ABSTRACT

Objectives. To test the hypothesis that the unusually low prevalences of insulin resistance (IR), metabolic syndrome (MS) and diabetes (DM) in Alaskan Eskimos, compared to American Indians, is related to the traditional Eskimo diet, high in C20-C22 ω-3 fatty acids (FAs). To determine if the relatively low blood pressures, low serum triglycerides and high HDL cholesterol levels in Eskimos result from high ω-3 FA consumption.

Study design. Cross-sectional study.

Methods. We measured plasma FA concentrations in 447 Norton Sound Eskimos (35-74 years of age) and screened for DM, CHD and associated risk factors. A dietary assessment (24-hr recall) was obtained for comparison the day before the blood sampling.

Results. Plasma ω-3 FA concentrations were highly correlated with dietary ω-3 FAs and HDL levels and inversely correlated with plasma levels of insulin, 2-h insulin (OGTT), HOMI-IR, 2-h glucose (OGTT), triglyceride levels and diastolic blood pressure.

Conclusions. High consumption of ω-3 FAs positively affects components of the MS, insulin sensitivity and glucose tolerance. This finding suggests that high consumption of C20-C22 ω-3 FAs protects against the development of the MS and glucose intolerance.

(Int J Circumpolar Health 2005; 64(4):396-408.)

Key words: Inuit, type 2 diabetes, insulin, cholesterol, triglycerides, blood pressure, HOMI-IR
INTRODUCTION

Recent studies have shown that Alaskan Eskimos have relatively low prevalences of insulin resistance (IR), metabolic syndrome (MS) and type 2 diabetes (DM; 1-3). Another study in this population revealed that DM and IGT were associated with lower plasma concentrations of ω-3 fatty acids (FA) than those observed in the normo-glycemics (4), suggesting that impaired glucose tolerance was related to a divergence from a traditional diet, high in ω-3 FAs. The aim of the current study was to further analyze those data, collected in the Alaska Siberia Project (ASP), to determine if there are any significant associations between the individual components of the MS and the plasma levels of C20-C22 ω-3 FAs derived from the traditional Eskimo diet of fish and marine mammals. Such associations might partially explain the low prevalences of IR, MS and DM in Eskimos. The new definition of MS according to the Adult Treatment Panel III (ATPIII; 5) includes the following variables: plasma concentrations of insulin, glucose, triglycerides, HDL cholesterol (HDLC), blood pressure and waist circumference.

MATERIAL AND METHODS

Study population
The 315 Eskimos (151 males and 164 females) between 35 and 74 years of age, from four villages in the Norton Sound Region of Alaska, were screened during a four-week period in 1994 for DM, CHD and associated risk factors using the Strong Heart Study protocol (1, 6) as part of an intervention study for DM (1). One Inupiat, one Central Yupik and two Siberian Yupik villages were represented. All age-eligible villagers were invited to participate and 67% of the females and 50% of the males in this age group participated (1). Data from a 1998 screening of a quasi-random sample (n = 152; 7) of participants in the 1994 screening are included here to show the similar associations of ω-3 FAs to components of the MS.

Study screening
The screening followed the Strong Heart Study Protocol (6) and consisted of a personal interview (including medical history), physical examination (including blood pressure measurements and ECG), blood sampling and nutritional interviews using 24-h recall and food frequency instruments (1, 8). The latter were conducted the day before the blood sampling. Blood chemistries were carried out at the Medlantic Research Institute, that also does the analysis for the Strong Heart Study (6). The methods used have been described elsewhere (6). Insulin was measured using a radioimmunoassay developed as a modification of the method of Morgan and Lazarow (9). The procedure for the 1998 sample was slightly different in that a different commercial grade antibody (Linco 1012) was used.

Anthropometric measurements included hip (at widest point) and waist (at umbilicus) circumferences (6). After the participant had rested for 5 minutes in the sitting position, three consecutive blood pressure measurements were made on the right arm with a standard stethoscope, an appropriate-sized cuff, and a Baum mercury sphygmomanometer (W.A. Baum Company, Copiaque, New York), using the first and fifth phase Korotkoff sounds. The means of the last two measurements were used to estimate the blood pressure.
Nutritional interviews
Dietary data for this study were collected during house-to-house interviews. Included in that interview was a 24-hour recall, which was collected for this project using the Nutritional Data System (NDS, Version 2.8, Food Database 10A, Nutrient Database 25, University of Minnesota), a software product run on laptop computers (8). The food frequency questionnaire (FFQ) included questions asked of participants regarding the portion size, quantity, frequency and season of intake of 117 foods. The food list was compiled during formative research in 1992, after which Native foods were added, and infrequently consumed, non-Native foods were removed (10,11).

