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Lipoprotein Composition and Lipoprotein Interrelations in 50-year-old Men with Hyperlipoproteinaemia

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ABSTRACT

The serum lipoprotein (LP) composition and LP lipid interrelations were studied in 50-year-old men with different types of hyperlipoproteinaemia (HLP) and in randomly sampled healthy controls from the same population.

The ratio cholesterol/triglycerides in very low density lipoproteins (VLDL) was high in HLP type III. The other types of HLP showed ratios not significantly different from the controls. The low density lipoprotein (LDL) cholesterol concentration was similar in controls, type III and type IV while, by definition, higher values were seen in type II A and II B. All types of HLP showed statistically significantly higher LDL triglycerides than the controls. HLP type II A and II B showed cholesterol/triglyceride ratios in LDL similar to the controls. The corresponding ratio in type IV was lower than in the control subjects but the lowest ratio was seen in type III with a mean value below the 5th percentile of healthy controls.

The high density lipoprotein (HDL) cholesterol concentration was decreased in HLP type IV. Apparently elevated HDL triglyceride levels were seen in all types of HLP with the highest mean value in type III.

The LP lipid interclass relationships were analysed in the random sample of healthy men and compared to corresponding relationships in the different types of HLP. Apart from HLP type III and HLP type IV with low LDL cholesterol levels all other types of LP patterns seemed to conform to a common model of LP interconversions. In type IV a significant negative correlation between VLDL concentration and LDL cholesterol levels was demonstrated in subjects with low LDL cholesterol as well as a direct relationship between LDL cholesterol concentration and the cholesterol/triglyceride ratio in VLDL. There were no significant correlations between LDL cholesterol concentration and VLDL lipid variables in other types of HLP and normolipidaemia.

INTRODUCTION

Hyperlipoproteinaemia (HLP) is one of the major risk factors for development of premature atherosclerotic cardiovascular disease (14, 3). According to suggestions by Fredrickson et al. (7, 8) HLP are divided into separate 'types'. The classification of HLP is based on the definition of upper 'normal' limits for the concentration of very low density lipoproteins (VLDL, $d<1.006$) and low density lipoproteins (LDL, $d=1.006$–1.063) (1). The prevalence of HLP in a population, and also the relative frequency of the different types of HLP (13), thus depends on which cutting points are chosen.

Lipid levels vary with sex and age as well as ethnic and geographic factors. This study was undertaken to characterize lipoprotein (LP) composition and LP lipid interrelations in different types of HLP in 50-year-old men. The lipid levels in the isolated LP density fractions and the statistical interrelationships between the LP fractions were studied and compared to corresponding relations in randomly sampled healthy controls.

MATERIAL AND METHODS

Subjects

During 1971–74 all men aged 50 (born 1921–24) living in and around the town of Uppsala in eastern Sweden were invited to a health screening for risk factors for coronary heart disease. The adherance rate was 84%. All men with triglyceride and/or cholesterol concentration in serum in the two top decentiles of the population at the initial screening were referred to the Department of Geriatrics for a complete LP analysis. The LP patterns were classified according to Fredrickson, Levy & Lees (8). Cutting points for HLP were for VLDL triglycerides and LDL cholesterol 1.5 mmol/l and 190 mg/100 ml respectively corresponding to the 85th percentile in a randomly sampled population of healthy 50-year-old men (13). In the present study all samples showing a characteristic LP pattern diagnostic for HLP according to WHO (1) analysed from January 2, 1972 through January 31, 1973 were included ($n=111$). Diagnosis of HLP type III was based on the demonstration of a typical 'floating β' pattern in VLDL.[1] No samples from subjects suffering from insulin-

[1] β-migrating lipoproteins demonstrated at agarose electrophoresis in the supernatant fraction of plasma after ultracentrifugation at $d=1.006$.

