REVIEW
OF
LITERATURE
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β₂ microglobulin is a LMW protein (11,800 dalton) and belongs to light chain part of membrane bound HLA antigen. It consist of two polypeptide chain, a heavy chain with antigenic structure and a light chain. β₂ microglobulin is synthesis in lymphatic system.

β₂ microglobulin is readily filtered across the glomeruli. In mature kidney approximately 99.9% of filtered β₂ microglobulin is reabsorbed by the tubuler so that normal concentration of the protein is very low in urine. Kidney is the only known site of excretion and catabolism of β₂ microglobulin. Reabsorption of β₂ microglobulin is limited to the proximal tubule which have high reabsorptive capacity for protein. In consequence elevated plasma level of β₂ microglobulin even though they result increased filtered load of protein are not translated in to increase urinary concentration of β₂ microglobulin. Tubular maxim value for β₂ microglobulin are high (400 to 600 µg). β₂ microglobulin is present in all biological fluid of body. Absorption of β₂ microglobulin occurs in proximal tubular by active transport.
Engle WD, Anant BS Jr. conducted study on neonates and show that renal handling of $\beta_2$ microglobulin developed fully by 34 week post conceptional age (CA) and suggest tubular reabortion of $\beta_2$ microglobulin as a useful indicator of renal tubular maturation. They also demonstrate that renal tubular maturation is independent of birth weight and varies with conceptional age i.e. even the full term low birth weight babies have tubular maturation.

Assadi FK conducted study to asses the usefulness of $\beta_2$ microglobulin in detecting the early stage of tubular damage by gentamicin and founded that the value of $\beta_2$ microglobulin were significantly elevated in neonates receiving gentamicin. There was no significant difference in serum creatinine and fractional tubular excretion of sodium in these neonates which again pointing out the usefulness of $\beta_2$ microglobulin in predicting subclinical tubular damage.

Zamardo V. conducted a study to find out the value of $\beta_2$ microglobulin in neonates with respiratory distress syndrome and find out subclinical tubular dysfunction with increase urinary $\beta_2$ microglobulin with normal serum creatinine and urinary sodium excretion.
Freedman conduct study to determine the usefulness of \( \beta_2 \) microglobulin in detecting fetal obstructive uropathy and find out that urinary \( \beta_2 \) microglobulin value were significantly elevated in these fetus and propose \( \beta_2 \) microglobulin as a useful marker to detect the presence of severe renal damage due to obstructive uropath.

J.W. Cole, R.J. Portman conducted study on full term neonates to find out the evidence of proximal tubular dysfunction in infant with meconium stained amniotic fluid and find out a higher value of \( \beta_2 \) microglobulin in these infant indicating the evidence of tubular dysfunction.

Eric D. Tack, MD, carried a study to evaluate renal injury in sick neonates using \( \beta_2 \) microglobulin concentration in urine. In this study he founded out that the values to \( \beta_2 \) microglobulin were considerable high in sick neonates in compression to normal infants. He also showed that the concentration of \( \beta_2 \) microglobulin were much more in neonates who suffer from birth anoxia in comparison to other sick neonates. The average concentration for birth anoxia neonates being 10±10mg/l in comparison to 8.32 ± 7.27 mg/l in non anoxic sick neonates.

K.P. Mehta U.S. Ali carried out a study to asses renal involvement in sick neonates referred to NICU using standard
renal parameter and urinary β2 microglobulin excretion and found out statically significant elevation in mean values of urinary β2 m in sick neonates when compared to normal controls irrespective of primary disease, indicating tubular dysfunction (41/46=90%) of the neonate while only 20% of them had abnormalities indicating renal involvement when judged by standard renal function test. Very high level were noted in cases of birth asphyxia, sepsis and renal involvement. Transient increase in the concentration of β2 microglobulin was noted in meconium aspiration syndrome.

