

Polyunsaturated Fatty Acids in Children

Ji-Hyuk Lee

Department of Pediatrics, College of Medicine and Medical Research Institute, Chungbuk National University, Cheongju, Korea

Polyunsaturated fatty acids (PUFAs) are the major components of brain and retina, and are the essential fatty acids with important physiologically active functions. Thus, PUFAs should be provided to children, and are very important in the brain growth and development for fetuses, newborn infants, and children. Omega-3 fatty acids decrease coronary artery disease and improve blood flow. PUFAs have been known to have anti-inflammatory action and improved the chronic inflammation such as auto-immune diseases or degenerative neurologic diseases. PUFAs are used for metabolic syndrome related with obesity or diabetes. However, there are several considerations related with intake of PUFAs. Obsession with the intake of unsaturated fatty acids could bring about the shortage of essential fatty acids that are crucial for our body, weaken the immune system, and increase the risk of heart disease, arrhythmia, and stroke. In this review, we discuss types, physiologic mechanism of action of PUFAs, intake of PUFAs for children, recommended intake of PUFAs, and considerations for the intake of PUFAs. (**Pediatr Gastroenterol Hepatol Nutr 2013; 16: 153 ~ 161**)

Key Words: Fatty acid, Unsaturated, Omega-3, Omega-6, Child

INTRODUCTION

In recent years, with the increasing concern about health, the concern about fats is also increasing. Fats are molecules that combined 1 glycerol and 3 fatty acids, which are used as major energy source of our body and are stored in hypodermis, muscle, and liver of our body. When our body absorbs fats, they are again decomposed into 1 glycerol and 3 fatty acids by lipase, and some fat molecules are absorbed as they are via intestines. The absorbed fats are first stored in

liver, hypodermic connective tissue, mesentery, or muscle, and later become energy source via decomposition as necessary.

In addition, depending on the presence of a double bond within the molecules of fatty acids, it is called saturated fatty acids if there is no double bond, and unsaturated fatty acids if there is a double bond. It is commonly known that saturated fatty acids are animal oil and harmful for health, and unsaturated fatty acids are vegetable oil and good for health. Therefore, polyunsaturated fatty acids (PUFAs) in-

Received : August 17, 2013, Accepted : August 25, 2013

Corresponding author: Ji-Hyuk Lee, Department of Pediatrics, Chungbuk National University College of Medicine, 52, Naesudong-ro, Heungdeok-gu, Cheongju 361-763, Korea. Tel: +82-43-269-6050, Fax: +82-43-264-6620, E-mail: e-z-up@daum.net

Copyright © 2013 by The Korean Society of Pediatric Gastroenterology, Hepatology and Nutrition

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

cluding omega-3 have drawn much attention. A lot of drugs and health supplement food are on the market, and especially, the number of products relevant to children has also increased. However, as there is concern about indiscriminate and excessive intake of PUFAs, it is important to understand the appropriate use of PUFAs.

Therefore, this paper aims to investigate the basic concepts, clinical applications, and the latest research results for PUFAs, and to examine future prospect.

TYPES OF PUFAS

Saturated fatty acids are mostly contained in animal oil such as beef, pork, and butter. Fish oil is also animal oil, but is classified as an unsaturated fatty acid. Vegetable fats are mostly unsaturated fatty acids, but coconut oil and palm oil are classified as saturated fatty acids.

Due to the stable nature, saturated fatty acids solidify and turn white at low temperatures, which are not easily denaturalized even though heat or pressure is applied, and are easy to store. Saturated fatty acids are problematic because they induce a number of problems related with blood circulation and blood vessels. Saturated fatty acids could induce arteriosclerosis, angina pectoris, and stroke by increasing blood cholesterol levels, and the blood flow could be

affected by saturated fatty acids which solidify at low temperatures.

Due to the structurally unstable nature, unsaturated fatty acids do not solidify and exist in liquid form at low temperatures, which are easily denaturalized when heat or pressure is applied, and go bad easily. In general, unsaturated fatty acids are known to have beneficial functions for health.

