Chemerin concentrations in SGA infants: correlations with triglycerides and parameters related to glucose homeostasis

A Léniz[1,2]; A Fernández-Quintela[1,3]; M del Hoyo[4]; I Díez-López[4]; MP Portillo[1,3]

[1]*Nutrition and Obesity Group. Department of Nutrition and Food Science, University of the Basque Country (UPV/EHU) and Lucio Lascaray Research Institute, Vitoria, Spain*

[2] *Araba Integrated Health Care Organization. Basque Health Service (Osakidetza).*

[3]*CIBERobn Physiopathology of Obesity and Nutrition, Institute of Health Carlos III, Spain*

[4]*Pediatric Endocrinology Unit, HU Araba Vitoria. Department of Pediatric University of the Basque Country (UPV/EHU)*

Corresponding author: Dr. Alfredo Fernández-Quintela, Dpt. Nutrición y Bromatología, Facultad de Farmacia, Paseo de la Universidad 7, 01006 Vitoria (España). Phone: +34-945-013066, fax: +34-945-013014, e-mail: alfredo.fernandez@ehu.eus

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Abstract:

Infants born small for gestational age (SGA) are known to have increased risk of developing several pathologies, including the metabolic syndrome, when they grow up. It has been described that both the growth pattern of these children as well as the risk of their presenting future metabolic disorders can be influenced by the expression of adipokines. Among them, chemerin has demonstrated to be implicated in lipid and glucose metabolism, presenting higher circulating concentration in diabetic and obese subjects. Thus, the aim of this study was to analyze the association of anthropometric parameters and plasmatic biochemical parameters with circulating chemerin concentration in SGA children. This prospective, longitudinal study was carried out in plasma samples of Caucasian children born SGA at Hospital Universitario de Álava-Txagorritxu. Significant positive correlations were observed between chemerin concentrations at 3 months and insulin values at 3 months and also with triglyceride levels at 24 months. These associations were maintained after adjustment by auxological parameters. Therefore, we suggest that circulating chemerin concentration, measured at an early age, might be an indicator of future metabolic alterations in SGA children.

Keywords: SGA; chemerin; glucose homeostasis; triglycerides, biochemical parameters

Introduction

Being born small for gestational age (SGA) can be due to several maternal, fetal and environmental factors like chronic diseases, exposition to environmental toxics (e.g., smoking and alcohol consumption), infections or an inadequate mother nutrition [7, 22, 30]. Usually, the catch-up occurs between 6 and 24 months, and about 85% of SGA children reach normal weight at 24 months [20]. It is well known that SGA infants can develop persistent short stature, perinatal morbidity, and metabolic alterations, such as type 2 diabetes, dyslipidemia, insulin-resistance, obesity or arterial hypertension, in adulthood [30, 31].

The level of circulating cytokines has been shown to be a key factor related to the prognosis of catch-up growth consequences [1]. These proteins, produced by several tissues and organs (adipokines secreted by white adipose tissue, mainly by visceral depots, myokines secreted by skeletal muscle and hepatokines secreted by liver) play important roles in metabolism. In addition, several cytokines act over the central nervous system, influencing subject adaptation and modifying energy resource management during the first years of life.

Chemerin, initially discovered in 2003, and also known as retinoic acid receptor responder protein 2, tazarotene-induced gene 2 protein, or RAR-responsive protein, is produced by white adipose tissue, liver, kidney, skin and intestine [17]. It acts through the binding receptors chemerin chemokine-like receptor 1, the chemerin receptor 23 (chem23) and CC-motif receptor-like 2 [32, 37, 39]. This protein plays a clear role in adipocyte metabolic pathways, such as adipogenesis, adipocyte differentiation triglyceride synthesis and lipolysis [25]. Moreover, it is involved in glucose homeostasis by acting on glucose transporter 4 (GLUT4) and adiponectin and leptin production [16, 19]. In humans chemerin has been associated with several components of metabolic

syndrome, such as serum triglycerides, total cholesterol and insulin resistance [5, 6, 33]. Moreover, several studies have shown higher chemerin concentrations in patients with type 2 diabetes mellitus (T2DM) [35, 38] and in obese subjects [11, 29].

