



Trabajo Original

Pediatría

Relationship between lipid profile, anthropometric indicators, and appetite-regulating hormones in infants according to type of feeding

Relación entre perfil lipídico, indicadores antropométricos y hormonas reguladoras del apetito en lactantes según tipo de alimentación

Edgar M. Vásquez-Garibay^{1,3}, Alfredo Larrosa-Haro¹, Nelly Muñoz-Esparza¹, Enrique Romero-Velarde^{1,3}, Elizabeth Guzmán-Mercado¹, Samuel García-Arellano², Felipe Martínez-Limón³, José Francisco Muñoz-Valle²

¹Instituto de Nutrición Humana. Universidad de Guadalajara; ²Instituto de Investigación en Ciencias Biomédicas. Universidad de Guadalajara; ³Nuevo Hospital Civil de Guadalajara Dr. Juan I. Menchaca. Guadalajara, Jalisco. México

Abstract

Background: infants receiving full breastfeeding (FBF) regulate their appetites differently from those receiving human milk substitutes (HMS). In addition, early exposure to the dietary cholesterol in human milk could lead to better cholesterol regulation in later stages of life. Therefore, the purpose was to compare lipid profiles in 4-month-old infants and to correlate lipid profile with anthropometric indicators and appetite-regulating hormones according to the type of feeding.

Methods: this was a cross-sectional and correlational study, which included 145 mother-infant dyads according to the type of feeding; 64 received FBF, 47 partial breastfeeding (PBF), and 34 HMS. The complete lipid profile, total ghrelin, leptin, peptide YY, and glucagon-like peptide type 1 were measured. Z-scores for weight/age, length/age, weight/length, triceps (TSF) and subscapular folds (SSF) and body mass index for age were also obtained.

Results: there were significant differences in triglycerides and LDL cholesterol according to the type of feeding. In the HMS group, an inverse relationship was observed between ghrelin and triglycerides ($p = 0.038$), ghrelin and total cholesterol (TC) ($p = 0.026$), and peptide YY and HDL cholesterol ($p = 0.017$). In the PBF group, a direct relationship was observed between length/age (z) and triglycerides ($p = 0.001$) and between subscapular folds and TC ($p = 0.049$). In infants receiving HMS, a direct correlation was observed between weight/age (z) and TC ($p = 0.045$) and between length/age (z) and LDL cholesterol ($p = 0.010$).

Conclusion: these findings show a relationship between growth, energy reserve, lipid profile, and modulation of appetite-regulating hormones according to the type of feeding they received.

Keywords:

Infants. Lipid profile. Appetite regulation. Growth indicators.

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Correspondence:

Edgar M. Vásquez Garibay, DSc. Instituto de Nutrición Humana. Universidad de Guadalajara. Hospital Civil de Guadalajara Dr. Juan I. Menchaca. Salvador Quevedo y Zubieta # 350, Col. Independencia. CP 44340, Guadalajara, Jalisco. México
e-mail: edgar.vgaribay@academicos.udg.mx; vasquez.garibay@gmail.com

Resumen

Introducción: los lactantes que reciben lactancia materna completa (LMC) regulan su apetito de manera diferente a los que reciben sucedáneos de la leche humana (SLH). Además, la exposición temprana al colesterol en la leche humana conduciría a mejor regulación del colesterol en etapas posteriores de la vida. El propósito fue de comparar el perfil lípidos en lactantes de cuatro meses y correlacionarlo con indicadores antropométricos y hormonas reguladoras del apetito según el tipo de alimentación.

Métodos: en un estudio transversal y correlacional se incluyeron 145 díadas madre-lactante según el tipo de alimentación; 64 recibieron LMC, 47 lactancia materna parcial (LMP) y 34 SLH. Se midió el perfil lipídico, grelina total, leptina, péptido YY y péptido tipo 1 similar al glucagón. Se obtuvieron puntajes Z para peso/edad, longitud/edad, peso/longitud, pliegue cutáneo tricipital y subescapular e índice de masa corporal para la edad.

