Journal of Nutrition and Health (J Nutr Health) 2013; 46(3): 226 ~ 238 pISSN 2288-3886 / eISSN 2288-3959
http://dx.doi.org/10.4163/jnh.2013.46.3.226

건강기능식품의 기능성을 중심으로 한 오메가-3 지방산 함유유지의 혈행개선 효과에 대한 체계적 고찰*

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Systematic review of the effect of omega-3 fatty acids on improvement of blood flow while focused on evaluation of claims for health functional food*

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ABSTRACT

Omega-3 polyunsaturated fatty acids are essential fatty acids because humans cannot synthesize them de novo and must obtain them in their diet. Fish and fish oil are rich sources of omega-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Significant evidence of the beneficial role of dietary intake of omega-3 fatty acids in blood flow has been reported and putative mechanisms for improvement of blood flow include anti-thrombotic effects, lowered blood pressure, improved endothelial function, and anti-atherogenic effects. Edible oils containing omega-3 fatty acids were registered as functional ingredients in the Korea Health Functional Food Code. Although omega-3 fatty acids have been evaluated by the Korea Food and Drug Administration (KFDA) based on scientific evidence, periodic re-evaluation may be needed because emerging data related to omega-3 fatty acids have accumulated. Therefore, in this study, we re-evaluated scientific evidence for the effect of omega-3 fatty acids as a functional ingredient in health functional food on improvement of blood flow. A comprehensive literature search was conducted for collection of relevant human studies using the Medline and Cochrane, KISS, and IBIDS databases for the years 1955−2012. Search keywords were used by combination of terms related to omega-3 fatty acids and blood flow. The search was limited to human studies published in Korean, English, and Japanese. Using the KFDA's evidence based evaluation system for scientific evaluation of health claims, 112 human studies were identified and reviewed in order to evaluate the strength of the evidence supporting a relation between omega-3 fatty acids and blood flow. Among 112 studies, significant effects on improvement of blood flow were reported in 84 studies and the daily intake amount was ranged from 0.1 to 15 g. According to this methodology of systematic review, we concluded that there was possible evidence to support a relation between omega-3 fatty acid intake and blood flow. However, because inconsistent results have recently been reported, future studies should be monitored. (J Nutr Health 2013; 46(3): 226 ~ 238)

KEY WORDS: systematic review, omega-3 fatty acids, blood flow, DHA, EPA, health functional food, re-evaluation.

서 론

오메가-3 지방산은 주로 식품을 통해 공급받을 수 있는 필수 지방산으로서 eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA)를 포함한다. 비록 EPA와 DHA의 전구체인 α-linolenic acid를 섭취할 경우 체내에서 EPA와 DHA가 합성되기는 하나 성인에서 α-linolenic acid가 DAH와 EPA로 전환되는 효율은 약 10~15 %, 어린이는 3~6%로 매우 낮기 때문에 DHA와 EPA가 풍부한 식품을 직접 섭취하는 것이 효과적

Received: Apr 9, 2013 / Revised: May 1, 2013 / Accepted: Jun 17, 2013
*This work was supported by grants of Korea Food and Drug Administration (12162-KFDA-036).
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인 것으로 알려져 있다.[1,2] 여러 연구들에 따르면 오메가-3 지방산이 혈전생성 억제, 죽상동맥경화를 유발시킬 수 있는 플라그의 생성 억제, 내피세포의 이완 촉진 등 혈행개선에 도움을 주는 것으로 보고되고 있으며,[3,4] 2004년부터 2007년까지 4년간 수행된 식품의약품안전처 고시형 건강기능식품 재평가 사업에서 EPA/DHA 함유제품의 경우 문헌검토만으로도 기능성에 대한 충분한 과학적 근거가 있다는 것이 확인된 바 있다. 하지만 재평가 사업 이후 새로운 연구들이 지속적으로 보고되고 있으며 특히 일부 인체적용시험에서는 오메가-3 지방산의 섭취가 혈행개선에 영향을 미치지 않는 것으로 보고되고 있어 최근의 연구 결과들을 포함하여 오메가-3 지방산의 혈행개선 기능성에 대해 재평가할 필요성이 있겠다. 이는 기능성 재평가에 대한 국제적 기류에 부합되는 것으로, 미국 FDA에서는 기평가된 health claim이나 qualified health claim의 재평가 필요성에 대해 Guideline에 언급하고 있으며,[5] 국제식품규격위원회 (Codex)에서도 기능성 표시의 재평가 필요성을 "Guidelines for use of nutrition and health claims-recommendations on the scientific substantiation of health claims"에서 강조하고 있다.[6]

따라서 본 연구에서는 식품의약품안전처에서 사용하고 있는 과학적 근거 중심의 체계적 고찰방법을 인체적용시험에 적합하도록 일부 변경하여 오메가-3 함유유지의 혈행개선 기능성에 대해 재평가를 수행하였다.

연구방법

문헌검색

문헌검색은 2012년 5월 31일까지 출판된 문헌을 대상으로 실시하였다. 국외 문헌 검색은 Pubmed, Cochrane, IBIDS (International Bilbliographic Information on Dietary Supplements)을 이용하였고 국내 문헌은 KISS (Koreanstudies Information Service System)을 이용하여 검색하였다. 사용된 검색어는 오메가-3 지방산 관련 검색어 omega-3, DHA, EPA, eicosapentaenoic acid, docosahexaenoic acid와 혈행 관련 검색어 coagulation, platelet aggregation, prothrombin, thrombosis, blood flow, thrombotic, 혈행, 혈액응고를 조합하여 사용하였다. 문헌은 검색을 실시한 2012년 5월 31일까지 출판된 문헌만을 검토하였다.

이번 체계적 문헌고찰에 포함된 문헌 선정 기준은 다음과 같다: 1) 인체를 대상으로 한 인체적용시험, 2) 오메가-3 지방산 함유 유지의 혈행 개선효과를 평가한 연구, 3) 오메가-3 지방산 함유 유지를 경구로 섭취한 연구. 연구 제외기준은 다음과 같다: 1) 시험관시험 및 동물시험, 2) 경구 섭취 연구가 아닌 연구, 3) 섭취량, 섭취기간 등의 시험 관련 정보가 부재한 연구, 4) 오메가-3 지방산 함유 유지를 섭취하였으나 다른 성분들과 함께 섭취한 복합물 이용 연구, 5) 학회 초록이나 총설, 6) 한국어, 영어, 일본어 이외의 언어로 게재된 문헌. 자료의 추출과 1차 문헌 선정은 초록의 제목 혹은 전문을 보고 선정하였으며, 체계적 문헌 고찰의 경험이 많은 영양학 전문가가 각기 시행하여 Endnote와 Excel에 정리하여 중복된 문헌을 검색하여 제외하였다 (Fig. 1).

자료의 평가 방법

선정된 문헌에 대하여는 시험물질, 표준화 여부, 연구설계, 피험자, 피험자에 대한 기본 정보 제공 여부, 피험자수 산출 방법의 적절성, 피험자 선정 및 제외 기준에 대한 설명, 시험기간, 섭취량, 섭취 방법, 기초식이 조절, 생활습관의 조절, 탈락율, 통계분석, 결과 해석, 혼동요인 보정 여부 등의 항목으로 구분하여 질 평가를 실시하였다. 연구의 질 평가 방법은 식품의약품안전청에서 사용하고 있는 질평가 도구[7]에 FDA 평가 가이드라인[5]을 참조하여 변형된 방법을 이용하였다. 이 도구는 총 27개 문항으로 되어 있으며 각 항목당 질평가 점수는 -1점에서 1점 사이로 산출된다. 자료의 종합평가는 식품의약품안전처에서 사용하고 있는 방법을 사용하였다. 오메가-3 지방산 함유유지의 혈행개선 기능성을 연구한 자료의 양, 결과의 일관성, 활용성을 모두 고려하여 종합적으로 검토하였다.

결 과

문헌검색 결과

문헌검색을 통해서 검색된 논문은 총 4,486건이었다. 연구제목과 초록, 원문검토를 통해 오메가-3 지방산 함유유지의 기능성과 관련이 없는 문헌이 986건, 생체 외 실험이나 동물시험 등의 기반연구가 204건, 시험 관련한 정보가 부족한 문헌이 67건, 복합물의 기능성을 확인한 연구가 34건, 경구투여가 아닌 근육주사 또는 정맥주사 등의 경로로 오메가-3 지방산 함유유지를 투여한 연구가 18건, 초록 등의 2차 문헌이 417건, 한국어, 일본어, 영어 이외의 언어로 작성된 문헌이 49건으로 총 4117건의 문헌이 검토에서 제외되었다. 결과적으로 총 158편 (한 개 논문에서 2건 이상의 연구를 수행한 경우가 있어 연구 건수로는 총 164건)의 문헌이 오메가-3 지방산 함유유지의 혈행개선 기능성 검토에 사용되었다 (Fig. 1).

자료의 평가

164건의 연구 중 낮은 평가를 받은 52건의 연구는 본 연구에서 제외하였다. 112건[8-115]의 연구는 모두 중재연구로서 88건이 무작위배정 대조군 비교 연구 (RCT)였고, 무작위 배정이 아

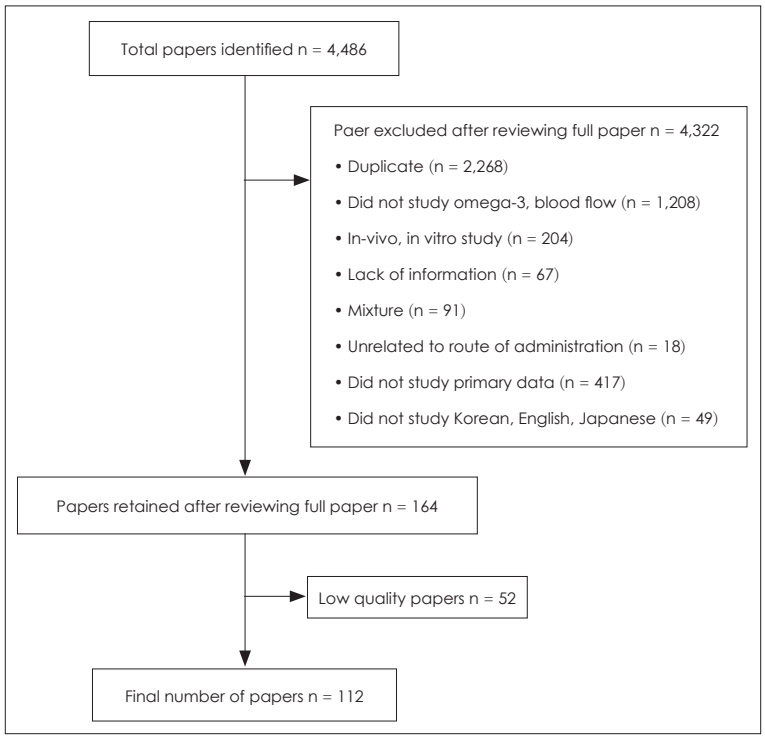

Fig. 1. Flow diagram of included and excluded studies.

