

Pleiotropic Effects of Dietary Fatty Acids and Fatty Acid Involvement in Chronic Mild Inflammation-related Diseases

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(Received March 30, 2010)

Changes in diet and lifestyle in recent years have led to unhealthy dietary patterns and inadequate physical activity, making it difficult to maintain an appropriate energy balance, which results in an increased prevalence of diet-related chronic diseases such as obesity, diabetes, cardiovascular disease, and certain types of cancer. The importance of the roles of lipids in these diseases is now recognized. Dietary fatty acids modulate inflammatory processes and contribute to the pathophysiological state of diet-related chronic diseases. Although there is insufficient evidence as to the involvement of monounsaturated fatty acids in inflammatory processes and limited evidence indicating a potential proinflammatory role of saturated and *trans* fatty acids, there is considerably stronger evidence suggesting that increasing the intake of n-3 polyunsaturated fatty acids brings about favorable antiinflammatory effects. Certain fatty acids may also produce therapeutic effects by modifying the activity of ghrelin, a growth hormone-releasing and appetite-stimulating peptide; such modification may yield reduction of food intake and enable clinical manipulation of energy metabolism.

Key words — dietary fatty acid, inflammation, cancer, cardiovascular disease, ghrelin, acylation

INTRODUCTION

In 1993, the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) held a consultation meeting to review scientific data on the optimal consumption of dietary fats and fatty acids to provide internationally valid recommendations; the report was published in 1994.¹⁾ A subsequent meeting of the Joint FAO/WHO Expert Consultation on the same subject was held in 2008. During the 15 years that elapsed between the 2 meetings, industrialization, urbanization, economic development, and market globalization have led to rapid changes in diets and lifestyles. This is particularly true in developing countries, where rapid socioeconomic changes occur. Improvements in the standard of liv-

ing have often been accompanied with unhealthy dietary patterns and insufficient physical activity, making it difficult to maintain an appropriate energy balance and a healthy weight, which results in an increased prevalence of diet-related chronic diseases such as obesity, diabetes, cardiovascular disease (CVD), and certain types of cancer that significantly affect human health.²⁾ It has been recognized that these disorders are associated with chronic mild inflammation in which the metabolism of fat tissue is involved.^{3,4)} The association of chronic inflammation with obesity and with increased cancer incidence is widely accepted.^{5,6)} In general, acute inflammation is a process that benefits the host by providing protection from invading pathogens and initiating wound healing.⁵⁾ The proinflammatory cytokines produced by activated macrophages have long-range effects that contribute to host defense mechanisms; tumor necrosis factor (TNF)- α and interleukin (IL)-1 β stimulate the release of IL-6, followed by the secretion of liver-derived C-reactive protein (CRP), and the production of IL-1 β and TNF- α is suppressed by the release of IL-1 receptor

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antagonist (IL-1ra) and soluble forms of TNF receptors (sTNF-Rs), respectively.⁵⁾ sTNF-Rs (sTNF-R1 and sTNF-R2) are produced by proteolytic cleavage of the extracellular domains of membrane-bound TNF receptors after induction of TNF or other cytokines such as IL-6, IL-1 β , or IL-2, and have a longer half-life and are detected with a higher sensitivity than TNF.^{7,8)} Chronic, low-grade, systemic inflammation has been introduced as a condition where there is a sustained, low-level (2- to 3-fold) increase in circulating levels of TNF- α , IL-1 β , IL-6, IL-1ra, sTNF-R, and CRP.⁹⁾ Although the initial stimuli that cause chronic systemic inflammation are not well defined, it is assumed that the origin of TNF- α in low-grade systemic inflammation is mainly the adipose tissue.⁹⁾ Numerous studies, including well-conducted, randomized controlled trials and prospective cohort studies on the incidence of disease outcomes and randomized controlled trials on physiological measures, continue to clarify the effects of dietary fats on health outcomes. It is now believed that lipids play critical roles in all diet-related diseases, and the relative amounts and types of dietary lipids consumed are important.^{2,10,11)}

Fatty acids are the main structural component and energy source for the human body. As more information on the physiological and pharmacological functions of dietary fatty acids is being obtained, the association of these compounds with disease is becoming clearer. Fatty acids have various structures depending on the number of carbon atoms and/or double bonds and their positions, and configuration (*cis* or *trans*). The chemical structure of fatty acids in lipids is crucial in determining the properties as well as the metabolic and functional behavior of lipids.

This review describes our current understanding of the molecular mechanisms underlying the action and pleiotropic effects of fatty acids. It also discusses recent clinical trials investigating the role of fatty acids in the prevention and treatment of chronic mild inflammation-associated diseases, and then addresses acyl modification of ghrelin, a peptide hormone, by fatty acids, which is crucial for physiological hormonal action.

