The impact of intrauterine and extrauterine weight gain in premature infants on later body composition

Growth, fat mass and HOMA-IR

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Clinical

ABSTRACT

BACKGROUND. The impact of intrauterine and extrauterine growth on later insulin resistance and fat mass (FM) in very low birth weight (VLBW) infants is not well established. Our study aim was to evaluate the effects of intrauterine and early/late extrauterine growth on later insulin resistance and body composition in VLBW infants from 6 months corrected age (CA) to 36 months.

METHODS. Prospective measurements of body composition by DEXA and insulin resistance by HOMA-IR along with other fasting plasma biochemistries were made in 95 VLBW infants at 6, 12, 18, 24 months CA and 36 months postnatal age. Mixed-effect models were used to evaluate the effects of age, sex, maturation status, and Δweight SD score on percentage FM (PFM), FM index (FMI), fat free mass index (FFMI) and HOMA-IR.

RESULTS. PFM and FMI were negatively associated with a decrease in weight-SD scores from birth to 36 weeks postmenstrual age (PMA; p=0.001) and from 36 weeks PMA to 6 months CA (p=0.003). PFM and FMI were higher in AGA than SGA infants. HOMA-IR was not associated with the Δweight-SD scores in either period.

CONCLUSIONS. Catch down growth in terms of weight is associated with persistently lower adiposity but not insulin resistance up to 36 months of age.

Introduction

The effects of prematurity, early growth impairment and catch-up growth of premature infants on their later metabolic health and adiposity remain unresolved. While premature birth is associated with a reduction in insulin sensitivity in childhood (1, 2), the effects of early growth patterns of preterm infants on insulin sensitivity are inconclusive. In two studies in preterm infants, associations between rapid weight gain in the first two weeks of life and decreased insulin sensitivity were observed in adolescents and prepubertal children (3, 4), although the fasting 32-33 split proinsulin concentration of formerly preterm infants with greater weight gain was not statistically different from controls during adolescence (3). Rapid infant weight gain until 3 months corrected age (CA) is reported to be associated with higher HOMA-IR at 19 years and marginally so at 5-7 years; however, the association was not statistically significant after correction for possible confounding variables (4, 5). Other studies failed to show any effect of growth between birth and 18 months of age on insulin concentrations at 9-12 years of age (6, 7).

The early postnatal period is purported to be critical for the development of adipose tissue (8). Preterm infants have a greater percentage fat mass (PFM) at term gestational age than full-term infants (9). Rapid growth in the first months of life in very low birth weight (VLBW) infants has been associated with increased adiposity at 6 and 19 years of age (10-12). In contrast, prematurity was associated with reduced body fatness in later childhood in one study (13) but greater fat mass and trunk fat, at 18 to 24 years of age compared to full-term subjects in another study

(14).

The effect of intrauterine weight gain in premature infants on later insulin sensitivity is unclear. Although size at birth influences plasma glucose levels 60 and 30 min after a glucose load in formerly preterm children at 20 days and 9-12 years, respectively (15, 6), it did not affect insulin sensitivity at 7 days of age or in adulthood (16, 7, 17). We previously reported higher HOMA-IR in the cord blood of preterm infants and a negative correlation between HOMA-IR and insulin levels and gestational age in this cohort (18).

To address these unresolved issues, our study aims were: (1) to determine the effect of intrauterine and early/ late extrauterine growth on later insulin resistance and body composition from 6 months CA to 36 months; (2) to analyse fasting plasma triglycerides, cholesterol, leptin, adiponectin, resistin and insulin-like growth factor I (IGF-I) concentrations from 6 months CA to 36 months; and (3) to test if these fasting plasma biochemistries correlate with percentage fat mass (PFM) and HOMA-IR in VLBW infants.

Materials and methods

A cohort study of VLBW was conducted between 6 and 36 months corrected for gestational age. Infants were recruited from La Paz University Hospital between November 2004 and October 2006 immediately after birth. Among all consecutive infants (n=341) who were born at < 34 weeks gestation and birth weight < 1500 g, parents of 111 gave written informed consent to participate. Exclusion criteria included presence of congenital diseases, chromosomal abnormalities and short bowel syndrome or others digestive disorders where absorption of nutrients was impaired. Data from VLBW infants were collected during initial admission.

The local research ethics committee of the La Paz University Hospital approved the study and written informed consent was obtained from the parent(s).

Recombinant human erythropoietin and a supplement of elemental iron (6 mg/kg per day) from the first days of life were administered to all VLBW infants included in the cohort during hospital stay. The early nutrition and clinical course of the premature infants were described previously (19). Data regarding human milk duration or formula feeding was collected. Weight (g), length (cm), and head circumference (cm) were measured at birth and at 36 weeks PMA and expressed as SD scores to correct for gestational age and sex with the use of Fenton growth chart (20). Infants were classified as AGA or SGA at birth regarding weight for age above or below 10 percentile.

