Original Article

Macronutrient innovations: The role of fats and sterols in human health

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Dietary intake of fats and sterols has long been known to play a critical role in human health. High proportions of saturated fat, which increase blood cholesterol levels, are mainly found in animal fat and some plant oil (e.g. cocoa butter, palm oil etc.). The predominant polyunsaturated fatty acid (PUFA) in the Western diet is linoleic acid (LA; 18:2n-6), an essential fatty acid, which is commonly found in vegetable seed oils. This is the parent fatty acid of n-6 series PUFA, which can be converted *in vivo* to C20 and C22 n-6 long chain (LC) PUFA. α-linolenic acid (ALA; 18:3n-3) is less abundant than LA and is another essential fatty acid; ALA is also present in some vegetable oils such as perilla, flaxseed, canola, soybean and walnut oils, and is the precursor of C20 and C22 n-3 LC PUFA. Sterols are widely distributed in animal tissue and plants, with cholesterol being the major sterol in animal tissue and β-sitosterol, campesterol and stigmasterol being the main sterols in plants. It has long been recognized that an increased dietary intake of saturated fat and (to a lesser extent) cholesterol, raises plasma/serum total and low-density lipoprotein (LDL)-cholesterol, and PUFA decreases these levels. Results from recent studies have shown that plasma/serum levels of lipids and lipoprotein lipids can also be decreased by plant sterols (phytosterols) and diacylglycerol (DAG). Conjugated linoleic acid (CLA, *cis*-9,*trans*-11–18:2) has been reported to have anticancer and antidiabetic activities. Fat as the DAG form has also been reported to have anti-obesity effects. Omega-3 PUFA have a beneficial effect on increased heart rate variability, decreased risk of stroke, reduction of both systolic and diastolic blood pressure and may be effective in managing depression in adults. Gamma-linolenic acid (GLA) and phytosterols have an anti-inflammatory activity. The GLA, when combined with docosahexaenoic acid (DHA), have been reported to have a beneficial effect in hyperactive children. These data show that various lipids are powerful bioactive compounds.

Key words: blood pressure, cancer, diabetes mellitus, fat, inflammation, lipoprotein lipids, neuropsychiatric disorders, obesity, sterol, thrombosis.

PLASMA/SERUM and LIPOPROTEIN LIPIDS

The relationship between dietary fats and serum cholesterol has been studied extensively for more than three decades. In 1965 Keys *et al.* and Hegsted *et al.* established that the saturated fatty acids (SFA) lauric (12:0), myristic (14:0) and palmitic acid (16:0), which were equally cholesterolemic, fatty acids with carbon chain lengths of less than 12, had little affect on blood cholesterol, while the SFA stearic acid (18:0) and monounsaturated fatty acid (MUFA) oleic acid (18:1) were neutral.[1,2] *Trans* fatty acids (TFA) from partially hydrogenated vegetable oils raise serum cholesterol levels.[3] Linoleic acid (LA) has been claimed to be the only fatty acid to appreciably lower plasma/serum total and low-density lipoprotein (LDL)-cholesterol when substituted for carbohydrate in the diet in early studies.[2,4] Results from recent studies suggest that saturates were not equally cholesterolemic, as reviewed by Kris-Etherton and Yu.[5] Myristic acid (14:0, mainly in dairy and meat fat) was more hypercholesterolemic than palmitic acid (16:0, high in meat, dairy fat and palm oil). Stearic acid (18:0, high in beef, lamb and chocolate) dose not raise total serum cholesterol. However, behenic acid (22:0) had a significantly total and LDL-cholesterol-raising effect compared with high-oleic acid sunflower oil in a more recent cross-over dietary intervention study in seven mildly hypercholesterolemic men aged 55–75 years.[6] Nestel *et al.* performed two studies on the effects of *trans* C18:1 on plasma lipoprotein lipid levels, in which the total fat provided 35% of energy. Low intake of TFA (4% of total energy) did not influence either LDL-C or high-density lipoprotein (HDL)-C levels. However, a high TFA intake (7% of total energy) raised LDL-C, while HDL-C levels were unaffected.[7,8] These results support previous findings by Zock and Katan that TFA are acting like SFA in their cholesterol-raising effect.[9] Plasma lipoprotein (a) levels were significantly higher in humans fed diets with TFA than diets with palmitic acid and with oleic

