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Fat and Fatty Acid Intake and Metabolic Effects in the Human Body

T.A.B. Sanders

Nutritional Sciences Division, King's College London, London, UK

Introduction

Dietary fat intake influences the physiological processes that transport fat between tissues as well as influencing the substrates for metabolic processes. Lipids need to be transported as lipoprotein complexes owing to the poor water solubility of lipids. Variations in plasma lipoprotein concentration influence the development of atherosclerosis. Atherosclerosis is the underlying pathological disorder underlying the major cardiovascular diseases (CVD; ischemic heart disease and ischemic cerebrovascular disease), which are leading causes of death worldwide. Clinical events usually result from the rupture of a plaque and subsequent thrombus formation. Elevated concentrations of apolipoprotein B100-containing lipoproteins (very-low-density lipoprotein (VLDL), intermediate-density lipoprotein and low-density lipoprotein (LDL)) are causally linked to the atherogenic process. Atherogenesis is a chronic inflammatory process that results from the accumulation of fatty streaks in large/medium arteries, which progress to form fibrous plaques over time [Ross, 1999]. The foam cells that constitute the initial lesion (the fatty streak) result from the uptake of apolipoprotein B100-containing proteins (mainly LDL) by tissue macrophages. Native LDL is not taken up by macrophages, but chemically modified (i.e., oxidated or glycated) apolipoprotein B100 is avidly taken up by the tissue macrophages, as are chylomicron remnants, to form foam cells. There is convincing evidence that foam cells can progress to form fibrous atherosclerotic plaques. There is a large body of scientific evidence, both in animal models and corroborated by human observational and intervention studies, showing that dietary fat intake is causally involved in atherogenesis and may also influence arterial thrombosis. With regard to the experimental feeding studies in animals, the evidence is convincing that elevations of plasma lipids caused by modification of dietary fat intake result in atherosclerosis. These animal studies indicate that fats high in saturated (SFA), monounsaturated (MUFA) and *trans* fatty acids (TFA) promote atherosclerosis [Brown et al., 2007], whereas diets containing oils high in polyunsaturated fatty acids (PUFA) inhibit atherosclerosis and low-fat diets do not promote atherosclerosis. This review focuses on the evidence from dietary intervention studies in man that dietary fat intake influences metabolic factors associated with risk of CVD.

Fasting Plasma Lipid and Lipoproteins and Dietary Fat Intake

Plasma total cholesterol (TC) concentration shows a continuous association with CVD risk without a threshold, but with the absolute risk increasing with age, smoking habit and raised blood pressure [Lewington et al.,

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Prof. T.A.B. Sanders
Nutritional Sciences Division, King's College London
4th Floor Franklin-Wilkins Building, Stamford Street
London SE1 9NH (UK)
Tel. +44 207 848 4273, Fax +44 207 848 4171, E-Mail tom.sanders@kcl.ac.uk

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Table 1. Summary of the change in serum lipids predicted from replacing 1% energy by individual fatty acids for carbohydrate based on the meta-analysis [adapted from EFSA, 2004] and changes from increasing intake of dietary cholesterol by 100 mg based on analysis of Weggemans et al. [2001]

	TC	LDL-C	HDL-C	TC:HDL-C
Lauric acid (12:0)	+0.069 (0.040 to 0.097)	+0.052 (0.026 to 0.078)	+0.027 (0.021 to 0.033)	–0.037 (–0.057 to –0.017)
Myristic acid (14:0)	+0.059 (0.036 to 0.082)	+0.048 (0.027 to 0.069)	+0.018 (0.013 to 0.023)	–0.003 (–0.026 to 0.021)
Palmitic acid (16:0)	+0.041 (0.028 to 0.054)	+0.039 (0.027 to 0.051)	+0.010 (0.007 to 0.013)	+0.005 (–0.008 to 0.019)
Stearic acid (18:0)	–0.010 (–0.026 to 0.006)	–0.004 (–0.019 to 0.011)	+0.002 (–0.001 to 0.006)	–0.013 (–0.030 to 0.003)
Elaidic acid (18:1 *trans*)	+0.031 (0.020 to 0.042)	+0.040 (0.020 to 0.060)	0.000 (–0.007 to 0.006)	+0.022 (0.005 to 0.038)
Oleic acid (18:1 *cis*)	–0.006 (0.020 to 0.042)	–0.009 (–0.014 to –0.003)	+0.008 (0.005 to 0.011)	–0.026 (–0.035 to –0.017)
PUFA	–0.021 (0.020 to 0.042)	–0.019 (0.020 to 0.060)	+0.006 (0.007 to 0.006)	–0.032 (0.005 to 0.038)
Dietary cholesterol (+100 mg/day)	+0.056 (0.046 to 0.065)	+0.050 (0.042 to 0.058)	+0.008 (0.042 to 0.058)	+0.020 (0.010 to 0.030)

Data presented in mmol/l with 95% CI in parentheses.

