CLINICAL RESEARCH ARTICLE

The relationship between IGF-I and -II concentrations and body composition at birth and over the first 2 months

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BACKGROUND: Insulin-like growth factor (IGF)-I and -II play an important role in prenatal growth. During the first 2 months from birth, body fat doubles, and rapid weight gain during this time increases future risk of cardiometabolic disease. The aim of this study was to determine whether IGF measurements at birth associate with body composition and the trajectory of its changes in the first 2 months.

METHODS: Umbilical cord IGF-I and -II concentrations were measured in term infants. Air displacement plethysmography was performed at birth and 2 months. Fat mass (FM) and fat-free mass (FFM) were corrected for infant length (L) to FM/L³ and FFM/L², respectively.

RESULTS: In 601 (317 male) infants, IGF-I concentrations at birth were associated with FM/L³ and FFM/L² Z-scores at birth ($R^2 = 0.05$ and 0.04 , respectively, $P < 0.001$), and IGF-II concentrations were associated with FFM/L² Z-scores at birth ($R^2 = 0.01$, $P = 0.02$). Lower IGF-I concentrations were weakly associated with increases in FM/L³ Z-scores over the first 2 months ($R^2 = 0.01$, $P = 0.003$).

CONCLUSION: IGF-I concentrations at birth are associated with adiposity and lean mass at birth and inversely with the trajectory of FM accumulation over the first 2 months. IGF-I measurements only account for a small amount of the variance in these measures.

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INTRODUCTION

The in utero environment and early infant growth play an important role in the development of adult disease. Low birth weight is associated with increased risk of cardiovascular disease in adulthood¹ and offspring of mothers exposed to famine during pregnancy have shown an increased risk of obstructive airway disease,² metabolic syndrome,³ and psychiatric disease.^{4,5} Following birth, rapid early weight gain also adversely affects risk of obesity,⁶ insulin resistance,⁷ premature adrenarche,⁸ and cardiovascular disease.^{1,6} These early-life weight changes may have additional implications for future health, as the obese phenotype often tracks from early childhood through adulthood.⁹

Insulin-like growth factor (IGF)-I and -II play an important role in regulating fetal growth. Infants with IGF-I and -II signaling defects have significant prenatal growth failure.¹⁰ Regulation of IGF-I and -II in utero appears to be more dependent on nutrition¹¹ than growth hormone (GH). Infants with GH deficiency have normal size at birth,¹² whereas infants with intrauterine growth restriction have reduced concentrations of IGF-I and -II.^{13,14} This correlation with weight at birth is stronger for IGF-I than for IGF-II concentrations.¹⁴ Animal models also show that expression of IGF-I and -II is reduced in response to intrauterine nutritional deprivation.¹⁵

Birth weight is often used as a proxy for adiposity, but these do not always correlate.^{16,17} It is possible that IGF-I and -II concentrations are associated more closely with lean and fat

mass (FM) than with birth weight. Infants born small for gestational age (SGA) have a greater deficit in body fat than in lean mass and have lower IGF-I concentrations,¹⁸ suggesting that IGF-I levels may be more closely associated with body fat than lean mass at birth. IGF-I measurement may also be useful in assessing early growth trajectories. In children born appropriate for gestational age, higher IGF-I concentrations at 3 months of age are associated with increased weight gain over the preceding 3 months.¹⁹

There are limited data describing the association of IGF-I and -II concentrations with detailed body composition measurements at birth or assessing the predictive value of IGF-I and -II concentrations at birth on subsequent dynamic changes in body composition. The aim of this study is to determine whether IGF-I and -II measurements at birth are associated with body composition at birth and with the trajectory of body composition changes in the first 2 months from birth.

METHODS

Subjects

The Cork BASELINE birth cohort study (ClinicalTrials.gov NCT: 01498965) is a prospective study that recruited infants born in Cork, Ireland between August 2008 and August 2011.²⁰ Children born between 37 and 42 weeks' gestation to low-risk first-time mothers were eligible for inclusion in this study. Exclusion criteria

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were non-singleton pregnancies, known major fetal anomalies, maternal prepregnancy hypertension, diabetes, renal disease, systemic lupus erythematosus, antiphospholipid syndrome, major uterine anomalies, cervical cone biopsy and ≥ 3 miscarriages. Ethical approval was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals.