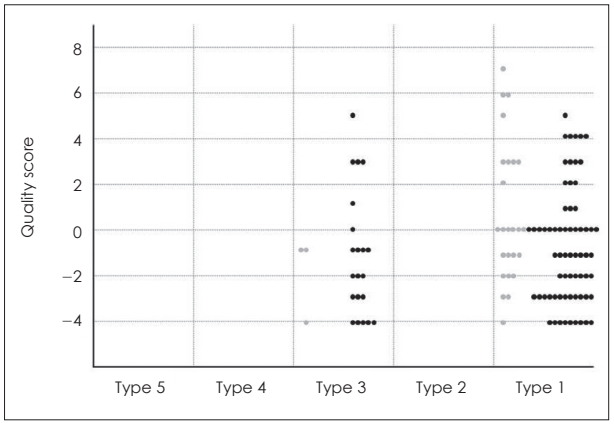

Fig. 2. Evidence table of systematic review for omega-3 fatty acids and effects on improvement of blood flow (Type 1, RCT; Type 2, Cohort study; Type 3, non-RCT/case-control study etc; Type 4, animal study; Type 5, in vitro study; ●, significant improvement in the blood flow-related biomarkers; ●, no significant improvement in the blood flow-related biomarkers).

닌 연구 24건 중 17건[22-24,31,48,49,51-53,55,83-86,107-109]은 질 평가 결과 −1~−4점으로 점수가 낮았다 (Fig. 2). 총 112건 (5,536명) 중 84건 (3,910명)[8-18,20-79,81-86,112-114]의 연구에서 오메가-3 지방산 함유유지의 섭취로 인해 통계적으로 유의하게 혈행개선 효과가 나타났다 ($p < 0.05$). 또한 유의한 효과를 나타낸 84건의 연구 중 33건의 연구 (1,665명)[33,44,56-79,81-83,85,86]에서는 대조군과 섭취군간의 군간 차이를 보였으며, 대상자는 대부분 건강한 성인, 노인, 지질수준이 높은 사람들이었다. 질평가 점수 분포를 보면 평균 점수는 −0.48점 (−4~7점)으로 0점 이상의 높은 점수를 받은 50건의 연구들 중 유의한 개선효과를 보인 연구결과는 36건이었다. 총 112건의 연구 중 환자 대상 연구 52건 (2,980명)을 제외하고 건강한 성인을 대상으로 한 60건 (2,824명)의 연구를 검토한 결과 48건 (1,934명)의 연구[8-11,16,18,20,21,23-28,30-32,37-40,44-47,49,50,52-57,62-65,68,70,76,78,83,85,86,112,114]에서 통계적으로 유의한 개선효과를 보였다 ($p < 0.05$)(Table 1).

오메가-3 지방산의 일일 섭취량에 따른 연구 결과

유의한 개선 효과를 보인 연구에서 오메가-3 지방산 함유 유지의 섭취기간은 단회에서 2년까지였으며, 일일 섭취량은 0.1~15 g으로 건강기능식품공전에서 제시된 섭취량 기준 (0.5~2 g)에 포함되는 연구가 23건 (1,499명),[8,10-12,14,25,30,36,41,42,52,55,57,58,62,64,65,68,69,72,76,78,82] 기준 보다 낮은 경우가 5건 (114명),[28,39,47,49,61] 기준보다 높은 경우가 56건 (2,297명)[9,13,15-18,20-24,26,27,29,31-35,37,38,40,43-46,48,50,51,53,54,56,59,60,63,66,67,70,71,73-75,77,79-81,83-86,112-114]이었다 (Fig. 3). 오메가-3 섭취로 인한 심각한 부작용사례는 보고되지 않았다.

오메가-3 지방산 함유유지의 순도에 따른 결과

오메가-3 지방산 함유유지의 순도 (purity)를 저순도 (low purity)와 고순도 (high purity)로 구분하여 연구결과를 분석하였다. 순도가 낮은 오메가-3 지방산 함유유지를 사용한 연구가 98건으로 유의한 개선효과가 관찰된 연구가 72건이었으며, 고순도 오메가-3 지방산 함유유지를 사용한 14건의 연구 중에는 12건의 연구에서 유의한 개선효과가 나타났다 (Fig. 4).

Table 1. Characteristics of studies included for systematic review

Reference	Study type[1]	Target	Subject No.	Purity[2]	Dose (g)	Result[3]	Quality score
Baldassarre et al. 2006[8]	RCT	Healthy	64	Low	1.8	+	5
Blonk et al. 1990[9]	RCT	Healthy	45	Low	1.5, 3.0	+	3
Engler et al. 2004[10]	RCT	Healthy	20	High	1.2	+	−1
Fahs et al. 2010[11]	RCT	Healthy	20	High	0.9	+	−2
Finnegan et al. 2003[12]	RCT	Patients	150	Low	0.7, 1.5	+	−2
Green et al. 1990[13]	RCT	Patients	27	Low	4.32	+	−4
Grundt et al. 2004[14]	RCT	Patients	300	Low	0.882	+	0
Herrmann et al. 1995[15]	RCT	Patients	53	Low	9.12	+	4
Park et al. 2002[16]	RCT	Healthy	33	High	4	+	−3
Passfall et al. 1993[17]	RCT	Patients	12	Low	2.16	+	−1
Prisco et al. 1995[18]	RCT	Healthy	20	Low	3.44	+	2
Møller et al. 1992[19]	RCT	Healthy	40	Low	1.06	Ø	−3
Freese et al. 1997[20]	Non-RCT	Healthy	46	Low	5.2	+	0
Piolot et al. 2003[21]	Non-RCT	Healthy	32	Low	3	+	1
Rillaerts et al. 1989[22]	Non-RCT	Patients	12	Low	2.7	+	−2
Walser et al. 2006[23]	Non-RCT	Healthy	13	Low	5	+	−2
Haglund et al. 1990[24]	Non-RCT	Healthy	20	Low	4.5 mL	+	−3
Agren et al. 1988[25]	RCT	Healthy	62	Low	0.8	+	−1
Andrioli et al. 1999[26]	RCT	Healthy	60	Low	3.6	+	−4
Bach et al. 1989[27]	RCT	Healthy	30	Low	1.26, 2.52	+	−4
Coates et al. 2009[28]	RCT	Healthy	33	Low	0.2	+	4
Derosa et al. 2009[29]	RCT	Patients	333	High	3	+	4
Mann et al. 2010[30]	RCT	Healthy	30	Low	0.79, 1.02	+	0
Mann et al. 1997[31]	Non-RCT	Healthy	29	Low	2.894	+	−2
Mesa et al. 2004[32]	RCT	Healthy	42	Low	5.5, 5.7	+	−3
Mori et al. 1992[33]	RCT	Patients	32	Low	4.6	+	0
Myrup et al. 2001[34]	RCT	Patients	36	Low	2, 2.6	+	−2
Schmidt et al. 1988[35]	RCT	Patients	36	Low	4.5	+	−3
Serebruany et al. 2011[36]	RCT	Patients	30	Low	0.84, 1.62	+	−3
Tremoli et al. 1995[37]	RCT	Healthy	16	Low	2.25	+	−3
Tremoli et al.1994[38]	RCT	Healthy	29	Low	2.25	+	0
Véricel et al. 1999[39]	RCT	Healthy	20	Low	0.18	+	−1
von Schacky et al. 1985[40]	RCT	Healthy	7	High	6	+	−3
Westerveld et al. 1993[41]	RCT	Patients	24	High	0.9, 1.8	+	0
Woodcock et al. 1984[42]	RCT	Patients	19	Low	1.8	+	−4
Wright et al. 2008[43]	RCT	Patients	60	High	3	+	1
Zucker et al. 1988[44]	RCT	Healthy	9	Low	5.4	+	0
Zucker et al. 1988[44]	Non-RCT	Patients	6	Low	5.4	+	0
Zucker et al. 1988[44]	RCT	Patients	10	Low	5.4	+	0
Toft et al. 1997[45]	RCT	Healthy	78	Low	3.4	+	3
Cobiac et al. 1991[46]	Non-RCT	Healthy	31	Low	4.5	+	3
Croset et al. 1990[47]	Non-RCT	Healthy	16	High	0.1	+	5
De Caterina et al. 1993[48]	Non-RCT	Patients	14	Low	3.77	+	−1
Driss et al. 1984[49]	Non-RCT	Healthy	19	Low	0.15	+	−3
Grundt et al. 1999[50]	RCT	Healthy	57	Low	3.4	+	−1
Landgraf-Leurs et al. 1990[51]	Non-RCT	Patients	13	Low	7.7	+	−4
Okumura et al. 2002[52]	Non-RCT	Healthy	15	Low	1.8	+	−4
von Schacky et al. 1985[53]	Non-RCT	Healthy	6	Low	4.64 mL	+	−2

