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Role of Fish Oil in Prevention of Cardiovascular Diseases: A Systematic Review

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WONG ET AL.: ***Role of Fish Oil in Prevention of Cardiovascular Diseases: A Systematic Review.*** *Epidemiological studies have shown that fish oil intake has cardioprotective effects. These benefits are ascribed to the active ingredients of fish oil, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Experimental and clinical studies have demonstrated that EPA and DHA exhibit their cardioprotective mechanisms via anti-arrhythmic, anti-atherogenic, anti-thrombotic and vasoprotective effects. In clinical trials, the clinical benefit of fish oil intake appears to be more prominent on secondary prevention than primary prevention. Furthermore, the triglyceride-lowering property of fish oil may be more beneficial for primary prevention in certain high risk patients, such as patients with Type II diabetes mellitus and metabolic syndrome. Nevertheless, fish oil has also been shown to be associated with worsening of glycaemic control, and increasing in plasma low-density lipoprotein cholesterol level. Therefore, whether fish oil supplement has cardioprotective effects in different selected subgroups of high risk subjects remain unclear, and further randomized controlled trials are required. (J HK Coll Cardiol 2007;15:1-11)*

Cardiovascular diseases, fish oil, omega-3, prevention

摘要

流行病學研究顯示攝入魚油對心臟具有保護作用。這些益處歸因於魚油中的活性成份，eicosapentaenoic acid(EPA)和docosahexaenoic acid (DHA)。實驗和臨床研究證實EPA和DHA通過抗心律失常、抗動脈硬化、抗血栓形成和血管保護作用來發揮對心臟的保護機制的。在臨床實驗表明魚油攝入的臨床益處，其二級預防作用更強於初級預防。此外，在高危人群，如II型糖尿病和代謝性疾病患者，魚油中低甘油三酯的特性具有更好的初級預防作用。儘管如此，有資料卻顯示魚油會加劇血糖的控制，增加低密度脂蛋白的水平。因此，魚油的補充是否對不同類型的高危病症具有心臟保護作用仍然尚不清楚，需要進一步的臨床隨機對照研究。

關鍵詞：心血管疾病　魚油　甘油三酯　預防

Introduction

Coronary heart disease (CHD) is an emerging health problem in Hong Kong and other developed countries. This rising incidence of CHD is ascribed to a 'westernized lifestyle' which consists of high-fat diets and a lack of exercises. Numerous epidemiological studies have demonstrated a positive correlation between CHD and the amount of lipid intake,[1,2] especially those rich in saturated fatty acids and trans-fatty acids which are easily obtained from meat.

On the other hand, Greenland Eskimos have a low CHD mortality despite a high intake of fat which contributes to about 40% of their total caloric intake.[3-6] Epidemiological studies in the 1970s suggested that this paradox was due to their high consumption of fish and fish-eating mammals which are rich in fish oil.[7,8] Fish oil contains abundant very long-chain omega-3

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polyunsaturated fatty acids (n-3 PUFA), which differs from those saturated fatty acids and trans-fatty acids in terms of their chemical structures and biochemical properties. Since then, other epidemiological studies of the coastal population of Japan and Alaska have also demonstrated the inverse relationship between n-3 PUFA from fish intake and CHD mortality,[9-13] suggesting the potential benefit of fish oil in the prevention of CHD.

Omega-3 polyunsaturated fatty acids

Fatty acids can be divided into saturated and unsaturated fatty acids, distinguished by the absence and presence of double bond(s) respectively. Monounsaturated fatty acid contains only 1 double bond in its long carbon chain, and polyunsaturated fatty acid contains more than 1 double bond.

There are two families of natural polyunsaturated fatty acids: the omega-6 (n-6) family and the omega-3 (n-3) family with the final double bond located at 6 carbon and 3 carbon atoms away from the end of the long carbon chain, respectively (Figure 1). These two classes of polyunsaturated fatty acid cannot be interconverted in the human body. The polyunsaturated fatty acid is considered very long-chain if its carbon chain contains more than 18 carbon atoms. The n-6 family is derived from linoleic acid, and the n-3 family is derived from alpha-linolenic acid (ALA). These two fatty acids are essential fatty acids, i.e. they have to be ingested from our diets. Dietary sources of n-6 PUFA include various plant oils such as corn, olive, safflower and sunflower seed oils, and dietary n-3 PUFA can be

