INTRODUCTION

Critically ill children are at increased risk of developing acute kidney injury (AKI). AKI is associated with a variety of short term and long term kidney impairment as well as high incidence of morbidity and mortality in the intensive care unit. Incidence of AKI following PICU admission is variable from 4.5 to 31 %, being much higher in children who are requiring invasive mechanical ventilation, or patients with sepsis/septic shock and those on vasopressor medications ***(McCaffrey et al., 2015).***

Despite the clinical importance of AKI, there are still no definite diagnostic and management tools for this disease till the present moment, where serum creatinine is still considered the basic diagnostic tool for AKI patients ***(McCaffrey et al., 2015)***. However, Serum creatinine (S.Cr) levels increase above the baseline levels only when about 25 to 50 % of the renal function has been lost which may cause a dissociation between deterioration of kidney functions and serum creatinine levels ***(Askenazi et al., 2009).***

Early diagnosis of AKI especially in critically ill patients is mandatory because it can allow early management procedures which will prevent further deterioration of the patient's condition. These interventions include stopping nephrotoxic drugs, and performing an accurate fluid and electrolyte balance for these patients ***(McCaffrey et al., 2015).***

Studies have identified many biomarkers which increase in number after being subjected to renal ischaemia after discovering some renal genes ***(Basu et al., 2011).*** These biomarkers include the following: human neutrophil gelatinase associated lipocalin (NGAL), cystatin-C (Cys-C), kidney injury molecule-1 (KIM-1), IL-18, and liver type fatty acid binding protein (L.FABP) ***(McCaffrey et al., 2015 and Han et al., 2008).***

In the recent years, Food and Drug Administration approved a new test that measures the level of cell cycle arrest biomarkers including urinary tissue Inhibitor of Metalloproteinase – 2 (TIMP2) for early detection of acute kidney injury cases ***(Ronco, 2015).***

Tissue inhibitor of metalloproteinase-2 (TIMP-2) is a marker which is released during the G1 cell cycle arrest in early phases of cell injury. During this early phase of renal injury following ischemia, the cells of the renal tubules enter short periods of G1 cell cycle arrest during which this marker is released. Therefore, an increased TIMP-2 level occurs early in the process of AKI ***(Westhoff et al., 2015 and Yamashita et al., 2014)*** It is considered as a marker for early prediction of AKI, especially in critically ill patients who have concomitant sepsis ***(Westhoff et al., 2015; Ronco, 2015; Yamashita et al., 2014).***

On the other hand, nutritional assessment is an essential tool for evaluating and monitoring patients who have acute

kidney injury (AKI). Acute loss of kidney function can affect the metabolism of macronutrients which are responsible for pro-inflammatory and catabolic states in ICU patients. The major nutritional problems usually found in AKI patients are hypercatabolic state and hyperglycemia.

Some studies have proved the correlation between some nutritional biomarkers and the clinical outcome in patients with AKI. The use markers like albumin, cholesterol and IGF-1 appears to be a useful screening parameter for bad prognosis and high mortality risk in patients with AKI ***(Berbel et al., 2011).***

AIM OF THE WORK

1. To study the frequency of occurrence of acute kidney injury in patients admitted to the pediatric intensive care unit.

2. To assess the role of urinary tissue inhibitor of metalloproteinase-2 in early detection of acute kidney injury.

3. To evaluate the relation of some nutritional biomarkers: Albumin, Cholesterol and Insulin like growth factor-1 (IGF-1) to the outcome (morbidity and mortality) of acute kidney injury in critically ill children.