Table 1. Continued

Reference	Study type[1]	Target	Subject No.	Purity[2]	Dose (g)	Result[3]	Quality score
Sanders et al. 1983[54]	RCT	Healthy	5	Low	1.63, 3.28, 6550	+	−4
Sanders et al. 1983[54]	RCT	Healthy	5	Low	5.96 mL	+	−4
Haglund et al. 1994[55]	Non-RCT	Healthy	12	Low	0.96	+	−3
Fumeron et al. 1991[56]	RCT	Healthy	36	Low	6	+	−4
Goyens et al. 2006[57]	RCT	Healthy	37	Low	1.6	+	3
Green et al. 1985[58]	RCT	Patients	18	Low	1.8	+	0
Hansen et al. 1993[59]	RCT	Patients	31	Low	3.4, 3.6	+	0
Hendra et al. 1990[60]	RCT	Patients	80	Low	3	+	0
Pirich et al. 1999[61]	RCT	Patients	26	Low	0.354	+	1
Rizza et al. 2009[62]	RCT	Healthy	50	Low	1.7	+	0
Vognild et al. 1998[63]	RCT	Healthy	266	Low	3.45 mL	+	−1
Phang et al. 2012[64]	Non-RCT	Healthy	30	High	2	+	3
Phang et al. 2012[65]	Non-RCT	Healthy	30	High	2	+	3
Axelrod et al. 1994[66]	RCT	Patients	20	Low	2.6	+	−1
Berrettini et al. 1996[67]	RCT	Patients	40	Low	2.58	+	2
Flaten et al. 1990[68]	RCT	Healthy	64	Low	1.4	+	−3
Haberka et al. 2011[69]	RCT	Patients	40	Low	0.84	+	−3
Honstra et al. 1990[70]	RCT	Healthy	84	Low	4.7	+	−4
Lau et al. 1995[71]	RCT	Patients	45	Low	2.8	+	−2
Lindman et al. 2004[72]	RCT	Patients	219	Low	1.44	+	−2
McVeigh et al. 1994[73]	RCT	Patients	20	Low	3	+	−3
Mehta et al. 1988[74]	RCT	Patients	8	Low	5.4	+	0
Moertl et al. 2011[75]	RCT	Patients	49	Low	0.882, 3.528	+	−1
Mori et al. 1997[76]	RCT	Healthy	138	Low	0.8, 1.6	+	2
Solomon et al. 1990[77]	RCT	Patients	10	Low	4.6	+	0
Wensing et al. 1999[78]	RCT	Healthy	67	Low	1.2	+	−1
Woodman et al. 2003[79]	RCT	Patients	59	High	4	+	1
Grundt et al. 2003[80]	RCT	Patients	300	Low	0.882	Ø	−3
Johansen et al. 1999[81]	RCT	Patients	54	Low	2.42	+	−4
Krishnan et al. 2007[82]	RCT	Patients	60	Low	0.6	+	−4
Brox et al. 1981[83]	Non-RCT	Healthy	10	Low	25 mL	+	−4
Mehta et al. 1988[84]	Non-RCT	Patients	8	Low	5.4	+	−4
Nordøy et al. 1994[85]	Non-RCT	Healthy	6	Low	4.86	+	−1
Wojenski et al. 1991[86]	Non-RCT	Healthy	9	High	3, 4	+	−1
Agren et al. 1997[87]	RCT	Healthy	55	Low	1.05, 1.68, 2.28	Ø	0
Almdahl et al. 1993[88]	RCT	Patients	18	Low	5.04	Ø	−2
Conquer et al. 1996[89]	RCT	Healthy	24	Low	1.62	Ø	5
Conquer et al. 1999[90]	RCT	Healthy	20	Low	3	Ø	6
Demke et al. 1988[91]	RCT	Patients	31	Low	1.7	Ø	3
Donnelly et al. 1992[92]	RCT	Patients	16	Low	1.08	Ø	3
Gajos et al. 2011[93]	RCT	Patients	54	Low	0.84	Ø	−1
Goodfellow et al. 2000[94]	RCT	Patients	28	Low	1.7	Ø	0
Grundt et al. 2003[95]	RCT	Patients	300	Low	0.882	Ø	−2
Hagve et al. 1993[96]	RCT	Healthy	16	Low	5.1	Ø	−4
Haines et al. 1986[97]	RCT	Patients	41	Low	4.6	Ø	−2
Hellsten et al. 1993[98]	RCT	Healthy	41	Low	2	Ø	−1
Montegaard et al. 2010[99]	RCT	Patients	8	Low	0.74, 3.84	Ø	−3
Neff et al. 2011[100]	RCT	Healthy	49	Low	2	Ø	0

Table 1. Continued

Reference	Study type[1)]	Target	Subject No.	Purity[2)]	Dose (g)	Result[3)]	Quality score
Nilsen et al. 1991[101)]	RCT	Patients	20	Low	5.04	Ø	−1
Poppitt et al. 2009[102)]	RCT	Patients	102	Low	1	Ø	2
Prisco et al. 1994[103)]	RCT	Healthy	20	Low	3.44	Ø	3
Saifullah et al. 2007[104)]	RCT	Patients	27	Low	0.671	Ø	6
Sanders et al. 2011[105)]	RCT	Healthy	367	High	0.45, 0.9, 1.8	Ø	7
Sirtori et al. 1992[106)]	RCT	Patients	12	Low	4.5	Ø	−1
DeCaterina et al. 1990[107)]	Non-RCT	Patients	30	Low	4.3	Ø	−1
Din et al. 2008[108)]	Non-RCT	Healthy	28	Low	0.7	Ø	−1
Nelson et al. 1997[109)]	Non-RCT	Healthy	12	Low	6	Ø	−4
Boberg et al. 1992[110)]	RCT	Patients	14	Low	3	Ø	0
Park et al. 2009[111)]	RCT	Healthy	158	Low	0.135, 0.27, 0.54	Ø	0
Brox et al. 2001[112)]	RCT	Healthy	120	Low	2.6, 3.3	+	3
Brox et al. 1983[113)]	RCT	Patients	17	Low	30 mL	+	−2
Hwang et al. 1997[114)]	RCT	Healthy	32	Low	9	+	4
Hwang et al. 1997[114)]	RCT	Healthy	36	Low	6, 15	+	4
Gajos et al. 2010[115)]	RCT	Patients	63	High	0.84	Ø	3

1) RCT: randomized clinical trial 2) Low: purity < 90%, high: purity ≥ 90% 3) +: significant improvement in blood flow-related biomarkers, Ø: no significant improvement in blood flow-related biomarkers

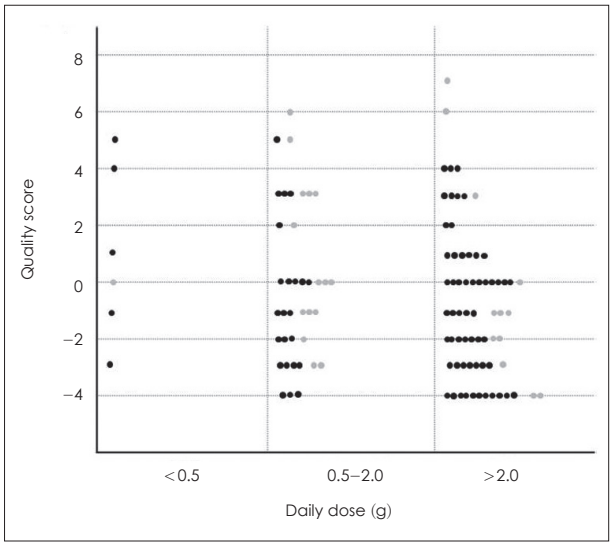

Fig. 3. Effects of omega-3 fatty acids on improvement of blood flow according to daily dose (●, significant improvement in the blood flow-related biomarkers; ●, no significant improvement in the blood flow-related biomarkers).

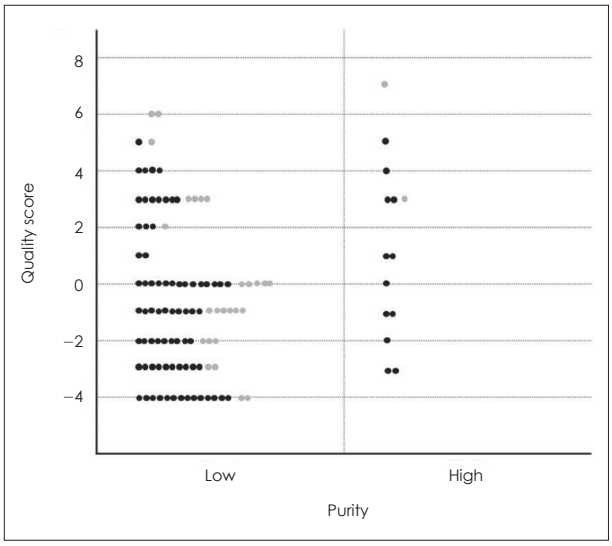

Fig. 4. Effects of omega-3 fatty acids on improvement of blood flow according to purity (Low: purity <90%; high: purity ≥ 90%; ●, significant improvement in the blood flow-related biomarkers; ●, no significant improvement in the blood flow-related biomarkers).

재평가 이후 출판된 연구들의 결과

오메가-3 지방산 함유유지의 건강기능식품 개별인정등록 이후에 출판된 연구 결과를 검토한 결과 2007년 이후 발표된 연구는 총 21건 (2007년 2건, 2008년 2건, 2009년 5건, 2010년 4건, 2011년 6건, 2012년 2건)[11,28-30,36,43,62,64,65,69,75,82,93,99,100,102,104,105,108,111,115]으로 이 중 12건의 연구 (765명)[11,28-30,36,43,62,64,65,69,75,82]에서 통계적으로 유의한 혈행개선 효과가 나타났으며 ($p < 0.05$), 9건의 연구 (856명)[93,99,100,102,104,105,108,111,115]에서는 개선효과가 관찰되지 않았다.