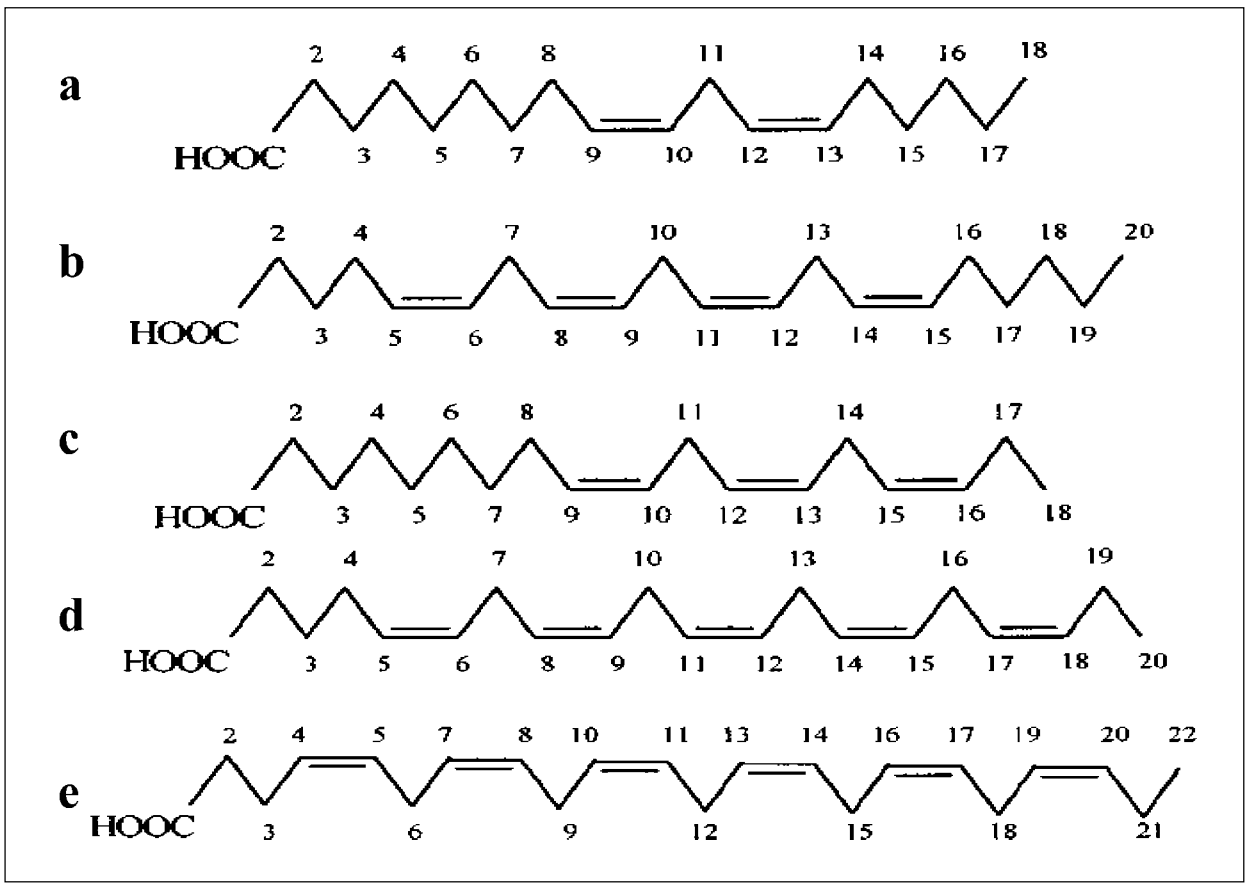

Figure 1. *(a) linoleic acid (18:2 n-6); (b) arachidonic acid (20:4 n-6); (c) alpha-linolenic acid (18:3 n-3); (d) eicosapentaenoic acid (20:5 n-3); (e) docosahexaenoic acid (22:6 n-3). The first number in the ratio denotes the number of carbon atoms in the long carbon chain, whereas the other one denotes the number of double bonds in the chain.*

found in other plant oils, such as linseed, soy and canola oils, as well as fatty fish, such as salmon, sardines, trout, mackerel and herrings. ALA is the only n-3 PUFA of plant origin. More unsaturated very long-chain n-3 PUFA, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are abundant in fish oil.

