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Low Levels of Apolipoprotein A_I Are Not Contributors to the Low Lecithin-Cholesterol Acyl Transferase Activity in Premature Newborn Infants

SANIA AMR, PARVEEN CHOWDHRY, PAUL HAMOSH, AND MARGIT HAMOSH

Departments of Pediatrics and Physiology and Biophysics, Georgetown University Medical Center, Washington, D.C. 20007

ABSTRACT. Umbilical cord sera were obtained from three groups of newborn infants; group I ($n = 8$) and group II ($n = 12$) weighed less than 1500 g and between 1500 and 2500 g, respectively. Group III ($n = 16$) was full term and weighed more than 2500 g. Lecithin-cholesterol acyl transferase activities, determined as the rates of esterification of [^{3}H]cholesterol, were 0.13 ± 0.01, 0.17 ± 0.01, and 0.26 ± 0.01 (mean ± SEM) nmol/h/ml for groups I, II, and III, respectively. The adult value ($n = 8$) was 0.96 ± 0.01 nmol/h/ml. The respective apolipoprotein A_I (apo-A_I) levels were 52 ± 6, 59 ± 4, and 67 ± 4 (mean ± SEM) mg/dl. Serum level of apo-A_I in adults was 137 ± 6 mg/dl. Plasma high-density lipoprotein cholesterol levels increased with gestational age. However, in newborn infants, high-density lipoprotein apo-lipoprotein B, total cholesterol, and triglyceride levels, were significantly lower than in adults. These data indicate that serum levels of lecithin-cholesterol acyl transferase activity significantly ($p < 0.01$) increase whereas the levels of apo-A_I do not significantly change with the gestational age. Also, in full-term newborns, lecithin-cholesterol acyl transferase activity is only 27%, whereas apo-A_I levels are 49% of adult values. Therefore, lower levels of apo-A_I do not account for the significantly lower activity of lecithin-cholesterol acyl transferase in preterm as compared to full-term newborn infants. (*Pediatr Res* 24: 191–193, 1988)

Abbreviations

LCAT, lecithin-cholesterol acyl transferase
Apo-A_I, apolipoprotein A_I
HDL, high-density lipoprotein
Apo-B, apolipoprotein B

LCAT is an enzyme that converts plasma lecithin and unesterified cholesterol to lysolecithin and cholesteryl ester, and therefore, it plays a key role in the metabolism of phospholipids (1, 2). The latter, as one of the components of fat emulsions, is commonly administered to low birth weight premature infants, who are maintained on total parenteral nutrition. In these newborns, Intralipid overload leads to phospholipid accumulation and hyperlipemia (3–8) that could be due to low LCAT activity. Indeed, LCAT activity was found to be lower at birth than in adults (9–12). Therefore, attempts to understand the mechanism(s) involved in lipid clearing and particularly the regulatory factors of LCAT activity, have been made (10, 13–16). Several investigators focused their attention on apo-A_I, which is the essential cofactor of LCAT activity and the principal apolipoprotein of plasma HDL (1, 2). Serum apo-A_I levels, like LCAT activities, were found to be lower at birth than in adults (10, 13–16). However, if the reduced enzyme activity is due to low levels of its cofactor remains unclear.

In our study, we examined the developmental patterns of apo-A_I levels and LCAT activities in preterm newborn infants. Umbilical cord sera, obtained from two groups of premature and one group of full-term newborns, were analyzed and compared to sera obtained from adults. We found no direct correlation between apo-A_I levels and LCAT activities.

MATERIALS AND METHODS

Three groups of infants were studied (Table 1). The experimental protocol was approved by the committee for research on human subjects of Georgetown University Hospital. Group I consisted of eight premature babies with birth weight less than 1500 g. In this group there was one case of sepsis and another case of HIV infection. Hyaline membrane disease was the common diagnosis in the six other newborns. Twelve newborns, weighing between 1500 and 2500 g, constituted group II; five infants were diagnosed as having transient respiratory distress. In both groups (I and II), and within each group, there was no significant difference between the infants with respect to the parameters studied. Group III was composed of 16 healthy full-term infants weighing more than 2500 g. A control group, consisting of eight healthy adults (four males, four females), was also studied.

