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Early markers of endocrinometabolic disease in newborns with delayed intrauterine growth

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SUMMARY

Introduction: The adjustments to malnutrition in growth restricted fetus (GRF) that lead to obesity, insulin resistance, diabetes and cardiovascular disease in adulthood are not well known. The most feasible explanation for this association is the hypothesis of catch up. Some studies postulate a greater influence of catch up growth than the low birth weight itself in developing metabolic and cardiovascular disease.
Material and methods: This is a prospective cohort study of newborns with intrauterine growth restriction (defined as weight percentile at birth less than 10th) born during a one-year period. Clinical data of patients were recorded (gender, gestational age, data about breastfeeding and anthropometry during follow-up every 3 months). Some details of pregnancy and characteristics of the mother were also registered. Serum biochemical parameters (IGF-1, IGF-BP3, insulin, glucose, total cholesterol, HDL cholesterol, DLD cholesterol, triglycerides, HOMA) were collected at birth from cord blood, 9 and 12 months. Two main comparative groups were established: those GRF who made a catch-up growth (increase in weight Z score higher than 0,67) during the follow-up and those who did not get it.
Results: 126 GRF children were born in the study period. 125 accepted the inclusion in the study and 67 of them completed the full monitoring for a year; 47 of them made recovery growth and 20 did not. A significant difference between both groups was found in glucose in umbilical cord and triglycerides at 12 months: GRF children with catch up growth showed lower glucose levels ($p = 0.03$) and higher levels of triglycerides ($p = 0.03$). There were no statistically significant differences in the rest of laboratory parameters analyzed (IGF-1, IGF-BP3, insulin, glucose, total cholesterol, HDL cholesterol, DLD cholesterol, HOMA at 9 and 12 months or triglycerides at 9 months).
Conclusions: Those GRF with catch up growth during the first year of life have early changes in the triglycerides at the end of that period with higher levels than those GRF children without catch up growth. This finding could be useful to develop a tool for early detection of GRF children with higher metabolic risk in order to prevent future pathology.

1. Introduction

An association between low birth weight and a higher risk of pathology in adulthood is known for years. Barker et al. [1] observed, in a cohort of men and women born between 1920 and 1943 in a region of the United Kingdom, an increased risk of coronary disease, hypertension and metabolic syndrome in adults with lower birth weight. They pointed out the relationship between low birth weight and endocrinometabolic pathology, postulating that fetal malnutrition gives rise to permanent structural and

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functional changes (among them, insulin resistance). This association known as Barker hypothesis has been subsequently confirmed in a considerable number of epidemiological studies [2–4].

However, restricted intrauterine growth is often the manifestation of the exposure to certain factors or conditions during prenatal life. Therefore, it is questionable whether low weight *per se* is a risk factor for future cardiometabolic diseases [5].

The term *perinatal programming* describes the fact that temporary environmental changes during fetal life or early childhood can lead to permanent alterations in some physiological processes. The theory of fetal programming in children with delayed intrauterine growth (GRF) began to be observed and studied after the Second World War. The traditional explanation is that the intrauterine deprivation of nutrients leads to a programming of the endocrine system and allows energy savings in fetal life. Nutrient deprivation continued after birth, therefore, is tolerated. However, the rapid recovery of energy supply and therefore hyperalimentation leads to an excess of energy. This further hypothesis is called as thrifty phenotype. It has postulated a potential relationship between reduced fetal nutrition and an excess of postnatal feeding aimed at rapidly increasing the weight of neonates [6].

This causes the deposit in adipose tissue predisposing to a pathological tolerance of glucose. Hyperalimentation seems to play an important physiopathological role in postnatal perinatal programming [7,8].

Postnatal growth is an important factor in the expression of posterior pathology: the pattern of growth and weight gain after birth is the key determinant of the future state of health of GRF [9–14]. There is an increased risk of metabolic syndrome among adults who were born small and who had a rapid recovery growth [15–17].

Not only prenatal growth determines the appearance of different conditions in children with delayed intrauterine growth but postnatal growth as well influences the possibility of the appearance of pathologies or factors that will condition the health of these patients. The main objective of this study was to evaluate the existence of differences in endocrinometabolic parameters that could be considered as early of future cardiovascular and endocrinometabolic pathology in the GRF population with recovery growth.

2. Patients and methods

This is a prospective cohort study. The target population was that of newborns with delayed intrauterine growth (GRF) with a gestational age greater than 32 weeks. GRF children were defined as those born with a weight percentile less than 10th for their gestational age and sex according to the tables of the Spanish cross-sectional study of 2010 A Carrascosa [18].

Exclusion criteria were the presence of major congenital anomalies, chromosomopathies or any clinical data that suggested any syndrome. Likewise, those children whose parents did not sign the informed consent were excluded from the study. The study was carried out after approval by the corresponding research and ethics committee.

Patients were included by consecutive sampling, so that all newborns who met the inclusion criteria and did not meet any exclusion criteria were included from the study start date.

Two main comparative groups were established: that of those GRF who made a recovery or catch up growth during the one-year follow-up (recuperators) and those who did not achieve such growth (non recuperators). Catch up growth was defined as a growth rate higher than the average for chronological age and sex during a defined period of time, after a growth inhibition phase. It was defined, as reported in the literature [19], as a gain in the Z weight score greater than 0.67 (0.67 is equivalent to the width of a percentile band in standard growth charts) during the follow-up period (one year).

For each study infant, details of pregnancy (complications such as hypertension or diabetes), characteristics of the mother (primiparity, smoking and anthropometric data such as height, weight and body mass index at the beginning and at the end of pregnancy), gestational age, sex, presence of antenatal corticosteroids and anthropometrics at birth (weight, height, head circumference and body mass index) were recorded.

In order to obtain data from early parameters related to the glycemic, lipid and growth factor profile of the GRF, a sample of cord blood was taken from every child and subsequently stored at −70 °C until its analysis.

After discharge, patients were followed-up every three months up to the first birthday. In each visit the following variables were recorded: weight, length, head circumference, body mass index and breastfeeding.