Resultados: hubo diferencias significativas en triglicéridos y colesterol LDL según el tipo de alimentación. En el grupo HMS se observó una relación inversa entre grelina y triglicéridos ($p = 0,038$), grelina y colesterol total (TC) ($p = 0,026$), y péptido YY y colesterol HDL ($p = 0,017$). En el grupo PBF hubo relación directa entre longitud/edad (z) y triglicéridos ($p = 0,001$) y entre pliegues subescapulares y CT ($p = 0,049$). En los lactantes que recibieron HMS, se observó una correlación directa entre peso/edad (z) y CT ($p = 0,045$) y entre longitud/edad (z) y colesterol LDL ($p = 0,010$).

Conclusión: los hallazgos muestran una relación entre perfil lipídico, crecimiento, reserva energética y modulación de las hormonas reguladoras del apetito según el tipo de alimentación.

Palabras clave:

Lactantes. Perfil lipídico.
Regulación del apetito.
Indicadores de crecimiento.

INTRODUCTION

An infant's lipid profile has been shown to differ significantly depending on the type of feeding. In industrialized countries, infants receiving full breastfeeding (FBF) have been found to have a different lipid profile than those receiving human milk substitutes (HMS) (1). Specifically, total serum cholesterol (TC) was found to be highest in infants receiving FBF. It has been suggested that this is due to increased lipase activity and a higher concentration of apolipoprotein E in human milk, which plays an important metabolic role at this stage of life (2,3). Kallio et al. (1) demonstrated that low-density lipoprotein (LDL) cholesterol concentration was lower in weaned infants than in infants fed exclusively human milk at two and six months of age. Although TC and LDL cholesterol are influenced by diet and adiposity in adults, early feeding in postnatal life could have a long-term "programming" effect on physiology and cholesterol metabolism. Therefore, breastfeeding could produce beneficial and lasting changes in lipid metabolism and consequently reduce the risk of cardiovascular disease later in life (4).

Owen et al. (5), in a systematic review and meta-analysis, showed that TC concentrations in breastfed infants were higher than that in HMS-fed infants, although they were similar in childhood and lower in adult life. Through these findings, they hypothesized that early exposure to the high cholesterol concentration of human milk could affect cholesterol metabolism in the long-term. Enteral exposure to high cholesterol in childhood reduces endogenous cholesterol synthesis, likely due to the low regulation of hepatic hydroxymethyl glutaryl coenzyme A reductase (6). However, these authors do emphasize that, from the small number of longitudinal studies that have examined this issue, there is no consistent evidence that breastfeeding results in a reduction in cardiovascular disease risk in adulthood.

Inverse relationships between breastfeeding and both adiposity and indicators of cardiometabolic risk have been demonstrated. Possible mechanisms include the self-regulation of energy intake and lower protein consumption in breastfed children than in those receiving HMS (7). Breastfed infants have also been speculated to have lower insulin secretion and insulin-like growth factor I and less weight gain during the first two years of life (8).

Regarding the lipid profile of infants receiving partial breastfeeding (PBF), a study in India showed that TC was significantly higher in infants receiving FBF than in those receiving PBF. It has been suggested that the higher TC concentration in infants fed FBF could be explained by the higher concentration of cholesterol in human milk compared to bovine milk (9). Another study (10) found that infants exclusively breastfed from 0 to 3 months old had lower TC and LDL cholesterol levels compared to HMS-fed infants at around 17.5 years of age, whereas no association was found for high-density lipoprotein (HDL) levels on PBF infants. Furthermore, the body mass index and the percentage of fat did not differ depending on the type of feeding. The authors, therefore, concluded that FBF could promote a healthier lipid profile in late adolescence through mechanisms not related to adiposity, which would imply possible long-term benefits for cardiovascular health.

FULL BREASTFEEDING AND APPETITE REGULATION

Infants receiving FBF regulate their appetites differently from those receiving HMS. This appears to be a result of the activity of adipokines (leptin and adiponectin) present in human milk. Over the long-term, this could help regulate body weight, improve insulin sensitivity, and increase fat metabolism (11,12). Furthermore, early exposure to the dietary cholesterol in human milk could lead to better cholesterol regulation in later stages of life (13).