Table I. *Triglyceride and cholesterol concentration in serum lipoprotein density fractions in 50-year-old men with normal lipoprotein pattern and hyperlipoproteinaemia (Mean ±S.E.)*

Lipoprotein pattern	(*n*)	VLDL[a] Triglyceride (mmol/l)	VLDL[a] Cholesterol (mg/100 ml)	LDL Triglyceride (mmol/l)	LDL Cholesterol (mg/100 ml)	HDL Triglyceride (mmol/l)	HDL Cholesterol (mg/100 ml)
Controls	(92)	1.03±0.06	21± 1	0.49±0.01	155± 3	0.24±0.01	48±1
II A	(38)	1.02±0.05	23± 2	0.68±0.03***	224± 8***	0.27±0.01**	46±2
II B	(28)	2.12±0.11***	41± 2***	0.70±0.02***	219± 4***	0.29±0.01***	43±1
III	(8)	2.18±0.26***	99±15***	0.71±0.10***	143±20	0.34±0.04***	44±3
IV	(37)	2.85±0.38***	53± 6***	0.61±0.03***	145± 5***	0.30±0.01***	36±1***

[a] The tests involving VLDL lipid concentrations were performed also on logarithmic transformed values with identical results regarding the demonstrated group differences.
*, **, ***=Significant on the 2, 1, and 0.1% level respectively compared with normals when tested with Student's *t*-test.

deficient diabetes, hypothyreosis or renal disease were included. One man had suffered from a myocardial infarction. One had angina pectoris and was treated with a β receptor blocking drug and one suffered from intermittent claudication. No other subjects were on regular treatment. Seventeen men had a reduced glucose tolerance at intravenous glucose tolerance test. Three of those showed a moderately increased fasting blood glucose concentration without glucosuria.

Controls

The control subjects ($n=92$) were apparently healthy men randomly sampled from the same population of 50-year-old men. Excluded from this material were obese persons (subjects with weight/height index above 1.10) and persons with clinical or laboratory signs of disease. The control population has earlier been described in detail (13).

LP analysis

Blood samples from subjects fasted over night were allowed to clot at room temperature and EDTA was added as a 5% solution to a final concentration of 0.05%. VLDL, LDL and high density LP (HDL, $d>1.063$) were isolated by consecutive spins at 15°C in a L2 65B Beckman preparative ultracentrifuge according to Havel et al. (11) using a 40.3 rotor. VLDL was isolated as the top fraction after centrifugation of serum at $d=1.006$ for 16 h at 40 000 rpm. The bottom fraction was then centrifuged at $d=1.063$ at 40 000 rpm for 20 h. The top and bottom fraction after the second centrifugation contained LDL and HDL respectively. A detailed description of the isolation procedure has been given (2). Whole serum as well as the isolated LP classes were extracted manually with isopropanol. Triglyceride and cholesterol concentrations in the LP fractions were determined in a Technicon Auto Analyzer Type II (23). The sum of cholesterol and TG concentrations in VLDL, LDL and HDL, was always within 100±10% of whole serum cholesterol and triglyceride concentrations respectively.

Immediately after the centrifugation whole serum and the top and bottom fraction at $d=1.006$ were subjected to agarose electrophoresis according to Noble (19). A 1% agarose gel containing 0.25% albumin was used. The electrophoresis was run in a barbital buffer, pH 8.6, at 16 V/cm for 1 hour and the gel was stained in Sudan Black.

Statistics

Significant differences between mean values were estimated with Student's *t*-test (two-tailed tests). VLDL triglyceride and cholesterol concentrations as well as LDL triglyceride concentrations were tested also after logarithmic transformation because of a skewed distribution of these variables (13). Correlation analyses (5) were performed at the Uppsala University Data Center on an IBM 370/155 computer using program BMD 02R (4). The accepted level for statistical significance was $p<0.02$. A significance at the 5% level would be expected to occur by chance alone in one test of 20. Because of the number of significance tests performed (e.g. Table I and IV–VI) the minimum requirement for statistical significance was set at 2% to reduce the risk of chance significances. Since the different groups of HLP were obtained by selection, i.e. by assigning subjects with values above and below certain limits for some variables to different groups, there is a certain accordance between the group comparisons of mean values and the reported correlation coefficients. By definition, significant group differences were obtained for the group assignment variables. Similarly, group differences should be expected for variables highly correlated with the group assignment variables.

