In type 1 DM, Uric Acid as the early predictor of diabetic complications compared to microalbuminuria

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Abstract

There is constant search for an early marker for diabetic complications. Microalbuminuria [MA] is recognized as the early predictor of diabetic nephropathy [DN]. Increased levels of serum uric acid [SUA] can be seen in later part of diabetes at the onset of complications. This study was done to know the significance of SUA levels when compared with MA in type 1 Diabetes Mellitus [DM] patients. Microalbuminuria was estimated and compared with serum uric acid levels along with diabetic duration and HbA1c.

Our results showed significantly increased mean levels of serum uric acid along with microalbuminuria in type 1 diabetes. Uric acid and microalbuminuria were also significantly increased in diabetes with >10 years duration and with HbA1c >10. It is emphasized that SUA levels increase with the tissue injury, consequence of glomerular basement membrane damage eventually leading to microalbuminuria. Hence uric acid can be one of the early predictor along with microalbumnuria in early onset of complications like nephropathy. It may also be used as prognostic marker of diabetic complications in type 1 diabetes mellitus.

Keywords: Diabetic complications, HbA1c, Microalbuminuria, Serum Uric acid, Type 1 diabetes mellitus.

Introduction

Diabetic nephropathy [DN] is a devastating chronic complication which is known to affect approximately 40% of diabetic patients[5]. It is one of the leading causes of kidney failure which requires renal transplant in one of four patients with type 1 diabetes[11]. The incidence of microalbuminuria [MA] in patients with type 1 DM was 12.6% in 7.3 years according to European Diabetes (EURODIAB) Prospective Complications Study Group and approximately 33% in an 18-year follow up study in Denmark[14]. The earliest clinical evidence of nephropathy is microalbuminuria (incipient nephropathy).

Without any specific interventions, approximately 80% of subjects with type 1 DM who develop sustained microalbuminuria, have their urinary albumin excretion [UAE] increase at a rate of ~10–20% per year to the stage of overt nephropathy over a period of 7 to 10 years, along with hypertension. This leads to a steady decline in glomerular filtration rate (GFR) and approximately 50% of individuals reach End Stage of Renal Disease (ESRD) in 10 to 15 years[5]. This increases the risk of death, mainly from cardiovascular causes. Studies have demonstrated that the onset and course of diabetic nephropathy can be reverted to a very significant degree by several interventions, but these interventions have their greatest impact if treated at a very early point in the course of the development of complications.

Humans convert major purine nucleosides to uric acid [UA] via the intermediates[11]. Uric acid exhibits a significant surge after tissue injury and has been implicated in diabetic complications. Studies have shown that hyperuricemia is associated with impaired renal function[11,13], poor glycemic control[13], stroke[27], cardiovascular risk[30], hypertension[8] and myocardial infarction[23] mediated by endothelial dysfunction and pathologic vascular conditions[2]. Overproduced uric acid is seen in ischemic tissues and has been associated with endothelial dysfunction by inhibiting nitric oxide release. Hence it was deduced that uric acid and/or its precursors might serve as injury signals in renal ischemia[23,30].

It was also shown that early appearance of serum uric acid was also strongly associated with microalbuminuria and decreased glomerular filtration rate in acute renal diseases[23]. Several studies have shown the association of high uric acid levels as a strong and early predictor of inflammatory response, oxidative stress and disturbances in autoregulation that occur with renal failure[2].

The worldwide incidence of type 1 diabetes varies widely, the average being around 18.5 per 100000 populations and the peak age is around 10-14 years[19,26]. The incidence in Karnataka is 3.8 per 100000 (0.32/yr) populations[17]. Auto-immune damage to pancreatic beta cells will be progressing for a variable period (3 - 36 months) till about 80% of the pancreatic beta cell mass has been irreversibly destroyed[29]. The prevalence of nephropathy in type1 diabetes in Karnataka is 8.6%[17]. The potential mechanisms for the chronic complications are unregulated glycation, sorbitol accumulation and haemodynamic changes leading to tissue damage which in turn increases uric acid levels.

Unregulated glycation changes protein structure and may alter function leading to tissue injury. All membranes, proteins and lipids become significantly glycated in diabetes. It has been found in all tissues like lens, retina, glomerular basement membrane, Schwann cells and coronary arteries leading to tissue injury and get damaged. Intensive control of blood glucose can prevent these complications. The degree of hyperglycemia also reflects the underlying metabolic process[9,29].

