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Growth and differentiation factor 15 (GDF15) levels predict adverse respiratory outcomes in premature neonates

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Abstract

Growth and differentiation factor 15 (GDF15) is a stress-responsive cytokine, and its expression increases during inflammation, hyperoxia, and senescence. Significantly, GDF15 is secreted by the placenta, and maternal levels increase throughout pregnancy. Serum GDF15 level is a promising biomarker for many lung diseases like pulmonary hypertension and pulmonary fibrosis. However, circulating GDF15 levels in preterm infants and their role as a predictor of respiratory outcomes have not been studied. We hypothesized that GDF15 levels would increase with gestational age at birth, and that postnatal GDF15 will be correlated with adverse respiratory outcomes in preterm infants.

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Authors contribution statement:

Dr. Almudares contributed significantly to conceptualizing, patient enrollment, project design, data and specimen acquisition, and drafting and revising the manuscript. Joseph Hagan contributed significantly by analyzing the data and reviewing and revising the manuscript. Xinpu Chen contributed significantly with specimen analysis and reviewing the manuscript. Dr. Devaraj contributed considerably by conceptualizing, overseeing the specimen acquisition and analysis, and reviewing the manuscript. Dr. Moorthy contributed by conceptualizing, reviewing, and revising the manuscript. Dr. Lingappan contributed substantially by conceptualizing, designing the project, data interpreting, and reviewing and revising the manuscript. All authors provided the final approval for the submitted manuscript.

Conflict of Interest

The authors have no conflict of interest to disclose.

Ethical Statement:

The study protocol was approved by the institutional review board of the Baylor College of Medicine. Written informed consent was obtained before enrolling the infants in the study.

Scavenged blood samples were retrieved from 57 preterm infants at five time points, from birth until 36-weeks postmenstrual age (PMA). GDF15 levels were measured using ELISA in 114 samples. We performed two-sample t-test, correlation and linear regression, logistic regression, and mixed-effects linear models for statistical analysis, and significance was identified when $p<0.05$.

Contrary to our hypothesis, for every one-week increase in gestational age at birth, the predicted GDF15 level decreased by 475.0pg/mL ($p<0.001$). Greater PMA was significantly associated with lower serum GDF15 levels ($p<0.001$). Interestingly, higher GDF15 levels were associated with a longer need for mechanical ventilation ($p=0.034$), prolonged respiratory support need ($p<0.001$), and length of hospital stay ($p=0.006$).

In conclusion, in preterm infants, GDF15 levels show an inverse correlation with gestational age at birth, with higher levels in more preterm babies, and levels trend down postnatally. Furthermore, longitudinal GDF15 levels through 36 weeks PMA predict adverse respiratory outcomes in preterm infants.

Keywords

Prematurity; respiratory support; biomarker; bronchopulmonary dysplasia; Growth differentiation factor 15

Introduction

Respiratory morbidity is a significant sequela of prematurity in the neonatal population [(1)]. Despite advances in perinatal care and a decrease in mortality, respiratory morbidity including bronchopulmonary dysplasia (BPD) remain high among these vulnerable patients. Long-term complications [(2)(3)(4)], including impaired pulmonary function and re-hospitalization, are also prevalent in this patient population. Serum biomarkers that could predict the development of these respiratory morbidities would be beneficial in predicting outcomes and directing therapies to babies most likely to develop long-term respiratory morbidities.

Growth differentiation factor (GDF15) is a divergent member of the transforming growth factor-B (TGF-beta) cytokine superfamily [(5)]. Under physiological conditions, GDF15 expression is low, except during pregnancy [(6)]. In pregnant women, the circulating GDF15 levels continue to increase throughout gestation, with evidence of fetal exposure [(7)(8)]. GDF15 expression increases during pathological states, including hypoxia, inflammation, oxidative stress, cancer, aging, and smoking [(9)(10)(11)]. Increased GDF15 expression may indicate ongoing cellular injury or protective response to biological stress depending on the stress signal and the organ or tissue.

