Léniz, A., Portillo, M.P., Fernández-Quintela, A. et al. *Has the adipokine profile an influence on the catch-up growth type in small for gestational age infants?*. **J Physiol Biochem** 75, 311–319 (2019).

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

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Aknowledgements: This work was supported by grants from Pfizer International (2012/13), Government of the Basque Country (IT-572-13) and Instituto de Salud Carlos III (CIBERobn).

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)) 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

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 [1-3]. SGA infants are at 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. 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 [4]. 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 [5].

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 [6]. 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 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 [7].

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 [8]. Another well-known adipokine is adiponectin, which is down-regulated in obese subjects, being inversely correlated with body mass

64 index (BMI) [9]. It plays an important role in glucose homeostasis[10]. Regarding the
65 SGA population, studies in pre-pubertal children have shown that low adiponectin serum
66 levels can interfere with insulin sensitivity and can also promote a pathogenic lipid profile
67 [11].

68 In addition, there are more recently discovered adipokines that have not been studied
69 in depth to date, especially in terms of their relationship with the SGA children`s growth.
70 One example is chemerin, whose circulating concentration has been related to higher BMI
71 values and development of metabolic syndrome [12, 13]. In cord blood, this adipokine is
72 associated with birth weight and fetal growth, underlining its importance in processes like
73 myogenesis, adipogenesis or energy balance [14]. Another relevant molecule is vaspin,
74 which has beneficial effects on obesity and the low-grade inflammation associated. In
75 addition, it could protect against the development of insulin resistance and metabolic
76 syndrome and is also able to reduce food intake [15, 16]. An experiment with cord blood
77 did not find an association between vaspin and birth weight in SGA children [17].
78 Omentin is mainly expressed in visceral adipose tissue and it mediates glucose uptake by
79 adipocytes, being inversely proportional to insulin resistance and other risk factors
80 associated with obesity [18]. Taking into account that SGA patients can develop
81 metabolic syndrome, another relevant newly discovered adipokine is nephroblastoma
82 overexpressed (NOV-CCN3). Plasma concentrations of this molecule are associated with
83 fat mass and BMI. Influence of this adipokine on obesity-mediated inflammation has been
84 suggested [19].

85 The first aim of this study was to compare plasma adipokine profiles (leptin,
86 adiponectin, vaspin, chemerin, and NOV) at 3 months old among SGA newborns with
87 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 grams and birth lengths ranging from 37 to 53 centimeters. 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 [20]. 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 hours of life. The mothers of the infants enrolled confirmed the normal course of the pregnancy, without any drug administration or pregnancy complications.

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 breast feeding 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 Δ <0.49 SD, normal catch-up Δ 0.5-1 SD, and fast catch-up Δ >1 SD.

Blood sample collection and adipokine assays

Newborn blood was obtained at three months of age by using EDTA tubes, plasma was obtained by centrifugation of blood at 1250 g for 20 minutes and was immediately frozen and stored at -70ºC until further analysis.

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 Autoanalyser system (Roche Diagnostics GmbH, Mannheim, Germany) in routine chemistry workflow of the diagnostics. Insulin resistance was estimated from fasting values as homeostatic model assessment (HOMA-IR) using the approximated equation of Matthews *et al*. [21].

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, (Abcam, Cambridge, UK) for chemerin ab155430, 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 2 paired samples was conducted with a paired Student

134 *t* test or a Wilcoxon signed ranks test, and comparison between unrelated variables was
135 conducted with a Student's *t* test or a Mann-Whitney's U test, as appropriate. Qualitative
136 variables, such as breastfeeding and catch-up growth type, were compared using
137 Pearson's $\chi 2$ test. Statistical significance was set-up at two-tailed $P<0.05$. Statistical
138 analysis was performed using IBM SPSS statistics v22.

139 **Results**

140 ***Study population profile***

141 The three experimental groups did not show significant differences in maternal age,
142 mother`s BMI, gestational age, parity and feeding method. With regard to newborns,
143 those with fast catch-up showed significantly lower birth weights than the other two
144 groups. No differences were observed in birth length. Moreover, head circumference was
145 higher in the normal catch-up group than in the other two experimental groups (Table 1).