Therefore, the purpose of this study was to show that the type of feeding an infant receives would lead to differences in its lipid profile, which would correlate to differences in anthropometric indicators and appetite-regulating hormones at 4 months of life.

METHODS

DESIGN

This was a cross-sectional comparative and correlational analysis of a sample of 145 mother-child dyads according to the

type of feeding. There were 64 in the FBF group, 47 in the PBF group, and 34 in the HMS group. We identified dyads of mothers and newborns who were admitted to the shared physiological puerperium room at the Nuevo Hospital Civil de Guadalajara. The inclusion and exclusion criteria and sample size estimation are described elsewhere (14).

DEPENDENT VARIABLES

Lipid Profile: the lipid profile included: triglycerides, TC, HDL cholesterol, and LDL cholesterol, all measured in mg/dL.

Serum concentration of appetite-regulating hormones: the appetite-regulating hormones studied were as follows: total ghrelin (pg/mL), leptin (ng/mL), peptide YY (pg/mL), and glucagon-like peptide type 1 (pM). The anthropometric indicators were as follows: weight (g), length (cm), head circumference (cm), arm circumference (cm), tricipital skin fold (TSF; mm), subscapular skin folds (SSF; mm), and z-scores for weight/age, length/age, weight/length, body mass index TSF and SSF.

INDEPENDENT VARIABLES

The independent study variables were: FBF, PBF, and cow's milk-based HMS.

INSTRUMENTS AND MEASUREMENT TECHNIQUES

Lipid profile measurement techniques and instruments: For lipid profile determination, serum was separated after collection of the blood sample from the infants. Serum samples were analyzed for lipid profile by the Beckman Coulter AU Analyzer (Beckman Coulter, Inc., 250 S. Kraemer Blvd. Brea, CA 92821, USA) for triglycerides (TG), total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C). Low density lipoprotein cholesterol (LDL-C) was calculated using the formulae, i.e., $LDL-C = TC - (HDL-C + VLDL-C)$.

Techniques and instruments for anthropometric measurements: After the standardization of the two observers (EGM and NME), anthropometric measurements were made with the techniques reported by Frisnacho (15) and described elsewhere (16). The z-scores of the anthropometric indicators and indices were obtained from the World Health Organization Child Growth Standards (17).

BLOOD COLLECTION AND ANALYSIS

Techniques for obtaining blood samples and tests for appetite-regulating hormones have been described elsewhere (14).

DATA COLLECTION, DATABASE, AND COMPUTER PROGRAM

After information was obtained, the database was created, and the data were captured, the statistical analysis was performed using SPSS software, version 24.

STATISTICAL ANALYSIS

The Levene test was used to assess the equality of the variations for two or more groups, and the Shapiro-Wilk and Kolmogorov-Smirnov tests were used to explore the normality of the distributions. An analysis of variance (ANOVA) was performed to compare the variances between the groups, and the unpaired Student *t*-test was used to show the contrast between two independent samples with normal distribution. In samples with abnormally distributed variables, the Mann-Whitney U-test was used. Linear regression and Pearson's correlation coefficient were used between parametric variables and Spearman's correlation was used between non-parametric variables. The level of significance was set at $p \leq 0.05$.

BIOSECURITY

The biological samples were handled in accordance with the specifications outlined in the Official Mexican Standard NOM-087-ECOL-SSA1-2002. The chemical substances were handled and stored in accordance with the official Mexican standards NOM-052-SEMARNAT-2005 and NOM-054-SEMARNAT-1993 and in accordance with the information indicated on the biosafety sheets for each chemical used.

ETHICAL CONSIDERATION

A written informed consent was obtained from the parents of participating dyads. The recommendations of the Declaration of Helsinki were followed in its last Amendment during the 64th Annual Assembly organized by the World Medical Association, 2013. The Committees of Bioethics and Research of the Hospital Civil Hospital of Guadalajara approved this study; and, the Committees of Biosecurity, Bioethical and Research of the University of Guadalajara, Center of Health Sciences (CI-01314).