Plasma FA analysis
The plasma fatty acid analysis was carried out at the University of Alaska Anchorage on plasma that was originally obtained after at least 12 hours fasting (4). Plasma was stored in EDTA for 2-6 days at -10°C, then at -70°C. The analysis of total FA in plasma was carried out using standard methods. (4, 12). The concentration of each fatty acid was determined for each sample using regression analysis. The ratio of the area of each fatty acid peak to the internal standard peak was plotted vs. the weight ratio of the fatty acid and the internal standard. The regression equation was used to calculate the concentration of each fatty acid in each sample. Typical correlations were 0.99, or better.

The percentage of total plasma content of C20 and C22 ω-3 FAs was used in the analysis, as these FAs are derived from fish and marine mammals, principal components of traditional Eskimo diets (4).

Statistics
The linear regression analyses were conducted on SPSS v 9.0, using sex, age and omega-3 fatty acids as independent variables to predict the analyzed dependent variables. Regression analysis involved adjustments for age and gender and removal of out-liers > 2 standard deviations (SD). Comparisons of upper and lowest quartiles of C20+C22 ω-3 FAs with MS variables were performed using the two-tailed T-test for independent samples after age and gender adjustments and removal of out-liers > 2 SD. Levene’s test for equality of variances was applied to all tests.
Calculations for HOMA index (13) are: [(glucose mmol x insulin microunits/l) /22.5]

RESULTS
The data from 1994 and 1998 are shown separately, as they largely confirm the association of C20-C22 ω-3 FA with MS variables (Table I). The data from the two screenings could not be pooled, because the chemical methods were slightly different for the analysis of plasma insulin and fatty acids. In both cases, greater “sensitivity” was obtained in 1998.

Relative plasma concentrations of C20-C22 ω-3 FAs were associated with lower plasma fasting insulin concentration, 2-h insulin concentration, HOMA IR index (13), triglyceride concentration, 2-h glucose levels, diastolic blood pressure and higher plasma HDLC levels (in 1998 only). Due to the small numbers, associations were not always statistically significant, but Figures 1-7 of C20-22 ω-3 FA quartiles clearly show the association, or lack of ω-3 FAs to a variety of variables trends that need to be verified in larger studies (Table II).
The results of the first screening in 1994 showed a good correlation between total dietary \( \omega-3 \) FA consumption (24-h recall) and plasma concentrations of C20+C22 \( \omega-3 \) FAs (\( P = 0.003 \)) that are principally derived from the consumption of fish and sea mammals (Fig. 1). Since we were not able to do a dietary assessment in 1998, we have relied on the plasma FA data from 1998 to reflect an estimate of consumption.

**DISCUSSION**

This is the first study to show that most components of the metabolic syndrome are improved by high consumption of C20-C22 \( \omega-3 \) FAs. The results explain a number of separate observa-
tions about the Eskimos that set them apart from other ethnic groups. Only thirty years ago, the low prevalence of DM (14-17) did not have a satisfactory explanation, although Bang and Dyerberg (17) made the observation that DM was rare among Greenlandic Eskimos and that they consumed large amounts of C20-C22 ω-3 FAs and mono-unsaturated fats, but relatively little saturated fats. They speculated on a relationship, but there was no study done to correlate ω-3 FA consumption, or plasma levels of ω-3 FAs, with plasma glucose levels, or DM. The first such study was not done until 1994 (4), when it was shown that plasma levels of ω-3 FAs were lower in those with impaired glucose tolerance (IGT) and DM than in normo-glycemic (NG) Eskimos. Those results also fit the observations from a questionnaire study of Alaskan Eskimos that showed an inverse correlation between fish and seal consumption and abnormal glucose tolerance and DM (18). However, potential variables, such as ω-3 FAs and oleic acid, were not identified, or measured in that study.

