Ingrid Løvold Mostad

Impact of dietary fat quantity and quality in type 2 diabetes with emphasis on marine n-3 fatty acids

Thesis for the degree doctor philosophiae

Trondheim, April 2007

Norwegian University of Science and Technology
Faculty of Medicine
Department of Cancer Research and Molecular Medicine

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HELSE OG REHABILITERING
Stiftelsen for norske helse- og rehabiliteringsorganisasjoner

NTNU
Norwegian University of Science and Technology

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Faculty of Medicine
Department of Cancer Research and Molecular Medicine

ISBN 978-82-471-1822-1 (printed version)
ISBN 978-82-471-1836-8 (electronic version)
ISSN 1503-8181

Doctoral theses at NTNU, 2007:83

Printed by NTNU-trykk

Betydning av mengde og type fett i kosten ved type 2 diabetes, med fokus på marine n-3 fettsyrer

Doktoravhandlingen bygger på tre kliniske studier av personer med type 2 diabetes**.**

Artikkel 1. Hensikten var å undersøke effekter av en 3-dagers intervensjon med fettfattig kost. Blodsukker, insulinfølsomhet, fettstoffer og fettvevshormoner ble målt. Nitten personer (10 menn og 9 kvinner, 40-75 år) uten insulinbehandling deltok, og alle hadde forhøyede nivå av triglyserider (et fettstoff) i blodet. Den fettfattige kosten hadde vesentlig mindre fett enn forsøkspersonenes vanlige kost. Til gjengjeld var innholdet av kornprodukter, frukt, grønnsaker, magre kjøtt- og meieriprodukter og fisk (både fet og mager), økt**.** Selv om denne kosten bare ble spist i 3 dager, var det signifikante forskjeller i blodprøvene tatt etterpå, sammenlignet med tilsvarende blodprøver etter vanlig kost. Følgelig ble fastende blodsukker, total kolesterol, HDL-kolesterol og hormonet leptin redusert. Nivået av hormonet adiponektin økte. Gjennomsnittlig blodsukker målt hver dag i kostperioden ble ikke endret, heller ikke insulinfølsomheten eller triglyseridnivået. Forsøkspersonene var sine egne kontroller.

Artikkel 2. Hensikten var å sammenligne insulinfølsomhet, insulinfrigjøring, blodsukker og energiomsetning etter 9 uker med enten fiskeolje (12 personer) eller maisolje (14 personer) som daglig tilskudd (20 ml). Fiskeoljens innhold av marine n-3 fettsyrer (omega-3 fettsyrer) var på 6 g/dag. Kosten ellers, samt vekta, var uforandret i forsøksperioden. Forsøket var dobbelt blindt. Ingen av forsøkspersonene (13 menn og 13 kvinner, 39-73 år) var behandlet med insulin, og alle hadde normale nivå av triglyserider. Gruppa som fikk fiskeolje kom ut med signifikant høyere blodsukker og dårligere insulinfølsomhet, samt tendens til større insulinfrigjøring, sammenlignet med gruppa som fikk maisolje. Energiomsetningen var uendret, men fettforbrenningen (målt i faste) økte signifikant i gruppa som fikk fiskeolje.

Artikkel 3. Hensikten var å sammenligne undergrupper av lipoproteiner etter 9 uker med enten fiskeolje eller maisolje, i samme forsøk som beskrevet i artikkel 2. Lipoproteiner (VLDL, LDL, HDL) er fettforbindelser som frakter kolesterol og triglyserider i blodet, og de kan deles inn undergrupper. Med fiskeolje ble partiklene av store VLDL mindre og konsentrasjonen av store VLDL og små HDL lavere.

Artikkel 4. Hensikten var å sammenligne effekter av n-3 fettsyrer (3 g) fra fiskeolje med soyaolje, når emulsjoner av disse ble gitt intravenøst i 4 timer. Insulinfølsomhet, insulinfrigjøring, energiomsetning og fettvevshormoner ble målt. Elleve forsøkspersoner (7 menn, 4 kvinner, 38-73 år, normale triglyseridnivå), utførte begge tester med to ukers mellomrom, dobbelt blindt. Rekkefølgen av hvilken olje som ble testet først, var tilfeldig. Resultatet var at fettsyrene fra fiskeolje ikke gjorde noen forskjell på det som ble målt, med unntak av en tendens til redusert fettforbrenning.

Tolkning av resultatene. Verken mengde eller type fett i kosten gir entydige resultat i sine effekter på blodsukker og fettstoffer i kroppen. Vi får bekreftet at det som er bra for å forebygge hjerte- og karsykdom, ikke nødvendigvis er like fra for reguleringen av blodsukkeret. At fettredusert kost gir et lavere fastende blodsukker, trenger ikke bety noe når dagens gjennomsnittlige blodsukker forblir uendret. Det viktigste funnet vårt er at mekanismen bak forhøyet blodsukker av stor dose marine n-3 fettsyrer, synes å være redusert insulinfølsomhet. Selv om blodsukkerstigningen var moderat, kan vi ikke ut fra våre resultater anbefale store, daglige mengder (6 g) marine n-3 fettsyrer til personer med type 2 diabetes. Vi har ingen grunn til å fraråde små, daglige mengder (1 g), som gis i 1 skje tran eller som 2-3 fiskeoljekapsler.

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Finansieringskilde: Helse og Rehabilitering, Stiftelsen for norske helse- og rehabiliteringsorganisasjoner

Ovennevnte avhandling er funnet verdig til å forsvares offentlig
for graden doctor philosophiae
Disputas finner sted i auditoriet, Kvinne-barn-senteret, St. Olavs Hospital,
onsdag 25. april 2007 kl. 13.15

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Acknowledgements

The work presented in this thesis was carried out at the Division of Endocrinology (B-11), Department of Medicine at St. Olavs Hospital in Trondheim. I have been employed as a research fellow at the Department of Cancer Research and Molecular Medicine (IKM), Faculty of Medicine at NTNU and financed for the most part from the Norwegian Foundation for Health and Rehabilitation. I am also thankful for the equipment and financial support from Peter Möller AS, Novo Nordisk, Abbot Norge AS, Norwegian Diabetes Association and NTNU. I thank Stein Kaasa, our previous, and Hans Krokan, the present chairman of the IKM for accepting me as a research fellow and for providing facilities. I thank Lise Støylen (Department of Clinical Service) and Else R. Holsdal (Division of Clinical Nutrition) at St. Olavs Hospital where I am employed halftime, for being flexible and supportive leaders in the process.

I am indebted to the participants in my studies for their endurance with the demanding protocols. Then, first of all: Valdemar Grill, my supervisor in full. You never discouraged me. With caution, respect and vast knowledge you have guided me into the scientific world of clinical research. "So far so good" has been a great phrase to me. I am impressed that I never had to wait for your response, contributing to the ever best teamwork. You made me feel comfortable at job.

Kristian S. Bjerve, you have always been there, for me. Can you imagine, this year we can celebrate 20 years as co-authors! Every time I meet you I learn more, and not only about the essential fatty acids. Thank you for all the analyses and manuscript work, and for giving me pleasure with kind e-mails (and SMSs when emergencies).

Elisabeth Qvigstad, you involved me in your project and introduced me to the world of clamps. (Does VG really know how troublesome they are)? Thanks for inspiring me as a forerunner in doing metabolic studies, and for your care and support during the hard days.

Marit R. Bjørgaas, your valuable help in developing the practice of insulinemic clamps calmed me down. Your linguistic knowledge has been a lot of help in the manuscript writing.

Stian Lydersen, "the day you entered my life" as a co-author was the 16th of December 2005 to be accurate, when I was in desperate need of a statistician. Lucky me. The teamwork with you has been a great pleasure, effective, informative and to the point.

Samar Basu, thanks for rapid analyses and contribution to the writing of Paper IV, and give my greetings to Eva Sejby for the assistance in your laboratory at Uppsala University.

For years the test room at B-11 was my second home. Thanks to my project nurses Anne Marit Aukan, Sissel Johnsen and Stine Lorentzen Lund: without you no clamps, no fun, no friendship; Ellen Gjerløw (leader) for creative solutions and stepping in if others were absent from any test; Tone Birgitte Bjørseth, Ruth Kari Holmli, Anne Mette Bredal, Gørild Carson and Lillian Bekkadal (performing the C-peptide glucagon tests, adipose tissue biopsies and/or DXA scans); the ever encouraging ladies in the secretariat: Grete Fossli, Aud Steiro, Elisabeth Skipnes, Vigdis Wågø, Ann-Synøve Hansen and Beate Waaden. Thanks also to the other diabetes nurses and the endocrinologists belonging to B-11 for showing interest in my projects and answering questions and contributing to discussions.

Thanks to the staff of the hematological laboratory of St. Olavs Hospital for access to the 4°C-centrifuge and a bench where I could prepare my buffer, every week for years; to Merete Mack, Erling Sagen, Ketil Thorstensen, Kristine Solem, Berit Valsø, Solveig Winther, Per H. Hepsø and Arnfinn Johansen for answering all my questions and performing fatty acid and urine analyses; to Per Farup, Peter Fayers and in particular Ingrid Lillevoll Lien for help with the minimization and oil bottle blinding procedures; to Vibeke Wist for managing the preparation of the Intralipid and Omegaven emulsions; to the hospital kitchen staff preparing the after-clamp-meals (however, at first they imagined the food was made for "a restaurant or something", namely "Valdemar's grill"); to Kari Solvoll, Kerstin Trygg, Magnhild Louise Pollestad and in particular Elin Bjørge Løken at UiO for advice and performing the nutritional analyses of all my projects; and the following for helping me with special issues and inspiring me in several ways: Harald Arnesen, Merete Askim, Gerd Bromseth, René Coffeng, Finn Drabløs, Keith Frayn, Thomas Haugen, Christian Hermstad, Lars Johansson, Ann-Christine Gottfries Kierulf, Aina Marie Lien, Stephen P Lock, Line Oldervoll, Tove Opdal, Jim Otvos, Trine Ranheim, Ingebjørg Seljeflot, Kristin Saarem, Per Thorsby, Inge Thyve, Bengt Vessby, Kjell Aarstad; further my colleagues Tove Drilen, Kjersti Gjermstad, Elisabeth Jacobsson, Xanthe Ann Johnson, Siv Tone Natland, Siren Nymo, Sara Severinsson, Ann Kristin de Soysa and Lene Thoresen.

So to my third home, IKM. To belong to the including and scientific working environment at IKM has been excellent when trying to complete a thesis. The lunch discussions have been through whatever parts of life there are, being the place of getting new inspiration and energy. All of you within the cancer research: nobody named, nobody left out.

Ingrid K. Hals Jørgensen, you have introduced me to the RIA-analyses with patience and precision. At last I made peace with the pipettes and standard curves and learned to love this work. I thank the rest of the "Grill Group" for help in the lab and/or scientific training in the meetings with Valdemar. I wish to thank Dagmar Moholdt and Mary Meland for secretarial, laboratorial and personal backing. Jon Lamvik, the grand old man of IKM: you never stopped challenging me by fruitful discussions. I thank you for that and for your whistling in the corridor and the steady asking for my father, whom you have known since the days of childhood at Tingvoll in Nordmøre.

Thanks to my father Arne's support and being proud of me, my mother Magnhild for advancing to be my personal quality controller of the thousands and thousands of numbers I had to punch into SPSS (she read, I wrote, I repeated, she controlled). Thanks to my parents-in-law, Synnøve and David, for their warm support. Thanks to my sister Liv for editing the draft of my thesis and my brother Magne for help with the photos.

What about my first home, then? There 5 children through the period of my thesis work have changed status from being children to be grown up sons and daughters, almost all of them. The youngest said a few days ago: *I feel sorry for dad, mom, he does everything, absolutely everything, also the things the ladies use to do, mom!* My small comfort is she actually *knows* what ladies, I suppose even moms, use to do. She never stops supporting you, Lars. You Lars never stop supporting me (*…well, so far,* I presume you may say, and nobody would know whether you were ironic, double ironic or just speaking the truth). Nevertheless, I trust in our experience through all these years: there ain't no cure for love. **LARS, Steinar, Ragne, Martin, Kari and Maghnild Synnøve**: I am grateful for your outstanding patience and love.

Ingrid Løvold Mostad, Trondheim, Feb 2007

Abbreviations

ANCOVA, analysis of covariance

ANOVA, repeated measures analysis of variance

BMI, body mass index

BMR, basal metabolic rate

CHD, coronary heart disease

CHO, carbohydrate or carbohydrates

CVD, cardiovascular disease

DHA, docosahexaenoic acid (22:6n-3)

DNSG, the Diabetes and Nutrition Study Group

DPA, docosapentaenoic acid (22:5n-3)

DXA, Dual Energy X-Ray Absorptiometry

EASD, the European Association for the Study of Diabetes

ELISA, enzyme linked immunoabsorbent assay

EPA, eicosapentaenoic acid (20:5n-3)

EPR, Energy Production Rate

E%, % of total energy

F, female

FDA, the Food and Drug Administration (US)

FFA, free fatty acids

FFQ, Food Frequency Questionnaire

HbA_{1c}, glycated hemoglobin

HDL, high density lipoprotein

HDL cholesterol, the cholesterol content of the high density lipoprotein

HOMA, Homeostatic Model Assessment

IDL, intermediate-density lipoprotein

ILM, Ingrid Løvold Mostad

LBM, lean body mass

LDL, low density lipoprotein

LDL cholesterol, the cholesterol content of the low density lipoprotein

LPL, lipoprotein lipase

l-VLDL, large VLDL lipoprotein particle concentration

M, male

MUFA, monounsaturated fatty acids

NEFA, non-esterified fatty acids

NMR, Nuclear Magnetic Resonance

PG, prostaglandin

PL, phospholipid or phospholipids

PUFA, polyunsaturated fatty acids

RIA, radioimmunoassay

RQ, respiratory quotient

SEM, standard error of the mean

SFA, Saturated Fatty Acids

s-HDL, small HDL lipoprotein particle concentration

s-LDL, small LDL lipoprotein particle concentration

VLCD, very low caloric diet

VLDL, very low density lipoprotein

VLDL cholesterol, the cholesterol content of the very low density lipoprotein

Papers included in this thesis

I. Mostad IL, Qvigstad E, Bjerve KS, Grill VE. Effects of a 3-day low-fat diet on metabolic control, insulin sensitivity, lipids and adipocyte hormones in Norwegian subjects with hypertriacylglycerolaemia and type 2 diabetes. Scand J Clin Lab Invest 2004; 64(6), 565-574.

II. Mostad IL, Bjerve KS, Bjorgaas MR, Lydersen S, Grill V. Effects of n-3 fatty acids in subjects with type 2 diabetes: reduction of insulin sensitivity and time-dependent alteration from carbohydrate to fat oxidation. Am J Clin Nutr 2006; 84(3), 540-550.

III. Mostad IL, Bjerve KS, Lydersen S, Grill V. Effects of marine n-3 fatty acid supplementation on lipoprotein subclasses measured by Nuclear Magnetic Resonance in subjects with type 2 diabetes. Eur J Clin Nutr 2007 Feb 28; [Epub ahead of print].

IV. Mostad IL, Bjerve KS, Basu S, Grill V. Effects of a 4 hour infusion of n-3 fatty acids on insulin sensitivity, insulin secretion, energy metabolism and F2-isoprostanes in subjects with type 2 diabetes. *Submitted to Clinical Nutrition the 20th of October 2006. Now under revision.*

1. Introduction

1.1 General

Nutritional aspects in diabetes often alternate focus between hyperglycemia and dyslipidemia. In the history of diabetes it may be correct to claim that when diet has been used as the only treatment, then the aim to achieve normoglycemia may have worsened the dyslipidemia. Turned around, the aim to achieve normolipidemia by diet may have worsened the hyperglycemia. A third aim of a recommended diet in overweight type 2 diabetes is to achieve weight reduction by energy restriction. Weight reduction, however, may mask other effects of dietary modifications. Effects of specific dietary changes could thus be secondary to weight reduction. When planning dietary studies in subjects with diabetes, it is preferable to avoid secondary effects. Further to be aware of the complexity of metabolic responses to dietary factors when interpreting the results to. We have tried to keep these considerations in mind.

1.2 Type 2 diabetes

1.2.1 Clarification and prevalence

Diabetes is classified into type 1 diabetes (due to islet β-cell destruction), type 2 diabetes (due to varying degrees of insulin resistance and/or insulin secretion defects), and into other specific types of diabetes. Type 2 diabetes accounts for >80% of all cases in Caucasian populations, affecting 5-7% of the world's population [1-3]. In Scandinavia the prevalence is reported to be 3-6 % [4,5]. Recent estimates in Norway for known (not total) diabetes are 3.4% for subjects aged ≥30 and ~ 8% for subjects aged 70-79 years [6]. Among South Asian immigrants in Norway the prevalence of known diabetes is assessed to be ~ 28% and 14% in women and men, respectively, compared with ~ 3% and 6%, respectively, in Norwegian women and men, aged 30-59

years [7]. The number of unknown cases may be nearly equal to the number of known cases in the age-groups ≥30 years in Norway [6].

Type 2 diabetes is a heterogeneous disease which is due both to environmental and genetic factors. Major environmental risk factors are obesity and physical inactivity. The genetic predisposition (polygenic, involving both insulin resistance and beta cell inadequacy) accounts for 40-80% of susceptibility to type 2 diabetes [8]. Both type 1 and 2 diabetes increase risk of cardiovascular disease [9,10].

1.2.2 Insulin resistance

Insulin resistance is defined as the inability of insulin to produce its usual biological actions at circulating concentrations that are effective in normal subjects [11].

Insulin acts by

- regulating glucose metabolism by inhibiting glucose production by the liver
- stimulating glucose uptake, particularly in skeletal muscle
- stimulating intravascular lipolysis and lipogenesis in adipose tissue
- inhibiting lipolysis in adipose tissue and
- Inhibiting very low density lipoprotein (VLDL) production of the liver.