2007]. Reductions in TC and LDL concentrations with statin therapy convincingly lower CVD risk, but the effects on CVD risk reductions using other agents (drug or diet) are less well established. Elevated plasma lipoprotein Lp(a) is associated with increased CVD risk, especially when it is associated with elevated plasma LDL cholesterol (LDL-C) concentrations [Seed et al., 1990]. The relationship between fasting plasma triacylglycerol (TAG) concentration and CVD risk is more complex because it can be transiently changed by diet, alcohol intake and physical activity. However, prolonged elevation of plasma TAG, which is often associated with the insulin-resistance syndrome and increased VLDL synthesis, generates small dense LDL particles (which are rich in apolipoprotein B relative to cholesterol) and causes a fall in high-density lipoprotein (HDL; measured as apolipoprotein A1 or HDL cholesterol (HDL-C)). This atherogenic dyslipidaemia (high TAG, small dense LDL-C and low HDL-C) is now recognized as conferring a substantial increase in CVD risk [Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001]. The ratio of TC:HDL-C (which indicates the ratio of apolipoprotein B:apolipoprotein A1) is twice as informative [Lewington et al., 2007] of individual CVD risk than TC or LDL-C, and differences in this ratio within and between populations are predominantly due to lifestyle factors (diet, physical activity, obesity, alcohol use). Thus, the ratio of TC:HDL-C is probably the most robust lipid metric to estimate lifestyle factor-related CVD risk.

Variation across population groups in plasma lipids has traditionally been due to differences in TC and LDL-C, although, with the worldwide obesity pandemic, atherogenic dyslipidaemia (raised TAG, low HDL-C) is increasingly prevalent. The equation developed by Keys has been widely used to predict changes in TC between diets [Keys and Parlin, 1966]:

$$\Delta\text{serum cholesterol mg/dl} = 2.3(\Delta S) - \Delta P + 1.5\,(\sqrt{\Delta C})$$

ΔS is the difference in % energy from SFA excluding stearic acid, ΔP is the difference in % energy from PUFA and ΔC is the difference in cholesterol content in mg/1,000 kcal; to convert to mmol/l divide by 38.5.

Table 1 summarizes the influence of different individual fatty acids on the different lipoprotein fractions that have been evaluated in a numerous controlled studies. Meta-analyses of these studies provide convincing evidence that SFA (C12–16) elevate TC, LDL-C and HDL-C compared with carbohydrates. The replacement of myristic (C14:0) and palmitic (C16:0) acids with carbohydrates results in little net change in the TC:HDL-C ratio. Lauric acid (C12:0) raises LDL-C and HDL-C and decreases the TC:HDL-C ratio by –0.037 for each 1% energy when it replaces carbohydrates [Mensink et al., 2003]. However, it is to be noted that coconut oil, which is the major dietary source of lauric acid, has a less favourable effect on the TC/HDL-C ratio than palm oil, which is rich in palmitic and oleic acid [Ng et al., 1992; Sundram et al., 1994]. Stearic acid (C18:0) does not have any significant effects on TC or LDL-C or the TC:HDL-C ratio compared with carbohydrates. There is possible evidence to suggest that the TC- and LDL-C-raising effects of palmitic acid are lower for vegetable than animal sources, because it is present predominantly in the sn–1 and sn–3

