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Analysis of long-chain ω-3 fatty acid content in fish-oil supplements

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Analyse des Gehalts langkettiger ω-3 Fettsäuren in Fischölpräparaten

Zusammenfassung. *Hintergrund:* In zahlreichen Studien wurden die verschiedensten vorteilhaften Effekte von mehrfach ungesättigten Omega 3 Fettsäuren auf Atherosklerose, Arrhythmie und Hypertriglyzeridämie nachgewiesen, was zahlreiche Gesundheitsorganisationen dazu veranlasst hat, einen täglichen Verzehr von einem Gramm Omega 3 Fettsäuren täglich für antiatherosklerotische sowie antiarrhytmische Wirkungen oder zwei bis vier g/d Omega 3 Fettsäuren zur Senkung der Plasmatriglyzeride zu empfehlen. Es sind zahlreiche Präparate auf dem Markt erschienen, welche die ω-3 PUFA-arme westliche Ernährung in Form von Kapseln ergänzen. Da diese Präparate beträchtlichen Variationen des Gehalts an langkettigen ω-3 PUFAs unterworfen sein können, haben wir neun kommerziell erhältliche Produkte bezugnehmend auf ihre Fettsäurekomposition getestet.

Methoden: Neun kommerziell erhältliche ω-3 PUFA Nahrungsergänzungsmittel wurden mittels kapillärer Gaschromatographie auf ihren Gehalt an langkettigen ω-3 PUFA untersucht.

Ergebnisse: Die neun von uns getesteten Präparate zeigen hinsichtlich der Konzentration an langkettigen ω-3 PUFA große Unterschiede von bis zu 63,7 ± 1,58 mol % (p = 0,002) und die Meisten scheitern daran, die empfohlene Tagesdosis von einem Gramm zu erzielen, selbst wenn sie in der höchsten vom Hersteller angegebenen Dosierung verabreicht werden. Acht der Präparate enthalten entweder gleiche oder signifikant höhere langkettige ω-3 PUFA Mengen als vom Hersteller angegeben und ein Hersteller macht keine Angabe. Die höchsten Anteile an Eicosapentaensäure (EPA) und Docosahexaensäure (DHA) wurden in Omacor® (95,80 ± 0,63%) und Percucor® (76,8 ± 7,11%) vorgefunden.

Konklusion: Verabreichung von langkettigen ω-3 Fettsäurepräparaten kann in großen Unterschieden der tatsächlich konsumierten Menge resultieren. Daher ist es empfehlenswert, die am höchsten standardisierten und gereinigten Produkte zu verwenden.

Summary. *Background:* Omega-3 polyunsaturated fatty acids (long-chain ω-3 PUFA) have proved to be beneficial in atherosclerosis, arrhythmia and hypertriglyceridemia in several studies, which has led national and international societies to recommend an intake of 1 g/d long-chain ω-3 PUFA for antiatherosclerotic and antiarrhythmic purposes or 2–4 g/d for a lipid lowering effect. Numerous preparations are marketed for supplementing western diet, which is low in long-chain ω-3 PUFA. Since these preparations vary in their long-chain ω-3 PUFA content, we tested nine commercially available products for their fatty acid composition.

Methods: Nine commercially available ω-3 fatty acid supplements were analyzed using capillary gas chromatography to determine their fatty acid content.

Results: The nine preparations showed huge differences, up to 63.7 ± 1.58 mol% ($P = 0.002$), in their long-chain ω-3 fatty acid content. Most of them failed to achieve the daily recommended dose of 1 g, even when administered at the highest dosage according to the manufacturer's recommendations. Eight of the preparations contained either equal or significantly greater amounts of long-chain ω-3 PUFA than denoted by the manufacturer; one preparation did not provide any information. The highest percentage of DHA and EPA was detected in Omacor® (95.80 ± 0.63%) and Percucor® (76.8 ± 7.109%).

Conclusion: Administering long-chain ω-3 fatty acid preparations may result in huge differences in terms of the actual amount ingested. It is therefore advisable to use the most standardized and purified products available.

Key words: ω-3 polyunsaturated fatty acid, food supplements, fish liver oil, gas chromatography, diet.