There are about 10 kinds of unsaturated fatty acids, and the ones with a physiologically important role are α -linolenic acid (ALA), linoleic acid, arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (Table 1). The ALA, linoleic acid, and AA are essential for normal growth and health, but are not synthesized in the body of mammals, and thus belong to essential fatty acids.

Unsaturated fatty acids can also be classified as omega series. This method classifies unsaturated fatty acids depending on the position of the first double bond from the omega, which is the carbon atom at the end of the carbon chain (CH₃ radical) within the molecular structure of fatty acids. The representative examples are omega-3 (n-3), omega-6 (n-6), and omega-9 (n-9).

In general, omega-3 is plentiful in fish oil (e.g., tuna, Japanese Spanish mackerel, Pacific saury, chub mackerel, salmon, Pacific herring, flathead mullet, and sardine), and is contained abundantly in vegetable oil such as perilla oil, flaxseed oil, soybean oil, and canola oil. The omega-3 series fatty acids that are nutritionally important are ALA, EPA, and DHA. Mammals are not able to synthesize omega-3 series fatty acids, and have a limited ability to synthesize EPA and DHA (long chain fatty acids) from ALA (short chain fatty acid).

Omega-6 series fatty acids are plentiful in grape seed oil, corn oil, cottonseed oil, soybean oil, and sunflower oil. The omega-6 series fatty acids include linoleic acid, γ -linolenic acid, and AA.

Omega-9 series fatty acids are oleic acids, and more than 80% of olive oil is composed of these fatty acids. The omega-9 series fatty acids are also included in lard, palm oil, and sesame oil.

Frequently mentioned along with unsaturated

Table 1. Unsaturated Fatty Acid

Variable	Carbon/double bond
Saturated fatty acid	
Myristic acid	C14/0
Stearic acid	C18/0
Monounsaturated fatty acid	
Palmitoleic acid	C16/1
Oleic acid	C18/1
Polyunsaturated fatty acid	
Linoleic acid	C18/2
Linolenic acid	C18/3
α -linolenic acid	C18/3
γ -linolenic acid	C18/3
Arachidonic acid	C20/4
Eicosapentaenoic acid	C20/5
Docosahexaenoic acid	C22/6

fatty acids are trans fatty acids. Trans fatty acids are seldom made naturally, and are artificial saturated fats which were made by adding hydrogen atom to the double bond of unsaturated fatty acids at the trans-position instead of the cis-position within fatty acid molecules. Unsaturated fats go bad easily and do not have a taste as good as that of saturated fats when cooking, and therefore, trans fats were made with much effort to resolve the problems. As trans fats were made from unsaturated fats, it was thought that the shortcomings of saturated fats could be eliminated, but there was absolutely no difference. Trans fats are plentiful in margarine and shortening, and are also contained abundantly in fast food such as bread, confectionery, French-fried potatoes, chicken, and popcorn.

PHYSIOLOGICAL MECHANISM OF ACTION OF PUFAS

PUFAs are essential fatty acids, which are crucial for normal growth and health, and are not synthesized in the body of mammals. Various symptoms could occur when PUFAs are insufficient, and thus, PUFAs have been considered medically important. Especially, the beneficial health functions of EPA and DHA are well known, which are the materials recognized as the omega-3 fatty acids functionality. EPA promotes blood circulation, and reduces blood cholesterol (low-density lipoprotein, LDL). DHA is the constituent that comprises brain tissue and optic nerve, and improves brain functions by revitalizing brain cells. In general, omega-3 fatty acids have the anti-inflammatory effect, anti-arrhythmic effect, and anti-thrombotic effect, while omega-6 fatty acids tend to cause inflammation and thrombus formation.