Table II. *Cholesterol/triglyceride ratio (Mean ±S.E.) in serum lipoprotein density fractions in 50-year-old men with normal lipoprotein pattern and hyperlipoproteinaemia*

Lipoprotein pattern	(*n*)	VLDL[a] mg/100 ml / mmol/l	LDL mg/100 ml / mmol/l	HDL mg/100 ml / mmol/l
Controls	(92)	20.4±0.6	325± 7	221± 9
II A	(38)	22.2±1.2	340±11	172± 8 ***
II B	(28)	19.9±0.8	317± 8	154± 7 ***
III	(8)	44.8±3.6 ***	202±10 ***	155±39
IV	(37)	19.3±0.7	251±11 ***	128± 7 ***

[a] The tests involving VLDL lipid concentrations were performed also on logarithmic transformed values with identical results regarding the demonstrated group differences.
*, **, ***=Significant on the 2, 1, and 0.1% level rspectively compard with normals when tested with Student's *t*-test.

RESULTS

By definition HLP type IV and II B had increased VLDL concentrations compared with the control subjects (Table I). The criteria for diagnosis of type III HLP do not include a requirement for increased lipid levels in VLDL or LDL (1). However, on the average HLP type III showed increased VLDL triglyceride levels. The VLDL cholesterol concentration was by far highest in type III.

The LDL cholesterol concentration was on the average similar in normals, type III and type IV. Significantly higher values were, by definition, seen in type II A and II B. All types of HLP showed significantly higher LDL triglycerides than the normal controls. Type III, II B and II A showed the most pronounced rise while type IV showed LDL triglyceride levels intermediate between normals and the other types of HLP with a significantly lower mean value than in type II B ($p<0.01$).

Also in HDL the lipid levels differed in the various types of HLP. Type II A showed HDL cholesterol concentrations similar to the normals. Types II B and III tended to show lower mean values than the controls but the differences were not statistically significant. In type IV there was a clearly lower HDL cholesterol concentration than in the control group. Apparently elevated HDL triglyceride concentrations were seen in all types of HLP. The highest mean value was seen in type III.

In an effort to gain further information regarding the lipid composition in different hyperlipoproteinaemic states the ratios between cholesterol and triglyceride concentrations in VLDL, LDL and HDL were computed and compared with normals (Table II). Although not significantly different there was a tendency to a higher VLDL ratio in II A and lower in type IV than in normals. Type III was characterized by a very high ratio in VLDL.

HLP types II A and II B showed cholesterol/triglyceride ratios in LDL similar to the controls. Type II A showed the highest mean value although not significantly different from the two other groups. The ratio in type IV was on the average

Table III. *Relationships between triglyceride (x) and cholesterol (y) concentration in serum lipoprotein in 50-year-old men with different lipoprotein patterns*

Linear correlation coefficients (*r*), slope (*b*) and intercept (*a*) of regression equations ($y=a+bx$)

Lipoprotein fraction	Lipoprotein pattern: Controls (*n*=92) *r*	*b*	*a*	II A (*n*=38) *r*	*b*	*a*	II B (*n*=28) *r*	*b*	*a*	III (*n*=8) *r*	*b*	*a*	IV (*n*=37) *r*	*b*	*a*
VLDL	0.89 ***	18.9	1.2	0.70 ***	22.8	−0.3	0.68 ***	12.6	14.6	0.84 **	50.6	−11.5	0.95 ***	14.9	10.3 **
LDL	0.60 ***	169	72 ***	0.49 **	140	129 ***	0.52 **	98	150 ***	0.94 ***	193	7	0.44 **	72	101 ***
HDL	0.10	21	44 ***	0.23	46	33 ***	−0.05	−8	46 ***	0.04	4	43 **	−0.06	−7	38 ***

*, **, ***=Significantly different from zero on the 2, 1, and 0.1% level respectively.

