"BIBLIOGRAFIA"

PREMESSA

Gli studi condotti sui principi attivi di **VitalOil** sono oltre 60.000. Qui pertanto ne sono riportati solo alcuni.

E' doveroso evidenziare che le nuove scoperte sul fronte degli acidi grassi essenziali Omega 3 e 6, pongono l'accento sui vantaggi di una dieta bilanciata Omega 3/Omega 6 prossima all'1:1.

Inoltre, si sta delineando meglio la diversa azione delle due classi di Omega 3 (ALA – origine vegetale, EPA, DHA – pesce):

VASI

l'ALA (il precursore vegetale), rispetto agli Omega 3 di Pesce, svolge una azione più marcata nei confronti della struttura vasale (**> elasticità**, **< ispessimento della placca**, **< pressione arteriosa**, **< ictus**).

CARDIOPROTEZIONE

l'azione (Elettrostabilizzazione) sembrerebbe essere a favore dell'EPA e DHA. Tuttavia in studi di ampia coorte e di durata pluriennale gli effetti cardioprotettivi dei tre acidi grassi sono molto simili. *(Probabilmente perché la trasformazione dell'ALA in EPA e DHA richiede diversi mesi per raggiungere l'equilibrio tissutale).*

COAGULAZIONE

L'EPA e il DHA allungano i tempi di coagulazione maggiormente dell'ALA. Tuttavia è bene sapere che l'assunzione anche dell'olio di Lino (1 cucchiaio /die) ha effetti marcati (+ 15%). Una maggiore neutralità si ha assumendo pari quantità di Omega 3 e Omega 6.
L'emostasi è un equilibrio particolarmente instabile, un eccesso di "fluidità" ematica, se da un verso riduce il rischio di trombosi, dall'altro aumenta quello di emorragie *(es. Ictus : l'Olio di Pesce (ricco solo in Omega 3) può alterare i parametri coagulativi ed essere correlato con un aumento delle Ischemie cerebrali: +30/+78% con 0,6-0,8 gr/die di EPA + DHA (The Lancet 1999; Neuroepidemiology 2002).*
E' consigliabile pertanto assumere molti Omega 3 solo se accompagnati da altrettanti Omega 6: **VitalOil** fornendo quantità elevate ed equilibrate di ALA-Omega 3 ed LA-Omega 6 è la risposta ottimale.

COLESTEROLO:

L'effetto sul colesterolo è proporzionale alla quantità di acidi grassi polinsaturi assunta, pertanto l'ALA-omega 3 risulta avvantaggiato in quanto se ne può assumere di più. (**VitalOil** apporta anche Omega 6 e i fitosteroli del gamma-Orizanolo, complesso antiradicali liberi Vit. A+E)

Livi sas - C.P. 16 - 35030 - Rubano PD – Tel 328 5684009, 049 9005684 - email: livinaturals@jumpy.it

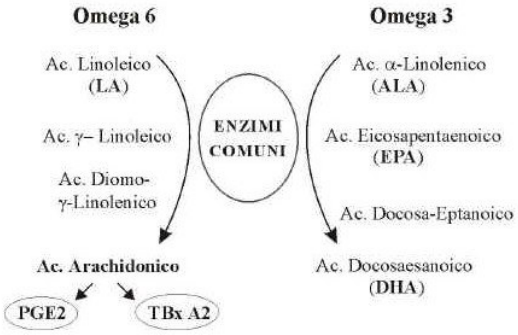
APPORTI NUTRIZIONALI di "VitalOil" : (20 ml)

ALA-Omega 3	3.0 gr
LA-Omega 6	2.9 gr
g-Orizanolo	80 mg
Vitamina E	13 mg (130% RDA)
Vitamina A	650 mmg (65 % RDA=100% LARN)

ABSTRACTS TRATTI DA PubMed

a service of the National Library of Medicine, provides access to over 12 million MEDLINE citations back to the mid-1960's and additional life science journals. PubMed includes links to many sites providing full text articles and other related resources.

Vital*Oil*: apporta 3 gr di ALA-Omega 3 e 2,9 di LA-Omega 6 ed è in grado di elevare i valori plasmatici di tutta la famiglia Omega 3: ALA +100%, EPA +44%, DHA+ 25%, senza modificare significativamente i parametri coagulativi, e pertanto senza aumentare il rischio emorraggico, al contrario dell'olio di lino non bilanciato (già con 1 cucchiai al giorno Riitta - Am J Clin Nutr 1997) ed ancora più marcatamente l'olio di pesce (già 0,8 gr di EPA+DHA aumentano il rischio di ictus emorraggico del 30 -78%, vedi studi sull'ictus)



J Nutr Sci Vitaminol (Tokyo) 1999 Dec;45(6):759-72

Long-term effects of dietary alpha-linolenic acid from perilla oil on serum fatty acids composition and on the risk factors of coronary heart disease in Japanese elderly subjects.

Ezaki O, Takahashi M, Shigematsu T, Shimamura K, Kimura J, Ezaki H, Gotoh T Division of Clinical Nutrition, National Institute of Health and Nutrition, Tokyo, Japan. ezaki@nih.go.jp

Although important roles of dietary n-3 fatty acids in the prevention of coronary heart disease (CHD) have been suggested, long-term effects of dietary alpha-**linolenic** acid (**ALA**, 18:3n-3) have not yet been established under controlled conditions.

We tested whether a moderate increase of dietary **ALA** affects fatty acids composition in serum and the risk factors of CHD.

Oxidized LDL (OxLDL) was directly measured by ELISA using antibody specific to OxLDL. By merely replacing soybean cooking oil (SO) with perilla oil (PO) (i.e., increasing 3 g/d of **ALA**), the n-6/n-3 ratio in the diet was changed from 4:1 to 1:1. **NOTA**: l'acido grasso n-6 era l'acido Linoleico (**LA**)

Twenty Japanese elderly subjects were initially given a SO diet for at least 6 mo (baseline period), a PO diet for 10 mo (intervention period), and then returned to the previous SO diet (washout period).

ALA in the total serum lipid increased from 0.8 to 1.6% after 3 mo on the PO diet, but EPA and DHA increased in a later time, at 10 mo after the PO diet, from 2.5 to 3.6% and 5.3 to 6.4%, respectively ($p<0.05$), and then returned to baseline in the washout period.

In spite of increases of serum n-3 fatty acids, the OxLDL concentration did not change significantly when given the PO diet.

Body weight, total serum cholesterol, triacylglycerol, glucose, insulin and HbA1c concentrations, platelet count and aggregation function, prothrombin time, partial thromboplastin time, fibrinogen and PAI-1 concentration, and other routine blood analysis did not change significantly when given the PO diet.

These data indicate that, even in elderly subjects, a 3 g/d increase of dietary **ALA** could increase serum EPA and DHA in 10 mo without any major adverse effects.

NOTA: TALI RISULTATI SONO ANCORA PIU' SIGNIFICATIVI CONSIDERANDO CHE NEGLI ANZIANI IL PROCESSO DI DESATURAZIONE ED ALLUNGAMENTO DEGLI ACIDI GRASSI OMEGA-3 E' MENO EFFICIENTE .

Am J Clin Nutr. 2003 Apr;77(4):819-25.

Dietary linolenic acid and carotid atherosclerosis: the National Heart, Lung, and Blood Institute Family Heart Study.

Djousse L, Folsom AR, Province MA, Hunt SC, Ellison RC; National Heart, Lung, and Blood Institute Family Heart Study. Section of Preventive Medicine & Epidemiology, Evans Department of Medicine, Boston University School of Medicine, MA 02118, USA. ldjousse@bu.edu

BACKGROUND: Dietary intake of linolenic acid (ALA-omega 3) is associated with a lower risk of cardiovascular disease mortality. However, it is unknown whether linolenic acid is associated with a lower risk of carotid atherosclerosis.

OBJECTIVE: The objective was to examine the association between dietary linolenic acid and the presence of atherosclerotic plaques and the intima-media thickness of the carotid arteries. DESIGN: In a cross-sectional design, we studied 1575 white participants of the National Heart, Lung, and Blood Institute Family Heart Study who were free of coronary artery disease, stroke, hypertension, and diabetes mellitus. High-resolution ultrasound was used to assess intima-media thickness and the presence of carotid plaques beginning 1 cm below to 1 cm above the carotid bulb. We used logistic regression and a generalized linear model for the analyses.

RESULTS: From the lowest to the highest quartile of linolenic acid intake, the prevalence odds ratio (95% CI) of a carotid plaque was 1.0 (reference), 0.47 (0.30, 0.73), 0.38 (0.22, 0.66), and 0.49 (0.26, 0.94), respectively, in a model that adjusted for age, sex, energy intake, waist-to-hip ratio, education, field center, smoking, and the consumption of linoleic acid, saturated fat, fish, and vegetables. Linoleic acid, fish long-chain fatty acids, and fish consumption were not significantly related to carotid artery disease. Alpha Linolenic acid (ALA) was inversely related to thickness of the internal and bifurcation segments of the carotid arteries but not to the common carotid artery.

CONCLUSION: Higher consumption of total linolenic acid (ALA) is associated with a lower prevalence odds of carotid plaques and with lesser thickness of segment-specific carotid intima-media thickness.

Am J Clin Nutr 2001 Nov;74(5):612-9

Relation between dietary linolenic acid and coronary artery disease in the National Heart, Lung, and Blood Institute Family Heart Study.

Djousse L, Pankow JS, Eckfeldt JH, Folsom AR, Hopkins PN, Province MA, Hong Y, Ellison RC.

Section of Preventive Medicine and Epidemiology, Evans Department of Medicine, the School of Medicine, Boston University.

BACKGROUND: Epidemiologic studies suggest that a higher consumption of

eicosapentaenoic acid and docosahexaenoic acid is associated with a reduced risk of cardiovascular disease. Studies in humans and animals also reported an inverse association between alpha-linolenic acid and cardiovascular disease morbidity and mortality.

OBJECTIVE: We examined the relation between dietary **linolenic acid** and prevalent coronary artery disease (CAD).

DESIGN: We studied 4584 participants with a mean (+/-SD) age of 52.1 +/- 13.7 y in the National Heart, Lung, and Blood Institute

Family Heart Study in a cross-sectional design. Participants' diets were assessed with a semiquantitative food-frequency questionnaire. For each sex, we created age- and energy-adjusted quintiles of linolenic acid, and we used logistic regression to estimate prevalent odds ratios for CAD.

RESULTS: From the lowest to the highest quintile of linolenic acid, the **prevalence odds ratios of CAD** were

1.0, 0.77, 0.61, 0.58, and 0.60 for the **men** (P for trend = 0.012) and

1.0, 0.57, 0.52, 0.30, and 0.42 for the **women** (P for trend = 0.014)

after adjustment for age, linoleic acid, and anthropometric, lifestyle, and metabolic factors. Linoleic acid was also inversely related to the prevalence odds ratios of CAD in the multivariate model (0.60 and 0.61 in the second and third tertiles, respectively) after adjustment for linolenic acid.

The combined effect of **linoleic and linolenic acids was stronger** than the individual effects of either fatty acid.

CONCLUSIONS: A higher intake of either linolenic or linoleic acid was inversely related to the prevalence odds ratio of CAD. The 2 fatty acids had synergistic effects on the prevalence odds ratio of CAD.

E' INTERESSANTE NOTARE COME I BENEFICI MAGGIORI SI OTTENGANO AUMENTANDO LA QUANTITA' DI **ALA** E **LA** ED IL RAPPORTO **ALA:LA**

British Medical Journal, July 1996

Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States.

Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer M, Willett WC. Harvard School of Public Health, Boston, MA 02115, USA.

OBJECTIVE--To examine the association between fat intake and the incidence of coronary heart disease in men of middle age and older.
DESIGN--Cohort questionnaire study of men followed up for six years from 1986.
SETTING--The health professionals follow up study in the United States.
SUBJECTS--43 757 health professionals aged 40 to 75 years free of diagnosed cardiovascular disease or diabetes in 1986.
MAIN OUTCOME MEASURE--Incidence of acute myocardial infarction or coronary death.
RESULTS--During follow up 734 coronary events were documented, including 505 non-fatal myocardial infarctions and 229 deaths. After age and several coronary risk factors were controlled for significant positive associations were observed between intake of saturated fat and risk of coronary disease. For men in the top versus the lowest fifth of saturated fat intake (median = 14.8% v 5.7% of energy) the multivariate relative risk for myocardial infarction was 1.22 (95% confidence interval 0.96 to 1.56) and for fatal coronary heart disease was 2.21 (1.38 to 3.54). After adjustment for intake of fibre the risks were 0.96 (0.73 to 1.27) and 1.72 (1.01 to 2.90), respectively. Positive associations between intake of cholesterol and risk of coronary heart disease were similarly attenuated after adjustment for fibre intake. Intake of **linolenic** acid 18:3 n3 (**ALA**) was inversely associated with **risk of myocardial infarction**; this association became significant only after adjustment for non-dietary risk factors and was strengthened after adjustment for total fat intake (**relative risk 0.41 for a 1% increase in energy, P for trend < 0.01**).

NOTA: 1 gr di **ALA** = 9 Kcal, dunque un incremento pari all'1 % del fabbisogno energetico quotidiano equivale a circa 1,8-2,5 gr al giorno

CONCLUSIONS--These data do not support the strong association between intake of saturated fat and risk of coronary heart disease suggested by international comparisons. They are compatible, however, with the hypotheses that saturated fat and cholesterol intakes affect the risk of coronary heart disease as predicted by their effects on blood cholesterol concentration.
They also support a specific preventive effect of alpha-**linolenic** acid intake.

Am J Clin Nutr 1999 May;69(5):890-7

Dietary intake of alpha-linolenic acid and risk of fatal ischemic heart disease among women.

Hu FB, Stampfer MJ, Manson JE, Rimm EB, Wolk A, Colditz GA, Hennekens CH, Willett WC. Department of Nutrition, Harvard School of Public Health, Boston, MA 02115, USA. Frank.Hu@channing.harvard.edu

BACKGROUND: Experimental studies in laboratory animals and humans suggest that alpha-**linolenic** acid (18:3n-3) may reduce the risk of arrhythmia.
OBJECTIVE: The objective was to examine the association between dietary intake of alpha-**linolenic** acid and risk of fatal ischemic heart disease (IHD).
DESIGN: This was a prospective cohort study. The intake of alpha-**linolenic** acid was derived from a 116-item food-frequency questionnaire completed in 1984 by 76283 women without previously diagnosed cancer or cardiovascular disease.
RESULTS: During 10 y of follow-up, we documented 232 cases of fatal IHD and 597 cases of nonfatal myocardial infarction.

After adjustment for age, standard coronary risk factors, and dietary intake of linoleic acid and other nutrients, a higher intake of alpha-**linolenic** acid was associated with a lower **relative risk (RR) of fatal IHD**; the RRs from the lowest to highest quintiles were 1.0, 0.99, 0.90, 0.67, and 0.55 (95% CI: 0.32, 0.94; P for trend = 0.01).

For nonfatal myocardial infarction there was only a modest, nonsignificant trend toward a reduced risk when extreme quintiles were compared (RR: 0.85; 95% CI: 0.61, 1.19; P for trend = 0.50).

NOTA: nel quintile più elevato, il consumo di **ALA** era 1,36 gr/g, quello più basso di 0,71 gr/giorno.

A higher intake of oil and vinegar salad dressing, an important source of alpha-linolenic acid, was associated with reduced risk of fatal IHD when women who consumed this food > or =5-6 times/wk were compared with those who rarely consumed this food (RR: 0.46; 95% CI: 0.27, 0.76; P for trend = 0.001).

CONCLUSIONS: This study supports the hypothesis that a higher intake of alpha-**linolenic** acid is protective against fatal IHD. Higher consumption of foods such as oil-based salad dressing that provide polyunsaturated fats, including alpha-**linolenic** acid, may reduce the risk of fatal IHD

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Am J Clin Nutr. 2003 Jul;78(1):65-71.

Comment in: Am J Clin Nutr. 2003 Jul;78(1):1-2.

n-3 Fatty acids and 5-y risks of death and cardiovascular disease events in patients with coronary artery disease.

Erkkila AT, Lehto S, Pyorala K, Uusitupa MI.

Department of Clinical Nutrition, University of Kuopio and Kuopio University Hospital, Kuopio, Finland. arja.erkkila@tufts.edu

BACKGROUND: Data on the association of n-3 fatty acid content in serum lipids with mortality in patients with coronary artery disease (CAD) are limited.

OBJECTIVE: We hypothesized that a high proportion of n-3 fatty acids in serum lipids would be associated with reduced risks of death and coronary events in patients with established CAD. DESIGN: We measured dietary intakes via food records and the fatty acid composition of serum cholesteryl esters (CEs) in 285 men and 130 women with CAD (x age: 61 y; range: 33-74 y). The patients participating in the **EUROASPIRE** *(European Action on Secondary Prevention through Intervention to Reduce Events)* study were followed up for 5 y.

RESULTS: During the follow-up, 36 patients died, 21 had myocardial infarctions, and 12 had strokes. The relative risks (RRs) of death adjusted for cardiovascular disease risk factors for subjects in the highest tertile of fatty acids in CEs compared with those in the lowest tertile were **0.33** (95% CI: 0.11, 0.96) for **alpha-linolenic acid**, **0.33** (0.12, 0.93**)** for **eicosapentaenoic acid**, and **0.31** (0.11, 0.87) for **docosahexaenoic acid** (P for trend = 0.063, 0.056, and 0.026, respectively). A high proportion of eicosapentaenoic acid in CEs was associated with a low risk of CAD death. Compared with no consumption, consumption of fish tended to be associated with a lower risk of death [1-57 g/d, RR = 0.50 (0.20, 1.28); > 57 g/d, RR = 0.37 (0.14, 1.00); P for trend = 0.059].

CONCLUSION: High proportions of n-3 fatty acids in serum lipids are associated with a substantially reduced risk of death.

Cardiovasc Drugs Ther 1997 Jul;11(3):485-91

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.

Singh RB, Niaz MA, Sharma JP, Kumar R, Rastogi V, Moshiri M.

Heart Research Laboratory, Medical Hospital and Research Centre, Civil Lines, Moradabad, India.

In a randomized, placebo-controlled trial, the effects of treatment with fish oil (**eicosapentaenoic acid, 1.08 g/day**) and mustard oil (**alpha-linolenic acid, 2.9 g/day**) were compared for 1 year in the management of 122 patients (fish oil, group A), 120 patients (mustard oil, group B), and 118 patients (placebo, group C) with **suspected acute myocardial infarction (AMI)**.

NOTA: In Italia i farmaci integratori di omega-3 di pesce (es. SEACORE) forniscono 0,8 gr/g di EPA+DHA, pari a circa il 70-75 % di quanto usato in questo studio. **VitalOil** fornisce 3 gr/g di ALA la medesima quantità dello studio.

Treatments were administered about (mean) **18 hours after the symptoms of AMI in all three groups**.

The extent of cardiac disease, rise in cardiac enzymes, and lipid peroxides were comparable among the groups at entry into the study.

After 1 year <u>total cardiac events</u> were significantly less in the fish oil and mustard oil groups compared with the placebo group (24.5% and 28% vs. 34.7%, p < 0.01).(pari ad una riduzione del - 19 % del gruppo ALA Vs controllo)

<u>Nonfatal infarctions</u> were also significantly less in the fish oil and mustard oil groups compared with the placebo group **(13.0% and 15.0% vs. 25.4%,** p a 0.05).(pari ad una riduzione del -41% del gruppo ALA Vs controllo)

Total cardiac deaths showed no significant reduction in the mustard oil group; however, the fish oil group had significantly less cardiac deaths compared with the placebo group (11.4% vs. 22.0%, p < 0.05).

Apart from the decrease in the cardiac event rate, the fish oil and mustard oil groups also showed a significant reduction in **total cardiac arrhythmias, left ventricular enlargement, and angina pectoris compared with the placebo group**.

Reductions in blood lipoproteins in the two intervention groups were modest and do not appear to be the cause of the benefit in the two groups.

Diene conjugates showed a significant reduction in the fish oil and mustard oil groups, indicating that a part of the benefit may be caused by the reduction in oxidative stress.

The findings of this study suggest that fish oil and mustard oil, possibly due to the presence of n-3 fatty acids, may provide rapid protective effects in patients with AMI. However, a large study is necessary to confirm this suggestion.

NOTA: IN CONSIDERAZIONE CHE LA TRASFORMAZIONE DELL'**ALA** IN **EPA** E **DHA** RAGGIUNGE IL PICCO DOPO DIVERSI MESI DALL'ASSUNZIONE, STUDI PIU' PROLUNGATI POTREBBERO ESSERE PIU' SIGNIFICATIVI (VEDI STUDIO SEGUENTE).

Am J Clin Nutr 1995 Jun;61(6 Suppl):1360S-1367S

Cretan Mediterranean diet for prevention of coronary heart disease.

Renaud S, de Lorgeril M, Delaye J, Guidollet J, Jacquard F, Mamelle N, Martin JL, Monjaud I, Salen P, Toubol P
INSERM Unit 63, Lyon-Bron, France.

As a result of the Seven Countries Study, the Mediterranean diet has been popularized as a healthy diet. Nevertheless, it has not replaced the prudent diet commonly prescribed to coronary patients. Recently, we completed a secondary, randomized, prospective prevention trial in 605 patients recovering from myocardial infarction in which we compared an adaptation of the Cretan Mediterranean diet with the usual prescribed diet.
After a mean follow-up period of 27 mo, **recurrent myocardial infarction, all cardiovascular events, and cardiac and total death were significantly decreased by > 70%** in the group consuming the Mediterranean diet.