These actions lower serum glucose, triglyceride and non-esterified fatty acids (NEFA or free fatty acids (FFA)), and increase lipoprotein lipase (LPL) activity in adipose tissue.

A resistance to these actions defines much of the phenotype of type 2 diabetes, i.e.:

- Hyperglycemia because of impaired suppression of endogenous glucose production under basal conditions as well as in the postprandial state
- Hypertriglyceridemia because the production of very low density lipoprotein (VLDL) in the liver is not suppressed, which in turn leads to lower high density lipoprotein (HDL) cholesterol and decreases the size of low density lipoprotein (LDL) particles (see below). Small dense LDL particles are highly atherogenic and can provide a link between insulin resistance and cardiovascular disease
- Elevated concentrations of plasma non-esterified fatty acids (NEFA, or FFA), because the “brake” on lipolysis is missing in insulin resistance.

1.2.3 Insulin secretion

The maintenance of normal glucose homeostasis depends on a balanced interaction between tissue sensitivity to insulin (especially in muscle and liver) and insulin secretion [12]. Hyperinsulinemia can be viewed as an attempt to overcome insulin resistance; however when type 2 diabetes is diagnosed, this adaptation is clearly not sufficient. Thus, insulin secretion is already defective at the time of diagnosis of type 2 diabetes. For reasons not completely elucidated, secretion is further attenuated with increasing duration of diabetes.

The interplay between insulin secretion and sensitivity makes it necessary in intervention studies to obtain measures not only of insulin sensitivity but also on insulin secretion. In the present studies we have tried to evaluate intervention effects on both parameters.

1.2.4 Energy metabolism

Energy requirements are determined by body size and composition, age and physical activity. Total energy expenditure consists of resting expenditure plus variable components due primarily to physical activity and "thermogenesis", i.e. heat production associated with meal digestion, nutrient absorption, and exposure to cold and stress [13]. Resting expenditure accounts for 50-70% of total energy expenditure. Energy metabolism is usually measured by indirect calorimetry and is termed energy production rate (EPR). Indirect calorimetry also allows calculation of the respiratory quotient (RQ), i.e. the ratio between CO_2 production and O_2 consumption. A high RQ signifies higher carbohydrate oxidation and simultaneously low fat oxidation and vice versa. An estimate of resting energy expenditure can also be obtained by calculating basal metabolic rate (BMR) by equations based on gender, age, weight (and height) [14].

A gradual increase in fasting RQ (i.e. lower fat oxidation) is reported after weight gain in subjects with and without type 2 diabetes [15]. A high RQ is claimed to be a predictor of weight gain in subjects with type 2 diabetes who are under treatment since a significant higher postabsorptive RQ is reported among those, compared with non-treated type 2 diabetes and healthy controls, with no difference between the non-treated diabetic and the healthy subjects [16].

1.2.5 Lipid variables

A "healthy" lipid profile is characterized by rapid removal of plasma lipids (triglycerides and cholesterol) from the circulation. The exogenous lipoprotein pathway includes triglycerides (and cholesterol) of dietary origin absorbed from the gut, and then repackaged into the large triglyceride-rich lipoproteins named chylomicrons. The chylomicrons are rapidly hydrolyzed, releasing FFA for fuel, or deposited and leaving excessive surface components to produce nascent HDL. The endogenous lipoprotein pathway includes triglycerides and cholesterol synthesized by the liver, released to the circulation into large, triglyceride-rich VLDL, rapidly hydrolyzed (releasing FFA) and transformed into intermediate-density lipoprotein (IDL) and eventually LDL. The density increases in parallel with the depletion of triglycerides and increase of the cholesterol content. The structure of each lipoprotein resembles that of VLDL as depicted in Figure 1.1.

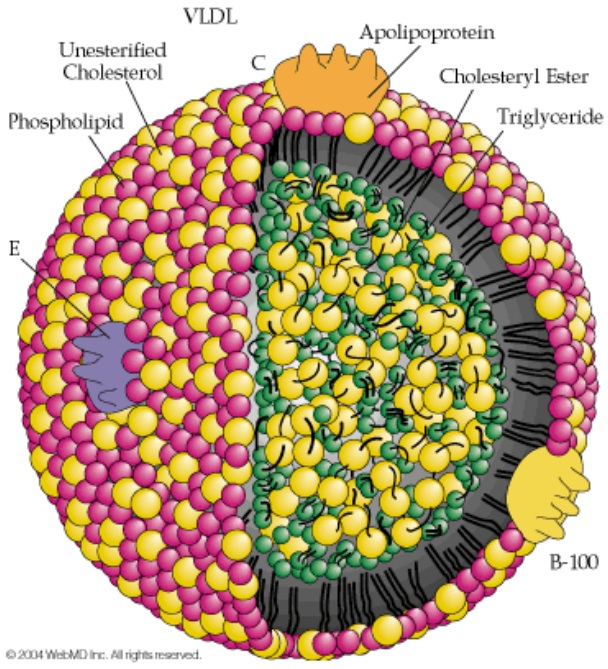

Figure 1.1 Lipoproteins

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Ref.: www.medscape.com

Brunzell JD and Failor A. Metabolism (chapter), Diagnosis and Treatment of Dyslipidemia (section), in ACP Medicine, Dale DC and Federman DD (Editors), Web.MD (Publisher), New York, 2006.

The lipoprotein shell is characterized by different apolipoproteins. They serve to activate surface receptors and enzymes essential for the uptake and metabolism of lipoproteins. Measuring apolipoprotein concentrations may have predictive value regarding cardiovascular disease for those apolipoproteins that are lipoprotein specific (but not for those who are not).

Similar to chylomicrons, also the catabolism of VLDL leaves excessive surface components to be used in the nascent HDL production. Nascent HDL is poor in cholesterol esters and can accept free cholesterol from various cells forming the large HDL (HDL_2), which deliver cholesterol to the liver. Increased levels of the large HDL_2 reflect effective catabolism of triglycerides, such catabolism being important in preventing LDL- cholesterol from ending up in endothelial cells; thus large HDL_2 are cardioprotective. Table 1.1 gives details of the composition of the main lipoproteins.

Table 1.1 Composition of the major lipoprotein complexes

Complex	Source	Density (g/ml)	%Protein	%TG[a]	%PL[b]	%CE[c]	%C[d]	%FFA[e]
Chylomicron	Intestine	<0.95	1-2	85-88	8	3	1	0
VLDL	Liver	0.95-1.006	7-10	50-55	18-20	12-15	8-10	1
IDL	VLDL	1.006-1.019	10-12	25-30	25-27	32-35	8-10	1
LDL	VLDL	1.019-1.063	20-22	10-15	20-28	37-48	8-10	1
*HDL_2	Intestine, liver (chylomicrons and VLDLs)	1.063-1.125	33-35	5-15	32-43	20-30	5-10	0
*HDL_3	Intestine, liver (chylomicrons and VLDLs)	1.125-1.210	55-57	3-13	26-46	15-30	2-6	6
Albumin-FFA	Adipose tissue	>1.281	99	0	0	0	0	100

[a]Triacylglycerols, [b]Phospholipids, [c]Cholesteryl esters, [d]Free cholesterol, [e]Free fatty acids *HDL2 and HDL3 derived from nascent HDL as a result of the acquisition of cholesteryl esters.
Ref.: http://www.med.unibs.it/~marchesi/lipoprot.html. The table is last updated 5.11.2002 and copied with permission from prof. Sergio Marchesini the 26th of January 2007 under the conditions to be used for educational purposes and may not be duplicated in any form for commercial purposes.

Dyslipidemia. The dyslipidemia in type 2 diabetes is characterized by hypertriglyceridemia, low concentrations of HDL cholesterol but almost normal concentrations of total cholesterol and LDL cholesterol [17]. The major abnormality is

elevation of VLDL (plasma triglyceride) due to its over-production and/or defective removal, contributing to an atherogenic lipoprotein phenotype with an atherogenic potential [18]. When less nascent HDL is produced, less cholesterol from LDL is transported to the liver. The endothelial cells of blood vessels have affinity for LDL, and cholesterol from LDL can enter the cells and damage the wall of the medium and large arteries. Another consequence of the elevated VLDL is the triglyceride enrichment of both HDL and LDL particles. This makes them a better substrate for hepatic lipase, which hydrolyses the triglycerides and makes HDL and LDL particles smaller and denser. Small dense LDL, typical for the dyslipoproteinemia in type 2 diabetes [19], is considered to be the most atherogenic among subclasses of lipoproteins [18]. Also the enlargement of the VLDL is suggested to be atherogenic [20]. When the HDL particle cores are loaded with triglycerides, these particles are broken down faster than normal HDL, which leads to a lower number of circulating total HDL (HDL particles) [21].

Measuring lipoprotein qualities. Measuring total plasma cholesterol to predict cardiovascular risk can obscure the contributions of different atherogenic or cardioprotective lipoprotein particles [22], since all lipoproteins contain cholesterol (Table 1.1). Quantifying individual lipoproteins by measuring their cholesterol contents also has limitations, since the cholesterol (and triglyceride) content of LDL, HDL and VLDL particles is not constant. Several reports indicate that the numbers and/or size of separate lipoproteins, rather than their cholesterol content, are associated with cardiovascular risk or events [23-26], or with the metabolic syndrome [27], insulin resistance [28] or type 2 diabetes [29,30]. Thus, the lipoprotein particle numbers and sizes may be clinically important [31]. Direct assessment of lipoprotein particle numbers was not possible until the advent of nuclear magnetic resonance (NMR) spectroscopic analysis [32,33]. This analysis is based on lipoproteins having magnetic properties that give them a “bell-like” behavior that produces a signal that can be recorded by NMR (Figure 1.2).

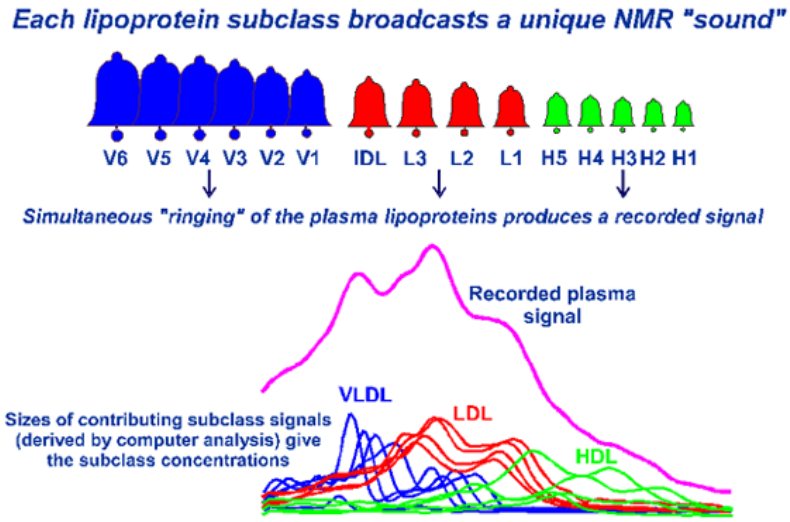


Figure 1.2
Lipoprotein subclasses behave like bells in the NMR anlyzer

Ref.: www.liposcience.com (Otvos,JD 2002 [22], measuring 6 different VLDL subclasses; IDL, 3 LDL and 5 HDL subclasses).

The figure is copied with permission of dr. Jim Otvos the 24th of January 2007.

The orientation order of the phospholipids in the lipoprotein shell (Figure 1.1) induces differences in magnetic susceptibility for lipoprotein particles of different size [34]. The equations describing this effect predict that every lipoprotein particle with a different diameter should have a different NMR signature. Neither the apolipoproteins in the shell nor the distribution between triglycerides and cholesterol in the core are decisive for the lipoprotein diameter and the NMR signal, thereby making it possible to measure the "pure" size and particle number concentration of each lipoprotein subclass, as illustrated in Figure 1.3.

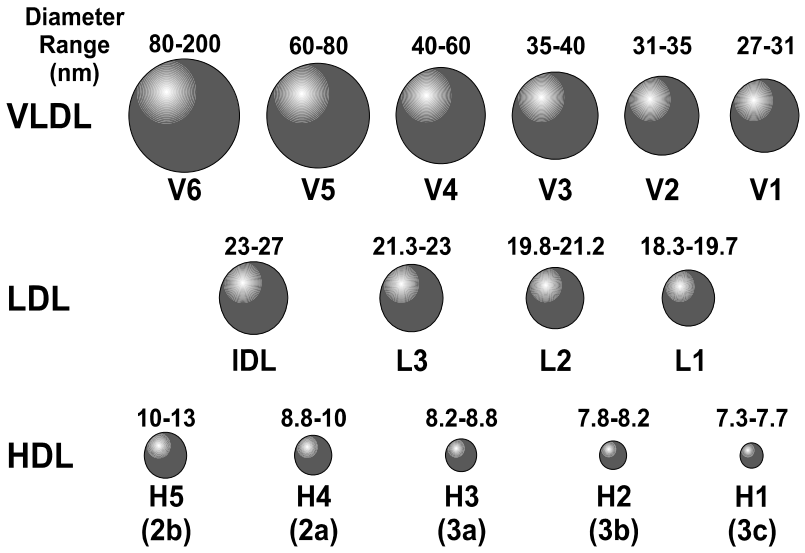


Figure 1.3
Lipoprotein subclasses nomenclature and size

Ref.: Otvos,JD 2002 [22], measuring 6 different VLDL subclasses; IDL, 3 LDL and 5 HDL subclasses.

The figure is copied with permission of dr. Jim Otvos the 24th of January 2007.

Oxidative products. Oxidative stress is associated with adiposity and insulin resistance in men [35]. Oxidative stress can be measured (indirectly) in many ways, such as levels of circulating oxidized LDL and isoprostanes. Oxidized LDL is found in monocyte-derived macrophages in atherosclerotic lesions [36,37] but not in healthy arteries [38]. Small, dense LDL particles typical of type 2 diabetes penetrate more easily than native LDL into the sub-endothelial space of the vessel walls where the oxidative modifications take place [39]. Circulating oxidized LDL are reported to associate with risk factors of the metabolic syndrome in middle-aged men [40], and are elevated in patients with coronary heart disease [41,42].

Isoprostanes are considered to be reliable biomarkers of oxidative stress [43] since they are relatively stable and found in most tissues and fluids [44,45].They are converted non-enzymatically by the free radical-catalyzed peroxidation of arachidonic acid. The major F_2-isoprostane (8-Iso-prostaglandin $F_{2\alpha}$) can be measured in both plasma and urine [46]. Isoprostanes may participate in pathophysiological processes by causing vaso- and bronchial constriction due to their ability to alter smooth muscle and platelet function [47].

1.2.6 Adipocyte hormones

Adiponectin and leptin are hormones produced by adipocytes. Subjects with type 2 diabetes, with impaired glucose tolerance or obesity without diabetes have lower levels of adiponectin compared with subjects not belonging to these categories. It is suggested that the positive correlation between adiponectin and insulin sensitivity [48,49] is linked to increased fat oxidation [50], and it is also proposed that adiponectin has anti-inflammatory and anti-atherogenic properties [50].

Circulating leptin concentrations are reported to be proportional to total body fat mass and therefore elevated in obese subjects and in subjects with type 2 diabetes [51]. It is unclear whether leptin improves or inhibits insulin sensitivity [52,53]. Thus both adiponectin and leptin have the potential to influence the phenotype of type 2 diabetes; these hormones were therefore measured in this thesis.

1.3 Marine n-3 fatty acids

Marine n-3 fatty acids (also named very long chain n-3 polyunsaturated fatty acids or omega-3 fatty acids) are the main part of the n-3 fatty acid family. The plant derived alpha-linolenic acid (18:3n-3) is the essential precursor of the n-3 fatty acid family. Linoleic acid (18:2n-6) is the essential precursor of the n-6 fatty acid family. These two fatty acids need to be provided by the food since the human organism lacks the enzymes capable of introducing double-bonds in the n-3 and n-6 positions of oleic acid (18:1n-9). Both n-3 and n-6 fatty acids use the same elongases and desaturases for further metabolism in the organism. The n-3 and n-6 fatty acids compete for the same enzymes, hence the balance between n-6 and n-3 fatty acids in the diet is important [54]. Marine n-3 fatty acids are produced by marine phytoplanctons, which accumulate in the food chain. The following marine n-3 fatty acids are therefore abundant in fatty fish, fish oils and sea mammals: 20:5n-3 (eicosapentaenoic acid (EPA)); 22:5n-3 (docosapentaenoic acid (DPA)) and 22:6n-3 (docosahexaenoic acid (DHA)). The 20:5n-3 and 22:5n-3, and to a limited extent, 22:6n-3, are formed from 18:3n-3 in humans. Marine n-3 fatty acids are reported to be twice as efficient as 18:3n-3 to reverse alpha-linolenic acid deficiency [55].

Both n-6 and n-3 fatty acids are important structural components of cell membranes, essential for various functions as fluidity, permeability, activity of membrane-bound enzymes and receptors, and for signal transduction [54]. In observational studies in the general population, consumption of moderate amounts fish or n-3 fatty acids from fish oil correlates with a lower risk of fatal coronary heart disease, in particular sudden cardiac death [56-62] via anti-arrhythmic effects [57,63]. A few secondary trials have been performed [64-66]; they report prevention of mortality due to CHD in patients with prior myocardial infarction.

It is obvious that effects of n-3 fatty acids are multi-faceted and may differ between humans, depending, for instance, on the absence or presence of diabetes and/or dyslipidemia. More studies are needed to clearly delineate the effects of n-3 fatty acids in relation to specific diseases or types of metabolic dysfunction.