Serum biochemical parameters (IGF-1, IGF-BP3, insulin, glucose, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, HOMA) were collected at birth (from cord blood), 9 and 12 months. IGF1 was determined by an immune-enzymatic method using the kit by Diasource (Louvain-la-Neuve, Belgium). IGFBP-3 was determined by an enzyme-linked immune-sorbent assay using monoclonal antibodies with high affinity and specificity (Biosource-Nivelles, Belgium). Insulin was determined by the immunoenzymatic method using and enhanced chemiluminescence Dxi 800 Beckman–Coulter analyser with reagents of the manufacturing company (Beckman–Coulter, Brea, CA). Glucose, cholesterol, triglycerides were determined using spectrophotometry in an automated analyser (Olympus AU 2700, Beckman–Coulter, Brea, CA). The homeostasis model assessment for insulin resistance (HOMA-IR) was assessed by the formula: [{insulin (mU/l) x glucose (mmol/l)}/22.5].

The main independent variable in the study was catch-up growth, defined as previously commented.

2.1. Statistics

The quantitative variables were expressed as mean and standard deviation, and qualitative variables as percentages. To analyze the association between the qualitative variables of the study, Chi-square test of Pearson was used. If the number of cells with expected values less than 5 was greater than 20%, Fisher's exact test was used instead. The Student's t-test was used for independent samples in the comparison of the mean values. The non-parametric alternatives used, if the use of the previous ones was not convenient, was the Mann–Whitney U test (for two groups) or the Kruskal Wallis H test (for more than two groups). The values of $p < 0.05$ were considered statistically significant. No adjustments were made for multiple testing. A multivariate analysis was done for those variables associated with the variable catch-up with $p < 0.1$ in the univariate analysis. The results were analyzed statistically with the SPSS 23.0 program.

3. Results

A total of 126 GRF children (54 males, 72 females) born in the one-year period of study were eligible. Fifty nine of them were excluded because the parents were unwilling to participate or to continue the follow-up (84,5% of the children who did not continue the follow-up did not come to their first medical consultation at 3 months). The clinical and socio-economic characteristics of the non-participating children did not differ from those of the study group. The remainder of the infants ($n = 67$) completed the monitoring for one full year: 47 of them made recovery growth and 20 did not. Forty-seven (70%) of them made a recovery growth in the first year: most in the first three

months (87%) and all with 9 months of life. Table 1 reflects the comparison of clinical and analytical basal characteristics of patients who completed the follow-up and lost patients, showing no significant differences between both groups. We also compared basal clinical characteristics with the endocrine metabolic parameters at 9 and 12 months, finding no significant differences except in total cholesterol at 12 months, which was higher in the group of smoking mothers (159.1 ± 20.4 mg/dl in smoking mothers *vs* 136.9 ± 31.9 mg/dl in non smoking mothers, p = 0.04) and primiparity, finding higher levels of LDL cholesterol at 9 months in children born from primiparous mothers (79 ± 23.1 mg/dl in primiparous *vs* 62.4 ± 22.4 mg/dl in non primiparous, p = 0.04). Thus, characteristics of the non-participating children did not differ from those of the study group.

Table 2 shows data related to pregnancy and mother's characteristics. No significant differences were found between recuperators and non-recuperators regarding complications during pregnancy (such as hypertension or diabetes), primiparity, smoking during pregnancy, nationality or anthropometric data (height, weight and body mass index at the and at the end of pregnancy).

Table 3 depicts general characteristics of GRF population, as well as breastfeeding and anthropometric data of the GRF infants throughout the study period. Most patients were female (57,4% in the recuperators group and 55% in the non-recuperators group), with a mean gestational age of 37.7 weeks (non-recuperators) and 38.8 weeks (recuperators) (p = 0.07). Most of them received breastfeeding at birth. We found significant differences in weight Z scores and BMI Z scores from the third month of follow up.

Variables that showed association with catch-up growth in the univariate analysis with p < 0.1 [breastfeeding at birth (p = 0.08) and gestational age at birth (p = 0.07)] were included in a logistic regression analysis in order to estimate the possible confounding effect. After this analysis, none of the variables maintained significant association although gestational age at birth was close to statistical significance (p = 0.09).

Regarding endocrine metabolic analytical parameters, Table 4 shows some glycemic and lipid parameters as well as two growth factors (IGF-1 and IGF-BP3).

Table 1
Comparison of basal characteristics (clinical data of pregnancy/mother/child and endocrine metabolic parameters at birth) of patients who finished the follow up and those who did not.

	Finished follow- up (n = 67)	Lost patients (n = 58)	p
HTA/preeclampsia	2 (3%)	6 (10.3)	0.1
Diabetes	4 (6%)	3 (5,2%)	0.8
Spanish nationality	55 (82.1%)	48 (82.8%)	0.8
In vitro fertilization	1 (1.5%)	1 (1.7%)	0.9
Primiparity	46 (68.7%)	35 (60.3%)	0.3
Smoking	22 (33.3%)	20 (34.5%)	0.9
Corticosteroids	2 (3%)	1 (1.7%)	0.6
Altered Doppler	2 (3%)	4 (6.9%)	0.3
Mother's weight beginning pregnancy (Kg)	61.8 ± 12.1	62.4 ± 13.5	0.8
Mother's height (cm)	161 ± 5	159 ± 5	0.3
Mother's body mass index (Kg/m^2)	23.6 ± 4.4	24.6 ± 5.0	0.2
Mother's weight gain (Kg)	11.3 ± 9.1	10.6 ± 3.6	0.5
Sex (female)	38 (56.7%)	32 (55.2%)	0.9
Prematurity	7 (10.4%)	6 (10.3%)	0.3
Gestational age (weeks)	38.5 ± 1.8	38.7 ± 1.7	0.9
Weight at birth (Kg)	2.5 ± 0.3	2.6 ± 0.3	0.3
Weight Z score at birth	−1.7 ± 0.4	−1.5 ± 0.6	0.2
Length at birth (cm)	46.7 ± 2.5	46.7 ± 2.5	0.8
Length Z score at birth	−1.5 ± 0.9	−1.5 ± 1.0	0.9
Head circumference at birth (cm)	32.9 ± 1.5	32.7 ± 1.4	0.6
Head circumference Z score at birth	−0.9 ± 0.8	−0.9 ± 0.8	0.9
Body mass index at birth (Kg/m^2)	11.7 ± 2.	11.8 ± 0.9	0.8
Body mass index Z score at birth	−1.4 ± 0.9	−1.2 ± 0.9	0.2
Systolic blood pressure (mmHg)	74.8 ± 8.1	74.7 ± 8.4	0.9
Diastolic blood pressure (mmHg)	44.4 ± 8.9	44.2 ± 7.6	0.9
Glucose cord blood (mg/dl)	85.6 ± 20.4	86.9 ± 23.5	0.7
Insulin cord blood (mU/ml)	3.9 ± 6.8	2.8 ± 5.2	0.4
HOMA cord blood	0.9 ± 1.9	0.7 ± 1.9	0.6
Total cholesterol cord blood (mg/dl)	68.4 ± 21.7	65.5 ± 14.3	0.5
LDL cholesterol cord blood (mg/dl)	34.4 ± 16.3	32.2 ± 9.3	0.4
HDL cholesterol cord blood (mg/dl)	25.0 ± 8.9	24.9 ± 8.1	0.9
Triglycerides cord blood (mg/dl)	43.3 ± 23.3	43.1 ± 18.7	0.9
IGF-1 cord blood (ng/dl)	37.5 ± 19.8	36.5 ± 18.3	0.8
IGF-BP3 cord blood (mg/l)	1.2 ± 0.3	1.2 ± 0.2	0.7

