources of essential fatty acids; however, their preformed long-chain metabolites are found mainly in animal foods. Food products of terrestrial animals are rich in n-6 fatty acids, whereas sea fishes are rich in n-3 fatty acids. Although oily fish and various other seafoods are excellent dietary sources of EPA and DHA, dietary intake of n-3 LCPUFA in the United States is only \approx 110 mg/day in women and \approx 170 mg/day in men. However, various dietary supplements containing several hundred milligrams of n-3 LCPUFAs per dose are widely available, so it is relatively easy to achieve a 10-fold increase in daily n-3 LCPUFA intake.

One of the practical difficulties of designing and carrying out clinical trials investigating the effect of n-3 LCPUFA supplementation is the lack of a generally accepted biomarker that reflects increased n-3 LCPUFA status in response to enhanced dietary intake. It is even more important in epidemiologic studies assessing health effects of n-3 LCPUFA status in populations over long periods to understand which biomarkers truly reflect n-3 LCPUFA status.

Methods

Ovid MEDLINE (www.ovid.com), EMBASE (Ovid) (www.ovid.com), and the Cochrane Library CENTRAL database (www.thecochranelibrary.com) were searched from inception to September 2007 for intervention studies of n-3 LCPUFA using text terms with appropriate truncation and relevant indexing terms. The search was in the form, [n-3 LCPUFA terms] and [intervention study terms] and [human studies]. We did not apply any language restriction.

To be included in the review, a study needed to meet all of the following characteristics: 1. an intervention study in humans (RCT, controlled clinical trial, or B/A study); 2. reported n-3 LCPUFA status at baseline and after supplementation; 3. involved supplementation with marine oils (fish, whale, or seal oil), seafoods (caviar or oily fish), single cell oils, or DHA-enriched eggs; 4. minimum duration of supplementation of 2 weeks; 5. described a daily dose of n-3 LCPUFA supplement; and 6. included participants who were healthy individuals.

Data for each included study were extracted into a Microsoft Access 2003 database file (Microsoft Corp, Redmond, WA). Where necessary, units of measurement were recalculated to percentage contribution of n-3 LCPUFA to total fatty acid composition of the relevant lipid fraction (% weight/weight). Meta-analysis was carried out with Cochrane software, Review Manager version 4.2 (Cochrane Collaboration; www.cochrane.org), with random-effects model.

We declare a biomarker effective (statistically significant pooled effect size; $P < 0.05$) or ineffective (statistically insignificant pooled effect size; $P \geq 0.05$) only where the pooling included ≥ 3 studies and ≥ 50 participants overall. Where there were < 3 studies or < 50 participants, it was stated that there were insufficient data to make a decision.

Results

Altogether 2733 titles and abstracts were identified, 255 of them appeared to be potentially relevant, and we attempted to collect them as full-text articles. Fifteen full articles (6%) could not be collected, but 240 full-text articles were available for detailed assessment for inclusion. Finally, 45 studies reported in 41 publications fulfilled the inclusion criteria. In the majority of cases, exclusion of articles was due to incomplete data presented or included nonhealthy subjects.

The majority of studies were carried out in Europe (26 studies) and North America (10 studies). The studies ranged in size from 7 to 341 participants. The supplement was marine oil or seafood in 35 studies, single cell oil in 5, and DHA-rich eggs in 3 studies. The most common placebo was vegetable oil (25 studies). The studies used a wide range of supplementation doses, from 83 mg/day DHA to 4900 mg/day DHA.

The method of randomization was poorly described in the majority of studies. There were only a moderate number of dropouts in most of the studies, but reasons often were not reported. Attempts were made to assess compliance objectively in 24 studies, but the results of the checks, i.e. levels of compliance, were not comprehensively reported. Overall the risk of bias was low in only 5 studies.

We included 41 studies reporting on 18 different potential biomarkers of n-3 LCPUFA status in this systematic review. There were sufficient data to state that plasma DHA, plasma phospholipid DHA, plasma triacylglycerol DHA, plasma cholesteryl ester DHA, plasma nonesterified DHA, erythrocyte DHA, erythrocyte phospholipid DHA, and platelet DHA were all effective biomarkers, peripheral blood mononuclear cell phospholipid DHA was an ineffective biomarker of DHA status and that plasma phospholipid EPA was an effective marker of EPA status (**Table 2**).

