

Review

n-3 Long-Chain Polyunsaturated Fatty Acids in Type 2 Diabetes: A Review

JOYCE A. NETTLETON, DSc, RD; ROBERT KATZ, PhD

ABSTRACT

Historically, epidemiologic studies have reported a lower prevalence of impaired glucose tolerance and type 2 diabetes in populations consuming large amounts of the n-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFAs) found mainly in fish. Controlled clinical studies have shown that consumption of n-3 LC-PUFAs has cardioprotective effects in persons with type 2 diabetes without adverse effects on glucose control and insulin activity. Benefits include lower risk of primary cardiac arrest; reduced cardiovascular mortality, particularly sudden cardiac death; reduced triglyceride levels; increased high-density lipoprotein levels; improved endothelial function; reduced platelet aggregability; and lower blood pressure. These favorable effects outweigh the modest increase in low-density lipoprotein levels that may result from increased n-3 LC-PUFA intake. Preliminary evidence suggests increased consumption of n-3 LC-PUFAs with reduced intake of saturated fat may reduce the risk of conversion from impaired glucose tolerance to type 2 diabetes in overweight persons. Reported improvements in hemostasis, slower progression of artery narrowing, albuminuria, subclinical inflammation, oxidative stress, and obesity require additional confirmation. Expected health benefits and public health implications of consuming 1 to 2 g/day n-3 LC-PUFA as part of lifestyle modification in insulin resistance and type 2 diabetes are discussed.

J Am Diet Assoc. 2005;105:428-440.

The increasing incidence of type 2 or non-insulin-dependent diabetes mellitus worldwide and in US adults and children poses an immense public health and medical challenge for the implementation of successful preventive and treatment strategies (1,2). The Centers for Disease Control and Prevention estimate that 17 million persons in the United States have diabetes, nearly 6 million of whom are undiagnosed (3). The con-

current rise in excess weight and obesity, which accompanies type 2 diabetes in 80% of cases, interferes with diabetes treatment and exacerbates the likelihood of hypertension, dyslipidemia, atherosclerosis, and polycystic ovarian syndrome (4). Further, the increased incidence of metabolic syndrome, a cluster of cardiovascular risk factors characterized by insulin resistance, visceral adiposity, dyslipidemia, hypertension, and a systemic proinflammatory state, greatly increases the risk of cardiovascular disease and type 2 diabetes (5). These clinical conditions are multifactorial in origin and treatment and all have a strong dietary component.

Type 2 diabetes and elevated blood glucose increase the risk of cardiovascular mortality from 40% to 200%, depending on the presence of other risk factors (6,7). Albert and colleagues (8) reported that risk of sudden cardiac death in US women was increased nearly threefold in the presence of diabetes after multiple risk factors were taken into consideration. Thus, control of diabetes and blood sugar is critical to reducing the toll of type 2 diabetes on cardiovascular mortality.

Currently, the most promising approach to mitigate and deter type 2 diabetes is lifestyle intervention—weight reduction, decreased total and saturated fat consumption, and increased physical activity—with appropriate pharmacotherapy as needed (9,10). From the public health perspective, prevention, by curbing obesity, increasing exercise, and improving diet, is the primary long-term strategy to ease the enormous health and economic burden of type 2 diabetes (11-13).

Healthful diets that avoid excess energy intake and reduce saturated fat consumption are a key component of lifestyle management in type 2 diabetes (14). The fatty acid profile of healthful type 2 diabetes diets can be improved by substituting monounsaturated and polyunsaturated fatty acids (PUFAs) for saturates and increasing the consumption of n-3 long-chain (LC) (≥ 20 carbon atoms) PUFAs (15-18). n-3 LC-PUFAs refer specifically to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are found mainly in fatty fish. Although there is some controversy about the relative merit of monounsaturates over polyunsaturates in diets designed for persons with type 2 diabetes, recent evidence has favored increasing the proportion of monounsaturates (15,19-21).

Increasing the consumption of n-3 LC-PUFAs improves several cardiovascular risk factors in persons with diabetes and may reduce the risk of conversion from impaired glucose tolerance to type 2 diabetes (22-24). Earlier studies led to concern about potential adverse effects of increased n-3 LC-PUFA intake on glucose control, insulin

J. A. Nettleton is principal, ScienceVoice Consulting, Denver, CO. R. Katz is president, Omega-3 Research Institute, Inc, Bethesda, MD.

Address correspondence to: Joyce A. Nettleton, DSc, RD, ScienceVoice Consulting, 2931 Race St, Denver, CO 80205. E-mail: sciencevoice@mindspring.com

Copyright © 2005 by the American Dietetic Association.

0002-8223/05/10503-0001\$30.00/0

doi: 10.1016/j.jada.2004.11.029

activity, and low-density lipoprotein (LDL) cholesterol levels and restrained recommendations for persons with type 2 diabetes to increase their intake of these fatty acids. Now, mounting evidence that increased consumption of n-3 LC-PUFAs benefits subjects with type 2 diabetes without adversely affecting glucose control has prompted the American Diabetes Association (13) and the American Heart Association (25) to recommend the consumption of two to three servings of fish per week. We review the literature on the effects of n-3 LC-PUFAs in insulin resistance and type 2 diabetes in human subjects and the potential of these fatty acids to enhance the effectiveness of current interventions in the prevention and treatment of type 2 diabetes.

EPIDEMIOLOGIC STUDIES

More than 30 years ago disease patterns among the Greenland Inuit, Alaskan natives, and other Arctic and subarctic natives showed far lower incidence of type 2 diabetes than in Danes, US residents, or others (26-29). Type 2 diabetes was less prevalent among Japanese islanders compared to their mainland counterparts (30). Lower prevalence of type 2 diabetes was attributed mainly to diets rich in n-3 LC-PUFAs. During the past 15 years, the incidence of type 2 diabetes has increased rapidly among native and migrant populations, as much as 80% among Alaskan natives (31). The increase has been associated with the greater consumption of nonindigenous foods, changes in lifestyle, and fatty acid imbalance (32,33).

In the Finnish and Dutch cohorts of the Seven Countries Study, Feskens and colleagues (34) reported that fish consumption was inversely related to 2-hour glucose levels during a 20-year follow-up of male participants. These investigators had previously reported that fish consumption was associated with reduced risk of developing impaired glucose tolerance in 175 men and women with normoglycemia aged 64 to 87 years (35).

Siscovik (36) reported that consumption by persons with diabetes over age 65 years of at least one or more meals per week of fatty fish that was not fried was associated with a significantly lower chance of primary cardiac arrest compared to subjects who consumed similar amounts of fried fish. These investigators had previously reported that an average of one fish meal per week was associated with a 50% reduction in risk of primary cardiac arrest (37).

Hu and coworkers (38) reported that in 5,103 nurses with type 2 diabetes followed for up to 16 years, those who consumed fish at least one to three times a month had a 40% lower risk of developing coronary heart disease compared to women with diabetes who ate fish less than once a month. Those who ate fish five or more times a week experienced a 64% reduction in coronary heart disease compared to those who ate fish less than once a month. Total mortality was also significantly reduced with fish consumption, ranging from 23% to 37% fewer deaths as fish consumption increased from one to three times a month to more than five times a week.

In Iceland, the prevalence of type 2 diabetes and coronary heart disease mortality are lower than in other Nordic countries, despite the high prevalence of overweight and obesity (39). Thorsdottir and coworkers (40)

reported that the prevalence of type 2 diabetes in Icelandic men was significantly and inversely associated with both the n-3 PUFA and EPA content of milk, and positively associated with the ratio of n-6/n-3 fatty acids in milk. Icelandic milk contains significantly more n-3 LC-PUFAs than milk in other Nordic countries, from three to eight times as much ($0.22\% \pm 0.05\%$ vs $0.06\% \pm 0.01\%$ for Norway and $0.03\% \pm 0.01\%$ for Denmark), mainly because animal fodder contains fish meal. Icelandic milk is also significantly lower in n-6 PUFAs. Mortality from coronary heart disease in women exhibited a similar inverse association with the EPA content of milk and positive association with the n-6/n-3 ratio. Daily consumption of 500 mL Icelandic milk for a week provides about the same amount of EPA as one 100-g serving of sea trout (176 vs 165 mg EPA). In this population, the unique composition of dairy fat could be protective against type 2 diabetes and cardiovascular disease.

By contrast, in a study of nearly 36,000 older Iowa women who did not have type 2 diabetes at enrollment, diabetes incidence after 11 years was positively associated with n-3 LC-PUFA consumption (41). After adjustment for other dietary fat, only vegetable fat was related to diabetes risk and appeared protective.

Van Dam and colleagues (42) reported that n-3 LC-PUFA intake was not associated with the risk of diabetes in more than 42,000 men in the US Health Professionals Follow-Up Study, but total and saturated fat intake increased risk. Linoleic acid consumption was associated with lower risk of type 2 diabetes in men younger than age 65 years who had body mass indexes less than 25 (calculated as kg/m^2), but not in older men with obesity.