Background

Starting with the hypothesis that the observed low cardiovascular mortality in the Inuit people of Greenland could be related to their marine diet, which contains omega-3 polyunsaturated fatty acids (long-chain ω-3 PUFA)

[1], a steadily growing body of evidence corroborating this assumption has emerged. As shown in the DART study, consumption of fatty fish twice a week showed beneficial effects on overall mortality in the secondary prevention of myocardial infarction [2]. The GISSI prevention study demonstrated that treatment with 1 g/d long-chain ω-3 PUFA in the form of supplements significantly decreased the rates of death, non-fatal myocardial infarction and stroke in patients surviving recent myocardial infarctions over 3.5 years [3], which underlines the therapeutic efficacy of long-chain ω-3 fatty acids. The mechanisms behind the data are still being explored, but many aspects have already been clarified.

The beneficial effects on atherosclerosis were among the first targets of examination following the observation that, among traditionally living native Alaskans, older persons had a significantly lower prevalence of atherosclerotic plaques and younger persons had fewer aortic fatty streaks than were present in non-natives [4]. These effects were proven in numerous studies [3, 5–11]. Antithrombotic effects [1, 12, 13] and antihypertensive effects [14, 15] have also been reported. Moreover, antiarrhythmic effects have been proven clinically, as seen in a risk reduction of 38% vs. placebo for confirmed arrhythmic events in post-myocardial infarction patients being treated with long-chain ω-3 fish oil for at least 11 months [16].

The triglyceride-lowering properties [17, 18] of long-chain ω-3 fatty acids also contribute to the beneficial effects on atherosclerosis and may prove of benefit in preventing the onset of type 2 diabetes mellitus [19]. Although the ideal consumption of long-chain ω-3 fatty acids is still under investigation, evidence from most prospective secondary prevention studies suggests that a daily intake of 0.5–1.8 g eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), be it in the form of fatty fish or as supplements, significantly reduces the incidence of underlying causes of heart disease and related fatalities. This has led the American Heart Association to recommend consumption of 1g/d EPA and DHA for patients with documented coronary heart disease, or even 2–4 g/d for triglyceride-lowering purposes in patients with hypertriglyceridemia [20].

Although consumption of sufficient amounts may be achieved by eating fatty fish, fish-oil preparations may be necessary in order to reach the recommended doses, especially in dyslipidemia, since achieving the recommended dose by eating fish alone (e.g. salmon) would require the patient to consume considerable amounts (110–220 g/d to reach the recommended 2–4 g/d [20]); this would result in bad compliance and consumption of large amounts of undesired fats as a side effect. In addition, the actual long-chain ω-3 fatty acid content in fish is highly variable, even within a single species, and is dependent on geographic origin, season and preparation.

Further, organochlorine contaminants are commonly found in farmed salmon [21], marking a potential risk for developing cancer and adverse neurobehavioral and immune effects. A significant association between incorporated long-chain ω-3 fatty acids derived from consumption of cold-water fish and intoxication with β-hexachlorcyclohexane, chlordanes, dichlorodiphenyltrichloroethane, hexachlorobenzene, mirex, polychlorinated biphenyls and toxaphenes has been demonstrated in the population of Greenland [22]. Although the beneficial effects still outweigh the estimated risks [23], intoxication with persistent organic pollutants could be avoided by consuming long-chain ω-3 fatty acids in the form of purified supplements. In addition, this form of administration may be helpful in reducing the mercury ingestion that accompanies fish consumption, a downside leading the Food and Drug Administration to recommend limiting fish consumption by pregnant women and children to not more than three or four meals per week [20].

Although long-chain ω-3 fatty acids in the form of supplements appear to be the safer and more controllable way of consuming long-chain ω-3 PUFA, all preparations rely on fish oil as a source of EPA and DHA, which may show the same variability as the natural product these preparations are derived from. Since long-chain ω-3 PUFA supplements are considered to be safe and beneficial in a wide variety of indications if administered appropriately, we tested the fatty acid content and composition of nine commercially available supplements by subjecting them to capillary gas chromatography in order to compare their quality and assess the potential clinical usefulness of different preparations available on the Austrian market.