1.4 Dietary fat quantity and quality in type 2 diabetes

1.4.1 Nutritional recommendations.

In health and type 2 diabetes. The Norwegian recommendations of macronutrient distribution prevailing the population in general [67], are based on the Nordic Nutrition recommendations [54]. Fat should provide 25-35 % of the total energy intake (E%), carbohydrates (exclusive fiber) 50-60 E% and protein 10-20 E%. Regarding fat quality, saturated (SFA) plus trans fatty acids should be limited to approximately 10 E%, cis-monounsaturated fatty acids (MUFA) 10-15 E% and polyunsaturated fatty acids (PUFA) 5-10 E%, including not less than 3 E% from essential PUFA (n-6 and n-3 fatty acids) and minimum 0.5 E% (preferably 1 E%) from the n-3 fatty acids in particular [67]. In Norway, subjects with type 2 diabetes are recommended the same food intake as to the population in general [68]. These guidelines are in accordance with the European ones [69], with exception of the encouragement to supplement the diet with cod liver oil (or other n-3 fatty acid supplements). In Europe there is no consensus on the use of supplements containing n-3 fatty acids in diabetes [69].

The Nordic recommendation of a minimal intake of 0.5 E% n-3 fatty acids includes all n-3 fatty acids. There are no specific recommendations on the intake of marine n-3 fatty acids separated from the sum of 18:3n-3 fatty acids. Reference energy requirements for women (74-31 y) are 1700-2300 kcal/d, ranging from sedentary to physically active, and the corresponding requirements for men are 2200-3300 kcal/d [54]. When adjusted to the lowest and highest energy requirements respectively, the sum of all n-3 fatty acids should thus vary from 0.9 to 1.8 g/d. The American guidelines include at least 2 servings/week of fish high in EPA and DHA (in sum ~ 230 g fish), which provide at least 0.5 g/d of EPA and/or DHA [70]. As a comparison, Norwegian 5 ml/d cod liver oil or 3 servings/week of fatty fish contribute with ~ 1 g/d marine n-3 fatty acids.

To summarize, subjects with type 2 diabetes are in general encouraged to increase the intake of dietary n-3 fatty acids in line with current recommendations for the general population. Also, available data are considered insufficient to make specific recommendations regarding the optimal ratio of dietary n-6/n-3 fatty acids [69].

In hospitalized patients. Surgical stress stimulates counter-regulatory hormone secretion, which in turn decreases insulin sensitivity and inhibits insulin release [71]. These changes are diabetogenic and favor catabolism. From the nutritional point of view, special efforts are needed to achieve energy and protein balance in surgical patients, patients with type 2 diabetes included. The optimal distribution between carbohydrate, fat and protein in parenteral nutrition has been discussed for a long time and recommendations on fat quantity have been given. For example, it has been recommended to infuse 2 g fat/kg/24 h, which covers 40 % of the basal energy requirement and ≥ 0.1 g/kg/24h 18:2n-6 fatty acid in order to avoid linoleic acid deficiency [72]. It has indeed been proposed to increase the content of n-3 fatty acids in parenteral nutrition [73].

Among hospitalized patients ~ 10 % have diabetes [74]. Among the heterogenic group of patients which needs parenteral nutrition, as many as 30% may have diabetes [75] . However, there appears to be no specific recommendations on the administration of n-3 fatty acids to hospitalized patients with type 2 diabetes.

Amounts of n-3 fatty acids in intervention and treatment. Previously 2-10 g/d of long-chain n-3 fatty acids have been used as supplements in intervention studies [76]. For long-term use, however, the US Food and Drug Administration (FDA) recommends 9 g/d natural fish oil (18% EPA, 12% DHA) as upper limit [77], based on the recommendation of 3 g/d of marine n-3 fatty acids as upper limit from Menhaden oil [78]. FDA does not claim that a higher intake poses a health hazard and there are indeed data from traditional Greenland Inuits, indicating that a high intake throughout life (8.5 g/d and up to ≥14 g/d of marine n-3 fatty acids [79,80]) is without apparent ill effects.

When n-3 fatty acids are used as treatment of severe hypertriglyceridemia, the upper limit recommended by FDA may be passed since the only registered preparation in Norway (Omacor, (Pharmacia&Upjohn)) is recommended in intakes of 1.7-3.4 g/d initially, and increased to 5 g/d if not effective at lower dosage [81].

1.4.2 The impact of fat quantity and quality on phenotypes of type 2 diabetes

Glycemic control. A low-fat/high carbohydrate (but low fiber) diet compared with a fat-modified diet (high in MUFA) is reported to increase postprandial glucose and reduce insulin sensitivity in subjects with type 2 diabetes [82]. Opposite results were obtained, i.e. a decrease in postprandial glucose and insulin resistance, when adding fiber-rich foods (especially soluble fibers from legumes, fruit and vegetables) to the low-fat diet [82]. The latter results are, however, not clearly confirmed by others [83,84].

Effects of n-3 fatty acids on glycemic control and insulin sensitivity in type 2 diabetes are equivocal. Deterioration of glycemic control has been found in some [85-90], but not in all studies [91-100]. However, none of the controlled intervention studies in subjects with type 2 diabetes found better insulin sensitivity after supplementation with n-3 fatty acids [93,100,101]. In healthy subjects (the KANWU study) the improvement of insulin sensitivity achieved by a high MUFA diet was not affected by adding marine n-3 fatty acids [102].

Neither the clinical relevance of low-fat studies nor the effects of n-3 fatty acids on glycemic control have been completely elucidated in subjects with type 2 diabetes. In particular, few studies have investigated both effects on insulin resistance and insulin secretion per se. Also knowledge of the impact of parenteral administration of n-3 fatty acids to subjects with type 2 diabetes is lacking.

Energy metabolism. A low-fat diet is reported to reduce EPR in morbidly obese subjects [103], however, this effect may be secondary to rapid weight loss. Different fatty acids are taken up and oxidized at different rates [104]. In theory, thus, increasing the proportion of n-3 fatty acids relative to other fatty acids could alter energy metabolism. Data on this subject are scarce in humans and subjects with type 2 diabetes. A small study in healthy humans reported a lower RQ (= increased fat oxidation) but no change in EPR after 3 wk intervention with 1.8 g marine n-3 fatty acids [105]. On the other hand intervention with 3.8 g of n-3 fatty acids for 6 wk in subjects with type 2 diabetes did not affect EPR or RQ [106]. The influence of marine n-3 fatty acids on energy metabolism in type 2 diabetes is largely unexplored.

Dyslipidemia. Marine n-3 fatty acids can reduce plasma triglycerides in hypertriglyceridemic subjects due to a reduced release of chylomicrons and VLDL [107]. Large doses (>3 g/d EPA+DHA) are reported to be necessary to lower triglycerides and VLDL cholesterol in non-diabetic [108], and diabetic [109,110] subjects, but doses < 2 g/d are also reported to be effective in type 2 diabetes [111]. Total cholesterol is not influenced by n-3 fatty acids [76]. As to effects on LDL cholesterol some studies report increased levels in type 2 diabetes [76,110], whereas others report tendencies for an increase [109,112], or no effects [113]. As to HDL cholesterol levels, these are reported to be increased by fish oil supplements in healthy subjects [114,115], but no effects were found in subjects with hypertriglyceridemia and/or type 2 diabetes [108-110,114].

In type 2 diabetes effects of n-3 fatty acids on lipoprotein subclasses by standard methods have so far given diverging results [113,116,117]. Intervention studies on lipoprotein subclasses measured by NMR in type 2 diabetes have, to our knowledge, so far not been performed. A controlled study of effects on lipoprotein subclass qualities by marine n-3 fatty acid intervention measured by NMR seems warranted in subjects with type 2 diabetes.

Oxidative products. In subjects with hypertension 3.4 g/d of marine n-3 fatty acids resulted in an increase of oxidized LDL [118]. In the KANWU study 2.4 g/d of marine n-3 fatty acids brought about a decrease in the non-enzymatic derived markers of oxidative stress (isoprostanes) in healthy subjects [38]. In diabetes there is little information on effects of n-3 fatty acids on oxidized LDL and isoprostanes, acutely and over time.

Adipocyte hormones. It is hard to find studies reporting effects on adipocyte hormones by fat reduction, in which concomitant weight reduction is not a confounding factor.

2. Aims

The overall aim was to investigate specific effects of changing the intake of fat quantity and/or quality in subjects with type 2 diabetes. Specifically I wanted to test

1. whether and to which extent a short-term (3 d) dietary intervention low-fat diet would affect glycemic control, lipids and hormones (Paper I)
2. whether and to which extent a long-term (9 wk) marine n-3 fatty acid supplementation (fish oil) would affect blood glucose, insulin sensitivity, insulin secretion and energy metabolism in subjects with type 2 diabetes and normotriglyceridemia (Paper II)
3. whether the same long-term intervention with n-3 fatty acids would affect lipoprotein size and subclasses and, if so, whether changes would relate to effects on insulin sensitivity (Paper III)
4. whether an acute (4 h) infusion of marine n-3 fatty acids would affect insulin sensitivity, insulin secretion, adipocyte hormones, energy metabolism and oxidative products in subjects with type 2 diabetes and normotriglyceridemia (Paper IV).

3. Subjects and methods

3.1 Study populations and design

All studies were carried out at St. Olavs Hospital, Trondheim in the Department of Medicine, Division of Endocrinology. The low fat study (Paper 1) was carried out October the 28th 1997 to October the 20th 1998. Study subjects for this study were recruited from patients treated at the diabetes out-patient clinic of the Division of Endocrinology. In the other two studies (Papers II-IV) study subjects were recruited from the primary health care. These later studies were performed from October the 1st 2001 to December the 17th 2002 (n-3 supplement study, Papers II and III) and from January the 9th to May 13th 2004 (n-3 infusion study, Paper IV).

An overview of study populations, design, interventions, endpoints and time-course is given in Table 3.1. Further details of the design are given in the flow diagrams of Figure 3.1.

For Paper I, pre-screening of patients was based on information in medical records. Criteria for inclusion were primarily set for a study protocol in which fatty acids were acutely lowered by Acipimox [119]. The low-fat intervention was initially a part of this study. Subjects thought to be eligible (n=61), were sent a letter with the information that they would be contacted by telephone. The following telephone call was made in order to acquire acceptance or not to send a second letter to the patients with detailed information and an invitation to participate in the study. The offer to participate was accepted by 42 persons. After screening and inclusion 21 subjects participated in the Acipimox study [119] and 19 of these also in the low-fat study reported in Paper I (Figure 3.1). Following the initial part of the study (after inclusion, Figure 3.1), the participants recorded - for the second time - their food intake by weighing their usual diet for 3 d (followed by measurements of fasting variables). Then they were instructed to go on living as usual for the next 2-3 wk until the 3 d of low-fat diet. To ensure a setting of free living the composition of the low-fat diet was given in general

Table 3.1 Overview of studies

	Low-fat study	n-3 supplement study	n-3 infusion study
Papers	I	II and III	IV
Study population	Type 2 diabetes n=19 (10 M, 9 F) Age 61 (40-69) y Hypertriglyceridemic No insulin treatment Smokers (n=5, 3 M, 2 F)	Type 2 diabetes n=26 (13 M, 13 F) Age 58 (39-73) y Normotriglyceridemic No insulin treatment No smokers	Type 2 diabetes n=11 (7 M, 4 F) Age 57 (38-73) y Normotriglyceridemic No insulin treatment No smokers
Study design	Before-after, pilot (Figure 3.1) Run-in period before baseline Usual diet before and after baseline Low-fat diet for 3 days	Parallel controlled (Figure 3.1) Double blind, randomized to corn or fish oil Wash-out period of marine n-3 fatty acids ≥6 months	Cross-over (Figure 3.1) Double blind, randomized Wash-out period of marine n-3 fatty acids ≥6 months
Study intervention	Normal food products Fat quantity reduction compared with the usual diet: - Low-fat diet, i.e. reduced intake of edible and invisible fats, in particular saturated fatty acids Dietary quality changes: - increased intake of whole-meal bread, vegetables, fruit and fish (including ~ 1 g n-3 fatty acids) - exchange from high-fat to low- fat diary products Energy intake not completely equal in the usual and low-fat diet	Liquid fish oil supplementation, per os Fat quality different between groups: - High dose (5.9 g) n-3 fatty acids (fish oil) in the intervention group - n-6 fatty acids (corn oil) in the control group Fat quantity increased equally in both groups Dietary quality were equal in both groups, except for the intervention oils Energy intake equal in both groups	Lipid emulsion added n-3 fatty acids infused, i.v. Fat quality different between test days: - moderate dose (3.1 g) n-3 fatty acids added standard lipid emulsion compared with the standard lipid emulsion alone Fat quantity nearly equal in both emulsions Dietary quality equal before each test day Energy intake nearly equal in both lipid emulsions
Study endpoints	Glycemic control Insulin sensitivity, insulin secretion Plasma and lipoprotein lipids Adipocyte hormones	Glycemic control Insulin sensitivity, insulin secretion Plasma and lipoprotein lipids, lipoprotein subclasses Adipocyte hormones Energy metabolism Oxidative products	Insulin sensitivity, insulin secretion FFA, triglycerides Adipocyte hormones Energy metabolism Oxidative products
Intervention time-course	Effects measured after 3 d with low-fat diet	Effects measured after 1 and 9 wk with n-3 fatty acid (fish oil) supplementation	Effects measured after 4 h with n-3 fatty acid infusion

For abbreviations, please refer to the abbreviation list.

but concrete terms (written and orally). The study subjects also measured their blood glucose 5 times daily and recorded quantity and quality of physical activity during each day of dietary recording.

In the n-3 supplement study the pre-screening process had fewer stages, since subjects who were eligible for participation had already expressed their willingness to participate by responding to an advertisement.

The discrepancy between the number of subjects willing to participate in the n-3 fatty acid intervention studies on one hand and those passing the screening criteria on the other (Figure 3.1), was due to stringent exclusion criteria, (such as smoking and regular use of supplements with marine n-3 fatty acids) which could not readily be formulated in an advertisement. Responders to the advertisement had the opportunity to cut smoking for ≥ 3 months or/and accept a wash-out period of n-3 supplements for ≥ 6 months. Many then declined participation.

The degree to which blinding was achieved, was evaluated by a post-study questionnaire (Appendix A) in which subjects were asked which oil (Photo 3.1) they thought they had ingested (details on the procedure are given in Paper II). As to the blinding of investigators, all analyses were performed before the randomization code was broken.

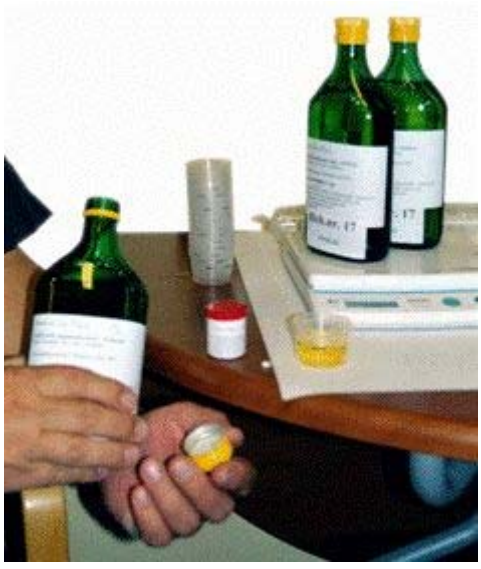


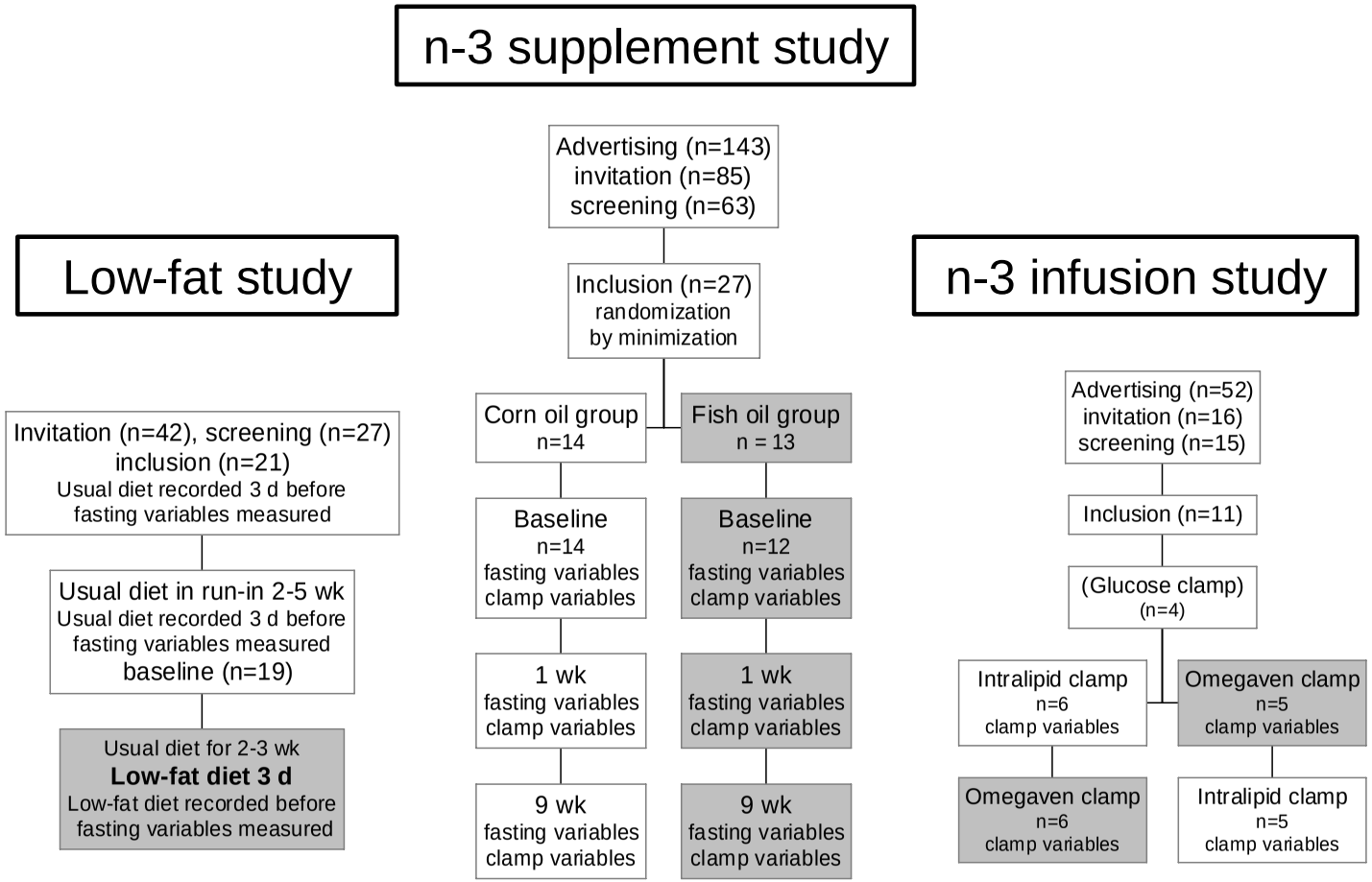
Photo 3.1

Study oils in the n-3 supplement study

Corn oil and fish oil flavored with lemon were distributed in liquid form in identical bottles. The subjects received disposable premarked 20-mL dose cups.

