Antioxidants and Cognitive Function: Misleading Concepts and New Strategies

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In a recent study, Yasuno et al. [1] reported promising results over the improvement of cognitive function by a combination of antioxidants in patients more than 65 years old. Forty-one patients with deterioration of cognitive function were evaluated after 3 years of follow up, during which patients undertook “antioxidant” supplementation. As a control, data of 622 patients without supplement intake were collected. The authors found that “antioxidants” improved cognitive function, arguing that antioxidants used in combination act synergistically in ameliorating cognitive function. According to author’s definition, supplement intake included a daily dose of 1182 mg n-3 fatty acids (FA), 83 mg lycopene from tomato extracts, and 240 mg Ginkgo Biloba leaf extract. In detail, n3-FA consisted of 1.182 mg purified fish oil, containing 290 mg eicosapentaenoic acid (EPA) and 203 mg docosahexaenoic acid (DHA).

The paper from Yasuno et al. [1] carries some misleading concepts that must be fixed to avoid the risk of further carry over in future papers by the mechanism of citation.

Firstly, “combination of antioxidant supplements” is the main misleading concept in the title that runs through the text. Actually, the authors used a combination of fish oil and two putative antioxidant supplements, i.e. tomato and Ginkgo Biloba extracts. Antioxidants, by definition, are molecules that can trap an array of free radicals, thereby interrupting chains reactions that lead to extensive biological damage. Fish oil enriched with n3-FA does not fall in the category of antioxidants. Contrarily, n3-FA contained in fish oil are, among the lipids, the most susceptible to the attack of free radicals, leading to the formation of bioactive and potentially hazardous by products [2,3].

Secondly, the purified fish oil used in this paper consisted of 1.182 mg purified fish oil, containing 41.7% n3-FA, i.e. 290 mg EPA and 203 mg DHA.

All the n3-FA supplements available for human use are fish oils enriched of n3-FA, but containing a variety of saturated and monounsaturated species, which differ from brand to brand [4]. We have analyzed the composition of a preparation of n3-FA (Esapent, Pharmacia Italia) commercially available in Italy with a nominal content of EPA plus DHA higher that 85%. Table 1 shows the distribution of the fatty acids in this preparation that still vehicles about 10% of non-n3-FA. What about the 58.3% of non-n3-FA in the supplement used in the study by Yasuno et al. [1]? The disregarded fatty acids present in the supplements must be taken into account because most of them, for example palmitoleic acid [5], have biological activity.

Third, the author gave 84 mg of the antioxidant lycopene through a tomato extract, and stating that the amount of a single dose of lycopene corresponds to that found in half of a standard tomato. The content of lycopene in tomato is 8.8-1.0 mg% [6] and, consequently, the authors supplemented an amount of lycopene that is equivalent to the amount contained in 1 kg tomatoes. In addition, did the tomato extract contain lycopene and other antioxidants, i.e. vitamin C and other carotenoids, or was it 100% lycopene? These considerations are crucial for future studies. If the authors have used pure lycopene, others should be able repeat the study with an equivalent amount of purified substance. If the authors used a tomato extract, containing 85 mg lycopene and...
additional antioxidants, others who may wish to repeat the study should be able to use the same supplement as refined from Lyco Red Co. This concept extends also to Ginkgo Biloba extracts. In studies using supplements, the authors should give the commercial name, if any, of the extract and, importantly, the corresponding nominal composition of ingredients in the formulation.

Aside from these considerations, the combination of fish oil and antioxidants supplements studied in cognitive decline deserves to be highlighted. N3-FA, which include α-linolenic acid, EPA and DHA, have been subject of intense investigation in the recent years for expected benefits in delaying cognitive decline in AD [7]. Subsequent large intervention trials, however, failed to confirm the expected beneficial effects of n3-FA on cognitive decline [7]. The reason of this failure is still unknown, but at least two aspects should be remarked, including the content of non-n3-FA in the fish oil used as a supplement and the high oxidizable capacity of n3-FA [8].

Using a supplement containing a mixture of FA, in different proportions, there is no way to attribute the effect to one of its components. Otherwise, effects of certain components might be masked or abolished by other components rising relevant bias. The varied composition of fish oil is amenable to such a kind of bias. On the other hand, the propensity of n3-FA to oxidize, producing potentially hazardous intermediates, is an underestimated factor that might contribute to explaining the failure of n3-FA on cognitive decline. The paper by Yasuno et al. offers a new strategy to further investigating n3-FA in cognitive decline: the association of n3-FA with antioxidants [1]. It is reasonable to speculate that antioxidants, given along with fish oil, could have acted favorably towards cognitive function by preserving n3-FA from in vivo peroxidation and delivering hazardous intermediates. Having no substantial treatment to counteract cognitive decline to date, fish oils in combination with antioxidants could be considered as a novel strategy for future studies in this clinical setting.

References