



# Has the adipokine profile an influence on the catch-up growth type in small for gestational age infants?

A. Léniz<sup>1,2</sup> · M. P. Portillo<sup>1,3,4</sup> · Alfredo Fernández-Quintela<sup>1,3,4</sup> · M. T. Macarulla<sup>1,3,4</sup> · A. Sarasua-Miranda<sup>5</sup> · M. del Hoyo<sup>5</sup> · I. Díez-López<sup>5</sup>

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## Abstract

Infants born small for gestational age (SGA) are at increased risk of perinatal morbidity, persistent short stature, and metabolic alterations in later life. Moreover, the post-natal growth pattern of SGA infants may be an important contributor to health outcomes later in life, which can be influenced by adipokines. The aims of this study were to compare plasma adipokine profiles (leptin, adiponectin, vaspin, chemerin, and nephroblastoma overexpressed (NOV/CCN3)) among SGA newborns aged 3 months, with low, normal, or high catch-up, to search for potential differences between males and females and to analyze the evolution of several adipokines in plasma from SGA newborns between 3 and 24 months. This prospective, longitudinal study was addressed in SGA Caucasian subjects at Hospital Universitario de Álava-Txagorritxu. We observed that infants with fast catch-up showed significantly lower birth weight than the other two groups. As far as adipokines are concerned, they could have an influence on catch-up type because differences among the three experimental groups were found. It may be proposed that health prognoses in infants with slow and fast catch-up are opposite, not only in adulthood but also during their first months. Finally, adipokine evolution patterns during the first 24 months of age differ, depending on the adipokine, and 24-month-old males show lower levels of leptin, adiponectin, and omentin than females.

**Keywords** SGA · Catch-up · Leptin · Adiponectin · Omentin · Chemerin · Vaspin · NOV/CCN3

## Introduction

Small for gestational age (SGA) status is characterized by a small birth length and/or birth weight with respect to reference curves, and can be induced by a wide variety of factors, such as

poor nutrition, chronic disease, and infections, as well as potential environmental toxins (e.g., smoking and alcohol consumption) in the mother [12, 34, 46]. SGA infants are at an increased risk of perinatal morbidity, persistent short stature, and metabolic alterations, such as dyslipidemia, type 2 diabetes, insulin resistance, obesity, or arterial hypertension in adulthood [46, 47]. Usually, from 6 months to 24 months after birth, catch-up growth occurs in a spontaneous way and 85% of SGA children have reached normal weight by the age of 24 months [27]. Although metabolic syndrome could be developed even with catch-up growth, improvements in the immune system and neurodevelopment, as well as normal adult height, have been demonstrated in this situation [36, 38, 47].

A key factor that has been shown to have a direct relationship with catch-up growth in SGA children is the level of circulating adipokines. These molecules are defined as cell signaling proteins secreted by adipose tissue, which nowadays are known to have a clear endocrine function [1]. They act on several regulation processes, such as bone formation, immune system, or overall metabolism. Interestingly, some adipokines act like a signal to the central nervous system, contributing to subject adaptation in

✉ Alfredo Fernández-Quintela  
alfredo.fernandez@ehu.eus

<sup>1</sup> Nutrition and Obesity Group, University of the Basque Country (UPV/EHU) and Lucio Lascaray Research Institute, Vitoria, Spain

<sup>2</sup> Araba Integrated Health Care Organization, Basque Health Service (Osakidetza), Vitoria, Spain

<sup>3</sup> CIBERobn Physiopathology of Obesity and Nutrition, Institute of Health Carlos III, Vitoria, Spain

<sup>4</sup> Department Nutrition and Food Sciences, University of the Basque Country, Paseo de la Universidad, 7, 01006, Vitoria, Spain

<sup>5</sup> Pediatric Endocrinology Unit, HU Araba Vitoria. Department of Pediatric, University of the Basque Country (UPV/EHU), Leioa, Spain

the first years of life through modification of energy resource management. All these changes are shown to be strongly associated with the length and weight, thus acting on the catch-up of the newborn [10].

One of the most frequently studied adipokines is leptin, which is associated with hepatic insulin sensitivity, through its role in energy homeostasis, as well as acting in tissues such as liver or pancreatic cells [33]. Another well-known adipokine is adiponectin, which is downregulated in obese subjects, being inversely correlated with body mass index (BMI) [2]. It plays an important role in glucose homeostasis [19]. Regarding the SGA population, studies in pre-pubertal children have shown that low adiponectin serum levels can interfere with insulin sensitivity and can also promote a pathogenic lipid profile [29].

