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Age-Related Changes in Lipid Metabolism (40957)[1]

DAVID KRITCHEVSKY

The Wistar Institute of Anatomy and Biology, Philadelphia, Pennsylvania 19104

Studies of lipids and aging in man have been concerned almost exclusively with measurement of serum lipid levels. In recent years more attention has been directed toward the vehicle of the serum lipids, namely, the serum lipoproteins. In animals it has also been possible to study lipid synthesis and degradation in various tissues and, from these studies, to obtain some idea of lipid turnover and accumulation. The ensuing discussion will cover both of these aspects of lipid metabolism in aging.

In general, serum or plasma lipid levels rise with age, although there are conflicting data. Page *et al.* (1) studied a small group of men aged 20–91 years and found no pattern of increasing cholesterol levels with aging. Eck and Desbordes (2) found that average cholesterol levels rose from 146 ± 5 mg/dl in a group of 10 subjects aged 5–15 years to 172 ± 16 mg/dl in 10 subjects aged 22–41 years; serum cholesterol levels in 10 subjects aged 60–81 years were 177 ± 16 mg/dl. These data suggested a sharp rise in cholesterol early in life and then a plateau. Kornerup (3), on the other hand, found no difference in cholesterol levels between men aged 1–14 years (202 mg/dl) and 19–46 years (203 mg/dl) but in a group aged 50–82 years the serum cholesterol levels had risen to 237 mg/dl.

Keys *et al.* (4) reported on cholesterol levels in over 2000 men aged 17–78 years and found a steady increase between the ages of 17 and 55 and a drop in the 60- to 78-year group (Table I). In 1970, Werner *et al.* (5) reported on serum cholesterol levels in men and women visitors to the 1968 San Francisco Health Fair. In men they found an increase (15%) in going from 13–19 to 20–29 years; another increase (7%) in the next decade and then a much slower increase in cholesterol values; women exhibited a somewhat similar pattern but between the ages of 50 and 79 their cholesterol levels were significantly higher than those of the men (Table II). Kipshidze (6) studied aging men in Russia and found peak serum cholesterol values in the group aged 50–59 years. The levels of the serum β-lipoproteins rose steadily with aging (Table III). A pattern of increasing serum cholesterol levels but decreasing high-density lipoproteins has also been seen in England (7).

Heiss *et al.* (8) have published on serum lipid levels in a series of more than 4000 patients. As can be seen in Table IV in men, the greatest single increase (10%) in cholesterol levels is seen between the ages of 20–24 and 25–29 years. In women, the pattern was similar. In both men and women HDL levels fell with advancing age but HDL levels were higher in women at every age level.

Glueck *et al.* (9) observed a preponderance of hyperalphalipoproteinemia among octagenarian kindreds.

Carlson *et al.* (10) studied plasma and tissue lipids in Sprague–Dawley rats aged 1–18 months. They observed a rise in plasma cholesterol, triglyceride, and phospholipid levels with age. Liver cholesterol levels rose but triglyceride levels were virtually unchanged (Table V).

TABLE I. SERUM CHOLESTEROL LEVELS AND AGE IN NORMAL MEN[a]

Age (years) Range	Mean	No.	Serum cholesterol (mg/dl)
17–25	21.3	916	177
23–27	25.0	310	184
25–30	27.4	205	192
28–32	29.9	98	194
30–45	37.3	116	210
45–55	49.9	287	248
50–60	53.2	145	251
60–78	69.3	42	227

[a] After Keys *et al.* (1).

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TABLE II. SERUM CHOLESTEROL LEVELS (mg/dl) IN AGING[a]

Age (years)	Men	Women
To 12	194	197
13–19	197	198
20–29	227	224
30–39	242	230*
40–49	246	215**
50–59	254	272**
60–69	259	285**
70–79	258	275*

[a] After Werner *et al.* (5).
* $P < 0.05$.
** $P < 0.001$.

