Review

Postprandial variability in plasma long-chain omega-3 is independent of supplement lipid structure

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Background and Objectives: Postprandial variations in plasma triacylglycerol (TAG) responses to vegetable oils are well established, but their origins remain unclear. This study examined the variability of postprandial plasma long-chain omega-3 fatty acids (LC omega-3) in response to commonly used supplements and foods and considers the biological implications of this variability. **Methods and Study Design:** A literature review was conducted to identify postprandial studies that reported variability in plasma LC omega-3 responses to supplementation. Studies were included if variability could be expressed as the coefficient of variation (CV) for the area under the curve (AUC). **Results:** Twenty-one studies encompassing 36 different treatments were identified. Supplements included LC omega-3 in the form of TAG, monoacylglycerols (MAG), free fatty acids (FFA), ethyl esters (EE), EE with emulsification agents, and whole foods. Variability was consistently observed across all forms; 65% of treatments showed a CV >50% for the AUC. Gastrointestinal (GI) symptoms were reported in some studies, suggesting possible malabsorption. **Conclusions:** Substantial inter-individual variability existed in postprandial LC omega-3 responses, independent of the chemical form of supplementation. This variability likely reflects differences in absorption, enterocyte metabolism, and including malabsorption. Postprandial variability may therefore contribute significantly to observed differences in tissue LC omega-3 status following LC omega-3 supplementation.

Key Words: long-chain omega-3 fatty acids, postprandial metabolism, inter-individual variability, triacylglycerol, supplementation

INTRODUCTION

After meals, the body produces triacylglycerol (TAG)-rich lipoproteins (chylomicrons) and their remnants. Elevated postprandial TAG concentrations have been linked to a higher risk of cardiovascular events, such as heart attacks and strokes. Studies indicate that chylomicron and remnant concentrations may be more predictive of such events than fasting TAG measurements.[1-3]

Variability in postprandial TAG responses between individuals is well known and is likely to drive advances in the use of personalized nutrition. Recent studies have reported substantial postprandial variability for meals containing oils such as palm oil or high-oleic sunflower oil. Newman et al.[4] studied the postprandial TAG response to a mixed ingredients meal containing palm oil in 340 subjects and reported significant variability in responses over 6-h, including that approx. 2% of subjects showed minimal plasma TAG appearance by 6-h. In another study by Berry et al.,[5] more than 1000 people consumed 8 meals differing in macronutrient composition with the fats/oils being mainly derived from high-oleic sunflower oil. Large inter-individual postprandial variations (over 6-h) were reported in TAG, glucose and insulin responses following consumption of identical meals (the coefficient of variation (CV) in the postprandial response for TAG was 103%, and 68% for glucose, and 59% for insulin). Amongst the statistically derived determinants of variability for postprandial TAG, serum lipid markers had the greatest influence (>20%), serum glycemic markers (>10%), other serum markers (>8%), anthropometry (8%), microbiome (7%), and gender (6%). Meal macronutrients (3.6%) and genetic variants (0.8%) had minimal impacts on predictions for postprandial lipaemia.

There have been many LC omega-3 supplementation studies reported in the literature over the past 30+ years,[6, 7] but few report the data for individual subjects or refer to between-subject variability. Some medium to long-term studies have reported the individual data or have referred to the variability in the blood LC omega-3 proportions

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following supplementation.[8-13] We hypothesized that one contributor to the variability in plasma and erythrocyte (RBC) LC omega-3 proportions following supplementation was variability which occurred during digestion and absorption of the LC omega-3. Therefore, we reviewed studies which examined plasma LC omega-3 concentrations in the postprandial period. We found consistent and substantial variability in the postprandial response to LC omega-3 supplementation and hypothesized that postprandial variability could be a significant contributor to variability in plasma and RBC LC omega-3 proportions.