RENAL PHYSIOLOGY

The human body homeostasis is maintained mainly by the kidneys and the urinary tract. Their major functions are water, electrolyte and acid–base balance. They also play a fundamental role in hormone secretion, red blood cell production and the blood pressure control (Figure 1) ***(Sinha and Marks, 2017).***

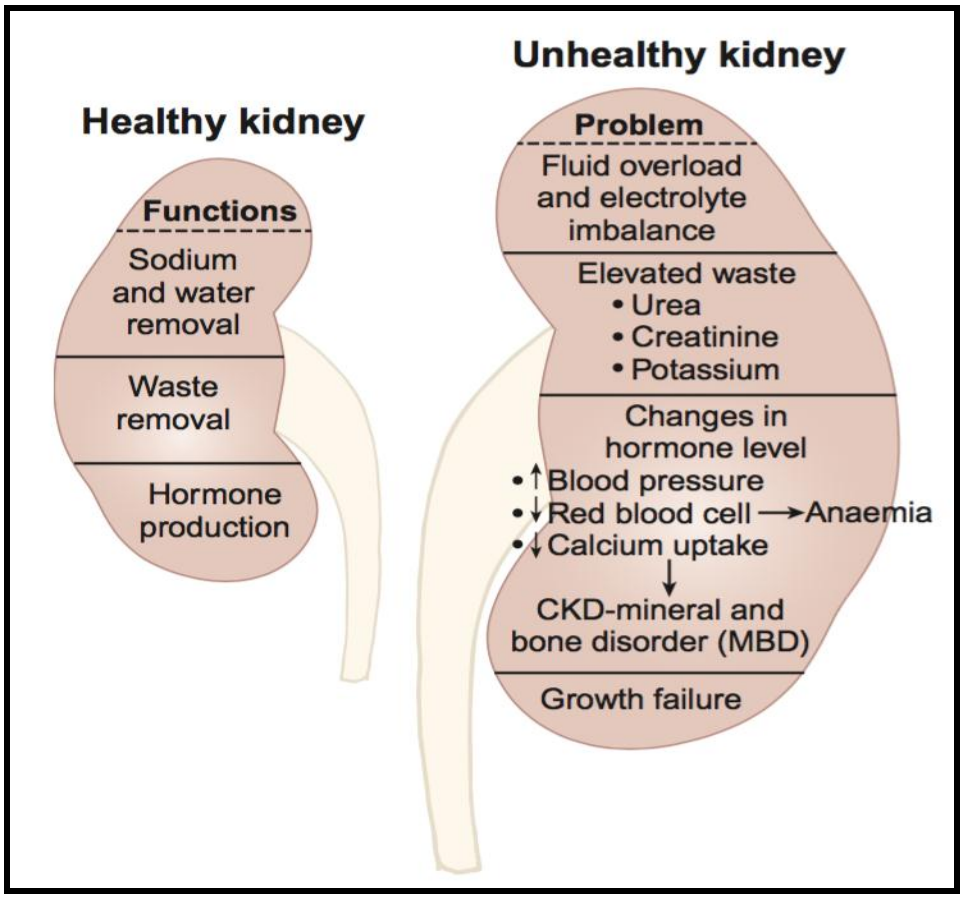

Fig. (1): Functions of the normal human kidneys and consequences of renal diseases ***(Fogo, 2009).***

Anatomy of the kidneys:

The kidneys are present in the paravertebral space are retroperitoneal organs; Right kidneys are slightly lower than left ones. At birth, the average length of the kidney is around 4.5–5.5 cm, whereas an adult kidney length is around 10–11.5 cm and its width around 5–7 cm ***(Sinha and Marks, 2017).***

The cortex is the outer layer of the kidney, it contains many structures including the glomeruli, the proximal and distal convoluted tubules, as well as the collecting ducts. On the other hand, the inner layer, which is the medulla, contains the straight parts of tubules, loop of Henle, vasa recta, and terminal collecting ducts ***(Fogo, 2009).***

Blood supply of the kidneys

The renal artery is the main blood supply to the kidneys. It arises from the aorta and divides into small branches in the medulla. These branches give the interlobar arteries that pass through the medulla to the corticomedullary junctions. The interlobar arteries then branch further to form the arcuate arteries, that run parallel to the surface of the kidneys. Finally, the interlobular arteries arise from arcuate arteries and give the afferent arterioles of glomeruli ***(Hunley et al., 2009).***