In addition, there are more recently discovered adipokines that have not been studied in depth to date, especially in terms of their relationship with the SGA children's growth. One example is chemerin, whose circulating concentration has been related to higher BMI values and development of metabolic syndrome [8, 9]. In cord blood, this adipokine is associated with birth weight and fetal growth, underlining its importance in processes like myogenesis, adipogenesis, or energy balance [40]. Another relevant molecule is vaspin, which has beneficial effects on obesity and the low-grade inflammation associated. In addition, it could protect against the development of insulin resistance and metabolic syndrome and is also able to reduce food intake [6, 13, 21]. An experiment with cord blood did not find an association between vaspin and birth weight in SGA children [3]. Omentin is mainly expressed in visceral adipose tissue. It mediates glucose uptake by adipocytes, being inversely proportional to insulin resistance and other risk factors associated with obesity [45]. Taking into account that SGA patients can develop metabolic syndrome, another relevant adipokine is the newly discovered nephroblastoma overexpressed (NOV-CCN3). Plasma concentrations of this molecule are associated with fat mass and BMI. Influence of this adipokine on obesity-mediated inflammation has been suggested [22].

The first aim of this study was to compare plasma adipokine profile (leptin, adiponectin, vaspin, chemerin, and NOV) at 3 months old among SGA newborns with slow, normal, or fast catch-up. Another aim was to look for potential differences between males and females. Finally, the evolution of several adipokines in plasma from SGA newborns from 3 months to 24 months was analyzed.

## Materials and methods

### Subjects

This prospective, longitudinal study addressed 27 SGA Caucasian subjects with gestational ages ranging from 33 to 41 weeks, birth weights ranging from 1100 to 2660 g, and

birth lengths ranging from 37 to 53 cm. All births took place at Hospital Universitario de Álava-Txagorritxu (HUA) in the period June 2013–March 2015. The selected subjects were infants defined as SGA at birth, that is having birth weight or birth length below 2 standard deviations (SD) of the Spanish standard birth weight/length curves [15]. Exclusion criteria were non-Caucasian children, children from multiple pregnancies, evidence of malformations or children with severe genetic malformations or children who had died during the first 24 h of life.

The mothers of the infants enrolled confirmed the normal course of the pregnancy, without any drug administration or pregnancy complications. Mothers were encouraged to follow general guidelines for a healthy diet during lactation period. However, in order to avoid specific nutrient deficiencies in the lactating period, mothers were advised to include 1 L of milk daily in their diets and they were supplemented with calcium (1500–1800 mg/day).

Gestational age was measured by dating the last menstrual period at the time of registration. Birth weight and birth length were obtained immediately after delivery using a standard electrical scale and an infantometer. Visits at 3, 12, and 24 months were scheduled. Information concerning breastfeeding or formula feeding was recorded. The protocol was approved by the Maternal Hospital Universitario de Álava (HUA) Ethical Committee (Ref. 2012-050) and all parents were provided with a written informed consent.

The distribution of children in the three types of catch-up was made according to the weight or length increase at visit 2 (12 months) compared with delivery: slow catch-up  $\Delta < 0.49$  SD, normal catch-up  $\Delta 0.5$ –1 SD, and fast catch-up  $\Delta > 1$  SD.

### Anthropometric parameters

For each age point (3, 12, 18, and 24 months), as well as at birth and at 4 years, body weight was measured using a scale and length, defined as the crown-to-heel length, using an infantometer or a stadiometer. The circumferences of the subjects were assessed to the closest millimeter using a tape measure. Waist circumference was measured mid-way between the lower side of the lowest rib and the upper side of the pelvis, on bare skin. Head circumference was measured at the temporal level and the arm circumference at the middle of the upper arm.  $\Delta$ BMI was calculated by subtracting the BMI (body mass index) at 18 months to the BMI at 4 years.

### Blood sample collection and adipokine assays

Newborn blood was obtained at 3 months of age by using EDTA tubes, plasma was obtained by centrifugation of blood at 1250 g for 20 min and was immediately frozen and stored at  $-70$  °C until further analysis. Newborns were fasted for 5 h before blood sample collection.

