

SERUM URIC ACID CORRELATES WITH THE PROGRESSION OF NEPHROPATHY IN PATIENTS WITH DIABETES MELLITUS

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ABSTRACT

Background: The heavy burden of end stage renal disease has made primary and secondary measures to prevent the development or progression of chronic kidney disease a priority. Search for markers of progression as in this study is necessitated by the fact that progression of kidney disease is multifactorial and for there to be some meaningful impact on the outcome all of the pathogenetic mechanisms will need to be identified and blocked.

Methods: We studied the hospital records of the diabetic patients with impaired renal function on presentation and who had a minimum period of follow up of 12 months. We sought any correlation between the progression of kidney disease (as measured by the reciprocal of serum creatinine against time) and known cardiovascular disease risk factors such as age, gender, smoking, cholesterol and proteinuria and serum uric acid.

Results: Fifty-five (35 male and 20 female) diabetic patients with a mean age of 64.9±10.4 years and a mean follow up period of 20 months were studied. The slope of the reciprocal of serum creatinine for the study population was -0.00531±0.000354dL/mg/ month. We observed a significant correlation between the slope of the reciprocal of serum creatinine and serum uric acid for the total study population ($r = 0.272$, $p = 0.044$) and male but not the female (male $r = -0.335$, $p=0.049$, female $r = -0.128$, $p = 0.590$).

Conclusion: In a cohort of diabetics with impaired renal function at presentation attaining satisfactory control of blood pressure, blood sugar and lipids, the serum uric acid correlates with the progression of the nephropathy.

KEYWORDS: Progression, nephropathy, diabetes, uric acid.

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INTRODUCTION

The contribution made by diabetes to the global burden of End Stage Renal Disease (ESRD) is increasing at an alarming rate worldwide. In the United States diabetics constitute greater than 40 % of the population of patients

requiring renal replacement therapy (RRT).¹ The developing countries are also experiencing an epidemic of diabetes coinciding with the phenomenon of increasing urbanisation and the adoption of Western lifestyles in the recently prosperous Asian countries. It has been estimated that the number of people suffering from diabetes will double from the present figure of about 154 million to close to 300 million by the year 2025.² Forty percent of the type 1 diabetics and 5-10 % of those with type 2 develop nephropathy³ and as a result of the global burden of the disease, very large numbers of diabetics go on to develop chronic kidney disease. A lot of advances have been made in the recent times in slowing the course of both diabetic and non diabetic nephropathies and thus delaying the time of onset kidney failure. Individuals with diabetes will benefit from the

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attainment of tight glycaemic control as that will reduce the risk of the development and the progression of nephropathy.⁴ Tight glycaemic control can decrease the progression of intima-media thickness of large arteries and also lead to the regression of microalbuminuria.^{5,6} The prospects of slowing the progression, achieving remission or even regression of nephropathy have further strengthened the need to intensify efforts at detecting and managing markers of progressive nephropathies. In this study we aimed at examining the association of some of the traditional cardiovascular risk markers such as blood pressure, lipids, smoking age, and sex on the progression of chronic kidney disease in patients with diabetes. We also examined the association between serum uric acid and the progression of diabetic renal disease seeing that elevated uric acid is linked to progressive renal disease in essential hypertension which is another important cause of kidney failure.

METHODS

The study was conducted in the Northern General Hospital Sheffield, United Kingdom where we examined and analysed the demographic, clinical, and laboratory data of patients with diabetes mellitus who were followed up for a minimum of 12 months. The study population consisted of diabetics with impaired renal function whose serum creatinine ranged between 200 and 600 μ mol/L. Smoking was