EFFECTS OF FATTY ACIDS ON INFLAMMATORY MARKERS

Inflammation plays a pivotal role in all phases of atherosclerosis, from initiation of the fatty streak

to the culmination, even in acute coronary syndromes.^{12,13)} Atherosclerosis was once considered to be simple lipid storage disease, but is now recognized as a chronic inflammatory condition of vessel walls where inflammatory cell infiltration and cytokine production occur.¹³⁾ The pathological mechanisms of obesity recapitulate many features of the inflammatory processes at work in atherosclerosis, and the long-term nutrient excess and unbalanced energy expenditure that characterizes obesity leads to fatty acid accumulation in the liver, muscles, and adipose tissue.¹³⁾ Adipose tissue produces and secretes a variety of molecules, such as leptin, IL-6, and TNF- α , that have characteristic local and systemic proinflammatory effects.^{3,14)} Several of these molecules over-released into the circulation in obese subjects lead to low grade chronic systemic inflammation,³⁾ which may induce insulin resistance and endothelial dysfunction and thus link latter phenomena with obesity and CVD.⁴⁾

The role of dietary factors in the prevention of CVD has attracted considerable attention. Numerous molecules, including cytokines, chemokines, cell adhesion molecules, and acute phase reactants such as fibrinogen, serum amyloid A, and CRP, have been identified as predictive markers of CVD. Among these, CRP is the prototypical marker of inflammation. Large amounts of published data have nominated CRP as a candidate factor to predict the future risk of CVD in apparently healthy people.^{15–18)} Limited studies have shown that certain dietary fatty acids reduced the levels of biomarkers of inflammation, whereas most of the studies with fish oil supplementation have shown null effects, and conflicting results have been reported with saturated and *trans* fatty acid intake.¹⁹⁾ The effects of these dietary fatty acids on inflammatory morbidity are discussed below.

Saturated and *trans* Fatty Acids

Double bonds of natural unsaturated fatty acids are in the *cis* configuration, while *trans* isomers are formed during the industrial hydrogenation process of liquid vegetable oils for food manufacturing. The configuration of the *trans* isomer is straighter as compared to the *cis* isomer and closely resembles that of saturated fats. There are several possible mechanisms by which *trans* fatty acids could affect inflammatory responses. For instance, the physical properties of *trans* fatty acids may affect membrane physiology, or the replacement of the *cis*-linoleic acid (a precursor of prostaglandin syn-

thesis) in the membrane by the *trans* isomer may affect production of prostaglandins.²⁰⁾ Positive correlations between diets with a high content of saturated or *trans* fatty acids and biomarkers of inflammation were demonstrated in several observational studies.^{16, 21–24)} A positive correlation was found between CRP and the Western diet, which is characterized by higher intakes of red meat, high-fat dairy products, and refined grains.²¹⁾ CRP levels did not correlate with individual foods or nutrients in the Western diet, but data did suggest a positive association between high fat intake (particularly of saturated and *trans* fatty acids from red and processed meats, full-fat dairy products, French fries, and high glycemic index carbohydrates in the Western diet) and inflammation.¹⁶⁾ A modest association between elevated CRP levels and saturated fat consumption was also found.²²⁾ Although women with a higher intake of *trans* fat had 73% higher CRP levels compared to those with a lower intake of such fat in Nurses' Health Study I cohort,^{23, 24)} *trans* fatty acid intake of generally healthy women was positively associated with levels of the sTNF-R1 and sTNF-R2 but not with IL-6 or CRP concentrations overall.²⁵⁾ In intervention trials, the levels of CRP and soluble E-selectin (sE-selectin), an adhesion molecule, increased when healthy subjects consumed *trans* fatty acids as much as 8% of energy in a high fat diet (39% of energy from fat),²⁶⁾ whereas 6% substitution of *trans* fatty acids in a standard fat diet (30% of energy from fat) showed no effects on CRP levels in moderately hypercholesterolemic subjects.²⁷⁾ Consumption of saturated acids (stearic, myristic, and palmitic acid) resulted in an increase in circulating concentrations of IL-6 and sE-selectin.²⁶⁾ Consumption of diets containing hydrogenated fats high in *trans* fatty acids increased *ex vivo* production of TNF- α and IL-6 from isolated peripheral blood mononuclear cells collected from subjects with moderately elevated low density lipoprotein (LDL) cholesterol levels.²⁰⁾ Consumption of food rich in stearic acid induced a significant increase in circulating levels of fibrinogen, while diets high in *trans* fatty acids did not.²⁶⁾ Increases in plasma levels of fibrinogen after consumption of a diet rich in stearic acid compared to one rich in lauric and myristic acids have also been reported.²⁸⁾ A study on postprandial endothelial activation reported as follows: in healthy subjects, a high-fat meal containing 59% fat (20.4 g of saturated fat) increased the postprandial plasma levels of TNF- α and IL-6 and the soluble forms of intercellular

adhesion molecule 1 (sICAM-1) and vascular cell adhesion molecule 1 (sVCAM-1), which are surrogate markers of endothelial activation and vascular inflammation, but high-carbohydrate meal did not, while in diabetic patients, both high-fat meal and high-carbohydrate meal increased the levels of these molecules.²⁹⁾ Findings have been inconsistent thus far.

