Compensatory mechanisms governing the concentration of plasma low density lipoprotein

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Abstract To evaluate factors regulating the concentrations of plasma low density lipoproteins (LDL), apolipoprotein B metabolism was studied in nine Pima Indians (25 ± 2 yr, 191 ± 20% ideal wt) with low LDL cholesterol (77 ± 7 mg/dl) and apoB (60 ± 4 mg/dl) and in eight age- and weight-matched Caucasians with similar very low density lipoprotein (VLDL) concentrations, but higher LDL (cholesterol = 104 ± 18; apoB = 82 ± 10; $P < 0.05$). Subjects received autologous ^{131}I-labeled VLDL and ^{125}I-labeled LDL, and specific activities of VLDL-apoB, intermediate density lipoprotein (IDL)-apoB, and LDL-apoB were analyzed using a multicompartmental model. Synthesis of LDL-apoB was similar (1224 ± 87 mg/d in Pimas vs 1218 ± 118 mg/d in Caucasians) but in Pimas the fractional catabolic rate (FCR) for LDL-apoB was higher (0.48 ± 0.02 vs 0.39 ± 0.04 d^{-1}, $P < 0.05$). In the Pimas, a much higher proportion of VLDL-apoB was catabolized without conversion to LDL (47 ± 3 vs 30 ± 5%, $P < 0.01$). When all subjects were considered together, LDL-apoB concentrations were negatively correlated with both FCR for LDL-apoB ($r = -0.79$, $P < 0.0001$) and the non-LDL pathway ($r = -0.43$, $P < 0.05$). Also, the direct removal (non-LDL) path was correlated with VLDL-apoB production ($r = 0.49$, $P = 0.03$), and the direct removal pathway and FCR for LDL-apoB were correlated ($r = 0.49$, $P = 0.03$). In conclusion, plasma LDL appear to be regulated by both the catabolism of LDL and the extent of metabolism of VLDL without conversion to LDL; both of these processes may be mediated by the apoB/E receptor, and appear to increase in response to increasing VLDL production. — **Howard, B. V., G. Egusa, W. F. Beltz, Y. A. Kesäniemi, and S. M. Grundy.** Compensatory mechanisms governing the concentration of plasma low density lipoprotein. *J. Lipid Res.* 1986. **27:** 11–20.

Supplementary key words plasma cholesterol • very low density lipoproteins • multicompartmental model

Studies of several kinds have demonstrated a relationship between plasma levels of low density lipoproteins (LDL) and atherosclerotic disease. This relationship has been shown in epidemiological studies among different populations (1) and within single populations (2), in patients with genetic forms of hypercholesterolemia (3), and in studies on experimental animals (4). Even within the so-called "normal" range of LDL levels in the United States, there is a graded relation between LDL concentrations and risk for coronary heart disease (CHD) (5). Therefore, factors regulating the levels of plasma LDL should be important determinants of CHD risk.

In general terms, levels of LDL are controlled by the balance between input and catabolism of this lipoprotein. The precursor of LDL is very low density lipoprotein (VLDL). VLDL are secreted into plasma by the liver and are catabolized to VLDL remnants by lipoprotein lipase (LPL). VLDL remnants can be either converted to LDL or removed directly by the liver or other tissues; this direct removal path has been called the "shunt" pathway because it was once thought that most VLDL particles are converted to LDL (6, 7). Recent studies (8–13), however, have shown that the direct removal pathway can be sizable in humans. Thus, the input of LDL depends on the balance between production rates of VLDL and the size of the direct removal pathway. The clearance of LDL also depends on two processes, uptake by specific cell-surface receptors for LDL and nonspecific uptake and degradation (14). Current evidence suggests that LDL and VLDL remnants are cleared by the same cell-surface receptors (15, 16). The magnitudes of these multiple pathways regulating input and exit of plasma LDL should determine levels of LDL in different populations.

The Pima Indians constitute one population in which

Abbreviations: VLDL, very low density lipoproteins, IDL, intermediate density lipoproteins, LDL, low density lipoproteins; FCR, fractional catabolic rate; CHD, coronary heart disease.

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concentrations of LDL cholesterol are relatively low (17). These reduced levels may account for their low occurrence of CHD (18) despite a high prevalence of two major risk factors for CHD—diabetes mellitus (19) and obesity (20). Thus, we have chosen to examine the lipoprotein metabolism in this population to determine the reasons for their low plasma LDL. Specifically, we carried out combined studies of the metabolism of VLDL and LDL in a group of male Pima Indians and in Causasians matched for age, sex, and weight. The results of this study reveal a combination of compensatory mechanisms affecting LDL concentrations.

METHODS

Subjects

Nine Pima Indian men were selected for investigation (**Table 1**). These men were obese, as is typical of the Pima population, and eight obese Caucasian men were selected for controls. The groups did not differ significantly in age, body weight, percent fat, or percent ideal body weight. All subjects had normal functions of kidneys, liver, and gastrointestinal tract as evaluated by physical examination, blood tests, and urinalysis. None had hypertension, evidence of CHD, or hyperlipidemia. The subjects were not diabetic as shown by a 75-g oral glucose tolerance test, and none were taking medications at the time of the study. Informed consent was obtained, and the protocol was approved by the Human Studies Committees of the National Institutes of Health and the Phoenix Indian Medical Center, and by the Gila River Indian Community. Two of the obese Caucasians were studied on the metabolic ward of the San Diego Veterans Administration Medical Center, San Diego, CA; a similar protocol was followed, except that body composition measurements were not available. In the remaining patients, body composition was determined by underwater weighing. Residual lung volume was measured simultaneously by a helium dilution technique. Fat-free mass was calculated according to Siri (21).