EPA and DHA are the active ingredients of fish oil which can be synthesized by elongation and desaturation of ALA in the human body, mainly in the liver (Figure 2). Nevertheless, the conversion of ALA to EPA is limited, and the whole body conversion of ALA to DHA is less than 5% in humans. Furthermore, their conversion in the body depend on the concentration of dietary n-6 PUFA and very long-chain PUFA intake.[14-18] Both EPA and DHA are incorporated into phospholipids of all cell membranes, especially in myocardium, retina and brain. They are crucial for the regulation of cell metabolism by influencing the membrane fluidity and ion transports. EPA also competes with arachidonic acid, which is an n-6 PUFA, for cyclooxygenases in eicosanoid synthesis (Figure 2). Eicosanoids derived from arachidonic acid, such as thromboxane A2 and leukotriene B4, are pro-thrombotic and pro-inflammatory, whereas those derived from EPA, such as prostacyclin, thromboxane A3 and leukotriene B5, are anti-thrombotic and anti-inflammatory.[19,20] EPA and DHA have been studied in a wide spectrum of diseases (Table 1), and the ratio between n-3 PUFA and n-6 PUFA in diets, rather than the absolute amount of n-3 PUFA, may be more important for disease prevention.[21, 22] Although the clinical efficacies of EPA and DHA in the prevention of cardiovascular diseases remain to be proven, there are several potential cardioprotective mechanisms, including anti-arrhythmic, anti-atherogenic, anti-thrombotic and vasoprotective effects as discussed