Monounsaturated Fatty Acids (MUFA)

Epidemiological studies demonstrate that the Mediterranean diet, in which olive oil is the major source of fat, reduces the risk of coronary heart disease and cancer.³⁰⁾ Virgin olive oil is a rich source of MUFA,³⁾ and the MUFA in olive oil is primarily oleic acid. A randomized trial investigating the antiinflammatory effects of a Mediterranean-style diet has been reported.³¹⁾ Patients with metabolic syndrome without CVD were randomly instructed to consume either a control diet or a Mediterranean-style diet; patients on the Mediterranean-style diet showed a concomitant decrease in serum concentrations of high-sensitivity-CRP and cytokines (IL-6, IL-7, and IL-18) and a decrease in insulin resistance compared with the control patients. Although the macronutrient composition of the 2 diets was similar (carbohydrates, 50–60%; proteins, 15–20%; and total fat, < 30%), the patients consuming the Mediterranean-style diet had higher intakes of vegetables, fruits, nuts, whole grains, and olive oil in comparison with the control patients. In contrast, null effects of a Mediterranean diet on biomarkers of inflammation in patients with medically treated coronary artery disease have also been reported.³²⁾ In addition, 8% substitution of oleic acid decreased IL-6 concentrations compared with consumption of a saturated or *trans* fatty acid-substituted diet, although there was no difference in the biomarkers of inflammation between an oleic acid diet (39% fat) and the standard-fat control diet (30% fat).²⁶⁾ Furthermore, a randomized and crossover study on diets enriched in refined olive oil, *i.e.*, rich in oleic acid, reported that eating meals with oleic acid for 1 week had a significant postprandial benefit on plasma levels of sICAM-1 and sVCAM-1 in healthy and, more importantly, in hypertriglyceridemic (normotensive and hypertensive) subjects.³³⁾ In another randomized, 4-week crossover diet study that evaluated the chronic effects of dietary fat on the postprandial expression of TNF- α genes in peripheral blood mononuclear cells from healthy subjects, a MUFA-enriched breakfast induced a lower

postprandial expression of TNF- α messenger RNA than one enriched in saturated fatty acids, however, significant effects of the MUFA-enriched diet on the plasma concentration of TNF- α were not shown.³⁴⁾ Thus, oleic acid does not promote inflammation and may actually offset the proinflammatory effects of a high-fat diet or diets with substitutions of saturated or *trans* fatty acids.¹⁶⁾

Polyunsaturated Fatty Acids (PUFA)

There are 2 classes of essential fatty acids, n-3 and n-6 PUFA. One important function of these PUFAs is related to their enzymatic conversion into eicosanoids.³⁵⁾ In most cases, animals have the enzymatic activity to convert linoleic acid (LA, 18:2 n-6) and α -linolenic acid (ALA, 18:3 n-3) to longer chain PUFAs, whereas they lack the 12- and 15-desaturase activities necessary to synthesize the precursor PUFAs, LA and ALA.³⁶⁾ Furthermore, the n-3 and n-6 PUFAs are not interconvertible in mammalian cells.³⁷⁾ Thus, LA, ALA, and their elongation and desaturation products are considered essential fatty acids in the human diet.^{11, 37, 38)} These 2 classes of essential fatty acids are metabolically and functionally distinct and often have important opposing physiological functions.^{37, 38)} Dietary n-6 and n-3 PUFAs can be enzymatically metabolized to prostaglandins, thromboxanes, hydroxyeicosate-traenoic acids, and leukotrienes by cyclooxygenases and lipoxygenases. Arachidonic acid (AA, 20:4 n-6), the major PUFA in cell membranes, produces the 2-series prostanoids and the 4-series leukotrienes, with 2 and 4 double bonds, while eicosapentaenoic acid (EPA, 20:5 n-3) is a substrate for the 3-series prostanoids and the 5-series leukotrienes.³⁵⁾ In general, eicosanoids derived from n-6 PUFAs have proinflammatory effects, while those derived from n-3 precursors have antiinflammatory effects.³⁹⁾ Likewise, eicosanoids derived from these 2 classes have opposing effects in cancer cell growth,^{40, 41)} invasion,⁴²⁾ and angiogenesis.^{43, 44)} In addition to eicosanoids, marine n-3 PUFAs can also be metabolized to resolvins from EPA and docosahexaenoic acid (DHA, 22:6 n-3), and protectins from DHA, which can accelerate and regulate the resolution of acute inflammation.⁴⁵⁾ n-3 PUFAs are also thought to exert indirect effects by inhibiting the n-6 series eicosanoid biosynthesis. n-3 PUFAs are incorporated into membrane phospholipids, where they partially replace AA and reduce the pool of available AA. They compete with n-6 PUFAs for desaturases, elongases, cyclooxygenases, and lipoxygenases, so