TABLE IV. MEAN PLASMA CHOLESTEROL AND TRIGLYCERIDE LEVELS (mg/dl) IN WHITE MALES AND FEMALES (20–59 yr)[a]

Age (years)	Males[b]			Females		
	CH	% HDL	TG	CH	% HDL	TG
20–24	162	28	89	162	32	68
25–29	179	25	104	174	32	71
30–34	193	24	122	174	32	74
35–39	201	21	141	188	29	89
40–44	205	21	152	196	29	92
45–49	213	21	143	205	28	105
50–54	213	21	154	222	27	112
55–59	215	22	134	231	26	132

[a] After Heiss *et al.* (8).
[b] CH, cholesterol; % HDL, % total cholesterol in high-density lipoprotein; TG, triglyceride. Males, over 2450 subjects; Females, over 1650 subjects.

Rat strain may be important in determining lipid levels. We have found that serum cholesterol levels of inbred BN, Lewis, or DA rats fell or were unchanged between the ages of 1 and 3 months but cholesterol levels were increased in Wistar rats (11). Serum cholesterol levels in rats may also vary as a function of their physical activity (12) and sex, being higher in males than in females (13).

In contrast to most rat strains Fisher 344 rats do not gain weight after reaching the age of 6–9 months. Their serum lipid levels begin to rise at 18–24 months (14). When compared with Sprague–Dawley rats their livers are smaller in size but represent the same proportion of total body weight (15, 16). Liver cholesterol levels of the two strains are similar (Table VI).

We have studied the plasma lipoproteins of young (1.5 months) and old (24 months) Wistar rats (17). The major differences are the increased levels of cholesterol, triglycerides, and free fatty acids in the lipoproteins of the old rats; increasing levels of sphingomyelin in the older rat plasma; and a decreasing ratio of polyunsaturated to saturated (P/S) fatty acids, the P/S ratio in the young rat plasma being 0.89 and that in older rats being 0.55 (Table VII).

Studies in young (under 2 years) and old (5–10 years) Rhesus monkeys (18) reveal that serum cholesterol and triglyceride levels rise with age, cholesterol from 140 to 173 mg/dl and triglycerides from 117 to 186 mg/dl. Phosphatidylcholine and phosphatidylethanolamine are significantly elevated in sera of the older monkeys. The serum

TABLE III. SERUM LIPIDS IN THE AGING[a]

Age group (years)	No.	Cholesterol (mg/dl)	Phospholipid (mg/dl)	C/PL[b]	β-Lipoprotein[c]
Under 20	37	190	166	1.14	1.00
20–29	35	181	167	1.08	1.07
30–39	33	202	201	1.00	1.21
40–49	28	216	225	0.96	1.50
50–59	23	243	211	1.15	1.57
60–69	31	217	219	0.99	1.57
70–79	31	214	228	0.94	1.64
80–89	30	192	206	0.93	1.64
90–99	26	209	196	1.07	1.64
100 +	26	200	226	0.88	1.71

[a] After Kipshidze (6).
[b] Cholesterol/phospholipid ratio.
[c] Levels of youngest group set arbitrarily as being equal to 1.00.

TABLE V. PLASMA AND TISSUE LIPIDS IN AGING RATS[a]

Tissue	Age (months)	Lipid			
		Cholesterol	Triglyceride	Phospholipid	FFA[b]
Plasma (mg/dl)	1	96	45	130	13
	4	94	73	142	15
	9	218	220	271	12
	18	307	224	353	16
Liver (mg/g)	1	3.4	7.4	30.9	—
	4	4.3	5.8	27.2	—
	9	4.9	6.4	24.3	—
	18	6.7	7.1	21.7	—
Heart (mg/g)	1	2.1	2.3	22.6	—
	4	2.0	1.2	26.4	—
	9	2.2	1.8	24.0	—
	18	2.1	1.3	24.5	—

[a] After Carlson *et al.* (10).
[b] Free fatty acids.