METHODS

Literature search strategy and selection criteria of articles

A systematic search was conducted in two databases—PubMed and Embase—up to September 2025. We used the following key words treated as title/abstract for the literature search: ("plasma docosahexaenoic acid" OR "plasma DHA" OR "plasma eicosapentaenoic acid" OR "plasma EPA" OR "plasma docosapentaenoic acid" OR "plasma DPA" OR "polyunsaturated fatty acid" OR "plasma LC omega-3 fatty acid" OR "plasma n-3 fatty acid" OR "fish oil" OR "krill" OR "algal oil" OR "wax esters" OR "ethyl esters" OR "FFA" OR "MAG" OR "n-3 FA enriched foods" OR "LC omega-3 enriched foods") AND ("postprandial" OR "acute"). Our search was restricted to studies in humans and studies published in English. The references of retrieved relevant articles were reviewed to identify potential publications. AJS and DL independently conducted the literature search, identified potential studies, and extracted detailed information from each included article. Inclusion criteria were controlled trials with postprandial design; the exposure of interest was any type of dietary long chain LC omega-3 fatty acid, the endpoint of interest was plasma LC omega-3 concentration expressed as area under the curve. We excluded studies in animals, controlled trials without mean ± SD/SEM, non-original research (reviews, editorials, or commentaries), abstracts, unpublished studies, and duplicated studies.

RESULTS

We identified 30 original LC omega-3 postprandial studies which reported area under the curve data (AUC). In this report, we only considered 21 of these studies since they reported the AUC curve data as mean with either SD or SEM. This allowed the expression of the variability by converting the mean responses to a coefficient of variation (CV%, SD/mean x 100). Studies reporting 25th and 75th percentile or other ranges were not included as it was not possible to derive a CV for the responses. The lipid type of LC omega-3 supplements varied considerably and included fish oils (FO) rich in TAG, lipid digestion products containing LC omega-3 (MAG and FFA), ethyl esters (EE) of EPA + DHA, krill oil typically rich in phospholipids (PL), algal oil (rich in polar lipids), EE of EPA + DHA mixed with novel emulsification agents and foods/meals rich in TAG containing LC omega-3.

Only two studies reported individual responses. Kohler et al.[12] compared the effects of a single dose of fish oil or krill oil (1700 mg EPA+DHA) on LC omega-3 concentrations in plasma PL and TAG fractions over a 72-h period in 15 adult subjects. There were large inter-individual variations in the incremental area under the curve (iAUC) in response to both the fish oil (rich in TAG) and the krill oil (rich in PL). The individual responses for fish oil and krill oil were not the same for the plasma PL and plasma TAG. Furthermore, in the plasma TAG fraction, for krill oil 2/15 subjects showed no response, while 1/15 (a different subject) showed no response to the fish oil; also 1/15 subjects for the fish oil group showed no response in the PL fraction. The reported results were converted into mean CV% for the iAUC72h responses (SD/ Mean x100). For the fish oil, the CVs for EPA+DHA in plasma PL and plasma TAG were 38% and 76%, respectively. For the krill oil, the CVs for EPA+DHA in plasma PL and plasma TAG were 37% and 72%, respectively. These results indicated that postprandial variability was evident for two different dietary lipid supplements, namely LC omega-3-TAG in the case of the fish oil and LC omega-3-PL (+FFA and TAG) in the case of krill oil. The other study reporting individual data was by Stonehouse et al.[14] The effects on plasma DHA concentrations of a single meal of soup or rice crackers, each containing encapsulated algal DHA, or capsules of DHA (440mg DHA in each treatment) were studied over a 24-h period in 27 male subjects. There was substantial variability between individuals for each treatment. The CVs for iAUC for plasma DHA were 68% for the soup meal, 76% for the rice crackers meal and 87% for the capsules of algal oil TAG.

Results of the variability of the 21 postprandial studies are summarized below and in Table 1 and presented in detail in Supplementary Table 1.

TAG oil studies (fish oil, re-esterified fish oil, blended fish oil, sardine/anchovy oil, algal oil, n=6 studies). The variability, expressed as CV for the AUC or iAUC, for EPA, DHA or EPA+DHA in plasma TAG or PL ranged from 38% to 102%, with 7 of 10 data points exceeding 50%. These studies involved from 7 to 27 subjects over periods from 8h to 72h and used doses which ranged from 415mg up to 1,700mg of EPA+DHA.[12, 14-17, 29]

