Original Article

Exploring the Effects of Early Nutritional Interventions on Growth, Metabolic Profiles, and Neurodevelopment in Preterm Rat Models

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Abstract

Background: During the critical window of development, malnutrition can have long-term metabolic and neuro-developmental consequences.

Objective: To evaluate the effect of early postnatal malnutrition and catch-up growth on metabolic profile and neurodevelopment in a preterm rat model, while adjusting for current body weight.

Methods: This experimental study was conducted on 142 neonatal rats. Rats were randomly allocated to normal (N) and malnourished (R) groups, from days 2-11 of postnatal life. Using litter size modification, malnourished rats were divided into three subgroups based on catch-up growth patterns (accelerated (RC), normal (RN) or no (RR) catchup), from days 11-21. Rats were provided food ad libitum from day 21 to 60. Growth velocity, serum glucose, insulin, leptin, triglycerides, and neurodevelopmental outcomes were compared among groups at day 60 while adjusting for body weight.

Results: During the catch-up growth phase, rats with accelerated growth (RC) exhibited significantly higher growth velocity ($p<0.001$) than normally fed rats (N), but this difference diminished by the study's end. Serum glucose concentrations were significantly higher in rats with rapid catch-up growth compared to those with normal ($p=0.003$) or no ($p<0.001$) catch-up growth. Serum insulin ($p=0.15$) and leptin ($p=0.97$) levels did not significantly differ among subgroups. Malnourished rats with normal catch-up growth demonstrated better-learned behaviour than rats with rapid ($p=0.013$) or no ($p=0.009$) catch-up growth.

Conclusion: Catch-up growth at a normal velocity after early postnatal malnutrition preserves metabolic health while limiting neurodevelopmental deficit. Accelerated catch-up growth, though transiently beneficial for growth, can increase vulnerability to neurodevelopmental deficits. These findings urge a nuanced approach in developmental biology and pediatric medicine for effective interventions and improved outcomes among preterm infants.

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Introduction

A drastic increase in the global preterm birth rate to 11% indicates a critical global health challenge.[1] This trend is particularly striking in low- and middle-income countries, with Pakistan ranked as the sixth

highest contributor.[2] Preterm infants are born before accumulating sufficient fat reserves during the third trimester.[3] So they confront formidable challenges during their early postnatal life, a critical window of development.[3] They are particularly susceptible to Extra-uterine Growth Restriction (EUGR), i.e. postnatal growth failure that arises from cumulative protein and energy deficits.[4] This EUGR is associated with long-term health implications.[4]

The concept of "nutritional programming" has gained prominence in the fields of developmental biology and pediatric medicine. This refers to early life malnutrition that triggers long-lasting epigenetic alterations which influence an individual's health throughout their lifetime.[5] Such programming can result from disturbances in the internal body environment, ranging from malnutrition to overfeeding, during this crucial developmental window.[5] These epigenetic modifications lead to enduring "developmental plasticity" in the genetic, nutritional, and endocrine signalling pathways that shape growth and neurodevelopment.[6]

Initial growth failure among preterm infants is often mitigated by accelerated catch-up growth. Accelerated catch-up growth exceeds the statistically expected limits for normal growth at that age.[7] This is deemed a potential solution to reduce the neurodevelopmental deficits and growth disparities that preterm infants face.[7] However, the benefits of catch-up growth are not without risks. While it may improve short-term neurodevelopment,[8] it has also been linked to metabolic disorders later in life.[9]

Previously animal and human studies have shown variable impact of catch-up growth on metabolic health and neurodevelopment of EUGR preterm infants.[8-10] These inconsistencies partly stem from non-standardised EUGR models, heterogeneity in nutritional protocols, variability in outcomes assessed and timing of measurement. However, results lack generalizability owing to the non-standardization of data including representative outcome measures, duration and intensity of catch-up growth induction. The intricate interplay of factors influencing growth velocity, such as nutrition and genetic predisposition, highlights the importance of using growth velocity as a standardized measure to compare outcomes among preterm infants, rather than focusing solely on absolute weight gain.[11] While studies address the impact of intrauterine growth restriction among small for gestational age infants, data specifically regarding EUGR in preterm infants is scarce.

