HYPERURICEMIA IN RENAL ALLOGRAFT

RECIPIENTS

A dissertation submitted to the Tamil Nadu Dr. M.G.R.
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BONAFIDE CERTIFICATE

This is to certify that the work presented in this dissertation titled "Hyperuricemia in renal allograft recipients" done towards fulfilment of the requirements of the **Tamil Nadu Dr. M.G.R. Medical University, Chennai for the D.M. (Branch–III) (Nephrology)** exams to be conducted in August 2013, is a bonafide work of Dr Suraj Kumar, done under my guidance and supervision. This dissertation has not been submitted, fully or in part to any other board or University.

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ABBREVIATIONS

e GFR – estimated glomerular filtration rate

RTR- Renal transplant recipients

MDRD- Modification of diet in renal disease

UA – Uric acid

CsA- Cyclosporine-A

CNI- Calcineurin inhibitor,

KDIGO- Kidney Disease : Improving global outcomes

KDOQI-Kidney Disease Outcomes Quality Initiative

NODAT- New onset diabetes after transplantation

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Abstract

TITLE OF THE ABSTRACT   : Hyperuricemia in renal allograft recipients

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AIM / OBJECTIVES:

The primary objective was to assess the prevalence, clinical and biochemical predictors of hyperuricemia in renal allograft recipients. The secondary objective was to find association of graft function with hyperuricemia.

MATERIAL AND METHODS:

We conducted a retrospective study on 283 renal allograft recipients with at least 6 month follow up. The data was recorded for each month till 6months and at 12th and 18th month and thereafter annually. We determined eGFR and occurrence of hyperuricemia, dyslipidemia, NODAT, acute rejection episodes. Hyperuricemia was defined as >6mg/dl in women and >7mg/dl in men and subdivided into early and late onset (<1>year) and mild and moderate to severe (<8>mg/dl). The statistical analyses were performed using SPSS software and independent t-test and Fisher's exact test or chi square test were performed depending on variables.

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RESULTS:

The prevalence of hyperuricemia was 26.8%. The mean time to onset of hyperuricemia was 6mths. Majority of the patients had early hyperuricemia (<12 months). Early onset moderate to severe hyperuricemia was seen in 29.5%. The incidence of NODAT and Dyslipidemia was 22% and 42% respectively. The nadir eGFR(73.0 ± 27.5ml/min vs. 81.9 ± 30.9ml/min, p value 0.03) and estimated GFR at 1month (68.5 ± 21.0ml/min vs. 74.5 ± 20.6ml/min, p value 0.04) were lower in patients with hyperuricemia.The incidence of NODAT (12.7% vs. 50.7%, p value 0.00) and serum triglyceride levels were higher (150.2 ± 67.5mg/dl vs. 131.9 ± 39.5mg/dl, p value 0.037) in patients with hyperuricemia. The recipients who had early onset moderate to severe hyperuricemia were found to have a lower estimated GFR at 1year (65.2 ± 18.8 vs. 78.2 ± 19.4, p value 0.014)where as early onset mild hyperuricemia had no association with GFR at any time interval.

CONCLUSIONS:

The prevalence of hyperuricemia was 26.8%. Hyperuricemia was associated with a higher BMI at transplant, lower graft function, presence of NODAT and higher triglyceride levels. There was no association with recipient gender, deceased donor allograft or acute rejection episodes.

REVIEW OF LITERATURE

Introduction

Hyperuricemia has been commonly associated with renal and cardiovascular diseases. In patients with gout, before the availability of antihyperuricemic treatment, 25% of patients developed proteinuria, 50% had chronic kidney disease, and 10–25% had end stage kidney disease.[1]

It is also more commonly seen in individuals with hypertension, obesity, metabolic syndrome etc. Over the years with widespread changes in dietary habits, there has been a worldwide epidemic of hyperuricemia, metabolic syndrome, obesity and type- 2-diabetes.[2] The animal models and experimental studies have further strengthened this association.

But large epidemiological studies have not been able to prove this association (Framinghan study).[3] The Modification of Diet in Renal Disease (MDRD) study also reported uric acid as a marker, rather than a predictor of renal function decline.[4] The JNC 7 recommendations as well as the KDOQI guidelines also do not recognize it as a risk factor.

There are also studies which support hyperuricemia as a primary risk factor for renal disease. In a study on Japanese population of 49000 males they showed that uric acid was one of the risk factors of renal failure with a relative risk (RR) of 8.52.[5] Hyperuricemia also have been shown as

a risk factor for hypertension, decline in renal function, and tubulointerstitial changes in IgA nephropathy.[6]

As the risk factors are so common in renal transplant setting hence it is even more common in the renal allograft recipients. The evidence for association of hyperuricemia with graft outcomes in renal allograft recipients is even more limited. In the precyclosporine era the prevalence of hyperuricemia was 25%. The use of cyclosporine led to a significant rise in the prevalence of hyperuricemia up to 80-85%. [7,8] Hyperuricemia also had a significant clinical impact with almost 10% patients developing gout.

Over the years the type of immunosuppression has changed from predominantly cyclosporine to low dose tacrolimus now which has also reflected in a change in the prevalence of hyperuricemia. The results from ELITE-Symphony trial have shown a prevalence of 19-55%.[9,10] The lowest prevalence of hyperuricemia was seen in patients on low dose tacrolimus which was approximately 20%. In other solid organ transplant recipients also hyperuricemia is very common (14%-50% in liver transplant recipients). [11,12]

The common predictors of hyperuricemia are same as general population like metabolic syndrome, dyslipidemia, obesity, hypertension, use of diuretics as well as the factors specific renal transplant setting like NODAT, CsA use, graft function, chronic allograft nephropathy. As most of the studies have been cross-sectional in nature hence the causality remains unproven.

Only a limited number of studies have evaluated the effect of hyperuricemia on graft survival and dysfunction in renal allograft recipients and the results obtained have been quite contradictory. Also it is difficult to separate this association of uric acid with graft function. The hyperuricemia may simply be a consequence of the reduced graft function, as well as it can directly contribute to graft dysfunction.

Hyperuricemia has frequently been associated with various disorders like chronic kidney disease, cardiovascular diseases. It has also been associated with hypertension, obesity, metabolic syndrome. The experimental evidence is indeed there but the causality has not been conclusively established. The role of hyperuricemia in renal transplant setting is even more controversial and the evidence has been very inconsistent.

- **Uric acid metabolism**

Uric acid is the catabolic end-product of purines exclusively, which is metabolized by uricase enzyme to allantoin in majority of the mammals, except for humans and apes like chimpanzees and gorillas where this enzyme is absent. The beneficial effect of this is the proposed free radical scavenging effect of uric acid. But the downside of the absence of this enzyme is the much higher level of uric acid seen in us compared to other mammals which has led to gout and other complications.

Biochemical pathway of uric acid synthesis in humans:

The primary enzyme of this pathway is xanthine oxiadse

1. It catalyzes the conversion of hypoxanthine to xanthine & then xanthine to uric acid.

2. In humans this enzyme is present in liver and mucosa of small intestine

- **Renal handling of Uric Acid and pathogenesis of Hyperuricemia**

Uric acid is freely filtered at the glomerulus, which is followed by reabsorption of almost 99% in proximal tubule, followed by 50% being secreted in S2 segment and 40% reabsorbed in S3 segment. Hence it is almost completely reabsorbed in proximal tubules and only 10-15% is secreted in the tubules distally which amounts to 300-500mg per day.

Hence uric acid is primarily handled by the kidneys and a significant proportion is reabsorbed leading to a fractional excretion of only 10%.

Mechanism of uric acid transport in the kidneys:

The full mechanism is not elucidated but proximal tubule is the predominant site of urate secretion as well as re-absorption. The urate transport is bidirectional proceeding in a secretory as well as re-absorptive direction in proximal tubule. There are several urate transporters in the proximal tubule involved in this process. URAT1 is the most important anion exchanger involved in the re-absorption. It is expressed on the apical membrane of the proximal tubules. Similarly Glut9a, present on basolateral side plays an important role in uric acid reabsorption. BothURAT1 and Glut9a transport urate in exchange of multiple monovalent anions like chloride, lactate, or PZA in an electroneutral manner. The transporter proteins involved in urate secretion include ABCG2, MRP4, NPT1, and NPT4 located on luminal side of tubular cells, and OAT1 on the basolateral side.