Materials and methods

The fatty acid content of the following commercially available preparations was analyzed: Abtei® Omega-3 Lachsoel 1000 (Abtei® Pharma, Germany), Ameu® Lachsoel-Konzentrat (Omega Pharma, Austria), Bilatin® (Stada Arzneimittel, Austria), Biogelat® Omega 3 Duo (Metochem Pharma, Austria), Blubio® Omega 3 (Blubiotech international, Germany), Dr. Boehm® Omega-3-forte (Apomedica, Austria), Omacor® (Solvay Pharma, Austria), Percucor® (Pharmaselect, Austria) and Omega 3 Supply® (the Wellness company, Austria).

According to the information from the manufacturers, Abtei® Omega-3 Lachsoel 1000 contains 1000 mg oil derived from salmon and 28.5% ω-3 fatty acids, without further differentiation on the types of ω-3 fatty acid; Ameu® Lachsoel-Konzentrat contains 500 mg salmon oil concentrate including 35% ω-3 PUFA, (18% EPA, 12% DHA, 5% others); Bilatin® contains 500 mg of purified salmon oil with 30% long chain ω-3 PUFA defined as EPA and DHA; Biogelat® Omega 3 Duo contains 400 mg of fish-oil concentrate (55% EPA and DHA) and 400 mg of perilla oil (60% α-linolenic acid); Blubio contains 495 mg salmon oil but no further information on ω-3 fatty acid content; Dr. Boehm is composed of 400 mg cold-water fish oil, 170 mg linseed oil and 30 mg olive oil containing 353 mg long-chain ω-3 fatty acids (132 mg EPA, 88 mg DHA); Omacor® contains ω-3 fatty acids in form of fatty-acid ethyl esters (46% EPA, 38% DHA); Percucor® contains 600 mg fat in the form of concentrated salmon oil with 60% EPA and DHA; and Omega 3 Supply® contains 850 mg fish oil with 30% EPA and DHA.

Fatty acids were analyzed according to the method described by Kang and Wang [24]. Briefly, aliquots (5 µl) of the samples were diluted 1:100 in hexane (Sigma Aldrich) and mixed with 1ml of hexane and 700 µl of 20% BF_3/MeOH reagent in a glass methylation tube. After blanketing with nitrogen, the mixture was methylated for 1 hour at 100 °C and then cooled to room temperature. Following the addition of 1 ml H_2O, fatty acid methyl esters were extracted in the hexane phase and centrifuged at 1770 g for 1 minute. The hexane

Table 1. Fatty acid composition in mol% of total fatty acid content within the analyzed supplements as determined by capillary gas chromatography

	Abtei®	Ameu®	Bilatin®	Biogelat®	Blubio®	Dr. Boehm®	Omacor®	Percucor®	Omega 3 Supply
	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD
Palmitic acid (C16:0)	21.4±2.06%	22.9±1.06%	24.2±1.19%	4.6±0.55%	20.3±2.07%	–	–	3.77±3.26%	18.4±1.80%
Palmitoleic acid (C16:1)	9.6±1.32%	10.7±0.55%	10.9±0.45%	–	10.3±1.12%	–	–	–	8.2±0.70%
Stearic acid (C18:0)	1.9±3.29%	2.0±3.41%	–	4.0±0.80%	3.7±3.36%	1.7±2.89%	–	2.73±2.37%	3.4±2.96%
Elaidic acid (C18:1 trans)	–	–	–	–	0.5±0.92%	–	–	–	–
Oleic acid (C18:1 cis)	26.4±3.70%	19.9±1.30%	19.5±0.55%	13.5±1.62%	17.1±4.23%	17.3±2.23%	–	11.53±3.10%	16.4±0.96%
Linoleic acid (C18:2)	–	–	–	6.6±0.72%	0.6±0.98%	4.1±3.52%	–	–	7.8±0.91%
Linolenic acid (C18:3)	–	–	–	27.5±2.80%	–	21.3±0.17%	–	–	–
EPA (C20:5)	16.93±1.44%	22.1±0.61%	23.7±1.71%	23.4±0.67%	23.3±3.15%	32.9±2.01%	53.8±0.25%	44.9±4.24%	20.5±0.99%
DPA (C22:5)	–	–	–	2.4±2.05%	0.8±1.33%	–	–	–	–
DHA (C22:6)	15.1±1.21%	13.9±0.23%	15.9±1.30%	16.1±0.15%	15.7±2.31%	22.7±1.32%	42.0±0.38%	31.9±2.87%	13.7±0.70%
LC ω-3 PUFA	32.0±1.33%	36.1±0.42%	39.6±1.51%	39.7±1.44%	39.0±3.39%	55.7±1.67%	95.8±0.32%	76.8±3.56%	34.2±0.85%
Others	8.7±7.58%	8.5±0.50%	5.8±5.05%	1.7±2.94%	7.7±7.85%	–	4.2±0.68%	5.2±4.69%	11.5±8.86%

