INTRODUCTION

The renal excretion of uric acid in children differs quantitatively and perhaps qualitatively, from that in adult humans. The younger the child, the greater the renal clearance of uric acid and the greater the excretion of uric acid expressed as mg per kg body weight ***(Baldree and Stapleton, 1990).***

Serum uric acid levels in humans are primarily determined by renal uric acid clearance, with 90% of clinically recognized hyperuricemia resulting from its impaired renal excretion ***(Le et al., 2008).***

Uric acid has been hypothesized to play a role in the early stages of vascular damage and contribute to the development of hypertension ***(Johnson et al., 2003).***

Hyperuricemia is a common feature in patients with chronic kidney disease (CKD) ***(Soliman et al., 2006).*** Patients with end stage renal disease (ESRD) often exhibit elevated serum uric acid levels due to decrease clearance. This was first noted in ***1958*** by ***Kasane et al.***

Hypertension is found in more than 50% of pediatric patients with CKD ***(VanDeVoorde and Mitsnefes, 2011).*** Factors contributing to CKD associated hypertension are

fluid overload, activation of the renin-angiotensin system, sympathetic hyperactivation, endothelial dysfunction and chronic hyperparathyroidism ***(Hadtstein and Schaefer, 2007).***

Chronic kidney disease (CKD) ad renal failure (RF) have been recognized as significant medical problems for most of the last 2 centuries. Scientific and technologic improvements during the second half of the 20th century provided renal replacement therapy as a life sustaining option for many individuals. The disease and management are classified according to stages of disease severity, which are assessed from glomerular filtration rate (GFR), albuminuria, and clinical diagnosis. Chronic kidney disease can be detected with routine laboratory tests, an some treatments can prevent development and slow disease progression, reduce complications of decreased GFR and risk of cardiovascular disease, and improve3 survival and quality of life ***(Levely and Coresh, 2013).***

Hemodialysis is one of three renal replacement therapies (the other two being renal transplant and peritoneal dialysis). The goals of pediatric hemodialysis (H.D.) are the same as those in adults undergoing H.D.: effective and safe clearance of uremic toxins, and removal of excess fluid ***(Rees, 2013).***

AIM OF THE WORK

To study the relation between serum uric acid in pediatric patients with end stage renal disease (ESRD) on regular hemodialysis and the prevalence of hypertension among those patients.

URIC ACID

Metabolism:

Uric acid is an end product of purine metabolism that is produced mainly by the liver and intestines, but also by other peripheral tissues, such as muscles, the endothelium, and the kidneys ***(Jalal et al., 2013).***

Urate is synthesized by the xanthine oxidoreductase enzyme, which successively oxidizes hypoxanthine to xanthine and then to urate. In the vast majority of mammals, urate is then converted to allantoin by urate oxidase. By contrast, in humans, urate constitutes the main end product of purine metabolism ***(Cipriani et al., 2010).***

Because it is a weak acid, uric acid circulates in plasma (pH 7.4) predominantly (98%) in the form of a monovalent sodium salt (urate) ***(Liebman et al., 2007).*** Although uric acid occurs predominantly as a urate anion under physiologic pH, more uric acid than urate is present in urine (pH 5-6) ***(Wright et al.,2010).*** In the collecting tubules of the kidneys, where the pH can fall to 5.0, uric acid formation is favored. The critical physical property of uric acid in the clinical setting is solubility. Uric acid is less

soluble than urate; thus, an acidic environment decreases solubility ***(Fahlen, 2013).***

The efficiency with which the human kidney reabsorbs urate may contribute to the higher serum uric acid levels in humans compared with other species; this in addition to an uricase mutation preventing further uric acid degradation in humans ***(Alvarez-Lario and Macarron-Vicente, 2010).***

Excretion:

In the kidney, uric acid and urate are initially filtered and additionally secreted. However, the largest part (90%) is usually reabsorbed and returns to blood ***(Alvarez-Lario and Macarron-Vicente, 2010).***

The factors that can influence the uptake of urate by the kidney are: plasma concentrations, volemia and renal plasma flow modulators. At this point, renal excretion of urate follows the same extra-renal limiting factors as those of glomerular filtration. Kidney participation is associated with glomerular filtration (90% filtrate), proximal reabsorption (by an active process) and post-secretory reabsorption in the distal tubule, ascending loop and collecting duct. In this phase, the renal excretion of urate follows the limiting factors that

accompany renal diseases (glomerular and medullary). The urate renal excretion phase is that of post-secretory reabsorption ***(Mount et al., 2006).***

The cell membrane is impermeable to the urate anion in the absence of specific transporters ***(Wright et al.,2010).*** A urate/anion exchanger (URAT1) has been identified in the brush-border membrane of the kidneys, a human organic anion transporter (hOAT1), while another urate transporter (UAT) has been found to facilitate urate efflux out of the cells. These transporters may account for the reabsorption, secretion, and reabsorption pattern of renal handling of urate. Urate secretion does appear to correlate with the serum urate concentration because a small increase in the serum concentration results in a marked increase in urate excretion ***(Qazi, 2012).***