Cardiovascular diseases

The study result that omega-3 fatty acids are related with coronary artery disease and blood flow became known in the 1970s by Danish researchers [1]. The researchers found that Greenlandic Inuit people have lower occurrence of acute myocardial infarction

than that of Danish people, and identified that it is closely related with omega-3 fatty acids. This study result is consistent with the statistical result that the Japanese people, who eat a lot of fish, have low occurrence of coronary artery disease [2]. Three epidemiologic surveys conducted in the United States are also consistent with this result. In the comparison of 80 adults who experienced primary cardiac arrest and 108 healthy adults, Siscovick et al. [3] found that the EPA and DHA contents of erythrocyte membrane are related with primary cardiac arrest. Albert et al. [4] examined the risk factors by taking the blood samples of 14,916 healthy males, and after 17 years, investigated the data of 94 males who died of heart disease, which showed that their omega-3 fatty acid contents were low. In addition, Lemaitre et al. [5] identified that blood EPA and DHA contents are related with fatal ischemic heart disease.

For most random assignment control experiments of omega-3 fatty acids, coronary artery disease was set as a direct endpoint. The representative study is diet and reinfarction trial (DART) (Burr et al. [6]), which indicated that the survival rate for myocardial infarction could be increased if one ingests 500-800 mg of omega-3 fatty acids every day. Also, the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto)-prevention study (1999) [7] identified that the death rate from cardiac arrest could be reduced if one ingests 300 mg of vitamin E and 850 mg of omega-3 fatty acids together. Harris et al. [8] reported that the intake of salmon oil could improve lipid profile by reducing the levels of plasma cholesterol, neutral fats, LDL cholesterol, and very-LDL cholesterol. Also, the intake of omega-3 fatty acids controls blood neutral fats depending on the concentration. Some study reported that ingesting 1-1.5 g of DHA and EPA reduces non-cholesterol blood neutral fats by 25-30% [9]. In addition, some study result indicated that fish oil, which has abundant DHA and EPA, suppresses the activity of endothelial lipase that increases the concentration of plasma high-density lipoprotein cholesterol. A recent meta-analysis study reported that the sufficient intake of ALA, which is an omega-3 series fatty acid, also reduces

the onset frequency of cardiovascular diseases [10].

The above-mentioned effects of omega-3 fatty acids are thought to be caused by the anti-thrombotic effect, but inconsistent results have been reported regarding the effect that inhibits thrombus formation. Consistent thrombus inhibition functionality was observed at high concentrations, but this was not the case at low concentrations [11]. Some study reported that the intake of salmon oil induces the integration of EPA into the phospholipids of platelet, and accordingly extends the bleeding time [12]. This study was verified as the report that fish oil can change the reactivity of blood vessels, and can favorably change the characteristics of artery walls. These changes could help maintain healthy blood flow [13].

Neurological diseases

PUFAs are the major components of brain and retina, and are the essential fatty acids with important physiologically active functions. Thus, PUFAs should be provided to children, and are very important in the brain growth and development for fetuses, newborn infants, and children.

Omega-3 series fatty acids also play an important role in dementia. When the intake of DHA and EPA is high, the occurrence of Alzheimer's disease is low, and the deterioration of cognitive function is also low.

Anti-inflammatory action

Fatty acids have been known to be involved in inflammatory reaction as eicosanoids such as AA are metabolized by cyclooxygenase (COX), and act as the precursor of inflammatory reaction. In this regard, PUFAs have been known to have anti-inflammatory action as the increase of EPA and DHA reduces the AA concentration, and suppresses a series of inflammatory reaction. Especially, Smith et al. [14] suggested that dietary fish oil reduces prostaglandin via three different mechanisms. First, the dietary intake of omega-3 fatty acids produces less prostaglandin than that of omega-6 series fatty acids. Second, omega-3 fatty acids compete against omega-6 fatty acids, to combine with the specific site

of COX 1 enzyme that converts omega-6 fatty acids into prostaglandin. Therefore, as more omega-3 fatty acids compete to combine with the specific site, the conversion of omega-6 fatty acids into prostaglandin could be reduced. Third, omega-3 fatty acids can also act as the precursor of prostaglandin, but the activity of this prostaglandin is 2-50 times lower than that of the prostaglandin produced by omega-6 fatty acids absorbed from dietary plants. In addition, another process for anti-inflammatory action has recently been reported, and this suggests that neutrophil secretes the inflammation resolution mediators which control and suppress inflammatory reaction using fatty acids as the precursor [15]. The examples are lipoxin (derived from AA), resolvin (derived from EPA and DHA), and epi-lipoxin. Also, in a study that used the nutritional supplements based on fish oil for the treatment of critical patients, it was reported that omega-3 fatty acids suppress a series of action of NF-kappaB, and the anti-inflammatory reaction is induced by the action of inflammation resolution mediators [16].