For most of these biomarkers, however, only limited data were available for subgroup analysis. In contrast, we were able to evaluate the effect of n-3 LCPUFA supplementation on the fatty acid composition of plasma phospholipids on the basis

Table 2: Primary analyses (the longest duration and the highest supplementation dose) for each of the identified biomarkers for supplementation with n-3 long-chain polyunsaturated fatty acids

Biomarker	No. of studies (no. of participants)	Pooled effect size, MD (95% CI) ¹	Heterogeneity I ² (%)	Appears effective as a biomarker?
Plasma DHA	6 (262)	1.13 [0.54 – 1.71]	88.7	yes
Plasma phospholipid DHA	21 (923)	2.45 [1.87 – 3.02]	94.0	yes
Plasma phospholipid EPA	16 (759)	4.07 [2.90 – 5.24] ²	99.0	yes
Plasma triacylglycerol DHA	5 (116)	0.86 [0.08 – 1.65]	92.1	yes
Plasma cholesteryl ester DHA	5 (110)	0.42 [0.13 – 0.71]	92.2	yes
Plasma nonesterified DHA	3 (72)	1.35 [0.11 – 2.59]	95.0	yes
Erythrocyte DHA	6 (277)	2.33 [0.86 – 3.81]	94.0	yes
Erythrocyte phospholipid DHA	6 (229)	0.97 [0.50 – 1.43]	72.3	yes
Young erythrocyte ghosts DHA	1 (17)	-1.00 [-4.07 – 2.07] ³	n.a.	unclear
Old erythrocyte ghosts DHA	1 (17)	1.70 [0.32 – 3.08] ³	n.a.	unclear
Platelet DHA	8 (235)	1.25 [0.87 – 1.64]	79.9	yes
Granulocyte DHA	1 (40)	0.60 [0.32 – 0.88]	n.a.	unclear
Neutrophil DHA	1 (20)	2.80 [0.01 – 5.59]	n.a.	unclear
Neutrophil phospholipid DHA	2 (28)	0.04 [-0.15 – 0.23]	n.a.	unclear
PBMC DHA	2 (36)	0.06 [-0.36 – 0.48]	0	unclear
PBMC phospholipid DHA	3 (94)	0.70 [-0.66 – 2.06]	93.9	no
LDL DHA	2 (73)	0.60 [0.59 – 0.61]	0	unclear
HDL phospholipid DHA	1 (7)	0.80 [0.07 – 1.53]	n.a.	unclear

Abbreviations: MD, mean difference; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; n.a., no available data; PBMC, peripheral blood mononuclear cell.

¹, all studies are in %DHA of total fatty acids unless otherwise stated; ², %EPA of total fatty acid; ³, µg/mg protein.

To claim that a biomarker was effective (reflected change in status) within a review, 3 conditions needed to be met: 1) statistical significance within a forest plot (95% CI did not include 0 or P <0.05), 2) ≥3 trials contributing data, and 3) ≥50 participants contributing data in the intervention and control arm. To claim that a biomarker was ineffective, 4 conditions had to be met: 1) lack of statistical significance within a forest plot (95% CI included 0 or P ≥0.05); 2) ≥3 trials contributing data; 3) ≥50 participants contributing data in the intervention and control arm.

of a considerable number of supplementation substudies. Plasma phospholipid DHA specifically appears to be a good marker of DHA status in adult men and women those with low, moderate, or high baseline DHA status; those who used either marine oil, seafood, or single cell oils. Although the response appeared to increase with increasing doses of DHA ≤2500 mg/day, additional dose increases did not appear to alter plasma phospholipid DHA further (**Figure 2**). Its usefulness is unclear in postmenopausal women, the elderly, and immigrants, and it appears to be an unsuitable marker in pregnant or lactating women.

One or 2 studies were found to include data on young erythrocyte ghost DHA, old erythrocyte ghost DHA, granulocyte DHA, neutrophil DHA, neutrophil phospholipid DHA, peripheral blood mononuclear cell total lipid DHA, low-density lipoprotein DHA, and high-density lipoprotein phospholipid DHA. There were insufficient data to assess whether these potential biomarkers of DHA status are effective.