Promising preliminary evidence that development of type 2 diabetes can be retarded or prevented by increased consumption of n-3 LC-PUFAs and reduced consumption of saturates was reported by Ebbesson (43). Forty-four Alaskan Inuit with impaired glucose tolerance, excess weight, or obesity were counseled to eat fewer foods high in saturated fats, palmitic acid, and *trans* fatty acids, and more traditional foods, especially fish and marine animals, as part of a 4-year diabetes prevention program. Prevention strategies emphasized increased physical activity and weight reduction. After 4 years, no participants developed type 2 diabetes, despite not losing weight (43). The degree of improvement in glucose tolerance was significantly correlated with the ratio of n-3 PUFAs to palmitic acid. The authors attributed these results largely to the altered pattern of fatty acid consumption and the increased intake of n-3 LC-PUFAs.

CLINICAL STUDIES

Glucose Control

In a review, Nettleton (44) noted that several clinical studies in the 1980s and early 1990s reported adverse effects on blood glucose control and insulin activity in subjects with type 2 diabetes who consumed large amounts of fish oil (45,46). It is now believed that these deleterious effects were largely attributable to the high doses used, like 10 g fish oil per day or more. Recent studies using low doses of n-3 LC-PUFAs, ranging from 1 to 2 g/day, have reported no deterioration in glucose control (23,47-49). In one study, the increase in glycated

hemoglobin associated with daily fish consumption providing 3.6 g n-3 PUFAs per day could be prevented by moderate exercise (55% to 65% maximum oxygen consumption/min) (50).

Two meta-analyses of trials with n-3 LC-PUFAs or fish oil in subjects with diabetes have further allayed fears of adverse effects on glucose control. Friedberg and colleagues (51) performed a meta-analysis of 26 trials in both patients with type 1 and type 2 diabetes and concluded that the use of fish oil had no adverse effect on glycated hemoglobin, and it lowered triglyceride levels by almost 30%. Montori and coworkers (52) conducted a meta-analysis of 18 randomized, placebo-controlled trials of a range of 3 to 18 g/day fish oil and concluded that fish oil supplementation lowered triglyceride levels an average of 0.56 mmol/L*, raised LDL cholesterol (0.21 mmol/L†), and had no statistically significant effect on glycemic control. Modest amounts of n-3 LC-PUFAs in the range of 1 to 2 g/day appear to pose no significant risk to glucose control in persons with type 2 diabetes.

Dyslipidemia in Type 2 Diabetes

It is now well established that n-3 LC-PUFAs lower triglyceride levels in subjects with type 2 diabetes or hypertriglyceridemia and may increase high-density lipoprotein (HDL) cholesterol levels, as well. Sirtori and colleagues (23) reported that 6 months' therapy with 2 to 3 g/day n-3 ethyl esters in 935 patients with hypertriglyceridemia, with and without type 2 diabetes, significantly reduced triglyceride levels in the patients with diabetes by 25.2% and increased HDL cholesterol levels by 7.4% on average, without changing glycemic parameters. Kesavulu and colleagues (24) reported that supplementation of 1.8 g/day n-3 LC-PUFAs for 2 months in 34 type 2 diabetes patients being treated with antidiabetic drugs significantly reduced triglyceride levels from 2.07 ± 0.94 mmol/L before treatment to 1.54 ± 0.49 mmol/L after treatment ($P < .05$, 25% reduction) and increased HDL cholesterol levels from 0.93 ± 0.99 mmol/L before treatment to 1.04 ± 0.098 mmol/L after ($P < .01$, 11% increase). Parameters of lipid peroxidation and antioxidant enzymes were also improved with combined treatment. Petersen and colleagues (53) reported that in 42 subjects with type 2 diabetes, 4 g/day fish oil compared with corn oil supplementation significantly reduced triglyceride levels (mean 0.54 mmol/L) and raised HDL-2b cholesterol levels (mean 0.05 mmol/L) after 8 weeks. Rivellese and colleagues (54) reported that the consumption of 2.7 g/day EPA and DHA for 2 months followed by 1.7 g/day for 4 months was accompanied by a 25% reduction in plasma triglyceride concentrations, with mean values diminishing from 3.85 ± 0.32 mmol/L to 2.92 ± 0.23 mmol/L in sub-

jects with type 2 diabetes and hypertriglyceridemia. Woodman and colleagues (55) reported that there were no significant changes in serum total, LDL, or HDL cholesterol levels in 39 subjects with type 2 diabetes who consumed 4 g EPA, DHA, or olive oil for 6 weeks, although fasting glucose was significantly elevated. Connor and colleagues (56) reported that 16 subjects with type 2 diabetes and hypertriglyceridemia who consumed 15 g/day olive oil or fish oil, containing 6.0 g/day n-3 LC-PUFAs, experienced a 42% reduction in triglyceride level (from 4.92 ± 2.99 mmol/L to 2.94 ± 1.11 mmol/L) and a significant increase in LDL cholesterol level after 6 months.

Elevated LDL cholesterol levels have been associated with the consumption of n-3 LC-PUFAs, but changes have tended to be inconsistent and modest. In their meta-analysis of 10 studies reporting LDL cholesterol levels, Montori and colleagues (52) concluded that fish oil was associated with a slight increase in LDL cholesterol level (0.21 mmol/L, range 0.02 to 0.41 mmol/L). Friedberg and colleagues (51) reported a slight but significant increase in serum LDL cholesterol level (mean 0.18 mmol/L) in their meta-analysis. A recent study of 259 adult Inuit in Greenland who consumed a marine diet high in n-3 LC-PUFAs reported inconsistent and insignificant effects on LDL cholesterol level (57). Woodman and colleagues (55) reported no significant effects of n-3 LC-PUFAs on LDL cholesterol levels in 39 subjects with type 2 diabetes. Most recent studies support the conclusion of the US government's evidence-based review of 13 randomized trials of persons with type 2 diabetes that there is strong evidence that n-3 LC-PUFAs reduce serum triglyceride levels, but have no effect on total, LDL, or HDL cholesterol levels (58).

n-3 LC-PUFAs have beneficial effects in reducing remnant lipoprotein (RLP) levels in persons with obesity and type 2 diabetes (59,60). RLPs are highly atherogenic lipoproteins produced in the hydrolysis of chylomicrons and very-low-density lipoproteins (VLDL). They are elevated in persons with insulin resistance, impaired glucose tolerance, type 2 diabetes, abdominal obesity, end-stage renal disease, and heart disease (61-65).

As early as 1991, n-3 LC-PUFAs (6 g/day) from fish oil were shown to reduce beta VLDL levels in nine patients with Type III hyperlipidemia, findings compatible with a reduction in RLP (66). Modest amounts of purified EPA, 0.9 to 1.8 g/day, reduced RLP levels significantly by 77% in 10 subjects with type 2 diabetes treated for 3 months (67). Purified EPA reduced RLP by 52% in 38 patients receiving dialysis treated for 3 months with 1.8 g/day, and had the additional benefit of lowering levels of oxidized LDL cholesterol (59).

Statin medication, which inhibits hydroxy-methylglutaryl coenzyme A reductase activity, is widely prescribed to patients with heart disease and type 2 diabetes to lower lipid levels. Recently published findings from the Collaborative Atorvastatin Diabetes Study (68) in which patients with type 2 diabetes were studied, report 36% fewer acute coronary heart disease events, a 31% reduction in coronary revascularizations, and a 48% reduction in stroke with 10 mg atorvastatin after a median follow-up time of 3.9 years. Fish oils or n-3 LC-PUFAs can enhance the effectiveness of some statins, with indepen-

*To convert mmol/L triglyceride to mg/dL, multiply mmol/L by 88.6. To convert mg/dL triglyceride to mmol/L, multiply mg/dL by 0.0113. Triglyceride of 1.80 mmol/L = 159 mg/dL.

†To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.7. To convert mg/dL cholesterol to mmol/L, multiply mg/dL by 0.026. Cholesterol of 5.00 mmol/L = 193 mg/dL.

dent and additive effects (69,70). Nakamura and colleagues (71) reported that EPA provided with hydroxymethylglutaryl coenzyme A reductase inhibitors reduced triglyceride levels by 10.8% and increased HDL cholesterol levels by 8.9% in subjects with hyperlipidemia. Nordoy and colleagues (69) reported an additive effect of a small amount of n-3 LC-PUFAs (1.7 g/day) combined with 10 mg/day atorvastatin in 42 patients with combined hyperlipidemia. As expected, atorvastatin alone reduced LDL cholesterol levels by 35% from baseline values (reduction 1.79 ± 1.16 mmol/L, $P < .001$) with a further nonsignificant decrease of 0.12 ± 0.51 mmol/L when n-3 LC-PUFAs were consumed. With atorvastatin alone, serum HDL cholesterol concentration increased significantly by 0.08 ± 0.09 mmol/L ($P < .001$), about 8%, but increased an additional 0.07 ± 0.08 mmol/L ($P < .001$) when fish oil was consumed. Triglyceride levels were also significantly reduced with atorvastatin by about 36% ($P < .001$), but fish oil did not significantly enhance this effect.

