Author’s response to reviews

Title: Alpha-tocotrienol is the most abundant tocotrienol isomer circulated in plasma and lipoproteins after postprandial tocotrienol-rich vitamin E supplementation

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Author’s response to reviews: see over
Response to Reviewers' Comments:

No amendments were required from Reviewer 1.

Corrections offered based on comments from Reviewer No. 2

Comment 1:
The title is not appealing because it is well know that tocotrienols are less preferentially circulated than α-tocopherol. Because tocopherols and tocotrienols serve different functions that hardly matters. Focus on tocotrienols make this work valuable. Furthermore, this is the first work (or among first) to show 4-5 micromolar α-tocotrienol in human circulation. Emphasis on that observation would make this report a powerful source.

Suggested title:
"alpha-Tocotrienol is the most abundant form of tocotrienol circulated in plasma and lipoproteins after postprandial tocotrienol-rich vitamin E supplementation"

OR

"Postprandial tocotrienol-rich vitamin E supplementation results in >4 micromolar concentration of alpha-tocotrienol in human circulation"

Response to Comment 1:
We have followed the reviewer's suggestion and amended the title as follows:

Alpha-tocotrienol is the most abundant tocotrienol isomer circulated in plasma and lipoproteins after postprandial tocotrienol-rich vitamin E supplementation

Comment 2:
Change all data from microgram/ml to micromolar

Response to Comment 2:
All measurements in tables and figures have been converted accordingly to micromolar (µM).

Comment 3:
Along the lines of revised title, suggest minor edits to BACKGROUND.

Suggested BACKGROUND: Tocotrienols (T3) and tocopherols (T) are both members of the natural vitamin E family with unique biological functions in human health and disease. α-T3 are known to be neuroprotective at nanomolar concentrations. This study evaluated the postprandial fate of T3 and α-T in plasma and lipoproteins.

Response to Comment 3:
We have modified this to reflect the concerns of the reviewer:

Background: Tocotrienols (T3) and tocopherols (T), both members of the natural vitamin E family have unique biological functions in humans. T3 are detected in circulating human plasma and lipoproteins,
although at concentrations significantly lower than α-tocopherol (α-T). T3, especially α-T3 is known to be neuroprotective at nanomolar concentrations and this study evaluated the postprandial fate of T3 and α-T in plasma and lipoproteins.

Comment 4:
Although it is OK to comment on comparison of T and T3 delivery in DISCUSSION do state that T3 have biological functions well below concentration noted in this study. Also, remove discussion of such comparison from INTRODUCTION and CONCLUSION as it is not novel and the biological relevance of such comparison is questionable.

Response to Comment 4:

To address the reviewer's reservation on the above statement we have amended the text (lines 279-281) as follows:

*Their occurrence throughout the postprandial state was apparent, only in significantly lower levels compared to α-T. Despite these observations, we note that T3 have been demonstrated to have biological functions well below plasma concentrations noted in this study (5, 8).*

Comment 5:
Emphasize in DISCUSSION and CONCLUSION which of the known functions of T3 are likely to work in humans on the basis of concentration needed for effect.

Response to Comment 5:

We are afraid that the scope of this current study does not really warrant us to make such a far reaching conclusion. However, we have looked into relevant references and have added reference 46 in support of a concluding statement (lines 375-377) that we are prepared to incorporate and which addresses the reviewer's concern:

*However, it is somewhat reassuring that even at the low concentration of circulating T3 in plasma (approximately 4 nanomolar) T3 could still have beneficial biological functions including that of neuroprotection as demonstrated by other workers [46].*

Comment 6:
Note that rapid disappearance of T3 could be because of preferential utilization

Response to Comment 6:
Agreed with the statement. There is a possibility that certain T3 isomers will be utilized first, based on in-vivo requirements (i.e. T3s are metabolized by side-chain degradation via β-oxidation pathway. CEHC is the final product of the process. We have amended the statements and the revised version is reflected as follows (lines 316 - 318) and supported by appropriate references:

There is no bio-discrimination between T and T3 during intestinal absorption after dietary intake of vitamin E [26,33-35]. However, the rapid disappearance of T3 may be associated with its preferential utilization in humans (8, 25, 34).

Comment 7: 
Because T3 and T serve different biological functions, suggest de-emphasizing comment on Vit E biological activity (Ref 22).

Response to Comment 7:
Reference 22 is an authoritative expert panel citation from the Food and Nutrition Board, Institute of Medicine, "Dietary reference intakes for vitamin C, vitamin E, selenium and carotenoids".

It would be a misrepresentation if this is de-emphasized since the science is still held to be correct. We have instead worked around this suggestion as follows while maintaining the relevance of Ref. 22: (see revised lines 252-255):

This is the main reason why α-T is the only vitamin E isomer that is currently used as the standard to estimate human vitamin E requirements [22]. However it is increasingly acknowledged that T3 and T serve different biological functions and benchmarking only α-T to estimate human vitamin E requirements may no longer be the most accurate measure [3,5,8].

Editorial Comments
Changes in the manuscript have been highlighted by red font.