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Effect of Weaning on Serum Lipoprotein(a) Concentration: The STRIP Baby Study

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ABSTRACT

Risk for coronary heart disease is increased in adult Caucasians with high serum lipoprotein(a) [Lp(a)] concentration. In adults the concentration is mainly regulated by genetic factors. Our previous study suggests that breast milk has a beneficial effect on serum Lp(a) concentration in infants. Now we analyzed the influence of weaning by measuring serum Lp(a) and cholesterol in 414 infants at 7, 13, 24, and 36 mo of age. At 7 mo the infants received, in addition to solid food, only breast milk (n = 148), breast milk and formula (n = 74), or formula only (n = 191). Median (range) serum Lp(a) concentrations were then 25 (≤12–743) mg/L, 35 (≤12–1188) mg/L, and 45 (≤12–577) mg/L in the three feeding groups, respectively (p = 0.0013). Breast milk and formula were changed to cow's milk in all infants before 12 mo of age. At 13 mo serum Lp(a) concentration had increased more in infants who were weaned from breast milk than in those who had been fed both breast milk and formula, or formula only (median increases 37, 26, and 20 mg/L, respectively; p = 0.0062). Thus the serum Lp(a) concentration was similar in all feeding groups at 13 mo. This finding was also observed at 24 and 36 mo. The increase in serum Lp(a) concentration was independent of the baseline Lp(a) level, apolipoprotein E phenotype, gender, and weight gain of the infants between 7 and 13 mo. The results imply that weaning from breast milk influences markedly serum Lp(a) concentration, suggesting the presence of a Lp(a) lowering factor in breast milk. (***Pediatr Res* 38: 522–527, 1995**)

Abbreviations

Lp(a), lipoprotein(a)
apo, apolipoprotein
BMI, body mass index

The composition of Lp(a) resembles that of LDL, but the protein moiety contains a unique glycoprotein apo(a) attached to apo B100 by disulfide bonds. Apo(a) is structurally and immunochemically related to plasminogen (1). The physiologic function of Lp(a) is obscure (2, 3), but in Caucasians a high serum Lp(a) concentration (≥250–300 mg/L) is probably associated with increased risk for coronary artery disease (4, 5).

Serum Lp(a) concentration is strongly influenced by genetic determinants. The concentration is inversely related to the size of the inherited apo(a) allele(s). Currently, some 34 apo(a) isoforms have been described (6). Serum Lp(a) concentration is independent of age and gender in adults, and commonly used lipid-lowering drugs and diets enriched with mono- and polyunsaturated fatty acids have not significantly diminished the serum Lp(a) concentration (7–9). In two preliminary studies supplementation of fish oil in capsule form in hypertriglyceridemic subjects and in one study palm oil has lowered serum Lp(a) concentrations (10–12). Interestingly, a high fat meal does not even temporarily increase the serum Lp(a) concentration (13).

Factors which influence serum Lp(a) concentration in early childhood are poorly known. Children who are ≥10 y old and live in families where one parent has coronary heart disease have significantly higher serum Lp(a) concentrations than children of healthy parents (5, 14). In the Bogalusa Heart Study, Caucasian children with parental history of myocardial infarction had markedly higher serum Lp(a) concentration than children of healthy families. Furthermore, black children had higher Lp(a) levels than white children, but they did not show the Caucasian association between parent's coronary artery disease and high serum Lp(a) concentration (15).

Breast milk's concentration of cholesterol and saturated fat is high. Consequently, infants fed solely breast milk (16) or

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mixed food and breast milk (17) have higher serum cholesterol concentration than infants fed formula, and weaning inhibits the age-related increase in serum cholesterol values (16). Meanwhile, serum Lp(a) concentration is lower in infants who receive breast milk as the only milk source than in infants who receive formula at the age of 7 mo (17).

We have now assessed the effect of weaning on serum Lp(a) concentration to obtain more definite proof of the possible Lp(a)-regulating effect of breast milk by measuring serum Lp(a) concentration in 414 healthy infants at the ages of 7, 13, and 24 mo and in most of them also at 36 mo of age, and compared changes in serum Lp(a) to changes in serum cholesterol concentration.

