Low density lipoprotein metabolism and lipoprotein cholesterol content in southwestern American Indians[1]

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Abstract The prevalence of ischemic heart disease is significantly lower in southwestern American Indians than in Caucasians. To investigate this difference, the metabolism of low density lipoprotein apoprotein (apo-LDL) and plasma lipoprotein cholesterol composition were studied in 10 southwestern American Indians and 5 Caucasian controls. The plasma concentration of LDL cholesterol in American Indians was 88 ± 5 mg/dl (mean ± SEM) and 111 ± 7 mg/dl in Caucasians. The corresponding values of apo-LDL concentrations were 53 ± 3 mg/dl and 77 ± 4 mg/dl, respectively. Conversely, high density lipoprotein cholesterol (HDL) concentrations were significantly higher in American Indians (56 ± 4 mg/dl) than in Caucasians (37 ± 3 mg/dl). There were no statistically significant differences in the biological half-life of apo-LDL, calculated from the second exponential of the plasma die-away curve (3.06 ± 0.15 days vs. 3.45 ± 0.11 days), the fractional catabolic rate of apo-LDL (0.432 ± 0.01 vs. 0.411 ± 0.01), or the fraction of total exchangeable apo-LDL in the intravascular space (70 ± 1 vs. 67 ± 3%). As derived from the absolute catabolic rate under steady-state conditions, the synthetic rate of apo-LDL in American Indians was, however, significantly lower than in Caucasians (334.6 ± 7.8 mg/m² per day vs. 507.2 ± 6.7 mg/m² per day; $P < 0.001$). These data indicate that the lower levels of plasma LDL cholesterol and apo-LDL in American Indians are due to a reduced rate of apo-LDL synthesis rather than to differences in fractional catabolic rates. These differences, in combination with higher HDL cholesterol levels, may contribute to the lower prevalence of ischemic heart disease in American Indians.

Supplementary key words low density lipoprotein · atherosclerosis · heart disease · high density lipoprotein · cholesterol · American Indians

Southwestern American Indians have a lower prevalence of coronary artery disease (CAD) and lower plasma cholesterol levels than Caucasians (1–10). Several studies have indicated that the overall prevalence of myocardial infarction and electrocardiographic evidence of ischemic heart disease in southwestern Indians is only 25% that of the Caucasian population studied in Framingham (8). Not only are the total plasma cholesterol levels lower in southwestern American Indians than in Caucasians, but they tend to rise little with advancing age (11). Measurement of cholesterol levels in Pima Indians has shown that values are 50–60 mg/dl lower in Indians than in Caucasians after the third decade. Despite their lowered prevalence of coronary artery disease, certain tribes of the Southwest (Pima) have the world's highest prevalence of diabetes mellitus (12); yet the prevalence of coronary artery disease in Pimas with long-standing diabetes is still lower than in nondiabetic Caucasians (13).

Elevated levels of low density lipoprotein (LDL), a major cholesterol-containing lipoprotein, have recently been implicated in the pathogenesis of arteriosclerotic cardiovascular disease. In patients with familial hypercholesterolemia (FH), reduced catabolism and increased synthesis of apoprotein LDL (apo-LDL, the protein moiety of LDL) is a genetic defect resulting in elevated levels of LDL cholesterol and apo-LDL (14–16) which, in turn, may be responsible for their premature coronary artery disease. In addition, decreased levels of high density lipoprotein (HDL) apoprotein and HDL cholesterol may also be involved in the development of CAD (17–19).

The low prevalence of CAD and low plasma cholesterol levels in American Indians suggested the need to

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Abbreviations: apo-LDL, low density lipoprotein apoprotein; HDL, high density lipoprotein; VLDL, very low density lipoprotein; FCR, fractional catabolic rate; CAD, coronary artery disease; FH, familial hypercholesterolemia; SGOT, serum glutamic oxaloacetic transaminase, also known as aspartate aminotransferase; SGPT, serum glutamic pyruvic transaminase, also known as alanine aminotransferase; VDRL, Venereal Disease Research Laboratory flocculation test for syphilis.

