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REVIEW

Saturated fat, carbohydrates and cardiovascular disease

R.S. Kuipers[1*], D.J. de Graaf[1], M.F. Luxwolda[1], M.H.A. Muskiet[2], D.A.J. Dijck-Brouwer[1], F.A.J. Muskiet[1]

[1]University Medical Center Groningen, Groningen, the Netherlands, [2]VU University Medical Center, Amsterdam, the Netherlands, *corresponding author: tel.:+31 (0)050-3612733, fax: +31 (0)50-3612290, e-mail: remkokuipers@hotmail.com

ABSTRACT

The dietary intake of saturated fatty acids (SAFA) is associated with a modest increase in serum total cholesterol, but not with cardiovascular disease (CVD). Replacing dietary SAFA with carbohydrates (CHO), notably those with a high glycaemic index, is associated with an increase in CVD risk in observational cohorts, while replacing SAFA with polyunsaturated fatty acids (PUFA) is associated with reduced CVD risk. However, replacing a combination of SAFA and *trans*-fatty acids with n-6 PUFA (notably linoleic acid) in controlled trials showed no indication of benefit and a signal toward increased coronary heart disease risk, suggesting that n-3 PUFA may be responsible for the protective association between total PUFA and CVD. High CHO intakes stimulate hepatic SAFA synthesis and conservation of dietary SAFA. Hepatic *de novo* lipogenesis from CHO is also stimulated during eucaloric dietary substitution of SAFA by CHO with high glycaemic index in normo-insulinaemic subjects and during hypocaloric high-CHO/low-fat diets in subjects with the metabolic syndrome. The accumulation of SAFA stimulates chronic systemic low-grade inflammation through its mimicking of bacterial lipopolysaccharides and/or the induction of other pro-inflammatory stimuli. The resulting systemic low-grade inflammation promotes insulin resistance, reallocation of energy-rich substrates and atherogenic dyslipidaemia that concertedly give rise to increased CVD risk. We conclude that avoidance of SAFA accumulation by reducing the intake of CHO with high glycaemic index is more effective in the prevention of CVD than reducing SAFA intake *per se*.

KEYWORDS

Saturated fatty acids, carbohydrates, diet heart, cardiovascular disease, fat

INTRODUCTION

In 2003, in the Netherlands, fat comprised about 34% of total energy intake (en%), and was, after carbohydrates (CHO), the main energy source. Grains, grain products and non-alcoholic beverages are the most important sources of dietary CHO in the Netherlands (*table 1*). Saturated (SAFA), monounsaturated and polyunsaturated fatty acids (PUFA) each constitute approximately 12.9, 10.8 and 7.1 en% of the total fat intake. Milk, milk products and meat are the main sources of dietary SAFA (*table 1*) in the Netherlands,[1,2] as well as in the United States.[3] Fatty acids are pleiotropic nutrients with important functions in the human body in addition to serving as substrates for energy production. Fatty acids are essential components of the phospholipids in all cell membranes, act as carriers of the fat-soluble vitamins A, D, E and K, and include the essential n-3 and n-6 PUFA, alpha-linolenic and linoleic acid, respectively.

The diet-heart hypothesis, also named the diet-heart paradigm, is based on the association between serum cholesterol and dietary SAFA with the risk of cardiovascular disease (CVD) that was found in the Seven Countries Study by Ancel Keys,[4] and the relationship between dietary SAFA and serum cholesterol that was demonstrated in short[5] and long-term feeding trials.[6,7] However, recent evidence from randomised controlled trials (RCTs) and observational studies has provided little support for the diet-heart paradigm and the causality of the association between dietary SAFA and CVD outcomes is increasingly questioned.[8-11]

In this paper we discuss the current scientific data on the effects of dietary SAFA, their controversies and the potential underlying (patho)physiological mechanisms for the role of SAFA in CVD.