Serum GDF15 levels and trends are associated with many cardiopulmonary disorders in adults, like chronic obstructive pulmonary disease [(12)], idiopathic pulmonary fibrosis [(13)], and pulmonary arterial hypertension [(14)]. However, GDF15 levels have been studied in limited pediatric conditions, including mitochondrial diseases [(15)], pulmonary arterial hypertension [(16)], and postnatal metabolic status and growth [(17)]. Pre-clinical studies have

shown increased GDF15 expression in pulmonary epithelial and endothelial cells upon exposure to hyperoxia [18]. GDF15 levels in term newborns are known to be elevated 5- to 10-fold compared to adults and show a rapid decline postnatally [17]. However, the circulating GDF15 levels in preterm infants and its longitudinal trends have not been studied, and the association between GDF15 and respiratory outcomes in preterm infants has yet to be identified.

In this study, we tested the hypothesis that there would be increasing GDF15 levels with gestational age and tested its correlation with respiratory outcomes in preterm neonates. We measured baseline GDF15 levels in premature infants and their longitudinal changes postnatally. This study is the first to report GDF15 levels in premature infants born at different gestational ages and its association with respiratory outcomes in this patient population.

Materials and Methods:

Study Population:

A total of 57 infants born at the Pavilion for Women at Texas Children's Hospital between October 2020 to January 2022 were enrolled in the study. The study was reviewed and approved by the institutional review board at Baylor College of Medicine, and written parental consent was obtained upon infant enrollment. Preterm infants born between 23 weeks and 0 days to 36 weeks and six days gestation admitted to the NICU were enrolled. Patients with major congenital anomalies were excluded from the study.

Specimens and data collection:

Serum samples were collected using scavenged specimens from the aliquots collected for routine laboratory tests. Samples were collected during the NICU stay at five-time points, when available, to measure the longitudinal changes in GDF15 levels postnatally. A total of 114 serum samples were retrieved from 57 patients, and two patients had no samples due to the inadequate volume of the scavenged specimens. The first sample was collected on the day of birth (N=33). The subsequent samples were collected on postnatal days 7, 14, and 28 and at the postmenstrual age of 36 weeks. After sample retrieval, the samples were de-identified and stored at −80°C until the analysis. Baseline characteristics and clinical data of each infant were gathered from birth until discharge or death. BPD was diagnosed in infants who required supplemental oxygen for at least the first 28 days postnatally [19].

GDF15 analysis:

Serum GDF-15 concentrations were quantified using the Quantikine ELISA kit (#DGD150, R&D Systems, Minneapolis, MN) according to the manufacturer's instructions. The serum samples were diluted 1:10, and the absorbance was read at 450 nm. The concentration of each sample was calculated using a standard curve.

Statistical methods:

Mixed-effects linear models with a first-order autoregressive covariance structure were used to analyze associations with longitudinal GDF15 measurements, while accommodating the

correlation among repeated measures from the same patient over time. Linear regression and correlation analysis was used to assess the association of GDF15 level in the first week of life with quantitative outcomes, and logistic regression was used for binary outcomes. GDF15 level in the first week of life was compared between groups using the two-sample t-test. Data were analyzed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina). A two-sided 5% significance level was used for all hypothesis tests. Power analysis indicated that 46 study patients would provide 80% statistical power to detect a true correlation of r = 0.4 between GDF15 level in the first week of life and gestational age at birth with a two-sided 5% significance level. Due to our approach of utilizing scavenged samples, we had planned to enroll additional subjects as we expected specimen availability might be compromised. Therefore, we continued the patient enrollment process until a sample size of 57 was reached.

Results

Study participants:

The characteristics of the study cohort are shown in Table 1. The average gestational age of our subjects was 30 ± 3.2 weeks (18% of the enrolled neonates were born at 23–27 weeks, 51% between 28–32 weeks, and 31% between 33–36 weeks), and their average birth weight was 1643 ± 635 g. Female infants represented 44% of the studied population. In our study population, among the preterm infants with birth weight <1500g, the frequency of BPD was 38.5%, and sepsis was 23% (Supplemental Table 1). The average length of hospital stay of our cohort was 52 days.