An important factor determining the renal excretion of uric acid is contraction in extracellular fluid volume, leading to increased proximal urate re-absorption. This frequently is a case with use of diuretics. The lowering of fractional excretion of urate, along with an increase in sodium reabsorption, has also been observed in hypertension and in hyperinsulinemia.

Table 1. Causes of hyperuricemia

Primary hyperuricemia	
Overproduction	Idiopathic
	Glucose-6-phosphatase deficiency (Von Gierke's disease)
	HGPRT deficiency (Lesch-Nyhan syndrome)
Decreased excretion:	Idiopathic

Secondary hyperuricaemia
Excess production:

Increased turnover of nucleic acid	Myeloproliferative disorder
	Lymphoma, leukemia
	Multiple myeloma
	Cytotoxic therapy for malignancies
	Psoriasis
Reduced ATP metabolism	Alcohol
	Tissue ischemia
Reduced excretion:	
Decreased glomerular filtration	- Renal failure
Decreased secretion (due to competition for tubular secretion)	- Lactic acidosis – alcohol, exercise
	Ketoacidosis due to alcohol, diabetes, starvation
	- Drugs – low dose salicylate
Increased reabsorption	Hypovolemia, eg diuretics

- **Factors associated with hyperuricemia**

Renal dysfunction is an important factor causing hyperuricemia, where the decline in GFR decreases the total filtered amount of uric acid. The organic acids like lactate, β-hydroxybutyrate and acetoacetate, which inhibit secretion of urate also cause hyperuricemia. Another important proposed cause of hyperuricemia is high fructose intake which has also been associated with the epidemic of obesity and metabolic syndrome.

- **Potential pathophysiologic mechanisms in hyperuricemia**

There are two ways to explain the renal injury and other poor cardiovascular outcomes associated with hyperuricemia. Hyperuricemia can be an innocent bystander with other factors being responsible, which occur commonly with it, e.g. type 2diabetes, insulin resistance and metabolic syndrome. Epidemiological studies have shown that hyperuricemia is more commonly seen in individuals with hypertension, metabolic syndrome, diabetes, stroke, cardiovascular events. It can directly also lead to renal injury and various studies have shown that hyperuricemia is an independent risk factor for initiation of renal disease in individuals with normal renal functions as well as in progression of renal impairment in patients with CKD.[13,14,15,16]

Role of Fructose intake in hyperuricemia and its association with metabolic syndrome.

In the recent years prevalence of hyperuricemia has shown a rise which is parallel to the rise in obesity and metabolic syndrome. An analysis of the NHANES data showed a prevalence of hyperuricemia of 21.2% and 21.6% in men and women respectively. The study also showed a similar and related rise over the last 2 decades of obesity. [2,17,18]

The important link which has been proposed between hyperuricemia and obesity is high fructose intake. Fructose is a monosaccharide present in honey and various fruits. It also amounts to 50% of table sugar which is a disaccharide composed of two monosaccharides, glucose and a fructose. Fructose is also used in soft drinks, baked eatables, candies/sweets, jams and yogurts as a sweetener in form of high fructose corn syrup. Although overall sucrose

intake has declined, the intake of high fructose corn syrup in US has risen by almost 30% over the last 35 year which was also linked to a parallel rise in obesity, hyperuricemia and type 2 diabetes .[19,20,21,22]

The NHANHES third report supported this hypothesis that intake of sugar-sweetened beverages is associated with serum uric acid levels.[23] Similar epidemiological studies have shown higher fructose consumption to be associated with gout and kidney stones.[24]

Proposed mechanism of hyperuricemia, insulin resistance and metabolic syndrome in high fructose intake:

Fructose is rapidly phosphorylated in hepatocytes to fructose-1phosphate with ATP acting as the phosphate donor. During this process the ADP which is generated is further changed into AMP depleting phosphate donors rapidly. This causes activation of enzyme AMP deaminase which in turn causes increase uric acid formation.

Fructose-1-phosphate is further metabolized to glycerol-3-phosphate, which is important in the synthesis of triglycerides leading to its accumulation in skeletal muscle. The increase in intramyocyte triglyceride level is important factor in insulin resistance. This also explains the increase in metabolic syndrome and insulin resistance. Another factor is inhibition of carnitine palmitoyltransferase I, an important enzyme of fatty acid oxidation pathway in the myocytes. [25]The skeletal muscles are the most important site of insulin dependent glucose metabolism; hence it impairs a major mechanism of insulin dependent glucose metabolism. This has been verified in animal models and the elevation of intramyocyte triglyceride level is quite common in rats fed diet rich in uric acid.[26,27,28]

Figure 1.

Pathway of uric acid synthesis from fructose

Fructose		ATP

Fructokinase

Fructose -1Phosphate		ADP

	AMP

AMPdeaminase
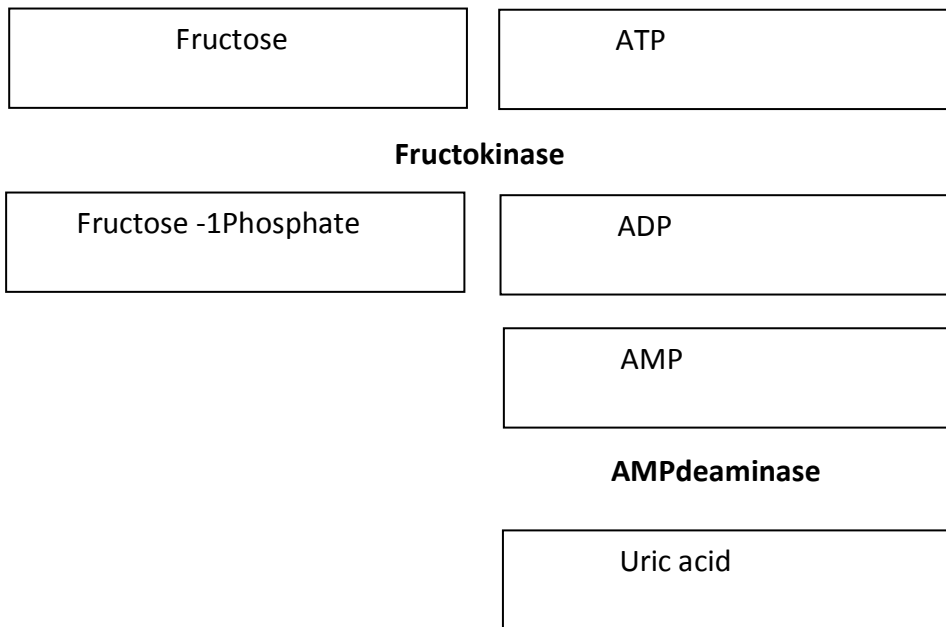
	Uric acid

Baron et al proposed a novel hypothesis linking higher fructose intake, uric acid elevation, and insulin resistance.[29] An important action of insulin is increase in blood flow to insulin sensitive tissues like skeletal muscle which promotes glucose utilization. This vasodilatory effect of insulin is mediated by endothelial nitric oxide synthase (eNOS).[30] In obese individuals this insulin mediated vasodilation is impaired which contributes to insulin resistance. As uric acid is a potent inhibitor of eNOS, hence a hyperuricemic state found in obese individuals may be involved in the pathogenesis of insulin resistance in them.

It's almost over 100 years ago that Osler advised diets low in fructose for prevention of gout. He wrote in 1893 that sugar to be reduced to a minimum and sweeter fruits not to be taken.[31] His astute observation indeed seems to be true in the light of the current knowledge.

Direct renal injury caused by hyperuricemia

The potential mechanisms behind it include inhibition of endothelial nitric oxide bioavailability, renin angiotensin system activation and direct actions on endothelial cells and vascular smooth muscle cells.

Animal models of hyperuricemia

In a rat model of hyperuricemia induced by feeding them oxonic acid (an inhibitor of uricase enzyme), Mazzali et al showed that hyperuricemic rats became hyperrtensive in 3 weeks, whereas control rats remained normotensive. They also noted that blood pressure could be reduced by treatment with either uricosuric agent (benziodarone) or a xanthine oxidase inhibitor (allopurinol) as well as oxonic acid withdrawal. The histological examination was normal by light microscopy whereas immunohistochemical stains showed ischemic damage with deposition of collagen and macrophage infiltration. These rats were also noted to have an increase in juxtaglomerular expression of renin with a reduction of neuronal NO synthase in macula densa and both the histopathological changes as well as hypertension were reduced with enalapril or L-arginine.[32]

In a similar study in rats made hyperuricemic by giving oxonic acid for 7weeks, the authors examined the renal biopsies. They compared hyperuricemic rats with control rats and there was a 30% increase in glomerular tuft area and it improved partially with use of enalapril.[33]

In a study by Kang et al in a 5/6 remnant kidney, the investigators examined the effect of hyperuricemia on renal disease progression, in rats fed oxonic acid for 6 wk with or without allopurinol or benziodarone.[34] They studied the renal function and histology at 6 wk. They observed that hyperuricemic rats had higher BP, more proteinuria along with poor renal function. These rats had more renal hypertrophy and glomerulosclerosis with interstitial fibrosis. These rats also showed thickening of preglomerular arteries along with proliferation smooth muscle cell. There was also evidence that rats on allopurinol and benziodarone had significantly less changes. Also the expression of COX-2 and renin also was increased in the preglomerular arterial vessels.