These protective effects were not related to serum concentrations of total, low-density-lipoprotein (LDL), or high-density-lipoprotein (HDL) cholesterol.
In contrast, protective effects were related to changes observed in plasma fatty acids: an increase in n-3 fatty acids and oleic acid and a decrease in linoleic acid that resulted from higher intakes of **linolenic** and oleic acids, but lower intakes of saturated fatty acids and linoleic acid.
In addition, higher plasma concentrations of antioxidant vitamins C and E were observed.
We conclude that a Cretan Mediterranean diet adapted to a Western population protected against coronary heart disease much more efficiently than did the prudent diet. Thus, it appears that the favorable life expectancy of the Cretans could be largely due to their diet.

NOTA:

E' da sottolineare (per eventuali confronti) che la minore mortalità è

da riferirsi a 27 mesi: pari a ca. -36% annuo.

Il gruppo sperimentale ha incrementato il consumo di ALA utilizzando al posto del burro 19 gr/g di Margarina "arricchita" di ALA.

Composizione della dieta (gr/g) (componente lipidica)

	Saturi	18:1 oleico	18:2 Linoleico LA	18:3 Alfa Linolenico ALA	EPA
Controllo	24,4	21,5	11,7	0,5	0,5
Sperimentale	17,7	27,5	7,7	1,7	0,6
di cui da margarina "arricchita" 19 gr:	2,9	8+1,1^{T}	3,1	0,9	
Confronto con VitalOil 19 gr:	**2,5**	**10,1**	**2,9**	**3,0**	

ISCHEMIA CEREBRALE

L'azione neuroprotettiva è ben nota per gli acidi grassi omega 3, tuttavia merita un distinguo sulla loro attività verso l'Ischemia cerebrale.

Merita di evidenziare come la probabile causa di tale differenza sia la maggiore attività anti-trombotica degli Omega 3 di pesce (EPA e DHA) che causerebbe l'aumento molto marcato di ictus emorragici.

Dai più recenti studi si evidenzia come tale effetto si manifesti marcatamente già a soli 0,6-0,8 gr di EPA+DHA: aumento dell'incidenza dell'ictus del **+30** e **+ 76%**

Al contrario, un apporto bilanciato di ALA-Omega3/LA-Omega 6 non altera significativamente i parametri coagulativi neppure a dosaggi di 8+8 gr/g (Atherosclerosis 1999 Jan;142(1):159-68 -Comparison of the effects of two low fat diets with different alpha-linolenic:linoleic acid ratios on coagulation and fibrinolysis-Allman-Farinelli MA)

Si ricorda che **Vital*Oil*** apporta **3+3 gr** di **ALA-w3**+**LA-w6**

E' interessante inoltre il risultato di uno studio in Giappone, (con una dieta già ricca di omega-3) **che evidenzia un netto beneficio di una dieta bilanciata anche in Omega 6.**

J Nutr Health Aging 2001;5(3):167-72

Diet and stroke.

Renaud SC.

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In industrialized countries, stroke is the most frequent life-threatening neurological disorder. The mortality trend for stroke appears to be similar to that of coronary heart disease (CHD) in different countries. Thus the dietary changes that protect from CHD, may also protect from stroke. The purpose of the present paper is not to review exhaustively the associations between foodstuffs and stroke. It is rather to emphasize a few important relationships that may be conducive to efficient recommendations in Public Health.

The intake of **saturated fat**, considered as the main environmental factor for CHD, does not appear to be also closely related to stroke. It has even been observed in the Framingham prospective study, that saturated fats were associated with a protective effect on stroke.

The multivariate analysis of the ecological study reported in the present paper suggests that the **villain for stroke could be the high intake of linoleic acid**, the main polyunsaturated fatty acid prescribed through the world, to most of the CHD patients.

Observation and intervention studies suggest that the fatty acid with the most efficient protective effect on stroke is alpha-linolenic acid (ALA) as for CHD clinical manifestations.

Also similarly to CHD, fruit, vegetables and folic acid, may have important protective effect on stroke.

Finally, at very moderate intake, alcohol may be related to a similar lowering on the risk of stroke as on that of CHD.

Nevertheless alcohol, at high intake for intoxication (binge drinking) has been associated with up to a 10 fold increased in the risk of stroke.

Finally, the diet recommendations suggested by the present analysis are similar to those used in the Lyon Diet Heart Study and in Finland, in the last 20 years. In both of these intervention studies mortality from CHD, cancer and stroke have been markedly reduced by more than 50 %.

The Lancet -Aug 1999, 447-55

Gissi-Prevenzione

Tutti gli studi che hanno analizzato le **correlazioni fra Ictus o Tia e la presenza degli Omega 3** hanno evidenziato l'**effetto protettivo per l'ALA-Omega 3**. Nello studio Italiano più importante (GISSI Prevenzione-1999 Lancet) che ha coinvolto 11324 soggetti post-infartuati il **rischio di Ictus aumentava del 30 %** assumendo solo 0,8 gr/g di olio di pesce (EPA+DHA).

Dalla tabella sottostante emerge che il **rischio di ictus è maggiore del beneficio cardiaco**, pertanto l'impiego degli Omega 3 di pesce (EPA+DHA) può essere **consigliato solo in pazienti ad alto rischio di infarto**

n=11324 post infarctuated subjects tested for 1260 gg, EPA + DHA 0,8 gr/day Vs placebo	Relative Risk (CI 95%)
Coronary **H**eart **D**esease deaths + not fatal **M**yocardial **I**nfarct	**0,75 (-25%)**
Fatal and not fatal Stroke	**1,30 (+30%)**
Tot. Death + not fatal MI + not fatal Stroke	**0,85 (-15%)**

Diversamente dall'ALA-Omega 3, tale correlazione è stata confermata anche da un'analisi sull'incidenza dell'Ictus in Groenlandia: **"n-3 fatty acids as a risk factor for haemorrhagic stroke"** Henning Sloth Pedersen, 1999 The Lancet, Vol. 353 (812-3) e dal seguente studio:

Neuroepidemiology 2002 May-Jun;21(3):107-14

Fish consumption and stroke: a community case-control study in Asturias, Spain.

Caicoya M. -Service of Clinical Epidemiology and Preventive Medicine, Monte Naranco Hospital, Oviedo, Spain.

BACKGROUND: The relationship between fish consumption and stroke is controversial. Actually, a low fish consumption may protect against ischemic stroke, while a fish diet is ecologically associated with an increased risk of hemorrhagic stroke.

OBJECTIVE: This study seeks to examine the relationship between fish consumption and stroke in a population with a high fish consumption and stroke incidence.
METHODS: A population-based case-control study was performed, lasting from September 1990 to December 1991. The study comprised 440 incident cases of stroke and 473 controls between the ages of 40 and 85. Cases were defined following WHO criteria, and controls were randomly selected from the study base population. Information on fish consumption was obtained with a food frequency questionnaire

RESULTS: After controlling for age, energy intake and several stroke risk factors, the risk of stroke increased with the consumption of fish, chi(2) 4.12, p = 0.04. Those in the highest quintile of consumption (46 g of fish/day) had a multivariate adjusted odds ratio (OR) of 1.95 (95% CI: 1.14-3.33) as compared to those in the lowest quintile of fish consumption (11 g/day). The risk of cerebral infarction also

increased with the consumption of fish, showing an OR of 1.98 (95% CI: 1.08-3.47). **Those in the highest quintile of n-3 fatty acid consumption (660 mg/day) were at borderline higher risk of stroke, with an OR of 1.76 (95% CI: 0.95-3.26), and also of cerebral infarction (OR: 1.89, 95% CI: 0.95-3.75), as compared to those in the lower quintile of n-3 fatty acids consumption (115 mg/day).**

CONCLUSION: Although misclassification of exposure and residual confounding by unmeasured factors cannot be ruled out, a high fish consumption was associated with an increased risk of stroke and cerebral infarction in this study. More studies should be done to clarify the effect of fish consumption on stroke and stroke subtype in order to issue recommendations regarding the consumption of fish and the risk of stroke.

EMBO J 2000 Apr 17;19(8):1784-93

Polyunsaturated fatty acids are potent neuroprotectors.

Lauritzen I, Blondeau N, Heurteaux C, Widmann C, Romey G, Lazdunski M

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Results reported in this work suggest a potential therapeutic value of polyunsaturated fatty acids for cerebral pathologies as previously proposed by others for cardiac diseases.

We show that the polyunsaturated fatty acid **linolenic acid** prevents neuronal death in an animal model of transient global ischemia even when administered after the insult.

Linolenic acid also protects animals treated with kainate against seizures and hippocampal lesions.

The same effects have been observed in an in vitro model of seizure-like activity using glutamatergic neurons and they have been shown to be associated with blockade of glutamatergic transmission by low concentrations of distinct polyunsaturated fatty acids.

Our data suggest that the opening of background K(+) channels, like TREK-1 and TRAAK, which are activated by arachidonic acid and other polyunsaturated fatty acids such as docosahexaenoic acid and linolenic acid, is a significant factor in this neuroprotective effect.

These channels are abundant in the brain where they are located both pre- and post-synaptically, and are insensitive to saturated fatty acids, which offer no neuroprotection.

NOTA: l'acido alfa-linolenico **ALA** aprendo i canali del K+ (potassio) determina una iperpolarizzazione di membrana, inibendo l'instaurarsi di un potenziale d'azione presinaptico che porterebbe al rilascio del glutammato e/o rendendo meno sensibile all'azione del glutammato la membrana post-sinaptica.

Stroke 1995 May;26(5):778-82

Serum fatty acids and the risk of stroke.

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BACKGROUND AND PURPOSE: To examine the relationship between serum fatty acids, which reflect dietary intake, and stroke, we conducted a nested case-control study of 96 men with incident stroke and 96 control subjects matched by age, clinical center, treatment group, and date of randomization who were enrolled in the Multiple Risk Factor Intervention Trial.
METHODS: After confirming the stability of the stored serum samples, we measured serum cholesterol ester and phospholipid fatty acid levels as the percentage of total fatty acids by

gas-liquid chromatography and examined their association with incident stroke. Using stepwise conditional logistic regression that controlled for risk factors for stroke, we determined which fatty acids were independent correlates of stroke.

RESULTS: In univariate models, a standard deviation (SD) increase (1.37%) in phospholipid stearic acid (18:0) was associated with a 37% increase in the risk of stroke, whereas an SD increase (0.06%) in phospholipid omega-3 alpha-**linolenic** acid (18:3) was associated with a 28% decrease in the risk of stroke (all P < .05).
Only alpha-**linolenic** acid in the cholesterol ester fraction was associated with the risk of stroke in multivariate models: an SD increase (0.13%) in the serum level of alpha-**linolenic** acid was associated with a **37% decrease in the risk of stroke (P < .05).**
Systolic blood pressure and cigarette smoking were also independently associated with stroke risk.

CONCLUSIONS: Our findings suggest that higher serum levels of the essential fatty acid alpha-**linolenic** acid are independently associated with a lower risk of stroke in middle-aged men at high risk for cardiovascular disease.

NOTA: la concentrazione plasmatica dell'ALA è usualmente 0,6-0,7 %, il che significa che innalzandola di un 0,13 % si porta la concentrazione plasmatica dell'ALA a c.a. 0,75 %

VitalOil è in grado di elevare il livello plasmatico dell'ALA a c.a. 1,2-1-4%

Vasc Med 1999;4(4):219-226
Essential fatty acids and cardiovascular disease: the Edinburgh Artery Study.
Leng GC, Taylor GS, Lee AJ, Fowkes FG, Horrobin D.
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The aim of this study was to determine whether plasma and red cell fatty acid levels were associated with cardiovascular disease, and whether any association was independent of other major risk factors.
Over 1100 subjects were examined in a random sample survey of the general population (the Edinburgh Artery Study).
Fatty acids were measured in three plasma fractions (triglyceride, cholesteryl ester and phospholipid) and in red cell phospholipids.
Fatty acid levels in groups with cardiovascular disease (myocardial infarction (MI), angina and lower limb disease) were compared with a no disease group.
- In the cholesteryl ester and phospholipid fractions there were significantly lower levels of eicosapentaenoic acid in the MI group on univariate analysis (p<0.05), but not when adjusted for age, sex, smoking and systolic blood pressure using logistic regression.

- In the red cell fraction, alpha-**linolenic** acid 18:3 n 3 (**ALA**) was significantly lower in those with stroke (p<0.01) and lower limb disease (p<0.05).

Linoleic 18:2 n 6 acid was significantly raised in the triglyceride fraction in those with MI, probably reflecting recent dietary changes.
- There were significant increases in dihomo-gamma-**linolenic** acid in the phospholipid and red cell fractions in those with MI, and in the phospholipid fraction in the stroke group.

These results do not support the hypothesis that n-6 fatty acids are protective against cardiovascular disease, although there may be some beneficial effects of the n-3 fatty acid, alpha-**linolenic** acid. Results from cross-sectional surveys must, however, be interpreted with caution because the presence of disease may affect dietary intake.

Stroke. 2002 Aug;33(8):2086-93.
Linoleic acid, other fatty acids, and the risk of stroke.

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BACKGROUND AND PURPOSE: The role of serum fatty acids as a risk factor for stroke and stroke subtypes is

largely unknown. METHODS: A prospective nested case-control study of Japanese 40 to 85 years of age was conducted through the use of frozen serum samples from 7450 participants in cardiovascular risk surveys collected from 1984 to 1989 for 1 community and 1989 to 1992 for the other 2 communities. By the end of 1998, we identified 197 incident strokes whose subtypes were confirmed by imaging studies. Three controls per case were selected by matching for sex, age, community, year of serum storage, and fasting status.

RESULTS: Compared with controls, total (n=197), hemorrhagic (n=75), and ischemic (n=122) strokes had similar proportions of n3 polyunsaturated fatty acids, lower proportions of linoleic and arachidonic acids, and higher proportions of saturated and monosaturated acids, determined by gas chromatography. The multivariate odds ratios associated with a 1-SD increase in linoleic acid (5%) after adjustment for hypertension, diabetes, serum total cholesterol, and other cardiovascular risk factors were 0.72 [95% confidence interval (CI), 0.59 to 0.89] for total stroke, 0.66 (95% CI, 0.49 to 0.88) for ischemic stroke, 0.63 (95% CI, 0.46 to 0.88) for lacunar infarction, and 0.81 (95% CI, 0.59 to 1.12) for hemorrhagic stroke. The respective odds ratios for saturated fatty acids (4%) were 1.13 (95% CI, 1.05 to 1.65), 1.35 (95% CI, 1.01 to 1.79), 1.44 (95% CI, 1.03 to 2.01), and 1.21 (95% CI, 0.82 to 1.80). Further adjustment for other fatty acids attenuated these relations, but the relation between linoleic acid and risk of ischemic stroke remained statistically significant.

CONCLUSIONS: A higher intake of linoleic acid may protect against ischemic stroke, possibly through potential mechanisms of decreased blood pressure, reduced platelet aggregation, and enhanced deformability of erythrocyte cells.

Arterioscler Thromb Vasc Biol 1997 Jun;17(6):1163-1170
Arterial compliance in obese subjects is improved with dietary plant n-3 fatty acid from flaxseed oil despite increased LDL oxidizability.
Nestel PJ, Pomeroy SE, Sasahara T, Yamashita T, Liang YL, Dart AM, Jennings GL, Abbey M, Cameron JD.
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The compliance or elasticity of the arterial system, an important index of circulatory function, diminishes with increasing cardiovascular risk.
Conversely, systemic arterial compliance improves through eating of fish and fish oil.
We therefore tested the value of high intake of alpha-**linolenic** acid, the plant precursor of fish fatty acids.
Fifteen obese people with markers for insulin resistance ate in turn four diets of 4 weeks each; saturated/high fat (SHF), alpha-**linolenic** acid/low fat (ALF), oleic/low fat (OLF), and SHF. Daily intake of alpha-**linolenic** acid was 20 g from margarine products based on flax oil.
Systemic arterial compliance was calculated from aortic flow velocity and aortic root driving pressure. Plasma lipids, glucose tolerance, and in vitro LDL oxidizability were also measured. Systemic arterial compliance during the first and last SHF periods was 0.42 +/- 0.12 (mean +/- SD) and 0.56 +/- 0.21 units based on milliliters per millimeter of mercury. It rose significantly to 0.78 +/- 0.28 ($P < .0001$) with ALF; systemic arterial compliance with OLF was 0.62 +/- 0.19, lower than with ALF ($P < .05$). Mean arterial pressures and results of oral glucose tolerance tests were similar during ALF, OLF, and second SHF; total cholesterol levels were also not significantly different. However, insulin sensitivity and HDL cholesterol diminished and LDL oxidizability increased with ALF.
The marked rise in arterial compliance at least with alpha-**linolenic** acid reflected rapid functional improvement in the systemic arterial circulation despite a rise in LDL oxidizability. Dietary n-3 fatty acids in flax oil thus confer a novel approach to improving arterial function.

Am J Clin Nutr 1986 Sep;44(3):336-40
Does dietary linolenic acid influence blood pressure?
Berry EM, Hirsch J.

Short-term intervention studies have shown that diets rich in polyunsaturated fats have hypotensive properties.
We have studied the long-term effects of dietary fat on blood pressure (BP) using adipose-tissue, fatty acid composition analysis in 399 free-living male subjects (average age, 47 yr).
Stepwise-regression analysis showed that adipose linoleic acid (18:2 n-6) was not associated with BP, whereas an absolute 1% increase in **linolenic** acid (18:3 n-3) (**ALA**) was associated with a decrease of 5 mm Hg in the systolic, diastolic, and composite mean arterial BP.
Linolenic acid (18:3) comprised only one-eighth the amount of linoleic acid (18:2)--the major polyunsaturate in adipose tissue and hence in the diet (2% vs 16%)--and yet it had a disproportionate association with BP.
This may be related to its role as a precursor for the production of prostaglandins and/or other vasoregulators. Dietary manipulation with n-3 fatty acids may be helpful in the treatment and prevention of hypertension.

Ann Med 1991 Aug;23(3):295-8
Dietary fats, antioxidants and blood pressure.
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Although obesity and alcohol intake as well as dietary sodium, potassium and magnesium are the major non-genetic determinants of blood pressure levels, interest has recently been stimulated in the function of fatty acids and antioxidants in the aetiology of hypertension. In the Kuopio Ischaemic Heart Disease Risk Factor Study both plasma ascorbic acid and serum selenium concentrations had a moderate, independent inverse association, estimated dietary intake of saturated fatty acids had a positive association and estimated dietary intake of **linolenic** acid had an inverse association with the mean resting blood pressure in 722 Eastern Finnish men

with neither self reported hypertension nor cerebrovascular disease.
· Even though these cross sectional observations do not prove causality, they warrant clinical trials to verify or disprove that dietary fats and antioxidants are factors in the development of hypertension.

J Hypertens Suppl 1987 Dec;5(5):S521-4
Vitamin C deficiency and low linolenate intake associated with elevated blood pressure: the Kuopio Ischaemic Heart Disease Risk Factor Study.
Salonen JT, Salonen R, Ihanainen M, Parviainen M, Seppanen R, Seppanen K, Rauramaa R.
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We investigated the association of dietary fatty acids and plasma antioxidative vitamins with blood pressure in 722 eastern Finnish men aged 54 years, examined in the Kuopio Ischaemic Heart Disease Risk Factor Study in 1984-1986, who had no known hypertension nor any cerebrovascular disease. Allowing for the major anthropometric, dietary, medical and psychological determinants of blood pressure in a multivariate regression analysis, plasma ascorbic acid concentration had a moderate, independent inverse association (P less than 0.0001) and the estimated dietary intake of **linolenic** acid an inverse (P = 0.026) independent association with mean resting blood pressure. **The marked elevation of blood pressure at the lowest levels of plasma vitamin C concentration supports the hypothesis of the role of antioxidants in the aetiology of hypertension.**

Med Hypotheses 1991 Sep;36(1):90-4
Stress and fatty liver--possible indications for dietary long-chain n-3 fatty acids.
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The favourable effects of eicosapentaenoic acid (EPA)- and doco-sahexaenoic acid (DHA)-rich diets (marine fish, fish oil) on several risk factors for cardiovascular disease are well established. The present survey describes possible new indications for diets supplemented with long-chain n-3 fatty acids.
During a standardized psychophysiological stress test (arithmetic, sentence completion tasks) systolic blood pressure after 2 weeks of diets supplemented with either 60 ml/day of sunflower or linseed oil was significantly decreased.
During the sunflower oil-rich diet 45 g/day of linoleic acid (LA) and during the linseed oil-rich period 38 g/day of alpha-**linolenic** acid (LNA) were ingested.
After a 2-week diet supplemented with mackerel (2 cans/day equivalent to 2.2 g/day of EPA and 2.8 g/day of DHA) systolic and diastolic blood pressure within the same test design appeared significantly lower.
After a herring diet providing 2 cans/day, equivalent to 1.0 g of EPA and 1.8 g of DHA, the blood pressure-lowering effect was minor.
The increase of thromboxane B2 (TxB2) during the stress test failed to occur after the fish diets.
The results suggest a stress-protective effect of polyenoic acid-rich diets, which appears most pronounced and dose-related after long-chain n-3 fatty acids.
In human liver an increase of fat droplet size in hepatocytes is associated with a decrease of the percentage of EPA in liver triglycerides.
A diminution of plasma free fatty acids (FFA) after a mackerel diet might contribute to a depressed synthesis of liver triglycerides.(ABSTRACT TRUNCATED AT 250 WORDS)

Am J Epidemiol 1999 Sep 1;150(5):492-500
Plasma fatty acid composition and 6-year incidence of hypertension in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study.
Zheng ZJ, Folsom AR, Ma J, Arnett DK, McGovern PG, Eckfeldt JH.
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The association of baseline fatty acid

composition in plasma cholesterol esters with 6-year incidence of hypertension was examined in middle-aged Minneapolis participants of the Atherosclerosis Risk in Communities (ARIC) Study (1987-1995). Compared with those who were never hypertensive (n = 1,975), incident hypertensives (n = 413) had statistically significantly higher baseline levels of palmitic (16:0) and palmitoleic (16:1n7) acids but lower levels of linoleic (18:2n6) acid and the polyunsaturated/saturated fatty acids ratio (P/S ratio).
Among polyunsaturated fatty acids, levels of :
- dihomo-gamma-linolenic (20:3n6) and
- arachidonic (20:4n6) acids were statistically significantly higher in incident hypertensives, compared with normotensives.