Photo taken by ILM, 2002.

Figure 3.1 Design of studies



For the n-3 infusion study (Paper IV), the procedure from advertising to inclusion was similar to the n-3 supplement study (Figure 3.1), as was also the clinical characteristics of the study population (Table 3.1). Included were subjects with appropriate veins for a 4-hour long infusion period. By this criterion we had to exclude some subjects. Subjects with hypertriglyceridemia were excluded because of our concerns about the lipid-increasing effects of the fat infusion (~ 80 g), given during 4 h. The same concerns resulted in that the meal served after each clamp was low-fat. Furthermore, the subjects were told to avoid intake of fat for the rest of that particular day.

3.2 Measurements

3.2.1 General

Taken all studies together, most endpoints are common (Table 3.1). The methods for each of them are presented in Table 3.2. Table 3.2 also gives an overview of other measurements (food intake, body composition and fatty acids, physical activity, compliance to the interventions and blinding).

3.2.2 Glycemic control

Fasting blood glucose. Venous blood serum samples after 12 h of fasting were analyzed in the Department of Medical Biochemistry (St. Olavs Hospital) on each day of testing. On the same days we also analyzed concentrations of fasting blood glucose with the YSI Glucose Analyzer in venous whole blood samples, which were drawn at 0 min of the clamps (Papers II and IV). Glucose values obtained from these whole blood sample values were – expectedly - lower (13-15%) than values obtained in serum. In addition, the study subjects measured fasting blood glucose themselves at home (in capillary whole blood), during both the low fat and the n-3 supplement studies (Papers I and II-III).

Day-time blood glucose. In the low-fat study (Paper I), subjects measured day-time blood glucose (capillary whole blood) 5 times a day (fasting, pre-lunch, pre-dinner, 2 h

Table 3.2 Measurements performed in the studies

Endpoint variables		**Low-fat study**	**n-3 supplement study**	**n-3 infusion study**
Glycemic control	Day-time blood glucose Fasting blood glucose HbA1c Insulin sensitivity Insulin secretion	At home 5xd in 3 d periods Standard methods Standard methods Fasting glucose/insulin ratio, Fasting HOMA	At home 5xd, various days Standard methods Standard methods Hyperinsulinemic clamp C-peptide glucagon test	• Standard methods Standard methods Hyperinsulinemic clamp C-peptide glucagon test
Energy metabolism	Energy production rate Respiratory Quotient	• •	Indirect calorimetry Indirect calorimetry	Indirect calorimetry Indirect calorimetry
Dyslipidemia	Plasma and lipoprotein lipids Free fatty acids Lipoprotein subclasses	Enzymatic methods Enzymatic method •	Enzymatic methods; NMR Enzymatic method NMR	Enzymatic methods Enzymatic method •
Oxidative products	Oxidized LDL Non-enzymatically peroxidation	• •	ELISA, monoclonal antibody •	• 8-iso-$PGF_{2\alpha}$ - specific RIA
Adipocyte hormones	Leptin, adioponectin	Human-specific RIA kits	Human-specific RIA kits	Human-specific RIA kits
Other hormones	C-peptide, insulin, proinsulin, glucagon	Human-specific RIA kits	Human-specific RIA kits	Human-specific RIA kits
Other variables				
Body composition	Weight (height, BMI) Waist and hip circumference Lean body mass, fat mass	Electronic scale Measuring tape •	Electronic scale; DXA scan Measuring tape DXA scan	Electronic scale, DXA scan Measuring tape DXA scan
Dietary intake	Retrospective intake Prospective intake	Quantitative FFQ Weighed records, 3 d periods	Quantitative FFQ •	Quantitative FFQ Estimated records, 1 d
Fatty acids	In diet In plasma phospholipids In subcutaneous adipose tissue	Software “BEREGN” Gas chromatography •	Software “BEREGN” Gas chromatography Methanolysis, gas chrom.graphy	Software ”Mat på data 4.2”. Gas chromatography •
Intervention	Prescribed vs. performed Blinding	Food and nutrient analysis •	Oil bottles weighed Double blinding documented	Lipid infusion registered Double blinding documented
Physical activity	Retrospective activity Prospective activity	Quantitative FQ, baseline Activity diary, 3 d periods	Quantitative FQ, baseline •	Quantitative FQ, baseline •

• = not investigated. For abbreviations, please refer to the abbreviation list.

after dinner, at bedtime) during the 3 d periods of dietary recording, using their own glucose measuring devices. In the n-3 supplement study (Papers II and III) all subjects used the same glucose measuring device (details in Paper II). For Paper I the values were recorded in the dietary recording form (Appendix B) and for Paper II in a separate blood glucose measurement form (Appendix C).

HbA_{1c} (glycated hemoglobin). In all studies subjects measured HbA_{1c} at baseline. HbA_{1c} was also measured after 9 wk intervention in the n-3 supplement study.

Insulin sensitivity. In the low-fat study (Paper I), insulin sensitivity was assessed as the ratio between fasting glucose (mg/L) and insulin (mU/L) [120,121]. For the n-3 intervention studies (Papers II - IV) we used isoglycemic hyperinsulinemic clamps. As others [122], we preferred isoglycemic to euglycemic clamps since we then could study the diabetic subjects in their native (hyperglycemic) conditions and avoid the confounding effect of insulin preinfusion (to achieve euglycemia). Subjects were thus clamped at the level of fasting glucose as measured the day of the baseline clamp. In the n-3 supplement study (Papers II and III) the clamp duration was 2 h and the insulin infusion 40 mU/min/m^2. Insulin sensitivity was assessed by glucose utilization, i.e. the amount of glucose (mg/min/kg lean body mass (LBM)) that was infused in order to maintain the fasting glucose concentration during the last 40 min of each clamp. In the n-3 infusion study (Paper IV), a higher rate of insulin infusion was chosen (80 mU/min/m^2) because we expected insulin resistance to progress during the infusion due to the co-infusion of lipid with glucose. These clamps lasted for 4 h in order to reach steady state. Again glucose utilization during the last 40 min was used to calculate insulin sensitivity.

Insulin secretion. In the low-fat study, fasting levels of insulin and glucose were used to assess insulin secretion. We calculated HOMA (Homeostatic Model Assessment) for β-cell function (20 x insulin mU/L / (glucose mmol/L – 3.5) as published [121,123].

In the n-3 supplement study, insulin secretion was assessed in the fasting mode by a C-peptide glucagon test [124,125]. This test is a long term validated one for assessing insulin secretion [126]. We performed the test on the day preceding a day of clamping. We considered potential variation in the response time to reach the maximum level of

C-peptide. Therefore we added measurements to include the time points 5, 6 and 7 min after the injection of glucagon. The maximum increment in C-peptide concentration obtained during min 5-7 was used for calculations.

In the n-3 infusion study we modified the standard C-peptide-glucagon test in so far that the test was performed not fasting but instead 15 min after end of the 4 h clamp.

3.2.3 Energy metabolism

EPR. Basal EPR (kcal/24 h) was measured by indirect calorimetry during 0 min in the resting mode after 12 h fasting. We performed indirect calorimetry measurements with a closed ventilated hood system (Photo 3.2) at baseline, and after 1 and 9 wk of intervention in the n-3 supplement study. Measurements were performed both in the fasted state and during clamps (Paper II). In the n-3 infusion study indirect calorimetry was measured during all clamps and additionally in the fasted state, but then only at baseline (Paper IV).

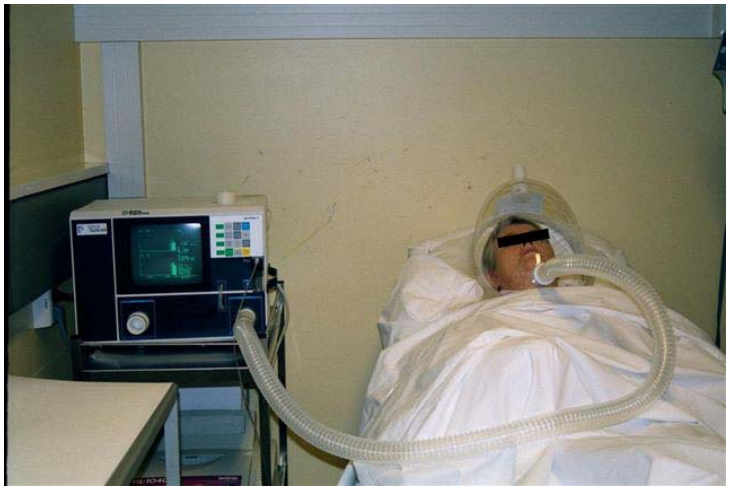


Photo 3.2

Indirect calorimetry in the resting mode

(Papers II and IV)

Photo taken by ILM and authorized by the subject, 2002.

Dietary macronutrient composition is associated with predictable rates of O2 consumption and CO2 production, while urinary nitrogen excretion rate reflects protein oxidation rates. From this information, energy expenditure is calculated from specific equations [13,127,128]. The conversion factors for carbohydrate, fat and protein in

terms of kcal/g are somewhat higher for indirect calorimetry (4.18, 9.46 and 4.32) than those used for food (4, 9, 4), [128] .

In the low-fat study, baseline BMR was calculated according to the equations given in Table 3.3.

Table 3.3 BMR calculated on the basis of gender, age and weight

GENDER	AGE, y	BMR (kcal/24 h)
women	30-59	8.7 x kg[a] – 25 x m[b] + 865
women	60+	9.2 x kg + 637 x m – 302
men	30-59	11.3 x kg + 16 x m + 901
men	60+	8.8 x kg + 1128 x m – 1071

[a]kg, measured to one decimal point; [b]m, measured to two decimal points [14].

RQ. When indirect calorimetry measures the respiratory gas exchange to estimate the rates of fat and carbohydrate oxidation, a stable protein oxidation is assumed, which is usually set to 81 g/d or 13 g/d nitrogen in the urine [128,129]. We sampled urine for 9 h during the night before fasting measurements of indirect calorimetry in the n-3 supplement study. Therefore we could calculate the urinary loss of g nitrogen (x 6.25=g protein metabolized, adjusted to 24 h). We used that information to calculate the non-protein RQ (details in Paper II).

3.2.4 Lipid variables

Fasting plasma lipids (triglyceride, total cholesterol) were measured at baseline and after interventions in all 3 study protocols. Lipoprotein lipids (HDL cholesterol, LDL cholesterol) were measured or calculated at the same occasions, with the exception of LDL cholesterol, which was not calculated in the hypertriglyceridemic subjects in the low-fat study (Paper I), since Friedewalds formula (Cholesterol – HDL cholesterol – 0.46 x triglycerides) can only be used when triglycerides are ≤4.0 mmol/L [130].

To avoid in vitro lipolysis, the samples to be used for analyzing free fatty acids were drawn into EDTA-containing tubes and handled quickly. In the n-3 infusion study duplicate samples (EDTA plasma) for all subjects were also analyzed at a second laboratory (Uppsala) in order to compare values analyzed at the Department of Medical Biochemistry at St. Olavs Hospital (Paper IV).

NMR measurements for lipoprotein subclasses were performed in the overnight fasted state at baseline, at 1 and at 9 wk of intervention in the n-3 supplement study (Paper III).

Oxidized LDL was measured (Paper III) using a standard method (Oxidized LDL competitive enzyme linked immunoabsorbent assay), as described [41,42]. Isoprostanes in plasma and urine were measured by a specific radioimmunoassay in the n-3 infusion study (Paper IV) [46].

3.2.5 Body composition

In the n-3 studies Dual energy X-ray Absorptiometry (DXA) scanning (Photo 3.3) was used to measure lean, fat and total body mass at baseline and also after 9 wk intervention in the n-3 supplement study. Insulin sensitivity (glucose utilization) and EPR is expressed relative to LBM in those studies, since we tried to avoid the confounding factor of different distribution between fat and LBM in men compared with women.

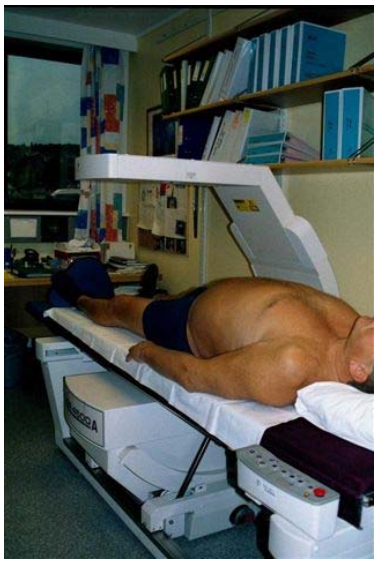


Photo 3.3

DXA scanning

Photo taken by ILM and authorized by the subject, 2002.

3.2.6 Dietary intake

Retrospective method. To assess energy and nutrient intake at baseline a Food Frequency Questionnaire (FFQ) for about 180 food items was used (Appendix D). The same FFQ was used in all studies (Table 3.2). This retrospective questionnaire is self-administered. It was sent by mail to the participants to be filled out at home. At baseline the filled-out questionnaire was checked during a personal interview (ILM) to eliminate

inconsistencies, misunderstandings and errors. The results were computed by using a food database (AKF96) and software systems (BEREGN) developed at the Department of Nutrition Research, University of Oslo. The food database was mainly based on the official Norwegian food table [131]. The analysis of the FFQs filled in by the participants in the low-fat study during 1997-1998 has not been published except in the present thesis (in the chapter of Results). When the Department of Nutrition Research evaluated these FFQs in 1998 they could not guarantee the validity of results of energy intake from the main groups of fatty acids since the composition of margarines in the database were updated only until 1995, whereas margarine factories in Norway frequently changed the composition of margarine during the time period of the low-fat study (1997-98). Since margarine is a main ingredient in cooking this uncertainty influenced the information obtainable from the analyzed FFQs. These results in the present thesis should therefore be interpreted with caution. However, the FFQ fatty acid results of the both n-3 studies (Papers II and IV) are based on an updated version of the database, which includes reliable information on the composition of margarine in Norway at the time of performance of these studies (2001-2004).

For all studies the sum of E% from SFA, MUFA, n-3 and n-6 or the sum of SFA, MUFA and PUFA are 3-4 E% lower than the calculated E% of total fat. This is because information of fat quality is missing for some food items. However, fat quantity information is never missing; thus, total fat intake was satisfactorily analyzed.

Prospective methods. Food recording by weighing was the prospective method chosen in order to assess each subject's usual and intervention diet in the low-fat study (Table 3.2). The weighed records of the usual diet (Appendix B) supplemented the retrospective records obtained by FFQ. The weighed records were analyzed almost a year later than the FFQs. Only total fat content is published in Paper I and also here (in the Results section). Nevertheless we could estimate the main intake of marine n-3 fatty acids from consumption of several fatty fish varieties, and these results are given in the text of Paper I.

Estimated records by household measures were the prospective method chosen to be carried out the day before each clamp in the n-3 infusion study (Table 3.2). The intention was to ensure similar food and beverage intake before the clamps since the

subjects were encouraged to eat the same food before the second clamp (Paper IV). Regarding the 1 day records, we had to use another database for nutrient analysis (Mat på data). This database gives the amounts of saturated, monounsaturated and polyunsaturated fatty acids, but does not calculate separate amounts of the n-6 and n-3 fatty acids.

3.2.7 Fatty acids in adipose tissue

Our study introduced the biopsy procedure (Photo 3.4) at St. Olavs Hospital (Paper II), [132].

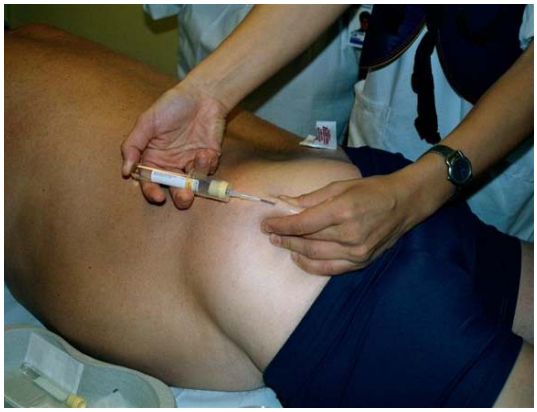


Photo 3.4

Subcutaneous adipose tissue biopsy

Adipose tissue was obtained from one buttock by needle aspiration.

The specimen was placed on ice and frozen immediately at -80ºC, pending later analyses of the fatty acid composition.

Photo taken by ILM and authorized by the subject, 2002.

