Review Article

Overview: Dietary fat and atherosclerosis

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Research on the effects of dietary fat on cholesterolemia and coronary risk began with comparisons of the amount and type of fat (saturated *vs* unsaturated). It then became clear that not all fatty acids had similar cholesterolemic effects and equations were derived which gave different weights to saturated and unsaturated fatty acids. We now find that the triglyceride structure also plays a role in cholesterolemia as suggested by the studies of Kritchevsky and Tepper in rabbits and McGandy *et al.* in human subjects.

Key words: atherosclerosis, cholesterolemia, dietary fat.

The amount of palmitic acid (16 : 0) present at the SN2 position of a triglyceride exerts important effects on the atherogenicity of that fat but has little effect on cholesterolemia. Lard and tallow both contain approximately 24% palmitic acid. In lard virtually all the 16 : 0 is present at SN2 and lard is significantly more atherogenic for rabbits than is tallow (4% of 16 : 0 at SN2). After randomization both fats carry 8% (or 1/3) of their total 16 : 0 at SN2. Randomization reduces the atherogenicity of lard by approximately 50% and raises that of tallow by approximately 10%. Similarly, randomization of cottonseed oil increases the amount of 16 : 0 at SN2 from approximately 2 to 10%. Atherogenicity is increased approximately three-fold. Palm oil (41% 16 : 0) carries only 3% of its 16 : 0 at SN2. Randomization of palm oil raises the amount of 16 : 0 at SN2 to 13.6% and increases its atherogenicity by 34%.

The mechanism of action is unclear but may be related to the degree of fat absorption and to the turnover time of specific triglycerides.

The earliest experiment involving the establishment of experimental atherosclerosis by dietary means was carried out almost a century ago by Ignatowski.[1] His study was based on the idea that a metabolite of animal protein was atherogenic for rabbits. He fed milk and egg yolks to weanling rabbits and horsemeat to adult rabbits and saw development of atherosclerotic lesions. A few years later Anitschkow and colleagues[2,3] and Wacker and Hueck[4] were able to induce atherosclerosis in rabbits by feeding them cholesterol suspended in sunflower oil or other fats. Their studies created an intense interest in the atherogenic effects of cholesterol and interest in the effects of proteins was eclipsed. For the 40 years following Anitschkow's experiments, studies of atherogenesis focused on cholesterol and the fat used to suspend cholesterol were ignored. In the 1950s Keys demonstrated a strong relationship between the level of dietary fat and cholesterolemia in a number of populations and attention began to centre on the level of dietary fat and cholesterolemia with the understanding that cholesterolemia was an indicator of risk of coronary heart disease.[5]

In 1954–56 Kritchevsky *et al.* showed that the severity of cholesterol-induced atherosclerosis in rabbits was a function of the level of unsaturation of the fat which accompanied the cholesterol.[6,7] At the same time Groen reviewed the literature and concluded that the level of fat saturation played an important role in cholesterolemia.[8] In 1957 Ahrens *et al.* fed human volunteers a liquid diet which contained 40% of its calories as fat and showed that, in general, plasma cholesterol levels were elevated as the level of saturation of the dietary fat decreased.[9] These studies laid the groundwork for the hypothesis that the level of cholesterolemia depended on the degree of saturation of dietary fat. The atherogenic effects of fats of varying iodine value are detailed in Table 1.[10]

Studies that showed that atherogenesis could be induced in rabbits by using a cholesterol-free, semipurified diet[11] demonstrated that even in the absence of dietary cholesterol the level of atherosclerosis was dictated by the extent of saturation of the dietary fat.[12,13]

In 1965 Keys *et al.*[14] and Hegsted *et al.*[15] and their colleagues developed formulas to predict cholesterol levels based on changes in the level of saturation of the dietary fat. The Keys formula was:

$$\Delta C = 1.35\ (2\Delta S – \Delta P) + 1.5\ \Delta Z,$$

where ΔC represents the change in serum or plasma cholesterol, S and P represent changes in saturated and unsaturated fat, respectively, and Z is the square root of mg/dietary cholesterol/4200 kJ of diet. The Hegsted formula[16] was:

$$\Delta C = 2.16\Delta S – 1.65\Delta P + 0.168\ \Delta C\ (mg/4200\ kJ) + 0.85.$$