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TABLE 1. Clinical data on Caucasian subjects during ^{125}I-LDL turnover studies

Initials	Age	Sex	Weight	Height	Calorie Intake	Polyunsaturated: Saturated Fat Ratio	Plasma Cholesterol			Plasma Triglyceride	Plasma Phospho-lipid
							Total	LDL	HDL		
	yr		*kg*	*cm*	*cal/day*			*mg/dl*		*mg/dl*	*mg/dl*
DiJa	26	F	61	164	2368	2.69	170	111	50	53	181
BJ	27	F	66	170	1971	2.77	147	106	33	62	155
JM	27	M	61	176	2315	2.21	149	94	35	83	181
JF	31	M	60	172	2633	2.74	186	136	31	96	239
TM	24	M	73	170	3486	2.72	162	109	38	69	153
Mean ± SEM							163 ± 7	111 ± 7	37 ± 3	73 ± 8	182 ± 16

further characterize their LDL metabolism and lipoprotein cholesterol composition. The present report describes these parameters and provides evidence for a diminished LDL synthetic rate, decreased LDL cholesterol and apo-LDL levels, and elevated HDL cholesterol levels in American Indians.

METHODS

As volunteer subjects, five normal Caucasians (3 men and 2 women) and 10 southwestern American Indians (7 men and 3 women of full Indian ancestry) were studied. The weights of the Indians were significantly larger than those of the Caucasians, but were representative of a typical Indian sample. The clinical data and caloric intake of these subjects during these studies are summarized in **Tables 1** and **2.**

A medical history, physical examination, and the following laboratory tests were performed on admission and found to be normal in all subjects: urinalysis, complete blood count, prothrombin time, serum electrolytes, blood urea nitrogen, serum creatinine, fasting and 2-hr postprandial blood glucose, serum uric acid, SGOT, SGPT, bilirubin, alkaline phosphatase, serum protein electrophoresis, total plasma cholesterol, triglycerides, thyroxine (T_4), triiodothyronine resin uptake (T_3RU), urine culture, VDRL, chest X-ray, hepatitis-associated antigen, and electrocardiogram. None of the female subjects was pregnant, as determined by menstrual history, pelvic examination, and a negative pregnancy test. None of the subjects ingested drug medication during the study period. There was no family history of cardiovascular disease or hyperlipoproteinemia in any subjects.

Protocol

All volunteers lived on the metabolic ward of the Phoenix Clinical Research Section during these studies. A high polyunsaturated fat study diet was consumed for 16–35 days before initiating low density lipoprotein isolation; the diet was continued throughout the studies. The caloric intake and daily cholesterol intake remained constant throughout the period of the turnover study. Eighteen to twenty percent of total calories were derived from protein, 38–42% from fat, and 38–42% from carbohydrates. Daily cholesterol intake was 300 mg. Evidence for the steady state was determined by measurement of body weight and plasma lipid and lipoprotein levels. Fasting total plasma cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, triglycerides, and plasma phospho-

TABLE 2. Clinical data on southwestern American Indian subjects during ^{125}I-LDL turnover studies

Initials/Tribe	Age	Sex	Weight	Height	Calorie Intake	Polyunsaturated: Saturated Fat Ratio	Plasma Cholesterol			Plasma Triglyceride	Plasma Phospho-lipid
							Total	LDL	HDL		
	yr		*kg*	*cm*	*cal/day*			*mg/dl*		*mg/dl*	*mg/dl*
GR/Pima	26	F	86	160	2548	2.70	148	81	48	92	168
DJ/Pima	22	F	98	155	2784	2.28	141	83	36	101	240
SS/Pima	25	F	112	163	2849	3.22	165	95	47	102	290
HS/Navajo	30	M	112	179	4050	2.26	157	85	52	106	118
SP/Hopi	31	M	71	164	2664	2.98	163	76	68	132	106
TK/Pima	28	M	99	170	3313	1.99	151	58	71	117	167
MH/Hopi	24	M	81	172	2818	2.12	186	94	73	97	243
HJ/Pima	61	M	61	162	2178	2.91	168	110	37	103	218
FC/Pima	22	M	97	160	2868	2.10	187	96	68	108	220
GS/Pima	27	M	109	183	3109	3.28	181	105	56	94	226
Mean ± SEM							165 ± 5	88 ± 5	56 ± 4	105 ± 4	220 ± 18

lipids were measured serially from the onset of LDL isolation to completion of turnover studies. All subjects received 1.0 g of supersaturated potassium iodide daily (SSKI 1 g/ml) in three divided doses prior to and during the ^{125}I-LDL turnover studies to prevent radioactive iodide uptake by the thyroid gland. All gave written informed consent. The Clinical Research Committees and Radiation Committee of the National Institutes of Health and the Phoenix Area Research Committee of the Indian Health Service approved all investigations.

