Growth and differentiation factor 15 (GDF15) in preterm infants and its relation to bronchopulmonary dysplasia – A pilot study.

Neonatal – Perinatal Medicine, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital
Faeq Almudares MD, Sridevi Devaraj Ph.D, Joseph Hagan ScD MSPH, Krithika Lingappan MD PhD

BACKGROUND

- Bronchopulmonary dysplasia (BPD) is one of the most common morbidities among surviving premature infants.
- A gap in BPD research is the lack of methods to identify infants at higher risk of developing BPD.
- Earlier identification will enable targeted postnatal interventions to prevent or attenuate its severity.
- GDF15 is a stress-responsive cytokine and a divergent member of the TGF-β superfamily.
- GDF15 expression increases under stress conditions, including inflammation, hyperoxia, and senescence. GDF15 levels increase in cardiopulmonary disorders.
- The circulatory GDF15 levels in preterm infants have not been studied, and its role as a biomarker in evolving lung injury is unknown.

HYPOTHESES

- GDF15 levels at birth in preterm neonates will be lower than in term neonates, and there will be a positive correlation between gestational age and initial serum GDF15 levels.
- Postnatal lung injury in the preterm neonate will be associated with increased serum GDF15.

METHODS

- Infants born between 23- to 36- weeks gestation were enrolled in the study (n=44).
- Scavenged blood samples were retrieved at five-time points: (day of life one (DOL 1), DOL 7, DOL 14, 4th week of life, and postmenstrual age 36 weeks) (n=83/135).
- The samples were stored at -80ºC until analysis.
- GDF15 levels were measured using the human GDF15 ELISA kit DGDF150.
- Statistical analysis was performed using simple linear regression and mixed-effects linear models. Significance was identified when *P*<0.05.