The long-term health consequences of early postnatal malnutrition and growth restriction, followed by catch-up growth, may resemble those of term-born small for gestational-age infants undergoing accelerated growth through overfeeding. However, the growth-restricted term newborn (whose principal fuel in utero is carbohydrates) offers an inaccurate model for preterm infants (whose primary fuel in early postnatal life is fat).[12] Therefore, current prenatal growth restriction models cannot adequately capture the metabolic consequences of postnatal malnutrition followed by catch-up growth. In experimental settings, early caloric restriction leads to postnatal malnutrition, whereas subsequent unrestricted feeding results in catch-up growth.

Considering these complex dynamics and the gap in available literature, the objective of this study is to evaluate the effect of early postnatal malnutrition and subsequent catch-up growth on metabolic profile and neurodevelopment in a rat model. The metabolic and neurodevelopmental evaluation was adjusted for current body weight to account for variation induced by size. The rat model offers translational relevance as its postnatal developmental period correspondingly models the human third trimester. This research aims to explore the intricate interplay between nutrition, somatic growth, metabolic health, and neurodevelopment. Findings may inform strategies for improving long-term outcomes in preterm infants at risk of EUGR.

Methods

This experimental study was conducted at the Department of Physiology, CMH Multan Institute of Medical Sciences (CIMS), Multan. The study was conducted from September to December 2022, after obtaining ethical approval from the Institutional Review Board (IRB) vide letter number TW/25/CIMS. Strict adherence to institutional guidelines for animal handling and compliance with ARRIVE guidelines was maintained throughout the data collection.[13]

A total of 24 timed pregnant Wistar rats were obtained on the 14th gestational day and housed in the institutional animal lab for acclimatization. Litters were delivered after one week. Dams were keenly observed for distress signs during the peripartum period. Pups were regularly observed to ensure feeding by their dams.

To study preterm and catch-up growth variation, the “litter size manipulation model” was used. This is considered a reliable method in rodent studies.[14,15] This model mimics the nutritional challenges of preterm infants and is preferable to models like maternal nutritional restriction, which raise ethical concerns. The litter size manipulation model modulates growth rate by varying

both the quantity and quality of milk intake, including milk availability and nutritional composition (fat and protein).[16] Factors like thermogenesis and protein utilization efficiency also vary with litter size, contributing to growth pattern differences.[16]

On the second postnatal day, 142 pups were randomly allocated to Group "N" (normal intake) and Group "R" (restricted intake) through litter size manipulation.[15] Group "R" (n=112) had large litters (16 pups/dam) for induction of malnourishment, while Group "N" (n=30) had small litters (10 pups/dam), considered normal. This intervention lasted from the 2nd to the 10th day, equivalent to the third trimester of intrauterine life in humans or early postnatal life of human preterm infants.[14] Randomization was performed at the litter level. Allocation concealment was not possible due to visible litter size differences.

On day 11, pups in Group R (n=112) with a weight below the 10th percentile of Group N (n=30) were labelled malnourished (n=92). The remaining pups (n=20) were excluded according to the predefined criteria, including mortality, congenital malformations, failure to nurse, or failure to achieve malnutrition, i.e., weight ≥ 10th percentile of group N. Ninety-two malnourished pups from Group R were randomly redistributed into subgroups. Pups in Group N (n=30) continued in normal-sized litters of 10 pups/dam each. Litter effects were reduced by randomization at the litter level, as pups were distributed across the litter during subgrouping.

Sample size was determined a priori, using G*Power (version 3.1.9.7).[17] The required sample size for an ANCOVA with four groups and one covariate was estimated, assuming a medium-to-large effect size (f = 0.32) according to Cohen's conventions,[18] an α error probability of 0.05, and a statistical power ($1-\beta$) of 0.80. The analysis indicated a minimum of 111 rats in total (approximately 27–28 per group). To account for potential attrition, a total of 122 rats were recruited. The experimental unit was the individual pup for growth and biochemical outcomes. Nesting within litters was acknowledged but not modeled statistically.