Recently, it was reported that the DHA and EPA of omega-3 fatty acids act as ligands for the G-protein receptor of cell membrane, and contribute to anti-inflammatory reaction and insulin sensitization reaction for mice [17].

In addition, the increase of interleukin 1 (IL-1) is observed in coronary artery disease, depression, senility phenomenon, and cancer. Similarly, the increase of IL-1 is observed in autoimmune diseases such as arthritis, Crohn's disease, ulcerative colitis, and lupus, and the increase of leukotrien (LTB4) formation, which is the inflammation precursor derived from omega-6 fatty acids, is observed. When EPA and DHA were administered to these diseases, it was reported that by suppressing both autoimmunity and T lymphocyte activity, the pathophysiology of inflammatory reaction or autoimmune disease could be improved, the clinically good effects were observed, and the use of the existing anti-inflammatory drugs could be reduced [18]. These results were also verified by a number of other placebo experiments. In addition, as leukotriene was found

to be an important element for immunity and inflammation system reaction, and be related with arthritis, lupus, asthma, or inflammation recovery, much attention was given to finding a method to control the synthesis of omega-6. At the present time, the simplest method is to use more omega-3 fatty acids and to reduce the use of omega-6 fatty acids. In the future, through more research, omega-3 fatty acids are expected to be used for the treatment of inflammatory diseases and autoimmune diseases such as lupus, ankylosing spondylitis, IgA nephropathy, psoriasis, or xerophthalmia.

Metabolic syndrome

Obesity is related with metabolic syndrome, and is especially an important risk factor for the occurrence of type 2 diabetes and cardiovascular diseases. Low-level chronic inflammation, occurring at the adipose tissue in the body of obese people, is related with insulin resistance and the etiology of metabolic syndrome. The exact trigger of this inflammation process is not known, but the hypoxia of adipose tissue, endoplasmic reticular stress, and the activation of innate immune system relevant to saturated fatty acids were identified as the important processes. Especially, the macrophage and T lymphocyte play an important role in mediating this immune process. It is known that omega-3 plays an important role in the above-mentioned process [19]. The actions of omega-3 fatty acids for adipose tissue are 1) preventing the hypertrophy and proliferation of adipose tissue, 2) inducing the biosynthesis of mitochondria within adipose cells, 3) inducing adiponectin, and 4) reducing the inflammation within adipose tissue [20]. According to a study, the DHA of marine origin prevents the inflammation of adipose tissue and insulin resistance for rodents, which were induced by a high fat diet, and also changes the symptoms in the reverse direction [21]. In addition, PUFAs affect the synthesis function of many transmitters of adipose cells by acting on many transcriptional factors in adipose cells [22].

A lot of studies found that omega-3 fatty acids reduce blood pressure slightly. However, plenty of

omega-3 fatty acids need to be taken to obtain clinically meaningful results, and care should be taken in the treatment because this increases the risk of bleeding.

INTAKE OF PUFAS FOR CHILDREN

Omega-3 and infants

Omega-3 is crucial for children's health. It was reported that infants, who had powdered formula containing abundant DHA (a type of omega-3), showed superior cooperation between eyes and hands, concentration, and social skills, and had higher scores in the intelligence test [23]. It was also reported that when long-chain polyunsaturated fatty acids (LCPUFAs) were taken during pregnancy, the frequency of preterm birth was decreased by increasing the duration of pregnancy [24]. In 2008, some study reported that children of mothers who had fish oil during pregnancy are less likely to have asthma in their teenage years [25]. Also, some study reported that powdered formula containing omega-3 helps the growth and brain development of preterm infants. It is not that the above-mentioned studies are decisive, but they could be the reason for ingesting omega-3 that contains DHA or EPA. Accordingly, a lot of powdered formula currently on the market contains DHA or EPA. In addition, breast milk is the most ideal source of omega-3 though it is largely affected by the food that mothers have ingested.