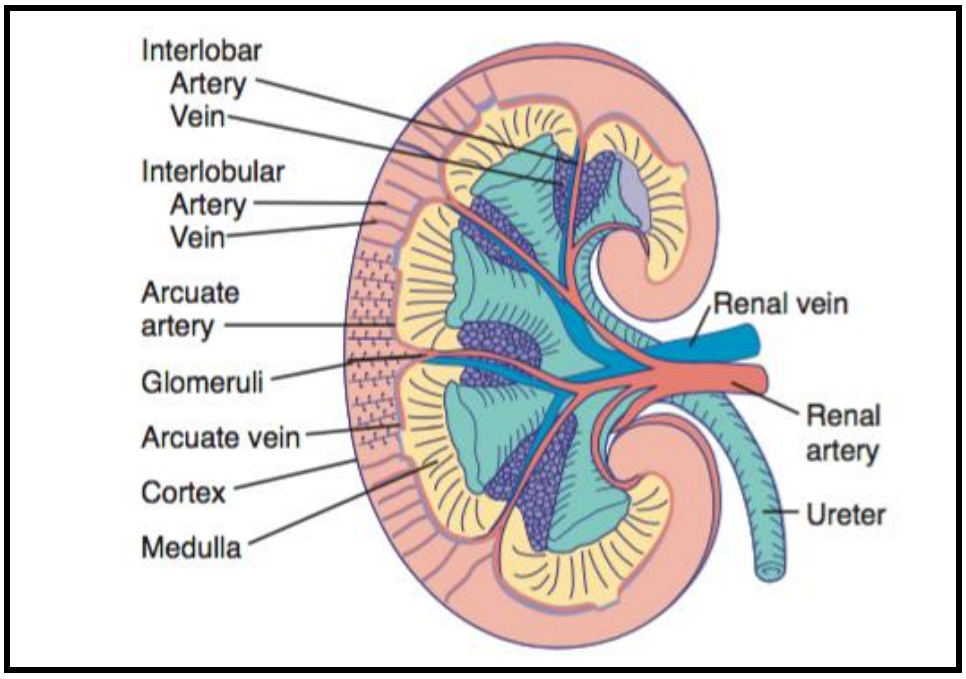

Fig. (2): Gross morphology of the renal circulation ***(Fogo, 2009).***

Gross microscopic differentiation

The kidneys are covered from outside by a thin capsule. On the other hand, other main constituents of the urinary tract are situated in the medial side of the kidneys, also known as hilum. The hilum opens into central space named renal pelvis. The pelvis of the kidneys extends to the outside to form the ureters, while its intrarenal portion divides to multiple calyces (6–10 in number). These calyces drain the renal pyramids. The papillae of these pyramids open into the calyces. The pelvi-ureteric and the vesico-ureteric junctions are narrow points present along the ureter and therefore are most prone to obstruction ***(Naish et al., 2014).***

