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final manuscript as submitted. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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ABSTRACT

Background: as chromium (Cr) is known to contaminate components of parenteral nutrition (PN), Cr-free PN is recommended for preterm

infants. Exposure to Cr by PN in preterm infants is scarcely investigated.

Objective: to describe Cr levels in plasma (Cr_p) and urine (Cr_u) during the first month of life in premature newborns ≤ 1500 g of birthweight (BW) receiving PN, and to evaluate the impact on postnatal clinical parameters.

Methods: a prospective observational study. Cr-free PN was administered at day 1 of life and continued until full enteral feeding with fortified breastmilk began. Cr_p levels at day 15 and 30 and Cr_u at day 30 of life were assessed according to demographic factors, biochemical markers and postnatal morbidity.

Results: 97 infants had a median gestational age (GA) of 29.9 weeks, and a median BW of 1205 g. Median Cr_p remained at 1.0 µg/L at 15 and 30 days (IQR 0.7-1.4 and 0.7-1.3, respectively). Premature babies < 26 weeks had a significantly higher Cr_p at one month than the remainder (p = 0.043) and higher Cr elimination in the urine (p = 0.026). Cr_p increased with prolonged PN (p < 0.001), even after adjusting for gestational age (p = 0.001). Laboratory parameters were not influenced by Cr_p or Cr_u, nor was morbidity. **Conclusion:** Cr_p increases with days of PN even when a trace mineral supplement without Cr is used, and the level reached persists during the first month of life with the introduction of Cr-supplemented breastmilk feeding. No relation to morbidity was observed.

Keywords: Chromium. Essential trace element. Preterm infant. Very low birth weight. Parenteral nutrition.

RESUMEN

Introducción: al ser el cromo (Cr) un posible contaminante de los componentes de la nutrición parenteral (NP), se recomienda esta sin Cr para los recién nacidos prematuros. Hay pocos estudios sobre la exposición al Cr a través de la NP en prematuros.

Objetivo: describir los niveles de Cr en plasma (Cr_p) y orina (Cr_o) durante el primer mes de vida en recién nacidos prematuros de ≤ 32 semanas y/o ≤ 1500 g de peso al nacer (PN) que recibieron NP, y evaluar el impacto sobre algunos parámetros clínicos postnatales.

Métodos: estudio observacional prospectivo. Se administró NP libre de Cr en el día 1 de vida y se continuó hasta conseguir la alimentación enteral completa con leche materna fortificada. Se evaluaron los niveles de Cr_p en los días 15 y 30 y los de Cr^o en el día 30 de vida, así como su posible relación con los factores demográficos, los marcadores bioquímicos y la morbilidad posnatal.

Resultados: los 97 lactantes tenían una edad gestacional (EG) media de 29,9 semanas y un peso al nacimiento (PN) medio de 1205 g. La media de Cr_p se mantuvo alrededor de 1,0 µg/L a los 15 y 30 días (IQR: 0,7-1,4 y 0,7-1,3, respectivamente). Los prematuros < 26 semanas tuvieron un Cr_p al mes significativamente mayor que el resto (p = 0,043) y una mayor eliminación de Cr en orina (p = 0,026). El Cr_p aumentó con los días de NP (p < 0,001), incluso ajustando la edad gestacional (p = 0,001). Los parámetros de laboratorio no se vieron influidos por el Cr_p o el Cr_o, ni tampoco la morbilidad.

Conclusiones: el Cr_p aumenta con los días de NP aunque se utilice un suplemento de elementos traza sin Cr, y los niveles alcanzados se mantienen estables durante el primer mes de vida, en el que se introduce la alimentación con leche materna fortificada con suplementos que sí contienen Cr. No observamos ninguna relación con la morbilidad.

Palabras clave: Cromo. Elemento traza. Oligoelemento. Prematuro. Muy bajo peso al nacer. Nutrición parenteral.

INTRODUCTION

Chromium is one of the most often studied trace elements in relation to human health as it is naturally occurring and also used in industrial processes. Despite this fact, literature about Cr in newborns is rare and mostly based on discovering the impact of high exposure to environmental Cr in pregnant women and the impact on babies' health (1-3). Research about Cr levels in preterm infants receiving parenteral nutrition is very scarce (4,5).

The transition element chromium (Cr) exists in several oxidation states. Hexavalent Cr is the most oxidized form. It is prevalent in industry and is potentially toxic. Trivalent Cr is stable and believed to be an essential trace element, though this is not clearly proved and evidence for this is only based on case reports (2). Individuals may be exposed to trivalent Cr through food, air, water, and soil or dietary supplements (6,7). It may improve glucose tolerance as it is thought to have an important function as a regulator of insulin action (8,9). Furthermore an interaction between Cr and iron has been reported as Cr is transported in the body bound to transferrin, where it binds competitively with iron (10).

In adults receiving prolonged parenteral nutrition (PN) without chromium supplementation, Cr deficiency has been related to glucose intolerance. (9,11-13).