Proposed mechanisms of renal injury with hyperuricemia:

- Effect on endothelial cell

Hyperuricemia may cause endothelial dysfunction, which is supported by the evidence that lowering uric acid with allopurinol helps improving endothelial function, measured by brachial artery vasodilatation.[35] It has also been proposed as an inhibitor of NO production in endothelial cells by oxidants scavenging induced by NADPH oxidase under hyperuricemia[36] and reduced bioavailability of NO. It also prevents endothelial repair by impairing endothelial cell proliferation.[37]

Uric acid also acts as an antioxidant by scavenging hydroxyl free radicals, singlet oxygen species and peroxynitrite. It has been proposed to be acting as an antioxidant protecting us from aging consequences and malignancies.[38] It has been shown to improve endothelial function in

diabetic patients after acute administration of uric acid[39] and improves oxidant stress.[40] But there have been contradictory views also where it has been shown to increase the oxidant stress.[41]

- Effect on arteriolar disease and glomerular hemodynamic

Hyperuricemia also alters glomerular hemodynamics.[42] It caused cortical vasoconstriction in renal arterioles in a rat model. This led to a decline in glomerular plasma flow and ultrafiltration coefficient resulting in 35% decline in SNGFR along with rise in glomerular pressure and these changes were restored by allopurinol.

Hyperuricemia also led to auto-regulation impairment in kidneys which led to an increase in transmission of increased systemic pressure to glomeruli causing glomerular hypertension.[42] It may be because of diseased afferent arteriole in hyperuricemic rats and allopurinol led to improvement in the same, improving renal autoregulatory response. Uric acid has also been shown to have an effect on plasma renin activity with amelioration of hypertension in hyperuricemia models with ACE inhibitors. [43, 34]

- **Hyperuricemia and hypertension**

Table 2. Susceptibility factors for renal disease in hypertension.

Factors favouring increased risk for progression of renal disease in patients with essential hypertension	Severe hypertension (systolic BP 170 mmHg)
	African Americans*
	Hyperuricemia
	Obesity / Metabolic syndrome*
	Use of diuretics *
	Decreased nephron endowment

*Among these the African Americans, diuretic use, obesity and metabolic syndrome are associated with hyperuricemia

Natural history studies before the era of effective of antihypertensive treatment noted that 35 to 65% of patients with essential hypertension developed proteinuria, with one third patients developing renal insufficiency and 6 to 10% dying of end stage kidney disease. [1,44]

The classic pathological findings consisted of medial hypertrophy of interlobular and arcuate arteries later progressing into medial fibrosis with neointimal hyperplasia. Afferent arterioles

also showed thickening with hyalinosis, with subendothelial deposition of homogenous eosinophilic material. These findings suggested a significant injury into the vascular compartment of the kidneys. [45,46]

These findings put new light on the effect of various risk factors. Based on these data hypertension has been divided into 2 phases.[47]

The initial phase is reversible whereas in the second phase the structural changes begin to start and then progress, leading to more and more kidney damage and other vascular changes.

1. The first phase in hypertension is initiated primarily by extrarenal stimuli, which cause induction of renal vasoconstriction. These stimuli include hyperuricemia, angiotensin II, catecholamines, and dysfunction of endothelium impairing release of nitric oxide or drugs like cyclosporine. During this phase, the vascular structure in the kidneys are normal, but there is diffuse arteriolar vasoconstriction, leading to decline in renal plasma flow causing renal ischemia, tubular injury and interstitial inflammation [35,43 ,48,49]

2. In the second phase, there is renal cortical vasoconstriction that is irreversible despite removal of the original stimuli.[50] It is associated with structural changes in the kidney which are arteriolosclerotic changes of the afferent arteriole along with interstitial inflammation. The importance of these changes have been delineated in animal models were both arteriolar and interstitial findings have been shown to have a key role in the hemodynamic response. The

inflammation (characterized by presence of monocyte/macrophages & T cells) plays a role by generating oxidants and angiotensin II, whereas structural changes in arteriole help in maintaining renal ischemia that incites this inflammatory reaction.

The vasoconstriction is associated with decline in ultra filtration coefficient, cortical plasma flow and single-nephron GFR.[43,51] But the GFR is decreased minimally because of the adaptation in juxtamedullary nephron.

Animal models have indeed shown that hyperuricemia induces systemic hypertension and kidney injury by causing renal vasoconstriction mediated by endothelial dysfunction and renin-angiotensin system activation. Over time, these models develop afferent arteriolar lesions, glomerular hypertension and hypertrophy, albuminuria, and finally glomerulosclerosis. [35, 43,52]

- **Epidemiological evidence**

Garrod and Frederick described the relation of gout with uric acid and hypertension in early 19th century. In a cross-sectional study of patients with gout, Keenan et al observed multiple co morbidities in these patients. The majority of patients had features of metabolic syndrome, with 90% being hypertensive, more than 60% having hyperlipidemia and many suffering from chronic kidney disease, diabetes, and ischemic heart disease.[53] There have been multiple epidemiological studies to determine whether uric acid is a risk factor for cardiovascular diseases with contradictory result.[3,5] Hence most authors have concluded uric acid as just a

marker rather than a risk factor for cardiovascular disease. Both JNC 7 and KDOQI guidelines for chronic kidney disease have not included uric acid as a major risk factor.

In recent studies role of uric acid in renal disease has been investigated in recent studies and has been supported as an independent risk factor for kidney disease in general population and for progression of renal diseases in those with established chronic renal disease and diabetes.[54] Also in a recent study in nontransplant population with an eGFR <60ml where the investigators randomized patients between allopurinol and conservative therapy found that allopurinol slowed renal progression.[55] These findings do not conclusively prove that uric acid is a risk factor but it may help in improving the renal functions with kidney disease.

Hyperuricemia has also been proposed as one of the components of metabolic syndrome[56,57] and as the prevalence of metabolic syndrome has increased, so is that of hyperuricemia. A recent study from United States using NHANES data showed a prevalence of hyperuricemia of 21.2% and 21.6% in men and women respectively. It also showed that prevalence may have increased over the last 2 decades, which may be related to rising rates of obesity and hypertension. [2]

Hyperuricemia is rising even in developing countries. As the percapita income has increased and dietary habits are changing, the estimates from developing world also show a prevalence between 10-21%.[7,8]

Hyperuricemia has been seen more commonly seen in individuals with hypertension, Dyslipidemia, obesity, metabolic syndrome, diabetes, alcoholism, renal dysfunction and who

are on drugs like diuretics, pyrazinamide etc. A significant number of these conditions are very commonly seen in renal transplant recipients. It makes quite logical that hyperuricemia would be seen very often in post transplant recipients. The prevalence of hyperuricemia with cyclosporine based regimens was 80% which declined significantly with the current practice of low dose of tacrolimus.[3] The data from Symphony trial shows the prevalence of hyperuricemia at 19-55%.[4]

- **Role of hyperuricemia in graft and patient survival**

Table 3. Role of immunosuppression in hyperuricemia

Immunosuppression	Serum Uric acid
Cyclosporin A	Increases
Steroid	Controversial
Azathioprine	No role (but requires dose modification if allopurinol is used)
Mycophenolate	No effect
Sirolimus	No role

- **Effect of immunosuppression on uric acid renal handling and metabolism**

    1. CsA :

        a. Increased net tubular urate reabsorption[58]

b. Decreased glomerular filtration rate[59]

c. Reduction in filtered load of uric acid.[60]

2. Steroid :

 a. Increased risk for insulin resistance and metabolic syndrome with well known association of metabolic syndrome and hyperuriccemia

 b. No direct effect on uric acid metabolism

 c. Controversial as effect confounded by other immunosuppressives.

 d. No studies of hyperuricemia from steroid free protocols

3. Tacrolimus

 a. It has similar properties as cyclosporine

 b. The prevalence in tacrolimus-based regimens is less than that seen in studies with cyclosporine based regimens.[61]

4. Azathiprine and Mycophenolate – No effect

5. Sirolimus –

 a. No effect on uric acid renal handling and metabolism

 b. Studies with mTOR inhibitors based regimens in cyclosporine-free regimens had lower rates of hyperuricemia

- **Evidence of hyperuricemia role in graft and patient survival**

Hyperuricemia is common in post-renal transplant setting. The role of hyperuricemia in renal allograft outcome has been very contrdictory and is based mainly on small and retrospective studies. The results have been inconsistent and there are no randomized trials of lowering of hyperuricemia showing benefit in graft outcome.