Table 2
Data related to pregnancy and mother's characteristics/anthropometry.

	Recuperators (n = 47)	Non recuperators (n = 20)	p
Hypertension	2.1%	5%	0.5
Diabetes	4.3%	10%	0.4
Primiparity	68.1%	70%	0.9
Smoking	32%	35%	0.8
Nationality Spanish	80.9%	85%	0.5
Weight (beginning of pregnancy) (kg)	63.5 ± 12.6	57.5 ± 9.6	0.2
Weight (end of pregnancy) (kg)	74.3 ± 12.7	67.8 ± 9.2	0.3
Height (cm)	163 ± 6	159 ± 6	0.9
BMI (Kg/m^2)	24 ± 4.7	22.5 ± 3.6	0.2

3.1. Glycemic profile

Data related to glycemic metabolism were collected in order to determine whether there was any difference in insulin resistance (IR) between GRF children with catch up and those without catch up. Glucose level in umbilical cord was significantly higher in non-recuperators (99.2 mg/dl vs 80.7 mg/dl, p = 0.03). No significant differences were observed between both groups regarding the rest of parameters (glucose, insulin or HOMA index) during the follow-up (Fig. 1).

3.2. Lipid profile

Higher levels of triglycerides were observed in recuperators-infants than in non-recuperators at 12 months (119.3 mg/dl vs 79.1 mg/dl, p = 0.03). No other significant difference was identified in the rest of lipid profile parameters (total- LDL-HDL cholesterol in the umbilical cord, at 9 and at 12 months or triglycerides at 9 months) between recuperators and non-recuperators (Fig. 2).

3.3. Growth factors

Regarding growth factors, IGF-1 and IGF-BP3 levels were similar in the umbilical cord, at 9 months and at 12 months in both GRF groups of infants (Fig. 3).

Table 3
-General characteristics of the studied GRF population during follow-up -up.

	Recuperators (n = 47)	Non recuperators (n = 20)	p
Gender (female/male)	27/20	11/9	0.9
Gestational age (mean weeks)	38.8 ± 1.3	37.7 ± 2.4	0.07
Prematurity (<37 weeks of gestational age)	4 (8.5%)	3 (15%)	0.4
Breastfeeding:			
at birth	33 (70%)	12 (60%)	0.08
at 3 months	26 (55.3%)	11 (55%)	0.5
at 6 months	16 (34%)	7 (35%)	0.6
at 9 months	6 (12.8%)	3 (15%)	0.6
at 12 months	3 (6.4%)	2 (10%)	0.5
Anthropometric data at birth			
Weight (Kg)	2.5 ± 0.2	2.4 ± 0.4	0.9
Z score of weight	−1.7 ± 0.4	−1.6 ± 0.3	0.1
Length (cm)	47.2 ± 0.2	45.2 ± 2.5	0.5
Z score of length	−1.5 ± 0.9	−1.4 ± 1.2	0.7
Head circumference (cm)	33.1 ± 1.4	32.2 ± 1.6	0.8
Z score of head circumference	−0.9 ± 0.8	−0.9 ± 0.8	0.9
BMI (Kg/m^2)	11.4 ± 0.9	11.8 ± 1.3	0.2
Z score of BMI	−1.4 ± 0.8	−1.4 ± 1.3	0.9
3 months			
Weight (Kg)	5.6 ± 0.5	4.9 ± 0.6	0.9
Z score of weight	−0.4 ± 0.5	−1.2 ± 0.6	<0.001
Length (cm)	59.2 ± 2.3	57.2 ± 2.3	0.7
Z score of length	−0.6 ± 0.7	−0.4 ± 0.9	0.4
Head circumference (cm)	39.8 ± 1.3	39.1 ± 1.3	0.9
Z score of head circumference	−0.5 ± 1.1	−0.9 ± 1.4	0.3
BMI (Kg/m^2)	16.1 ± 1.2	14.9 ± 1.1	0.7
Z score of BMI	−0.2 ± 0.8	−1.0 ± 0.8	<0.001
6 months			
Weight (Kg)	7.4 ± 0.7	6.4 ± 0.6	0.3
Z score of weight	−0.3 ± 0.6	−1.2 ± 0.5	<0.001
Length (cm)	66.3 ± 3.2	64.2 ± 2.8	0.4
Z score of length	−0.5 ± 1.3	−0.2 ± 0.6	0.4
Head circumference (cm)	43.2 ± 1.3	42.2 ± 1.3	0.9
Z score of head circumference	−0.1 ± 1.2	−0.2 ± 0.9	0.8
BMI (Kg/m^2)	16.9 ± 1.4	15.6 ± 0.9	0.2
Z score of BMI	−0.3 ± 0.9	−1.1 ± 0.6	<0.001
9 months			
Weight (Kg)	8.3 ± 1.5	7.4 ± 0.8	0.7
Z score of weight	−0.4 ± 0.6	−1.4 ± 0.7	<0.001
Length (cm)	71.8 ± 2.8	68.0 ± 3.6	0.6
Z score of length	−0.6 ± 1.1	−0.1 ± 1.1	0.7
Head circumference (cm)	44.9 ± 1.4	44.1 ± 1.5	0.7
Z score of head circumference	−0.1 ± 0.9	−0.2 ± 1.2	0.8
BMI (Kg/m^2)	16.6 ± 1.1	16.1 ± 1.6	0.1
Z score of BMI	−0.6 ± 0.7	−1.2 ± 0.7	<0.001
12 months			
Weight (Kg)	9.3 ± 0.7	8.0 ± 0.9	0.4
Z score of weight	−0.5 ± 0.3	−1.7 ± 0.7	<0.001
Length (cm)	75.0 ± 2.9	72.8 ± 3.6	0.4
Z score of length	−0.03 ± 1.1	−0.1 ± 1.3	0.9
Head circumference (cm)	36.5 ± 4.0	45.1 ± 1.3	0.4
Z score of head circumference	−0.1 ± 1.2	−0.3 ± 0.8	0.6
BMI (Kg/m^2)	16.7 ± 1.2	15.1 ± 1.1	0.6
Z score of BMI	−0.6 ± 0.8	−1.7 ± 0.7	<0.001