Table 1. *Dietary intakes and the average contributions of different dietary resources in 2003 in a typical Dutch population*[a,b]

	Energy	Protein	Fat	SAFA	MUFA	PUFA	Trans	CHO	MS & DS	PS	Fibre
Total daily intake (kcal and g/day)	2328	81	90	33	28	19	3	277	144	133	19.3
Total daily intake (en%)		14.3	34.4	12.9	10.8	7.1		48.2	24.9	23.1	2.1
Potatoes and other tuberous organs (g%)	3.8	2.9	1.2	1.7	1.0	0.8	3.4	6.2	0.7	12.2	15.1
Vegetables (g%)	1.1	2.2	0.3	0.2	0.5	0	0	1.3	1.6	1.0	12.2
Legumes (g%)	0.1	0.3	0	0	0		0	0.2	0	0.4	1.1
Fruits[c] (g%)	3.9	2.6	3.7	1.9	4.9	6.1	0	4.8	8.2	1.1	12.3
Milk and milk products (g%)	14.5	25.1	18.1	30.8	13.0	2.5	19.8	9.9	17.8	1.3	1.9
Cheese	5.0	9.2	10.7	18.0	7.9	1.5	13.3	0.1	0.2	0	0
Grains and grain products[d] (g%)	23.0	20.8	10.8	6.7	9.2	17.2	25.4	34.0	5.2	65.2	43.0
Bread	16.4	16.9	5.8	3.6	4.1	11.3	3.8	25.3	4.1	48.3	35.9
Meat and meat products[e] (g%)	11.4	29.9	20.1	20.3	25.9	10.3	10.0	0.7	0.2	1.2	0.1
Fish and shellfish (g%)	0.5	2.1	0.6	0.4	0.8		0.2	0.1	0	0.2	0
Eggs (g%)	0.7	1.7	1.3	0.8	1.4		0.1	0	0	0	0
Fats[f] (g%)	6.4	0.1	18.8	14.5	16.5	33.5	13.1	0	0.1	0	0
Sugar and candy (g%)	7.7	1.7	5.2	6.3	5.5	3.6	3.3	11.7	20.6	2.1	3.6
Cookies, cake and biscuits (g%)	7.0	3.2	7.7	9.0	7.2	5.2	18.6	8.3	7.7	8.9	4.7
Non-alcoholic beverages (g%)	8.2	1.6	0.2	0.3	0.1	0	0.1	16.3	30.6	0.8	1.8
Alcoholic beverages (g%)	5.1	1.0	0.1	0.1	0.1	0	0.1	2.9	4.4	1.3	0
Sauces, seasonings, herbs and spices (g%)	4.0	0.9	9.4	4.4	12.3	16.3	0.7	1.5	2.1	0.9	0.8
Soups and bouillon (g%)	0.8	1.3	0.8	0.8	0.8		0.7	0.6	0.3	0.9	1.9
Miscellaneous (g%)	1.7	2.5	1.8	1.9	1.2		4.4	1.5	0.7	2.4	1.4
Total	100	100	100	100	96	96	100	100	100	100	100

a. data derived from the Dutch VCP reference population (n=750) of Dutch men (352) and women (398) between 19-30 years of age in 2003.[1,2]
b. SAFA = saturated fatty acids; MUFA = monounsaturated fatty acids; PUFA = polyunsaturated fatty acids; trans = trans-fatty acids; CHO = carbohydrates; MS = monosaccharides; DS = disaccharides; PS = polysaccharides
c. including seeds and nuts
d. including flour, bread, pasta, rice and cereals
e. including poultry
f. including oils, butter, margarines and other frying fats

LIPOPROTEINS, CHOLESTEROL, SAFA AND CVD

A high serum total cholesterol, and especially LDL cholesterol, is associated with an increased risk of CVD, whereas a high HDL cholesterol has a protective association.[12] The serum total cholesterol/HDL cholesterol ratio is the consensus risk factor for the estimation of coronary heart disease risk. The reduction of this ratio by 1 point is classically associated with a coronary heart disease risk reduction of 52%.[13] The metabolic syndrome, also called the insulin resistance syndrome, which is characterised by obesity, impaired glucose homeostasis, hypertension and atherogenic dyslipidaemia ('deadly quartet'), is a major risk factor for CVD.[14] Similarly, atherogenic dyslipidaemia,[15] which is characterised by elevated triglycerides, small dense LDL particles and reduced HDL cholesterol ('deadly lipid triad'),[16] is also a major risk factor for CVD. These small dense LDL particles are susceptible to structural modifications by oxidation[17] and notably oxidised LDL particles affect atherosclerotic plaque formation[18] by promoting foam cell generation, endothelial dysfunction and local inflammation.