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position as opposed to the sn–2 position as in animal fats such as lard [Choudhury et al., 1995; Zhang et al., 1997]. Animal fats also contain dietary cholesterol, and while the influence of dietary cholesterol on plasma TC and LDL-C is often dismissed as trivial, Keys and Parlin [1966] estimated that each 100 mg of dietary cholesterol raised TC by 4 mg/dl (0.11 mmol/l). A more recent meta-analysis [Weggemans et al., 2001] concluded that for most individuals over the range of practical intake (0–400 mg/day), each 100 mg leads to increases in TC by 0.056 mmol/l (95% CI: 0.046–0.065 mmol/l) and HDL-C by 0.008 mmol/l (95% CI: 0.005–0.010 mmol/l), increasing the TC:HDL-C ratio by 0.02. However, some individuals, especially those carrying the apolipoprotein E $\varepsilon 4$ allele, are more sensitive to dietary cholesterol and a 10% increase in TC can result from an additional 300 mg cholesterol/day [Sarkkinen et al., 1998]. There is also some evidence to suggest an interaction between SFA and TFA intake with dietary cholesterol. Plant sterols and stanols block the absorption of dietary and biliary cholesterol, and lower TC, LDL-C and the TC:HDL-C ratio independent of changes in fatty acid composition, but these effects are only significant following the consumption of food products fortified with plant sterols/stanols [Law, 2000].

Compared with carbohydrates, the major MUFA (oleic acid; C18:1n–9) has a neutral effect on plasma LDL-C, and PUFA (mainly linoleic acid; C18:2n–6) have a slight lowering effect on TC and LDL-C. Compared with oleic acid, SFA increase HDL-C, and intakes of linoleic acid above 12% energy lower HDL-C. There is convincing evidence that the replacement of SFA with unhydrogenated vegetable oils rich in *cis* unsaturated fatty acids results in a reduction in the TC:HDL-C ratio by approximately 0.029, and by 0.035 for each 1% energy of SFA replaced with oleic acid and linoleic acid, respectively [Mensink et al., 2003]. This meta-analysis indicated that replacement of saturated or C18 *cis* unsaturated fats with carbohydrate increases fasting TAG, at least in the short term.

Compared with carbohydrate, TFA raise LDL-C, but have a similar effect as carbohydrate on HDL-C [Mensink and Katan, 1990; Nestel et al., 1992; Judd et al., 1994; Almendingen et al., 1995; Aro et al., 1997; Lichtenstein et al., 1999; Sanders et al., 2003b; Mozaffarian and Clarke, 2009]. Replacing 1% energy TFA by carbohydrate, oleic acid or linoleic acid lowers the TC:HDL-C ratio by 0.022, 0.054 and 0.067, respectively. Most studies have investigated the effect of partially hydrogenated vegetable oil, although 3 studies used chemically isomerized high oleic sunflower oil as a source of TFA [Mensink and Katan, 1990; Aro et al., 1997; Sanders et al., 2003b]. A recent study compared the effects of 5% energy of TFA (11–12 g/day) from natural sources compared to those derived from industrial sources in men and women. This study reported that only industrially produced TFA lowered HDL-C [Chardigny et al., 2008], but the natural sources raised LDL-C compared with the industrial sources. Subgroup analysis suggested the effect was more marked in women. A second study [Motard-Bélanger et al., 2008] compared low (4.2 g/day) and high intakes (10.2 g/day) of ruminant TFA with industrial TFA in 38 men. This study showed a significant increase in TC and LDL-C, with the high intake of *trans* from either natural or industrial sources, and in the TC:HDL-C ratio. The reduction in HDL-C following an increased intake of TFA is a consequence of a fall in HDL2 cholesterol concentrations [Judd et al., 1994; Sanders et al., 2003b; Motard-Bélanger et al., 2008], which is not dissimilar to the effect observed when carbohydrate replaces fat. However, the LDL-C:HDL-C ratio is higher following an increased intake of TFA compared with the diets high in carbohydrate. Some [Nestel et al., 1992; Judd et al., 1994; Almendingen et al., 1995; Aro et al., 1997; Motard-Bélanger et al., 2008] have reported that TFA increase Lp(a) concentration, but this difference could equally be explained by differences in fatty acid chain length of the predominant fatty acids in the diet [Sanders et al., 1997]. Many of the comparisons have used palmitic-, myristic- and lauric-rich fats to replace C18:1 *trans*, and this might explain why palm oil resulted in a lower Lp(a) concentration compared with partially hydrogenated soybean oil [Sundram et al., 1997]. Sanders et al. [2003b], in a head-to-head comparison of C18:1 provided either as *cis* or *trans,* found no difference in Lp(a) concentrations; a result echoed in a recent comparison [Chardigny et al., 2008] of industrially produced and naturally occurring TFA.