Chan and colleagues (70) studied 52 men with obesity, dyslipidemia, and insulin resistance, who consumed 4 g/day fish oil or 40 mg/day atorvastatin or both treatments for 6 weeks. They compared their findings to 10 men with normolipidemia and baseline values. Subjects consuming atorvastatin or atorvastatin plus fish oil had significantly reduced LDL cholesterol concentrations at 6 weeks compared to baseline values (3.8 ± 0.16 vs 1.8 ± 0.12 , mmol/L before and after atorvastatin, $P < .001$) and (4.0 ± 0.28 vs 2.2 ± 0.19 mmol/L before and after atorvastatin plus fish oil, $P < .001$). Only those consuming both treatments had significantly increased HDL cholesterol concentrations (1.00 ± 0.05 vs 1.04 ± 0.05 mmol/L before and after atorvastatin, not significant) and (1.10 ± 0.09 vs 1.25 ± 0.09 mmol/L before and after atorvastatin plus fish oil, $P < .01$). Fish oil consumption alone had no effect on LDL or HDL cholesterol concentrations. These investigators have since shown that atorvastatin increases hepatic clearance of apolipoprotein B-containing lipoproteins, whereas fish oils reduce the secretion of VLDL apolipoprotein B, thereby providing a possible explanation for the enhanced effects of the combined treatment.

Hypertension

Kriketos and colleagues (72) studied the effect of different types of fat in an energy-restricted diet consumed by 52 subjects with moderate obesity and hypertension for 10 weeks. Compared to the diets rich in n-6 or saturated fatty acids, the diet rich in n-3 LC-PUFAs tended to protect against the loss of fat-free tissue mass, but had no additional effect on blood pressure, insulin sensitivity, or lipid profile. Mori and colleagues (73) showed that when fish providing 3.6 g n-3 LC-PUFAs was included daily as part of a weight-loss diet, those consuming fish compared to those not eating fish had greater improvements in glucose and insulin metabolism and lipid profiles. Weight loss was similar in the two groups. Likewise, in subjects with overweight and hypertension consuming an energy-restricted diet, daily fish (3.65 g/day n-3 LC-PUFAs), or energy restriction plus daily fish, those consuming the energy-restricted diet with fish had significantly greater reductions in blood pressure (reduction in systolic/diastolic pressure, 13.0/9.3 mm Hg) than those on the energy-

restricted diet (5.5/2.2 mm Hg) or just daily fish (6.0/3.0 mm Hg) (74). Even in those not losing weight, the consumption of fish was accompanied by a reduction in blood pressure that was absent in those not eating fish. Thus, regular consumption of fish may improve blood pressure in subjects with obesity and hypertension.

Yosefy and colleagues (75) examined the effect of moderate doses of n-3 LC-PUFAs in subjects with hypertension and obesity with type 2 diabetes using a 13-day period with 20-hour fasting on days 1, 5, 9, and 13 and the provision of 4.5 g/day EPA and DHA as fish oil concentrate for the 13-day period. This intermittent fasting technique rapidly exchanges n-3 LC-PUFAs for n-6 LC-PUFAs in serum phospholipids. Following 13 days of n-3 LC-PUFA supplementation, the 19 subjects had significant reductions in systolic and diastolic blood pressure (from 157.6/83.2 to 141.9/75.6 mm Hg, $P < .001$) and triglyceride level (from 2.36 to 1.73 mmol/L, $P < .001$). Changes were similar to those observed in subjects with obesity and hypertension without type 2 diabetes. Jain and colleagues (76) also reported significant improvements in blood pressure in 25 patients with type 2 diabetes consuming a diabetic diet plus 0.6 g n-3 LC-PUFAs daily. However, Woodman and colleagues (55) reported that the consumption of 4 g/day n-3 LC-PUFAs had no significant effect on blood pressure in 39 subjects with type 2 diabetes whose body mass index averaged less than 35.

DHA, but not EPA, was shown to improve vascular reactivity and blood flow in studies conducted on the forearms of overweight men with mild hyperlipidemia by Mori and colleagues (77). DHA enhanced vasodilator mechanisms and reduced constrictor responses, which could contribute to the blood pressure-lowering effects associated with n-3 LC-PUFA intake.

Stroke

Several studies have shown a protective effect of n-3 LC-PUFA in ischemic or thrombotic stroke, the most prevalent type of stroke in Western countries. In a 12-year study of 43,671 male health professionals, He and colleagues (78) reported that fish consumption had a significant protective effect against risk of ischemic stroke. Compared to men who consumed fish less than once a month, those who ate fish one to three times per month had a relative risk of 0.57 (95% confidence interval=0.35 to 0.95). Higher fish consumption did not confer additional reduction in risk. Fish consumption was not associated with risk of hemorrhagic stroke. Iso and colleagues (79) also reported a protective association between fish consumption and thrombotic stroke in a study of 79,839 US nurses. Unlike findings in the study of male health professionals, risks of all strokes and ischemic stroke in these women were related to the amount of fish consumed. In multivariate analysis, the relative risk of all strokes with fish consumption one to three times per month was 0.93 (confidence interval=0.65 to 1.34). For fish intake once, two to four times, or five or more times per week, relative risks were 0.78, 0.73, and 0.48, respectively (P for trend=.06). Risk of hemorrhagic stroke also declined with fish consumption, but the trend was not statistically significant.

Consumption of very high levels of n-3 LC-PUFAs (>10

g/day) has been associated with increased risk of hemorrhagic stroke. In the two studies just described, no statistically significant association between fish consumption and risk of hemorrhagic stroke was observed with modest fish and n-3 LC-PUFA intake. However, these studies were not specific to subjects with type 2 diabetes.

It was first reported in the 1980s that the incidence of hemorrhagic cerebrovascular disease and mortality was greater in Greenland Inuit than in the white Danish population (27,80,81). Hemorrhagic stroke was associated with high dietary and tissue levels of n-3 LC-PUFA (27,82). Pedersen and colleagues (82) reported that Greenlanders who experienced fatal hemorrhagic stroke all had significantly higher levels of DHA in their perirenal adipose tissue compared to those with nonhemorrhagic cerebrovascular death. Conclusions are limited by the small number of subjects (four hemorrhagic fatalities). In these studies, consumption of n-3 LC-PUFAs was in the range of 15 g/day, amounts greatly exceeding the current n-3 LC-PUFA recommendations of 1 to 2 g/day. The US Food and Drug Administration evaluated the safety of n-3 LC-PUFA consumption and concluded that intakes up to 3 g/day posed no health risk.

Endothelial Function

The vascular endothelium is actively involved in maintaining blood circulation, fluidity, and various hemostatic processes (83). It is involved in the development of atherosclerosis and is associated with impaired function in cardiovascular disease and type 2 diabetes (84). When the endothelium becomes activated, as occurs in inflammation and cardiovascular disease, it increases its production of soluble adhesion molecules and cytokines that attract diverse cells and particles to its surface. The endothelium is also critical for vasomotor function, synthesizing several substances that affect vasoconstriction and vasodilation.

n-3 LC-PUFAs have been reported to decrease markers of endothelial cell activation or improve vasodilation significantly in healthy subjects (85), those with hypercholesterolemia (86,87), hypertriglyceridemia and type 2 diabetes (88), hypertriglyceridemia without type 2 diabetes (89), and heart disease (90). McVeigh and colleagues (91) reported significantly improved forearm blood flow responses in 23 patients with type 2 diabetes who consumed fish oils for 6 weeks, compared to baseline values or subjects consuming olive oil. Abe and colleagues (88) noted that the reduction in soluble adhesion molecules with n-3 LC-PUFA supplementation was greatest for subjects with diabetes. In vitro studies are consistent with reduced endothelial activation as a result of n-3 LC-PUFA treatment. However, Johansen and colleagues (92) and Seljeflot and colleagues (93) observed increased levels of adhesion molecules in heart patients undergoing angioplasty and smokers with hyperlipidemia, respectively. At the same time, markers of endothelial hemostatic function improved with n-3 fatty acid supplementation, suggesting both beneficial and detrimental effects. In a study of 29 subjects with type 2 diabetes and 21 controls, Sampson and colleagues (94) reported that supplementation with 2 g n-3 LC-PUFA for 21 days did not influence the expression of soluble adhesion molecules. Although the findings are inconsistent, too few studies of

sufficient duration have been conducted in patients with type 2 diabetes to permit firm conclusions about the effects of n-3 LC-PUFAs on endothelial activation and function.

Progression of Atherosclerosis

Recently, Erkkila and colleagues (95) reported that the consumption of two or more fish servings a week over a 3-year period significantly reduced the narrowing of coronary arteries in postmenopausal women with diabetes and coronary artery disease compared to similar women without diabetes. Change in percent stenosis, a measure of artery narrowing, in women with diabetes who ate two or more servings of fish per week was $2.36 \pm 0.71\%$ compared to $5.71 \pm 0.67\%$ in those who ate less than two servings per week ($P < .001$). Adjustment for serum lipids, inflammatory markers, education, or strenuous physical activity did not appreciably alter the relationship. When the type of fish consumed was examined separately, women with diabetes who consumed tuna or other dark fish once or more per week had significantly less increase in artery narrowing ($2.84 \pm 0.61\%$) compared to women who ate tuna or other dark fish less than once per week ($6.17 \pm 0.79\%$) ($P = .007$). Changes in artery narrowing with tuna consumption were not statistically significant in women without diabetes. Although the study did not measure n-3 LC-PUFAs directly, the observation that changes did not occur in women with diabetes who ate fish other than tuna or dark fish suggests the results were linked to n-3 LC-PUFA consumption. Further, the effects of tuna or dark fish were observed with consumption once or more per week, compared with two or more servings per week for the category "all fish."