4. Discussion

Our results show that GRF infants who achieve catch up during the first year of age are more likely to present lower glucose level at birth and higher triglycerides at 12 months than infants who will not get it.

Epidemiological studies have shown a relationship between low birth weight caused by intrauterine growth restriction and glycemic metabolism disorders in adulthood [20]. The relationship between preterm birth, low weight, and development of type II diabetes remained unproven until the publication in 2008 of a systematic review on this matter [21] In relation to earlier alterations, cohort studies such as CASyMIR [22] or Soto et al. [23] did not find significant differences in glycemia between GRF infants compared to control population at birth or at 12 months of age. However, they found significant differences in umbilical cord insulin between both groups, with lower fasting insulin levels in GRF cord blood. This difference was not observed at one year of age. The study by Soto et al. also compared insulin levels between GRFs who made recovery growth and those who did not, showing higher fasting insulin levels at one year of age in those who did recovery growth.

On the other hand, experimental studies with animals in which a growth restriction is induced have found early differences

Table 4
Quantitative variables of endocrine-metabolic analytical parameters in recovery and non-recovery GRF infants.

	Recuperators (n = 47)	Non recuperators (n = 20)	p
Glucose (mg/dl)			
Umbilical cord	80.7 (15.3)	99.2 (26.6)	0.03
9 months	82.7 (9.7)	84.1 (9.0)	0.5
12 months	79.1 (7.1)	85.5 (31.8)	0.5
Total Cholesterol (mg/dl)			
Umbilical cord	65.3 (17.4)	76.6 (29.8)	0.2
9 months	144.1 (24.8)	140.0 (25.5)	0.6
12 months	155.78 (21.0)	144.3 (34.3)	0.4
HDL Cholesterol (mg/dl)			
Umbilical cord	24.67 (9.0)	26.0 (8.9)	0.6
9 months	44.73 (13.1)	46.7 (15.3)	0.7
12 months	42.84 (10.1)	49.6 (24.7)	0.5
LDL Cholesterol (mg/dl)			
Umbilical cord	31.3 (11.8)	42.8 (23.4)	0.1
9 months	76.0 (21.4)	71.8 (29.4)	0.6
12 months	89.1 (29.4)	87.5 (32.4)	0.9
Triglycerides (mg/dl)			
Umbilical cord	46.1 (24.5)	35.3 (18.0)	0.2
9 months	115.8 (77.0)	105.8 (86.3)	0.7
12 months	119.3 (70.2)	79.1 (21.5)	0.03
Insulin (mU/ml)			
Umbilical cord	3.13 (4.31)	6.1 (11.3)	0.4
9 months	4.24 (4.54)	4.2 (3.9)	0.6
12 months	4.07 (4.80)	1.9 (0.7)	0.2
HOMA			
Umbilical cord	0.6 (0.7)	1.7 (3.4)	0.3
9 months	0.8 (0.6)	0.9 (0.9)	0.6
12 months	0.7 (0.8)	0.4 (0.1)	0.2
IGF-1 (ng/dl)			
Umbilical cord	36.8 (21.7)	39.3 (14.0)	0.7
9 months	59.4 (56.5)	44.0 (13.7)	0.3
12 months	89.9 (107.4)	54.2 (29.1)	0.4
IGF-BP3 (mg/l)			
Umbilical cord	1.2 (0.3)	1.2 (0.3)	0.8
9 months	2.8 (0.5)	2.5 (0.5)	0.5
12 months	3.1 (0.6)	2.7 (0.5)	0.4

between those who made a rapid recovery from those who did not: the glucose intolerance observed in young pigs was probably linked to insulin resistance and to early recovery growth in previously growth restricted pigs. Otherwise, results of studies in rats have shown that, not only the low weight in itself, but also the recovery growth is partly responsible for the programming effects observed at a later age [24–26].

We found differences in glucose at birth between recuperators and non-recuperators GRF infants. However, insulin levels or the glucose/insulin ratio have shown to be more useful as an index of possible metabolic pathology than glucose level alone. The measurement of glucose in cord blood was made both in infants with mothers with and without a fasting situation during labor, and we didn't record that item during data collection. The significant differences found in our study in umbilical cord glucose levels between both groups may be partly explained by different fasting situations.

In the present study, no statistically significant differences were found in the levels of fasting insulin or in the HOMA index during the follow-up in any of the groups during the first year of life. This may be due to the sample size. It is also possible that the alteration is of later appearance since the tendency with time seems to be an alteration in the regulation of blood glucose according to literature [27].

On the other hand, the non-compliance of fasting by some patients prior to the analytical extraction may have influenced the results as well: despite the indications, it is possible that our patients have not strictly complied with the fasting hours prior to the analysis.

