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Invited commentary

Omega-3 fatty acids: Benefits for cardio-cerebro-vascular diseases

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ABSTRACT

Background and purpose: Intracranial artery stenosis (ICAS) is a narrowing of an intracranial artery, which is a common etiology for ischemic stroke. In this commentary, we review key aspects of the discrimination between non-stroke controls and ischemic stroke patients on the background of phospholipid ω3-fatty acid (DHA, EPA) composition. The discussion is embedded in the presentation of general effects of long-chain ω3 polyunsaturated fatty acids (PUFAs) in cardio-cerebro-vascular diseases (CCVDs) and Alzheimer dementia (AD).
Summary of commentary: ICAS is a common stroke subtype and has emerged as a major factor in recurrent stroke and vascular mortality. DHA and EPA are important fatty acids to distinguish between NCAS (no cerebral arteriosclerotic stenosis) and ICAS in stroke. The risk of ICAS is inversely correlated with the DHA content in phospholipids. Furthermore, a mechanistic explanation has been proposed for the beneficial effects of PUFAs in CCVDs and AD.
Conclusions: Whereas the beneficial effects of EPA/DHA for cardiovascular diseases and stroke seem to be beyond question, preventive effects in patients with very mild cognitive dysfunction and beginning Alzheimer's disease undoubtedly need confirmation by larger clinical trials. A collaborative international basic science approach is warranted considering cautiously designed studies in order to avoid ethical problems.

Fat *per se* as independent coronary risk factor has been scientifically shelved. A number of scientific investigations have shown how differentiated fatty acids are to be judged. Saturated fatty acids and trans-fatty acids are particularly harmful to the heart and blood vessels. Omega-3 fatty acids range on top of the list of good fats [1]. Clinical trials have delivered sufficient convincing arguments in this regard. Against this background, a paradigm change has happened in the recommendations for fat supply. The daily intake of eicosapentaenoic acid (EPA, C20:5n-3) and docosahexaenoic acid (DHA, C22:6n-3) should amount to 0.5–1.8 g.

1. Benefits of ω3 fatty acids in cardiovascular diseases

Long-chain ω3 fatty acids of fish diminished fatal myocardial events in patients after infarction [2–4]. This may be attributable to a membrane-stabilizing effect in cardiac muscle cells [5] and a fast plaque stabilizing effect [6]. The best-known field of application of the long-chain, polyunsaturated ω3 fatty acids substantiated by numerous clinical trials, is the normalization of the lipid level via a drastic reduction in serum triglycerides [7,8]. Besides a diminished cardiovascular risk [4,9], these ω3 fatty acids were proven to have antiarrhythmic [10] and antiinflammatory effects [11,12], positive actions on oxidative stress [13,14] and plaque stability [6] as well as a reducing impact on the cardiovascular risk factor concentrations of Lp(a) [15] and oxLDL [16]. In epidemiologic studies, it appeared a striking quantitative agreement between optimal daily demand for these essential fatty acids and the significant effect on mortality rate of coronary heart disease [17,18].

OxLDL promotes the build-up and progression of plaques [19,20]. Therefore, the reduction of the oxLDL/LDL quotient observed under fish oil treatment is so significant, because oxLDL leads preferably to the formation of unstable plaques via induction of apoptosis [21]. The Lp(a) level is determined genetically to about 74% [22]. Thus, it is difficult to influence Lp(a) therapeutically [23]. On the other hand, the plasma Lp(a) concentration is attentively balanced by inflammatory cytokines [24]. Moreover, this parameter, independent of the other lipid values, has an effect on the oxLDL level and vice versa. Witztum and co-workers point out that

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in settings of enhanced oxidative stress and chronically elevated Lp(a) levels, the atherogenicity of Lp(a) may stem from its capacity as carrier of pro-inflammatory oxidation by-products [25].