Oxidative Stress

Oxidative stress refers to an abundance of free radicals or highly reactive oxygen species that can result from lipid peroxidation. In seeking stability, these highly reactive oxygen species interact with and may damage other molecules such as lipids, proteins, and nucleic acids. Oxidized lipids increase the risk of cardiovascular disease. Increased oxidative stress observed in type 2 diabetes may be related to the increased risk of cardiovascular disease in these patients (96). Because n-3 LC-PUFAs are highly unsaturated, there has been concern that increased consumption might increase oxidative stress.

Pedersen and colleagues (97) recently concluded that 4 g/day fish oil supplementation leads to increased oxidation in vivo and in vitro in patients with type 2 diabetes. Other studies have concluded that low doses of fish oil (0.6 to 1.8 g EPA+DHA/day) consumed by patients with type 2 diabetes have beneficial effects on measures of oxidative stress (24,76). Recent assessment of oxidative stress that measured the excretion of F_2 -isoprostanes, the products of free radical peroxidation of arachidonic acid, demonstrated that consumption of either EPA or DHA by subjects with hypertension and type 2 diabetes reduced in vivo oxidant stress (98). In a double-blind, randomized, placebo-controlled study, 59 patients with type 2 diabetes were randomized to consume 4 g/day EPA, DHA, or olive oil for 6 weeks. Excretion of F_2 -isoprostanes was signifi-

cantly reduced by EPA (19%) and DHA (20%) compared to olive oil, with no change in inflammatory markers. These researchers had previously reported that the consumption of a daily fish meal providing 3.6 g/day n-3 LC-PUFAs by 55 patients with dyslipidemia and type 2 diabetes significantly reduced lipid peroxidation (99). Although additional studies are needed, it appears that increased oxidative stress in type 2 diabetes may be improved by the moderate consumption of n-3 LC-PUFAs.

Obesity and Metabolic Syndrome

Whereas obesity clearly increases the risk of developing type 2 diabetes, the effect of total dietary fat and its composition in the development of obesity and insulin resistance remains controversial. High-fat diets combined with physical inactivity are associated with obesity, reduced insulin sensitivity, and increased prevalence of type 2 diabetes (100). Diets low in fat and high in protein and complex carbohydrates help maintain healthy weight in normal-weight subjects and promote weight loss in those with overweight. Reduced-fat diets (26% of energy from fat) are associated with weight loss and improved glucose tolerance (101), but whether high-fat diets actually promote obesity and type 2 diabetes is uncertain (17,102). Diets high in saturated fat and low in polyunsaturates and n-3 LC-PUFAs have generally been associated with increased adiposity, greater risk of type 2 diabetes, reduced insulin sensitivity, and diminished insulin action in skeletal muscle (42,103,104). For example, in the Health Professionals Follow-Up Study (42), risk of developing type 2 diabetes was determined in men aged 40 to 75 years who were followed for 12 years. Subjects were divided according to percent energy intake from fat, with quintiles of consumption ranging from a median low of 24% of energy from fat to 39% of energy from fat. Relative risk of developing type 2 diabetes ranged from 1.22 at 29% of energy from fat to 1.88 at 39% of energy from fat ($P < .0001$). For quintiles of saturated fat intake, relative risk ranged from 1.51 in the second quintile to 2.01 in the highest quintile ($P < .0001$). Intakes of linoleic, α -linolenic, and n-3 LC-PUFAs were not associated with risk.

A recent multinational study reported that 204 subjects recently diagnosed with type 2 diabetes were significantly more likely than control subjects without diabetes to consume more fat ($30.2 \pm 0.5\%$ of energy from fat vs $27.8 \pm 0.5\%$, $P < .001$) and more animal fat ($12.2 \pm 0.3\%$ of energy from fat vs $10.8 \pm 0.3\%$, $P < .01$) (104). Similarly, total fat and animal fat intake was significantly greater in those with undiagnosed type 2 diabetes compared with control subjects without diabetes.

Changing the fatty acid composition of the diet from one rich in saturates to one rich in polyunsaturates improved insulin sensitivity in 11 subjects with type 2 diabetes, with or without obesity, and in six lean subjects (18). There was also a decrease in abdominal subcutaneous fat area, but weight remained unchanged. At baseline, all subjects consumed on average 36.0 ± 14.5 g/day saturated fatty acids and 16.8 ± 7.0 g/day polyunsaturated fatty acids. After 5 weeks of dietary change with dietary counseling, those randomized to consume either a high saturated or polyunsaturated fatty acid diet consumed on average 58.7 ± 15.9 or 21.7 ± 7.1 g/day saturated

or polyunsaturated fatty acids, respectively. These changes represented a 63% and 29% increase in consumption of saturated or polyunsaturated fatty acids, respectively, and were made largely at the expense of saturated fatty acid intake. At baseline, insulin sensitivity was 0.6 ± 0.3 and 0.5 ± 0.4 in the subjects without obesity and in subjects with obesity or diabetes, respectively, but after 5 weeks of dietary change insulin sensitivity in those consuming more polyunsaturated fatty acids increased to 0.64 ± 0.43 $\mu\text{mol/L/mU}^{-1}/\text{kg}^{-1}/\text{min}^{-1}$, whereas insulin sensitivity in those on the saturated fatty acid diet remained at 0.51 ± 0.35 $\mu\text{mol/L/mU}^{-1}/\text{kg}^{-1}/\text{min}^{-1}$. The difference between the two dietary groups was statistically significant ($P = .02$). Other studies have suggested that polyunsaturated fatty acids, particularly n-3 LC-PUFAs, may be at least partly protective against weight gain, perhaps because they are less readily deposited in adipose tissue and more readily oxidized (34,103).

There is limited evidence that n-3 LC-PUFAs may be associated with reduced incidence of obesity, ease of weight loss, and maintenance of body weight (105). In a study of 84 obese men and women in Spain, central obesity was inversely associated with monounsaturated and n-3 LC-PUFAs in subcutaneous and omental (peritoneal) adipose tissue, respectively (105). These observations suggest that n-3 LC-PUFAs may be protective against abdominal obesity, the type of obesity most directly associated with insulin resistance and type 2 diabetes.

The metabolic syndrome, of which abdominal obesity, dyslipidemia, hypertension, and impaired glucose tolerance are characteristic, afflicts some 47 million US adults. In a recent study of 5,974 men in western Scotland, having one of the metabolic characteristics of this syndrome doubled risk of diabetes; having four characteristics or more increased the risk 24-fold (5). Because n-3 LC-PUFAs have beneficial effects in improving lipid profiles, reducing blood pressure, reducing insulin resistance, and reducing markers of systemic inflammation, they have considerable potential to reduce the adverse consequences of this syndrome.

Albuminuria and Renal Disease

One possible vascular complication of type 2 diabetes is microalbuminuria, a condition that may foreshadow the progression of diabetes to end-stage renal disease, and strongly predicts end-stage renal disease (106). n-3 LC-PUFAs have been shown in some studies to reduce albuminuria (107,108), but not in others (109,110). Patients with diabetes with deteriorating kidney function may require dialysis, a procedure with greater than 50% incidence of vascular access thrombosis that necessitates additional surgery (111). Administration of fish oil or purified n-3 LC-PUFAs was reported to improve dramatically the duration of graft patency and survival of dialysis patients (112). In a trial of 24 patients with polytetrafluoroethylene grafts, subjects were randomized within 2 weeks of graft placement to consume either 4 g/day fish oil or corn oil ethyl esters for 1 year. Primary graft patency rates for those consuming fish oil were dramatically improved at the end of 1 year, 75.6% patency compared to 14.9% in the control oil group ($P < .05$). Mean venous pressure at the end of the study was significantly lower in fish oil-treated patients compared to controls (88 ± 7 vs

112±10 mm Hg), and systolic and diastolic blood pressures were significantly reduced by an average of 30 and 15 mm Hg, respectively ($P<.05$), in fish oil–treated subjects. Thus, moderate treatment with 4 g/day fish oil was accompanied by striking improvements in graft patency and blood pressure in these patients.

C-Reactive Protein (CRP)

C-reactive protein (CRP) is one of several acute phase reactants present in inflammatory conditions. Its elevation in type 2 diabetes, heart disease, and other conditions signals subclinical inflammation. Its presence is unrelated to lipid profile. Elevated CRP has emerged as a strong independent predictor of cardiovascular disease and an important predictor of the likelihood of developing type 2 diabetes. In several large prospective trials, those with the highest CRP levels were two to four times more likely to develop type 2 diabetes than those with the lowest levels (113-116). Among persons with diabetes, elevated CRP is associated with major coronary events, duration of diabetes and retinopathy, and subsequent development of microalbuminuria, a marker for impaired kidney function.

In a study of patients undergoing coronary angiography, CRP level was inversely associated with the DHA content of granulocytes and directly associated with significant coronary stenoses. Patients with no significant angiographic changes had the highest levels of granulocyte DHA, suggesting that patients with stable coronary artery disease may have benefited from the anti-inflammatory properties of n-3 LC-PUFAs (117). In contrast, Chan and colleagues (118) reported that in subjects with dyslipidemia and obesity without type 2 diabetes, fish oil had no effect on plasma CRP levels.

Studies with n-3 LC-PUFAs in critically ill patients have reported reduced CRP levels following n-3 LC-PUFA supplementation. In patients with pancreatic cancer and cachexia, 4 weeks of n-3 LC-PUFA consumption was followed by a 93% decrease in serum CRP level (119). Other studies have shown that in severely ill patients and those undergoing major abdominal surgery, provision of enteral formula containing arginine, n-3 LC-PUFAs, and nucleotides was associated with significantly reduced CRP levels and improved immunocompetence (119-121). Although much more data are needed, it appears that n-3 LC-PUFAs have beneficial effects on CRP levels and immune function.