that the biosynthesis of the 2-series prostanoids and the 4-series leukotrienes is reduced.¹¹⁾ In addition, an *in vitro* study proposed that production of 2-series prostanoids from AA by cyclooxygenase-2 would decrease in proportion to the compensatory decrease in the AA content of membrane phospholipids via increased incorporation of n-3 PUFAs such as EPA since cyclooxygenase-2 preferentially oxygenates AA at low concentrations of substrate when presented with a mixture of AA and EPA.⁴⁶⁾

The relationship between dietary n-3 PUFA and inflammation has been relatively well examined and clinically studied among the major dietary macronutrients.¹⁹⁾ The theory that n-3 PUFAs may play a major role in modulating inflammation is supported by several studies. A cross-sectional study performed among healthy men and women indicated that intake of EPA and DHA was inversely associated with plasma levels of sTNF-R1 and sTNF-R2.⁴⁷⁾ This antiinflammatory effect of EPA and DHA has also been observed in other cross-sectional studies performed among healthy individuals^{48, 49)} or in patients with established coronary artery disease.⁵⁰⁾

In an interventional study, decreases in CRP and IL-6 levels were observed in postmenopausal women who consumed dietary fish oil.⁵¹⁾ The antiinflammatory effects of ALA have also been observed in several interventional studies; dietary ALA decreased CRP, serum amyloid A, and IL-6 in dyslipidemic patients⁵²⁾ and lowered CRP levels in moderately hypercholesterolemic men and women.⁵³⁾ However, in a substitution study, both ALA-enriched diet and LA-enriched diet significantly decreased levels of sICAM-1 and sE-selectin in hypercholesterolemic subjects, in addition to a significant decrease in CRP levels in the ALA-enriched diet.⁵⁴⁾ In this substitution study, it should be noted that both substitution diets had high levels of LA (10.5 and 12.6%) and had half the total fats derived from walnuts, walnut oil, and flaxseed oil. Furthermore, saturated fatty acids provided only 8% of the total energy, and there may be a role of specific amino acids found in walnuts (*e.g.*, arginine) that contributes to a decrease in inflammation in the 2 dietary groups.¹⁶⁾ Authors' previous study indicates that preoperative oral administration of a supplement rich in n-3 PUFAs and arginine may improve inflammatory and immune responses as well as nutritional status in patients undergoing major surgery for cancer, in which perioperative circulating levels of inflammatory markers such as CRP,

polymorphonuclear leukocyte (PMN)-elastase, α_1 -acid glycoprotein, cytokines (TNF- α , IL-6, and IL-8), and soluble cytokine receptors (sTNF-R1 and sTNF-R2) were investigated.⁵⁵⁾ Composition of the supplement is shown in Fig. 1, and subject characteristics are summarized in Table 1. Subject patients ingested 1000 ml/day of the supplement for 5 days before surgery (Fig. 2), and the control patients consumed an ordinary diet. As shown in Figs. 3, 4, and 5, the levels of inflammatory markers, cytokines, and cytokine receptors in the supplemented patients were lower in comparison to the control patients on day 0 (just before surgery) and/or on postoperative day 1 and 3. Significantly lower levels of PMN-elastase and IL-8 in the supplemented patients compared to the control patients were observed on postoperative day 3 (Figs. 3 and 4). These antiinflammatory effects of the supplement might result from not only n-3 PUFAs but also from arginine.

Conjugated Linoleic Acid (CLA)

CLA is a term for LA (18:2 n-6) isomers in which the 2 double bonds are conjugated. In 1979, mutagenic inhibitory activity of an extract of fried ground beef was reported,⁵⁶⁾ and the active agents were subsequently identified as CLAs.⁵⁷⁾