TABLE VI. BODY AND LIVER WEIGHT AND SERUM AND LIVER CHOLESTEROL LEVELS OF AGING FISHER 344 (F) AND SPRAGUE–DAWLEY (SD) RATS

Age (months)	Strain	Body weight (g)	Liver weight (g)	Cholesterol	
				Serum (mg/dl)	Liver (mg/100 g)
2	F	297 ± 18 a	9.3 ± 1.0 d	32 ± 2 g	153 ± 6 j
	SD	413 ± 20 a	13.5 ± 1.1 d	40 ± 3 g	181 ± 10 j
6	F	405 ± 38	11.6 ± 1.0 e	38 ± 3 h	148 ± 3
	SD	458 ± 25	14.9 ± 1.0 e	49 ± 2 h	167 ± 9
12	F	440 ± 29	14.5 ± 1.0	61 ± 5	144 ± 8
	SD	614 ± 83	18.3 ± 2.8	47 ± 5	153 ± 6
18	F	434 ± 14 b	14.4 ± 0.9 f	68 ± 5 i	177 ± 7
	SD	680 ± 70 b	20.3 ± 2.3 f	102 ± 10 i	173 ± 7
24	F	392 ± 20 c	13.9 ± 0.6	102 ± 16	176 ± 9
	SD	701 ± 47 c	20.2 ± 4.2	98 ± 22	178 ± 9

Note. Six rats per group. Values followed by same letter are significantly different ($P \leq 0.05$).

TABLE VII. LIPID CONTENT OF PLASMA LIPOPROTEINS OF YOUNG (6 weeks) AND OLD (24-months) WISTAR RATS

Lipoprotein class	Lipid (mg/dl)[a]				
	FC	EC	TG	FFA	PL
$d = 1.006$					
Young	4.35	3.90	74.39	7.89	13.75
Old	3.87	5.74	51.06	9.03	14.55
$d = 1.006–1.019$					
Young	1.15	2.12	8.72	3.25	4.10
Old	1.30	2.83	5.23	6.04	7.37
$d = 1.019–1.063$					
Young	1.20	7.06	3.31	2.89	7.20
Old	2.69	14.41	7.03	6.40	14.35
$d = 1.063–1.21$					
Young	1.30	14.55	2.40	6.37	17.00
Old	2.65	34.12	5.33	10.79	22.85
$d > 1.21$					
Young	0.57	3.95	1.57	14.11	17.57
Old	1.59	3.71	42.90	24.66	22.72

[a] FC, free cholesterol; EC, esterified cholesterol; TG, triglycerides; FFA, free fatty acids; PL, phospholipids.

TABLE VIII. HEPATIC CHOLESTEROGENESIS IN AGING FISHER 344 (F) AND SPRAGUE–DAWLEY (SD) RATS

Age (months)	Rat	Cholesterol (dpm × 10^{-5} ± SEM) Acetate	Mevalonate
2	F	0.99 ± 0.38	8.01 ± 1.1
	SD	0.49 ± 0.11	11.40 ± 2.5
6	F	0.44 ± 0.10	10.12 ± 1.2
	SD	0.59 ± 0.16	11.19 ± 1.2
12	F	0.26 ± 0.03	8.56 ± 1.3
	SD	0.38 ± 0.07	10.61 ± 1.6
18	F	0.30 ± 0.03	6.47 ± 1.0
	SD	0.35 ± 0.09	6.56 ± 1.0
24	F	0.42 ± 0.09	4.87 ± 1.1
	SD	0.28 ± 0.03	6.57 ± 1.0

Note. Six rats per group.

P/S ratios are 0.80 in the young monkeys and 0.70 in the older ones.

