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Circulating visfatin levels in healthy preterm infants are independently associated with high-density lipoprotein cholesterol levels and dietary long-chain polyunsaturated fatty acids

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Abstract

The adipokine visfatin has been proposed to exert insulin-mimicking effects and to play a role in the development of metabolic syndrome. Preterm infants are at risk for the later development of insulin resistance and, possibly, for other components of metabolic syndrome. Dietary long-chain polyunsaturated fatty acids (LCPUFAs) during the perinatal period may reduce the risk of metabolic syndrome. The authors' objective was to study the circulating concentrations of visfatin in preterm infants and to examine associations of visfatin with anthropometric measurements, metabolic indices, and dietary LCPUFAs. Serum visfatin concentrations were determined by enzyme-linked immunosorbent assay at mean (SD) 33.8 (11.7) days of life in 60 healthy preterm infants (gestational age, 32.7 [1.9] weeks) randomly assigned to be fed since birth either a formula containing LCPUFA (arachidonic and docosahexaenoic acid) (+LCPUFA group) or the same formula without LCPUFA (−LCPUFA group). Associations of visfatin with anthropometric parameters, serum glucose, insulin, homeostasis model assessment index of insulin resistance, blood lipids, and adiponectin levels were examined. Serum visfatin levels were significantly higher in the +LCPUFA than in the −LCPUFA group ($P < .001$) and correlated positively with body weight z score ($\beta = 0.31$, $P = .02$), total cholesterol ($\beta = 0.34$, $P = .01$), high-density lipoprotein cholesterol (HDL-C) ($\beta = 0.47$, $P < .001$), and adiponectin levels ($\beta = 0.29$, $P = .03$), but not with indices of insulin sensitivity. In multiple regression analysis, HDL-C and dietary LCPUFAs correlated independently with serum visfatin levels. Circulating visfatin levels in preterm infants are independently associated with HDL-C levels and dietary LCPUFAs. Whether the higher visfatin levels in the +LCPUFA preterm infant group are beneficial for the later health of these infants remains to be determined.

1. Introduction

Visfatin, also known as *pre–B-cell colony-enhancing factor* and as *nicotinamide phosphoribosyltransferase*, a cytokine predominantly produced in adipose tissue, has been identified (1) as a novel insulin-mimetic factor, (2) as an enzyme in the catalysis of the rate-limiting step in the production of nicotinamide adenine dinucleotide (NAD) from nicotinamide, and (3) as a regulatory factor in proinflammatory and immunomodulating processes [1,2]. Although there is controversy regarding the insulin-mimicking effects and the protective role of visfatin against the development of insulin resistance [1,3,4], several studies in human adolescents and adults have shown that circulating visfatin levels are associated with a beneficial lipid profile and increased high-density lipoprotein cholesterol (HDL-C) levels [5-8]. Interestingly, visfatin secretion and messenger RNA gene expression were significantly increased in primary cultured rat adipocytes after a 24-hour treatment with eicosapentaenoic acid, an n-3 long-chain polyunsaturated fatty acid (LCPUFA) [9]. Dietary n-3 LCPUFAs have been linked to beneficial effects against insulin resistance and to a favorable impact on lipidemic profile [10]. It is also worth noting that dietary LCPUFAs during the perinatal period may affect neonatal programming and reduce the risk of metabolic syndrome in later life [11,12].

Institutional approval: The Hospital Ethics Committee approved the study, and informed parental consent was also obtained.

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Preterm infants are at risk for the later development of insulin resistance and possibly other components of the metabolic syndrome [13,14]. To our knowledge, circulating visfatin levels have not been determined in preterm infants so far. Furthermore, we are not aware of studies examining the effects of dietary LCPUFAs on circulating visfatin levels in humans. In a previous randomized controlled study in preterm infants, we showed that feeding with a formula containing LCPUFAs (arachidonic and docosahexaenoic acid) had favorable effects on serum adiponectin levels and on lipidemic profile [15]. The present study aims to expand the previous study by evaluating the circulating visfatin concentrations in the same sample of preterm infants and to examine the associations of visfatin with anthropometric measurements, metabolic indices (serum lipid, glucose and insulin levels, homeostasis model assessment of insulin resistance [HOMA-IR]), adiponectin levels, and also with the supplementation of diet with LCPUFA.