After adjustment for age, sex, body mass index, waist/hip ratio, smoking status, ethanol intake, education level, physical activity, and baseline systolic blood pressure in separate models, the odds ratio estimates of incident hypertension for an interquartile increment of a fatty acid in cholesterol esters were 1.26 (95% confidence interval (CI): 1.05, 1.51) for 16:0, 1.11 (95% CI: 0.96, 1.28) for 16:1n7, 1.01 (95% CI: 0.85, 1.21) for 20:3n6, 1.14 (95% CI: 1.03, 1.27) for 20:5n3, 0.81 (95% CI: 0.68, 0.96) for 18:2n6, and 0.83 (95% CI: 0.70, 0.99) for the P/S ratio.
The authors conclude that reduced levels of linoleic acid and the P/S ratio and elevated levels of palmitic and arachidonic acids are associated with a higher risk of hypertension.

NOTA: l'acido alfa **linolenico** 18:3 n 3 (**ALA**) riduce la trasformazione dell'ac. Linoleico 18:2 n 6 in di-omo-gamma -linlenico e arachidonico.

Eur J Clin Nutr 2000 Dec;54(12):865-871
Associations of alpha-linolenic acid and linoleic acid with risk factors for coronary heart disease.
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BACKGROUND: Prevention of coronary heart disease (CHD) in high-risk subjects.
OBJECTIVE: To investigate the associations of dietary intake of alpha-**linolenic** acid (**ALA**) and linoleic acid (LA) as assessed by food frequency questionnaire and in the plasma cholesteryl ester (CE), with CHD risk factors.
DESIGN: Baseline data of a double-blind, randomized placebo-controlled trial. Subjects have hypercholesterolemia (6.0-8.0 mmol/l) and at least two other CHD risk factors (n=266).
RESULTS: The reported dietary **ALA** and LA intakes and the LA/**ALA** ratio were associated with the contents in the CE (r=0.37, r=0.21, and r=0.42, respectively; P<0.01).
In multivariate analysis, CE **ALA** was inversely associated with diastolic blood pressure (r=-0.13; P<0.05)
and positively with serum triacylglycerol (r=0.13; P<0.05), and CE LA was inversely associated with serum triacylglycerol (r=-0.32; P<0.01). The CE LA/**ALA** ratio was strongly inversely associated with CE **ALA** (r=-0.95; P<0.01).
In the lowest quintile of CE **ALA**, mean dietary intake was 0.4 energy % **ALA** (1.2 g/day), 8.4 energy % LA and an LA/**ALA** ratio of 21, and in the highest quintile 0.6 energy % **ALA** (1.7 g/day), 6.8 energy % LA and 12 (ratio). In the lowest quintile of CE **ALA** the diastolic blood pressure was 4 mm Hg lower (P trend<0.05), and the serum triacylglycerol 0.3 mmol/l higher (P trend NS) when compared with the top quintile.

CONCLUSIONS: In a CHD high-risk population with LA-rich background diet, these cross-sectional data suggest that replacing LA in the diet by **ALA** may decrease diastolic blood pressure, and may increase serum triacylglycerol concentration.

Vopr Pitan 1997;5:15-17
[Effect of antiatherosclerotic diet, containing polyunsaturated fatty acids of the omega-3 family from flax oil, on fatty acid composition of cell membranes of patients with ischemic heart disease. Hypertensive disease and hyperlipoproteinemia].[Article in Russian]Rozanova IA, Pogozheva AV, Kupakova SN, Lupinovich VL, Karagodina ZV, Levachev MM, Samsonov MA.Use flax oil as a vegetative source of PUFA omega-3 in diet of patients with ischemic heart disease, hyperlipidemia and high blood pressure resulted in positive dynamic of clinical manifestation, blood lipids and coagulograms of the patient. Pronounced influence on membrane lipids of erythrocytes was revealed: significantly increased a quota an linolenic, eicosapentaenic and docosahexaenic PUFA against a background of reducing a level of linoleic acid.

Curr Opin Clin Nutr Metab Care
2001 Mar;4(2):115-21

Polyunsaturated fatty acids and rheumatoid arthritis.

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Rheumatoid arthritis is characterized by infiltration of T lymphocytes, macrophages and plasma cells into the synovium, and the initiation of a chronic inflammatory state that involves overproduction of proinflammatory cytokines and a dysregulated T-helper-1-type response. Eicosanoids synthesized from arachidonic acid and cytokines cause progressive destruction of cartilage and bone.

The n-6 polyunsaturated fatty acid gamma-linolenic acid is the precursor of di-homo-gamma-linolenic acid.

The latter and the n-3 polyunsaturated fatty acid eicosapentaenoic acid, which is found in fish oil, are able to decrease the production of arachidonic acid-derived eicosanoids and to decrease the production of proinflammatory cytokines and reactive oxygen species, and the reactivity of lymphocytes.

A number of double-blind, placebo-controlled trials of gamma-linolenic acid and fish oil in rheumatoid arthritis have shown significant improvements in a variety of clinical outcomes.

These fatty acids should be included as part of the normal therapeutic approach to rheumatoid arthritis.

However, it is unclear what the optimal dosage of the fatty acids is, or whether there would be extra benefit from using them in combination.

Br J Nutr 2001 Mar;85(3):251-69

Antioxidants and fatty acids in the amelioration of rheumatoid arthritis and related disorders.

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The generation of reactive oxygen species (free radicals) is an important factor in the development and maintenance of rheumatoid arthritis in humans and animal models.

One source of free radicals is nitric oxide produced within the synoviocytes and chondrocytes and giving rise to the highly toxic radical peroxynitrite.

Several cytokines, including tumour necrosis factor-alpha (TNFalpha) are involved in the formation of free radicals, partly by increasing the activity of nitric oxide synthase.
Indeed, nitric oxide may mediate some of the deleterious effects of cytokines on bone resorption.

Aspirin, tetracyclines, steroids and methotrexate can suppress nitric oxide synthase.

Dietary antioxidants include ascorbate and the tocopherols and beneficial effects of high doses have been reported especially in osteoarthritis.

There is also evidence for beneficial effects of beta-carotene

and selenium, the latter being a component of the antioxidant enzyme glutathione peroxidase.

The polyunsaturated fatty acids (PUFA) include the n-3 compounds, some of which are precursors of eicosanoid synthesis, and the n-6 group which can increase formation of the pro-inflammatory cytokines TNFalpha and interleukin-6, and of reactive oxygen species.

Some prostaglandins, however, suppress cytokine formation, so that n-3 PUFA often oppose the inflammatory effects of some n-6-PUFA.

gamma-linolenic acid (GLA) is a precursor of prostaglandin E1, a fact which may account for its reported ability to ameliorate arthritic symptoms.

Fish oil supplements, rich in n-3 PUFA such as eicosapentaenoic acid have been claimed as beneficial in rheumatoid arthritis, possibly by suppression of the immune system and its cytokine repertoire.

Some other oils of marine origin (e.g. from the green-lipped mussel) and a range of vegetable oils (e.g. olive oil and evening primrose oil) have indirect anti-inflammatory actions, probably mediated via prostaglandin E1.

Overall, there is a growing scientific rationale for the use of dietary supplements as adjuncts in the treatment of inflammatory disorders such as rheumatoid arthritis and osteoarthritis.

Am J Clin Nutr 2000 Jul;72(1):42-8

Biochemical effects of a diet containing foods enriched with n-3 fatty acids.

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BACKGROUND: Results of many studies indicate that consumption of n-3 fatty acids can benefit persons with cardiovascular disease and rheumatoid arthritis. However, encapsulated fish oil is unlikely to be suited to lifetime daily use and recommendations to increase fish intake have not been effective.
OBJECTIVE: The objective was to examine the effectiveness of a diet that incorporates foods rich in n-3 fatty acids in elevating tissue concentrations of eicosapentaenoic acid and in suppressing the production of inflammatory mediators.

DESIGN: Healthy male volunteers were provided with foods that were enriched in alpha-linolenic acid (cooking oil, margarine, salad dressing, and mayonnaise) and eicosapentaenoic and docosahexaenoic acids (sausages and savory dip) and with foods naturally rich in n-3 fatty acids, such as flaxseed meal and fish. Subjects incorporated these products into their food at home for 4 wk. Fatty acid intakes, cellular and plasma fatty acid concentrations, and monocyte-derived eicosanoid and cytokine production were measured.

RESULTS: Analyses of dietary records indicated that intake of eicosapentaenoic acid plus docosahexaenoic acid averaged 1.8 g/d and intake of alpha-linolenic acid averaged 9. 0 g/d. These intakes led to an average 3-fold increase in eicosapentaenoic acid in plasma, platelet, and mononuclear cell phospholipids. Thromboxane B(2),

prostaglandin E(2), and interleukin 1beta synthesis decreased by 36%, 26%, and 20% (P < 0.05), respectively.

CONCLUSIONS: Foods that are strategically or naturally enriched in n-3 fatty acids can be used to achieve desired biochemical effects without the ingestion of supplements or a change in dietary habits. A wide range of n-3-enriched foods could be developed to support large-scale programs on the basis of the therapeutic and disease-preventive effects of n-3 fatty acids.

Am J Clin Nutr 2000 Jan;71(1 Suppl):343S-8S

Dietary polyunsaturated fatty acids and inflammatory mediator production.

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Many antiinflammatory pharmaceutical products inhibit the production of certain eicosanoids and cytokines and it is here that possibilities exist for therapies that incorporate n-3 and n-9 dietary fatty acids. The proinflammatory eicosanoids prostaglandin E(2) (PGE(2)) and leukotriene B(4) (LTB(4)) are derived from the n-6 fatty acid arachidonic acid (AA), which is maintained at high cellular concentrations by the high n-6 and low n-3 polyunsaturated fatty acid content of the modern Western diet. Flaxseed oil contains the 18-carbon n-3 fatty acid alpha-linolenic acid, which can be converted after ingestion to the 20-carbon n-3 fatty acid eicosapentaenoic acid (EPA). Fish oils contain both 20- and 22-carbon n-3 fatty acids, EPA and docosahexaenoic acid. EPA can act as a competitive inhibitor of AA conversion to PGE(2) and LTB(4), and decreased synthesis of one or both of these eicosanoids has been observed after inclusion of flaxseed oil or fish oil in the diet. Analogous to the effect of n-3 fatty acids, inclusion of the 20-carbon n-9 fatty acid eicosatrienoic acid in the diet also results in decreased synthesis of LTB(4). Regarding the proinflammatory ctyokines, tumor necrosis factor alpha and interleukin 1beta, studies of healthy volunteers and rheumatoid arthritis patients have shown < or = 90% inhibition of cytokine production after dietary supplementation with fish oil. Use of flaxseed oil in domestic food preparation also reduced production of these cytokines. Novel antiinflammatory therapies can be developed that take advantage of positive interactions between the dietary fats and existing or newly developed pharmaceutical products.

Proc Nutr Soc 1998 Nov;57(4):555-62

Dietary n-6 and n-3 fatty acids in immunity and autoimmune disease.

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Clearly there is much evidence to show that under well-controlled laboratory and dietary conditions fatty acid intake can have profound effects on animal models of autoimmune disease. Studies in human autoimmune disease have been less dramatic; however, human trials have been subject to uncontrolled dietary and genetic backgrounds, infection and other environmental influences, and basic trial designs have been

inadequate. The impact of dietary fatty acids on animal autoimmune disease models appears to depend on the animal model and the type and amount of fatty acids fed. Diets low in fat, essential fatty acid-deficient, or high in n-3 fatty acids from fish oils increase the survival and reduce disease severity in spontaneous autoantibody-mediated disease, whilst linoleic acid-rich diets appear to increase disease severity. In experimentally-induced T-cell-mediated autoimmune disease, essential fatty acid-deficient diets or diets supplemented with n-3 fatty acids appear to augment disease, whereas n-6 fatty acids prevent or reduce the severity. In contrast, in both T-cell and antibody-mediated auto-immune disease the desaturated and elongated metabolites of linoleic acid are protective. Suppression of autoantibody and T lymphocyte proliferation, apoptosis of autoreactive lymphocytes, and reduced pro-inflammatory cytokine production by high-dose fish oils are all likely mechanisms by which n-3 fatty acids ameliorate autoimmune disease. However, these could be undesirable long-term effects of high-dose fish oil which may compromise host immunity. The protective mechanism(s) of n-6 fatty acids in T-cell- mediated autoimmune disease are less clear, but may include dihomo-gamma-linolenic acid- and arachidonic acid-sensitive immunoregulatory circuits such as Th1 responses, TGF beta 1-mediated effects and Th3-like responses. It is often claimed that n-6 fatty acids promote autoimmune and inflammatory disease based on results obtained with linoleic acid only. It should be appreciated that linoleic acid does not reflect the functions of dihomo-gamma-linolenic and arachidonic acid, and that the endogenous rate of conversion of linoleic to arachidonic acid is slow (Hassam et al. 1975, 1977; Phylactos et al. 1994; Harbige et al. 1995). In addition to effects of dietary fatty acids on immunoregulation, inflammation as a consequence of immune activation in autoimmune disease may also be an important mechanism of action whereby dietary fatty acids modulate disease activity. In conclusion, regulation of gene expression, signal transduction pathways, production of eicosanoids and cytokines, and the action of antioxidant enzymes are all mechanisms by which dietary n-6 and n-3 fatty acids may exert effects on the immune system and autoimmune disease. Probably the most significant of these mechanisms in relation to our current understanding of immunoregulation and inflammation would appear to be via fatty acid effects on cytokines. The amount, type and balance of dietary fatty acids and associated antioxidant nutrients appear to impact on the immune system to produce immune-deviation or immunosuppressive effects, and to reduce immune-mediated inflammation which will in turn affect the susceptibility to, or severity of, autoimmune disease.

Br J Nutr 2002 Jan;87 Suppl 1:S77-82

n-3 fatty acids in psoriasis.

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Increased concentrations of free arachidonic acid (AA) and its proinflammatory metabolites have been observed in psoriatic lesions. Replacement of arachidonic acid by alternative precursor polyunsaturated fatty acids (PUFA), especially eicosapentaenoic acid (EPA), which can be metabolized via the same enzymatic pathways as AA, might be a therapeutic option in psoriasis. However the results of studies evaluating the therapeutic benefit of dietary fish oil have been conflicting and not clearly dose-dependent. To overcome the slow kinetics and limited availability of oral supplementation, we have performed three studies to assess the efficacy and safety of an intravenously administered fish oil derived lipid emulsion on different forms of psoriasis. Patients received daily infusions of either an n-3 fatty acid-based lipid emulsion (Omegaven) or a conventional n-6 lipid emulsion (Lipoven) in different time and dose regimens. In addition to an overall

assessment of the clinical course of psoriasis, EPA- and AA-derived neutrophil 5-lipoxygenase (LO)--products, thromboxane (TX) B2/B3, PAF and plasma free fatty acids were investigated. Treatment with n-3 fatty acids resulted in a considerably higher response rate than infusion of n-6 lipids. A more than 10-fold increase in neutrophil EPA-derived 5-LO product formation was noted in the n-3 group, accompanied by a rapid increase in plasma-free EPA within the first days. In conclusion, intravenous n-3-fatty acid administration causes reduction of psoriasis, which may be related to changes in inflammatory eicosanoid generation. The rapidity of the response to intravenous n-3 lipids exceeds by orders of magnitude the hitherto reported kinetics of improvement of psoriatic lesions upon use of oral supplementation.

Drugs 1998 Apr;55(4):487-96

Lipid mediators in inflammatory disorders.

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During the past few decades, intensive collaborative research in the fields of chronic and acute inflammatory disorders has resulted in a better understanding of the pathophysiology and diagnosis of these diseases. Modern therapeutic approaches are still not satisfactory and shock, sepsis and multiple organ failure remain the great challenge in intensive care medicine. However, the treatment of inflammatory diseases like rheumatoid arthritis, ulcerative colitis or psoriasis also represents an unresolved problem. Many factors contribute to the complex course of inflammatory reactions. Microbiological, immunological and toxic agents can initiate the inflammatory response by activating a variety of humoral and cellular mediators. In the early phase of inflammation, excessive amounts of interleukins and lipid-mediators are released and play a crucial role in the pathogenesis of organ dysfunction. Arachidonic acid (AA), the mother substance of the pro-inflammatory eicosanoids, is released from membrane phospholipids in the course of inflammatory activation and is metabolised to prostaglandins and leukotrienes. Various strategies have been evaluated to control the excessive production of lipid mediators on different levels of biochemical pathways, such as inhibition of phospholipase A2, the trigger enzyme for release of AA, blockade of cyclooxygenase and lipoxygenase pathways and the development of receptor antagonists against platelet activating factor and leukotrienes. Some of these agents exert protective effects in different inflammatory disorders such as septic organ failure, rheumatoid arthritis or asthma, whereas others fail to do so. Encouraging results have been obtained by dietary supplementation with long chain omega-3 fatty acids like eicosapentaenoic acid (EPA). In states of inflammation, EPA is released to compete with AA for enzymatic metabolism inducing the production of less inflammatory and chemotactic derivatives.

J Am Acad Dermatol 1998
Apr;38(4):539-47

Omega-3 fatty acid-based lipid infusion in patients with chronic plaque psoriasis: results of a double-blind, randomized, placebo-controlled, multicenter trial.

Mayser P, Mrowietz U, Arenberger P, Bartak P, Buchvald J, Christophers E, Jablonska S, Salmhofer W, Schill WB, Kramer HJ, Schlotzer E, Mayer K, Seeger W, Grimminger F.

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BACKGROUND: Profound changes in the metabolism of eicosanoids with increased concentrations of free arachidonic acid (AA) and its proinflammatory metabolites have been observed in psoriatic lesions. Free eicosapentaenoic acid (EPA) may compete with liberated AA and result in an antiinflammatory effect.

OBJECTIVE: Our purpose was to assess the efficacy and safety of intravenously administered fish-oil-derived lipid emulsion on chronic plaque-type psoriasis. METHODS: A double-blind, randomized, parallel group study was performed in eight European centers. Eighty-three patients hospitalized for chronic plaque-type psoriasis with a severity score of at least 15 according to the Psoriasis Area and Severity Index (PASI) participated in a 14-day trial. They were randomly allocated to receive daily infusions with either a omega-3 fatty acid-based lipid emulsion (Omegavenous; 200 ml/day with 4.2 gm of both EPA and docosahexaenoic acid (DHA); 43 patients) or a conventional omega-6-lipid emulsion (Lipovenous; EPA+DHA < 0.1 gm/100 ml; 40 patients). The groups were well matched with respect to demographic data and psoriasis-specific medical history. Efficacy of therapy was evaluated by changes in PASI, in an overall assessment of psoriasis by the investigator, and a self-assessment by the patient. In one center neutrophil 4- versus 5-series leukotriene (LT) generation and platelet 2- versus 3- thromboxane generation were investigated and plasma-free fatty acids were determined.

RESULTS: The total PASI score decreased by 11.2 +/- 9.8 in the omega-3 group and by 7.5 +/- 8.8 in the omega-6 group (p = 0.048). In addition, the omega-3 group was superior to the omega-6 group with respect to change in severity of psoriasis per body area, change in overall erythema, overall scaling and overall infiltration, as well as change in overall assessment by the investigator and self-assessment by the patient. Response (defined as decrease in total PASI of at least 50% between admission and last value) was seen in 16 of 43 patients (37%) receiving the omega-3 emulsion and 9 of 40 patients (23%) receiving omega-6 fatty acid-based lipid emulsion. No serious side effects were observed. Within the first few days of omega-3 lipid administration, but not in the omega-6 supplemented patients, a manifold increase in plasma-free EPA concentration, neutrophil leukotriene B5 and platelet thromboxane B3 generation occurred.

CONCLUSION: Intravenous omega-3-fatty acid administration is effective in the treatment of chronic plaque-type psoriasis. This effect may be related to changes in inflammatory eicosanoid generation.

Pediatrics 2003 Jan;111(1):e39-44

Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age.

