Neutrophil Gelatinase-associated Lipocalin (NGAL) as a Marker of Renal Tubular Injury in Metabolic Syndrome Patients with Hyperuricemia

Ritu Karoli¹, Nikhil Gupta², Yogesh Karoli³, Manish Raj Kulshreshtha⁴, Vandana Tiwari⁵

Original Article

Abstract

Background: Hyperuricemia has been associated with chronic kidney disease, evidence suggests that hyperuricemia might play a role in progression of renal damage. Whether hyperuricemia can lead to renal tubular injury remains unclear. In this study we aimed to determine serum NGAL and urinary NGAL/creatinine ratio as markers of renal tubular injury in metabolic syndrome patients with hyper or normouricemia.

Material and Methods: In this hospital based cross-sectional study, 180 participants with metabolic syndrome were included, 90 patients had hyperuricemia and 90 were with normouricemia. Clinical biochemical parameters of serum NGAL and urinary NGAL were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit. Receiver operating characteristic (ROC) curve was analysis was employed to assess the sensitivity and specificity of serum NGAL and urine NGAL/creatinine ratio.

Results: Out of all, 96 were males and 84 were females. The mean age of participants was 45 ± 7 years. Serum NGAL levels and Urinary NGAL/creatinine ratio were higher in metabolic syndrome patients with hyperuricemia. High Serum NGAL was positively correlated with presence of hypertension; HbA1c and waist-hip ratio and negatively correlated with HDL.

Conclusion: Serum NGAL levels and urinary NGAL/creatinine ratio were higher in metabolic syndrome patients with hyperuricemia that indicates presence of renal tubular injury in these patients. High Serum NGAL was positively correlated with presence of hypertension; HbA1c and waist-hip ratio.

Introduction

In recent years there has been a renewed interest in hyperuricemia and its association with a number of clinical disorders other than gout, including hypertension, atherosclerosis, cardiovascular disease, and chronic kidney disease.¹² Indeed, hyperuricemia is commonly part of the cluster of metabolic and hemodynamic abnormalities including obesity, glucose intolerance, dyslipidemia, and hypertension often subsumed under the term “metabolic syndrome”.² Metabolic syndrome is highly prevalent in patients of CKD and its components are associated with progression of CKD.³ Recent data suggest that uric acid may be an important factor in the pathogenesis of chronic kidney disease (CKD) rather than just a marker of decreased renal uric acid excretion.⁴ The debate remains ongoing on whether renal impairment is due to a direct nephrotoxic effect of uric acid or due to other pathologic mechanisms caused by hyperuricemia.⁵ Most studies have focused on uric acid-induced endothelial dysfunction, oxidative stress and inflammation in the kidney.⁶⁻⁷

Neutrophil gelatinase-associated lipocalin (NGAL) protein originally purified from human neutrophils, is a promising biomarker for early detection of renal tubular injury.⁸ Whether chronic asymptomatic hyperuricemia can be related to renal tubular injury in presence of metabolic abnormalities is not clear. Therefore, the aim of this study was to test the hypothesis that serum and urinary levels of NGAL are elevated in patients with hyperuricemia.

Material and Methods

A hospital based cross sectional, observational study was conducted at department of medicine, Dr RMLIMS, Lucknow.

Participant selection- The study included 180 patients who had an age of >20 years with normal renal functionshad metabolic syndrome. The metabolic syndrome (MS) was defined according to International Diabetes Federation (IDF) criteria.⁹ MS by IDF is defined as Central obesity [defined as waist circumference ≥94 cm (male), ≥80 cm or (female)] and any two of the following:

1. BP Systolic ≥ 130 mmHg or BP diastolic ≥ 85 mmHg
2. TG ≥ 150 mg/dl
3. HDL ≤ 40 mg/dl in men and ≤50 mg/dl in women.
4. FBS ≥100 mg/dl

Hyperuricaemia was defined as serum uric acid levels >6.8 mg/dL in both males and females.¹⁰ Estimated glomerular filtration rate (eGFR) was calculated using Equation from the Modification of Diet in Renal Disease study- Estimated GFR (mL/min per 1.73 m²) = 1.86 x (P_creat)[–1.154] x (age)[–0.203] Multiply by 0.742 for women.

