The Role Of Hepatic And Renal Functions In The Development Of Retinopathy Of Prematurity: Is Proteinuria A New Risk Factor?

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Abstract

Purpose: To investigate the association of hepatic and renal parameters with the development of retinopathy of prematurity (ROP) in premature infants with a gestational age ≤ 32 weeks.

Methods: Medical records of 240 preterm infants were reviewed retrospectively, 85 of them were grouped as type 1, type 2 ROP and control group. These groups test results of first-month hepatic and renal function were compared for the risk of development of ROP and the development of type 1 ROP.

Results: In this study, 12, 35 and 38 infants were enrolled in the type 1, type 2 ROP and control group, respectively. The average gestational age and birth weight were higher; however, the duration of oxygen treatment was lower in the control group ($p<0.001$). The blood glucose level was significantly higher in the type 1 ROP group than in the other groups ($p=0.023$). The mean of total serum bilirubin of the type 1 ROP group was significantly lower than those of the type 2 ROP and control group ($p=0.032$). Proteinuria was present in 85.7% of preterms with treatment-requiring ROP and proteinuria increased the risk of ROP by 3.9 times (OR with 95% CI: 3.9 (1.19-12.75), $p=0.042$).

Conclusion: We found significantly higher blood glucose and lower total bilirubin level in the type 1 ROP group. Moreover, our findings suggest that proteinuria seems to be a new and important risk factor for both ROP and type 1 ROP in preterm infants.

Introduction

Retinopathy of Prematurity (ROP) is an important disease, which can lead to significant visual impairment with the disruption of retinal vascular development [1, 2]. In order to prevent ROP and blindness, reliable and simple criteria are necessary to discriminate against premature newborns at risk. Determination of these criteria may provide several benefits, such as eliminating frequent ROP examinations, minimizing the number of advanced stage ROP cases by appropriate treatment on time. Several reports reveal the relationship between ROP and lungs, brain or intestinal problems, such as bronchopulmonary dysplasia, respiratory distress syndrome, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, eryptosis and patent ductus arteriosis [3]. However, as far as we can find in the literature, there is no study concerning the potential association between ROP and renal or hepatic parameters representing their maturity and/or disorders.

Evaluation of renal-glomerular functions may provide valuable data about the involvement of a wide vascular network and the deterioration of these vessels may be a component of immaturity and organ insufficiency. The results of a recent study reveal that elevated blood urea levels due to impaired renal function deteriorate endothelial function [4]. Urea related endothelial damage is due to free oxygen radical production, similar to hyperglycemia related endothelial damage [5, 6] According to the presented data, we aimed to investigate the relationship between ROP and renal functions.

As several products (i.e., bilirubin) have a role in both the synthesis and degradation of cytokines and autacoids and so homeostasis, hepatic function probably has a crucial effect on ROP development. In the literature, there are several studies about the relationship between bilirubin, hyperglycemia and ROP [3, 7–13]. On the other hand, no report is present about the role of hepatic function tests, which give some clue about the organ maturation and ROP.

Within this scope, the aim of this study was to investigate the potential relationship between ROP and the biochemical tests reflecting hepatic and renal function, among premature infants.

Subjects And Methods

This retrospective comparative study was approved by the Aydin Adnan Menderes University Ethical Committee and Review Board and was conducted in accordance with the Declaration of Helsinki. Hospital records of 240 premature neonates, who had been followed up for 4 years in the ROP clinic of the ophthalmology department were reviewed. Infants were divided into type 1 and type 2 ROP groups according to the third edition of ICROP classification criteria, revisited recently [14]. The babies born with a gestational age of ≤ 32 weeks without any ROP findings were considered as a control group. ROP examinations were carried out by the same physician (AIAU), considering the third edition of ICROP criteria for diagnosis and ETROP criteria for treatment. All type 1 ROP group infants were treated with laser photocoagulation. To assess hepatic and renal functions of the groups, blood glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total and direct bilirubin, albumin, blood urea nitrogen (BUN), creatinine, minerals (sodium, potassium, chloride, calcium, phosphorus, magnesium) and presence of proteinuria were evaluated with serologic tests and with urinalysis. The results compared between the groups.

Statistical Analysis

A Kolmogorov-Smirnov test was conducted to determine a normality of the distribution. For the variables normally distributed, a comparison between groups was performed by a one-way ANOVA test. Kruskal Wallis test was made for the variables that were not normally distributed. Descriptive statistics were presented as mean ± standard deviation (SD). A chi-square test was used to analyze the categorical data and descriptive statistics were presented as frequency (%). The p values < 0.05 indicated a statistically significant difference.