Omega-3 fatty acids contribute in different ways to cardiac and vascular protection [26–28]. An increased incorporation of ω3 fatty acids into cell membranes augments their fluidity. Therefore, blood viscosity diminishes. Moreover, the polyunsaturated fatty acids further endothelial function and NO formation, which results in an improvement of blood perfusion. In addition, ω3 fatty acids influence adhesion molecules as well as the arachidonic acid cascade. Thus, they act upon the formation of various eicosanoids and have an inhibiting effect on inflammation [29]. The latter is even amplified by EPA since it competitively blocks the enzyme cyclooxygenase. In addition, the cardiovascular risk is decreased by lowering blood pressure and plasma triglycerides, proven antithrombotic effects and slowing down the growth of arteriosclerotic plaques [30,31].

Therefore, ω3 fatty acids have a secured place in the overall concept of secondary prevention besides acetylsalicylic acid, ACE inhibitors, statins and β-receptor blockers (ESC, AHA, ACC). All drugs that are of significance in secondary prevention after myocardial infarction have shown that they prevent further cardiovascular events like re-infarction, sudden cardiac death, heart insufficiency and death [26,32,33].

2. Benefits of ω3 fatty acids in stroke

In previous studies, fish consumption was associated with lower risk of stroke [34–37] and incident dementia [38,39]. In the Zutphen and NHANES I studies, the authors concluded that consumption of at least one portion of fish per week may be associated with a reduced stroke incidence [34,35]. This was the first time that an inverse relation between fish consumption and ischemic stroke incidence has been reported. Mechanistically, a reduction in the formation of thromboxane A_2 by long-chain ω3 polyunsaturated fatty acids (PUFAs), including marine-derived EPA and DHA, and thus a diminished aggregability of blood platelets, an enhanced deformability of erythrocytes, an altered fluidity and activity of membrane-associated enzymes and receptors, resulting in protection of the vessel wall against ischemic damage, lowering of plasma triglycerides, VLDL, blood pressure and insulin resistance as well as an improvement of glucose tolerance were discussed [28,34,35,37,40,41]. In a large prospective cohort study, a diet high in cereal fiber, folate, and ω3 fatty acids, with a high ratio of polyunsaturated to saturated fat, and low in *trans* fat and glycemic load combined with abstinence from smoking, moderate alcohol consumption, regular exercise and low body mass index was associated with a significantly reduced risk of total and ischemic stroke but not of hemorrhagic stroke [42]. In the JELIS trial, administration of highly purified EPA appeared to reduce the risk of recurrent stroke, particularly of ischemic events, in a Japanese population of hypercholesterolemic patients receiving low-dose statin therapy [43]. In a transgenic mice model, diet-induced accumulation of DHA in the brain protected against post-ischemic inflammation and injury, e.g., by preventing microglial activation after ischemic harm and reducing the ischemic lesion size. Increased DHA intake may provide protection against acute immune response/brain damage in ischemic stroke, the authors concluded [44].

The strengths of a large cohort study from the Karolinska Institutet of 34,670 middle-aged and elderly women include the prospective and population-based design and the almost complete follow-up of participants by linkage with various population-based Swedish registers [45]. During a mean follow-up of 10.4 years, the authors ascertained 1680 stroke events, including 1310 cerebral infarctions, 233 hemorrhagic strokes, and 137 unspecified strokes. After adjustment for other stroke risk factors, intake of long-chain ω3 PUFAs was inversely associated with risk of total stroke, whereas dietary cholesterol was positively correlated with risk of total stroke and cerebral infarction. While in this clinical trial no differentiation of total stroke patients in relation to their intake of EPA/DHA has been undertaken, this is examined in the paper published by M.-J. Shin et al. in this issue of Atherosclerosis [46]. Stroke is generally classified as derived from extracranial arteriosclerosis, intracranial artery stenosis (ICAS) [cf. 41], small vessels (lacunar stroke), cardioembolic and cryptogenic events. ICAS is a narrowing of an intracranial artery, which is a common etiology for ischemic stroke and has been implicated as a major factor in recurrent stroke and vascular mortality [46]. Given the high risk of stroke in patients who were randomized soon after their qualifying events, early identification of ICAS is important for prognosis and possible intervention [47]. Indeed, Shin et al. [46] showed that fatty acid