An increase in the consumption of SAFA by 1 energy percent (en%) raises serum total cholesterol by 0.052 mmol/l.[6] However, in the same study, the total cholesterol of subjects consuming 15 en% SAFA ranged from 4 to 6 mmol/l, indicating that most variation in the serum total cholesterol is not on account of the differences in SAFA intake *per se*.[6] Because of the presumed relationship between SAFA and CVD, it is nowadays recommended to replace dietary fat, and especially SAFA, by *cis*-unsaturated fatty acids.[19,20] Between 1987/1988 and 1997/1998 the intake of *cis*-unsaturated fatty acids, refined CHO and monosaccharides and disaccharides in the Netherlands increased at the expense of fat, SAFA and *trans*-fatty acids.[19,20] In this review, we will evaluate the current consensus on the relationship between SAFA and CVD while the consequences of replacing SAFA by CHO,

monounsaturates and PUFA will be examined with regard to their influence on atherogenic dyslipidaemia.

SAFA AND CVD

A recent meta-analysis of prospective cohort studies[21] showed that the intake of SAFA is not associated with an increased risk of coronary heart disease, stroke or those two combined (i.e. cardiovascular disease, CVD), before[21] or after[22] adjustment for serum total cholesterol. Additionally, the consumption of milk and milk products was not related to CVD in a meta-analysis of prospective cohort studies. Consumption of milk and milk products may even decrease CVD risk,[23] although this meta-analysis of prospective cohort studies was not supported by a recent prospective cohort study in the Netherlands.[24]

REPLACING SAFA BY CHO

Replacing 5 en% SAFA with 5 en% CHO reduced serum total cholesterol by 0.18 mmol/l, LDL cholesterol by 0.16 mmol/l and HDL cholesterol by 0.05 mmol/l, increased the serum triglycerides by 0.11 mmol/l and had no effect on the total cholesterol/HDL cholesterol ratio.[5] LDL cholesterol reduction from isocaloric substitution of SAFA by CHO is accompanied by an increase in the amount of atherogenic small dense LDL particles and a decrease in the less atherogenic large LDL particles.[15] Because of the increase in triglycerides and small dense LDL and no change in the total cholesterol/HDL cholesterol ratio, replacing SAFA by CHO seems unfavourable with regard to CVD prevention.

A pooled analysis of 11 cohort studies showed that replacing 5 en% SAFA by CHO was associated with a slightly increased risk of coronary events (7%), but there was no difference in mortality.[25] In practice, however, SAFA are often replaced by CHO with a high glycaemic index. A subsequent analysis by Jakobsen *et al.*[26] showed that replacement of 5 en% SAFA by CHO with a low glycaemic index was associated with a non-significant reduction in CVD risk, while replacing SAFA by CHO with a high glycaemic index was associated with a 33% increased risk of myocardial infarction.[26]

REPLACING SAFA BY MONOUNSATURATED FATTY ACIDS

Replacing 5 en% SAFA by 5% monounsaturated fatty acids reduced total cholesterol by 0.21 mmol/l, LDL cholesterol by 0.20 mmol/l, and HDL cholesterol by 0.01 mmol/l, and increased the serum triglycerides by 0.01 mmol/l. The 0.145 reduction in the total cholesterol/HDL cholesterol ratio is predicted to translate into a coronary heart disease risk reduction of 7.5%.[13] However, in the recent pooled analysis of prospective observational cohorts by Jakobsen *et al.*,[26] the intake of monounsaturated fatty acids was associated with a 19% higher risk of CVD events, but not with coronary heart disease mortality. This outcome contrasts with the beneficial effects of the so-called Mediterranean diet, which is typically high in monounsaturated fatty acids,[27] and the theoretical decrease of the total cholesterol/HDL cholesterol ratio, when SAFA are replaced by monounsaturated fatty acids.[5] Consequently, it was recently concluded that there is insufficient evidence to advise the replacement of SAFA by monounsaturated fatty acids.[28]