LDL isolation

Approximately 150 ml of blood was collected in a sterile, pyrogen-free plastic bag (Fenwal Laboratories, Buena Park, CA) containing a 1% solution of disodium ethylenediaminetetraacetic acid (EDTA). The plasma was immediately separated by centrifugation at 4°C and its density adjusted to 1.019 g/ml by the addition of a solution of NaCl–KBr of *d* 1.085 g/ml; it was then centrifuged in a Beckman 60 Ti rotor (Beckman Instruments, Inc., Palo Alto, CA) at 60,000 rpm for 14 hr (14). After the infranate was removed by tube slicing and its density was adjusted to 1.063 g/ml by the addition of a solution of NaCl–KBr of 1.35 g/ml, it was subjected to further ultracentrifugation for 16 hr at 60,000 rpm. The supernate, containing lipoprotein of density range 1.019–1.063 g/ml, was isolated by tube slicing and ultracentrifuged for 12 hr at 65,000 rpm in a Beckman 65 rotor after carefully overlaying the LDL with a NaCl–KBr solution of *d* 1.063 g/ml. The supernate was then reisolated and spun again for 12 hr at 65,000 rpm with the 65 rotor at a density of 1.063 g/ml. The concentrated LDL was then dialyzed for 3 hr against 4 l of 0.15 M NaCl containing 0.1% EDTA, pH 7.4, to remove the KBr and return the preparation to plasma density. An aliquot was taken for protein determination (20).

Each preparation of LDL was pure and free of contaminating lipoproteins and other serum protein as determined by agarose gel immunoelectrophoresis employing specific antisera against high density (alpha) and low density (beta) apoproteins, whole human serum, albumin, and gamma globulin (14) (Behring Diagnostics, Somerville, NJ). Lipoprotein Lp(a) was not measured during the course of these investigations (21).

LDL apoprotein was radioiodinated using a modification of McFarlane's iodine monochloride technique (22). Purified LDL protein (8–12 mg/ml) in a volume of 1 ml was labeled with carrier-free ^{125}I at 4°C in 1.0 M glycine buffer, pH 10. The efficiency of iodination was 18–25%. The reaction at this pH maximizes protein binding and minimizes lipid binding of the label (14). Unbound iodine was removed by dialysis against a total of 10 l of 0.15 M NaCl, 0.1% Na_2EDTA, pH 7.4, divided into a series of smaller volumes. The percentage of free ^{125}I was determined by precipitation with 10% trichloroacetic acid and 5% phosphotungstic acid in the presence of carrier albumin or plasma. Lipid labeling of LDL was determined by extraction with chloroform–methanol 2:1 (23).

The percentage of ^{125}I attached to the peptide moiety of LDL averaged 95.5%, while lipid labeling accounted for an average of 3.7% and free ^{125}I for 0.8%. The mobility of radiolabeled LDL was unchanged as detected by immunoelectrophoresis after iodination.

Immediately after dialysis of the ^{125}I-LDL, sterile human serum albumin (25%) and sterile saline were added; each dilution contained 35 mg/ml of albumin and approximately 12–15 μCi/ml of ^{125}I-LDL. The preparation was then sterilized by Millipore filtration (0.45 μm) (Millipore Corp., Bedford, MA), and tested for sterility and pyrogenicity before in vivo use (24). The labeled LDL was ready for reinfusion 120 hr after the initial venipuncture.

At the beginning of the turnover study, fasting supine subjects received 20–35 μCi of autologous ^{125}I-LDL in a volume of 1–2 ml (1–2 mg LDL protein) through an intravenous saline infusion. Thereafter, 10-ml blood samples were obtained in glass tubes (containing EDTA) from a vein in the opposite arm at 10 min ("zero time"), 1, 2, 4, 8, 12, 24, 32, 48, 56, 72 hr, and then daily (AM, fasting) for 14 or 21 days. Forty ml of blood were obtained on days 2, 5, 8, 11, 14, and 17 for determination of LDL, HDL, and VLDL cholesterol, LDL apoprotein, plasma triglyceride, and phospholipid. T_4 and T_3 resin uptake were determined on days 7 and 14 after LDL injection in several subjects. Twenty-four-hour urine specimens were collected in glass jars to which KI, $NaHSO_3$, and NaOH were added to minimize volatilization of ^{125}I (14). During the first 72 hr of the Caucasian studies, each voided urine sample was collected in a separate glass jar in order to characterize further the early excretion of the radioactivity. Plasma and urine aliquots were counted for radioactivity at the end of each respective study in a Packard Autogamma spectrometer (Packard Instrument Co., Inc., Downers Grove, IL). There was no residual ^{125}I activity in the intravenous tubing after LDL injection.