Results

Of a total 240 preterm infants, 85 were analyzed in this study. Out of these 85 premature neonates, 12 (14.1%), 35 (41.2%) and 38 (44.7%) were classified as type 1, type 2 ROP and control group, respectively. All of the infants with ROP, 63.8% were male. Table-1 shows gestational age (GA), birth weight and duration of oxygen treatment of these groups. The mean gestational age at birth was 26.08 ± 3.05 weeks in type 1 ROP and 27.51 ± 1.90 weeks in type 2 ROP and 30.76 ± 1.51 weeks in the control group (p <

0.001). The mean birth weight was 979.16 ± 464.52, 1098.85 ± 457.71 and 1671.61 ± 331.17 grams in type 1, type 2 ROP and control group, respectively ($p < 0.001$). The duration of oxygen treatment was statistically lower in the control group than in the other groups (type 1: mean 44.5 ± 27.26 days; type 2: mean 29.57 ± 24.43 days; control: 7.05 ± 12.38 days ($p < 0.001$). Nevertheless, there is no statistically significant difference between the type 1 and type 2 ROP groups in terms of the mean gestational age, the birth weight and the duration of oxygen treatment ($p = 0.735$, $p = 1.000$, $p = 0.539$, respectively).

Table-1: Gestational age, birth weight, and duration of oxygen treatment of the groups.

	Type-1 ROP (N:12)	Type-2 ROP (N:35)	Control (N:38)	p
Gestational age (Weeks)	26.08 ± 3.05	27.51 ± 1.90	30.76 ± 1.51	0.735*/**<0.001**†
Birth weight (Gram)	979.16 ± 464.52	1098.85 ± 457.71	1324.87 ± 465.61	1.00*/**<0.001**†
Duration of oxygen treatment (Days)	44.5 ± 27.26	29.57 ± 24.43	6.74 ± 2.45	0.539*/**<0.001**†

ROP: retinopathy of prematurity, N: number of infants, *: p value between type 1 and type 2 ROP group. †: p value between control and ROP groups

Urinalysis showed that there was proteinuria in 85.7% of infants with type 1 ROP, whereas there were 32.0% of infants with type 2 ROP and 16.7% of the control group (Figure). The difference was statistically significant ($p = 0.001$). Furthermore, 73.7% of premature neonates who had proteinuria developed type 1 or 2 ROP. The risk of severe ROP development was 3.9 times in babies with proteinuria (OR with 95% CI: 3.9 (1.19–12.75), $p = 0.042$).

Figure: Frequency of proteinuria in type 1 ROP, type 2 ROP, and control group. There was proteinuria in 85.7% of infants with type 1 ROP, 32% of infants with type 2 ROP and 16.7% of the control group ($p = 0.001$).

Table-2 summarizes the renal biochemical parameters (BUN, creatinine) and minerals (sodium, potassium, chloride, calcium, phosphorus, magnesium) according to the groups. Serologic tests revealed that BUN and creatinine values in the type 1 ROP group were higher than in other groups, but the difference was not statistically significant (Table-2). Serum mineral levels, except sodium and chloride, were insignificant between groups. Sodium and chloride levels in groups, which were statistically significant, are shown in Table-2.

Table-2: Renal biochemical parameters and minerals of the groups.				
Renal parameters	Type 1 ROP	Type2 ROP	Control group	p
Urea (mg/dL)	50.08 ± 67.73	41.10 ± 22.42	26.18 ± 19.14	**0.020**
Creatinine (mg/dL)	0.73 ± 0.63	0.56 ± 0.15	0.49 ± 0.13	0.238
Sodium (mEq/L)	133.25 ± 2.99	137.45 ± 4.38	138.15 ± 6.19	**0.003**
Potassium (mEq/L)	4.75 ± 092	5.02 ± 0.67	5.07 ± 0.76	0.442
Chloride (mEq/L)	103.58 ± 6	108.72 ± 8	111.10 ± 7.24	**0.015**
Calcium (mEq/L)	9.80 ± 0.89	9.5 ± 0.85	9.61 ± 0.99	0.642
Phosphor (mEq/L)	4.43 ± 1.08	5.12 ± 1.29	5.69 ± 1.42	**0.020**
Magnesium (mEq/L)	2.33 ± 0.70	2.20 ± 0.31	2.18 ± 0.32	0.844
ROP: retinopathy of prematurity				

Table-3 shows the hepatic biochemical parameters of the groups. Total blood bilirubin level was significantly lower in type 1 ROP group than type 2 ROP and control group (1.69 ± 1.56 U/L, 4.56 ± 5.63 U/L, 5.28 ± 4.68 U/L, respectively) (p = 0.032). Furthermore, blood glucose level at the first month of birth was significantly higher in type 1 ROP group (mean: 100.75 ± 12.40 mg/dL in type 1 ROP, mean: 86.60 ± 28.58 mg/dL in type 2 ROP and mean: 83.15 ± 29.49 mg/dL in control group) (p = 0.023); but the difference of direct bilirubin, albumin, AST, ALT, ALP levels amongst the groups were insignificant (p = 0.594, p = 0.628, p = 0.0.694, p = 0.633, p = 0.516, respectively).