GDF15 levels show a significant inverse correlation with gestational age, with higher levels in more preterm babies:

Previous studies had reported increasing maternal GDF15 levels with advancing gestation leading us to hypothesize that GDF15 levels would be higher with greater gestational age at birth. However, contrary to our hypothesis, in preterm infants, GDF15 levels within the first week of life were 7201 ± 3880 pg/mL (in infants <= 30 weeks) vs. 3718 ± 2336 pg/mL (in infants > 30 weeks), ($p<0.001$, Supplemental Table 2). For every one-week increase in gestational age at birth, the predicted GDF15 level in the first week of life decreased by 475.0 pg/ml ($r^2 = 0.209$, $p<0.001$, Figure 1). The average serum GDF15 level within the first week of life in the entire cohort was 5062 ± 3620 pg/mL.

Serum GDF15 changes decline with postnatal age in preterm infants:

After controlling for gestational age at birth, for each additional day of life, the predicted GDF15 level decreased by 118.7 pg/ml ($p<0.001$). Greater postmenstrual age in the preterm infants was significantly correlated with lower serum GDF15 levels ($r = -0.618$, $p<0.001$) (Figure 2). The serum GDF15 levels reached their lowest levels at the postmenstrual age of 36 weeks, with an average of 2033±1052 pg/mL (Supplemental Table 3).

Longitudinal GDF15 levels are associated with adverse respiratory outcomes in preterm neonates:

A mixed-affect linear model was fit for the respiratory outcome with GDF15 levels, using a first-order autoregressive covariance structure to accommodate the correlation among repeated GDF15 measurements from the same patient over time and after controlling for gestation age at birth and day of life (since both variables were shown to be significantly associated with the longitudinal GDF15 levels). After controlling for gestational age, the longitudinal GDF15 levels were significantly higher in preterm infants who required longer invasive mechanical ventilator support ($p = 0.034$), more extended period of respiratory support ($p<0.001$), and increasing length of hospital stay ($p=0.006$) (Table 2). However, longitudinal GDF15 levels were not significantly different for patients with versus without BPD ($p=0.173$).

GDF15 levels within the first week of life predict severe IVH in premature neonates:

We investigated the association between the longitudinal GDF15 levels in preterm infants and prematurity-related outcomes, including intraventricular hemorrhage, retinopathy of prematurity, and necrotizing enterocolitis. After adjusting for the gestational age, and the postnatal day of life, there were no statistically significant associations between the trend in GDF15 levels over time in preterm infants and intraventricular hemorrhage, retinopathy of prematurity, and necrotizing enterocolitis (Table 3). Additionally, no associations were detected with the baseline characteristics of the study subjects, such as birth weight, gender, or exposure to prenatal steroids (Table 3). Since many outcomes in preterm neonates are predicted by their early postnatal clinical course, we assessed the relationship between the GDF15 levels within the first week of life and prematurity-related outcomes. Interestingly, higher initial GDF15 levels were associated with higher grades of intraventricular hemorrhage ($p=0.015$), even though longitudinal levels were not ($p=0.538$).

Discussion:

Using a prudent approach of scavenged blood specimens from preterm neonates, we report the baseline GDF15 levels in premature infants born at different gestational ages and the association of longitudinal GDF15 levels with respiratory outcomes in preterm neonates. We show that the initial GDF15 level shows an inverse correlation with gestational age in preterm infants, with higher levels in more premature infants. Postnatal GDF15 levels decrease after birth, with their lowest level at 36 weeks PMA. This result was contrary to our hypothesis, based on the rising GDF15 during pregnancy in previous studies, with maternal GDF15 levels peaking at term [(6)]. The higher GDF15 levels in preterm infants may be related to the stress from to preterm birth, as GDF15 is a stress-responsive cytokine. Higher initial GDF15 levels in more preterm neonate may be related to higher induced maternal levels or greater placental production, and the subsequent transfer to the preterm neonates. Increased production in the fetus during an impending preterm birth may be another factor leading to higher GDF15 levels in preterm neonates.

In a human study, circulating GDF-15 was increased in women preceding the development of preeclampsia and in women with diagnosed preeclampsia compared to controls. Maternal

levels were higher in women with preterm deliveries due to preeclampsia [20]. Other studies, however, have not replicated this association [21]. Based on our analysis, there was no association between the initial levels or the trend of GDF15 in preterm infants born to a mother who had a diagnosis of hypertensive disorders of pregnancy.

