# FIBROBLAST GROWTH FACTOR 21 IS INVERSELY ASSOCIATED WITH GROWTH RATES IN INFANCY

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**DISCLOSURE:**
**Nothing to disclose**

## I. BACKGROUND

- Nutrition is one of the most important determinants growth. Human and experimental evidence indicate that Growth Hormone (GH) insensitivity is a major hormonal mechanism underlying malnutrition-related poor growth, yet the molecular signals leading to GH insensitivity are ill-defined.
- Fibroblast growth factor 21 (FGF21) is a member of the FGF family, primarily known to regulate multiple metabolic pathways. FGF21 is induced in the liver by fasting, and its increased expression/activity leads to increased fatty acid oxidation and ketogenesis.
- Recent evidence also indicates that FGF21 may be an important regulator of growth:
- Transgenic mice overexpressing FGF21 exhibit ↓ longitudinal bone growth and GH sensitivity and sustained caloric reduction in mice leads to ↑ expression of FGF21 in the liver and in the growth plate, which in turn results in reduced GH receptor binding and action, possibly through endocrine and paracrine effects of FGF21.
- Little is known about the regulation of FGF21 in humans :circulating [FGF21] are ↑ in subjects with overweight, have type 2 DM or impaired glucose tolerance and also in those on a very-low calorie diet. In addition in anorexia nervosa FGF21 was positively associated with integrated [GH], suggesting that FGF-21 may mediate a state of GH resistance

## II. AIM

**To investigate the role of FGF21 during growth in infancy**

## III. SUBJECTS AND METHODS

Prospective design and study approval by the IRB of the institution. Two groups of infants:
-Group 1 cross-sectional group, n=95 ,cord blood 55 Term / 40 preT
-Group 2 longitudinal group, n= 80, 40 term/40 preT (VLBW ): birth –+ 6 & 12m.
-Blood samples for FGF21, leptin, insulin and glucose collected from cord blood (cross-sectional group), and at 6 and 12 months of life in (long. group).
-Length and weight were measured at birth, 6 months, and 12 months.

*Assays*
Serum FGF21 = ELISA (Millipore Corporation, Billerica, MA, USA). Serum insulin (IRMA) and serum leptin by RIA. IRMA and RIA kits (Diasource Immunoassays SA (Nivelles, Belgium).

*Calculations and statistical analysis (STATA v. 12.0)*
-Significant weight catch-up (CU) was defined as a change in weight, between 0 and 12 months, greater than 0.67 SDS.
-Differences between groups were assessed by Student's t test or nonparametric test (Mann-Whitney U) depending on the normality of the data and exact Fisher test was used for categorical variables.
-Correlation between length SDS or weight SDS changes (0-12m, 0-6m, 6-12 m) variables and serum concentrations of hormones evaluated using Spearman's correlation.
- The temporal evolution of height SDS was associated with the temporal evolution of growth and metabolic parameters by regression analysis for repeated measures estimated through mixed models.

## IV. RESULTS

Figure 1 Postnatal Weight (A) and length (B) SDS changes in the first semester (Δ 0-6m) and in the second semester (Δ 6-12m) of life, comparing the term (T) and preterm (PT) grouped according to by BW SDS (AGA or SGA) mean ± SEM * p <0.05 **p<0.01

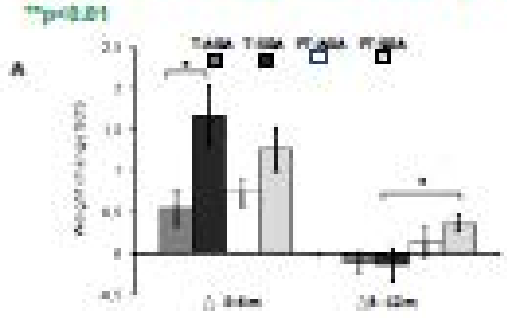


Figure 2 Serum FGF21 concentrations (median and interquartile range q25-q75) in the two groups of term (T) and preterm (PT) infants (A), and the T and PT infants grouped according to by BW SDS (AGA or SGA) (B). FGF21 was measured in the cord blood (CB), at 6 months (6m) and 12 months (12m) of life