The hypothesis of all the studies have been based on the experimental evidence that hyperuricemia plays an important role in the pathogenesis of cardiovascular and renal disease by causing endothelial dysfunction by reducing nitric oxide and increasing smooth muscle proliferation. But whether uric acid is directly involved in the progression of renal worsening or it is just a marker of poor graft function is still an open question. The initial studies have mainly suggested it as a marker of poor graft function.

 The data from the study by Gores et al in 1980 which analyzed patients on CsA with asymptomatic hyperuricemia showed no difference between hyperuricemic vs. normouricaemic patients in terms of graft outcome.[62] They also showed a very low prevalence of gout in this cohort and suggested that asymptomatic hyperuricemia needs no treatment. In a recent study by Akgul et al in where they studied graft outcome at 3yr along with biopsy proven chronic allograft nephropathy and compared it with hyperuricemia at 3months.[63] They found no relation between hyperuricemia at 3months with chronic allograft nephropathy and graft outcome at 3years but the prevalence of hyperuricemia increased over time. A recent study which analyzed the data from Symphony trial by Meier-Kriesche et al also showed a similar result.[9] The authors studied 3-year follow-up data from Symphony trial and compared uric acid level at 1month with graft survival at 3 years. The predictor of elevated uric acid levels were

obesity, poor baseline graft function, initial randomization to Cyclosporin-A and deceased donor allograft. In a multivariate analysis they found that poor graft outcome at 3years, when adjusted for poor baseline graft function had no association with higher uric acid level.

Compared to these findings some studies have shown entirely contrasting results. In a study by Gerhardt *et al.*, the investigators retrospectively analyzed the data of 350 kidney transplant patients. They found a significantly reduced graft survival in patients with elevated uric acid levels at 2, 4, and 5years post-transplant (92.2, 70.6, and 68.8% vs. 98.1, 85.6, and 83.3%) compared to recipients with normal uric acid levels. There was a significant association of uric acid levels with diuretic therapy and gender. They concluded that graft survival at 5yrs post-transplantation was worse in hyperuricemic compared to normouricemic patients but they were unable to find any association of allopurinol therapy with graft outcome.[64] Armstrong et al compared uric acid levels with estimated GFR at 2years and showed a significant association of uric acid levels with hypertension and graft function at 2years. [65] The investigators retrospectively analyzed data of 90 RTR with a median duration of follow-up of 7 years. The prevalence of hyperuricemia was 70% at baseline which increased to 80% after 2.2 years. UA levels were higher in patients who were taking ≥3 antihypertensive medications. The other predictors were prednisolone dose, estimated GFR and beta-blocker therapy. But the study had a very small sample size and a short period of follow-up. The investigators also measured the cyclosporine levels during this study. There was no association between uric acid and drug levels.

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Similarly in a retrospective study, Haririan et al evaluated the predictive value of mean uric acid in the initial 6 months after transplant for graft function and survival. They recruited 212 live donor renal allograft recipients. The majority of patients were on tacrolimus and mycophenolate. The mean follow-up period was around 7years. They found that uric acid level and hyperuricemia were associated with graft loss independent of other variables. The risk of death also was more but did not achieve significance. The hyperuricemic patients were had a lower estimated GFR and graft loss also was 20% higher.[66]

In another important retrospective study from Seoul by Min et al the authors analyzed the outcome of 281 renal transplant recipients. [67] They defined hyperuricaemia as early onset when it occurred within 1 year of transplant and late onset as after 1year and moderate to severe hyperuricemia as ≥8mg/dl. On multivariate analysis only early-onset moderate-to-severe hyperuricaemia was associated with chronic allograft nephropathy (P = 0.035) and poor graft survival (P = 0.026). The effect of moderate-to-severe hyperuricemia on graft survival was time dependent. The predictive value of moderate to severe hyperuricemia was seen even in recipients with preserved graft function (> 60 ml/min) at 1 year where it was found to be a marker of long-term graft dysfunction and failure. They also showed that early onset moderate to severe hyperuricemia was an independent risk factor for chronic allograft nephropathy. There was a dose response relationship with higher uric acid levels having poor graft function. Bandukwala et al in a retrospective study analyzed the association of hyperuricemia with inflammation, graft dysfunction, and cardiovascular events in 405 renal transplant recipients with stable renal function.[68]They included 405 stable renal allograft recipients who had ≥3 uric

acid and CRP measurement to determine the association of uric acid with CRP, rate of decline in the estimated glomerular filtration rate and cardiovascular events. They noted a prevalence of hyperuricemia of 44%. Hyperuricemia showed a negative association with estimated GFR and positive association with diuretic use, transplant vintage, and triglycerides. But the association of uric acid with CRP was rendered insignificant after adjustment for estimated GFR. The rate of decline in graft function was significantly higher in hyperuricemic recipients (p 0.003). Also there was a higher incidence of cardiovascular events in hyperuricemic recipients compared to recipients whose uric acid levels were normal (17 vs. 4, p = 0.001). Overall hyperuricemia was an independent predictor of lower eGFR and higher triglyceride level and higher cardiovascular morbidity.

Recently in a meta-analysis by Huang et al in 2012 where they included twelve studies, they found that the renal transplant recipients with hyperuricemia had a lower estimated GFR (P, 0.0001, 95%CI 6.34-6.14) and higher SCr (p 0.00001, 95%CI 0.17-0.31) compared to recipients with normal uric acid levels. The meta-analysis also noted that hyperuricemia was a risk factor of chronic allograft nephropathy (OR = 2.85, 95%CI 1.84-4.38) and loss of graft (OR = 2.29, 95%CI 1.55-3.39).[69] The results of this meta-analysis was important as it involved multiple studies which included patients from Asia, Mediterranean, Europe and North America making it representative of various races. The second aspect was that the effect on renal function of uric acid levels was consistent even after adjusting for other confounding variables

Also to establish causality the other important evidence is improvement in graft function with uric acid lowering drug. There are no randomized trials but which have tested this hypothesis there are 2 nonrandomized trials which reported the effect of uric acid lowering therapy on renal allograft recipients. In a study by Flury et al published in 1977, the authors compared the effects of allopurinol vs. benzbromarone for uric acid lowering after kidney transplantation. They enrolled 17 renal allograft recipients with hyperuricemia who were treated with either allopurinol or benzbromarone. Both drugs reduced uric acid levels effectively. With allopurinol, the adverse reactions were increased azathioprine mediated bone marrow toxicity whereas in benzbromarone group no interactions were observed. The investigators did not observe any difference in the graft function. Hence they concluded that hypouricemic drugs were safe and effective but without an effect on graft function.[70] A similar study by Navascues et al showed that allopurinol use for uric acid lowering was safe in renal transplant recipients but similarly there was no difference in graft function[71] as the serum creatinine did not show a significant change after treatment (2.35±0.92 mg/dl vs. 2.39±1.03 mg/dl).

There was a recent small randomized controlled trial[72] although in nontransplant patients where the investigators randomized 54 patients to allopurinol or the continuation of usual therapy for 1year. The serum creatinine level in the treatment arm was less but it did not reach a statistical significance (P = 0.08). Overall, After 12 months of treatment 16% in the treatment arm reached the combined end points of >40% deterioration in renal function and dialysis dependence vs. 46.1% in the control group. Although the limitation of this study was that it was a very small study.

Management of hyperuricemia in post renal allograft recipients

- There are no recommendations, but mainly suggestions

- KDIGO working group[74] –

  1. To achieve weight loss

  2. To decrease meat and alcohol consumption

  3. To avoid diuretics

  4. Losartan is associated with 8% reduction in uric acid concentrations which is not a class effect. Can be substituted if any ARB/ACEi is indicated

  5. Asymptomatic hyperuricemia treatment is not advised

  6. Allopurinol is commonly used as a hypouricemic drug.

  7. If used together along with azathioprine can cause severe life threatening bone marrow suppression. It requires a 50% reduction of azathioprine dose

- American Society of Transplantation[73]

  1. Measure uric acid every 2–3 months

  2. More frequent screening is needed in recipients with impaired graft function   and especially those who are on diuretics.