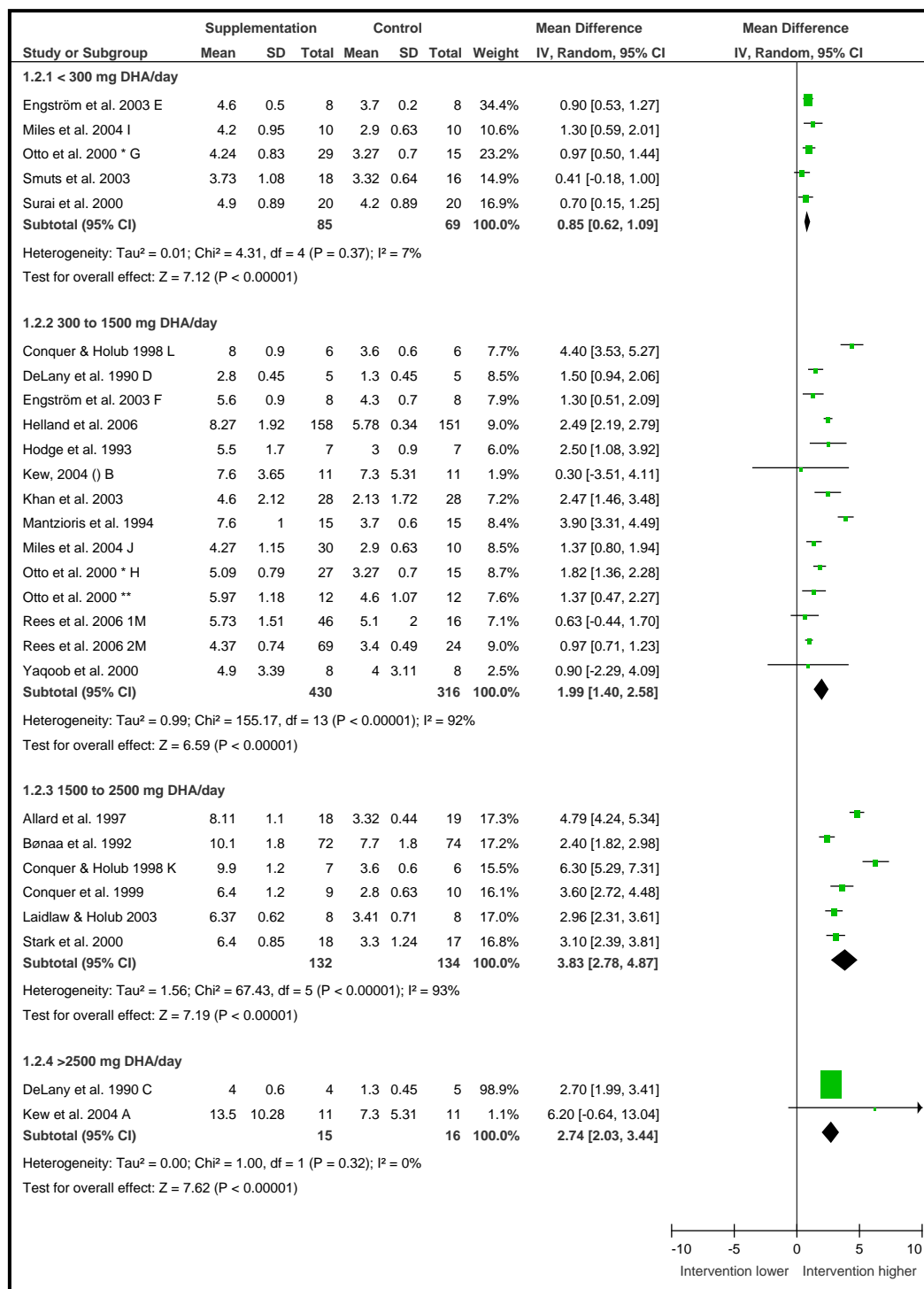


Figure 2: Response of plasma phospholipid docosahexaenoic acid (DHA) to supplementation with DHA [%DHA/total fatty acid composition (weight/weight)]

Specification of the groups as represented in the original articles: A, DHA group; B, eicosapentaenoic acid (EPA) group; C, 20-g fish oil group; D, 5-g fish oil group; E, ordinary caviar paste group; F, fish oil-enriched caviar paste group; G, combined data of low fish oil and low DHA groups; H, combined data of high fish oil and high DHA groups; I, blend 3 group; J, combined data of eicosapentaenoic acid, blend 1, and blend 2 groups; K, high DHA group; L, low DHA group; and M, combined data of low, moderate, and high EPA groups. 1 indicates the older group within the study, and 2, the younger group within the study.