The levels of glucose, insulin, total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides (TG), insulin-like growth factor 1 (IGF-1), insulin-like growth factor-binding protein 3 (IGF-BP3), cortisol, C-reactive protein (CRP), thyroid-stimulating hormone (TSH), and thyroxine (T4) in plasma were measured using an automated Roche Autoanalyzer system (Roche Diagnostics GmbH, Mannheim, Germany) in routine chemistry workflow of the diagnostics. Insulin resistance was estimated from fasting values as homeostatic model assessment–insulin resistance (HOMA-IR) using the approximated equation of Matthews et al. [23].

Adipokine concentrations were measured by using the following commercial human ELISA kits: RD191001100 (BioVendor, Brno, Czech Republic) for leptin, RD195023100 (BioVendor, Brno, Czech Republic) for adiponectin, RD191100200R (BioVendor, Brno, Czech Republic) for omentin, ab155430 (Abcam, Cambridge, UK) for chemerin, RD191097200R (BioVendor, Brno, Czech Republic) for vaspin, and ab193710 (Abcam, Cambridge, UK) for NOV.

## Statistical analysis

Normality of the data was tested using the Shapiro–Wilk test. Data are presented as mean (SD). Comparison between two paired samples was conducted with a paired Student's *t* test or a Wilcoxon signed ranks test, and comparison between unrelated variables was conducted with a Student's *t* test or a Mann–Whitney *U* test, as appropriate. Bivariant correlations among all adipokines, among each adipokine and biochemical parameters, and finally among each adipokine and anthropometric parameters were tested using Pearson's *r* or Spearman's rho, according to the data distribution. Correlations with  $r < -0.6$  or  $r > 0.6$  were taken into account. Qualitative variables, such as breastfeeding and catch-up growth type, were compared using Pearson's  $\chi^2$  test. Statistical significance was set up at two-tailed  $P < 0.05$ . Statistical analysis was performed using IBM SPSS statistics v22.

## Results

### Study population profile

The three experimental groups did not show significant differences in maternal age, mother's BMI, gestational age, parity, and feeding method. Mother dietary patterns were not analyzed.

With regard to newborns, those with fast catch-up showed significantly lower birth weight than the normal catch-up group. Further, those infants in the slow catch-up group showed lower weights as compared to those in the normal

catch-up group in every visit (3, 12, 18, and 24 months). Regarding infants' length, whereas no differences among groups were observed in birth length, babies were smaller in the slow catch-up group at 12 and 18 months as compared to those infants in the normal and fast catch-up groups. Moreover, head circumference was higher in the normal catch-up group than in the other two experimental groups. No statistical differences among groups were found in the brachial or abdominal perimeters (Table 1).

### Adipokine profile in the three catch-up groups at 3 months

As shown in Table 2, infants from slow catch-up group, at 3 months, showed lower concentrations of circulating leptin and vaspin and higher levels of adiponectin, chemerin, and omentin, when compared with normal catch-up group. By contrast, no significant differences were observed between normal and fast catch-up groups.

### Plasma biochemical parameters in the three catch-up groups at 12 months

Table 3 summarizes plasma biochemical parameters of the three catch-up groups at 12 months. Infants in the slow catch-up group presented higher concentrations of insulin than infants with normal catch-up, without changes in glucose concentrations. Consequently, HOMA-IR values were also higher. No differences were found in the other biochemical parameters measured. Similarly, no differences were found between infants with normal and fast catch-up. By analyzing correlations, only five of them were significant. Positive correlations were found between leptin at 12 months and glucose at 12 months ( $r = 0.73$ ), NOV/CCN3 at 12 months and HDL-cholesterol at 12 months ( $r = 0.63$ ) and vaspin at 24 months and height at 4 years of age ( $r = 0.64$ ). Negative correlations were observed between NOV/CCN3 at 24 months and cortisol levels at 12 months ( $r = -0.82$ ) and between vaspin at 12 months and CRP at 12 months ( $r = -0.68$ ) (Fig. 1).

### Evolution of adipokine concentrations during the 24 first months of life

Plasma concentrations of the measured adipokines at 3, 12, and 24 months of age are summarized in Table 4. Leptin and NOV were decreased during the two first years of life, and the opposite pattern was observed in omentin, with increasing concentrations during the 2-year period. Finally, adiponectin, chemerin, and vaspin remained unchanged during the two first years of life.