Experimental procedures

Patients were admitted to the metabolic ward at least 7 days before the study and placed on a solid food weight-maintaining diet consisting of 40% fat (P/S ratio = 0.35), 45% carbohydrate, 15% protein, and 500 mg of cholesterol/day. In addition, patients received 150 mg of potassium iodide daily. Each patient was weighed daily and caloric intake was adjusted to maintain constant body weight during the study. Levels of plasma cholesterol and triglyceride were shown to be constant during the study period, with mean coefficients of variation of 8.3% and 15.5%, respectively.

Autologous VLDL and LDL were isolated under sterile conditions from plasma obtained by plasmapheresis (13). VLDL (d < 1.006 g/ml) were isolated by preparative ultracentrifugation for 18 hr at 40,000 rpm and concentrated and rewashed by centrifugation at 40,000 rpm for 18 hr. After removal of VLDL the infranatant was adjusted to d 1.025 g/ml and, after centrifugation for 20 hr at 40,000 rpm (15°C), intermediate density lipoproteins (IDL) were removed and discarded. The infranatant was adjusted to d 1.060 g/ml, and LDL were isolated by centrifugation at 50,000 rpm for 20 hr. LDL were rewashed and concentrated by adjusting the density to 1.070 g/ml and centrifuging at 40,000 rpm for 20 hr.

The isolated VLDL and LDL were dialyzed for several hours against 0.15 M NaCl containing 2 mM EDTA, pH 7.4 (EDTA-saline); VLDL were labeled with ^{131}I and LDL were labeled with ^{125}I by the method of McFarlane (22). Unbound iodine was removed by extensive dialysis against EDTA-saline. ^{131}I-Labeled VLDL and ^{125}I-labeled LDL were diluted in the patient's own serum to obtain a final activity of approximately 10 μCi/ml and were passed through a 0.22-micron Millipore filter. Sterility and lack of pyrogenicity were confirmed in aliquots of the final preparations. Preliminary experiments indicated that

TABLE 1. Study subjects

	Pima		Caucasian	
N	9		8	
Age (yr)	25 ± 2	(18-38)	35 ± 5	(18-61)
Height (cm)	173 ± 2	(164-184)	178 ± 3	(164-192)
Weight (kg)	131 ± 14	(91-216)	124 ± 11	(71-148)
BMI[a]	44 ± 4	(30-74)	39 ± 3	(26-50)
Percent ideal wt	191 ± 20	(132-322)	173 ± 9	(139-220)
Percent fat[b]	36 ± 3	(26-53)	36 ± 2	(32-43)
Plasma volume (ml)	4396 ± 329	(3347-6033)	4051 ± 273	(2640-4887)
Mean insulin (μU/ml)[c]	94 ± 16	(34-176)	43 ± 7	(30-70)

[a] Body mass index, equal to wt (kg)/ht^2 (m^2).
[b] Data available for six subjects.
[c] Insulin value is the mean during the first 6 hr of the turnover study. Values were significantly higher in Pimas than in Caucasians ($P < 0.05$).

iodinated VLDL and LDL prepared in this way were similar in composition and structure (by gel filtration chromatography) to the native lipoprotein.

Approximately 5 days after plasmapheresis, 23–29 μCi of ^{131}I-labeled VLDL (0.2–2.6 mg of protein, average % label in B = 47%) was injected. Forty-eight hr later 36–51 μCi of ^{125}I-labeled LDL (0.6–3.8 mg of protein, average % label in B greater than 95%) was injected. For 24 hr prior to and 24 hr after the injection of ^{131}I-labeled VLDL, the diet consisted of 60% of maintenance calories in a fat-free formula preparation (75% carbohydrate, 25% protein) which was fed every 3 hr. This diet was used to eliminate the influx of chylomicrons during assessment of VLDL metabolism (23) and to minimize hourly fluctuations of VLDL concentrations during the time when frequent samples were obtained for VLDL. Concentrations of VLDL and LDL during the period of formula diet were not significantly different compared to those in the remaining 14 days of the study. Therefore, it was assumed that the measurements of VLDL kinetics during the period of formula feeding are applicable to the remaining days of the study. Venous blood samples were collected into EDTA at −30, 15, 30, 60 min, and 2, 3, 4, 5, 9, 12, 18, 24, 30, 36, 42, and 48 hr after injection of VLDL, and 15, 30, and 60 min and 6, 12, and 24 hr after injection of LDL, and then daily thereafter before breakfast for 15 days. Urine specimens were collected throughout the study.

Lipoproteins were separated from each plasma sample as follows. Four ml of plasma was overlaid with a solution of 0.15 M NaCl, 1 mM EDTA, pH 7.4, d 1.006 g/ml, and centrifuged for 18 hr at 40,000 rpm. After VLDL were harvested, the infranatant was adjusted to d 1.019 g/ml, and the samples were centrifuged for 20 hr at 40,000 rpm. Intermediate density lipoproteins were removed and then LDL were similarly isolated after the infranatant was adjusted to d 1.063 g/ml and centrifuged for 20 hr at 40,000 rpm. The specific activity of apoB in each lipoprotein fraction was determined using isopropanol to isolate apoB as described previously (24). ApoB concentrations in VLDL, IDL, and LDL were measured as the difference between total protein in each fraction and isopropanol-soluble protein as described previously (24). In this report IDL refers to the particles isolated between densities 1.006 and 1.019 g/ml, and it is not known how these relate to VLDL "remnants" which may be present both in this density range as well as in the VLDL fraction.

Plasma volume was determined by isotopic dilution of ^{125}I-labeled LDL using plasma samples obtained at 5, 10, 15, and 20 min after injection of ^{125}I-labeled LDL. The plasma ^{125}I radioactivity at time of injection was computed by linear regression. This estimate, A, did not differ significantly from an estimate of intercept computed from fitting the complete curve, B (A/B = 0.98 ± 0.03).