However, a recent meta-analysis relevant to omega-3 suggested that there is no convincing evidence to conclude whether the intake of LCPUFAs during pregnancy helps cognitive development or visual development [26], and more research is necessary in this respect in the future.

There is no clear evidence on the appropriate duration of intake. Several studies reported that it is helpful for visual development if omega-3 fatty acids are continuously ingested until 12 months [27,28], but more research is necessary.

PUFAs for children and adolescents

Several studies reported that children with atten-

tion deficit hyperactivity disorder (ADHD) have lower omega-3 levels than those of normal children. A few studies are taking note of fish oil as the medicine, and actually reported that behavior is improved, hyperactivity is reduced, and concentration is improved. However, a Cochrane review reported that there is still no clear evidence to determine whether PUFAs are helpful for ADHD [29]. Recently, another Cochrane review reported that the intake of PUFAs improves the learning ability of children with learning disorder [30]. Also, in a recent 20-year study of young adults in the United States, it was reported that more intake of PUFAs is associated with lower prevalence rate of asthma [31]. When DHA was administered to child patients with familial hyperlipidemia, the elasticity of vascular endothelium was improved, and it is thought that this could help prevent the progress to the onset of early coronary artery heart disease [32].

RECOMMENDED INTAKE OF PUFAS

For the recommended daily intake of omega-3, a number of literatures were examined to determine the intake that improves blood flow and controls blood neutral fats. Based on the results of DART study [6] and Krishnamurti et al. [11], the minimum intake was set to 500 mg. This is consistent with the intake recommended by the International Society for the Study of Fatty Acids and Lipids (ISSFAL). For the adequate intake of DHA and EPA in international health functional food, the daily intake of 0.5-2 g was proposed, considering the intake of less than 3 g suggested by the FDA and considering that omega-3 can be ingested from a diet. This recommended intake is the amount that can be ingested in dietary life if one has about 2 chub mackerels every week. For the patients with coronary artery disease, the American Heart Association recommends ingesting 1 g of EPA and DHA per day, from fish or from medicine according to doctor's prescription.

In the case of pregnant women or lactating women, the ISSFAL recommends ingesting at least 200 mg of DHA per day to help the brain development of

fetuses or newborn infants. For pregnant women or lactating women, the United States Environmental Protection Agency (USEPA) recommends ingesting less than 180 g of fish per week.

As for the intake of omega-6 fatty acids, evidence is still insufficient. However, to maintain good health, it is appropriate to ingest linoleic acid so that it constitutes about 2% of total daily calories. As mentioned earlier, omega-3 and omega-6 compete with each other, and therefore, it is important to maintain a proper intake ratio between the two, whether they are ingested from food or medicine. The World Health Organization (WHO) recommends an intake ratio of 5-10 : 1 (omega-6 : omega-3).

In the case of PUFAs for children, studies are insufficient regarding the types, amount, and duration of the intake of PUFAs. A lot of powdered formula currently on the market contains omega-3 fatty acids, but the effective intake for children has not been clearly investigated. For young children, the USEPA recommends ingesting less than 60 g of fish per week, considering the potential risk of environmental contamination, and also recommends never ingesting a fish oil tablet without doctor's prescription. As for the recommended intake of omega-3 fat-

Table 2. Adequate Intake for Omega-Fatty Acids

Life stage	Source	Male (g/day)	Female (g/day)
Infants (mo)			
0-6	ALA, EPA, DHA	0.5	0.5
7-12	ALA, EPA, DHA	0.5	0.5
Children (yr)			
1-3	ALA	0.7	0.7
4-8	ALA	0.9	0.9
9-13	ALA	1.2	1.0
Adolescents (yr)			
14-18	ALA	1.6	1.1
Adults (yr)			
≥19	ALA	1.6	1.1
Pregnancy (all ages)	ALA	-	1.4
Lactation (all ages)	ALA	-	1.3

ALA: α -linoleic acid, EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid.