Table IV. *Relationships between lipoprotein lipid variables in the very low and low density lipoproteins in 50-year-old men with different types of serum lipoprotein patterns*

Linear correlation coefficients (r)

	LDL											
	Controls (n=92)			II A (n=38)			II B (n=28)			IV (n=37)		
VLDL[a]	TG	Chol	Chol/TG	TG	Chol	Chol/TG	TG	Chol	Chol/TG	TG	Chol	Chol/TG
TG	* 0.26	0.06	** −0.27	0.22	0.03	−0.21	−0.08	−0.08	0.06	0.05	*** −0.62	*** 0.55
Chol	** 0.35	0.11	** −0.30	*** 0.52	0.08	*** −0.55	0.27	0.00	−0.28	0.33	* −0.40	*** −0.68
Chol/TG	0.21	0.11	−0.10	*** 0.59	0.06	*** −0.66	* 0.44	0.13	−0.41	*** 0.62	** 0.43	−0.32

[a] VLDL triglyceride and cholesterol concentrations were logarithmic transformed before calculations.
*, **, ***=Significant on the 2, 1, and 0.1% level.

clearly lower than the controls. The lowest ratios, however, were seen in type III where the mean ratio was well below the 5th percentile of randomly sampled healthy controls.

In HDL all types of HLP exhibited a mean value for the cholesterol/triglyceride ratio below the controls. Type II A showed a moderately decreased ratio, in type IV the ratio was reduced with nearly 50%. Types II B and III showed similar average ratios.

The relation between cholesterol and triglycerides in the LP fractions were studied by correlation analysis in the different types of HLP and compared to those found in the population of randomly sampled healthy controls (Table III). In the controls a strong positive correlation was seen between VLDL triglycerides and cholesterol (r=0.89). A less pronounced but clearly significant correlation was also seen in LDL (r=0.60). In HDL, however, there was no significant correlation between triglycerides and cholesterol (r=0.10). The same pattern was seen in all types of HLP: A significant positive correlation between cholesterol and triglycerides in VLDL and LDL, no correlation in HDL (Table III).

When LP lipid interclass relationships were analyzed in the control sample certain significant lipid relationships were revealed. These were basically similar to those distinguished also in HLP types II A, II B and IV (Tables IV–VI). These correlations were not studied in HLP type III because of the low number of subjects in this group.

The LDL triglyceride concentration tended to

Table V. *Relationships between lipoprotein lipid variables in the very low and high density lipoproteins in 50-year-old men with different types of serum lipoprotein patterns*

Linear correlation coefficients (r)

	HDL											
	Controls (n=92)			II A (n=38)			II B (n=28)			IV (n=37)		
VLDL[a]	TG	Chol	Chol/TG	TG	Chol	CHol/TG	TG	Chol	Chol/TG	TG	Chol	Chol/TG
TG	*** 0.36	*** −0.41	*** −0.51	0.07	** −0.43	** −0.42	0.23	−0.01	−0.12	*** 0.47	*** −0.52	*** −0.54
Chol	*** 0.37	*** −0.46	*** −0.54	0.26	*** −0.54	*** −0.60	0.27	−0.04	−0.20	*** 0.52	** −0.42	*** −0.57
Chol/TG	0.07	−0.14	−0.13	0.28	* −0.41	** −0.50	0.03	−0.03	−0.08	0.15	0.18	0.09

[a] VLDL triglyceride and cholesterol concentrations were logarithmic transformed before calculations.
*, **, ***=Significant on the 2, 1, and 0.1% level.