Supplementation with Cr in parenteral nutrition also resulted in better glucose tolerance and caloric delivery during the first week of life in very low birth weight infants (14).

On the other hand, Cr is a known contaminant of components of PN solutions, showing increased 10- to 50-fold of normal reference levels in sera of patients receiving Cr-free PN solutions. Contamination is reported to vary greatly between 2.4 and 10.5 µg/day (11). There is little evidence that trivalent Cr is toxic due to its poor absorption, but intravenous trivalent Cr received by PN may have an impact on renal function in adults and in newborns.

Preterm infants with low glomerular filtration rates may be at risk of Cr toxicity even by non-supplemented parenteral solutions (15-17).

The objective of the present study was to determine Cr status of preterm babies with a birthweight < 1500 g receiving PN in order to obtain plasma and urine chromium levels (Cr_p and Cr_u) for our population and find out a possible impact on infants' clinical parameters and morbidity.

We hypothesized that preterm infants receiving Cr-free trace element solution (Fresenius-Kabi Peditrace®) during the first weeks of life continued by fortified (PreNan HMF®) breastmilk may show a relation between the duration of parenteral nutrition and Cr levels with a possible impact on renal function, iron storage and glucose levels.

METHODS

Study design and participants

Mother-infant dyads were recruited from the NEOTRACE cohort, which is a prospective observational single-center study in mother-child cohorts in the Neonatal Intensive Care Unit of the Son Espases University Hospital, Palma de Mallorca, Spain. Data collection began in June 2019 and continued until October 2021.

Premature infants with a gestational age (GA) ≤ 32 weeks and/or ≤ 1500 g of birth weight (BW) were included. All infants without parental consent were excluded.

Mothers were interviewed on their dietary habits, smoking status, intake of iron and other supplements taken during pregnancy and the living area (rural or city).

Plasma Cr levels in newborns were measured at day 15 and 30 of life and urine Cr at 30 days of life, alongside a basic metabolic panel including a complete blood count, glucose, creatinine, electrolytes, bilirubin, calcium, phosphorus, triglyceride, C-reactive protein (CRP) and ferritin. All premature infants received parenteral nutrition with a combined trace element product (Fresenius-Kabi Peditrace®) which did not contain Cr as a supplement. Premature babies continued

nutrition with fortified mothers' or donors' milk for the first month of life.

Mothers' milk was added after 12 hours (1001-1500 g BW) or after 24 hours (≤ 1000 g BW), increasing in aliquots of 20-25 ml/kg/day; meanwhile PN was reduced until withdrawal, when a total of approximately 150 ml of enteral feeding was reached (Supplementary Table I). Fortifier (PreNAN HMF, Nestle® with 0.2 µg of chromium per gram) was introduced after milk intake reached 100 ml/kg/day and was given until hospital discharge. The fortifier dosage was 1 g per 25 ml of breastmilk. Cr content in breastmilk was calculated as an average intake of 1.6 µg/L following the study by Cocho *et al.* in Spanish women (18).

Plasma chromium, urine assessment and analysis of material

Chromium concentrations were measured in plasma lithium heparin and urine samples by inductively-coupled plasma mass spectrometry (ICP-MS) on the NexION x300 platform (PerkinElmer, Finland) using ^{103}Rh as internal standard. Sample preparation included a 1:12 dilution with a solution of 0.5 % HNO_3 and calibration was done by standard addition. Quality was ensured thanks to the ClinChek Serum control materials (RECIPE, Germany) and the participation in the OELM-SEQC external quality assurance program.

All other biochemical tests were also performed in plasma lithium heparin samples on the Architect platform (Abbott Laboratories, USA), while complete blood counts were performed in K_3EDTA whole blood samples using the CellDyn Sapphire flow cytometer (Abbott Laboratories, USA).

All biochemical and hematological tests are accredited according to the ISO 15189.

Anthropometrical and clinical data were taken from electronic patient reports on the hospital information system. For mothers, the following parameters were registered: age, body-mass index (BMI), previous miscarriage, and previous children. For the newborn: GA, BW, Apgar,

umbilical cord pH, days of parenteral nutrition, need for blood transfusions, need for invasive or non-invasive mechanical ventilation (IMV, NIMV), early or late septicemia, intraventricular haemorrhage (IVH), leukomalacia, respiratory distress syndrome (RDS), bronchodysplasia (BDP), retinopathy (ROP), cholestasis, and death.

Statistical analyses

A descriptive analysis of all variables was carried out to define the characteristics of the study group with frequencies and percentages for the qualitative variables and with the median and interquartile range (IQR) for the quantitative variables. To analyze the differences between the different Cr determinations on the same subjects, that is, intragroup differences, Friedman's and Wilcoxon´s tests for paired samples were used. In addition, the differences between groups were analyzed using the Mann-Whitney's U-test for quantitative variables and the chi-square test or Fisher's exact test for qualitative variables. The correlations between numerical variables have been evaluated using the Spearman's rho correlation coefficient. Additionally, all bivariate analyses were adjusted for the GA and PN using the respective simple and multiple linear and logistic regressions. For accurate identification of which factors reached significance, correction for multiple comparisons with the Bonferroni method was used and significance threshold was indicated.