As for the fat profile, we found statistically significant differences regarding triglycerides during the follow-up of the GRF in their first year of life: GRF infants with catch up presented higher levels of triglycerides. We found no differences between recuperators and non-recuperators in other parameters of fat profile.

Regarding triglycerides, significant differences were found in our study at 12 months (higher levels in GRF with recovery growth). Therefore, this would support the theory of a differentiating and early change (already with one year of life) between both groups; thus, GRF with recovery growth would tend to higher triglyceride levels. This finding agrees with that of some studies: Leunissen et al. describe the presence of significantly higher triglyceride levels in early adulthood in those GRF with a rapid weight gain in the first three months of life [11]. Soto et al. also find a trend to higher levels of triglycerides in GRF population compared to control population at one year of age [23]. However, when assessing the difference between GRF that perform recovery growth (of weight and/or height) and those that do not, they do not find statistically significant differences at one year of age. Previous studies indicate that the development of insulin resistance may be related to an interaction between birth weight and postnatal growth rate [28]. On the other hand, the level of serum triglycerides is accepted as a good indicator of insulin resistance [29]. These data, together with a greater trend to insulin resistance in GRF with rapid recovery growth could explain our findings regarding triglycerides.

There is contradictory evidence regarding the correlation of the lipoprotein profile in cord blood and parameters of fetal development as indicated by García Díaz et al. [30]. They showed a lack of relationship between lipid concentrations at birth and anthropometric parameters in their prospective study of 265 GRF children. They also pointed out the disparity of the results of studies that had analyzed this issue: some of them showed relationship between lipid concentrations in cord blood and anthropometric data and others did not. This fact does not prejudge the possibility that later, during childhood, there may be effects dependent or related to low birth weight. These effects may depend on greater insulin resistance (genetic or acquired during the fetal stage) and on the interaction of nutritional factors and lifestyle. Thus, authors such as Leunissen et al. found in an observational study conducted among GRF infants that those with a rapid weight gain during the first three months of life had lower HDL cholesterol levels and a higher total cholesterol/HDL cholesterol index in early adulthood [28].

In the present study, total cholesterol as well as LDL and HDL cholesterol levels during the first year of life were similar in those GRF with recovery group and those without it. These data agree with the findings shown by Soto et al. with no statistically significant differences in cholesterol levels between the GRF group and the control group or between GRF with or without recovery growth [23]. Thus, cholesterol levels do not seem to be a good indicator of future endocrinometabolic pathology at least in early stages. The relationship between total cholesterol and delay of intrauterine growth seems to be strongly influenced by gender as well as body mass index (BMI) [6] It is possible that, if a longer follow-up is done, these levels could be altered in the context of the metabolic syndrome.

On the other hand, it has been shown a strong relationship between some hormones and serum proteins such as IGF-1 and IGF-BP3 and fetal growth. These have shown an important role in fetal and postnatal growth as well as in development. Thus, several studies point to a significantly lower number of these proteins in cord blood of GRF compared to controls [22,31,32]. The hypothesis of recovery growth proposed by Cianfarani observes that newborn children with an altered development often

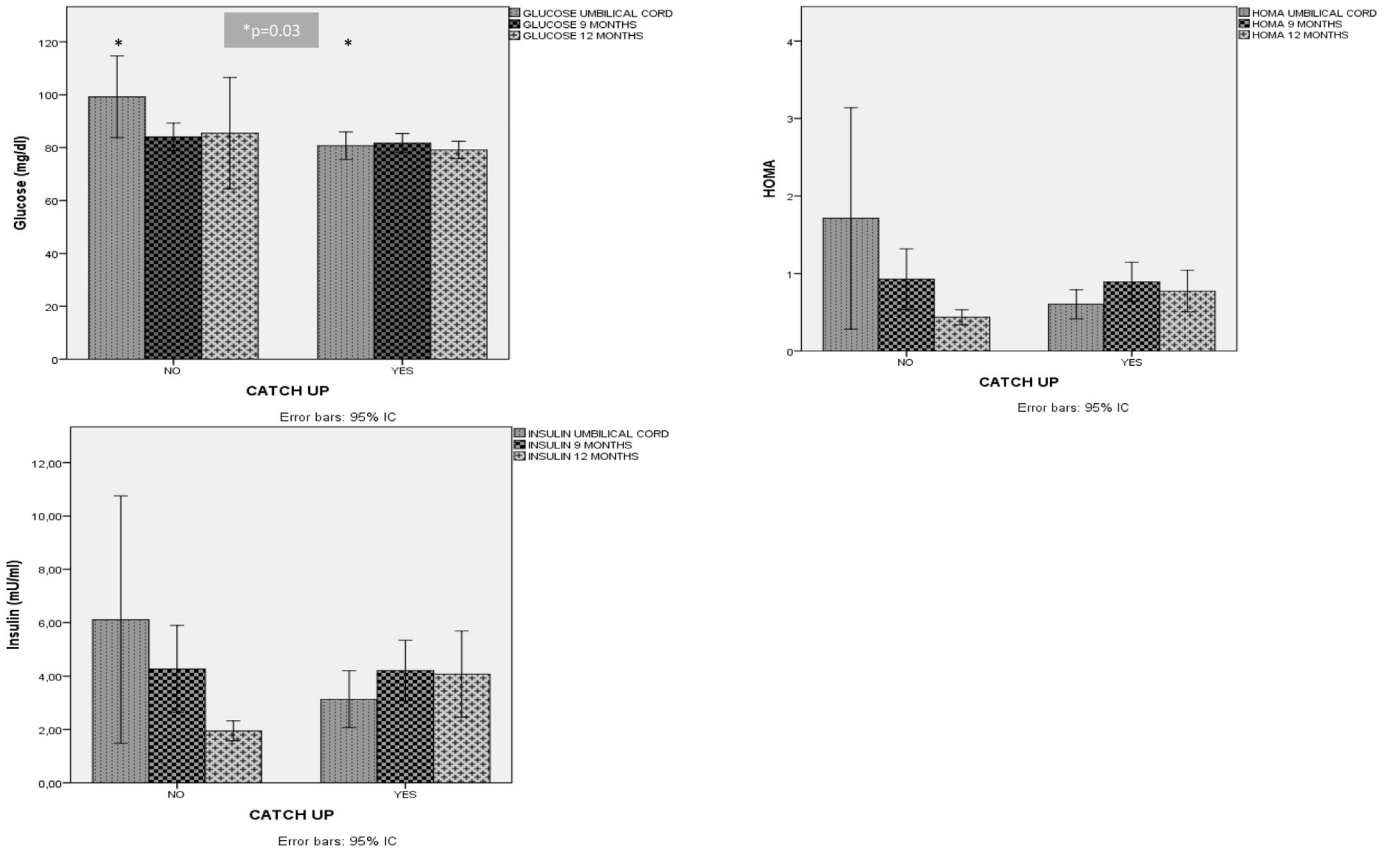

Fig. 1. Glycemic profile.