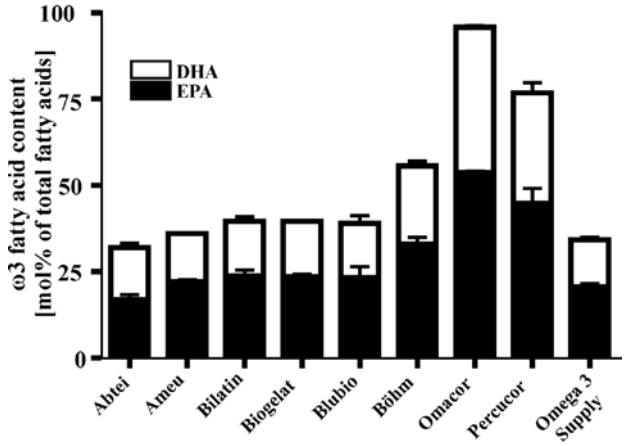

Fig. 1. EPA and DHA content in mol% of fatty acids contained (bars represent mean ± SD)

layer was removed and dried under N_2. Afterwards the esters were resuspended in 100 µl hexane and analyzed using capillary gas chromatography. An Agilent 6890N gas chromatography system (Agilent Technologies) equipped with an Agilent HP-88, 100 m × 25 mm, 0.2 µm column was used, and a 3 µl sample at an initial temperature of 240 °C and a split ratio of 25:1 was injected.

The recovery rate was monitored by adding 1 µg/ml tridecanoic acid (Fluka, Switzerland) as an internal standard at the beginning of the extraction procedure and peaks were identified by comparison with known fatty acid standards (Supelco, USA and Biotrend Chemicals, Germany). Our standard mixture included tridecanoic acid (C13:0), palmitic acid (C16:0), palmitoleic acid (C16:1), stearic acid (C18:0), elaidic acid (C18:1 trans), oleic acid (C18:1 cis), linoleic acid (C18:2), linolenic acid (C18:3), EPA (C20:5), docosapentaenoic acid (DPA, C22:5) and DHA (C22:6). All were analyzed at three different concentrations for calibration.

GC ChemStation software (rev. 10.02 [1757]) was used for data analysis and peak integration. The mean CV for detected fatty acids, as determined by repeated measures of a known fatty acid mix at each run, was 5.74 ± 3.62%. For the main fatty acids of interest, EPA and DHA, CV was 5.87% and 6.04% respectively. From each preparation, three capsules were extracted and analyzed. Percentages of fatty acid concentrations are given in mole percent.

SPSS 11.5 software was used for statistical analysis. One-way ANOVA was used for comparisons between groups. Since variances between groups were inhomogeneous as determined by the Levene test, Welch statistics were used. Accordingly, Dunnett's T3 was used for pairwise post hoc comparisons. To assess significant differences in the information supplied by the manufacturers, the stated EPA and DHA content for each preparation was set to one and the one sample t-test was used for comparisons with this reference value. The Spearman ρ correlation coefficient was determined to analyze parallels in fatty acid composition. Results are expressed as mean ± standard deviation; two-sided P values <0.05 were considered statistically significant.

