INTRODUCTION

Parenteral Nutrition (PN) can be defined as provision of nutrition for metabolic requirements and growth through the parenteral route ***(Chaudhari, 2006).***

There is growing evidence that inadequate nutrition in the first weeks of life of premature infants results in growth failure that is often difficult to correct and may lead to permanent detrimental effects ***(Embleton, 2001 and Ehrenkram, 2007).***

The early use of adequate PN minimizes weight loss, improves growth and neurodevelopmental outcome, and appears to reduce the risk of mortality and later adverse outcomes, such as necrotizing enterocolitis and bronchopulmonary dysplasia ***(Moyses, 2013 and Christtnann, 2013).***

There has been reluctance to provide early and high protein parenteral nutrition because of fear of potential amino acid toxicity, uremia and metabolic acidosis. These complications were seen more frequently during the earlier days of parenteral nutrition support when solutions that were being used were unbalanced with a relatively low essential amino acids content and a high in non-essential, potentially, toxic amino acid ***(Thureen, 2003).***

Cystatin C (Cys-C), a protein of the cysteine protease inhibitor family, is produced by all nucleated cells and is measurable in body fluids. Cys-C has regulatory roles in

protein catabolism, antigen presentation, bone reabsorbtion, and hormone processing. It is also involved in tissue remodeling, cancer cell invasion, and tumor metastasis ***(Donadio et al., 2001).***

Cys-C is a low molecular weight protein (13-kDa) that is almost completely filtered by the glomerulus and largely catabolized by proximal t ubular cells. In adults, serum Cys-C concentration is closely correlated with the glomerular filtration rate (GFR) ***(Stickle et al., 1998).***

Assessment of glomerular filtration-cystatin C concentration is considered an excellent correlate of the level of glomerular filtration that is not significantly influenced by other effects (diet, infections, liver function, malignancies, myopathies, body fat content). An indicator of glomerular filtration used to date - creatinine, in practice is only a rough estimate because it reflects changes with low sensitivity and specificity. Its value depends on muscular mass and thus it depends on age and sex, tubular secretion (changeable intra- and interindividually), urine collection levels and analytical measurement problems. It has been demonstrated that cystatin C level increases even with creatinine clearance decrease below 1.57 $ml.s^{-1}$ when the creatinine level has not yet changed ***(Galteau et al., 2001; Bokenkamp et al., 2001).***

AIM OF THE WORK

To study the effect of protein parentral nutrition on serum cytatin C as a marker for renal function in preterm neonates.

THE KIDNEY

Embryological development:

At 5th week of embryogenesis, the ureteric bud appears. From mesenchyme of the nephrogenic ridge. Uretric bud forms the ureter. And from week 6 onward repeated branching gives rise to the calyces, papillary ducts and collecting tubules by week 12. The branching elements also induce the mesenchyme to develop into nephrons proximal and distal tubules, and glomeruli. Branching and nephron induction continues until week 36. There are about 600.000 nephrons per kidney, Figure (1). Premature birth and low weight for gestational age may both be associated with reduced nephron numbers ***(Boundless, 2016).***

Nephron:

Functional unit of kidney (0.6-1.5 million per kidney) composed of glomerules, proximaltubule, lobe of henle, distal tubule, collecting duct.