In 1983 William D Engle carried out a study to determine the renal handling of β2 microglobulin in human neonates and found out that glomerular balance β2 microglobulin in human kidney occurs after offers 34 weeks and suggested that fractional tubular reabsorption of β2 microglobulin can serve as useful marker for renal tubular maturation.

In 1985 J. W. cole carried out a study to determine the renal dysfunction in neonates with meconium stained amniotic fluid using β2 microglobulin in urine. When compared with the normal infants values for the infants with meconium stained amniontic fluid were increase significantly day 1 (1.64 ± 2.16mg/l) and day 3 (2.12 ± 2.04 mg/l). Levels exceeding two standard deviation
above the normal mean in 12 out of 26 infants. All infants with meconium stained amniotic fluid with one minute Apgar score of 6 or less had on elevated urinary β₂ microglobulin concentration. The elevated levels of urinary β₂ microglobulin in infants with meconium stained amniotic fluid indicate the existence of tubular dysfunction, probably mild acute tubular necrosis secondary to hypoxia.

In 1990 J Floege, M.F. wilk carried out study to determine renal elimination of β₂ microglobulin in patients with normal and impaired renal function. In this study he calculate renal arteriovenous extraction β₂ micro, poly/ruction and a second low molecular Weight protein, myoglobin in 16 human kidney with normal renal function and 22 kidney with reduce function in kidney with normal function, the exbaction of β₂ micro significantly exceeded that of poly fradate while that of myoglobin was not different from that of polyfructure. In kidney with reduce function the extraction of polyfrutios was not significant altered. In contrast the β₂m extraction decreased this decreas was significantly correlated with the decrees of endogenocis createns cleane. These results indicate that in normal renal function the glomerular filtration of β₂m may be supplemented by a perilubular mode of removal. The mechanism
underlying the selective decrease of $\beta_2m$ extraction in kidney with reduce function remain speculative.

In 1991 FOUAD A. RASHAD carried out a study 'Altered urinary $\beta_2$-microglobulin excretion as a index of nephrotoxicity. In this study he use dialrizonate mequlmine (DMG) a radio groupaphic contrast agent having a direct nephrotoxic effect on proximal convoluted tubule as suggested by data of Gold Stein et al. In 9 patient out of 20 on whose this study was carried out show abnormal value of $B_2$ microglobulin with in 4 hr of administration of dye. This study futher strengthen the view that $\beta_2$ Microglobulin in handle at the level of proximal convoluted tubule.

In 1979 A. APERIA carried out a study "$\beta_2$ microglobulin an indicator of renal tubular maturation and dysfunction in the newborn". The urinary excretion and proximal tubular reabsorption of $\beta_2$ microglobulin was studied in 17 healthy newborn infant in relation to gestational and postnatal age. The effect of IRDS and non-conjugate hyperbilirubine on the tubular reabsorption of beta-2 microglobulin was studied in 10 IRDS infants and 14 infants with non – conjugation hyperbilrubinemia. The filtered load of $\beta_2$ microglobulin was found to increase with
increases gestational age. This was due to rise in plasma $\beta_2$ microglobulin concentration as well as to a rise in the G.F.R.

APGAR SCORE

The apgar score devised in 1952 by Dr. Virginia Apgar. It is quick method of assessing the state of newborn (Curr Res Anaesth Analg, 1953). Although apgar score continues to provide a convenient short hand for reporting the state of the baby and the effectiveness of resuscitation, the purpose of this statement is to place the apgar score in its proper prospective as a tool for assessing asphyxia and for prognostication. The apgar score was developed to identify quickly the newborn in need of resuscitation (Apgar, 1983).

The apgar score is comprised of five components heart rate, respiratory effort, tone, irritability and colour. Each of which can be given a score of 0,1 and 2.