The results of the 4-year ASP intervention study also revealed that those with improved glucose tolerance had significantly higher plasma concentrations of ω-3 FAs than those that did not, suggesting a significant role of ω-3 FAs in insulin sensitivity and glucose tolerance (7). It is noteworthy that the improvement of glucose tolerance occurred without weight loss.

Considering that the results of the present study indicate a potential role of C20+C22 ω-3 FAs in most components of the metabolic syndrome, it became apparent from the literature that fragments of this role have been described in a variety of studies over the years.

**Insulin resistance**

Insulin resistance is at the core of the metabolic syndrome (19). The results presented here clearly show an inverse association between plasma concentrations of fasting and 2-h insulin and C20+C22 ω-3 FAs (Tables I-II, Fig. 2), perhaps explaining earlier observations that Eskimos have, on average, significantly lower plasma concentrations of insulin and, hence, greater insulin sensitivity, than American Indians (3, 20) and other ethnic groups (21). Insulin sensitivity associated with ω-FAs has
also been noted by other investigators (22-25). Bjorkman et al. (26) showed that hyperinsulinemia/insulin resistance is inversely associated with the amount of C20-C22 FAs in muscle cell membrane phospholipids in patients with CHD and normal volunteers, i.e. insulin sensitivity is positively related to C20-C22 FAs. An increase in C20-C22 ω-3 FAs leads to (a) increased membrane fluidity, (b) increases in the number of insulin receptors, and (c) increases in insulin action (27). It is important to note that trans FAs have the opposite effect after being incorporated into cell membrane phospholipids: decreased fluidity, decreased insulin and binding to its receptor, leading to impaired insulin action, insulin resistance and hyperinsulinemia (27). Trans FAs have not been measured in Eskimos, although we know that they consume relatively large quantities (4).

**Glucose intolerance**

There is a clear inverse association of plasma concentrations of 2-h glucose and C20-C22 ω-3 FAs, revealing a significant effect of these ω-3 FAs on glucose tolerance (Fig. 3). The lack of correlation with fasting plasma glucose levels is not understood, but suggests that ω-3 FAs affect the response to a rapid increase of the glucose load, presumably by the increased insulin sensitivity. The ASP intervention study also showed that improved glucose tolerance was highly correlated with increased plasma concentrations of ω-3 FAs (7). This confirmed the pre-intervention measures, which revealed lower plasma concentrations of ω-3 FAs in those with IGT and DM compared to the normoglycemic participants. The findings in the ASP studies are in agreement with those of Adler et al. (18), if ω-3 FAs were the active ingredient in their

Figure 3. Plasma concentrations (mg·dL⁻¹) of fasting glucose and 2-h glucose (OGTT) of participants with high (upper quartile; open circle) and low (lower quartile; closed circle) concentrations of plasma C20+C22 ω-3 FAs (%).
findings of an inverse correlation between fish and seal consumption and impaired glucose tolerance. Those findings are similar to those of Feskens et al., who determined that fish consumption (high ω-3) was protective against glucose intolerance and DM during a 20-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study (28).

**Obesity**

Obesity is a major independent risk factor for IR, IGT and DM affecting all variables related to the metabolic syndrome. It is interesting that the development of obesity is dependent not only on genetic risk factors and total dietary fat etc., but also on the type of fat consumed (29-34). The more unsaturated the FA profile of the diet, the more resistant animals are to obesity. This would be consistent with the relative ease with which the ω-3 PUFA and mono-unsaturated fats, in particular, are used for energy compared to saturated fats (35). ω-3 FAs may in fact be protective against weight gain (32), as is a high consumption of protein, as determined by the principal component analysis of our data set (Risica et al. unpublished). Plasma FA profiles of overweight Eskimos are significantly different from those with normal weight after adjusting for age, gender and impaired glucose tolerance (Ebbesson, unpublished). It is clear from our data set that a lower consumption of ω-3 FAs (Fig. 4a) and lower plasma concentrations of C20+C22 FA (Fig. 4b) are correlated with body weight, but the correlation does not reach statistical significance.