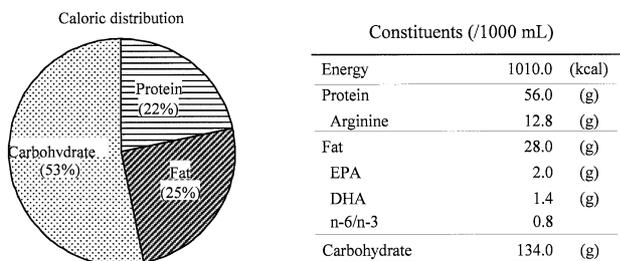


Fig. 1. Supplement Composition

Since then, additional biological effects of CLA have been reported, and evidence now suggests that these fatty acids function as modulators of immune responses, cell growth, nutrient utilization, nutrient storage, and lipid metabolism.⁵⁸⁾ CLAs are produced naturally by bacterial hydrogenation and isomerization in the gut of ruminant animals, or they can be generated chemically by alkali isomerization of LA. Although there are as many as 28 possible isomeric forms of CLA, by far the most abundant isomer in nature is *cis*-9, *trans*-11 CLA.^{58,59)} In the human diet, CLAs are consumed in milk fat and in meats derived from ruminant animals, whereby they represent 0.5–2% of fatty acids, and the *cis*-9, *trans*-11 CLA isomer in these foods is more than 70%.^{58,60)} Studies in animal models have indicated promoting effects of CLA

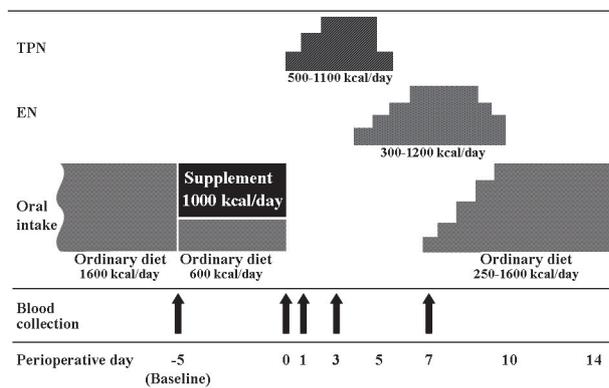


Fig. 2. Perioperative Nutritional Management and Blood Collection in the Supplement Group

Control group subjects received an ordinary diet before the surgery, and their postoperative nutritional management was the same as that in the supplement group. Blood samples were collected on the same day as in the supplement group, except for 5 days before the surgery (baseline). TPN, total parenteral nutrition; EN, enteral nutrition.

Table 1. Subject Characteristics⁵⁵⁾

	Supplement group (n = 12)	Control group (n = 14)	
Bile duct cancer	6	4	
Pancreatic cancer	3	4	
Gastric cancer	2	3	
Esophageal cancer	1	3	
Male/female	11/1	11/3	n.s.
Age	64 ± 10	64 ± 15	n.s.
Body mass index (kg/m ²)	19 ± 3	19 ± 8	n.s.
Operation time (min)	498 ± 58	476 ± 52	n.s.
Blood loss (mL)	952 ± 412	934 ± 372	n.s.

n.s., no significant differences between the two groups.

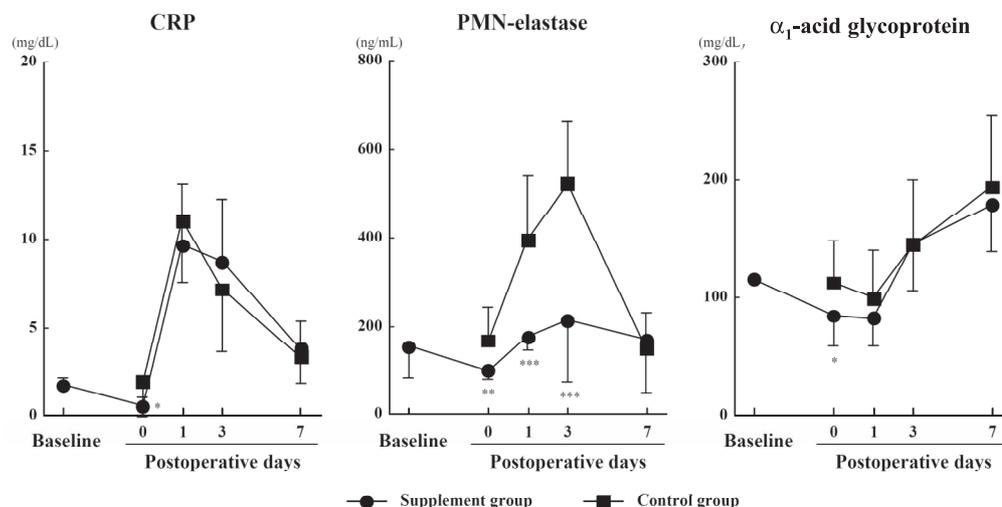


Fig. 3. Perioperative Changes in Inflammatory Markers⁵⁵⁾

Each point represents the mean and standard deviation. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared with the control group.