<table>
<thead>
<tr>
<th>Component</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Absent</td>
</tr>
<tr>
<td>Respiration</td>
<td>Absent</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Limp</td>
</tr>
<tr>
<td>Reflex</td>
<td>No response</td>
</tr>
<tr>
<td>Colour</td>
<td>Blue or pale</td>
</tr>
</tbody>
</table>
It is important to recognise that elements of the score such as tone, colour and reflex irritability are partially dependent on the physiologic maturity of the infant. The normal premature infant may thus attain a low score purely because of immaturity with no evidence of anoxic insult.

One Minute Apgar Score

A low one minute apgar score indicates an infant who may need resuscitation. Although a score of less than 6 is listed in the international classification of diseases revision 9, codes as asphyxia a low score at one minute neither indicates that substantial hypoxia or ischemia has occurred not has much prognostic significance.

In the collaborative perinatal project 4.8 percent of surviving infants has a one minute apgar score of 3 or less (Nelson et al1979). The one minute apgar score should not itself be used as indication of prior asphyxia or as a predictor of future deficit.

Five Minute Apgar Score

The apgar score at five minutes indicates the infant who needs continued resuscitative efforts. The score is affected by all the conditions noted to affect the one minute Apgar score.
Ten Minute Apgar Score

An apgar score that continues to be 3 or less at 10 minutes indicates that the infant has remained hypoxic or hypeperfused despite resuscitative efforts. Only a small fraction of one percent of all full term infants in the collaborative perinatal project has such a score of these 34 percent died during the first year. However, if they survived most of these infants did well.

Fifteen And Twenty Minute Apgar Score

A score of 3 or less at fifteen or twenty minutes after delivery despite resuscitative efforts indicates that the full term infant has suffered a severe antecedent injury with the possibility of additional post natal effects Often but not always, this may be a result of intrauterine hypoxia The mortality rate of these infants is 53 percent and 59 percent respectively. Failure of low scores to increase at 5,10 or 20 minutes indicates an on going insult that could affect, or further effect outcome. Continued low scores at 10, 15 and 20 minutes are associated with increasing mortality and long term morbidity. However, only a small fraction of 1 percent of infants had a score of less than 3 at 20 minutes and survived. Rapid improvement of scores by five to ten minutes indicate that the prior insult was unlikely to have been sufficiently severe to result in permanent deficit (Nelson, Elenberg, 1981).
In an infant with a low apgar score, umbilical cord acidemia, in the absence of maternal acidemia, large base deficit and presence of nucleated RBC in the peripheral blood provide supporting evidence of asphyxia. Liver, renal and cardiac dysfunctions may also provide evidence of asphyxia.

It should be noted that apgar score partially depends upon the maturity of the new born (Call in et al, 1986). Immature infants are more likely to be hypotonic to have cyanotic extremities and to have decreased responsiveness. Therefore a score of 7 may be 'maximum' for a normal premature infant.

DEVELOPMENTAL RENAL PHYSIOLOGY

During intrauterine life the function of the nephric system apparently is minimal. The task of maintaining the homeostasis of the fetus is fulfilled by the placenta, as evidenced by the absence of abnormalities in fluid and electrolyte balance in newborns with bilateral renal agenesis.

At birth, the kidneys have a combined weight of about 25 gm, compared to 40 gm at 3 months of age and 300 gm in the adult. They often demonstrate persistence of a fetal, lobular structure and because of the laxity of the abdominal wall they are readily palpable. On cut section the superficial renal cortex appears thin, whereas the juxtamedullary and medullary areas are
relatively; well developed. This corresponds to the more advanced state of development reached by the deeper (more central) parts of the kidney and reflects the centrifugal pattern which characterizes the growth of this organ. Despite its small size and the thin cortex kidney of the full term newborn contains its full complement of nephrons (800,000 to 1,000,000 per kidney).