Most studies that have demonstrated effects of TFA on serum lipids have used very high intakes, and the impact of lowering intakes from 2 to 1% of the energy would have a smaller impact on the TC:HDL-C ratio than decreasing the intake of SFA by 5% energy. For example, replacing 1% energy TFA with 1% energy from oleate would lower TC by 0.036 mmol/l and increase HDL-C by 0.008 mmol/l, whereas replacing 5% energy from SFA (3.3% from C16:0, 1.2% from C18:0, 0.3% from C14:0) with oblate would lower TC by 0.2 mmol/l without changing HDL-C.

Interesterification is a technique increasingly being used by the food industry to generate fats with defined physical properties as an alternative to the partial hydrogenation of fats. However, the health effects of these changes have received little attention. Zock et al. [1995]

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noted a greater increase in LDL-C of 0.08 mmol/l when palmitate was in the sn–2 position in men, but not in women. Sundram et al. [2007], in a cross-over study of 30 Malaysian subjects (20 female and 10 male), reported that palm olein had a more favourable effect on the TC:HDL-C ratio than partially hydrogenated soybean oil or an interesterified fat made from fully hydrogenated soybean oil and unhydrogenated soybean oil, which was rich in stearic acid. Mensink [2008] compared products made from a high-palmitic-acid *trans*-free semi-liquid fat or a high-oleic-acid low-*trans* high-stearic-acid semi-liquid fat and found that the palmitic acid-rich diet raised LDL-C and HDL-C by 0.34 and 0.06 mmol/l, respectively, compared with the high-oleic interesterified blend. Berry et al. [2007a] compared native shea butter, rich in stearic acid and naturally present exclusively in the sn–1 and sn–3 positions, with randomized shea butter in 19 male subjects before and after a low-stearate diet and found no difference in TC or HDL-C between randomized and native shea butter or with the low-stearate run-in period. The evidence to date thus suggests that interesterified fats where stearic acid is present in the sn–2 position probably have a neutral effect on blood lipids [Berry, 2009]. However, further research is urgently needed on whether the commercial interesterification of vegetable fats (including fully hydrogenated fats), which is widely carried out in the food industry, influences plasma LDL-C and HDL-C and other indices of CVD risk.

Long-chain n–3 PUFA [n–3 LCP: mainly eicosapentaenoic acid (C20:5n–3; EPA) and docosahexaenoic acid (C22:6n–3; DHA)] generally supplied in the diet by oily fish have no effect on TC [Bays, 2006], but lower plasma TAG and VLDL cholesterol and raise LDL-C concentrations [Theobald et al., 2004; Caslake et al., 2008] in amounts exceeding 0.7 g/day (~0.3% energy). Dietary supplements, usually providing in excess of 3 g n–3 LCP/day, lower plasma TAG on average by 27%, but have variable effects on LDL-C and HDL-C depending on the dose, type of fatty acid and lipoprotein phenotype: on average they increase both LDL-C (6%) and HDL-C (1.4%) concentrations, but also LDL and HDL particle size [Minihane et al., 2000; Griffin et al., 2006; Kelley et al., 2007]. DHA from algal sources in the range of 0.7–1.5 g/day raises TC and LDL-C between 6 and 12%, but has little influence on the TC:HDL-C ratio [Theobald et al., 2004; Geppert et al., 2006; Sanders et al., 2006a]. Linolenic acid does not share the effects shown by n–3 LCP and does not influence plasma lipid concentrations within the range of intakes likely to be encountered in human diets [Balk et al., 2006].

There is convincing evidence [Whitlock et al., 2009] that individuals who maintain a healthy weight are less likely to develop a raised TC:HDL ratio. Furthermore, weight loss in overweight or obese subjects results in improvements in circulating lipid concentrations, including raising HDL-C, lowering TAG and TC, and improving the TC:HDL-C ratio [Yu-Poth et al., 1999].