Serum uric acid concentration is determined by a combination of the rate of purine metabolism (both endogenous and exogenous) and the efficiency of renal clearance**.** It has been difficult to identify the specific role of elevated serum uric acid because of its association with established cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia and obesity. Possible mechanism could be advanced glycated end [AGE] products, sorbitol accumulation and free radical injury when exposed to chronic hyperglycemia leading to early tissue damage and consequently, increased uric acid levels.

Increased understanding of the mechanisms underlying these associations may allow a clearer interpretation of the importance of elevated serum uric acid concentrations and the potential value of uric acid in diabetic complications. It was shown that serum uric acid levels were also related with CRP levels, calcium/phosphate metabolism, dyslipidemia and inflammation in chronic kidney disease patients[6,7,20]**.** Mild hyperuricemia was shown to significantly increase inflammation and renal tubular injury.

Mild or moderate hyperuricemia may be a contributing factor in the renal injury[22,24]. The NHANES I epidemiologic follow-up Study from 1971-1992, showed a strong, significant, specific and independent association of serum uric acid to cardiovascular mortality[16]. Several studies add to the increasing evidence that uric acid may have a true role in chronic disorders. Uric acid has been found to promote LDL oxidation *in vitro*, a key step in the progression of atherosclerosis[3,25] and these effects are inhibited by vitamin C[1] indicating an important interaction between aqueous anti-oxidants. Uric acid can also stimulate granulocyte adherence to the endothelium[4] and peroxide and superoxide free radical liberation[4,12].

Therefore, uric acid may have a deleterious effect on the endothelium through leukocyte activation and interestingly, a consistent relationship has been noted between elevated serum uric acid concentration and circulating inflammatory markers[10,15,18]. Uric acid travers's dysfunctional endothelial cells and accumulates as crystal within atherosclerotic plaques[21]. These crystals may contribute to local inflammation and plaque progression[28].

The literature reviews show the link between increased UA and chronic disorders especially in type 2 diabetics. Microalbuminuria, an early indicator of diabetic nephropathy due to basement membrane damage, has been associated with elevated serum uric acid levels in type 2 diabetes. Most of the studies are on type 2 diabetes and very little studies are available on type 1 diabetes. Early measurement of these parameters may help in early diagnosis and management of diabetic complications and may help in reverting them. Hence it is imperative to know the UA levels along with microalbumnuria in type 1 Diabetes mellitus, which also helps to know the relationship between glycemic control. Objective of the study was to determine the significance of serum uric acid levels compared to microalbuminuria in type 1 Diabetes Mellitus patients.

Material and Methods

Study was done at Kempegowda Institute of Medical Sciences and Bangalore Diabetic Hospital, Bangalore on 50 people having type 1 Diabetes Mellitus cases along with 50 age and sex matched controls. Type 1 Diabetes Mellitus on treatment in all age groups formed Inclusion criteria. Exclusion criteria established vascular complications, all conditions and drugs which alter serum uric acid levels, were excluded. Data for the study was collected from all those who fulfill the inclusion and exclusion criteria after taking a detailed case history. Baseline data including detailed medical history, conventional risks factors, clinical examinations and relevant investigations were included as part of the methodology. After obtaining ethical clearance and an informed written consent, blood samples were collected by venepuncture. 24 hours of urine sample was collected for microalbuminuria.

Estimation of uric acid was done by uricase method by fully automated auto-analyzer. Microalbuminuria was estimated by immunoturbidimetric method. Ready to use reagent was used in all estimations and samples were analyzed in an auto analyzer and the readings were tabulated. SPSS and Systat were used for the analysis of data and MS Excel has been used to generate graphs and tables.