The first day of the last menstrual period (LMP) was used to determine gestational age. Ultrasound gestational age was used if performed before 16 weeks' gestation and if there was a discrepancy of >6 days between this and LMP. Ultrasound gestational age was also used if there was a discrepancy of >10 days between LMP and the ultrasound measurement at 20 weeks' gestation.

Body composition assessment

Air displacement plethysmography (ADP) (PEAPOD™ Infant Body Composition System, Life Measurement Inc, Concord, CA)²¹ was used to measure body composition at birth and 2 months of age. Standardized protocols were used to assess body composition as per the manufacturer's specifications. The naked infant, without umbilical cord clip, was weighed on a high precision scale and placed in a closed chamber. Pressure and volume changes in the chamber were used to calculate air displacement, and body density was determined. Age- and sex-specific fat-free mass (FFM) density values and the density of fat were then used to calculate FM and FFM.^{22,23}

Birth measurements were included if they occurred within the first 4 days from birth. In this cohort, 90% of 2-month measurements were taken between 49 and 86 days of age, and 2-month measurements were included if they occurred within this window. FM and FFM are dependent on infant size, so these measurements were adjusted for infant length in order to remove the confounding effect of size.^{24,25} We have previously shown that $FM/length^3$ (FM/L^3) and FFM/L^2 are the optimal indices for this correction in the first 3 months from birth.¹⁶ Age- and sex-specific Z-scores for FM/L^3 and FFM/L^2 parameters have been determined from this birth cohort and have been previously described elsewhere.¹⁶

Sample collection and storage

Umbilical cord samples were collected at birth. They were processed to serum within 3 h of collection and stored at -80°C until analyzed.

Mass spectrometry

IGF-I and -II concentrations were measured using liquid chromatography-mass spectrometry (LCMS) (Quest Diagnostics, Madison, NJ). This methodology is described in detail elsewhere.^{26,27} Isotopically labeled IGF-I was added to the sample as an internal standard to correct for any analyte lost in binding protein extraction. IGF-I and -II were separated from their binding proteins by an acid ethanol extraction followed by automated online extraction and analytical chromatography using an Aria TX-4 (Thermo-Fisher, San Jose, CA). IGF-I and -II were quantified using a time-of-flight mass spectrometer using narrow mass extraction of full-scan spectra. Performance characteristics of this assay have been previously described.^{26,27} For IGF-I measurement, the interassay coefficient of variation and percentage of recovery were, respectively, 5 and 104% at 100 ng/mL, 5.2 and 103% at 400 ng/mL, and 3.5 and 103% at 700 ng/mL. For IGF-II measurement, the interassay coefficient of variation and percent recovery were, respectively, 6.1 and 102% at 200 ng/mL, 3.2 and 99% at 500 ng/mL, and 5.3 and 99% at 1200 ng/mL.

Statistical analysis

Analysis of FM/L^3 and FFM/L^2 also utilized age- and sex-specific Z-scores at birth and 2 months. The change in Z-score between birth and 2 months was calculated by subtracting the age- and

sex-specific Z-score at birth from the 2-month Z-score. Gestational age- and sex-specific Z-scores for IGF-I and -II concentrations were also used in this analysis, and the development of these reference data are described elsewhere.¹⁴ The LCMS assay cannot detect IGF-I concentrations <16 ng/mL or IGF-II concentrations <32 ng/mL. When samples had concentrations below these values, a concentration of 15 ng/mL for IGF-I or 31 ng/mL for IGF-II was assigned.

Linear regression analysis was used to test associations between IGF-1 and -II concentration Z-scores and body composition. When evaluating the relationship between IGF Z-scores at birth and changes in FM/L^3 and FFM/L^2 Z-scores over the first 2 months, partial correlations were used to correct for FM/L^3 and FFM/L^2 Z-scores at birth.