Due to the fact that studies devoted to analyzing chemerin in children are scarce in the literature, the aim of the present study was to analyze for the first time the association in SGA infants between chemerin circulating concentration and plasma biochemical parameters on one hand and anthropometric parameters on the other hand.

Materials and Methods

Subjects

This prospective longitudinal study was conducted with twenty-seven SGA Caucasian children born in Hospital Universitario de Álava-Txagorritxu (HUA), over the period of June 2013 to March 2015. SGA condition was assessed as infants with birth and/or length below 2 standard deviations (SD) of the Spanish standard birth weight/length curves [9]. Births from multiple pregnancies, non-Caucasian children and subjects with evidence of malformations or endocrine malfunction were excluded from the study. A normal course of the pregnancy was confirmed by the enrolled mothers, as well as by the absence of drug administration or complications during pregnancy.

Newborn length ranged from 37 to 53 cm, weight from 1100 to 2660 grams and gestational age, established by dating the last menstrual period at the time of registration, from 33 to 41 weeks. All parents signed a written informed consent, and the protocol was approved by the Hospital Universitario de Álava (HUA) Ethical Committee (Ref. 2012-050).

Anthropometric parameters

Body weight was measured using an electronic scale at birth, 3 months and 24 months. The crown-to-heel length was determined with an infantometer or a stadiometer. Head circumference was assessed at the temporal level, waist circumference mid-way between the lower side of the last rib and the upper side of the pelvis, and arm circumference at the middle of the upper arm. All circumferences were measured to the closest millimeter and over bare skin.

Blood collection and chemerin assay

Blood samples were obtained using EDTA tubes at 3 and 24 months of age after 5h fasting. Blood was centrifuged at 1250 g for 20 minutes, and the plasma obtained was stored at -70ºC until analysis. The levels of glucose, insulin, total cholesterol, LDL-c, high density lipoprotein cholesterol (HDL-c), TG, IGF-1, IGF-BP3, cortisol, CRP, TSH and T4 in plasma were measured using an automated Roche Autoanalyser system (Roche Diagnostics GmbH, Mannheim, Germany). Sensitive and specific enzyme-linked inmunoassay was used to determine chemerin concentration in plasma samples. The ELISA kit was obtained from Abcam (ab155430; Cambridge, UK) and the measurements performed with a Labsystems iEMS Reader MF analyzer plate photometer (Labsystems Diagnostics Oy, Helsinki, Finland).

The Homeostasis model assessment (HOMA-IR) was used to evaluate insulin sensitivity. Calculations of insulin sensitivity by the HOMA-IR technique were performed by the approximated equation of Mathews *et al.* (1985) based on fasting glucose and insulin levels [18].

Statistical analysis

Data are presented as mean values (SD). The statistical analyses were performed using IBM SPSS statistics v25 (SPSS, Chicago, IL, USA). Normality of the data was

tested using Saphiro-Wilks W test, and logarithmical transformation was performed in non-normally distributed parameters for multivariate analysis. Differences in two paired samples were elucidated with a paired Student's *t* test or a Wilcoxon signed ranks test, and comparisons between unrelated variables were conducted with a Student's *t* test or a Mann-Whitney's U test, where appropriate. Correlation between variables was assessed using either Pearson or Spearman`s rank tests as appropriate. Multivariate linear regression analyses were used to adjust the effects of covariates and to identify independent relationships. Statistical significance was set-up at *P* value of <0.05.

Results

Study population profile

Table 1 shows demographic and anthropometric parameters at birth. Figures 1A and 1B show body weight and body length at 3 and 24 months.