Keys and Hegsted both found that fats rich in stearic acid did not give the predicted response and concluded that stearic acid was 'neutral' (that is, had no effect on cholesterolemic response). Monounsaturated fat was also considered neutral, but Mattson and Grundy have shown that fats rich in oleic

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Table 1. Effect of several saturated fats on atherosclerosis in rabbits*

Fat	Iodine value	Serum cholesterol (mg/dl)	Average atherosclerosis[a] Aortic arch	Thoracic aorta
Coconut oil (12)[b]	9	2831	3.1	2.5
Lard (9)	63	2251	2.7	2.0
Hydrogenated corn oil (13)	79	1988	2.5	1.7
Corn oil (13)	124	1910	1.6	1.3

Rabbits were fed 2% cholesterol and 6% fat for 2 months.
*See reference 10; [a]Graded on a 0–4 scale; [b]No. survivors of 14/group.

Table 2. Major triglycerides of some natural fats and oils*

Fat or oil	Major triglycerides		
Butter	PPB	PPC	POP
Lard	SPO	OPL	OPO
Tallow	POO	POP	POS
Cocoa butter	POS	SOS	SOP
Corn oil	LLL	LOL	LLP
Cottonseed oil	PLL	POL	LLL
Olive oil	OOO	OOP	OLO
Palm oil	POP	POO	POL
Peanut oil	OOL	POL	OLL
Soybean oil	LLL	LLO	LLP
Safflower oil	LLL	LLO	LLP
Sunflower oil	LLL	OLL	LOO

*See reference 26; B, butyric acid; C, capric acid; P, palmitic acid; O, oleic acid; S, stearic acid; L, linoleic acid.

acid will reduce serum cholesterol levels.[17,18] Whereas polyunsaturated fats lower both low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, monounsaturated fats only affect the former, resulting in a more favourable LDL cholesterol : HDL cholesterol ratio. Since the original formulas were introduced many others have been proposed. With the availability of better analytical methods it became possible to adduce specific effects for individual fatty acids. For example, a formula proposed by Derr *et al.* offers coefficients for specific fatty acids:[19]

$$\Delta C = 2.3\Delta 14 : 0 + 3.0\Delta 16 : 0 – 0.8\Delta 18 : 0 – 1.0 \text{ PUFA},$$

where PUFA represents polyunsaturated fatty acids. On the basis of their studies in monkeys and hamsters, Hayes and his colleagues concluded that myristic acid is hypercholesterolemic at any dietary level, linoleic acid exerts a hypocholesterolemic effect until its level in the diet approaches 5–6% of calories after which it has no further effect, and palmitic acid is hypercholesterolemic in subjects whose cholesterol levels exceed 225 mg/dL or when ingested with more than 400 mg of cholesterol per day.[20–22] An excellent review of the effects of dietary fatty acids on plasma cholesterol has been published recently.[23] It is also becoming increasingly evident that levels of plasma cholesterol are more dependent on fat saturation than on levels of dietary cholesterol.[24] The relatively small effect of dietary cholesterol was observed by Gertler *et al.* in 1950.[25]

Recently, attention has been turned to the effects of triglyceride structure on experimental atherogenesis. The structure of naturally occurring triglycerides is determined genetically. Small[26] summarized the composition of the major triglycerides in a number of fats and oils (Table 2). The table demonstrates the uniqueness of each fat. The major triglyceride of corn oil, soybean oil, safflower oil or sunflower oil is trilinolein, for example, but there are differences in structure among their second and third most common triglycerides. The differences are important because they dictate the composition of circulating triglycerides. In the course of fat digestion, the fatty acid at the SN2 position is conserved to 75–80% in the triglyceride present in lymph.[27] Tristearin is virtually unabsorbed but the stearic acid of mixed triglycerides is fairly well absorbed[28] albeit at a slow rate relative to other triglycerides.[29,30]