According to Potter and Thierstein, formation of new glomeruli ceases in the normal fetus when length reaches 46-49 cm and weight, 2100 to 2500 gm. As a consequence, these authors have proposed the use of morphological glomerular development as an indicator of fetal maturity. Since the size of the kidney is significantly smaller than later in life whereas the number of the constituent units is the same, size of the individual units must, of necessity, be smaller. Microdissection studies performed by Fetterman and associates have shown the diameter of the glomerulus in the newborn to be only half that of the adult, and the length of the tubule no more than one-tenth. This relative predominance of glomerular tissue over tubular is considered to influence the functional pattern of kidney during infancy. However, this concept is subjected to controversy.
The most important distinctive physiological feature of the newborn kidney is its relatively low level of function. Renal blood flow and glomerular filtration rate in the fetus are maintained at low levels.

For the first few days after birth, a striking increase in these functions is observed followed by a progressive rise over subsequent weeks and months. Mature levels were, achieved towards the end of the first year of life.

**Comparison of renal function parameter at different ages.**

<table>
<thead>
<tr>
<th>Age</th>
<th>Glomerular filtration rate (ml/min/1.73m²)</th>
<th>Renal plasma flow (ml/min/1.73m²)</th>
<th>Max. urine osmolarity (mosm/liter)</th>
<th>Bicarbonate threshold (mosm/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Newborn</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>28 – 32 weeks</strong></td>
<td>15 - 20</td>
<td>40 - 60</td>
<td></td>
<td>17 - 18</td>
</tr>
<tr>
<td><strong>33 – 36 weeks</strong></td>
<td>20 - 25</td>
<td></td>
<td></td>
<td>18 - 22</td>
</tr>
<tr>
<td><strong>36 – 38 weeks</strong></td>
<td>26 – 30</td>
<td>88 ± 4.2</td>
<td>700</td>
<td>21 - 22</td>
</tr>
<tr>
<td><strong>38 – 40 weeks</strong></td>
<td>30 - 40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>6 – 1 yr</strong></td>
<td>77 ± 14</td>
<td>352 ± 73</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1 – 3 yr.</strong></td>
<td>96 ± 22</td>
<td>537 ± 122</td>
<td></td>
<td>22 - 24</td>
</tr>
<tr>
<td><strong>Adult</strong></td>
<td>118 ± 18</td>
<td>612 ± 92</td>
<td>1300</td>
<td>26 - 28</td>
</tr>
</tbody>
</table>
The rate of glomerular filtration in the newborn is about 26 ml/min/1.73m² (Table 1) as compared with the glomerular filtration rate of 125ml/min/1.73m² of the average adult male and explains why the newborn is unable to dispose rapidly and efficiently excessive water and solute. Since the process of growth results in a high degree of anabolism of substances such as nitrogen, potassium, sodium, calcium, phosphorus and water, the excretory burden the kidney would otherwise; have to carry is minimized. Infants switched abruptly to milk rich in sodium content have been shown to gain weight and become edematous. These infants respond to sodium load similar to those observed in adult, but response is limited because of low glomerular filtration resulting is low absolute rate of sodium excretion. Following water deprivation young infants generally fail to concentrate their urine to levels commonly observed in older children and adults.

The fact that the newborn is unable to reach levels of urine osmolarity in excess of 700 mosm/litre compared to 1300 mosm/liter in the older child is only in small part the result of morphological immaturity. The main reason is the limited availability of urea, which constitutes about half the total osmolality of the renal medullary interstitium in the mature kidney. The almost complete anabolism of proteins which characterizes the healthy newborn, results in relatively little urea
for excretion. If protein is provided in sufficient amounts within 2 or 3 months, the kidney reaches a concentrating ability approaching that of the mature organ. A situation similar to sodium excess exists with regard to water diuresis. The poor diuretic response to a water load in the young infant has been attributed to limitation to excrete water in absolute forms limited by the low filtration rate.

