



Urinary Citrates and NPN Substances Index for the Evaluation of Chronic Renal Failure Patients

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ABSTRACT

Chronic renal failure is usually the end results of variety of chronic conditions which include glomerulonephritis, obstructive uropathy, polycystic disease, renal artery stenosis and tubular dysfunction. Excretion of urinary citrate levels is dependent on renal functions i.e. glomerular filtration, tubular reabsorption, and excretion. Acid base status is thought to play a significant role in urinary citrate excretion. Alkalosis enhances citrate excretion, while acidosis decreases it. In acidosis, increased citrate utilization by the mitochondria in the tricarboxylic acid cycle occurs. This results in lower intracellular levels of citrate, facilitating citrate reabsorption and hence reducing citrate excretion. Citrate excretion is impaired by acidosis, hypokalemia (causing intracellular acidosis), a high-animal protein diet (with an elevated acid-ash content), and urinary tract infection (UTI). It has been assumed that decreased urinary citrate & increased serum citrate levels in renal failure and renal stone formers. The aim of this study was to confirm the association of decreased urinary citrate levels in renal failure patients.

Keywords: Urinary citrate, NPN substances, chronic renal failure (CRF), Kidney stones.

1. INTRODUCTION

In recent years, renal handlings of citrate and citrate excretion in the urine have attracted renewed interest because of several considerations. First, modern techniques in renal physiology (such as, transport studies in brush border membrane vesicles and perfused proximal tubules) have provided insights into the cellular and molecular mechanisms of citrate transport^[1].

Citrate is normally excreted in the urine as a byproduct of oxidative pathways in the body^[2]. Also, excretion of urinary citrate (and other organic anions) has been recognized to influence systemic acid-base status, at least in certain species. Citrate is known to inhibit precipitation of calcium oxalate and phosphate and growth of their crystals^[3].

Citrate, an alkalinizing agent, is reabsorbed in the renal proximal tubule by a sodium-coupled transporter, the Na⁺/dicarboxylate cotransporter, with broad substrate specificity for Krebs's cycle intermediates^[4, 5]. Tanner et al have recently demonstrated^[6-8] that citrate salts improve renal function in rats with polycystic kidney disease, mainly by its alkalinizing effect. The citrate utilized by the

kidneys is supplied predominantly by reabsorption of filtered by the citrate, with peri-tubular uptake of citrate accounting for the remainder (up to 30 to 40%) of citrate utilized by the kidneys^[11]. Citrate is thought to be freely filterable at the glomerulus. In humans, 65 to 90% of the filtered citrate is reabsorbed; therefore 10 to 35% of filtered citrate is excreted in the urine^[9, 10]. However, there are some reports of low urinary citrate output in stone formers (SF) and renal failure as compared with healthy subjects^[12, 13, 19], while other studies found no differences^[14, 15].

This study was aimed to evaluate the 24 hour citrate excretion in chronic renal failure patients and compare it with those of healthy subjects in order to determine the prevalence of this defect in our population.

2. PATIENTS AND METHODS:

Between November, 2012 and March, 2013, twenty five adult male & female recurrent chronic renal failure patients who underwent treatment in Shridevi Institute of Medical Sciences and Research Hospital, Tumkur were

selected as cases for the study group. Twenty five ages matched healthy volunteers with no evidence of chronic renal failure or any positive history of renal stones who agreed to take part in the study were included as controls group. In both groups subjects were on their usual diet and were not taking any regular medications that could interfere with the biochemical results. Patients with diabetes, hypertension, renal impairment, and documented urinary tract infection were excluded from the study. Both groups detailed history has taken and physical examination is performed. Each study participant received clear verbal and written instructions about collection of 24 hour urine sample and was provided with a special container. Twenty four hour urinary citrate excretion was measured in both groups. All samples were tested in the same laboratory. For the purposes of this study, citrate levels were taken as more than 320 mg/24hr urine^[16]. 24 hr urine was collected in a container with 10ml of 10N Sulfuric acid as preservative^[17, 18].

After collecting 24hr urine citrate was determined by the quantitative method (Colorimetric kit method). Urine creatinine (Mod. jaffe’s Kinetic method), uric acid (uricase/PAP method), urea (Modified Berthelot Method) and routine urine analysis was carried out for all study subjects & controls.

2.1. Analytical methods

Urinary citrate excretion was assayed by the colorimetric method with pentabromoacetone (PBA). Citric acid is oxidized to pentabromoacetone (PBA) by bromine. PBA formed is extracted with ether and reacts with borax buffer solution to form yellow color, which is measured calorimetrically using blue violet filter (or) spectrophotometer at 445nm.

3. RESULTS:

There were twenty five healthy peoples in control group and twenty five patients in Study group. The mean age of the patients in Study and Control Group was 33 to 57 years respectively. The mean 24 hour urinary citrate values in control group was 323.9 ± 4.304 while it was 293.3 ± 8.343 in Study group. The mean value of urinary citrate is significantly decreased in study group. Urinary citrate values in both groups are shown in Fig 1. By applying two samples to *t*- test on citrate values in all participants in both groups, P value was < 0.001 i.e. the difference in citrate values in chronic renal failure and healthy controls was low statistically significant in chronic renal failure patients compare to healthy controls.

NPN values in both groups are shown in Fig 2. By applying *t* tests on NPN values in all participants in both groups, P value was < 0.001. The mean blood urea level in the study group was increased (100.6 ± 37.95) when compared to that of the control group (26.27 ± 4.143). The mean difference was statistically significant. It has been

corroborated in various texts that a very high serum urea level is associated with an azotemic +state, where the kidneys fail to excrete the substance.