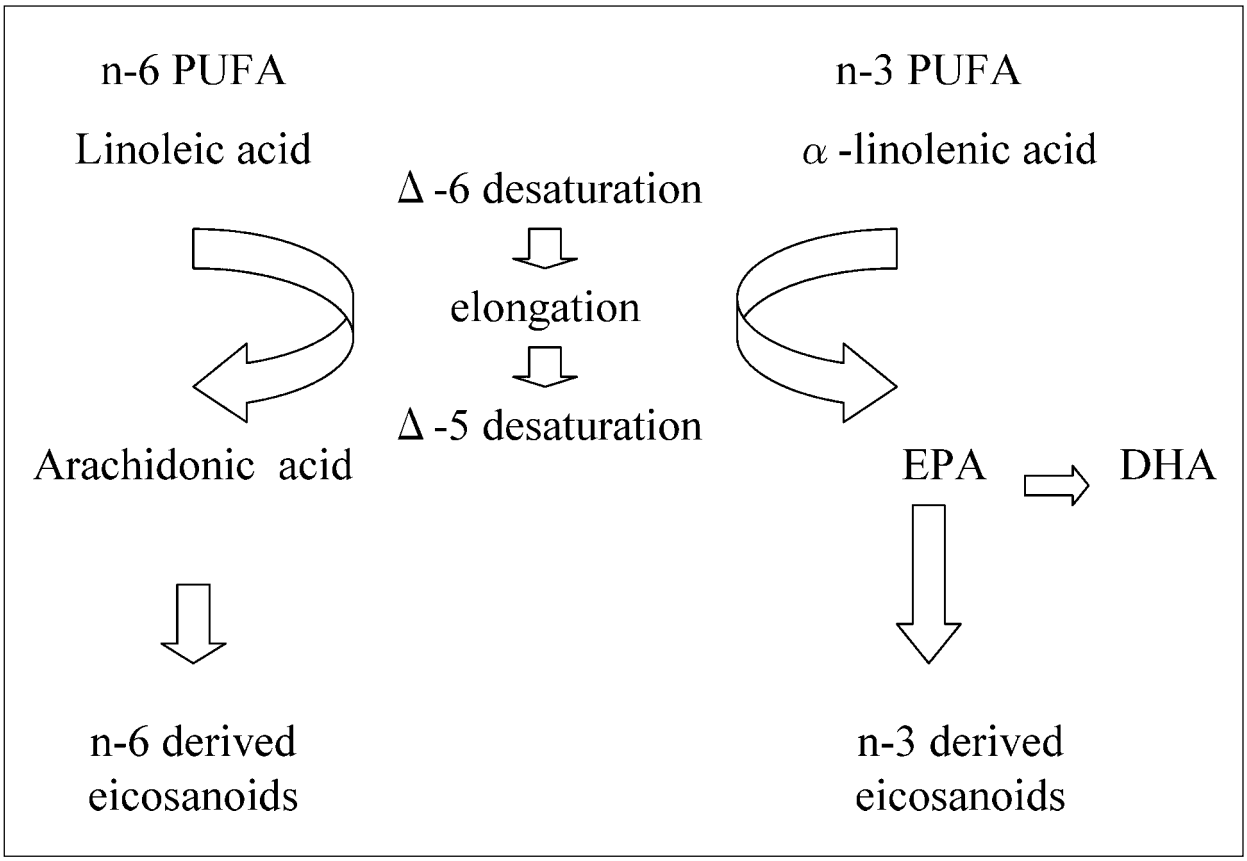

Figure 2. *Metabolism of n-3 and n-6 PUFA and synthesis of eicosanoids. EPA is converted to DHA by further desaturation and elongation processes.*

Table 1. Potential spectrum of benefits from n-3 PUFA

- Cardiovascular diseases
- Retinal and brain development, especially during infancy
- Autoimmue diseases, e.g. systemic lupus erythmatosis, rheumatoid arthritis
- Crohn's disease
- Cancers of breast, prostate and colon

below. Furthermore, these effects also appear be shown a dose-response relationships.

Anti-arrhythmic effect

In the DART trial,[23] 2033 Welsh men with recent myocardial infarction (MI) were randomized to receive at least 2 servings of fatty fish per week or capsules with 0.5 gram of fish oil daily. There was a significant 29% reduction in both cardiac and total mortality within 4 months compared with the control group. However, there was no significant reduction in the incidence of recurrent non-fatal MI. As a result, the anti-arrhythmic effects of fish oil have been postulated to account for these beneficial effects by reducing sudden cardiac death elicited by ventricular arrhythmias.

GISSI-Prevenzione trial,[24] the largest randomized controlled trial on fish oil provided further support for the anti-arrhythmic mechanism. In this study, 11324 patients with post-MI randomized to receive 1 gram fish oil capsule daily (containing 850-882 mg of EPA and DHA) had a significant 20% reduction in cardiovascular mortality, non-fatal MI and stroke after 3.5 years follow-up. Subsequent time-course reanalysis showed that the total mortality was significantly lowered by 41% after 3 months and a significant 53% reduction in sudden death after 4 months.[25] It is worth to note that the majority of patients in this trial were already on aspirin, beta-blockers, angiotensin converting enzyme inhibitors and/or statins. A further 30% significant reduction in cardiovascular mortality in this trial suggests the potency of EPA and DHA in secondary prevention after MI.[25] Moreover, this group of patients was Italian who consumed Mediterranean diet including moderate fish consumption. Therefore, a greater benefit may be conferred to populations with a 'westernized' lifestyle.

Despite these suggestions of the apparent anti-arrthythmic effect of EPA and DHA, the exact cardiac electrophysiology is still unclear. The incorporation of EPA and DHA into the membrane phospholipids in cardiac myocytes can increase the membrane fluidity. This may also inhibit the conductances of the voltage-dependent sodium and L-type calcium ion channels, as well as the voltage-dependent potassium and transient outward channels, either as incorporated form or free circulating form.[26,27] These changes in the compositions of membrane phospholipids may influence the synthesis of eicosanoids to reduce the vulnerability to develop ventricular fibrillation during myocardial ischemia and reperfusion.[26,28] Furthermore, EPA and DHA may have indirect anti-arrhythmic effects through modulation of autonomic nervous system with increased heart rate variability and baroreflex sensitivity, and reduced premature ventricular complexes.[27,28]

Anti-atherogenic effect

Several mechanisms have been postulated to account for the potential anti-atherogenic effects of fish oil, including lowering of plasma triglyceride with a moderate increase in high-density lipoprotein cholesterol (HDL-C), anti-inflammatory effect due to changes in eicosanoid synthesis, and reducing the expression of cell adhesion molecules.[26,29] In contrast to the anti-arrhythmic effect which can be exerted on a low dose (smaller than 1g daily), the antiatherogenic effect requires a higher dose.[26]

Type II diabetes mellitus (DM) is associated with hypertriglyceridaemia, low levels of HDL-C and an abnormal composition of low-density lipoprotein

cholesterol (LDL-C), so EPA and DHA may be beneficial to these patients. Nevertheless, the use of EPA and DHA may result in a poor glycaemic control in patients with impaired glucose tolerance or DM.[30,31] Previous studies have suggested that insulin secretion might be reduced by the intake of n-3 PUFA due to the changes in membrane fluidity and responsiveness of pancreatic islet cells to normal stimuli.[32] Furthermore, the use of EPA and DHA may increase oxidative stress through lipid peroxidation due to their polyunsaturated property, which may contribute to the development of atherosclerosis.[33]