2. Methods

2.1. Study population

The study population consisted of 60 preterm infants (28 girls and 32 boys) who were randomly assigned to be fed since birth either a commercial formula containing LCPUFAs (arachidonic acid, 12.0 mg and docosahexaenoic acid, 7.1 mg per 100 mL of formula) (+LCPUFA group, n = 30) or a formula without LCPUFAs (−LCPUFA group, n = 30). The 2 formulas were produced by the same manufacturer (S-26; Wyeth Nutritionals, Askeaton, Ireland), and their nutrient composition was identical apart from the LCPUFAs. Criteria for inclusion in the study were as follows: gestational age of at least 28 weeks, birth weight greater than 1000 g, no family history of hyper- or hypolipidemias, no congenital malformation, and mothers who elected formula feeding. Gestational age was estimated from the last menstrual period and confirmed by fetal ultrasound measurements and clinical examination of the neonate according to the new Ballard score [16]. In addition, to avoid a confounding effect of neonatal morbidity on outcome measures, only infants who did not present major neonatal morbidity (respiratory distress requiring assisted ventilation for more than 3 days, hypotension with need for inotropes, intraventricular hemorrhage greater than grade I according to the criteria of Volpe [17], sepsis, necrotizing enterocolitis, chronic lung disease) and who also tolerated full enteral feeding (≥150 mL/[kg d]) until the 10th day of life were included in the study. The amount of formula consumed at each meal was recorded, and the infants' growth (body weight and length, head circumference) was evaluated periodically during hospitalization. Body mass index (BMI) and body weight *z* score (SD scores from the mean after adjustment for gestational age and sex) [18] were assessed at discharge.

The protocol of randomization of the infants, the formula composition, and the assessment of the infants' growth were described in detail previously [15]. Venous samples were drawn from all infants, before feeding, on the morning of the day of discharge for determining serum visfatin, adiponectin, glucose, insulin, and lipid (triglycerides, total cholesterol [total-C], HDL-C, and low-density lipoprotein cholesterol [LDL-C]) levels. Serum was separated after centrifugation and stored at −80°C until further analyses. The HOMA-IR index was calculated as fasting glucose (in millimoles per liter) times fasting insulin (in milli-international units per liter) divided by 22.5 [19]. Demographic characteristics, growth measurements, and serum adiponectin and lipids levels of preterm infants were reported previously [15] and are summarized in Table 1. According to a previous report on circulating visfatin concentrations in full-term neonates [20], it was estimated that a sample size of 30 infants in each group would be sufficient to detect a significant difference of 1 SD in mean visfatin levels between +LCPUFA and −LCPUFA groups assuming an α risk of 0.01, a power of 0.80, and a bilateral test.

The Hospital Ethics Committee approved the study, and informed parental consent was also obtained.

2.2. Assays

Serum visfatin levels were measured using a commercial enzyme immunoassay kit (Visfatin C-Terminal [Human]

Table 1
Demographic characteristics, growth measurements, and serum adiponectin and lipid levels of the 2 infant groups