Data analyses were performed using SPSS 21.0 (IBM, New York). Mean (SD) were reported for normally distributed data and compared using Student's independent sample *T* tests. Linear

Fig. 1 The number of subjects recruited who (1) were born at term, (2) had umbilical cord blood samples available, and (3) had body composition measurement performed at birth and 2 months

Table 1. Characteristics of population

	Males	Females	All
Number, <i>n</i>	317	284	601
Gestational age, weeks	40.2 (1.1)	40.2 (1)	40.2 (1.1)
Birth weight, kg	3.57 (0.45)	3.49 (0.45)	3.53 (0.45)
Weight at 2 months, kg	5.66 (0.68)	5.3 (0.57)	5.49 (0.66)
Length at birth, m	0.51 (0.02)	0.50 (0.02)	0.50 (0.02)
Length at 2 months, m	0.59 (0.02)	0.58 (0.02)	0.59 (0.02)
IGF-I, ng/mL	49.6 (23.9)	56.6 (24.3)	52.9 (24.3)
IGF-I, Z-score	0.07 (1)	-0.004 (1)	0.03 (1)
IGF-II, ng/mL	421.4 (98.1)	428.5 (103.7)	424.8 (100.8)
IGF-II, Z-score	0 (1)	-0.01 (1)	-0.004 (1)
FM/L^3 at birth, kg/m^3	2.7 (1.2)	3.2 (1.2)	2.9 (1.2)
FM/L^3 at birth, Z-score	0 (1)	-0.02 (1)	-0.01 (1)
FM/L^3 at 2 m, kg/m^3	5.9 (1.5)	6.2 (1.4)	6 (1.5)
FM/L^3 at 2 m, Z-score	0 (1)	0.09 (1)	0.04 (1)
FFM/L^2 at birth, kg/m^2	11.8 (0.9)	11.5 (0.9)	11.7 (0.9)
FFM/L^2 at birth, Z-score	0 (1)	0.06 (1)	0.02 (1)
FFM/L^2 at 2 m, kg/m^2	12.8 (0.8)	12.1 (0.8)	12.5 (0.9)
FFM/L^2 at 2 m, Z-score	0.04 (1)	0.04 (1)	0.04 (1)
Change in FM/L^3 Z-score from birth to 2 months	0 (1.2)	0.1 (1.2)	0.05 (1.2)
Change in FFM/L^2 Z-score from birth to 2 months	0.04 (1)	-0.02 (1.1)	0.01 (1)

Unless otherwise stated, mean (SD) are presented
FM fat mass, FFM fat-free mass, IGF insulin growth factor

regression analysis was used to evaluate the relationship between continuous variables.

RESULTS

There were 2137 infants enrolled in the Cork BASELINE birth cohort. Of these, 105 were excluded from this study due to gestational age <37 weeks, 932 did not have sufficient cord blood available for IGF measurement, and a further 499 did not have body composition measurement performed both at birth and 2 months. Complete measurements of IGF-I and -II at birth and ADP measurements at birth and 2 months of age were available in 601 term infants (317 males) (Fig. 1). Characteristics of these subjects are shown in Table 1. At birth, IGF-I concentration Z-score correlated positively with IGF-II concentration Z-score ($R^2 = 0.08$, $P < 0.001$).

Association of IGF-I and -II concentrations at birth with body composition at birth

Increased IGF-I concentrations were associated with higher FM/L³ and FFM/L² Z-scores at birth ($R^2 = 0.05$, $P < 0.001$ and $R^2 = 0.04$, $P = 0.016$, respectively), although these accounted for a small amount of the variance in body composition at birth (Fig. 2). IGF-II concentrations at birth were associated with FFM/L² Z-score at birth ($R^2 = 0.01$, $P = 0.02$) but not with FM/L³ Z-score at birth ($R^2 = 0.002$, $P = 0.4$).