have low levels of insulin, IGF-1, IGF-BP3 but high concentrations of growth hormone (GH), IGF -BP1 and IGF-BP2 in comparison with newborns with normal growth [33]. The normalization of insulin levels and IGF growth factor usually occurs during the first three months of postnatal life. This concurs with the rapid recovery growth that occurs in children with altered development. In our study, we found no significant differences in IGF-1 and IGF-BP3 between both groups of GRF infants. If we had followed more children and during a longer period perhaps we could have found some differences between recuperators and non-recuperators.

Finally, comparing clinical characteristics of recuperators and non-recuperators, we found no significant differences regarding data related to pregnancy and mother's characteristics/anthropometry. Analysing general characteristics of the studied GRF population during follow-up, we found gestational age at birth and breastfeeding at birth or more showed an association close to statistical significance. After the multivariate analysis, none of the variables maintained an independent association with catch up: only the lower gestational age at birth showed an association close to statistical significance with catch up growth. Comparing with previous literature, it seems that preterm babies usually show an extrauterine growth restriction or postnatal growth failure, but this usually reflects only the situation in the first weeks after delivery [34].

Regarding evolution of anthropometric data, we observed that children who made a catch up growth during the follow up already showed-from the third month-a trend in this sense since their Z scores of weight and BMI were statistically different in children that did not make a catch up growth at 12 months. This point agrees with other studies that show that most GRF with catch up growth do it during the first 3–6 months [35]. However we have not found any differences with reference to other anthropometric data such as length or head circumference.

Our study has some limitations. It seems to show that those children with a lower gestational age at birth tend to have a catch up growth less frequently. However, few preterm babies have been included and they are not less than 32 weeks of gestational age due to the characteristics of our hospital. Thus, we cannot make a categorical affirmation, but our results suggest some kind of association between lower gestational age at birth and no catch up. We think more and larger studies are necessary including a sample with more preterm babies of different gestational ages at birth.

Losses of patients during follow-up is another limitation of our study. In order to understate the possible selection bias, we made a comparison of basal clinical and analytical characteristics of patients who finished follow-up and those who did not, and we did no find significant differences. We also made a comparison of basal clinical characteristics of the patients with endocrine metabolic parameters at 9 and 12 months and did not find significant differences except in total cholesterol at 12 months (higher in the group of smoking mothers) and LDL cholesterol at 9 months (higher in children from primiparous mothers). Thus, we think the selection bias due to losses could have little influence in the results obtained and probably do not invalidate them.

Finally we made no adjustments for multiple testing so some different results could be found in similar studies.