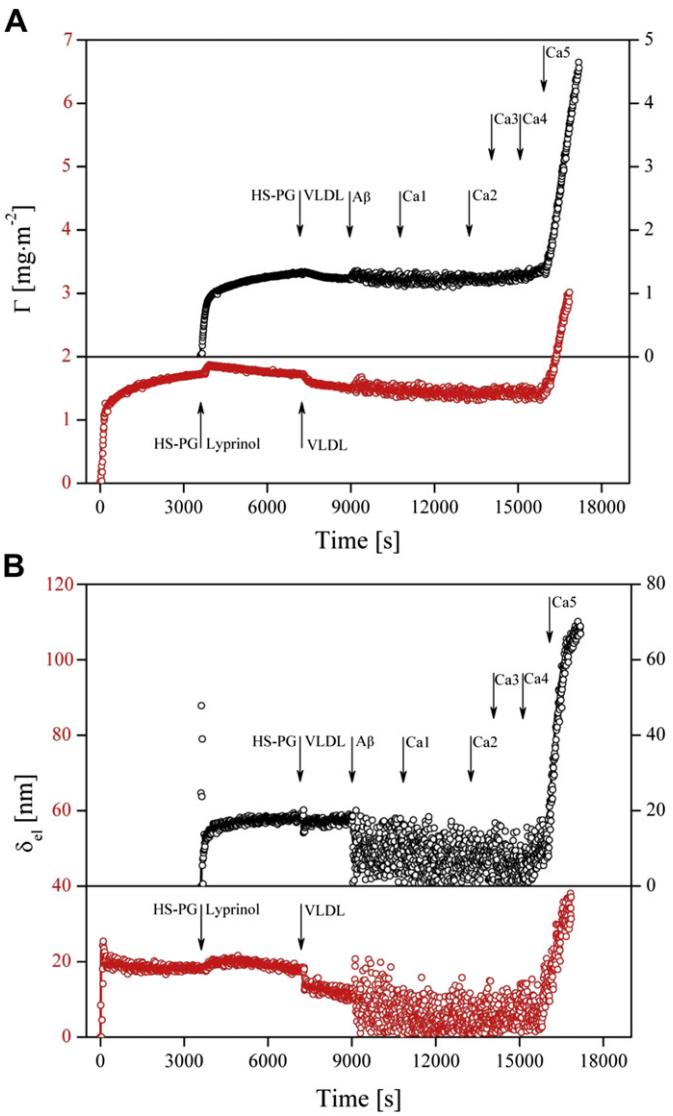

Fig. 1. Total adsorbed amount (A) and layer thickness (B) versus time. At time zero, HS-PG (0.1 mg/mL) was adsorbed on hydrophobic silica from a Ca^{2+}-free Krebs solution. The first arrow indicates the addition of the plasma VLDLapoE4/E4 fraction (10 mg/dL) from a genotypized patient either without (○, black curve) or with PUFAs (EPA 15.9 μmol/L; DHA 7.2 μmol/L) (○, red curve). Thereafter, human Aβ (0.1 mg/mL) was applied. Total Ca^{2+} concentrations in solution are indicated at the arrows (Ca1 2.52, Ca2 5.04, Ca3 7.56, Ca4 10.08, Ca5 17.64 mmol/L). The thick, solid lines were computed by an iterative parameter fit of the nonlinear allosteric-cooperative, simple saturative or exponential kinetics to the experimental points using an algorithm for least-squares estimates. The pH was 7.34 (○) and 7.23 (○), respectively.

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composition of phospholipids is significantly different between non-stroke controls and ischemic stroke patients and especially between NCAS (no cerebral arteriosclerotic stenosis) and ICAS among stroke patients. DHA and EPA were important fatty acids for distinguishing between NCAS and ICAS in stroke. Furthermore, the risk of ICAS was inversely correlated with DHA contents in phospholipids. Considering plasma DHA reflects dietary intake, these results indicate a potential benefit of sufficient amounts of DHA in plasma or in the diet in reducing the risk of ICAS [46].