- Caring for Australasians with Renal Impairment guidelines for patients with CKD [74]

  1. Treatment of hyperuricemia does not reduce progression of kidney disease and is not recommended.

- European Best Practice guideline[75]

    1. The combination of allopurinol and azathioprine is to be avoided.

Hence the conclusion can be drawn that there is enough experimental evidence for uric acid being a major risk factor for renal diseases but there is limited evidence from the trials, mainly from cross-sectional studies and there are even fewer randomized trials on benefit of treating hyperuricemia.

So the jury is still out despite the experimental evidence, whether uric acid is just a marker of poor graft function or is it directly involved in the decline of graft function.

Primary objective

- To assess the prevalence of hyperuricemia in renal allograft recipients.

- To look for the clinical and biochemical predictors of hyperuricemia in renal allograft

  recipients.

Secondary objective

- To look for the association between graft function and hyperuricemia

STUDY DESIGN:

- Retrospective observational study.

SAMPLE SIZE:

- Study was conducted on 284 consecutive recipients of renal allograft who underwent the transplant between 2008 July and 2011 June in the department of nephrology in Christian medical college, Vellore.

INCLUSION CRITERIA

- Consecutive patients who underwent renal transplant between 2007 january and 2011 June

EXCLUSION CRITERIA

Patients who did not have follow-up of at least 6months.

METHODS

- Patients were studied till the last follow-up of June 2012 or till graft loss or death whichever was earliest.

- Observation was recorded at each month till 6months post transplant and then at 12 and 18th month. Thereafter it was recorded annually.

- A detailed proforma was filled to document

  1. Demographics details including the age, height, weight and sex of the patient

  2. Clinical history including the native kidney disease along

  3. Biochemical parameters were also noted which included

     a. serum level of creatinine and lipid profile which is done monthly.

  4. Uric acid was recorded at the time of diagnosis of hyperuricemia.

  5. Treatment details especially the induction therapy, maintenance immunosuppression and antirejection therapy were noted.

  6. Presence of CMV disease and viremia also noted

  7. Estimated GFR was calculated at each visit using abbr. MDRD equation

  8. The donor details including the age, sex and weight were also included.

- The data was collected from the transplant charts and hospital electronic data   base.

DEFINITIONS

Hyperuricemia[76]

Defined by working group of KDIGO taskforce for care of kidney transplant recipients as

1. women >0.36 mmol/L (6.0 mg/dL)

2. men >0.42 mmol/L (7.0 mg/dL)

Dyslipidemiia –

ATPIII guideline[77]

1. LDL cholesterol <100mg/dl

2. Triglyceride < 150mg/dl

3. HDL cholesterol (in men) < 40mg/dl

4. HDL cholesterol (in women) <50mg/dl

NODAT

As defined by International consensus guidelines (published in 2003)[78,79]

HbA1c (glycated hemoglobin) should not be used before 3 months after transplant

Standard WHO and ADA criteria for diabetes mellitus diagnosis

1. Symptoms of diabetes (polyuria, polydipsia, and unexplained weight loss) + random

   plasma glucose ≥200 mg/dL (11.1 mmol/L)

2. Fasting (at least eight hours) plasma glucose ≥126 mg/dL (7.0 mmol/L)

3. 2 hour plasma glucose ≥200 mg/dL (11.1 mmol/L) upon oral glucose tolerance test

   (glucose load equivalent to 75 g anhydrous glucose in water)

- Hypertension[64]

- Defined by working group of KDIGO taskforce for care of kidney transplant recipients as

1. 140 mm Hg and/or diastolic blood pressure ≥90 mm Hg

2. History of use of antihypertensives

- Abbr. MDRD equation[80] –

  4 parameter equation (demographic variables only)

  estimated GFR (ml/min/1.73m$^{2)}$ = 175*(serum creatinine in mg/dL)$^{-1.154}$*[Age in years]$^{-0.203}$*

  [0.742 if patient is female] * [1.212 if patient an African American]

STATISTICAL METHODS

- Statistical analyses were performed using SPSS software.

- For continuous variables data was expressed as means ± standard deviations and for discrete variables as frequencies (percentages).

- Means were compared using Student's t-test, independent t-test for continuous variables.

- Non-continuous variables were compared by using chi square and Fisher's exact Test.

- Error bar plot was plotted for triglycerides, nadir eGFR and at eGFR 1month for showing the distribution of these variables in patients.

We recruited 284 patients who underwent live related or deceased donor renal transplantation in our institution from June 2008 to June 2011 and who satisfied our inclusion and exclusion criteria. Baseline characteristics have been summarized in the following table.

Table 4. Demographic characteristics

Demographic characteristics	
Recipient (Male:Female)	2:1
Recipient Age (in years) (mean±SD)	36.7±11.97
Donor (Male:Female)	1:2
Donor Age (in years) (mean±SD)	41.08±11.6

Demographic parameters

Ours was relatively a younger cohort with a mean age of the patients being 36.7±12.0 years with a range of 7-63 years. Recipient group was skewed towards males with more number of males getting a renal transplant with male to female ratio of 2:1. Most of the donors were female with a male to female donor ratio of 1:2. The mean (±SD) donor age was 41.08±11.6 years.

Baseline parameters

Among the recipients diabetes was quite common with the prevalence of diabetes pretransplant being 34.5% (98recipients). Hypertension was also very common with 71.5% (203 patients) being hypertensive pre-transplant. Majority of the patients were on hemodialysis prior to undergoing transplant (89.4%). Only 5patients were on peritoneal dialysis and 25 (8.8%) patients had a preemptive renal transplant. The mean duration of dialysis was 7.6months.

Table 5. Baseline parameters

Baseline parameters	
Live related donors % (n)	90.5%(256)
Deceased donors % (n)	9.5%(28)
Pre-transplant Hypertension % (n)	71.5%(203)
Pre-transplant Diabetes % (n)	34.5%(98)
BMI(Body Mass Index) kg/m^2	20.8±3.4
Preemptive renal transplantation% (n)	8.8%(25)
Mean duration of dialysis (months)	7.6±8.06

Native kidney disease:

The underlying chronic kidney disease was unknown in the majority of the patients with 55.6% patients in this group. The other most important cause of chronic kidney disease was diabetic nephropathy. 20.4% patients had diabetic nephropathy. Patients with focal segmental

glomerulosclerosis and other chronic glomerulonephritis constituted 5.6% and 11.6% respectively. There were 5 patients in this cohort who had autosomal dominant polycystic kidney disease (1.8%). 5% patients had obstructive uropathy as the native kidney disease.

. **Figure 2. Native kidney disease**
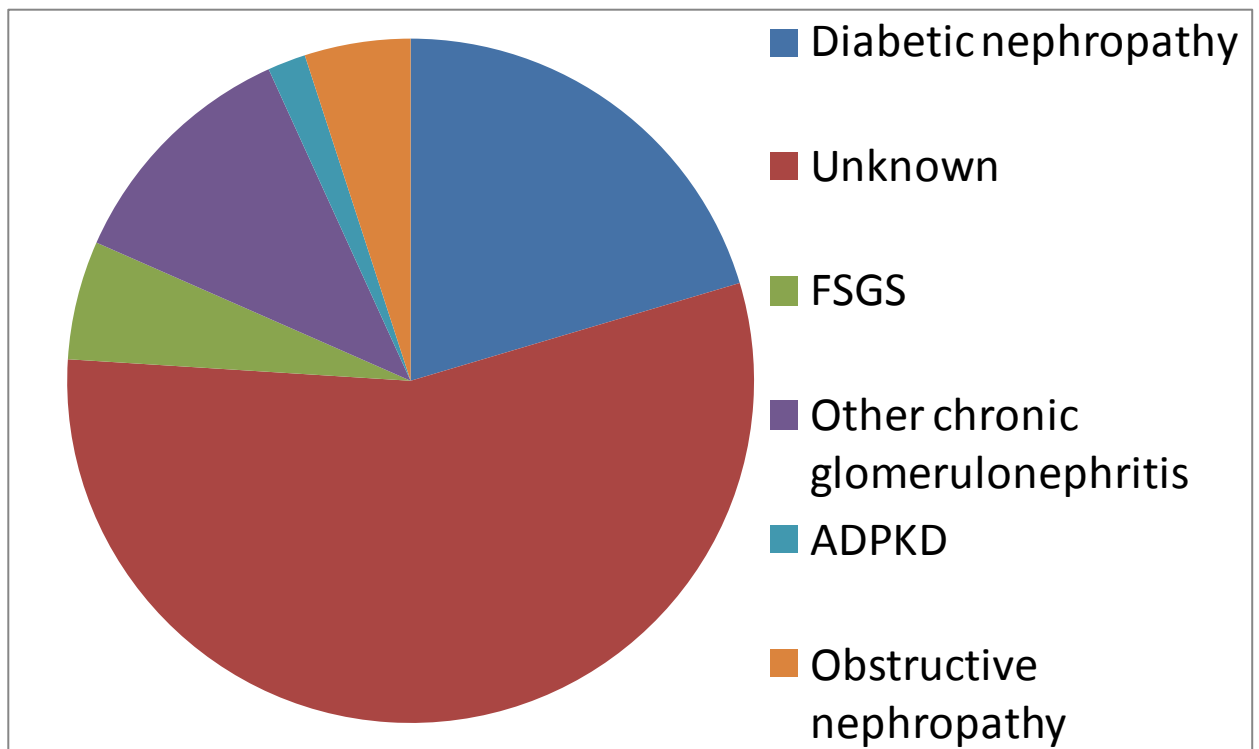
- **Transplant details**