A total of 142 pups were born across 24 litters, which served as the initial biological cohort. Of these, 20 pups were excluded due to predefined criteria. While n= 122 pups were retained for subgroup allocation on day 11, that exceeded the minimum calculated sample size (n=111).

- Sub-group RC (Restricted then catch-up growth): 5 litters of 6 pups/dam each (n=30), target >+1 SD growth velocity above Group N
- Sub-group RN (Restricted then normal growth): 3 litters of 10 pups/dam each (n=30), target growth velocity within ±1 SD of Group N
- Sub-group RR (Restricted then restricted intake): 2 litters of 16 pups/dam each (n=32), target growth velocity <-1 SD of Group N

This nutritional intervention continued from day 11 to day 21, broadly equivalent to the first two years of human life, representing the catch-up growth phase in human preterm infants.[14] Catch-up growth variation among subgroups was confirmed by calculating the mean difference in growth velocity from day 11 to day 21, as described below. A statistically significant difference confirmed the variation in catch-up growth. From day 21 to day 60, pups were shifted to weaning and provided water and rodent diet ad libitum.

Somatic growth was assessed via serial weight measurements of pups by a digital measuring scale (Sonex S9 Plus). Growth velocity[19] of rats was calcu-lated as [GV = ((Wy – Wx) × 1000) / ((Wx + Wy)/2)].[9] Where Wx and Wy show the body weight in grams, at the start and end of specified period. Growth assessors were not blinded due to visible size differences.

Neurodevelopmental outcome was assessed through the Passive Avoidance Test[20] on day 45 (training day) and day 46 (testing day). Rats were trained on day 45 to avoid the dark room due to an aversive electric shock. On the testing day, latency to enter the dark chamber was noted for each pup.

Blood sampling was performed on day 60, which is broadly equivalent to young adulthood in humans.[14] Rats were anesthetized with ether and blood was collected via terminal cardiac puncture.[21] Rats were euthanized post-sampling as per institutional protocol. Separated sera were used for glucose measurement by glucose oxidase mediated peroxidase method. Rest of the sera were used for analysis of serum parameters using Glory Science Co, Ltd Rat ELISA kits for insulin, leptin, and triglycerides. Biochemical assays and neurodevelopmental testing were performed by blinded analysts.

Data analysis was conducted unblinded using Statistical Package for Social Sciences (SPSS) version 26. A two-way mixed ANOVA compared the effect of nutritional group and day of life on serial growth velocity. Serum biochemistries and passive avoidance test performance were compared among subgroups by univariate ANCOVA, with weight as a covariate. If significant, a Tukey post hoc test was used, significant at $p<0.05$. Chi square/Fischer exact test compared the groupwise percentage timed-out event of passive avoidance test,

subjected to fulfilling of assumptions.

For ANCOVA, linearity between body weight and serum parameters was confirmed by scatterplots. Homogeneity of regression slopes was confirmed by interaction term testing. Homoscedasticity was evaluated by residual inspection. No leverage or influential points were identified.

Results:

Two-way repeated measures ANOVA for growth velocity in rats (N=30, RC=30, RN=30, RR=32) showed a statistically significant interaction between day of life and subgroup ($F=11.38$, $p<0.001$). Figure 1 shows the statistically significant effect of nutritional intervention on serial growth velocity of rats for specified intervals.

Table 1 shows the pairwise comparison among subgroups for the effect of nutritional intervention on growth velocity of rats. During catch-up growth induction phase (day 11-21), malnourished rats with accelerated growth (RC) grew at a significantly higher velocity than normally fed rats (N), $p<0.001$. Malnourished rats with normal (RN) or no (RR) catch-up growth, continued growing at a higher velocity than normally fed rats (N), even after the catch-up growth intervention was over at day 21. After all groups were shifted to ad libitum feeding from day 21–60, growth velocity differences became non-significant by day 60.