**Blood pressure (BP)**

Blood pressures in Eskimos have been reported to be lower than in most other populations (3, 36). In 1992, mean systolic BPs (SBP) in Yupic Eskimos were 115 mm Hg among men and 123 among women, while the comparable diastolic BPs (DBPs) were 69 and 69 mm Hg, respectively (3). Lower blood pressures have only been recorded in a few Asian and Amazonian populations (36). The data presented here
suggest that the documented low blood pressures in Eskimos is partially due to the long chain ω-3 FA consumption. Furthermore, it is possible to hypothesize that the diet and resulting low blood pressures could, over thousands of years, have led to an evolutionary and potentially dangerous thinning of blood vessel walls, and that the recent obesity and associated increased SBP partially explain increases in the risks for aneurysms and stroke when combined with thin blood vessel walls in this population. The death rate from stroke in Alaskan Eskimos is now 1.5x the rate for the US White population (37).

Blood pressure, especially diastolic, appears to be inversely associated with an increased consumption of long chain ω-3 FAs, both in our study and in others (Table I, Fig. 5; 38,39). In Eskimos, we have observed significantly lower DBP, but not SBP, in those that improved their glucose tolerance during an intervention study that resulted in increased ω-3 FA consumption (7). An earlier study revealed that DBP, but not SBP, was significantly associated with fasting insulin levels (3). The present study shows that insulin is significantly related to 20+22C ω-3 FA concentrations.

A wide range of mechanisms may explain the vascular effects of ω-3 FAs (38,39). In rats, studies have shown that fish oil can lower basal vascular tone (40). Possible mechanisms include the enhancement of endothelial (nitric oxide-mediated) vasodilation and the inhibition of intrinsic thromboxane-like vasoconstriction. ω-3 FAs increase endothelium-derived relaxing factor (EDRF), presumably nitric oxide, which facilitates relaxation in large arteries and vessels (41). In the presence

Figure 5. Systolic and diastolic blood pressure (mmHg) with high (upper quartile; open circle) and low (lower quartile; closed circle) concentrations of plasma C20+C22 ω-3 FAs (%).
of eicosapentaenoic acid (EPA, 20:5-ω-3), endothelial cells in culture increase the release of relaxing factors, indicating a direct effect of ω-3 FAs on the cells. Clinical studies have shown the positive effect of fish oil on flow-mediated dilation (42).

The ASP intervention study was the first to demonstrate improved blood pressure with changes in fat diet without weight loss (7). We know that blood pressure is proportional to the degree of obesity (43) and that BP will fall 1.6-1.3 mmHg per Kg of weight reduction in overweight subjects (43). After a number of studies, it has become clear that, without weight loss, a reduction of fat intake per se is not likely to lower blood pressure (44-46). Large changes in total (47), or saturated fat (48, 49) had no effect on BP. The ASP studies on Eskimos appear to add the dimension that specific fats, such as C20+20C ω-3 FAs, can reduce BP without weight loss. The association of plasma FA concentrations with BP adds credence to that hypothesis, which now needs confirmation in larger studies.

With regards to hypertensives, it is noteworthy that patients on β-blockers and diuretics benefit by fish oil treatment, not only by improved BP, but by a significant reduction of plasma triglycerides and a rise in plasma HDL2 cholesterol, thus counteracting the main adverse effect of these drugs and, presumably, restoring their full potential to reduce cardiovascular morbidity (50). The latter is also improved by the anti-arrhythmic function of ω-3 FAs, especially DHA (51).

Triglycerides (TG)
The results of the present investigation clearly show an inverse relationship between plasma triglyceride and C20-C22 ω-3 FA concentrations (Tables I-II, Fig. 6). The exceptionally low triglyceride levels observed in Eskimos (52) can now be partially attributed to the high consumption of ω-3 FAs. It has been known for three decades that dietary fish oil rich in highly unsaturated EPA (20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) decrease plasma TG levels in both healthy (22, ) and hyper-triglyceridemic subjects (53, 54). It has recently been shown that eicosapentanoic acid (EPA) is primarily responsible for the hypo-triglyceridemic effects of fish oil in humans and rats (55-57) and that DHA, in contrast to EPA, does not inhibit hepatic TG production (58).

The ω-3 FAs have the potential to suppress the accumulation of TG in the heart and skel-

![Figure 6. Plasma triglyceride levels in participants with high (upper quartile; open circle) and low (lower quartile; closed circle) concentrations of plasma C20+C22 ω-3 FAs (%).](image-url)
etal muscle when included in high-sucrose, or high-fat diets (59, 60-61). The mechanisms are not understood, but some studies suggest that the ω-3 FAs inhibit lipogenesis (61) by suppressing TG synthesis and secretion in the liver (62).