Results

Using standards, we identified 94.1 ± 5.63% of the total peak area in the samples. As shown in Table 1 all preparations analyzed contained considerable amounts of long-chain ω-3 PUFA, with the highest percentage of EPA and DHA (95.80 ± 0.63%) and total amount of long-chain ω-3 fatty acids per capsule (958.0 ± 6.25 mg/capsule) present in Omacor®. Preparations differed widely from each other in percentage of EPA and DHA (Fig. 1; $P<0.001$). Pairwise comparisons of combined EPA and DHA content did not yield any significant difference between Abtei®, Ameu®, Bilatin®, Biogelat®, Blubio® and Omega 3 Supply®. Dr. Boehm® contained significantly higher percentages than Abtei® (mean difference: 23.63 ± 2.46%; $P=0.01$), Ameu® (19.60 ± 1.98%; $P=0.045$), Bilatin® (16.03 ± 2.59%; $P=0.043$) and Omega 3 Supply® (21.43 ± 2.14%; $P=0.022$) and lower amounts than Omacor® (–40.13 ± 1.96%; $P=0.011$). Omacor® differed significantly from all products except Percucor®, which also did not show significant differences from Dr. Boehm® but differed significantly from the rest of the preparations in that it contained more long-chain ω-3 PUFA.

Comparison with the manufacturers' information (Fig. 2) showed that four supplements (Abtei®, Ameu®, Dr. Boehm® and Percucor®) did not differ significantly from the concentrations given, four preparations held significantly more EPA and DPA than stated (Bilatin® 32.13 ± 10.04% higher content than denoted, Biogelat® 44.20 ± 2.94%, Omacor® 14.07 ± 0.74% and Omega 3 Supply® 14.10 ± 5.35%), and one manufacturer (Blubio®) did not declare the amount of long-chain ω-3 PUFA contained in their product. Regarding manufacturers' recommendations for daily intake, only one of the preparations (Ameu®) slightly exceeded the amount suggested by most health-care organizations by recommending ingestion of up to six capsules per day (1082.0 ± 24.98 mg EPA and DHA). Except for Omacor® and Percucor®, which only differed by 42.00 ± 6.25 mg and 78.4 ± 85.3 mg from the advised 1 g/d, all preparations lacked more than 30% EPA and DHA to meet AHA recommendations. Furthermore, two preparations, Blubio® (385.77 ± 54.05 mg) and Dr. Boehm® (440.88 ± 26.391 mg), failed to achieve the range of 0.5–1.8 g found to be effective in most studies. The ratio of DHA to EPA (DHA/EPA) was highest in Abtei® (0.89 ±

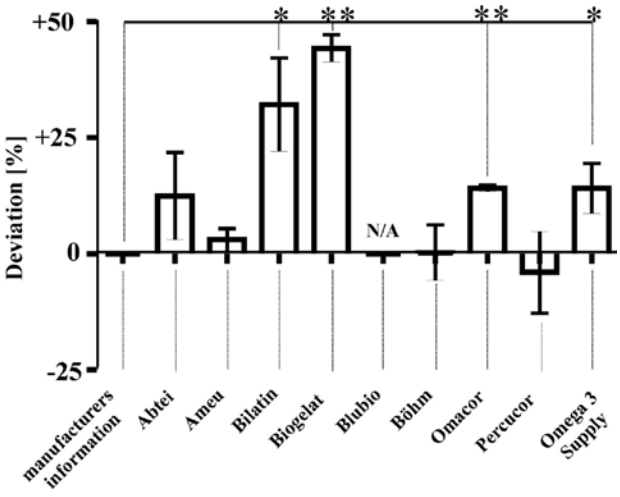

Fig. 2. Deviation from manufacturers' information on EPA and DHA content in percent (bars represent mean ± SD; $*P<0.01$, $**P<0.001$)

0.004) and the highest overall percentage of DHA was found in Omacor® (41.96 ± 0.38%). When correlating the fatty acid composition of the preparations, six of the products, Abtei®, Ameu®, Bilatin®, Blubio®, Percucor® and Omega 3 Supply®, showed a highly significantly correlating pattern regarding their fatty acid composition (mean r = 0.903 ± 0.07; mean $P < 0.001$).