RESULTS

Total lipid profile samples were taken at 16 weeks postpartum for 145 infants. The parents' sociodemographic data and the infants' anthropometric indicators are described elsewhere (14). The infants' serum lipid concentrations classified according to the three types of feeding are described in table I. The ANOVA test showed significant differences in triglycerides, TC, and

LDL cholesterol. Overall, a significantly higher concentration of all components of the lipid profile was observed in infants receiving FBF compared to PBF or HMS, except for HDL cholesterol, of which infants receiving HMS had higher concentrations than those receiving FBF.

Table II shows an inverse trend in the FBF group between peptide YY (anorectic hormone) and TC that was not significant ($p = 0.059$). For the PBF group, there was a direct trend between leptin and TC ($p = 0.075$) and a direct and significant correlation between leptin and HDL cholesterol ($r = 0.319$, $p = 0.033$). With HMS, an inverse and significant relationship was observed between ghrelin and triglycerides ($p = 0.038$), ghrelin and TC ($p = 0.026$), ghrelin and HDL cholesterol ($p = 0.039$), and between peptide YY and HDL cholesterol ($p = 0.017$). Additionally, an in-

verse trend was observed between peptide YY and triglycerides, but it was not significant ($p = 0.077$).

Table III shows the correlations coefficients between the lipid profiles and anthropometric indicators. For infants who received FBF, a direct trend was observed between length/age and serum TC, but it was not significant. For infants who received PBF, a direct and significant correlation was observed between length/age (z) and triglycerides ($p = 0.01$), and between SSF and TC ($p = 0.049$). A direct trend was also observed between weight/age (z) and triglycerides and between TSF (z) and TC, but these were also not significant. For infants who received HMS, a direct and significant correlation was observed between weight/age (z) and TC ($p = 0.045$) and between length/age (z) and LDL cholesterol ($p = 0.010$).

Table I. Lipid profile in 145 four-month-old infants according to type of feeding*

Lipid profile	FBF			PBF			HMS			p
	n	X	SD	n	X	SD	n	X	SD	
Triglycerides (mg/dL)	63	160	70.6	47	137	64.8	33	121	54.8	0.014
Total cholesterol	64	135	21.9	47	119	25.1	34	119	22.4	< 0.001
HDL cholesterol (mg/dL)	62	32.5	7.7	47	34.3	7.8	34	35.8	7.8	0.114
LDL cholesterol (mg/dL)	64	67.9	21.9	46	57.6	20.6	34	57.1	18.6	0.012

*Data are presented as the mean and standard deviation (SD); there were some missing values in the measurement techniques. ANOVA statistical analyses of one factor and post-hoc analyses (Tukey) of significant comparisons between groups. FBF: full breastfeeding; PBF: partial breastfeeding; HMS: human milk substitutes. Triglycerides: FBF vs HMS, $p = 0.008$; total cholesterol: FBF vs PBF, $p = 0.003$; FBF vs HMS, $p = 0.003$; LDL cholesterol: FBF vs. PBF, $p = 0.035$; PBF vs HMS, $p = 0.031$; HDL cholesterol: FBF vs HMS, $p = 0.031$.

Table II. Serum concentrations of lipids and appetite-regulating hormones according to type of feeding*

Type of feeding	ARH	Triglycerides			Total cholesterol			HDL cholesterol		
		r	R ²	p	r	R ²	p	r	R ²	p
FBF (n = 65)	Peptide YY	-			0.243	0.060	0.059	-		
PBF (n = 47)	Leptin	-			0.268	0.072	0.075	0.319	0.101	0.033 [†]
HMS (n = 33)	Ghrelin	-0.369	0.136	0.038	-			0.367	0.135	0.039
	Peptide YY	0.317	0.100	0.077	-			-		

*Pearson's correlation coefficient and simple linear regressions; only significant or trend values were included in the table. ARH: appetite-regulating hormones; FBF: full breastfeeding; PBF: partial breastfeeding; HMS: human milk substitute. There was no correlation between GLP-1 (glucagon-like peptide type 1) and lipid profile or between LDL cholesterol and ARH in any feeding type. [†]Spearman's correlation.