HDL cholesterol (HDLC)

The results of this investigation showed a significant association between plasma concentrations of HDLC and C20-C22 ω-3 FAs in the 1998 screening, but did not reach statistical significance in 1994 (Table I, Fig. 7). The relationship of ω-3 FAs with plasma HDL levels has been observed before (54, 63, 64). The ingestion of gram quantities of ω-3 FAs leads to a small, but significant, increase in plasma HDL (HDL2). This increase in HDL often takes place simultaneously with a fall in VLDL concentration. The increased concentration of HDL may be explained by the reduced concentration of FFA in plasma (65, 66), thus causing a reduced flux of cholesterol ester from HDL to LDL and VLDL via the cholesteryl ester transfer protein (cETP) (67, 68). It is noteworthy that the high HDL levels routinely observed in ANs may not be as protective against CVD as originally thought, because the high levels may be due to an elevation of the HDL2 subclass, which is less protective than HDL3 (69, 70).

Conclusions

The results presented here suggest that the consumption of C20-C22 ω-3 FAs found in fish oils improve glucose tolerance and most variables in the MS by a) improving peripheral and hepatic insulin sensitivity, as previously shown in animal studies (27), which in turn corrects the dyslipidemia in the IRS, i.e. the hyper-triglyceridemia, decreased plasma HDL etc., b) improving DBP by increasing EDRF (nitric oxide) secretion, resulting in relaxation of large blood vessels c) reducing the oxygen demand of the working heart, resulting in increased cardiac efficiency and, perhaps, slower heart rate, which in turn would reduce arrhythmic events (71, 72) and d) improving the efficiency of fat metabolism by reducing the lipogenesis that results in the development of obesity (29-35).
Acknowledgements
The authors are grateful to the Norton Sound Health Corporation (NSHC) and the inhabitants of the villages participating in this study. The authors are also grateful to Dr. Cynthia Schraer, Dr. Amanda Adler and Anne Marie Mayer for their enormous contributions in the screenings. This study was approved by the NSHC, the Institutional Review Boards of the University of Alaska Fairbanks and the Alaska Native Health Center. This research was supported by grant ROI-47099 from the National Institute for Diabetes, Digestive and Kidney Diseases.