3.3 Statistics

Statistical analyses were performed with SPSS versions 11.5 and 13.0 (SPSS Inc, Chicago, IL, 2003 and 2005). Assumptions of normality were checked by Shapiro-Wilks' test in Paper I and by visual inspection of normal Q-Q Plots in Papers II-IV. Randomization was performed by the method of minimization [133]. Results are given as median values and the variability as the interquartile range (IQR; the distance between the 75th and 25th percentile values) in text and the most tables in all Papers, and as means (variability as 95% CI or SEM) as indicated in some tables and figures. Table 3.4 gives a brief overview of the methods of significance testing used. A *P*-value ≤0.05

(two-sided) was considered significant. Spearman's correlation coefficients (*r*) were used to evaluate bivariate correlations. Statistical details are described in each Paper.

Table 3.4 Statistical methods

	Papers			
	I	**II**	**III**	**IV**
The paired Wilcoxon signed ranks test	x	x		x
The unpaired Mann-Whitney test	x	x	x	
The independent samples *t* test		x		
ANCOVA, General linear model, Univariate procedure		x	x	
ANOVA, General linear model, Repeated measures procedure		x	x	x
Bonferroni adjustments		x		

For abbreviations, please refer to the abbreviation list.

4. Results

4.1. General

In Papers 1-IV results were generally presented as medians and inter-quartile ranges (IQR). In the following Results section of this thesis some main results are given as mean values and (95% CI).

4.2 Baseline results

4.2.1 Study subjects

Baseline characteristics of all study participants are given in Table 4.1. The subjects in the low-fat study were more overweight and their glycemic control and lipid profile was more abnormal compared with the participants in the other two studies. The n-3 fatty acid relative concentration of plasma phospholipids expressed as weight% was ~ 13 g/100 g in the low-fat study compared with 9-10 g/100 g in the n-3 studies (Table 4. 1). Among the 19 subjects of the low-fat study 5 were regular users of n-3 fatty acid supplements. The use of supplements corresponded with an increased n-3 fatty acid weight% to ≥15 g/100g plasma phospholipid fatty acids (not published in Paper I). The concentrations of total plasma phospholipid fatty acids correlated positively to the triglyceride concentrations in all studies but significantly only among the hypertriglyceridemic subjects in the low-fat study ($r=0.691$, $P=0.001$).

4.2.2 Energy intake

Baseline energy intake and macronutrient distribution are summarized for all three studies in Table 4.2. In the low-fat study, the FFQ and weighing records showed close agreement regarding total energy intake but discrepancy as to the energy distribution between carbohydrate, fat and alcohol. In the n-3 supplement study, baseline diet was recorded by FFQ only. In the n-3 infusion study, the total energy intake calculated from

Table 4.1 Study subjects at baseline

Variables[1]		**Low-fat study**			**n-3 supplement study**			**n-3 infusion study**		
		Baseline, n=19 (10 M, 9 F)			Baseline, n=26 (13 M, 13 F)			Baseline, n=11 (7 M, 4 F)		
		mean	*95% CI*		mean	*95% CI*		mean	*95% CI*	
Age	years	56	*51*	*61*	59	*55*	*62*	56	*49*	*63*
Duration of diabetes	years	6.6	*4.7*	*8.5*	3.6	*2.4*	*4.8*	5.0	*2.7*	*7.3*
Weight	kg	91.2	*83.8*	*98.6*	85.5	*80.2*	*90.7*	84.4	*75.7*	*93.1*
BMI	kg/m^2	30.5	*28.2*	*32.8*	29.5	*28.4*	*30.5*	28.4	*26.6*	*30.1*
Waist	cm	105	*99*	*112*	101	*97*	*104*	100	*95*	*105*
Lean Body Mass	kg	•			57.6	*53.1*	*62.0*	58.2	*50.9*	*65.6*
Fat mass	kg	•			25.4	*23.4*	*27.5*	23.6	*20.6*	*26.7*
Systolic blood pressure	mm Hg	147	*139*	*156*	138	*132*	*143*	128	*120*	*137*
Diastolic blood pressure	mm Hg	87	*82*	*91*	82	*78*	*86*	80	*74*	*87*
HbA_{1c}	%	7.8	*7.1*	*8.4*	6.9	*6.6*	*7.2*	7.4	*6.5*	*8.3*
Serum glucose	mmol/L	9.7	*8.3*	*11.1*	7.9	*7.3*	*8.5*	9.5	*7.8*	*11.2*
Serum glucose	mg/L	175	*150*	*200*	143	131	154	171	*140*	*202*
Insulin	mU/L	14.0	*11.1*	*16.9*	14.2	*11.5*	*16.8*	13.9	*8.7*	*19.1*
C-peptide	nmol/L	1.13	*0.91*	*1.33*	1.02	*0.81*	*1.22*	0.90	*0.64*	*1.16*
Glucagon	pmol/L	38	*30*	*45*	85	*75*	*96*	88	*68*	*108*
Proinsulin	pmol/L	17	*12*	*21*	33	*26*	*40*	31	*17*	*45*
Leptin	ng/mL	13.2	*10.2*	*16.2*	11.0	*8.4*	*13.6*	11.8	*7.6*	*16.1*
Adiponectin	µg/mL	9.6	*7.4*	*11.9*	8.6	*7.0*	*10.2*	6.2	*4.0*	*8.4*
Total cholesterol	mmol/L	6.4	*5.9*	*6.9*	5.0	*4.5*	*5.4*	5.0	*4.1*	*5.8*
LDL cholesterol	mmol/L	•			3.1	*2.7*	*3.4*	3.1	*2.4*	*3.8*
HDL cholesterol	mmol/L	1.13	*1.04*	*1.23*	1.20	*1.10*	*1.31*	1.22	*0.98*	*1.46*
Triglycerides	mmol/L	3.4	*2.4*	*4.5*	1.5	*1.2*	*1.8*	1.44	*1.00*	*1.87*
Free fatty acids	mmol/L	0.81	*0.62*	*0.99*	0.55	*0.48*	*0.62*	0.50	*0.43*	*0.58*
Plasma PL^2 fatty acids, total	mg/L	1642	*1516*	*1768*	1151	*1067*	*1235*	1147	*1013*	*1281*
Saturated fatty acids	g/100 g	41.0	*40.5*	*41.5*	45.1	*44.8*	*45.3*	45.3	*44.9*	*45.7*
Monounsaturated fatty acids	g/100 g	12.1	*11.3*	*12.7*	12.7	*12.2*	*13.3*	13.4	*12.5*	*14.3*
n-6 fatty acids	g/100 g	33.6	*31.8*	*35.3*	32.3	*31.1*	*33.4*	31.5	*30.0*	*33.0*
n-3 fatty acids	g/100 g	13.2	*11.5*	*14.9*	9.9	*8.9*	*11.0*	9.7	*8.2*	*11.2*
n-6/n-3 ratio	g/100 g	2.8	*2.3*	*3.4*	3.5	*3.1*	*4.0*	3.4	*2.9*	*3.9*

[1]All metabolic variables are measured after 12 h fast; [2]Phospholipid; • = not investigated. For abbreviations, please refer to the abbreviation list.

FFQ differed from the 1 d estimated records by household measures but showed lesser discrepancy regarding the E% of carbohydrate and fat. A comparison of energy intake and distribution based on FFQ in all three studies shows (by eye-glance) somewhat lower energy intake in the n-3 supplement study compared with the others (Table 4.2).

4.2.3 Energy expenditure and distribution

Baseline resting energy expenditure (EPR or BMR) is given as kcal/24 h for all studies in Table 4.2. Results of the relative contribution of protein, fat and carbohydrate as fuels are also given for the n-3 studies (Table 4.2). The subjects of the n-3 supplement study displayed higher RQ than those of the n-3 infusion study.

4.3 Endpoint results

4.3.1 General

An overview of endpoint fasting variables (Papers I, II and III) and endpoint test variables (Papers II and IV) is given in Table 4.3.

4.3.2 Glycemic control

In the low-fat study, the fasting blood glucose concentration was reduced (median – 0.4 mmol/L, P=0.049) when measured at home, and also when measured in serum samples at hospital (-0.6 mmol/L, P=0.049), after 3 d intervention (Paper I). The day-time blood glucose was not affected. In the n-3 supplement study, 5.9 g/d of marine n-3 fatty acids increased fasting blood glucose by 1.0 mmol/L (P=0.035) and day-time concentrations by 0.9 mmol/L, after 9 wk intervention compared with corn oil (Paper II). Further the insulin sensitivity (glucose utilization) was reduced by 1.56 mg/min/kg lean body mass (P=0.049) when compared with corn oil (Paper II). There was a tendency to increased insulin secretion in response to glucagon in the fish oil group compared with the corn oil group, P=0.078 (Paper II). Neither insulin secretion nor insulin sensitivity were measurably affected by the low-fat (Paper I) or n-3 infusion (Paper IV) interventions, Table 4.3.

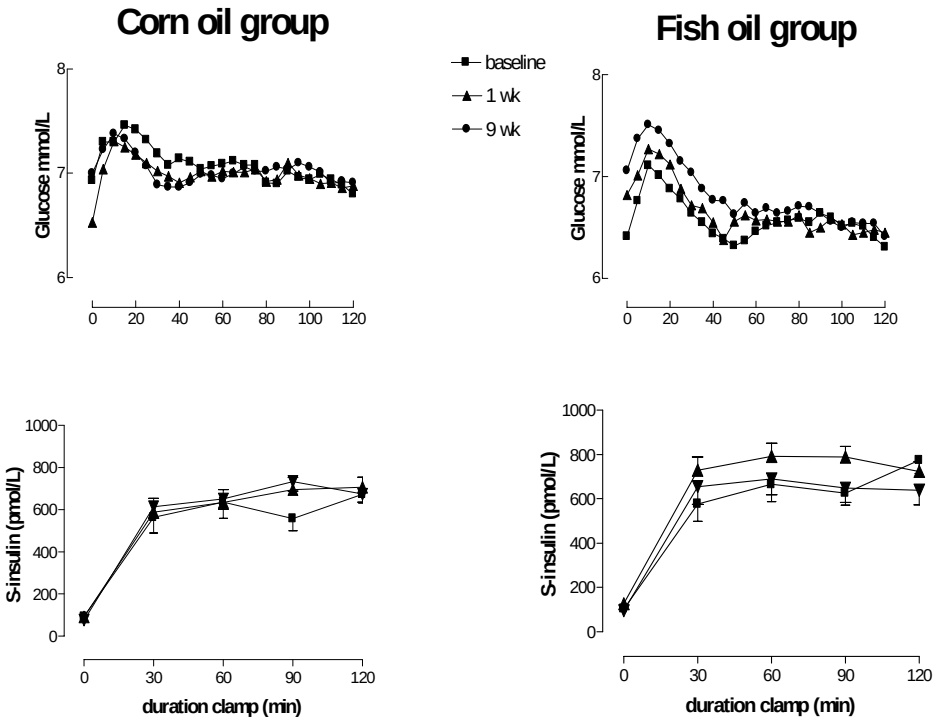
Table 4.2 Energy intake, expenditure and distribution at baseline

Baseline variables		**Low-fat study**			**n-3 supplement study**			**n-3 infusion study**		
		Baseline, n=19			Baseline, n=26			Baseline, n=11		
		mean	*95% CI*		mean	*95% CI*		mean	*95% CI*	
Energy intake by FFQ[1]	kcal	2133	*1745*	*2522*	1931	*1754*	*2109*	2087	*1788*	*2386*
	Protein, E%	17.7	*16.5*	*19.0*	17.8	*17.1*	*18.5*	18.0	*16.9*	*19.1*
	Fat, E%	34.0	*32.3*	*35.7*	32.0	*30.1*	*33.9*	35.2	*32.5*	*37.8*
	CHO, E%	47.7	*44.9*	*50.4*	49.0	*47.0*	*51.1*	45.0	*42.8*	*47.3*
	Alcohol, E%	1.2	*0.4*	*1.9*	1.1	*0.3*	*2.0*	1.7	*0.5*	*2.9*
	SFA, E%	13.0	*12.0*	*14.0*	12.1	*11.3*	*13.0*	13.6	*12.0*	*15.2*
	MUFA, E%	12.2	*11.5*	*12.9*	10.3	*9.5*	*11.1*	11.5	*10.4*	*12.6*
	n-6 FA, E%	4.5	*3.8*	*5.2*	5.5	*5.0*	*6.0*	5.9	*4.8*	*7.1*
	n-3 FA, E%	1.2	*0.9*	*1.5*	1.2	*1.1*	*1.3*	1.3	*1.1*	*1.4*
	PUFA, E%	6.2	*5.5*	*7.0*	6.9	*6.4*	*7.4*	7.2	*6.0*	*8.4*
	n-6/n-3 ratio	4.6	*3.6*	*5.6*	4.7	*4.2*	*5.1*	4.6	*4.0*	*5.3*
Energy intake by food records[2,3]	kcal	2049[2]	*1762*	*2336*	•			1760[3]	*1552*	*1967*
	Protein, E%	17.2	*15.7*	*18.6*	•			19.4	*17.1*	*21.8*
	Fat, E%	38.4	*35.9*	*40.9*	•			37.3	*33.1*	*41.4*
	CHO, E%	41.9	*39.0*	*44.7*	•			43.3	*38.4*	*48.2*
	Alcohol, E%	2.5	*0.6*	*4.4*	•			0.0	*0.0*	*0.0*
Resting energy expenditure[4,5]	kcal/d	1772[4]	*1630*	*1913*	1592[5]	*1487*	*1698*	1695[5]	*1490*	*1899*
	RQ	•			0.84	*0.82*	*0.87*	0.80	*0.77*	*0.84*
	% CHO	•			41.5	*32.7*	*50.4*	27.1	*15.9*	*38.2*
	% fat	•			34.2	*25.7*	*42.7*	51.6	*40.0*	*63.2*
	% protein	•			24.1	*21.4*	*26.8*	21.3	*18.8*	*23.8*

[1]Food Frequency Questionnaire; [2]Weighed records, 3 d-period; [3]Estimated records, 1 d; [4]BMR calculated by weight, height, gender, age [13];
[5]EPR measured by indirect calorimetry, fasting; • = not investigated
For abbreviations, please refer to the abbreviation list.

The clamp conditions regarding isoglycemia and hyperinsulinemia were comparable in the two groups of the n-3 supplement study (Figure 4.1). Also baseline fasting insulin and glucose concentrations were comparable- (Paper II).

Figure 4.1 Hyperinsulinemic, isoglycemic clamps in the n-3 supplement study
corn oil group (n=14), fish oil group (n=12).Mean values (and SEM, S-insulin)



4.3.3 Energy metabolism

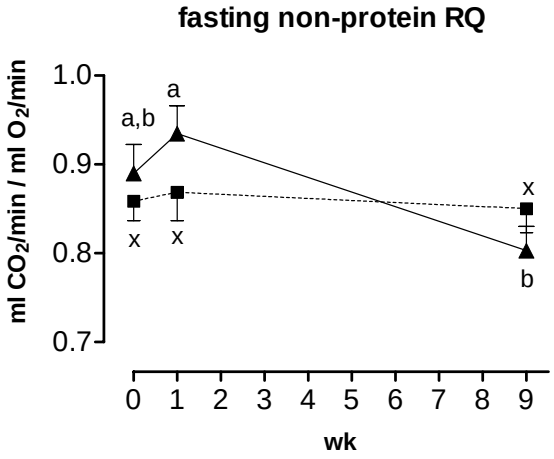
In the n-3 supplement study. The resting EPR was stable from baseline to 1 and 9 wk (Paper II). The non-protein RQ was increased after 1 wk, followed by a decrease at 9 wk in the fish oil group compared with the corn oil group (Figure 4. 2). That is, fat utilization as fuel was temporarily decreased after 1 wk (but NS), after which it was significantly increased with a concomitant decrease in carbohydrate utilization (Paper II).

Table 4.3 Endpoint results (of intervention compared with control)

Endpoint variables		**Low-fat study** (results after 9 wk intervention)	**n-3 supplement study**	**n-3 infusion study** (results after the lipid clamps)
Glycemic control	Fasting blood glucose	↓	↑	•
	Day-time blood glucose	→	↑	•
	HbA1c	•	→	•
	Insulin sensitivity	→	↓	→
	Insulin secretion	→	(↑)	→
Energy metabolism	EPR, fasting	•	→	•
	Non-protein RQ, fasting	•	↓ (↑ after 1 wk)	•
	Fat burning (E%), fasting	•	↑ (↓ after 1 wk)	•
	EPR, clamp	•	→	→
	Non-protein RQ, clamp	•	(↓)	→
	Fat burning (E%), clamp	•	(↑)	(↓)
Dyslipidemia	Triglyceride	→	→	→ (the clamp increase was similar)
	Total cholesterol	↓	→	•
	LDL cholesterol	•	→	•
	HDL cholesterol	↓	→	•
	FFA, fasting	→	→	•
	FFA, clamp	•	↓\	(↑)\
	Lipoprotein size	•	Size VLDL↓, HDL (↑),LDL→	•
	Lipoprotein subclasses	•	l-VLDL ↓, s-HDL ↓, s-LDL(↑)	•
Lipid oxidation	Oxidized LDL	•	→	•
	Non-enzymatically peroxidation	•	•	→ (in both plasma and urine)
Adipocyte hormones	Leptin	↓	→	→
	Adioponectin	↑	→	→
Other hormones	C-peptide	→	→	•
	insulin	→	→	•
	proinsulin	→	(↑)	•
	glucagon	→	→	•

↓ ↑ = significant reduced or increased compared with the control group; (↑)(↓) = tendency to decrease or increase compared with the control group; ↓\ = less marked decrease and (↑)\ = tendency of lower increase, compared with the control group
→ = no treatment difference between groups; • = not investigated. For abbreviations, please refer to the abbreviation list.