The mean serum creatinine level in the study group was (5.817 ± 4.186) and the controls was (0.8967 ± 0.179) the mean difference was statistically significant.

The mean serum Uric Acid level in the study group was (7.563 ± 1.337) and the controls was (4.19 ± 0.544) the mean difference was statistically significant.

Parameter (mg/24hr)	Control group	Study group	P-value
Urinary Citrate	323.9±4.304	293.3±8.343	< 0.00

Table 1. Mean & Std. Dev of Urinary Citrate.

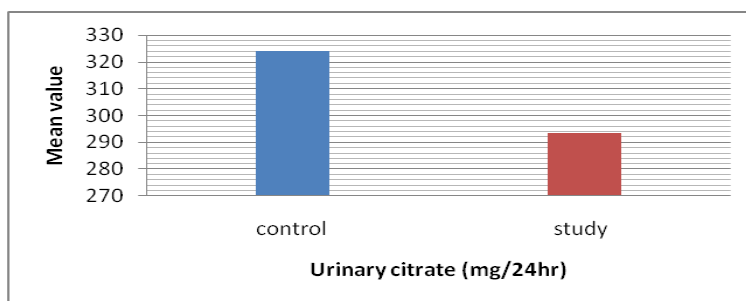


Fig 1: Urinary citrate values in both groups

PARAMETERS (mg/dl)	Control mean & Std. Dev	Study mean & Std. Dev	P- value
Blood Urea	26.27 ± 4.143	100.6 ± 37.95	<0.001
Serum creatinine	0.8967 ± 0.179	5.817 ± 4.186	<0.001
Serum uric acid	4.19 ± 0.544	7.563 ± 1.337	< 0.001

Table 2: Mean ± SD in NPN in control group & study groups

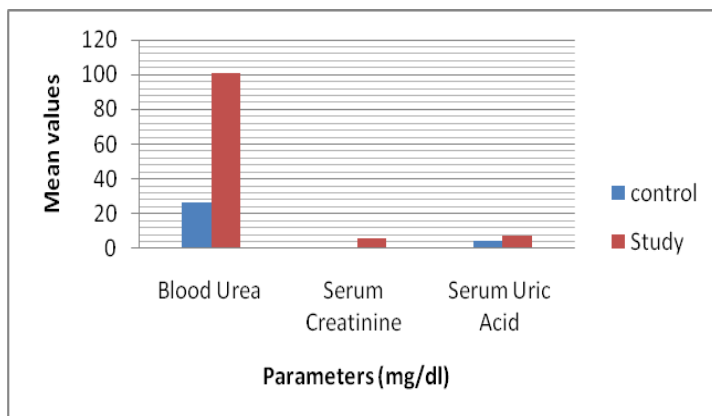


Fig 2: NPN values in both groups

4. CONCLUSION

Chronic Renal failure (CRF) is a worldwide health problem. According to WHO Global Burden of Disease Project, it ranks as the 12th leading cause of death. It is estimated that approximately one lakh new patients develop ESRD in India annually. Change in lifestyle leading to obesity, hypertension, and diabetes all contribute to increased risk of CRF.

As there is steep rise in cases of Diabetes and Hypertension there is increase as well as in the cases of CRF which virtually end in ESRD, which is causing a great burden for the country in terms of morbidity & mortality.

As glomerular filtration rate (GFR) decreases, there is a stepwise decrease in the amount of citrate that is filtered; however, in the early stages of CRF, the increased fractional excretion of citrate prevents an abrupt decline in urinary citrate, such that overt hypocitraturia is not usually observed until advanced stages of CRF^[20]. Urinary citrate excretion depends upon the urinary volume, calcium, magnesium excretion and GI - alkali load. High meat intake increases the urinary excretion of calcium, oxalate, and uric acid and decreases urinary pH and citrate excretion. The use of high-protein, low-carbohydrate diets for weight loss has led to concern about increased risk of stone formation, as these diets have been shown to be associated with decreased urinary citrate and pH levels and increased urine calcium and sodium levels in the induction and maintenance phases^[21]. Hypocitraturia enhances urine calcium salt supersaturation and reduces calcium crystallization inhibition, increasing the risk of calcium nephrolithiasis. It also may play a role in uric acid solubility and uric acid stone formation. The hypocitraturia of indeterminate causes or idiopathic hypocitraturia may be secondary to intrinsic renal defects (dysfunction of the sodium-citrate co-transport or disorder red intracellular citrate regulation etc), in appropriate intestinal citrate or alkali absorption, or a normal physiologic response to animal protein-rich diets.

The major outcomes of CRF, as well as ARF to some extent, regardless of specific diagnosis, (i.e. type of kidney disease), include progression to kidney failure and complications from decreased kidney function. Increasing evidence shows that early detection followed by treatment often can delay or prevent some of these adverse outcomes.

Our study was aimed to evaluate urinary citrates, non protein nitrogenous substances in the serum in cases of CRF. Mean urinary citrates decreased significantly when compared with controls. It was observed that mean Blood Urea, Serum creatinine & Serum uric acid were significantly increased when compared with controls. Early diagnosis and treatment as well as regular monitoring of these cases will help in decreasing the morbidity and delaying the fatality.

Overall there was a major difference between the two groups in urinary citrate as risk factors that predispose to stone formation in chronic renal failure patients.

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Conflict of Interest: None Declared

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