Table-3: Hepatic biochemical parameters of the groups.				
Hepatic parameters	Type 1 ROP	Type 2 ROP	Control group	p
Glucose (mg/dL)	100.75 ± 12.40	86.6 ± 28.58	83.15 ± 29.49	**0.023**
AST (U/L)	29.5 ± 9.18	41.10 ± 42.97	34.12 ± 14.00	0.694
ALT (U/L)	10.92 ± 4.89	18.14 ± 26.94	13.84 ± 10.04	0.633
ALP (U/L)	404.58 ± 183.62	440.07 ± 163.76	396.90 ± 156.12	0.516
Total Bilirubin (U/L)	1.69 ± 1.56	4.56 ± 5.63	5.28 ± 4.68	**0.032**
Direct Bilirubin (mg/dL)	0.52 ± 0.50	0.64 ± 0.87	0.43 ± 0.15	0.594
Albumin (g/dL)	2.97 ± 0.51	3.14 ± 0.54	2.92 ± 0.66	0.638
ROP: retinopathy of prematurity				

Discussion

The most important risk factors related to ROP are the gestational age and the birth weight of the infants [15]. The others are long-term exposure to high concentration of oxygen and immature lungs [16]. However, there was no paper about the relationship between ROP and the hepatic and renal functions of premature infants who had multiorgan immaturity.

The most significant finding of this study is the presence of proteinuria in 85.7% of treatment-requiring ROP patients. Of all the premature neonates who had proteinuria, 73.7% developed type 1 or 2 ROP. Furthermore, the risk of severe ROP development was 3.9 times higher in preterm babies with proteinuria. Although increased rates of renal dysfunction or chronic kidney disease in their later life has been shown in premature infants, there are no reports in the literature addressing the coexistence of proteinuria and ROP development [17]. It has been found that prematurity and low birth weight are associated with fewer nephrons and lower glomerular density [18]. Nephrogenesis in humans begins around 9 weeks of gestation and continues through the 36th weeks. During the last trimester of pregnancy, there is a rapid development with nearly 60% of nephron formation. Therefore, premature infants are born with a reduced number of glomeruli due to the cessation of nephron development, which results in glomerular hyperfiltration [19]. We believe that a decreased number of nephrones at birth can cause proteinuria. Besides, the significant decrease of sodium and chloride in our type 1 ROP patients may also be the result of this glomerular maldevelopment and hyperfiltration or due to several clinical situations such as prolonged concentration defect of the kidney, immaturity of the surrenal cortex and drugs such as diuretics for bronchopulmoner displasia treatment. Moreover, post-mortem studies evaluating the postnatal glomerulogenesis in extremely preterm infants showed that the kidney continues to develop in the postpartum period but glomerulogenesis ceases [20, 21]. They conclude that premature birth alone causes decreased glomerulogenesis irrespective of size for GA and predisposes to focal glomerulosclerosis and proteinuria similar to pathologic retinal vasculogenesis and fibroproliferation. It is also expected that marked retardation in intrauterine growth implies profound effects on renal and retinal development. In a recent review about oxidative stress (OS) in preterm newborns, Lembo et al. drawn an attention of the accumulation of oxidants in the early stage of life may represent a huge problem of organ maturation including eye and kidney [22]. They have explained how a preterm infant vulnerable to OS, because of their immaturity of antioxidant systems, and how this OS contributes to premeture's immature organ damage in their neonatal period, especially retinas, kidneys, brain, intestine and lungs. OS-induced renal damage has shown by using biomarkers in the first two weeks of life in preterm babies [23]. Some other oxidative products have been used for early detection of the ROP [24]. Lembo et al have concluded that OS is the main cause responsible for the development of typical premature infant diseases such as retinopathy of prematurity and kidney damage [22]. Therefore we had expected to find in our study that ROP patients could be more susceptible to renal dysfunction. Thus the result of our study showing proteinuria as a risk factor for ROP may be reflect the immaturity and dysgenesis of both renal and retinal tissues and it might explain why the infants with type 1 or 2 ROP also had 73.7% proteinuria or why the preterm infants with proteinuria have 3.9 times greater risk of severe ROP development in our study. Furthermore, an experimental study investigating the effect of preeclampsia as a causative factor for proteinuria showed that glomerular podocyte damage decreases vascular

endothelial growth factor (VEGF) levels in the embryogenesis phase [25]. Decreased VEGF levels lead to interruption of intersegmental vessel sprouting at angiogenesis and the eye appears dark according to the loss of green fluorescent plasma proteins in the Zebra fish with proteinuria [25] Therefore, we concluded that increased proteinuria levels showing renal immaturity could be an informative marker in the course of the disease in preterm newborns at risk of developing ROP.