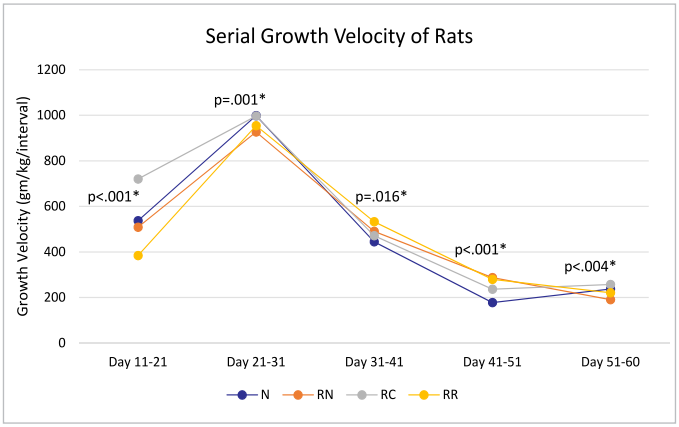

Figure 1: *Effect of nutritional intervention on serial growth velocity rats from Day 11 to 60 of postnatal life*

**Significant at Bonferroni adjusted alpha level of p< 0.05, N; Normally Fed, RN; Restricted then normal Growth, RC; Restricted then Accelerated catch-up growth, RR; Restricted then restricted growth. (N/RN/RC : n=30 each, RR: n=32)*