Figure 4.2 Non-protein RQ before clamps at baseline, 1 and 9 wk, n=26



■…■ Corn oil group
▲—▲ Fish oil group

Time x group effect analysed by the repeated measurements ANOVA. Means not sharing a common superscript letter are significantly different at $P<0.05$ (Bonferroni correction).

In the n-3 infusion study. EPR increased significantly during both lipid infusions compared with the fasting mode (Paper IV). However, EPR did not differ between the standard lipid infusion and the one to which n-3 fatty acids had been added. The non-protein RQ was lowered by the lipid infusions (i.e. they led to higher utilization of fat as fuel) compared with the glucose clamp. However, we found a tendency to higher non-protein RQ, i.e. lower utilization of fat as fuel, during the infusion with n-3 fatty acids compared with the standard lipid infusion, $P=0.062$ (Paper IV). In other words, the increase in fat oxidation compared to the fasting mode appeared less pronounced during the infusion with n-3 fatty acids.

4.3.4 Variables of lipid metabolism.

Plasma triglycerides were not affected by the low-fat diet (Paper I). However, total and HDL cholesterol were reduced with 0.4 ($P<0.005$) and 0.03 mmol/L ($P<0.05$), respectively. Plasma lipids or lipoprotein lipids were not influenced by the n-3 supplement intervention (Paper III) or by the infusion of n-3 fatty acids (Paper IV).

Fasting concentrations of FFA were not affected by the low-fat (Paper I) or the n-3 fatty acid intervention (Paper II). However, the reduction of FFA concentration brought about by insulin during hyperinsulinemic clamps was moderately antagonized after 9 wk of intervention in the fish oil group compared with the corn oil group (Paper II). On the other hand the acute infusion of n-3 fatty acids tended to influence concentrations of

FFA by dampening the rise during lipid infusion. The mechanisms behind the latter effect are unclear (Paper IV).

Lipoprotein size and subclasses were affected in several respects by the intervention of 5.9 g marine n-3 fatty acids (Paper III, and summarized here in Table 4.4).

Oxidized LDL was not significantly affected by fish oil compared with corn oil (Paper III). As to isoprostanes, the marked increase of plasma F_2-isoprostanes (8-iso-PGF_{2a}) during lipid infusion was not modified when n-3 fatty acids were added to the standard lipid infusion (Paper IV).

Table 4.4 Lipoprotein size and subclass particle concentrations at baseline, 1 and 9 wk, n=26

Variables		**Corn oil group**			**Fish oil group**			***P*-values**	
		n=14 mean	*95% CI*		n=12 mean	*95% CI*		ANOVA[1]	ANCOVA[2]
VLDL size, baseline	nm	45.6	*41.6*	*50.0*	46.1	*43.0*	*49.1*		
1 wk		44.7	*41.7*	*47.8*	41.5	*38.2*	*44.7*		
9 wk		45.5	*41.5*	*49.5*	38.9	*36.3*	*41.5*	0.001	<0.001
Large VLDL, baseline	nmol/L	2.7	*0.3*	*5.1*	2.3	*0.5*	*4.2*		
1 wk		1.6	*0.1*	*3.1*	1.1	*-0.6*	*2.9*		
9 wk		1.8	*0.3*	*3.4*	0.3	*-0.3*	*1.0*	0.041	0.015
Small LDL, baseline	nmol/L	982	*751*	*1212*	1009	*685*	*1333*		
1 wk		928	*719*	*1137*	1118	*939*	*1298*		
9 wk		1076	*821*	*1331*	1271	*978*	*1564*	0.068	0.061
HDL size, baseline	nm	9.1	*8.9*	*9.3*	9.0	*8.8*	*9.3*		
1 wk		9.2	*9.0*	*9.3*	9.1	*8.9*	*9.4*		
9 wk		9.0	*8.8*	*9.2*	9.1	*8.9*	*9.4*	0.063	0.033
Total HDL, baseline	µmol/L	26.4	*23.4*	*29.5*	29.6	*27.5*	*31.7*		
1 wk		28.3	*25.2*	*31.3*	28.6	*26.2*	*31.0*		
9 wk		27.9	*24.8*	*30.9*	28.7	*25.6*	*31.8*	0.044	0.269
Small HDL, baseline	µmol/L	16.9	*14.8*	*19.0*	20.6	*18.8*	*22.5*		
1 wk		18.3	*16.2*	*20.3*	19.3	*17.2*	*21.3*		
9 wk		18.7	*16.3*	*21.0*	18.5	*15.9*	*21.0*	0.004	0.051

[1]Repeated measurements analyses of variance for time (baseline, 1 wk, 9 wk) x group interaction; [2]Analyses of covariance with the 9 wk measurements as the dependent variable and baseline measurement and group as covariates. For abbreviations, please refer to the abbreviation list.

4.3.5 Adipocyte hormones.

In the low-fat study (Paper I) the concentrations of fasting leptin decreased from 12.1 to 9.9 ng/mL (P<0.005) after 3 d of low-fat diet compared to the usual diet. Levels of adiponectin increased from 8.6 to 10.5 µg/mL (P=0.048) (Paper I). These adipocyte

hormones were not affected by n-3 fatty acid supplement (Paper II) or by the infusion of n-3 fatty acids (Paper IV).

4.3.6 Fatty acids in plasma and adipose tissue

The changes that we observed in fatty acid composition of plasma phospholipids indicated good compliance to the dietary intervention both in the low-fat study (Paper I) and the n-3 supplement study (Paper II, Supplemental Tables). The changes observed in the supplement study were in agreement with changes in fatty acids in subcutaneous adipose tissue, which was biopsied after 9 wk of intervention (Paper II).

4.3.7 N-3 fatty acid infusion results

Acute infusion of n-3 fatty acids added to a standard lipid infusion did not affect energy metabolism, levels of oxidative products (isoprostanes) or adipocyte hormones but, tended to reduce fat oxidation and dampen the lipid-induced rise in FFA (Paper IV).

5. Discussion

5.1 Methodological considerations

5.1.1 Study populations and design

All three study populations consisted of subjects with type 2 diabetes not treated with insulin and were well defined. Subjects of the low-fat study were less well controlled in terms of glycemia and lipid profile compared to the subjects of the other studies (Table 4.1). This may be due to their hypertriglyceridemia, which was part of the design. Hypertriglyceridemic subjects were chosen for the low-fat study since we assumed that such dyslipidemic individuals had the most to gain from a low-fat diet. In the n-3 supplementation study, subjects with normotriglyceridemia were chosen to avoid secondary effects on insulin resistance by the known ability of n-3 fatty acids to reduce hypertriglyceridemia. Since the n-3 infusion study was to some extent inspired by the results of the in-3 supplement study, we chose a study population that resembled the former.

Subjects of the low-fat study had higher concentration of plasma phospholipid n-3 fatty acids than subjects in the n-3 fatty acids supplement study (Table 4.1). This difference indicates the importance of incorporating a wash-out period in studies concerning effects of n-3 fatty acids. Further, the above-mentioned differences seem to indirectly confirm that the use of n-3 fatty acid supplements (cod-liver oil, fish oil capsules) is widespread in Norway, as reported to prevail 35-40% of the population during winter [134,135]. It is interesting to note that the levels that we obtained were similar [136] to the reported ones in Inuits in the 1990s and higher than in Canadian native populations [137]. The choice of a long wash-out period (≥6 months) was based on previous observations that 2-4 [138,139] or 6 months [140] are necessary to presumably eliminate an influence of marine n-3 fatty acid supplementation on phospholipid composition. It follows that many cross-over studies in the field have used a too short wash-out period in between the cross-over periods. Still we estimate that 2 wk was

enough in our own cross-over study (Paper IV) because we used a single dose of n-3 fatty acids only.

When dealing with dietary oils the choice of placebo is not an easy one. The need for the placebo oil to be acceptable to Norwegian food habits motivated our choice of corn oil (Paper II).

5.1.2 Measurements

Insulin sensitivity. The need for glucose infusion to uphold a certain level of blood glucose depends both on glucose uptake and endogenous glucose production. Production (glucose output from the liver) is sensitive to insulin effects; therefore it should be possible in principle to infuse enough insulin to block glucose output completely. The insulin level during an euglycemic hyperinsulinemic clamp should be around 400 pmol/L in order to suppress glucose output from the liver [127], and we achieved 6-700 pmol/L and ~ 1000 pmol/L in the n-3 supplement respective infusion study. However, other investigators report the need of even higher insulin levels to insure blocking the glucose release from liver in insulin resistant subjects [141]. Thus, we cannot exclude the possibility that glucose utilization as measured here reflects both glucose uptake and production rather than glucose uptake alone.

Lipid variables. Some studies fail to find good correlations between NMR measurements and the standardized, validated method of ultracentrifugation. That does not necessarily mean that the NMR method is invalid but rather that NMR measures other lipoprotein qualities than the cholesterol parts. Indeed, Packard CV et al argue that novel types of measurements (such as NMR) will provide insight into regulation of subfraction lipoprotein distribution [18].

Dietary intake. Using retrospective methods a disadvantage is that one depends on the subjects' capacity to remember and generalize his/her mean intake of food. Using prospective methods you may instead interfere with the subjects' food habits by the mere asking for continuous documentation. Clearly, then, there exists no perfect method of diet registration.

In the low-fat study the intention was to check how the subjects translated general dietary principles (to reduce saturated fat, promote fibre-rich foods and unsaturated fat,

especially n-3 fatty acids) into concrete food choices. For that purpose we considered weighing to be the best method. We were somewhat surprised that energy intake reported from the weighed records was similar to the FFQ recording at baseline (because weighing usually underestimates [142,143], whereas FFQ records a higher energy intake compared with weighing [144-146]. Nevertheless, the method of FFQ is found to report lower E% from fat and higher E% from carbohydrate, compared with weighed records [144,147]. This discrepancy was also found in our study.

The weighing method was not used in the protocol for the n-3 fatty acid supplement study, the reasons being that a) the intervention protocol was demanding on the participants and b) the FFQ performed at baseline and at the end of intervention were deemed sufficient to assess stability of food intake.

As to the n-3 infusion study, the baseline FFQ was performed mostly to describe the subjects at baseline in the same manner as the other study subjects of this thesis. The choice of using household measures to estimate portions instead of weighing was to minimize the burden on the participants. However, the results demonstrated the difficulties in first describing food portions and then converting those descriptions to amounts in g. Therefore it was not a surprise the energy intake was reported as markedly lower by this method than by FFQ. All in all we consider the chosen dietary recording methods as appropriate for assessing diet during the study conditions.

5.2 Main results

5.2.1 Glycemic control

We focus in Paper I on the fact that the day-time average blood glucose was not affected by the low-fat diet. However, in terms of glycemic control one should acknowledge that the fasting blood glucose was significantly decreased by the low-fat diet. It seems possible that a discrepancy between effects on day-time and fasting blood glucose levels could be caused by improved insulin sensitivity of the liver (i.e. reduced glucose production) and not to the same extent a reduction of glucose uptake by skeletal muscles. However, we did not perform trace experiments, such as with radioactive glucose and therefore have no hard data to support this notion. Also, the low-fat diet

was different from the usual diet not only with regard to quantity and quality of fats but also with regard to carbohydrates and led to a slight energy deficit. The reasons why the diet was positive for the fasting component of glycemic control may thus be multiple.

All evidence indicates that the moderate increase in blood glucose levels by the 9 wk n-3 fatty acid intervention (Paper II) was the result of increased insulin resistance and not reduced insulin secretion, as suggested elsewhere [86-88,90]. The improved glucose utilization in the control group is likely an unspecific effect of trial participation. In any case, I find it reasonable to state that secondary effects of weight reduction as confounder can be ruled out, since the subjects were weight stable throughout the entire 9 wk of this study (Paper II).

How important was the large dose of ~ 6 g/d n-3 fatty acids for the negative result on the glycemic control - and is such a dose clinically relevant? In spite of the high dose we observed only moderate effects on insulin sensitivity, suggesting that lower doses may have only marginal effects. However, we cannot be completely sure, since we did not perform a dose-response study.

We deliberately chose a high dose of n-3 fatty acids for the following reasons. First, if beneficial rather than negative results had been found in our study, then n-3 fatty acids could be recommended to subjects with type 2 diabetes without restrictions on dosage. Second, for detection of possible effects a high dose would give us better possibilities to register effects (as was also apparent for insulin sensitivity measurements). Third, we thought that the use of a high dose would facilitate delineation of time-course effects.

One may question whether one can tolerate a high dose (5-6 g/d) of n-3 fatty acids in a life-time perspective. Inuits have in the 1970s been reported to eat ~ 9 g /d [79], in the same period also intakes ~ 14 g/d/3000 kcal were reported [80], all without apparent negative effects of n-3 fatty acids [79]. From a medical point of view, doses up to 5-6 g/day have been reported to be useful in treatment of hypertriglyceridemia and perhaps other pathological conditions. Hence, besides being helpful in a research perspective, the choice of a high dose on n-3 fatty acids in our study seems to be at least partly relevant in an epidemiological and clinical perspective.

However, the dose used here is far above the recommended intake of n-3 fatty acids of about 1 g/d to prevent cardiovascular disease in the general population. Furthermore, it was not our intention to extrapolate the present results in type 2 diabetic subjects to non-diabetic subjects. In any case, the present results offer no justification for taking away the daily spoon of cod liver oil from the man in street!

5.2.2 Energy metabolism

Our results on n-3 effects on RQ (Paper II) appear not to have been reported before. The main finding was increased fatty acid oxidation at the end of the intervention. The mechanisms behind are not elucidated here. It has been proposed that n-3 fatty acids enhance fatty acid oxidation by utilization of PPAR receptors [107].

We found a strong tendency for lowered fat oxidation after 1 wk of intervention with n-3 fatty acids. This would mean that metabolic handling of n-3 fatty acids is characterized by some delay. It cannot be explained as inhibited fat oxidation due to energy surplus [148] since the diet was energy stable. We suggest in Paper II that the time-dependency of an increase in fatty acid utilization (taking at least more than 1 wk and less than 9 wk) indicates induction of enzymes essential for fatty acid mitochondrial or peroxisomal oxidation.

5.2.3 Lipid variables

Plasma and lipoprotein lipids. In the low-fat study we were aware of the possibility that triglycerides could increase, because of the known effect in that direction by the concomitant increase of the carbohydrate intake [82]. In that context it was a positive result that the triglyceride concentrations were unaffected. One explanation for this finding is that the triglyceride increasing effect of carbohydrates is weakened by the simultaneously increased fibre intake [82]. A moderate increase in the intake of marine n-3 fatty acids may also have contributed. A third explanation could be the slightly negative energy balance, which (unintentionally) was a result of the low-fat diet.

One may anticipate that a reduction of saturated fat and a concomitant increase in fibre intake would lower total cholesterol [149,150]. It is however noteworthy that such an effect was observed after only 3 d of diet alteration. On the other hand, a reduction of

HDL cholesterol was not unexpected in view of the markedly reduced intake of fat [149-151].

Lipoprotein subclasses. My first incentive to measure lipoprotein subclass variables was the results of Dunstan DW et al, namely that 3.6 g/d n-3 fatty acids (from fatty fish, not supplement) added a low fat diet for 8 wk increased the levels of large HDL (HDL_2) but decreased the levels of small HDL (HDL_3), explaining the observation that the total HDL cholesterol did not change [152]. Our results of decreased particle concentration of small HDL (Paper III) are in accordance with the results of Dunstan WE [152]. Taken together with the reduced VLDL size and reduced particle concentration of large VLDL these results can be viewed as anti-atherogenic since they reflect a rapid removal of plasma triglycerides. As to the tendency for increased particle concentration of small LDL this could be a consequence of a n-3 fatty acid induced moderate reduction of insulin sensitivity in the liver [153]

5.2.4 Adipocyte hormone results.

In observational studies low levels of adiponectin is usually associated with insulin resistance; however this was not found in the n-3 supplement study (Paper II). The absence of effect could be due to a neutralizing effect by fatty acid oxidation, which was increased at the end of the intervention study. Indeed, previous reports indicate that increased fatty acid oxidation per se increases adiponectin levels [50].

The lack of effect on leptin concentrations by n-3 fatty acid supplementation (Paper II) could, at least in part, be due to the stability of energy intake, fat intake, and body fat mass throughout the study (since leptin levels are regulated, at least in part, by changes in these [51,154]).

6. Conclusions

To conclude:

1. A 3-day low-fat diet reduced fasting but not day-time blood glucose concentrations in subjects with type 2 diabetes and hypertriglyceridemia. Insulin sensitivity and insulin secretion were not affected, nor concentrations of triglycerides and free fatty acids. Total and HDL cholesterol concentrations were reduced, as were leptin concentrations. Adiponectin concentrations were increased (Paper I).
2. A 9 wk intervention with a high dose of marine n-3 fatty acids (fish oil) increased fasting and day-time blood glucose concentrations in subjects with type 2 diabetes and normal levels of triglycerides. These effects were due to increased insulin resistance as documented by isoglycemic hyperinsulinemic clamps. The intervention with fish oil time-dependently increased fat oxidation, i.e. after 9 but not after 1 wk of treatment (Paper II).
3. The fish oil intervention did not affect plasma lipids (triglycerides, total cholesterol) or lipoprotein lipids (LDL cholesterol, HDL cholesterol, oxidized LDL). However, lipoprotein subclass qualities were affected: i.e. the VLDL size, large VLDL and small HDL particle concentrations were all reduced (Paper III). The effects on these lipoprotein subclasses occurred concomitant with a decrease in insulin sensitivity.
4. In subjects with type 2 diabetes and normal levels of triglycerides adding an n-3 fatty acid emulsion to a standard lipid emulsion did not affect insulin sensitivity, energy metabolism or markers of oxidative stress as measured during a 4 h hyperinsulinemic clamp (Paper IV).

7. References

Reference List

[1] Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988-1994. Diabetes Care 1998; 21(4): 518-24.