Total plasma cholesterol, triglyceride, and phospholipid determinations

Total plasma cholesterol was determined daily and total plasma triglyceride was determined serially throughout each study using the AutoAnalyzer AAII

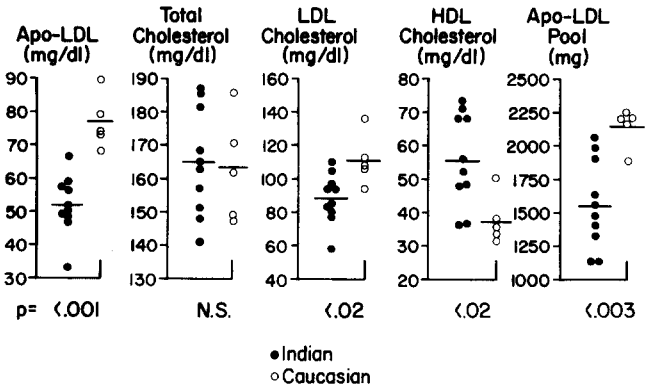

Fig. 1. Comparison of apo-LDL concentration values, total and lipoprotein cholesterol values, and apo-LDL pool size between Indians and Caucasians. Total cholesterol values are similar, but statistically significant differences are noted in all other parameters. Horizontal line represents mean value.

(Technicon Instruments Co., Tarrytown, NY) (25). Plasma phospholipids were determined serially using previously published methods (26).

Lipoprotein cholesterol and apoprotein determinations

Very low density lipoprotein (VLDL) and intermediate density lipoprotein were removed after ultracentrifugation in a Beckman type 65 rotor (Beckman Instruments, Inc., Palo Alto, CA) at 60,000 rpm for 14 hr at d 1.019 g/ml. The infranate was then adjusted to 1.063 g/ml and ultracentrifuged for 16 hr at 60,000 rpm, allowing separation of the LDL fraction from the HDL fraction. These two fractions were then isolated by tube slicing. The cholesterol determination was performed in each fraction (VLDL, LDL, HDL). HDL was the only lipoprotein in the density range >1.063 g/ml, as determined by immunoelectrophoresis. The heparin–manganese chloride precipitation method for HDL-cholesterol was also used (26). Apoprotein-LDL was determined by the method of Lowry et al. (20). A protein:cholesterol ratio for LDL was then determined in each sample on separate days.

Data analysis

The kinetics of LDL turnover were fitted to the mathematical model of an open two-compartment system, described by Mathews and Nosslin (27, 28). A regression line was computed for the log linear portion of the plasma die-away curve; the y intercept and slope of the peeled exponential of this line were determined to obtain the fractional catabolic rate (FCR) of apo-LDL, percentage of apo-LDL in the intravascular space, and biological half-life of intravascular apo-LDL. The ratio of the urinary excretion of ^{125}I radioactivity to that remaining in the plasma (U/P ratio) from day 2 to the end of the study provided an independent measurement of the FCR. Plasma volume (PV) was determined by isotopic dilution using the 10-min plasma sample (14). The synthetic rate (SR) of apo-LDL is equal to the absolute catabolic rate under steady-state conditions. The synthetic rate of apo-LDL, expressed as milligrams of apo-LDL synthesized daily, was calculated using the formula SR = (PV)(FCR)(Apo-LDL concentration). The absolute catabolic rate was also expressed as mg apo-LDL catabolized/m^2 body surface per day (14).

Statistical analysis

The statistical significance of differences between Indian and Caucasian mean values of the lipoprotein parameters was determined by analysis of variance using the Statistical Analysis System program (29).

RESULTS

All subjects remained in a steady state throughout the LDL isolation period and the period during which the turnover studies were performed. During this period each subject received a constant diet and caloric intake, maintained a steady weight (±0.4 kg), and had similar plasma lipid and lipoprotein levels throughout the period of the study.

Lipid and lipoprotein parameters in Caucasians and Indians (Tables 1–4, Fig. 1)

Values of apo-LDL (52 ± 3 mg/dl (Table 4) and LDL cholesterol (88 ± 5 mg/dl) (Table 2) were significantly lower in the Indians than in Caucasians (77 ± 4 mg/dl and 111 ± 7 mg/dl, respectively) (Tables 3 and 1), while total plasma cholesterol values were similar. HDL cholesterol values (56 ± 4 mg/dl) (Table 2) were significantly higher in the Indians than in the Caucasians (37 ± 3 mg/dl) (Table 1). The percentage of total cholesterol represented by HDL cholesterol was significantly higher in the Indians, while that of LDL cholesterol was significantly lower (see **Fig. 3**). The apo-LDL pool size (Fig. 1) [product of (plasma volume)(apo-LDL concentration)] was also significantly lower in the Indians (1560 ± 103 mg) than in Caucasians (2143 ± 66 mg). Statistically significant higher plasma triglyceride levels were noted among the more obese Indian volunteers.