The ratio of urine to plasma radioactivity (U/P ratio) was calculated for ^{125}I from the total ^{125}I radioactivity in urine collected daily. No significant declines in U/P ratios were observed in the majority of the subjects during the collection period. Values for ^{125}I urine radioactivity were also used in the modeling procedure to obtain the best estimate of LDL FCR. Urinary creatinine (25) was monitored to confirm complete collection.

Cholesterol in total plasma and each lipoprotein fraction was measured by the extract method of Rush, Leon, and Turrell (26) and triglyceride was measured by the enzymatic method of Bucolo and David (27). These measurements were standardized to be comparable to those of the Lipid Research Clinics, using calibration pools supplied by the Centers for Disease Control, Atlanta, GA (17). Glucose was measured on a glucose analyzer (Beckman Instruments). Protein in lipoprotein fractions was measured by the Lowry method as modified by Markwell et al. using 1% SDS (28). Plasma insulin was measured by the Herbert et al. modification (29) of the radioimmunoassay method of Yalow and Berson (30).

The kinetic data generated in this study were analyzed using the linear first order compartmental model described by Beltz et al. (31) which is an extension of the model of Berman et al. (9). This model was developed using studies from a range of individuals who differed widely in plasma lipoprotein distribution. Analysis of VLDL-apoB employed a stepwise conversion of VLDL-apoB into IDL. A small quantity of slowly removed VLDL-apoB is contained in an additional pool (compartment 21). The number of pools in the delipidation chain was allowed to vary to give the best fit of the data. This provides a model which is flexible enough to be used in studies with VLDL of varying degrees of heterogeneity. The kinetics of LDL-apoB were analyzed by the standard two-pool model. Appearance of ^{125}I in urine was modeled using a plasma iodine compartment and a single urine pool. Parameters obtained in these analyses were the fractional catabolic rates (FCRs) and transport rates. Transport rates (also referred to in this paper as "synthesis" or "production") in LDL were computed after the best estimate of FCR was obtained from the composite of ^{125}I-labeled LDL, ^{131}I-labeled LDL, and ^{125}I urine curves. By combining all the data, it was possible to obtain an integrated picture of apoB kinetics. The mass of VLDL-apoB converted to LDL and that removed directly from the circulation were estimated. It was assumed that IDL is an intermediate in the conversion of VLDL to LDL; the direct removal pathway came out of both VLDL and IDL. The magnitude of "direct" input of LDL also was obtained (31).

Compartmental modeling was performed on a VAX computer (Digital Equipment Corp.) using the SAAM/CONSAM computer programs (32, 33). Statistical analyses were performed using the Statistical Analysis System

(Cary, NC). Differences between means were evaluated using Student's unpaired *t*-test assuming central distribution, and relationships between variables were evaluated by computing Pearson simple correlation coefficients.

RESULTS

Mean concentrations of cholesterol and triglycerides in total plasma, VLDL, and LDL are compared for the two groups in **Table 2**. The average total cholesterol was higher in Caucasians, but total triglyceride values were similar. There were no differences in levels of VLDL-apoB, triglyceride, or cholesterol. For Caucasians, the LDL-cholesterol and apoB were higher than in Pimas but the ratio was similar. The ratios of triglycerides/apoB in VLDL and apoB/cholesterol in VLDL were similar for the two groups.

Fig. 1 shows turnover data for VLDL, IDL, and LDL for a typical Pima and Caucasian subject with both the experimental points and the model simulated curve. Data from both populations could be accounted for using the model previously described by Beltz et al. (31). The mean square errors (weighted) for the Pimas and Caucasians (10.5 ± 1.2 and 18.0 ± 3.4) were not significantly different; the model, therefore, fit the data from the two populations equally well.

Numerical values for kinetic parameters for VLDL-apoB and LDL-apoB and their interconversions for individuals are presented in the Appendix. Kinetics of VLDL-apoB are summarized in **Fig. 2**. Despite similar concentrations of VLDL-apoB in the two groups, the synthetic rate of VLDL-apoB was significantly higher in the Pimas. The FCR of VLDL-apoB was marginally higher in Pimas, but not at a significance of $P < 0.05$. Compartment numbers in the delipidation chain for Pimas and Caucasians were not significantly different (3.8 ± 0.4 and 4.1 ± 0.4, respectively).

TABLE 2. Lipids and lipoproteins

	Pima	Caucasian	*P*
Total			
Cholesterol[a]	149 ± 5	205 ± 24	0.05
Triglyceride	139 ± 6	147 ± 16	
VLDL			
Cholesterol	17 ± 4	23 ± 4	NS
Triglyceride	114 ± 21	116 ± 19	NS
ApoB	10.1 ± 1.3	11.0 ± 2.2	NS
TG/apoB	11.0 ± 1.1	11.0 ± 1.7	NS
LDL			
Cholesterol	77 ± 7	104 ± 18	0.08
Triglyceride	24 ± 2	23 ± 5	NS
ApoB	60 ± 4	82 ± 10	0.05
CH/apoB	0.80 ± 0.05	0.84 ± 0.06	NS

[a] All concentrations are given as mg/dl.

Synthetic rates of LDL-apoB were similar in Pimas and Caucasians (**Fig. 3**). However, the FCR of LDL-apoB was significantly higher in Pimas (Fig. 3).