고 찰

건강기능식품의 기능성은 근거중심평가방법에 의해 평가시점에서의 모든 연구결과들을 종합하여 평가한다. 체계적 고찰방법이라고도 불리는 이 방법은 연구자의 편견이나 견해를 최대한 배제하여 좀 더 객관적이고 정확하게 현재까지의 연구결과들을 종합할 수 있다는 장점이 있다. 하지만 체계적 고찰방

법에 의해 평가되는 경우에도 평가된 시점 이후 새로운 과학적 증거들이 보고된다면 이에 기반한 재평가가 다시 수행되어야 할 것이다. 따라서 본 연구에서는 오메가-3 지방산 함유유지의 혈행개선 기능성을 재평가하기 위해 식약청에서 기능성 평가에 사용하고 있는 방법을 인체적용시험의 평가에 적합하도록 일부 보완한 체계적인 고찰 방법으로 재평가를 실시하였다. 문헌검색을 통해 총 112건의 연구를 선별하였고 각각의 연구에 대하여 질평가를 수행하였다. 질평가는 피험자, 시험디자인, 혼동요인, 순응도, 표준화된 시험물질 사용 여부, 측정한 바이오마커, 통계분석 방법의 항목에 대해 구분한 후 실시하였다. 개별평가에 따라 질평가 점수가 낮았던 52건[24,55,116-165]의 연구는 이후의 평가에서 제외되었다. 질평가 점수가 낮았던 연구들은 대부분 피험자의 선정/제외 기준에 대한 설명이 없거나, 무작위배정이 아니거나, 기초 식이조사를 실시하지 않은 등 시험 설계와 관련하여 중요한 정보가 기재되어 있지 않은 연구들 이었다

총 112건 연구 중 84건[8-18,20-79,81-86,112-114]에서 유의한 혈행개선 효과가 확인되었으며 피험자 수로 환산하면 총 5,804명의 피험자 중 2/3가 넘는 3,910명의 연구에서 오메가-3 지방산 함유유지 섭취로 유의한 혈행개선 효과가 나타난 것으로 평가되었다 ($p < 0.05$). 유의하게 개선된 바이오마커를 보면 bleeding time, platelet adhesion, platelet aggregation, thromboxane A2, plasma fibrinogen level, platelet count 등으로 확인되었다. 또한 건강인을 대상으로 한 60건의 연구를 분석한 결과에서는 2/3 이상인 48건의 연구 결과에서 유의한 혈행개선 효과를 보임이 확인되었다.

오메가-3 지방산의 일일 섭취량은 0.1~15 g으로 유의한 개선효과를 보인 연구들을 보면 건강기능식품공전에서 제시된 섭취량 기준 (0.5~2 g)에 포함되는 연구가 23건 (1,499명), 기준 보다 낮은 경우가 5건 (114명), 기준보다 높은 경우가 56건 (2,297명)[9,13,15-18,20-24,26,27,29,31-35,37,38,40,43-46,48,50,51,53,54,56,59,60,63,66,67,70,71,73-75,77,79-81,83-86,112-114]이었다. 오메가-3 지방산 함유유지의 순도에 따라 층화분석한 결과 저순도 (low purity) 오메가-3 지방산 함유유지를 사용한 98건의 연구 중 72건에서 유의한 결과가 관찰되었으며, 고순도 (high purity) 함유유지를 사용한 14건의 연구 중 12건에서 유의적인 개선효과가 나타났다.

오메가-3 지방산 함유유지가 건강기능식품으로 인정받은 이후에 출판된 논문들만을 분석한 결과에서도 총 21건[11,28-30,36,43,62,64,65,69,75,82,93,99,100,102,104,105,108,111,115] 중 12건의 연구[11,28-30,36,43,62,64,65,69,75,82]에서 통계적으로 유의한 혈행개선 효과가 나타났으며, 개선효과가 없었던 연구를 보면 시험식품을 단회투여한 연구가 1건,[99] 혈행개선에 적합하지 않은 대상자에게서 효과를 확인한 연구가 3건,[93,102,104] 대상자의 특성을 파악할 수 없는 연구가 1건,[115] 피험자들의 식이조절이 잘 이루어지지 않은 연구가 3건[83,102,111]이었다. 이들 연구들은 본 연구에서 실시하는 오메가-3 지방산 함유 유지의 혈행개선 기능 재평가 결과에 영향을 주지는 않았으나 오메가-3 지방산 함유유지의 혈행개선 기능성에 대한 일관성을 약화시켰으므로 향후 연구 결과 추이를 지켜볼 필요가 있을 것으로 판단된다.

요약 및 결론

오메가-3 지방산 함유유지의 혈행개선 기능성을 건강기능식품 재평가 기준에 맞추어 체계적 고찰을 실시하였다. 2012년 5월 기준 DB 검색을 통해 4,486건의 자료를 수집하여, 선정/제외 기준에 따라 선별한 결과 총 112건의 연구가 평가되었다. 112건 (5,804명) 중 84건 (3,910명)의 연구에서 통계적으로 유의한 개선 효과 나타났으며 ($p < 0.05$), 일일 섭취량은 0.1~15 g으로 공전에서 제시되어 있는 섭취량 (0.5~2 g) 기준을 포함하였다. 건강인을 대상으로 한 60건의 연구를 검토한 결과 48건의 연구에서 유의한 개선 효과를 보였다. 이들 문헌 중 건강기능식품 개별인정 등록 후 발표된 연구는 21건으로서 종합평가에 의하면 오메가-3 지방산 함유유지 섭취는 혈행개선 기능성을 나타낼 수 있는 것으로 판단되었다. 따라서 현재시점에서 건강기능식품인 오메가-3 지방산 함유유지의 혈행개선 기능성은 인정될 것으로 판단되나 일부 연구에서 개선효과가 없는 것으로 보고되고 있으므로 향후 연구결과 추이를 지속적으로 지켜볼 필요가 있을 것이다.

Literature cited

1) Yamada M, Omata K, Abe F, Ito S, Abe K. Changes in prostacyclin, thromboxane A2 and F2-isoprostanes, and influence of eicosapentaenoic acid and antiplatelet agents in patients with hypertension and hyperlipidemia. Immunopharmacology 1999; 44 (1-2): 193-198
2) Holub BJ. Clinical nutrition: 4. Omega-3 fatty acids in cardiovascular care. CMAJ 2002; 166(5): 608-615
3) Kris-Etherton PM, Harris WS, Appel LJ; Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Arterioscler Thromb Vasc Biol 2003; 23(2): e20-e30
4) Connor WE. Importance of n-3 fatty acids in health and disease. Am J Clin Nutr 2000; 71(1 Suppl): 171S-175S
5) U.S. Food and Drug Administration. Guidance, compliance, & regulatory information. Silver Spring (MD): U.S. Food and Drug Administration; 2009 [cited 2012 Dec 27]. Available from: http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm073332.htm
6) Joint FAO/WHO Codex Alimentarius Commission; World Health Organization; Food and Agriculture Organization of the United Nations. Guidelines for use of nutrition and health claims (CAC/GL 23-1997, Rev. 1-2004). Rome: Food and Agriculture Or-