Blood samples were taken from the umbilical cords of newborns and kept at 4° C overnight. After centrifugation, the sera were stored at −20° C. The blood samples, taken from adults, were similarly treated.

LCAT activity was determined as the rate of esterification of [^{3}H]cholesterol, according to the technique of Albers *et al.* (17). Apo-A_I and Apo-B were measured by radioimmunoassay, using kits purchased from Ventrex Laboratories (Portland, ME). Serum triglycerides and total and HDL cholesterol levels were determined enzymatically according to the manufacturer's protocol (Sigma Chemical Co., St. Louis, MO).

For statistical analysis, Student's t test and analysis of variance were used.

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Correspondence and requests for reprints Dr. Sania Amr, Basic Science Building, Room 207, Georgetown University Medical Center, 3800 Reservoir Road, N.W., Washington, D.C. 20007-2197.
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Table 1. *Clinical parameters of different groups of newborn infants**

Group	*n*	Birth wt (g)	Gestational age (wk)
I	8 (3 males, 5 females)	943 ± 58 (790–1195)	28.7 ± 1.3 (25–36)
II	12 (7 males, 5 females)	1987 ± 78 (1590–2340)	33.4 ± 0.5 (31–36)
III	16 (6 males, 10 females)	3283 ± 94 (2610–3960)	39.7 ± 0.2 (38–41)

* The data are expressed as the means ± SEM (range).

RESULTS

LCAT activity was measured as the rate of esterification of cholesterol/h/ml of serum. The results showed that the enzyme activity increased significantly with the gestational age (Fig. 1), but remained, in full-term infants, much lower than in adults (27%). In these newborns, apo-A_I levels, which were only 49% of those observed in adults, did not differ significantly from the levels measured in preterm infants (Fig. 2). Therefore, the increment in LCAT activity was not parallel to the change in apo-A_I levels. As shown in Figure 3, there was no direct correlation between LCAT activity and apo-A_I levels in newborn infants.

To further investigate the lipid profiles of these groups, we simultaneously determined the serum levels of Apo-B, triglycerides, and cholesterol. Total and HDL cholesterol varied with the gestational age (Table 2). Total cholesterol was higher in infants with very low birth weight than in full-term babies. In contrast, HDL cholesterol increased significantly with gestational age. In full-term infants, although plasma HDL cholesterol constituted 45% of total cholesterol levels, the amount remained lower than in adults, where HDL cholesterol levels were only 19% of total cholesterol. Apo-B and triglyceride levels were lower in newborn infants than in adults (Table 2).

DISCUSSION

In our study, we determined the levels of LCAT activity and apo-A_I in umbilical cord sera of preterm and full-term newborn infants. We found that the enzyme activity significantly increased, whereas apo-A_I levels did not vary with the gestational age. Also, in full-term newborns, LCAT activity was only 27%, whereas apo-A_I levels were 49% of adult values. These data strongly support the lack of correlation between the levels of LCAT activity and apo-A_I concentration in newborn infants. Previous studies have shown that cord plasma LCAT activity and apo-A_I levels in full-term infants are much lower than those in adults (10, 13–16). Inasmuch as apo-A_I is the essential cofactor in the activation of LCAT it was hypothesized that the reduced levels of the former might account for the low levels of the latter (2). Our data, showing the patterns of both parameters during gestation, argue against this hypothesis. We found that plasma HDL cholesterol levels increased with the gestational age in a manner parallel to the increase in LCAT activity. Such an increase was earlier reported (18). Inasmuch as HDL are the substrate for LCAT, it is plausible that the low levels of the former could be responsible for the very low activity of the latter in premature infants. However, at term, LCAT activity was proportionally much lower than the levels of its substrate (HDL) in adults (27 and 73% of the adult values, respectively). Although it is possible that low concentration of apo-A_I and/or HDL might contribute to the lower LCAT activity, it is unlikely that the lack of substrate and/or activator is the major factor. More likely is the possibility that low levels of the enzyme per se are responsible for low LCAT activity in newborn infants. Further