[2] King H, Rewers M. Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. WHO Ad Hoc Diabetes Reporting Group. Diabetes Care 1993; 16(1): 157-77.

[3] King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care 1998; 21(9): 1414-31.

[4] Lundman B, Engstrom L. Diabetes and it's complications in a Swedish county. Diabetes Res Clin Pract 1998; 39(2): 157-64.

[5] Midthjell K, Krüger Ø, Holmen J, Tverdal A, Claudi T, Bjørndal A, Magnus P. Rapid changes in the prevalence of obesity and known diabetes in an adult Norwegian population. The Nord-Trøndelag Health Surveys: 1984-1986 and 1995-1997. Diabetes Care 1999; 22(11): 1813-20.

[6] Stene LC, Midthjell K, Jenum AK, Skeie S, Birkeland KI, Lund E et al. [Prevalence of diabetes mellitus in Norway]. Tidsskr Nor Laegeforen 2004; 124(11): 1511-4.

[7] Jenum AK, Holme I, Graff-Iversen S, Birkeland KI. Ethnicity and sex are strong determinants of diabetes in an urban Western society: implications for prevention. Diabetologia 2005; 48(3): 435-9.

[8] Katsilambros N, Tentolouris N. Type 2 diabetes: an overview. In: Pickup JC, Williams G, eds, Textbook of Diabetes 1. Oxford: Blackwell Science Ltd. 2003; 4.1-4.19.

[9] Grant PJ, Davies JA. Cardiovascular diseases and diabetes. In: Pickup JC, Williams G, eds, Textbook of Diabetes 2. Oxford: Blackwell Science Ltd. 2003; 56.1-56.24.

[10] Poirier P, Després J-P. Lipid disorders in diabetes. In: Pickup JC, Williams G, eds, Textbook of Diabetes 2. Oxford: Blackwell Science Ltd. 2003; 54.1-54.21.

[11] Yki-Jarvinen H. Action of insulin on glucose metabolism in vivo. Baillieres Clin Endocrinol Metab 1993; 7(4): 903-27.

[12] DeFronzo RA. Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 1988; 37(6): 667-87.

[13] Kruszynska YT. Normal metabolism: the physiology of fuel homeostasis. In: Pickup JC, Williams G, eds, Textbook of Diabetes 1. Oxford: Blackwell Science Ltd. 2003; 9.1-9.38.

[14] FAO/WHO/UNU. Energy and protein requirements. Report of a joint expert consultation. 724. 1985. World Health Organization. Technical Report Series. Ref Type: Report

[15] Poynten AM, Markovic TP, Maclean EL, Furler SM, Freund J, Chisholm DJ, Campbell LV. Fat oxidation, body composition and insulin sensitivity in diabetic and normoglycaemic obese adults 5 years after weight loss. Int J Obes Relat Metab Disord 2003; 27(10): 1212-8.

[16] Nakaya Y, Ohnaka M, Sakamoto S, Niwa Y, Okada K, Nomura M et al. Respiratory quotient in patients with non-insulin-dependent diabetes mellitus treated with insulin and oral hypoglycemic agents. Ann Nutr Metab 1998; 42(6): 333-40.

[17] Verges B. New insight into the pathophysiology of lipid abnormalities in type 2 diabetes. Diabetes Metab 2005; 31(5): 429-39.

[18] Packard CJ. Small dense low-density lipoprotein and its role as an independent predictor of cardiovascular disease. Curr Opin Lipidol 2006; 17(4): 412-7.

[19] Steinmetz A. Treatment of diabetic dyslipoproteinemia. Exp Clin Endocrinol Diabetes 2003; 111(5): 239-45.

[20] Freedman DS, Otvos JD, Jeyarajah EJ, Barboriak JJ, Anderson AJ, Walker JA. Relation of lipoprotein subclasses as measured by proton nuclear magnetic resonance spectroscopy to coronary artery disease. Arterioscler Thromb Vasc Biol 1998; 18(7): 1046-53.

[21] Syvanne M, Taskinen MR. Lipids and lipoproteins as coronary risk factors in non-insulin-dependent diabetes mellitus. Lancet 1997; 350 Suppl 1: SI20-SI23.

[22] Otvos JD. Measurement of lipoprotein subclass profiles by nuclear magnetic resonance spectroscopy. Clin Lab 2002; 48(3-4): 171-80.

[23] Rosenson RS, Otvos JD, Freedman DS. Relations of lipoprotein subclass levels and low-density lipoprotein size to progression of coronary artery disease in the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I) trial. Am J Cardiol 2002; 90(2): 89-94.

[24] Goldberg RB, Kendall DM, Deeg MA, Buse JB, Zagar AJ, Pinaire JA et al. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. Diabetes Care 2005; 28(7): 1547-54.

[25] Otvos JD, Collins D, Freedman DS, Shalaurova I, Schaefer EJ, McNamara JR et al. Low-density lipoprotein and high-density lipoprotein particle subclasses predict coronary events and are favorably changed by gemfibrozil therapy in the Veterans Affairs High-Density Lipoprotein Intervention Trial. Circulation 2006; 113(12): 1556-63.

[26] Mora S, Szklo M, Otvos JD, Greenland P, Psaty BM, Goff DC, Jr. et al. LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis 2006.

[27] Kathiresan SSOJJ. Increased small low-density lipoprotein particle number: a prominent feature of the metabolic syndrome in the Framingham Heart Study. Circulation 2006; 113(1): 20-9.

[28] Goff DC, Jr., D'Agostino RB, Jr., Haffner SM, Otvos JD. Insulin resistance and adiposity influence lipoprotein size and subclass concentrations. Results from the Insulin Resistance Atherosclerosis Study. Metabolism 2005; 54(2): 264-70.

[29] Garvey WT, Kwon S, Zheng D, Shaughnessy S, Wallace P, Hutto A et al. Effects of insulin resistance and type 2 diabetes on lipoprotein subclass particle size and concentration determined by nuclear magnetic resonance. Diabetes 2003; 52(2): 453-62.

[30] Festa A, Williams K, Hanley AJ, Otvos JD, Goff DC, Wagenknecht LE, Haffner SM. Nuclear magnetic resonance lipoprotein abnormalities in prediabetic subjects in the Insulin Resistance Atherosclerosis Study. Circulation 2005; 111(25): 3465-72.

[31] Jeyarajah EJ, Cromwell WC, Otvos JD. Lipoprotein particle analysis by nuclear magnetic resonance spectroscopy. Clin Lab Med 2006; 26(4): 847-70.

[32] Otvos JD, Jeyarajah EJ, Bennett DW. Quantification of plasma lipoproteins by proton nuclear magnetic resonance spectroscopy. Clin Chem 1991; 37(3): 377-86.

[33] Otvos JD, Jeyarajah EJ, Bennett DW, Krauss RM. Development of a proton nuclear magnetic resonance spectroscopic method for determining plasma lipoprotein concentrations and subspecies distributions from a single, rapid measurement. Clin Chem 1992; 38(9): 1632-8.

[34] Lounila J, la-Korpela M, Jokisaari J, Savolainen MJ, Kesaniemi YA. Effects of orientational order and particle size on the NMR line positions of lipoproteins. PHYSICAL REVIEW LETTERS 1994; 72(25): 4049-52.

[35] Urakawa H, Katsuki A, Sumida Y, Gabazza EC, Murashima S, Morioka K et al. Oxidative stress is associated with adiposity and insulin resistance in men. J Clin Endocrinol Metab 2003; 88(10): 4673-6.

[36] Steinberg D. Low density lipoprotein oxidation and its pathobiological significance. J Biol Chem 1997; 272(34): 20963-6.

[37] Heinecke JW. Oxidants and antioxidants in the pathogenesis of atherosclerosis: implications for the oxidized low density lipoprotein hypothesis. Atherosclerosis 1998; 141(1): 1-15.

[38] Nalsen C, Vessby B, Berglund L, Uusitupa M, Hermansen K, Riccardi G et al. Dietary (n-3) fatty acids reduce plasma F2-isoprostanes but not prostaglandin F2alpha in healthy humans. J Nutr 2006; 136(5): 1222-8.

[39] Scheffer PG, Bos G, Volwater HG, Dekker JM, Heine RJ, Teerlink T. Associations of LDL size with in vitro oxidizability and plasma levels of in vivo oxidized LDL in Type 2 diabetic patients. Diabet Med 2003; 20(7): 563-7.

[40] Sigurdardottir V, Fagerberg B, Hulthe J. Circulating oxidized low-density lipoprotein (LDL) is associated with risk factors of the metabolic syndrome and LDL size in clinically healthy 58-year-old men (AIR study). J Intern Med 2002; 252(5): 440-7.

[41] Holvoet P, Vanhaecke J, Janssens S, Van de WF, Collen D. Oxidized LDL and malondialdehyde-modified LDL in patients with acute coronary syndromes and stable coronary artery disease. Circulation 1998; 98(15): 1487-94.

[42] Holvoet P, Mertens A, Verhamme P, Bogaerts K, Beyens G, Verhaeghe R et al. Circulating oxidized LDL is a useful marker for identifying patients with coronary artery disease. Arterioscler Thromb Vasc Biol 2001; 21(5): 844-8.

[43] Morrow JD, Hill KE, Burk RF, Nammour TM, Badr KF, Roberts LJ. A series of prostaglandin F2-like compounds are produced in vivo in humans by a non-cyclooxygenase, free radical-catalyzed mechanism. Proc Natl Acad Sci U S A 1990; 87(23): 9383-7.

[44] Liu T, Stern A, Roberts LJ, Morrow JD. The isoprostanes: novel prostaglandin-like products of the free radical-catalyzed peroxidation of arachidonic acid. J Biomed Sci 1999; 6(4): 226-35.

[45] Morrow JD, Roberts LJ. The isoprostanes: unique bioactive products of lipid peroxidation. Prog Lipid Res 1997; 36(1): 1-21.

[46] Basu S. Radioimmunoassay of 8-iso-prostaglandin F2alpha: an index for oxidative injury via free radical catalysed lipid peroxidation. Prostaglandins Leukot Essent Fatty Acids 1998; 58(4): 319-25.

[47] Cracowski JL, Stanke-Labesque F, Souvignet C, Bessard G. [Isoprostanes: new markers of oxidative stress in human diseases]. Presse Med 2000; 29(11): 604-10.

[48] Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001; 86(5): 1930-5.

[49] Salmenniemi U, Zacharova J, Ruotsalainen E, Vauhkonen I, Pihlajamaki J, Kainulainen S et al. Association of adiponectin level and variants in the adiponectin gene with glucose metabolism, energy expenditure, and cytokines in offspring of type 2 diabetic patients. J Clin Endocrinol Metab 2005; 90(7): 4216-23.

[50] Diez JJ, Iglesias P. The role of the novel adipocyte-derived hormone adiponectin in human disease. Eur J Endocrinol 2003; 148(3): 293-300.

[51] Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y et al. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat Med 1995; 1(11): 1155-61.

[52] Arner P. Insulin resistance in type 2 diabetes -- role of the adipokines. Curr Mol Med 2005; 5(3): 333-9.

[53] Wilding JP. Obesity and nutritional factors in the pathogenesis of type 2 diabetes mellitus. In: Pickup JC, Williams G, eds, Textbook of Diabetes 1. Oxford: Blackwell Science Ltd. 2003; 21.1-21.16.

[54] Nordic nutrition recommendations : NNR 2004 : integrating nutrition and physical activity. 4th ed ed. Copenhagen: Nordic Council of Ministers. 2005.

[55] Bjerve KS. n-3 fatty acid deficiency in man. J Intern Med Suppl 1989; 731: 171-5.

[56] Marckmann P, Gronbaek M. Fish consumption and coronary heart disease mortality. A systematic review of prospective cohort studies. Eur J Clin Nutr 1999; 53(8): 585-90.

[57] Albert CM. Fish consumption and risk of sudden cardiac death. JAMA 1998; 279(1): 23-8.

[58] Yuan JM. Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. American journal of epidemiology 2001; 154(9): 809-16.

[59] Bucher HC. N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. The American journal of medicine 2002; 112(4): 298-304.

[60] Erkkilä AT. n-3 Fatty acids and 5-y risks of death and cardiovascular disease events in patients with coronary artery disease. The American Journal of Clinical Nutrition 2003; 78(1): 65-71.

[61] Nordoy A. n-3 polyunsaturated fatty acids and cardiovascular diseases. Lipids 2001; 36 Suppl: -9.

[62] Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC, Ma J. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. N Engl J Med 2002; 346(15): 1113-8.

[63] Jones PJ. Effect of n-3 polyunsaturated fatty acids on risk reduction of sudden death. Nutrition reviews 2002; 60(12): 407-9.

[64] Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet 1989; 2(8666): 757-61.

[65] Singh RB, Niaz MA, Sharma JP, Kumar R, Rastogi V, Moshiri M. Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian experiment of infarct survival--4. Cardiovasc Drugs Ther 1997; 11(3): 485-91.

[66] Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet 1999; 354(9177): 447-55.

[67] SHDIR. Norske anbefalinger for ernæring og fysisk aktivitet. 2005. Oslo, Sosial- og helsedirektoratet.
Ref Type: Pamphlet

[68] Vaaler Sr, Møinichen T, Grendstad I. Diabeteshåndboken (Handbook of Diabetes). *In Norwegian.* Third ed. Oslo: Gyldendal Norsk Forlag AS. 2004.

[69] Mann JI, De Leeuw I, Hermansen K, Karamanos B, Karlstrom B, Katsilambros N et al. Evidence-based nutritional approaches to the treatment and prevention of diabetes mellitus. Nutr Metab Cardiovasc Dis 2004; 14(6): 373-94.

[70] 2005 Dietary Guidelines Advisory Committee. Nutrition and your health: dietary guidelines for Americans. 2005.
Ref Type: Data File

[71] Gill GV. Surgery in patients with diabetes mellitus. In: Pickup JC, Williams G, eds, Textbook of Diabetes 1. Oxford: Blackwell Science Ltd. 2003; 41.1-41.10.

[72] Mossberg T. Klinisk nutrition och vätskebehandling (Clinical nutrition and fluid treatment). *In swedish.* Uppsala, Sweden: Fresenius Kabi AB, Marknadsbolag Sverige, 751 74 Uppsala. 2001.

[73] Fürst P, Kuhn KS. Fish oil emulsions: what benefits can they bring? Clin Nutr 2000; 19(1): 7-14.

[74] Panser LA, Naessens JM, Nobrega FT, Palumbo PJ, Ballard DJ. Utilization trends and risk factors for hospitalization in diabetes mellitus. Mayo Clin Proc 1990; 65(9): 1171-84.

[75] Wright J. Total parenteral nutrition and enteral nutrition in diabetes. Curr Opin Clin Nutr Metab Care 2000; 3(1): 5-10.

[76] Harris WS. n-3 fatty acids and serum lipoproteins: human studies. Am J Clin Nutr 1997; 65(5 Suppl): 1645S-54S.

[77] FDA (U.S.Food and Drug Administration). Agency Response Letter, GRAS Notice. Rulis AM, editor. No. GRN 000105, 1-5. 15-10-2002. Department of Health and Human Services, Center for Food Safety and Applied Nutrition, Office of Food Additive Safety.
Ref Type: Report

[78] FDA (Food and Drug Administration) DoHaHS. Substances Affirmed as Generally Recognized as Safe: Menhaden Oil, 21 CFR Part 184. Federal Register 1997; 62(108): 30751-7.

[79] Deutch B, Dyerberg J, Pedersen HS, Asmund G, Moller P, Hansen JC. Dietary composition and contaminants in north Greenland, in the 1970s and 2004. Sci Total Environ 2006; 370(2-3): 372-81.

[80] Bang HO, Dyerberg J, Sinclair HM. The composition of the Eskimo food in north western Greenland. Am J Clin Nutr 1980; 33(12): 2657-61.

[81] Felleskatalogen (the Norwegian physician desk reference). 48:e utgave ed. Oslo: Felleskatalogen AS. 2006.

[82] Riccardi G, Parillo M. Comparison of the metabolic effects of fat-modified vs low fat diets. Ann N Y Acad Sci 1993; 683: 192-8.

[83] Storlien LH, Borkman M, Jenkins AB, Campbell LV. Diet and *in vivo* insulin action: of rats and man. Diabetes Nutr Metab 1991; 4: 227-40.

[84] Berry EM. Dietary fatty acids in the management of diabetes mellitus. Am J Clin Nutr 1997; 66(4 Suppl): 991S-7S.

[85] Vessby B, Boberg M. Dietary supplementation with n-3 fatty acids may impair glucose homeostasis in patients with non-insulin-dependent diabetes mellitus. J Intern Med 1990; 228(2): 165-71.

[86] Boberg M, Pollare T, Siegbahn A, Vessby B. Supplementation with n-3 fatty acids reduces triglycerides but increases PAI-1 in non-insulin-dependent diabetes mellitus. Eur J Clin Invest 1992; 22(10): 645-50.

[87] Schectman G, Kaul S, Kissebah AH. Effect of fish oil concentrate on lipoprotein composition in NIDDM. Diabetes 1988; 37(11): 1567-73.

[88] Borkman M, Chisholm DJ, Furler SM, Storlien LH, Kraegen EW, Simons LA, Chesterman CN. Effects of fish oil supplementation on glucose and lipid metabolism in NIDDM. Diabetes 1989; 38(10): 1314-9.

[89] Axelrod L, Camuso J, Williams E, Kleinman K, Briones E, Schoenfeld D. Effects of a small quantity of omega-3 fatty acids on cardiovascular risk factors in NIDDM. A randomized, prospective, double-blind, controlled study. Diabetes Care 1994; 17(1): 37-44.

[90] Hendra TJ, Britton ME, Roper DR, Wagaine-Twabwe D, Jeremy JY, Dandona P et al. Effects of fish oil supplements in NIDDM subjects. Controlled study. Diabetes Care 1990; 13(8): 821-9.

