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Research Article

Study of Bone Mineralization and Renal Function Biochemical Parameters in Preterm and Term Infants

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Abstract: The objective of the presented work was to study and compare different biochemical parameters of bone mineralization and renal function in preterm and term infants. The study included 150 newborn babies admitted in the neonatal unit, of the hospital. The enrolled neonates were divided into study group [further divided into subgroups according to their gestational age (GA) - Group-IA (30-32 weeks of GA &IB (34-36 weeks of GA), 50 neonates in each group] and control group (Group-II also including 50 neonates). Serum calcium, phosphorus, alkaline phosphatase (ALP), creatinine, sodium, and potassium were measured in all the three groups. Serum calcium and phosphorous levels were found to be significantly decreased withP<.001 and p<0.05 respectively, and serum ALP, creatinine, and potassium were found to be significantly increased (P<0.05) in Group-IA as compared Group-II. Serum sodium levels did not show any significant difference. There was no significant difference in calcium and phosphorous levels although they were decreased, whereas serum ALP and creatinine levels were found to be significantly(P<0.05) increased in Group-IA as compared to Group-IB. High serum ALP and creatinine levels and low serum calcium and phosphorus levels were seen inpreterm babies. Group-IB did not show any significant difference when compared to Group-II (control group). It can be concluded that high serum ALP activity and low serum calcium and phosphorus levels are associated with preterm babies. A significant difference in the mean values of the renal function parameters was also obtained, except for serum sodium and potassium levels.
Keywords: Gestational Age, Neonates, Bone Mineral Density, Glomerulogenesis.

INTRODUCTION

Premature infants, also called preterm infants, are babies born earlier than 37 weeks of gestation. Preterm birth is among the most common causes of death in infants worldwide [1]. Those born before 32 weeks are called "early preterm while the majority of premature babies are born between 34 and 37 weeks of gestation and are called as late preterm infants. Late preterm infants have no health problems and they generally do better than those born earlier [2].

Maternal disorders such as genital tract infections, anemia, hypertension, gestational or non-gestational diabetes, obesity, metabolic and antiphospholipid syndromes [3-10] affect the environment where the fetus is developing and may produce metabolic, immune, vascular, hemodynamic and renal alterations [11-14].

Premature infants are known to be at risk of developing metabolic bone disease (MBD) [15]. MBD is characterized by a failure of complete mineralization of the osteoid and encompasses disturbances ranging from mild under mineralization (osteopenia) to severe bone disease with fractures (rickets). The cause being usually inadequate calcium and phosphate intake. The risk of MBD is inversely proportional to gestationalage (GA) and birth weight and directly related to postnatal complications [16].

Development of the fetal skeleton requires large amounts of energy, protein and minerals. Minerals, such as calcium and phosphorus, are actively acquired by the fetus from the mother. By the 2nd semester of pregnancy, fetal serum Calcium and Phosphorous concentrations are ~20% higher than maternal serum concentrations. Mineralization of the bones occurs predominantly during the 3rd semester. If the increased fetal demand in minerals is not met, then inadequate fetalbone mineralization of the bones occurs [17].

Bone mineralisation is the result of the action of the osteoblasts forming the matrix vesicles. Alkaline phosphatase (ALP) in the vesicles of membranes transports phosphate into the vesicle. Calcium diffuses

passively through the membrane, and, together with phosphate, forms a crystallisation product. After enough minerals have been crystallised, alkaline phosphatase is released by vesicle rupturation. Thus serum ALP is regarded as an indicator of the active crystallisation process. Active and usually more efficient crystallisation takes place in utero, but serum ALP is always low in the first few days of life, when bone mineralisation is thought to occur at an almost normal rate, as reflected by the fall in serum calcium [18].

MBD is due to low intake of calcium and phosphorus [19-21]. The use of simple biochemical indicators of bone mineralisation are serum ALP and, to some extent, serum phosphate and serum calcium levels. They have been suggested to be an easy way of identifying premature infants with MBD [22, 23].