Discussion

Our results show a huge variety in the content of long-chain ω-3 fatty acids in the preparations analyzed and even greater variation in the recommended daily intake. Consumption of the same amounts of fish-oil supplements may result in differences of up to 63.7% in long-chain ω-3 fatty acids. Furthermore, we found a similarity in the fatty acid composition of six preparations, probably because they all contain fish oil derived from salmon and, regarding the degree and significance of correlation, probably obtained from the same supplier. The difference in composition in Dr. Boehm® and Biogelat® can be explained by the addition of linseed and perilla oils respectively, whereas Omacor®, unlike any of the other products, undergoes an esterification and purification process that explains the difference in fatty acid composition. Most of the information from the manufacturers on long-chain ω-3 fatty acid content was confirmed by our results (Fig. 2), with all but one product containing equal or significantly greater amounts of EPA and DHA than denoted. For one product, Blubio®, the comparison could not be made since the manufacturer does not provide any information. Even when using the highest recommended dosage, all but one product failed to exactly reach the recommended 1 g/d EPA and DHA. The only manufacturer slightly exceeding the recommendations (Ameu®) suggests consumption of 1–2 capsules three times a day, which led us to calculate six capsules per day as the suggested total intake. Seven of the preparations were found to be within a range considered therapeutically effective in secondary prevention studies [20] when consuming the highest amount recommended by the manufacturer, but two supplements failed to achieve even the lower limit of AHA recommendations (0.5 g/d) [20].

Table 2. Manufacturers' advice on daily intake and number of capsules needed to reach the daily dose of 1 g long-chain ω-3 PUFA as recommended for secondary CHD prevention in the AHA's scientific statement [20]

	Highest recommended dosage	Dosage needed to reach AHA recommendation	SD
Abtei®	1	3.14	±0.25
Ameu®	6	5.55	±0.13
Bilatin®	3	5.06	±0.37
Biogelat®	2	3.08	±0.09
Blubio®	2	5.25	±0.73
Böhm®	2	4.55	±0.28
Omacor®	1	1.04	±0.01
Percucor®	2	2.17	±0.19
Omega 3 Supply®	2	3.44	±0.17

One of the preparations analyzed (Dr. Boehm®) contained considerable amounts of α-linoleic acid (ALNA) derived from linseed oil, possibly as a source for endogenous conversion into EPA and DHA. The existence of such a pathway has been demonstrated in rodents [25]. The conversion involves sequential desaturation and C-chain elongation to form EPA and DPA, with further elongation leading to the formation of DHA. However, studies addressing the question of bioconversion of ALNA to EPA and DHA have concluded that in adult men conversion to EPA is limited: results range from 8% [26] to 0.2% [27] and conversion to DHA is extremely low (<0.01%) [28]. Even high daily doses (9.5 g/d) of ALNA have no effect on plasma EPA and DHA levels, whereas such effects are seen in low (0.8 g/d) doses of EPA and DHA [29]. Data on the capability of ALNA to evoke beneficial effects in the manner of EPA and DHA are inconsistent [9], therefore it is doubtful whether the addition of linseed oil has any beneficial effects.

Although oleate and DHA appear to compete for different lipid pools and may act additively, the benefit of adding olive oil to a preparation is also uncertain, since oleic acid is not essential, the body having the ability to synthesize limited amounts endogenously. Further, olive oil is abundant in a wide variety of foods found in western diet. Similar considerations apply to the addition of soybean or perilla oil to Omega 3 Supply and Omega 3 Duo respectively.

Since many effects seem to be more pronounced with DHA than with EPA [30], we determined which preparation had the highest ratio of DHA to EPA. This was found to be Abtei®, and the highest percentage and total amount of DHA was found in Omacor®.

Omacor's standard deviation was the lowest, which most probably results from its different manufacturing process. Also, its form of administration as ethyl esters differs from all other supplements, which all deliver long-chain ω-3 fatty acids in the form of acylglycerols, and results in a delayed and more continuous absorption of fatty acids, as has been shown in animal models [31].

The addition of α-tocopherol to most preparations is mainly for preservational purposes as an antioxidant and, as shown in the GISSI study [3], does not appear to contribute to the mechanism of action of long-chain ω-3 fatty acids in reducing cardiovascular mortality.

Conclusions

Whereas most preparations tested show similar long-chain ω-3 PUFA acid composition, there are considerable differences in four of the supplements (Biogelat®, Dr. Boehm®, Omacor®, and Percucor®). Omacor® contains long-chain ω-3 fatty acids in their purest form and has the highest total amount of DHA, which apparently is superior to EPA as an active agent in reducing the incidence of arrhythmic events.

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