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acid.[8,10] α-linolenic acid (ALA, 18:3n-3), an n-3 polyunsaturated fatty acid (PUFA) from plant sources had a parallel effect on plasma/serum total and LDL-cholesterol compared with LA.[11,12] The n-3 PUFA, especially those from marine oils, reduce serum triacylglycerol (TAG) levels.[13,14] Recent studies have challenged the idea that the hypocholesterolemic effect of vegetable oils does not simply depend on the PUFA content, but also on the phytosterol component of vegetable oils.[15,16] In two studies Jones *et al.* investigated the effect of phytosterol on plasma levels of TAG, total, HDL- and LDL-cholesterol. In the first study 22 healthy free-living subjects (male, 18; female, four) aged 20–58 years consumed two experimental diets over two 10-day periods with or without 21.2 mg/kg bodyweight per day tall oil phytosterols in a cross-over study with a 14-day wash period between the diets (tall oil is derived from pulping of pine wood). In the diet with phytosterol, plasma total and LDL-cholesterol concentrations decreased by 6% and 9%, respectively, compared with the diet without the phytosterol ($P < 0.01$).[17] In the second study, 15 hypercholesterolemic subjects aged 37–61 years were randomly assigned to one of the three diets for a period of 3 weeks, followed by a 5-week 'wash-out period', before being assigned to the other diet. One diet contained margarine alone as control, a second contained margarine with 8% phytosterol from rapeseed oil (1.84 g/day) and a third contained margarine with 8% phytostanol, a hydrogenated phytosterol from rapeseed oil, saturation of phytosterols at the 5-α position (1.84 g/day). Plasma LDL-cholesterol concentration was significantly reduced after 21 days phytosterol and phytostanol diets compared with control diet ($P < 0.05$). Plasma total cholesterol concentration was significantly reduced after 21 days phytosterol diet ($P < 0.05$), but not phytostanol diet compared with control diet. Plasma concentrations of TAG and HDL-cholesterol did not differ across diets.[18] Subsequently, these compounds have been intentionally added into food products such as margarine, mayonnaise, yogurt and cereal bars in various countries. Phytosterols are compounds similar in structure to cholesterol. It was visualized that their structural similarity might allow competition between phytosterols and cholesterol for absorption in the gut. Ikeda and Sugano proposed that it might due to the ability of phytosterols to interfere with cholesterol-bile salt micelle solubility in the intestine.[19] Neuvonen *et al.* suggested that it might involve the enterohepatic circulation of bile acid[20] because phytosterols have been reported to enhance bile acid excretion.[21] Serum TAG levels were significantly decreased in 13 (female, nine; male, four) hyperlipidemic or obese children aged 7–17 years when they consumed oil as a diacylglycerol (DAG) form for 5 months when compared with baseline.[22] The TAG concentrations of post-prandial serum and chylomicron were significantly lower in the DAG diet at post-prandial 4 and 6 h compared with the TAG diet in 40 healthy men (aged 33 ± 8 years).[23] The mechanism of the hypotriacylglycerolemia of dietary DAG has been proposed due to the reduction of re-esterification (by glycerol and free fatty acid) and chylomicron assembly in the small intestine or to the reduction of subsequent secretion of chylomicron into the circulation.[23]