Urinary excretion accounts for two-thirds of total elimination of uric acid and the remainder is excreted in feces. Uric acid is excreted into bile and intestinal lumen, and most of the uric acid is secreted directly into the intestinal lumen from blood, but not via the bile ducts, as an extra-renal elimination pathway. Furthermore, endogenous uric acid is secreted from blood directly into the intestinal lumen at all intestinal segments, and the

secretion at the ileum was about three- and two-times greater than in jejunum and colon, respectively ***(Hosomi et al., 2012).***

The renal excretion of uric acid in children differs quantitatively and perhaps qualitatively, from that in adult humans. The younger the child, the greater the renal clearance of uric acid and the greater the excretion of uric acid expressed as mg per kg body weight ***(Baldree and Stapleton, 1990).***

Typically, net reabsorption occurs in infants and children. The fractional excretion of urate in infants and children ranges from about 0.1-0.6. The concentration of uric acid in plasma depends on dietary ingestion, de novo purine synthesis, and uric acid elimination by the kidneys and intestine ***(Shaykh, 2013).***

Normal uric acid serum level is shown in the table below:

Table (I):

	1-5 years	6-11 years	12-19 years	
			Male	Female
Uric Acid serum level (mg/dl)	1.7-5.8	2.2-6.6	3-7.7	2.7-5.7

(Nicholson and Pesce, 2007)

Effect of uric acid in the body:

The blood levels of uric acid are a function of the balance between the breakdown of purines and the rate of uric acid excretion. Theoretically, alterations in this balance may account for hyperuricemia, although clinically defective elimination accounts for most cases of hyperuricemia ***(Qazi, 2012).***

Elevated uric acid levels can be seen in the following:

- Gout
- Renal failure
- Destruction of massive amounts of nucleoproteins (leukemia, anemia, chemotherapy, toxemia of pregnancy, psoriasis, sickle cell anemia, hemolytic anemia, polycythemia, resulting pneumonia)
- Drugs (especially diuretics, barbiturates)
- Lactic acidosis
- Hypothyroidism
- Chronic kidney disease
- Parathyroid diseases
- Low-dose salicylates
- Metabolic acidosis

- Diet (high-protein weight-reducing diet, alcohol, liver, and sweetbread)
- Chronic lead poisoning
- Down syndrome
- Polycystic kidney disease
- Sarcoidosis
- Lesch-Nyhan syndrome
- von Gierke disease
- Chronic berylliosis.

(Devkota, 2014)

Decreased uric acid levels can be seen in the following:

- Drugs such as uricosuric drugs (salicylates, probenecid, allopurinol), estrogen, phenothiazines, indomethacin, corticotropin
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH) with hyponatremia
- Wilson disease
- Fanconi syndrome
- Acromegaly
- Celiac disease
- Xanthinuria

(Devkota, 2014)

Uric acid and ESRD:

Discovery of uric acid happened in the 1700's with the analysis of a bladder stone. In fact, the condition defined as "gouty nephropathy" was originally attributed to the deposition of urate crystals in the tubules and renal interstitium heading to a local inflammatory reaction ***(Talbott and Terplan, 1960).***

Individuals with increased serum uric acid levels secondary to high dietary purine intake also may have lower than normal urinary pH, favoring even more uric acid in urine than urate. Considering that uric acid is less soluble than urate, this milieu would favor uric acid crystal formation ***(Coe, 1983).*** Uric acid crystals have the capacity to adhere to the surface of renal epithelial cells ***(Koka et al., 2000)*** and induce an acute inflammatory response in such cell lines ***(Umekawa et al., 2003).*** In addition to an increased risk of kidney stone formation, such effects have been shown to reduce glomerular filtration rate (GFR) ***(Spencer et al., 1976).***

However recent renal hemodynamic studies conducted in hyperuricemic rates documented an arteriolopathy of preglomerular vessels, which impairs the autoregulatory response of afferent arterioles, resulting in

glomerular hypertension. Lumen obliteration induced by vascular wall thickening produces severe renal hypoperfusion. The resulting ischemia is a potent stimulus that induces tubulointerstitial inflammation and fibrosis, as well as arterial hypertension ***(Sánchez-Lozada et al., 2005).*** This would explain why the expression "gout nephropathy" has been abandoned and local crystal deposit have no longer been thought to be the reason for renal damage ***(Cerezo and Ruilope, 2012).*** These studies provide a potential mechanism by which hyperuricemia can mediate hypertension and renal disease ***(Sánchez-Lozada et al., 2005).*** The importance of these findings in relation to human disease is uncertain. One must be careful in extrapolating from animal models to human disease ***(Sánchez-Lozada et al., 2002).***

Although there is increasing evidence supporting hyperuricemia as a true risk factor of chronic kidney disease, there are still discrepancies regarding the contributing role of uric acid in the onset or worsening of kidney disease ***(Weiner et al., 2008).***