Analysis of GDF15 levels in amniotic fluid and fetal membranes in preterm labor and premature rupture of membranes did not reveal any differences in levels compared to term deliveries [22]. Sugulle *et al.* reported higher circulating and placental GDF15 levels in mothers with preeclampsia and diabetes mellitus. In addition, GDF-15 was elevated in the amniotic fluid and fetal circulation in pregnancies complicated by preeclampsia and superimposed preeclampsia in diabetes mellitus, as compared with controls [23]. Based on the above, maternal and placental GDF15 levels may be higher in conditions that increase the risk of preterm birth.

GDF15 levels in preterm infants under the postmenstrual age of 31 weeks were higher than those observed in term infants [17]. The reported GDF15 levels by Díaz *et al.* for term infants were comparable to the GDF15 levels for preterm infants at a postmenstrual age of 32 to 36 weeks in our study. Similar to our findings, in a study with 18 neonates (mean gestational age of 37.2 weeks), Kinoshita *et al.* showed that GDF15 levels were negatively correlated with postnatal period and z-score of birth weight. Interestingly, they also noticed a positive correlation of GDF-15 levels with N-terminal pro-brain natriuretic peptide and lactate levels, speculating the association of GDF-15 levels with mitochondrial function [24].

We also demonstrate in this study cohort, that preterm infants who required longer invasive mechanical ventilator support and longer period of any respiratory support had higher GDF15 levels. Higher production of GDF15 in the lung or from other tissues as a response to systemic illness in these neonates, could underlie the higher serum levels. Circulating GDF15 levels are increased in various lung diseases [25], pulmonary hypertension [16], chronic obstructive pulmonary disease (COPD) [26], and idiopathic pulmonary fibrosis [13]. GDF15 levels were elevated in those with interstitial lung abnormalities in two large adult cohorts (Farmingham heart study and the COPDGene study) [27]. In a mouse model of bleomycin-induced lung injury, lung epithelial cells were the source of GDF15 production and associated with cellular senescence [13]. GDF15 expression is also induced in pulmonary endothelial and epithelial cells upon exposure to hyperoxia *in vitro*, increased cellular viability, and decreased cellular oxidative stress [18]. GDF15 expression in lung tissue is linked to cellular senescence, as it expression is increased when epithelial cells are exposed to bleomycin [13]. Whether the role of GDF15 overexpression is protective to increase the cellular viability, as shown by Tiwari et al, or a marker of cellular that needs to be discerned. The only known specific receptor identified for GDF15 is the glial-cell-line-derived neurotrophic factor family (GFRAL) receptor, located in the hindbrain [28][29][30]. Whether all effects of GDF15 are mediated through GFRAL or other GDF15 receptors in different organs are involved is unknown. The binding of GDF15 to GFRAL activates ERK, AKT and PLC-gamma downstream signaling [31]. Moreover, GDF15 was found to activate SMAD-mediated signaling in other tissues like airway epithelial cells [32] and cardiomyocytes [33]. The metabolic, anti-obesity, and cachectic effects of GDF15 are mediated through its interaction with GFRAL [31]. However, this receptor has not been

identified in the human lung [13]. Díaz et al. reported a more significant decline in GDF-15 levels in small for gestational age (SGA) infants at four months compared to appropriate for gestational age (AGA) infants. They speculated that this might be needed to allow for the catch-up growth in SGA infants [17]. In the NICU, extrauterine growth retardation increases morbidity in preterm neonates [34]. Higher GDF15 levels could contribute to this phenomenon and thus indirectly modulate other morbidities such as adverse respiratory outcomes.