Exclusion criteria comprised of

¹Professor (Sr Gr), ²Associate Professor, Department of Medicine, ³Senior Consultant, Department of Orthopedics, ⁴Associate Professor, ⁵Professor (Sr Gr), Department of Biochemistry, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh; ⁶Corresponding Author
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between groups was performed using Student’s unpaired t test and chi square analysis. We used Pearson’s correlation coefficient to assess the relationships. Receiver operating characteristic (ROC) curve was analysis was employed and area under the curve (AUC) was calculated to assess the sensitivity and specificity of serum NGAL and urine NGAL/creatinine ratio to discriminate hyperuricemia from normouricemia. 95% Confidence interval was calculated as needed. P < 0.05 was considered statistically significant.

Results

In this hospital based cross-sectional study, 180 participants with metabolic syndrome were included. 90 patients had hyperuricemia and 90 with normal uricemia. Out of all, 96 were males and 84 were females. The mean age of participants was 45 ± 7 years. Table 1 shows that there were no statistically significant differences across the groups in age, gender, BMI, waist circumference and waist hip ratio. Prevalence of hypertension and glucose intolerance was more in subgroup of patients with hyperuricemia.

As far as biochemical parameters were concerned as depicted in Table 2, it was observed that HbA1c, serum creatinine and serum NGAL were significantly higher in patients with hyperuricemia. Urinary NGAL/creatinine ratio was also found to be significantly higher in metabolic syndrome patients with hyperuricemia. Serum NGAL in hyperuricemia group was higher than normouricemia (median 458 ng/ml, IQR: 268-698 ng/ml). Serum NGAL was positively correlated with systolic and diastolic blood pressure and waist hip ratio.

Table 1: Clinical and Anthropometric data of study Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Metabolic syndrome patients with hyperuricemia (n=90)</th>
<th>Metabolic syndrome patients with normouricemia (n=90)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46 ± 12.6</td>
<td>45 ± 14</td>
<td>0.57</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>24 (53)</td>
<td>23 (51)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.1 ± 4.36</td>
<td>25.7 ± 4.33</td>
<td>0.23</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>89.62 ± 8.73</td>
<td>88.8 ± 6.8</td>
<td>0.12</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>1.2 ± 0.45</td>
<td>1.08 ± 0.45</td>
<td>0.8</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>162.62±7.49</td>
<td>148.25±7.56</td>
<td>0.02*</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>96±6.4</td>
<td>82.6 ± 0.03</td>
<td>0.003*</td>
</tr>
</tbody>
</table>

Data is shown as Mean±SD (Standard deviation); *statistically significant

Table 2: Biochemical parameters of study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Metabolic syndrome patients with hyperuricemia (n=90)</th>
<th>Metabolic syndrome patients with normouricemia (n=90)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C (%)</td>
<td>6.2±1.6</td>
<td>5.7±0.85</td>
<td>0.04*</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>192±24</td>
<td>188.98±18</td>
<td>0.07</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>36.85±8</td>
<td>34.85±6</td>
<td>0.6</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>178.4±34</td>
<td>180.6±30</td>
<td>0.12</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>112.8±16</td>
<td>108±12.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>7.8±1.6</td>
<td>3.2±1.56</td>
<td>0.01*</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.3±0.2</td>
<td>0.8±0.3</td>
<td>0.01*</td>
</tr>
<tr>
<td>Fasting glucose(mg/dl)</td>
<td>109.2±10.09</td>
<td>106±12</td>
<td>0.12</td>
</tr>
<tr>
<td>Serum NGAL (ng/ml)</td>
<td>352.6±34</td>
<td>214±27.8</td>
<td>0.01*</td>
</tr>
<tr>
<td>Urinary NGAL/creatinine ratio</td>
<td>25.2±8</td>
<td>16.2±5.6</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

Data is shown as Mean±SD (Standard deviation); *statistically significant

Table 3: Correlation analysis with high NGAL

<table>
<thead>
<tr>
<th>Parameter</th>
<th>rho value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>0.42</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.56</td>
<td>0.01</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.36</td>
<td>0.002</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.48</td>
<td>0.01</td>
</tr>
<tr>
<td>HDL</td>
<td>-0.32</td>
<td>0.04</td>
</tr>
</tbody>
</table>
blood pressure, HbA1c and waist-hip ratio and negatively correlated with HDL as shown in Table 3.