	+LCPUFA (n = 30)	−LCPUFA (n = 30)
At baseline and during hospitalization		
Girls/boys, n	14/16	14/16
Gestational age, wk	32.7 (1.7)	32.7 (2.0)
Birth weight, g	1634 (285)	1652 (251)
Birth weight *z* score	−1.2 (0.7)	−1.1 (0.7)
Age at full enteral feeding, d	7.5 (1.9)	7.8 (2.0)
Caloric intake, cal/(kg d) (last study week)	154.1 (16.7)	155.4 (20.7)
Weight gain, g/(kg d)		
Entire study period	8.3 (1.6)	7.9 (3.2)
Last week of study	16.7 (3.2)	15.6 (4.5)
At the end of intervention		
Postnatal age at testing, d	32.1 (11.6)	35.6 (11.8)
Anthropometric measurements		
Body weight, g	2281 (165)	2248 (163)
Body weight *z* score	−1.9 (0.5)	−2.0 (0.4)
Body length, cm	46.8 (1.2)	46.9 (0.8)
BMI (kg/m^2)	10.3 (0.2)	10.2 (0.3)
Head circumference, cm	33.1 (1.3)	33.2 (0.9)
Adiponectin, mg/L	55.2 (25.8)*	36.7 (18.4)
Triglycerides, mg/dL	110.6 (38.6)†	133.9 (56.1)
Total-C, mg/dL	101.5 (13.9)	95.9 (19.0)
HDL-C, mg/dL	42.5 (10.1)‡	36.0 (9.6)
LDL-C, mg/dL	36.8 (9.3)	33.1 (12.8)

Values represent the mean (SD), except from sex.
* $P = .002$, in comparison with the −LCPUFA group.
† $P = .06$, in comparison with the −LCPUFA group.
‡ $P = .01$, in comparison with the −LCPUFA group.

EIA; Phoenix Pharmaceuticals, Belmont, CA) according to manufacturer's instructions. The intra- and interassay coefficients of variation (CVs) were 5% and 12%, respectively. The sensitivity limit was 0.1 ng/mL.

Serum adiponectin and lipids concentrations were measured as described previously [15]. Briefly, adiponectin levels were assayed using a human adiponectin enzyme-linked immunosorbent assay kit (Linco Research, St. Charles, MO), whereas triglycerides, total-C, and HDL-C levels were measured using the Bayer ADVIA 1650 Clinical Chemistry System (Bayer, Tarrytown, NY). The LDL-C values were estimated using the Friedewald formula, as follows: LDL-C = total-C − (triglycerides/5 + HDL-C).

Determination of serum insulin concentrations was performed by an electrochemiluminescence immunoassay using the automated analyzer Cobas e 411 (Roche Diagnostics, Mannheim, Germany). The intra- and interassay CVs did not exceed 2.0% and 2.8%, respectively; the sensitivity limit was 0.2 mIU/L. Serum glucose was assessed by an enzymatic glucose oxidase method, and the determination was performed using the Siemens ADVIA 1800 Clinical Chemistry System (Siemens Healthcare Diagnostics, Erlangen, Germany). The intra- and interassay CVs were less than 0.9% and 1.5%, respectively; and the sensitivity limit was less than 0.001 mmol/L.

2.3. Statistical analyses

Data are presented as mean (SD), apart from insulin and HOMA-IR values that were expressed as median (25th-75th percentiles) because their distribution was not normal. Groups were compared for quantitative variables by the Student *t* or Mann-Whitney *U* test, as appropriate. Univariate and multiple regression analyses were used to examine relations among the variables of interest. Values of visfatin were normally distributed (Kolmogorov-Smirnov test). Levels of statistical significance were set at $P < .05$. All statistical analyses were performed using the SPSS statistical package (version 10.0; SPSS, Chicago, IL).

3. Results

Serum visfatin, glucose, and insulin concentrations, as well as HOMA-IR values, in the 2 groups and the entire population of preterm infants are shown in Table 2. Mean (SD) serum visfatin levels were significantly higher in the +LCPUFA group than in the −LCPUFA group ($P < .001$). No significant correlation was found between visfatin levels and gestational age, sex, birth weight, body weight and length or BMI at testing, weight gain, glucose, insulin, HOMA-IR values, triglycerides, and LDL-C levels both in the entire population of preterm infants and in the +LCPUFA and −LCPUFA groups separately.