Despite the global increase in obesity, TC and LDL-C have fallen in several economically developed countries [Vartiainen et al., 2000; Evans et al., 2001; Carroll et al., 2005] where the fat supply has changed from predominantly animal fats (dairy fats, lard, lamb and beef fat), rich in SFA, to vegetable oils rich in *cis* unsaturated fatty acids [Vartiainen et al., 2000]. In contrast, there is evidence to suggest that TC and LDL-C are increasing in some emerging economies such as China [Critchley et al., 2004], and that this is accompanied by an increase in total and saturated fat from both animal and vegetable sources. However, in many developing countries, it is not possible to dissociate the effect on TC of an increase in BMI from lean to moderately elevated BMI [Whitlock et al., 2009].

Postprandial Lipid Metabolism

While most attention has focused on fasting lipid and lipoprotein concentrations, for most of the time humans are in the postprandial state, and variations in the non-fasting lipid concentrations may also influence the atherogenic process. Elevated postprandial lipid concentrations, resulting from meals typically containing 30–50 g fat, and persistent elevation of postprandial plasma TAG are associated with progression of atherosclerosis and increased risk of thrombosis. Impaired postprandial lipaemia is associated with obesity, insulin resistance and type 2 diabetes. Compared with meals low in fat and high in carbohydrate, meals high in long-chain fatty acids (C14–18) result in substantial lipaemia. Short- and medium-chain fatty acids (C2–C12) do not result in substantial lipaemia [Oakley et al., 1998; Sanders et al., 2000, 2001]. Stearic-rich fats result in variable effects on postprandial lipaemia according to the physical properties of the fat [Sanders et al., 2000, 2001, 2003a; Tholstrup et al., 2001; Berry et al., 2007a]. Most stearic-rich TAG result in decreased postprandial lipaemia compared to oleic acid-rich TAG, and this appears to be a consequence of the high melting point of the TAG delaying its absorption.

Trans isomeric fatty acids have similar effects compared to *cis* isomeric fatty acids [Sanders et al., 2000,

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2003b; Tholstrup et al., 2001]. Intakes in excess of 1.5 g n–3 LCP result in decreased postprandial lipaemia, both acutely and chronically [Harris and Muzio, 1993; Zampelas et al., 1994; Griffin et al., 2006], probably by way of their effects on reducing VLDL synthesis, which in turn reduces competition for clearance of chylomicron remnants. There is consistent evidence that prolonged elevations of plasma TAG concentrations result in an increased proportion of small dense LDL particles that are associated with increased progression of atherosclerosis and increased risk of coronary heart disease [Kwiterovich, 2002]. Diets containing a higher proportion of carbohydrate in place of fat result in an increase in plasma TAG concentrations in the fasting state, but a lower plasma TAG concentration in the postprandial state. However, there is no consistent evidence from randomized controlled trials to indicate that diets with a reduced proportion of energy from fat result in an increased proportion of small dense LDL. There is, however, evidence to show that weight loss, leading to a reduction in adipose tissue, decreases the proportion of small dense LDL [Siri-Tarino et al., 2009].

Insulin Sensitivity

Regular physical activity and weight loss in overweight or obese subjects improve insulin sensitivity [Costacou and Mayer-Davis, 2003; Roumen et al., 2008]. Animal studies indicate that diets rich in SFA impair insulin sensitivity, and that n–3 LCP improve insulin sensitivity. The euglycaemic insulin clamp technique is regarded as the gold standard for the measurement of insulin sensitivity. However, few studies have investigated the effect of fat modification using this technique, and where it has been employed, the sample size is insufficient to come to any clear conclusion. Most of the larger studies have assessed insulin sensitivity using the intravenous glucose tolerance test. While this technique measures tissue sensitivity to insulin, it does not fully measure the response to diet, which is also influenced by incretins secreted in the gut in response to food.

There is limited evidence that replacing SFA from animal sources with MUFA from plant sources improves insulin sensitivity and glycaemic control in type 2 diabetes [Garg, 1998]. However, randomized controlled trials [Vessby et al., 2001; Griffin et al., 2006; Tardy et al., 2009] have generally failed to show any consistent effect of changing either the level of fat or the type of fat on insulin sensitivity when changes in weight or physical activity are taken into account. Where a reduction in the dietary intake of fat is accompanied by a reduction in energy intake and weight loss, an improvement in insulin sensitivity is likely.