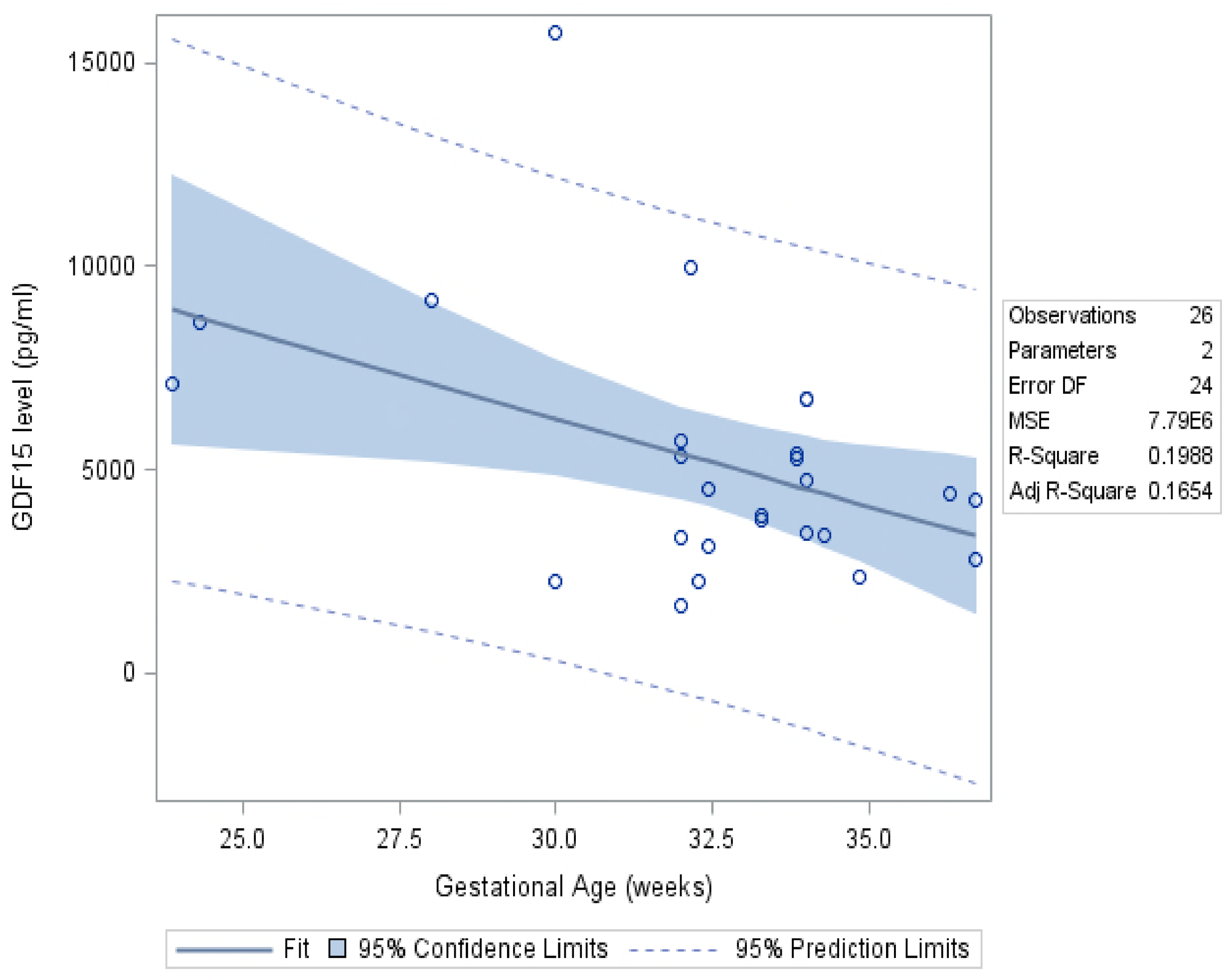

Fig 1: Scatterplot of GDF15 serum level vs. gestation age at birth. The circulating GDF15 levels of the 26 subjects were plotted as open circles. Linear regression analysis showed significant negative correlations. (r = -0.479, p = 0.016).