Table VI. *Relationships between lipoprotein lipid variables in the low and high density lipoproteins in 50-year-old-men with different types of serum lipoprotein patterns*

Linear correlation coefficients (r)

	HDL											
	Controls (n=92)			II A (n=38)			II B (n=28)			IV (n=37)		
LDL	TG	Chol	Chol/TG	TG	Chol	Chol/TG	TG	Chol	Chol/TG	TG	Chol	Chol/TG
	**		**			**						*
TG	0.28	−0.19	−0.30	0.28	−0.37	0.43	0.30	−0.10	−0.27	0.29	−0.09	−0.39
Chol	0.04	−0.04	−0.11	0.09	0.01	0.12	0.03	−0.11	−0.11	−0.22	0.30	0.17
	**				**	***				***		***
Chol/TG	−0.28	0.20	0.22	−0.31	0.43	0.59	−0.34	0.01	0.22	−0.54	0.31	0.59

*, **, ***=Significant on the 2, 1, and 0.1% level.

vary positively with VLDL lipid levels (significant in controls and type II A) (Table IV) and was significantly positively correlated to the cholesterol/triglyceride ratio in VLDL in both HLP types II A, II B and IV. The LDL cholesterol/triglyceride ratio tended to vary inversely with VLDL lipid concentration (significant in controls, types II A and IV) and with the VLDL ratio (significant in type II A). The LDL cholesterol concentration on the other hand did not show any significant relationships with lipids in other LP classes in either controls, II A or II B with remarkably low correlation coefficients when related to all other lipid variables. In type IV, however, a negative correlation to VLDL lipid concentrations as well as a positive correlation to the VLDL cholesterol/triglyceride ratio was demonstrated. The negative correlation to VLDL as well as the positive correlation to the VLDL ratio was due to the presence of a number of patients with HLP type IV with high VLDL triglyceride levels and low LDL cholesterol levels.

HDL triglyceride and cholesterol concentrations generally tended to show a positive and negative relation to VLDL lipid concentration respectively (Table V). The HDL ratio was negatively correlated to the VLDL lipid concentration. The HDL triglyceride concentration was positively respectively negatively correlated to LDL triglyceride levels and the LDL cholesterol/triglyceride ratio in the control groups (Table VI). The HDL cholesterol concentration in type II A and the HDL triglyceride concentration in type IV were positively respectively negatively correlated to the LDL ratio. In contrast to the other variables which showed apparently linear interrelationships the HDL ratio gave curved relations to other variables when plotted.

DISCUSSION

LP lipid composition and LP lipid interrelations were studied in HLP and in an apparently healthy control population of 50-year-old men. It was shown (Table I) that the LP patterns in HLP differed from the normal LP pattern not only in regard of VLDL triglyceride and LDL cholesterol concentration. In spite of great variations in VLDL concentration the lipid composition, as mirrored by the cholesterol/triglyceride ratio (Table II) did not differ from normal in types II A, II B and IV. HLP type III was characterized by a high cholesterol/triglyceride ratio (Table II) caused by a dramatically increased cholesterol level in VLDL (Table I).

The HLP discovered in the investigated population were moderate as can be expected when a screening of a general population is performed. The mean values for LDL cholesterol in type II were about 220 mg/100 ml. Concomitant with the increased cholesterol levels, type II A and II B showed increased LDL triglyceride concentrations of a similar relative magnitude resulting in a 'normal' cholesterol/triglyceride ratio (Table II). Slack and Mills (26) reported a low proportion of triglycerides in the total LDL lipid in patients with familial hyper-β-lipoproteinaemia and suggested the presence of an abnormal LP in this disease. In a recent report (20) type II A with tendon xanthomata

were found to have particularly high cholesterol content in relation to triglyceride content. In the mild cases of type II without xanthoma tendinosum, most of which probably were of non-familial origin, in the present population, no abnormality was found in regard of the cholesterol/triglyceride ratio.

The linear relation between the cholesterol and triglyceride content in LDL in healthy 50-year-old men does not pass through the origin, i.e. the intercept (a) is significantly different from zero (Table III). Thus, the ratio cholesterol/triglycerides is a somewhat artificial concept which will increase with decreasing lipid content of LDL. A change of the ratio may not necessarily mean a change in LP composition, especially at low lipid concentrations in LDL. As HLP types III and IV (Table II) showed a low mean ratio in spite of normal LDL cholesterol levels this, however, seems to imply a real change in LP composition in these types of HLP compared to normal LP composition.