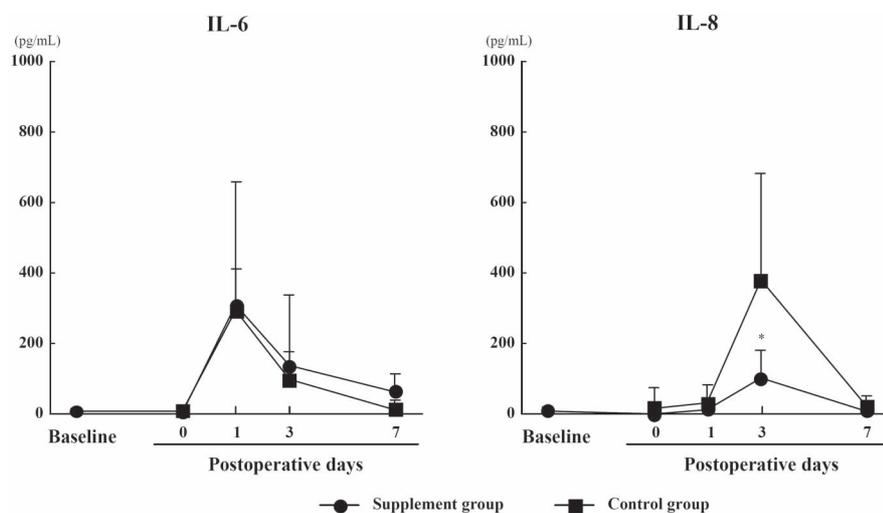


Fig. 4. Perioperative Changes in Cytokines⁵⁵⁾

Each point represents the mean and standard deviation. * $p < 0.001$ compared with the control group.

on lipid and glucose metabolism, such as anti-diabetic, antiatherogenic, hypocholesterolemic, and hypotriglyceridemic effects as well as beneficial effects on the immune systems and adipose tissue.^{61,62)} Studies in humans have confirmed the beneficial effects of CLA on body composition and profile of plasma lipoproteins.^{63,64)} The most studied CLA isomers are *cis*-9, *trans*-11 and *trans*-10, *cis*-12 CLA; the first has anticarcinogenic effects and the second reduces body weight and fat percentage.⁶²⁾ Although the list of purported benefits of CLA is impressive, there have been several reports that dispute the antiatherogenic, hypocholesterolemic, and hypotriglyceridemic effects of CLA

in animals.^{65–68)} The effect of these isomers on endothelial dysfunction leading to inflammation and atherosclerosis is of interest because of the enormous effect of the disease on society. Chemically produced and commercially available CLA is a mixture of *cis*-9, *trans*-11 and *trans*-10, *cis*-12 CLA (CLA mixture) and contains 40% of each of the 2 isomers.^{58,60)} A supplementation study of *trans*-10, *cis*-12 CLA, CLA mixture, or placebo in men with metabolic syndrome revealed a significant increase in CRP levels (110%) in the *trans*-10, *cis*-12 CLA-supplemented group compared with placebo.⁶⁹⁾ CLA mixture supplementation reduced fibrinogen concentration but had no effect on CRP

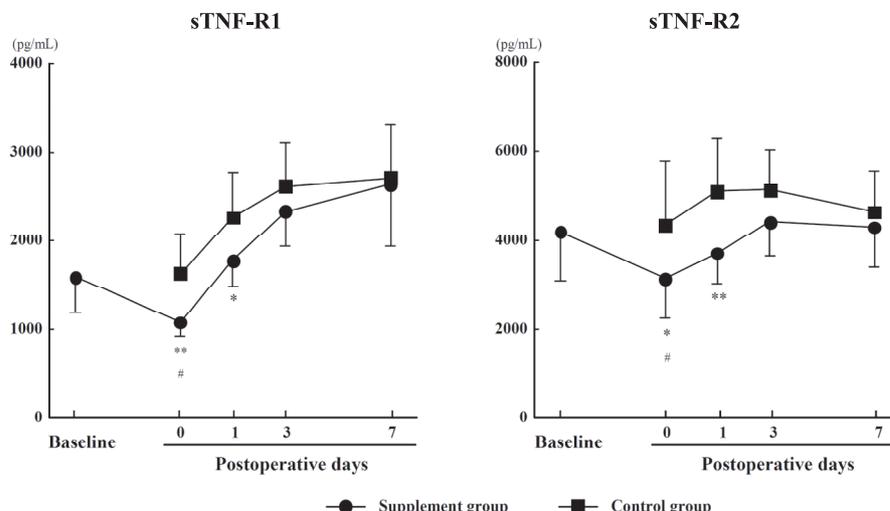


Fig. 5. Perioperative Changes in Cytokine Receptors⁵⁵⁾

Each point represents the mean and standard deviation. * $p < 0.05$, ** $p < 0.01$ compared with the control group. # $p < 0.05$ compared with the baseline value.