The total and percentage conversions of VLDL-apoB to LDL-apoB are compared in **Fig. 4**. Although the total input of VLDL-apoB was greater in Pimas (Fig. 2), the masses of apoB converted to LDL were similar for the two groups. Thus, the percentage of VLDL-apoB converted to LDL was significantly lower in the Pimas, and the absolute quantity of VLDL-apoB not converted to LDL, but lost through direct removal, or non-LDL pathway, was significantly higher. Indeed, the percentage of total VLDL-apoB leaving the VLDL compartment but not converted to LDL was almost twofold higher in Pimas than in Caucasians.

By combining data for patients of both groups, additional information about factors regulating LDL levels was obtained. As synthesis of VLDL-apoB increased, more of apoB was removed by the direct removal (non-LDL) pathway (**Fig. 5**); this increment in the direct removal pathway thus dampened the rise in conversion of VLDL-apoB to LDL. An increasing proportion of apoB metabolized via the direct removal (non-LDL) path was associated with lower concentrations of LDL-apoB (**Fig. 6**), and LDL-apoB concentration was negatively associated with the FCR for LDL-apoB (**Fig. 7**). Furthermore, the magnitude of the direct removal (non-LDL) pathway and the FCR of LDL-apoB were positively associated (**Fig. 8**). Among the current subjects, the quantity of apoB entering LDL was not significantly correlated with levels of LDL-apoB ($r = 0.16$, NS). This was consistent with the observed increase in FCR.

Plasma insulin concentrations were measured on samples drawn during the first 6 hr of the metabolic study. Mean concentrations were higher in the Pimas than in Caucasians (Table 1), and there were weak positive correlations between plasma insulin and both the FCR for LDL-apoB ($r = 0.46$, $P = 0.08$) and the percent VLDL-apoB removed by the direct removal pathway ($r = 0.40$, $P = 0.14$).

DISCUSSION

The objective of this study was to elicit the mechanisms regulating concentrations of plasma LDL. We investigated a group of Pima Indians who, in spite of their obesity, diet, and westernized life style, have relatively low levels of LDL-cholesterol (17), and a low prevalence of CHD (18). Their lipoprotein metabolism was compared to that of a group of obese Caucasians who had higher plasma LDL. The studies indicated that apoB metabolism in the two groups differed quantitatively but not qualitatively; thus the lipoprotein metabolic system of the Pimas has

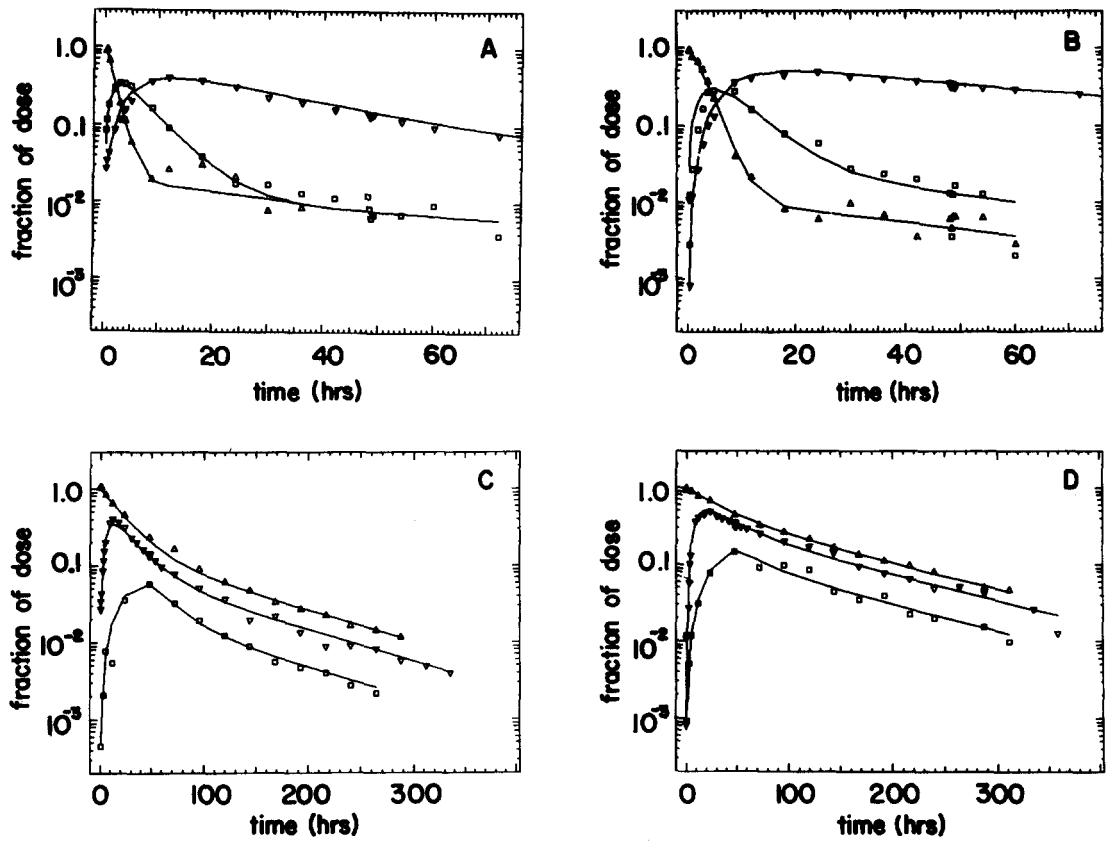

Fig. 1. Specific activity data for VLDL-, IDL-, and LDL-apoB metabolism in a typical Pima (A and C) and Caucasian (B and D). Data points are the experimental data; the curve is the computer-simulated fit to the observed data. A and B are ^{131}I-labeled VLDL (△), ^{131}I-labeled IDL (□), and ^{131}I-labeled LDL (▽) data; C and D are ^{131}I-labeled LDL (▽), and ^{125}I-labeled LDL (△) data, and ^{125}I in urine (□) data.

responded to physiologic and/or environmental factors in ways that result in lower LDL concentrations. This comparison, combined with the examination of associations observed by pooling of the data from all subjects, provides new insight into factors controlling LDL concentrations.