In the course of our work on the effects of different fats in atherogenesis we obtained fats enriched in one specific fatty acid. The fats were obtained by randomizing pure trilaurin trimyristin, tripalmitin and tristearin with corn oil. This provided us with randomized fats containing 19% lauric acid, 18% myristic acid, 30% palmitic acid and 23% stearic acid. The greater concentration of palmitic acid (30%) is due to the fact that corn oil contains approximately 11% palmitic acid. Thus, the randomized palmitic acid-rich fat contained approximately 10% palmitic acid at SN2 whereas the other three fats only had approximately 3.1% palmitic acid at that position. The palmitic acid-rich fat was the most atherogenic.

In a series of studies, rabbits were fed diets containing special fats and cholesterol comprising 6% fat and 2% cholesterol for 8 weeks.[30] The control groups were native and randomized corn oil. As Table 3 shows, there were no significant differences in atherogenicity among the four special fats. The palmitic acid-rich fat (presumably 10% C16 : 0 at SN2) was significantly more atherogenic than the control fats, which were of identical atherogenicity. If the average atherogenicity (arch plus thoracic ÷ 2) of corn oil is set at 1.00, the average atherogenicities of the other fats would be: randomized corn oil, 0.97; lauric acid-rich fat, 1.14; myristic acid-rich fat, 1.11; palmitic acid-rich fat, 1.23; and stearic acid-rich fat, 1.03.[31]

McGandy *et al.* used special fats prepared by interesterification of natural fats with trilaurin, trimyristin, tripalmitin or hydrogenated soybean oil (85% stearic acid) in a ratio of 3 : 1.[32] When the fats were fed to human subjects, the authors did not see the anticipated changes in cholesterol levels. They concluded that the position of a fatty acid in a triglyceride influences its metabolism.

We have continued to examine the effects of triglyceride structure on atherogenicity of different fats. The studies have been carried out in rabbits fed a semipurified diet containing 14–15% fat and 0.1–0.5% cholesterol.

Tallow and lard are used interchangeably in experimental diets requiring animal fat. Both fats contain approximately 24% palmitic acid but its distribution within those fats differs markedly. Almost all of the palmitic acid of lard is found at the SN2 position whereas only 3.8% of the palmitic acid of tallow is at SN2. Lard is significantly more atherogenic than is tallow (Table 4). After the fats are randomized they both have approximately 8% palmitic acid at SN2 and possess similar atherogenic potential[33] (Table 5). Cottonseed oil also contains approximately 24% of palmitic acid, only 1.7% of

which is present at SN2. After randomization the amount of palmitic acid at the SN2 position was increased to 9.9% and its atherogenicity for rabbits was increased almost three-fold[34] (Table 6).

Table 3. Effect of fats prepared by randomizing appropriate triglyceride into corn oil on experimental atherosclerosis in rabbits* (average of 5 experiments)

Fat	No. rabbits	Serum cholesterol (mg/dL)	Atherosclerosis (0–4 scale) Aortic arch	Thoracic aorta
Corn oil (CO)	43/46	2633	1.65	1.10
Randomized CO	42/46	2022	1.59	1.08
Lauric (19%, 12 : 0)	41/46	2003	1.98	1.15
Myristic (18.2%, 14 : 0)	34/36	1883	1.82	1.24
Palmitic (30%, 16 : 0)	42/46	2080	2.07	1.30
Stearic (23.4%, 18 : 0)	40/46	1988	1.74	1.08

Rabbits were fed 2% cholesterol in 6% fat for 2 months.
*See reference 31.