[91] Sirtori CR, Paoletti R, Mancini M, Crepaldi G, Manzato E, Rivellese A et al. N-3 fatty acids do not lead to an increased diabetic risk in patients with hyperlipidemia and abnormal glucose tolerance. Italian Fish Oil Multicenter Study. Am J Clin Nutr 1997; 65(6): 1874-81.

[92] Connor WE, Prince MJ, 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; 337-40.

[93] Rivellese AA, Lilli S. Quality of dietary fatty acids, insulin sensitivity and type 2 diabetes. Biomed Pharmacother 2003; 57(2): 84-7.

[94] Pelikanova T, Kohout M, Valek J, Kazdova L, Base J. Metabolic effects of omega-3 fatty acids in type 2 (non-insulin-dependent) diabetic patients. Ann N Y Acad Sci 1993; 683: 272-8.

[95] McManus RM, Jumpson J, Finegood DT, Clandinin MT, Ryan EA. A comparison of the effects of n-3 fatty acids from linseed oil and fish oil in well-controlled type II diabetes. Diabetes Care 1996; 19(5): 463-7.

[96] Annuzzi G, Rivellese A, Capaldo B, Di ML, Iovine C, Marotta G, Riccardi G. A controlled study on the effects of n-3 fatty acids on lipid and glucose metabolism in non-insulin-dependent diabetic patients. Atherosclerosis 1991; 87(1): 65-73.

[97] Morgan WA, Raskin P, Rosenstock J. A comparison of fish oil or corn oil supplements in hyperlipidemic subjects with NIDDM. Diabetes Care 1995; 18(1): 83-6.

[98] Westerveld HT, de Graaf JC, van Breugel HH, Akkerman JW, Sixma JJ, Erkelens DW, Banga JD. Effects of low-dose EPA-E on glycemic control, lipid profile, lipoprotein(a), platelet aggregation, viscosity, and platelet and vessel wall interaction in NIDDM. Diabetes Care 1993; 16(5): 683-8.

[99] Luo J, Rizkalla SW, Vidal H, Oppert JM, Colas C, Boussairi A et al. 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(5): 717-24.

[100] Storlien LH, Baur LA, Kriketos AD, Pan DA, Cooney GJ, Jenkins AB et al. Dietary fats and insulin action. Diabetologia 1996; 39(6): 621-31.

[101] Montori VM, Farmer A, Wollan PC, Dinneen SF. Fish oil supplementation in type 2 diabetes: a quantitative systematic review. Diabetes Care 2000; 23(9): 1407-15.

[102] Vessby B, Unsitupa M, Hermansen K, Riccardi G, Rivellese AA, Tapsell LC et al. Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: The KANWU Study. Diabetologia 2001; 44(3): 312-9.

[103] Valtuena S, Salas-Salvado J, Lorda PG. The respiratory quotient as a prognostic factor in weight-loss rebound. Int J Obes Relat Metab Disord 1997; 21(9): 811-7.

[104] Storlien LH, Tapsell LC, Calvert GD. Diabetic diets--whither goest? Nutrition 1998; 14(11-12): 865-7.

[105] Delarue J, Couet C, Cohen R, Brechot JF, Antoine JM, Lamisse F. Effects of fish oil on metabolic responses to oral fructose and glucose loads in healthy humans. Am J Physiol 1996; 270(2 Pt 1): E353-E362.

[106] Puhakainen I, Ahola I, Yki-Jarvinen H. Dietary supplementation with n-3 fatty acids increases gluconeogenesis from glycerol but not hepatic glucose production in patients with non-insulin-dependent diabetes mellitus. Am J Clin Nutr 1995; 61(1): 121-6.

[107] Davidson MH. Mechanisms for the hypotriglyceridemic effect of marine omega-3 fatty acids. Am J Cardiol 2006; 98(4A): 27i-33i.

[108] Connor WE. Importance of n-3 fatty acids in health and disease. Am J Clin Nutr 2000; 71(1 Suppl): 171S-5S.

[109] Malasanos TH, Stacpoole PW. Biological effects of omega-3 fatty acids in diabetes mellitus. Diabetes Care 1991; 14(12): 1160-79.

[110] Montori VM, Farmer A, Wollan PC, Dinneen SF. Fish oil supplementation in type 2 diabetes: a quantitative systematic review. Diabetes Care 2000; 23(9): 1407-15.

[111] Ouguerram K, Maugeais C, Gardette J, Magot T, Krempf M. Effect of n-3 fatty acids on metabolism of apoB100-containing lipoprotein in type 2 diabetic subjects. Br J Nutr 2006; 96(1): 100-6.

[112] Carpentier YA, Portois L, Malaisse WJ. n-3 fatty acids and the metabolic syndrome. Am J Clin Nutr 2006; 83(6 Suppl): 1499S-504S.

[113] Petersen M, Pedersen H, Major-Pedersen A, Jensen T, Marckmann P. Effect of fish oil versus corn oil supplementation on LDL and HDL subclasses in type 2 diabetic patients. Diabetes Care 2002; 25(10): 1704-8.

[114] Harris WS. n-3 fatty acids and lipoproteins: comparison of results from human and animal studies. Lipids 1996; 31(3): 243-52.

[115] Nestel PJ. Fish oil and cardiovascular disease: lipids and arterial function. Am J Clin Nutr 2000; 71(1 Suppl): 228S-31S.

[116] Luo J, Rizkalla SW, Vidal H, Oppert JM, Colas C, Boussairi A et al. 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(5): 717-24.

[117] Patti L, Maffettone A, Iovine C, Marino LD, Annuzzi G, Riccardi G, Rivellese AA. Long-term effects of fish oil on lipoprotein subfractions and low density lipoprotein size in non-insulin-dependent diabetic patients with hypertriglyceridemia. Atherosclerosis 1999; 146(2): 361-7.

[118] Suzukawa M, Abbey M, Howe PR, Nestel PJ. Effects of fish oil fatty acids on low density lipoprotein size, oxidizability, and uptake by macrophages. J Lipid Res 1995; 36(3): 473-84.

[119] Qvigstad E, Mostad IL, Bjerve KS, Grill VE. Acute lowering of circulating fatty acids improves insulin secretion in a subset of type 2 diabetes subjects. Am J Physiol Endocrinol Metab 2003; 284(1): E129-E137.

[120] Legro RS, Finegood D, Dunaif A. A fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with polycystic ovary syndrome. J Clin Endocrinol Metab 1998; 83(8): 2694-8.

[121] Albareda M, Rodriguez-Espinosa J, Murugo M, de Leiva A, Corcoy R. Assessment of insulin sensitivity and beta-cell function from measurements in the fasting state and during an oral glucose tolerance test. Diabetologia 2000; 43(12): 1507-11.

[122] Pelikanova T, Kazdova L, Chvojkova S, Base J. Serum phospholipid fatty acid composition and insulin action in type 2 diabetic patients. Metabolism 2001; 50(12): 1472-8.

[123] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28(7): 412-9.

[124] Faber OK, Binder C. C-peptide response to glucagon. A test for the residual beta-cell function in diabetes mellitus. Diabetes 1977; 26(7): 605-10.

[125] Scheen AJ, Castillo MJ, Lefebvre PJ. Assessment of residual insulin secretion in diabetic patients using the intravenous glucagon stimulatory test: methodological aspects and clinical applications. Diabetes Metab 1996; 22(6): 397-406.

[126] Gottsater A, Landin-Olsson M, Fernlund P, Gullberg B, Lernmark A, Sundkvist G. Pancreatic beta-cell function evaluated by intravenous glucose and glucagon stimulation. A comparison between insulin and C-peptide to measure insulin secretion. Scand J Clin Lab Invest 1992; 52(7): 631-9.

[127] Pinkney J. Clinical research methods in diabetes. In: Pickup JC, Williams G, eds, Textbook of Diabetes 1. Oxford: Blackwell Science Ltd. 2003; 35.1-35.20.

[128] Takala J, Meriläinen P. Handbook of gas exchange and indirect calorimetry. 2001. Helsinki, Finland, Datex-Engstrom Division, Instrumentarium Corp.
Ref Type: Report

[129] Ferrannini E. The theoretical bases of indirect calorimetry: a review. Metabolism 1988; 37(3): 287-301.

[130] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18(6): 499-502.

[131] Rimestad AH, Blaker B, Flåten A-M, Nordbotten A. Den store matvaretabellen (The Norwegian Food Table). *In norwegian.* Oslo: Universitetsforlaget. 1995.

[132] Beynen AC, Katan MB. Rapid sampling and long-term storage of subcutaneous adipose-tissue biopsies for determination of fatty acid composition. Am J Clin Nutr 1985; 42(2): 317-22.

[133] Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975; 31(1): 103-15.

[134] Johansson LR, Solvoll K, Bjorneboe GE, Drevon CA. Intake of very-long-chain n-3 fatty acids related to social status and lifestyle. Eur J Clin Nutr 1998; 52(10): 716-21.

[135] Grimsgaard S. Individual fatty acids and cardiovascular risk factors. 1-62. 2001. Institute of Community Medicine, University of Tromsø, Norway.
Ref Type: Thesis/Dissertation

[136] Dewailly E, Blanchet C, Lemieux S, Sauve L, Gingras S, Ayotte P, Holub BJ. n-3 Fatty acids and cardiovascular disease risk factors among the Inuit of Nunavik. Am J Clin Nutr 2001; 74(4): 464-73.

[137] Dewailly E, Blanchet C, Gingras S, Lemieux S, Holub BJ. Cardiovascular disease risk factors and n-3 fatty acid status in the adult population of James Bay Cree. Am J Clin Nutr 2002; 76(1): 85-92.

[138] Haban P, Zidekova E, Klvanova J. Supplementation with long-chain n-3 fatty acids in non-insulin-dependent diabetes mellitus (NIDDM) patients leads to the lowering of oleic acid content in serum phospholipids. Eur J Nutr 2000; 39(5): 201-6.

[139] Brown AJ, Pang E, Roberts DC. Persistent changes in the fatty acid composition of erythrocyte membranes after moderate intake of n-3 polyunsaturated fatty acids: study design implications. Am J Clin Nutr 1991; 54(4): 668-73.

[140] Marangoni F, Angeli MT, Colli S, Eligini S, Tremoli E, Sirtori CR, Galli C. Changes of n-3 and n-6 fatty acids in plasma and circulating cells of normal subjects, after prolonged administration of 20:5 (EPA) and 22:6 (DHA) ethyl esters and prolonged washout. Biochim Biophys Acta 1993; 1210(1): 55-62.

[141] Bergman RN, Finegood DT, Ader M. Assessment of insulin sensitivity in vivo. Endocr Rev 1985; 6(1): 45-86.

[142] Schoeller DA. How accurate is self-reported dietary energy intake? Nutr Rev 1990; 48(10): 373-9.

[143] Black AE, Goldberg GR, Jebb SA, Livingstone MB, Cole TJ, Prentice AM. Critical evaluation of energy intake data using fundamental principles of energy physiology: 2. Evaluating the results of published surveys. Eur J Clin Nutr 1991; 45(12): 583-99.

[144] Nes M, Frost AL, Solvoll K, Sandstad B, Hustvedt BE, Lovo A, Drevon CA. Accuracy of a quantitative food frequency questionnaire applied in elderly Norwegian women. Eur J Clin Nutr 1992; 46(11): 809-21.

[145] Solvoll K, Lund-Larsen K, Søyland E, Sandstad B, Drevon CA. A quantitative food frequency questionnaire evaluated in a group of dermatologic outpatients. Scandinavian Journal of Nutrition 1993; 37: 150-5.

[146] Block G, Hartman AM. Issues in reproducibility and validity of dietary studies. Am J Clin Nutr 1989; 50(5 Suppl): 1133-8.

[147] Andersen LF, Solvoll K, Johansson LR, Salminen I, Aro A, Drevon CA. Evaluation of a food frequency questionnaire with weighed records, fatty acids, and alpha-tocopherol in adipose tissue and serum. Am J Epidemiol 1999; 150(1): 75-87.

[148] Ravussin E, Tataranni PA. Dietary fat and human obesity. J Am Diet Assoc 1997; 97(7 Suppl): S42-S46.

[149] Grundy SM, Denke MA. Dietary influences on serum lipids and lipoproteins. J Lipid Res 1990; 31(7): 1149-72.

[150] Clarke R, Frost C, Collins R, Appleby P, Peto R. Dietary lipids and blood cholesterol: quantitative meta-analysis of metabolic ward studies. BMJ 1997; 314(7074): 112-7.

[151] Mancini M, Parillo M. Role of diet in the treatment of hyperlipidemias. In: Grepaldi G, Tiengo A, Enzi G, eds, Diabetes, Obesity and Hyperlipidemias. New York: Elsevier Science Publisher. 1990; 91-7.

[152] 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(6): 913-21.

[153] Yki-Jarvinen H. Insulin resistance in type 2 diabetes. In: Pickup JC, Williams G, eds, Textbook of Diabetes 1. Oxford: Blackwell Science Ltd. 2003; 22.1-22.19.

[154] Reseland JE, Anderssen SA, Solvoll K, Hjermann I, Urdal P, Holme I, Drevon CA. Effect of long-term changes in diet and exercise on plasma leptin concentrations. Am J Clin Nutr 2001; 73(2): 240-5.

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126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.

142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
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160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.

174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
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183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
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186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS

203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING

231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

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248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS

260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
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264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

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269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION
279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS
280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
282. Idar Kirkeby-Garstad: CLINICAL PHYSIOLOGY OF EARLY MOBILIZATION AFTER CARDIAC SURGERY
283. Linn Getz: SUSTAINABLE AND RESPONSIBLE PREVENTIVE MEDICINE. CONCEPTUALISING ETHICAL DILEMMAS ARISING FROM CLINICAL IMPLEMENTATION OF ADVANCING MEDICAL TECHNOLOGY
284. Eva Tegnander: DETECTION OF CONGENITAL HEART DEFECTS IN A NON-SELECTED POPULATION OF 42,381 FETUSES
285. Kristin Gabestad Nørsett: GENE EXPRESSION STUDIES IN GASTROINTESTINAL PATHOPHYSIOLOGY AND NEOPLASIA
286. Per Magnus Haram: GENETIC VS. AQUIRED FITNESS: METABOLIC, VASCULAR AND CARDIOMYOCYTE ADAPTATIONS
287. Agneta Johansson: GENERAL RISK FACTORS FOR GAMBLING PROBLEMS AND THE PREVALENCE OG PATHOLOGICAL GAMBLING IN NORWAY

288. Svein Artur Jensen: THE PREVALENCE OF SYMPTOMATIC ARTERIAL DISEASE OF THE LOWER LIMB
289. Charlotte Björk Ingul: QUANITIFICATION OF REGIONAL MYOCARDIAL FUNCTION BY STRAIN RATE AND STRAIN FOR EVALUATION OF CORONARY ARTERY DISEASE. AUTOMATED VERSUS MANUAL ANALYSIS DURING ACUTE MYOCARDIAL INFARCTION AND DOBUTAMINE STRESS ECHOCARDIOGRAPHY
290. Jakob Nakling: RESULTS AND CONSEQUENCES OF ROUTINE ULTRASOUND SCREENING IN PREGNANCY – A GEOGRAPHIC BASED POPULATION STUDY
291. Anne Engum: DEPRESSION AND ANXIETY – THEIR RELATIONS TO THYROID DYSFUNCTION AND DIABETES IN A LARGE EPIDEMIOLOGICAL STUDY
292. Ottar Bjerkeset: ANXIETY AND DEPRESSION IN THE GENERAL POPULATION: RISK FACTORS, INTERVENTION AND OUTCOME – THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
293. Jon Olav Drogset: RESULTS AFTER SURGICAL TREATMENT OF ANTERIOR CRUCIATE LIGAMENT INJURIES – A CLINICAL STUDY
294. Lars Fosse: MECHANICAL BEHAVIOUR OF COMPACTED MORSELLISED BONE – AN EXPERIMENTAL IN VITRO STUDY
295. Gunilla Klensmeden Fosse: MENTAL HEALTH OF PSYCHIATRIC OUTPATIENTS BULLIED IN CHILDHOOD
296. Paul Jarle Mork: MUSCLE ACTIVITY IN WORK AND LEISURE AND ITS ASSOCIATION TO MUSCULOSKELETAL PAIN
297. Björn Stenström: LESSONS FROM RODENTS: I: MECHANISMS OF OBESITY SURGERY – ROLE OF STOMACH. II: CARCINOGENIC EFFECTS OF *HELICOBACTER PYLORI* AND SNUS IN THE STOMACH

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298. Haakon R. Skogseth: INVASIVE PROPERTIES OF CANCER – A TREATMENT TARGET ? IN VITRO STUDIES IN HUMAN PROSTATE CANCER CELL LINES
299. Janniche Hammer: GLUTAMATE METABOLISM AND CYCLING IN MESIAL TEMPORAL LOBE EPILEPSY
300. May Britt Drugli: YOUNG CHILDREN TREATED BECAUSE OF ODD/CD: CONDUCT PROBLEMS AND SOCIAL COMPETENCIES IN DAY-CARE AND SCHOOL SETTINGS
301. Arne Skjold: MAGNETIC RESONANCE KINETICS OF MANGANESE DIPYRIDOXYL DIPHOSPHATE (MnDPDP) IN HUMAN MYOCARDIUM. STUDIES IN HEALTHY VOLUNTEERS AND IN PATIENTS WITH RECENT MYOCARDIAL INFARCTION
302. Siri Malm: LEFT VENTRICULAR SYSTOLIC FUNCTION AND MYOCARDIAL PERFUSION ASSESSED BY CONTRAST ECHOCARDIOGRAPHY
303. Valentina Maria do Rosario Cabral Iversen: MENTAL HEALTH AND PSYCHOLOGICAL ADAPTATION OF CLINICAL AND NON-CLINICAL MIGRANT GROUPS
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