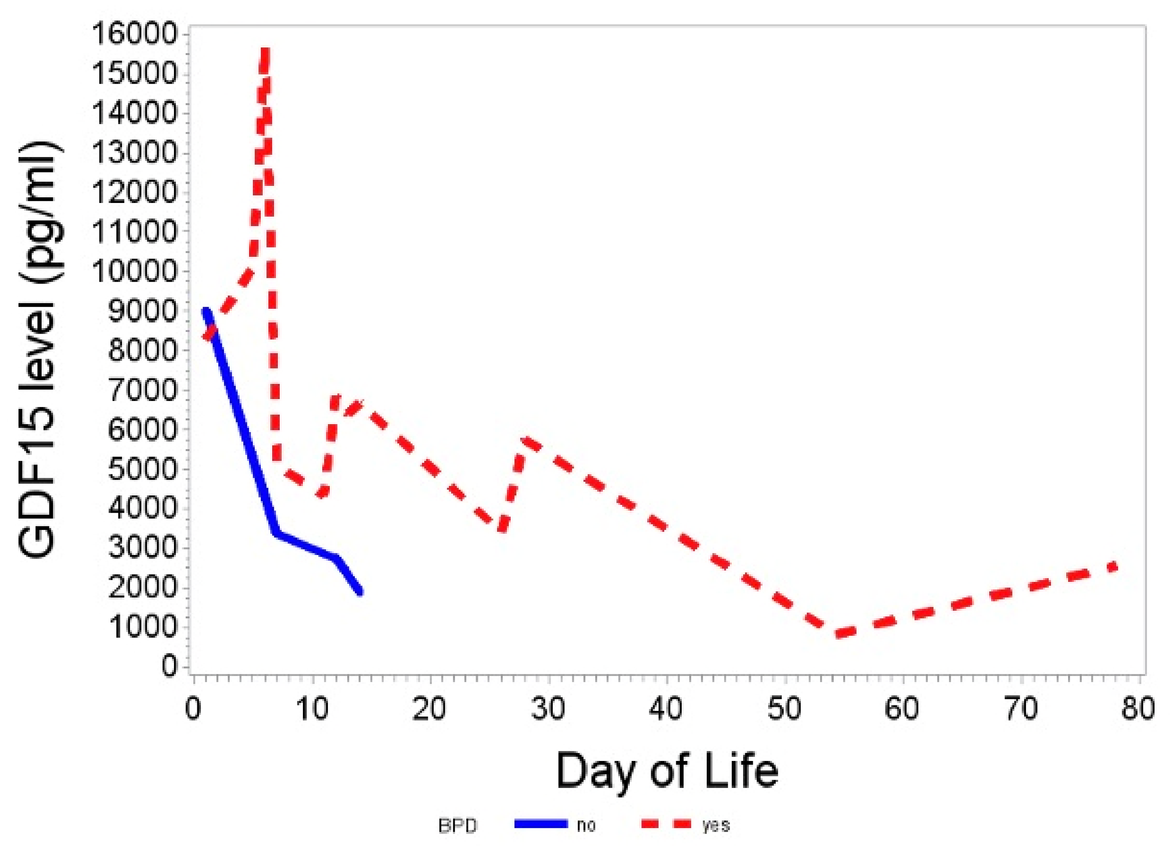

Fig 3: Linear plot shows the longitudinal trend of GDF15 over time in infants born at ≤30 weeks gestation. Subjects with BPD (blue line, n=5) compared to subjects without BPD (red dotted line, n=7). The mixed-effects linear model showed no significant correlation between GDF15 and the longitudinal trend of GDF15 (p=0.273).