REPLACING SAFA BY N-6 AND N-3 PUFA

Replacing 5 en% SAFA by 5 en% PUFA decreased total cholesterol by 0.29 mmol/l, LDL cholesterol by 0.26 mmol/l, HDL cholesterol by 0.02 mmol/l, triglycerides by 0.03 mmol/l and the total cholesterol/HDL cholesterol ratio by 0.175, which theoretically corresponds to a coronary heart disease risk reduction of 9.1%.[13] A pooled analysis of 11 cohort studies showed that replacement of 5 en% SAFA by (n-3 and n-6) PUFA was associated with a significant 13% reduction in coronary events and a 26% reduction in coronary heart disease mortality.[25] These results are consistent with a meta-analysis of RCTs,[29,30] which showed that replacing 5 en% SAFA by (n-3 and n-6) PUFA reduced coronary heart disease risk by 10%. These results have been interpreted as providing strong concordant evidence to support current recommendations to replace SAFA with the n-6 PUFA linoleic acid, and were recently translated into an American Heart Association (AHA) advice,[31] to consume 'at least 5 to 10 % of energy as n-6 PUFA'. Importantly, however, neither of these pooled analyses made a clear distinction between n-6 and n-3 PUFA species, and the Mozaffarian *et al.*[29] meta-analysis of RCTs did not consider the potential confounding role of *trans*-fatty acids. The n-3 PUFA[32] and *trans*-fatty acids[33] have been positively and negatively related to CVD development, respectively. If distinction is made between interventions that selectively replaced SAFA and *trans*-fatty acids with n-6 PUFA/linoleic acid, and those that substantially increased both n-3 and n-6 PUFAs, a whole different picture emerges.[34] Linoleic acid selective PUFA interventions produced no indication of benefit but rather a fairly consistent, but non-significant, signal toward *increased* risk of coronary heart disease and death.

These potentially negative effects of n-6 PUFA acid may even have been underestimated, since PUFA also replaced *trans*-fatty acids. If SAFA is replaced by both n-3 and n-6 PUFA, a significant (22%) decreased coronary heart disease risk is found. However, this reduction may also be attributable, at least in part, to the reduced consumption of *trans*-fatty acids.[34]

RISK REDUCTION IN PERSPECTIVE

Besides the already mentioned large variability in the relationship between serum total cholesterol and SAFA intake,[6] there is the well-known example of the African Maasai who had very high intakes of both cholesterol (500 to 2000 mg/day) and SAFA from milk,[35,36] but exhibited remarkably low serum cholesterol levels[8,11,35,36] and although accompanied by extensive atherosclerosis, with lipid infiltration and fibrous changes, they had a very low incidence of cardiovascular events.[8] Secondly, comparison with other risk factors and the feasibility of a reduced SAFA consumption also require some attention. In 2003 the average SAFA intake in the Netherlands was estimated at 12.9% of total energy (en%). This intake should be lowered by 38%, i.e. to 7.9 en%, to achieve a 10% risk reduction in CVD.[30] The Dutch National Institute for Public Health and the Environment (RIVM) calculated that a 5% reduction in SAFA intake would reduce the annual incidence of CVD by 4300 persons per year and CVD mortality by 1000 people per year,[37] at an annual mortality from CVD of approximately 40,000/year in the Netherlands.[38] For comparison, the estimated mortality attributable to overweight, insufficient fruit and vegetable intake, and low fish intake is 6900, 7300, and 4500 persons per year, respectively.[37] A recent report from the UK predicted that an increase in the intake of fruits and vegetables from 279-356 g to 440 g/day would save as many lives as a reduction in the current SAFA consumption in the UK from >14 to 3 en% and a reduction in salt intake from >8.1 to 3.5 g/day.[39] Consequently, other risk factors seem much simpler to be addressed and their role seems at least comparable, if not more important, in the current high incidence of CVD. Recommendations to increase intake of n-3 PUFA, fruit and vegetables and reduce sodium intake,[30] to increase physical activity,[40] to reduce *trans*-fatty acid intake[30] and reduce the intakes of CHO with high glycaemic index, such as notably found in soft drinks and candy (*table 1*), seem more prudent candidates in the battle against CVD[41] than to reduce SAFA intake to the recommended <10 en%[19,20], and also because in daily practice SAFA are mostly replaced by CHO with high glycaemic index.[42]