The SPSS v.26 software (IBC Corporation, US) was used for all statistical analyses.

Ethics statement

The study protocol including all materials and procedures was approved by the Ethics Committee of the Balearic Islands (IB 3826/18 PI) and all mothers signed informed consent before inclusion. At every stage of the study, mothers had the possibility to withdraw their babies' participation.

RESULTS

A total of 97 babies participated with a median gestational age of 29.9 weeks (IQR, 27.7 to 31.6), and median birth weight of 1205.0 g (IQR, 895.0 to 1432.5 g). Thirteen were twins; 56 were male (58 %). The mothers' median age was 34 years (IQR, 29.0 to 37.0) with a pre-gestational body mass index of 23.8 (IQR, 21.5 to 26.8). A total of 187 serum, 187 plasma, and 68 urine samples were obtained. Premature babies received PN with a median of 8.0 days (IQR, 7.0 to 14.0). At day 15 (first day of measurement) most infants were on full enteral nutrition with fortified breastmilk.

Mothers´ dietary habits (> once a week intake of broccoli, organ meat, potatoes, whole grains, seafood, chicken, eggs and cooking with tap water), were not related to their babies' chromium levels in plasma or urine, after adjusting for GA and Bonferroni method. Neither living area (urban or countryside) nor smoking status or intake of supplements were related to Cr levels.

Median Cr_p levels were 1.0 µg/L (IQR, 0.72 to 1.44) at 15 days and 0.95 µg/L (IQR, 0.72 to 1.27) at 30 days of chronological age. Median Cr elimination in urine was 0.6 µg/L (IQR, 0.2 to 1.3) (Figs. 1 and 2).

Plasma chromium concentration decreased during the first month of life, but the trend was not significant ($p = 0.076$) when comparing premature newborns which had a Cr_p value on both days ($n = 59$). In premature babies < 26 weeks a significant higher Cr_p value at one month of age could be observed ($p = 0.043$) together with a higher Cr elimination in urine ($p = 0.026$) (Figs. 1 and 2).

Plasma chromium at 30 days was significantly increasing with more days of parenteral nutrition ($p < 0.001$), and lower gestational age (GA) and lower birth weight ($p = 0.005$ and 0.015) (Table III). After adjusting for GA, PN remained a positive factor for the increasing Cr_p (adjusted B: 0.03; CI, 0.01 to 0.04, $p = 0.001$). Also Cr_u at day 30 was inversely related to GA and BW and increased with day of parenteral nutrition (Tables I and II).

Data were adjusted for both GA and PN. A positive association was found between Cr in plasma and Cr in urine at day 30 of life (RHO, 0.52, $p < 0.001$) (Fig. 3).

Regarding renal function, median creatinine in serum decreased from day 15 (0.6 mg/dL; IQR, 0.5 to 0.6) to day 30 (0.4 mg/dL; IQR, 0.4 to 0.5), without significant relation to Cr_p.

Creatinine in urine at day 30 was increased with increased Cr_u ($p < 0.013$; adjusted B, 0.08; CI, 0.02-0.15), but this was not significant after adjusting with the Bonferroni method for multiple comparisons. Serum urea was not related to Cr_p at any day of measurement (Table III).

Serum glucose levels were not related to Cr_p, nor the diagnosis of any alteration of glucose levels (hyper- or hypoglycemia). Also, neither hemoglobin nor ferritin levels at 30 days of age were related to Cr levels in plasma or urine. Other laboratory parameters like C-reactive protein, triglycerides, calcium, phosphorus, bilirubin and number of blood transfusions received during the first month of life were not seen to influence Cr levels.

Complications like early or late septicemia, respiratory distress syndrome, bronchopulmonary dysplasia, cholestasis, retinopathy, ventricular hemorrhage or leukomalacia had no significant relation to plasma chromium levels (Table III).

Only the duration of invasive mechanical ventilation had a statistical relation as Cr increased with longer ventilation time, even after adjusting for GA and PN ($p = 0.001$) (Table III).

DISCUSSION

In this longitudinal cohort study, an inverse relation between Cr_p and GA and BW (RHO, -0.292; $p = 0.005$, and RHO, -0.256; $p = 0.015$) at 30 days of age was found, though not for preterm babies' percentiles. Also, Cr_u was related to GA and BW (RHO, -0.338; $p = 0.005$ and RHO, -0.370; $p = 0.002$).