3. Benefits of ω3 fatty acids in Alzheimer dementia

Besides the aforementioned advantages of long-chain ω3 PUFAs, the authors [46] discuss for DHA a reduction of neuroinflammation [48], activation of anti-apoptotic pathways [49] and a protection against post-ischemic inflammation and injury [44]. Moreover, in these communications the protective role of ω3 fatty acids in neurodegenerative diseases, mixed pathologies of dementia [50] and Alzheimer's disease was explained [cf. 38,39,51,52]. Since PUFAs are essential nutrients and essential components of neuronal and glial cell membranes and regulate both prostaglandin and pro-inflammatory cytokine production, PUFA deprivation of neurons can lead to neuronal cell death and neurodegeneration [48]. Therefore, it is understandable that dietary intake of ω3 fatty acids, especially DHA, and weekly consumption of fish reduced the risk of incident Alzheimer disease [39]. In this prospective study of a stratified random sample from a geographically defined community, participants who consumed fish once per week or more had 60% less risk of Alzheimer disease compared with those who rarely or never ate fish in a model adjusted for age, intake of other dietary fats, vitamin E and cardiovascular conditions. Even though the same authors weakened their findings in a following prospective cohort study, they concluded that fish consumption may be associated with a slower cognitive decline with age [53].

In line with this, a Swedish group from the Karolinska Institutet and University Hospital found in a randomized, double-blind, placebo-controlled clinical trial that in a small subgroup with very mild cognitive dysfunction, a significant reduction in MMSE (Mini-Mental State Examination) decline rate could be observed in the ω3 fatty acid-treated group compared with the placebo group [54]. The study rated the patients on a 30-point scale, where a lower score indicated a more severe state of Alzheimer dementia. At the beginning of the trial, the patients were ranked at 28, a mild level of dementia. After six months, those taking the placebo had deteriorated to 26, while those who had taken ω3 had not changed at all. In a later study, the same authors showed positive effects on agitation symptoms in *APOE4* carriers with mild to moderate Alzheimer's disease supplemented with ω3 fatty acids for six months [55].

These encouraging results prompted us to look out for additional mechanistic explanations. Utilizing nanotechnologic biosensor ellipsometry [56], it is possible to simulate Alzheimer nanoplaque formation *in vitro* and to investigate the impact of any drug on plaque formation and size [57–59]. The devastating neurodegeneration in Alzheimer's disease may be caused by deposition of amyloid β-peptide (Aβ) in plaques in brain tissue [60–62]. Diffuse Aβ deposits can be seen analogous to early fatty streaks of cholesterol that are the harbingers of mature, symptom-producing arteriosclerotic plaques. Additionally, apolipoprotein E4 (apoE4) has been linked to the formation of the amyloid plaques by *in vitro* studies demonstrating that apoE4 forms a very stable complex with the Aβ peptide, whereas apoE3 interacts less avidly [63]. Incubation of Aβ with apoE4 resulted in a much more complex, dense network of fibers compared to that formed with apoE3 [64]. Furthermore, Mahley [65] has shown in a very elegant study, that the HS-PG (heparan sulfate proteoglycan)/LRP (LDL receptor-related protein) pathway is involved in the delivery of apoE to neurons, where apoE alters neurite growth and cytoskeletal activity in these cells. Specifically, apoE4, which has been associated with the pathogenesis of Alzheimer's disease, inhibits neurite extension and microtubule formation subsequent to the interaction of apoE4 with the HS-PG/LRP pathway. Indeed, we could confirm in ellipsometry measurements [66] earlier observations [63–65] that LDLapoE4/E4, IDLapoE4/E4 and HDLapoE4/E4 lead to dramatic Alzheimer nanoplaque formation, while the apoE3/E3 lipoproteins do so only very restrictedly, and incubation media devoid of Aβ not at all.