The density range 1.006–1.063 comprises two LP fractions: LDL_1 (d=1.006–1.019 corresponding to Sf 12–20) and LDL_2 (d=1.019–1.063, Sf 0–12). The LDL_1 particles are bigger and relatively more triglyceride rich than LDL_2 (25). Normally LDL_2 is the quantitatively totally dominating fraction, as is also seen in HLP type II (4). The LDL cholesterol/triglyceride ratio in normals, types II A and II B is thus mainly reflecting the composition of the LDL_2 particles. The heterogeneity of the LDL density fraction may explain the lower correlation recorded between cholesterol and triglyceride concentration in LDL than in VLDL (Table III).

Both HLP types III and IV were characterized by considerably increased LDL triglyceride concentrations when compared with normals (Table I). As the LDL cholesterol levels were normal, the LDL cholesterol/triglyceride ratios in type III and IV were low. The lower ratio in type III than in type IV was caused by a higher mean value for LDL triglycerides (Tables I–II).

The very low LDL ratio in type III mirrors a change in the relation between LDL_1 and LDL_2 first reported by Gofman et al. (16) in patients with xanthoma tuberosum (e.g. probably type III). An increased concentration of LDL_1 in relation to LDL_2 probably reflects the accumulation of particles metabolically intermediate between VLDL and LDL_2 because of a block in the normal catabolism of VLDL (21).

The group of lipid patterns classified as HLP type IV is probably heterogeneous representing pathogenetically different disorders with an incrased VLDL concentration in common but with diverging LDL concentration and composition. Some type IV may be genetically related to combined hyperlipidaemia (22). Other LP patterns classified as type IV have been suggested to be associated with a retarded conversion of VLDL to LDL because of a relatively decreased VLDL triglyceride clearance (28).

Also the density fraction >1.063 contains two or more populations of LP particles with different lipid composition (24). HDL_2 (d=1.063–1.125) contains somewhat less triglycerides and more cholesterol than HDL_3 (d=1.125–1.21) which is also more rich in protein content. Nichols reported (17) that HDL_2 and HDL_3 may vary in concentration relatively independent of each other. He did not find any relationship between the cholesterol and triglycerides in HDL in either normals or HLP. In this study low cholesterol levels in HDL in combination with an increased VLDL lipid concentration was seen i type IV which may reflect the redistribution of some LP components (mainly HDL_2) from HDL to VLDL after the introduction of triglyceride-rich VLDL into the circulation (12). A reciprocal relationship between HDL and VLDL concentration is present during conditions of varying VLDL concentration (15).

HDL triglyceride concentration was significantly increased in all types of HLP compared with the normal controls (Table I). These 'HDL triglyceride' determinations probably measure not only HDL LP triglycerides but also some diglycerides and monoglycerides produced during the hydrolysis of triglyceriderich LP and recovered in the ultracentrifuge fraction with d>1.063. The HDL 'triglyceride' determinations is certainly both less specific and less accurate (2) than the triglyceride determination in the other LP classes.

One explanation for actually incrased HDL triglyceride levels in HLP may be a suggested nonenzymic exchange of HDL esterified cholesterol for VLDL triglycerides secondary to lecithin cholesterol acyl transferase (LCAT) dependent esterification of free cholesterol in HDL (18). High HDL triglyceride concentrations may possibly be regarded as reflecting an accelerated break down of triglyceride-rich LP particles with a requirement of disposal of much VLDL surface material. No significant correlation was found between HDL triglyc-

eride and cholesterol concentrations (Table III). Thus no conclusion can be drawn from changes in the HDL cholesterol/triglyceride ratio regarding changes in HDL lipid composition.

When lipid variables show either a strongly positive or a strongly negative interrelationship, some common determinant of the serum concentrations of these lipids seems probable. We have studied linear correlations between LP lipid variables in the random sample of healthy men and in different types of HLP (Table IV–VI). Although the conclusions drawn from this study are valid only for middle-aged men the results were in good agreement with those found in investigations of other populations.

The positive relationship between VLDL concentration and the triglyceride concentration in LDL and HDL as well as the negative relationship between VLDL concentration and HDL cholesterol content is in agreement with earlier studies by Lindgren, Freeman & Nichols (16) and Ewing, Freeman & Lindgren (6).