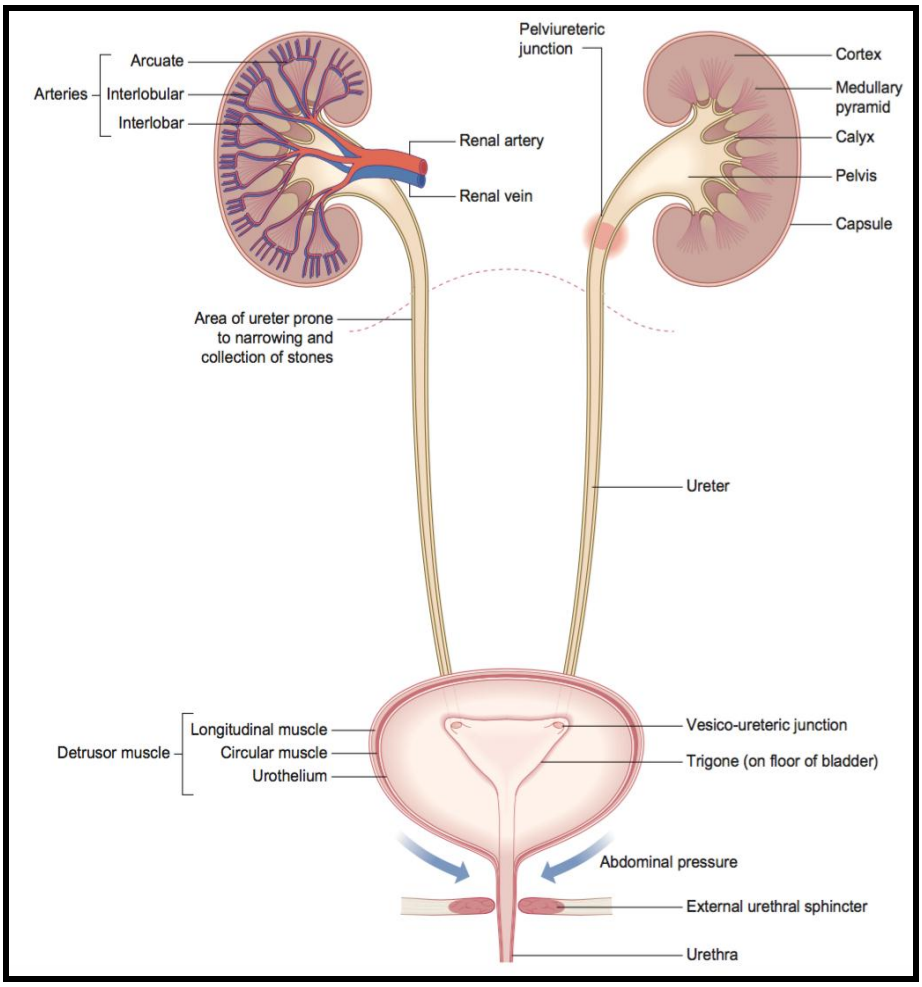

Fig. (3): Longitudinal cut section in the kidneys and its relationship to the other urinary tract structures ***(Naish et al., 2014).***

The kidney contains about 1 million nephrons (each one is formed of glomerulus and tubules). Nephron number in humans varies greatly from 200,000 up to 2 million nephrons per kidney. This large variation may have a major significance as a risk factor for developing hypertension and progressive renal dysfunction later. In human beings, the formation of the nephrons is completed by 36 to 40 weeks of gestation.

However, the maturation of the nephrons functionally as well as tubular growth continues throughout the 1st 10 years of age ***(Fogo, 2009).***

The Nephrons

The Nephron (Figure 4) is a structural unit of the kidney. There are around one million nephrons in each kidney. Each nephron contains a glomerulus which is connected to tubules that drain into the collecting duct. Then, the ducts join each other to drain into the renal calyces present in the renal pyramids. Glomeruli are responsible for generating the glomerular filtrate. This is done by ultra-filtration of the blood that enters the kidney through afferent arterioles. This ultra-filtrate accumulates in Bowman's space and then it crosses the tubules, where it transforms to the final urine ***(Sinha and Marks, 2017).***