146

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 (n=11)	Normal catch-up (n=9)	Fast catch-up (n=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)❖❖	1606(463)
Birth length (cm)	43.3(3.8)	46.8(3.5)	42.1(3.7)
Head circumference (cm)	30.6(2.2)	32.8(1.0)§§,❖❖	29.2(1.2)
Brachial perimeter (cm)	11.2(0.9)	10.6(0.9)	10.3(0.9)
Abdominal perimeter	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

Mann-Whitney`s U/ Student`s t test used according to the distribution

§: Slow vs normal. §§ P <0.01

❖: Normal vs fast. ❖❖ P <0.01

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.

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

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

Mann-Whitney`s U/ Student`s t test were used according to the distribution.

§: Slow *vs* normal. § P <0.05; §§ P <0.01

*: Slow *vs* fast. * P <0.05; ** P <0.01

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 rest of the biochemical parameters measured. Similarly, no differences were found between infants with normal and fast catch-up.

Table 4. Plasma biochemical parameters at 12 months.

	Slow catch-up (n=11)	Normal catch-up (n=9)	Fast catch-up (n=7)
Glucose (mg/dL)	78 (7)	80(9)	82(9)
Insulin (µU/mL)	3.5(1.3) §	1.6(0.8)	1.8(1.3)
HOMA-IR	0.69(0.31) §	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_3 (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_4 (ng/dL)	1.07(0.07)	1.13(0.10)	1.11(0.19)

[§]: Slow *vs* normal. [§] P <0.05; [§§] P <0.01

LDL-c: low density lipoprotein cholesterol, HDL-c: high density lipoprotein cholesterol TG: triglycerides; IGF-1: insulin-like growth factor 1; IGF-BP_3: insulin-like growth factor-binding protein 3; CRP: C reactive protein; TSH: thyroid-stimulating hormone; T_4: thyroxine.

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 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)##; ¤	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)#; ¤	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 (ng/mL)	120.17 (37.39)##; ¤¤	88.03 (24.56)	73.15 (17.74)

Mann-Whitney`s U/ Student's *t* test used according to the distribution.

[#]: visit 1 (3 months) *vs* visit 2 (12 months). # $P<0.05$; ## $P<0.01$

¤: visit 1 (3 months) *vs* visit 3 (24 months). ¤ $P<0.05$; ¤¤ $P<0.01$

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).

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 (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)

Mann-Whitney`s U/ Student`s t test used according to the distribution
* $P<0.05$; ** $P<0.01$

Discussion

In SGA infants, catch-up growth is defined as the acceleration in growth soon after birth [22]. Maximum catch-up growth usually occurs in the first 6 months of life but may continue up to 24 months [23]. 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 post-natal growth pattern of SGA infants, rather than SGA status itself, may be a more important contributor to health outcomes later in life [24]. 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 [1, 25, 26]. Moreover, it has been reported that exclusive breastfeeding during the first months of life, instead of artificial and/or fortifying formulas in these low-weight infant, is essential to avoid excessive weight gain during the first months and years of life, which is associated with an increased cardiovascular risk in the adult stage [27, 28]. 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 [29-31]. 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 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 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 [10, 32]. 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 [26]. 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 [16, 19, 33].

As indicated before in this Discussion section, postnatal growth pattern of SGA infants may be an important contributor to health outcomes later in life [23]. 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 [34, 35], the present results show that, during the first months of life, this growth pattern leads to a transitory impairment in glycaemic 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 [7]. In this study, leptin showed a significant 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 [36].

With regard to adiponectin, in our study the evolution of this adipokine is similar to that showed by Bozzola *et al*. (2010) [7], 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 [37].

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 [38]. However, in this cohort of infants, no significant differences in brachial and abdominal perimeters were found.

Our study has strengths and limitations. One limitation is the small sample size. The reason is that SGA represent a small percentage of newborns in Hospital Universitario de Alava-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. A strength is that a wide panel of adipokines was measured, some of them (omentin, vaspin and NOV) 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.

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

Funding Sources: This work was supported by grants from Pfizer International (2012/13), Government of the Basque Country (IT-572-13) and Instituto de Salud Carlos III (CIBERobn).

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.