ganization of the United Nations; 2004 [cited]. Available from: http://std.gdciq.gov.cn/gssw/JiShuFaGui/CAC/CXG_023e.pdf
7) Ministry of Food and Drug Safety. Regulation for evaluation on efficacy of health functional food. Cheongwon: Ministry of Food and Drug Safety; 2012 [cited 2012 Dec 27]. Available from: http://www.foodnara.go.kr/hfoodi/industry/
8) Baldassarre D, Amato M, Eligini S, Barbieri SS, Mussoni L, Frigerio B, Kozàkovà M, Tremoli E, Sirtori CR, Colli S. Effect of n-3 fatty acids on carotid atherosclerosis and haemostasis in patients with combined hyperlipoproteinemia: a double-blind pilot study in primary prevention. Ann Med 2006; 38(5): 367-375
9) Blonk MC, Bilo HJ, Nauta JJ, Popp-Snijders C, Mulder C, Donker AJ. Dose-response effects of fish-oil supplementation in healthy volunteers. Am J Clin Nutr 1990; 52(1): 120-127
10) Engler MM, Engler MB, Malloy M, Chiu E, Besio D, Paul S, Stuehlinger M, Morrow J, Ridker P, Rifai N, Mietus-Snyder M. Docosahexaenoic acid restores endothelial function in children with hyperlipidemia: results from the EARLY study. Int J Clin Pharmacol Ther 2004; 42(12): 672-679
11) Fahs CA, Yan H, Ranadive S, Rossow LM, Agiovlasitis S, Wilund KR, Fernhall B. The effect of acute fish-oil supplementation on endothelial function and arterial stiffness following a high-fat meal. Appl Physiol Nutr Metab 2010; 35(3): 294-302
12) Finnegan YE, Howarth D, Minihane AM, Kew S, Miller GJ, Calder PC, Williams CM. Plant and marine derived (n-3) polyunsaturated fatty acids do not affect blood coagulation and fibrinolytic factors in moderately hyperlipidemic humans. J Nutr 2003; 133(7): 2210-2213
13) Green P, Fuchs J, Schoenfeld N, Leibovici L, Lurie Y, Beigel Y, Rotenberg Z, Mamet R, Budowski P. Effects of fish-oil ingestion on cardiovascular risk factors in hyperlipidemic subjects in Israel: a randomized, double-blind crossover study. Am J Clin Nutr 1990; 52(6): 1118-1124
14) Grundt H, Nilsen DW, Hetland Ø, Mansoor MA. Clinical outcome and atherothrombogenic risk profile after prolonged washout following long-term treatment with high doses of n-3 PUFAs in patients with an acute myocardial infarction. Clin Nutr 2004; 23(4): 491-500
15) Herrmann W, Biermann J, Kostner GM. Comparison of effects of N-3 to N-6 fatty acids on serum level of lipoprotein (a) in patients with coronary artery disease. Am J Cardiol 1995; 76(7): 459-462
16) Park Y, Harris W. EPA, but not DHA, decreases mean platelet volume in normal subjects. Lipids 2002; 37(10): 941-946
17) Passfall J, Philipp T, Woermann F, Quass P, Thiede M, Haller H. Different effects of eicosapentaenoic acid and olive oil on blood pressure, intracellular free platelet calcium, and plasma lipids in patients with essential hypertension. Clin Investig 1993; 71(8): 628-633
18) Prisco D, Filippini M, Francalanci I, Paniccia R, Gensini GF, Serneri GG. Effect of n-3 fatty acid ethyl ester supplementation on fatty acid composition of the single platelet phospholipids and on platelet functions. Metabolism 1995; 44(5): 562-569
19) Møller JM, Svaneborg N, Lervang HH, Varming K, Madsen P, Dyerberg J, Schmidt EB. The acute effect of a single very high dose of N-3 fatty acids on coagulation and fibrinolysis. Thromb Res 1992; 67(5): 569-577
20) Freese R, Mutanen M. Alpha-linolenic acid and marine long-chain n-3 fatty acids differ only slightly in their effects on hemostatic factors in healthy subjects. Am J Clin Nutr 1997; 66(3): 591-598
21) Piolot A, Blache D, Boulet L, Fortin LJ, Dubreuil D, Marcoux C, Davignon J, Lussier-Cacan S. Effect of fish oil on LDL oxidation and plasma homocysteine concentrations in health. J Lab Clin Med 2003; 141(1): 41-49
22) Rillaerts EG, Engelmann GJ, Van Camp KM, De Leeuw I. Effect of omega-3 fatty acids in diet of type I diabetic subjects on lipid values and hemorheological parameters. Diabetes 1989; 38(11): 1412-1416
23) Walser B, Giordano RM, Stebbins CL. Supplementation with omega-3 polyunsaturated fatty acids augments brachial artery dilation and blood flow during forearm contraction. Eur J Appl Physiol 2006; 97(3): 347-354
24) Haglund O, Wallin R, Luostarinen R, Saldeen T. Effects of a new fluid fish oil concentrate, ESKIMO-3, on triglycerides, cholesterol, fibrinogen and blood pressure. J Intern Med 1990; 227(5): 347-353
25) Agren JJ, Hänninen O, Laitinen M, Seppänen K, Bernhardt I, Fogelholm L, Herranen J, Penttilä I. Boreal freshwater fish diet modifies the plasma lipids and prostanoids and membrane fatty acids in man. Lipids 1988; 23(10): 924-929
26) Andrioli G, Carletto A, Guarini P, Galvani S, Biasi D, Bellavite P, Corrocher R. Differential effects of dietary supplementation with fish oil or soy lecithin on human platelet adhesion. Thromb Haemost 1999; 82(5): 1522-1527
27) Bach R, Schmidt U, Jung F, Kiesewetter H, Hennen B, Wenzel E, Schieffer H, Bette L, Heyden S. Effects of fish oil capsules in two dosages on blood pressure, platelet functions, haemorheological and clinical chemistry parameters in apparently healthy subjects. Ann Nutr Metab 1989; 33(6): 359-367
28) Coates AM, Sioutis S, Buckley JD, Howe PR. Regular consumption of n-3 fatty acid-enriched pork modifies cardiovascular risk factors. Br J Nutr 2009; 101(4): 592-597
29) Derosa G, Maffioli P, D'Angelo A, Salvadeo SA, Ferrari I, Fogari E, Gravina A, Mereu R, Randazzo S, Cicero AF. Effects of long chain omega-3 fatty acids on metalloproteinases and their inhibitors in combined dyslipidemia patients. Expert Opin Pharmacother 2009; 10(8): 1239-1247
30) Mann NJ, O'Connell SL, Baldwin KM, Singh I, Meyer BJ. Effects of seal oil and tuna-fish oil on platelet parameters and plasma lipid levels in healthy subjects. Lipids 2010; 45(8): 669-681
31) Mann N, Sinclair A, Pille M, Johnson L, Warrick G, Reder E, Lorenz R. The effect of short-term diets rich in fish, red meat, or white meat on thromboxane and prostacyclin synthesis in humans. Lipids 1997; 32(6): 635-644
32) Mesa MD, Buckley R, Minihane AM, Yaqoob P. Effects of oils rich in eicosapentaenoic and docosahexaenoic acids on the oxidizability and thrombogenicity of low-density lipoprotein. Atherosclerosis 2004; 175(2): 333-343
33) Mori TA, Vandongen R, Mahanian F, Douglas A. Plasma lipid levels and platelet and neutrophil function in patients with vascular disease following fish oil and olive oil supplementation. Metabolism 1992; 41(10): 1059-1067
34) Myrup B, Rossing P, Jensen T, Parving HH, Hølmer G, Gram J, Kluft C, Jespersen J. Lack of effect of fish oil supplementation on coagulation and transcapillary escape rate of albumin in insulin-dependent diabetic patients with diabetic nephropathy. Scand J Clin Lab Invest 2001; 61(5): 349-356
35) Schmidt EB, Kristensen SD, Dyerberg J. The effect of fish oil on lipids, coagulation and fibrinolysis in patients with angina pectoris. Artery 1988; 15(6): 316-329
36) Serebruany VL, Miller M, Pokov AN, Lynch D, Jensen JK, Hallén J, Atar D. Early impact of prescription Omega-3 fatty acids on platelet biomarkers in patients with coronary artery disease and hypertriglyceridemia. Cardiology 2011; 118(3): 187-194
37) Tremoli E, Maderna P, Marangoni F, Colli S, Eligini S, Catalano I, Angeli MT, Pazzucconi F, Gianfranceschi G, Davi G, Str-

agliotto E, Sirtori CR, Galli C. Prolonged inhibition of platelet aggregation after n-3 fatty acid ethyl ester ingestion by healthy volunteers. Am J Clin Nutr 1995; 61(3): 607-613
38) Tremoli E, Eligini S, Colli S, Maderna P, Risè P, Pazzucconi F, Marangoni F, Sirtori CR, Galli C. n-3 fatty acid ethyl ester administration to healthy subjects and to hypertriglyceridemic patients reduces tissue factor activity in adherent monocytes. Arterioscler Thromb 1994; 14(10): 1600-1608
39) Véricel E, Calzada C, Chapuy P, Lagarde M. The influence of low intake of n-3 fatty acids on platelets in elderly people. Atherosclerosis 1999; 147(1): 187-192
40) von Schacky C, Weber PC. Metabolism and effects on platelet function of the purified eicosapentaenoic and docosahexaenoic acids in humans. J Clin Invest 1985; 76(6): 2446-2450
41) Westerveld HT, de Graaf JC, van Breugel HH, Akkerman JW, Sixma JJ, Erkelens DW, Banga JD. Effects of low-dose EPA-E on glycemic control, lipid profile, lipoprotein(a), platelet aggregation, viscosity, and platelet and vessel wall interaction in NIDDM. Diabetes Care 1993; 16(5): 683-688
42) Woodcock BE, Smith E, Lambert WH, Jones WM, Galloway JH, Greaves M, Preston FE. Beneficial effect of fish oil on blood viscosity in peripheral vascular disease. Br Med J (Clin Res Ed) 1984; 288(6417): 592-594
43) Wright SA, O'Prey FM, McHenry MT, Leahey WJ, Devine AB, Duffy EM, Johnston DG, Finch MB, Bell AL, McVeigh GE. A randomised interventional trial of omega-3-polyunsaturated fatty acids on endothelial function and disease activity in systemic lupus erythematosus. Ann Rheum Dis 2008; 67(6): 841-848
44) Zucker ML, Bilyeu DS, Helmkamp GM, Harris WS, Dujovne CA. Effects of dietary fish oil on platelet function and plasma lipids in hyperlipoproteinemic and normal subjects. Atherosclerosis 1988; 73(1): 13-22
45) Toft I, Bønaa KH, Ingebretsen OC, Nordøy A, Jenssen T. Fibrinolytic function after dietary supplementation with omega3 polyunsaturated fatty acids. Arterioscler Thromb Vasc Biol 1997; 17(5): 814-819
46) Cobiac L, Clifton PM, Abbey M, Belling GB, Nestel PJ. Lipid, lipoprotein, and hemostatic effects of fish vs fish-oil n-3 fatty acids in mildly hyperlipidemic males. Am J Clin Nutr 1991; 53 (5): 1210-1216
47) Croset M, Véricel E, Rigaud M, Hanss M, Courpron P, Dechavanne M, Lagarde M. Functions and tocopherol content of blood platelets from elderly people after low intake of purified eicosapentaenoic acid. Thromb Res 1990; 57(1): 1-12
48) De Caterina R, Caprioli R, Giannessi D, Sicari R, Galli C, Lazzerini G, Bernini W, Carr L, Rindi P. n-3 fatty acids reduce proteinuria in patients with chronic glomerular disease. Kidney Int 1993; 44(4): 843-850
49) Driss F, Vericel E, Lagarde M, Dechavanne M, Darcet P. Inhibition of platelet aggregation and thromboxane synthesis after intake of small amount of icosapentaenoic acid. Thromb Res 1984; 36(5): 389-396
50) Grundt H, Nilsen DW, Hetland O, Mansoor MA, Aarsland T, Woie L. Atherothrombogenic risk modulation by n-3 fatty acids was not associated with changes in homocysteine in subjects with combined hyperlipidaemia. Thromb Haemost 1999; 81(4): 561-565
51) Landgraf-Leurs MM, Drummer C, Fröschl H, Steinhuber R, Von Schacky C, Landgraf R. Pilot study on omega-3 fatty acids in type I diabetes mellitus. Diabetes 1990; 39(3): 369-375
52) Okumura T, Fujioka Y, Morimoto S, Tsuboi S, Masai M, Tsujino T, Ohyanagi M, Iwasaki T. Eicosapentaenoic acid improves endothelial function in hypertriglyceridemic subjects despite increased lipid oxidizability. Am J Med Sci 2002; 324(5): 247-253
53) von Schacky C, Fischer S, Weber PC. Long-term effects of dietary marine omega-3 fatty acids upon plasma and cellular lipids, platelet function, and eicosanoid formation in humans. J Clin Invest 1985; 76(4): 1626-1631
54) Sanders TA, Roshanai F. The influence of different types of omega 3 polyunsaturated fatty acids on blood lipids and platelet function in healthy volunteers. Clin Sci (Lond) 1983; 64(1): 91-99
55) Haglund O, Mehta JL, Saldeen T. Effects of fish oil on some parameters of fibrinolysis and lipoprotein(a) in healthy subjects. Am J Cardiol 1994; 74(2): 189-192
56) Fumeron F, Brigant L, Ollivier V, de Prost D, Driss F, Darcet P, Bard JM, Parra HJ, Fruchart JC, Apfelbaum M. n-3 polyunsaturated fatty acids raise low-density lipoproteins, high-density lipoprotein 2, and plasminogen-activator inhibitor in healthy young men. Am J Clin Nutr 1991; 54(1): 118-122
57) Goyens PL, Mensink RP. Effects of alpha-linolenic acid versus those of EPA/DHA on cardiovascular risk markers in healthy elderly subjects. Eur J Clin Nutr 2006; 60(8): 978-984
58) Green D, Barreres L, Borensztajn J, Kaplan P, Reddy MN, Rovner R, Simon H. A double-blind, placebo-controlled trial of fish oil concentrate (MaxEpa) in stroke patients. Stroke 1985; 16(4): 706-709
59) Hansen JB, Olsen JO, Wilsgård L, Lyngmo V, Svensson B. Comparative effects of prolonged intake of highly purified fish oils as ethyl ester or triglyceride on lipids, haemostasis and platelet function in normolipaemic men. Eur J Clin Nutr 1993; 47(7): 497-507
60) Hendra TJ, Britton ME, Roper DR, Wagaine-Twabwe D, Jeremy JY, Dandona P, Haines AP, Yudkin JS. Effects of fish oil supplements in NIDDM subjects. Controlled study. Diabetes Care 1990; 13(8): 821-829
61) Pirich C, Gaszo A, Granegger S, Sinzinger H. Effects of fish oil supplementation on platelet survival and ex vivo platelet function in hypercholesterolemic patients. Thromb Res 1999; 96(3): 219-227
62) Rizza S, Tesauro M, Cardillo C, Galli A, Iantorno M, Gigli F, Sbraccia P, Federici M, Quon MJ, Lauro D. Fish oil supplementation improves endothelial function in normoglycemic offspring of patients with type 2 diabetes. Atherosclerosis 2009; 206(2): 569-574
63) Vognild E, Elvevoll EO, Brox J, Olsen RL, Barstad H, Aursand M, Osterud B. Effects of dietary marine oils and olive oil on fatty acid composition, platelet membrane fluidity, platelet responses, and serum lipids in healthy humans. Lipids 1998; 33(4): 427-436
64) Phang M, Sinclair AJ, Lincz LF, Garg ML. Gender-specific inhibition of platelet aggregation following omega-3 fatty acid supplementation. Nutr Metab Cardiovasc Dis 2012; 22(2): 109-114
65) Phang M, Lincz L, Seldon M, Garg ML. Acute supplementation with eicosapentaenoic acid reduces platelet microparticle activity in healthy subjects. J Nutr Biochem 2012; 23(9): 1128-1133
66) Axelrod L, Camuso J, Williams E, Kleinman K, Briones E, Schoenfeld D. Effects of a small quantity of omega-3 fatty acids on cardiovascular risk factors in NIDDM. A randomized, prospective, double-blind, controlled study. Diabetes Care 1994; 17(1): 37-44
67) Berrettini M, Parise P, Ricotta S, Iorio A, Peirone C, Nenci GG. Increased plasma levels of tissue factor pathway inhibitor (TF-PI) after n-3 polyunsaturated fatty acids supplementation in patients with chronic atherosclerotic disease. Thromb Haemost 1996; 75(3): 395-400
68) Flaten H, Høstmark AT, Kierulf P, Lystad E, Trygg K, Bjerke-