Blood pressure

The effect of long chain (LC) n-3 PUFA from fish on blood pressure (BP) has been evaluated in a meta-analysis of 31 placebo controlled trials in 1356 subjects. The results indicated that systolic BP fell by 3.4 mmHg and diastolic BP fell 2.0 mmHg following ingestion of fish oil 5.6 g/day in a number of hypertensive studies.[24] Two human studies recently provided further evidence of the importance of LC n-3 PUFA on BP. In a dietary invention study, 69 overweight (BMI > 25 kg/m^2) medication-treated hypertensive subjects were randomized to a daily fish meal (approx. 3.65 g/day of LC n-3 PUFA), weight reduction, the two regimens combined, or a control regimen for 16 weeks, and 63 subjects completed the study. Both systolic and diastolic BP, bodyweight and heart rate were significantly decreased in the fish diet group compared with a control diet even after adjustment for changes in urinary sodium, potassium, or the sodium/potassium ratio, as well as dietary macronutrients.[25] The second study was an observational study in which the effect of n-3 PUFA from fish on blood pressure, platelet fatty acid levels and heart rate variability was investigated in 43 subjects (male, 24; female, 19) aged 18–62 years who were patients with type 1 diabetes mellitus and 38 subjects (male, 24; female, 14) aged 37–77 years who were patients with type 2 diabetes mellitus. Each patient completed a food frequency questionnaire and gave a blood sample. Blood pressure, heart rate variability, plasma and lipoprotein lipids and platelet fatty acid composition were measured. The study found that fish intake was significantly positively associated with platelet membrane docosahexaenoic acid (DHA) levels. According to the platelet DHA level, patients were divided into three tertiles: patients in the 1st tertile ($n = 14$) had the lowest, patients in the 3rd tertile ($n = 15$) had the highest, and patients in the 2nd tertile had moderate DHA levels. Compared with patients in the 1st tertile, patients in the 3rd tertile had a significantly lower diastolic BP and higher 24-h heart rate variability (increased heart rate variability has a beneficial effect on dysrhythmia). Platelet DHA level was significantly positively associated with 24-h heart rate variability in patients with type I diabetes mellitus, but this association was not significant in patients with type II diabetes mellitus.[26] Mori *et al.* found that eicosapentaenoic acid (EPA) and DHA differed in their effect in BP and heart rate in a double blind, randomized placebo-controlled human study. In this study 55 overweight (BMI 25–30) subjects aged 20–65 years were randomized to 4 g/day of purified EPA, DHA, or placebo (olive oil) capsules for 6 weeks. Compared with the placebo group, DHA significantly reduced both systolic and diastolic BP (measured over 24 h) by 5.8 and 3.3 mmHg, and the waking systolic and diastolic BP by 3.5 and 2.0 mmHg, respectively ($P < 0.05$). Relative to the placebo group, 24-h heart rate, when awake and when asleep, were significantly reduced by 3.5 ± 0.8, 3.7 ± 1.2 and 2.8 ± 1.2 b.p.m., respectively. However, EPA

had no significant effect on BP and heart rate.[27] A recent animal study found that n-3 PUFA deficiency in the perinatal period resulted in an increase in BP later in life in Sprague–Dawley rats.[28] In this study 40 Sprague–Dawley rats were randomly divided to a diet deficient in n-3 PUFA (α-linolenic acid; DEF) and a diet adequate in n-3 PUFA (CON) for 64 days, then half of the animals on DEF crossed to CON (DEF–CON) and vice-versa (CON–DEF) for 150 days. The results showed that mean BP was significantly higher in the DEF–DEF group compared with the three other groups, and significantly higher in DEF–CON than CON–CON. Although the study was carried out on rats, the implication of these findings is that an adequate n-3 PUFA intake at an early age may prevent increased BP in later life in humans.[28]