**Table 1** Demographic data and baseline anthropometric parameters of the subjects involved in the study, distributed according to their catch-up type

	Slow catch-up ( <i>n</i> = 11)	Normal catch-up ( <i>n</i> = 9)	Fast catch-up ( <i>n</i> = 7)
Gender (male/female)	5/6	6/3	3/4
Gestational age (weeks)	36 (3)	38 (1)	35 (3)
Birth weight (g)	1903 (485)	2300 (297) <sup>+††</sup>	1606 (463)
Birth length (cm)	43.3 (3.8)	46.8 (3.5)	42.1 (3.7)
Weight at 3 months (g)	4482 (610)	5234 (507) <sup>§§</sup>	4761 (588)
Length at 3 months (cm)	55.2 (3.2)	57.3 (1.6)	55.5 (1.7)
Weight at 12 months (kg)	7.69 (0.50)	8.54 (0.45) <sup>§§</sup>	8.63 (1.21)
Length at 12 months (cm)	70.5 (1.8)	72.5 (2.0) <sup>§-***</sup>	73.4 (2.2)
Weight at 18 months (kg)	9.15 (0.83)	9.91 (0.42) <sup>§</sup>	9.91 (0.42)
Length at 18 months (cm)	77.5 (1.7)	79.5 (1.6) <sup>§-*</sup>	80.1 (2.6)
Weight at 24 months (kg)	10.24 (0.86)	10.94 (0.45) <sup>§</sup>	10.45 (0.44)
Length at 24 months (cm)	83.8 (2.3)	85.1 (1.9)	85.1 (3.0)
Weight at 4 years (kg)	14.51 (2.17)	14.87 (0.93)	15.59 (2.13)
Length at 4 years (cm)	98.6 (4.3)	100.1 (3.8)	102.0 (4.2)
ΔBMI	-0.50 (0.70)	-0.69 (0.25)	-0.61 (0.45)
Head circumference (cm)	30.6 (2.2)	32.8 (1.0) <sup>§§,†††</sup>	29.2 (1.2)
Brachial perimeter (cm)	11.2 (0.9)	10.6 (0.9)	10.3 (0.9)
Abdominal perimeter (cm)	34.1 (2.0)	34.1 (2.0)	33.5 (3.1)
Maternal age (years)	35.6 (3.1)	35.7 (3.3)	31.3 (4.1)
Mother's BMI	25.5 (6.0)	21.8 (2.3)	26.9 (7.5)
Breastfeeding (yes/no)	5/6	5/4	3/4

Data are presented as mean (SD)

$\chi^2$  test or Mann-Whitney *U*/ Student's *t* test used according to the distribution

*BMI*, body mass index

Slow vs normal <sup>§</sup> *P* < 0.05, <sup>§§</sup> *P* < 0.01

Normal vs fast <sup>†</sup> *P* < 0.05, <sup>†††</sup> *P* < 0.01

Slow vs fast <sup>\*</sup> *P* < 0.05, <sup>\*\*</sup> *P* < 0.01

## Gender differences

When the gender factor was examined in each visit, statistical differences were observed between males and females, showing females higher levels of leptin, adiponectin, and omentin at 24 months, but not before this age. Also, in the case of NOV sexual dimorphism was observed, with higher concentration in males only in the first visit that is at 3 months. By contrast, vaspin and chemerin were similar in both genders in the three visits (Table 5).

## Discussion

In SGA infants, catch-up growth is defined as the acceleration in growth soon after birth [4]. Maximum catch-up growth usually occurs in the first 6 months of life but may continue up to 24 months [7]. It is well

known that catch-up type has a clear influence on the metabolic features of infants later in their life. In fact, it has been proposed that the postnatal growth pattern of SGA infants, rather than SGA status itself, may be a more important contributor to health outcomes later in life [35]. If catch-up growth is achieved gradually without accumulation of abdominal fat in the first 24 months, the incidence of the associated metabolic syndrome is not significant. With regard to fast catch-up, there is a concern because, although it can benefit infants by improving their nutritional status, resistance to infection, and survival, it can also contribute to the development of obesity, impaired glucose tolerance, and increased mortality from coronary heart disease later in life.