Lower pH and concentration of bicarbonate in blood in infants has been attributed to low renal threshold for bicarbonate. Also responsible for this tendency in premature infants is an increased production of organic acids, low phosphate intake and the inability of the newborn kidney to establish a steep groupadient of hydrogen ions. Finally, ammonia also is diminished during the first few weeks of life, even under conditions of stress such as administration of ammonium or calcium chloride.

The response of the kidney to acid loading becomes comparable to the adult by the end of the first month of life. In summary, the low rate of glomerular filtration observed in newborns limits the ability of the kidney to dispose rapidly of a fluid or solute load. The even greater limitation in tubular reabsorption may result in inappropriate loss in urine of
substances such as glucose, amino acids, bicarbonate, and phosphate. Although none of these limitations has a detrimental effect on a healthy, newborn they restrict the capacity of the newborn to respond under conditions of stress.

**RENAL FUNCTIONS IN PERINATAL ASPHYXIA**

Stark and Geiger (1973) reported renal tubular dysfunctions in 3 infants following renovascular accidents in the newborn period. Out of 3 patients, two developed rickets and one neonates developed rickets along with acidosis and growth retardation. This was contributed to result of renal damage following renal ischemia.

Salha and Daniel (1978) studied renal response of lamb foetus to partial occlusion of umbilical cord. Role of foetal kidney during impairment of placental exchange was studied in 3 foetal lambs intact in utero. A standard asphyxial insult for a period of one hour was produced by occluding the umbilical cord sufficiently to lower the foetal heart rate by $35 \pm 10$ beats/min and pH by 0.15 units and this asphyxial stress caused a fall in urinary output and glomerular filtration rate.

Guignard et al (1976) assessed renal functions in 20 newborn infants with respiratory distress syndrome. They concluded that a state of acute reversible renal insufficiency can
occur during acute phase of respiratory distress syndrome. This was because of hypoxia arising from respiratory distress leading to renal insufficiency,

Dauber et al (1976) reported seven cases of perinatal renal failure following perinatal anoxia and they also reported that condition is reversible but prolonged renal insufficiency will cause increased damage tending to irreversible cortical or medullary necrosis.

Norman et al (1977) conducted a prospective study of incidence diagnosis and early course of acute renal failure in newborns following perinatal asphyxia. 72 out of 314 patients were diagnosed as a case of acute renal failure on the basis of arbitrarily defined criteria of oliguria (urine output less than 1-2 ml/kg/hr) azotemia (BUN more than 20-100 mg/dl) 94% patients responded to challenge by intravenous infusion and intravenous furosemide.

Anand et al (1978) studied the clinical course and followed up 14 neonates who developed acute renal failure. They reported that renal failure was secondary to major perinatal disorders. 13 patients had hypoxia and 9 were in shock when renal failure developed 5 patients died during acute phase and 5 sustained residual renal damage.
Robert et al (1989) studied occurrence and prognostic factors in 16 infants. Out of 16 infants, 9 had acute renal failure secondary to perinatal asphyxia 3 had congenital cardiovascular anomalies and 1 had heart failure. They reported that in neonates with ischemic acute renal failure, lack of oliguria and presence of identifiable renal uptake of nuclide suggest a favourable prognosis. They concluded that renal functions in neonates were influenced by hypoxia which may be reversible if diagnosed and treated early.

Pereria and Pereria (1990) studied the pattern of renal dysfunctions in the tropics and they reported that perinatal hypoxia and respiratory distress syndrome which are the leading causes of acute renal failure in the west were comparatively less important in India, where acute gastroenteritis and septicemia are the leading causes.

Jayshree et al (1990) evaluated the renal functions and occurrence of renal failure following perinatal asphyxia in the newborns. They observed that 43% of asphyxiated babies developed acute renal failure and 69.2% had oliguric renal failure. They did not find significant correlation between apgar scores at 5 and 10 minutes and development of oliguric acute renal failure carried a poorer prognosis as compared to nonoliguric one.
Roberts et al (1990) conducted a study on twenty one infants of 34-41 weeks gestational age with birth asphyxia (5 minutes apgar score less than or equal to 5 or umbilical artery pH less than or equal to 7.2) during the first two days of life to find out whether the urinary excretion of tubular markers of renal function is of value in the early diagnosis, of acute renal failure. Urinary retinal binding protein, myoglobin and N.acetylene beta D.glocosaminidase (NAG), expressed as a ratio with urinary creatinine were measured and excretion profiles repeated at 3-6 days in 15 infants and at 7-14 days in 12 infants.