RELATION BETWEEN INFLAMMATION AND LIPOPROTEIN METABOLISM

The causal relationship between LDL cholesterol *per se* and CVD[6] is still subject of debate.[8-11] However, both oxidised and small dense LDL have been related to increased CVD risk.[17,18] Moreover, there is convincing evidence that the LDL cholesterol reducing statins reduce CVD risk,[43-46] but statins have pleiotropic effects. Statins also have anti-inflammatory effects and equally reduce C-reactive protein (CRP) and the concentration of LDL cholesterol.[43-47] This observation supports the endotoxin-lipoprotein hypothesis[48] stating that chronic systemic low-grade inflammation connects LDL cholesterol to CRP. There is increasing evidence that changes in serum lipoproteins might be a response to a state of chronic inflammation *secondary* to our current lifestyle that in turn is composed of many factors. Besides the influence of dietary changes, environmental changes such as stress, sleep deprivation and environmental pollution, including smoking, have also been related to chronic inflammation.[49] It was recently re-emphasised that these so-called gene-environment interactions play important roles in de development of many, if not all, current diseases of civilization,[50,51] while a primary role for 'faulty' genes, is grossly overestimated.[52,53]

Common metabolic disorders, such as obesity, type 2 diabetes and the metabolic syndrome, are associated with low-grade inflammation and elevations in acute phase proteins such as CRP.[54] It has become increasingly clear that insulin resistance develops secondary to systemic inflammation and that the compensatory hyperinsulinaemia aims primarily at balancing glucose homeostasis.[55,56] The insulin resistant state, induced by pro-inflammatory cytokines, is indispensable for the reallocation of energy-rich substrates. Glucose is conserved for the metabolically highly active brain and for the activated immune system, which both rely on glucose metabolism for their energy supply.[55] Organs that would normally also use glucose become insulin resistant and use triglycerides and free fatty acids, distributed by the liver and adipose tissue, respectively, as energy sources. At the same time, the lipoprotein profile might act to fight off inflammation and support the repair of tissue damage secondary to the inflammatory reaction.[57-66] This is executed via: 1) an increase in cholesterol-rich lipoproteins (mainly LDL and VLDL), which have the ability to bind bacterial lipopolysaccharide (LPS) in proportion to their cholesterol content,[16,67,68] although the best determinant of the capacity of lipoprotein to bind LPS is a high phospholipid/cholesterol ratio (i.e. surface/volume ratio);[69] 2) the suppression of reverse cholesterol transport via multiple pathways[66] (i.e. low HDL); 3) increased oxidation

of LDL and VLDL, while HDL becomes proinflammatory;[62] 4) increased cholesterol delivery to the immune system,[62] and 5) the production of small dense LDL particles.[70] The last-mentioned become enriched in sphingolipids, are poorly cleared by the LDL receptor, cross the endothelial barrier more effectively, bind to the vascular wall intima and are accumulated in macrophages because of their susceptibility to oxidative modification.[62] Taken together, the proatherogenic dyslipidaemia of the metabolic syndrome is in support of the recovery from inflammation-induced damage.[48,55] However, when these changes in the lipoprotein profile last for prolonged periods of time, such as in the chronic low-grade inflammation of the metabolic syndrome,[14] they give rise to the development of atherosclerosis.[62,66]