The reasons that determine catch-up type in SGA infants are not clear. It has been suggested that sensitivity to growth factors like insulin, insulin-like growth factors, or growth hormone (GH) may be involved [32, 46, 49]. Moreover, it has been reported that exclusive breastfeeding during the first

**Table 2** Plasma adipokine concentrations in SGA infants with slow, normal, and fast catch-up growth at 3 months of age

	Slow catch-up ( <i>n</i> = 11)	Normal catch-up ( <i>n</i> = 9)	Fast catch-up ( <i>n</i> = 7)
Leptin (ng/mL)	3.41 (1.15) <sup>§§</sup>	5.77 (2.69)	4.52 (3.19)
Adiponectin (μg/mL)	81.96 (42.27) <sup>*</sup>	56.61 (36.78)	31.51 (13.62)
Omentin (ng/mL)	434.98 (117.37) <sup>§§,**</sup>	312.80 (113.81)	305.95 (81.77)
Chemerin (ng/mL)	207.78 (35.46) <sup>§§</sup>	191.00 (19.68)	201.03 (22.06)
Vaspin (ng/mL)	0.14 (0.07) <sup>§</sup>	0.20 (0.10)	0.17 (0.07)
NOV/CCN3 (ng/mL)	141.77 (45.70) <sup>*</sup>	114.93 (18.54)	91.11 (20.06)

Data are presented as mean (SD)

Mann–Whitney *U*/ Student's *t* test used according to the distribution

NOV/CCN3, nephroblastoma overexpressed

Slow vs normal <sup>§</sup> *P* < 0.05; <sup>§§</sup> *P* < 0.01

Slow vs fast. <sup>\*</sup> *P* < 0.05; <sup>\*\*</sup> *P* < 0.01

months of life, instead of artificial and/or fortifying formulas in these low-weight infants, is essential to avoid excessive weight gain early in life, which is associated with an increased cardiovascular risk in the adult stage [14, 43]. In our cohort of SGA infants, differences in catch-up type do not seem to be due to different feeding types after birth.

When we looked at body weight at birth, it was realized that those infants with fast catch-up showed significantly lower birth weight than the other two groups. Thus, it seems that this parameter plays a role in the type of catch-up showed by infants during the first 24 months of age [28, 31, 48, 50].

Early adiposity rebound (AR), which is defined as a rise in the BMI curve ( $\Delta$ BMI) that appears between 5 and 7 years,

has been associated with increased risk of metabolic syndrome [44]. Interestingly, Maeyama et al. observed that 7% of SGA children presented adiposity rebound before 3 years of age [37]. Other studies have revealed that BMI changes at this age could predict adult cardiometabolic risk [18]. Unfortunately, children in our cohort did not achieve yet the age needed to assess the AR values (7 years). Thus, in the present study,  $\Delta$ BMI was calculated by subtracting the BMI (body mass index) at 18 months to the BMI at 4 years but no significant differences were observed among groups.

In order to gain more insight into catch-up type, in the present work, we analyzed potential differences in adipokine plasma concentrations at 3 months of age. We observed that