PL-rich oil studies (krill oil, PL-enhanced fish oil, polar-rich algal oil, n = 6 studies). The variability, expressed as CV for the AUC or iAUC, for EPA, DHA or EPA+DHA in plasma TAG or PL ranged from 28% to 76%, with 5 of 9 data points exceeding a CV of 50%. These studies involved from 10 to 24 subjects over periods from 10h to 72h and used doses which ranged from 206mg up to 1,700mg of EPA+DHA.[12,15,18,19]

FFA studies (Epanova, OM3-CA, unspecified, n=3 studies). The variability, expressed as CV for the AUC or iAUC, for EPA, DHA or EPA+DHA in plasma ranged from 34% to 53%, with 3 of 5 data points equal to or exceeding a CV of 50%. These studies involved from 14 to 26 subjects over 24h and used doses which ranged from 3,264 mg up to 4,000 mg of EPA+DHA.[20-22]

Monoacylglycerol (MAG) studies (2-MAG, 1(3)-MAG, MAG unspecified, n=3 studies). The variability, expressed as CV for the AUC, for EPA, DHA or EPA+DHA in plasma ranged from 19% to 93%, with 2 of 4 data points equal to or exceeding a CV of 50%. These studies involved from 7 to 24 subjects over 24h and used

Table 1. Studies included in this review

Omega-3 lipid supplement	Number of treatments†	Variability in AUC (iAUC) expressed as coefficient of variation (CV%)‡
TAG	6	38-102%, with 7/10 data points§ >50%
PL or polar lipid	6	28-76%, with 5/9 data points >50%
FFA	3	34-53%, with 3/5 data points >50%
MAG	3	19-93%, with 2/4 data points >50%
Ethyl esters (EE)	9	32-154%, with 9/12 data points >50%
Wax esters	1	42% with 0/1 data points >50%
EE or TAG with enhanced emulsification	4	31-137%, with 4/6 data points >50%
Whole foods	9	21-138%, with 7/10 data points > 50%
Total	41	19-154%, with 37/57 data points >50%

†Treatments = individual treatments within a study.
‡Coefficient of variation (CV%) = SD/mean x 100
§Data points = number of AUC/iAUC outcomes in each study (eg. plasma TAG, plasma PL, whole plasma, blood).

doses which ranged from 1,247 mg up to 3,000 mg of EPA+DHA.[17,21,23]

Ethyl ester of LC omega-3 studies (Omacor, KD Pharma or unspecified sources, n = 9 studies). The variability, expressed as CV for the AUC or iAUC, for EPA, DHA or EPA+DHA in plasma or plasma PL ranged from 32% to 154%, with 9 of 12 data points exceeding a CV of 50%. These studies involved from 10 to 40 subjects over 24 h to 72 h and used doses which ranged from 680 mg up to 3,360 mg of EPA+DHA.[15,20,21, 23-28]

Wax ester study (*Calanus finmarchicus* oil, n = 1). The variability, expressed as CV for the iAUC, for EPA+DHA in plasma was 42%. This study involved 18 subjects over 72h and used a dose of 416mg of EPA+DHA. Wax esters are considered mostly undigestible due to the poor efficacy of the carboxylester lipase and the poor solubility of the wax esters. However, this study showed that the bioavailability of the wax esters was similar to that of the comparative EE group.[27]

Ethyl esters or TAG with enhanced emulsification properties studies (n = 4 studies). The variability, expressed as CV for the AUC or iAUC, for EPA, DHA or EPA+DHA in plasma or whole blood ranged from 31% to 137%, with 4 of 6 data points exceeding a CV of 50%. These studies involved from 12 to 40 subjects over 24h to 72h and used doses which ranged from 374mg up to 1680mg of EPA+DHA. The data revealed that the enhanced emulsification properties significantly improved the bioavailability of the EE compared with standard EE, as judged by the AUC, but variability was still evident.[24-26,29]

Whole food studies (TAG) (herring, fish oil, foods with fish oil, novel foods with algal oil, n = 4 studies). The variability, expressed as CV for the iAUC for EPA, DHA or EPA+DHA in ranged from 21 to 138%, with 7 of 10 data points exceeding a CV of 50%. The studies involved from 17 to 27 subjects over 6h to 24h and used doses which ranged from 415 mg up to 3200 mg of EPA+DHA. These studies demonstrated that the food matrix did not alter the highly variable postprandial plasma LC omega-3 responses to whole food containing TAG-rich in LC omega-3.[14,30-32]

In summary, the variability in the plasma or blood LC omega-3 concentrations of the 21 postprandial studies revealed that there was significant variability in the data independent of the type of lipid supplement. More than 64% of the treatments had a CV more than 50% for the AUC or iAUC for plasma EPA, plasma DHA, whole blood EPA+DHA or plasma EPA+DHA.