METHODS

Beginning in March 1990, 1062 healthy 6-mo-old infants (56.2% of the eligible age cohort) were recruited in an intervention study for prevention of atherosclerosis (the STRIP baby project, Special Turku coronary Risk factor Intervention Project for babies). Recruiting was done by nurses at the well baby clinics in the city of Turku. At the Cardiorespiratory Research Unit a pediatrician met the parents and explained the background, purpose, and design of the study. The infants were divided randomly into an intervention and a control group. The intervention group received individualized dietary counseling which aimed at adequate energy supply with 30–35% of energy from fat and a polyunsaturated:monounsaturated:saturated fatty acid ratio of 1:1:1, and cholesterol intake <200 mg/day.

All infants had received increasing amounts of solid food since the age of 3–5 mo. Based on the type of liquid milk the infants used at the age of 7 mo groups which received only breast milk (n = 148), breast milk and formula (n = 74), or formula only (n = 191) were formed. Because the effect of weaning on serum Lp(a) level was similar in the intervention and control groups of the project, results of the intervention and control group infants were combined for analyses of the effects of the milk type used. Serum Lp(a) values of the parents of solely breast or formula-fed infants were also measured to exclude the possibility that the breast- and formula-fed infants differed genetically from each other.

Fifteen infants were fed cow's milk already at 7 mo of age; their data were excluded from this analysis. At the age of 13 mo all children received as their milk source cow's milk; the fat content of the milk used ranged from 0 to 3.9%.

Venous nonfasting blood samples were successfully drawn for measurement of serum Lp(a) and cholesterol concentration at the ages of 7, 13, and 24 mo from 414 children. Until now, 341 of these children blood was obtained also at 36 mo of age. Samples were collected under cutaneous anesthesia with Emla (Astra, Södertälje, Sweden), separated by centrifugation (3500 rpm) and stored at −25°C before analyses within 2 mo, a time known to be without any effect on serum Lp(a) concentration (18). Lp(a) concentration was measured using a solid phase two-site immunoradiometric assay (Pharmacia, Uppsala, Sweden) based on direct sandwich technique in which two MAb are directed against separate antigenic determinants on the apo(a) molecule (19). Serum plasminogen concentration up to 5 g/L gives no measurable cross-reactivity in the assay. The detection limit of the assay was 12 mg/L, and the intraassay (interassay) coefficients of variation for the determination were 1.9% (4.4%) at 180 mg/L, and 2.3% (4.9%) at 45 mg/L. Serum cholesterol concentration was analyzed with a fully enzymatic CHOD-PAP method (Merck, Darmstadt, Germany) (20). The intraassay (interassay) coefficient of variation for cholesterol was 1.5% (2.0%) at 4.5 mmol/L. Weight-for-height of the infants was expressed as percentages of the mean weight-for-height of healthy Finnish children at the ages of 7 or 13 mo (21). Apo E phenotype was determined by isoelectric focusing (22).

The study has been approved by the Joint Ethics Committee of the University of Turku and Turku University Hospital. Informed consent was obtained from the parents of the children.

Because of the skewed distribution of Lp(a) concentrations and frequently encountered values which were below the detection limit of the assay (*e.g.* at 7 mo in 31.8% of breast-fed and 20.3% of formula-fed infants), median values were used. The significancies of the differences between the groups and the changes between 7 and 13, 24, and 36 mo of age were tested using Kruskall-Wallis test and Wilcoxon rank sum test, respectively. Serum cholesterol concentrations were expressed as means ± SD; in their statistical analyses a t test was used.

RESULTS

There was a pronounced increase in the infants' median Lp(a) concentration between 7 and 13 mo of age ($p < 0.0001$) (Table 1). The largest increase in median values (37 mg/L) occurred in infants who had received breast milk as their only milk source at 7 mo of age; the increase was smallest (20 mg/L) in infants who had received formula, and intermediate (26 mg/L) in those who had received both formula and breast milk at 7 mo of age. A slight but significant decrease in median Lp(a) values occurred in all three feeding groups between the ages of 13 and 24 mo. These changes were similar in the three groups. The values remained almost unchanged between 24 and 36 mo. All three feeding groups had a similar median Lp(a) concentration at 13 mo, as well as 24 and 36 mo of age. There was no difference in the dietary composition with respect to the percentage of polyunsaturated, monounsaturated, and saturated fat intake as measured by 3–4-d dietary records between the initially breast-fed infants and formula-fed infants at the ages of 13 and 24 mo.