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OBJECTIVES: Docosahexaenoic acid (DHA; 22:6 n-3) and arachidonic acid (AA; 20:4 n-6) are important for development of the central nervous system in mammals. There is a growth spurt in the human brain during the last trimester of pregnancy and the first postnatal months, with a large increase in the cerebral content of AA and DHA. The fetus and the newborn infant depend on maternal supply of DHA and AA. Our hypothesis was that maternal intake of DHA during pregnancy and lactation is marginal and that high intake of this fatty acid would benefit the child. We examined the effect of supplementing pregnant and lactating women with very-long-chain n-3 polyunsaturated fatty acids (PUFAs; cod liver oil) on mental development of the children, compared with maternal supplementation with long-chain n-6 PUFAs (corn oil).

METHODS: The study was randomized and double-blinded. Pregnant women were recruited in week 18 of pregnancy to take 10 mL of cod liver oil or corn oil until 3 months after delivery. The cod liver oil contained 1183 mg/10 mL DHA, 803 mg/10 mL eicosapentaenoic acid (20:5 n-3), and a total of 2494 mg/10 mL summation operator n-3 PUFAs. The corn oil contained 4747 mg/10 mL linoleic acid (18:2 n-6) and 92 mg/10 mL alpha-linolenic acid (18:3 n-3). The amount of fat-soluble vitamins was identical in the 2 oils (117 micro g/mL vitamin A, 1 micro g/mL vitamin D, and 1.4 mg/mL dl-alpha-tocopherol). A total of 590 pregnant women were recruited to the study, and 341 mothers took part in the study until giving birth. All infants of these women were scheduled for assessment of cognitive function at 6 and 9 months of age, and 262 complied with the request. As part of the protocol, 135 subjects from this population were invited for intelligence testing with the Kaufman Assessment Battery for Children (K-ABC) at 4 years of age. Of the 135 invited children, 90 came for assessment. Six children did not complete the examination. The K-ABC is a measure of intelligence and achievement designed for children aged 2.5 years through 12.5 years. This multisubtest battery comprises 4 scales: Sequential Processing, Simultaneous Processing, Achievement (not used in the present study), and Nonverbal Abilities. The Sequential Processing and Simultaneous Processing scales are hypothesized to reflect the child's style of problem solving and information processing. Scores from these 2 scales are combined to form a Mental Processing Composite, which serves as the measure of intelligence in the K-ABC.

RESULTS: We received dietary information from 76 infants (41 in the cod liver oil group and 35 in the corn oil group), documenting that all of them were breastfed at 3 months of age. Children who were born to mothers who had taken cod liver oil (n = 48) during pregnancy and lactation scored higher on the Mental Processing Composite of the K-ABC at 4 years of age as compared with children whose mothers had taken corn oil (n = 36; 106.4 [7.4] vs 102.3 [11.3]). The Mental Processing Composite score correlated significantly with head circumference at birth (r = 0.23), but no relation was found with birth weight or gestational length. The children's mental processing scores at 4 years of age correlated significantly with maternal intake of DHA and eicosapentaenoic acid during pregnancy. In a multiple regression model, maternal intake of DHA during pregnancy was the only variable of statistical significance for the children's mental processing scores at 4 years of age.

CONCLUSION: Maternal intake of very-long-chain n-3 PUFAs during pregnancy and lactation may be favorable for later mental development of children.

Am J Clin Nutr 2002 Jul;76(1):232-8

Acute ingestion of a meal rich in n-3 polyunsaturated fatty acids results in rapid gastric emptying in humans.

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BACKGROUND: n-3 Polyunsaturated fatty acids (PUFAs) have proven benefits for both the development of atherosclerosis and inflammatory conditions. The effects on atherosclerosis may be partly mediated by the observed reduction in fasting and postprandial triacylglycerol concentrations after both acute and chronic n-3 PUFA ingestion.

OBJECTIVE: The aim of this study was to assess gastric emptying and gastrointestinal hormone release after the consumption of mixed meals rich in n-3 PUFAs or other classes of fatty acids.

DESIGN: Ten healthy women (aged 50-62 y) completed 4 separate study visits in a single-blind, randomized design. On each occasion, subjects consumed 40 g oil rich in either saturated fatty acids, monounsaturated fatty acids, n-6 PUFAs, or n-3 PUFAs as part of a mixed meal. [1-(13)C]Octanoic acid (100 mg) was added to each oil. Gastric emptying was assessed by a labeled octanoic acid breath test, and concentrations of gastrointestinal hormones and plasma lipids were measured. RESULTS: Recovery of (13)C in breath was enhanced after n-3 PUFA ingestion ($P < 0.005$). The cholecystokinin response after the n-3 PUFA meal was significantly delayed ($P < 0.001$), and the glucagon-like peptide 1 response was significantly reduced ($P < 0.05$).

CONCLUSION: The inclusion of n-3 PUFAs in a meal alters the gastric emptying rate, potentially as the result of changes in the pattern of cholecystokinin and glucagon-like peptide 1 release

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Dietary fish oil increases acetylcholine- and eicosanoid-induced contractility of isolated rat ileum.

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The long-chain (n-3) polyunsaturated fatty acids (PUFA) have been reported to exhibit health benefits and healing properties for the gastrointestinal tract.

The aim of this study was to investigate the effects of dietary fish oil supplementation on the in vitro contractility of gut tissue.

Rats (9 wk old) were fed synthetic diets supplemented with 170 g/kg Sunola oil (SO; 850 g/kg as oleic acid [18:1(n-9)]) or with 100 g/kg of the SO replaced by saturated animal fat (SF) or fish oil (FO) for 4 wk. In the colon, there was no difference in the sensitivity (50% effective concentration) or the maximal contraction among the three dietary groups induced by acetylcholine or 8-iso-prostaglandin (PG)E(2) with the rat colon being relatively insensitive to the thromboxane mimetic U-46619. However, in the ileum, the FO group had greater maximal contractions induced by acetylcholine and 8-iso-PGE(2) compared with the SO and SF groups ($P < 0.05$), and greater maximal contractions induced by PGE(2), PGF(2alpha) and U-46619 compared with the SF group ($P < 0.05$). FO feeding increased the incorporation of (n-3) PUFA (eicosapentaenoic [20:5(n-3)], docosapentaenoic [22:5(n-3)] and docosahexaenoic acids [22:6(n-3) primarily at the expense of (n-6) PUFA (linoleic [18:2(n-6)] and arachidonic acids [20:4(n-6)]) in the ileum and colon phospholipid fatty acids ($P < 0.05$). The FO group had a lower cecal digesta pH ($P < 0.001$) and a greater butyrate concentration than the SF group ($P < 0.05$).

These results suggest that dietary (n-3) PUFA may modulate the contractility of the small intestine.

Nippon Heikatsukin Gakkai Zasshi. 1980 Mar;16(1):47-55.

Effects of gamma-oryzanol on the movements of stomach and ileum in the dog (author's transl)]
[Article in Japanese]
Mizonishi T, Semba T.

Gastric and ileal movements were measured after administration of gamma-Oryzanol in the dog. 1. Gastric and ileal movement were enhanced after intravenous administration of 1 mg/kg body weight of gamma-Oryzanol. The higher dose of gamma-Oryzanol produced the shorter latency of these enhanced movements and thereafter, induced the inhibition of these movements. 2. When bilateral vagal nerves and the splanchnic nerves were previously transected or administered atropine, no enhancement of the gastric and ileal movement were observed by administration of gamma-Oryzanol. Furthermore, these enhanced movement produced with gamma-Oryzanol were abolished by atropine injection during these enhanced movement. 3. The inhibitory movement of the stomach and the ileum produced by administration of gamma-Oryzanol of 10 mg/kg body weight were reversely existed by the transection of vagal nerves in the cervical region or by administration of quinidine. These results indicate that gamma-Oryzanol produces the enhancement as well as inhibition of gastric and ileal movements. These effects may be produced by reaction to the central nervous system of the gastric and ileal movements.

Nippon Yakurigaku Zasshi. 1976 May;72(4):475-81.

[Studies of gamma-oryzanol (1). Effects on stress-induced ulcer]
[Article in Japanese]
Itaya K, Kiyonaga J.

In clinical trials, it is well known that gamma-oryzanol is effective against the syndromes of autonomic nervous unbalance and climacteric disorders. The authors studied the action of gamma-oryzanol on restraint, water-immersion stress ulcer under various conditions in rats. The drug, given 1 to 100 mg/kg s.c. daily for five days, reduced the ulcer index dose-dependently, and slightly prevented the rate of increase in serum level of 11-OHCS. These effects were observed in adrenalectomized as well as sham operated rats. It is likely that the antiulcerogenic action of gamma-oryzanol is due to participation of the autonomic nervous system, but not the hypophyseoadrenal axis.

APPROFONDIMENTO:

ACIDI GRASSI ESSENZIALI NELLA TERAPIA DI MANTENIMENTO DELLA MALATTIA DI CROHN

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Le malattie infiammatorie croniche sono condizioni la cui eziopatogenesi rimane ancora oggi di origine sconosciuta.
I metaboliti dell'acido arachidonico, gli eicosanoidi, vengono ritenuti responsabili della cascata infiammatoria che automantiene la flogosi iniziale. Tali metaboliti vengono prodotti a partire dagli acidi grassi a 20 atomi di carbonio.

Si possono distinguere due vie metaboliche:
a - attraverso la via della ciclossigenasi, l'acido arachidonico viene trasformato in prostaglandine, prostacicline e trombossani

b - attraverso la via della 5-lipossigenasi, attiva a livello dei granulociti eosinofili e dei monociti, deriva la produzione di leucotrieni.
Il leucotriene B4 e l'acido 5-idrossieicosatetraenoico costituiscono i principali metaboliti flogogeni prodotti a livello dei granulociti

E' stato dimostrato che il leucotriene B4 è presente nella mucosa colica dei pazienti con malattia infiammatoria cronica intestinale in concentrazioni 50 volte superiori a quelle riscontrabili in condizioni di normalità. Inoltre agisce attraverso un secondo messaggero amplificando la risposta infiammatoria secondaria alla produzione di citochine ad azione flogogena. Infine, avendo elevate proprietà chemiotattiche, favorisce la migrazione di cellule direttamente responsabili dei processi di flogosi.

I farmaci attualmente più utilizzati nella terapia delle malattie infiammatorie croniche intestinali agiscono interferendo a vari livelli di tale cascata infiammatoria. I glucocorticoidi (cortisonici) prevengono la formazione di molecole libere di acido arachidonico, attraverso l'inibizione dell'attività delle fosfolipasi A_2 e C sui fosfolipidi di membrana. La mesalazina agisce attraverso l'inibizione della 5-lipossigenasi nella mucosa colica.

Lee e coll. suggerirono possibili effetti degli acidi grassi contenuti nell'olio di pesce sui processi metabolici cellulari di tipo infiammatorio.

L'**acido eicosapentaenoico (EPA)**, acido grasso polinsaturo a 20 atomi di carbonio (Figura 3), prodotto dal metabolismo dell'**acido α-linolenico (ALA)**, si differenzia dall'acido arachidonico per la presenza di un doppio legame in più in posizione 17.

Esso rappresenta un buon substrato per la 5-lipossigenasi e compete con l'acido arachidonico per l'utilizzazione di tale enzima insieme al suo omologo acido docosaesaenoico (DHA). L'incorporazione di acido eicosapentaenoico e di docosaesaenoico nelle membrane dei granulociti neutrofili è il presupposto fondamentale per il realizzarsi del meccanismo d'azione competitivo nei confronti dell'acido arachidonico. Tale effetto comporta una ridotta sintesi di leucotriene B4 e la sintesi di un nuovo leucotriene B5 il quale non possiede alcun effetto flogogeno.

Gli effetti antinfiammatori dell'olio di pesce sono stati verificati su modelli animali, su coliti indotte nel ratto da acido trinitrobenzensulfonico. Accanto agli effetti sulla cascata dell'acido arachidonico, gli acidi grassi omega 3 contenuti nell'olio di pesce, riducono i livelli circolanti e tissutali delle principali citochine flogogene (IL-1,TNFα) e limitano la sintesi del "platelet activating factor", fosfolipide con potente azione flogogena.

NOTA "VitalOil": in uno studio con pazienti anziani, (pertanto a ridotta attività enzimatica), l'arrichimento della dieta con 3 gr di **ALA** - Omega 3 + 3 gr di **LA** - Omega 6 ha dimostrato di **elevare i livelli plasmatici** di tutti gli acidi grassi Omega 3: **- ALA** (**+100%**), **- EPA** (**+44%**) e **DHA** (**+20%**)[1] (i suoi metaboliti).

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ALTRI STUDI

J Gastroenterol. 1995 Nov;30 Suppl 8:98-101.
Therapeutic efficacy of N-3 polyunsaturated fatty acid in experimental Crohn's disease.

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We investigated the therapeutic efficacy of n-3 polyunsaturated fatty acids (PUFAs) on trinitrobenzene sulfonic acid (TNBS)-induced colitis in the rats, which condition is considered an experimental Crohn's disease (CD). In rats with TNBS-induced colitis, feeding with an elemental diet (ED) plus 2% n-3 PUEA-rich perilla oil significantly suppressed plasma leukotriene (LT) B4 and ulcer index compared to that in rats fed with ED plus 2% n-6 PUFA-rich safflower oil (34.2 +/- 12.3 s 63.8 +/- 13.2 pg/ml and 8.8 +/- 12.1 vs 66.4 +/- 33.1, P < 0.01, respectively). Moreover, the plasma LTB4 and the ulcer index were significantly correlated (P < 0.05).
Feeding with ED plus 2% **alpha-linolenic acid (ALA-omega 3)-rich vegetable oil significantly reduced plasma LTB4 and colonic weight** compared to that in rats fed with ED plus 2% eicosapentaenoic acid (EPA)/docosahexaenonic acid (DHA)-rich fish oil in this model (61.6 +/- 10.5 vs 85.0 +/- 20.9 pg/ml and 0.83 +/- 0.13 vs 0.96 +/- 0.08g, P < 0.05, respectively). This study suggested that dietary fat manipulation with perilla oil can reduce colonic damage and that this is correlated with the suppression of plasma LTB4.

The therapeutic efficacy of ALA in controlling intestinal inflammation in experimental CD may be superior to that of EPA and DHA.

Br J Nutr. 2002 Jan;87 Suppl 1:S83-8.

Impact of parenteral n-3 fatty acids on experimental acute colitis.

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The present study was undertaken to investigate the effects of parenteral lipid emulsions (LE) enriched with n-3 fatty acids (n-3 FA) in experimental acute colitis. Seventy-four adult male Wistar rats were randomized into six groups, five of which had acetic acid-induced colitis. The animals received a fat-free diet and water ad libitum in individual metabolic cages. By a central venous catheter, saline was infused (0.5 ml/h) into the control groups CS (without colitis) and CC (with colitis), while the test groups received specific LE for 7 days. The n-3/n-6 FA ratio and the lipidic compositions regarding long chain (LCT) and medium chain (MCT) triglycerides were: group L--1:7.7 (LCT, n = 12), M--1:7.0 (MCT and LCT, n = 12), LW-3--1:4.5 (LCT plus n-3 FA, n = 12) and MW-3--1:3.0 (MCT and LCT plus n-3 FA, n = 13). The frequency of diarrhea, oral intake/body weight ratio, intestinal alterations, macrophage cellularity were evaluated and colonic concentrations of leukotrienes (LTB4, LTC4), prostaglandins (PGE2) and thromboxanes (TXB2) were measured. Groups M, MW-3 and LW-3 had less diarrhea than the CC group (P<0.05). Average oral intake/body weight ratio in MW-3 animals was comparable to the CS and better than the CC group. n-3 FA treated rats (LW-3 and MW-3) presented less intestinal inflammatory alterations than CC rats. Mucosal ulcer formation in MW-3 group did not differ from CS rats. M and MW-3 rats had less macrophages in the colon than the CC group. Compared with CC group, lower concentrations of LTB4 in the CS, LW-3 and MW-3 groups; of PGE2 in the CS, M and MW-3 groups; and of TXB2 in the CS and MW-3 groups were found. Mean concentrations of LTC4 did not differ among the groups. Thus, a LCT-containing LE with a low n-3-n-6 ratio does not modify inflammatory colitis manifestations; LE with a high n-3-n-6 ratio reduces diarrhea, preserves oral intake-weight ratio, attenuates morphological consequences and decreases colonic concentrations of inflammatory mediators; MCT/LCT-containing LE with 1:3 n-3-n-6 ratio exerts the most profound beneficial impact on the inflammatory response.

Vopr Pitan.

1996;(6):35-7.
Optimization of dietary fat composition in erosive and ulcerative diseases of the gastroduodenal area

Matushevskaia VN, Shakhovskaia AK, Karagodina ZV, Lupinovich VL, Korf II, Loranskaia TI, Levachev MM.

Fish oil preparation "Polyen" was used for treatment 21 patients with ulcerative diseases of the stomach or duodenum. The cicatrization of ulcer was diagnosed in 85% of patients treated by "Polyen" and in 60% of those who did not take fish oil. "Polyen" influenced fatty acid composition of erythrocyte membranes and lipid peroxidation. Authors draw a conclusion that omega-3 PUFA's can stimulate the reparative processes.

Food Chem Toxicol. 1995 Jul;33(7):553-8.

Effect of acute administration of fish oil (omega-3 marine triglyceride) on gastric ulceration and secretion induced by various ulcerogenic and necrotizing agents in rats.

al-Harbi MM, Islam MW, al-Shabanah OA, al-Gharably NM.

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The fish oil commercially known as Marine-25 (omega-3 marine triglyceride) is an eicosapentaenoic acid (EPA)-rich oil. It was investigated for its ability to inhibit gastric secretion and to protect the gastric mucosa against the injuries caused by pyloric ligation, non-steroidal anti-inflammatory drugs (NSAIDs--aspirin and indomethacin), reserpine, hypothermic restraint stress and necrotizing agents [0.6 M HCl 0.2 M NaOH or 80% (v/v) aqueous ethanol]. The results showed that the fish oil, at a dose of 5 or 10 ml/kg body weight, provided significant protection in the various experimental models used. It produced a significant inhibition of gastric mucosal damage induced by pyloric ligation, NSAIDs, reserpine or hypothermic restraint ulcers. Fish oil also exerted a significant inhibitory action on gastric mucosal lesions produced by various necrotizing agents. Our findings show that fish oil rich in eicosapentaenoic acid possesses both antisecretory and antiulcerogenic effects.

Gut. 1994 Nov;35(11):1557-61.

Inhibitory effect of polyunsaturated fatty acids on the growth of Helicobacter pylori: a possible explanation of the effect of diet on peptic ulceration.

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Diets high in polyunsaturated fatty acids may protect against duodenal ulcer, possibly through inhibiting the growth of Helicobacter pylori. This hypothesis was tested in vitro by incubating H pylori microaerophilically with a range of polyunsaturated fatty acids. omega-3 alpha-Linolenic acid (ALA) significantly, but reversibly, inhibited growth at 1.8, 2.5, and 5 x 10(-4) M ($p < 0.01$), while concentrations of 10(-3) M killed virtually all organisms, with cell lysis observed by electron microscopy. Similar inhibitory effects were seen with other polyunsaturated fatty acids, at concentrations of 2.5 x 10(-4) M the relative inhibitory potencies were oleic (C18:1) < linoleic (C18:2) < arachidonic (C20:4) < omega-3 linolenic (C18:3) = omega-6 linolenic (C18:3) = eicosapentanoic (C20:5) acid. Cell fractionation studies with 14C labelled linolenic acid showed that the linolenic acid was associated with the membrane fraction. Commonly ingested dietary polyunsaturated fatty acids inhibit the growth of H pylori in vitro, an effect which deserves further in vivo study.

Gli Omega 3, svolgono un'azione antinfiammatoria ed intervengono nel metabolismo osseo, **aumentando l'assorbimento del Calcio** e **riducendo il riassorbimento osseo** *(inibizione degli osteoclasti stimolati dalla PGE2, che viene ridotta dagli omega 3)*

Altri studi dimostrano un **aumento della sintesi del collagene dei legamenti**

Eur J Med Res. 2003 Aug 20;8(8):381-7. Related Articles, Links

Dietary fatty acids and immune reactions in synovial tissue.

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Inflammation of the synovial membrane in rheumatoid arthritis is mediated by specialized cells necessary for immune response. The most prominent features are the accumulation of mononuclear phagocytes, lymphocytes and leukocytes in the proliferating tissue. Pro-inflammatory and proliferative signals are transmitted to the bone marrow and to the synovial membrane. The result is a monoclonal stimulation of specific cell lines, and synovial proliferation in the inflamed joint. Angiogenesis, synovial hypertrophy, and increased perfusion facilitate the accumulation of inflammatory cells. Components of the autoimmune reaction are described in the international system of classification, the CD-System (cluster of differentiation). Pro-inflammatory signals are mediated by metabolites of arachidonic acid. Prostaglandins, leukotrienes, lipoxines and hydroxy fatty acids, derived from this PUFA, stimulate the formation and the activity of adhesion molecules (integrines), cytokines (gamma-interferon, interleukin-1, interleukin-6, tumor-necrosis factor), chemokines (interleukine-8, macrophage-chemotactic peptide, RANTES and colony -stimulating factors ((CSF, granulocytes/ monocytes-CSF, Multi-CSF (= IL-3)). Dietary means to mitigate inflammation comprise reduction of arachidonic acid, and increased intake of eicosapentaenoic acid and antioxidants. In the literature 12 randomized, placebo-controlled double-blind studies, fulfilling GCP-criteria, demonstrate a moderate but consistent improvement of clinical findings and laboratory parameters in patients with RA. A dose-response relationship was established up to an daily dose of 2.6 gram fish oil, equivalent to about 1.6 gram EPA. In these experiments EPA was the omega-3 fatty acid responsible for improvement, with distinct effects on inhibition of cytokines formation (IL-1 to IL-6, IL-8, TFN-alpha, GM-CSF), decreased induction of proinflammatory adhesion molecules (selectines, intercellular adhesions molecule-1 (ICAM-1)), and degrading enzymes (e.g. phospholipase A2, cyclooxygenase-2, inducible NO-synthetase). Only one study reports the relevance of the background diet. From this study it became apparent that reduction of dietary arachidonic acid improves the incorporation and the clinical benefit of EPA.