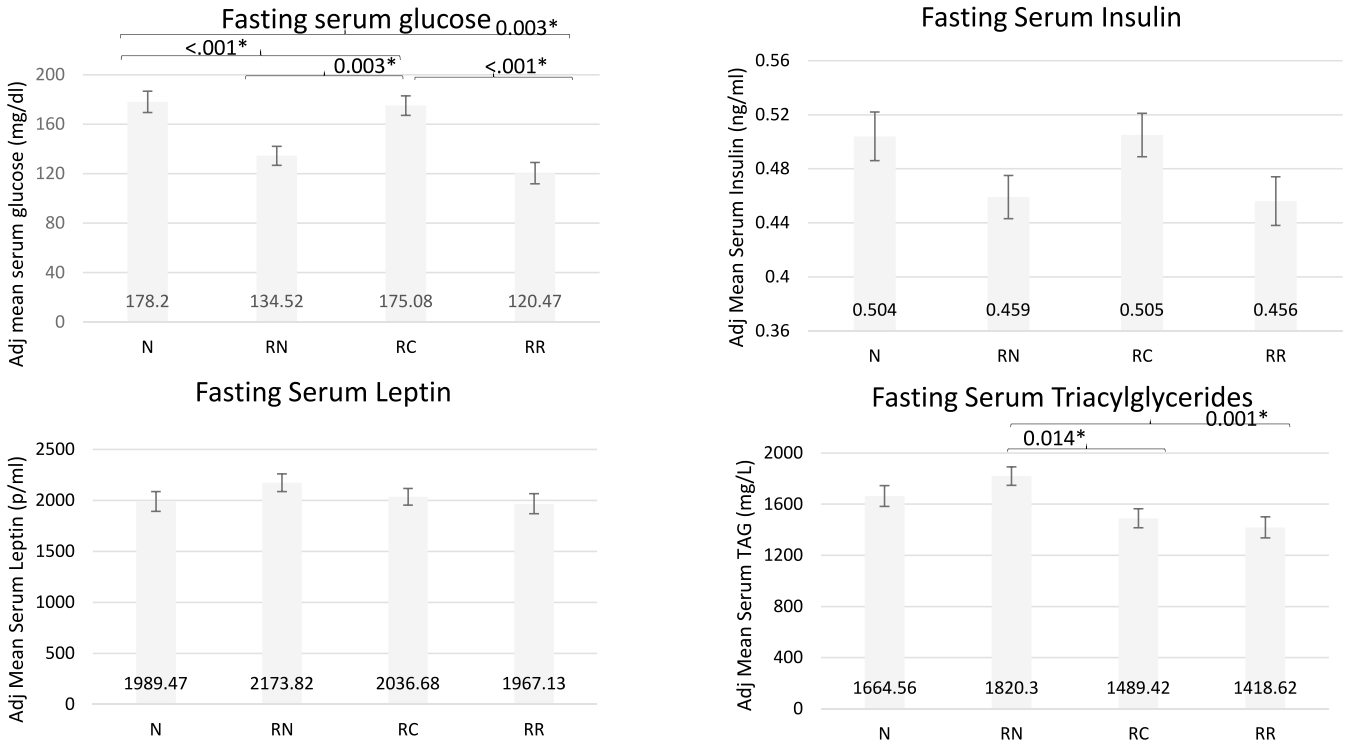

Figure 2: *Effect of nutritional intervention on serum parameters of rats at day 60 of postnatal life*
**Significant at Bonferroni adjusted alpha level of p< 0.05, Error bars: ±1 SEM N; Adj: Adjusted for weight Normally Fed, RN; Restricted then normal Growth, RC; Restricted then Accelerated catch-up growth, RR; Restricted then restricted growth. (N/RN/RC: n=30 each, RR: n=32)*

Table 1: *Effect of nutritional intervention on growth velocity of rats, Day 11 - 60 of postnatal life*

Subgroup Pair (a-b)		Mean ± SEM	p-value	Mean ± SEM	p-value	Mean ± SEM	p-value	Mean ± SEM	p-value	Mean ± SEM	p-value
a	b	Day 11- 21		Day 21- 31		Day 31- 41		Day 41- 51		Day 51- 60	
N	RN	28.29± 42.53	1.00	71.52± 20.79	0.01*	-45.79± 28.15	0.64	-109.89± 24.88	<.001*	46.36± 18.36	0.08
N	RC	-183.06± 42.53	<.001*	1.36± 20.79	1.00	-26.6± 28.15	1.00	-59.02± 24.88	0.12	-19.78± 18.36	1.00
N	RR	152.65± 41.86	0.002*	43.87± 20.46	0.20	-88± 27.71	0.01*	-102.09± 24.49	<.001*	16.54± 18.07	1.00
RN	RC	-211.35± 42.53	<.001*	-70.17± 20.79	0.01*	19.19± 28.15	1.00	50.87± 24.88	0.26	-66.14± 18.36	0.01*
RN	RR	124.36±41.86	0.02*	-27.66± 20.46	1.00	-42.22± 27.71	0.78	7.81± 24.49	1.00	-29.82± 18.07	0.61
RC	RR	335.71± 41.86	<.001*	42.51± 20.46	0.24	-61.41± 27.71	0.17	-43.07± 24.49	0.49	36.31± 18.07	0.28

**Significant at Bonferroni adjusted alpha level of p< 0.05, SEM: Standard error of mean*
N; Normally Fed, RN; Restricted then normal Growth, RC; Restricted then Accelerated catch-up growth, RR; Restricted then restricted growth, (N/RN/RC: n=30 each, RR: n=32).

Univariate ANCOVA for the serum glucose of rats in subgroups was statistically significant (p< 0.001), while adjusting for body weight. Figure 2 shows pairwise comparisons indicating that mean serum glucose concentrations of N and RC were significantly higher than RN and RR, p<0.01.