IMPLICATIONS

Promising results from studies of patients with insulin resistance and type 2 diabetes indicate that consumption of n-3 LC-PUFAs improves lipid profiles, may retard disease progression, modestly reduces blood pressure, and may deter the onset of more serious cardiovascular complications, including mortality. However, proof that n-3 LC-PUFAs can prevent subjects with insulin resistance or impaired glucose tolerance from developing type 2 diabetes remains to be established. Effects of n-3 LC-PUFAs on insulin signaling pathways, expression and activity of glucose metabolizing enzymes, decreased expression of lipogenesis enzymes, and increased fatty acid

oxidation are all consistent with reduced insulin resistance (122). Epidemiologic data on n-3 LC-PUFA consumption and type 2 diabetes are relatively few and subject to the limitations of retrospective analysis. However, where seafood or n-3 LC-PUFA consumption has been robust, several studies have reported the association between fish consumption and reduced prevalence of type 2 diabetes or its cardiovascular consequences. Controlled prospective studies and appropriately designed intervention trials in subjects with insulin resistance or type 2 diabetes would contribute important information with potentially huge influence on public health.

A summary of the expected physiologic effects of moderate n-3 LC-PUFA consumption in subjects with type 2 diabetes is shown in the Figure. Clearly, as recognized by the dietary recommendations of the American Diabetes Association and American Heart Association, subjects with type 2 diabetes can achieve the cardioprotective effects of regular consumption of modest amounts of n-3 LC-PUFAs, without jeopardizing glucose or insulin control.

To date, the most effective intervention to mitigate type 2 diabetes, if not halt its progression, involves lifestyle change (9,10,123). This includes weight reduction, increased physical activity, and a healthful diet that avoids excess fat and saturated fat. The value of diet and exercise has been emphasized repeatedly (12). Dietary change can be made more strategically effective, without adversely affecting glucose control, by the regular inclusion of modest amounts of n-3 LC-PUFAs in a low-saturated-fat diet.

For dietetics professionals in clinical practice, appropriate dietary guidance for patients at risk of type 2 diabetes, including patients with overweight, obesity, insulin resistance, and metabolic syndrome, should incorporate the recommendation to consume fatty fish, such as salmon, rainbow trout, sardines, mackerel, and herring, at least twice a week. Two to three 3-oz servings of fatty fish per week, containing at least 1 g per serving of EPA and DHA, would provide about 300 to 450 mg n-3 LC-PUFAs per day. Slightly larger serving size (3.5 to 4 oz) of certain fatty fish, such as king, sockeye, pink, and Atlantic (farmed) salmon, consumed three times per week easily provides about 850 mg EPA and DHA per day.

Patients who have type 2 diabetes or documented cardiovascular disease, or are at high risk of cardiovascular disease, may be advised to consume 1 g/day n-3 LC-PUFAs from fatty fish or n-3 LC-PUFA supplements, with a physician's concurrence (25). Patients with hypertriglyceridemia may benefit from 2 to 4 g/day n-3 LC-PUFAs under a physician's supervision (25). Patients who cannot or will not consume fish may consider the consumption of fish oil or n-3 LC-PUFA supplements to provide the suggested doses of EPA and DHA. With appropriate pharmacotherapy to control blood sugar, hypertension, dyslipidemia, obesity/metabolic syndrome, and other medical conditions that may be present, increased n-3 LC-PUFA consumption has the potential to stem the rising tide of type 2 diabetes and its cardiovascular sequelae. Additional cardiovascular benefit might be realized from the synergistic effect of n-3 LC-PUFAs with statin therapy on improved lipoprotein profiles, reduced disease progression, and lower risk of mortality.

Markers and conditions	Expected effect(s)	Comments
Glucose control	No significant effect	1-2 g/day n-3 LC-PUFAs not associated with adverse effects
Risk of conversion from insulin resistance to type 2 diabetes	Delay or possibly prevent conversion	Insulin resistance may improve; preliminary evidence that conversion can be prevented by dietary change with n-3 LC-PUFAs
Insulin homeostasis	Small improvement or no change	Insulin resistance and hyperinsulinemia not adversely affected by n-3 LC-PUFAs
Triglycerides (TG)	Significant ↓ in circulating levels, up to 30%; effects are related to dose and are greater with higher TG levels	Improved lipid profile and ↓ risk of cardiovascular disease (CVD)
High-density lipoproteins (HDL)	Modest to moderate ↑ in the range of 0%-11%	Improved lipid profile and ↓ risk of CVD
Low-density lipoproteins (LDL)	Possible modest ↑ ranging from 0%-8%; LDL particle size may ↑	Possible ↑ risk of CVD outweighed by favorable changes in TG and HDL; ↑ particle size may be less atherogenic
Remnant lipoproteins	↓ levels by 50% or more	↓ risk of CVD
C-reactive protein (CRP)	↓ CRP	↓ CRP reduces risk of subclinical inflammation, type 2 diabetes, and CVD
Endothelial function	Docosahexaenoic acid ↑ vasodilation, improves microcirculation	Improved function; ↓ risk of CVD; may retard progress of type 2 diabetes; effects may ↓ blood pressure
Blood pressure	May ↓ up to 10% both systolic and diastolic pressure independent of weight loss	May ↓ risk of stroke and CVD
Hemostasis	Possible improvement	May ↓ risk of CVD and thrombosis by ↓ platelet aggregability; ↑ bleeding not observed with doses <3 g/day
Microalbuminuria	May ↓ risk	May significantly improve graft patency in advanced kidney disease
Type 2 diabetes	↓ disease progression, ↓ risk of CVD	↓ CVD mortality; may ↓ conversion from insulin resistance to type 2 diabetes and slow progress of the disease; improved lipid profiles, inflammatory responses, and microcirculation
CVD	↓ risk, ↓ mortality, ↓ risk of sudden death	Improved lipid profiles, inflammatory responses, endothelial function, cardiac electrical stability, blood pressure, microcirculation; ↑ effectiveness of statin medication in raising HDL and lowering TG levels
Stroke	↓ risk of thrombotic stroke	Consumption of 1-3 g/day n-3 LC-PUFAs does not ↑ risk of hemorrhagic stroke
Obesity	May ↓ insulin sensitivity	May ↓ abdominal subcutaneous fat
Metabolic syndrome	↓ dyslipidemia, progression to diabetes, sudden cardiac death	

Figure. Expected effects of 1 to 2 g/day intake of n-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFAs)^a on markers and diseases in subjects with type 2 diabetes. ^aLong-chain= ≥ 20 carbon atoms; mainly eicosapentaenoic acid and docosahexaenoic acid.