Thrombosis

Arterial thrombosis is generally recognized to play a major role in the transition from stable to acute ischaemic heart and cerebral diseases, manifested by unstable angina, acute thrombotic infarction and sudden death. Platelet aggregation is an early event in the development of thrombosis. It is initiated by thromboxane A_2 (TXA_2), a potent platelet aggregation agent and vascular contractor, produced from arachidonic acid (AA; 20:4n-6), a LC n-6 PUFA in the platelet membrane.[29,30] Eicosapentaenoic acid (20:5n-3), a LC n-3 PUFA, is released from phospholipids of the platelet membrane and, as a 'false' substrate, competes with AA for access to cyclooxygenase and produces an alternative form of thromboxane (TXA_3), which is relatively inactive in promoting platelet aggregation and vasoconstriction.[31] This situation can lead to a reduced TXA_2 production and thus a lower thrombosis tendency.[32,33] A diet with a high n-6 to n-3 PUFA ratio can cause a high tissue n-6 to n-3 PUFA ratio (i.e. increased AA to EPA ratio), which may promote production of TXA_2, leading to an increased thrombosis tendency.[34] Evidence from dietary intervention studies has found that the production of TXA_2 was decreased by LC n-3 PUFA in humans[35,36] and in animals,[37,38] and by plant n-3 PUFA (ALA) in humans[39] and in animals.[40,41] Two current prospective cohort studies from the USA Nurses' Health study examined the effect of the intake of n-3 PUFA from plants and fish on ischaemic heart and cerebrovascular diseases in women. In the first study the dietary intake of ALA was calculated from a food frequency questionnaire completed in 1984 by 76 283 nurses aged 38–63 years who were free from previously diagnosed cardiovascular disease and cancer. There were 597 cases of non-fatal myocardial infarction and 232 cases of fatal ischaemic heart disease documented during 10 years of follow up. After the adjustment of confounding factors the results showed that higher intakes of ALA were significantly associated with a reduced risk of fatal ischaemic heart disease in this study population.[42] In the second study 79 839 female nurses, aged 34–59 years in 1980, who were without prior diagnosed cardiovascular disease, cancer, and history of diabetes and hypercholesterolaemia completed a food frequency questionnaire. After 14 years follow up 574 incident strokes were documented with 303 ischaemic strokes (264 thrombotic and 39 embolic infarctions). Compared with women who ate fish less than once per month, those with a higher intake of LC n-3 PUFA from fish had a lower risk of total stroke. Among stroke subtypes, a significantly reduced risk of thrombotic infarction was found among women who ate fish two or more times per week. These data indicate that higher consumption of fish is associated with a reduced risk of thrombotic infarction.[43] These results confirm that an increased dietary n-3 PUFA intake is protective against cardiovascular thrombotic infarction. Hornstra suggested that SFA were prothrombotic based on studies using an animal model.[44] It has been found that plasma factor VII activity was significantly positively correlated with plasma stearic acid concentration.[45,46] Mitropoulos *et al.* proposed that dietary fat induced changes in plasma factor VII activation through an effect on plasma free stearic acid concentration.[45] However, dietary intake of stearic acid has been reported to have an antithrombogenic effect.[47,48]

Cancers

Many studies have investigated the effect of dietary fat and sterol on cancers in experimental models. In general, high intake of n-6 PUFA favoured the development of tumours, whereas equivalent consumption of n-3 PUFA reduced or protected tumour development, as reviewed by Cave.[49] However, there are only a few publications on human studies. Conjugated linoleic acid (CLA), which is commonly a mixture of several isomers (the main ones being *cis*-9,*trans*-11-18:2 and *trans*-10,*cis*-12-18:2[50]), has been shown to exhibit anticarcinogenic properties in various animal models and cultured human tumour cells, which have been reviewed by others.[51–55] The interest in CLA was stimulated by the observation in 1987 that CLA was an effective inhibitor of benzo(a)pyrene-initiated mouse epidermal neoplasia.[56] Since then there have been numerous reports of biological and physiological effects of CLA (the literature on which can be followed on the following Internet address: http://www.wisc.edu/fri/clarefs.htm). The major CLA isomer found in foods derived from ruminant animals (cattle, goats and sheep) is *cis*-9,*trans*-11-18:2, and this isomer is found at a level of 3.2 ± 0.2 mg/g in milk fat (Ma *et al.*).[57] Most studies on anticarcinogenic properties have been conducted using a mixture of CLA isomers chemically produced from vegetable oils.[58] In a recent study Igarashi and Miyazawa compared the effect of CLA and conjugated linolenic acid on cultured human tumour cells, and the results have indicated that conjugated linolenic acid is more cytotoxic to human tumour cells than CLA.[59] Consumption of fatty fish, high in LC n-3 PUFA, showed a decreased risk of prostate cancer in a population-based prospective study from Sweden in 6272 men. In this study it was reported that men who ate moderate or high amounts of fish had a two- to threefold lower frequency of prostate cancer compared with men who ate no fish.[60] Docosahexaenoic acid manifested more effective inhibitory activity than EPA on transcription