Adapted from Trumbo et al. J Am Diet Assoc 2002;102:1621-30 [33].

Table 3. Adequate Intake for Omega-6 Fatty Acids

Life stage	Source	Male (g/day)	Female (g/day)
Infants (mo)			
0-6	Omega-6 PUFA	4.4	4.4
7-12	Omega-6 PUFA	4.6	4.6
Children (yr)			
1-3	LA	7	7
4-8	LA	10	10
9-13	LA	12	10
Adolescents (yr)			
14-18	LA	16	11
Adults (yr)			
19-50	LA	17	12
≥51	LA	14	11
Pregnancy (all ages)	LA	-	13
Lactation (all ages)	LA	-	13

PUFA: polyunsaturated fatty acid, LA: linoleic acid.
Adapted from Trumbo et al. J Am Diet Assoc 2002;102:1621-30 [33].

ty acids for infants, the WHO suggests 400 mg per 10 kg of body weight, and the ISSFAL suggests 350-750 mg per 10 kg of body weight. In 2002, the Council on Food and Nutrition of the American Medical Association published the recommended intake of omega-3 and omega-6 fatty acids depending on age, as shown below (Tables 2 and 3) [33].

CONSIDERATIONS FOR THE INTAKE OF PUFAS

As discussed earlier, many large-scale epidemiologic surveys demonstrated that the intake of omega-3 fatty acids is related with the occurrence of coronary artery diseases. However, this includes both the intake from general diets and the intake from supplements. Hence, the intake from supplements such as medicine or health supplement food needs to be examined.

Until recently, many of the coronary artery disease-related epidemiologic surveys have been performed based on the Western diets such as that of the United States. Considering the Korean diets which have high intake of fish, it will be difficult to accurately apply the correlation with the occurrence of coronary artery diseases obtained from the epi-

demologic surveys to Korean population. Also, considering the dosage forms of health functional food that are only applied to supplements, the disease occurrence risk reduction function of health functional food needs to be approached carefully.

It is not that every unsaturated fatty acid is beneficial. On the contrary, obsession with the intake of unsaturated fatty acids could bring about the shortage of essential fatty acids that are crucial for our body, weaken the immune system, and increase the risk of heart disease, arrhythmia, and stroke. When fish oil is ingested for a long period of time (several months), it is better to ingest vitamin E (antioxidant) together, in preparation for lipid peroxidation. Also, as the toxicity of vitamin A or D could be increased, care should be taken in this regard.

DHA and EPA should not be ingested prior to surgery because their thrombus dissolution action would make it difficult to stop bleeding. For omega-3 series fatty acids and omega-6 series fatty acids that are essential fatty acids, the competition between the two fatty acids and the balance between the requirements are very important at the desaturation-chain extension step in the body. Therefore, health functional food should not be excessively ingested above the proposed intake, besides the fatty acids ingested from diets.

Omega-3 fatty acids are the food that has safely been ingested for a long period of time, but the FDA recommends not ingesting more than 3 g of fish oil-derived omega-3 fatty acids per day. Though it is not serious toxicity, these fats and oil contain a lot of fat-soluble vitamins, and care should be taken. However, the dose-response effect for omega-3 fatty acids is not clear. For the Inuit people, no particular side effect was observed though 6.5 g of omega-3 fatty acids was ingested every day, and no particular side effect was reported except for the side effect of gastro-intestinal tract when 3 g of DHA and EPA was ingested every day [34].