Nutritional management after discharge of the VLBW infants entailed the following recommendations: 1) a supplement of elemental iron at 2 mg/kg per day starting at month 2 of age and extending through 12 months of age; 2) exclusive breastfeeding

for a minimum of 4 months but preferably for 6 months, without supplementation after discharge; 3) if human milk was not available, post discharge formula was used until 3 months CA and preterm formula was used only for infants with bronchopulmonary dysplasia. The iron requirements for toddlers (1-3 years of age) were presumed to be met with naturally iron-enriched foods.

For the research protocol, infants were scheduled a visit to La Paz University Hospital at 6, 12, 18, 24 months CA and at 36 months. Two physicians performed anthropometric measures included weight, length and head circumference according to standardized procedures. During the study, standardization was carried out to maximize inter-observer reliability, coefficient of variations less than 5% were achieved and maintained during the study period. A nude weight was obtained in duplicate using a Seca electronic infant scale accurate to the nearest 10 g (Seca 375, Hamburg, Germany) and length was obtained in duplicate on an infant length board to the nearest 0.1 cm (Seca 210, Hamburg, Germany). Circumference measurement was taken to the nearest mm by using a flexible measuring tape. Whole body FM and FFM and regional (truncal) FM, whole-body bone mineral content (BMC) and bone mineral density (BMD) were measured by using DXA (Lunar- DPX-MD; GE Healthcare, Chalfont St. Giles, UK). For the measurement of truncal fat, a line of delineation was drawn between the head of the humerus and the glenoid fossa of the scapula to separate the upper limb from the trunk, and the leg consisted of the parts of the body between the inferior border of the ischial tuberosity to the most distal tip of the toes.

Scans were analyzed by using infant whole body analysis software (General Electric, Chalfont St. Giles, UK). All DXA scans were performed with the same device and

software. No sedation was used. The study was performed after a feeding. Previously reported precision values for DXA are <1% for FFM and <2% for FM (21). FM was normalized to body weight using the FMP, and FM and FFM were normalized to body height to give fat mass index (FMI) and fat-free mass index (FFMI) as follows FMI = FM/height^2 and FFMI = FFM/height^2. The percentage of truncal fat (PTF) was calculated using the following formula: PTF = 100 x TF/FM.

Blood samples were drawn under fasting conditions, at least six hours after the previous meal, centrifuged and the serum stored at -80ºC until assayed. Glucose, total cholesterol and triglycerides were immediately quantified by enzymatic methods in an auto analyzer. Insulin (Diagnostic Products Corporation, Los Angeles, CA), leptin, adiponectin and IGF-I (Mediagnost, Tübingen, Germany) were determined by radioimmunoassay and resistin by enzyme-linked immunosorbent assay (ELISA) from Merck Millipore (Billerica, MA). In all cases intra- and inter-assay coefficients of variations were lower than 10%. HOMA-IR was calculated according to the formula: [glucose (mmol/l) X insulin (mU/ml)]/22.5.

At 6 to 36 months, weight, length and head circumference z scores were computed using OMS growth curves through the macro for SPSS. From 6 to 24 months corrected age was used, chronological age was use at 36 months. Extra uterine growth retardation between birth and 36 weeks PMA (early) and between 36 weeks PMA and 6 months CA (late) were computed as Δ-SD scores. The number of participants completing the 6 to 36-month visits was 95; the parents of 16 infants refused to participate in the follow up study.

The study was originally designed to evaluate the effect of early growth retardation on body composition and metabolic outcomes. Mixed-Effect Model Repeat Measurement analyses were performed to assess associations between prenatal (as a dichotomous variable, AGA vs SGA), early and late extra uterine growth retardation (both continuous variables, changes in SDS) and percentage fat mass, FMI, FFMI and HOMA-IR, from 6 to 36 months, using the MIXED procedure for SAS 9.1 software (SAS Institute, Cary, NC). The models included AGA-SGA at birth, the age at evaluation (6, 12, 18, 24 and 36 months), and early and late Δ-SD scores. Sex was used as a covariate. An estimate of fixed effect was calculated for percentage fat mass, FMI, FFMI and HOMA-IR regarding prenatal, early and late extra uterine growth retardation. To demonstrate relevant univariant associations, simple linear regression was used, examining leptin concentration against percentage fat mass and HOMA. Descriptive statistics are expressed as mean (±SD) for continuous variables or n (%) for categorical variables.