J Hum Nutr Diet. 2003 Apr;16(2):97-109. Related Articles, Links

Nutritional management of rheumatoid arthritis: a review of the evidence.

Rennie KL, Hughes J, Lang R, Jebb SA.

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Rheumatoid arthritis (RA) is a debilitating disease and is associated with increased risk of cardiovascular disease and osteoporosis. Poor nutrient status in RA patients has been reported and some drug therapies, such as nonsteroidal anti-inflammatory drugs (NSAIDs), prescribed to alleviate RA symptoms, may increase the requirement for some nutrients and reduce their absorption. This paper reviews the scientific evidence for the role of diet and nutrient supplementation in the management of RA, by alleviating symptoms, decreasing progression of the disease or by reducing the reliance on, or combating the side-effects of, NSAIDs. Supplementation with long-chain n-3 polyunsaturated fatty acids (PUFA) consistently demonstrates an improvement in symptoms and a reduction in NSAID usage. Evidence relating to other fatty acids, antioxidants, zinc, iron, folate, other B vitamins, calcium, vitamin D and fluoride are also considered. The present evidence suggests that RA patients should consume a balanced diet rich in long-chain n-3 PUFA and antioxidants. More randomized long-term studies are needed to provide evidence for the benefits of specific nutritional supplementation and to determine optimum intake, particularly for n-3 PUFA and antioxidants.

Maturitas. 2002 May 20;42(1):13-22. Related Articles, Links

Polyunsaturated fatty acids. Is there a role in postmenopausal osteoporosis prevention?

Albertazzi P, Coupland K.

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OBJECTIVE: To review the effect of a diet supplemented with polyunsaturated fatty acids (PUFA) on prevention or treatment of osteoporosis. METHODS: MEDLINE (1966-April 2001), Allied Complementary Medicine (1985-2001), Cochrane Library and Database of Systematic Reviews (1st Quarter 2001) was searched. Five reviews and no systematic reviews were found on this topic in the Cochrane Library. Eleven relevant in-vivo studies were identified on the effect of these compounds on bone. Eight were animal studies and three were randomised control trials (RCT) in human.

RESULTS: There are two classes of PUFA designated as n-3 and n-6 with alpha-linolenic acid (ALA). These two different types of PUFA differently influence prostaglandin formation and hence modulate bone metabolism differently. These are several in vitro and animal data suggesting that diet with a low n-6/n-3 ratio may have beneficial effects on bone mineral density. Only three, short-term, small studies have been performed in human so far. Two studies, one performed with bone markers and one with bone density showed a positive effect of PUFA on bone. While a third study showed no effect.

CONCLUSIONS: Preliminary, data have suggested that a diet with a low n-6/n-3 ratio may have beneficial effects on bone mineral density. Further studies are, however, required to fully assess the dose and type of PUFA to be used for optimum bone effects. This may be useful particularly for the prevention of disease in the elderly, since a diet rich in n-3 PUFA has been shown to have additional benefit on the cardiovascular, central nervous system and joints.

Aging (Milano). 1998 Oct;10(5):385-94. Related Articles, Links

Calcium, gamma-linolenic acid and eicosapentaenoic acid supplementation in senile osteoporosis.

Kruger MC, Coetzer H, de Winter R, Gericke G, van Papendorp DH.

Department of Physiology, University of Pretoria, South Africa.

Recent animal work suggests that gamma-linolenic acid (GLA) and eicosapentaenoic acid (EPA) enhance calcium absorption, reduce excretion and increase calcium deposition in bone. A pilot study was set up to test the interactions between calcium and GLA + EPA in humans. Sixty-five women (mean age 79.5), taking a background diet low in calcium, were randomly assigned to GLA + EPA or coconut oil placebo capsules; in addition, all received 600 mg/day calcium as the carbonate. Markers of bone formation/degradation and bone mineral density (BMD) were measured at baseline, 6, 12 and 18 months. Twenty-one patients were continued on treatment for a second period of 18 months, after which BMD (36 months) was measured. At 18 months, osteocalcin and deoxypyridinoline levels fell significantly in both groups, indicating a decrease in bone turnover, whereas bone specific alkaline phosphatase rose indicating beneficial effects of calcium given to all the patients. Lumbar and femoral BMD, in contrast, showed different effects in the two groups. Over the first 18 months, lumbar spine density remained the same in the treatment group, but decreased 3.2% in the placebo group. Femoral bone density increased 1.3% in the treatment group, but decreased 2.1% in the placebo group. During the second period of 18 months with all patients now on active treatment, lumbar spine density increased 3.1% in patients who remained on active treatment, and 2.3% in patients who switched from placebo to active treatment; femoral BMD in the latter group showed an increase of 4.7%. This pilot controlled study suggests that GLA and EPA have beneficial effects on bone in this group of elderly patients, and that they are safe to administer for prolonged periods of time.

J Nephrol. 2002 Nov-Dec;15(6):601-4. Related Articles, Links

Fatty acids, calcium and bone metabolism.

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Epidemiological, clinical and experimental evidence suggests that fatty acids may have an effect (due to their chemical structure) on calcium metabolism in animals and man. Fatty acid deficiency in animals can lead to a loss of bone calcium and matrix, resulting in marked bone demineralization, and treatment with a mixture of omega-3 and omega-6 polyunsaturated fatty acids can induce significant reduction in some biochemical markers of bone reabsorption. A relationship, between phospholipid fatty acid content, calcium-regulating hormones and intestinal, renal, and bone calcium metabolism alterations, has been reported in patients with renal stones and hypercalciuria. Recent studies have shown specific effects of fatty acids on the gene expression of some bone cytokines. Fatty acids might be involved in calcium metabolism influencing cellular calcium ion transport directly, as second messengers, or generating, through the cyclooxygenase pathway, potential biological mediators which have complex effects on bone remodeling. Experimental and clinical documentation of the specific and indirect effects of fatty acids on calcium and bone metabolism could open up new and interesting clinical prospects.

Prostaglandins Leukot Essent Fatty Acids. 2003 Jun;68(6):423-9. Related Articles, Links

Omega-3 fatty acids modulate ATPases involved in duodenal Ca absorption.

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Dietary supplementation with fish oil that contains omega-3 polyunsaturated fatty acids has been shown to enhance bone density as well as duodenal calcium uptake in rats.

The latter process is supported by membrane ATPases.

The present in vitro study was undertaken to test the effect of omega-3 fatty acids on ATPase activity in isolated basolateral membranes from rat duodenal enterocytes. Ca-ATPase in calmodulin-stripped membranes was activated in a biphasic manner by docosahexanoic acid (DHA) (10-30 microg/ml) but not by eicosapentanoic acid (EPA). This effect was blocked partially by 0.5 microM calphostin (a protein kinase C blocker). DHA inhibited Na,K-ATPase (-49% of basal activity, [DHA]=30 microg/ml, P <0.01). This effect could be reversed partially by 50 microM genistein, a tyrosine kinase blocker. EPA also inhibited Na,K-ATPase: (-47% of basal activity, [EPA]=30 microg/ml, P <0.01), this effect was partially reversed by 100 microM indomethacin, a cyclo-oxygenase blocker. Omega-3 fatty acids are thus involved in multiple signalling effects that effect ATPases in BLM.

J Nutr. 2002 Sep;132(9):2667-72. Related Articles, Links

Modulation of essential (n-6):(n-3) fatty acid ratios alters fatty acid status but not bone mass in piglets.

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Dietary (n-6) and (n-3) fatty acids have been implicated as important regulators of bone metabolism. The main objective of this research was to define the response of whole-body growth, fatty acid status and bone mass to a reduced dietary (n-6):(n-3) fatty acid ratio. A secondary objective was to determine whether there is an amount of fat x fatty acid ratio interaction for these outcomes. Piglets (n = 32) were randomized to 1 of 4 diets: group 1: [30 g fat/L + (n-6):(n-3) ratio 4.5:1]; group 2: [30 g fat/L + (n-6):(n-3) ratio 9.0:1]; group 3: [60 g fat/L + (n-6):(n-3) ratio 4.5:1]; and group 4: [60 g fat/L + (n-6):(n-3) ratio 9.0:1]. After 21 d, outcomes assessed included growth, fatty acid status and bone mass and metabolism. Growth and bone mass did not differ among the four groups nor did arachidonic acid (AA as g/100 g fatty acids) in plasma, adipose and brain. **Piglets fed diets 1 and 3 with the lower (n-6):(n-3) ratio had lower liver AA (P < 0.001).** Those fed diets 1 and 2 containing 30 g fat/L had lower docosahexaenoic acid (DHA as g/100 g fatty acids) in liver (P < 0.001), plasma (P = 0.019) and adipose tissue (P = 0.045). However, piglets fed diets 1 and 3 had higher (P < 0.001) brain DHA than those fed diets with a higher (n-6):(n-3) ratio. **Higher plasma DHA was associated with less bone resorption (r = -0.44, P = 0.01).** Therefore, elevation of dietary (n-3) fatty acids supports growth and fatty acid status while not compromising bone mass. The results may be of relevance to the nutritional management of preterm infants whose DHA status is often too low and bone resorption too high.

Maturitas. 2002 May 20;42(1):13-22. Related Articles, Links

Polyunsaturated fatty acids. Is there a role in postmenopausal osteoporosis prevention?

Albertazzi P, Coupland K.

Centre for Metabolic Bone Disease, H. S Brocklehurst Building, Hull Royal Infirmary, 220-236 Anlaby Road, Hull, UK. p.albertazzi@medschool.hull.ac.uk

OBJECTIVE: To review the effect of a diet supplemented with polyunsaturated fatty acids (PUFA) on prevention or treatment of osteoporosis. METHODS: MEDLINE (1966-April 2001), Allied Complementary Medicine (1985-2001), Cochrane Library and Database of Systematic Reviews (1st Quarter 2001) was searched. Five reviews and no systematic reviews were found on this topic in the Cochrane Library. Eleven relevant in-vivo studies were identified on the effect of these compounds on bone. Eight were animal studies and three were randomised control trials (RCT) in human. RESULTS: There are two classes of PUFA designated as n-3 and n-6 with alpha-linolenic acid (ALA). These two different types of PUFA differently influence prostaglandin formation and hence modulate bone metabolism differently. These are several in vitro and animal data suggesting that diet with a low n-6/n-3 ratio may have beneficial effects on bone mineral density. Only three, short-term, small studies have been performed in human so far. Two studies, one performed with bone markers and one with bone density showed a positive effect of PUFA on bone. While a third study showed no effect. CONCLUSIONS: Preliminary, data have suggested that a diet with a low n-6/n-3 ratio may have beneficial effects on bone mineral density. Further studies are, however, required to fully assess the dose and type of PUFA to be used for optimum bone effects. This may be useful particularly for the prevention of disease in the elderly, since a diet rich in n-3 PUFA has been shown to have additional benefit on the cardiovascular, central nervous system and joints.

Clin Sci (Lond). 2002 Apr;102(4):403-9. Related Articles, Links

Fatty acids and cytokine mRNA expression in human osteoblastic cells: a specific effect of arachidonic acid.

Priante G, Bordin L, Musacchio E, Clari G, Baggio B. Department of Medical-Surgical Sciences, University of Padova, Via Giustiniani 2, 35128 Padua, Italy.

Epidemiological, clinical and experimental evidence suggests that fatty acids have a modulatory effect on bone metabolism in animals and humans. To investigate this hypothesis, we evaluated the effects of three different fatty acids, arachidonic acid (AA), eicosapentaenoic acid (EPA) and oleic acid (OA), on the expression of cytokines involved in bone remodelling. Cytokine mRNAs in the human osteoblast-like cell line MG-63 were quantified by reverse transcription-PCR. AA induced increased expression of interleukin-1alpha, interleukin-1beta, tumour necrosis factor-alpha and macrophage colony-stimulating factor mRNAs in a time- and dose-dependent manner. EPA and OA had no stimulatory effects, but instead caused a significant inhibition of AA-induced cytokine mRNA expression. Cell treatment with calphostin C, an inhibitor of protein kinase C (PKC), and cellular PKC down-regulation experiments independently resulted in significant inhibition of AA-induced cytokine expression, suggesting that a PKC-dependent mechanism accounts for the effects of AA on cytokine production. In conclusion, our study demonstrates specific effects of fatty acids on cytokine gene expression in human osteoblast-like cells. The clinical relevance of our findings requires further investigation.

Exp Biol Med (Maywood). 2001 Jun;226(6):485-97. Related Articles, Links

Omega-3 polyunsaturated fatty acids and skeletal health.

Watkins BA, Li Y, Lippman HE, Seifert MF.

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This minireview on skeletal biology describes the actions of prostaglandins and cytokines involved in the local regulation of bone metabolism, it documents the role of lipids in bone biology, and it presents relationships between fatty acids and other factors that impact skeletal metabolism. The data presented herein show consistent and reproducible beneficial effects of omega-3 (n-3) fatty acids on bone metabolism and bone/joint diseases. Polyunsaturated fatty acids modulate eicosanoid biosynthesis in numerous tissues and cell types, alter signal transduction, and influence gene expression. These effects have not been explored in the skeletal system. Future research on n-3 fatty acids in bone biology should focus on the following two aspects. First, the further elucidation of how n-3 fatty acids alter biochemical and molecular processes involved in bone modeling and bone cell differentiation, and second, the evaluation of the potential pharmaceutical applications of these nutraceutical fatty acids in maintaining bone mineral status and controlling inflammatory bone/joint diseases.

Altern Med Rev. 2001 Feb;6(1):61-77. Related Articles, Links

Can manipulation of the ratios of essential fatty acids slow the rapid rate of postmenopausal bone loss?

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The rapid rate of postmenopausal bone loss is mediated by the inflammatory cytokines interleukin-1, interleukin-6, and tumor necrosis factor alpha. Dietary supplementation with fish oil, flaxseeds, and flaxseed oil in animals and healthy humans significantly reduces cytokine production while concomitantly increasing calcium absorption, bone calcium, and bone density. Possibilities may exist for the therapeutic use of the omega-3 fatty acids, as supplements or in the diet, to blunt the increase of the inflammatory bone resorbing cytokines produced in the early postmenopausal years, in order to slow the rapid rate of postmenopausal bone loss. Evidence also points to the possible benefit of gamma-linolenic acid in preserving bone density.

Prog Lipid Res. 2001 Jan-Mar;40(1-2):125-48. Related Articles, Links

Bioactive fatty acids: role in bone biology and bone cell function.

Watkins BA, Lippman HE, Le Bouteiller L, Li Y, Seifert MF.

Department of Food Science, Lipid Chemistry and Molecular Biology Laboratory, Purdue University, 47907, West Lafayette, IN, USA

Bone is a unique tissue providing support, movement, and mineral balance for the body. Bone growth is achieved in the young by a process called modeling, and maintained during adulthood by a process termed remodeling. Three types of cells are responsible for the formation of cartilage and bone; the chondrocyte, osteoblast, and osteoclast. These cells are under the influence of a plethora of regulatory molecules, which govern their action to provide an individual optimal bone mass. Interruption of this homeostatic machinery, especially in the elderly, often results in a loss of bone mass (osteoporosis) or cartilage damage (rheumatoid arthritis). Many pharmacological agents have been made available in an effort to prevent or alleviate these pathologies, however, one vector often overlooked is the diet. This review focuses on the relationship between dietary polyunsaturated fatty acids and bone biology, both in vivo and in vitro.

J Cell Biochem. 2003 Oct 1;90(2):347-60.

Effects of long-term administration of N-3 polyunsaturated fatty acids (PUFA) and selective estrogen receptor modulator (SERM) derivatives in ovariectomized (OVX) mice.

Zeitlin L, Segev E, Fried A, Wientroub S.

Department of Pediatric Orthopaedics, Dana Children's Hospital, Tel Aviv Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Israel.

We studied the beneficial effects of dietary consumption of n-3 polyunsaturated fatty acids (PUFA) and two selective estrogen receptor modulator (SERM) derivatives (SERM-I and SERM-II) and their combined effect on serum lipids, skin dermis and adipose layers, bone marrow adipogenesis, and cytokine secretion in mice. Two different ovariectomized (OVX) models were studied: treatment began immediately post-OVX in one and 3 months post-OVX in the other. Our results showed that n-3 PUFA and both SERMs decreased triglyceride levels in the serum, and that SERMs also decreased serum cholesterol levels while n-3 PUFA had no similar effect. SERMs had no effect on IL-6, IL-1 beta, or IL-10 levels, but they decreased ex vivo tumor necrosis factor (TNF-alpha). N-3 PUFA decreased secretion of non-induced IL-6 and TNF-alpha from cultured BMC and IL-1 beta levels in vivo (i.e., in bone marrow plasma), but its main effect was a significant elevation in the secretion of IL-10, a known anti-inflammatory cytokine. OVX-induced B-lymphopoiesis was not affected by LY-139481 (SERM-I) while LY-353381 (SERM-II) exhibited an estrogen-antagonistic effect in sham and OVX mice and elevated the amount of B-cells in bone marrow. Fish oil consumption prevented the elevation in B-lymphopoiesis caused by OVX, but had no curative effect on established augmented B-lymphopoiesis. This activity could be mediated via the elevation of IL-10 which was shown to suppress B-lymphopoiesis. Both SERMs and n-3 PUFA inhibited the increase in adipose tissue thickness caused by OVX in mice. Our results showed that n-3 PUFA, could prevent some of the deleterious outcomes of estrogen deficiency that were not affected by SERMs. We observed no significant beneficial effects of the combined administration of SERM-I, SERM-II, and PUFA on the studied parameters.The exact mechanism by which polyunsaturated fatty acids exert their activities is still not clear, but peroxisome proliferator-activated receptors (PPARs) might be involved in processes which are modulated by n-3 PUFA. J. Cell. Biochem. 90: 347-360, 2003.

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J Nutr. 2000 Sep;130(9):2274-84. Related Articles, Links

Dietary ratio of (n-6)/(n-3) polyunsaturated fatty acids alters the fatty acid composition of bone compartments and biomarkers of bone formation in rats.

Watkins BA, Li Y, Allen KG, Hoffmann WE, Seifert MF.

Department of Food Science, Lipid Chemistry and Molecular Biology Laboratory, Purdue University, West Lafayette, IN 47907, USA.

The effects of dietary polyunsaturated fatty acids (PUFA) on ex vivo bone prostaglandin E(2) (PGE(2)) production and bone formation rate were evaluated in rats. Weanling male Sprague-Dawley rats were fed AIN-93G diet containing 70 g/kg of added fat for 42 d. The dietary lipid treatments were formulated with safflower oil and menhaden oil to provide the following ratios of (n-6)/(n-3) fatty acids: 23.8 (SMI), 9.8 (SMII), 2.6 (SMIII), and 1.2 (SMIV). Ex vivo PGE(2) production in liver homogenates and bone organ cultures (right femur and tibia) were significantly lower in rats fed diets with a lower dietary ratio of (n-6)/(n-3) fatty acids than in those fed diets with a higher dietary ratio. Regression analysis revealed a significant positive correlation between bone PGE(2) and the ratio of arachidonic acid (AA)/eicosapentaenoic acid (EPA), but significant negative correlations between bone formation rate and either the ratio of AA/EPA or PGE(2) in bone. Activities of serum alkaline phosphatase isoenzymes, including the bone-specific isoenzyme (BALP), were greater in rats fed a diet high in (n-3) or a low ratio of (n-6)/(n-3), further supporting the positive action of (n-3) fatty acids on bone formation. These results demonstrated that the dietary ratio of (n-6)/(n-3) modulates bone PGE(2) production and the activity of serum BALP in growing rats.

Clin Nutr. 2000 Aug;19(4):271-6. Related Articles, Links

Serum fatty acid imbalance in bone loss: example with periodontal disease.

Requirand P, Gibert P, Tramini P, Cristol JP, Descomps B.

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Among the numerous factors of bone remodelling, the local action of arachidonic acid metabolites together with cytokines, is particularly important, especially that of prostaglandin PGE2. It has been suggested that the alveolar bone destruction in periodontal disease and osteoporosis can be treated by reducing the ratio of arachidonic acid in phospholipids, which would diminish prostaglandin production. The aim of this study was to evaluate the main serum polyunsaturated fatty acids and a possible alteration in the level of arachidonic acid in patients suffering from periodontal bone loss. Of the 105 patients who participated the study, 78 were suffering from periodontal bone loss and 27 served as a control group. The fatty acids were measured in serum by gas-chromatography. The results showed that the level of fatty acids of the n-6 pathway was higher in our patients with bone loss than in the control group, whereas the reverse was observed with fatty acids of the n-3 pathway. In conclusion, our patients' bone losses are linked with an imbalance between n-6 and n-3 fatty acids, which seems to justify a diet increase in 20- and 22-carbon fatty acids.

Proc Soc Exp Biol Med. 2000 Jan;223(1):88-95. Related Articles, Links

Omega-3 fatty acids enhance ligament fibroblast collagen formation in association with changes in interleukin-6 production.