The intake of unsaturated fatty acids for pregnant women or lactating women needs to be treated carefully. In the case of pregnant women, heavy met-

als (e.g., mercury and lead), dioxins, and polychlorinated biphenyl compounds, accumulated within fish due to marine environment contamination, could have an adverse effect on fetuses. Especially, as mercury is accumulated in fish meat, the intake of fish oil would be safer. However, fish oil could also be risky if it is not well refined. There is no convincing evidence on the benefits for infants when pregnant women or lactating women ingest omega-3 fatty acids. If DHA is ingested in large quantities during pregnancy, birth weight is increased, but the risk of bleeding is also increased.

CONCLUSION

PUFAs are the major components of brain and retina, and are the essential fatty acids with important physiologically active functions. Thus, PUFAs should be provided to children, and are very important in the brain growth and development for fetuses, newborn infants, and children. PUFAs have been known to decrease coronary artery disease and improve blood flow. PUFAs have anti-inflammatory action and improve the chronic inflammation such as auto-immune diseases or degenerative neurologic diseases. PUFAs are used for metabolic syndrome related with obesity or diabetes. However, there are several considerations related with intake of PUFAs. There is no clear evidence on the appropriate duration or dose to intake PUFAs in children, so more researches are needed in the future.

REFERENCES

1. Bang HO, Dyerberg J, Sinclair HM. The composition of the Eskimo food in north western Greenland. *Am J Clin Nutr* 1980;33:2657-61.
2. Kagawa Y, Nishizawa M, Suzuki M, Miyatake T, Hamamoto T, Goto K, et al. Eicosapolyenoic acids of serum lipids of Japanese islanders with low incidence of cardiovascular diseases. *J Nutr Sci Vitaminol (Tokyo)* 1982;28:441-53.
3. Siscovick DS, Raghunathan TE, King I, Weinmann S, Wicklund KG, Albright J, et al. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *JAMA* 1995;274:1363-7.
4. Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC, et al. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *N Engl J Med* 2002;346:1113-8.
5. Lemaitre RN, King IB, Mozaffarian D, Kuller LH, Tracy RP, Siscovick DS. n-3 Polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. *Am J Clin Nutr* 2003;77:319-25.
6. Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989;2:757-61.
7. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. *Lancet* 1999;354:447-55.
8. Harris WS, Connor WE, McMurry MP. The comparative reductions of the plasma lipids and lipoproteins by dietary polyunsaturated fats: salmon oil versus vegetable oils. *Metabolism* 1983;32:179-84.
9. Harris WS, Rambjør GS, Windsor SL, Diederich D. n-3 fatty acids and urinary excretion of nitric oxide metabolites in humans. *Am J Clin Nutr* 1997;65:459-64.
10. Pan A, Chen M, Chowdhury R, Wu JH, Sun Q, Campos H, et al. α -linoleic acid and risk of cardiovascular disease: a systematic review and meta-analysis. *Am J Clin Nutr* 2012;96:1262-73.
11. Krishnamurti C, Stewart MW, Cutting MA, Rothwell SW. Assessment of omega-fatty-acid-supplemented human platelets for potential improvement in long-term storage. *Thromb Res* 2002;105:139-45.
12. Goodnight SH Jr, Harris WS, Connor WE. The effects of dietary omega 3 fatty acids on platelet composition and function in man: a prospective, controlled study. *Blood* 1981;58:880-5.
13. 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;14:1425-9.
14. Federation of American Societies for Experimental Biology. Anti-inflammatory effects of omega 3 fatty acid in fish oil linked to lowering of prostaglandin [Internet]. Rockville (MD): Science Daily; 2006 [cited 2013 Sep 13]. Available from: <http://www.sciencedaily.com/releases/2006/04/060404085719.htm>.