Results

Anthropometric data of the VLBW infants at birth and at 36 weeks postmenstrual age (PMA) are shown in **Table 1**. Catch-down growth, defined as a decrease in SD score greater than 0.67, as it is stated by Ong KK et al (22), was observed in the weight of 86 infants (92%) and in the length of 77 infants (85%) between birth and 36 weeks PMA. Anthropometric data from 6 months CA to 36 months of age are presented in **Table 2** and **Figure 1**. Body weight, length and head circumference increased over time (P <0.001). Weight SD-scores decreased and length SD-scores increased from 6 months CA to 36 months (P <0.001). Catch-up growth, defined as a change in z-score >0.67 (16), was observed for weight in 18 (19%) of the infants between 6 months CA and 36 months. Head circumference z-score increased from 6 months CA to 36 months (P =0.006). In the follow-up study, 26% of infants were reported to be formula fed from birth, 74% received human milk for an average of at least 9 weeks, while only 14 infants were still receiving human milk at three months corrected age (unpublished data).

FM, PFM, fat mass index (FMI), percentage trunk-fat mass, fat-free mass (FFM), fat-free mass index (FFMI) and bone mineral density (BMD) are presented in **Table 2** and **Figure 1**. FM, FFM and BMD increased gradually from 6 months CA to 36 months (P <0.001). Whereas PFM remained stable (P =0.714), FMI and FFMI decreased over time (P =0.004 and P <0.001, respectively). Percentage trunk-fat mass decreased from 6 to 18-24 months CA, and then increased at 36 months to values similar to those observed at 6 months CA (P <0.001) (**Table 2**). PFM and FMI were lower for SGA (n=24) than AGA infants (n = 71) from 6 months CA to 36 months (p<0.001).

Cholesterol, triglycerides, resistin and HOMA-IR are presented in **Table 2** and IGF-I, leptin and adiponectin are displayed in **Figure 2**. Cholesterol increased, particularly between 6 and 12 months CA, whereas triglycerides steadily decreased during the study period ($p<0.001$). Leptin decreased from 6 to 12 months CA and then remained stable. Adiponectin decreased from 6 to 18 months CA. No effects of time on resistin were observed. HOMA-IR decreased initially and then increased ($p<0.001$). HOMA-IR was not statistically different between SGA and AGA infants throughout the study ($p=0.076$).

PFM correlated positively with serum leptin concentrations throughout the study from 6 months CA to 36 months ($r = 0.444$ to 0.583, $P<0.001$). HOMA-IR tended to be positively correlated with serum leptin concentration at 6 months CA but this did not attain statistical significance ($r = 0.303$; $P=0.061$). HOMA, however, was positively associated with leptin at 12, 18, 24 months CA and 36 months ($r=0.341$, $P=0.008$; $r = 0.356$, $P=0.011$; $r = 0.345$, $P=0.008$ and $r = 0.392$, $P=0.003$, respectively). The other biochemistries did not correlate consistently with PFM or HOMA-IR throughout the study period.

The effects of age, sex, being AGA vs. SGA status, and experiencing early and late extrauterine weight-SD score on PFM, FMI, FFMI and HOMA-IR from 6 months CA to 36 months are shown in **Table 3**. PFM and FMI were negatively associated with a decrease in weight-SD score from birth to 36 weeks PMA (early extrauterine period) ($p<0.001$) and from 36 weeks PMA to 6 months CA (late extrauterine period) ($p=0.003$). FFMI was negatively associated with a decrease in early, but not late extrauterine weight-SD score. PFM (+4.3 ±1.03 %) and FMI (+0.09 ± 0.02 g/cm^2)

were higher in AGA than SGA in infants from 6 months CA to 36 months. Overall, PFM and FMI did not differ by sex, but females had significantly less PFM than males at 6 and 12 months CA (-2.80 ± 1.36% (p=0.045) and -2.89 ± 1.29% (p=0.028)), respectively. FMI was lower in females than males at 12 months CA (-0.06±0.03 g/cm^2 (p=0.037)). FFMI and bone mineral density (p=0.001) were also lower in females than males during the entire study period.

HOMA-IR was no significantly associated with early or late extrauterine Δweight SD scores. Nor was HOMA-IR associated with PFM.

Discussion

A decrease in weight-SD score before 6 months CA was associated with a lower accretion of fat mass and fat-free mass in VLBW preterm infants. Prenatal growth retardation and insufficient early/late extrauterine weight gain were associated with less fat mass from 6 months CA to 36 months. A deficit in weight gain during the last trimester and in early postnatal life had a persistent effect on PFM and FMI through 36 months of age. We did not detect an effect of prenatal or postnatal growth on HOMA-IR in this cohort up to 36 months of age. Given the potential impact of poor growth during a relatively short timeframe on later metabolic health, this study clarifies the effect of intrauterine and early postnatal growth on later body fatness and insulin resistance between 6 months CA and 36 months in VLBW infants.