Table 2 summarizes the clinical trials[33-56] on the effect use of EPA and DHA supplement in patients with type II DM. Sirtori et al randomized 418 patients with type II DM to 1.5 g EPA and 1.0 g DHA for the first 2 months and then a total of 1.0 g EPA and 0.7 g DHA for the subsequent 6 months, and showed a significant 15% reduction of plasma triglyceride compared with placebo. Nevertheless, there were no changes in major glycaemic indexes including fasting blood glucose, haemoglobin A1c (HbA1c), insulinaemia and oral glucose tolerance. Furthermore, meta-analysis[57] also demonstrated that fish oil supplementation in patients with type II DM lowered plasma triglyceride level, and had no statistically significant effect on glycaemic control. Nevertheless, the use of higher dose of fish oil in patients with hypertriglyceridaemia significantly increased LDL-C level. There is very limited clinical data on the effect of EPA and DHA on oxidative stress, and the results from clinical trials showed inconsistent results.[33,46,52]

Anti-thrombotic effect

Previous studies have shown that fish oil improved platelet function in patients with hypertension or DM.[43,56,58] This effect has been attributed to EPA which compete with arachidonic acid in eicosanoid synthesis, causing a decrease in the thromboxane A2: thromboxane A3 ratio and an increase in prostacyclin I3. However, while DHA is not a substrate for cyclooxygenase, evidences have shown that purified DHA can also reduce platelet aggregation.[59,60] Woodman et al have suggested that highly purified DHA may be even more effective than EPA for the anti-thrombotic effect.[56] This may be owing to the replacement of arachidonic acid by DHA in platelet membrane phospholipids, inhibition of cyclooxygenases, or direct effects of DHA on platelet function independent of eicosanoid production.[56]

Vasoprotective effect

EPA and DHA improve vascular endothelial function by increasing the availability of nitric oxide.[26,27,61] Previous studied have suggested that supplement of DHA with pure n-3 PUFA, but not EPA, contributed to the improvement in endothelial function.[62] Nevertheless, there is only very limited clinical data on the effects of fish oil on vascular endothelial function.[56] Further studies are required to investigate the effects of fish oil supplement on vascular endothelial function in different subgroup of high risk subjects.

Conclusions

In summary, fish oil supplement has been shown to improve clinical outcomes in post-MI patients, possibly attributed by its anti-arrhythmic effects. Furthermore, existing data demonstrated that fish oil supplement reduced plasma triglyceride level without significant effect of blood glucose level over short term usage, which may contribute to an anti-atherogenic effect. However, the potential cardioprotective effects of fish oil, including anti-thrombotic and vasoprotective effects remain unproved. Furthermore, the long term effects and the optimal dosage of fish oil supplement remain unclear. Therefore, further randomized controlled trials will be required to prove the beneficial effect of fish oil on the prevention of cardiovascular diseases.

Acknowledgement

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Table 2. Summary of clinical trials

