To Protect Memory High-Dose DHA Reaches the Brain but Fails

A clinical trial published found that high-dose docosahexaenoic acid (DHA) supplementation successfully increased brain DHA levels in older adults at risk of dementia, including those carrying the APOE ε4 Alzheimer's risk variant. However, despite reaching the brain, the supplement did not improve cognitive performance or brain structure over two years, raising new questions about how DHA is used within the brain.

Study

DHA is a fatty acid that is part of the nerve cell membrane, playing a key role in synaptic function and modulating neuroinflammation. Its levels tend to be lower in the presence of dementia-linked changes like amyloid deposition and cognitive decline, and in patients with late-onset Alzheimer's disease (AD).

The APOE ε4 gene variant is the strongest genetic risk factor for AD. Previous research suggests it is associated with accelerated DHA catabolism and lower plasma and cerebrospinal fluid DHA levels in people with AD dementia compared with non-carriers.

Observational studies have suggested modest associations between higher omega-3 intake and lower risk of cognitive decline, but randomized trials have produced inconsistent results. Of 24 randomized trials in people without dementia, only five reported positive cognitive effects following DHA supplementation. Conversely, no improvement was seen in patients with AD.

Thus, two important questions remain unanswered: is early intervention necessary in patients with low omega-3 levels before dementia sets in, and are higher doses required to ensure adequate brain uptake? Previous imaging studies suggest that younger cognitively healthy carriers have increased brain DHA incorporation, which may reflect greater DHA demand, compared to non-carriers. This has not been studied in older adults prior to the onset of dementia.

In the current study, researchers investigated whether high-dose DHA supplementation could effectively raise brain DHA levels and potentially support cognitive and structural brain health in older adults with low dietary omega-3 intake before dementia develops.

Findings

The 365 participants were divided into two arms: 181 in the LP arm and 184 in the non-LP arm. In both arms, DHA supplementation significantly increased the CSF DHA/AA ratio at six months compared with placebo, indicating successful delivery of DHA to the brain. There was also a 17% increase in CSF DHA. The red cell omega-3 index also increased from 4.9% to 11%.

The increases in DHA delivery to the brain and in the red cells were independent of APOE ε4 status. This suggests that the gene variant did not influence this process.

However, APOE ε4 non-carriers showed greater improvement in cognitive scores than carriers, with a mean improvement of 3.8 and 1.6 in the two groups, respectively, regardless of treatment group. Importantly, the study demonstrates that inadequate brain delivery is unlikely to explain the disappointing results of previous DHA supplementation trials, because high-dose supplementation successfully increased CNS DHA levels.

The authors hypothesize that simply improving DHA delivery to the brain may not be sufficient to enhance cognitive function, given the enzymatic catabolism of DHA within synaptic membranes, which are crucial for cognitive processing.

There was no difference in brain volumes or in cognitive performance over the whole study period between the intervention and control groups. Adverse events were comparable between groups, and the treatment was generally safe and well-tolerated.

Conclusion

The findings show that high-dose DHA supplementation can substantially increase brain DHA levels within six months in older adults at risk of dementia, regardless of APOE ε4 status. Conversely, this did not translate into observable improvements in cognition or brain structure over 24 months.

These results suggest that high DHA intake alone may not be sufficient to improve cognitive outcomes or preserve brain structure in relatively healthy older adults over a 2-year period, despite adequate brain delivery. They also imply that APOE ε4 carriers experience normal DHA delivery to the brain before dementia, despite the dysregulation in established dementia reported in prior research.

Future research should focus on examining DHA metabolism in the brain rather than on additional supplementation trials. Because brain DHA delivery was successfully achieved without improving cognition, future work should focus on how DHA is processed and used within brain cells rather than simply increasing DHA intake.

Source:

https://www.news-medical.net/news/20260625/High-dose-DHA-reaches-the-brain-but-fails-to-protect-memory.aspx