dal T, Osland A. Fish-oil concentrate: effects on variables related to cardiovascular disease. Am J Clin Nutr 1990; 52(2): 300-306
69) Haberka M, Mizia-Stec K, Mizia M, Janowska J, Gieszczyk K, Chmiel A, Zahorska-Markiewicz B, Gąsior Z. N-3 polyunsaturated fatty acids early supplementation improves ultrasound indices of endothelial function, but not through NO inhibitors in patients with acute myocardial infarction: N-3 PUFA supplementation in acute myocardial infarction. Clin Nutr 2011; 30(1): 79-85
70) Honstra G, van Houwelingen AC, Kivits GA, Fischer S, Uedelhoven W. Influence of dietary fish on eicosanoid metabolism in man. Prostaglandins 1990; 40(3): 311-329
71) Lau CS, McLaren M, Belch JJ. Effects of fish oil on plasma fibrinolysis in patients with mild rheumatoid arthritis. Clin Exp Rheumatol 1995; 13(1): 87-90
72) Lindman AS, Pedersen JI, Hjerkinn EM, Arnesen H, Veierød MB, Ellingsen I, Seljeflot I. The effects of long-term diet and omega-3 fatty acid supplementation on coagulation factor VII and serum phospholipids with special emphasis on the R353Q polymorphism of the FVII gene. Thromb Haemost 2004; 91(6): 1097-1104
73) McVeigh GE, Brennan GM, Cohn JN, Finkelstein SM, Hayes RJ, Johnston GD. Fish oil improves arterial compliance in non-insulin-dependent diabetes mellitus. Arterioscler Thromb 1994; 14(9): 1425-1429
74) Mehta JL, Lopez LM, Lawson D, Wargovich TJ, Williams LL. Dietary supplementation with omega-3 polyunsaturated fatty acids in patients with stable coronary heart disease. Effects on indices of platelet and neutrophil function and exercise performance. Am J Med 1988; 84(1): 45-52
75) Moertl D, Berger R, Hammer A, Hutuleac R, Koppensteiner R, Kopp CW, Steiner S. Dose-dependent decrease of platelet activation and tissue factor by omega-3 polyunsaturated fatty acids in patients with advanced chronic heart failure. Thromb Haemost 2011; 106(3): 457-465
76) Mori TA, Beilin LJ, Burke V, Morris J, Ritchie J. Interactions between dietary fat, fish, and fish oils and their effects on platelet function in men at risk of cardiovascular disease. Arterioscler Thromb Vasc Biol 1997; 17(2): 279-286
77) Solomon SA, Cartwright I, Pockley G, Greaves M, Preston FE, Ramsay LE, Waller PC. A placebo-controlled, double-blind study of eicosapentaenoic acid-rich fish oil in patients with stable angina pectoris. Curr Med Res Opin 1990; 12(1): 1-11
78) Wensing AG, Mensink RP, Hornstra G. Effects of dietary n-3 polyunsaturated fatty acids from plant and marine origin on platelet aggregation in healthy elderly subjects. Br J Nutr 1999; 82 (3): 183-191
79) Woodman RJ, Mori TA, Burke V, Puddey IB, Barden A, Watts GF, Beilin LJ. Effects of purified eicosapentaenoic acid and docosahexaenoic acid on platelet, fibrinolytic and vascular function in hypertensive type 2 diabetic patients. Atherosclerosis 2003; 166(1): 85-93
80) Grundt H, Nilsen DW, Mansoor MA, Hetland Ø, Nordøy A. Reduction in homocysteine by n-3 polyunsaturated fatty acids after 1 year in a randomised double-blind study following an acute myocardial infarction: no effect on endothelial adhesion properties. Pathophysiol Haemost Thromb 2003; 33(2): 88-95
81) Johansen O, Seljeflot I, Høstmark AT, Arnesen H. The effect of supplementation with omega-3 fatty acids on soluble markers of endothelial function in patients with coronary heart disease. Arterioscler Thromb Vasc Biol 1999; 19(7): 1681-1686
82) Krishnan PV, Anuradha S, Bhattacharjee J, Gaiha M. Effects of low dose omega-3 fatty acids on platelet functions and coagulation profile in Indian patients with type 2 diabetes mellitus with vascular complications: a prospective, preliminary study. J Indian Acad Clin Med 2007; 8(1): 45-52
83) Brox JH, Killie JE, Gunnes S, Nordøy A. The effect of cod liver oil and corn oil on platelets and vessel wall in man. Thromb Haemost 1981; 46(3): 604-611
84) Mehta J, Lawson D, Saldeen TJ. Reduction in plasminogen activator inhibitor-1 (PAI-1) with omega-3 polyunsaturated fatty acid (PUFA) intake. Am Heart J 1988; 116(5 Pt 1): 1201-1206
85) Nordøy A, Hatcher L, Goodnight S, Fitzgerald GA, Conner WE. Effects of dietary fat content, saturated fatty acids, and fish oil on eicosanoid production and hemostatic parameters in normal men. J Lab Clin Med 1994; 123(6): 914-920
86) Wojenski CM, Silver MJ, Walker J. Eicosapentaenoic acid ethyl ester as an antithrombotic agent: comparison to an extract of fish oil. Biochim Biophys Acta 1991; 1081(1): 33-38
87) Agren JJ, Väisänen S, Hänninen O, Muller AD, Hornstra G. Hemostatic factors and platelet aggregation after a fish-enriched diet or fish oil or docosahexaenoic acid supplementation. Prostaglandins Leukot Essent Fatty Acids 1997; 57(4-5): 419-421
88) Almdahl SM, Nilsen DW, Osterud B, Sørlie DG, Vaage J. Thromboplastin activities and monocytes in the coronary circulation of reperfused human myocardium. No effect of preoperative treatment with n-3 fatty acids. Scand J Thorac Cardiovasc Surg 1993; 27(2): 81-86
89) Conquer JA, Holub BJ. Supplementation with an algae source of docosahexaenoic acid increases (n-3) fatty acid status and alters selected risk factors for heart disease in vegetarian subjects. J Nutr 1996; 126(12): 3032-3039
90) Conquer JA, Cheryk LA, Chan E, Gentry PA, Holub BJ. Effect of supplementation with dietary seal oil on selected cardiovascular risk factors and hemostatic variables in healthy male subjects. Thromb Res 1999; 96(3): 239-250
91) Demke DM, Peters GR, Linet OI, Metzler CM, Klott KA. Effects of a fish oil concentrate in patients with hypercholesterolemia. Atherosclerosis 1988; 70(1-2): 73-80
92) Donnelly SM, Ali MA, Churchill DN. Effect of n-3 fatty acids from fish oil on hemostasis, blood pressure, and lipid profile of dialysis patients. J Am Soc Nephrol 1992; 2(11): 1634-1639
93) Gajos G, Zalewski J, Rostoff P, Nessler J, Piwowarska W, Undas A. Reduced thrombin formation and altered fibrin clot properties induced by polyunsaturated omega-3 fatty acids on top of dual antiplatelet therapy in patients undergoing percutaneous coronary intervention (OMEGA-PCI clot). Arterioscler Thromb Vasc Biol 2011; 31(7): 1696-1702
94) Goodfellow J, Bellamy MF, Ramsey MW, Jones CJ, Lewis MJ. Dietary supplementation with marine omega-3 fatty acids improve systemic large artery endothelial function in subjects with hypercholesterolemia. J Am Coll Cardiol 2000; 35(2): 265-270
95) Grundt H, Hetland Ø, Nilsen DW. Changes in tissue factor and activated factor XII following an acute myocardial infarction were uninfluenced by high doses of n-3 polyunsaturated fatty acids. Thromb Haemost 2003; 89(4): 752-759
96) Hagve TA, Lie O, Grønn M. The effect of dietary N-3 fatty acids on osmotic fragility and membrane fluidity of human erythrocytes. Scand J Clin Lab Invest Suppl 1993; 215: 75-84
97) Haines AP, Sanders TA, Imeson JD, Mahler RF, Martin J, Mistry M, Vickers M, Wallace PG. Effects of a fish oil supplement on platelet function, haemostatic variables and albuminuria in insulin-dependent diabetics. Thromb Res 1986; 43(6): 643-655
98) Hellsten G, Boman K, Saarem K, Hallmans G, Nilsson TK. Effects on fibrinolytic activity of corn oil and a fish oil preparation enriched with omega-3-polyunsaturated fatty acids in a long-term study. Curr Med Res Opin 1993; 13(3): 133-139