Study	Duration	Participants	Interventions	Outcomes	
				Significant	**Insignificant**
Schectman et al 1988[34]	4 weeks	13 participants with type 2 DM 46% hyper-triglyceridaemia, 46% hypertension, 15% CHD	Low dose: 2.6 g EPA + 1.4 g DHA; High dose: 5 g EPA + 2.5 g DHA vs. 12 g safflower oil	TG ↓24% at low dose and 39% at high dose	HDL-C, apoA1
Borkman et al 1989[35]	3 weeks	10 participants with mild type 2 DM, 20% hypertension, 10% CHD	1.8 g EPA + 1.2 g DHA vs. 10 g safflower oil	FBG ↑ 14 % compared with baseline	TG, LDL-C, HDL-C, TC
Hendra et al 1990[36]	6 weeks	80 participants with type 2 DM; 70% of intervention group had microvascular complications compared with 42.5% in control group, 35% of control group had CAD compared with 7.5% in fish oil group.	1.8 g EPA + 1.2 g DHA vs. 10 g olive oil	TG ↓ FBG ↑ after 3 weeks Spontaneous platelet aggregation in whole blood ↓ after 6 wk Factor VII ↑	TC, FBG after 6 weeks
Annuzzi et al 1991[37]	2 weeks	8 males with type 2 DM	1.8 g EPA + 1.2 g DHA vs. 10 g olive oil	TG ↓ LDL-C ↑	FBG, average daily blood glucose
Boberg et al 1992[38]	8 weeks	14 participants with type 2 DM 43% hypertension 7% CAD	1.8 g EPA + 1.2 g DHA vs. 10 g olive oil	TG and VLDL-TG ↓ by 27% and 36% respectively compared with baseline FBG and HbA1c ↑ compared with baseline Plasminogen inhibitor-1 ↑ 21% compared with baseline	LDL-C ↑, FBG, HbA1c
Connor et al 1993[39]	24 weeks	16 participants with type 2 DM and hypertriglyceridaemia	4.1 g EPA + 1.9 g DHA vs. 15 g olive oil	TG, VLDL-TG and VLDL-C ↓ LDL-C ↑	TC, HDL-C
Westerveld et al 1993[40]	8 weeks	20 participants with type 2 DM	Low dose: 0.9 g EPA High dose: 1.8 g EPA vs. 1.6 g olive oil	Platelet-activating factor-induced platelet aggregation ↓ in both high and low dose groups LDL-C ↑	Triglycerides, glycemic control

Table 2. Summary of clinical trials (con't)

Study	Duration	Participants	Interventions	Outcomes	
				Significant	**Insignificant**
McVeigh et al 1993[41]	6 weeks	23 participants with type 2 DM	1.8 g EPA + 1.2 g DHA vs. olive oil	By venous occlusion plethysmography, forearm blood flow ↑ by acetylcholine Forearm blood flow ↓ by N c monomethyl-L-arginine	Forearm blood flow by GTN
McVeigh et al 1994[42]	6 weeks	20 participants with type 2 DM	1.8 g EPA + 1.2 g DHA vs. olive oil	Large-artery compliance estimate ↑ Oscillatory compliance value ↑	
Axelrod et al 1994[43]	6 weeks	18 participants with type 2 DM	1.1 g EPA + 1.5 g DHA vs. 5 g safflower oil	TG ↓ by 44 mg/dl SBP ↓ by 8 mmHg HbA1c ↓ by 0.56% TC ↓ by 20 mg/dl	FBG, HDL-C, LDL-C, collagen-induced thromboxane A2 production, ADP-induced platelet aggregation or TXA2 generation
Puhakainen et al 1995[44]	6 weeks	9 participants with type 2 DM	2.16 g EPA + 1.44 g DHA vs. 12 g corn + olive oil (6 g each)	TG, VLDL-TG, HDL3-TG ↓ by 16%, 23% and 21% respectively	FBG, HbA1c, body weight
Morgan et al 1995[45]	12 weeks	40 participants with well controlled type 2 DM and hyper-triglyceridaemia	Low dose: 2.6 g EPA + 2.4 g DHA High dose: 5.2 g EPA + 4.8 g DHA vs. 9 or 18 g corn oil	TG, VLDL-TG, VLDL-C ↓, LDL-C ↑ at week 6	LDL-C at week 12, TC, HDL-C, FBG, HbA1c, weight, BP
McGrath et al 1996[46]	6 weeks	23 participants with type 2 DM	1.8 g EPA + 1.2 g DHA vs. 10 g olive oil	Thiobarbituric acid reacting substances ↑ by 32%; vitamin E ↓ by 19%	TG ↓ by 14%, FBG ↑ by 3.5%, HDL, HbAlc, LDL, apolipoprotein B
McManus et al 1996[47]	3 months	11 participants with well controlled type 2 DM 36% obese	1.8 g EPA + 1.2 g DHA vs. 35 mg/kg linseed oil	TG ↓	Weight, FBG, insulin levels, HbA1c, TC, LDL-C, HDL-C
Sirtori et al 1997[48]	8 months	418 participants with type 2 DM and hyperlipidaemia	1.5 g EPA + 1.0 g DHA for 2 months, then 1.0 g EPA + 0.7 g DHA for 6 months vs. 3 g olive oil for 8 months	TG ↓ by 15%	FBG, HbA1c, insulin, and oral glucose tolerance

Table 2. Summary of clinical trials (con't)