References

1. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: Prevalence, numerical estimates, and projections. *Diabetes Care*. 1998;21:1414-1431.
2. Silink M. Childhood diabetes: A global perspective. *Horm Res*. 2002;57(suppl 1):S1-S5.
3. Centers for Disease Control and Prevention. National diabetes fact sheet. Available at: <http://www.cdc.gov/diabetes/pubs/estimates.htm#prev>. Accessed December 2, 2004.
4. Hensrud DD. Dietary treatment and long-term weight loss and maintenance in type 2 diabetes. *Obes Res*. 2001;9(suppl 4):S348-S353.
5. Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, Isles C, Macfarlane PW, Packard CJ, Cobbe SM, Shepherd J. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation*. 2003;108:414-419.
6. DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: Comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med*. 2001;161:397-405.
7. Saydah SH, Loria CM, Eberhardt MS, Brancati FL. Subclinical states of glucose intolerance and risk of death in the US. *Diabetes Care*. 2001;24:447-453.
8. Albert CM, Chae CU, Grodstein F, Rose LM, Rexrode KM, Ruskin JN, Stampfer MJ, Manson JE. Prospective study of sudden cardiac death among women in the United States. *Circulation*. 2003;107:2096-2101.
9. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393-403.
10. McAuley KA, Williams SM, Mann JI, Goulding A, Chisholm A, Wilson N, Story G, McLay RT, Harper MJ, Jones IE. Intensive lifestyle changes are necessary to improve insulin sensitivity: a randomized controlled trial. *Diabetes Care*. 2002;25:445-452.
11. Lindstrom J, Eriksson JG, Valle TT, Aunola S, Cepaitis Z, Hakumaki M, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Mannelin M, Martikkala V, Moltchanov V, Rastas M, Salminen V, Sundvall J, Uusitupa M, Tuomilehto J. Prevention of diabetes mellitus in subjects with impaired glucose tolerance in the Finnish diabetes prevention study: Results from a randomized clinical trial. *J Am Soc Nephrol*. 2003;14(7 suppl 2):S108-S113.
12. Hamdy O, Goodyear LJ, Horton ES. Diet and exercise in type 2 diabetes mellitus. *Endocrinol Metab Clin North Am*. 2001;30:883-907.
13. American Diabetes Association. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care*. 2002;25(suppl 1):S50-S60.
14. Franz MJ, Bantle JP, Beebe CA, Brunzell JD, Chasson JL, Garg A, Holzmeister LA, Hoogwerf B, Mayer-Davis E, Mooradian AD, Purnell JQ, Wheeler M. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care*. 2003;26(suppl 1):S51-S61.
15. Parillo M, Rivellese AA, Ciardullo AV, Capaldo B, Giacco A, Genovese S, Riccardi G. A high-monounsaturated-fat/low-carbohydrate diet improves peripheral insulin sensitivity in non-insulin-dependent diabetic patients. *Metabolism*. 1992;41:1373-1378.
16. Hu FB, van Dam RM and Liu S. Diet and risk of type II diabetes: The role of types of fat and carbohydrate. *Diabetologia*. 2001;44:805-817.
17. Salmeron J, Hu FB, Manson JE, Stampfer MJ, Colditz GA, Rimm EB, Willett WC. Dietary fat intake and risk of type 2 diabetes in women. *Am J Clin Nutr*. 2001;73:1019-1026.
18. Summers LK, Fielding BA, Bradshaw HA, Ilic V, Beysen C, Clark ML, Moore NR, Frayn KN. Substituting dietary saturated fat with polyunsaturated fat changes abdominal fat distribution and improves insulin sensitivity. *Diabetologia*. 2002;45:369-377.
19. Madigan C, Ryan M, Owens D, Collins P, Tomkin GH. Dietary unsaturated fatty acids in type 2 diabetes: Higher levels of postprandial lipoprotein on a linoleic acid-rich sunflower oil diet compared with an oleic acid-rich olive oil diet. *Diabetes Care*. 2000;23:1472-1477.
20. Perez-Jimenez F, Lopez-Miranda J, Pinillos MD, Gomez P, Paz-Rojas E, Montilla P, Marin C, Velasco MJ, Blanco-Molina A, Jimenez Pereperez JA and Ordovas JM. A Mediterranean and a high-carbohydrate diet improve glucose metabolism in healthy young persons. *Diabetologia*. 2001;44:2038-2043.
21. Rocca AS, LaGreca J, Kalitsky J, Brubaker PL. Monounsaturated fatty acid diets improve glycemic tolerance through increased secretion of glucagon-like peptide-1. *Endocrinology*. 2001;142:1148-1155.
22. Grundt H, Nilsen DW, Hetland O, Aarsland T, Baksaas I, Grande T, Woie L. Improvement of serum lipids and blood pressure during intervention with n-3 fatty acids was not associated with changes in insulin levels in subjects with combined hyperlipidaemia. *J Intern Med*. 1995;237:249-259.
23. Sirtori CR, Crepaldi G, Manzato E, Mancini M, Rivellese A, Paoliet R, Pazzucconi F, Pamparana F, Stragliotto E. One-year treatment with ethyl esters of n-3 fatty acids in patients with hypertriglyceridemia and glucose intolerance: Reduced triglyceridemia, total cholesterol and increased HDL-C without glycemic alteration. *Atherosclerosis*. 1998;137:419-427.
24. Kesavulu MM, Kameswararao B, Apparao Ch, Kumar EG, Harinarayan CV. Effect of omega-3 fatty acids on lipid peroxidation and antioxidant enzyme status in type 2 diabetic patients. *Diabetes Metab*. 2002;28:20-26.
25. Kris-Etherton P, Harris WS, Appel LJ, AHA Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids and cardiovascular disease. *Circulation*. 2002;106:2747-2757.

26. Mouratoff GJ, Carroll NV, Scott EM. Diabetes mellitus in Athabaskan Indians in Alaska. *Diabetes*. 1969;18:29-32.
27. Kromann N, Green A. Epidemiological studies in the Upernavik district, Greenland: Incidence of some chronic diseases, 1950-1974. *Acta Medica Scand*. 1980;208:401-406.
28. Adler AI, Boyko EJ, Schraer CD, Murphy NJ. Lower prevalence of impaired glucose tolerance and diabetes associated with daily seal oil or salmon consumption among Alaska Natives. *Diabetes Care*. 1994;17:1498-1501.
29. Schraer CD, Risica PM, Ebbesson SO, Go OT, Howard BV, Mayer AM. Low fasting insulin levels in Eskimos compared to American Indians: Are Eskimos less insulin resistant? *Int J Circumpolar Health*. 1999;58:272-280.
30. Kagawa Y, Nishizawa M, Suzuki M, Miyatake T, Hamamoto T, Goto K, Motonaga E, Izumikawa H, Hirata H, Ebihara A. Eicosapolyenoic acids of serum lipids of Japanese islanders with low incidence of cardiovascular diseases. *J Nut Sci Vitaminol (Tokyo)*. 1982;28:441-453.
31. Schraer CD, Mayer AM, Vogt AM, Naylor J, Brown TL, Hastie J, Moore J. The Alaska Native diabetes program. *Int J Circumpolar Health*. 2001;60:487-494.
32. Murphy NJ, Schraer CD, Thiele MC, Boyko EJ, Bulkow LR, Doty BJ, Lanier AP. Dietary change and obesity associated with glucose intolerance in Alaska Natives. *J Am Diet Assoc*. 1995;95:676-682.
33. Ebbesson SO, Kennish J, Ebbesson L, Go O, Yeh J. Diabetes is related to fatty acid imbalance in Eskimos. *Int J Circumpolar Health*. 1999;58:108-119.
34. Feskens EJM, Loeber JG, Kromhout D. Diet and physical activity as determinants of hyperinsulinemia: The Zutphen Elderly Study. *Am J Epidemiol*. 1994;140:350-360.
35. Feskens EJ, Bowles CH and Kromhout D. Inverse association between fish intake and risk of glucose intolerance in normoglycemic elderly men and women. *Diabetes Care*. 1991;14:935-941.
36. Siscovick D. Prevention of sudden death by low intakes of n-3 polyunsaturated fatty acid. Presented at Omega-3 Fatty Acids, Diabetes and Cardiovascular Risk: An International Workshop. Bethesda, MD, November 30-December 2, 2000.
37. Siscovick DS, Raghunathan T, King I, Weinmann S, Bovbjerg VE, Kushi L, Cobb LA, Copass MK, Psaty BM, Lemaitre R, Retzlaff B, Knopp RH. Dietary intake of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *Am J Clin Nutr* 2000;71(suppl 1):S208-S212.
38. Hu FB, Cho E, Rexrode KM, Albert CM, Manson JE. Fish and long-chain ω -3 fatty acid intake and risk of coronary heart disease and total mortality in diabetic women. *Circulation*. 2003;107:1852-1857.
39. Vilbergsson S, Sigurdsson G, Sigvaldason H, Hreidarsson AB, Sigfusson N. Prevalence and incidence of NIDDM in Iceland: Evidence for stable incidence among males and females 1967-1991—the Reykjavik Study. *Diabet Med*. 1997;14:491-498.
40. Thorsdottir I, Hill J, Ramel A. Omega-3 fatty acid supply from milk associates with lower type 2 diabetes in men and coronary heart disease in women. *Prev Med*. 2004;39:630-634.
41. Meyer KA, Kushi LH, Jacobs Jr. DR, Folsom AR. Dietary fat and incidence of type 2 diabetes in older Iowa women. *Diabetes Care*. 2001;24:1528-1535.
42. Van Dam RM, Willett WC, Rimm EB, Stampfer MJ, Hu FB. Dietary fat and meat intake in relation to risk of type 2 diabetes in men. *Diabetes Care*. 2002;25:417-424.
43. Ebbesson S. Fats and diabetes prevention in Inuits [abstract]. Paper presented at the International Society for the Study of Fatty Acids and Lipids, Montreal, Canada, May 7-11, 2002.
44. Nettleton JA. *Omega-3 Fatty Acids and Health*. New York, NY: Chapman and Hall; 1995.
45. Borkman M, Chisholm DJ, Furler SM, Storlien LH, Draegen EW, Simons LA, Chesterman CN. Effects of fish oil supplementation on glucose and lipid metabolism in NIDDM. *Diabetes*. 1989;38:1314-1319.
46. Vessby B. n-3 Fatty acids and blood glucose control in diabetes mellitus. *J Int Med Suppl*. 1989;225:207-210.
47. 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;16:683-688.
48. Axelrod L, Camuso J, Williams E, Kleinman K, Briones E and 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;17:37-44.
49. Luo J, Rizkalla SW, Vidal H, Oppert JM, Colas C, Boussairi A, Guerre-Millo M, Chapuis AS, Chevalier A, Durand G, Slama G. Moderate intake of n-3 fatty acids for 2 months has no detrimental effect on glucose metabolism and could ameliorate the lipid profile in type 2 diabetic men. Results of a controlled study. *Diabetes Care*. 1998;21:717-724.
50. Dunstan DW, Mori TA, Puddey IB, Beilin LJ, Burke V, Morton AR, Stanton KG. The independent and combined effects of aerobic exercise and dietary fish intake on serum lipids and glycemic control in NIDDM. A randomized controlled study. *Diabetes Care*. 1997;20:913-921.
51. Friedberg CE, Janssen MJ, Heine RJ, Grobbee DE. Fish oil and glycemic control in diabetes. A meta-analysis. *Diabetes Care*. 1998;21:494-500.
52. Montori VM, Farmer A, Wollan PC, Dinneen SF. Fish oil supplementation in type 2 diabetes. A quantitative systematic review. *Diabetes Care*. 2000;23:1407-1415.
53. Petersen M, Pedersen H, Major-Pedersen A, Jensen T, Marckmann P. Effects of fish oil versus corn oil supplementation on LDL and HDL subclasses in type 2 diabetic patients. *Diabetes Care*. 2002;25:1704-1708.
54. Rivellese AA, Maffettone A, Iovine C, Di Marino L, Annuzzi G, Mancini M, Riccardi G. Long-term effects of fish oil on insulin resistance and plasma