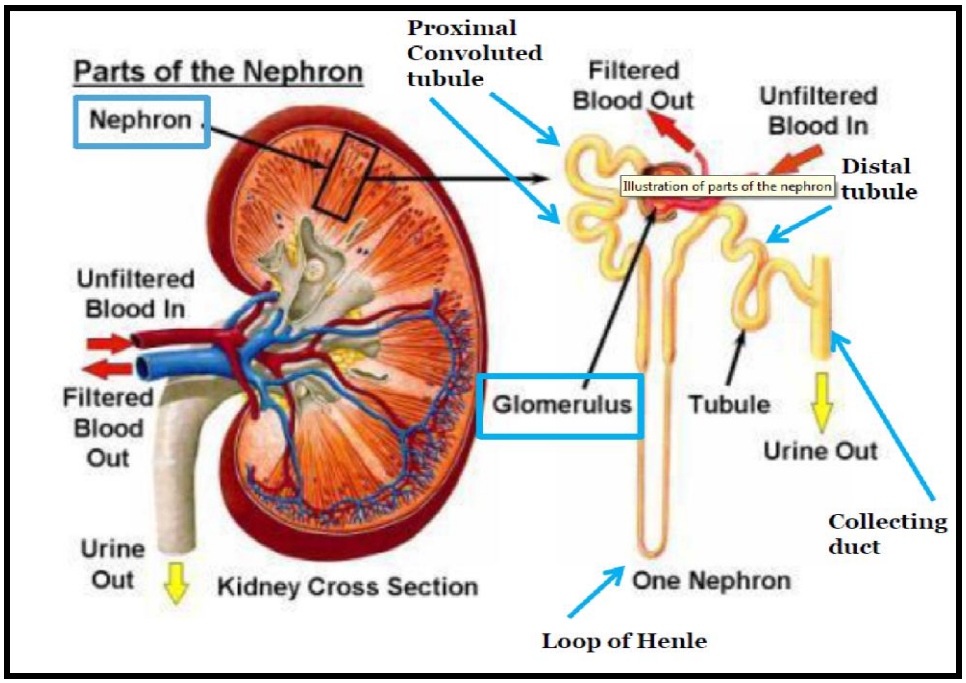

Figure (1): Parts of nephron.

In humans, formation of nephrons is complete at birth, but functional maturation with tubular growth and elongation continues during the first decade of life. Because new nephrons cannot be formed after birth, progressive loss of nephrons may lead to renal insufficiency ***(Carlo, 2016).***

Functional development: At birth, the kidney replaces the placenta in maintaing fluid and electrolytes and removing waste products. This occur by change in renal blood flow (RBF) and glomerular filtration rate (GFR) and tubular functions. Kidney function depend after birth on gestational age and postnatal age ***(Boundless, 2016).***

Glomerular function

At birth, systemic blood pressure (BP) is low and the intravascular resistance high, resulting in a very reduced kidney perfusion. The kidneys of the newborn receive only 15-20% of the cardiac output, in contrast to the 25% observed in the adult ***(Boundless, 2016).***

This hypoperfusion in combination with a severely limited filtration surface are the basic reasons of the very low GFR of the neonate. Thus, in a healthy term neonate the GFR at birth is just 20 ml/min/1.73m^2 and about 10-15 ml/min/1.73m^2 in a premature one, this low GFR limits all renal functions, especially with regard to water and electrolyte homeostasis and the excretion of waste products. During the first month of life GFR increases rapidly due to a rise of systemic BP and a concomitant fall renal vascular resistance, but it hardly exceeds 40 ml/min/1.73m^2 in the term neonate ***(Cayabyab et al., 2009).***

Tubular function

Contrary to glomerular function which increases rapidly but remains defective during neonatal period, tubular function, responsible for water, electrolytes and acid-base balance, matures more progressively and is more efficient in some mechanisms than it is in adult life ***(Woroniecki, 2011).***

Water management

During feotal life water is abundant and is exchanged freely between mother and foetus without any concentrative mechanisms. At birth the total body water (TBW) accounts for 75% of the weight of the newborn, most of which is extracellular fluid (ECF). Within days the total amount of water starts to decrease due to very little fluid intake and the increasing GFR and at the same time a shift of fluids between compartments commences. The ECF space contracts and water enters the cells, which increase in number and size.

These changes result in the so called "physiological weight loss" of 5-10% of birth weight for the term neonate and somewhat higher in premature neonates, which occurs within the first week of life ***(Woroniecki, 2011).***

After this period the kidneys concentrating capacity increases and water loss is minimised. However, because the renal concentration mechanism matures in the 2nd month of life, the neonatal concentrating capacity remains low and conditions of water depletion, such as vomiting, diarrhea or phototherapy may lead to dehydration ***(Guinard, 2003).***

On the other hand, the dilutional mechanism function is much more effective during the neonatal period. This does not mean that the infant can excrete water load efficiently, because of low GFR of this newborn ***(Woroniecki, 2011).***

Sodium management

Sodium is essential for growth and a positive sodium balance is important for adequate growth and development. The increased water loss right after birth is accompanied by sodium loss, which is more prominent in premature neonates ***(Meglosa, 2012)***.