factor activator protein 1 (AP-1), which is implicated in the development of cancer in an experimental animal model.[61] A recent prospective cohort study from Finland reported the effect of dietary fat and cholesterol on colorectal cancer in 9959 men and women free of diagnosed cancer. Baseline information was collected from the subjects between 1967 and 1972, and 109 cases of colorectal cancer were documented in late 1999. After adjustment for other confounding factors, a high cholesterol intake was associated with colorectal cancer while total fat, saturated fat, monounsaturated fat and PUFA were not significantly associated with colorectal cancer risk.[62] Compared with n-6 PUFA, LC n-3 PUFA from fish oil had a protective effect on development of colon cancer in rats.[63] In a review by Awad and Fink it was suggested that dietary phytosterol may offer protection from the many common cancers in Western societies, such as colon, breast and prostate cancer.[64] However, in 120 852 subjects in a 6.3-year cohort follow-up study from the Netherlands there was no association between dietary intake of phytosterols and the risk of colon and rectal cancer.[65]

Inflammation

Arachidonic acid (20:4n-6) is a substrate of pro-inflammatory eicosanoids such as prostaglandin E $(PGE)_2$ and leucotriene B $(LTB)_4$, while LC n-3 PUFA DHA and EPA from fish oil, and n-6 PUFA gamma-linolenic acid (GLA; 18:3n-6) are substrates for eicosanoids, which are antagonistic towards these produced from AA.[66] The LC n-3 PUFA and GLA are claimed to have an anti-inflammatory effect, and the LC n-3 PUFA are thought to result in the amelioration of rheumatoid arthritis and related disorders.[67] Arachidonic acid-derived leucotrienes (LT), recognized as 'slow-reacting substance anaphylaxis', are mediators of allergic responses and inflammation.[68] Arachidonic acid can increase the formation of other pro-inflammatory substances such as cytokines, tumour necrosis factor (TNF)-α, interleukin (IL)-6 and reactive oxygen species as reviewed by Darlington and Stone.[69] The LC n-3 PUFA EPA and DHA compete with AA at the cyclooxygenase and lipoxygenase level, which results in a decreased production of AA-derived pro-inflammatory eicosanoids, cytokines, IL-6 and reactive oxygen species.[70] The 5-series of LT can be produced from EPA, and they are inactive relative to the AA-derived 4-series of LT.[67,71] Gamma-linolenic acid can be elongated *in vivo* to 20:3n-6, which is an immediate precursor of PGE_1, an eicosanoid with known anti-inflammatory and immunoregulatory properties.[72,73] A recent study found that GLA reduces IL-1B (an important mediator of joint tissue injure and inflammation) production by human monocytes *in vitro*.[74] Phytosterol, β-sitosterol and stigmasterol have been reported to generate anti-inflammatory activity in acute animal inflammatory models by the inhibition of neutrophil migration into inflamed tissue[75] and myeloperoxidase activity.[76] Recent results from a placebo-controlled trial in marathon runners showed that phytosterols had a beneficial effect on inhibition of inflammation. Namely, the ratio of cortisol to dehydroepiandrosterone sulphate (a marker of inflammation) and IL-6 (a mediator of inflammation) were significantly decreased after an ultra-marathon in the runners ($n = 9$) who received the phytosterol capsules (a mixture of beta-sitosterol and beta-sitosterol glucoside), compared with their counterparts ($n = 8$) who received placebo capsules.[77]