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Altering dietary ratios of n-3 and n-6 polyunsaturated fatty acids (PUFA) represents an effective nonpharmaceutical means to improve systemic inflammatory conditions. An effect of PUFA on cartilage and bone formation has been demonstrated, and the purpose of this study was to determine the potential of PUFA modulation to improve ligament healing. The effects of n-3 and n-6 PUFA on the in vitro healing response of medial collateral ligament (MCL) fibroblasts were investigated by studying the cellular coverage of an in vitro wound and the production of collagen, PGE2, IL-1, IL-6, and TNF. Cells were exposed to a bovine serum albumin (BSA) control or either eicosapentaenoic acid (EPA, 20:5n-3) or arachidonic acid (AA, 20:4n-6) in the form of soaps loaded onto BSA for 4 days and wounded on Day 5. AA and EPA improved the healing of an in vitro wound over 72 hr. EPA increased collagen synthesis and the overall percentage of collagen produced, but AA reduced collagen production and total protein. PGE2 production was increased in the AA-treated group and decreased in the EPA-treated group, but was not affected by wounding. IL-1 was not produced at the time point evaluated, but TNF and IL-6 were both produced, and their levels varied relative to the PUFA or wounding treatment. There was a significant linear correlation ($r2 = 0.57$, $P = 0.0045$) between IL-6 level and collagen production. These results demonstrate that n-3 PUFA (represented by EPA in this study) positively affect the healing characteristics of MCL cells and therefore may represent a possible noninvasive treatment to improve ligament healing. Additionally, these results show that MCL fibroblasts produce PGE2, IL-6, and TNF and that IL-6 production is related to MCL collagen synthesis.

Angle Orthod. 1999 Aug;69(4):365-71. Related Articles, Links

Influence of dietary n-3 polyunsaturated fatty acid on experimental tooth movement in rats.

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This study was conducted to investigate the influence of dietary n-3 polyunsaturated fatty acid on experimental tooth movement. This acid substantially reduces the production of arachidonic acid. Sixty 4-week-old male Wistar strain rats were divided into experimental and control groups. Animals in the experimental group were fed a purified diet containing 10% refined fish oil (rich in n-3 fatty acid); control animals were fed a diet containing 10% corn oil (rich in n-6 fatty acid). After 6 weeks, the maxillary first molars were moved buccally with an initial force of 20 g for periods of 0, 3, 7, or 14 days. Tooth movement in the experimental group was 80% of that seen in the controls. The number of osteoclasts on the pressure side during tooth movement was nearly 60% of that seen in controls, and the degree of bone resorption was 80%. The data suggest that a diet enriched with fish oil reduces osteoclastic activity and subsequent alveolar bone resorption that is the key to experimental tooth movement.

Aging (Milano). 1998 Oct;10(5):385-94. Related Articles, Links

Calcium, gamma-linolenic acid and eicosapentaenoic acid supplementation in senile osteoporosis.

Kruger MC, Coetzer H, de Winter R, Gericke G, van Papendorp DH.

Department of Physiology, University of Pretoria, South Africa.

Recent animal work suggests that gamma-linolenic acid (GLA) and eicosapentaenoic acid (EPA) enhance calcium absorption, reduce excretion and increase calcium deposition in bone. A pilot study was set up to test the interactions between calcium and GLA + EPA in humans. Sixty-five women (mean age 79.5), taking a background diet low in calcium, were randomly assigned to GLA + EPA or coconut oil placebo capsules; in addition, all received 600 mg/day calcium as the carbonate. Markers of bone formation/degradation and bone mineral density (BMD) were measured at baseline, 6, 12 and 18 months. Twenty-one patients were continued on treatment for a second period of 18 months, after which BMD (36 months) was measured. At 18 months, osteocalcin and deoxypyridinoline levels fell significantly in both groups, indicating a decrease in bone turnover, whereas bone specific alkaline phosphatase rose indicating beneficial effects of calcium given to all the patients. Lumbar and femoral BMD, in contrast, showed different effects in the two groups. Over the first 18 months, lumbar spine density remained the same in the treatment group, but decreased 3.2% in the placebo group. Femoral bone density increased 1.3% in the treatment group, but decreased 2.1% in the placebo group. During the second period of 18 months with all patients now on active treatment, lumbar spine density increased 3.1% in patients who remained on active treatment, and 2.3% in patients who switched from placebo to active treatment; femoral BMD in the latter group showed an increase of 4.7%. This pilot controlled study suggests that GLA and EPA have beneficial effects on bone in this group of elderly patients, and that they are safe to administer for prolonged periods of time.

Lipids. 1997 Mar;32(3):293-302. Related Articles, Links

Incorporation of long-chain n-3 fatty acids in tissues and enhanced bone marrow cellularity with docosahexaenoic acid feeding in post-weanling Fischer 344 rats.

Atkinson TG, Barker HJ, Meckling-Gill KA.

Department of Human Biology and Nutritional Sciences, University of Guelph, Ontario, Canada.

We wanted to examine the effects of an oil rich in docosahexaenoic acid (DHA), without eicosapentaenoic acid, on the composition of membrane phospholipid in a variety of tissues. Our in vitro studies had previously shown that DHA could modify glucose and nucleoside transport in cells in culture and also increase selectivity of the nucleoside drug, arabinosylcytosine (araC) toward tumor cells. Here we wanted to examine what effect DHA supplementation would have in the whole animal in terms of the chemosensitivity of normal bone marrow, the dose-limiting tissue during chemotherapy, to araC. The purpose was to determine whether fatty acid supplementation might be useful as an adjuvant to chemotherapy. We fed diets containing 5% (w/w) low fat-corn oil (LF-CO group), 10% moderate fat-safflower oil (MF-SO group), or 10% DHASCO (MF-DHA group) to weanling Fischer 344 rats for 8-9 wk. Feed intake and growth were not different between the different diets. Similarly, treatment of animals with the chemotherapeutic drug araC did not differentially affect growth, feed intake, or tissue fatty acid composition for the different diet groups. Fatty acid compositions of bone marrow, liver, red blood cells, plasma phospholipid and triglyceride, as well as skeletal and cardiac muscle, were substantially different between the dietary groups. The DHASCO oil contained 46% DHA (22:6n-3) and resulted in profound incorporation of DHA in all tissues examined. The most dramatic response was seen in skeletal muscle of MF-DHA fed animals where DHA represented 46% of membrane phospholipid fatty acids. This is likely to have consequences to muscle function. Although DHASCO contains a similar level of saturated fatty acids (42%), few differences in saturates were noted between the various dietary groups for most of the tissues examined. Both LF-CO and MF-SO diets were hypercholesterolemic, and the LF-CO was also hypertriglyceridemic compared to the chow-fed animals. Animals fed the MF-DHA diet had the lowest triglyceride levels of any of the treatment groups and cholesterol levels comparable to chow-fed animals. MF-DHA had substantially higher numbers of colony-forming units-granulocyte macrophage (CFU-GM) as reflected in a twofold higher bone marrow cellularity than either chow or LF-CO animals, suggesting expansion of the bone marrow compartment with DHA feeding. Although higher than LF-SO, the number of CFU-GM in MF-SO animals was not significantly higher than animals fed chow. Bone marrow from LF-CO animals appeared to be more resistant to araC treatment than either MF group. Thus, DHA, fed as DHASCO, has advantages over low or moderate n-6 diets and chow as it is has both hypolipidemic- and bone marrow-enhancing properties in weanling Fischer 344 rats. This suggests that DHA supplementation may be useful in adjuvant chemotherapy.

Diabetes Res Clin Pract. 1995 Oct;30(1):37-42. Related Articles, Links

Effect of eicosapentaenoic acid and docosahexaenoic acid on diabetic osteopenia.

Yamada Y, Fushimi H, Inoue T, Matsuyama Y, Kameyama M, Minami T, Okazaki Y, Noguchi Y, Kasama T.

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To evaluate the effect of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are polyunsaturated fatty acids, on diabetic osteopenia, we measured the bone fragility in streptozotocin-induced diabetic rats. The fragility of femur was increased in diabetic rats, which was prevented in part by EPA or DHA. Moreover, EPA prevented osteopenia even in diabetic rats fed a low zinc feed, which was a potent accelerator of diabetic osteopenia. Plasma alkaline phosphatase activity and parathyroid hormone level showed no difference between the two groups of diabetic rats with or without EPA. Urinary excretion of calcium and phosphate was increased and plasma inorganic phosphate level was high in diabetic rats, suggesting severe mineral loss. In diabetic rats fed EPA, although urinary and plasma calcium levels did not change significantly, urinary phosphate excretion and plasma inorganic phosphate concentration were slightly lowered, which suggested that EPA may have an effect in suppressing phosphate release from bones in diabetic rats. These data suggest that EPA and DHA could be effective on diabetic osteopenia, but to elucidate the precise mechanisms, further examinations will be needed.

Prostaglandins Leukot Essent Fatty Acids. 1995 Jul;53(1):13-9. Related Articles, Links

The effect of different n-6/n-3 essential fatty acid ratios on calcium balance and bone in rats.

Claassen N, Coetzer H, Steinmann CM, Kruger MC.

Department of Physiology, Faculty of Medicine, University of Pretoria, South Africa.

Prostaglandins (PGs) are known to have various effects on bone metabolism. The supplementation of essential fatty acids (EFAs), the precursors of PGs, leads to increased intestinal calcium absorption and calcium balance. It is, however, not known whether increased calcium absorption and calcium balance will enhance the calcium content in bone. Male Sprague-Dawley rats (n = 40) aged 5-12 weeks were supplemented with EFAs. The main dietary EFAs, linoleic acid (LA) and alpha-linolenic acid (ALA) were administered in a ratio of 3:1 as a control group. The conversion of LA to ALA to the PG precursors is slow, with the first step, delta-6-desaturation being rate limiting. Fatty acids beyond this rate-limiting step, gamma-linolenic acid (GLA, n-6) and eicoapentaenioc acid (EPA, n-3), were administered to different groups in the ratios 3:1, 1:1 and 1:3 to explore the impact of different ratios of n-6 and n-3 EFAs. Intestinal calcium absorption (mg/24 h) increased by 41.5% in the 3:1 supplemented group, compared with the control group. The decrease in urinary calcium (mg/24 h) correlated with the increase in n-3 level. The calcium balance (mg/24 h) and bone calcium (mg/g bone ash) increased significantly in the 3:1 (41.5% and 24.7%) group, compared with the control. The increase in bone calcium might be attributed to an EFA-induced increase in circulating PGs. An increased synthesis of PGs acting on target bone cells, as well as changes in membrane fluidity, may underlie these observations

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Bone. 1995 Apr;16(4 Suppl):385S-392S. Related Articles, Links

Supplemented gamma-linolenic acid and eicosapentaenoic acid influence bone status in young male rats: effects on free urinary collagen crosslinks, total urinary hydroxyproline, and bone calcium content.

Claassen N, Potgieter HC, Seppa M, Vermaak WJ, Coetzer H, Van Papendorp DH, Kruger MC.

Department of Physiology, Faculty of Medicine, University of Pretoria, Republic of South Africa.

The effect of different ratios of the prostaglandin precursors gamma-linolenic (GLA) and eicosapentaenoic (EPA) acids on bone status in growing rats measured as a function of free urinary pyridinium crosslinks and hydroxyproline levels was investigated. Male Sprague-Dawley rats were weaned onto an essential fatty acid deficient diet and from their fifth week, different groups of rats received a balanced, semisynthetic diet, supplemented with different ratios of GLA:EPA supplied as a mixture of evening primrose oil (EPO) and fish oil (FO). Controls were supplemented with linoleic (LA; sunflower oil) and alpha-linolenic (ALA; linseed oil) acids (3:1) or a commercially available rat chow. Animals were terminated at 84 days and femur length, ash weight, calcium content, free urinary pyridinium crosslinks (Pyd and Dpyd), total hydroxyproline (Hyp), and creatinine levels measured. Free urinary Pyd and Dpyd are good indicators of bone status and they correlated well with Hyp. Pyd and Dpyd excretion were significantly decreased in the higher GLA:EPA dietary groups and correlated well (r = 0.7) with Hyp levels. Concomitantly, bone calcium content increased significantly in the same dietary groups.

These results suggest that diet supplementation with relatively high GLA:EPA ratios are more effective in inhibiting bone resorption than LA:ALA.

Prostaglandins Leukot Essent Fatty Acids. 1994 Feb;50(2):81-4. Related Articles, Links

Eicosapentaenoic acid inhibits bone loss due to ovariectomy in rats.

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Section of Physiological Chemistry, Graduate School, Tokyo Medical and Dental University, Japan.

Eicosapentaenoic acid (EPA), one of the polyunsaturated fatty acids, is well-known to have a wide variety of beneficial biological functions. In the present work we demonstrate another new beneficial effect of EPA on bone metabolism in vivo. Ovariectomized rats were divided into 4 groups under the same calorie intake condition; (1) normal diet, (2) low calcium diet (1.5 mg/day), (3) EPA-enriched diet (160 mg/day/kg), (4) EPA-enriched and low calcium diet. These diets were continued for 35 consecutive days. The bone weight of the femora and tibiae decreased significantly in the low calcium group, but the decrease was inhibited in the EPA-low calcium group. Moreover, in the rupture test, which indicates bone strength, the femora in the low calcium group were easier to break than in the normal calcium diet groups. In the EPA-low calcium group the strength of the bone was equivalent to that in the normal diet group. These results suggest that an EPA-enriched diet prevents the loss of bone weight and strength caused by oestrogen deficiency or inadequate nutrition. There is a possibility that EPA could be developed to be a novel anti-osteoporosis drug.

Modulatory effect of omega-3 polyunsaturated fatty acids on osteoblast function and bone metabolism.

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Recent investigations indicate that the type and amount of polyunsaturated fatty acids (PUFA) influence bone formation in animal models and osteoblastic cell functions in culture. In growing rats, supplementing the diet with omega-3 PUFA results in greater bone formation rates and moderates ex vivo prostaglandin E(2) production in bone organ cultures. A protective effect of omega-3 PUFA on minimizing bone mineral loss in ovariectomized rats has also been reported. The actions of omega-3 fatty acids on bone formation appear to be linked to altering osteoblast functions. Herein we describe experiments with MC3T3-E1 osteoblast-like cells that support findings in vivo where omega-3 PUFA modulated COX-2 protein expression, reduced prostaglandin E(2) production, and increased alkaline phosphatase activity. Other studies indicate that the dietary source of PUFA may affect protein expression of Cbfa1 and nodule formation in fetal rat calvarial cells.

Biochem Biophys Res Commun. 2003 Jan 24;300(4):957-64. Related Articles, Links

Role of prostaglandin E produced by osteoblasts in osteolysis due to bone metastasis.

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Prostaglandin E2 (PGE2) is produced in bone mainly by osteoblasts and stimulates bone resorption. Osteolytic bone metastasis of cancers is accompanied by bone resorption. In this study, we examined the roles of PGE2 in osteolysis due to bone metastasis of breast cancer. Injection of human breast cancer cells, MDA-MB-231 (MDA-231), into nude mice causes severe osteolysis in the femur and tibia. The expression of cyclo-oxygenase-2 (COX-2) and the receptor activator of NF-kappaB ligand (RANKL), a key molecule in osteoclast differentiation, mRNAs was markedly elevated in bone with metastasis. When MDA-231 cells were cocultured with mouse calvaria, COX-2-induced PGE2 production and bone resorption progressed. The contact with MDA-231 cells could induce the expression of COX-2 and RANKL in osteoblasts by mechanisms involving MAP kinase and NF-kappaB. The blockage of PGE2 signal by indomethacin and EP4 antagonist abrogated the osteoclast formation induced by the breast cancer cells. Here, we show a PGE-dependent mechanism of osteolysis due to bone metastasis.

Prostaglandins. 1989 May;37(5):615-25. Related Articles, Links

Effects of prostaglandin E3 and eicosapentaenoic acid on rat bone in organ culture.

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To assess the possibility that diets rich in eicosapentaenoic acid (EPA) could have adverse effects on the skeleton, we examined the resorptive response to its major project, PGE3, and the effects and metabolism of EPA itself in cultured fetal rat long bones and neonatal rat calvaria. PGE3 stimulated bone resorption with a potency similar to that of PGE2. However, EPA was a much less effective precursor for PGE3 than was arachidonic acid (AA) for PGE2. In bones cultured with complement sufficient rabbit serum, which stimulates endogenous PGE release, addition of EPA had little effect on bone resorption while AA produced a substantial increase. Bones labeled with [3H]-AA and incubated with transforming growth factor-alpha (TGF-alpha), which stimulates endogenous PGE production, produced substantial amounts of PGE2, while bones labeled with [3H]-EPA and treated similarly produced less than 1/10th as much labeled PGE3. Thus, EPA appears to be a less effective precursor for the production of bone resorbing prostanoids than AA in cultured rat bone. However, since PGE3 is a potent stimulator of bone resorption, the possibility that dietary EPA can effect the production of bone resorbing prostanoids in man requires further study

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Nutritional and biochemical aspects of the hypolipidemic action of rice bran oil: a review.

Author: Rukmini C; Raghuram TC
Address: National Institute of Nutrition, Indian Council of Medical Research, Hyderabad.
Source: J Am Coll Nutr, 10(6):593-601 1991 Dec

In this paper, we review the effects of rice bran oil (RBO), an unconventional oil recently introduced onto the Indian market for human use.

RBO contains oleic acid (38.4%), linoleic acid (34.4%), and **linolenic** acid (2.2%) as unsaturated fatty acids, and palmitic (21.5%) and stearic (2.9%) acids as saturated fatty acids.

The unsaponifiable fraction (4.2%) has total tocopherols (81.3 mg%), gamma-oryzanol (1.6%), and squalene (320 mg%).

Oryzanol is a mixture of Ferulic acid esters of triterpene alcohols such as Cycloartenol (CA) (106 mg%) and 24-methylene Cycloartanol (494 mg%).

Studies on experimental rats demonstrated a hypolipidemic effect of RBO. The unsaponifiable fraction of RBO lowers cholesterol levels.
Feeding phytosterols, CA, and 24-methylene cycloartanol in amounts present in RBO to hypercholesterolemic rats for 8 weeks indicates that CA alone reduces cholesterol and triglyceride levels significantly.
Endogenous sterol excretion increases in animals given CA.
The accumulation of CA in the liver inhibits cholesterol esterase activity, which in turn leads to reduction in circulating cholesterol levels. **Cycloartenol is structurally similar to cholesterol and may compete with the binding sites of cholesterol and sequestrate cholesterol,** which is metabolized to its derivatives.

RBO, which is rich in tocopherols and tocotrienols, may improve oxidative stability. **Tocotrienols inhibit HMG CoA reductase, resulting in hypocholesterolemia.** The hypolipidemic effect of RBO has also been established in human subjects. Thus, RBO could be a suitable edible oil for patients with hyperlipidemia.

Phytother Res 2001 Jun;15(4):277-89

Atherosclerosis and Dysmetabolic Disease Study Center 'G. Descovich', Clinical Medicine and Applied Biotechnology Dept. 'D. Campanacci', University of Bologna, Italy.
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Diet is the first (and sometimes the only) therapeutic approach to hyperlipoproteinaemias.

Rice bran oil and its main components (unsaturated fatty acids, triterpene alcohols, phytosterols, tocotrienols, alpha-tocopherol) have demonstrated an ability to improve the plasma lipid pattern of rodents, rabbits, non-human primates and humans, reducing total plasma cholesterol and triglyceride concentration and increasing the high density lipoprotein cholesterol level.
Other potential properties of rice bran oil and gamma-oryzanol, studied both in vitro and in animal models, include modulation of pituitary secretion, inhibition of gastric acid secretion, antioxidant action and inhibition of platelet aggregation.
This paper reviews the available data on the pharmacology and toxicology of rice bran oil and its main components with particular attention to those studies relating to plasma lipid altering effects. Copyright 2001 John Wiley & Sons, Ltd.

Title: Effects of gamma-oryzanol on serum lipids and apolipoproteins in dyslipidemic schizophrenics receiving major tranquilizers.

Author: Sasaki J; Takada Y; Handa K; Kusuda M; Tanabe Y; Matsunaga A; Arakawa K
Address: Department of Internal Medicine, School of Medicine, Fukuoka University, Japan.

Source: Clin Ther, 12(3):263-8 1990 May-Jun

The subjects were 20 chronic schizophrenic patients with dyslipidemia (total cholesterol levels greater than or equal to 220 mg/dl, triglycerides greater than or equal to 150 mg/dl, or high-density lipoprotein cholesterol less than or equal to 40 mg/dl) who had been receiving neuroleptics for a mean of ten years. Each patient was given 100 mg of gamma-oryzanol three times daily for 16 weeks.
Total cholesterol decreased, from 204 at baseline to 176 mg/dl at week 12.
Low-density lipoprotein cholesterol level decreased significantly from 124 mg/dl at baseline to 101 mg/dl at week 12.
High-density lipoprotein cholesterol levels were 36.1 mg/dl at baseline and 35.9 mg/dl at week 12.
Apolipoprotein (apo) B levels decreased significantly from 116 mg/dl to 101 mg/dl at week 16;
Apo A-II levels increased significantly from 31.7 mg/dl to 34.7 mg/dl;
Apo B/apo A-I ratio declined significantly from 0.99 to 0.84.
No treatment side effects were recorded. It is concluded that gamma-oryzanol is safe and effective in the treatment of dyslipidemia.