In the present study LDL cholesterol concentration varied remarkably independent of all other LP lipid variables in the controls, types II A and II B. In type IV, however, the LDL cholesterol concentration showed a significant negative relationship to VLDL lipid levels and a positive correlation to the cholesterol/triglyceride ratio in VLDL due to the presence of a group of patients with high VLDL triglyceride levels and low LDL cholesterol levels. Gofman & Tandy reported (10) that a regression curve of LDL on VLDL levels studied in two large samples of human males showed a steady rise in LDL levels with increasing levels of VLDL. At very high levels of VLDL, however, the curve sloped downwards and the relationship between those two classes became inverse rather than direct. The reason for this may be a retarded interconversion of VLDL to LDL because of a relatively deficient triglyceride removal capacity (28). The negative correlation between LDL cholesterol and the VLDL cholesterol/triglyceride ratio is also compatible with this hypothesis.

The tendency to a negative relationship between LDL and VLDL ratios seen in HLP type II A as well as the positive correlation between LDL triglycerides and the VLDL ratio in types II A, II B and IV may be due to a certain accumulation of particles with a density and composition intermediate between VLDL and LDL in some patients associated with a 'late pre-β' pattern in $d < 1.006$ on agarose electrophoresis (27).

In conclusion all the moderate HLP studied in this investigation showed similar LP lipid interclass interrelationships although they are conventionally divided into different types of HLP because of diverging mean values for LP lipid concentrations. Apart from HLP type III and HLP type IV with low LDL cholesterol levels all other types of LP patterns seemed to conform to a common model of LP interconversions where the different HLP types represented different tails of the same spectrum. No clear qualitative differences in LP interrelationships between the HLP types were observed. The basically quantitative differences in the statistical correlations between the LP lipids in the healthy controls and types II A, II B and some of the type IV may be due to the 'truncation' of the spectrum caused by the classification. By simple measures such as dietary modifications, many of these moderately expressed HLP may be transformed to other types of HLP patterns or to a normal LP pattern.

HLP type III is probably due to a block in the catabolism between VLDL and LDL with accumulation of 'intermediary' LP. In type IV a negative correlation exists between VLDL concentration and LDL cholesterol levels which also at least in some cases, may be caused by a block in the conversion of VLDL to LDL although at an earlier step in the catabolism of triglyceride-rich LP.

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REFERENCES

1. Beaumont, J. C., Carlson, L. A., Cooper, G. R., Fejfar, Z., Fredrickson, D. S. & Strasser, T.: Classification of hyperlipidemias and hyperlipoproteinemias. Bull Wld Hlth Org *43*: 891, 1970.
2. Carlson, K.: Lipoprotein fractionation. J Clin Pathol, Suppl. *5*: 32, 1973.
3. Carlson, L. A. & Böttiger, L. E.: Ischaemic heart disease in relation to fasting value of plasma triglycerides and cholesterol. Lancet *I*: 865, 1972.
4. Dixon, W. J. (ed.): BMD Biomedical Computer Programs. University of California Press, Berkeley, 1973.
5. Draper, N. R. & Smith, H.: Applied Regression Analysis. John Wiley & Sons Inc., New York, 1966.