The majority of the patients received an allograft from a live related donor. Out of 284 patients there were 256 (90.5%) live related renal transplantation and 28(9.5%) received a deceased donor kidney.

Immunosuppression

Most of the patients received induction prior to the transplant. Out of 283 patients 246 (86.9%) patients received induction. The most common induction regimen was Basiliximab (2 doses were given on day 0 and 4), which was given to 73.1% patients. 39(13.8%) patients received antithymoglobulin as induction agent whereas 37(13.1%) patients underwent transplant without induction. Post transplant 11patients (3.9%) had delayed graft function, requiring hemodialysis. Overall in the immediate post-transplant period, the nadir estimated GFR (mean±SD) was 79.2ml/min±30.2 and time period after which they achieved it was 9.2 ±9.4 days.

Table 6. Induction Regimen

	n(%)
Basiliximab	207(73.1%)
Antithymocyte globulin	39(13.8%)
No induction	37(13.1%)

Table 7. Maintenance immunosuppression

	n(%)
Mycophenolate	267(94)
Tacrolimus	258(90.8)
Cyclosporin-A	15(5.3)

	n(%)
Azathioprine	11(3.9)

The predominant immunosuppression used in our cohort was triple immunosuppression which included Mycophenolate, Tacrolimus and steroid. 94% patients were on mycophenolate and 90.8% patients were on Tacrolimus. Cyclosporin-A was given to only 15 patients (5.3%) and Azathioprine to11 patients (3.9%).

Table 8. Post transplant complications

	n(%)
Graft loss	9
Death	11
Dyslipidemia	120(42.1)
NODAT	64(22.8%)

Post transplant complications:

The mean (±SD) duration of follow-up was 27.1±13 months. During the follow-up period 9 patients had graft loss and 11 patients died, out of which 7 died with a functioning graft. There were 120 patients (42.1%) who had dyslipidemia post transplant period and 64 patients (22.8%) developed NODAT. Also 67(23.6%) patients had biopsy proven acute rejection.
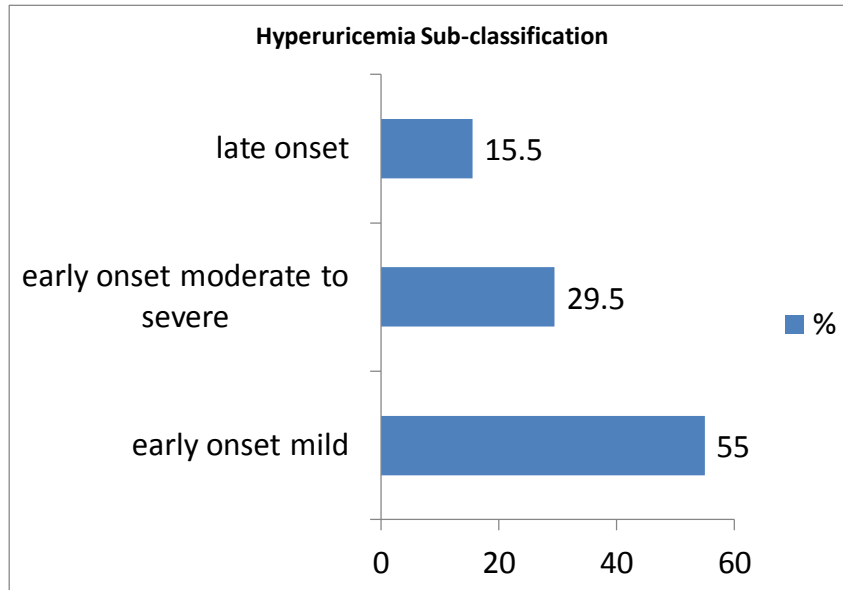
Hyperuricemia

Post transplant 85(26.8%) patients had hyperuricemia. The mean time to onset of hyperuricemia was 6mths. Majority of the patients had early onset hyperuricemia (<12 months) with only 11% patients having onset of hyperuricemia after 12months. The mean uric acid level in patients who had hyperuricemia was 7.8±0.96mg/dl. Among the patients who had hyperuricemia, around one third (29.5%) had moderate to severe hyperuricemia (>8mg/dl). We subdivided the hyperuricemic recipients on the basis of time of onset and severity. There were no differences in the baseline variables between early and late onset hyperuricemia

Table 9. Distribution of baseline parameters between early and late onset hyperuricemia

	Early onset hyperuricemia	Late onset hyperuricemia	p value
Age (year)	36.9	34.0	0.44
BMI (kg/m$^{2)}$	21.2	22.0	0.60
Dur^{n} of dialysis pre-transplant (month)	8.1	8.4	0.93
Donor age	39.3	46.0	0.08
Pre-transplant DM	37.9	36.4	0.8

Figure 3. Hyperuricemia Sub-classification

Association of hyperuricemia with baseline parameters

The baseline demographic variables were similar among the hyperuricemic and normouricemic recipients. These included age (36.7±11.6 vs 36.6±12.2, p value 0.93), donor age (40.9±11.9 vs. 41.1±11.5, p value 0.93), recipient sex and donor sex.

The duration of dialysis prior to transplant was (7.5±0.9 months vs. 8.3±0.6 months, p value 0.98) was also similar among the two groups. The number of patients who had pre-transplant

39

hypertension (78.3% vs. 78.1%, p value 0.9) or diabetes (38.7 vs. 32.2, p value 32.2) was also similar in both recipients with elevated uric acid levels and in those with normal levels. Among the baseline parameters only the BMI (body mass index) was significantly higher (21.8±4.7 vs. 20.4±2.9, p value 0.98) in the hyperuricemic recipients.

Among the immunosuppressive drugs there was no significant difference in terms of treatment with mycophenolate, tacrolimus and azathioprine in hyperuricemic and normouricemic patients. But the proportion of patients using cyclosporine-A was significantly more common in hyperuricemic patients (10.7% and 3.4%, p value 0.031).

Table 10. Association of hyperuricemia with baseline parameters

|	Hyperuricemia	Normouricemia	p value
Recipient Age(yr)	36.7±11.6	36.6±12.2	0.93
Recipient BMI (kg/m^2) (at transplant)	21.8±4.7	20.4±2.9	0.024
Donor Age (yr)	40.9±11.9	41.1±11.5	0.892
Pre-transplant diabetes	38.7	32.2	0.321
Pre-transplant hypertension (%)	78.3	78.1	0.9
Duration of dialysis	7.5±0.9	8.3±0.6	0.98

(months)pre-transplant			

Association of hyperuricemia with graft function

The proportion of patients who had delayed graft function after transplant among hyperuricemic was higher compared to the normouricemic recipients but it did not achieve statistical significance (4.1% vs. 1.5%, p value 0.19). The hyperuricemic recipients had a significantly lower nadir estimated GFR (73.0±27.5ml/min vs. 81.9±30.9ml/min, p value 0.03) and estimated GFR at 1month (68.5±21.0ml/min vs. 74.5±20.6ml/min, p value 0.04). The estimated GFR at all other time intervals did not show any significant association with hyperuricemia. We also calculated the estimated GFR decline weighted for the time of follow-up (nadir eGFR – eGFR at last visit /duration of follow-up in months). This also was similar between the groups.