Table III. Correlations and simple linear regressions between the serum lipid profile and anthropometric indicators according to the type of feeding*

Anthropometric indicators	Triglycerides				Total cholesterol				LDL cholesterol			
	<i>n</i>	<i>r</i>	<i>R</i> ²	<i>p</i>	<i>n</i>	<i>r</i>	<i>R</i> ²	<i>p</i>	<i>n</i>	<i>r</i>	<i>R</i> ²	<i>p</i>
Full breastfeeding												
Length/Age (z) [†]					62 [‡]	0.213	0.045	0.096				
Partial breastfeeding												
Length/Age (z) [†]	47	0.469	0.220	0.001								
Weight/Age (z)	47	0.254	0.064	0.085								
TSF/Age (z)		-	-	-	47	0.249	0.062	0.091				
SSF/Age (z)		-	-	-	47	0.340	0.120	0.049				
Human milk substitutes												
Length/age (z) [†]		-	-	-		-	-	-	34	0.438	0.192	0.010
Weight/age (z) [†]		-	-	-	34	0.346	0.120	0.045				

*Only significant or trend values were included in the table. [†]Spearman's correlation. [‡]There were two missing values in the measurement techniques. TSF: tricipital skin fold; SSF: subscapular skin folds.

DISCUSSION

The comparison of variances analysis demonstrated that at 16 weeks of postnatal life, the lipid profiles were significantly different between the FBF, PBF, and HMS groups in all elements studied except HDL cholesterol. The FBF group had significantly higher lipid profile concentrations than the HMS group ($p = 0.008$), particularly for triglycerides. The TC concentration in the FBF group was significantly higher than that in the PBF group ($p = 0.003$) and the HMS group ($p = 0.003$). LDL cholesterol levels were significantly higher in the FBF group than in both the PBF group ($p = 0.035$) and the HMS group ($p = 0.031$). Whereas HDL cholesterol was significantly higher in the HMS group than in the FBF group ($p = 0.031$).

The higher concentrations of TC and LDL cholesterol in infants receiving FBF compared to that in infants receiving HMS has been widely documented (3-5,18) and, less frequently, the same finding has also been observed when comparing FBF to PBF (9,19). These findings do not coincide with those of Ramirez-Silva et al. (7), however, who studied Mexican children at three months of age. Some of these authors have suggested that the highest concentrations of TC and LDL cholesterol in infants receiving FBF could be physiological and useful for cognitive development and lipid metabolism programming in adulthood. Additionally, exclusive breastfeeding could initiate lasting changes in lipid metabolism, potentially reducing the risk of cardiovascular disease later in life (4).

Some interesting correlations were observed between lipid profiles and appetite-regulating hormones. In the FBF group, there was an inverse non-significant correlation between peptide YY and TC ($p = 0.059$). This hormone is known to have an anorectic function that increases the efficiency of digestion and absorption of nutrients after a meal. Furthermore, the higher concentration of peptide YY in infants receiving FBF has been shown to exert a protective effect against obesity (20), which

would explain the inverse relationship between these indicators. In infants who received PBF, a direct correlation trend was observed ($p = 0.075$) between TC and leptin concentrations, which makes sense considering that leptin and high cholesterol would be associated with greater adiposity.

The most noteworthy findings were observed in the HMS group. The inverse and significant correlation between ghrelin and triglycerides in this group ($r = -0.369$, $p = 0.038$) could be explained by the higher concentration of triglycerides causing a lower serum concentration of ghrelin, a powerful orexigenic. However, since the same finding was observed between ghrelin and HDL cholesterol ($r = -0.387$, $p = 0.026$), it seems that ghrelin is sensitive to lipid elevation regardless of its function in infants who receive HMS. This could also explain the trend towards an inverse correlation between peptide YY and triglyceride concentrations ($r = 0.317$, $p = 0.077$) and the inverse and strongly significant correlation between peptide YY and HDL cholesterol ($r = -0.412$, $p = 0.017$). It is particularly interesting that these findings occurred in the HMS but not FBF group.

