Eur J Nutr (2015) 54:859–860
DOI 10.1007/s00394-015-0874-5

LETTER TO THE EDITOR

Commentary to "Randomized controlled trial of oral glutathione supplementation on body stores of glutathione"

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Published online: 20 March 2015

In regard to the article "Randomized controlled trial of oral glutathione supplementation on body stores of glutathione" published in Eur J Nutr [1], there is a point in the conclusion of the article that may be confusing and misleading to your readers. The body of the Eur J Nutr article reports data derived from the use of a non-liposomal glutathione, but the conclusion of the Eur J Nutr article references "[68]," a study on liposomal glutathione [2].

The authors of the Eur J Nutr [1] article state "The use of GSH itself in HIV infection may have advantages over its precursors since it would not require GSH resynthesis within cells via GCL, the activity of which is reduced in HIV+ macrophages [68]." The article offers no direct support of this statement. The article misleadingly cites reference "[68]," an article in J Interferon Cytokine Res by Morris D et al. [2] for substantiation of the statement. The "[68]" citation is to Morris D, Guerra C, Khurasany M, Guilford F, Saviola B, Huang Y, Venketaraman V (2013) *Glutathione supplementation improves macrophage functions in HIV*. J Interferon Cytokine Res. 2013 May;33(5):270–9 [2].

The cited article "[68]" is an article that describes the function of liposomal glutathione, not plain unformulated (non-liposomal) glutathione. This distinction is made in the abstract and in the body of the article by referring to a liposomal formulation of glutathione (lGSH), which is GSH encapsulated in lipid vesicles and obtained from Your Energy Systems, LLC. The properties of liposomal glutathione have been characterized in numerous articles [2–9].

It may help your readers to point out that there are several methods of supporting glutathione: (1) cysteine containing precursor of glutathione material such as whey protein or *N*-acetyl cysteine (NAC) [10], (2) non-liposomal glutathione as used in the Eur J Nutr article [1] and (3) liposomal glutathione, which has numerous publications describing its unique properties [2–9]. As described below, only liposomal glutathione has been demonstrated to have direct intracellular activity.

In describing the difference between liposomal glutathione and non-liposomal glutathione, the reader is referred to the article "Liposomal glutathione provides maintenance of intracellular glutathione and neuroprotection in mesencephalic neuronal cells" [5], which demonstrates that liposomal glutathione is much more efficient than non-liposomal glutathione in repleting glutathione-depleted astrocyte cells. In comparing liposomal glutathione to non-liposomal glutathione, the article states "liposomal GSH was 100-fold more potent; EC50s 4.75 and 533 μM for liposomal and non-liposomal GSH, respectively" [5]. The article goes on to demonstrate "Liposomal-GSH spared endogenous GSH during PQMB [paraquat and maneb] exposure, but did not require GSH biosynthesis for protection" [5]. The procedures associated with this finding show that liposomal glutathione is not catabolized outside the cell as one would find with a non-liposomal glutathione preparation [5]. Clearly, the difference in construction between non-liposomal GSH and liposomal GSH gives enhanced absorption properties to liposomal glutathione.

The ability of liposomal glutathione to have properties of enhanced absorption is pointed out in other studies

This comment refers to the article available at doi:10.1007/s00394-014-0706-z.

A reply to this article available at doi: 10.1007/s00394-015-0873-6

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showing the distinction between liposomal glutathione and glutathione precursor materials like NAC. These studies use human innate immune cells in which NAC and liposomal glutathione (lGSH) were used to replete glutathione in cell culture [2, 8, 9]. One of the studies, published in J Interferon Cytokine Res [2], uses HIV+ macrophages to show liposomal glutathione is able to provide antioxidant support directly to cells and demonstrated that liposomal glutathione can replete intracellular GSH dramatically more efficiently than NAC by showing that "doses of lGSH given (5 and 10 μM) were 1000 times lower than the dosage of NAC given (10 mM)" [2].

These studies are cited to demonstrate that there is a difference in construction and function between liposomal and non-liposomal glutathione.

The conclusion cited in the Eur J Nutr article on non-liposomal glutathione [1] may create confusion for the reader by stating that "GSH [non-liposomal] is more effective in restoring immune function in macrophages from HIV-infected individuals than is *N*-acetylcysteine [68]" [1]. This reference actually refers to the liposomal glutathione (lGSH) studies published in the J Interferon Cytokine Res [2] and does not support any conclusion with respect to non-liposomal glutathione.

In addition, there is reason to question the assertion that non-liposomal glutathione will be effective in a condition like HIV. It is demonstrated in the J Interferon Cytokine Res article [2] that there is decreased production of the enzyme catalytic subunit of glutamine-cysteine ligase (GCLC) resulting in decreased formation of GSH in HIV+ cells [2]. Blood glutathione is usually broken down by the ectoenzyme ɣ-glutamyltranspeptidase into its constituent amino acid components prior to absorption into cells [5]. The J Interferon Cytokine Res article [2] explains that the loss of GCLC enzyme prevents efficient use of the cysteine from NAC and explains why liposomal glutathione is 1000 times more efficient in replenishing GSH than NAC in HIV+ macrophages. The Eur J Nutr article [1] offers no data from which an assertion of effectiveness in HIV may be made.

Summary

In the Eur J Nutr article [1], the following statement is made: "The use of GSH [non-liposomal glutathione] itself in HIV infection may have advantages over its precursors since it would not require GSH re-synthesis within cells via GCL, the activity of which is reduced in HIV+ macrophages [68]. Indeed, in vitro studies indicate that GSH is more effective in restoring immune function in macrophages from HIV-infected individuals than is N-acetylcysteine [68]." The context of the statement refers to non-liposomal glutathione, while the article cited in support of this conclusion refers to studies with liposomal glutathione [2].

It may be useful to point out to your readers the differences in non-liposomal and liposomal glutathione. Explaining this distinction will help clarify any confusion that may have arisen from the conclusion of the Eur J Nutr article that uses data on non-liposomal glutathione [1], but makes a conclusion citing a study using liposomal glutathione [2].

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