In neonatology, biomarkers have been studied in various clinical conditions, including chronic lung disease [35], necrotizing enterocolitis, sepsis [36], and patent ductus arteriosus [37]. Biochemical markers identify high-risk populations, detect responses to interventions, and predict outcomes. This information can guide clinicians to utilize specifically directed therapies to alleviate or prevent disease and avoid high-risk interventions. The pathophysiology of lung disease in preterm infants is highly complex and mediated by genetic and environmental interactions. Previous studies have highlighted biomarkers that have shown an association with chronic lung disease, like interleukin-6 (IL-6), IL-10, and vascular endothelial growth factor (VEGF) [38]. A recent study focusing on the identification of biomarkers for persistence of patent ductus arteriosus in extremely premature (22–27 weeks) infants identified high levels of GDF-15 as one of the candidates among B-type natriuretic peptide, interleukin-6, -8, -10 and -12 [39]. A persistent hemodynamically significant PDA is associated with adverse respiratory outcomes in the preterm population. The association in our study between high GDF15 levels and adverse respiratory outcomes could be direct or indirect because of another pathological factor such as a persistent PDA.

Our study highlighted the association of higher initial GDF15 levels in preterm infants with severe IVH. This may reflect the systemic inflammatory stress in these neonates. However, GDF15 might play a causative role, as GDF15 exhibits an inhibitory role on platelet integrins [40] and higher GDF15 levels have been associated with higher incidence of atrial fibrillation-related bleeding in patient on anti-platelet medications [41]. GDF15 is also known as nonsteroidal anti-inflammatory drug-activated gene (NAG-1) and is induced by the administration of NSAIDs, including indomethacin [42]and ibuprofen [43]. Many preterm neonates are exposed to NSAIDs to prevent IVH or treat a hemodynamically significant PDA. However, there are no long-term benefits of these drugs despite the closure of PDA [44]. The indirect effects of these drugs with the possible induction in GDF15 levels in this patient population need to be further explored.

The limitation of our study is the small size of the cohort and the absence of follow-up beyond the NICU discharge regarding the GDF15 levels and long-term respiratory and clinical outcomes. Also, maternal and cord blood GDF15 levels were not measured and were not compared to the initial GDF15 levels in neonates. The strength of our study is that utilizing scavenged specimens avoided any additional blood loss or painful procedures in this vulnerable population, and samples were collected longitudinally from the same patient at different time points, enabling the correlation of GDF15 levels with the clinical course.

In summary, in this pilot study, we show for the first time that GDF15 levels in preterm infants display a significant inverse correlation with gestational age, with higher levels