Current Therapeutic Res. 45(4),543-552 (1989)

Effects of gamma-Orizanol on Hyperlipidemic Subjects

Yoshino, G., Kazuni, T., Amano, M. Takeiwa, M., Yamasaki, T.

The hypocholesterolemic effect of gamma oryzanol was investigated in 67 patients with hyperlipidemia: 35 (WHO type IIa), 19 (IIb), 13 (IV).
300 mg of gamma Oryzanol were administered daily for 3 months.
In type IIa and IIb patients, plasma cholesterol (251 ± 7 and 268 ± 8 mg/dl, respectively) significantly decreased from the second month (8% and 12% respectively; $P<0.001$)
The mean plasma triglyceride levels of all subjects decreased significantly after three months
($p< 0.05$).
HDL-Cho lipoprotein was also significantly elevated in the type IIb subjects after three months.
The reduction in plasma-cholesterol was attributable to the decrease in LDL-Cho lipoprotein in the type IIa and IIb subjects.
Thus a mild but significant hypocholesterolemic effect of gamma-oryzanol was observed.
Together with a long term history of clinical use, this indicates the potential use of this drug as a treatment of first choice for mild hypercholesterolemia.

ATTIVITA' **ANTI-TUMORALE** DELL' **ALA-OMEGA-3**

Maggiori informazioni sono disponibili alle pagine seguenti:

Gli acidi grassi Omega-3, come l'acido alfa-Linolenico (ALA) e l'EPA, sono noti come agenti preventivi ed anticachettici.

Si ritiene che ciò sia dovuto a:
- azione inibitoria degli Omega 3 nei confronti della trasformazione dell'acido LA-Omega 6 in sostanze mitogene, come l'acido13-idrossioctadecadienoico (13-HODE).
- ostacolando l'attecchimento di cellule cancerogene ai tessuti sani e quindi l'invasività dei tumori.
- producendo dei composti perossidati che inibiscono la crescita cellulare e potenziano l'effetto di alcuni chemioterapici, (tassolo e cisplatino)

La relazione con gli acidi grassi Omega 6, rende evidente l'importanza di un'assunzione bilanciata degli acidi grassi essenziali Omega-3 ed Omega-6.

In tre studi francesi su 632 donne, e in un più recente studio americano su 1120 donne è stata evidenziata una netta riduzione dell'incidenza del carcinoma mammario (-50/64%) in relazione all'aumento del contenuto di acidi grassi Omega 3 nel tessuto adiposo. (rapporto Omega 3/Omega 6 1:3 equivalente ad una dieta con 2,5 gr ALA-Omega 3 e 7,5 gr Omega 6, facilmente praticabile con VitalOil)

Studi su modelli evidenziano un effetto potenziante della Melatonina associata all'acido ALA-Omega 3 fornito ad un rapporto Omega-3 : Omega-6 di circa 1:1 e di potenziamento dell'effetto del tassolo.

Molto frequentemente la comune dieta apporta 0,6-0,8 gr di ALA-Omega 3 ed il rapporto Omega 3/Omega 6 è prossimo all'1:10. VitalOil fornisce un rapporto ALA-Omega 3/LA-Omega 6 di 1:1 . Desiderando si può personalizzare la formula giungendo fino ad un rapporto Omega 3:Omega 6 di 3:2 , con la massima stabilità e mantenendo una buona palatabilità.

Cancer Res 2000 Sep 15;60(18):5289-95

Mechanism for the antitumor and anticachectic effects of n-3 fatty acids.

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Dietary intake of the n-6 fatty acid (FA) linoleic acid (LA) has a strong growth-promoting effect on many rodent tumors and human tumor xenografts grown in immunodeficient rodents. n-3 FAs such as alpha-linolenic and eicosapentaenoic acids (EPAs), which differ from LA and arachidonic acid, respectively, by only a single double bond in the n-3 position, are recognized cancer chemopreventive and anticachectic agents. Understanding how this seemingly small structural difference leads to such remarkable functional differences has been a challenge. In a previous study, we showed that LA uptake, [3H]thymidine incorporation into DNA, and total DNA content were decreased in tissue-isolated hepatoma 7288CTC perfused in situ with arterial blood containing alpha-linolenic acid, EPA, or docosahexaenoic acids. The Ki for the inhibition of LA uptake and [3H]thymidine incorporation by alpha-linolenic acid was 0.18 and 0.25 mM, respectively. Here we show that the addition of alpha-linolenic acid or EPA to arterial blood inhibits tumor FA uptake, including LA, and the subsequent conversion of LA to the mitogen 13-hydroxyoctadecadienoic acid (13-HODE) in vivo and during perfusion in situ.

[3H]Thymidine incorporation during perfusion in situ was also inhibited. Addition of 13-HODE to the arterial blood reversed the inhibition of [3H]thymidine incorporation but had no effect on FA uptake. These two n-3 FAs also inhibited FA transport in inguinal fat pads in vivo and during perfusion in situ in fed (FA uptake) and fasted (FA release) rats. The effects of EPA and talinolenic acid on transport of saturated, monounsaturated, and n-6 polyunsaturated FAs in hepatoma 7288CTC and inguinal fat pads during perfusion in situ were reversed by the addition of forskolin (1 microM), pertussis toxin (0.5 microg/ml), or 8-bromo-cyclic AMP (10 microM) to the arterial blood. We conclude that the antitumor and anticachectic effects of n-3 FAs on hepatoma 7288CTC and inguinal fat pads in vivo result from an inhibition of FA transport. These inhibitions are mediated by a putative n-3 FA receptor via a Gi protein-coupled signal transduction pathway that decreases intracellular cyclic AMP. **A specific decrease in LA uptake and its conversion to the mitogen 13-HODE causes the tumor growth inhibition.**

J Nutr. 2003 May;133(5):1409-14. Related Articles, Links

Dietary (n-3)/(n-6) fatty acid ratio: possible relationship to premenopausal but not postmenopausal breast cancer risk in U.S. women.

Goodstine SL, Zheng T, Holford TR, Ward BA, Carter D, Owens PH, Mayne ST.

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Recent research has suggested that an increased (n-3) fatty acid intake and/or increased (n-3)/(n-6) polyunsaturated fatty acid (PUFA) ratio in the diet is associated with a lower breast cancer risk. This case-control study investigated the association between intake of (n-3) and other fatty acids and the (n-3)/(n-6) PUFA ratio and breast cancer risk. After combining data from two related case-control studies in Connecticut, we had information available on a total of 1119 women (565 cases and 554 controls). Cases were all histologically confirmed, incident breast carcinoma patients. Controls were hospital-based (Yale-New Haven Hospital study site) and population-based (Tolland County study site). Information on dietary intake was obtained through a validated food-frequency questionnaire. Standard multivariate methods were used to address the independent effects of specific fatty acids, fat classes and macronutrients on breast cancer risk. In the full study population, there were no significant trends for any macronutrient/fatty acid when comparing the highest to the lowest quartile of intake.

When the analysis was restricted to premenopausal women, consumption of the highest compared with the lowest quartile of the (n-3)/(n-6) PUFA ratio was associated with a nonsignificant **41% lower risk of breast cancer** [odds ratio (OR) = 0.59, 95% confidence interval (CI) 0.29, 1.19, P for trend = 0.09].

A higher (n-3)/(n-6) PUFA ratio was significantly associated with a lower risk of breast cancer when the data were restricted to the Tolland County (population-based) study site; OR = 0.50, 95% CI 0.27, 0.95, P for trend = 0.02.

These results are consistent with the hypothesis that a higher (n-3)/(n-6) PUFA ratio may reduce the risk of breast cancer, especially in premenopausal women.

nt J Cancer 2002 Mar 1;98(1):78-83

N-3 and N-6 fatty acids in breast adipose tissue and relative risk of breast cancer in a case-control study in Tours, France.

Maillard V, Bougnoux P, Ferrari P, Jourdan ML, Pinault M, Lavillonniere F, Body G, Le Floch O, Chajes V.

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Experimental studies have indicated that n-3 fatty acids, including alpha-linolenic acid (18:3 n-3) and long-chain n-3 polyunsaturated fatty acids inhibit mammary tumor growth and metastasis. Earlier epidemiological studies have given inconclusive results about a potential protective effect of dietary n-3 polyunsaturated fatty acids on breast cancer risk, possibly because of methodological issues inherent to nutritional epidemiology. To evaluate the hypothesis that n-3 fatty acids protect against breast cancer, we examined the fatty acid composition in adipose tissue from 241 patients with invasive, nonmetastatic breast carcinoma and from 88 patients with benign breast disease, in a case-control study in Tours, central France. Fatty acid composition in breast adipose tissue was used as a qualitative biomarker of past dietary intake of fatty acids. Biopsies of adipose tissue were obtained at the time of surgery. Individual fatty acids were measured as a percentage of total fatty acids, using capillary gas chromatography. Unconditional logistic regression modeling was used to obtain odds ratio estimates while adjusting for age, height, menopausal status and body mass index. We found inverse associations between breast cancer-risk and n-3 fatty acid levels in breast adipose tissue. **Women in the highest tertile of alpha-linolenic acid (18:3 n-3) had an odds ratio of 0.39 (95% confidence intervals [CI] = 0.19-0.78) compared to women in the lowest tertile (trend p = 0.01).** In a similar way, women in the highest tertile of docosahexaenoic acid (22:6 n-3) had an odds ratio of 0.31 (95% CI = 0.13-0.75) compared to women in the lowest tertile (trend p = 0.016). Women in the highest tertile of the long-chain n-3/total n-6 ratio had an odds ratio of 0.33 (95% confidence interval = 0.17-0.66) compared to women in the lowest tertile (trend p = 0.0002). In conclusion, our data based on fatty acids levels in breast adipose tissue suggest a protective effect of n-3 fatty acids on breast cancer risk and support the hypothesis that the balance between n-3 and n-6 fatty acids plays a role in breast cancer.

Eur J Cancer 2001 Feb;37(3):402-13

Effects of gamma-linolenic acid and oleic acid on paclitaxel cytotoxicity in human breast cancer cells.

Menendez JA, del Mar Barbacid M, Montero S, Sevilla E, Escrich E, Solanas M, Cortes-Funes H, Colomer R.

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It has been suggested that dietary interventions may improve the effectiveness of cancer chemotherapy. We have examined the combined in vitro cytotoxicity of paclitaxel and the fatty acids gamma-linolenic acid (GLA, 18:3n-6) and oleic acid (OA, 18:1n-9) in human breast carcinoma MDA-MB-231 cells. The effect of fatty acids on paclitaxel chemosensitivity was determined by comparing IC(50) and

IC(70) (50 and 70% inhibitory concentrations, respectively) obtained when the cells were exposed to IC(50) and IC(70) levels of paclitaxel alone and fatty acids were supplemented either before or during the exposure to paclitaxel. The 3-4,5-dimethylthiazol-2-yl-2,5-diphenyl-tetrazolium bromide (MTT) assay was used to determine cell growth inhibition. GLA by itself showed antiproliferative effects, and a possible GLA-paclitaxel interaction at the cellular level was assessed by the isobologram and the combination-index (CI) methods. Isobole analysis at the isoeffect levels of 50 and 70% revealed that drug interaction was predominantly synergistic when GLA and paclitaxel were added concurrently for 24 h to the cell cultures. Interaction assessment using the median-effect principle and the combination-index (CI) method showed that exposure of MDA-MB-231 cells to an equimolar combination of concurrent GLA plus paclitaxel for 24 h resulted in a moderate synergism at all effect levels, consistent with the results of the isobologram analysis. When exposure to GLA (24 h) was followed sequentially by paclitaxel (24 h) only an additive effect was observed. The GLA-mediated increase in paclitaxel chemosensitivity was only partially abolished by Vitamin E, a lipid peroxidation inhibitor, suggesting a limited influence of the oxidative status of GLA in achieving potentiation of paclitaxel toxicity. When OA (a non-peroxidisable fatty acid) was combined with paclitaxel, an enhancement of chemosensitivity was found when OA was used concurrently with paclitaxel, although less markedly than with GLA. Pretreatment of MDA-MB-231 cells with OA for 24 h prior to a 24 h paclitaxel exposure produced greater enhancement of paclitaxel sensitivity at high OA concentrations than the concurrent exposure to OA and paclitaxel. The OA-induced sensitisation to paclitaxel was not due to the cytoxicity of the fatty acid itself. When these observations were extended to three additional breast carcinoma cell lines (SK-Br3, T47D and MCF-7), simultaneous exposure to GLA and paclitaxel also resulted in synergism. GLA preincubation followed by paclitaxel resulted in additivity for all cell lines. Simultaneous exposure to paclitaxel and OA enhanced paclitaxel cytotoxicity in T47D and MCF-7 cells, but not in SK-Br3 cells, whereas preincubation with OA failed to increase paclitaxel effectiveness in all three cell lines. For comparison, the effects of other fatty acids on paclitaxel chemosensitivity were examined: **GLA was the most potent at enhancing paclitaxel cytotoxicity, followed by alpha-linolenic acid (ALA; 18:3n.3), eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3), whereas linoleic acid (LA; 18:2n-6) did not increase paclitaxel toxicity.** These findings provide experimental support for the use of fatty acids as modulators of tumour cell chemosensitivity in paclitaxel-based therapy.

Breast Cancer Res Treat 2000 Dec;64(3):287-96

Effect of melatonin and linolenic acid on mammary cancer in transgenic mice with c-neu breast cancer oncogene.

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Breast cancer is one of the most common cancers and is a leading cause of mortality in women. The TG.NK transgenic mouse line expresses the c-neu breast cancer oncogene under the control of a MMTV promoter and appears to be a useful animal model for evaluation of intervention strategies to delay/prevent breast cancer.

Fiber-rich nonpurified diet (NTP-2000) and some retinoid analogues have been shown to significantly delay the development of mammary cancer in the TG.NK model.

Four-week-old hemizygous TG.NK female mice with MMTV/c-neu oncogene fed NTP-2000 diet were gavaged with 0.05-0.2 ml of flaxseed oil as the source of omega-3 rich PUFA, or melatonin at 50-200 mg/kg or a combination of 0.10 ml flaxseed oil and 50 mg/kg melatonin in a gavage volume of 0.2 ml per mouse with corn oil as the vehicle for 30 weeks.

The time course of the mammary tumor incidence pattern was advanced by flaxseed oil compared to the control.

At the high dose (0.2 ml) of flaxseed oil, when the omega-6: omega-3 PUFA ratio was closer to 1, there was some delay in the growth of mammary tumors.

Melatonin delayed the appearance of palpable tumors and the growth of the tumors with a dose-related statistically significant negative trend for the incidence of tumors.

The combination of flaxseed oil and melatonin caused a significant decrease in the number of tumors and tumor weight per mouse compared to the control and to flaxseed oil but not to melatonin alone.

Flaxseed oil may delay the growth of mammary tumors if the omega-6:omega-3 PUFA ratio of fat consumed is closer to 1.

Melatonin has the potential to markedly delay the appearance of palpable mammary tumors.

Studies are in progress with the TG.NK mouse model to understand the histological and molecular changes associated with the dose-response pattern of mammary tumor incidence and growth after treatment with a broad range of doses of melatonin.

Eur J Cancer 2000 Feb;36(3):335-40

Low alpha-linolenic acid content of adipose breast tissue is associated with an increased risk of breast cancer.

Klein V, Chajes V, Germain E, Schulgen G, Pinault M, Malvy D, Lefrancq T, Fignon A, Le Floch O, Lhuillery C, Bougnoux P.

Laboratoire de Biologie des Tumeurs, d'anatomo-pathologie, Clinique d'Oncologie-Radiotherapie, Service de Gynecologie-Obstetrique, E. A. 2103, Unite de Recherche Associee Universite-INRA, CHU, Tours, France.

Data derived from experimental studies suggest that alpha-linolenic acid may have a protective effect in breast cancer. Observations obtained from epidemiological studies have not allowed conclusions to be drawn about a potential protective effect of dietary alpha-linolenic acid on breast cancer, possibly because of methodological issues. This case-control study conducted in an homogeneous population from a central area in France was designed to explore the hypothesis that alpha-linolenic acid inhibits breast cancer, using fatty acid levels in adipose breast tissue as a biomarker of past qualitative dietary intake of fatty acids. Biopsies of adipose breast tissue at the time of diagnosis were obtained from 123 women with invasive non-metastatic breast carcinoma. 59 women with benign breast disease served as controls. Individual fatty acids were analysed by capillary gas chromatography. An unconditional logistic regression model was used to obtain odds ratio estimates whilst adjusting for age, menopausal status and body mass index (BMI). No association was found between fatty acids (saturates, monounsaturates, long-chain polyunsaturates n-6 or n-3) and the disease, except for alpha-linolenic acid which showed an inverse association with the risk of breast cancer. The relative risk of breast cancer for women in the highest quartile of adipose breast tissue alpha-linolenic acid level was 0.36 (95% confidence interval=0.12-1.02) compared with those in the lowest quartile (P trend=0.026), suggesting a protective effect of alpha-linolenic acid in the risk of breast cancer. The effects of dietary alpha-linolenic on the risk of breast cancer warrant further study.

Br J Cancer 1994 Aug;70(2):330-4

alpha-Linolenic acid content of adipose breast tissue: a host determinant of the risk of early metastasis in breast cancer.

Bougnoux P, Koscielny S, Chajes V, Descamps P, Couet C, Calais G.

Laboratoire de Biologie des Tumeurs, Tours, France.

The association between the levels of various fatty acids in adipose breast tissue and the emergence of visceral metastases was prospectively studied in a cohort of 121 patients with an initially localised breast cancer. Adipose breast tissue was obtained at the time of initial surgery, and its fatty acid content analysed by capillary gas chromatography.

A low level of alpha-linolenic acid (18:3n-3) in adipose breast tissue was associated with positive axillary lymph node status and with the presence of vascular invasion, but not with tumour size or mitotic index.

After an average 31 months of follow-up, 21 patients developed metastases. Large tumour size, high mitotic index, presence of vascular invasion and low level of 18:3n-3 were single factors significantly associated with an increased risk of metastasis. A Cox proportional hazard regression model was used to identify prognostic factors. Low 18:3n-3 level and large tumour size were the two factors predictive of metastases. These results suggest that host alpha-linolenic acid has a specific role in the metastatic process in vivo. Further understanding of the biology of this essential fatty acid of the n-3 series is needed in breast carcinoma.

Nutr Cancer 2000;36(1):33-41

Effect of an alpha-linolenic acid-rich diet on rat mammary tumor growth depends on the dietary oxidative status.

Cognault S, Jourdan ML, Germain E, Pitavy R, Morel E, Durand G, Bougnoux P, Lhuillery C.

Laboratoire de Nutrition et Securite Alimentaire, Institut National de la Recherche Agronomique, Jouy-en-Josas, France.

To investigate whether the oxidative status of an 18:3(n-3) polyunsaturated fatty acid (PUFA)-enriched diet could modulate the growth of chemically induced rat mammary tumors, three independent experiments were performed. Experiments I and II examined the variation of tumor growth by addition of antioxidant (vitamin E) or a prooxidant system (sodium ascorbate/2-methyl-1,4-naphthoquinone) to a 15% linseed oil diet rich in 18:3(n-3). Experiment III addressed the role of PUFA in the tumor growth modulation by vitamin E. For this purpose, we compared the effect of vitamin E in 15% fat diets containing a high level of 18:3(n-3) (linseed oil, high-PUFA diet) or devoid of 18:3(n-3) (hydrogenated palm/sunflower oil, low-PUFA diet). In Experiments I-III, tumor growth increased in the presence of vitamin E compared with control (without vitamin E). Furthermore, it decreased when prooxidant was added. In contrast, no difference was observed when the diet was low in PUFA, suggesting that sensitivity of PUFA to peroxidation may interfere with tumor growth. This observation was supported by growth kinetic parameter analysis, which indicated that tumor growth resulted from variations in cell loss but not from changes in cell proliferation. These data show that, in vivo, PUFA effects on tumor growth are highly dependent on diet oxidative status.

Carcinogenesis 2003 Mar;24(3):385-92
Related Articles, Links

The role of cyclooxygenase in n-6 and n-3 polyunsaturated fatty acid mediated effects on cell proliferation, PGE(2) synthesis and cytotoxicity in human colorectal carcinoma cell lines.

Dommels YE, Haring MM, Keestra NG, Alink GM, van Bladeren PJ, van Ommen B.

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This study was conducted to investigate the role of the enzyme cyclooxygenase (COX) and its prostaglandin product PGE(2) in n-6 and n-3 polyunsaturated fatty acid (PUFA)-mediated effects on cellular proliferation of two human colorectal carcinoma cell lines. The long chain PUFAs eicosapentaenoic acid (EPA; 20:5n-3) and arachidonic acid (AA; 20:4n-6) both inhibited cell proliferation of Caco-2 cells compared with the long chain fatty acids alpha-linolenic acid (ALA; 18:3n-3) and linoleic acid (LA; 18:2n-6). Neither incubation with PGE(2) nor reduction in PGE(2) synthesis by EPA compared with AA led to differential effects on cell proliferation in Caco-2 cells. This suggests that n-6 and n-3 PUFA-mediated cell proliferation in Caco-2 cells is not regulated via PGE(2) levels. AA and EPA had no effect on growth of HT-29 colon cancer cells with a low COX activity. However, stimulation of COX-2 activity by IL-1 beta resulted in a decrease in cell proliferation and an induction of cytotoxicity by AA as well as by EPA. Both inhibition of the COX pathway by indomethacin as well as inhibition of direct lipid peroxidation by antioxidants such as vitamin E and C diminished the anti-proliferative effects of AA as well as EPA. Also, malondialdehyde, a product of lipid peroxidation and COX-activity was decreased by addition of vitamin E and partially decreased by indomethacin. These data support the hypothesis that growth inhibitory and cytotoxic effects of PUFAs with methylene-interrupted double bonds such as AA and EPA are due to peroxidation products that are generated during lipid peroxidation and COX activity.