DISCUSSION

We showed that in all studies there was significant variability in the postprandial accretion of LC omega-3 into plasma (and whole blood) over periods ranging from 6h to 72 h. Furthermore, the variability was independent of the lipid type (structure) of the LC omega-3 supplement, or for LC omega-3 present in whole foods. There have been few investigations into the causes of the variability of LC omega-3 responses in the postprandial period, however there are some indications from the literature which suggest that some of the variability could result from some of the LC omega-3 supplements escaping digestion in the duodenum and being excreted into the colon.

To examine which stages of digestion, absorption and re-assembly of fatty acids into TAG and PL in the enterocyte, the studies can be looked at from the stages of digestion and absorption, as outlined in Figure 1.

Lipases and carboxylesterases. LC omega-3 lipid supplements requiring enzymatic digestion (TAG, PL, ethyl esters and wax esters) all showed substantial variability (72 % of treatments had CV >50 %). This implies/indicates that within these studies there were individuals with either high, medium or low plasma accretion of LC omega-3. This suggests variability in the lipid digesting enzymes and/or the micelle formation which facilitate the enzymatic processes. To partially address the issue of micelle formation, it was shown that the ethyl ester preparations with enhanced micelle formation properties led to significantly higher plasma LC omega-3 accretion than ethyl esters, however despite this, the enhanced preparations still showed high CV values (31-115 %). Thus, factors other than micelle formation are likely playing a role in the observed variability. In the case of those individuals with putatively low plasma LC omega-3 accretion, some of the undigested LC omega-3 oils will lead to malabsorption of the oils meaning the undigested lipids will reach the large bowel and be subject to faecal excretion.