These results caused us to test PUFAs (Lyprinol®, PCSO-524™ Lipid-Komplex, Pharmalink International, Leichlingen, Germany) for Alzheimer nanoplaque formation and size under worst conditions, i.e., with homozygous VLDLapoE4/E4 from genotypized patients and with human β-amyloid peptide (1–42). Fig. 1 shows at a first glance that after monomolecular coating of the silica surface with proteoheparan sulfate, ω3 fatty acids bind strongly to HS-PG (Fig. 1A) and induce a compaction of the binary complex (Fig. 1B). The VLDL docking process is markedly diminished, Aβ leads to large scattering (particle formation) immediately after binding to VLDL

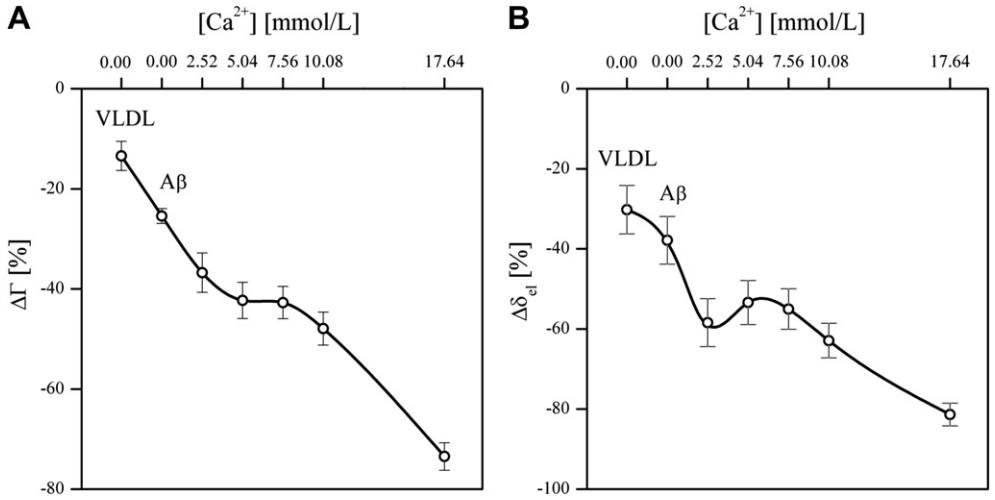

Fig. 2. Reduction in Ca^{2+}-induced changes in adsorbed amount (A, Alzheimer nanoplaque formation) and layer thickness (B, Alzheimer nanoplaque size) as derived from the curves in Fig. 1. The reductions upon application of the VLDLapoE4/E4 fraction and human Aβ were calculated as a ratio to the control values ($n = 3$).

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[67], Ca^{2+} titration complexes are diminished (Fig. 1A), and the adsorbed layer thickness is approximately halved for Ca1-Ca5 (Fig. 1B). The exact evaluation of these experiments is depicted in Fig. 2. Preincubation of HS-PG with ω3 fatty acids reduced VLDL docking and nanoplaque size by 13.4% (size by 30.2%), ternary plaque formation with Aβ by 25.4% (size by 37.9%), and quaternary calcified Alzheimer nanoplaque formation by 36.8% (size by 58.4%). In conclusion, this reduction of Alzheimer nanoplaque neoformation and size, detected here for the first time as a novel pleiotropic action of ω3 fatty acids, may have a beneficial effect on the cognitive functions in dementiae of the Alzheimer type, in the prevention of TIA and stroke.

4. Summary

Whereas the beneficial effects of EPA/DHA for cardiovascular diseases and stroke seem to be beyond question, preventive effects in patients with very mild cognitive dysfunction and beginning Alzheimer's disease undoubtedly need confirmation by larger clinical trials. Such studies have to be carefully designed because all the patients included should participate in possible benefits.

Note added in proof

Just recently, in a meta-analysis a correlation between the intake of omega-3 fatty acids and the risk of cardiovascular events in different patient populations was critically questioned [68], especially when the patients were treated by actual evidence-based prevention strategies. In future, it has to be proven whether these arguments are lasting.

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