Growth and body composition were measured longitudinally from 6 months CA to 36 months in a cohort of preterm infants whose protein and energy intakes approached recommended levels during the first weeks of life (19). Prenatal and/or early postnatal growth retardation followed by catch-up growth between 6 months CA and 36 months was not associated with the expected accretion of FM before 36 months. Although absolute FM and FFM increased from 6 months CA to 36 months, PFM remained stable. Even the AGA infants had similar FM, not higher than term infants from 18 months CA on, as would have been expected at term gestational age (9). Griffin IJ et al. reviewed published data and concluded that preterm infants generally show less FM and FFM than term infants, as published by Butte et al (23) in the first year (24). In contrast, Ramel et al. showed higher fat mass in preterm

infants compared with term infants at term age and similar fat mass at 4 months CA (25). To the best of our knowledge, our study is the first to evaluate the effect of prenatal and early growth of VLBW infants on later body composition up to 36 months of age.

Rapid postnatal growth in preterm infants from preterm birth up to term age, and in the first 3 months after term age is supposedly harmful for development of body fat (13). Intrauterine and extrauterine growth retardation did not promote higher fat mass in our cohort possibly because no catch-up occurred before 6 months CA. In children, prematurity is associated with reduced body fatness. The findings of Fewtrell et al related to reduced body fatness in 8-12 y of age in formerly premature children, are particularly pertinent to the results presented here (12). As in our study, Fewtrell et al. (6) found a relationship between AGA at birth and insulin resistance and FM during the first years of life. This effect seems to be lost in adulthood (reviewed by Lapillonne, 26). We found that the early and late extrauterine decrease in weight-SD score was associated with lower FM and the early extra uterine decrease in weight-SD score was associated with lower FFM during the first 36 months of life. The use of FMI and FFMI, adjusted for height, allowed us to quantify the effect of growth independently on FM and FFM. No association was found in our study between adiposity and HOMA-IR, although a relationship was found between leptin and insulin resistance from 12 months CA to 36 months. In formerly VLBW infants, insulin resistance may develop during childhood (1,25) and adulthood, as assessed by fasted insulin concentrations or insulin resistance tests (reviewed by Lapillonne, 26). Most of the studies do not

support a relationship between rapid weight gain in preterm infants during the first 18 months of life and later risk of insulin resistance. Weight gain from birth to 40 weeks gestation is not associated with insulin resistance in children aged 4-10 years born prematurely (27). Growth in the first year of life did not affect glucose tolerance (14). Insulin concentrations at 9-12 years were associated with an increase in weight from 18 months to age of measurement, but not with weight gain before 18 months (6). In adults born at term, there was no direct effect of postnatal weight velocity (0-4 months) on adult HOMA-IR, however weight velocity from 0 to 24 months positively predicted HOMA-IR (28). In SGA infants, the percentage of body fat in adulthood explained the differences in insulin sensitivity of those with rapid weight gain in the first three months of life (29). Our study showed no association between early and late extrauterine growth and insulin resistance, suggesting growth retardation during initial hospitalization and after discharge did not affect HOMA-IR up to 36 months of age. Caution, however, must be taken in interpreting our results given that not all the parents of the infants born during the recruitment period consented to participation in the study and only a small percentage of infants experienced significant catch-up growth. The effects of the study design were already considered previously (19); however, clinical characteristics presented here are representative of our NICU population. Parents of the infants included in our study received nutritional recommendations but they are not obliged to follow a strict feeding protocol and our short-term follow-up.

In conclusion, our study indicates that reduced weight gain during gestation and the first months of life has a significant impact on FM from 6 months CA to 36 months in

VLBW infants. Furthermore, early postnatal growth retardation does not influence insulin sensitivity. Postnatal growth retardation is a frequent clinical feature in VLBW infants. Our data do not support the hypothesis that interventions aimed at discouraging weight gain during hospitalization and after discharge would improve body composition or insulin resistance in preterm infants.

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Figure 1. Weight SD score (lines) and percentage fat mass from 6 months CA to 36 months (bars) in AGA (black, n = 71) vs. SGA (open, n = 24). Mixed-Effect Model Repeat Measurement analyses were performed. Percentage fat mass is significantly different between AGA and SGA from 6 months CA to 36 months ($P < 0.001$). Weight SD score do not differ significantly between groups

Figure 2. (a) IGFI, (b) leptin and (c) adiponectin of AGA (grid bars, n = 61) and SGA (open bars, n= 20) infants from 6 months CA to 36 months. Mixed-Effect Model Repeat Measurement analyses were performed. No significant differences between groups were observed