**Table 3** Plasma biochemical parameters at 12 months

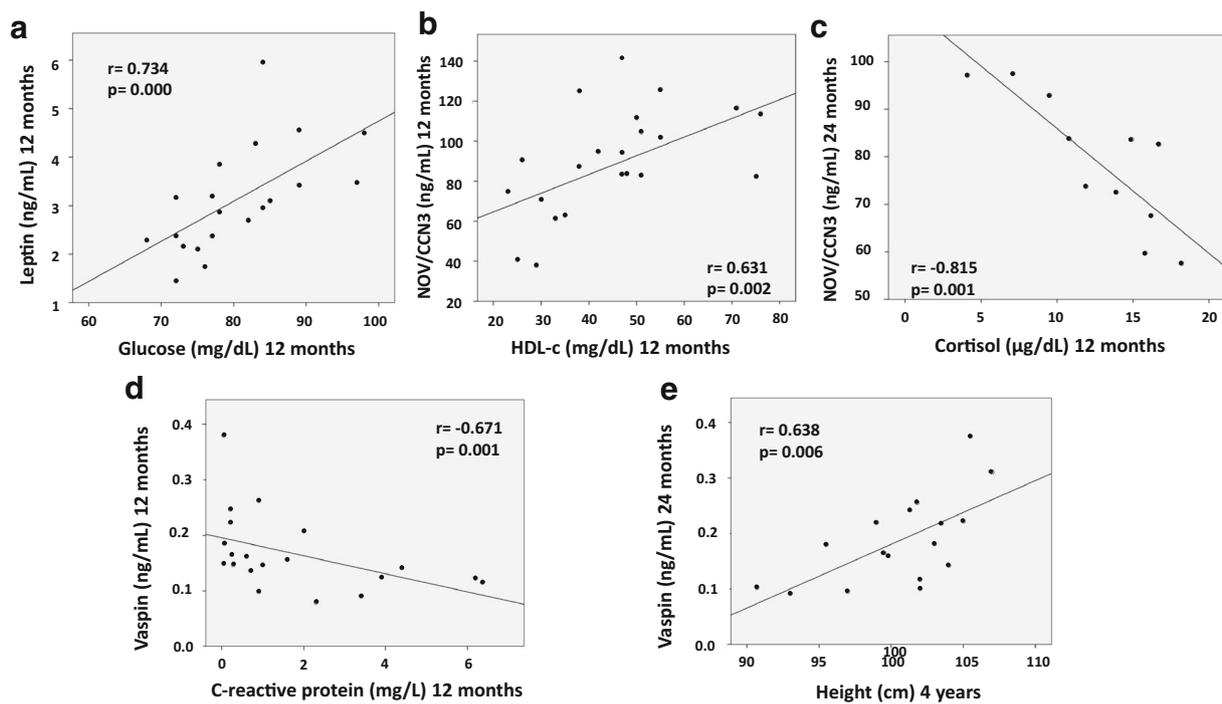
	Slow catch-up ( <i>n</i> = 11)	Normal catch-up ( <i>n</i> = 9)	Fast catch-up ( <i>n</i> = 7)
Glucose (mg/dL)	78 (7)	80 (9)	82 (9)
Insulin (μU/mL)	3.5 (1.3) <sup>§</sup>	1.6 (0.8)	1.8 (1.3)
HOMA-IR	0.69 (0.31) <sup>§</sup>	0.33 (0.21)	0.39 (0.32)
Cholesterol (mg/dL)	164 (35)	158 (28)	151 (38)
LDL-c (mg/dL)	89 (49)	103 (22)	83 (41)
HDL-c (mg/dL)	51 (13)	40 (14)	46 (20)
TG (mg/dL)	104 (28)	89 (36)	109 (52)
IGF-1 (ng/mL)	34 (6)	43 (19)	51 (27)
IGF-BP <sub>3</sub> (μg/mL)	2.3 (0.4)	2.8 (0.8)	2.6 (0.7)
Cortisol (μg/dL)	13.94 (3.37)	12.50 (3.56)	10.55 (5.24)
CRP (mg/L)	7.72 (10.66)	1.38 (1.13)	1.86 (2.10)
TSH (μU/mL)	1.90 (1.19)	2.74 (0.69)	3.17 (2.17)
T <sub>4</sub> (ng/dL)	1.07 (0.07)	1.13 (0.10)	1.11 (0.19)

Data are presented as mean (SD)

Mann–Whitney *U*/ Student's *t* test used according to the distribution

HOMA-IR, homeostasis model assessment–insulin resistance; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; TG, triglycerides; IGF-1, insulin-like growth factor 1; IGF-BP<sub>3</sub>, insulin-like growth factor-binding protein 3; CRP, C-reactive protein; TSH, thyroid-stimulating hormone; T<sub>4</sub>, thyroxine

Slow vs normal. <sup>§</sup> *P* < 0.05; <sup>§§</sup> *P* < 0.01



**Fig. 1** Correlations between different parameters: **a** leptin at 12 months and glucose at 12 months, **b** NOV/CCN3 at 12 months and HDL-cholesterol at 12 months, **c** NOV/CCN3 at 24 months and cortisol at

12 months, **d** vaspin at 12 months and CRP at 12 months, and **e** vaspin at 24 months and height at 4 years

infants with slow catch-up showed different adipokine profile to normal catch-up infants. By contrast, no differences were observed between normal and fast catch-up. Thus, it can be suggested that adipokines, at a very early life, could have an influence on catch-up type.