Neuropsychiatric disorders

Manic-depressive illness (bipolar disorder), depression and schizophrenia are common neuropsychiatric disorders. Results from the case control and clinical trails have shown that LC n-3 PUFA play a regulating role in neuropsychiatry performance. A lowed serum/plasma cholesterol concentration has been suggested to be associated with an increased risk of suicide and depression.[78] Results from a recent 4-month double-blind, placebo-controlled trial in 30 patients with type I or II bipolar disorder aged 18–65 years showed that episodes of severe mania and depression were significantly reduced in the LC n-3 PUFA supplementation group ($n = 14$; 9.6 g/day) compared with the placebo group ($n = 16$).[79] Decreased LC n-3 PUFA has been reported in serum phospholipid and cholesteryl ester of depressive patients,[80,81] and in erythrocyte membranes of schizophrenic patients.[82,83] As reviewed by Richardson and Puri, and Kidd, abnormalities of 20- and 22-carbon PUFA such as 20:4n-6, 20:5n-3 and 22:6n-3 are associated with attention-deficit/hyperactivity disorder (ADHD).[84,85] A recent prospective 5–8-year follow-up study in 29 133 men aged 50–69 years showed that low serum cholesterol concentrations were associated with low mood, which resulted in an increased risk of hospital treatment due to major depressive disorder and suicide.[86] A recent case-control study found that serum cholesterol concentration was significantly lower in parasuicide subjects with a mean age of 44 ± 21 years compared with 331 sex- and age-matched controls ($P < 0.001$).[87] Mufti *et al.* reported that a low serum cholesterol level was strongly associated with violent behaviour among 20 psychiatric patients.[88] These results suggested that the widespread use of cholesterol-lowering drugs could lead to increased changes in mood. Mechanisms of the n-3 PUFA effect on neuropsychiatric disorders may be due to influencing the biophysical properties of the neuronal membrane.[78] Biophysical properties of synaptic membranes directly affect neurotransmitter biosynthesis, signal transduction, uptake of serotonin, binding of α-adrenergic and serotonergic receptors and monoamine oxidase activity. These factors are all implicated in the neurobiology. It has been reported that 20:5n-3 is able to reverse the phospholipid abnormalities in schizophrenia via inhibition of PUFA-specific phospholipase A_2, an enzyme that removes PUFA from the sn-2 position of membrane phospholipids or by activation of a fatty acid coenzyme A ligase.[82] It may also be possible that n-3 PUFA are operating through the *N*-acylethanolamines (NAE) and 2-acylglycerols because these lipids are endogenous ligands for the cannabinoid receptors found predominantly in the brain.[89] In piglets, brain levels of NAE increased fourfold for 20:4n-6, fivefold for 20:5n-3, ninefold for 22:5n-3 and 10-fold for 22:6n-3 after being fed a diet

with 20:4n-6 and 22:6n-3 for 18 days compared with a diet without 20:4n-6 and 22:6n-3.[90]

Diabetes mellitus and obesity

Evidence from dietary intervention and prospective follow-up studies indicates that dietary intake of PUFA and phytosterol could be beneficial, whereas cholesterol, *trans* and saturated fatty acids could adversely affect insulin resistance and glucose metabolism. In a large (n = 110 660) and long-term (6 years) intervention study from China (the Da Qing IGT and Diabetes Study), the dietary treatment group and physical exercise group had a significantly lower cumulative diabetes incidence compared with the control group. The 110 660 subjects aged 25–74 years were recruited from 33 health-care clinics in 1986. After health examination screening tests, 577 subjects were classified as having impaired glucose tolerance. The subjects were randomized into a clinical trial group, either to a control group or to one of three active intervention groups: diet only (low total fat, PUFA replacing saturated fat and high fibre); physical exercise only; and diet plus exercise. After 6 years the cumulative diabetes incidence was significantly lower in the dietary treatment group (43.8%), the physical exercise group (41.1%) and the diet plus exercise group (46.0%) than in the control group (67.7%) ($P < 0.05$).[91] A more recent similar randomized intervention study from Finland involved 522 overweight (BMI = 31 ± 4.6) subjects aged 55 ± 7 years, with impaired glucose tolerance who were divided into the intervention group (n = 265) and control group (n = 257). The subjects in the intervention group were given individual advice on dietary intake of energy, total and saturated fat, and moderate physical exercise. After 4 years the intervention group had a significantly lower cumulative diabetes incidence than the control group (11% *vs* 23%; $P < 0.001$).[92] Two recent large prospective follow-up studies from the USA showed that PUFA and vegetable fat have a protective effect on type II diabetes. The first study examined the relationship between dietary fat intake and risk of type II diabetes in 84 204 female nurses aged 34–59 years in 1980. A total of 2507 cases of type II diabetes were documented during 14 years of follow up. The risk of type II diabetes was significantly positively associated with dietary intake of *trans* fatty acids and cholesterol, and negatively associated with vegetable fat, n-3 and n-6 PUFA.[93] In the second study the association between intake of dietary fat and incident type II diabetes was examined in 35 988 older Iowa women aged 55–69 years in 1986, in which a total of 1890 incident cases of type II diabetes was reported during 11 years of follow up.[94] However, some results were not consistent with the first study because the dietary intake of *trans* fatty acids was negatively, and n-3 PUFA was positively, associated with the incidence of type II diabetes. As reviewed by McCarty, CLA has a beneficial effect on adipocyte insulin resistance that might be found to aid diabetic glycemic control.[95] Results from an animal study in male diabetic fatty rats showed that CLA is able to normalize impaired glucose tolerance and improve hyperinsulinemia.[96] Phytosterols may also have a beneficial effect on diabetes because phytosterols reduce plasma lipids via the inhibition of the absorption of cholesterol in type I diabetes[97] and type II diabetic patients,[98] while increased plasma lipids may cause muscle lipid accumulation, and later will induce chronic insulin resistance.[99]