99) Montegaard C, Tulk HM, Lauritzen L, Tholstrup T, Robinson LE. Acute ingestion of long-chain (n-3) polyunsaturated fatty acids decreases fibrinolysis in men with metabolic syndrome. J Nutr 2010; 140(1): 38-43
100) Neff LM, Culiner J, Cunningham-Rundles S, Seidman C, Meehan D, Maturi J, Wittkowski KM, Levine B, Breslow JL. Algal docosahexaenoic acid affects plasma lipoprotein particle size distribution in overweight and obese adults. J Nutr 2011; 141(2): 207-213
101) Nilsen DW, Dalaker K, Nordøy A, Osterud B, Ingebretsen OC, Lyngmo V, Almdahl S, Vaage J, Rasmussen K. Influence of a concentrated ethylester compound of n-3 fatty acids on lipids, platelets and coagulation in patients undergoing coronary bypass surgery. Thromb Haemost 1991; 66(2): 195-201
102) Poppitt SD, Howe CA, Lithander FE, Silvers KM, Lin RB, Croft J, Ratnasabapathy Y, Gibson RA, Anderson CS. Effects of moderate-dose omega-3 fish oil on cardiovascular risk factors and mood after ischemic stroke: a randomized, controlled trial. Stroke 2009; 40(11): 3485-3492
103) Prisco D, Paniccia R, Filippini M, Francalanci I, Bandinelli B, Comeglio P, Rostagno C, Abbate R, Neri Serneri GG. No changes in PAI-1 levels after four-month n-3 PUFA ethyl ester supplementation in healthy subjects. Thromb Res 1994; 76(3): 237-244
104) Saifullah A, Watkins BA, Saha C, Li Y, Moe SM, Friedman AN. Oral fish oil supplementation raises blood omega-3 levels and lowers C-reactive protein in haemodialysis patients--a pilot study. Nephrol Dial Transplant 2007; 22(12): 3561-3567
105) Sanders TA, Hall WL, Maniou Z, Lewis F, Seed PT, Chowienczyk PJ. Effect of low doses of long-chain n-3 PUFAs on endothelial function and arterial stiffness: a randomized controlled trial. Am J Clin Nutr 2011; 94(4): 973-980
106) Sirtori CR, Gatti E, Tremoli E, Galli C, Gianfranceschi G, Franceschini G, Colli S, Maderna P, Marangoni F, Perego P, Stragliotto E. Olive oil, corn oil, and n-3 fatty acids differently affect lipids, lipoproteins, platelets, and superoxide formation in type II hypercholesterolemia. Am J Clin Nutr 1992; 56(1): 113-122
107) DeCaterina R, Giannessi D, Mazzone A, Bernini W, Lazzerini G, Maffei S, Cerri M, Salvatore L, Weksler B. Vascular prostacyclin is increased in patients ingesting omega-3 polyunsaturated fatty acids before coronary artery bypass graft surgery. Circulation 1990; 82(2): 428-438
108) Din JN, Harding SA, Valerio CJ, Sarma J, Lyall K, Riemersma RA, Newby DE, Flapan AD. Dietary intervention with oil rich fish reduces platelet-monocyte aggregation in man. Atherosclerosis 2008; 197(1): 290-296
109) Nelson GJ, Schmidt PS, Bartolini GL, Kelley DS, Kyle D. The effect of dietary docosahexaenoic acid on platelet function, platelet fatty acid composition, and blood coagulation in humans. Lipids 1997; 32(11): 1129-1136
110) Boberg M, Pollare T, Siegbahn A, Vessby B. Supplementation with n-3 fatty acids reduces triglycerides but increases PAI-1 in non-insulin-dependent diabetes mellitus. Eur J Clin Invest 1992; 22(10): 645-650
111) Park Y, Harris WS. Dose-dependent effects of n-3 polyunsaturated fatty acids on platelet activation in mildly hypertriglyceridemic subjects. J Med Food 2009; 12(4): 809-813
112) Brox J, Olaussen K, Osterud B, Elvevoll EO, Bjørnstad E, Bratteboøg G, Iversen H. A long-term seal- and cod-liver-oil supplementation in hypercholesterolemic subjects. Lipids 2001; 36 (1): 7-13
113) Brox JH, Killie JE, Osterud B, Holme S, Nordøy A. Effects of cod liver oil on platelets and coagulation in familial hypercholesterolemia (type IIa). Acta Med Scand 1983; 213(2): 137-144
114) Hwang DH, Chanmugam PS, Ryan DH, Boudreau MD, Windhauser MM, Tulley RT, Brooks ER, Bray GA. Does vegetable oil attenuate the beneficial effects of fish oil in reducing risk factors for cardiovascular disease? Am J Clin Nutr 1997; 66(1): 89-96
115) Gajos G, Rostoff P, Undas A, Piwowarska W. Effects of polyunsaturated omega-3 fatty acids on responsiveness to dual antiplatelet therapy in patients undergoing percutaneous coronary intervention: the OMEGA-PCI (OMEGA-3 fatty acids after pci to modify responsiveness to dual antiplatelet therapy) study. J Am Coll Cardiol 2010; 55(16): 1671-1678
116) Ahmed AA, Holub BJ. Alteration and recovery of bleeding times, platelet aggregation and fatty acid composition of individual phospholipids in platelets of human subjects receiving a supplement of cod-liver oil. Lipids 1984; 19(8): 617-624
117) Atkinson PM, Wheeler MC, Mendelsohn D, Pienaar N, Chetty N. Effects of a 4-week freshwater fish (trout) diet on platelet aggregation, platelet fatty acids, serum lipids, and coagulation factors. Am J Hematol 1987; 24(2): 143-149
118) Bakken AM, Farstad M, Holmsen H. Fatty acids in human platelets and plasma. Fish oils decrease sensitivity toward N2 microbubbles. J Appl Physiol 1991; 70(6): 2669-2672
119) Bakken AM, Hervig T, Thorsen T, Holmsen H. Fatty acids in human platelets and plasma. Dietary seal oil decreases sensitivity toward microbubbles. Platelets 1995; 6(5): 259-264
120) Beitz J, Schimke E, Liebaug U, Block HU, Beitz A, Honigmann G, Sziegoleit W, Müller G, Mest HJ. Influence of a cod liver oil diet in healthy and insulin-dependent diabetic volunteers on fatty acid pattern, inhibition of prostacyclin formation by low density lipoprotein (LDL) and platelet thromboxane. Klin Wochenschr 1986; 64(17): 793-799
121) Bradlow BA, Chetty N, van der Westhuyzen J, Mendelsohn D, Gibson JE. The effects of a mixed fish diet on platelet function, fatty acids and serum lipids. Thromb Res 1983; 29(6): 561-568
122) Brister SJ, Buchanan MR. Effects of linoleic acid and/or marine fish oil supplements on vessel wall thromboresistance in patients undergoing cardiac surgery. Adv Exp Med Biol 1997; 433: 275-278
123) Brown AJ, Roberts DC. Fish and fish oil intake: effect on haematological variables related to cardiovascular disease. Thromb Res 1991; 64(2): 169-178
124) Eritsland J, Arnesen H, Smith P, Seljeflot I, Dahl K. Effects of highly concentrated omega-3 polyunsaturated fatty acids and acetylsalicylic acid, alone and combined, on bleeding time and serum lipid profile. J Oslo City Hosp 1989; 39(8-9): 97-101
125) Fischer S, Weber PC. Thromboxane A3 (TXA3) is formed in human platelets after dietary eicosapentaenoic acid (C20:5 omega 3). Biochem Biophys Res Commun 1983; 116(3): 1091-1099
126) Gibney MJ, Bolton-Smith C. The effect of a dietary supplement of n-3 polyunsaturated fat on platelet lipid composition, platelet function and platelet plasma membrane fluidity in healthy volunteers. Br J Nutr 1988; 60(1): 5-12
127) Harris WS, Rothrock DW, Fanning A, Inkeles SB, Goodnight SH Jr, Illingworth DR, Connor WE. Fish oils in hypertriglyceridemia: a dose-response study. Am J Clin Nutr 1990; 51(3): 399-406
128) Hawthorne AB, Filipowicz BL, Edwards TJ, Hawkey CJ. High dose eicosapentaenoic acid ethyl ester: effects on lipids and neutrophil leukotriene production in normal volunteers. Br J Clin Pharmacol 1990; 30(2): 187-194
129) Hirai A, Terano T, Hamazaki T, Sajiki J, Kondo S, Ozawa A, Fujita T, Miyamoto T, Tamura Y, Kumagai A. The effects of the oral administration of fish oil concentrate on the release and the metabolism of [14C]arachidonic acid and [14C]eicosapentaenoic acid by human platelets. Thromb Res 1982; 28(3): 285-298