- lipoproteins in NIDDM patients with hypertriglyceridemia. *Diabetes Care*. 1996;19:1207-1213.
55. Woodman RJ, Mori TA, Burke V, Puddey IB, Watts GF, Beilin LJ. Effects of purified eicosapentaenoic and docosahexaenoic acids on glycemic control, blood pressure, and serum lipids in type 2 diabetic patients with treated hypertension. *Am J Clin Nutr*. 2002;76:1007-1015.
 56. Connor W, Prince M, Ullmann D, Riddle M, Hatcher L, Smith FE, Wilson D. The hypotriglyceridemic effect of fish oil in adult-onset diabetes without adverse glucose control. *Ann N Y Acad Sci*. 1993;683:337-340.
 57. Bjerregaard P, Pedersen HS, Mulvad G. The associations of a marine diet with plasma lipids, blood glucose, blood pressure and obesity among the Inuit in Greenland. *Eur J Clin Nutr*. 2000;54:732-737.
 58. MacLean CH, Mojica, WA, Morton SC, Pencharz J, Hasenfeld Garland R, Tu W, Newberry SJ, Jungvig LK, Grossman J, Khanna P, Rhodes S, Shekelle P. Effects of Omega-3 Fatty Acids on Lipids and Glycemic Control in Type II Diabetes and the Metabolic Syndrome and on Inflammatory Bowel Disease, Rheumatoid Arthritis, Renal Disease, Systemic Lupus Erythematosus, and Osteoporosis. Rockville, MD: Agency for Healthcare Research and Quality; 2004. Evidence Report/Technology Assessment No. 89. AHRQ Publication No. 04-E012-2.
 59. Ando M, Sanaka T, Nihei H. Eicosapentaenoic acid reduces plasma levels of remnant lipoproteins and prevents in vivo peroxidation of LDL in dialysis patients. *J Am Soc Nephrol*. 1999;10:2177-2184.
 60. Chan DC, Watts GF, Mori TA, Barrett PH, Redgrave TG, Beilin LJ. Randomized controlled trial of the effect of n-3 fatty acid supplementation on the metabolism of apolipoprotein B-100 and chylomicron remnants in men with visceral obesity. *Am J Clin Nutr*. 2003;77:300-307.
 61. Watanabe N, Taniguchi T, Taketoh H, Kitagawa Y, Namura H, Yoneda N, Kurimoto Y, Yamada S, Ishikawa Y. Elevated remnant-like lipoprotein particles in impaired glucose tolerance and type 2 diabetic patients. *Diabetes Care*. 1999;22:152-156.
 62. Hirany S, O'Byrne D, Devaraj S, Jialal I. Remnant-like particle-cholesterol concentrations in patients with type 2 diabetes mellitus and end-stage renal disease. *Clin Chem*. 2000;46:667-672.
 63. McNamara JR, Shah PK, Nakajima K, Cupples LA, Wilson PW, Ordovas JM, Schaefer EJ. Remnant-like particle (RLP) cholesterol is an independent cardiovascular disease risk factor in women: results from the Framingham Heart Study. *Atherosclerosis*. 2001;154:229-236.
 64. Bard JM, Charles MA, Juhan-Vague I, Vague P, Andre P, Safar M, Fruchart JC, Eschwege E. Accumulation of triglyceride-rich lipoprotein in subjects with abdominal obesity: The biguanides and the prevention of the risk of obesity (BIGPRO) 1 study. *Arterioscler Thromb Vasc Biol*. 2001;21:407-414.
 65. Schaefer EJ, McNamara JR, Shah PK, Nakajima K, Cupples LA, Ordovas JM, Wilson PW. Elevated remnant-like particle cholesterol and triglyceride levels in diabetic men and women in the Framingham Offspring Study. *Diabetes Care*. 2002;25:989-994.
 66. Dallongeville J, Boulet L, Davignon J, Lussier-Cacan S. Fish oil supplementation reduces beta-very low density lipoprotein in type III dysbetalipoproteinemia. *Arterioscler Thromb*. 1991;11:864-871.
 67. Nakamura N, Hamazaki T, Kobayashi M, Ohta M, Okuda K. Effects of eicosapentaenoic acids on remnant-like particles, cholesterol concentrations and plasma fatty acid composition in patients with diabetes mellitus. *In Vivo*. 1998;12:311-314.
 68. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685-696.
 69. Nordoy A, Hansen JB, Brox J, Svensson B. Effects of Atorvastatin and omega-3 fatty acids on LDL subfractions and postprandial hyperlipemia in patients with combined hyperlipemia. *Nutr Metab Cardiovasc Dis*. 2001;11:7-16.
 70. Chan DC, Watts GF, Barrett PH, Beilin LJ, Redgrave TB, Mori TA. Regulatory effects of HMG CoA reductase inhibitor and fish oils on apolipoprotein B-100 kinetics in insulin-resistant obese male subjects with dyslipidemia. *Diabetes*. 2002;51:2377-2386.
 71. Nakamura N, Hamazaki T, Ohta M, Okuda K, Urakaze M, Sawazaki S, Yamazaki K, Satoh A, Temaru R, Ishikura Y, Takata M, Kishida M, Kobayashi M. Joint effects of HMG-CoA reductase inhibitors and eicosapentaenoic acids on serum lipid profile and plasma fatty acid concentrations in patients with hyperlipidemia. *Int J Clin Lab Res*. 1999;29:22-25.
 72. Kriketos AD, Robertson RM, Sharp TA, Drougas H, Reed GW, Storlien LH, Hill JO. Role of weight loss and polyunsaturated fatty acids in improving metabolic fitness in moderately obese, moderately hypertensive subjects. *J Hypertens*. 2001;19:1745-1754.
 73. Mori TA, Bao DQ, Burke V, Puddey IB, Watts GF, Beilin LJ. Dietary fish as a major component of a weight-loss diet: Effect on serum lipids, glucose, and insulin metabolism in overweight hypertensive subjects. *Am J Clin Nutr*. 1999;70:817-825.
 74. Bao DQ, Mori TA, Burke V, Puddey IB, Beilin LJ. Effects of dietary fish and weight reduction on ambulatory blood pressure in overweight hypertensives. *Hypertension*. 1998;32:710-717.
 75. Yosefy C, Viskoper JR, Laszt A, Priluk R, Guita E, Varon D, Illan Z, Berry EM, Savion N, Adan Y, Lugassy G, Schneider R, Raz A. The effect of fish oil on hypertension, plasma lipids and hemostasis in hypertensive, obese, dyslipidemic patients with and without diabetes mellitus. *Prostaglandins Leukot Essent Fatty Acids*. 1999;61:83-87.
 76. Jain S, Gaiha M, Bhattacharjee J, Anuradha S. Effects of low-dose omega-3 fatty acid substitution in type-2 diabetes mellitus with special reference to