Study	Duration	Participants	Interventions	Outcomes	
				Significant	**Insignificant**
Goh et al 1997[49]	12 weeks	28 participants with type 2 DM divided into a low polyunsaturated/ saturated fat (P/S) and a high P/S diet group	1.4 g EPA + 0.88 g DHA VS 35 mg/kg linseed oil	TG ↓ by 43% in low P/S diet TG ↓ by 71% in high P/S diet LDL-C ↑ by 2.5% in low P/S diet LDL-C ↑ by 4.5% in high P/S diet	
Luo et al 1998[50]	2 months	12 male participants with type 2 DM, Not on insulin; 20% hypertension; 10% Hyperlipidaemia	1.08 g EPA + 0.72 g DHA VS 6 g sunflower oil	TG ↓ by 14%	FBG, insulin, HbA1c, TC, LDL-C, HDL-C
Patti et al 1999[51]	6 months	16 hyper-triglyceridaemia type 2 DM participants	2.5 g ω-3 fatty acids for 2 months, then 1.7 g ω-3 fatty acids for 4 months VS 3 g olive oil for 2 months, then 2 g olive oil for 4 months		Significant: Small LDL-C ↑ by 10% Insignificant: Other LDL and VLDL distribution and size
Mori et al 1999[52]	8 weeks	55 participants with type 2 DM, hyper-triglyceridaemia and/ or hypoHDL-Cemia	Low-fat (30% of daily energy) diet with daily fish (3.6 g ω-3 fatty acids) vs. Low-fat diet alone vs. Moderate exercise vs. Moderate exercise with low-fat (30% of daily energy) diet with daily fish (3.6 g ω-3 fatty acids)	Urinary F2-isoprostanes ↓ by 20% by fish diet Urinary F2-isoprostanes correlated with BMI, and TG at baseline	Urinary F2-isoprostanes ↓ by 20% by moderate exercise
Woodman et al 2002[53]	6 weeks	51 participants with type 2 DM and drug treatment for hypertension	4 g EPA vs. 4 g DHA vs. 4 g olive oil	FBG ↑ by 1.40 mmol/L and 0.98 mmol/L in EPA and DHA groups respectively TG ↓ by 19% and 15% in EPA and DHA groups respectively HDL2-C ↑ by 16% and 12% in EPA and DHA groups respectively HDL3-C ↓ by 11% with EPA	HbA1c, BP, TC, LDL-C, HDL-C

Table 2. Summary of clinical trials (con't)

Study	Duration	Participants	Interventions	Outcomes	
				Significant	Insignificant
Petersen et al 2002[54]	8 weeks	42 participants with type 2 DM, hyper-triglyceridaemia and low or moderate alcohol intake	4 g fish oil containing 2.6 g EPA+DHA vs. 4 g corn oil Both containing 13.4 mg vit. E	TG ↓ 12 times more HDL2b-C ↑ 0.05 mmol/L more HDL2a-C ↓ 66% less	LDL-C, HDL-C, conc. of small dense LDL particles
Pedersen et al 2003[55]	8 weeks	49 participants with type 2 DM and hypertriglyceridaemia	4 g fish oil containing 2.6 g EPA+DHA vs. 4 g corn oil	LDL oxidation mean lag time and mean propagation time ↓ by 16% and 17% TG ↓ HDL ↑	HbA1c, FBG
Woodman et al 2003[56]	6 weeks	51 participants with type 2 DM and drug treatment for hypertension	4 g EPA VS 4 g DHA vs. 4 g olive oil	Collagen aggregation ↓ by 16.9% Collagen-stimulated thromboxane release ↓ by 18.8%	PAF-stimulated platelet aggregation, fibrinolytic function, vascular function by FMD and NMD
Mori et al 2003[33]	6 weeks	51 participants with type 2 DM and drug treatment for hypertension	4 g EPA vs. 4 g DHA vs. 4 g olive oil	Urinary F2-isoprostanes ↓ by 19% and 20% with EPA and DHA respectively	CRP, IL-6, TNF-α

Abbreviations: CHD= coronary heart disease; CRP=C-reactive protein; DHA=docosahexaenoic acid; DM=diabetes mellitus; EPA= eicosapentaenoic acid; FMD=flow mediated dilation; FBG=fasting blood glucose; HDL-C=high density lipoprotein-cholesterol; LDL-C= low density lipoprotein-cholesterol; NMD=nitroglycerin mediated dilation; SBP=systolic blood pressure; TC= total cholesterol; TNF= tumor necrosis factor; TG=triglyceride

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