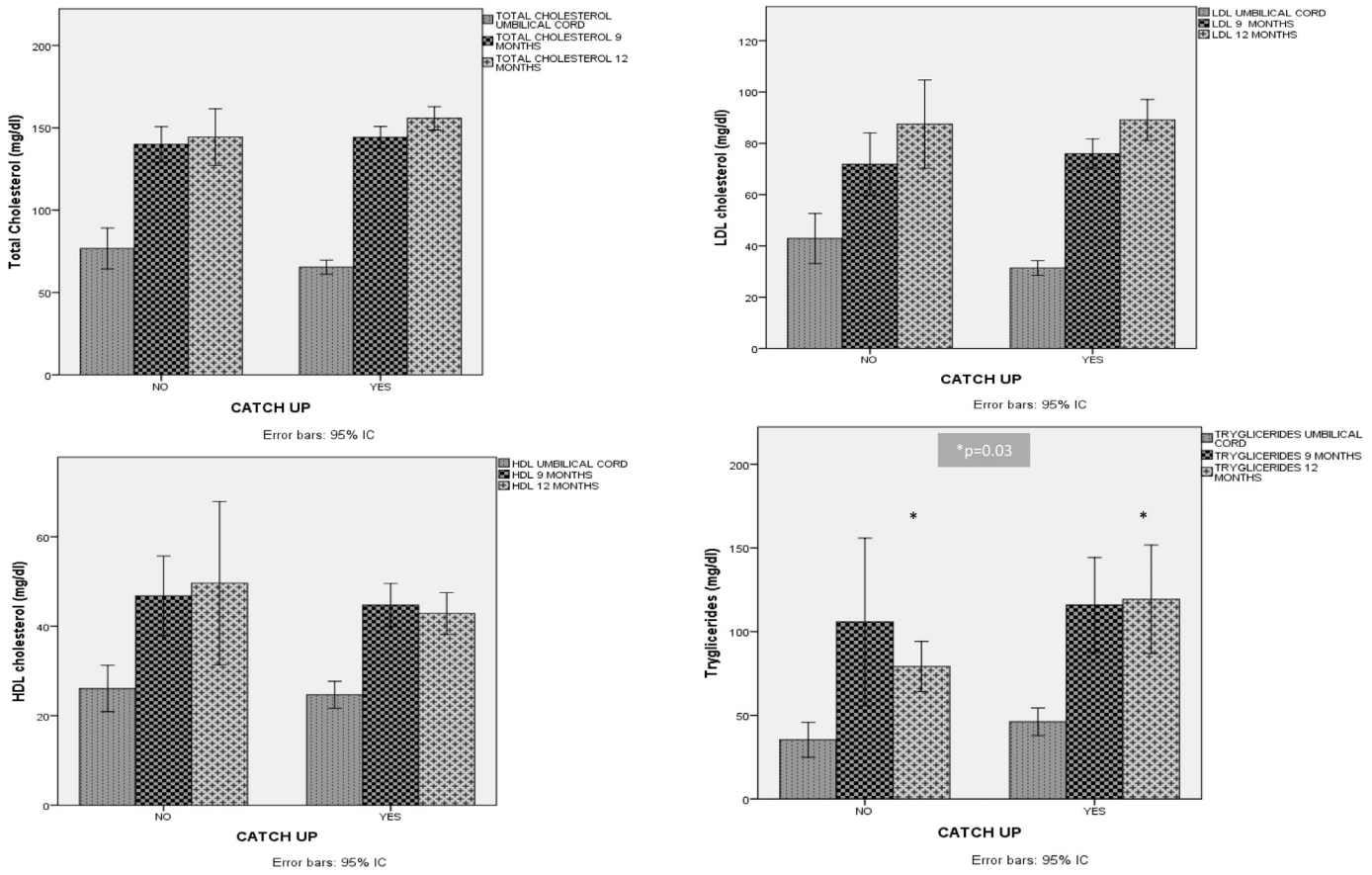

Fig. 2. Fat profile.

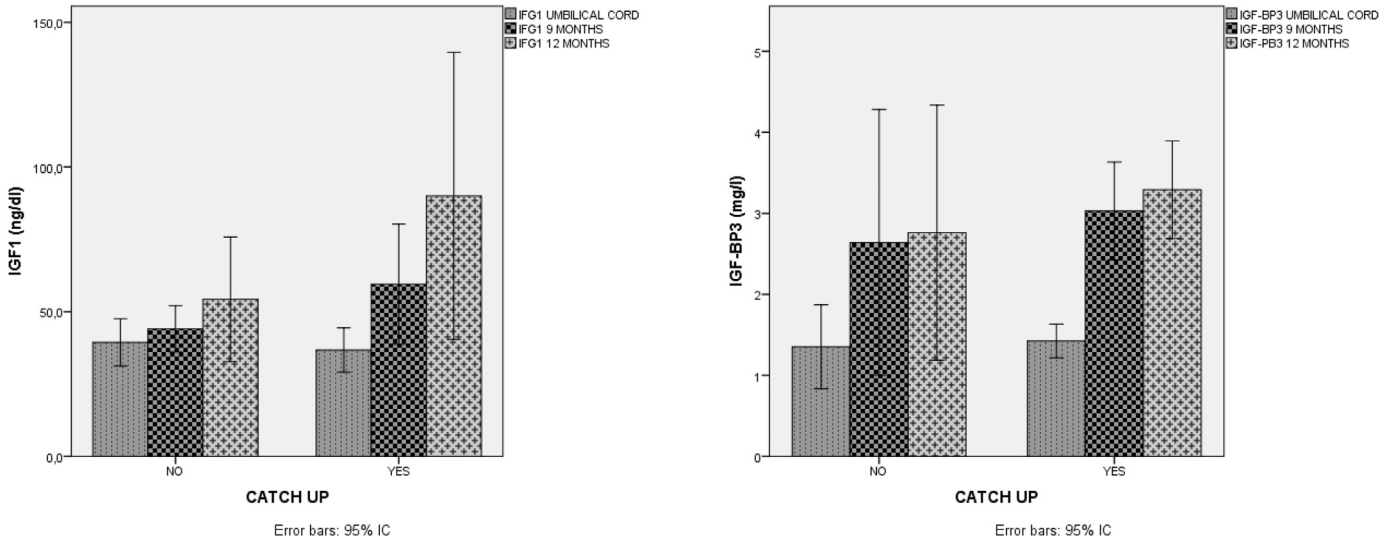

Fig. 3. IGF-1 and IGF-BP3.

Summarizing our results suggest that there may be early markers of future endocrinometabolic pathology (higher triglycerides) in GRF population with recovery growth at the first year of life. More studies are needed to confirm these findings. If our results are confirmed, this could be useful to develop a tool for early detection of children with higher metabolic risk in order to prevent future pathology.

5. Conclusions

We found early differentiating analytical markers (triglycerides) in GRF children with recovery growth during the first year of life. There may be some early differences in biomarkers for insulin resistance between GRF with and without catch up. Catch up growth may be a risk factor for the development of insulin

resistance in later life. A screening in GRF with catch up growth might be useful at some later age during childhood.