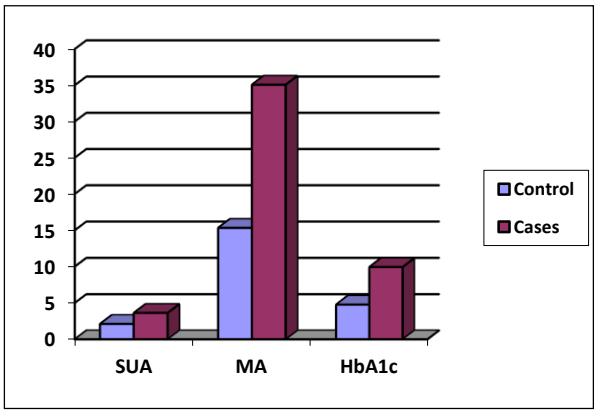

Fig. 1: SUA, HbA1c and MA levels compared to controls

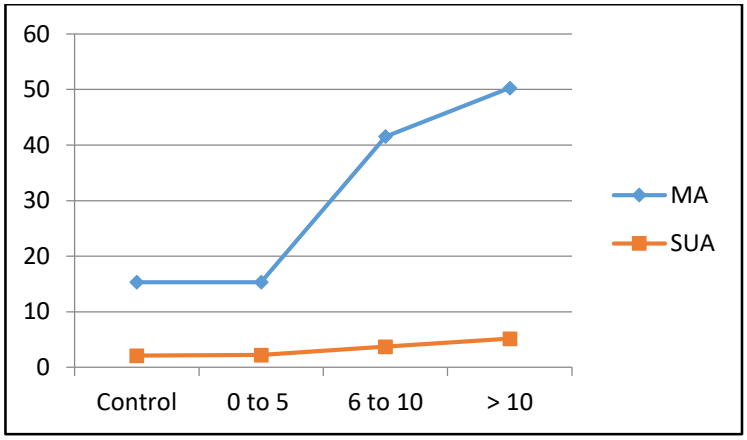

Fig. 2: Comparison of SUA and MA depending on duration of DM

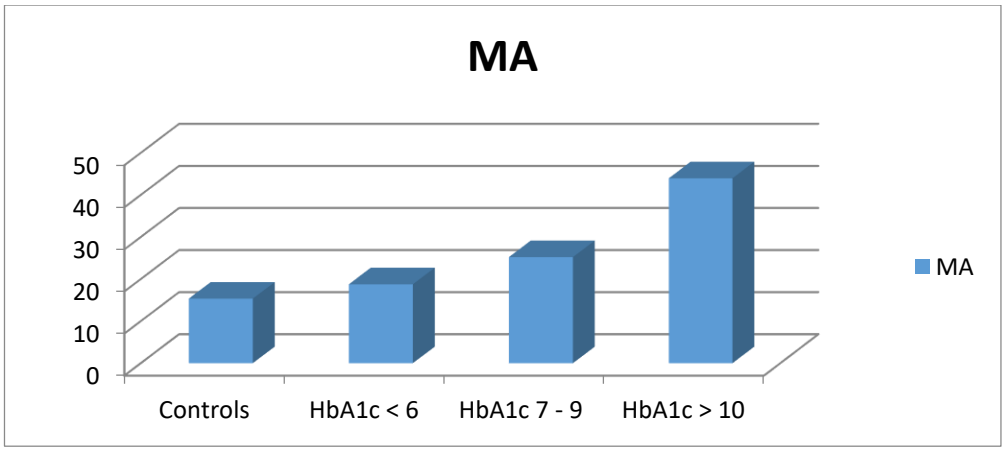

Fig. 3: Microalbuminuria levels at different levels of HbA1c

Table 1
SUA, HbA1c & MA compared with controls and their significance

	Range	Min	Max	Mean	SD	P value
SUA_Control	3.0	0.5	3.5	2.11	0.86	0.000
SUA mg/dl cases	8.0	0.8	8.8	3.63	1.93	
HBA1c_Control	1.8	4.0	5.8	4.77	0.53	0.001
HBA1c % cases	9.4	6.0	15.4	9.94	2.27	
MA_Control	9.5	10.5	20.0	15.34	2.59	0.000
MA mg/L cases	214.0	2.5	216.5	35.08	40.37	

Table 2
SUA and MA levels at depending on duration of diabetes

DM duration	Control	<5 yrs	6-10 yrs	>10 yrs
SUA	2.11±0.86	2.23±0.90	3.74±1.77	5.16±1.89
P value		0.564	0.004	0.001
MA	15.34±2.59	15.35±10.73	41.53±30.32	50.27±62.52
P value		0.771	0.002	0.067

Table 3
MA at different levels of HbA1c

	Range	Minimum	Maximum	Mean	SD	Sig. (2-tailed)
MA in Controls	9.5	10.5	20.0	15.34	2.59	
MA in HbA1c < 6	21.5	8.0	29.5	18.75	15.20	0.808
MA in HbA1c 7 – 9	117.5	2.5	120.0	25.22	26.06	0.098
MA in HbA1c > 10	213.8	2.7	216.5	43.96	48.57	0.005

Results and Discussion

This study was conducted on 100 subjects with 50 people having type 1 diabetics on insulin with 50 controls. The age and gender matched as far as possible. The average age of cases and control was 17.96±5.4 and 18.98±5.6 years respectively. Type 1 diabetes is commonly seen in younger individuals. The duration of diabetes varied from 2.5 months to 23 years with the average being 7.78±5.0 years. The life expectancy of type 1 diabetes is very less due to improper monitoring and poor control of blood sugars. Also there is early onset of chronic complications in them.