^{125}I-LDL metabolic parameters in Caucasians and Indians (Tables 3 and 4, Fig. 2)

The synthetic rate of apo-LDL, expressed as mg apo-LDL/day or mg/m^2 per day was 677 ± 54 mg/day or 334.6 ± 7.8 mg/m^2 per day in the Indians. Under steady-state conditions, this synthetic rate is indicative of the absolute catabolic rate. These rates were signifi-

TABLE 3. Metabolic parameters for ^{125}I-labeled LDL turnover studies—Caucasians

Initials	Plasma Volume	Plasma apo-LDL	Intravascular Distribution[a]	FCR[b] (a)	FCR[b] (b)	T½ for Exponential Decay[c] (c)	Rate of Synthesis and Catabolism of apo-LDL	
	ml	*mg/dl*	%			*days*	*mg/day*	*mg/m²/day*
DiJa	2793	79	62.6	0.381	0.322	3.84	841	509.7
BJ	3005	74	61.5	0.420	0.323	3.58	934	530.7
JM	2764	68	69.4	0.398	0.347	3.28	748	429.9
JF	2459	70	77.0	0.402	0.360	3.26	890	523.5
TM	3005	73	62.4	0.455	0.407	3.31	998	542.4
Mean ± SEM	2805 ± 100	77 ± 4	67 ± 3	0.411 ± 0.01	0.351 ± 0.02	3.45 ± 0.11	882 ± 42	507.2 ± 6.7

[a] Percent of apo-LDL contained in intravascular space.
[b] Fraction of the intravascular apo-LDL catabolized each day: (a) calculated from the plasma die-away curve; (b) calculated from the U/P ratio.
[c] Calculated from the second (c) exponential of the plasma die-away curve. (c) Represents the biological half-life of apo-LDL.

cantly lower than Caucasian rates (882 ± 42 mg/day or 507.2 ± 6.7 mg/m² per day; $P < 0.001$). No significant differences were found in the percentage of apo-LDL in the intravascular space, fractional catabolic rate or apo-LDL (fraction or intravascular pool of apo-LDL catabolized/daily), or the biological half-life of apo-LDL, as calculated from the second exponential of the plasma die-away curve.

Urinary:plasma (U/P) ratios of ^{125}I-LDL (Table 5, Fig. 4)

The fractional catabolic rates of apo-LDL (the fraction of the intravascular pool of apo-LDL catabolized daily) derived from the urinary plasma ratio determinations were in reasonably good agreement with the fractional catabolic rates derived independently from the plasma die-away curves, but in all studies, the U/P determination gave slightly lower results. The U/P ratios of radioactivity also declined with time, after the initial delay and peak in excretion of radioactivity.

DISCUSSION

These studies are consistent with the hypothesis that southwestern American Indians have a reduced synthetic rate of apo-LDL, lower plasma values of apo-LDL and LDL cholesterol, and higher values of HDL cholesterol than Caucasians with similar cholesterol levels. No differences in these parameters were found between the sexes of either race, confirming a previous finding by one of us (14). Because elevated levels of LDL cholesterol may predispose to coronary artery disease, the present findings of both lower apo-LDL and LDL cholesterol provide a possible explanation for the diminished prevalence of this disease among American Indians.

TABLE 4. Metabolic parameters for ^{125}I-labeled LDL turnover studies—Indians

Initials	Plasma Volume	Plasma apo-LDL	Intravascular Distribution[a]	FCR[b] (a)	FCR[b] (b)	T½ for Exponential Decay[c] (c)	Rate of Synthesis and Catabolism of apo-LDL	
	ml	*mg/dl*	%			*days*	*mg/day*	*mg/m²/day*
GR	2722	49	72.7	0.444	0.428	2.74	592	313.2
DJ	2929	50	68.5	0.527	0.474	2.68	772	393.9
SS	3019	52	69.6	0.528	0.432	2.43	829	385.6
HS	3922	50	64.2	0.449	0.390	3.42	880	384.3
SP	2383	48	77.1	0.350	0.302	3.72	400	226.0
TK	3466	33	72.1	0.459	0.459	2.48	525	250.0
MH	2928	56	73.6	0.367	0.343	3.30	602	310.3
HJ	2123	66	68.4	0.382	0.350	3.54	538	328.1
FC	3267	58	70.9	0.378	0.365	3.52	716	358.0
GS	3479	59	67.6	0.444	0.436	2.82	911	396.1
Mean ± SEM	3024 ± 170	52 ± 3	70 ± 1	0.432 ± 0.01	0.397 ± 0.01	3.06 ± 0.15	677 ± 54	334.6 ± 7.8