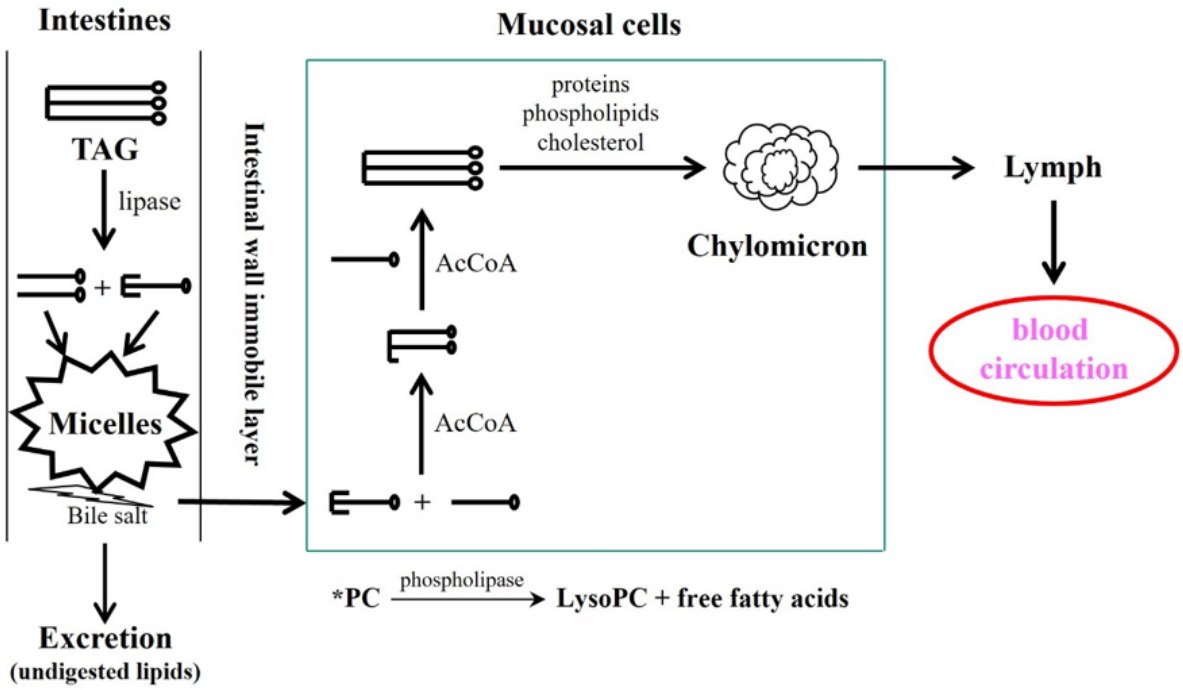

Figure 1. The various elements in the digestion and absorption of dietary lipids (in supplements or food).[33, 34]

Lipid digestion products (FFA and MAG). These lipid products also showed considerable variability in their accretion into plasma (67 % of treatments had CV >50 %). Again, there will be individuals with either high, medium or low plasma accretion of LC omega-3 and in the latter case the malabsorption will mean some of these unabsorbed products (FFA & MAG) will reach the large bowel and be excreted.

We examined whether the variability was related to the dose of the LC omega-3 supplement, as shown in Figure 2a. It was clear that dose was not a significant factor in the variability (r^2 = 0.002, p >0.05). Another possible source of variability could be the analytical method and/or laboratory conditions. Since all studies examined the postprandial accretion of at least two different lipid LC omega-3 supplements, we plotted the pairs of treatments conducted in each laboratory as shown in Figure 2b. It was evident from this that there was a weak relationship between the pairs of studies, with the regression explaining only 28 % of the variance, and with only 10/27 of the treatment pairs having a CV within 10 % of each other. This suggests that neither the analytical method nor the laboratory conditions were likely to be major sources of the postprandial variability reported here. We then compared the variability between supplements requiring enzymatic digestion (TAG + PL) with lipid digestion products (FFA + MAG). While these studies were not conducted in the same individuals, there was no significant difference between the pre- and post-lipid digestion lipid supplements (TAG+PL, CV = 58 ± 18 % (n = 19 studies, mean ± SD) versus FFA+DAG, CV= 49 ± 20% (n = 9 studies) p >0.05). This matter requires a detailed investigation comparing pre- and post-lipase digestion supplements in the same subjects.

Since variability was found with all the different lipid formulations, it is logical that some of the variability was in the post-digestion and emulsification steps and the absorption of digested lipids into the enterocytes via fatty acid transporters, and/or assembly of the absorbed lipids in the endoplasmic reticulum into TAG and PL, and then export of these lipids in chylomicrons into the lymph.[33, 34] These processes collectively involve multiple proteins, including those related to the apical uptake of fatty acids into enterocytes (fatty acid translocase CD36, fatty acid transport protein FATP-4 and plasma membrane fatty acid binding protein FABP); cytosolic trafficking of bound fatty acids to the endoplasmic reticulum (FABP-1, FABP-2); re-esterification of FFA and 2-MAG into TAG (monoacylglycerol acyltransferase 2 MGAT2, diacylglycerol acyltransferases DGAT1/2); chylomicron assembly (formation and transport) (apolipoprotein B48 ApoB48, microsomal triglyceride transfer protein MTTP, GTPase/SAR1B, ApoA-IV); and secretion of chylomicrons into the lymph (Rab8, Rab11, Caveolin-1).[35-37] Polymorphisms have been reported for many of these proteins, and include polymorphisms in CD36,[38,39] iFABP/FABP-2,[40-42] FABP-4,[43] MTTP,[41, 44] ApoB,[45] and chylomicron secretion.[46] These polymorphisms could contribute to variability in postprandial responses to LC omega-3 supplements as discussed here. Furthermore, it has been reported that the partition of TAG between storage in cytoplasmic lipid droplets in the enterocytes and secretion in chylomicrons is altered in obesity,[36] and this partition is a possible source of variability in response to lipid supplements between subjects.