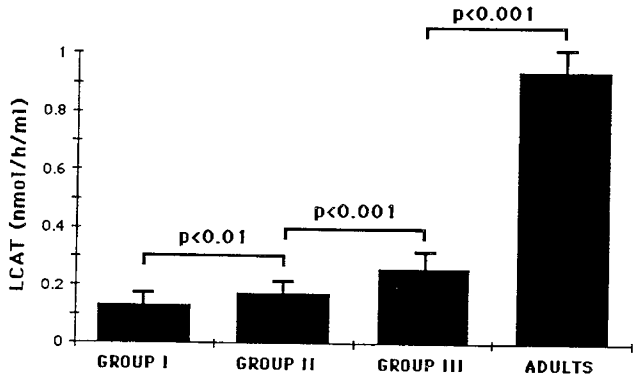

Fig. 1. LCAT activity in serum samples obtained from umbilical cords of newborn infants and from adults. The data represent the means ± 2 SD.

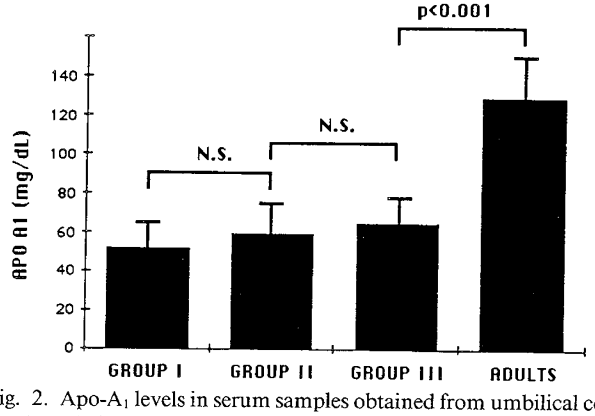

Fig. 2. Apo-A_I levels in serum samples obtained from umbilical cords of newborn infants and from adults. The data represent the means ± 2 SD.

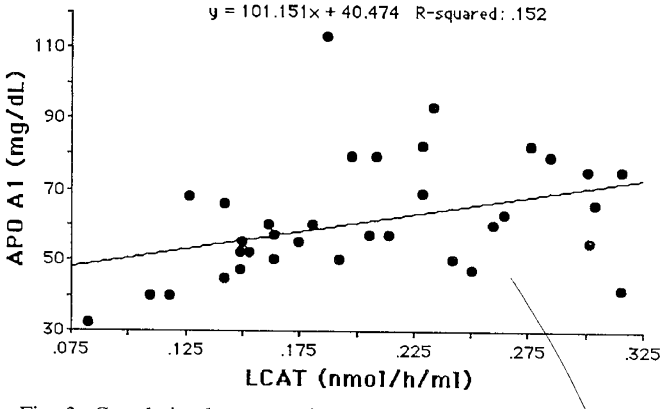

Fig. 3. Correlation between LCAT activity and apo-A_I levels in preterm and full-term newborn infants.

investigations aiming at the quantitative determination of LCAT concentration in addition to its activity, will be necessary to confirm this possibility.

The deficiency of LCAT is of clinical importance in newborns and particularly in very low birthweight infants, to whom administration of Intralipid is commonly used. Indeed, in adult humans (19) and in young rats (20) parenteral nutrition with Intralipid leads to decrease in LCAT activity and impairs the metabolism of exogenous lecithin present in Intralipid. Consequently, an increase not only in serum phospholipid and triglyceride, but also in cholesterol levels occurs (3–8, 21). The resulting hyperlipemia points to the importance of careful monitoring of

Table 2. *Serum levels of Apo-B, total and HDL cholesterol and triglycerides in newborn infants and adults**

Group	Cholesterol		Apo-B	Triglycerides
	Total	HDL		
I	75 ± 12 †	11 ± 1	31 ± 4	60 ± 12
II	51 ± 4	16 ± 2 ‡	28 ± 2 †	42 ± 4
III	55 ± 3	25 ± 1	22 ± 1	49 ± 4
Adults	175 ± 14	34 ± 2	76 ± 6 ‡	100 ± 11 ‡

* The data represent the means ± SEM (mg/dl).
† $p < 0.05$.
‡ $p < 0.001$.

preterm infants parenterally fed with Intralipid, with respect to their serum lipids and plasma LCAT and lipoprotein lipase and hepatic lipase activities. Therefore the dose and modality of administration of Intralipid will have to be established based on the basal levels of these parameters. Also, in some cases, a modification of the lipid emulsion, especially with respect to its lecithin content, might have to be considered.

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