Association of IGF-I and -II concentrations at birth with body composition trajectory over the first 2 months

FM/L³ and FFM/L² Z-scores at 2 months were not associated with IGF-I ($R^2 = 0.002$, $P = 0.3$ and $R^2 = 0.001$, $P = 0.5$, respectively)

or IGF-II ($R^2 = 0.004$, $P = 0.1$ and $R^2 = 0.002$, $P = 0.3$, respectively) Z-scores at birth (Table 2). This indicates that body composition at 2 months was not predicted by IGF-I or -II concentration at birth.

Although IGF-I and -II concentrations at birth were not associated with body composition at 2 months, there was a weak but significant association with change in body composition over the first 2 months. Higher IGF-I Z-scores at birth were associated with reductions in FM/L³ Z-scores ($R^2 = 0.05$, $P < 0.001$) and FFM/L² Z-scores ($R^2 = 0.03$, $P < 0.001$) between birth and 2 months of age. However, IGF-II concentrations were not associated with changes in FM/L³ Z-scores ($R^2 = 0.006$, $P = 0.05$) or FFM/L² Z-scores ($R^2 = 0.003$, $P = 0.02$) over the same timeframe (Fig. 3).

To control for the potential effect of FM/L³ or FFM/L² at birth on growth and body composition over the subsequent 2 months, further analyses were performed. When controlled for FM/L³ Z-score at birth, higher IGF-I Z-scores at birth were associated with a reduction in FM/L³ Z-score between birth and 2 months of age ($R^2 = 0.01$, $P = 0.003$). This association was not seen with IGF-II Z-scores at birth ($R^2 = 0.01$, $P = 0.07$). When controlling for FFM/L² Z-score at birth, there was no association between the change in FFM/L² Z-score over the first 2 months with IGF-I ($R^2 = 0.01$, $P = 0.08$) or IGF-II ($R^2 = 0$, $P = 0.88$) Z-scores at birth.

DISCUSSION

This study demonstrated the relationships between IGF-I and -II concentrations at birth and neonatal body composition in a large well-defined cohort of healthy, term infants in Ireland. Lower IGF-I concentrations at birth were associated with reduced adiposity and lean mass, while lower IGF-II concentrations at birth were

Fig. 2 Scatter plot and linear regression comparing insulin growth factor (IGF)-I (a, b) and IGF-II (c, d) concentrations with age- and sex-corrected fat mass (FM)/L³ and fat-free mass (FFM)/L² Z-scores at birth. The associations between IGF-I concentration and FM/L³ and FFM/L² Z-scores and the association between IGF-II concentration and FFM/L² Z-score at birth were significant

Table 2. Relationship between sex- and gestational age-corrected FM/L³ and FFM/L² Z-scores at birth and 2 months, with sex- and gestational age-corrected IGF-I and IGF-II Z-scores at birth

	IGF-I Z-score			IGF-II Z-score		
	R ²	Regression coefficient (SEM)	P	R ²	Regression coefficient (SEM)	P
FM/L ³ Z-score at birth	0.05	0.23 (0.04)	<0.001	0.001	0.04 (0.04)	0.4
FM/L ³ Z-score at 2 months	0.002	−0.05 (0.04)	0.3	0.004	−0.06 (0.04)	0.1
FFM/L ² Z-score at birth	0.04	0.2 (0.04)	<0.001	0.01	0.1 (0.04)	0.02
FFM/L ² Z-score at 2 months	0.001	0.03 (0.04)	0.5	0.002	0.04 (0.04)	0.3
Change in FM/L ³ Z-score from birth to 2 months ^a	0.01	−0.12 (0.04)	0.003	0.01	−0.07 (0.04)	0.07
Change in FFM/L ² Z-score from birth to 2 months ^b	0.01	−0.07 (0.04)	0.08	0	−0.01 (0.04)	0.88

For this analysis, IGF-I and -II Z-scores are the dependent variables and FM/L³ or FFM/L² measures are independent variables

FM fat mass, FFM fat-free mass, IGF insulin growth factor

^aPartial correlation controlling for FM/L³ Z-score at birth

^bPartial correlation controlling for FFM/L² Z-score at birth

Fig. 3 Scatter plot and linear regression comparing insulin growth factor (IGF)-I (a, b) and IGF-II (c, d) concentrations at birth with age- and sex-corrected fat mass/L³ and fat-free mass/L² Z-scores at 2 months

associated with reduced lean mass. Despite these significant associations, IGF concentrations accounted for a small amount of the variance in these body composition parameters. IGF-I and -II concentrations at birth were not associated with body composition parameters at 2 months. However, lower IGF-I concentrations at birth were associated with a greater increase in both adiposity and lean body mass in both sexes between birth and 2 months.