- oxidative stress—A prospective preliminary study. *J Assoc Physicians India*. 2002;50:1028-1033.
77. Mori TA, Watts GF, Burke V, Hilme E, Puddey IB, Beilin LJ. Differential effects of eicosapentaenoic acid and docosahexaenoic acid on vascular reactivity of the forearm microcirculation in hyperlipidemic, overweight men. *Circulation*. 2000;102:1264-1269.
 78. He K, Rimm EB, Merchant A, Rosner BA, Stampfer JM, Willett WC, Ascherio A. Fish consumption and risk of stroke in men. *JAMA*. 2002;288:3130-3136.
 79. Iso H, Rexrode KM, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, Hennekens CH, Willett WC. Intake of fish and omega-3 fatty acids and risk of stroke in women. *JAMA*. 2001;285:304-312.
 80. Kristensen MO. Increased incidence of bleeding intracranial aneurysms in Greenlandic Eskimos. *Acta Neurochir*. 1983;67:37-43.
 81. Bjerregaard P, Dyerberg J. Mortality from ischaemic heart disease and cerebrovascular disease in Greenland. *Int J Epidemiol*. 1988;17:514-519.
 82. Pedersen HA, Mulvad G, Seidelin KN, Malcom GT, Boudreau DA. N-3 fatty acids as a risk factor for haemorrhagic stroke. *Lancet*. 1999;353:812-813.
 83. Brown AA, Hu FB. Dietary modulation of endothelial function: Implications for cardiovascular disease. *Am J Clin Nutr*. 2001;73:673-786.
 84. Hogikyan RV, Galecki AT, Pitt B, Halter JB, Greene DA, Supiano MA. Specific impairment of endothelium-dependent vasodilation in subjects with type 2 diabetes independent of obesity. *J Clin Endocrinol Metab*. 1998;83:1946-1952.
 85. Thies F, Miles EA, Nebe-von-Caron G, Powell JR, Hurst TL, Newsholme EA, Calder PC. Influence of dietary supplementation with long-chain n-3 or n-6 polyunsaturated fatty acids on blood inflammatory cell populations and functions and on plasma soluble adhesion molecules in healthy adults. *Lipids*. 2001;36:1183-1193.
 86. Goode GK, Garcia S, Heagerty AM. Dietary supplementation with marine fish oil improves in vitro small artery endothelial function in hypercholesterolemic patients: A double-blind placebo-controlled study. *Circulation*. 1997;96:2802-2807.
 87. Goodfellow J, Bellamy MF, Ramsey MW, Jones CJ, Lewis MJ. Dietary supplementation with marine omega-3 fatty acids improves systemic large artery endothelial function in subjects with hypercholesterolemia. *J Am Coll Cardiol*. 2000;35:265-270.
 88. Abe Y, El-Masri B, Kimball KT, Pownall H, Reilly CF, Osmundsen K, Smith CW, Ballantyne CM. Soluble cell adhesion molecules in hypertriglyceridemia and potential significance on monocyte adhesion. *Arterioscler Thromb Vasc Biol*. 1998;18:723-731.
 89. 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;324:247-253.
 90. Fleischhauer FJ, Yan WD, Fischell TA. Fish oil improves endothelium-dependent coronary vasodilation in heart transplant recipients. *J Am Coll Cardiol*. 1993;21:982-989.
 91. McVeigh G, Brennan G, Johnston G, McDermott B, McGrath L, Henry W, Andrews JQ, Hayes JR. Dietary fish oil augments nitric oxide production or release in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia*. 1993;36:33-38.
 92. Johansen O, Seljeflot I, Hostmark 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;19:1681-1686.
 93. Seljeflot I, Arnesen H, Brude IR, Nenseter MS, Drevon CA, Hjermmann I. Effects of omega-3 fatty acids and/or antioxidants on endothelial cell markers. *Eur J Clin Invest*. 1998;28:629-635.
 94. Sampson MJ, Davies IR, Brown JC, Morgan V, Richardson T, James AJ, Sampson AP, Hughes DA. n-3 polyunsaturated fatty acid supplementation, monocyte adhesion molecule expression and pro-inflammatory mediators in Type 2 diabetes mellitus. *Diabet Med*. 2001;18:51-58.
 95. Erkkila AT, Lichtenstein AH, Mozaffarian D, Herrington DM. Fish intake is associated with a reduced progression of coronary artery atherosclerosis in postmenopausal women with coronary artery disease. *Am J Clin Nutr*. 2004;80:626-632.
 96. Lipinski B. Pathophysiology of oxidative stress in diabetes mellitus. *J Diabetes Complicat*. 2001;15:203-210.
 97. Pedersen H, Petersen M, Major-Pedersen A, Jensen T, Nielsen NS, Lauridsen ST, Marckmann P. Influence of fish oil supplementation on in vivo and in vitro oxidation resistance of low-density lipoprotein in type 2 diabetes. *Eur J Clin Nutr*. 2003;57:713-720.
 98. Mori TA, Woodman RJ, Burke V, Puddey IB, Croft KD, Beilin LJ. Effect of eicosapentaenoic acid and docosahexaenoic acid on oxidative stress and inflammatory markers in treated-hypertensive type 2 diabetic subjects. *Free Radical Bio Med*. 2003;35:772-781.
 99. Mori TA, Dunstan DW, Burke V, Croft KD, Rivera JH, Beilin LJ, Puddey IB. Effect of dietary fish and exercise training on urinary F2-isoprostane excretion in non-insulin-dependent diabetic patients. *Metabolism*. 1999;48:1402-1408.
 100. Arner P. Insulin resistance in type 2 diabetes: Role of fatty acids. *Diabetes Metab Res Rev* 2002;18(suppl 2):S5-S9.
 101. Swinburn BA, Metcalf PA, Ley SJ. Long-term (5-year) effects of a reduced-fat diet intervention in individuals with glucose intolerance. *Diabetes Care*. 2001;24:619-624.
 102. Vessby B. Dietary fat and insulin action in humans. *Br J Nut* 2000;83(suppl 1):S91-S96.
 103. Storlein LH, Kriketos AD, Jenkins AB, Baur LA, Pan DA, Tapsell LC, Calvert GD. Does dietary fat influence insulin action? *Ann NY Acad Sci*. 1997;827:287-301.
 104. Thanopoulou AC, Karamanos BG, Angelico FV, Asaad-Khalil SH, Barbato AF, Del Ben MP, Djordjevic PB, Dimitrijevic-Sreckovic VS, Gallotti CA, Katsilambros NL, Migdalis IN, Mrabet MM, Pet-

- kova MK, Roussi DP, Tenconi MT. Dietary fat intake as risk factor for the development of diabetes: Multinational, multicenter study of the Mediterranean Group for the Study of Diabetes (MGSD). *Diabetes Care*. 2003;26:302-307.
105. Garaulet M, Perez-Llamas F, Perez-Ayala M, Martinez P, de Medina FS, Tebar FJ, Zamora S. Site-specific differences in the fatty acid composition of abdominal adipose tissue in an obese population from a Mediterranean area: Relation with dietary fatty acids, plasma lipid profile, serum insulin, and central obesity. *Am J Clin Nutr*. 2001;74:585-591.
 106. American Diabetes Association. Diabetic nephropathy. *Diabetes Care*. 2002;25(suppl 1):S85-S89.
 107. Hamazaki T, Takazakura E, Osawa K, Urakaze M, Yano S. Reduction in microalbuminuria in diabetics by eicosapentaenoic acid ethyl ester. *Lipids*. 1990; 25:541-545.
 108. Shimizu H, Ohtani K, Tanaka Y, Sato N, Mori M, Shimomura Y. Long-term effect of eicosapentaenoic acid ethyl (EPA-E) on albuminuria of non-insulin dependent diabetic patients. *Diabetes Res Clin Pract*. 1995;28:35-40.
 109. Rossing P, Hansen BV, Nielsen FS, Myrup B, Holmer G, Parving HH. Fish oil in diabetic nephropathy. *Diabetes Care*. 1996;19:1214-1219.
 110. Lungershausen YK, Howe PRC, Clifton PM, Hughes CRT, Phillips P, Graham JJ, Thomas DW. Evaluation of an omega-3 fatty acid supplement in diabetics with microalbuminuria. *Ann NY Acad Sci*. 1997; 827:369-381.
 111. Miller PE, Carlton D, Deierhoi MH, Redden DT, Allon M. Natural history of arteriovenous grafts in hemodialysis patients. *Am J Kidney Dis*. 2000;36: 68-74.
 112. Schmitz PG, McCloud LK, Reikes ST, Leonard CL, Gellens ME. Prophylaxis of hemodialysis graft thrombosis with fish oil: Double-blind, randomized, prospective trial. *J Am Soc Nephrol*. 2002;13:184-190.
 113. Barzilay JI, Abraham L, Heckbert SR, Cushman M, Kuller LH, Resnick HE, Tracy RP. The relation of markers of inflammation to the development of glucose disorders in the elderly: The Cardiovascular Health Study. *Diabetes*. 2001;50:2384-2389.
 114. Rost NS, Wolf PA, Kase CS, Kelly-Hayes M, Silbershatz H, Massaro JM, D'Agostino RB, Franzblau C, Wilson PW. Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: the Framingham study. *Stroke*. 2001; 32:2575-2579.
 115. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*. 2001;286:327-334.
 116. Freeman DJ, Norrie J, Caslake MJ, Gaw A, Ford I, Lowe GD, O'Reilly DS, Packard CJ, Sattar N. C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. *Diabetes*. 2002; 51:1596-1600.
 117. Madsen T, Skou HA, Hansen VE, Fog L, Christensen JH, Toft E, Schmidt EB. C-reactive protein, dietary n-3 fatty acids, and the extent of coronary artery disease. *Am J Cardiol*. 2001;88:1139-1142.
 118. Chan DC, Watts GF, Barrett PH, Beilin LJ, Mori TA. Effect of atorvastatin and fish oil on plasma high-sensitivity C-reactive protein concentrations in individuals with visceral obesity. *Clin Chem*. 2002; 48:877-883.
 119. Wigmore SJ, Fearon KC, Maingay JP, Ross JA. Down-regulation of the acute-phase response in patients with pancreatic cancer cachexia receiving oral eicosapentaenoic acid is mediated via suppression of interleukin-6. *Clin Sci (Lond)*. 1997;92:215-221.
 120. Weimann A, Bastian L, Bischoff WE, Grotz M, Hansel M, Lotz J, Trautwein C, Tusch G, Schlitt HJ, Regel G. Influence of arginine, omega-3 fatty acids and nucleotide-supplemented enteral support on systemic inflammatory response syndrome and multiple organ failure in patients after severe trauma. *Nutrition*. 1998;14:165-172.
 121. Schilling J, Vranjes N, Fierz W, Joller H, Gyurech D, Ludwig E, Marathias K, Geroulanos S. Clinical outcome and immunology of postoperative arginine, omega-3 fatty acids, and nucleotide-enriched enteral feeding: A randomized prospective comparison with standard enteral and low-calorie/low-fat IV solutions. *Nutrition*. 1996;12:423-429.
 122. Delarue J, Le Foll C, Corporeau C, Lucas D. N-3 long chain polyunsaturated fatty acids: A nutritional tool to prevent insulin resistance associated to type 2 diabetes and obesity? *Reprod Nutr Dev*. 2003;44:289-299.
 123. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Aunola S, Cepaitis Z, Moltchanov V, Hakumaki M, Mannelin M, Martikkala V, Sundvall J, Uusitupa M. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;344: 1343-1350.