Although the blood urea level between the groups was not significantly different, it was slightly higher in our ROP groups than in the control group. Several studies have reported that increased blood urea levels may also damage vascular health even in the absence of chronic renal insufficiency [4]. Increased blood urea levels and hyperglycemia have similar effects on blood vessels. They increase free oxygen radicals, decrease prostacycline synthesis, cause endoplasmic reticulum stress and insulin resistance, which are responsible for vessel injury. D'apolito et al. have shown that urea raises mitochondrial reactive oxygen species production in arterial endothelial cells, activates pro-atherosclerotic pathways and inactivates a critical endothelial-specific anti-atherosclerotic enzyme in vitro and in vivo [5]. They also stated that the aim of the treatment of endothelial damage should be the reduction of free oxygen radical production induced by increased urea levels [5]. Therefore, although without statistical significance, the higher urea level, found in the patients with ROP, may also have contributed to the retinal vascular endothelial damage resulting in retinopathy in our preterm neonates.

Another notable finding from this study was the association between blood glucose levels and ROP development. Blood glucose level at the first month of birth was higher in the type 1 ROP group and the difference was statistically significant. It has been reported in the literature that insulin insensitivity, inadequate pancreatic response and immature hepatic glucose production are responsible for the cause of hyperglycemia in premature infants [26]. A recent meta-analysis study of the association between neonatal hyperglycemia and ROP have concluded that there is a tendency to increase the risk of ROP in the patients with hyperglycemia [13]. For the link between hyperglycemia and ROP, it is proposed by a rat study that higher glucose concentration increases VEGF protein expression in retinal Muller cells [27]. Furthermore, Sone H. et al. have shown that long-term high glucose concentration induces VEGF and it is also up-regulated by acute glucose deprivation in cultured bovine retinal pigmented epithelial cells [28]. In contrast, after adjustment for factors such as birth weight and gestational age, another systemic review and meta-analysis study of the association between hyperglycemia and ROP found only a borderline significant association between the duration of hyperglycemia and ROP but not between mean glucose level and ROP (adjusted OR 5 1.08, P50.15) [29]. According to this systemic review and meta-analysis study, hyperglycemia could not be definitely considered as a risk factor for ROP. In our study, the relationship between the duration of hyperglycemia and ROP was not evaluated. Further studies adjusting for potential confounding variables are needed to clarify this association.

Finally, in our study, the serum total bilirubin level of the type 1 ROP group was found to be significantly lower than the other groups. Although high bilirubin levels can be noxious, it has been revealed that the cycling between bilirubin and biliverdin provides an antioxidant effect and it is protective against oxidative stress, a presumed cause of ROP [30]. The issue of whether elevated serum bilirubin reduces the

risk of ROP in preterm infants is still controversial [10]. Some studies reported that it has a protective effect against ROP, but other studies found no association between ROP and serum bilirubin level [11]. We found statistically higher bilirubin levels in our control group and the ROP group that did not need laser therapy. This might be explained by the anti-oxidant effect of bilirubin. Furthermore, it is well known that extremely high levels of bilirubin can lead to severe neurological damage and needs to be treated. However, knowing the lower limit of bilirubin to maintain its antioxidant effect may be as important as knowing the upper limit to avoid its toxic side effects. Fereshtehnejad SM et al have shown that the mean total serum bilirubin of more than 5.1 U/L significantly affects the prevalence of ROP and they recommend stopping lowering serum bilirubin whenever it reaches this cutoff point [11]. Therefore, this issue should be considered when these patients were treated by phototherapy for elevated serum bilirubin levels.

The most striking result of our study was proteinuria in 71.4% of the patients with ROP at type 1 or 2 ROP. Furthermore, 91.7% of the patients with type 1 ROP had proteinuria and the infants ≤ 32 weeks of gestation with proteinuria were nearly four times more vulnerable to developing severe ROP. Besides, more than half of preterm infants with ROP were male, blood glucose level was significantly higher in the type 1 ROP group, but bilirubin was lower.