During the follow-up period 9 patients lost their graft. The number of patients (6.8%) who lost their graft in the hyperuricemic group was higher compared to patients whose uric acid levels were normal (2%) but it was not statistically significant (p value 0.059). There was also no significant difference in terms of induction and acute rejection among the 2 groups.

The incidence of NODAT was significantly higher in patients with hyperuricemia (50.7%, vs. 12.7%, p value 0.00). The prevalence of dyslipidemia was higher but it did not achieve statistical significance (52% vs. 39.2%, p value 0.058). The level of serum triglyceride was higher in the patients with hyperuricemia (150.2±67.5mg/dl vs. 131.9±39.5mg/dl, p value 0.037). The levels of serum LDL cholesterol (93.9±25.3mg/dl vs. 96.0±31.0mg/dl, p value 0.583) and HDL

cholesterol (47.2±12.5mg/dl vs. 48.7±9.7mg/dl, p value 0.34) were similar. Also the incidence of

CMV disease post transplant was similar in 2 groups.
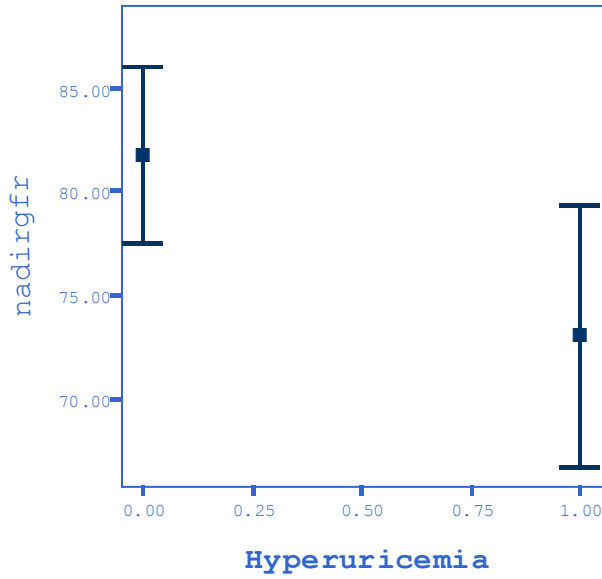
Figure 4. Error bar plot between hyperuricemia and nadir eGFR
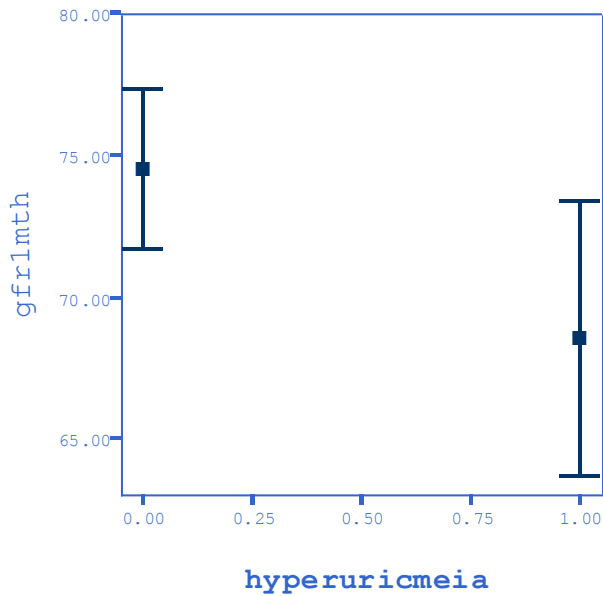
Figure 5. Error bar plot between hyperuricemia and eGFR at 1mth

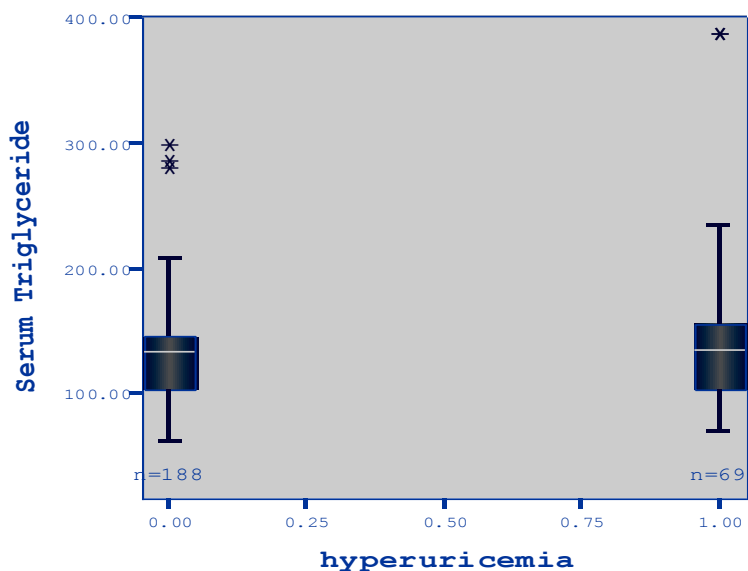**Figure 6. Error bar plot between hyperuricemia and triglycerrides**

Table 11. Association of hyperuricemia with NODAT and dyslipidemia

	Hyperuricemia	Normouricemia	pvalue
NODAT	50.7%	12.7%	0.00
Dyslipidemia	52%	39.2%	0.058
Serum Triglyceride	150.2±67.5mg	131.9±39.5	0.037
Serum LDL	93.9±25.3	96.0±31.0	0.58
Serum HDL	47.2±12.5	48.7±9.7	0.34

DISCUSSION

We undertook a retrospective longitudinal study in the Department of nephrology, Christian medical college, Vellore to determine the factors influencing the occurrence of hyperuricemia in the patients undergoing renal transplantation in our department. We recruited 284 patients in the study who underwent either a live related or a deceased donor renal transplantation between the period of 2008, July to 2011 June. Our study population was skewed towards males. The male to female ratio in our cohort was approximately 2:1. Our study population mainly comprised of young adults to middle age group individuals with people in the group between 20-50 years comprising of almost 80% of the total recipients. The mean age of the recipients was 36.7±12.0 years. The mean BMI of our patient was 20.8kg/m^2 with one fourth of the patients being underweight and with only 10% being overweight. Prior to transplant 71.5% patients had hypertension and 34.5% patients had diabetes. Ours was predominantly a live related renal transplant recipient population (90.5%). Among the live related renal recipients majority of the donors were females with the male to female ratio of 1:2. The mean donor age was 41.08±11.6 years. There was a gender bias, which is expected as other studies have also shown a similar trend. A retrospective study from PGI Chandigarh showed that among a cohort of 682 patients, 90% were males and among the donors 66% were females which is similar to our study.[81]

The most common native kidney disease was of unknown etiology which constituted 55.6% of the population followed by diabetic nephropathy (20.4%). Other etiologies were obstructive

uropathy (5.0%), focal segmental glomerulosclerosis (5.6%), other chronic glomerulonephritis (11.6%) and ADPKD (1.8%). Only 9% patients underwent a preemptive renal transplantation, with majority being on dialysis with a mean duration of dialysis of 7.6months. Majority of the patients received an induction therapy prior to transplant with the maintenance immunosuppression being tacrolimus and mycophenolate based triple regimen.

Post transplant the prevalence of dyslipidemia and NODAT were 42% and 22% respectively. Other studies also have shown a similar incidence of NODAT and dyslipidemia depending on the duration of follow-up and other risk factors. In a prospective study from Spain[82] with a similar Tacrolimus based maintenance immunosuppression regimen, they showed an incidence of NODAT of 20% at 1year where as in another study where the investigators did an OGTT (oral glucose tolerance test) at 10 weeks found the incidence of NODAT to be 14%.[83] Graft loss and death were uncommon event (9 and 11 respectively) but the mean duration of follow-up was less (27 months). Among the patients who died, 7 died with a functioning graft.