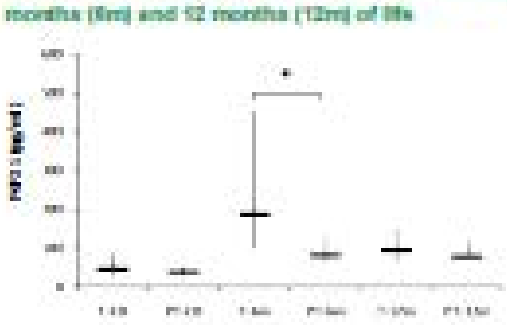


Figure 3

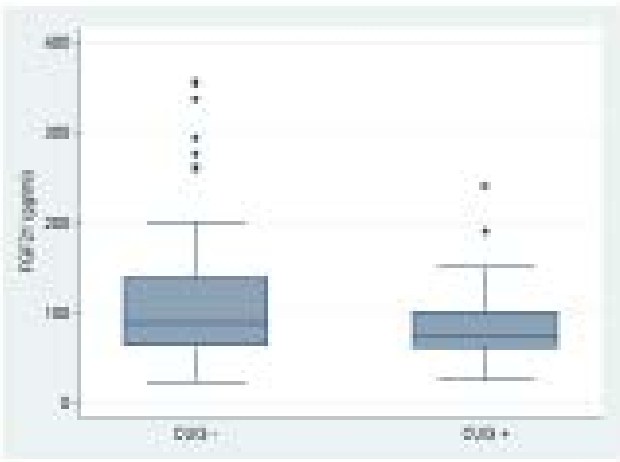


Table 1 Anthropometric characteristics at birth and gestational age of infants enrolled in the cross-sectional and in the longitudinal groups ** =p<0.01, for comparisons within the same group and same gestational age , between those born appropriate (AGA) or small for gestational age (SGA)

**Cross-sectional group**

| | Term AGA (28) | Term SGA (27) | Preterm AGA (21) | Preterm SGA (19) |
|---|---|---|---|---|
| GA (weeks) | 39.3 ± 1.2 | 39.3 ± 1.2 | 34.4 ± 2.1 | 33.2 ± 3.1 |
| BW (SDS) | 0.02 ± 0.83 | -1.81 ± 0.26** | -0.53 ± 0.58 | -2.03 ± 0.62** |
| BL (SDS) | -0.25 ± 0.90 | -1.77 ± 0.83** | -0.89 ± 1.05 | -1.76 ± 0.91** |

**Longitudinal group**

| | Term AGA (23) | Term SGA (17) | Preterm AGA (20) | Preterm SGA (20) |
|---|---|---|---|---|
| GA (weeks) | 39.2 ± 0.2 | 39.6 ± 0.3 | 29.0 ± 0.4 | 31.3 ± 0.5 |
| BW (SDS) | 0.11 ± 0.13 | -1.98 ± 0.15** | -0.91 ± 0.11 | -2.66 ± 0.18** |
| BL (SDS) | 0.59 ± 0.19 | -1.34 ± 0.31** | -0.49 ± 0.15 | -1.95 ± 0.22** |

-From birth →12 m of age, preT infants' linear growth and weight gain were larger than those of term infants, irrespective of birth weight (BW) SDS.
-At birth and at 12 months, there was no difference in FGF21 levels between preT and T infants; in contract, at 6 months serum FGF21 in T infants was significantly higher than that of preT ones.
-In the 0-6m period, in the whole longitudinal group serum FGF21 was inversely correlated to the length change SDS, (r= -0.5, p<0.05) and no correlation with the weight change. and such significant inverse correlation persisted in the preT-AGA group in the 6-12m period (r=-0.46,p<0.04)
-Length catch-up (increase in length ≥ 0.67 SD) in the 0-12m period was inversely associated to FGF21 at 12 months (r=-0.22 , p<0.06). The association almost reached statistical significance at 6 months (r=- 0.22, p= 0.06). Those infants who performed length catch –up had a lower concentration of FGF21 ( p<0.06) (figure 3).

## V. CONCLUSIONS

Our findings suggest that circulating FGF21 levels are inversely correlated with linear growth velocity in infants during their first year of life, and such correlation does not depend on gestational age or birth weight SDS. Due to the importance of FGF21 as a metabolic regulator during states of under-nutrition, our findings suggest a causative role for FGF21 in nutritional stunting, which is the most common type of growth failure in the world. Yet, these findings do not enable us to shed light on the hormonal/molecular mechanisms linking FGF21 action and linear growth in humans. We believe that future studies based on a larger population sample followed since birth, and including the evaluation of a wider range of growth-regulating factors and more specific markers of insulin sensitivity, are warranted.