Cholesterol synthesis is depressed in aging rats. Bloch *et al.* (19) studied the incorporation of deuterium-labeled acetate into liver cholesterol in rats and found a progressive decrease with increasing body weight (hence age). Yamamoto and Yamamura (20) studied cholesterol synthesis in rats aged 2, 5, or 8 months. Whether biosynthesis was studied *in vivo* or *in vitro*, there was a 45–55% reduction at 5 months and a 60–70% reduction at 8 months. Cholesterogenesis from alanine is reduced in aging male and female rats, but at every age level the rate of sterol synthesis is higher in the females (13). In Fisher 344 rats cholesterol synthesis whether measured as incorporation of [^{14}C]acetate or activity of HMG-CoA reductase is highest in 2-month-old rats, then levels off (14). When compared with Sprague–Dawley rats, Fisher 344 rats show increased cholesterol synthesis from acetate only at 2 months (15, 16). Cholesterol synthesis from mevalonate is actually somewhat higher in Sprague–Dawley rats (Table VIII). Fatty acid synthesis from acetate is unaffected by age in Fisher 344 rats (14). When the activities of hepatic acetyl-CoA carboxylase (ACC) and fatty acid synthesis (FAS) are assayed in 2- to 24-month Fisher 344 or Sprague–Dawley rats, the activity of both enzymes increases with age. Generally, ACC and FAS activity is slightly higher in livers of Fisher rats (21). Skin, tendon, and aorta of young rats incorporate more acetate into cholesterol than do similar tissues of older rats (22, 23). We (24) have compared incorporation of acetate into cholesterol in kidney, spleen, and colon of 45-day-old or 18-month-old Fisher 344 and Sprague–Dawley rats. Young Fisher rats incorporate more acetate into kidney and colon; the incorporation of precursors in the older rats is similar in the two strains (Table IX).

Triglyceride synthesis and palmitic acid oxidation are also reduced in old rats (25).

Cholesterol degradation and turnover also decrease in aging rats. Yamamoto and Yamamura (20) observed reduced levels of biliary and fecal bile acids in aging rats. Mitochondrial preparations from young Wistar rats oxidize more [26-^{14}C]cholesterol to $^{14}CO_2$ than do old Wistar rats and microsomal cholesterol 7α-hydroxylase activity is 32% lower in old than in young Wistar rats (26). Fisher 344 and Sprague–Dawley

TABLE IX. INCORPORATION OF [1-^{14}C]ACETATE INTO TISSUE STEROLS IN YOUNG AND OLD FISHER 334 OR SPRAGUE–DAWLEY RATS

Rats	dpm × 10^{-4}/mg tissue ± SEM Kidney	Spleen	Colon
Young Fisher 344	1.96 ± 1.07[a]	0.10 ± 0.01	2.49 ± 1.04[c]
Young Sprague–Dawley	0.18 ± 0.02	0.16 ± 0.02[a]	0.39 ± 0.04[b]
Old Fisher 344	0.10 ± 0.02	0.04 ± 0.004	1.98 ± 0.55
Old Sprague–Dawley	0.11 ± 0.02[b]	0.06 ± 0.001	1.62 ± 0.59[b]

Note. Eight rats per group except as noted: [a] seven rats; [b] six rats; [c] five rats.

TABLE X. SYNTHESIS AND HYDROLYSIS OF CHOLESTERYL OLEATE BY RAT AORTA PREPARATIONS

Age (months)	No. pools	Protein (mg/ml)	Synthesis (S)	Hydrolysis (H)	S/H
2	4	2.04	3.9 ± 0.17	2.0 ± 0.62	1.95
12	3	1.49	5.5 ± 1.62	6.9 ± 2.36	0.80
24	4	0.90	7.0 ± 0.41	23.2 ± 2.46	0.31

Note. Results are expressed as nmole (synthesized or hydrolyzed)/mg protein/hr.

rats, however, show little change in cholesterol 7α-hydroxylase activity as they age (15, 16). Cholesterol turnover either in the normal physiological state or under the influence of hormones is higher in young (6 weeks) rats than in old (13 months) ones (27).

A reduction in synthesis, degradation, and turnover might be expected to lead to increased tissue deposition and such is indeed the case in the rabbit (28). In men, too, cholesterol in skin increases from 267 to 343 mg/100 g when tissue from young (20–29 years) men is compared with that from older (60–79 years) men. Cholesterol content of muscle (mg/100 g) increases from 259 to 359; of adipose tissue from 180 to 224; and of connective tissue from 278 to 825 (29). Overall there would appear to be a 180% increase in tissue cholesterol.