Table-I: Demographic Characteristics of study population

| Characteristic | Result |
|--------------------|-----------------|
| Age (years) | |
| · Mean age (SD) | 64.9 \pm 10.8 |
| · Range | 39-82 |
| Sex | |
| · Male | 35 |
| · Female | 20 |
| Race | |
| · White Caucassian | 50 |
| · Asian | 4 |
| · Black African | 1 |
| Smoking | |
| · Yes | 22 |
| · No | 33 |

present if the patients smoked at presentation or on follow up. The outcome of blood pressure measurements at presentation and on follow up visits were used to generate the variables of systolic (SBP), diastolic (DBP) and mean arterial blood pressures (MAP). The study population received treatment for hypertension, diabetes and dyslipidaemia with the aim of attaining the current goals of treatment of the conditions. As a result angiotensin converting enzyme inhibitors (ACEi) angiotensin receptor blockers (ARB) along with other antihypertensive drugs and statins were used as indicated. We analysed the results of biochemical tests such as 24 hour urinary protein excretion, serum lipids, serum uric acid, and serum creatinine at presentation and at the follow up clinic visits. We determined the rate of progression of the nephropathy by plotting the reciprocal of the serum creatinine against time in the course of the follow up visits.

Statistical Analysis: The data was presented as mean \pm standard deviation. The results were analysed by the use of the SPSS software version 11.5 and p-values <0.05 were regarded as significant. Parametric (t-test) was used to compare differences between group means while Pearson correlation was used to analyse baseline and time dependent variables.

RESULTS

Patients Characteristics: Fifty-five patients (35 males, 20 females) suffering from diabetes and impaired renal function constituted the study

Table-II: Clinical and Laboratory Characteristics at Presentation

| Feature | Result |
|--------------------------------|------------------|
| Diagnosis | |
| · Type 1 Diabetes | 13 |
| · Type 2 Diabetes | 42 |
| Blood Pressure (BP) | |
| · Systolic (SBP) | 162.8 \pm 16.6 |
| · Diastolic (DBP) | 91.2 \pm 11.3 |
| · MAP | 115.1 \pm 12.1 |
| Serum uric acid (mmol/L) | 401.6 \pm 92.8 |
| Serum cholesterol (mmol/L) | 5.9 \pm 1.1 |
| Serum albumin (g/L) | 35.8 \pm 5.5 |
| Duration of Follow up (months) | 20.8 \pm 2.9 |
| HbA1c | 8.2 \pm 1.3 |

Table-III: Mean Blood pressures at Presentation and follow up

| Blood pressure | Presentation | Follow up |
|---------------------|--------------|-----------|
| Systolic BP (mmHg) | 162.8 | 146.0 |
| Diastolic BP (mmHg) | 91.2 | 83.6 |
| MAP (mmHg) | 112 | 101 |

population. Forty-two of the patients had type 2 diabetes while 13 had type 1 diabetes. The patients were aged between 39 and 82 years with a mean age of 64.9 ± 10.8 years (Table-I). The majority of the study population was made up of white Caucasians (50 in number) while the rest were Asians⁴ (4 in number) and a black African¹ (one patient). Table-II shows the clinical and biochemical features of the study group at baseline. There was no statistical difference between the sexes with regards to their mean age, blood pressure levels the length of follow up, the urinary protein excretion rate and lipids levels. We compared the mean blood pressures at presentation and on follow up (Table-III).

Progression of kidney disease: The rate of progression of the nephropathy was estimated by the plot of the reciprocal of the serum creatinine against time that gave a slope of -0.00531 ± 0.000354 dL/mg per month for the study population. Although there was no gender difference in the plot of reciprocal of serum creatinine against time the plot of the slope against serum uric acid revealed significant differences between male and female patients (male $r = -0.335$, $p = 0.049$, female $r = -0.128$, $p = 0.590$) (Fig-1). There was a significant correlation between the slope of the reciprocal of serum creatinine and serum uric acid for the study population ($r = 0.272$, $p = 0.044$) (Fig-2). The slope of the reciprocal of the serum creatinine did not correlate significantly with the age of the patients ($r = -0.108$, $p = 0.431$) or cigarette smoking habit. There was no significant difference between the proteinuria at presentation and on follow up