The medians of the mid-parent serum Lp(a) values of those infants who had received breast milk or formula as their only milk source at 7 mo of age were 113.5 mg/L and 112.5 mg/L, respectively, (p = 0.92). This finding excludes the possibility that genetic differences in Lp(a) isoforms could explain the differences in the Lp(a) values between the breast milk-fed and the formula-fed groups. Serum cholesterol concentrations as well as BMI of the mothers and fathers in both feeding groups were similar, suggesting that there were no major differences in the nutrition between the parents in the two groups (serum

Table 1. *Serum Lp(a) concentration in children at 7, 13, 24, and 36 mo according to milk type fed at 7 mo of age (BM = breast milk, F = infant formula)*

	Milk type at 7 mo			*p* for difference between the groups
	BM (*n* = 148)	BM + F (*n* = 74)	F (*n* = 192)	
Median value at 7 mo (mg/L) (range)	25 (≤12–743)	35 (≤12–1188)	45 (≤12–577)	overall 0.0013 BM *vs* F 0.0003
Median value at 13 mo (mg/L) (range)	67* (≤12–1605)	62* (≤12–1880)	80* (≤12–1125)	NS
Median value at 24 mo (mg/L) (range)	51† (≤12–1495)	59† (≤12–1495)	65† (≤12–1295)	NS
Median value at 36 mo (mg/L) (range)	53‡ (≤12–1620)	55‡ (≤12–928)	59‡ (≤12–898)	NS
Median change in absolute values (mg/L)				
From 7 to 13 mo	+37	+26	+20	overall 0.0062 BM *vs* F 0.0024
From 13 to 24 mo	−6	−5	−7	NS
From 24 to 36 mo	+3	+2	+1	NS
Relative change in median values (%)				
From 7 to 13 mo	+122	+67	+44	Overall <0.0001 BM *vs* F <0.0001
From 13 to 24 mo	−10	−7	−12	NS
From 24 to 36 mo	+8	+7	+6	NS

Difference within groups:

* Between Lp(a) values at 7 and 13 mo of age, $p < 0.0001$, sign rank test.

† Between Lp(a) values at 7 and 24 mo of age, $p < 0.0001$, sign rank test.

‡ Between Lp(a) values at 13 and 24 mo of age, $p < 0.0001$ in children fed only breast milk or only formula at the age of 7 mo, $p = 0.024$ in children fed both breast milk and formula at the age of 7 mo.

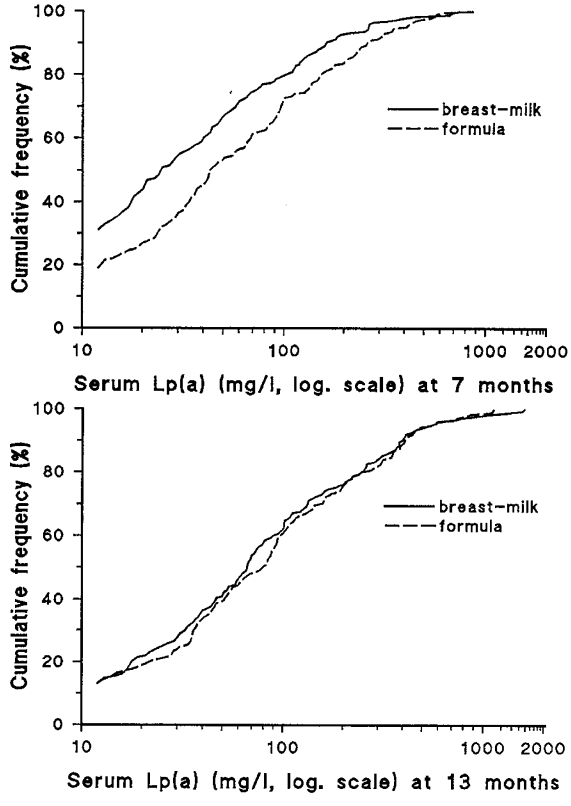

Figure 1. Cumulative distribution of serum Lp(a) concentrations in infants at 7 mo of age (*top*) and at 13 mo of age (*bottom*).