Hyperuricemia

The prevalence of hyperuricemia in our study was 26.8%. This is similar to studies which have been based on a similar maintenance immunosuppression. The ELITE – Symphony study also showed a similar prevalence of hyperuricemia ranging from 19-55%.There was no association between hyperuricemia and donor age, sex, deceased donor allograft, delayed graft function, pre-transplant diabetes or hypertension. Among the baseline variables only BMI at transplant had a significant association with hyperuricemia. We also could not find any association of

hyperuricemia with type of induction, maintenance immunosuppression and acute rejection except for the use of cyclosporine. But the number of patients on cyclosporine was very small. This was in contrast to the results of Min et al where they found that age and BMI at time of transplant, gender, history of hypertension and diabetes prior to transplant, deceased donor allograft, duration of dialysis were significantly associated with hyperuricemia. But other studies have shown similar results as our study. In a study by Akalin et al,[84] the investigators could not find any association with recipient age, BMI and donor gender. The predictors of hyperuricemia in this study were male gender (63.9% and 49.7%, p0.012), deceased donor allograft (54.2% and 33.1%, p 0.001), older donor age (41.8yr and 38.yr, p 0.014) and use of cyclosporine as maintenance immunosuppression. But similar to our study the incidence of acute rejection episodes was not higher in hyperuricemic recipients.   Hence the results have been contradictory.

We also found that the incidence of NODAT was higher in patients with hyperuricemia compared to those whose uric acid levels were normal (12.7% vs. 50.7%, p value 0.00). Although dyslipidemia was not significantly associated with hyperuricemia but the mean level of serum triglyceride was higher in the patients with hyperuricemia (150.2±67.5mg/dl vs. 131.9±39.5mg/dl, p value 0.037). These results were similar to previous studies. The study by Akalin et al[84] also showed a higher incidence of NODAT in patients with hyperuricemia (14.1% vs. 7.6%, p value 0.07) although it did not reach statistical significance. Similarly the study by Bandukwala et al[68] found a significantly higher triglyceride levels in patients with elevated levels of uric acid (140±80mg/dl vs. 157±80, p value 0.02). As the diabetes, obesity, hyperuricemia are

all components of metabolic syndrome so it was expected. Although in the available literature there is a paucity of data on association of NODAT with hyperuricemia and also the risk factors of NODAT in transplant are different than in non-transplant setting.[85,86]

In a recent study by Min et al[67] they proposed that the early onset moderate to severe hyperuricemia is more strongly associated with graft dysfunction. So we also separately analyzed the data for patients with early onset moderate to severe hyperuricemia. Majority of patients had an early onset hyperuricemia (89%) which was similar to the study by Min et al[67] where the authors found that 3/4th of the patients had early onset hyperuricemia. The baseline variables in our study were similarly distributed between the early and late onset hyperuricemia groups.

Association of hyperuricemia with graft function

The incidence of delayed graft function was statistically not different (4.1% vs. 1.9%, p value 0.19). We also found that hyperuricemic patients had a lower nadir estimated GFR (73.0±27.5ml/min vs 81.9±30.9ml/min, p value 0.033) and estimated GFR at 1month (68.5±21.0ml/min vs 74.5±20.6ml/min, p value 0.034) post transplant compared to the patients with normal uric acid levels. But there was no difference in the graft function at subsequent time interval during the follow up. We also estimated the rate of decline in estimated GFR per month in recipients with hyperuricemia and that too was similar as in those with normal levels. This was similar to the study by Meier-Kriesche et al[10] in which they showed that hyperuricemia correlated well with baseline estimated GFR but upon multivariate analysis there was no correlation with GFR at 3years. We also analyzed the association of early onset moderate to

severe hyperuricemia with graft function. The estimated GFR at 1 yr post-transplant was lower in patients with early onset moderate to severe hyperuricemia (65.2±18.8 vs. 78.2±19.4, p value 0.014) although it did not have any association with nadir estimated GFR and GFR at 1 month post-transplant. We also analyzed the association of early onset mild hyperuricemia (<8mg/dl) with graft function and similar to Min et al[67] there was no association with graft function at any time interval. Hence our results also supported the dose response relationship of hyperuricemia with graft function proposed by Min et al.

Conclusion:

- Prevalence of hyperuricemia was 26.8%.

- Hyperuricemia was predominantly early onset 89%.

- Early onset moderate to severe hyperuricemia as defined in our study was seen in 29.5% patients.

- Among the baseline characteristics only body mass index was associated with hyperuricemia which was higher in this group.

- Predominant maintenance immunosuppression was tacrolimus and mycophenolate based regimen in our study.

- The nadir eGFR and eGFR at 1month was lower in hyperuricemic patients

- Among the patients who had an early onset moderate to severe hyperuricemia the eGFR at 1 year was lower.

- There was no association of early onset mild hyperuricemia with eGFR at any time post-transplant.

- The incidences of NODAT and serum level of triglycerides were higher in hyperuricemic recipients.

- There was no association between deceased donor, recipient gender, type of induction regimen and delayed graft function.

Table 12. Summary of studies on hyperuricemia in renal allograft recipients

Study	Study design	No. of patients	Immunosupression	Prevalence of hyperuricemia	Graft outcome	Association
Gores et al[62]	Prospective	131	CsA	80%	No diff.	--------
Akgul et al[63]	Retrospective	133	CsA	84.6%	No diff.	--------
Meier-Kriesche et al[10]	Prospective (Symphony trial)	1645	Csa/Tac/mTor inh.	19-55%	No diff	Obese, CsA use, deceased donor, poor baseline graft function
Akalin et al[84]	Retrospective	307	----------	47%	No diff	Male sex, deceased donor,higher CAN, graft loss, poor baseline graft function
Gerhardt et al[64]	Retrospective	350	CsA/Tac	--------------	Adverse	--------
Armstrong et al.[65]	Retrospective	90	CsA/Tac	80%	Adverse	Hypertension, eGFR at 2years
Bandukwala et al[68]	Retrospective	405	Tac/CsA	44%	Adverse	diuretic use, duration of followup, and triglycerides
Our study	Retrospective	284	Tac	27%	Adverse	High BMI at transplant, low nadir GFR and GFR at1mth, dyslipidemia, elevated triglyceride

Proforma

DEPARTMENT OF NEPHROLOGY
CHRISITIAN MEDICAL COLLEGE AND HOSPITAL
VELLORE

Case Number:

1) Recipient Name:

2) Recipient HT :

3) Recipient WT:

4) R. Hosp. No:

5) R. Age:

6) R. Sex: Female -1 / Male -0

7) Dialysis: No - 0 /   HD-1   /   CAPD-2

8) Duration of Dialysis:

9) Pre Tx DM : No – 0   /   Yes – 1

10) Pre Tx HTN: No – 0   /   Yes – 1

11) Live related -0 / Cadaver -1

12) Donor Age:

13) Donor Sex: Female -0 / Male -1

14) HLA Match:

15) Induction: Nil – 0 / Simulect – 1 / ATG – 2

16) Nadir Creat:

17) Post Tx day of nadir creat(the lowest creatinine just before an increase noted-Day O)

18) Subsquent eGFR of Recipient

mth	GFR	weight	mth	GFR	weight
1			5		
2			6		
3			12		
4			18		
24			48		
36					

19) DGF Yes-0, No-1

20) Prednisolone: No -0 / Yes -1

21) Cyclosporin: No -0 / Yes -1

22) Tacrolimus: No -0 / Yes -1

23) Azathioprine: No -0 / Yes -1

24) MMF: No -0   /   Yes – 1

25) Presence of acute rejection

26) No. of Rejection episodes:

27) Post HTN (number of drugs used for BP control) : No -0 / Yes (num):

28) New Onset diabetes after transplant DM: No -0 / Yes -1

29) Hyperuricemia : Yes-1/No-0

30) Hyperuricemia after transplant duration – (mth)

31) Early /Late hyperuricemia(</>1yr) : Yes-1/Late -0

32) Graft loss – Yes -1/No-0

   Death – Yes-1/No-0

33) Graft function of last visit

34) Native kidney disease

   1- DN

   2- unknown

   3- FSGS

   4- CGN

   5- ADPKD

   6- Obstructive uropathy

35) Dyslipidemia at time of diagnosis of hyperuricemia – Yes-1/No-0

      LDL- /TG-/HDL-/ Totalcholesterol

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Hyperuricemia in renal allograft recipients A dissertation submitted to the Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment of the University regulations for the award of D . M . (B r a n c h – I I I) (N e p h r o l o g y) 1 DEPARTMENT OF NEPHROLOGY CHRISTIAN MEDICAL COLLEGE, VELLORE BONAFIDE CERTIFICATE This is to certify that the work presented in this dissertation titled "Hyperuricemia in renal allograft recipients" done towards fulfilment of the requirements of the Tamil Nadu Dr. M.G.R. Medical University, Chennai for the D.M. (Branch–III) (Nephrology) exams to be conducted in August 2013, is a bonafide work of Dr Suraj Kumar, done under my guidance and supervision....