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

Merlq V1, De Luca F2, Hernandez M1, Peña V4, Roesel K4, Garcia M4, Avalia A1, Cavada G3, Iñiguez G1

1 Institute of Maternal and Child Research, School of Medicine, University of Chile, 2Section of Endocrinology and Diabetes, St. Christopher's Hospital for Children, Drexel University College of Medicine, Philadelphia, PA, USA.
3Public health department, University of Chile and University of los Andes, 4Obstetrics and fetal medicine unit, San Borja Arturo Grand Hospital

DISCLOSURE:
Nothing to disclose

I. BACKGROUND
- Nutrition is one of the most important determinants of 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, anorexia nervosa FGF21 was positively associated with integrated GH, suggesting that FGF21 may mediate a state of GH resistance.

II. SUBJECTS AND METHODS
- Prospective design and study approval by the IRB of the institution. Two groups of infants:
  - Group 1 cross-sectional group, n=66 cord blood at term and preterm (VLBW): birth = 6 to 12 months.
  - Group 2 longitudinal group, n=80, 40 term and preterm (VLBW): birth = 6 to 12 months.
- Blood samples for FGF21, leptin, insulin and glucose collected from cord blood (cross-sectional group), and at 6 and 12 months of life (long-term).
- Length and weight were measured at birth, 6 months, and 12 months.

Assays
- Serum FGF21 = ELISA (Millipore Corporation, Billerica, MA, USA). Serum Insulin (RMA) and serum leptin by RIA. RMA and RIA kits (Diasorin Immunoassays S.A. Nivelles, Belgium).
- Calculations and statistical analysis (STATIA v. 12.0). Significant weight catch-up (WCU) was defined as a change in weight, between 6 and 12 months, greater than 85.7 SDS.
- Differences between groups were assessed by Student's t-test or non-parametric 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 (6-12m, 6-9m, 6-12m) 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.

III. AIM
To investigate the role of FGF21 during growth in infancy

IV. RESULTS

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

Cross-sectional group

<table>
<thead>
<tr>
<th>Term AGA</th>
<th>Term SGA</th>
<th>Preterm AGA</th>
<th>Preterm SGA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(26)</td>
<td>(24)</td>
<td>(28)</td>
</tr>
<tr>
<td>GA (weeks)</td>
<td>35.9 ± 0.4</td>
<td>36.0 ± 0.4</td>
<td>35.7 ± 0.4</td>
</tr>
<tr>
<td>BW (SDS)</td>
<td>0.2 ± 0.3</td>
<td>-0.2 ± 0.3</td>
<td>-0.5 ± 0.3</td>
</tr>
<tr>
<td>BL (SDS)</td>
<td>-2.5 ± 0.5</td>
<td>-2.7 ± 0.5</td>
<td>-2.9 ± 0.5</td>
</tr>
</tbody>
</table>

Longitudinal group

<table>
<thead>
<tr>
<th>Term AGA</th>
<th>Term SGA</th>
<th>Preterm AGA</th>
<th>Preterm SGA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(17)</td>
<td>(16)</td>
<td>(18)</td>
</tr>
<tr>
<td>GA (weeks)</td>
<td>36.0 ± 0.4</td>
<td>35.8 ± 0.4</td>
<td>35.7 ± 0.4</td>
</tr>
<tr>
<td>BW (SDS)</td>
<td>0.1 ± 0.2</td>
<td>-0.1 ± 0.2</td>
<td>-0.2 ± 0.2</td>
</tr>
<tr>
<td>BL (SDS)</td>
<td>0.9 ± 0.1</td>
<td>-1.3 ± 0.1</td>
<td>-1.4 ± 0.1</td>
</tr>
</tbody>
</table>

- From birth to 12 months of age, preterm 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 preterm and term infants; in contrast, at 8 months of age FGF21 in preterm infants was significantly higher than that of term infants.
- In the 0-6m period, in the whole longitudinal group serum FGF21 was inversely correlated with the length change SDS, (r = -0.5, p<0.06) and no correlation with the weight change, and thus significant inverse correlation persisted in the preterm 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 with FGF21 at 12 months (r = -0.22, p=0.06). Those infants who performed length catch-up had a lower concentration of FGF21 (p<0.06).

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 undernutrition, our findings suggest a causative role for FGF21 in nutritional clamping, 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 larger population samples followed since birth, and including the evaluation of a wider range of growth-regulating factors and more specific markers of insulin sensitivity, are warranted.