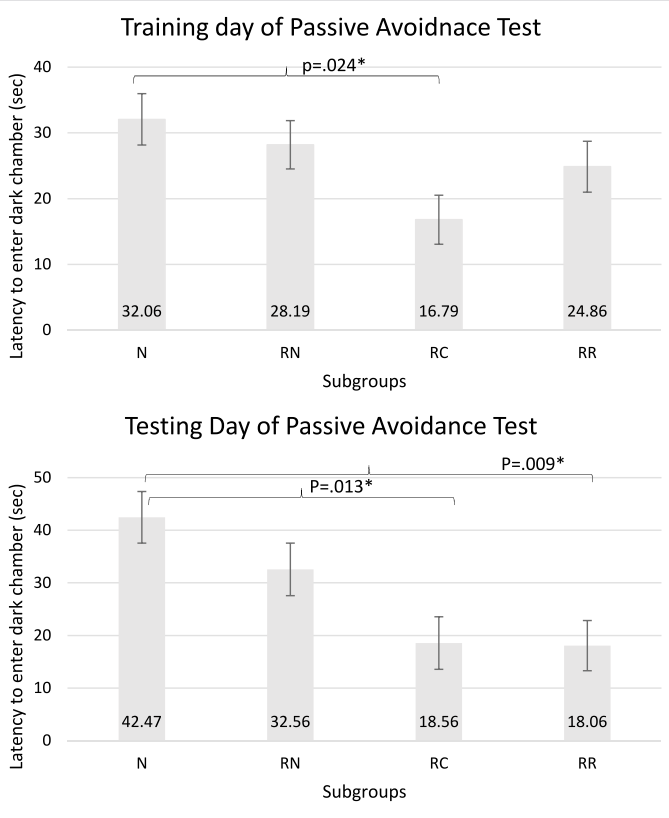

Figure 3: *Effect of nutritional intervention subgroups on passive avoidance test performance*

**Significant at Bonferroni adjusted alpha level of p< 0.05, Error bars: ±1SEM,*

N; Normally Fed, RN; Restricted then normal Growth, RC; Restricted then Accelerated catch-up growth, RR; Restricted then restricted growth. (N/RN/RC: n=30 each, RR: n=32)

Table 2: *Effect of nutritional intervention on "Timed-out" event of Passive avoidance Test*

Sub-groups	Training Day		Testing Day	
	Entered dark chamber. n (%)	Timed-out at 60 sec n (%)	Entered dark chamber. n (%)	Timed-out at 120 sec n (%)
N	25 (83.3%)	5 (16.7%)	25 (83.3%)	5(16.7%)
RN	24 (80%)	6 (20%)	27 (90%)	3 (10%)
RC	29 (96.7%)	1 (3.3%)	29 (96.7%)	1 (3.3%)
RR	25 (78.1%)	7 (21.9%)	32 (100%)	0 (0%)

N; Normally Fed, RN; Restricted then normal Growth, RC; Restricted then Accelerated catch-up growth, RR; Restricted then restricted growth. (N/RN/RC: n=30 each, RR: n=32)

Univariate ANCOVA for insulin (p=0.15) and leptin (p=0.97), both adjusted for final body weight, showed no significant subgroup effect. Therefore, post hoc testing was not performed. Figure 2 presents the adjusted means for insulin and leptin levels.

Univariate ANCOVA for serum triglyceride (TAG) levels showed a significant subgroup effect (p=0.001), adjusting for body weight. Figure 2 shows that subgroup RN had significantly higher TAG levels than RC (p= 0.014) and RR (p=0.001).

Univariate analysis for passive avoidance test latency showed significant subgroup differences on training (p=0.03) and testing (p=0.004) days. Figure 3 shows significantly longer latency in N compared with RC on training (p=0.024) and testing (p=0.013) days, and longer latency in N compared with RR on testing day (p=0.009).

Chi-square analysis of the proportion of rats who timed out showed no significant subgroup difference on train-

ing day (p=0.15), but was significant on testing day (p=0.04). Table 2 shows subgroup-wise percentages of timed-out rats.

Discussion

This study explores the interplay between early postnatal malnutrition, catch-up growth, and their impacts on glucose homeostasis and neurodevelopment in a rat model. During the catch-up growth phase, malnourished rats with accelerated growth exhibited significantly higher growth velocity than normally fed rats, aligning with previous research indicating short-term growth advantages.[22] Despite initial growth retardation, preterm infants typically catch up to their genetic growth potential with adequate nutrition.[23]

However, the subsequent normalization of growth velocity between malnourished and normally fed rats by the study's end emphasizes the transient nature of these effects, contrary to studies suggesting persistent weight gain and obesity after rapid catch-up growth.[24] Many observational studies and review articles among human preterm infants have reported a high risk of later obesity among protein supplemented formula-fed infants.[24,25] Previous rodent research has shown similar results relating early postnatal overfeeding to overweight and adiposity later in life.[26]