In the total study population, serum visfatin concentrations correlated positively with body weight *z* score (β = 0.31, $P = .02$), total-C ($\beta = 0.34$, $P = .01$), HDL-C ($\beta = 0.47$, $P < .001$) (Fig. 1), and adiponectin levels ($\beta = 0.29$, $P = .03$) by univariate regression analysis. The significant correlation between serum visfatin and HDL-C levels in the entire study population was entirely driven by the +LCPUFA group, whereas no significant correlation was found between visfatin and HDL-C levels in the −LCPUFA group (Fig. 1). Visfatin levels also correlated significantly with total-C concentrations in the +LCPUFA group ($\beta = 0.58$, $P = .002$) but not in the −LCPUFA group ($P = .46$), whereas they did not correlate significantly with weight *z* score or adiponectin levels in either the +LCPUFA or −LCPUFA group separately.

As expected, the correlations between visfatin and body weight *z* score values, as well as between visfatin and adiponectin levels, did not remain significant after adjustment for the type of feeding. On multiple regression analysis modeling with gestational age, sex, body weight *z* score, total-C, HDL-C, adiponectin, HOMA-IR values, and the type of feeding entered into the model, only HDL-C and

Table 2
Serum glucose, insulin, HOMA-IR, and visfatin values in preterm infants studied

	Total population (N = 60)	+LCPUFA (n = 30)	−LCPUFA (n = 30)	*P* value[a]
Glucose, mmol/L	4.1 (0.6)	4.3 (0.6)	4.0 (0.6)	.10
Insulin, mIU/L	3.0 (1.7-6.6)	4.0 (1.8-7.9)	2.6 (1.9-6.0)	.59
HOMA-IR	0.6 (0.3-1.4)	0.7 (0.3-1.6)	0.5 (0.3-1.1)	.55
Visfatin, ng/mL	8.6 (4.0)	10.6 (4.7)	6.7 (1.7)	<.001

The data represent the mean (SD) except for insulin and HOMA-IR values expressed as median (25th-75th percentiles).

[a] *P* value for comparison between the +LCPUFA and the −LCPUFA group.

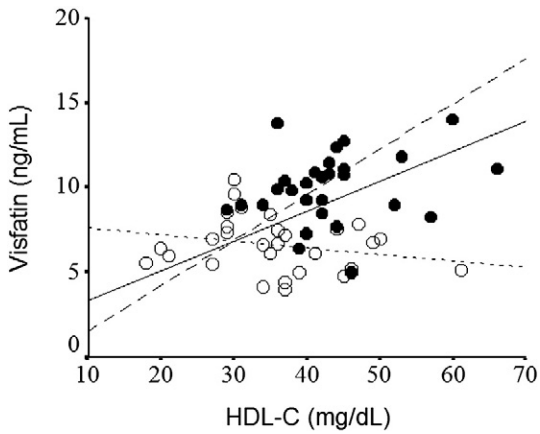

Fig. 1. Correlations between serum visfatin and HDL-C levels. ●, preterm infants fed the LCPUFA-supplemented formula (+LCPUFA group); ○, preterm infants fed the LCPUFA-free formula (−LCPUFA group). The lines represent the regression slope separately for the +LCPUFA group (— — —; $\beta = 0.59$, $P = .001$) and the −LCPUFA group (- - - - - -; $\beta = -0.20$, $P = .31$) and for the entire study population (——; $\beta = 0.47$, $P < .001$).

Table 3
Multiple regression analysis showing factors independently associated with serum visfatin levels in preterm infants studied

Independent variables	β	t	P value
Gestational age	−0.06	−0.35	.72
Sex	0.23	1.42	.17
Body weight z score	0.03	0.16	.87
Total-C	−0.08	−0.38	.70
HDL-C	0.58	2.17	.03
Adiponectin	−0.22	−1.06	.29
HOMA-IR	0.12	0.84	.40
Dietary LCPUFA	0.36	2.34	.02

β, standardized regression coefficient; R^2 (%) = 44.0, P = .01; dependent variable: visfatin levels.

feeding with the +LCPUFA formula correlated independently with serum visfatin levels (Table 3).