and IL-6 levels in subjects with type 2 diabetes meli-
litus.⁷⁰⁾ A significant increase in CRP levels after
3 months of supplementation of the CLA mixture
(4.2 g/day) compared with placebo in healthy volun-
teers was also reported.⁷¹⁾ A double-blind, random-
ized, parallel intervention study in postmenopausal
women supplemented with oil rich in the CLA mix-
ture, the naturally occurring *cis*-9, *trans*-11 CLA
(CLA milk), or olive oil for 16 weeks was con-
ducted. Results from this study indicated that di-
ets supplemented with the CLA mixture had sev-
eral adverse effects on CVD markers such as higher
levels of CRP, fibrinogen, and plasminogen activa-
tor inhibitor-1, whereas supplementation with the
CLA milk oil resulted in only a small but signifi-
cant increase in lipid peroxidation compared with
olive oil.⁶⁰⁾ Thus, supplementation with CLA in the
human diet may not be recommended until addi-
tional information is obtained from studies on the
mechanisms of CLA and specific CLA isomers at
the molecular level. Since purified preparations of
the *cis*-9, *trans*-11 and *trans*-10, and *cis*-12 isomers
of CLA are now commercially available, studies us-
ing purified isomers are anticipated.

CANCER AND DIETARY PUFAs

The cancer promoting and suppressing effects
of n-6 and n-3 PUFAs, respectively, have been
suggested, which include alterations in the prop-
erties of cancer cells (proliferation, invasion, metas-

tasis, and apoptosis) as well as those of host cells
(inflammation, immune response, and angiogen-
esis).^{11, 35, 72)} Although recent observational stud-
ies supporting suppressive effects of n-3 PUFAs
on colorectal cancer^{73, 74)} and a case-control study
demonstrating an inverse correlation between long-
chain n-3 PUFAs and overall prostate cancer risk⁷⁵⁾
have been published, many epidemiological studies
failed to demonstrate a statistically significant as-
sociation between n-3 PUFAs and reduced cancer
risk.¹¹⁾ The poor correlation of fatty acid consump-
tion with reduced cancer risk might be in part ex-
plained by the characteristics of the population and
ecological studies, which mainly rely on data from
self-reported dietary fatty acids intakes or from es-
timates based on national consumption, and there
were wide variations in the amount and source of
n-3 PUFAs consumed in each study.¹¹⁾ Therefore,
an interventional study is necessary to estimate the
effects of PUFAs on cancer. Several clinical in-
tervention trials using fish oil or n-3 PUFAs have
been performed to investigate the cancer suppress-
ive effects and utility of nutritional support for
cancer patients to reduce weight loss or modulate
the immune system. Initial clinical trials suggested
that nutritional supplements containing n-3 PUFAs
could relieve weight loss or lead to weight gain in
advanced cancer patients with cachexia.^{76–79)} Al-
though a recent review failed to find sufficient evi-
dence to support the use of oral EPA in the treat-
ment of cancer cachexia,⁸⁰⁾ weight stabilization or
weight gains could be achieved when patients were

able to consume high doses of the dietary supplement for prolonged periods with limited gastrointestinal side effects^{81,82}) Thus, it is suggested that high-dose intake of n-3 PUFAs may have a role in nutritional support of cancer patients. Inflammation appears to play a critical role even in the development of human cancer.^{6,83,84}) It is indicated that antiinflammatory agents, which primarily block the metabolism of AA, are beneficial in the prevention of colon⁸⁵) and prostate⁸⁶) cancer, but the cardiovascular risk of cyclooxygenase-2 inhibitors, including celecoxib, may limit the clinical use of these drugs.⁸⁷) An approach to reduce the intake of n-6 PUFAs and increase the proportion of n-3 PUFAs in our diet to suppress the production of proinflammatory eicosanoids and thus decrease the risk of cancer is of interest. However, a review of a large number of literature reports did not find a significant, consistent association between n-3 PUFA intake and cancer prevention.⁸⁸) Nutritional supplements enriched in n-3 PUFAs have also been tested in clinical trials for their ability to improve the outcome of other cancer treatments. Several studies have shown reduced infectious complications or inflammatory responses after major abdominal surgery for cancer.^{56,89,90}) In addition, DHA supplementation during anthracycline-based chemotherapy in breast cancer patients with rapidly progressing visceral metastases was devoid of adverse side effects and can improve the outcome of chemotherapy such as the response rate, time to progression, and overall survival.⁹¹)

BIOACTIVE GHRELIN AND FATTY ACIDS

Ghrelin, a 28-amino acid peptide hormone produced principally by stomach tissue, was discovered as an endogenous ligand for the growth hormone secretagogue receptor (GHSR) 1a with potent growth hormone releasing activities.⁹²) Numerous

studies have identified multiple physiological functions for ghrelin. In addition to stimulating growth hormone release from the pituitary,^{92–95}) ghrelin promotes food intake, induces adiposity,^{96–99}) and influences metabolic fuel preference.¹⁰⁰) Ghrelin can also improve cardiac function.^{101–103}) Thus, multiple physiological functions for ghrelin have been identified. Ghrelin levels are modulated by changes in nutritional status such as feeding and fasting or exposure to high-fat diets.^{104,105}) The major active form of ghrelin is modified by an acyl group with a fatty acid at the third amino acid from the N-terminus, serine (Ser3) and acyl modification is essential for the activation of the GHSR1a, which induces growth hormone release and has orexigenic, metabolic, and insulin secretory effects.^{92,106})