15. Serhan CN. Novel omega -- 3-derived local mediators in anti-inflammation and resolution. *Pharmacol Ther* 2005;105:7-21.
16. Singer P, Shapiro H, Theilla M, Anbar R, Singer J, Cohen J. Anti-inflammatory properties of omega-3 fatty acids in critical illness: novel mechanisms and an integrative perspective. *Intensive Care Med* 2008;34: 1580-92.
17. Oh DY, Talukdar S, Bae EJ, Imamura T, Morinaga H, Fan W, et al. GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-ensitizing effects. *Cell* 2010;142:687-98.
18. Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. *J Am Coll Nutr* 2002;21: 495-505.
19. Kalupahana NS, Claycombe KJ, Moustaid-Moussa N. (n-3) Fatty acids alleviate adipose tissue inflammation and insulin resistance: mechanistic insights. *Adv Nutr* 2011;2:304-16.
20. Kopecky J, Rossmeis M, Flachs P, Kuda O, Brauner P, Jilkova Z, et al. n-3 PUFA: bioavailability and modulation of adipose tissue function. *Proc Nutr Soc* 2009;68:361-9.
21. Kalupahana NS, Claycombe K, Newman SJ, Stewart T, Siriwardhana N, Matthan N, et al. Eicosapentaenoic acid prevents and reverses insulin resistance in high-fat diet-induced obese mice via modulation of adipose tissue inflammation. *J Nutr* 2010;140:1915-22.
22. Madsen L, Petersen RK, Kristiansen K. Regulation of adipocyte differentiation and function by polyunsaturated fatty acids. *Biochim Biophys Acta* 2005; 740:266-86.
23. Birch EE, Garfield S, Hoffman DR, Uauy R, Birch DG. A randomized controlled trial of early dietary supply of long-chain polyunsaturated fatty acids and mental development in term infants. *Dev Med Child Neurol* 2000;42:174-81.
24. Decsi T. Effects of supplementing LCPUFA to the diet of pregnant women: data from RCT. *Adv Exp Med Biol* 2009;646:65-9.
25. Olsen SF, Østerdal ML, Salvig JD, Mortensen LM, Rytter D, Secher NJ, et al. Fish oil intake compared with olive oil intake in late pregnancy and asthma in the offspring: 16 y of registry-based follow-up from a randomized controlled trial. *Am J Clin Nutr* 2008;88:167-75.
26. Gould JF, Smithers LG, Makrides M. The effect of maternal omega-3 (n-3) LCPUFA supplementation during pregnancy on early childhood cognitive and visual development: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2013;97: 531-44.
27. Morale SE, Hoffman DR, Castañeda YS, Wheaton DH, Burns RA, Birch EE. Duration of long-chain polyunsaturated fatty acids availability in the diet and visual acuity. *Early Hum Dev* 2005;81:197-203.
28. Hoffman DR, Theuer RC, Castañeda YS, Wheaton DH, Bosworth RG, O'Connor AR, et al. Maturation of visual acuity is accelerated in breast-fed term infants fed baby food containing DHA-enriched egg yolk. *J Nutr* 2004;134:2307-13.
29. Gillies D, Sinn JKH, Lad SS, Leach MJ, Ross MJ. Polyunsaturated fatty acids (PUFA) for attention deficit hyperactivity disorder (ADHD) in children and adolescents. *Cochrane Database Syst Rev* 2012;7: CD007986.
30. Tan ML, Ho JJ, Teh KH. Polyunsaturated fatty acids (PUFAs) for children with specific learning disorders. *Cochrane Database Syst Rev* 2012;12:CD009398.
31. Li J, Xun P, Zamora D, Sood A, Liu K, Daviglius M, et al. Intakes of long-chain omega-3 (n-3) PUFAs and fish in relation to incidence of asthma among American young adults: the CARDIA study. *Am J Clin Nutr* 2013;97:173-8.
32. Engler MM, Engler MB, Malloy M, Chiu E, Besio D, Paul S, et al. Docosahexaenoic acid restores endothelial function in children with hyperlipidemia: results from the EARLY study. *Int J Clin Pharmacol Ther* 2004;42: 672-9.
33. Trumbo P, Schlicker S, Yates AA, Poos M; Food and Nutrition Board of the Institute of Medicine, The National Academies. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. *J Am Diet Assoc* 2002;102: 1621-30.
34. Leaf A, Jorgensen MB, Jacobs AK, Cote G, Schoenfeld DA, Scheer J, et al. Do fish oils prevent restenosis after coronary angioplasty? *Circulation* 1994;90:2248-57.