Malabsorption of LC omega-3 oils is referred to as a side effect of LC omega-3 oil consumption in the literature,[47,48] with effects reported including burping, fishy taste and gastrointestinal (GI) upsets such as looser stools, flatulence, malodorous stools and diarrhoea. A review of five trials which used fish oils in the prevention of restenosis following coronary angioplasty reported that there was a strong relationship between the dose of fish oil and GI side effects (trend p <0.0001).[47] There has been

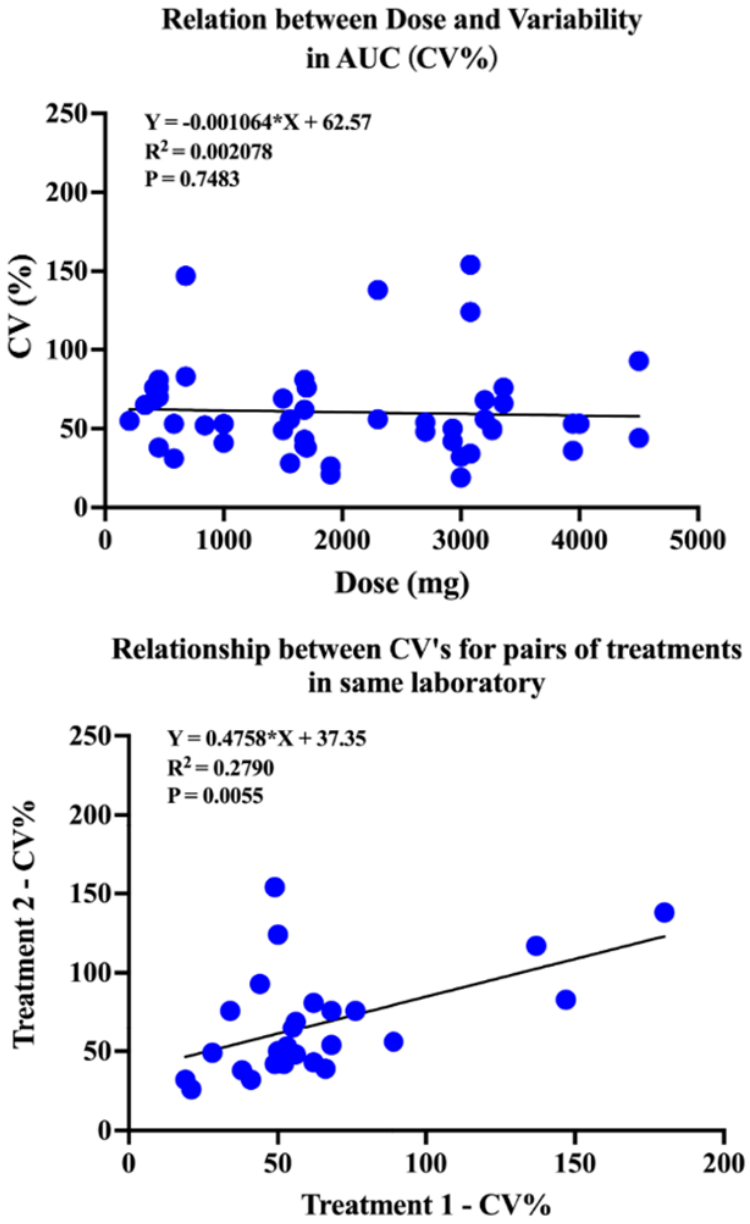

Figure 2. (a) Relationship between the dose of supplement (mg) and variability of postprandial LC omega-3 AUC, expressed as CV%; (b) Relationship between the postprandial LC omega-3 CV's (%) for pairs of treatments within the same laboratory (for example, in Kohler et al.,[12] the AUC for the postprandial LC omega-3 in plasma PL from fish oil (treatment 1) and krill oil (treatment 2) were determined with the results yielding a CV of 38% for each treatment. In contrast, in Offman et al.,[20] the AUC for the postprandial LC omega-3 in plasma PL from free fatty acids (treatment 1) and ethyl esters (treatment 2) were determined with the results yielding a CV of 34% and 76%, respectively)

inconsistent reporting of adverse events in either postprandial or longer-term LC omega-3 studies, however GI-related adverse effects were reported in three of the postprandial studies referred to above (Supplementary Table 1). An example of GI side effects of LC omega-3 ingestion was reported in a 24-h postprandial study by Cuenoud et al[21] which used doses of approx. 3g of LC omega-3; in this study, there were 22 treatment emergent adverse effects in 11/24 subjects including nausea, diarrhoea, and headache. Since these effects were not consistently reported in all subjects, malabsorption of LC omega-3 could contribute to inter-individual variability.