REFERENCES

1. Ebbesson SOE, Schraer CD, Risica PM, et al. Diabetes mellitus and impaired glucose tolerance in three Alaskan Eskimo populations: The Alaska-Siberia Project. Diabetes Care 1998; 21:563-569.
2. Schraer CD, Risica PM, Ebbesson SOE, and Go OT, Howard BV. Low fasting insulin levels in Eskimos compared to American Indians: Are Eskimos less insulin resistant? Int J Circumpolar Health 1999; 58: 272-280.
3. Schraer CD, Ebbesson SOE, Adler A, Cohen JS, Boyko EJ, Nobmann ED. Glucose tolerance and insulin-resistance syndrome among St. Lawrence Island Eskimos: The Alaska-Siberia Project. Proc. X Int. Congress Circumpolar Health 1997; 348-354.
4. Ebbesson SOE, Kennish J, Ebbesson LOE, Go O, Yeh J. Diabetes is related to fatty acid imbalance in Eskimos. Int J Circumpolar Health 1999; 58:108-119.
5. Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Full Report. http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3_rpt.htm
6. Lee ET, Welty TK, Fabsitz R, et al. The Strong Heart Study - a study of cardiovascular disease in American Indians: Are Eskimos less insulin resistant? Int J Circumpolar Health 1999; 58: 272-280.
7. Ebbesson SOE, Ebbesson LOE, Swenson M, Kennish JM, Robbins DC. A successful diabetes prevention study in Eskimos: The Alaska Siberia project. Int J Circumpolar Health 2005; 64(4):409-424.
8. Risica P, Nobmann ED, Ebbesson SOE, Schraer C, Caufield L, Caballer B. Springtime Macronutrient Intake of Alaska Natives of the Norton Sound Area. Int J Circumpolar Health 2005; 64(3): 222-233.
9. Morgan CR, Lazarow A. Immunoassay of insulin: two antibody system. Plasma insulin levels in normal, subdiabetic and diabetic rats. Diabetes. 1963; 12: 115-26.
10. Nobmann ED, Ebbesson SOE, White RG, Schraer CD, Lanier AP, Bulkow LR. Dietary intakes among Siberian Yupiks of Alaska and implications for cardiovascular disease. Int J Circumpolar Health 1998; 57:4-17.
11. Nobman EAD. Diet Among Siberian Yup’iks of Alaska and the Implications for Cardiovascular Disease, University of Alaska Fairbanks, May 1996 (Ph. D. thesis).
12. Anderson Gj, Conner WE, Corliss JD, Lin DS. Rapid modulation of the n-3 docosahexaenoic acid levels in the brain and retina of the newly hatched chick. J Lipid Res 1989; 30:433-441.
13. Matthews DR, Hosker JP, Rudensky AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting glucose and insulin concentrations in man. Diabetologia 1985; 28:412-419.
14. Scott EM, Griffith I V: Diabetes mellitus in Eskimos. Metabolism 6:320-325(1957).
15. Mourtzoff G, Carroll NV, Scott EM: Diabetes mellitus in Eskimos. JAMA 1967;199: 107-112.
16. Mourtzoff G, Scott EM: Diabetes mellitus in Eskimos after a decade. JAMA 1973; 226: 1345-1346.
17. Bang HO, Dyberg J, Hjorne N. The Composition of Food Consumed by Greenland Eskimos. Acta Med Scand 1976; 200: 69-73.
18. Adler Al, Boyko EJ, Schraer CD, Murphy NJ. Lower prevalence of impaired glucose tolerance and diabetess associated with daily seal oil or salmon consumption among Alaska Natives. Diabetes Care 1994; 17: 1498-1501.
19. Reaven, GM. Banting lecture: Role of insulin resistance in human disease. Diabetes 1988; 37: 1595-1607.
20. Greenland J, Valdez R, Casper M. Prevalence and correlates of the insulin resistance syndrome among Native Americans. Diabetes Care1999; 22:441-7.
21. Ferrannini E, Vichi S, Beck-Nielsen H, Laakso M, Paolillo G, Smith U. Insulin action and age. Diabetes 1996; 45: 947-53.
22. Dewaillie E, Blanchet C, Lemieux S, et al. N-3 Fatty acids and cardiovascular disease risk factors among the Inuit of Nunavik. Amer J Clin Nutr 2001; 74:4: 464-73.
23. Clarke SD. Polyunsaturated fatty acid regulation of gene transcription: a mechanism to improve energy balance and insulin resistance. Br J Nutr 2000;83(suppl):S59-66.
24. Storlien LH, Kriketos AD, Calvert GD, Baur LA, Jenkins AB. Fatty acids, triglycerides and syndromes of insulin resistance. Prostaglandins Leukot Essent Fatty Acids 1997; 57:379-85.
25. Lardinois CL. The role of omega-3 fatty acids on insulin secretion and insulin sensitivity. Med Hypotheses 1987; 24:243-8.
26. Bjorkman M, Storlien DA, Pan AB, Jenkins DJ, Chisholm DJ, Campbell LV. The relation between insulin sensitivity and the fatty-acid composition of skeletal-muscle phospholipids. N Engl J Med 1993; 328: 238-44.
27. Simopoulos AP. Omega-6/Omega-3 fatty acid ratio and trans fatty acids in non-insulin-dependent diabetes mellitus. In: Lipids and Syndromes of Insulin Resistance. Klimes I, et al. Ann NY Acad Sci 1997; 827:327-38.
28. Feskens EJM, Virtanen SM, Räsänen L, et al. Dietary factors determining diabetes and impaired glucose tolerance: a 20-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study. Diabetes Care 1995; 18:1104-12.

29. Pan DA, Storlien LH. Effect of dietary lipid profile on the metabolism of ω-3 fatty acids: implications for obesity prevention. In: Omega-3 Fatty Acids: Metabolism and Biological Effects 1993; 97-106 Birkhäuser. Basel.

30. Shimomura Y, Tamura T, Suzuki M. Less body fat accumulation in rats fed a safflower oil diet than in rats fed a beef tallow diet. J Nutr 1990; 120: 1291-96.

31. Hainault I, Carlotti M, Hajduch E, Guichard C, Lavau M. fish oil in a high lard diet prevents obesity, hyperlipemia, and adipocyte insulin resistance in rats. Ann. N Y Acad Sci 1993; 683: 98-101.