There was a significant elevated level of SUA, HbA1c and MA when compared to controls ($P < 0.01$) in type 1 diabetes mellitus. An elevated level of SUA indicates increased tissue damage. Increased levels of MA indicate damage to basement membrane of nephrons and these parameters are increased in uncontrolled diabetes indicated by increased levels of HbA1c.

Depending on DM duration: To study the correlation of UA and MA, duration of diabetes was categorized into three groups as <5years, 6–10years and >10years. SUA and MA were estimated in these groups. Paired sample t test was applied (table 2). There was not much difference between controls and cases with <5 years duration of diabetes indicating no complications ($P>0.05$). But as the duration of diabetes increases, there is statistically significant ($P < 0.01$) elevated levels of SUA and MA at 6-10 years. This clearly demonstrates the development of complications and renal involvement in this group. In >10years of diabetic duration, there is further significant increase of SUA indicating progression of tissue injury (table 3). The mean levels of MA also increased in this group of diabetes though statistically not significant ($P>0.05$). Possible explanations could be nephropathy with decreased GFR in this group.

There is considerable increase of UA with the duration of diabetes, even though the values were not in pathologic levels. With increasing duration of diabetes irrespective of age and sex, there was significant increase of SUA levels with 6 - 10 years of DM and further increase with >10 years duration of diabetes compared to controls. There is constant increase of UA possibly due to progressive tissue damage as the duration of diabetes advances. Microalbuminuria was comparable with controls when duration of diabetes is <5 years. But as the duration of diabetes increases, there is a significant increased level with 6-10 years duration of diabetes. The mean levels of MA kept on increasing even with >10 years duration though statistically not significant, indicating early renal involvement. The parallel increase of these parameters indicates possible tissue damage and also glomerular basement membrane damage leading to microalbuminuria.

At different levels of HbA1c: To know the significance of MA in glycemic control, the microalbuminuria levels are studied at different levels of HbA1c <6%, 7-9% and >10% (table 3). With HbA1c <6 level, no difference was noted with controls indicating absence of renal involvement. But with HbA1c level 7-9, there are increased levels of microalbuminuria though statistically not significant indicating progressive tissue damage (table 3). Microalbuminuria levels were significantly increased ($P<0.01$) in poor glycemic control with HbA1c >10 indicating glomerular basement damage and leaking of proteins.

As the HbA1c levels increases with poor glycemic control, there are increased levels of microalbuminuria. With poor glycemic control, significant glycation occurs with plasma proteins and lipids. This leads to the formation of advanced glycated end products which is accumulated in all the tissues like glomerular basement membrane, lens and capillary bed etc. In turn it causes tissue damage leading to increased levels of uric acid and microalbuminuria which is the pathophysiology in chronic complications of diabetes like nephropathy.

Our study implicates the utility of measurement of SUA levels along with MA in type 1 diabetes mellitus, to predict the development of chronic complications and also to monitor the prognosis of nephropathy, which would be helpful for an early medical intervention.

Conclusion

In this study, there is an increasing trend of serum uric acid level concentrations in the high-normal range with microalbuminuria. There is also increased level of microalbuminuria with poor glycemic control (HbA1c) indicating glycation of glomerular basement membrane leading to leakage of albumin and this is clearly evident as the duration of diabetes increases. Here the uric acid acts as an acute phase reactant and gives an injury signal with glycated tissue and damage to the endothelium and basement membrane of kidneys in type 1 diabetes mellitus.

A positive correlation was observed between serum uric acid and microalbuminuria levels. Since this is an inflammatory process, elevated levels of acute phase reactants like serum uric acid probably act as diagnostic and early marker for the assessment of systemic complications in type 1 diabetes mellitus. Continuous glycation and consequent formation of glycated end products may possibly be the cause of glomerular basement damage leading to increased levels of uric acid levels resulting in microalbuminuria. The present study has explored the possible usefulness of these parameters as early markers of development of complications in type 1 DM.

Hence this study highlights the facts that all type 1 diabetes should be screened periodically for serum uric acid levels and microalbuminuria to detect and to prevent future complications. Follow up studies may be required to confirm that this level of serum uric levels is a risk factor for diabetic complications in type 1 diabetes and to determine whether

its reduction by strict euglycemia would prevent the complications.

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