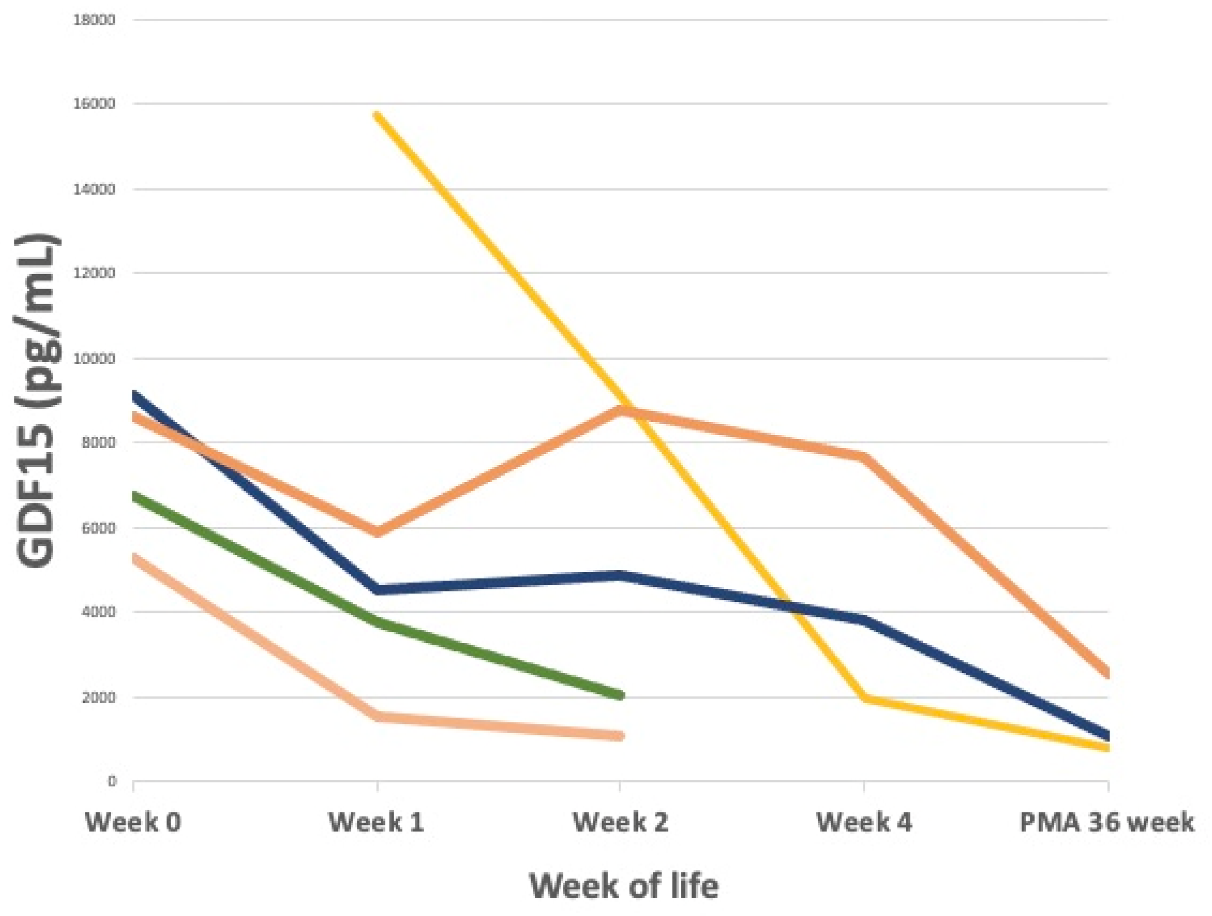

Fig 2: Linear plot for the longitudinal trend of circulating GDF15 levels in the surviving premature infants over time. A different colored line represents each subject (n=5).

RESULTS

- The serum GDF15 levels at DOL 1 (n=26) showed that for each additional week of gestational age at birth, the level decreased by 334.2 pg/mL (*r* = -0.479, *P* = 0.016).
- After controlling for gestational age at birth, the longitudinal predicted GDF15 level decreased by 113.2 pg/mL (*P* <0.001) for each additional DOL.
- Higher circulatory GDF15 levels were associated with longer mechanical ventilation time (*P* =0.024), higher oxygen requirement (*P* <0.001), and more prolonged respiratory support need (*P* <0.001).
- In infants born at ≤30 weeks gestation (n= 12), the change in serum GDF15 levels over time was not significantly different for infants with versus without BPD (n = 5 vs. n =7, *P* = 0.273).

CONCLUSION

- In premature infants, the circulating GDF15 levels, at 24 hour of life, are higher in infants born at lower gestation age.
- The circulating GDF15 levels trend down postnatally in preterm infants.
- The circulating GDF15 levels were significantly higher in preterm infants who required higher and longer respiratory support.
- The change in GDF15 level over time was not significantly different for patients with versus without BPD.

REFERENCES

Bootcov, M., et al. MIC-1, a novel macrophage inhibitory cytokine, is a divergent member of the TGF-beta superfamily. Proc Natl Acad Sci USA. 94, 11514-11519 (1997).
Tiwari, K., Moorthy, B., Lingappan, K. Role of GDF15 (growth and differentiation factor 15) in pulmonary oxygen toxicity. *Toxicol Vitr*. 29, 1369-1376 (2015).
Mirna M, Rohm I, Jirak P, Wernly B, Bäz L, Paar V, et al. Analysis of novel cardiovascular biomarkers in patients with pulmonary hypertension (PH). Hear Lung Circ. 29, 337-344 (2020).
Zhang, Y., Jiang, W., Wang, L., Lingappan, K. Sex-specific differences in the modulation of Growth Differentiation Factor 15 (GDF15) by hyperoxia in vivo and in vitro: Role of Hif-1α. *Toxicol Appl Pharmacol.* 332, 8-14 (2017).
Al-Mudares, F., et al. Role of Growth Differentiation Factor 15 in Lung Disease and Senescence: Potential Role Across the Lifespan. *Front Med*. 7, 1-8 (2020).
Verhamme F, Freeman C, Brusselle G, Bracke K, Curtis J. GDF-15 in pulmonary and critical care medicine. Am J Respir Cell Mol Biol. 60:621–8 (2019).
Díaz M, Campderrós L, Guimaraes M, López-Bermejo A, de Zegher F, Villarroya F, et al. Circulating growth-and-differentiation factor-15 in early life: relation to prenatal and postnatal growth and adiposity measurements. Pediatr Res. 87:897–902 (2019).