Comparison of Pima and Caucasian groups

One factor that should affect LDL levels is the rate of input of VLDL, the precursor of LDL. It might have been expected, therefore, that the secretion rate of VLDL-apoB would have been lower in Pimas than in Caucasians. In fact, synthesis of VLDL-apoB was somewhat higher in Pimas than in Caucasians. One possibility that could account for differences in VLDL kinetics between the two groups would be differences in VLDL composition or structure. In the present study there were no apparent differences in VLDL composition as measured by triglycerides, cholesterol, and apoB concentrations. A comparison of VLDL size by chromatography on agarose A-5 columns indicated no differences between VLDL from Pimas and Caucasians (B. Daniels and B. V. Howard, unpublished data). Although these measurements do not represent a complete comparison of VLDL structure in Pimas and Caucasians, they suggest that the kinetic differ-

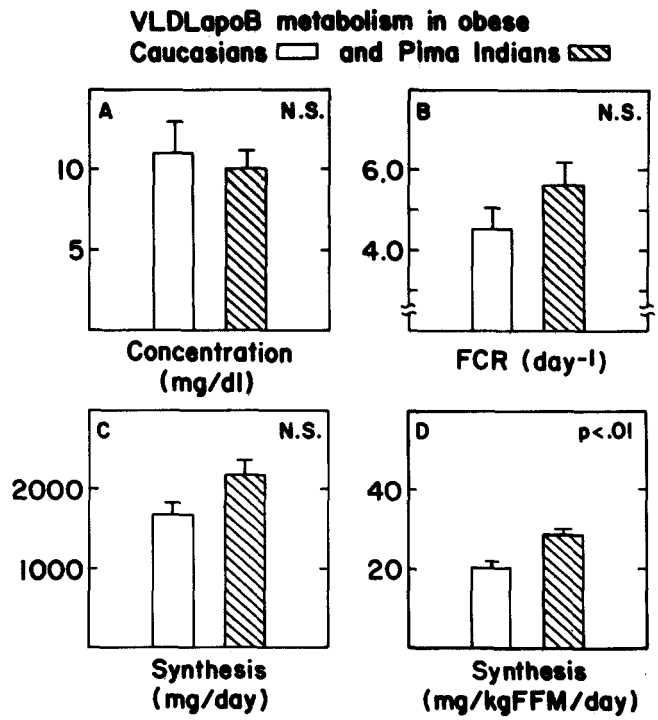

Fig. 2. Comparison of VLDL-apoB metabolism in obese Caucasians and Pima Indians.

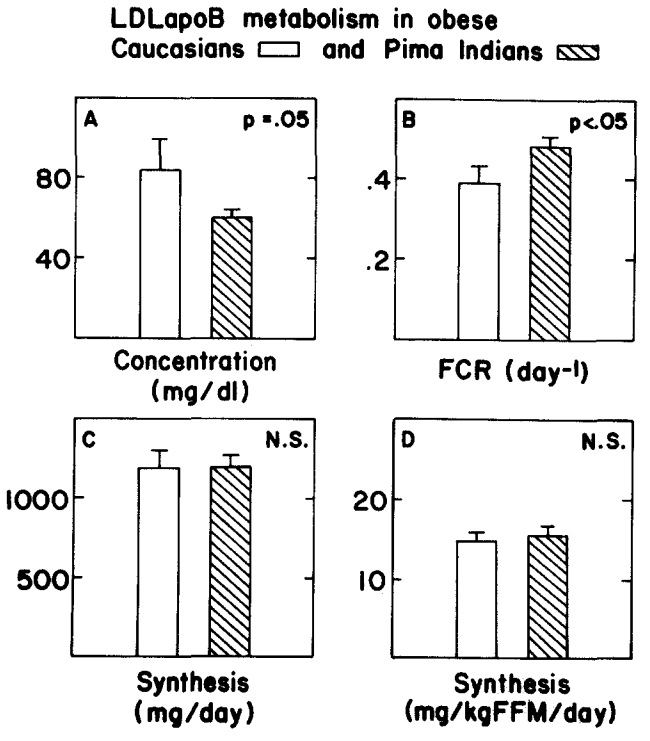

Fig. 3. Comparison of LDL-apoB metabolism in obese Caucasians and Pima Indians.

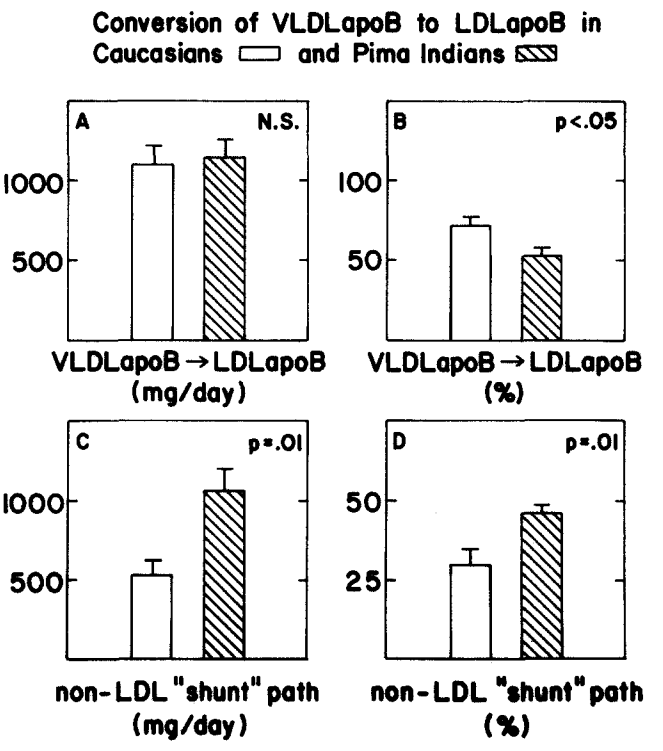

Fig. 4. Conversion of VLDL-apoB to LDL-apoB in Caucasians and Pima Indians. The direct removal (non-LDL) pathway refers to the amount of VLDL metabolized without conversion to LDL. Values are expressed both as mg/day and also as percent of the VLDL that is either converted to LDL (B) or metabolized without conversion to LDL (D).