In a cohort study in Hubei, China, exposure to higher chromium levels during pregnancy was potentially related to the risk of delivering a premature infant (19). In Portland (Oregon, USA) researchers identified prenatal exposure to chromium as a risk factor for preterm birth and small-for gestational age (20). In a prospective cohort of 3041 women in Wuhan, China, Cr in maternal urine samples was associated to lower fetal growth, and Cr was suggested to be a toxic metal regarding fetal growth (21).

BW and GA seemed to point towards increased Cr levels in plasma and urine in our cohort, but both lost significance after adjusting for the days of PN. Comparison to previous studies may be difficult as we do not have data of mothers' Cr levels during pregnancy and most of the cited studies did not measure infants' Cr status. We did not find any relation between mothers' dietary habits and life circumstances, including living in a rural area or city, nor smoking status. The increase in chromium levels in plasma and urine with decreased GA and BW may be due solely to the fact that these infants received more days of parenteral nutrition.

Glucose levels, renal function and ferritin

No relation was found between Cr_u or Cr_p and serum glucose levels, ferritin levels and renal function reflected in creatinine and urea levels in serum.

Cr improves glucose tolerance by enhancing the action of insulin. A few case reports in adults receiving long term PN and developing glucose intolerance which improved after Cr supplementation led to the conclusion that insulin resistance in these cases was due to decreased Cr levels (9,12,13). In a large cohort of very low birth weight infants chromium supplementation in PN resulted in better glucose tolerance during the first week of life (14). To our knowledge, the latter has been the only study focusing on Cr supplementation in PN and glucose levels in preterm infants. The authors of the study gathered data on glucose intake via PN and based on those data and

amount of supplemented Cr they found a higher caloric intake due to the better tolerance of glucose in the Cr supplemented infants. Children in the non-supplemented cohort were of lower gestational age (31.7 vs 32.9 weeks) than among the supplemented children, a fact which may have been reflected in the results as babies with a lower GA tend to be affected with more alterations in the glucose metabolism.

Our Cr_p levels were obtained after 15 days and showed no association with glucose levels at 15 days of life in the logistic regression analysis and even a positive association at 30 days of life lost significance after adjusting for PN and GA. The diagnosis of hyperglycemia or hypoglycemia was also not related to Cr_p or Cr_u.

Importantly, serum creatine was not influenced by higher Cr_p levels. Studies reporting renal impairment after high Cr intake are based on just a few case reports in adults (15,16).

However those data support the recommendation of a Cr-free PN in premature babies as glomerular filtration rates are lower in premature babies than in adults.

Ferritin levels in our cohort were not altered by Cr_p. The few other studies dedicated to the competitive binding effect of chromium and iron on transferrin pointed towards lower levels of Cr_p being related to higher transferrin binding iron. Studies regarding the competitive action of Cr with iron are scarce and based on small groups of patients, there is so far no recent literature about this relation and comparison to our group of patients also might be difficult as we did not measure transferrin (10,22).

Chromium values and parenteral and enteral nutrition

Even though a trace element product without supplemental Cr was administered, the most influential factor of increasing Cr_p levels at day 30 of life was days of having received PN which had a positive B-coefficient of 0.03 (CI, 0.01-0.04, $p = 0.001$).

We calculated chromium intake by the study of Cocho et al in Spanish women of 1.6 µg/L breastmilk even though other studies reported lower Cr content in breastmilk at around 0.22 µg /L (18,23,24).

The fortifier given in our center contains 0.2 µg/1 g of Cr. On an estimated intake of 180 ml/kg/d in a full enteral fed preterm infant with 1 g fortifier per 25 ml breastmilk a full intake of Cr would be 0.29 µg/kg/d by breastmilk and an additional 1.44 µg /kg/d by the fortifier, so a total intake of 1.73 µg /kg/day. The recommended adequate intake of Cr for infants between 0-6 months is 0.2 µg/day of chromium or 0.029 µg/kg/day (25). So our preterm babies received an unknown amount of Cr via PN due to contaminated components and more than the recommended intake of Cr via oral nutrition. During the first 15 days of life when receiving PN, Cr_p levels were similar (1.0 µg/L; IQR, 0.72-1.44) to levels at 30 days of life (0.95 µg/L; IQR, 0.72-1.27). There are only a few studies in newborns to establish normal Cr plasma and/or urine levels. Our urine Cr levels in comparison with reported “normal” levels in literature were similar to a pediatric cohort in Buenos Aires (median level 1.5 µg/L with a range of 1.2-2.8 µg/L). Plasma Cr levels were higher than published in a meta-analysis (range, 0.07 µg/L to 0.2 µg/L) (26,27). A decrease of levels with increasing age is commented on in the literature (28).

CONCLUSION

Infants with a lower gestational age, lower birthweight and more days of PN had higher Cr_p and Cr_u levels. Even if PN is not supplemented with Cr, an increase in Cr_p levels according to days of parenteral nutrition seems to be evident. This is possibly due to contamination of PN components. However, plasma and urine chromium levels did not reach levels which could be considered toxic in our population of preterm babies. No associations were found with blood glucose, ferritin or creatinine levels, nor to morbidities.