*, Otto et al. Nutr Res 2000.; **, Otto et al. Prostaglandins Leukot Essent Fatty Acids 2000.

New findings of the thesis

Plasma zinc concentration responded in a dose-dependent manner to dietary manipulation in adults, women, men, pregnant and lactating women, the elderly, and those at low and moderate baseline zinc status. Urinary zinc excretion responded to zinc status overall and in all subgroups for which there were sufficient data. Hair zinc concentration also responded, but there were insufficient studies for subgroup analysis. These results indicate that in healthy individuals, plasma, urinary and hair zinc concentrations are reliable biomarkers of zinc status. Platelet, polymorphonuclear cell, mononuclear cell, and erythrocyte zinc concentration and alkaline phosphatase activity did not appear to be effective biomarkers of zinc status.

There were sufficient data to determine that plasma DHA, plasma phospholipid DHA, plasma triacylglycerol DHA, plasma cholesteryl ester DHA, plasma nonesterified DHA, erythrocyte DHA, erythrocyte phospholipid DHA, and platelet DHA were all effective biomarkers of DHA status, whereas peripheral blood mononuclear cell phospholipid DHA does not appear to be a good biomarker of DHA status and that plasma phospholipid EPA was an effective marker of EPA status. Plasma phospholipid DHA was the most frequently investigated biomarker; it appears to be a good marker of DHA status in adult men and women irrespective of DHA baseline status or supplementation dose, but ineffective marker in pregnancy and lactation; its usefulness in other population subgroups is unclear.

Practical applications

At the present time, plasma zinc concentration is the only biomarker of status that can be used to measure zinc status in individuals with either a low or a high supply of dietary zinc, but with many limitations and constraints. Urinary zinc excretion and hair zinc can provide useful information on zinc status in zinc-supplemented individuals, but whether these reflect zinc status in depleted individuals is not certain. It is clear that there is an urgent need to develop new biomarkers of zinc status.

Data presented in this thesis may be useful in designing novel studies on n-3 LCPUFA supplementation, especially those aimed at answering the question as to which biomarker might be sensitive enough to detect changes of a given dose of n-3 LCPUFA supplementation in a given clinical setting. There appears to be a range of useful biomarkers of DHA status in humans, but further research is needed to characterize which work best in particular population subgroups.

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List of publications

Publications in the topic of the thesis

Nicola M Lowe, **Katalin Fekete**, Tamás Decsi. Methods of assessment of zinc status in humans: a systematic review. *Am J Clin Nutr* 2009;89:2040S–2051S.

IF₂₀₀₉: 6.307
Independent citations: 39

Katalin Fekete, Tamás Marosvölgyi, Viktória Jakobik, Tamás Decsi. Methods of assessment of n-3 long-chain polyunsaturated fatty acid status in humans: a systematic review. *Am J Clin Nutr* 2009;89:2070S–2084S.

IF₂₀₀₉: 6.307
Independent citations: 20

Further publications

Fekete Katalin és Decsi Tamás. A cink szerepe gyermekek egészségének megőrzésében és helyreállításában. *Gyermekorvos Továbbképzés* 2009;8:169–172.

Katalin Fekete, Cristiana Berti, Irene Cetin, Maria Hermoso, Berthold V Koletzko, Tamás Decsi. Perinatal folate supply: relevance in health outcome parameters. *Matern Child Nutr* 2010;6:23–38.

IF₂₀₁₀: 2.311
Independent citations: 0

Katalin Fekete and Tamás Decsi. Long-chain polyunsaturated fatty acids in inborn errors of metabolism. *Nutrients* 2010;2:965–974.

IF₂₀₁₀: still computing
Independent citations: 0

Cumulative IF: 14.925
Total independent citations: 59

Abstracts

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