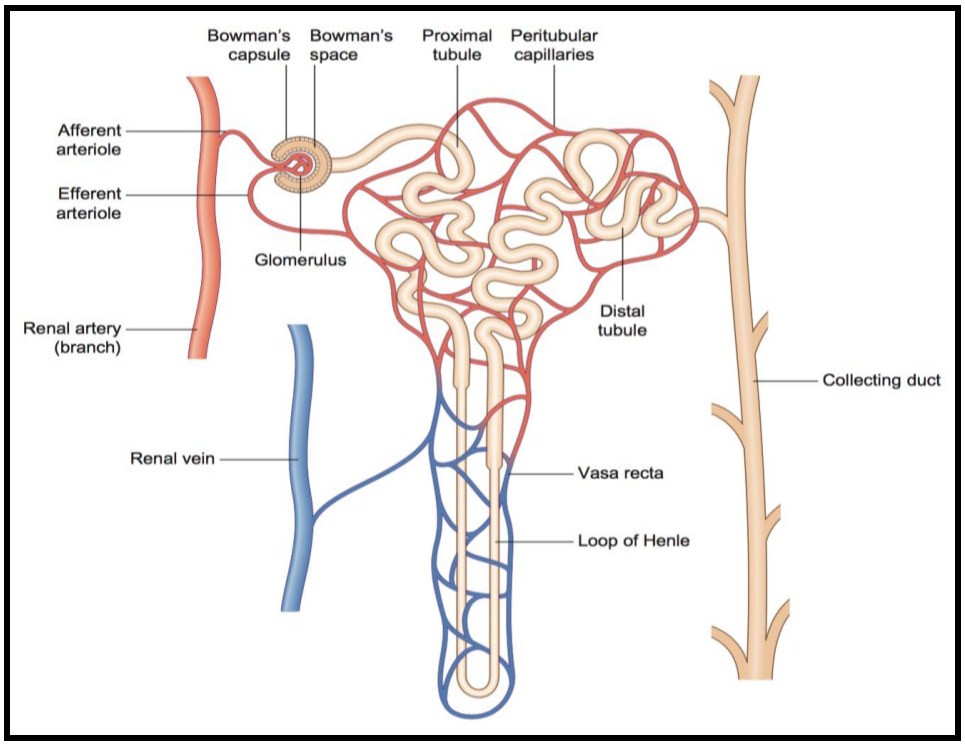

Fig. (4): Diagram of the structure of the nephron ***(Fogo, 2009).***

Solutes pass in the tubular fluid through the renal tubules. This is where they are absorbed through a highly selective mechanism ***(Naish et al., 2014).***

Glomerular filtrate consists of macromolecules, glucose, electrolytes like sodium, potassium, chloride, bicarbonate, amino acids as well as water. Proximal tubules are the main site for reabsorption of most of the glucose filtered, and also electrolytes and essential nutrients. The reabsorption of bicarbonate at the the proximal tubules affects the acid–base homeostasis. Some toxic metabolites, anions and cations are also secreted by these tubules. The loop of Henle forms the

main site for urinary concentration. The rest of sodium, chloride and water reabsorption occurs in the Distal tubules and collecting ducts. These actions are controlled by vasopressin and aldosterone ***(Sinha and Marks, 2017).***