ences are probably not due to structural differences in the VLDL from the two groups. Another possibility is that there were dietary differences between the two groups. Both groups consumed a diet identical in caloric content and composition during the study, and the 7-day stabilization period would bring the slowest compartment more than 90% toward equilibrium (3.5 half-times). Also, a diet survey indicates Pima calorie intake and distribution is very similar to the typical American diet (34). Thus, dietary factors seemingly cannot account for this difference. Hormonal differences, on the other hand, could be a factor. The Pimas frequently have insulin levels that are higher than can be explained by obesity alone (35). These unusually elevated levels of insulin are associated with increased resistance to the peripheral action of insulin (36); high insulin levels or insulin resistance in some way may thus accentuate the usual overproduction of VLDL found in obese subjects.

Although the Pima produced more VLDL, more VLDL was removed by the direct removal, or non-LDL pathway. Early attempts to estimate the quantity of VLDL converted to LDL suggested that the transformation was almost quantitative (6, 7). This claim was in conflict with findings in many experimental animals in which a major fraction of VLDL remnants is cleared by the liver (37, 38). More recent studies in humans also indicate that a substantial quantity of VLDL remnants is removed from circulation by the direct removal pathway (8–13). The present results support these latter findings. The percentage of VLDL-apoB cleared by the direct removal pathway in all our patients ranged from 0% to 62%. In the Pima group, the magnitude of the direct removal pathway, whether in absolute or percentage terms, was greater than in Caucasians. Thus, while more VLDL-apoB entered plasma in the Pimas, their higher direct

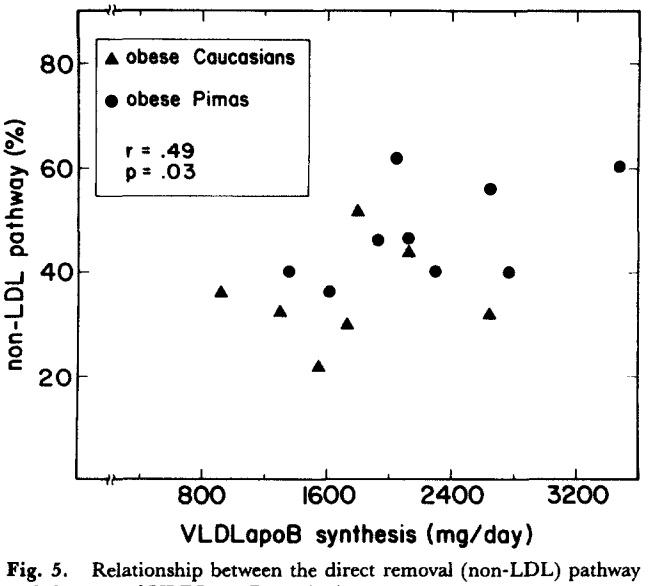

Fig. 5. Relationship between the direct removal (non-LDL) pathway and the rate of VLDL-apoB synthesis.

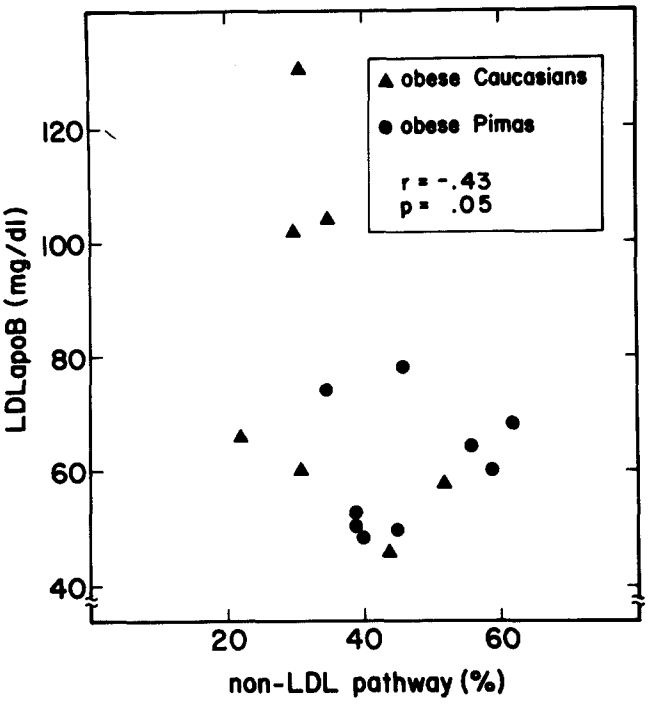

Fig. 6. Relationship between plasma LDL-apoB concentration and the direct removal (non-LDL) pathway.

removal pathway reduced the amount of VLDL converted to LDL. It should be noted that IDL isolated as in the present study are not equivalent to VLDL remnants; the latter are most likely distributed in both the VLDL and LDL compartments. The results of the kinetic analysis using the present model suggest that the direct removal pathway occurs primarily from the VLDL compartment (31).