Taken together that our current lifestyle includes many factors that 1) initiate and propagate inflammation; 2) give rise to an inadequate capacity to terminate inflammatory responses; and 3) lead to insufficient protection from the collateral damage caused by the chronic immune activation. One of these factors is our dietary SAFA intake, which can cause inflammation by their mimicking of a part of bacterial LPS[48] and/or by providing other pro-inflammatory stimuli.[67,68,71] Whether dietary SAFA cause inflammation depends on the accumulation of SAFA in the body and not on the dietary SAFA intake *per se*. Accumulation of SAFA can also occur by the synthesis of SAFA from CHO via *de novo* fatty acid synthesis. This mainly occurs in the liver, which secretes these *de novo* synthesised fatty acids as VLDL.[16,72]

SAFA *VS* CARBOHYDRATES, THE METABOLIC SYNDROME AND THE IMMUNE SYSTEM

The adverse effects of high SAFA intake on lipid metabolism are particularly noted when SAFA are combined with a high CHO intake. Under these conditions, dietary SAFA are preserved, while the surplus of the consumed CHO is converted to SAFA by hepatic *de novo* fatty acid synthesis. Although the conservation of SAFA during excessive intake of CHO with a high glycaemic index is well known,[73-76] the synthesis of SAFA from (surplus) CHO may not have received sufficient attention. Contrary to widespread belief, *de novo* fatty acid synthesis is not restricted to hypercaloric conditions or to excessive intake of CHO, but also depends on the type of ingested CHO. A low-fat eucaloric diet with a high sugar/starch ratio stimulated *de novo* fatty acid synthesis and increased serum triglycerides in normal weight individuals.[72] When subjects with the metabolic syndrome, i.e. with pre-existing insulin resistance, were fed either a hypocaloric low-CHO/high-fat diet with high SAFA content or a hypocaloric high-CHO/low-fat diet with low SAFA content, the low-CHO/high-SAFA diet resulted in *lower* SAFA levels in plasma lipids compared with the high-CHO/low-SAFA diet.[75,76] Finally, in subjects with the hepatic manifestation of the metabolic syndrome, i.e. non-alcoholic fatty liver disease, 26% of the fatty acids in the liver triglycerides and 23% of the fatty acids in VLDL triglycerides derive from *de novo* fatty acid synthesis in the liver.[77] Importantly, as much as 25 to 30% of Western adults are suffering from non-alcoholic fatty liver disease[78] in which the hepatic synthesis of fat, including SAFA, has become independent of the metabolic state, i.e. is independent of the feeding-fasting cycle.[77] Taken together, SAFA accumulate: 1) under eucaloric conditions in normal weight subjects who consume a CHO-rich diet with high glycaemic index; and 2) under hypocaloric conditions in subjects with the metabolic syndrome and non-alcoholic fatty liver disease who consume CHO-rich diets. Thus CHO, particularly those with a high glycaemic index, and pre-existing insulin resistance are confounding factors in the discussion on the relation between CVD and dietary SAFA. This observation underscores the importance of a renewed discussion about the possible dangers of dietary SAFA.

CONCLUSIONS

The total body of evidence suggests that attention should be shifted from the harmful effects of dietary SAFA *per se*, to the prevention of the accumulation of SAFA in body lipids. This shift would emphasise the importance of reducing dietary CHO, especially CHO with a high glycaemic index, rather than reducing dietary SAFA. The chronic interaction of SAFA with our immune system elicits so-called chronic systemic low-grade inflammation, which underlies the metabolic changes referred to as the (atherogenic) dyslipidaemia of the metabolic syndrome or the lipidaemia of sepsis. The ultimate goal of the ensuing insulin resistance is the re-allocation of energy-rich substrates, such as glucose, to the immune system while the change in our lipoprotein profile aims at the limitation of the inflammatory responses and the repair of the resulting tissue damage. Dietary SAFA belong to the many false triggers of inflammation that result from the conflict between our slowly adapting genome and our rapidly changing lifestyle, but among these many factors they are not the most important. A reduction in the consumption of CHO with a high glycaemic index, *trans*-fatty acids and linoleic acid, and an increased consumption of fish, vegetables and fruit, and a reduction of inactivity, sleep deprivation and chronic stress seem more realistic approaches to fight the current pandemic of cardiovascular disease resulting from chronic systemic low grade inflammation.

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