[a] Percent of apo-LDL contained in intravascular space.
[b] Fraction of the intravascular apo-LDL catabolized each day: (a) calculated from the plasma die-away curve; (b) calculated from the U/P ratio.
[c] Calculated from the second (c) exponential of the plasma die-away curve. (c) Represents the biological half-life of apo-LDL.

TABLE 5. Plasma and urine counts and urine volume in Indian subjects

Time (hr)	GR			DJ			SS		
	Plasma Counts[ab]	Urine Counts[c]	Urine Volume (ml)	Plasma Counts[ab]	Urine Counts[c]	Urine Volume (ml)	Plasma Counts[ab]	Urine Counts[c]	Urine Volume (ml)
"0"	36678			33597			28075		
1	35893			33550			27172		
2	34456			31994			25644		
4	30767			28212			23015		
8	27756			25435			20425		
12	26140			23411			19184		
24	20612	18353	2290	16616	29545	1440	13440	39825	850
32	17557			14390			11496		
48	13388	29056	1649	9371	37274	1390	7840	34640	1080
56	11116			8699			6939		
72	8887	12966	2028	6295	26691	1060	5010	20394	1100
96	6205	12147	1990	4100	15689	1200	3577	10148	1450
120	4346	8992	1783	2983	8417	1080	2523	6105	1130
144	3299	11669	1063	2157	6139	1010	1904	6260	740
168	2501	7526	1110	1628	3532	1380	1473	5044	650
192	1909	3596	1921	1234	2553	1470	1005	3111	620
216	1462	2536	1940	943	2013	980	839	2475	720
240	1154	2023	1780	762	1730	1150	677	1580	860
264	896	1151	2300	613	1032	1410	567	948	1350
288	692	2214	980	528	1375	985	503	912	1050
312	628	852	2120	433	735	1390	321	624	1230
336	498	761	1881	—	—	—	—	—	—

Time (hr)	FC			HS			SP		
	Plasma Counts[ab]	Urine Counts[c]	Urine Volume (ml)	Plasma Counts[ab]	Urine Counts[c]	Urine Volume (ml)	Plasma Counts[ab]	Urine Counts[c]	Urine Volume (ml)
"0"	40362			21519			32716		
1	38701			21058			31336		
2	39523			20283			32439		
4	34688			18323			30402		
8	33177			16301			27357		
12	29331			14863			26242		
24	22871	25570	1267	11498	28542	1935	23423	14323	1386
32	20705			9625			20905		
48	14593	39854	1075	6636	31965	821	17288	26531	985
56	13784			5769			15407		
72	10538	34648	1285	4392	21000	1222	13243	25352	828
96	7528	20023	2275	3008	13795	1215	10044	14564	1160
120	5567			2317	7066	1095	8295	12226	862
144	4486	10254	1375	1781	6316	845	5896	12463	985
168	3489	4162	2845	1413	3982	1195	4782	9230	940
192	2718	6231	1020	1113	3516	855	4017	5854	985
216	2206	5143	1115	902	2464	1285	3269	3834	1423
240	1873	1777	1885	764	1771	1282	2814	3199	905
264	1403	2344	1855	659	1183	1392	2298	3064	930
288	1258	2011	1747	544	839	1735	1837	1203	1482
312	987	1159	2035	430	881	1622	1684	1360	1120
336	827	1562	1187	390	830	1420	1460	1846	1450

[a] 60% counting efficiency, 60–300 window at 80% gain.
[b] Per 2 ml counted.
[c] Per 5 ml counted.