Indices of Oxidative Stress

There is convincing mechanistic evidence [Griendling and FitzGerald, 2003] to implicate lipoprotein oxidation in the pathogenesis of atherosclerosis, but the consequences of altering lipoprotein oxidation [Reaven et al., 1991; Finnegan et al., 2003; Caslake et al., 2008] in human studies through increasing/decreasing the proportion of dietary PUFA are not well established. A number of biomarkers of oxidative damage are available, but none are strongly predictive of risk of CVD, and there is no convincing evidence to demonstrate that modifying the composition of dietary fat has a significant impact on the process of lipoprotein oxidation in vivo. Furthermore, randomized controlled trials of antioxidant compounds have failed to demonstrate any benefit on cardiovascular risk [Bjelakovic et al., 2007].

Inflammatory Markers

Chronic inflammation results in the elevation of acute-phase proteins, including fibrinogen and C-reactive protein, and is believed to be mediated by elevated production of cytokines, particularly IL-6. Chronic inflammation, as indicated by mild elevations of C-reactive protein, increases the risk of CVD – especially if the TC:HDL-C ratio is high [Ridker, 2001]. Obesity may directly contribute to the increased production of IL-6 from adipose tissue. Postprandial lipaemia may also stimulate the production of inflammatory cytokines. One mechanism suggested is that postprandial lipaemia may increase the absorption of endotoxin from the gut [Erridge et al., 2007]. Evidence has also been presented [Byrne et al., 1998; Grainger et al., 2000] that TAG-rich lipoproteins sequester the active form of the atheroprotective cytokine TGFβ1. High intakes of n–3 LCP (>3 g/day) in the form of dietary supplements [Meydani, 2000; Vedin et al., 2008] decrease cytokine production and probably decrease inflammatory markers, but randomized controlled trials, using lower intakes as may habitually be consumed in usual diets, have failed to demonstrate any clear effects on cytokines, adhesion molecules or C-reactive protein [Blok et al., 1997; Balk et al., 2006; Theobald

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et al., 2007]. There is possible evidence that TFA increase systemic inflammation [Baer et al., 2004], but not all studies have consistently shown such effects [Motard-Bélanger et al., 2008].

Procoagulant and Fibrinolytic Activity

Elevated procoagulant FVII and fibrinogen and decreased indices of fibrinolytic activity (as assessed by measures of clot lysis time or elevated plasminogen activator inhibitor PAI-1 activity) are associated with an increased risk of atherothrombosis [Meade et al., 1993; Heinrich et al., 1994; Folsom et al., 2001]. Hyperlipidaemia is associated with elevated FVII and fibrinogen, and insulin resistance syndrome is associated with elevated PAI-1. There is possible evidence that n–3 LCP, provided as dietary supplements, increase FVIIc [Sanders et al., 2006a], but this effect was not evident with an increased intake from oily fish [Sanders et al., 2006b]. There is convincing evidence that meals high in fat (usually 50 g fat) compared to meals high in carbohydrate and low in fat (<15 g fat) acutely increase the concentration of FVIIa [Oakley et al., 1998; Sanders et al., 1999, 2000, 2001, 2003b, 2006b; Tholstrup et al., 2003; Sanders and Berry, 2005]. There is probable evidence that the increase in FVIIa is greater following meals rich in MUFA (oleic acid) than for some sources of SFA [Sanders et al., 2000, 2006b; Tholstrup et al., 2003; Sanders and Berry, 2005; Berry et al., 2007a, b]. There is insufficient evidence to demonstrate chronic effects of different types of fatty acids on fibrinogen or fibrinolytic activity [Miller, 2005; Sanders et al., 2006b], but fibrinolytic activity improves with intensive lifestyle intervention (weight reduction and increased physical activity) [Hamalainen et al., 2005].

Blood Pressure and Arterial Stiffness

Both systolic and diastolic blood pressure increase with age in economically developed communities and show a continuous association with risk of CVD without a threshold [Lewington and Clarke, 2005]. Elevated blood pressure is a self-amplifying condition and is strongly associated with BMI. There is also a strong association between the development of hypertension and hyperlipidaemia. There is convincing evidence that weight loss results in a fall in blood pressure [Neter et al., 2003]. A 5-kg loss in weight results in systolic/diastolic blood pressure falls of 4.4/3.6 mm Hg. In this respect, a reduction in total fat intake that results in lower energy intake and weight loss will lower blood pressure. However, there is no clear evidence to indicate the superiority of low-calorie diets that contain a higher proportion of fat than carbohydrate.