Table-IV: Correlation of Blood pressures with slope of Reciprocal of serum creatinine

| | | SBP | DBP | MAP |
|-------------|---|--------|-------|-------|
| Slope 1/ Cr | r | -0.081 | 0.180 | 0.089 |
| Slope 1/ Cr | p | 0.558 | 0.187 | 0.518 |

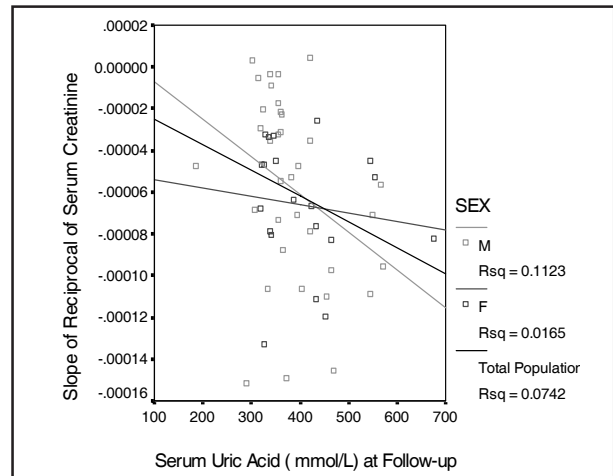


Fig-1: Correlation plot Serum Uric Acid and the Slope of 1/Serum Creatinine ($\mu\text{mol/L}$) in Males and Females. Males: $r = -0.335$, $p = 0.049$, Females: $r = -0.128$, $p = 0.590$, Total Population: $r = -0.272$, $p = 0.044$

for the study population as a whole or between males and females. In addition the slope of the reciprocal of serum creatinine however did not significantly correlate with either proteinuria at presentation ($r = -0.059$, $p = 0.67$), proteinuria at follow up ($r = -0.074$, $p = 0.59$) or with cholesterol at follow up ($r = 0.046$, $p = 0.738$). Over the follow up period neither the systolic blood pressure, the diastolic blood pressure nor the mean arterial blood pressure correlated with the slope of the reciprocal of serum creatinine (Table-IV).

DISCUSSION

Chronic Kidney disease in most instances progresses relentlessly to kidney failure with patients requiring one or the other form of renal replacement to stay alive. The rate of progression of the CKD depends on several factors including the nature of the underlying disease and differs from one individual to another.⁷ Individual variations in the rate of progression of the nephropathy have been attributed to age gender, ethnicity, genetics, urinary protein excretion rate, blood pressure levels, lipids, and cigarette smoking. Whereas some patients demonstrate a constant rate of loss of renal function some others have a less predictable course with periods of accentuation and slowing of progression.⁸ The plot of the reciprocal of the serum creatinine against time is a simple method of estimating the

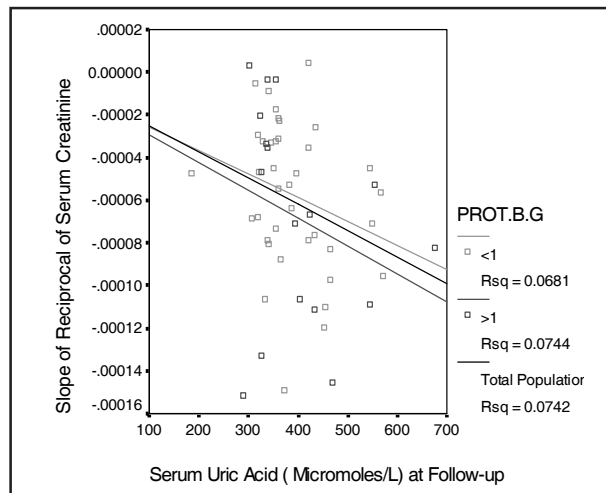


Fig- 2: Correlation plot of Follow-up Serum Uric acid and the Slope of 1/Serum Creatinine in patients with proteinuria <1g and > 1g/24 hours respectively. <1g/24hours: $r=-0.262$, $p=0.114$, >1g/24hours: $r=0.273$, $p=0.290$, Study Population: $r=0.272$, $p=0.044$