Fractional excretion of sodium (FENa) immediately after birth can be as high as 5% compared with 1% in the adult, but it falls within days as the mechanisms for concentrating and saving sodium develop quickly to compensate for the very low concentration in salt of the human milk in term neonate. This process is delayed in premature infants who may require sodium supplementation to remain in positive balance. After the first few days and throughout early infancy the babies' kidneys are in a sodium-conserving state ***(Meglosa, 2012).***

Acid-base balance and other substances

The tight regulation of acid-base homeostasis is achieved through buffer systems and appropriate respiratory and renal adaptation. At birth, respiratory adaptive responses are adequate and work immediately in a spontaneously breathing and neurologically intact neonate ***(Guinard and Drukker, 2013).***

The renal compensatory mechanisms are slower and limited due to low neonatal GFR and the not yet developed tubular transport systems of bicarbonate and hydrogen ions

Thus neonates are in a physiological acidotic state, with healthy term newborns to have bicarbonate levels of 18-20 mEq/L compared with 24-26 mEq/L in the adult, a level which is reached at about 1 year of age. Premature infants may have bicarbonate levels as low as 14 mEq/L ***(George et al., 2012).***

Potassium excretion is low during gestation and remains so during the first months of life. Thus tissue and serum potassium levels are higher in neonatal period and early infancy than later. Thus, potassium values of 6 mEq/L or even 6.2 mEq/L in premature babies are considered normal in early infancy ***(Meglosa, 2012).***

Phosphorus is an essential element not only for growth but also for metabolism and its mechanisms of reabsorption are well developed at birth and work more efficiently than they do in adult life. Phosphate values are high during neonatal period and infancy, especially in breast-fed infants ***(Meglosa, 2012).***

Clinical Manifestations of Renal Diseases in neonate:

Many renal diseases are initially asymptomatic and first detected during a routine physical examination. Abdominal masses may be found, It may be renal or related to genitourinary system, edema also may be found in congenital nephrotic syndrome from low oncotic pressure, fluid over load lead also to edema as input exceed output. Tubular defects or use of diuretics may lead to dehydration. Oliguria also is a symptom of renal injury ***(Cerda, 2011).***

Renal Function Tests:

1) **Urine analysis**
2) **Glomerular filtration rate**
3) **Serum creatinine**
4) **Serum urea**
5) **Blood urea nitrogen**
6) **Blood urea nitrogen**
7) **Cystatin - c**

c1. Urine analysis:

A multiple urine test strip can be employed. Urine analysis may reveal the following macroscopically.

a) Proteinuria
b) Hematuria
c) Glucosuria

(Andreson et al., 2012)

a. Proteinuria:

Protein excretion varies with gestational age. urinary protein execretion is higher in premature infants and decreases progressively with postnatal age. Heavy proteinuria with edema suggests nephrotic syndrome.

Measurements of protenuria on 24 - hour urine collections have now been replaced by measuring protein to creatinine ratios on spot urine sample (normal ratio < 20mg / mmol) ***(Andreson, 2012).***

b. Haematuria:

It is uncommon in newborns and should always be investigated. Hematuria has many causes in newborns and microscopy of urine should always be performed to confirm the presence of red blood cells rather than a false - positive test due to free hemoglobin, myoglobin, drugs or confectionary dyes ***(Phillips, 2016).***

c. Glucosuria:

Is commonly present in premature infants <34 weeks gestational age. The tubular reabsorption of glucose is <93% in infants born before 34 weeks.

Osmolality & Urine Ph: Normal urine pH is between 5 and 7. Neonatal concentrating ability is limited with maximum specific gravity of 1.021 to 10.025 ***(Andreson, 2012).***

Leukocyte & Nitrite tests: Many test strips now incorporate nitrite detection which can indicate the presence of urinary infection when nitrate is reduced to nitrite. Leucocytes may also indicate infection but false-positive and negative tests may occur as in contamination, exposure of dipstick to air ***(Finnel, 2011).***

Microscopy: This may give useful information especially in the presence of proteinuria or haematuria. Urine should be examined for the casts. Red blood cell casts suggest glomerulonephritis. The presences of increased white blood cells, above 5 per high powered field, or motile bacteria suggest urinary tract infection ***(Andreson, 2012).***

Glomerular filtration rate

Kidney function is best measured as glomerular filtration rate (GFR). The GFR can be calculated by varity of marker. The ideal characterities of marker freely filterd through glomerulus, no tublar secration or reabsorption, no Renal or tubular metabolism.

The marker may be exogenous (inulin) or endogenous (creatianine), may be readio labeled or non radio labeled.