MH			HJ		
Plasma Counts[ab]	Urine Counts[c]	Urine Volume (ml)	Plasma Counts[ab]	Urine Counts[c]	Urine Volume (ml)
42574			35895		
39300			35178		
37687			33421		
36771			31085		
34049			26669		
31480			24547		
23462	25233	1725	21328	12057	2210
20527			17880		
15915	36268	1625	13585	10427	2625
—			11493		
11605	35245	1015	9191	9108	4105
8281	18605	1627	7280	6444	1605
6533	8989	2345	5124	4546	2750
4940	10536	1407	3899	4186	2425
4031	3848	3205	3021	2524	2765
3053	3657	2455	2590	1523	3205
2548	3186	2205	2065	1318	2820
1875	3971	1460	1681	637	3230
1606	2114	2175	1401	574	3215
1354	956	3620	1215	561	3385
1074	875	3525	1088	453	3575
958	1103	2300	975	301	3415

TK			GS		
Plasma Counts[ab]	Urine Counts[c]	Urine Volume (ml)	Plasma Counts[ab]	Urine Counts[c]	Urine Volume (ml)
33944			23168		
31826			22131		
32420			21659		
29386			21569		
26570			18083		
23689			16458		
19254	40736	1465	13127	18188	1865
15255			11181		
11768	54164	930	8309	33686	765
9785			7320		
7534	39239	925	5528	25819	1325
5209	26684	1230	3876	15534	1575
3812	10036	1885	2972	9710	1285
2870	9691	1370	2348	7204	1205
2337	4124	2165	1727	5475	1215
1665	6733	985	1435	3378	1495
1336	4637	645	1144	2323	1605
1023	2246	1630	888	2064	1285
928	1550	2025	687	1581	1190
734	1946	1145	583	1108	1625
619	1635	1135	510	898	1425
526	1243	1305	336	921	1205

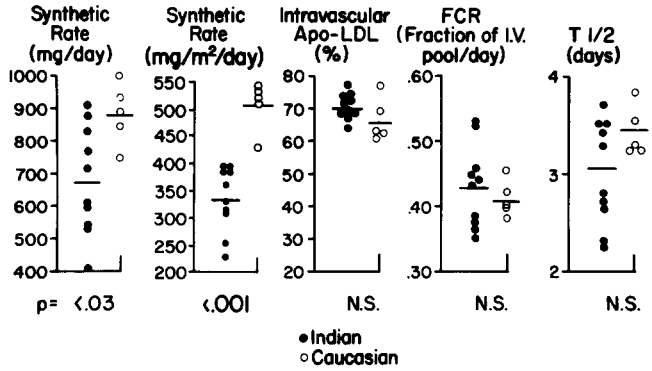

Fig. 2. Comparison of parameters of LDL metabolism between Indians and Caucasians. The absolute synthetic rate of apo-LDL is significantly lower in Indians. Horizontal line represents mean value.

The metabolic parameters of LDL metabolism and LDL cholesterol levels in our Caucasians are comparable to the values previously reported in normolipidemic subjects by Langer, Strober, and Levy (14), Sigurdsson, Nicoll, and Lewis (30), and Bilheimer et al. (31). HDL cholesterol values in our Caucasians are consistent with those reported by Fredrickson and Levy (32). Apo-LDL values determined during the course of these studies in Caucasians are in accord with values in normolipidemic subjects studied by Albers, Cabana, and Hazzard (33) using a radioimmunoassay technique.

Statistically significant differences in LDL metabolism and lipoprotein levels were demonstrated in the American Indians. The absolute catabolic rate of apo-LDL, expressed as mg/day or mg/m² per day, was significantly lower in the Indians in spite of a greater degree of obesity than in the Caucasians, whereas no differences were noted in the fractional catabolic rate of apo-LDL, biological half-life of apo-LDL (calculated from the second exponential of the plasma die-away curve), and the percentage of exchangeable apo-LDL in the intravascular space.

The Indian group had higher plasma triglyceride levels than the Caucasians. The higher levels are probably the result of an increased synthesis of VLDL related to their greater degree of obesity (34). If so, accelerated VLDL and triglyceride synthesis might have been expected to result in increased LDL synthesis in the more obese Indian group. VLDL turnover studies, however, are needed to determine this with certainty, since an alternate pathway might be postulated to explain the higher triglyceride levels in the face of lower apo-LDL synthesis among the Indians.