progression of CKD⁹ which we employed in this study. In this study the slope of the reciprocal of the serum creatinine of 0.00531dL/mg/mo was comparable to the rate of progression reported by Hakim and Lazarus¹⁰ but smaller than the between 0.0087 and 0.0133 dL/mg /mo reported by Muthusepathi et al¹¹ in the era prior to the widespread use of ACEi and ARB. Our study showed a significant correlation between the slope of the reciprocal of the serum creatinine and the serum uric acid. Whereas the association between chronically elevated uric acid and kidney disease has been recognized, it remains controversial whether the renal disease is a direct consequence of the hyperuricaemia or not.¹² Domrongkitchaiporn et al identified hyperuricaemia greater than 6.29mg/dl along with elevated systolic blood pressure and body mass index as risk factors for the development of decreased kidney function in a 12 year cohort study.¹³ Johnson et al in their review stated that hyperuricaemia and /or low nephron number are the two possible pathways responsible for impaired renal autoregulation in patients with salt sensitive hypertension that are at increased risk of progressive renal disease.¹⁴ Lead exposure has been linked to hyperuricaemia consequent upon proximal tubular damage and a resultant impairment

of uric acid excretion. Some epidemiologic studies have associated low level lead exposure with progressive nephropathy and/or hypertension in the general population.¹⁵ Tseng had shown a correlation between serum uric acid and urinary albumin excretion in Taiwanese type 2 diabetics.¹⁶ In a Japanese study of more than 6,000 individuals with normal renal functions at baseline, elevated serum uric acid was associated with the risk of developing renal insufficiency within two years.¹⁷

There is an increasing recognition of kidney disease as a cardiovascular risk marker but the precise pathogenetic mechanism linking the two is not yet established. Endothelial cell dysfunction has been suggested to be a possible explanation for the high cardiovascular risk that is associated with CKD in the general population.^{18,19} Diabetics have impaired endothelial function that is possibly related to free radical generation and is amenable to xanthine oxidase inhibition with allopurinol therapy which also decreases serum uric acid levels.^{20,21} Feig et al hypothesized that uric acid is one of the principal mediators that inhibit endothelial cell proliferation in the setting of intrauterine growth retardation, low nephron number and risk of hypertension²² which in turn predicts cardiovascular disease.²³ It does appear to us that uric acid through the intermediacy of endothelial dysfunction contributes to the progression of the renal disease of diabetics. Rossing et al reported that several modifiable factors such as baseline albuminuria, systolic blood pressure, Hb A1c, GFR, age, and degree of retinopathy enhanced the progression of kidney disease in type 2 diabetics.²⁴ Our study population had received renoprotective agents such as ACEi, ARBs and statin treatments even at presentation thereby blunting the impact of such modifiable factors. This scenario may explain the observed non-significant correlation of such factors as proteinuria, cholesterol with progression of the renal disease in this study. Moreover the follow up period of 20 months can be regarded as short relative to duration of the course of most chronic diseases that run for years rather than months thus supporting the observations made

by Levey et al.²⁵ They had noted that the precision of estimates of progression in individual patients increased with duration of follow up and as a result we recommend further studies with longer follow up durations involving larger numbers of patients.

CONCLUSION

Serum uric acid correlated with progression of nephropathy in a cohort of diabetic patients who had impaired kidney function at presentation in addition to them having satisfactory control of modifiable risk factors for progression such as for blood sugar, blood pressure, urinary protein excretion rate and serum lipids. Future studies are indicated to examine the impact that the inhibition of uric acid synthesis may have on the course of chronic kidney disease in diabetic patients.

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