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References

[1] Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet 1989:577–80.
[2] Barker DJ, Bull AR, Osmond C, Simmonds SJ. Fetal and placental size and risk of hypertension in adult life. BMJ 1990;301(6746):259–62.
[3] Barker DJ, Hales CN, Fall CH, Osmond C, Phipps K, Clark PM. Type 2 (non-insulin dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. Diabetologia 1993;36(1):62–7.
[4] Kopec G, Shekhawat P, Mhanna M. Prevalence of diabetes and obesity in association with prematurity and growth restriction. Diabetes Metab Syndr Obes Targets Ther 2017 Jul 6;10:285–95. Dove Press.
[5] Reinehr T, Kleber M, Toschke AM. Small for gestational age status is associated with metabolic syndrome in overweight children. Eur J Endocrinol 2009:579–84.
[6] Mercuro G, Bassareo PP, Flore G, Fanos V, Dentamaro I, Scicchitano P, et al. Prematurity and low weight at birth as new conditions predisposing to an increased cardiovascular risk. Eur J Prev Cardiol 2013 Apr;20(2):357–67.
[7] Ravelli AC, van der Meulen JH, Michels RP, Osmond C, Barker DJ, Hales CN, et al. Glucose tolerance in adults after prenatal exposure to famine. Lancet 1998:173–7.
[8] Singhal A, Cole TJ, Fewtrell M, Kennedy K, Stephenson T, Elias-Jones A, et al. Promotion of faster weight gain in infants born small for gestational age: is there an adverse effect on later blood pressure? Circulation 2007:213–20.
[9] Ben-Shlomo Y, McCarthy A, Hughes R, Tilling K, Davies D, Smith GD. Immediate postnatal growth is associated with blood pressure in young adulthood: the Barry Caerphilly Growth Study. Hypertension 2008:638–44.
[10] Brufani C, Grossi A, Fintini D, Tozzi A, Nocerino V, Patera PI, et al. Obese children with low birth weight demonstrate impaired beta-cell function during oral glucose tolerance test. J Clin Endocrinol Metab 2009:4448–52.
[11] Leunissen RW, Kerkhof GF, Stijnen T, Hokken-Koelega A. Timing and tempo of first-year rapid growth in relation to cardiovascular and metabolic risk profile in early adulthood. JAMA 2009:2234–42.
[12] Meas T, Deghmoun S, Alberti C, Carreira E, Armoogum P, Chevenne D, et al. Independent effects of weight gain and fetal programming on metabolic complications in adults born small for gestational age. Diabetologia 2010;53(5):907–13.
[13] Chernausek SD. Update: consequences of abnormal fetal growth. J Clin Endocrinol Metab 2012:689–95.
[14] Neitzke U, Harder T, Plagemann A. Intrauterine growth restriction and developmental programming of the metabolic syndrome: a critical appraisal. Microcirculation 2011;18(4):304–11.
[15] Thorn SR, Rozance PJ, Brown LD, Hay Jr WW. The intrauterine growth restriction phenotype: fetal adaptations and potential implications for later life insulin resistance and diabetes. Semin Reprod Med 2011;29(3):225–36.
[16] Mericq V, Ong KK, Bazaes R, Pena V, Avila A, Salazar T, et al. Longitudinal changes in insulin sensitivity and secretion from birth to age three years in small- and appropriate-for gestational-age children. Diabetologia 2005;48(12):2609–14.
[17] Ong KK, Petry CJ, Emmett PM, Sandhu MS, Kiess W, Hales CN, et al. Insulin sensitivity and secretion in normal children related to size at birth, postnatal growth, and plasma insulin-like growth factor-I levels. Diabetologia 2004;47(6):1064–70.
[18] Carrascosa A, Fernández JM, Ferrández A, López Siguero JP, López D, Sánchez E. Estudios Españoles de Crecimiento. Disponible en, http://www.aeped.es/noticias/estudios-españolescrecimiento-2010.
[19] Hemachandra A, Howards P, Furth S, Klebanoff M. Birth weight, postnatal growth, and risk for high blood pressure at 7 years of age: results from the collaborative perinatal project. Pediatrics 2007;119(6):1264–9.
[20] Huang TT, Johnson MS, Goran MI. Development of a prediction equation for insulin sensitivity from anthropometry and fasting insulin in prepubertal and early pubertal children. Diabetes Care 2002;25(7):1203–10.
[21] Whincup PH, Kaye SJ, Owen CG, Huxley R, Cook DG, Bhargava SK, et al. Birth weight and risk of type 2 diabetes a systematic review 2015;300(24).
[22] Verkauskiene R, Beltrand J, Claris O, Chevenne D, Deghmoun S, Dorgeret S, et al. Impact of fetal growth restriction on body composition and hormonal status at birth in infants of small and appropriate weight for gestational age. Eur J Endocrinol 2007:605–12.
[23] Soto N, Bazaes RA, Peña V, Salazar T, Avila A, Iñiguez G, et al. Insulin sensitivity and secretion are related to catch-up growth in small-for-gestational-age infants at age 1 year: results from a prospective cohort. J Clin Endocrinol Metab 2003;88(8):3645–50.
[24] Poore KR, Fowden AL. Insulin sensitivity in juvenile and adult Large White pigs of low and high birthweight. Diabetologia 2004;47(2):340–8.
[25] Yuan QX, Zhou JY, Teng LP, Liu CP, Guo J, Liu LJ, et al. Intrauterine growth retardation leads to the functional change of insulin secretion in the newborn rats. Horm Metab Res 2010;42(7):491–5.
[26] Chamson-Reig A, Thyssen SM, Arany E, Hill DJ. Altered pancreatic morphology in the offspring of pregnant rats given reduced dietary protein is time and gender specific. J Endocrinol 2006:83–92.
[27] Singhal A, Cole TJ, Fewtrell M, Deanfield J, Lucas A. Is slower early growth beneficial for long-term cardiovascular health? Circulation 2004;109:1108–13. United States.
[28] Eriksson JG, Forsen T, Tuomilehto J, Winter PD, Osmond C, Barker DJ. Catch-up growth in childhood and death from coronary heart disease: longitudinal study. BMJ 1999;318(7181):427–31.
[29] McAuley KA, Williams SM, Mann JI, Walker RJ, Lewis-Barned NJ, Temple LA, et al. Diagnosing insulin resistance in the general population. Diabetes Care 2001;24(3):460–4.
[30] Dios García Díaz Jd, Gaspar Blázquez MJ, Bienvenido Villalba M, Granizo Domínguez V, Jiménez Bustos JM. Relationship between lipoprotein profile in cord blood with obstetric variables and anthropometry in newborns. Differences related with sex. Clín Investig Arterioscler 2007;19(05):215–22.
[31] Lo HC, Tsao LY, Hsu WY, Chen HN, Yu WK, Chi CY. Relation of cord serum levels of growth hormone, insulin-like growth factors, insulin-like growth factor binding proteins, leptin, and interleukin-6 with birth weight, birth length, and head circumference in term and preterm neonates. Nutrition 2002:604–8.
[32] Albertsson-Wikland K, Boguszewski M, Karlberg J. Children born small-for-gestational age: postnatal growth and hormonal status. Horm Res 1998;49(2):7–13.
[33] Cianfarani S, Germani D, Branca F. Low birthweight and adult insulin resistance: the "catch-up growth" hypothesis. Arch Dis Child Fetal Neonatal 1999;81(1):71–3.
[34] Fenton TR, Chan HT, Madhu A, Griffin IJ, Hoyos A, Ziegler EE, et al. Preterm infant growth velocity calculations: a systematic review. Pediatrics 2017;139(3):e20162045.
[35] Boguszewski MC, Mericq V, Bergada I, Damiani D, Belgorosky A, Gunczler P, et al. Latin American consensus: children born small for gestational age. BMC Pediatr 2011:66–72.