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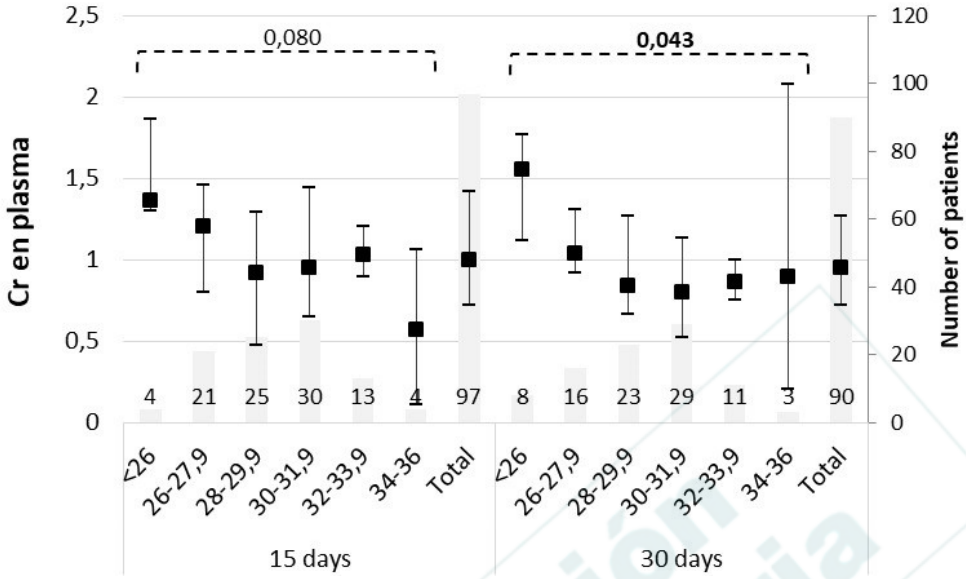

Figure 1. Chromium in plasma in µg/L during the first month of life. Description: premature babies with a GA of < 26 weeks had significantly higher levels of Cr at 30 days ($p = 0.043$).

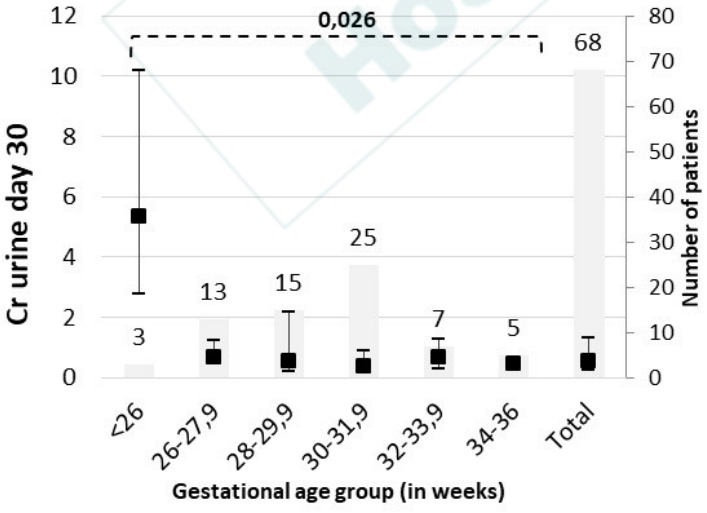

Figure 2. Chromium in urine in µg/L at 30 days of age. Description: infants with a GA < 26 weeks had a significant higher elimination of Cr ($p = 0.026$).