Table 1. Anthropometric parameters and demographic data of study population

	Mean	Standard Deviation
Gender (male/female)	14/13	
Gestational age (weeks)	36.75	2.75
Birth weight (g)	1958.00	492.20
Birth length (cm)	44.04	3.99
Weight at 3 months (kg)	4.81	0.64
Length at 3 months (cm)	55.95	2.56
Weight at 24 months (kg)	10.54	0.72
Length at 24 months (cm)	84.56	2.39
⊿BMI	-0.59	0.51
Head circumference (cm)	31.06	2.15
Brachial perimeter (cm)	34.00	3.10
Abdominal perimeter (cm)	10.85	1.13
Maternal age (years)	34.48	3.82
Mother's BMI	24.59	5.63
Breastfeeding (yes/no)	13/14	

Comentado [ALR1]: Esto lo pusimos porque nos lo pidió el referee (el tema del adiposity rebound). Valorar ponerlo o no en este paper

Comentado [ALR2]: Tanto esto como el género, no son una media

BMI, body mass index

Plasma biochemical parmeters

Plasma biochemical parameters at 3 and 24 months are shown in Table 2. At 3 months, children presented higher values of glucose, triglycerides (TG), thyroid-stimulating hormone (TSH), thyroxine (T4) and C reactive protein (CRP), and lower values of low density lipoprotein cholesterol (LDL-c), insulin-like growth factor 1 (IGF-1) and insulin-like growth factor 1 (IGF-BP3) than at 24 months. No significant differences were observed in the remaining parameters. Circulating chemerin concentrations were not significantly different at 3 and 24 months. These data were reported in a previous study from our group [36], but they have been included again in this study as necessary.

Table 2. Differences in plasma biochemical parameters between 3 and 24 months

	3 months (n=27)	**24 months** (n=18)
Glucose (mg/dL)	85.04(7.87) **	79.70(6.99)
Insulin (μU/mL)	4.66(2.74)	6.28(7.98)
HOMA-IR	1.04(0.75)	1.23(1.52)
Cholesterol (mg/dL)	147.07(37.37)	157.83(39.24)
LDL-c (mg/dL)	73.64(26.67) **	103.95(29.33)
HDL-c (mg/dL)	50.06(20.51)	46.11(12.59)
TG (mg/dL)	116.86(65.53) *	58.31(23.46)
IGF-1 (ng/mL)	42.22(15.20) *	67.94(39.16)
IGF-BP_3 (μg/dL)	2.06(0.42) **	2.77(0.70)
Cortisol (μg/dL)	9.59(5.65)	12.22(2.74)
CRP (mg/dL)	1.52(3.14) *	1.29(1.96)
TSH (μU/mL)	3.44(1.68) **	2.47(1.03)
T_4 (ng/dL)	1.20(0.21) *	1.03(0.10)

Mann-Whitney`s U/ Student's *t* test used according to the distribution.
* P <0.05; ** P <0.01

Correlations

144 Correlations between chemerin concentration and biochemical and anthropometric
145 parameters are shown in Figure 2. Positive significant correlations were found between
146 chemerin, measured at 3 months, and TG (r=0.43), insulin (r=0.45), glucose (r=0.40), and
147 consequently HOMA-IR values (r=0.44) at 3 months. Also, chemerin at 3 months was
148 positively correlated to TG at 24 months (r=0.48). No significant correlations were
149 observed between chemerin and other biochemical parameters or anthropometric
150 parameters.

151 ***Multiple linear regression analysis***

152 Multiple linear regression analysis between chemerin at 3 months and biochemical
153 parameters at the same age, as dependent variables, showed that the association between
154 chemerin and insulin was maintained after adjustment for weight and length at birth and
155 gestational age (R-square=0.08; P= 0.046) (Table 3). By contrast, the associations with
156 glucose, HOMA-IR and TG were lost. In the case of TG at 24 months, the association
157 persisted after adjustment for weight and length at birth and 24 months and gestational
158 age (P=0.031), and the coefficient of determination (R-square) values was 0.28 (Table 4).