Among all the adipokines analyzed in the present study, leptin and adiponectin are implicated in metabolism and energy balance of fetuses, newborns, and adults, and have been suggested to play a role in fetal growth [11, 19]. Infants with slow catch-up showed lower concentrations of leptin and similar levels of adiponectin than infants with normal catch-up. Thus, the low concentration of leptin may be involved in the slow growth of these infants. This fact could be related to the well-known effect of leptin on growth hormone production. It has been demonstrated that leptin induces GH release due to the inhibition of hypothalamic somatostatin [49]. In addition, infants with slow catch-up showed lower concentrations of vaspin, and higher levels of chemerin and omentin at 3 months, when compared with normal catch-up group. Among these alterations, only that concerning chemerin was maintained at 12 months. Furthermore, they showed insulin resistance according to insulin and HOMA values. Taking into account that vaspin concentrations are related to insulin sensitivity, omentin can be taken as a biomarker of insulin resistance, and chemerin is related to insulin resistance and type 2 diabetes, altogether our results suggest that the altered adipokine profile can be responsible, at least in part, for the impaired glycemic control [6, 22, 26].

As indicated before in this “Discussion” section, postnatal growth pattern of SGA infants may be an important contributor to health outcomes later in life [7]. Bearing this in mind, we decided to analyze whether catch-up type influenced metabolic status of infants early in life. For this purpose, we measured several biochemical serum parameters at 12 months of age. The results obtained show that infants with slow catch-up showed significantly higher values of insulin and, therefore, HOMA-IR than infants in the other two groups, meaning that, at this age, they have worse glucose homeostasis control. In the case of infants with fast catch-up, no significant differences were found when compared with infants with normal catch-up. Whereas it has been clearly demonstrated that later in life, SGA infants with slow catch-up are less prone to develop metabolic alterations than SGA infants with fast catch-up [24, 42], the present results show that, during the first months of life, this growth pattern leads to a transitory impairment in glycemic control.

We also analyzed the evolution of adipokine profile during the first 24 months of age in the whole cohort of infants because reported data are scarce and somehow controversial. The results show that the evolution pattern is different, depending on the adipokine. Thus, whereas leptin and NOV decreased during the 24 first months of life, omentin increased in the same period of time, and chemerin and vaspin remained unchanged. With regard to leptin, our results are in good accordance with those reported by Bozzola et al. (2010) in adequate for gestational age (AGA) and SGA infants [10]. In this study, leptin showed a significant

**Table 4** Evolution of plasma adipokine concentrations during the 24 first months of life

	Visit 1 3 months (n = 27)	Visit 2 12 months (n = 21)	Visit 3 24 months (n = 18)
Leptin (ng/mL)	4.47 (2.40) <sup>###,‡</sup>	3.39 (1.60)	3.09 (1.87)
Adiponectin (µg/mL)	61.12 (39.21)	54.65 (28.10)	75.00 (57.87)
Omentin (ng/mL)	363.13 (119.94) <sup>#,‡</sup>	394.77 (102.43)	423.51(116.01)
Chemerin (ng/mL)	205.38 (29.20)	201.95 (19.33)	192.58 (24.72)
Vaspin (ng/mL)	0.17 (0.08)	0.16 (0.07)	0.19 (0.08)
NOV-CCN3 (ng/mL)	120.17 (37.39) <sup>###,‡,‡</sup>	88.03 (24.56)	73.15 (17.74)

Data are presented as mean (SD)

Mann–Whitney *U*/Student’s *t* test used according to the distribution

NOV-CCN3, nephroblastoma overexpressed

Visit 1 (3 months) vs visit 2 (12 months). # *P* < 0.05; ## *P* < 0.01

Visit 1 (3 months) vs visit 3 (24 months). ‡ *P* < 0.05; ‡‡ *P* < 0.01

increase in the first month of life and then decreased until 12 months of life. Our study provides additional data, demonstrating that values remained unchanged at least until 24 months of age. However, other studies have shown higher levels of leptin at 12 months of age probably due to different environmental factors derived from the origin of children [5].

With regard to adiponectin, in our study, the evolution of this adipokine is similar to that shown by Bozzola et al. (2010) [10], but when analyzing data at 12 and 24 months, our study did not show the significant reduction observed by Iñiguez et al. (2004) in AGA and SGA infants [30].

When the gender factor was examined, statistical differences were observed between males and females, mainly at 24 months of age. Males showed lower levels of leptin, adiponectin, and omentin. Taking into account that adiponectin is exclusively produced by white adipose tissue, which is the main producer of leptin and omentin, this difference may be due to the differences in body fat mass gain between males and

females during the first years of life [16, 17]. However, in this cohort of infants, no significant differences in brachial and abdominal perimeters were found.