Renal clearance is calculated by the following formula:

C_s (mL/min) = U_s (mg/mL) x V(mL/min)/P_s(mg/mL)

where C, equals the clearance of substance s, U_s reflects the urinary concentration of s, *V* represents the urinary *(low* rate, and P_s equals the plasma concentration of s. To correct the clearance for individual body surface area, the formula is:

Corrected clearance (mL/min/1.73 m^2)

$$C_s\,(mL/\min)\times\frac{1.73}{Surface\,area\,(m^2)}$$

(Filler et al., 2014)

Because the inulin clearance technique is cumbersome for use in clinical practice, the GFR is commonly estimated by the clearance of endogenous creatinine ***(Filler et al., 2014).*** The "bedside" Schwartz formula is the most widely used pediatric formula and is based on the serum creatinine, patient height, and an empirical constant ***GFR = K x Body length (cm)/SCr (SCr: serum creatinine, mg/dL)***. K is a constant which depends on urinary creatinine per unit of body size and **its values for different ages are as follows:**

K, 0.34 in premature infants <34 weeks. The accuracy of this equation is further improved utilizing an endogenous marker, cystatin C, in addition to serum creatinine ***(Gao et al., 2013).***

This technique does not require any urine collection, thus making it suitable for routine clinical use ***(Levely et al., 2006).***

Serum Creatinine: serum creatinine is the most commonly used in expensive method evaluating renal dysfunction. Creatinine is a waste product of creatine. Creatinine production is continuous and is proportional to muscle mass. Creatinine is not only freely filtered by glomerules but also secreted by proximal tubule and depend on GFR. Renal dysfunction diminishes the ability to filter creatinine and the serum creatinine rises. Serum creatinine is not sensitive enough to detect early stages of renal damage as when serum creainine level doubles, the GFR is considered to be halved so it is not adequate marker for pediatric and neonatal population ***(Gao et al., 2013).***

Although the serum creatinine levels and GFR using this marker helps clinicians to assess renal function in neonates, but it is better to use markers that are stable over time and is not affected by muscle mass, tubular reabsorption and/or secretion. This stable marker can show the physiologic changes of renal function in children less than 1 year including neonates more precisely ***(Filler et al., 2014),*** acute kidney injury in neonate can be diagnosed as follow:

Table (1): Acute Kidney Injury Criteria in Neonates

Stage	Serum Creatinine Criteria	Urinary Output Criteria
1	SCr increase of ≥0.3 mg/dL or SCr increase to 150%-199% of baseline	UOP >0.5 mL/kg/hour and ≤1 mL/kg/hour
2	SCr increase to 200%-299% of baseline	UOP >0.1 mL/kg/hour and ≤0.5 mL/kg/hour
3	SCr increase to ≥300% of baseline or SCr ≥2.5 mg/dL or receipt of dialysis	UOP ≤0.1 mL/kg/hour

(Samuels et al., 2016)

Creatinine clearance test

A creatinine clearance test measures how well creatinine is removed from blood by kidneys. Creatinine clearance tests measure the level of the waste product creatinine in blood and urine. A creatinine clearance test gives better information than a blood creatinine test on how well kidneys are working. A creatinine clearance test is done on both a blood sample and on a

sample of urine collected over 24 hours (24-hour urine sample). In children it is difficult to collect urine for 24 hour thus we use schwartaz formula to collect GFR depend on serum creatinene and height. According to Creatinine clearance and urine out put.

Serum Urea

Urea is the end product of protein catabolism. The urea is produced from the amino group of the amino acids and is produced in the liver by means of the Urea cycle.

Urea undergoes filtrations at the glomerulus as well as secretion and re absorption at the tubular level. The rise in the level of serum urea is generally seen as a marker of renal dysfunction specially glomerular dysfunction. Urea level only rises when the glomerular function is reduced below 50% ***(Filler et al., 2014)***.

Blood Urea Nitrogen (BUN)

Sometimes the Serum urea level is expressed as blood urea nitrogen. BUN can be easily calculated from the serum urea level. The molecular weight of urea is 60 and it contains two nitrogen atoms of combined atomic weight of 28. Hence the contribution of nitrogen to the total weight of urea in serum is 28/60 that is equal to 0.47. Hence the serum urea levels can be easily converted to BUN by multiplying it by 0.47. A rise in blood nitrogen level is known as azotemia ***(Filler et al., 2014)***.