Although the primary acyl chain-modified ghrelin molecules in humans and rodents are esterified by an n-octanoyl group (8:0),⁹²) a minor population of ghrelin peptide exists with different acyl modifications: n-decanoyl (10:0) and n-decenoyl (10:1).^{107,108}) According to an examination using a variety of synthetic acyl-modified ghrelin peptides, the potency of ghrelin biological activity was altered by different acyl groups, and octanoic acid was not the only modification of Ser3 to sustain the activity of ghrelin as other acyl acid modifications maintained activity.¹⁰⁹) A structural schema of representative active ghrelin and inactive ghrelin is shown in Fig. 6. It is reported that ingestion of either medium-chain fatty acids such as n-hexanoic, n-octanoic, and n-decanoic acid or medium-chain triacylglycerols including glyceryl trihexanoate, glyceryl tri-octanoate, and glyceryl tridecanoate increased acylated ghrelin concentrations in the stomach without increasing either total (acyl- and desacyl-) or mRNA expression of ghrelin, indicating that exogenous free fatty acids are utilized as the direct source of acyl modification of ghrelin; therefore, modification of ghrelin activity through administration of exogenous free fatty acids may be a potential therapeutic modality for the clinical manipulation of en-

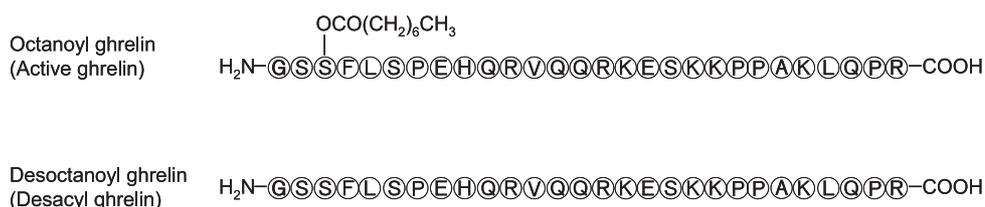


Fig. 6. Schematic of Human Ghrelin

ergy metabolism.¹¹⁰⁾ Desacyl ghrelin was initially thought to be inactive, but recent *in vitro* and *in vivo* evidence have identified biological actions of this desacyl peptide, and its action is independent of GHSR.¹¹¹⁾ The enzyme catalyzing the transfer of acyl groups to ghrelin Ser3 was recently identified as ghrelin O-acyltransferase (GOAT). GOAT is a membrane-bound enzyme that attaches octanoate to Ser3 of ghrelin.^{106, 112)} The tissues of the stomach and pancreas in humans express transcripts for both ghrelin and GOAT, which is consistent with GOAT being the acyltransferase for ghrelin.¹⁰⁶⁾ It is well established that the stomach is the principal tissue for acylated ghrelin production, and that changes in ghrelin production in this tissue greatly impact fluctuations caused by metabolic adaptation in organisms.¹¹³⁾ GOAT is an attractive target because ghrelin is the only protein known to be octanoylated; therefore, GOAT inhibition is likely to interfere with ghrelin action through GHSR and might protect against obesity in humans.^{114, 115)} RIA and ELISA kits to distinguish acylated ghrelin from desacyl-ghrelin are commercially available and have been used clinically to determine their respective plasma levels.^{8, 116–119)}

CONCLUSIONS

In addition to the role as major substrates for energy production and storage, fatty acids modulate inflammatory processes and contribute to the pathophysiological states of chronic mild inflammation-related diseases such as CVD, diabetes, obesity, and certain types of cancer. Although there is insufficient evidence as to the involvement of MUFAs in inflammatory process and limited evidence indicating a potential proinflammatory role of saturated and *trans* fatty acids, there is considerably stronger evidence suggesting that increasing the intake of n-3 PUFAs results in favorable antiinflammatory effects. Certain fatty acids may also have therapeutic effects by modifying the activity of ghrelin, which may result in the reduction of food intake and enable clinical manipulation of energy metabolism. The physiological function and pharmacological effects of fatty acids may be affected by an individual's age, sex, or nutritional status, and thus recommendations for optimal intake for the prevention and treatment of inflammatory processes should be tailored to each individual's needs.¹²⁰⁾ Further extensive and carefully planned studies are necessary

to determine the optimal intake of fatty acids.

Conflict of Interest Declaration The authors have no conflicts of interest to declare.

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