32. Pan DA, Hulbert AJ, Storlien LH. Dietary fats, membrane phospholipids, and obesity. J Nutr 1994; 124: 1555-66.

33. Dreon DM, Frey-Hewitt B, Ellsworth N, Williams PT, Terry B, Wood PD. Dietary fat: carbohydrate ratio and obesity in middle-aged men. Am J Clin Nutr 1988; 47:995-1000.

34. Romieu I, Willett WC, Stampfer MJ, et al. Energy intake and other determinants of relative weight. Am J Clin Nutr 1988; 47: 406-12.

35. Leyton J, Drury PJ, Crawford MA. Differential oxidation of saturated and unsaturated fatty acids in vivo in the rat. Br J Nutr 1987; 57:383-92.

36. Bjerregaard P, Dewailly E, Young TK, et al. Blood pressure among the Inuit (Eskimo) populations in the Arctic. Scand J Pub Health 2003; 31:92-99.

37. Lanier AP, Ehrsam G, Sandidge J. Alaska Native Mortality 1989-1998. Office of Alaska Native Health Research, Division of Community Health Services, Alaska Native Tribal Health Consortium, July, 2002.

38. Chin JPF, Dart AM. How do fish oils affect vascular function? Clin Exp Pharmacol Physiol 1995; 22:71-81.

39. Howe PRC. Dietary fats and hypertension: Focus on fish oil. In:Lipids and Syndromes of Insulin Resistance. Klimes I et al. Ann NY Acad Sci 1997; 827: 339-52.

40. Howe PRC, Lungerhausen Y, Rogers PF, Gerkens JF, Head RJ, Smith RM. Effects of dietary sodium and fish oil on blood pressure development in stroke-prone spontaneously hypertensive rats. J Hypertens 1991; 9:639-44.

41. Shimokawa H, Vanhoutte PM. Dietary cod-liver oil improves endothelium dependent responses in hypercholesterolemic and atherosclerotic porcine coronary arteries. Circulation 1998; 78:1421.

42. Goodfellow J, Bellamy MF, Ramsey MW, Jones CJ, Lewis MJ Dietary supplementation with marine omega-3 fatty acids improve systemic large artery endothelial function in subjects with hypercholesterolemia. J Am Coll Cardiol. 2000 Feb;35(2): 265-70.

43. Staessen J, Fagard R, Lunen P, Amery A. Body weight, sodium intake, and blood pressure. J Hypertens 1989; 7 (suppl. 1):S19-S23.

44. Beilin LJ. Diet and hypertension: critical concepts and controversies. J Hypertens 1987; 5(suppl. 5): S447-S457.

45. Sacks FM. Dietary fats and blood pressure: a critical review of the evidence. Nutr Rev 1989; 47: 291-300.

46. Pietinen P, Aro A. The role of nutrition in the prevention and treatment of hypertension. Adv Nutr Res 1990; 8:35-78.

47. Mensink RP, Janssen m-C, Katan MB. Effect on blood pressure of two diets differing in total fat, but not in saturated and polyunsaturated fatty acids in healthy volunteers. Am J Clin Nutr 1988; 47:976-980.

48. Sacks FM, Rouse IL, Stamperet MJ, Bishop LM, Lenherr CF, Walther RJ. Effect of dietary fats and carbohydrate on blood pressure of mildly hypertensive patients. Hypertension 1987; 10: 452-60.

49. Margetts BM, Beilin LJ, Armstrong BK, Rouse IL, Vandongen R, Croft KD, McMurchie EJ. Blood pressure and dietary polyunsaturated and saturated fats: a controlled trial. Clin Sci 1985; 69: 165-75.

50. Lungerhausen YK, Abbey M, Nestel PJ, Howe PRC. Reduction of blood pressure and plasma triglycerides by omega-3 fatty acids in treated hypertensives. J Hypertens 1994; 12: 1041-45.

51. Pepe, S, McLennan Dietary fish oil confers direct antiarrhythmic properties on the myocardium of rats. J Nutr 1996; 126: 34-42.

52. Ebbesson SOE, Schraer DC, Nobmann ED, Ebbesson LOE. Lipoprotein profiles in Alaskan-Siberia project. Arctic Med Res 1996; 55:165-173.