cholesterol in mothers of the breast-fed infants 5.02 ± 0.86 mmol/L and in mothers of formula-fed infants 5.08 ± 1.05 mmol/L; $p = 0.56$. The respective values in fathers were 5.37 ± 1.04 and 5.40 ± 1.10 mmol/L; $p = 0.78$. BMI in mothers of breast-fed infants 23.0 ± 3.2 kg/m^2 and in mothers of formula-fed infants 23.6 ± 3.7 kg/m^2; $p = 0.09$. The respective values in fathers were 24.9 ± 3.2 and 24.8 ± 3.2 kg/m^2; $p = 0.60$)

The cumulative distributions of Lp(a) concentrations, which had differed markedly between breast- and formula-fed groups at 7 mo, showed no differences between the two groups at 13 mo of age (Fig 1). The distribution curves at the ages of 24 and 36 mo were almost identical to those at 13 mo of age.

Because of the expected influence of genetic factors on serum Lp(a) concentration, we subdivided the infants in the breast- and formula-fed groups into infants with Lp(a) values <37 mg/L (median for age) or ≥37 mg/L at the age of 7 mo (Table 2). The differences between the breast milk-fed and formula-fed groups in absolute and relative changes which occurred in the Lp(a) values between 7 and 13 mo of age were significant irrespective of the 7-mo Lp(a) level [high *versus* low Lp(a)].

The age-associated increases in serum Lp(a) values differed significantly between the two feeding groups (breast milk and formula) in boys as well as in girls. In boys the median increase in serum Lp(a) among breast-fed infants was 31 mg/L (112%) and in formula-fed infants 17 mg/L (41%; *p* for difference in change <0.001). The respective figures in girls were 37 mg/L (112%) and 24 mg/L (46%; *p* for difference in change <0.001).

The mean increases in height, relative weight, and weight-for-height between 7 and 13 mo of age were similar in the breast milk, breast milk and formula, and formula groups (data not shown). Because growth may influence Lp(a) values, the infants were divided into growth rate quartiles which were based on their relative weight increases between 7 and 13 mo of age. In all quartiles, the differences between breast milk-fed and formula-fed infants in the changes which were recorded

Table 2. *Absolute and relative changes in serum Lp(a) concentration between 7 and 13 mo of age who were fed breast milk or formula as their only milk source at 7 mo, stratified according to serum Lp(a) concentration (< or ≥ median = 37 mg/L) at 7 mo*

	Lp(a) < median at 7 mo		Lp(a) ≥ median at 7 mo	
	Breast milk-fed at 7 mo of age (n = 100)	Formula-fed at 7 mo of age (n = 107)	Breast milk-fed at 7 mo of age (n = 73)	Formula-fed at 7 mo of age (n = 135)
Median absolute change (mg/L)	+19	+5*	+121	+48†
Median relative change (%)	+109	+26‡	+24	+49§

Difference between breast milk-fed and formula-fed infants:
* p = 0.003.
† $p < 0.0001$.
‡ p = 0.0006.
§ $p < 0.0001$.

in the Lp(a) values between 7 and 13 mo were significant (Table 3).

The infants were also divided into two groups according to their apo E phenotype: infants with apo ϵ4 allele (apo $E4^+$) and infants without apo ϵ4 allele (apo $E4^-$). In both groups the increase in serum Lp(a) concentration between 7 and 13 mo was significantly higher in breast-fed infants than in formula-fed infants (Table 4). Within the milk groups there was no difference in the change in serum Lp(a) levels between the apo $E4^+$ and apo $E4^-$ infants. In breast-fed children with apo E2/E2 or E3/E2 phenotype (n = 16) Lp(a) concentration rose after weaning from 33.5 mg/L to 88 mg/L, and the median increase was 121%, which was not different from the increase in all breast-fed children (median increase 122%).