In humans, rapid development of important functional cell structures in the lungs, pancreas, and kidneys takes place until the last few weeks of gestation and preterm birth may affect final development [24, 25]. As nephrogenesis continues until the GA of 34-36 weeks, preterm babies have a diminished number of nephrons at birth. Their number is highly correlated to GA and that glomerulogenesis had stopped after 40 days postnatal. A limited postnatal glomerulogenesisoccurs in preterm born individuals and postnatal renal failure inhibits glomerulogenesis. In a small study an active glomerulogenesisin preterm birth was seen but also ceased after a short period [26-29]. Therefore, nephron deficit (oligonephronia) in preterm born individuals probably exists throughout life placing the patient at risk for renal function deterioration [30].

Perinatal hypoxia is a common feature in preterm born babies. Spontaneous hypoxic events occur often in premature born infants, hypoxia-induced tissue injury increase the risk for neurological but also renal morbidity [31]. Hypoxia may lead to acute tubules necrosis and acute kidney injuryand deterioration of renal function. The damage seems reversible, but loss of nephrons is not repaired and therefore is likely to increase the risk for renal disease in later life [32].

MATERIAL AND METHODS

The study was approved by the Ethics Review Committee of the institute. All patients were recruited after obtaining informed consent from the parents. The study was a prospective study, conducted in the Department of Paediatrics PGIMS Rohtak between June 2013 and June 2014.

The study included 150 newborn babies admitted inneonatal unit.The enrolled neonates were divided into study group [further divided into subgroups according to their GA - Group-IA (30-32 weeks of GA &IB (34-36 weeks of GA), 50 neonates in each group] and control group (Group-II also including 50 neonates). Serum calcium, phosphorus, alkaline phosphatase, creatinine, sodium, and potassium were measured in all the three groups.

RESULT AND DISCUSSION

Table 1 shows that there is significant decrease inserum calcium and phosphorus levels in Group-IA as compared to Group-II, but it was insignificantly decreased in Group-IA as compared to Group-IB (shown in Table 3) and in Group-IB as compared to Group-II (as Table 2 shows).

Serum ALP levels were significantly increased at 30–32 weeks as compared to term infants(shown in Table 1) and in Group-IA compared to Group-IB(Table 3), but it was insignificantly increased in Group-IB as compared to Group-II (Table 2 shows).

Table 1 and 2 shows that serum creatinine was significantly increased in Group-IA as compared to Group-II and in Group-IA as compared to Group-IB (Table 3), but it was insignificantly increased in Group-IB as compared to Group-II (Table 2 shows). Table 3 shows it was insignificantly increased in Group-IA as compared to Group-IB.

Decreased serum calcium and phosphorus levels in preterm babies signifies inadequate calcium and phosphate intake, reduced opportunity for transplacental mineral delivery and excessive mineral loss after birth in preterm babies, decreased bone mineralization and increased bone resorption, increased calcitonin, and increased urinary calcium and phosphorus excretion in preterm babies. Chronic damage to placenta may alter the phosphate transport; therefore babies with intrauterine growth restriction may be osteopenic [33]. Two studies had reported that preterm normal and osteopenic infants had a significant increase of serum ALP compared with full term infants [34, 35]. ALP level is negatively associated with both body weight and gestational age in preterm infant [34]. Beyers *et al*., in their study showed that raised serum ALP and high urinary hydroxyproline indicate increase in bone turnover. Bone resorption may be more important than bone formation in preterm infants [36]. Increased ALP level signifies increased bone cellular or osteoblastic activity in preterm babies [37]. In case of neonates, increase in total ALP has been attributed to the raised levels of its bone isoenzyme [38].