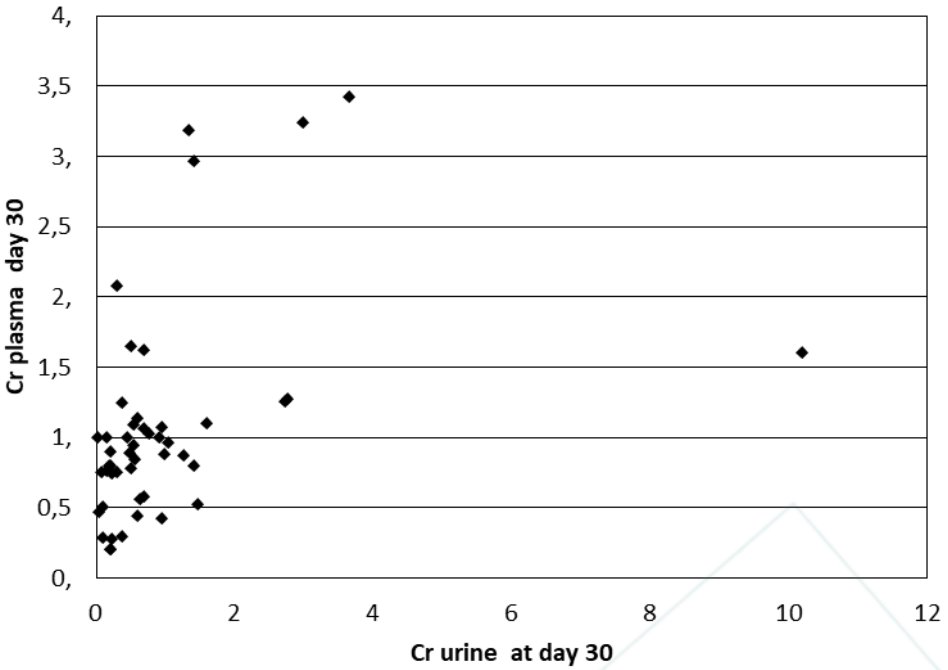

Figure 3. Relation between Cr levels in plasma and urine in µg/L at 30 days of age. Description: 48 patients had values in plasma and urine at day 30. A positive association could be observed between plasma and urine levels of Cr. A high level in plasma led to high elimination in urine (Spearman´s Rho: 0.52, $p < 0.001$), simple coefficient: 0.2 (95 % CI, 0.07-0.33), adjusted coefficient: 0.21 (95 % CI, 0.05-0.36).

Table I. Bivariate associations between numeric variables and plasma Cr levels, adjusted for PN and BW

	Cr_p day 15							Cr_p day 30						
	n	**RHO**	***p***	**B (CI)**	***p***	**Adjusted B (CI)**	***p***	***n***	**RHO**	***p***	**B (CI)**	***p***	**Adjusted B (CI)**	***p***
Gestational age	97	-0.148	0.149	-0.04 (-0.09-0.02)	0.186	-0.04 (-0.09-0.02)	0.186	90	-0.292	*0.005**	-0.05 (-0.12-0.01)	0.095	-0.05 (-0.12-0.01)	0.095
Birth weight	97	-0.183	0.073	0.00 (0.00-0.00)	0.124	0.00 (0.00-0.00)	0.356	90	-0.256	*0.015**	0.00 (0.00-0.00)	*0.042**	0.00 (0.00-0.00)	0.211
Percentile	97	-0.048	0.638	0.00 (-0.01-0.00)	0.613	0.00 (-0.01-0.01)	0.951	90	-0.036	0,734	0.00 (-0.01-0.00)	0.163	0.00 (-0.01-0.00)	0.166
Days of PN	97	0.327	*0.001†*	0.02 (0.01-0.04)	*0.002†*	0.02 (0.01-0.04)	*0.004**	90	0.402	*< 0.001†*	0.03 (0.01-0.04)	*< 0.001†*	0.03 (0.01-0.04)	*0.001†*
Glucose day 15	95	0.265	*0.009**	0.00 (0.00-0.01)	0.149	0.00 (0.00-0.01)	0.662	86	0.402	*< 0.001†*	0.01 (0.01-0.02)	*< 0.001†*	0.01 (0.00-0.02)	*0.013**
Glucose day 30	88	-0.030	0.783	0.00 (-0.01-0.01)	0.973	0.00 (-0.01-0.01)	0.511	85	0.028	0.797	0.01 (0.00-0.01)	0.149	0.00 (0.00-0.01)	0.456
Creatinine (s) day 15	94	0.162	0.118	-0.01 (-0.29-0.26)	0.939	-0.02 (-0.29-0.25)	0.893	86	0.279	*0.009**	0.16 (-0.16-0.49)	0.327	0.18 (-0.14-0,49)	0.271
Creatinine (s) day 30	90	0.176	0.097	-0.03 (-0.20-0.13)	0.687	-0.02 (-0.18-0.14)	0.808	88	0.204	0.057	0.06 (-0.13-0.26)	0.534	0.07 (-0,11-0.26)	0.451
Creatinine (u) day 15	90	0.078	0.462	0.01 (-0.01-0.04)	0.351	0.02 (-0.01-0.04)	0.188	82	-0.110	0.326	-0.01 (-0.04-0.02)	0.437	0.00 (-0.03-0.02)	0.884
Creatinine (u) day 30	77	0.168	0.144	0.00 (-0.02-0.03)	0.752	0.00 (-0.02-0.03)	0.772	77	0.069	0.548	0.00 (-0.03-0.03)	0.984	0.00 (-0.04-0.03)	0.779
Urea day 15	94	-0.077	0.462	0.00 (-0.01-0.00)	0.396	0.00 (-0.01-0.00)	0.166	86	0.113	0.298	0.00 (-0.01-0.01)	0.924	0.00 (-0.01-0.00)	0.599
Urea day 30	89	-0.121	0.260	-0.02 (-0.04-0.00)	0,083	-0.01 (-0.03-0.01)	0.178	87	-0.074	0.493	0.00 (-0.02-0.01)	0.758	-0.01 (-0.03-0.00)	0.138
Ferritin day 30	89	0.067	0.530	0.00 (0.00-0.00)	0.189	0.00 (0.00-0.00)	0.873	89	0.132	0.218	0.00 (0.00-0,00)	0.965	0.00 (0.00-0.00)	*0.016**

PN:

parenteral nutrition; (*p*): plasma; (u): urine. Spearman’s rank correlation coefficient (Spearman’s Rho) to analyze the association between two continuous variables. Associations were adjusted by newborns' gestational age and days of PN using linear regression analysis with Cr levels as dependent variable. Simple regressions are expressed by crude Beta coefficient (B) and multiple regressions by adjusted Beta coefficient. *$p < 0.05$; †after adjusting for multiple comparisons with the Bonferroni method, $p < 0.0038$.