Interestingly, the changes between 7 and 13 mo of age in serum cholesterol concentration were different from the changes in serum Lp(a) concentration in all groups of infants which were formed according to milk type used at 7 mo of age. Mean serum cholesterol remained unchanged (mean ± SD at 7 mo 4.1 ± 0.78 mmol/L and at 13 mo 4.11 ± 0.77 mmol/L; p = NS) in the infants who had been breast-fed at 7 mo, and increased by 0.30 mmol/L (from 3.76 ± 0.69 at 7 mo to 4.06 ± 0.68 mmol/L at 13 mo; $p < 0.001$) in the infants who had been formula-fed at 7 mo (p for the difference in the change between the groups <0.0001). Indeed, the changes in serum Lp(a) concentration did not correlate with the changes in serum cholesterol concentration neither in the infants fed breast milk (r = 0.064, p = NS) nor in the infants fed formula (r = 0.081, p = NS). At 13 mo and later, mean serum cholesterol concentrations and the changes in serum cholesterol concentration were similar in both groups (data not shown).

Table 3. *Relative change (%) in serum Lp(a) concentration in infants who received breast milk or formula as their only source of milk at 7 mo of age stratified according to the change in relative weight between 7 and 13 mo of age*

	Quartiles of change in relative weight*			
Change	I	II	III	IV
Absolute change (mg/L)				
Breast-fed at 7 mo of age	+48	+28	+34	+23
Formula-fed at 7 mo of age	+13	+24	+22	+21
p†	<0.001	<0.001	0.005	0.018
Relative change (%)				
Breast-fed at 7 mo of age	+157	+117	+112	+87
Formula-fed at 7 mo of age	+33	+48	+47	+41
p	0.001	<0.001	0.01	0.008

* I quartile represents the smallest and IV quartile the largest increase in the relative weight between 7 and 13 mo of age.
† Wilcoxon rank sum test after logarithmic transformation.

DISCUSSION

We showed previously in a large cohort of infants that those who received breast milk as their only milk source had significantly lower serum Lp(a) concentration than those who received formula (17). On the other hand, Van Biervliet *et al.* (23) in a sample of 27 children found no difference in serum Lp(a) between infants fed breast milk or formula at the age of 3 mo. The current study is in accordance with our previous findings showing in a sample of 414 infants that the age-related increase in Lp(a) is higher when the infants switch to adult-like diet from breast milk than when they switch from feeding which is based on formula. Furthermore, the increase was intermediate in the group which switched from a diet which included both breast milk and formula. Breast milk-associated factors thus influence serum Lp(a) concentrations markedly, but the influence is transient.

Boerwinkle *et al.* (24) have shown that the apo(a) gene mainly accounts for the variance in plasma Lp(a) concentration in the adult population. Therefore, one might argue that there could be a possible genetic predisposition for lower Lp(a) levels in breast-fed infants. However, we have two arguments against this possibility: first, the difference in change in serum Lp(a) concentration between breast-fed and formula-fed infants was independent of the baseline Lp(a) value; and second, the parents of breast-fed and formula-fed infants had similar median mid-parent values of serum Lp(a) concentrations. In adults, some dietary factors may also affect serum Lp(a) levels (10–12, 25, 26). Therefore, there is a theoretical possibility that serum Lp(a) levels in parents of breast- and formula-fed infants could be similar as a result of different nutrition acting in opposite directions. However, there was no difference in serum total cholesterol concentrations and BMI values between the parents of breast-fed and formula-fed infants; these rough estimates of nutrition suggest that there were no major dietary differences between the parents in the two feeding groups. Our findings clearly imply that exogenic factors also influence Lp(a) levels in early childhood. This regulation might in theory be mediated by nutritional components, or hormones and growth factors (27) in the breast milk that may inhibit synthesis

Table 4. *Serum Lp(a) concentration at 7 and 13 mo of age in infants stratified according to apo E phenotype (apo E4$^+$ and apo E4$^-$) and milk type fed at 7 mo*