There is convincing evidence for a blood pressure-lowering effect of replacing SFA with MUFA as part of a healthy lifestyle diet [Appel et al., 2003, 2005] with an increased proportion of fruit and vegetables, wholegrains and reduced salt intake. There is insufficient evidence that replacement of saturated fats with MUFA alone has a significant effect on blood pressure [Shah et al., 2007]. There is possible evidence from cross-sectional studies that linoleic acid may contribute to the prevention of raised blood pressure [Miura et al., 2008]. High intakes (>2 g/day) of n–3 LCP convincingly lower blood pressure [Geleijnse et al., 2002], and there is possible evidence that habitual intakes at lower levels have the same effect [Ueshima et al., 2007]. Over the age of 60 years, systolic blood pressure increases more than diastolic blood pressure, and this is likely in part to be a consequence of arterial stiffening. Arterial stiffness is emerging as a strong predictor of CVD risk in the elderly [Terai et al., 2008; Anderson et al., 2009]. There is possible evidence that n–3 LCP may decrease arterial stiffening [Hamazaki et al., 1988; Yamada et al., 2000; Tomiyama et al., 2005; Terai et al., 2008].

Endothelial Function

Impaired endothelial function plays a central role in atherogenesis and also increases the risk of arterial thrombosis. The capacity of the vascular endothelium to synthesize nitric oxide (NO) and NO bioavailability are important determinants of normal endothelial function. NO appears to have both anti-thrombotic and anti-atherosclerotic properties. The capacity of the endothelium to synthesise NO can be assessed in vivo by measuring flow-mediated dilatation of the brachial artery. Impaired flow-mediated dilatation is associated with the risk of atherosclerotic disease [Yeboah et al., 2007]. Hyperlipidaemia and hyperglycaemia are 2 factors known to impair endothelial function. Meals high in long-chain fatty acids, which induce substantial lipaemia compared with meals low in fat but high in carbohydrate, result in an impairment of endothelial function in the postprandial period in healthy subjects [Vogel et al. 1997, 2000; Ong et al., 1999; Bae et al., 2001; Cortés et al., 2006]. There is possible evidence that n–3 LCP may improve [Goodfellow et al., 2000; Leeson et al., 2002; Engler et al., 2004]

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Table 2. Summary of strength of evidence for metabolic risk factors excluding fasting lipids

	Blood pressure	Arterial stiffness	Endothelial function	Fibrinogen	FVII	Fibrinolytic activity	Inflammation	Insulin sensitivity	Postprandial lipaemia
Total fat	P – NR	I	PS↑	P – NR	C↑	P – NR	I	P – NR	C↑
Trans fatty acid	P – NR	I	PS↑	P – NR	C↑	P – NR	PS↑	PS – NR	C↑
SFA	PS↑	I	I	P – NR	P↑	P – NR	I	I	C↑
Lauric	P – NR	I	I	P – NR	C↓	I	I	I	P – NR
Myristic	P – NR	I	I	P – NR	P↑	I	I	I	C↑
Palmitic	P – NR	I	I	P – NR	C↑	P – NR	P – NR	I	C↑
Stearic	P – NR	I	I	P – NR	P↓	PS – NR	P – NR	I	C↓
Oleic	P – NR	I	I	P – NR	C↑	PS – NR	P – NR	PS↓	C↑
MUFA	P – NR	I	I	P – NR	C↑	P – NR	I	PS↓	C↑
PUFA	PS↓	I	I	P – NR	P↑	P – NR	I	P – NR	C↑
n–6 PUFA	PS↓	I	I	P – NR	P↑	P – NR	I	P – NR	C↑
Linoleic acid	PS↓	I	I	PS – NR	P↑	P – NR	P – NR	P – NR	C↑
Arachidonic acid	I	I	I	I	I	I	I	I	I
n–3 LCP	P↓	PS↓	PS↓	P – NR	P↑	P – NR	PS↓	P – NR	C↓
α-Linolenic acid	P – NR	I	I	P – NR	PS↑	P – NR	I	P – NR	PS↑
EPA	I	PS↓	I	I	I	I	I	I	C↓
DHA	PS↓	PS – NR	PS↓	P – NR	PS↑	P – NR	I	P – NR	P↓

C = Convincing; P = probable; PS = possible; I = Insufficient; ↑ increased risk; ↓ decreased risk; NR = no relationship.

and TFA [de Roos et al., 2001] may impair endothelial function. Early chronic feeding studies have been subject to operator-dependent variability [Hall, 2009]. Consequently, there is insufficient evidence to conclude that there are any other differences between MUFA, PUFA and SFA.