As of yet, there is still no agreement as to whether treating asymptomatic hyperuricemia in renal individuals with uric acid-lowering therapy will offer more renoprotection. Large prospective trials are needed to solve that ***(Cerezo and Ruilope, 2012).***

On the other hand, Uric acid clearance is impaired in CKD ***(Johnson et al., 2003)*** and therefore, significant amounts of uric acid may accumulate in patients approaching end-stage renal disease (ESRD) ***(Sombolos et al., 1997).***

Relation between hyperuricmia and hypertension:

At the end of the 19th century and the first two decades of the 20th century, uric acid was already linked with hypertension and cardiovascular diseases. The investigation of a link between uric acid and hypertension made relatively little progress through much of the 20th century ***(Feig, 2012).*** While some of the cardiovascular risk trials measured uric acid and suggested an association between uric acid and hypertension, or cardiovascular disease, the lack of plausible mechanistic evidence linking the two led most investigators to conclude that uric acid was an associated surrogate marker for more important risk factors such as obesity, diabetes, and chronic kidney disease (CKD) ***(Culleton et al., 1999).*** Animal models support a two-phase mechanism for the development of hyperuricemic hypertension. Initially, uric acid induces vasoconstriction by activation of the renin-angiotensin system and reduction of circulating nitric oxide, which can be reversed by lowering uric acid. Over time, uric acid uptake into vascular smooth muscle cells causes cellular

proliferation and secondary arteriolosclerosis that impairs pressure natriuresis, causing sodium-sensitive hypertension. Consistent with the animal model data, small clinical trials performed in adolescents with newly diagnosed essential hypertension demonstrate that at least in certain young patients, reduction of serum uric acid can mitigate blood pressure elevation. While more research is clearly necessary, the available data suggest that uric acid is likely causative in some cases of early-onset hypertension ***(Feig, 2012).***

On the other hand, the increase in serum uric acid in hypertension may be due to the decrease in renal blood flow that accompanies the hypertensive state, since a low renal blood flow will stimulate urate reabsorption ***(Messerli et al., 1980).*** Hypertension also results in microvascular disease, and this can lead to local tissue ischemia ***(Puig and Ruilope, 1999).*** In addition to the release of lactate that blocks urate secretion in the proximal tubule, ischemia also results in increased uric acid synthesis ***(Friedl et al., 1991).*** With ischemia, ATP is degraded to adenine and xanthine, and there is also increased generation of xanthine oxidase. The increased availability of substrate (xanthine) and enzyme (xanthine oxidase) results in increased uric acid generation as well as oxidant (O_2^-) formation ***(Many et al., 1996).***

Messerli et al. (1980) hypothesized that the frequent presence of hyperuricemia in hypertensive patients reflects underlying renal dysfunction or reduced renal perfusion. Three possible conclusions can be drawn from the association of hypertension with raised sUA levels; Hypertension may arise as a result of hyperuricemia, hypertension can cause hyperuricemia and the duration and severity of hypertension is related directly to the sUA levels.

The antioxidant role of uric acid:

Uric acid has been shown to have antioxidant properties in vitro ***(Hink et al., 2002)*** and in vivo ***(Kandar et al., 2006)***, it contributes as much as 2/3rd of all free radical scavenging capacity in plasma and it is particularly effective in quenching hydroxyl, superoxide, peroxal and peroxynitrite radical and may serve protective physiological role by preventing lipid per oxidation ***(Squadrito et al., 2000).*** Peroxynitrite is a particularly toxic product formed by the reaction of superoxide anion with nitric oxide that can injure cells by nitrosylating the tyrosine residues (nitrotyrosine formation) of proteins. Uric acid can also block this reaction ***(Squadrito et al., 2000).***

Hink et al. (2000) reported that uric acid may prevent the degradation of extracellular superoxide dismutase

(SOD3), an enzyme critical in maintaining endothelial and vascular function. SOD3 is an extracellular enzyme that catalyzes the reaction of superoxide anion (O2−•) to hydrogen peroxide (H2O2). The removal of O2−• by SOD3 prevents the reaction and inactivation by O2−• of the important endothelial vasodilator, nitric oxide (NO). SOD3, by removing O2−•, therefore helps to maintain NO levels and maintain endothelial function.

Normally, SOD3 is inactivated in the presence of H2O2, suggesting a feedback inactivation of the enzyme. However, uric acid blocks SOD3 inactivation by H2O2 by regenerating SOD3 with the production of a urate radical ***(Hink et al., 2000).*** This latter radical, although potentially a pro-oxidant, has been found to be markedly less reactive than classic oxidants and can be rapidly regenerated back to urate in the presence of ascorbate ***(Maples and Mason, 1988).***

Several lines of evidence have demonstrated that soluble UA is a strong antioxidant, also, Urate circulating in elevated concentrations was proposed to be one of the major antioxidants of the plasma that protects cells from oxidative damage, thereby contributing to an increase in life span of our species ***(Ames et al., 1981).***