The diminished synthesis of apo-LDL cannot be accounted for by either differences in plasma volume or differences in fractional catabolic rate. Since the absolute catabolic rate of LDL is equal to the absolute synthetic rate in steady-state conditions, it is clear that

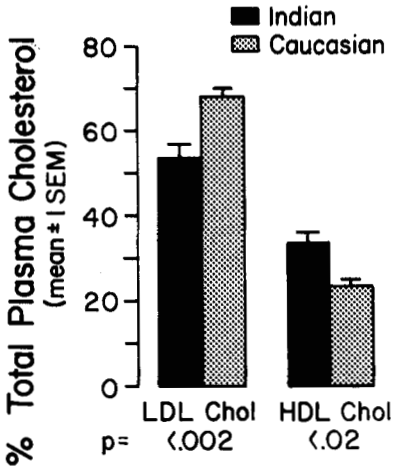

Fig. 3. LDL and HDL cholesterol expressed as percentage of total cholesterol. Indians have a significantly lower proportion of LDL cholesterol and higher proportion of HDL cholesterol for a similar level of total cholesterol than Caucasians.

American Indians both catabolize less apoprotein and synthesize less apoprotein than Caucasians. If the synthetic rate of apo-LDL were similar in Caucasians and southwestern American Indians, a reduction in the absolute catabolic rate in the latter group would be accompanied by an accumulation of plasma apo-LDL. However, the reduced levels of apo-LDL in the Indians reflect both the diminished synthetic rate of apo-LDL as well as the correspondingly lower absolute catabolic rate. Significant differences in apo-LDL pool size between Indians and Caucasians were not associated with changes in the fractional catabolic rate, but were well correlated with absolute synthetic rate (**Fig. 5**). These data are also consistent with the observation that the fractional catabolic rate of apo-LDL is independent of the apo-LDL pool size (14).

The lower synthetic rate of apo-LDL in the Indians probably accounts for the lower plasma levels of LDL-cholesterol and, in part, for the higher ratio of HDL/LDL cholesterol found in the Indians than in the Caucasians. The apo-LDL synthetic rate (mg/m² per day) correlates with the plasma apoprotein levels in both the Indians (r = 0.48) and Caucasians (r = 0.47), which in turn are highly correlated with the plasma LDL cholesterol levels (r = 0.97 in Indians; 0.98 in

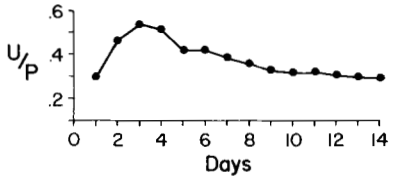

Fig. 4. Urinary–plasma ratio of ^{125}I-labeled LDL excretion in both Indians and Caucasians. After an initial delay, peak excretion was followed by a slight decline. U/P ratios provided an independent estimate of fractional catabolic rate (fraction of intravascular pool of LDL catabolized daily) of apo-LDL.

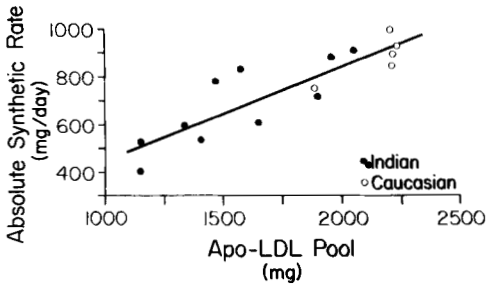

Fig. 5. Relationship between absolute synthetic rate of apo-LDL and apo-LDL pool size. The smaller apo-LDL pool size in Indians is a result of a diminished synthetic rate.

Caucasians). Thus apo-LDL synthesis is related to LDL cholesterol levels in both races (r = 0.59 in Indians; 0.56 in Caucasians).

Although the total plasma cholesterol level was similar in the two groups, the findings of low LDL cholesterol fractions in the Indians is consistent with the levels reported in a population of Tarahumara Indians living in Mexico (35). Our observation of similar total cholesterol levels between the Indians and Caucasians in the age range studied is consistent with the report that median cholesterol levels are similar between Pimas and Caucasians in the third decade (11). After this age, total cholesterol levels become significantly higher in Caucasians but remain similar in the Indians, suggesting that the differences in apo-LDL synthesis and LDL cholesterol levels, which we have demonstrated, may be accentuated in older age groups.

The higher levels of HDL cholesterol found in Indians are also of interest in view of the lower rate of CAD in the Indians. Recent evidence suggests that low HDL cholesterol levels may predispose to the development of coronary heart disease (17–19) and a role for HDL in promoting tissue clearance of cholesterol has been suggested by studies of Tangier disease in which HDL levels are low or absent (36). Although firm conclusions concerning the reasons for the infrequency of ischemic heart disease among the Indians cannot be made with certainty, the lower apo-LDL synthetic rates, lower LDL cholesterol levels, and elevated HDL cholesterol levels found in the southwestern American Indians are consistent with the hypothesis that these measures have an important role in the genesis of coronary artery disease.

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