Dietary Interactions with Genotype

Several gene polymorphisms for lipid and haemostatic risk factors have been identified that may have interactions with dietary fat intake. Subjects who carry the ε4 allele for apolipoprotein have higher TC and LDL-C concentrations compared to those carrying the common ε3 allele. These ε4 carriers appear to show greater absolute (but not proportionately different) falls in TC and LDL-C compared with ε3 carriers when they decrease their intakes of SFA and cholesterol [Lefevre et al., 1997]. However, the LDL-C-raising effect of n–3 LCP does not differ between ε4 and ε3 carriers [Theobald et al., 2004; Caslake et al., 2008]. Cross-sectional data do not suggest that the apolipoprotein E genotype is an important determinant in the LDL-C response to SFA [Wu et al., 2007]. Subjects who are homozygous for the ε2 allele do not show an increase in serum cholesterol in response to dietary cholesterol, but this genotype is associated with an increased prevalence of WHO type II hyperlipoproteinaemia, which responds to a low-fat diet.

About 1:500 people carry mutations for the LDL receptor. These individuals have higher TC and LDL-C and a 25-fold increased risk of developing premature CVD. Plasma TC and LDL-C concentrations in individuals who carry this mutation are relatively unresponsive to changes in the level or type of dietary fat [Poustie and Rutherford, 2001].

Conclusions

There is convincing evidence that the major determinants of differences in metabolic risk factors within and across populations are due to behavioural and lifestyle factors (diet, physical activity, obesity, smoking, alcohol use) rather than genetic differences. Decreasing the intake of SFA C12–16 and their replacement with oleic and linoleic acids lowers TC and LDL-C without lowering HDL-C and has a more favourable effect on the TC: HDL-C ratio than replacement with carbohydrate, particularly in populations where a high proportion of the

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population is overweight or obese. The intake of SFA has fallen close to 10% in several economically developed countries because the fat supply has changed from predominantly animal fats (dairy fats, lard, lamb and beef fat), rich in SFA, to vegetable oils rich in *cis* unsaturated fatty acids. Consequently, in those countries, the capacity to decrease SFA much further is limited without major changes in dietary patterns, and is only likely to result in modest reductions in TC and LDL-C. TFA have adverse effects on the TC:HDL-C ratio. Therefore, replacing TFA with *cis* unsaturated fatty acids is preferred, but some food applications require high-melting-point fats. Stearic acid appears to have no effect on the LDL-C or TC:HDL-C ratio. Thus, this need could be met by the use of fully hydrogenated vegetable oils interesterified with unhydrogenated fat, which results in the production of TAG with a significant proportion of stearic acid in the sn–2 position, or by blending with fats that have high melting points, such as palm oil. Further research on the health effects of these approaches is required.

The effects of total fat and the various fatty acids on other CVD risk factors are shown in table 2. There is possible evidence to suggest that long-chain n–3 fatty acids may influence arterial stiffening and have favourable effects on endothelial function, but this requires further research. Dietary fat intake has no clear effect on blood pressure, inflammation, fibrinolysis or insulin sensitivity, whereas these risk factors are strongly influenced by obesity. Meals high in fat, however, cause postprandial lipaemia and may promote atherosclerosis as well has having a potentially adverse influence on the risk of thrombotic events by way of effects on procoagulant activity and endothelial function. There is a need for further research in this area as the modulation of risk of thrombosis may be of greater importance in older populations who have established atherosclerosis and are most at risk of cardiovascular events.

Disclosure Statement

T.A.B.S. has acted as a consultant to Seven Seas, he is a member of the Scientific Advisory Committee for the Global Dairy Platform, he is a member of the external scientific review committee of the Malaysian Palm Oil Board, he chairs Cadbury's Global Nutrition Advisory Panel. His research group has received oils and fats from Unilever, Archer Daniel Mills and Croda gratis for research. He has received payments from several industrial companies for attending workshops and giving lectures. He receives research funding from the UK Food Standards Agency.

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