Notably, serum glucose concentrations were significantly higher in malnourished rats with rapid catch-up growth compared to those undergoing normal or no catch-up growth. This suggests that the metabolic consequences of catch-up growth extend beyond the immediate growth phase, emphasizing the need for careful consideration of nutritional interventions in the postnatal period. These results support the concept of nutritional programming, indicating that extremely low birth weight (EUGR) infants not only fail to thrive but also experience long-term adverse consequences, including an increased risk of adult-onset type 2 Diabetes Mellitus and cardiovascular diseases among overweight preterm infants.[23,27] However, current study showed no difference in serum glucose of normally fed rats and rats with rapid catch-up growth. Previously, rodent, and human studies have variably associated preterm birth and rapid catch-up growth with deranged glucose homeostasis; still, the results are inconclusive because of heterogeneity of data available.[3,14,28]

Surprisingly, serum insulin and leptin levels did not show significant differences among subgroups when adjusting for body weight, raising concerns about the intricate relationship between catch-up growth, metabolic factors, and the potential role of compensatory mechanisms. Insulin and leptin are both critical regulators in growth and metabolism.[29] Previous studies have linked accelerated catch-up growth to increased insulin resistance and deranged leptin levels.[3,30] Inadequate nutrition during the perinatal period often results in altered leptin levels, which can adversely impact hypothalamic development and energy balance regulation.[29] The variation observed in this study may be due to the timing of the assessment. Measurements on day 60 may not capture the significant effects of insulin and leptin, which could be more evident during catch-up growth or later metabolic adaptation. A strength of this study is the use of ANCOVA to adjust for weight at assessment, a factor often not fully addressed in other studies. Although ANCOVA controlled key confounders, it may not have captured hormonal or stage-specific metabolic influences on insulin and leptin.

In contrast, serum triglyceride levels demonstrated significant differences, with malnourished rats undergoing normal catch-up growth showing higher mean levels compared to those with restricted catch-up growth. Previously, catch-up growth was also associated with an increased risk of dyslipidemia and cardiovascular disorders among low birth weight and preterm infants.[3] These findings underscore the need for a comprehensive understanding of the metabolic consequences associated with catch-up growth in the context of early malnutrition.

In this study, malnourished rats with normal catch-up growth demonstrated significantly better learned behavior than rats with rapid or no catch-up growth. Conversely, previous studies largely associate accelerated catch-up growth with improved neurodevelopment of preterm infants at the cost of metabolic derangements.[22,24] Consistent with this study, Beyerlein et al. proposed a linear relationship between cognition and weight gain velocity from −1 to +2 standard deviation, and no further advantage at >+2 standard deviation.[31] Conversely, previous studies largely associate accelerated catch-up growth with improved neurodevelopment of preterm infants at a cost of metabolic derangements.[22,24] However, the direction and magnitude of the relation between catch-up growth velocity and neurocognitive/ metabolic consequences are still controversial.

In conclusion, this study provides valuable insights into the intricate relationship between early postnatal malnutrition, catch-up growth, and subsequent metabolic and neurodevelopmental outcomes. These findings offer a foundation for future research and potential interventions in the realm of developmental biology and pediatric medicine.

Limitations and Recommendations:
This study is limited to using a rat model, which may not perfectly mirror the complexities of human development. The results from this rat model may not directly apply to human infants due to differences in metabolism and neurodevelopment. Also, the Passive Avoidance Test measures only one aspect of neurodevelopment.
Future research could explore additional markers of metabolic health and extend the observation period to elucidate the long-term consequences further. More sophisticated measures of neurocognitive outcome could be used, such as the Morris Water Maze, T-Maze, or Barnes Maze.

Conclusion

Catch-up growth at a normal velocity after early postnatal malnutrition preserves metabolic health while limiting neurodevelopmental deficit. Accelerated catch-up growth, though transiently beneficial for growth, can increase vulnerability to neurodevelopmental deficits. These findings urge a nuanced approach in developmental biology and pediatric medicine for effective interventions and improved outcomes among preterm infants.

Ethical Approval: The Institutional Review Board/ Ethical Committee, CMH Multan Institute of Medical Sciences (CIMS), Multan approved this study vide Case No. TW/25/ CIMS.
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Authors' Contribution

FI: Conception & design, acquisition of data, analysis & interpretation, drafting of article, critical revisions for important intellectual content, final approval of the version to be published

AR: acquisition of data, analysis & interpretation, drafting of article

SA: Acquisition of data, analysis & interpretation

UB: Critical revisions for important intellectual content

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