159

160 **Table 3**. Multiple linear regression analyzes between triglyceride concentration and
161 chemerin concentration in plasma, adjusting by auxological parameters.

Triglyceride concentration at 24 months as dependent variable	**Standardized coefficient (β)**	**P value**
Chemerin at 3 months	0.584	0.031
Gestational age	-0.543	0.487
Weight at birth	1.076	0.283

Height at birth	-0.638	0.282
Weight at 24 months	0.200	0.470
Height at 24 months	-0.302	0.341

Table 4. Multiple linear regression analysis between triglyceride concentration at 24 months of age and chemerin concentration at 3 months of age, adjusting by auxological parameters.

Triglyceride concentration at 24 months as dependent variable	**Standardized coefficient (β)**	**P value**
Chemerin at 3 months	0.584	0.031
Gestational age	-0.543	0.487
Weight at birth	1.076	0.283
Height at birth	-0.638	0.282
Weight at 24 months	0.200	0.470
Height at 24 months	-0.302	0.341

Discussion

As indicated in the Introduction section, it has been widely described that SGA infants can develop alterations involved in the development of metabolic syndrome, such as visceral obesity, insulin-resistance, high concentrations of LDL-cholesterol and TG or

arterial hypertension, in adulthood. This fact was first described by Barker *et al.* (1992) and further confirmed by other studies [21, 31, 36]. By contrast, data concerning the potential metabolic alterations, and the evolution of biochemical parameters involved in metabolic syndrome, during the catch-up period are scarcer. Moreover, in some cases controversial results have been reported.

A meta-analysis published by Owen *et al.*, (2003) showed a significant inverse association between total cholesterol and birth weight [27]. De Jong *et al*. (2015) observed high prevalence of high TG levels at 1 year of age in SGA and very-low-birth-weight (VLBW) infants, compared to appropriate for gestational age (AGA) children [14]. Moreover, at 2 years of age VLBW children showed higher glucose levels than AGA children. However, no significant differences in insulin levels and HOMA-IR values were observed among groups. In other studies, Dominguez-Hernández *et al.*, (2016) found that total cholesterol and LDL-cholesterol levels were not significantly different between obese SGA and obese non-SGA children and Castanis-Muñoz *et al.*, (2017) reported no association between postnatal growth and lipid levels [10, 15].

In the present study, we evaluated biochemical parameters very soon after birth (3 months) and at the end of the catch-up period (24 months). By comparing data at these two ages, it can be observed that whereas some parameters remained unchanged, others were modified. Focusing on lipids and parameters related to glucose homeostasis, we observed that insulin, HOMA-IR, total cholesterol and HDL-cholesterol remained unchanged, glucose and TG were significantly reduced, and LDL-cholesterol was significantly increased at 24 months of age.

This study was limited by the absence of a control group (AGA infants) and consequently, the cut-off values were based on studies in other populations and on

196 reference values for Spanish children [13, 28]. According to these data, all values in the
197 present study, either at 3 or at 24 months, were in the range of physiological values for
198 healthy children. This means that the significant differences observed between these two
199 ages lack pathological consequences. Importantly however, this fact demonstrates that
200 SGA children showed a healthy biochemical profile in spite of the alterations in weight
201 and/or length during the catch-up period (24 months).

202 In a previous study carried out in this precise cohort of SGA children, we measured
203 serum concentrations of several adipokines [23]. In the present study we hoped to gain
204 more insight concerning chemerin because it has been reported that this protein plays an
205 important role in TG metabolism and glucose homeostasis, which in turn are closely
206 related to metabolic syndrome. For this purpose we analyzed correlations between
207 chemerin and biochemical parameters.