53. Goodnight SH Jr, Harris WS, Connor WE, Illingworth D. Polyunsaturated fatty acids, hyperlipidemia, and thrombosis. Arteriosclerosis 1982; 2: 87-113.

54. Harris WS. Fish oils and plasma lipid and lipoprotein metabolism in humans: a critical review. J Lip Res 1989; 30: 785-807.

55. Willumsen N, Skorve J, Hexeberg S, Rustan AC, Berge RK. The hypotriglyceridemic effect of eicosapentaenoic acid in rats is reflected in increased mitochondrial fatty acid oxidation followed by diminished lipogenesis. Lipids 1993; 28: 683-90.

56. Rambjor GS, Wålen Al, Windsor SL, Harris WL. Eicosapentaenoic acid is primarily responsible for hypotriglyceridemic effect of fish oil in humans. Lipids 1996; 31: S45-S49.

57. Froyland L H, Vaagenes H, Asiedu DK, Gaarras A, Lie O, Berge RK. Chronic administration of eicosapentaenoic acid and docosahexaenoic acid as ethyl esters reduced plasma cholesterol and changed the fatty acid composition in rat blood and organs. Lipids 1996; 31: 169-78.

58. Willumsen N, Hexeberg S, Skorve J, Lundquist M, Berge RK. Docosahexaenoic acid shows no triglyceride-lowering effects, but increases the peroxisomal fatty acid oxidation in liver of rats. J Lipid Res 1993; 34: 13-22.

59. Storlien LH, Pan DA, Kriketos AD, Baur LA. High fat diet-induced insulin resistance: lessons and implications from animal studies. Ann NY Acad Sci 1993; 683: 82-90.

60. Klimes I, Sebőkővá E, Vrána A, Kazdová L. Dietary fish oil confers direct antiarrhythmic properties on the myocardium of rats. J Nutr 1996; 126: 34-42.
61. Sebôková E, Klimes I. Molecular and cellular determinants of triglyceride availability. In: Lipids and Syndromes of Insulin Resistance. Klimes I, et al. Ann NY Acad Sci 1997; 827:200-14.

62. Rustan AC, Nossen JO, Christianses EN, Drevon CA. Eicosapentaenoic acid reduces hepatic synthesis and secretion of triacylglycerol by decreasing the activity of acyl-coenzyme A:1, 2-diacylglycerol acyltransferase. J Lipid Res 1988; 29:1417-26.

63. Schmidt EB, Dyerberg J. Omega-3 fatty acids: current status in cardiovascular medicine. Drugs 1994; 47: 405-24.

64. Saynor R, Gillott T. Changes in blood lipids and fibrinogen with a note on safety in a long-term study on the effects of n-3 fatty acids in subjects receiving fish oil supplements and followed for seven years. Lipids 1992; 27: 533-38.

65. Singer P, Wirth M, Berger. A possible contribution of decrease in free fatty acids o low serum triglyceride levels after diets supplemented with n-6 and n-3 polyunsaturated fatty acids. Atherosclerosis 1990; 83:167-75.

66. Sullivan DR, Sanders TA, Trayner IM, Thompson GR. Paradoxical elevation of LDL apoprotein B levels in hypertriglyceridemic patients and normal subjects ingesting fish oil. Atherosclerosis 1986; 61: 129-34.

67. Packard CJ, Munro A, Lorimer AR, Gorro AM, Shepherd J. Metabolism of apoliprotein B in large triglyceride-rich very low density lipoproteins of normal and hypertriglyceridemic subjects. J Clin Invest 1984; 74: 2178-92.

68. Barter PJ. Enzymes involved in lipid and lipoprotein metabolism. Curr Opin Lipidol 1990; 1: 518-23.

69. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study: implications for treatment. Circulation 1992; 85:37.

70. Sweetnam PM, Bolton CH, Yarnell JW, et al. Associations of HDL2 and HDL3 cholesterol subfractions with the development of eschemic heart disease in British men. The Caerphilly and Speedwell Collaborative Heart Disease Studies. Circulation 1994; 90: 769.

71. Pepe S, McLennan PL. Dietary fish oil confers direct antiarrhythmic properties on the myocardium of rats. J Nutr 1996; 126: 34-42.

72. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fiber intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet 1989; ii: 757-761.