Table II. Bivariate associations between numeric variables and urine Cr levels adjusted for PN and BW

	Urine Cr day 30						
	n	**RHO**	***p***	**B (CI)**	***p***	**Adjusted B (CI)**	***p***
Gestational age	68	-0.338	*0.005†*	-0.27 (-0.41 to 0.14)	*< 0.001†*	-0,19 (-0.34 to -0.04)	*0.012**
Birth weight	68	-0.370	*0.002†*	0.00 (0.00 to 0.00)	*< 0.001†*	0,00 (0.00 to 0.00)	0.212
Percentile	67	-0.080	0.519	-0.01 (-0.02 to 0.01)	0.307	-0,01 (-0.02 to 0.00)	0.091
Days of PN	68	0.372	*0.002†*	0.08 (0.04 to 0.12)	*< 0.001†*	0,05 (0.01 to 0.10)	*0.016**
Ferritin day 30	67	0.213	0.084	0.00 (0.00 to 0.00)	*0.017**	0,00 (0.00 to 0.00)	0.629
Glucose day 30	64	-0.104	0.411	0.00 (-0.02 to 0.02)	0.839	0,00 (-0.02 to 0.02)	0.789
Creatinine (*p*) day 30	66	0.216	0.081	5.60 (-0.15 to 11.36)	0.056	0,66 (-6.05 to 7.36)	0.846
Creatinine (u) day 30	66	0.391	*0.001†*	0.10 (0.03 to 0.17)	*0.010**	0,08 (0.02 to 0.15)	*0.013**
Urea day 30	67	-0,079	0.525	-0,02 (-0.07 to 0.04)	0.558	0,00 (-0.5 to 0.05)	0.968

PN: parenteral nutrition; (*p*): plasma; (u): urine. Spearman's rank correlation coefficient (Spearman's Rho) to analyze the association between two continuous variables. Associations were adjusted by newborns' gestational age and days of PN using linear regression analysis with Cr levels as dependent variable. Simple regressions are expressed by crude Beta coefficient (B) and multiple regressions by adjusted Beta coefficient. *$p < 0.05$; †after adjusting for multiple comparisons with the Bonferroni method, $p < 0.0056$.

Table III. Bivariate associations between plasma Cr levels and clinical outcomes, adjusted OR by gestational age and days of PN

		Cr15							Cr30						
		n	Med (IQR)	*p*	OR (CI)	*p*	Adjusted OR (CI)	*p*	*n*	Med (IQR)	*p*	OR (CI)	*p*	Adjusted OR (CI)	*p*
Early sepsis (1-7 days)	No	87	1.0 (0.7-1.4)	0.072	2.57 (1.02-6.50)	0.046	2.71 (0.84-8.73)	0.095	80	0.9 (0.7-1.2)	0.023	2.28 (1.12-4.63)	0.023	1.46 (0.56-3.83)	0.443
	Yes	10	1.4 (0.8-2.0)						10	1.3 (0.9-1.6)					
Late sepsis (7-28 days)	No	73	1.0 (0.7-1.3)	0.123	1.72 (0.83-3.59)	0.145	0.48 (0.11-2.08)	0.325	62	0.9 (0.6-1.1)	0.010	1.65 (0.91-2.99)	0.101	0,39 (0.09-1.75)	0.219
	Yes	23	1.3 (0.8-1.8)						27	1.1 (0.9-1.6)					
IVH > 2	No	87	1.0 (0.7-1.4)	0.794	0.89 (0.30-2.64)	0.834	0.59 (0.14-2.48)	0.471	79	0.9 (0.7-1.3)	0.211	1.32 (0.62-2.82)	0.467	1.26 (0.49-3.21)	0.628
	Yes	10	1.1 (0.5-1.4)						11	1.0 (0.9-1.3)					
Leukomalacia	No	80	1.0 (0.8-1.4)	0.824	1.05 (0.45-2.41)	0.916	0.41 (0.10-1.60)	0.197	67	0.9 (0.7-1.2)	0.091	1.75 (0.95-3.24)	0.073	1.28 (0.58-2.79)	0.538
	Yes	17	1.3 (0.7-1.5)						22	1.1 (0.9-1.6)					
RDS	No	42	1.0 (0.7-1.5)	0.810	0.93 (0.49-1.77)	0.825	0.59 (0.25-1.40)	0.232	34	0.8 (0.7-1.2)	0.112	1.19 (0.65-2.17)	0.578	0.72 (0.33-1.59)	0.417
	Yes	55	1.0 (0.8-1.4)						56	1.0 (0.8-1.4)					
BPD	No	73	1.0 (0.7-1.4)	0.210	1.51 (0.74-3.08)	0.262	0.49 (0.11-2.24)	0.355	61	0.9 (0.6-1.1)		1.94 (1.05-3.61)		1.10 (0.37-3.22)	0.865