Appetite-regulating hormones may attempt to protect infants from excessive saturated fat intake and long-term cardiovascular risk when they do not receive FBF (10). According to these authors, FBF can promote a healthier lipid profile in late adolescence through mechanisms not related to adiposity, implying that these mechanisms would have potential long-term benefits for cardiovascular health. There is "a lot of weight in the evidence, obtained from full-term newborns" that feeding with human milk in early life can fundamentally and permanently change an infant's biology (21). However, a systematic review by Güngör et al. (22) showed that when comparing shorter or longer durations of any form of human milk feeding with blood lipid profiles in childhood and adulthood, the evidence was inconclusive.

Regarding the correlation between the lipid profile and the anthropometric indices (z), several findings were observed. For

infants receiving FBF, there was a direct correlation between length/age, as an expression of growth, and TC, but it was not significant ($p = 0.096$). In the PBF group, there was a direct and significant correlation between the length/age index (z) and triglycerides ($r = 0.469$, $p = 0.001$). Trends were also observed between the weight/age index (z) and triglycerides, but it was not significant ($p = 0.085$). There was also a trend towards a direct relationship between the TSF, energy reserve indicator (z), and TC ($p = 0.091$) and a direct and significant correlation between the SSF indicator (z) and TC ($r = 0.340$, $p = 0.049$). Finally, in the group that received HMS, a direct and significant correlation was observed between the weight/age index (z) and TC ($r = 0.346$, $p = 0.045$) and between the length/age index (z) and LDL cholesterol ($r = 0.438$, $p = 0.010$).

These findings showed that during the first four months of postnatal life, significant correlations and direct and/or inverse trends between lipid profile indicators and the length/age index, the weight/age index, and adiposity indicators such as skin folds were present regardless of the type of feeding (although they were more prominent with PBF). We could consider these anthropometric indicators to be both growth indicators (since an infant increase 100 % of its weight in the first four months of postnatal life) and energy reserve indicators, essential substrates for growth.

Why were the correlations more significant in the PBF group? This is difficult to interpret. One explanation is that the classification system used (23) to identify this group seems to be imprecise. This classification divides breastfeeding into frequent breastfeeding > 80 %, intermediate 20-80 %, and infrequent < 80 %. With these criteria, it is difficult to determine the amount of human milk that an infant actually received, especially in the intermediate group. In this way, the anthropometric indicators of growth and adiposity, the serum concentration of lipids, and the appetite-regulating hormone concentrations would be influenced by the variability in this group, as previously observed (14,24).

STRENGTHS AND LIMITATIONS

The main strength of this study was its originality, since it explores the correlation of lipid profiles to appetite-regulating hormones and various indicators of growth and fat for three types of feeding (FBF, PBF, and HMS) in infants after the first four months of postnatal life. The main limitation of the study was that the number of cases was unequal between the groups, the FBF group had the most participants, and the HMS group had the fewest. Even though the total sample came from a cross section of a cohort from birth, for ethical reasons they could not be divided into groups with the same number of participants.

CONCLUSION

There were significant differences in the lipid profiles of infants at 16 weeks of postnatal life between the FBF, PBF, and HMS groups. The ghrelin concentration, therefore, appears to be sensitive to serum lipid concentrations. An inverse and significant

correlation was also observed between peptide YY and HDL cholesterol levels. These findings occurred in infants receiving HMS but not in infants receiving FBF.

In the PBF group, there was a direct and significant correlation between the length/age index (z) and triglycerides, and between the SSF indicator (z) and TC. In the group that received HMS, a direct and significant correlation was observed between the weight/age index (z) and TC and between the length/age index (z) and LDL cholesterol. These findings show that during the first semester of postnatal life, there is a strong correlation between growth, energy reserve, lipid profile, and modulation of appetite-regulating hormones. Longitudinal studies during the breastfeeding period are necessary to observe the strength of the correlations between the lipid profile with indicators of growth and body composition and between the lipid profile and appetite-regulating hormones.

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