Cancer Res 2003 Mar 1;63(5):972-9 Related Articles, Links

Modulation of inducible nitric oxide synthase and related proinflammatory genes by the omega-3 fatty acid docosahexaenoic acid in human colon cancer cells.

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Epidemiological and preclinical studies demonstrate that consumption of diets high in omega-3 polyunsaturated fatty acids reduces the risk of colon cancer. Inhibition of colon carcinogenesis by omega-3 polyunsaturated fatty acids is mediated through modulation of more than one signaling pathway that alters the expression of genes involved in colon cancer growth. In our earlier studies on global gene expression with cDNA microarrays, we have shown that treatment of CaCo-2 colon cancer cells with docosahexaenoic acid (DHA) down-regulated the prostaglandin family of genes, as well as cyclooxygenase 2 expression and several cell cycle-related genes, whereas it up-regulated caspases 5, 8, 9, and 10 that are associated with apoptosis. It is known that nitric oxide activates the cyclooxygenase 2 enzyme, which plays a pivotal role in the progression of colon cancer via prostaglandin synthesis and angiogenesis. The present study was undertaken to examine the multifaceted role of DHA in the expression of inducible nitric oxide synthase (iNOS) and of related proinflammatory genes, as those have been shown to play a role in tumor progression. In addition, we aimed to identify associated target genes by DNA microarray, reverse transcription-PCR analysis, and cellular localization of iNOS expression in CaCo-2 cells. Results of this study demonstrate that treatment with DHA down-regulates iNOS in parallel with a differential expression and down-regulation of IFNs, cyclic GMP, and nuclear factor kappa B isoforms. More importantly, our findings clearly demonstrate the up-regulation of cyclin-dependent kinase inhibitors p21((Waf1/Cip1)) and p27, differentiation-associated genes such as alkaline phosphatases, and neuronal differentiation factors. These finding strongly suggest that the antitumor activity of DHA may be attributed, at least in part, to an effect on iNOS regulatory genes. In addition, our results indicate the presence of specific gene expression profiles in human colon cancer that

can be used as molecular targets for chemopreventive agents.

Nutr Cancer 2002;43(1):1-21 Related Articles, Links

Most effective colon cancer chemopreventive agents in rats: a systematic review of aberrant crypt foci and tumor data, ranked by potency.

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Potential chemopreventive agents for colorectal cancer are assessed in rodents. We speculated that the magnitude of the effect is meaningful and ranked all published agents according to their potency. Data were gathered systematically from 137 articles with the aberrant crypt foci (ACF) end point and from 146 articles with the tumor end point. The potency of each agent to reduce the number of ACF is listed in one table and the potency of each agent to reduce the tumor incidence in another table. Both tables are shown in this review and on a website with sorting abilities (http://www.inra.fr/reseau-nacre/sci-memb/corpet/indexan.html). Potency was estimated as the ratio of the value in control rats to the value in treated rats. From each article, only the most potent agent was kept, except in articles reporting the effect of more than seven agents. Among the 186 agents in the ACF table, the median agent reduced the number of ACF by one-half. **The most potent agents to reduce azoxymethane-induced ACF** were Pluronic, polyethylene glycol, **perilla oil (ALA Omega 3) with beta-carotene**, and sulindac sulfide. Among the 160 agents in the tumor table, the median agent reduced the tumor incidence in rats by one-half. The most potent agents to reduce the incidence of azoxymethane-induced tumors were celecoxib, a protease inhibitor from soy, difluoromethylornithine with piroxicam, polyethylene glycol, and a thiosulfonate. For the 57 agents present in both tables, a significant correlation (r) was found between the potencies against ACF and tumors ($r = 0.45$, $P < 0.001$); without celecoxib, a major outlying point in the correlation, $r = 0.68$ ($P < 0.001$, $n = 56$). In conclusion, this review gathers most known chemopreventive agents, ranks the most promising agents against colon carcinogenesis in rats or mice, and further supports the use of ACF as a surrogate end point for tumors in rats.

J Biol Chem 2003 Mar 28;278(13):11167-74 Related Articles, Links

Role of cyclooxygenase 2 in protein kinase C beta II-mediated colon carcinogenesis.

Yu W, Murray NR, Weems C, Chen L, Guo H, Ethridge R, Ceci JD, Evers BM, Thompson EA, Fields AP.

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Elevated expression of protein kinase C beta II (PKC beta II) is an early promotive event in colon carcinogenesis (Gokmen-Polar, Y., Murray, N. R., Velasco, M. A., Gatalica, Z., and Fields, A. P. (2001) Cancer Res. 61, 1375-1381). Expression of PKC beta II in the colon of transgenic mice leads to hyperproliferation and increased susceptibility to colon carcinogenesis due, at least in part, to repression of transforming growth factor beta type II receptor (TGF-beta RII) expression (Murray, N. R., Davidson, L. A., Chapkin, R. S., Gustafson, W. C., Schattenberg, D. G., and Fields, A. P. (1999) J. Cell Biol., 145, 699-711). Here we report that PKC beta II induces the expression of cyclooxygenase type 2 (Cox-2) in rat intestinal epithelial (RIE) cells in vitro and in transgenic PKC beta II mice in vivo. Cox-2 mRNA increases more than 10-fold with corresponding increases in Cox-2 protein and PGE2 production in RIE/PKC beta II cells. PKC beta II activates the Cox-2 promoter by 2- to 3-fold and stabilizes Cox-2 mRNA by at least 4-fold. The selective Cox-2 inhibitor Celecoxib restores expression of TGF-beta RII both in vitro and in vivo and restores TGF beta-mediated transcription in RIE/PKC beta II cells. Likewise, the omega-3 fatty acid eicosapentaenoic acid (EPA), which inhibits PKC beta II activity and colon carcinogenesis, causes inhibition of Cox-2 protein expression, re-expression of TGF-beta RII, and restoration of TGF-beta1-mediated transcription in RIE/PKC beta II cells. Our data demonstrate that PKC beta II promotes colon cancer, at least in part, through induction of Cox-2, suppression of TGF-beta signaling, and establishment of a TGF-beta-resistant, hyperproliferative state in the colonic epithelium. Our data define a procarcinogenic PKC beta II --> Cox-2 --> TGF-beta signaling axis within the colonic epithelium, and provide a molecular mechanism by which dietary omega-3 fatty acids and nonsteroidal

antiinflammatory agents such as Celecoxib suppress colon carcinogenesis.

Nutr Cancer 2002;42(1):125-30
Effects of n-6 and n-3 polyunsaturated fatty acids on gap junctional intercellular communication during spontaneous differentiation of the human colon adenocarcinoma cell line Caco-2.

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Gap junctional intercellular communication (GJIC), which modulates cell growth and differentiation, may play an important role in tumor growth. Cancer cells have dysfunctional GJIC, but it is not known whether GJIC is mechanistically involved in the carcinogenic and anti-carcinogenic effects of n-6 and n-3 polyunsaturated fatty acids (PUFAs) on colon tumor cells. Caco-2 cells were used as an in vitro model to study the effects of PUFAs on differentiated as well as undifferentiated human colon cells.
The GJIC capacity of this cell line increased during spontaneous differentiation. However, no differential effects between n-6 and n-3 PUFAs on GJIC were observed. Short-term incubation with linoleic acid (18:2n-6), alpha-linolenic acid (18:3n-3), arachidonic acid (AA, 20:4n-6), and eicosapentaenoic acid (EPA, 20:5n-3) did not influence GJIC, while long-term incubation (> 10 days) with linoleic acid and alpha-linolenic acid inhibited GJIC of these colon cells. Long-chain metabolites such as AA and EPA were not formed after incubation with linoleic acid and alpha-linolenic acid, thus excluding the involvement of prostaglandins in the observed effects.
Although the exact mechanism of GJIC inhibition is unclear, cytotoxicity probably mediated by lipid peroxidation products seems to be related, because incubation with more PUFAs (AA and EPA) completely abolished GJIC.

Carcinogenesis 2002 Sep;23(9):1519-29
Induction of tumors in the colon and liver of the immunodeficient (SCID) mouse by 2-amino-3-methylimidazo[4,5-f]quinoline (IQ)-modulation by long-chain fatty acids.

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We have recently shown that immunodeficient (SCID) mice, which lack functional T and B cells, are highly susceptible to low dose site specific induction of colon aberrant crypt foci (ACF), surrogates for colon tumors, by 2-amino-3-methylimidazo[4,5-f]quinoline (IQ). To test whether long-term exposure to a high dose in the diet might prove carcinogenic to the SCID mouse colon, in contrast to other mice strains tested to date, the compound was administered at 300 p.p.m. in the diet to female 6-7-week-old SCID mice for 32 weeks. IQ induced high numbers of ACF, hyperplastic polyps, dysplasia, and colon adenomas, as well as hepatocellular altered foci and liver adenomas. Induction of colon tumors did not correlate with the main sites where ACF developed, the proximal colon, however, being seen mainly in the mid and distal colon. Induction of colon tumors correlated significantly with the incidence of dysplasia, crypt height, the mitotic index, cell proliferation and numbers of 8-hydroxydeoxyguanosine (8-OHdG)-positive cells in the colon crypt, particularly in mid and distal colon. Administration of 20% omega-6 polyunsaturated fatty acids (corn oil), omega-3 polyunsaturated fatty acids (perilla oil: acido alfa-linolenico), or monounsaturated fatty acids (olive oil) simultaneously with IQ in the diet resulted in: (i) inhibition of colon and liver tumor induction by corn and perilla oil, whereas olive oil showed no effects; (ii) no reduction in total numbers of ACF by corn oil or perilla oil but significant suppression in the olive oil treated group; (iii) inhibition of tumor development particularly by omega-3 polyunsaturated fatty acids in perilla oil, correlating significantly with decreased cell proliferation in both colon and liver and a marked decrease in crypt heights and mitotic indices. Selective reduction in the numbers of 8-OHdG-positive nuclei, mainly in the middle and distal colon crypts, was also found to correlate with tumor inhibition. **Thus, the results indicate carcinogenicity of IQ in the colon of the SCID mouse and preventive effects of polyunsaturated fatty acids**.

Surgery 2002 Nov;132(5):805-14 Related Articles, Links

Preoperative oral arginine and n-3 fatty acid supplementation improves the immunometabolic host response and outcome after colorectal resection for cancer.

Braga M, Gianotti L, Vignali A, Carlo VD.

Department of Surgery, San Raffaele University, Milan, Italy.

BACKGROUND: Previous trials showed that perioperative immunonutrition improved outcome in patients with gastrointestinal cancer. This study was designed to appraise the impact of the simple preoperative oral arginine and n-3 fatty acids supplementation on immune response, gut oxygenation, and postoperative infections. METHODS: Two hundred patients with colorectal neoplasm were randomized to: (a) oral intake for 5 days before surgery of a formula enriched with arginine and n-3 fatty acids (pre-op group; n = 50); (b) same preoperative treatment prolonged after surgery by jejunal infusion (peri-op group; n = 50); (c) oral intake for 5 days before surgery of a standard isoenergetic, isonitrogenous formula (control group; n = 50); and (d) no supplementation before and after operation (conventional group; n = 50). The immune response was measured by phagocytosis ability of polymorphonuclear cells and delayed hypersensitivity response to skin tests. Gut oxygenation and microperfusion were assessed by polarographic probes and laser Doppler flowmetry, respectively. RESULTS: The 4 groups were comparable for demographics, comorbidity, and surgical variables. The 2 groups receiving immunoutrients (pre-op and peri-op) had a significantly better immune response, gut oxygenation, and microperfusion than the other 2 groups. Intent-to-treat analysis showed an overall infection rate of 12% in pre-op, 10% in peri-op, 32% in control, and 30% in conventional groups (P <.04 pre-op and peri-op vs control and conventional).

CONCLUSION: Preoperative oral arginine and n3-fatty acids **improves the immunometabolic response and decreases the infection rate**. Postoperative prolongation with such supplemented formula has no additional benefit.

Cancer Lett 2002 Dec 10;187(1-2):169-77 Related Articles, Links

Influence of omega-3 fatty acids on the growth of human colon carcinoma in nude mice.

Kato T, Hancock RL, Mohammadpour H, McGregor B, Manalo P, Khaiboullina S, Hall MR, Pardini L, Pardini RS.

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The present study investigated the influence of dietary omega-3 fatty acid supplementation on the growth of human colon carcinoma xenograft in athymic nude mice. Four diets were fed to evaluate the effect of levels and types of fat on colon tumor growth. Animals were maintained on a standard diet modified by addition of fats containing omega-3 and omega-6 fatty acids to represent high and low fat intakes for 53 days. The final mean estimated tumor weight for the high fat corn oil (24%) fed group was 2,302 mg, whereas the low fat (8% corn oil) group was 1,681 mg. The final mean tumor weight of the high fat menhaden oil fed group was 782 mg representing a 66% decrease in growth compared to the high fat corn oil group and a decrease of 54% compared to the low corn oil fed group. The high fat golden algae oil fed group resulted in a mean final tumor weight of 223 mg representing a 90% inhibition of tumor growth relative to the high fat corn oil fed group and 87% inhibition of growth compared to the low fat corn oil fed group. These findings indicate that dietary omega-3 fatty acids possess significant tumor suppressing properties and that the primary tumor suppressing fatty acid is docosahexaenoic acid. Histopathologic examination of control and treated tumors and expression array analyses (**human cytokine and apoptosis arrays) support the tumor growth inhibition data and provide evidence for discussion of possible mechanisms for the observed growth inhibition.**

Carcinogenesis 1996 Sep;17(9):1897-901
Synergistic suppression of azoxymethane-induced foci of colonic aberrant crypts by the combination of beta-carotene and perilla oil in rats.

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The modulating effect of the combined dietary feeding of beta-carotene and perilla oil, which is rich in alpha-linolenic acid, on the development of azoxymethane (AOM)-induced colonic aberrant crypt foci (ACF) was investigated in male F344 rats. Rats received oral administration of beta-carotene (0, 50 or 200 mg/kg body weight/day) and fed a basal diet containing either 12% olive oil, 3% perilla oil plus 9% olive oil, or 12% perilla oil. A dose-dependent suppressive effect of perilla oil was found. The numbers of ACF were 42.0 and 18.4% of those of the 12% olive oil-fed controls in the rats fed 3% perilla oil plus 9% olive oil and 12% perilla oil, respectively. The development of ACF was also reduced significantly by the addition of dietary beta-carotene in each of the oil-fed groups ($P < 0.05$, respectively). The suppression by the combination of beta-carotene and perilla oil was synergistic, as the numbers of ACF were 12.9 and 8.9% of those of the 12% olive oil-fed controls in beta-carotene-treated rats fed 3% perilla oil plus 9% olive oil and 12% perilla oil, respectively. beta-carotene plus perilla oil also suppressed the numbers of silver-stained nucleolar organizer regions and the expression of ras mRNA in the colonic mucosa (cell proliferation biomarkers). Following administration of beta-carotene, a significant increase in the concentration of intact beta-carotene molecules was found in the colonic mucosa, livers, and sera. However, no accumulation of retinoids was observed in the colonic mucosa, suggesting that the inhibitory effect may not be related to the provitamin A activity. **These results suggest that the combination of beta-carotene and perilla oil (rich in alpha linolenic acid omega 3) may be useful in the prevention of colon cancer.**

Cancer 1994 Apr 15;73(8):2069-75 Related Articles, Links
Colon cancer prevention with a small amount of dietary perilla oil high in alpha-linolenic acid in an animal model.

Narisawa T, Fukaura Y, Yazawa K, Ishikawa C, Isoda Y, Nishizawa Y.

Akita University College of Allied Medical Science, Japan.

BACKGROUND. Epidemiologic and experimental studies suggest that dietary fish oil and vegetable oil high in omega-3 polyunsaturated fatty acids (PUFAs) suppress the risk of colon cancer. The optimal amount to prevent colon carcinogenesis with perilla oil high in omega-3 PUFA alpha-linolenic acid in a 12% medium-fat diet was investigated in female F344 rats. For comparison, safflower oil high in omega-6 PUFA linoleic acid was used. METHODS. Thirty or 25 rats at 7 weeks of age in each group received an intrarectal dose of 2 mg N-methyl-N-nitrosourea 3 times weekly in weeks 1 and 2 and were fed the diets with various levels of perilla oil and safflower oil throughout the experiment. RESULTS. The incidence of colon cancer at the termination of the experiment at week 35 was 40%, 48% and 32% in the rats fed the diets with 3% perilla oil plus 9% safflower oil, 6% perilla oil plus 6% safflower oil, and 12% perilla oil plus 0% safflower oil, respectively, whereas it was 67% in the rats fed the control diet with 0% perilla oil plus 12% safflower oil. The amount of diet consumed and the body weight gain were identical in all of the dietary groups. The ratios of omega-3 PUFA to omega-6 PUFA in the serum and the colonic mucosa at week 35 were increased in parallel to the increased intake of perilla oil.

CONCLUSIONS. The results suggest that a relatively small fraction of perilla oil, 25% of total dietary fat, may provide an appreciable **beneficial effect in lowering the risk of colon cancer**.

Biomed Pharmacother 2002 Jul;56(5):215-22 Related Articles, Links

Polyunsaturated fatty acids (PUFA) and eicosanoids in human health and pathologies.

Tapiero H, Ba GN, Couvreur P, Tew KD.

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Linoleic and alpha-linolenic acids, obtained from plant material in the diet are the precursors in tissues of two families with opposing effects which are referred to as "essential fatty acids" (EFA): arachidonic acid (AA) and pentaene (eicosapentaenoic acid: EPA) and hexaene (docosahexaenoic acid: DHA) acids. The role of EFA is crucial, without a source of AA or compounds which can be converted into AA, synthesis of prostaglandins (PGs) by a cyclooxygenase (COX) enzyme would be compromised, and this would seriously affect many normal metabolic processes. COX, also known as prostaglandin endoperoxide synthase (Pghs) or as prostaglandin G/H synthase, is a key membrane bound enzyme responsible for the oxidation of AA to PGs. Two COX isoforms have been identified, COX-1 and COX-2 that form PGH2, a common precursor for the biosynthesis of thromboxane A2 (TxA2), prostacyclin (PGI2) and PGs (PGD2, PGE2, PGF2alpha. COX-1 enzyme is expressed constitutively in most cells and tissues. Its expression remains constant under either physiological or pathological conditions controlling synthesis of those PGs primarily involved in the regulation of homeostatic functions. In contrast, COX-2 is an intermediate response gene that encodes a 71-kDa protein. COX-2 is normally absent from most cells but highly inducible in certain cells in response to inflammatory stimuli resulting in enhanced PG release. PGs formed by COX-2 primarily mediate pain and inflammation but have multiple effects that can favour tumorigenesis. They are more abundant in cancers than in normal tissues from which the cancers arise. COX-2 is a participant in the pathway of colon carcinogenesis, especially when mutation of the APC (Adenomatous Polyposis Coli) tumour suppressor gene is the initiating event. In addition, COX-2 up-regulation and elevated PGE2 levels are involved in breast carcinogenesis. It seems that there is a correlation between COX-2 level of expression and the size of the tumours and their propensity to invade underlying tissue. Inhibition by non-steroidal anti-inflammatory drugs (NSAIDs) of COX enzymes which significantly suppress PGE2 levels, reduced breast cancer incidence and protected against colorectal cancer. Therefore it is suggested that consumption of a diet enriched in n-3 PUFA (specifically EPA and DHA) and inhibition of COX-2 by NSAIDs may confer cardioprotective effects and provide a significant mechanism for the prevention and treatment of human cancers.

Br J Cancer 1998 Jun;77(11):1978-83 Related Articles, Links

Abnormalities in plasma and red blood cell fatty acid profiles of patients with colorectal cancer.

Baro L, Hermoso JC, Nunez MC, Jimenez-Rios JA, Gil A.

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We evaluated total plasma fatty acid concentrations and percentages, and the fatty acid profiles for the different plasma lipid fractions and red blood cell lipids, in 17 patients with untreated colorectal cancer and 12 age-matched controls with no malignant diseases, from the same geographical area. Cancer patients had significantly lower total plasma concentrations of saturated, monounsaturated and essential fatty acids and their polyunsaturated derivatives than healthy controls; when the values were expressed as relative percentages, cancer patients had significantly higher proportions of oleic acid and lower levels of linoleic acid than controls. With regard to lipid fractions, cancer patients had higher proportions of oleic acid in plasma phospholipids, triglycerides and cholesterol esters, and lower percentages of linoleic acid and its derivatives. **On the other hand, alpha-linolenic acid was significantly lower in triglycerides from cancer patients and tended to be lower in phospholipids.** Its derivatives also tended to be lower in phospholipids and triglycerides from cancer patients. Our findings suggest that colorectal cancer patients present abnormalities in plasma and red blood cell fatty acid profiles characterized by lower amounts of most saturated, monounsaturated and essential fatty acids and their polyunsaturated derivatives, especially members of the n-6 series, than their healthy age-matched counterparts. These changes are probably due to metabolic changes caused by the illness per se but not to malnutrition.