in more preterm babies and postnatally declining levels. We highlight the potential of using GDF15 as a biomarker for predicting adverse respiratory outcomes in preterm infants. Studies in animal models with loss-of-function and gain-of-function of GDF15 will be needed to establish causality for the disease phenotype and further elucidate the cell-autonomous or non-cell-autonomous role of GDF15 will be required. Further studies in larger cohorts will be needed to correlate the GDF15 levels in maternal, placental, and cord blood with its postnatal levels and the role of GDF15 levels in predicting BPD and associated morbidities such as BPD- associated pulmonary hypertension.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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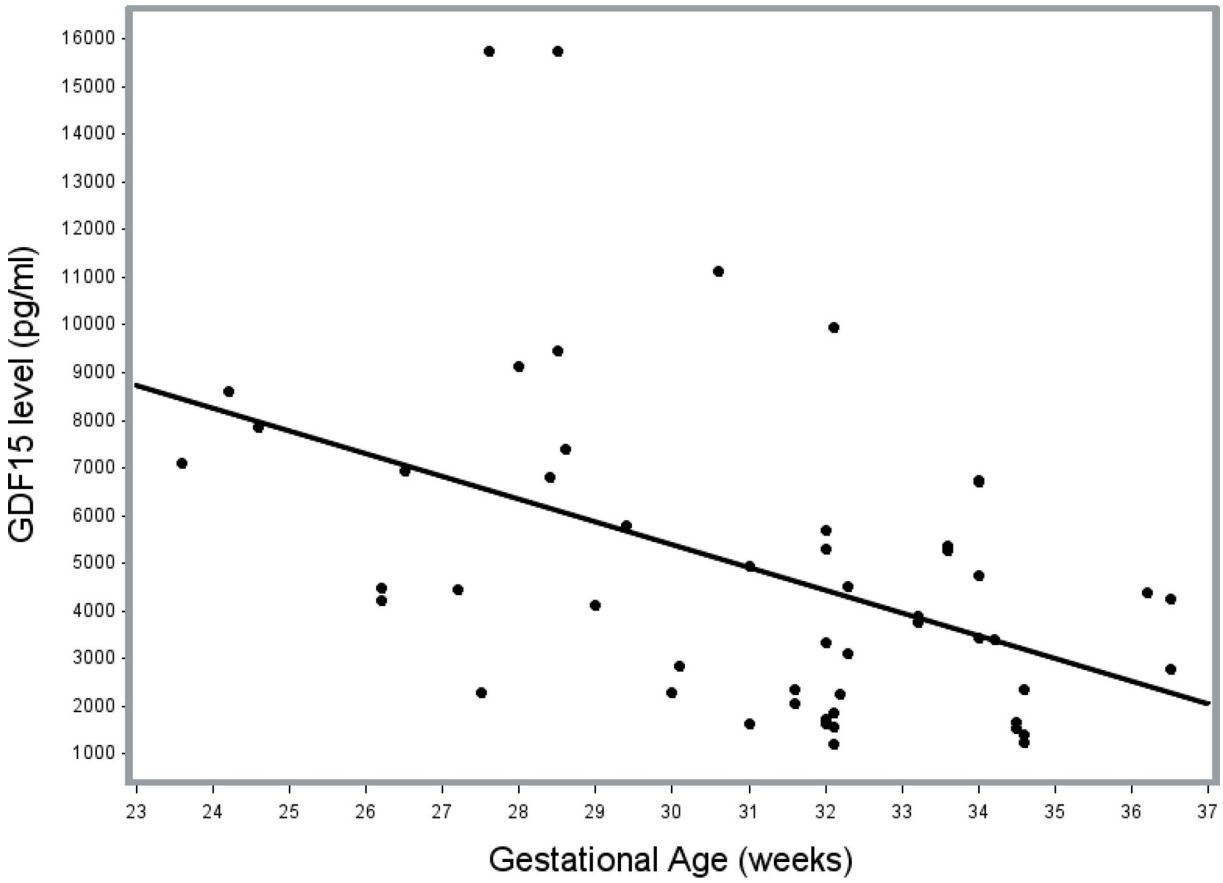

Figure 1:

Scatterplot of GDF15 serum levels within the first week of life vs. Gestational age, with superimposed linear regression line. Linear regression analysis showed that for every one-week increase in gestational age at birth, the predicted GDF15 level in the first week of life decreased by 475.0 pg/ml ($p<0.001$).

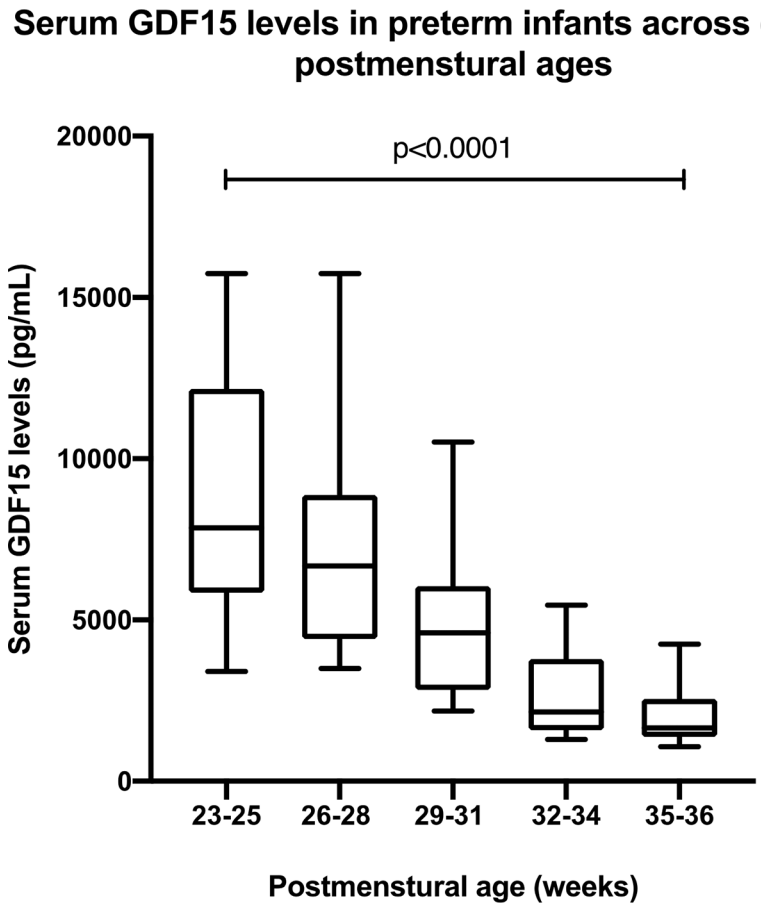

Figure 2:

A box and whisker plot showing the serum GDF15 levels in infants at different postmenstrual ages. The data are represented as boxes for the medians and the interquartile ranges, and the whiskers represent the 10th percentile. Pearson's correlation showed a significant inverse relationship between PMA and GDF15 level. ($r = -0.618$, $p<0.0001$).

Table 1:

The baseline characteristics and outcomes of the study cohort. A total number of 55 preterm infants are shown in the table.

		Study Cohort (n = 55) [a]
Infants Baseline Characteristics		
Gestational age – n (%)		
	23 – 27 weeks	10 (18)
	28 – 32 weeks	28 (51)
	33 – 36 weeks	17 (31)
Birth weight (g) – mean ± standard deviation		1643 ± 635
Female – n (%)		24 (44)
Exposure to antenatal steroids – n (%)		41 (75)
Delivered via Cesarean Section – n (%)		47 (85)
APGAR <7 at 1 minute – no.(%)		18 (33)
Pregnancy – n (%)		
	Singleton Multiparity	31 (56) 24 (44)
Race or ethnic groups, n (%)		
	White Black Hispanic Others	20 (36) 17 (31) 17 (31) 1 (2)
Hypertensive disorders of pregnancy, n (%)		20 (36)
Chorioamnionitis, n (%)		5 (9)
Infants Outcomes		
Bronchopulmonary dysplasia, n (%)		10 (18)
Duration of respiratory support (days) – mean ± standard deviation		27 (42)
Patent ductus arteriosus treatment, n (%)		6 (11)
Necrotizing enterocolitis, n (%)		4 (7)
Sepsis, n (%)		6 (11)
Retinopathy of prematurity, n (%)		11 (20)
Intraventricular hemorrhage, n (%)		9 (16)
Mortality, n (%)		1 (2)
Length of stay (days) – mean ± standard deviation		52 ± 45

[a]Two subjects out of the enrolled 57 were excluded, due to inability to retrieve scavenged specimens.

Table 2.

After controlling for gestational age and day of life, the associations of longitudinal GDF15 levels with respiratory outcomes and length of stay in preterm infants

	Slope Coefficient (Standard Error)	p-value
Respiratory Outcomes		
Duration of mechanical ventilation (days)	26.0 (11.4)	0.034
Duration of any respiratory support (days)	37.4 (8.8)	<0.001
Oxygen requirement at PMA 36 week	290.3	0.044
Bronchopulmonary dysplasia	1191.2 (842.5)	0.173
Length of stay (days)	27.7 (8.9)	0.006

Table 3.

After controlling for gestational age and day of life, the associations between the longitudinal GDF15 levels, cohort baseline characteristics, and other outcomes related to prematurity in preterm infants.

	Slope Coefficient (Standard Error)	p-value
Baseline Characteristics		
Birth weight – g	−1.35 (0.65)	0.051
Birth Length – cm	−40.7 (56.0)	0.476
Gender – female	−218.0 (363.7)	0.556
Mode of Delivery – Cesarean Section	−345.5 (704.7)	0.629
Prolonged rupture of membrane	−730.6 (687.7)	0.301
Exposure to antenatal steroid	−1309.3 (709.9)	0.080
Chorioamnionitis	853.9 (934.4)	0.372
Hypertensive disorders of pregnancy	127.0 (569.2)	0.826
Outcomes related to prematurity		
Intraventricular hemorrhage	215.9 (326.6)	0.538
Retinopathy of prematurity	742.2 (906.9)	0.423
Necrotizing enterocolitis	747.8 (453.4)	0.116