Although input rates of LDL-apoB were similar in Pimas and Caucasians, the FCRs of LDL were higher in the Pimas. Consequently the Pimas had lower levels of LDL-apoB and LDL-cholesterol. At face value, the results of this study might suggest that the FCR of LDL was the critical factor responsible for the relatively low levels of LDL in Pimas. However, when all the kinetic data are examined together, a somewhat different picture emerges for the interaction of factors determining LDL concentrations.

Compensatory mechanisms for regulation of LDL levels

Three factors can possibly determine LDL levels: *a*) secretion rates of VLDL-apoB, *b*) rates of clearance of VLDL remnants (the direct removal pathway), and *c*) fractional clearance rates of LDL. The second (*b*) seems more important than the first (*a*). Despite very high rates of VLDL secretion, the Pimas were able to curtail the conversion of VLDL to LDL by a compensatory increase in clearance of VLDL remnants. The magnitude of the direct removal pathway, thus, was critically important in determining LDL levels. The positive correlation between VLDL-apoB production and the direct removal pathway suggests that a progressive rise in the size of the direct removal pathway, in response to increasing secretion rates of VLDL, played a major role in preventing the development of hypercholesterolemia in the obese subjects of both populations, but particularly in the Pimas.

In the present data the magnitude of the direct removal pathway and the LDL FCR were positively related. Recent evidence indicates that clearance of both VLDL remnants and LDL are mediated by the same cell-surface receptors, namely, apoB/E receptors (15, 16). These receptors, which reside on many cells but predominately on hepatocytes, appear to be specific for apoB-100, the form of apoB present on VLDL, VLDL remnants, and LDL (14). Affinities of these different lipoproteins for apoB/E receptors, however, are not identical. Of the three classes of lipoproteins, the VLDL remnants are removed most rapidly by apoB/E receptors. LDL, which has lost most of its apoE, has much less affinity for the receptor and is removed much more slowly. Nevertheless, the apoB/E receptor pathway seemingly removes more LDL than does nonreceptor clearance, since fractional clearance by nonreceptor mechanisms is relatively fixed (39). Thus, variability in nonreceptor mechanisms seems a much less important determinant of LDL levels.

Finally, a less likely possibility is that affinity of lipoproteins for the receptor was greater in individuals with lower LDL. Although complete composition of lipoproteins was not determined, the VLDL-triglyceride/apoB ratios and LDL-apoB/cholesterol ratios were similar in the

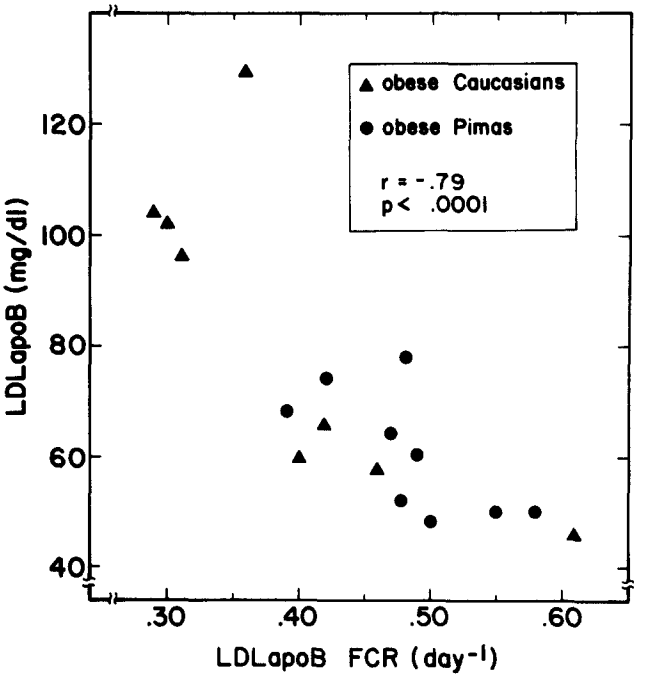

Fig. 7. Relationship between plasma LDL concentration and the fractional catabolic rate for LDL.

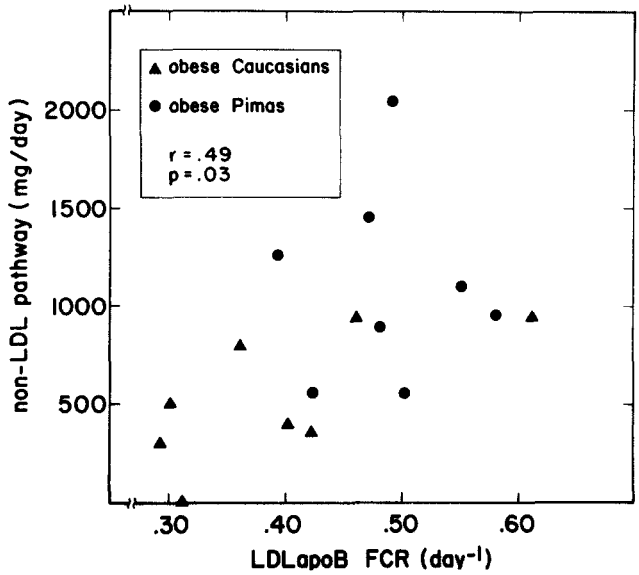

Fig. 8. Relationship between the direct removal (non-LDL) pathway and the fractional catabolic rate for LDL.

Pimas and Caucasians, and variation in these ratios was not significantly related to plasma LDL concentrations.