References

1. Saenger P, Czernichow P, Hughes I, Reiter EO (2007) Small for gestational age: Short stature and beyond. Endocr Rev 28:219-51

2. Britt C, Sven C, Ove A (2005) Preterm and term births of small for gestational age infants: A population-based study of risk factors among nulliparous women. Br J Obstet Gynaecol 105:1011-7

3. Lee PA, Chernausek SD, Hokken-Koelega A, Czernichow P (2003) International small for gestational age advisory board consensus development conference statement: Management of short children born small for gestational age, April 24-October 1, 2001. Pediatrics 111:1253-61

4. Hokken-Koelega AC1, De Ridder MA, Lemmen RJ, Den Hartog H, De Muinck Keizer-Schrama SM, Drop SL (1995) Children born small for gestational age: Do they catch up? Pediatr Res 38:267-71

5. Levy-Marchal C, Jaquet D (2004) Long-term metabolic consequences of being born small for gestational age. Pediatr Diabetes 5:147-53

6. Ahima RS, Flier JS (2000) Adipose Tissue as an Endocrine Organ. Trends Endocrinol Metab 11:327-32

7. Bozzola E, Meazza C, Arvigo M, Travaglino P, Pagani S, Stronati M, Gasparoni A, Bianco C, Bozzola M (2010) Role of adiponectin and leptin on body development in infants during the first year of life. Ital J Pediatr 36:26

8. Kistner A, Vanpée M, Hall K (2013) Leptin may enhance hepatic insulin sensitivity in children and women born small for gestational age. Endocr Connect 2:38-49

9. Ahima RS, Qi Y, Singhal NS, Jackson MB, Scherer PE (2006) Brain adipocytokine action and metabolic regulation. Diabetes 55 Suppl 2:S145-54

10. Dos Santos E, Duval F, Vialard F, Dieudonné MN (2015) The roles of leptin and adiponectin at the fetal-maternal interface in humans. Horm Mol Biol Clin Investig 24:47-63

11. Huang Y, Li Y, Chen Q, Chen H, Ma H, Su Z, Du M (2015) Low serum adiponectin levels are associated with reduced insulin sensitivity and lipid disturbances in short children born small for gestational age. Clin Endocrinol (Oxf) 83:78-84

12. Bozaoglu K, Bolton K, McMillan J, Zimmet P, Jowett J, Collier G, Walder K, Segal D. (2007) Chemerin is a novel adipokine associated with obesity and metabolic syndrome. Endocrinology 148:4687-94

13. Bozaoglu K, Segal D, Shields KA, Cummings N, Curran JE, Comuzzie AG, Mahaney MC, Rainwater DL, VandeBerg JL, MacCluer JW, Collier G, Blangero J,

355 Walder K, Jowett JBM 2009 Chemerin is associated with metabolic syndrome
356 phenotypes in a mexican-american population. J Clin Endocrinol Metab 94:3085-8

357 14. Mazaki-Tovi S, Kasher-Meron M, Hemi R, Haas J, Gat I, Lantsberg D, Hendler I,
358 Kanety H. (2012) Chemerin is present in human cord blood and is positively correlated
359 with birthweight. Am J Obstet Gynecol 207:412.e1-10

360 15. El-Mesallamy HO, Kassem DH, El-Demerdash E, Amin AI. Vaspin and
361 visfatin/Nampt are interesting interrelated adipokines playing a role in the pathogenesis
362 of type 2 diabetes mellitus. Metabolism. 2011 Jan;60:63-70

363 16. Blüher M (2012) Vaspin in obesity and diabetes: Pathophysiological and clinical
364 significance. Endocrine Endocrine 41:176-82

365 17. Akcay A, Akar M, Demirel G, Canpolat FE, Erdeve O, Dilmen U (2013) Umbilical
366 cord and fifth-day serum vaspin concentrations in small-, appropriate-, and large-for-
367 gestational age neonates. J Pediatr Endocrinol Metab 26:635-8

368 18. Rong-Ze Yang, Mi-Jeong Lee, Hu H, Pray J, Hai-Bin Wu, Hansen BC, Shuldiner
369 AR, Fried SK, McLenithan JC, Da-Wei Gong (2006) Identification of omentin as a
370 novel depot-specific adipokine in human adipose tissue: Possible role in modulating
371 insulin action. Am J Physiol Endocrinol Metab 290:E1253-61

372 19. Escoté X, Gómez-Zorita S, López-Yoldi M, Milton-Laskibar I, Ferández-Quintela
373 A, Martínez AJ, Moreno-Aliaga J, Portillo MP (2017) Role of Omentin, Vaspin,
374 Cardiotrophin-1, TWEAK and NOV/CCN3 in Obesity and Diabetes Development. Int J
375 Mol Sci 18 pii: E1770

376 20. Carrascosa A, Fernández JM, Ferrández A, López-Siguero JP, López D, Sánchez E
377 (2010) Estudios españoles de crecimiento Available from:
378 http://www.aeped.es/noticias/estudios-espanoles-crecimiento-2010.