Both CLA and DAG have been reported to be associated with either changes in body composition or weight loss in animals and humans. In the case of CLA it now appears that *trans*-10, *cis*-12 CLA is the isomer that induces body composition changes via a reduced uptake of lipid by adipocytes, which results from an effect of the CLA on upregulating lipoprotein lipase and downregulating stearoyl CoA desaturase.[100] In rats, pigs and possibly humans, CLA may enhance lean body mass gain relative to fat mass gain (see 100 for review). Furthermore, the *cis*-9, *trans*-11 CLA isomer enhanced feed efficiency and growth in young rodents with no effects on body fat levels, while the *trans*-10, *cis*-12 CLA isomer reduced body fat levels but did not enhance body growth or feed efficiency.[100] Pariza *et al.* believe it is likely to be necessary to feed both isomers to achieve optimal effects on growth, feed efficiency and body composition in young growing animals.[100]

Consumption of 1,3-DAG is associated with a reduced post-prandial increase in plasma TAG compared with consumption of TAG.[23] Furthermore, short- and long-term consumption of DAG in adults is associated with weight loss.[101] A recent study on 1,3-DAG, in which the amount of α-linolenic acid (ALA) was 61%, showed a reduction of bodyweight and visceral fat in mice fed a high sucrose diet; in this study the leptin and insulin levels increased in the high TAG group over a 20-week period, but replacement of 3% (weight percentage) of TAG by the ALA-DAG was associated with a reduction in insulin and leptin levels.[102] A study in humans on calorie-restricted diets using 2.5–3.7 g/day of an ALA-DAG, containing 49% ALA, for 12–16 weeks showed a significant reduction in body fat area.[103] A second study in humans, using 2 g/day of an ALA-DAG with 59% ALA, for 6–12 weeks showed a significant reduction in visceral fat area, a significant reduction in very-low-density lipoprotein (VLDL) TAG levels and a significant increase in resting oxygen consumption. The authors concluded that the reduction in visceral fat area was the result of a reduced TAG synthesis and increased oxidation of fatty acids.[104]

Conclusions

Results from recent human and animal studies show that various lipids are powerful bioactive compounds. α-linolenic acid from plant sources had a parallel effect on plasma/serum total and LDL-cholesterol compared with LA. The marine LC n-3 PUFA reduce serum triacylglycerol. Phytosterol reduces plasma levels of TAG, total- and LDL-cholesterol. Diacylglycerol reduces plasma TAG levels and has also been reported to have anti-obesity effects. Conjugated linoleic acid has been reported to have anticancer, antidiabetic activities and effects on growth, feed efficiency and body composition in young growing animals. Omega-3 PUFA have a beneficial effect on increased heart rate

variability, decreased risk of stroke, reduction of both systolic and diastolic BP and may be effective in managing depression in adults. Gamma-linolenic acid and phytosterols have an anti-inflammatory activity. Gamma-linolenic acid and DHA have been reported to have a beneficial effect in hyperactive children. Decreased tissue levels of LC n-3 PUFA and cholesterol are associated with neuropsychiatric disorders. These data showed that fat and sterol play a critical role in human health in relation to cardiovascular disease, inflammation, cancer, diabetes mellitus, obesity and neuropsychiatric disorders.

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