At birth, the newborn serum creatinine reflects maternal concentrations and this is because maternal creatinine equilibrates with fetal concentrations across the placenta [39, 40, 41]. However, preterm birth is often associated with gestational diseases affecting placental function and/or maternal renal function. Some gestational diseases also affect fetal glomerular development by inducing intrauterine growth restriction [42]. Once the umbilical cord is severed, the perfect intrauterine maternal-fetal biochemical balance is disturbed. Thereafter, creatinine will rapidly disappear

in the first urine specimens passed by the newborn infants. A new steady state is achieved in due time, based on independent neonatal factors, of which the unusual occurrence of tubular creatinine reabsorption is the one. We hypothesize that this latter temporary phenomenon is attributable to back-flow of creatinine across leaky immature tubular and vascular structures. With time, Maturational renal changes impose a barrier to creatinine excretion [43].

Bueva and Guignard [44] showed a negative correlation between plasma creatinine and GA in one study comparing preterm infants versus term infants between the first and the second day of life. Increased serum creatinine and electrolytes signifies lower GFR in preterms. Glomerular function shows a progression directly correlated to GA and postnatal age in preterm infants [45]. The more is the immature infancy, the more pronounced the contraction of the extracellular space and higher the insensible water loss; both these factors predispose to hypernatremia in the first few days of life [46].

In the first 24 to 72 h after birth serum potassium concentrations rise moderately to markedly in premature infants, even in the absence of exogenous potassium intake and in the absence of renal dysfunction [46, 47]. This increase seems to be the result of a shift of potassium from the intracellular to extracellular space. The magnitude of this shift roughly correlates with the degree of immaturity. In markedly premature infants, this shift can result in life-threatening hyperkalemia [46].

Table 1: Comparison of serum calcium, phosphorus, alkaline phosphatase, creatinine and electrolyte levels at 30–32 weeks and at 37 or more weeks of GA

Parameter	Group-IA	Group-II	p-value
Serum Calcium (mg/dl)	8.88±0.92	10.32+0.76	HS(p<.001)
Serum phosphorus (mg/dl)	5.46±0.97	6.96±1.58	S(p<.05)
Serum alkaline phosphatase (IU/L)	235.1±75.81	166.9±42.23	S(p<.05)
Serum creatinine (mg/dl)	1.46±0.52	0.88±1.93	S(p<.05)
Serum sodium(mEq/L)	142.6±6.72	137.2±6.97	NS
Serum potassium (mEq/L)	5.71±0.47	5.01±0.36	S(p<.05)

Table 2: Comparison of serum calcium, phosphorus, alkaline phosphatase, creatinine and electrolyte levels at 34–36 weeks and at 37 or more weeks of GA

Parameter	Group-IB	Group-II	p-value
Serum Calcium (mg/dl)	9.78±1.05	10.32+0.76	NS
Serum phosphorus (mg/dl)	6.35±1.39	6.96±1.58	NS
Serum alkaline phosphatase (IU/L)	172.7±42.01	166.9±42.23	NS
Serum creatinine (mg/dl)	1.04±0.31	0.88±1.93	NS
Serum sodium(mEq/L)	139.9±5.1	137.2±6.97	NS
Serum potassium (mEq/L)	5.37±0.49	5.01±0.36	NS

Table 3: Comparison of serum calcium, phosphorus, alkaline phosphatase, creatinine and electrolyte levels at 30–32 weeks and at 34-36 weeks of GA

Parameter	Group-IA	Group-IB	p-value
Serum Calcium (mg/dl)	8.88±0.92	9.78±1.05	NS
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Serum creatinine (mg/dl)	1.46±0.52	1.04±0.31	S(P<.05)
Serum sodium(mEq/L)	142.6±6.72	139.9±5.1	NS
Serum potassium (mEq/L)	5.71±0.47	5.37±0.49	NS