379 accessed 4 Jul 2018

380 21. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC
381 (1985) Homeostasis model assessment: insulin resistance and beta-cell function from
382 fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412-9.

383 22. Albertsson-Wikland K, Boguszewski M, Karlberg J 1998 Children born small-for-
384 gestational age: Postnatal growth and hormonal status. Horm Res Paediatr 49 suppl 2:7-
385 13

386 23. Boersma B, Wit JM (1997) Catch-up growth. Endocr Rev 18:646-61

387 24. Lei X, Chen Y, Ye J, Ouyang F, Jiang F, Zhang J (2015) The optimal postnatal
388 growth trajectory for term small for gestational age babies: A prospective cohort study.
389 J Pediatr 166:54-8

25. Karlberg JP, Albertsson-Wikland K, Kwan EY, Lam BC, Low LC (1997) The timing of early postnatal catch-up growth in normal, full-term infants born short for gestational age. Horm Res 48 Suppl 1:17-24

26. Tannenbaum GS, Gurd W, Lapointe M (1998) Leptin is a potent stimulator of spontaneous pulsatile growth hormone (GH) secretion and the GH response to GH-releasing hormone. Endocrinology 139:3871-5

27. Carling SJ, Demment MM, Kjolhede CL, Olson CM (2015) Breastfeeding duration and weight gain trajectory in infancy. Pediatrics 135:111-9

28. Parikh NI, Hwang S, Ingelsson E, Benjamin EJ, Fox CS, Vasan RS, Murabito JM (2009) Breastfeeding in infancy and adult cardiovascular disease risk factors. Am J Med Am J Med 122:656-63

29. Jornayvaz FR, Vollenweider P, Bochud M, Mooser V, Waeber G, Marques-Vidal P (2016) Low birth weight leads to obesity, diabetes and increased leptin levels in adults: The CoLaus study. Cardiovasc Diabetol 15:73

30. Xiao X, Zhang Z, Li W, Feng K, Sun Q, Cohen HJ, Xu T, Wang H, Liu A, Gong X, Shen Y, Yi Z 2010 Low birth weight is associated with components of the metabolic syndrome. Metabolism 59:1282-6

31. Hovi P, Andersson S, Eriksson JG, Järvenpää AL, Strang-Karlsson S, Mäkitie O, Kajantie E (2007) Glucose regulation in young adults with very low birth weight. N Engl J Med 356:2053-63

32. Briffa JF, McAinch AJ, Romano T, Wlodek ME, Hryciw DH (2015) Leptin in pregnancy and development: A contributor to adulthood disease? Am J Physiol Endocrinol Metab 308:E335-50

33. Helfer G, Wu Q (2018) Chemerin: A multifaceted adipokine involved in metabolic disorders. J Endocrinol 238:R79-94

34. Ong KKL, Ahmed ML, Emmett PM, Preece MA, Dunger DB (2000) Association between postnatal catch-up growth and obesity in childhood: Prospective cohort study. BMJ. 320:967-71

35. Giapros V, Vavva E, Siomou E, Kolios G, Tsabouri S, Cholevas V, Bairaktari E, Tzoufi M, Challa A (2017) Low-birth-weight, but not catch-up growth, correlates with insulin resistance and resistin level in SGA infants at 12 months. J Matern Fetal Neonatal Med. 30:1771-1776

36. Amador-Licona N, Martinez-Cordero C, Guizar-Mendoza JM, Malacara JM, Hernandez J, Alcala JF (2007) Catch-up Growth in Infants Born Small for Gestational Age - A Longitudinal Study. J Pediatr Endocrinol Metab 20:379-86 DOI: 10.1515/JPEM.2007.20.3.379Amador-Licona N., Martinez-Cordero C., Guizar-Mendoza J.M., Malacara J.M., Hernandez J. and Alcala J.F. Generic197

427 37. Iñiguez G, Soto N, Avila A, Salazar T, Ong K, Dunger D, Mericq V (2004)
428 Adiponectin levels in the first two years of life in a prospective cohort: Relations with
429 weight gain, leptin levels and insulin sensitivity. J Clin Endocrinol Metab 89:5500-3

430 38. Cheng G, Bolzenius K, Joslowski G, Günther AL, Kroke A, Heinrich J, Buyken AE
431 (2015) Velocities of weight, height and fat mass gain during potentially critical periods
432 of growth are decisive for adult body composition. Eur J Clin Nutr 69:262-8