	Milk type fed at 7 mo of age			p for difference between the groups
	n (Breast/formula)	Breast milk only	Formula only	
Median value at 7 mo (mg/L) (range)				
Apo E4$^+$	69/75	30 (≤12–743)	50 (≤12–559)	0.010
Apo E4$^-$	98/157	21 (≤12–676)	40 (≤12–862)	0.0041
Median value at 13 mo (mg/L) (range)				
Apo E4$^+$	69/75	72 (≤12–1300)	87 (≤12–1125)	0.56
Apo E4$^-$	98/157	66 (≤12–1605)	68 (≤12–1120)	0.50
Median absolute change (mg/L)				
Apo E4$^+$		+40	+25	0.036
Apo E4$^-$		+28	+16	0.025
Median relative change (%)				
Apo E4$^+$		+124	+51	<0.0001
Apo E4$^-$		+108	+38	<0.0001

or accelerate degradation of the Lp(a) particles. The possible active components of breast milk are discussed below in detail.

Lp(a) concentrations which are low at birth, often below the detection level of the current assay methods, increase during the first year of life, and reach adult concentrations during the second year (28, 29). Intestinal mucosa matures and intestinal permeability decreases during the first year of life (30). This change in intestinal leakiness might explain why breast milk feeding influences serum Lp(a) concentrations in infancy, but nutritional changes, *e.g.* those examined in many intervention studies, have minimal effects on Lp(a) concentration later in life. Breast milk and formula differ in many nonprotein components but also in the protein composition. In particular, immunologically active proteins and growth factors differ (27), and these differences are at least in theory possible factors behind the differences in the effect between the two milk types on serum Lp(a). However, the increased permeability of the intestinal mucosa to proteins disappears usually between 0 and 6 mo of age, and major changes in the leakiness are unlikely to occur as late as between 7 and 13 mo of age.

Significant differences in the fatty acid composition of breast milk and infant formula do exist. Large amounts of trans-fatty acids in the diet increase serum Lp(a) levels in adults (25, 26), but the trans-fatty acid concentration in human milk (31) and in the most commonly used infant formula in Finland are closely similar (4.4 and 4.7%, respectively). Therefore, differences in trans-fatty acid intake are an unlikely explanation for our findings.

Breast milk contains significantly more gestagenic hormones than formula (32). Use of norethisterone, a synthetic gestagen, is associated with a decreased concentration of serum Lp(a) in postmenopausal women (33). These findings suggest that hormones in breast milk may at least to some extent account for its Lp(a) lowering effects.

Another factor which has been associated with decreases in serum Lp(a) concentrations in adults is weight loss, as in adult women weight loss decreases high (>300 mg/L) serum Lp(a) concentrations (34). We found no difference in the change in Lp(a) concentrations between the children whose weight-for-height decreased and children whose weight-for-height increased between 7 and 13 mo of age when the growth rate is rapid.

Due to breast milk's high cholesterol and saturated fat content, serum cholesterol concentration was higher in infants who received breast milk as their only milk source than in infants who received formula at 7 mo of age. Serum cholesterol concentration remained unchanged in infants who were weaned from breast milk between 7 and 13 mo of age, but increased markedly in infants who had been fed formula at 7 mo of age. The changes in serum cholesterol were thus different from those in serum Lp(a), suggesting that the serum Lp(a) concentration is regulated independently from serum cholesterol in infants. The effect of breast milk on Lp(a) seems to be transient, because of the lack of difference between the groups in the later measurements. Similarly, breast milk probably has no long-term effects on cholesterol in children (35), although in animal studies differences in cholesterol metabolism later in life have been reported (36).

In summary, our results show that breast milk feeding has marked effects on the serum Lp(a) concentration in infants and that differences in serum Lp(a) concentration between previously breast milk fed and formula-fed infants disappear rapidly after weaning. We hypothesize that breast milk hormones or growth factors are responsible for the difference between the Lp(a) levels in the breast milk-fed and formula-fed infants. The biologic significance of the decreased serum Lp(a) values due to breast milk feeding is unknown with regard to initiation of atherogenesis. However, knowing that earliest precursors of atherosclerosis, fatty streaks, can develop during the first years of life, a potentially favorable effect of low Lp(a) during the first 12 mo of age cannot be excluded. After all, the main message of our finding is that, contrary to previous reports, physiologic dietary factors can affect serum Lp(a) levels.

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