The lipids of human aorta show a marked increase between the ages of 6 and 56 with the major increase being in cholesteryl ester (30). The level of esterified cholesterol is higher in diseased aorta than it is in adjacent normal tissue (31). In the rat, an animal which is very resistant to atherosclerosis, aortic lipolytic activity increases with age (32, 33). We studied the synthesis and hydrolysis of cholesteryl oleate with acetone powders prepared from aortas of 2-, 12-, and 24-month Sprague–Dawley rats. Both synthesis and hydrolysis increased with age, with the ratio of synthesis to hydrolysis falling from 1.95 (2 months) to 0.80 (12 months) to 0.31 (24 months) (34) (Table X). These findings may explain, in part, the resistance of the rat to atherosclerosis. Stein and Stein (35) found that the sphingomyelin content (μg P/mg DNA) of young (30 days old) rat aorta was 4.3 and that it rose to 13.1 in old (18–24 months) rats. In old rabbits the sphingomyelin level (26.9 μg P/mg DNA) was three times higher than that in young rabbits. We (17, 36) have found increasing levels of sphingomyelin in the sera of aging rats and have examined aspects of the metabolism of this phospholipid. Analysis of the phospholipids of young and old Fisher 344 and Sprague–Dawley rats (Table XI) indicates no interstrain differ-

TABLE XI. RAT LIVER PHOSPHOLIPIDS

	mg/100 g liver ± SEM					
	Fisher 344			Sprague–Dawley		
Phospholipid	3 months[a]	12 months[b]	18 months[b]	3 months[b]	12 months[b]	18 months[b]
LPC	58 ± 36	91 ± 36	116 ± 59	35 ± 6	57 ± 20	77 ± 31
Sph	112 ± 10	109 ± 2	115 ± 7	120 ± 7	121 ± 2	116 ± 5
PC	1460 ± 56	1520 ± 60	1460 ± 35	1650 ± 100	1740 ± 21	1750 ± 68
PS + PI	338 ± 12	310 ± 41	320 ± 12	366 ± 50	393 ± 19	361 ± 27
PE	737 ± 59	658 ± 47	655 ± 9	868 ± 60	897 ± 46	805 ± 52

Note. LPC, lysophosphatidyl choline; Sph, Sphingomyelin; PC, phosphatidyl choline; PS + PI, phosphatidyl serine plus phosphatidyl inositol; PE, phosphatidylethanolamine.

[a] Five rats.

[b] Four rats.

TABLE XII. HEPATIC ENZYMES OF PHOSPHOLIPID METABOLISM

	Activity ± SEM					
	Fisher 344			Sprague–Dawley		
	3 months	12 months	18 months	3 months	12 months	18 months
Sphingomyelinase[a]	132 ± 19	118 ± 13	138 ± 6	139 ± 24	152 ± 42	150 ± 27
Dihydrosphingosine[b] biosynthesis	2.49 ± 0.10	2.09 ± 0.09	2.25 ± 0.18	1.91 ± 0.12	2.26 ± 0.25	2.28 ± 0.27
Choline kinase[c]	30.3 ± 3.8	29.5 ± 3.6	31.9 ± 2.3	24.9 ± 2.7	21.0 ± 3.7	26.4 ± 2.0

[a] μg Sphingomyelin hydrolyzed/30 min/mg protein. Three rats per group, except 3-month Fisher 344, four rats.
[b] nmole palmitic acid incorporated/60 min/mg protein. Two rats per group.
[c] nmole choline phosphorylated/10 min/mg protein. Three rats per group.

ences or age-related differences in sphingomyelin levels. Phosphatidylcholine and phosphatidylethanolamine levels are somewhat higher in Sprague–Dawley rats. Studies of hepatic sphingomyelinase or dihydrosphingosine synthesis show no differences either (Table XII). The sphingomyelin increase may be specific to the aorta.

As animals age they become increasingly unable to metabolize lipid. They synthesize less but also degrade and excrete less. The result is a net accumulation of lipid in tissues and blood. Energy expenditure and genetic background affect lipid accumulation.

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