208 Several studies have reported significant correlations between chemerin and
209 parameters related to glycemic control, such as serum glucose, HbA1c and insulin
210 concentrations, and HOMA-IR values in different cohorts. Bobbert *et al.* (2015) carried
211 out a study in 440 adult subjects of both sexes with no baseline diabetes and a mean age
212 of 60 years, devoted to analyzing whether chemerin predicted type 2 diabetes mellitus
213 (T2DM) in adult population. They observed that peripheral chemerin was significantly
214 correlated to fasting glucose and HbA1c [3]. In view of these results, the authors proposed
215 chemerin as a potential indicator of T2DM. In the same way, Bozaoglu *et al.* (2009)
216 showed a positive correlation between this adipokine and fasting glucose, insulin and
217 HOMA-IR in non-diabetic adult subjects, in a sample of 969 subjects with a mean age of
218 36 years [6]. Similarly, in a pediatric population Sledzińska *et al.* (2017) found that
219 chemerin was associated with circulating insulin and HOMA-IR values in 5-17-year-old
220 children with normal or excess body weight [34].

The results obtained in the present study are in good accordance with those reported in adults and children, because we observed a positive correlation between chemerin and serum glucose and insulin concentrations, as well as HOMA-IR values, at 3 months of age. As far as we know, this is the first time that this correlation has been evidenced in SGA infants at that early age. The studies reported addressing SGA infants have only analyzed these parameters in cord blood. Our study demonstrates that the relationship between chemerin and parameters related to glucose homeostasis observed in adults and children also exist in SGA infants. Nevertheless, it should be emphasized that, in the case of glucose and HOMA-IR, the significance of these correlations disappears when adjustments are made for height, length and gestational age in the multiple regression analysis.

Regarding TG concentrations, as in the case of glucose homeostasis-related parameters, several studies have reported significant correlations with chemerin in different cohorts. Cheon *et al.* (2017) observed a strong correlation between circulating chemerin and TG in obese adults showing T2DM [12]. This correlation was also present in adult population with other diseases, such as atrial fibrillation, chronic obstructive pulmonary disease or non-alcoholic fatty liver disease among others [4, 26, 40]. In children and adolescents, the correlation was also found in obese and non-obese subjects, confirming the relation of the chemerin with lipid metabolism in different cohorts [2, 24].

In the present study, a positive correlation was found between serum chemerin and TG at 3 months. These results show that the association between these two parameters observed in adult population and children also is present in SGA infants at an early age. It is important to point out that in the above mentioned reported studies, correlations between chemerin and biochemical parameters were carried out by using data obtained at the same time, as is the case in the present study when we analyzed correlations between

chemerin and biochemical parameters obtained at 3 months of age. But, in addition to that, we analyzed the correlations between chemerin at 3 months and biochemical parameters at 24 months. In this case we found that chemerin was significantly correlated to TG, and this correlation was maintained after adjustments in multiple regression analysis. This is an important result because it means that this adipokine could be proposed as a biomarker of prognosis for serum TG. Nevertheless, further studies are needed to give support and stronger scientific evidence to this hypothesis based on limited results.

In order to better assess the conclusions of the present study, its strengths and limitations should be declared. One strength is that the study has been performed in infant peripheral blood, extracted by venopunction at 3 months, while the vast majority of the studies carried out in SGA children used cord blood. Among the limitations, the small sample size should be mentioned. This is due to the small percentage of infants born SGA in Txagorritxu Hospital, where the study was conducted, and the difficulty in obtaining their progenitors' informed consent to extract blood samples at 3 months of age for no other reason than research. Another important limitation is the lack of an AGA infant group. Finally, we analyzed total chemerin, but it has been described that isoforms of this adipokine have different activities as well as different distribution and concentration in tissues [8].

Compliance with Ethical Standards

- Parents of all subjects have given their written consent informed consent to take part in the study
- The study protocol has been approved by the Ethical Committee of the Hospital Universitario de Álava-Txagorritxu (HUA) (Ref. 2012-050)
- The authors have no conflicts of interest to declare

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Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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