	Yes	24	1.2 (0.7-1.6)						29	1.1 (0.9-1.6)				
Hyperglycemia	No	75	1.0 (0.7-1.4)	0.529	1.47 (0.71-3.05)	0.305	1.34 (0.61-2.96)	0.472	71	0.9 (0.7-1.2)	0.022	1.56 (0.84-2.9)	0.164	1.36 (0.68-2.73)	0.383
	Yes	22	1.1 (0.7-1.5)						19	1.3 (0.8-1.6)					
NEC	No	85	1.0 (0.7-1.4)	0.172	1.46 (0.60-3.56)	0.411	0.49 (0.12-2.10)	0.339	78	0.9 (0.7-1.3)	0.436	1.25 (0.58-2.71)	0.565	0.59 (0.18-1.92)	0.385
	Yes	12	1.3 (0.9-1.6)						11	1.1 (0.5-1.6)					
ROP	No	82	1.0 (0.7-1.4)	0.511	1.50 (0.62-3.64)	0.375	1.15 (0.25-5.24)	0.852	71	0.9 (0.6-1.2)		1.79 (0.94-3.38)	0.075	1.24 (0.49-3.18)	0.649
	Yes	12	1.1 (0.7-1.7)						16	1.1 (0.9-1.4)					
Cholestasis	No	90	1.0 (0.7-1.4)	0.083	2.35 (0.84-6.60)	0.104	1.33 (0.28-6.33)	0.722	83	0.9 (0.7-1.2)		3.02 (1.37-6.67)	0.006	2.10 (0.60-7.31)	0.243
	Yes	7	1.5 (1.0-2.0)						7	1.4 (1.1-3.4)					
Death < 30 days	No	96	1.0 (0.7-1.4)	0.093	0.00 (0.00-11020756.05)	0.317	0.00 (0.00-.)	0.981	90	1.0 (0.7-1.3)	#N/A	#N/A	#N/A	#N/A	#N/A
	Yes	1	0.1 (0.1-0.1)						0	0.0 (0.0-0.0)					
	N		RHO	P	B (IC)	P	Adjusted B (IC)	*p*	N	RHO	*p*	B (IC)	*p*	Adjusted B (IC)	*p*
IMV (days)	95		0.399	**<0.001**	2.84 (0.96-4.72)		1.18 (-0.33 to 2.68)	0.123	90	0.317	**0.002**	4.15 (1.96 to 6.35)	**<0.001**	0.98 (-0.56 to 2.53)	0.210
NIMV (days)	95		0.181	0.079	2.19	0.36	-0.49	0.77	9	0.235		3.59 (-0.62 to	0.093	0.07	0.96

				(-2.53 to 6.90)	0	(-3.90 to 2.91)	4	0		7.80)	(-3.00 to 3.14)	5
O_2 (days)	95	0.164	0.112	5.86 (-3.32 to 15.03)	0.208	-1.72 (-8.29 to 4.84)	0.603	90	0.261	11.59 (3.14 to 20.03)	2.14 (-3.69 to 7.97)	0.468

BPD: bronchodysplasia: NEC: necrotizing enterocolitis; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity; IMV: invasive ventilation; NIMV: non-invasive ventilation. Median comparisons with Mann-Whitney U-test were used to analyze differences in Cr between two groups, and Spearman's rank correlation coefficient (Rho) was used to analyze associations between Cr levels and continuous variables. Associations were adjusted by newborns' GA and days of parenteral nutrition using regression analysis with the clinical outcomes as dependent variables. Logistic regression was applied when a dependent variable was categorical (expressed by crude and adjusted OR) and linear regression was applied when a dependent variable was continuous (expressed by crude and adjusted Beta coefficient (B). *$p < 0.05$; †after adjusting for multiple comparisons with Bonferroni method, $p < 0.0036$.

Supplementary Table I. Administration of total liquids in ml/kg/day

Day of life	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Birth weight < 1000 g	80	100	110	120	130	140	150-160	170-180
> 1000-1500 g	70	90	100	110	120	130	150	170-180

Notes: Feeding was started in < 1000 g at 24 hours of life in > 1000-1500 g of BW at 12 hours of life in aliquots of 25 ml/kg per day and up until the withdrawal of parenteral nutrition at 150 ml/kg/day, approximately.