In conclusion, the results of this study suggest that proteinuria seems to be a new and important risk factor for both ROP and type 1 ROP in preterm infants. There was a significant association between blood glucose level and ROP development. Bilirubin may help protect preterm infants from ROP. We suggest that the use of these parameters in the follow-up of ROP may be useful. However, prospective, multi-center studies with a larger sample size are still needed to determine the neonatal risk factors for ROP.

Declarations

Conflict of interest: None

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Declaration of Conflicting Interest

Author declares no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Figures

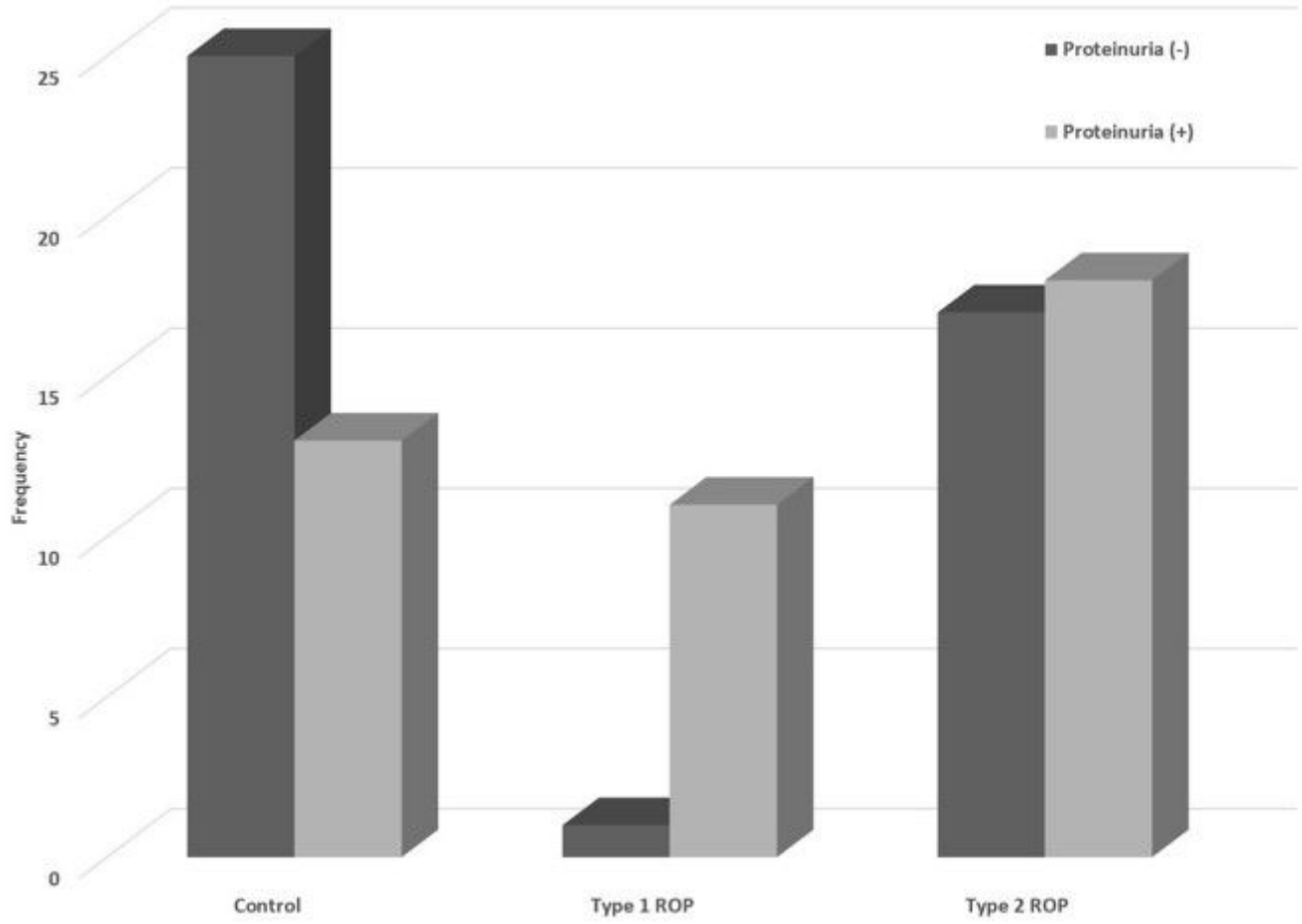

Figure 1

Frequency of proteinuria in type 1 ROP, type 2 ROP, and control group. There was proteinuria in 85.7% of infants with type 1 ROP, 32% of infants with type 2 ROP and 16.7% of the control group (p=0.001).