130) Hirai A, Terano T, Takenaga M, Kobayashi S, Makuta H, Ozawa A, Fujita T, Tamura Y, Kitagawa H, Kumagai A, Yoshida S. Effect of supplementation of highly purified eicosapentaenoic acid and docosahexaenoic acid on hemostatic function in healthy subjects. Adv Prostaglandin Thromboxane Leukot Res 1987; 17B: 838-845
131) Hirai A, Terano T, Makuta H, Ozawa A, Fujita T, Tamura Y, Yoshida S. Effect of oral administration of highly purified eicosapentaenoic acid and docosahexaenoic acid on platelet function and serum lipids in hyperlipidemic patients. Adv Prostaglandin Thromboxane Leukot Res 1989; 19: 627-630
132) Kobayashi S, Hamazaki T, Sawazaki S, Nakamura H. Reduction in the ADP release from shear-stressed red blood cells by fish oil administration. Thromb Res 1992; 65(3): 353-364
133) Lands WE, Culp BR, Hirai A, Gorman R. Relationship of thromboxane generation to the aggregation of platelets from humans: effects of eicosapentaenoic acid. Prostaglandins 1985; 30(5): 819-825
134) Lorenz R, Spengler U, Fischer S, Duhm J, Weber PC. Platelet function, thromboxane formation and blood pressure control during supplementation of the Western diet with cod liver oil. Circulation 1983; 67(3): 504-511
135) Lox CD. The effects of dietary marine fish oils (omega-3 fatty acids) on coagulation profiles in men. Gen Pharmacol 1990; 21 (2): 241-246
136) Lund EK, Harvey LJ, Ladha S, Clark DC, Johnson IT. Effects of dietary fish oil supplementation on the phospholipid composition and fluidity of cell membranes from human volunteers. Ann Nutr Metab 1999; 43(5): 290-300
137) Nelson GJ, Schmidt PC, Corash L. The effect of a salmon diet on blood clotting, platelet aggregation and fatty acids in normal adult men. Lipids 1991; 26(2): 87-96
138) Nomura S, Kanazawa S, Fukuhara S. Effects of eicosapentaenoic acid on platelet activation markers and cell adhesion molecules in hyperlipidemic patients with Type 2 diabetes mellitus. J Diabetes Complications 2003; 17(3): 153-159
139) Olivieri O, Negri M, De Gironcoli M, Bassi A, Guarini P, Stanzial AM, Grigolini L, Ferrari S, Corrocher R. Effects of dietary fish oil on malondialdehyde production and glutathione peroxidase activity in hyperlipidaemic patients. Scand J Clin Lab Invest 1988; 48(7): 659-665
140) Pschierer V, Richter WO, Schwandt P. Primary chylomicronemia in patients with severe familial hypertriglyceridemia responds to long-term treatment with (n-3) fatty acids. J Nutr 1995; 125(6): 1490-1494
141) Rylance PB, George MP, Saynor R, Weston MJ. A pilot study of the use of MaxEPA in haemodialysis patients. Br J Clin Pract Suppl 1984; 31: 49-54
142) Rylance PB, Gordge MP, Saynor R, Parsons V, Weston MJ. Fish oil modifies lipids and reduces platelet aggregability in haemodialysis patients. Nephron 1986; 43(3): 196-202
143) Sakamoto N, Nishiike T, Iguchi H, Sakamoto K. Effects of eicosapentaenoic acid intake on plasma fibrinolytic and coagulation activity by using physical load in the young. Nutrition 2000; 16(1): 11-14
144) Sanders TA, Hinds A. The influence of a fish oil high in docosahexaenoic acid on plasma lipoprotein and vitamin E concentrations and haemostatic function in healthy male volunteers. Br J Nutr 1992; 68(1): 163-173
145) Sanders TA, Hochland MC. A comparison of the influence on plasma lipids and platelet function of supplements of omega 3 and omega 6 polyunsaturated fatty acids. Br J Nutr 1983; 50(3): 521-529
146) Saynor R, Verel D, Gillott T. The long-term effect of dietary supplementation with fish lipid concentrate on serum lipids, bleeding time, platelets and angina. Atherosclerosis 1984; 50(1): 3-10
147) Singer P, Berger I, Lück K, Taube C, Naumann E, Gödicke W. Long-term effect of mackerel diet on blood pressure, serum lipids and thromboxane formation in patients with mild essential hypertension. Atherosclerosis 1986; 62(3): 259-265
148) Smith P, Arnesen H, Opstad T, Dahl KH, Eritsland J. Influence of highly concentrated n-3 fatty acids on serum lipids and hemostatic variables in survivors of myocardial infarction receiving either oral anticoagulants or matching placebo. Thromb Res 1989; 53(5): 467-474
149) Tagawa H, Shimokawa H, Tagawa T, Kuroiwa-Matsumoto M, Hirooka Y, Takeshita A. Long-term treatment with eicosapentaenoic acid augments both nitric oxide-mediated and non-nitric oxide-mediated endothelium-dependent forearm vasodilatation in patients with coronary artery disease. J Cardiovasc Pharmacol 1999; 33(4): 633-640
150) Takimoto G, Galang J, Lee GK, Bradlow BA. Plasma fibrinolytic activity after ingestion of omega-3 fatty acids in human subjects. Thromb Res 1989; 54(6): 573-582
151) Tamura Y, Hirai A, Terano T, Kumagai A, Yoshida S. Effects of eicosapentaenoic acid on hemostatic function and serum lipids in humans. Adv Prostaglandin Thromboxane Leukot Res 1985; 15: 265-267
152) Tamura Y, Hirai A, Terano T, Yoshida S, Takenaga M, Kitagawa H. Anti-thrombotic and anti-atherogenic action of eicosapentaenoic acid. Jpn Circ J 1987; 51(4): 471-477
153) Terano T, Hirai A, Hamazaki T, Kobayashi S, Fujita T, Tamura Y, Kumagai A. Effect of oral administration of highly purified eicosapentaenoic acid on platelet function, blood viscosity and red cell deformability in healthy human subjects. Atherosclerosis 1983; 46(3): 321-331
154) Thorngren M, Gustafson A. Effects of 11-week increases in dietary eicosapentaenoic acid on bleeding time, lipids, and platelet aggregation. Lancet 1981; 2(8257): 1190-1193
155) Thorngren M, Shafi S, Born GV. Delay in primary haemostasis produced by a fish diet without change in local thromboxane A2. Br J Haematol 1984; 58(4): 567-578
156) Tremoli E, Mosconi C, Maderna P, Colli S, Stragliotto E, Sirtori CR, Galli C. Effects of EPA and DHA ethylesters on plasma fatty acids and on platelets, PMN and monocytes in healthy volunteers. Adv Prostaglandin Thromboxane Leukot Res 1991; 21A: 233-236
157) Tsuruta K, Ogawa H, Yasue H, Sakamoto T, Miyao Y, Tanae H, Kaiga K. Effect of purified eicosapentaenoate ethyl ester on fibrinolytic capacity in patients with stable coronary artery disease and lower extremity ischaemia. Coron Artery Dis 1996; 7 (11): 837-842
158) Turini ME, Powell WS, Behr SR, Holub BJ. Effects of a fish-oil and vegetable-oil formula on aggregation and ethanolamine-containing lysophospholipid generation in activated human platelets and on leukotriene production in stimulated neutrophils. Am J Clin Nutr 1994; 60(5): 717-724
159) Vanschoonbeek K, Feijge MA, Paquay M, Rosing J, Saris W, Kluft C, Giesen PL, de Maat MP, Heemskerk JW. Variable hypocoagulant effect of fish oil intake in humans: modulation of fibrinogen level and thrombin generation. Arterioscler Thromb Vasc Biol 2004; 24(9): 1734-1740
160) Yao JK, Magan S, Sonel AF, Gurklis JA, Sanders R, Reddy RD. Effects of omega-3 fatty acid on platelet serotonin responsivity in patients with schizophrenia. Prostaglandins Leukot Essent Fatty Acids 2004; 71(3): 171-176
161) Yosefy C, Viskoper JR, Varon D, Ilan Z, Pilpel D, Lugassy G, Schneider R, Savyon N, Adan Y, Raz A. Repeated fasting and

refeeding with 20:5, n-3 eicosapentaenoic acid (EPA): a novel approach for rapid fatty acid exchange and its effect on blood pressure, plasma lipids and hemostasis. J Hum Hypertens 1996; 10 Suppl 3: S135-S139
162) Yoshimura T, Matsui K, Ito M, Yunohara T, Kawasaki N, Nakamura T, Okamura H. Effects of highly purified eicosapentaenoic acid on plasma beta thromboglobulin level and vascular reactivity to angiotensin II. Artery 1987; 14(5): 295-303
163) Baumann KH, Hessel F, Larass I, Müller T, Angerer P, Kiefl R, von Schacky C. Dietary omega-3, omega-6, and omega-9 unsaturated fatty acids and growth factor and cytokine gene expression in unstimulated and stimulated monocytes. A randomized volunteer study. Arterioscler Thromb Vasc Biol 1999; 19 (1): 59-66
164) Eritsland J, Seljeflot I, Abdelnoor M, Arnesen H. Long-term influence of omega-3 fatty acids on fibrinolysis, fibrinogen, and serum lipids. Fibrinolysis 1994; 8(2): 120-125
165) Gazso A, Kaliman J, Horrobin D, Sinzinger H. Effects of omega-3 fatty acids on the prostaglandin system in healthy volunteers. Prog Clin Biol Res 1989; 301: 517-521