6. Ewing, E. M., Freeman, N. K. & Lindgren, F. T.: The analysis of human serum lipoprotein distribution. Advan Lipid Res *3:* 25, 1965.
7. Fredrickson, D. S. & Lees, R. S.: A system for phenotyping hyperlipoproteinemia. Circulation *32:* 321, 1965.
8. Fredrickson, D. S., Levy, R. I. & Lees, R. S.: Fat transport in lipoproteins: an integrated approach to mechanisms and disorders. New Engl J Med *276:* 34, 1967.
9. Gofman, J. W., de Lalla, O., Glazier, F., Freeman, N. K., Lindgren, F. T., Nichols, A. V., Strisower, B. & Tamplin, A. R.: The serum lipoprotein transport system in health, metabolic disorders, atherosclerosis and coronary heart disease. Plasma (Milan) *2:* 413, 1954.
10. Gofman, J. W. & Tandy, R.: *In* Atherosclerotic Vascular Disease, p. 162. Appleton-Century-Crofts, New York, 1967.
11. Havel, R. J., Eder, H. A. & Bragdon, J. H.: The determination and chemical composition of ultracentrifugally separated lipoproteins in human serum. J Clin Invest *34:* 1345, 1955.
12. Havel, R. J., Kane, J. P. & Kashyap, M. L.: Interchange of apolipoproteins between chylomicrons and high density lipoproteins during alimentary lipemia in man. J Clin Invest *52:* 32, 1973.
13. Hedstrand, H. & Vessby, B.: Serum lipid levels and lipoprotein composition in healthy 50-year-old men in Sweden. Upsala J Med Sci 81: 37, 1976.
14. Kannel, W. B., Castelli, W. P., Gordon, T. & McNamara, P. M.: Serum cholesterol, lipoproteins, and the risk of coronary heart disease. Ann Intern Med *74:* 1, 1971.
15. Levy, R. I., Lees, R. S. & Fredrickson, D. S.: The nature of prebeta (very low density) lipoproteins. J Clin Invest *45:* 63, 1966.
16. Lindgren, F. T., Freeman, N. K. & Nichols, A. V.: *In* Metabolism of Lipids as Related to Atherosclerosis, p. 62. Ch. C. Thomas, Springfield, Illinois, 1965.
17. Nichols, A. V.: Human lipoproteins and their interrelationships. Adv Biol Med Phys *11:* 109, 1967.
18. Nichols, A. V. & Smith, L.: Effect of very low density lipoproteins on lipid transfer in incubated serum. J Lipid Res *6:* 206, 1965.
19. Noble, R. P.: Electrophoretic separation of plasma lipoproteins in agarose gel. J Lipid Res *9:* 693, 1968.
20. Olsson, A. G. & Carlson, L. A.: Studies in asymptomatic primary hyperlipidaemia. I. Types of hyperlipoproteinaemias and serum lipoprotein concentrations, compositions and interrelations. Acta Med Scand, Suppl. *580*, 1975.
21. Quarfordt, S. H., Levy, R. I. & Fredrickson, D. S.: The kinetic properties of very low density lipoprotein triglyceride in type III hyperlipoproteinemia. Biochim Biophys Acta *296:* 572, 1973.
22. Rose, H. G., Kranz, P., Weinstock, M., Juliano, J. & Haft, J. I.: Combined hyperlipoproteinemia. Evidence for a new lipoprotein phenotype. Atherosclerosis *20:* 51, 1974.
23. Rush, R. L., Leon, L. & Turrel, J.: Automated simultaneous cholesterol and triglyceride determination on the Auto Analyzer® II instrument. Advances in Automated Analysis *1:* 503, 1971.
24. Scanu, A. & Granda, J. L.: Effects of ultracentrifugation on the human serum high-density ($1.063 < p < 1.21$ g/ml) lipoprotein. Biochemistry *5:* 446, 1966.
25. Shore, B. & Shore, V.: Some physical and chemical properties of the lipoproteins produced by lipolysis of human serum Sf 20–400 lipoproteins by postheparin plasma. J Atherosclerosis Res *2:* 104, 1962.
26. Slack, J. & Mills, G. L.: Anomalous low density lipoproteins in familial hyperbetalipoproteinaemia. Clin Chim Acta *29:* 15, 1970.
27. Vessby, B., Carlson, L. A. & Hedstrand, H.: Cholesterol and Triglyceride Composition of Very Low and Low Density Lipoproteins in Hyperlipoproteinaemias, p. 882. Springer Verlag, Berlin, Heidelberg, New York, 1974.
28. Vessby, B. & Lithell, H.: Dietary effects on lipoprotein levels in hyperlipoproteinemia. Delineation of two subgroups of endogenous hypertriglyceridemia. Artery *1:* 63, 1974.

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