4. Discussion

To our knowledge, this study is the first to determine circulating visfatin concentrations in preterm infants; and it is also novel in evaluating whether dietary LCPUFAs have any effect on circulating visfatin levels in humans. Serum visfatin levels in our study population were lower than levels reported previously in full-term infants [20,21], adolescents [6], and adults [22] probably because of the lower amount of adipose tissue in preterm infants. Adipocytes are potential, although not unique [23], sources of visfatin production/release [24]; and the synthesis of visfatin messenger RNA is further induced—more than 3-fold increase—during adipogenesis [24]. This fact possibly explains the positive correlation between visfatin concentrations and body weight score values in our study population because body weight accounts for almost 80% of the variance of fat mass in neonates as assessed by dual-energy x-ray absorptiometry [25]. A positive correlation between serum visfatin levels and body weight customized (adjusted) centiles has also been reported in full-term newborns on days 1 and 4 of life [26]. In addition, an adipogenetic effect of visfatin has previously been shown [1]. Whether visfatin has a role in fetal and/or neonatal growth, similar to that proposed for other adipocytokines such as leptin and adiponectin [27,28], needs to be further explored.

The positive association between visfatin and adiponectin has been previously reported, although not consistently [1,29-31]. As regards the association between visfatin and HDL-C, circulating visfatin levels were identified as an indicator of beneficial lipid profile in nondiabetic white adults and correlated positively with HDL-C and negatively with triglycerides independently of adiposity and insulin resistance [5]. Positive correlations between visfatin and HDL-C have also been shown in other studies in adolescents [6] and adults [7,8] and have been attributed to the enzymatic function of visfatin in NAD biosynthesis. Visfatin salvages the nicotinamide that is formed during NAD metabolism to replenish the cellular NAD level [5,32]; oral administration of nicotinamide significantly increases cellular NAD and serum HDL-C levels [33].

The n-3 LCPUFAs are possibly common modulators for the production of both adiponectin and HDL-C, possibly through activation of transcription factors and nuclear receptors such as the peroxisome proliferator activated receptor−γ in the liver and the adipose tissue [10]. Moreover, n-3 LCPUFAs were shown to stimulate the production of visfatin in vitro [9], whereas recently, in vivo, in human volunteers, a 3-week treatment with rosiglitazone—a peroxisome proliferator activated receptor−γ agonist—increased the mean circulating visfatin concentrations by 283% [34]. In our study population, serum visfatin levels were significantly higher in the +LCPUFA than in the −LCPUFA group of preterm infants; and dietary LCPUFAs were recognized as an independent predictor of serum visfatin concentrations. Whether this association reflects an influence of only n-3 or both n-3 and n-6 LCPUFAs is not known, as the role of n-6 LCPUFAs on visfatin production has not been studied so far. Aside from dietary LCPUFAs, HDL-C but not adiponectin correlated independently with serum visfatin levels in multiple regression analysis. The finding that HDL-C correlated significantly with visfatin levels only in the +LCPUFA, but not in the −LCPUFA, group of infants might be suggestive of a synergic effect of LCPUFAs and visfatin on HDL-C levels.

Studies investigating the association between visfatin and indices of insulin resistance have yielded conflicting results. In several trials, no significant correlations between visfatin and insulin or glucose levels were found [7,20,22,35], in accordance with the results of the present study. However, in other studies, visfatin levels correlated significantly with insulin levels and insulin sensitivity [36,37]. Furthermore, in a recent study, hypervisfatinemia after the injection of pcDNA3.1-visfatin plasmid in rats led to enhanced whole-body insulin sensitivity as determined by euglycemic-hyperinsulinemic clamps [38]. It has also been shown that visfatin exhibits important autocrine effects on sensitivity of liver cells to insulin action possibly through its effects on NAD biosynthesis [39]. Differences in study populations and methodology applied might have contributed to the conflicting results of relevant studies [1,3,40]. Follow-up of our study population may be helpful to determine whether the higher visfatin levels in the +LCPUFA preterm infant group and their positive association with HDL-C are beneficial for the later health of these infants by exerting a protective effect against the development of insulin resistance and metabolic syndrome. The precise role of visfatin in preterm infants needs to be further explored.

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