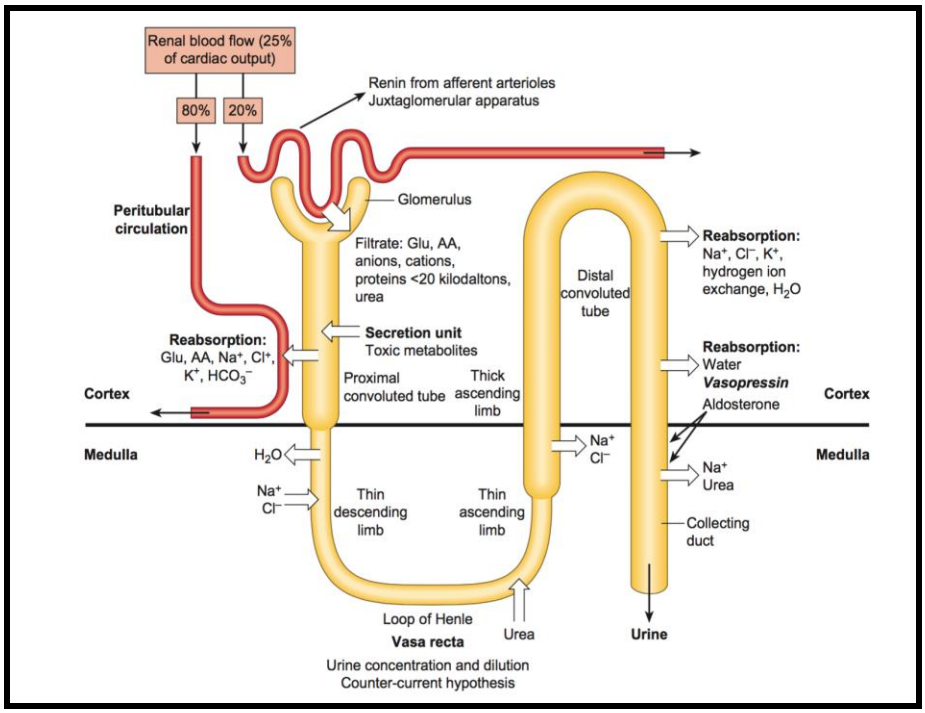

Fig. (5): Diagrammatic representation of the major transport sites across the nephron ***(Naish et al., 2014).***

The glomeruus

The glomerular capillaries are considered as filtering mechanism of the kidneys. Glomerular capillaries are lined by endothelial cells. They have very thin cytoplasm which contains holes also known as fenestrations. Glomerular basement membrane (GBM) forms a continuous layer between endothelial and mesangial cells ***(Hunley et al., 2009).***

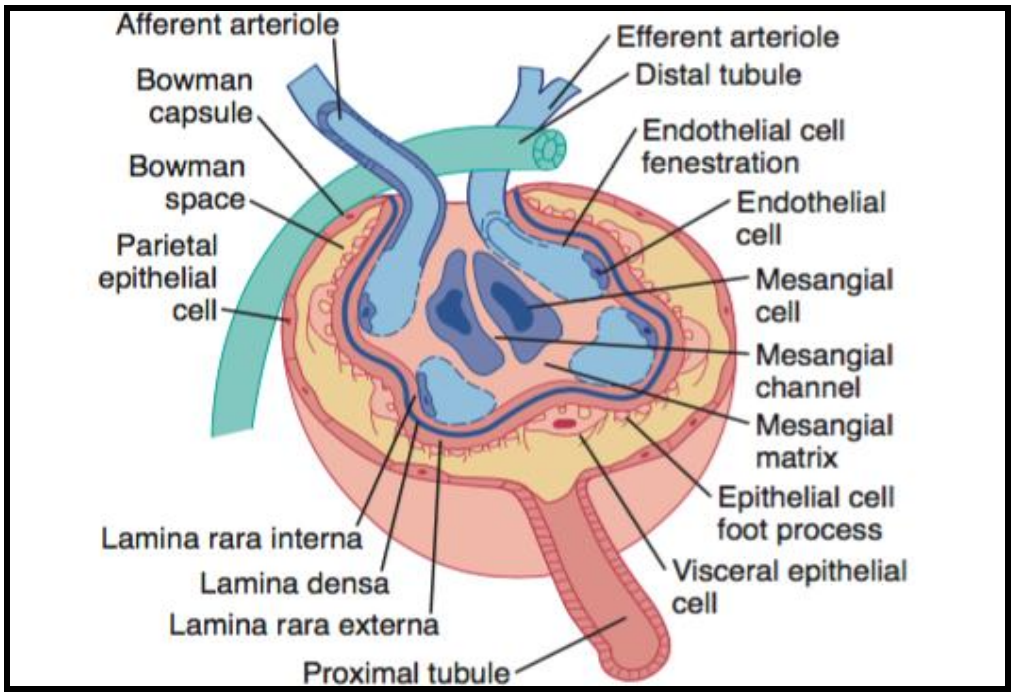

Fig. (6): The glomerulus and its surrounding structures ***(Hunley et al., 2009).***

Renal functions

Glomerular filtration rate (GFR) is the standard tool used for measurement of kidney functions. The glomerular capillaries filters the plasma through capillary walls. The resulting ultra-filtrate contains all of plasma substances including (electrolytes, phosphate, glucose, creatinine, and low-molecular-weight proteins) except the proteins that have high molecular weight of more than 68 kDa (like albumin and globulin) ***(Hunley et al., 2009).***