Table 4. Influence of lard and tallow on atherosclerosis in rabbits* (Data ± SEM); (Summary of two experiments with 14/group)

	Group	
	Lard	Tallow
Plasma lipids (mg/dL)		
Cholesterol (C)	662 ± 24	600 ± 48
% HDL-C	6.4 ± 0.6	9.2 ± 0.8[a]
Triglycerides	332 ± 62	253 ± 31
Liver lipids (g/100 g)		
Cholesterol	3.12 ± 0.42	1.99 ± 0.24[b]
Triglycerides	1.97 ± 0.22	2.15 ± 0.44
Atherosclerosis		
Aortic arch	1.44 ± 0.19	0.69 ± 0.16[a]
Thoracic aorta	1.06 ± 0.18	0.41 ± 0.13[a]

*See reference 33.
Rabbits were fed semipurified diets containing 14% fat and 0.5% cholesterol for 2 months.
Aortas graded visually on a 0–4 scale. [a]$P < 0.01$; [b]$P < 0.05$.

Palm oil has been characterized as an atherogenic fat because of its high concentration of palmitic acid (41.2%). However, most of the palmitic acid of palm is at positions SN1 and SN3 and only 3.3% is at SN2. Randomization of palm oil increases the amount of palmitic acid at SN2 to 13.6% and significantly increases its atherogenicity[35] (Table 7). Finally, experiments in which rabbits have been fed diets containing 15% fat, one-third of which is a specifically prepared fat (1,3 stearoyl-2-oleoylglycerol (SOS), 1,2 stearoyl-2-oleoylglycerol (SSO), 1,3 palmitoyl-2-oleoylglycerol (POP) or 1,2 palmitoyl-2-oleoylglycerol (PPO)), show that PPO is the most atherogenic fat[35] (Table 8). The foregoing studies are consistent in showing the increased atherogenicity of fats with palmitic acid at SN2. Understanding the mechanism might provide insight into the atherogenic process.

One possibility is that the structure of the triglyceride affects LDL size. It has been shown by Krauss and Burke[36] that LDL can be subfractionated into small, dense and large fluffy particles and that the former are more atherogenic. However, we have shown that the triglyceride structure does not affect LDL size.[34,37] The structure of a triglyceride affects its rates of turnover,[38,39] but this has not been tested using the specific triglycerides that we are investigating.

The positional distribution of the fatty acids of human milk or infant formula influences their absorption, which appears to be related linearly to the amount of palmitic acid at the SN2 position.[40–42] Co-randomization of coconut and palm oils increases the amount of palmitic acid at SN2 and renders the fat more absorbable in rats than does a simple mixture of the two fats.[42,43] The structure of triglycerides also affects absorption of formulas by piglets and is related to the triglyceride structure, particularly the amount of palmitic acid at SN2.[44,45] Thus, the ongoing research relating type of dietary fat to cholesterolemia and risk of coronary heart disease has progressed through the stages of total fat, to comparison of saturated and unsaturated fat, to specific effects of individual fatty acids and now to influence of triglyceride structure.

Atherogenicity of these various fats may be related to the extent of absorption of the fat. In the study comparing SOS, SSO, POP and PPO the two palmitic acid-rich fats were absorbed to a greater extent than were the fats containing stearic acid.[35] The relation of degree of atherogenicity with degree of absorption may mean that more of a specific fat is available to allow its metabolites to interact with vascular

Table 5. Atherogenic effects in rabbits of native and randomized lard and tallow* (Data ± SEM)

	Group			
	Lard	Rand. lard	Tallow	Rand. tallow
Plasma lipids (mg/dL)				
Cholesterol	926 ± 184	834 ± 153	1177 ± 156	1189 ± 165
Triglycerides	175 ± 51[a]	58 ± 5[abc]	144 ± 28[b]	223 ± 43[c]
Liver lipids (g/100 g)				
Cholesterol	3.41 ± 0.63	3.34 ± 0.44[a]	3.77 ± 0.56	5.07 ± 0.51[a]
Triglycerides	0.97 ± 0.10	0.88 ± 0.14	1.26 ± 0.16	1.26 ± 0.18
Atherosclerosis				
Aortic arch	2.69 ± 0.28[ab]	1.50 ± 0.28[a]	1.29 ± 0.24[b]	1.50 ± 0.53
Thoracic aorta	1.75 ± 0.28[abc]	0.69 ± 0.19[a]	0.79 ± 0.28[b]	0.79 ± 0.29[c]

*See reference 33. Rabbits (8/group) were fed semipurified diets containing 14% fat and 0.5% cholesterol for 3 months. Aortas were graded visually on a 0–4 scale. Values in horizontal row bearing same letter are significantly different. Rand, randomized.