The relationship between IGF-I concentration at birth and adiposity is not surprising. There are strong associations between IGF-I concentrations and birth weight^{14,28} and nutritional status.¹¹ IGF-II is an important prenatal growth factor. Chorionic villi expression of *IGF2* mRNA is associated with birth weight²⁹ and paternally inherited *IGF2* mutations are associated with growth restriction.³⁰ Animal models also support this important role of IGF-II in regulating prenatal growth.³¹ It is possible that IGF-II is

more critical to growth prior to the third trimester,³² and this may explain the small association between body composition and IGF-II concentration at birth.

Although IGF-I and -II concentrations at birth are not directly associated with body composition parameters at 2 months, there is a weak association with trajectory of accumulation of adiposity. Significant changes occur in body composition during the first 3 months from birth, with a two-fold increase in FM corrected for length. Lean mass remains relatively stable during this time.¹⁶ The inverse relationship between IGF-I at birth and the change in adiposity may simply reflect the early “catch-up” accumulation of body fat in infants with relative intrauterine growth restriction at birth. The same inverse association was seen between change in lean mass and IGF-I concentration at birth, indicating that this “catch-up” is not limited to adiposity but also occurs in lean mass. While significant, it should be noted that IGF-I concentrations accounted for only 5% of the variance in changes in FM/L³ and over the first 2 months, and this reduced to 1% when corrected for FM/L³ at birth. This suggests that IGF-I concentrations at birth only predict a small fraction of observed subsequent body composition changes.

The consequences of this relationship may extend to the interplay between intrauterine nutritional status, the GH/IGF axis, and fetal programming of postnatal growth. Pregnancies complicated by limited access to nutrition are associated with increased IGF-I concentrations in adulthood, and it is hypothesized that chronic IGF suppression in utero results in an irreversible “overshoot” of this axis in later life.³³ Children who have rapid early weight gain have increased body mass index and insulin resistance as early as 8 years of age,³⁴ and SGA children with rapid early weight gain have persistent increases in adiposity when compared with similar weight, control children who were not born SGA.³⁵ Although the mechanisms for these persistent metabolic complications are unknown, it is possible that low IGF-I concentration at birth is a biomarker for future risk.

Strengths of this study include the large, well-defined, relatively homogenous study population. All children were term, healthy, and Caucasian, making confounding factors unlikely to contribute to these findings. However, this homogeneity may limit the generalizability of our findings to other populations. The large number of children with available body composition measurement is also unique for investigating these relationships. IGF-I and -II measurement by standard radioimmunoassays can be subject to assay interference by IGF-binding proteins. However, LCMS was used in this study and this technique is not subject to interference from binding proteins.^{26,27} A weakness of the study is the lack of available IGF-I and -II measurements at 2 months, to further investigate the hypothesis that IGF-I and -II may be useful biomarkers of metabolic risk during catch-up growth. Also, this study only included term infants and it is not known whether the association is similar for preterm infants. Data were not available for the entire birth cohort, and it is not known whether this introduced bias to our analysis.

We conclude that IGF-I concentrations at birth are associated with adiposity and lean mass at birth and the trajectory of FM accumulation over the first 2 months, although this only accounts for a small proportion of the variability seen in these parameters. Although IGF-I and -II play a significant role in prenatal growth, we have found that, in a cohort of healthy term infants, IGF-I and -II concentrations at birth are not major determinants of body composition changes over the first 2 months.

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ADDITIONAL INFORMATION

Competing interests: A.G. serves on the Steering Committee of the Pfizer International Growth Study Database. M.J.M. and M.P.C. are employees of Quest Diagnostics. The other authors declare no competing interests.

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