The glomerular filtrate results from counter regulatory forces applied on the capillary wall. The capillary hydrostatic

pressure of the glomerulus is responsible for ultra-filtration. It results from systemic arterial pressure, which is modified by the afferent and efferent arteriolar tone ***(Gao et al., 2013).***

The glomerular filtrate begins early in fetal life. However, the placenta is the organ responsible for fetal excretion and therefore a normal kidney function is not mandatory for homeostasis during fetal life. The kidneys stop growing by the age of 18 to 20 years in the majority of people, and GFR continues to rise since birth till the kidneys reach their maximum growth. The GFR can be estimated by the measurement of serum creatinine. Creatinine is derived from the metabolism of muscles. It's excreted through glomerular filtration. The serum creatinine level is influenced mainly by the muscle mass and level of glomerular function. This is in contrast to blood urea nitrogen concentration which is affected by the hydration status and the nitrogen balance. A patient can have normal serum creatinine levels despite affected renal function very shortly after onset of acute kidney injury with anuria. In that case, serum creatinine is considered an insensitive tool to measure the decline in renal functions because its level does not rise above the normal levels until GFR decrease by 30 to 40% ***(Filler et al., 2014).***

The best way to measure the glomerular filtration rate is through the clearance of inulin (a fructose polymer). However, this measurement is quite difficult, therefore GFR is commonly measured by estimation of the endogenous creatinine clearance.

There are many formulas used to estimate creatinine clearance in clinical settings. The most commonly used formula in pediatrics is the "bedside" Schwartz formula. This formula is based on serum creatinine, patient's height, and a constant ***(Gao et al., 2013; Schwartz et al., 2009).***

The proximal tubules is responsible for most of the transport in the kidneys. Its luminal membrane forms the 'brush border' of microvilli to offer a large surface area for the reabsorption process. The organic solutes like low-molecular-weight proteins, amino acids and glucose are largely reabsorbed in this segment with more 98%. Moreover, the absorption of inorganic solutes and of water also occur in the PCT. Subsequent tubules are responsible for the fine-tuning of water and solutes reabsorption by the kidneys ***(Bitsori, 2012).***

Overall, the glomerular and tubular functions are decreased at birth compared to later childhood and adult levels, even when corrected to the adult body surface area of 1.73 m2. However, neonatal kidneys can accurately manage homeostasis and sustain a normal development and maturation since birth ***(Bitsori, 2012).***

The urinary excretion and GFR increase with the child growth, and the concentration capacity also improves until the renal functions reach adult levels by 2 years of age. The maturation changes are more rapid in the first six months of life then they get slower with age ***(Adalat et al., 2010).***

The renal functions can be evaluated clinically by the measurement of substances in urine and serum. The normal values of commonly measured parameters of renal functions in the first years of life are illustrated in Table 1 ***(Bitsori, 2012).***

Table (1): Renal function changes according to the age ***(Bitsori, 2012).***

	1st week		2nd week	8 weeks	1-2 years
	Premature	**Term infant**			
Daily excretion of urine (ml/kg/24hrs)	15-75	20-75	25-120	80-130	40-100
GFR (ml/min/1.73m^2)	10-15	15-20	35-45	60-75	90-110
Serum creatinine (mg/dl)	0.9	0.7	0.5	0.3-0.4	0.3-0.4
Max urine osmolality (mOsm/kg H_2O)	400-500	500-600	700-800	1000-1200	1200-1400

Measurement of blood urea is not an accurate tool for the estimation of renal functions during the first months of life. This is because it reflects the infant's metabolic status rather than his renal functions. It is usually lower during anabolic situations like rapid growing in infancy. It also increases with the catabolic states that occur with many diseases not only with renal dysfunction. Later on in childhood, lots of other conditions can affect the level of urea apart from the GFR. These conditions are highlited in Table 2 ***(Woroniecki et al., 2011).***