Plasma creatinine concentration, creatinine clearance, plasma myoglobin concentration, and fractional sodium excretion were measured in asphyxiated infants. Four asphyxiated infants had acute renal failure. Four had tubular dysfunction without glomerular disturbance and 13 had normal renal function.

Bertolli et al (1990) studied the utility of measuring tubular enzymes in neonates with hypoxic ischemic encephalopathy, with nephropathy. They concluded that fact foetal neonatal hypoxia can cause a functional kidney impairment which is often temporary and not clinically overt but sometimes leading to acute renal failure. Hypoxic stress may result in a tubulointerstitial damage and kidney tubular enzyme determination has proved to
be an easy, early and non invasive method to define a tubular interstitial lesion. A major target of nephrotoxicity is the proximal tubular cells, alterations in brush border membrane and cytoplasm result in increased turnover process in the kidney cortex followed by a corresponding increased excretion of alanine amino peptidase (AAP) and N acetyl glucosaminidase (NAG) from the proximal tubular cells long before glomerular or tubular functions are impaired.

Karlowij and Adelman (1992) studied the incidence of acute renal failure among neonates and they found that it is a common occurrence in the neonatal intensive care unit and commonest cause being birth asphyxia.

Roca et al (1992) studied the systemic effects i.e. non neurological manifestation in hypoxic ischemic encephalopathy in newborns after neonatal asphyxia. A total of 145 full term neonates affected by hypoxic ischemic encephalopathy were studied. 47(32.4%) infants presented systemic abnormalities i.e. arterial hypotension, acute renal failure, pulmonary abnormalities and necrotising enterocolitis.

**Acute renal failure** is define as a clinical syndrome in which a sudden deterioration of renal function result in inability of the kidney to maintain fluid and electrolyte homeostasis.
**Probable diagnosis** - The condition is, suspected when any one of the following criteria is present -

- Urine output < .5 ml/kg/hour
- BUN > 20 mg/dl
- Serum creatinine > 1 mg/dl

**Definitive diagnosis**

- Urinary sodium excretion of more than 50 mEq/L.
- Fractional excretion of sodium greater than 2.

ARF should also be suspected in any neonate if serum creatinine fail to decline below maternal level by 5-7th day or rising by 0.3 mg/dl/day or above.

**Urine output and micturation**

About 1/3 of neonates micturate at birth or soon after birth, 93% by 24 hours and 99.4% by 48 hours of life. Failure to pass urine by 48 hours should raise the suspicion of renal pathology. The average infant excrete 15 to 60 ml of urine per 24 hour during the first 2 days of life and 50 to 100 ml per kg during the next four week. Oligouria is defined as urine output of less than 0.5 ml per kg per hour.
Blood urea nitrogen

Plasma concentration of urea is below 42 mg/dl at birth and remains so during the neonatal period. The value of blood urea are influence by protein intake and a misleading rise in BUN level are seen in catabolic state such as sepsis, trauma. In a study of ARF in NICU conducted by Reimald 13/24 infant had a blood urea concentration within normal range at the time of diagnosis.

Serum Creatinine

Serum creatinine level in first 72 hours reflects maternal level (.7-1.5 mg/dl) which falls in next few day of life to .2 to .4 mg/dl. By 5-7th day normal creatinine value are reach. A serial rise in serum craetinine or failure to fall by 7-10 day of life is a reliable indicator or renal pathology.
MATERIALS
AND
METHODS