The data from the present subjects thus suggest that LDL are controlled by apparently linked compensatory mechanisms of increasing shunt pathway and increasing LDL clearance. It might be reasonable to question how generally applicable these are, since the data are from significantly obese individuals. When data from lean subjects, reported previously (12, 13), were included in the present analyses (N = 30) LDL-apoB levels were highly related to the non-LDL path ($r = -0.48$, $P = 0.007$) and LDL FCR ($r = -0.65$, $P = 0.0001$). Furthermore, the non-LDL path and FCR for LDL were related ($r = 0.49$, $P = 0.005$), reaffirming the possible key role of the apoB/E receptor in these processes.

If we can assume then that the apoB/E receptor activity is greater in subjects with lower LDL, the reason is of interest. One difference between the Pimas and Caucasians was the higher insulin levels in Pimas. Also, for all patients, plasma insulin levels appeared to be positively related to both the direct removal pathway and the FCR of LDL; others have proposed that insulin may directly stimulate LDL catabolism (40). Another likely mechanism for lower LDL levels is the presence of greater activity of apoB/E receptors on a genetic basis. If so, this suggests that apoB/E receptors are predominant determinants of both rates of input and exit of LDL, and hence LDL levels, and that a high activity of receptors in the Pimas may account for their low prevalence of CHD.

APPENDIX Kinetic data for apoB metabolism in each study subject

	VLDL Metabolism						LDL Metabolism					
			Turnover						Turnover			
Subjects	Pool	FCR	mg/d	mg/kg/d	mg/kgFFM/d[a]	mg/dl/d[b]	Pool	FCR	mg/d	mg/kg/d	mg/kgFFM/d[a]	mg/dl/d[b]
	mg	*d*					*mg*	*d*				
Pimas												
10	446	7.8	3493	26.9	40.2	70.5	2951	0.49	1446	11.1	16.6	29.2
11	589	3.2	1908	20.2	27.2	57.0	2580	0.48	991	10.5	14.2	29.6
12	385	4.1	1595	16.8	23.8	47.3	2521	0.42	1063	11.2	15.9	31.5
13	371	7.1	2621	21.3	34.5	69.2	2448	0.47	1162	9.4	15.3	30.7
14	244	8.8	2114	16.6	30.3	47.7	2198	0.58	1266	10.0	18.2	28.6
15	399	5.1	2047	15.6	24.4	43.7	3170	0.39	1234	9.4	14.7	26.3
16	202	6.7	1360	14.9	20.9	39.7	1623	0.50	807	8.9	12.4	23.6
17	845	3.3	2764	12.8	27.1	45.8	3059	0.55	1686	7.8	16.5	27.9
18	486	4.7	2268	13.3	21.8	41.0	2834	0.48	1358	7.9	13.1	24.6
Mean ± SEM	441 ± 64	5.6 ± 0.7	2241 ± 216	17.6 ± 1.5	27.8 ± 2.1	51.3 ± 3.9	2598 ± 161	0.48 ± 0.02	1224 ± 87	9.6 ± 0.4	15.2 ± 0.6	28.0 ± 0.9
Caucasians												
1	502	1.8	904	12.7		34.2	2728	0.29	791	11.1		30.0
2	799	3.3	2637	21.1		69.0	4967	0.36	1788	14.3		46.8
3	393	4.6	1807	17.0	25.0	45.5	2275	0.46	1057	10.0	14.6	26.6
4	491	3.0	1469	12.9	19.3	39.5	4461	0.31	1445	9.2	13.8	28.2
5	226	7.0	1573	10.8	19.0	32.8	3163	0.42	1317	9.1	15.9	27.4
6	352	4.8	1706	11.5	18.3	34.9	4946	0.30	1484	10.0	15.9	30.4
7	256	5.0	1289	11.9	17.5	34.7	2189	0.40	879	8.1	11.9	23.7
8	316	6.7	2106	12.0	19.1	43.4	2254	0.61	1380	7.8	12.5	28.4
Mean ± SEM	417 ± 65	4.5 ± 0.6	1686 ± 185	13.7 ± 1.2	19.7 ± 1.1	41.8 ± 4.2	3397 ± 442	0.39 ± 0.04	1268 ± 118	10.0 ± 0.7	14.1 ± 0.7	30.2 ± 2.5

[a] Data expressed per kg fat-free mass.
[b] Data expressed per dl plasma volume.
[c] Calculated as the sum of VLDL apoB production plus "direct" input of LDL incremented by the % of direct removal from this pathway.
[d] Amount of apoB mass entering the LDL compartment.

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Appendix, continued

Conversion of VLDL to LDL						
	Shunt		LDL Turnover/	Total ApoB	"Direct"	U/P
VLDL → LDL	%	mg/d	VLDL Turnover	Production[c]	Synthesis[d]	Ratio
mg/d				*mg/d*	%	
1432	59	2060	0.41	3556	2	0.42
992	46	878	0.52	1908	0	0.53
1021	35	558	0.67	1649	3	0.44
1127	56	1468	0.44	2696	3	0.57
1163	45	951	0.60	2298	8	0.54
757	62	1269	0.60	3315	39	0.42
802	40	544	0.59	1360	0	0.48
1686	39	1078	0.61	2770	0	0.46
1338	39	885	0.60	2284	1	0.48
1146 ± 100	47 ± 3	1077 ± 158	0.56 ± 0.3	2426 ± 244	6 ± 4	0.48 ± 0.02
579	35	316	0.87	1245	28	
1767	31	817	0.68	2663	1	
831	52	940	0.58	2069	21	0.33
1440	0	0	0.74	1469	1	0.38
1133	22	346	0.84	1809	14	0.52
1143	30	512	0.87	2215	24	0.29
877	31	400	0.68	1301	1	0.28
1158	44	927	0.65	2515	16	0.44
1116 ± 131	30 ± 5	532 ± 118	0.74 ± 0.4	1910 ± 192	13 ± 4	0.37 ± 0.03

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