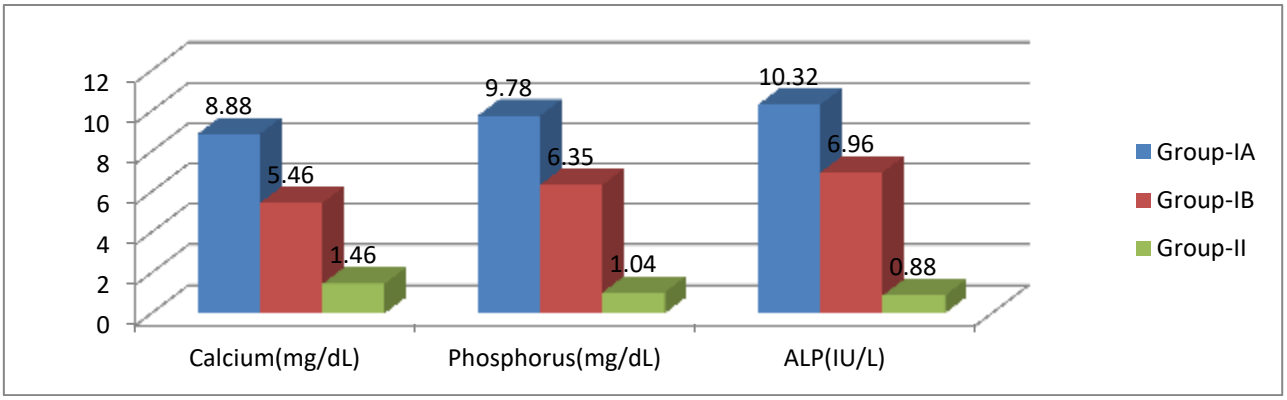

Figure 1: Showing Mean Value of Calcium, Phosphorus and ALP

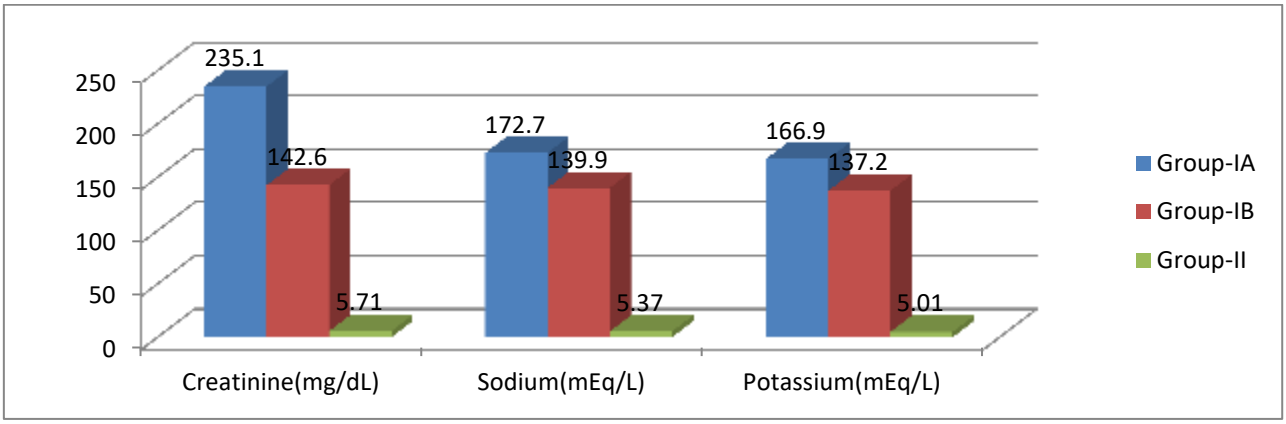

Figure 2: Showing Mean Value of Creatinine, Sodium and Potassium

CONCLUSION

It can be concluded that high serum ALP activity and low serum calcium and phosphorus levels are associated with pretermbabies. A significant difference in themean values of the renal function parameters was also obtained, except for serum sodium and potassium levels.

Of course, future prospective studies are necessary to explore the development of renal function in very preterm infants and also to determine whether multifactors events acting early in postnatal life could have long-term consequences on renal outcome in later life.

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