Table 6. Effect of native and randomized cottonseed oil (CSO) on atherosclerosis in rabbits* (Data ± SEM)

	Group	
	Native CSO $n = 12$	Randomized CSO $n = 12$
Serum lipids (mg/dL)		
Cholesterol	546 ± 32	542 ± 25
Triglycerides	57 ± 5	60 ± 4
Liver lipids (g/100 g)		
Cholesterol	1.81 ± 0.01	2.08 ± 0.08[a]
Triglycerides	0.85 ± 0.01	0.84 ± 0.05
Atherosclerosis (0–4 scale)		
Aortic arch	0.58 ± 0.16	1.38 ± 0.19[a]
Thoracic aorta	0.13 ± 0.09	0.71 ± 0.23b

Rabbits were fed semipurified diets containing 14% fat and 0.1% cholesterol for 90 days.
*See reference 34. [a]$P < 0.01$; [b]$P < 0.05$

Table 7. Effect of native and randomized palm oil (PO) on atherosclerosis in rabbits* (Data ± SEM)

	Group	
	Native PO $n = 8$	Randomized PO $n = 8$
Serum lipids (mg/dL)		
Cholesterol	620 ± 36	779 ± 29[a]
% HDL-C	6.8 ± 0.42	6.4 ± 0.88
Triglycerides	70 ± 5	122 ± 13[a]
Liver lipids (g/100 g)		
Cholesterol	1.22 ± 0.87	1.18 ± 0.07
Triglycerides	0.98 ± 0.13	1.33 ± 0.12
Atherosclerosis (0–4 scale)		
Aortic arch	1.63 ± 0.23	2.13 ± 0.18[b]
Thoracic aorta	1.31 ± 0.28	1.81 ± 0.30

Rabbits were fed semipurified diets containing 14% fat and 0.2% cholesterol for 65 days.
*See reference 35. [a]$P < 0.01$; [b]$P < 0.05$.

Table 8. Influence of special fats on experimental atherosclerosis in rabbits* (Data ± SEM)

	Group			
	SOS $n = 5/8$	SSO $n = 7/8$	POP $n = 7/8$	PPO $n = 6/8$
Serum lipids (mg/dL)				
Cholesterol (C)	325 ± 81	272 ± 55	308 ± 55	415 ± 103
% HDL-C	7.14 ± 1.87	9.34 ± 3.03	8.27 ± 3.02	7.92 ± 3.14
Triglycerides	68 ± 8	83 ± 10	94 ± 16	81 ± 25
Liver lipids (mg/100 g)				
Cholesterol	1.16 ± 0.14	1.16 ± 0.10	1.17 ± 0.14	1.20 ± 0.21
Triglycerides	0.71 ± 0.05	0.79 ± 0.03	0.77 ± 0.08	0.79 ± 0.07
Atherosclerosis (0–4 scale)				
Aortic arch	1.60 ± 0.10	1.36 ± 0.34	1.36 ± 0.26	2.42 ± 0.51
Thoracic aorta	1.10 ± 0.33	0.57 ± 0.28	0.29 ± 0.18	1.17 ± 0.21

Rabbits were fed semipurified diets containing 0.05% cholesterol and 15% fat, one-third of which was the special fat.
*See reference 36. SOS, 1,3 stearoyl-2-oleoylglycerol; SSO, 1,2 stearoyl-3-oleoylglycerol; POP, 1,3 palmitoyl-2-oleoylglycerol.; PPO, 1,2 palmitoyl-3-oleoylglycerol.

tissue. This suggestion should be amenable to laboratory verification. Eventually, we should be able to understand the specific features of fat structure and metabolism that result in atherosclerosis. This should do much to clarify the chemistry and physiology of aortic fat deposition.

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