In order to obtain more information from adipokine profile, a correlation analysis was carried out. A positive correlation between leptin and plasma glucose was found. Taking into account that this adipokine shows glucose-lowering effects, independent of its effects on energy balance, the elevated concentration of leptin may represent a potential compensatory mechanism promoted by the increased glucose level [41]. The glucose-lowering action of leptin is shown to be mediated by several pathways such as normalization of plasma glucagon levels or the hypothalamic-pituitary-adrenal (HPA) axis [20]. In addition, CRP was negatively correlated with vaspin. This is an expected result because vaspin has been described as an anti-inflammatory adipokine [25, 52]. Moreover, at 2 years, vaspin was also positively correlated with height at 4 years. Zhu et al. (2013) observed that vaspin could attenuate the apoptosis of osteoblasts through

**Table 5** Differences in plasma adipokine concentrations between male and female SGA infants at each visit

	Visit 1 (3 months)		Visit 2 (12 months)		Visit 3 (24 months)	
	Males (n = 14)	Females (n = 13)	Males (n = 9)	Females (n = 12)	Males (n = 9)	Females (n = 9)
Leptin (ng/mL)	4.32 (2.41)	4.64 (2.48)	4.17 (2.00)	2.81 (0.94)	2.24 (0.77)	3.95(2.28)*
Adiponectin (µg/mL)	61.53 (44.70)	60.67 (34.14)	49.26 (21.96)	58.69 (32.31)	50.79 (41.51)	106.12(63.67)*
Omentin (ng/mL)	364.29 (136.79)	361.88 (104.39)	353.77 (77.94)	425.52 (110.68)	344.54 (52.48)	502.48 (108.68)**
Chemerin (ng/mL)	207.78 (30.91)	202.80 (28.26)	197.27 (17.25)	205.45 (20.78)	188.88 (19.59)	196.27 (29.74)
Vaspin (ng/mL)	0.16 (0.05)	0.19 (0.10)	0.15 (0.05)	0.17 (0.09)	0.19 (0.08)	0.19 (0.09)
NOV-CCN3 (ng/mL)	136.32 (40.96)	102.79 (24.08)*	93.93 (25.88)	83.60 (23.67)	67.08 (20.47)	79.21 (12.92)

Data are presented as mean (SD)

Mann–Whitney *U*/Student’s *t* test used according to the distribution

NOV-CCN3, nephroblastoma overexpressed

\**P* < 0.05

\*\**P* < 0.01

ERK signaling pathway [51]. Knowing that these cells are needed for bone development, it can be hypothesized that higher vaspin levels at 2 years may have contributed to increased height at 4 years. Finally, with regard to NOV/CCN3, although it has been related to the obesity-associated insulin-resistance [39], to the best of our knowledge, very little information is available concerning its physiological actions on lipid metabolism. Consequently, further research is needed to discuss the correlations found in the present study between NOV/CCN3 and cortisol or HDL-cholesterol.

Our study has strengths and limitations. One limitation is the small sample size. The reason is that SGA represents a small percentage of newborns in Hospital Universitario de Álava-Txagorritxu and also that it is difficult to obtain parent consent for blood collection in infants at 3 months of age. Consequently, power limitations and type II errors should therefore be taken into account when interpreting the results. Another limitation is that our study was carried out in a Caucasian population and thus data cannot be directly extrapolated to other population groups. Finally, it should be pointed out that this study does not allow us to determine whether differences in adipokine profile are the cause or the consequence of differences in adipose tissue development. A strength is that a wide panel of adipokines was measured, some of them (omentin, vaspin, and NOV/CCN3) very little studied in infants and children. Moreover, to the best of our knowledge, adipokine studies in SGA infants commonly focus on cord blood, which is not considered the ideal material because it may present contradictory factors. In our study, we worked with plasma samples, not at birth, but at a very early age (3 months).

Taken together our results show that (a) the lowest weight in SGA infants is related to a fast catch-up growth, (b) adipokines, very early in life, can have an influence on catch-up type, (c) health prognoses for infants with slow and fast catch-up are opposite, between the first months of life and later in life, (d) adipokine evolution pattern during the first 24 months of age is different, depending on the adipokine, and (e) males show lower levels of leptin, adiponectin, and omentin than females at 24 months old.

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### Compliance with ethical standards

**Ethical approval** The study protocol has been approved by the Ethical Committee of the Hospital Universitario de Álava-Txagorritxu (HUA) (Ref. 2012-050). 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** Parents of all subjects have given their written informed consent to take part in the study. Informed consent was obtained from all individual participants included in the study.

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