These GI-related events support the notion that some of the ingested fish oil escapes digestion and passes into the colon and is possibly excreted in the faeces. In support of this, a review by Costantini et al[49] reported that dietary LC omega-3 supplementation can exert effects on the intestinal environment in humans including significantly altering the composition of the gut microbiome, likely indicating that some of the ingested LC omega-3 escaped digestion and absorption in the duodenum and exerted effects on the composition of the microbiota in the large intestine.

One consequence of variability in the postprandial absorption and subsequent uptake of LC omega-3 by the liver would be a variability of the effect of LC omega-3 in lowering plasma TAG concentrations. Such variability has been frequently reported and was summarized in a recent review by Rundblad et al.[50] which identified a number of determinants of the variability, including genetic variants, epigenetics and gene expression profiles, gut microbiota and habitual intake of LC omega-3. The

review by Rundblad et al. did not consider variability in the postprandial response to LC omega-3 supplementation as a potentially influential factor.[50]

Several postprandial and longer-term LC omega-3 supplementation studies have identified individuals who showed little (less than 10% increase over initial baseline value) or no increase in plasma or RBC LC omega-3 proportions.[8-10,15] These subjects could be categorised as non-responders, a topic which has not been pursued in the literature in the context of LC omega-3 supplementation; therefore, it is important to define more precisely what constitutes a non-responder. Clearly, the response to LC omega-3 supplementation will depend on the dose given and the length of time of the study. Based on the study by Sparkes et al. (lowest dose was 0.35g of EPA+DHA for 8 weeks) we propose that a non-responder could be defined as an individual whose response increases by less than 10 % of the initial value for the plasma or RBC EPA+DHA proportions.[8] A recent study used an n = 1 trial design to precisely characterize the individual glucose responses to high carbohydrate or high fat meals.[51] Perhaps this approach could be adopted in characterizing individuals' responses to LC omega-3 supplements? Following the identification of such individuals, this would presumably lead to further studies investigating the proteomic and genomic characteristics of these individuals.

There are several limitations to the current study. Firstly, since we solely used AUC variability. we did not capture the potential variability in kinetic parameters such as time to peak response and the peak postprandial value. This indicates that further analyses of the collected data could be investigated to explore the variability of these additional parameters. The other limitation is that we did not consider the baseline value of the subjects in each study as this has been reported to influence the postprandial response.[6,7]

Future directions

We hypothesize that the variability in the digestion and absorption of LC omega-3 fatty acids, resulting in a variable postprandial response, would lead to variability in plasma and RBC LC omega-3 proportions following supplementation.

The implications of variability in RBC LC omega-3 proportions, if supported by the above hypothesis, are that the utility of RBC omega 3 as a measure of status might be called into question if it is found that there are low and high responders to LC omega-3 intakes. Furthermore, this could have significant implications for LC omega-3 trials: for example, should low responders be excluded from trials? Finally, there are significant implications for consumers taking LC omega-3 supplements, including whether low responders gain any biological benefits from consuming LC omega-3 supplements? These matters will all need further study.

Conclusions

Postprandial variability in response to TAG ingestion is a common phenomenon, not restricted to oils rich in LC omega-3. This paper highlighted the postprandial variability in response to LC omega-3 oils, with the suggestion that part of the variability could stem from [a] maldigestion of these oils leading to excretion into the large bowel, and possibly in faeces and [b] variability in the absorption of the FFA and/or 2-MAG, either into the enterocytes, and/or the processing of the absorbed lipids into chylomicrons and/or the export of these into the lymph. The paper proposes that postprandial variability in plasma LC omega-3 responses might contribute to variations in LC omega-3 proportions in both plasma and RBC following LC omega-3 supplementation.

SUPPLEMENTARY MATERIALS

All supplementary materials are available upon request to the editorial office.

CONFLICT OF INTEREST AND FUNDING DISCLOSURES

The authors declare no conflict of interest.

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