To estimate utility of serum NGAL and urinary NGAL/creatinine ratio in differentiation of hyperuricemia and normouricemia, ROC curve was used and AUC was calculated and cut off values for serum NGAL and urinary NGAL/creatinine ratio at various sensitivity and specificity levels studied. It was observed that at level of 502ng/ml (AUC 0.88, 95 % CI, 0.80-0.95, p=0.01), sensitivity and specificity for hyperuricemia were 89% and 77%, (Figure 1). For urinary NGAL/creatinine ratio, (Figure 2), AUC was 0.88(95% CI 0.6-0.98, p=0.01) a value of 27 had 88% sensitivity and 72% specificity for detecting hyperuricemia.

**Discussion**

Uric acid, an end-product of purine metabolism is excreted via kidney. Many epidemiologic studies have suggested that hyperuricemia is associated with hypertension, cardiovascular diseases and insulin resistance, and uric acid as independent predictor of renal damage.

CKD is a devastating illness which is rapidly approaching epidemic proportions globally. Patients with CKD have high uric acid levels because of reduced renal clearance. The growing evidence suggests that hyperuricemia may have role in progression of CKD but whether chronic asymptomatic hyperuricemia can cause renal tubular injury is not known. Metabolic syndrome has become an important public health problem with increasing prevalence which is often associated with hyperuricemia. This study was aimed to assess presence of renal tubular injury as reflected by serum and urinary NGAL in patients of metabolic syndrome who have hyperuricemia and to study any correlation of these markers with individual components of metabolic syndrome. We included all metabolic syndrome patients to avoid any selection bias and divided into 2 groups depending upon uric acid levels. Renal tubular injury markers serum NGAL and urinary NGAL were determined and both were significantly greater in patients with hyperuricemia than normouricemia.

It is well known that acute hyperuricemia leads to acute kidney injury by precipitation of uric acid crystals causing direct renal toxicity. Experimental studies suggest that non crystallopathic mechanisms may also act to cause indirect injury such as renal vasoconstriction, oxidative stress inflammation and endothelial dysfunction. NGAL, It is a member of the lipocalin family a 25-kDa small protein that is expressed at low levels in several human tissues and rapidly released from renal by damaged renal tubular epithelium in response to various insults to the kidney. NGAL is well known biomarker of renal tubular injury. In contrast to serum creatinine which rises when renal function is substantially decreased, serum NGAL and urinary NGAL are specifically increased in the early phase of renal damage. The studies have shown that NGAL they are not only the markers of AKI but also elevated in patients with chronic tubulointerstitial disease, and may predict of long-term decline in renal function in patients with CKD.

Similar to the results of present study, Tomczak et al have studied the relation of hyperuricemia and markers of renal tubular injury. In their study on male, obese, hypertensive adolescents with hyperuricemia, they demonstrated that patients with hyperuricemia had higher urine NGAL and KIM-1 levels relative to controls with normouricemia. This study also suggested the possibility that hyperuricemia may be linked to tubular injury. Pathogenic role of uric acid in causation of renal dysfunction is indicated by the fact that lowering uric acid levels by allopurinol retards renal damage. Experimental studies have shown that induction of hyperuricemia led to progressive glomerular injury and tubulointerstitial fibrosis. Ryu et al have also demonstrated that uric acid stimulates fibrogenic process in renal tubular epithelium.

High Serum NGAL was positively correlated with presence of hypertension; HbA1c and waist-hip ratio and negatively correlated with HDL. This finding suggests that components of metabolic syndrome have added effects on renal tubular markers along with hyperuricemia. Our findings are in concordance with Tomczak et al who have reported similar correlations of components of metabolic syndrome with NGAL in patients of hyperuricemia. Greater urinary NGAL levels have been reported by other researchers also in patients with hypertension.

Our study has few limitations. It has cross sectional design so causal relationship between hyperuricemia and renal tubule-interstitial injury could not be delineated. Secondly, study had small sample size and only NGAL could be assessed.

More prospective studies with large number of patients having long-term follow-up will be needed to validate our data and determine the roles of NGAL, urine NGAL/Cr ratio and other markers in patients with hyperuricemia in predicting tubulointerstitial disease and renal outcomes.

**Conclusion**

Serum NGAL levels and urinary NGAL/creatinine ratio were higher in metabolic syndrome patients with hyperuricemia that indicates presence of renal tubular injury in these patients. High Serum NGAL was positively correlated with presence of hypertension; HbA1c and waist-hip ratio Further research is needed to determine long-term prognostic values of both hyperuricemia and NGAL for recognition of complications of hyperuricemia to prevent renal damage in the early phase.

**References**


Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from insulin resistance, insulin action, or both. Despite availability of various treatment modalities it is difficult to achieve the desired glycemic control in many patients. In such patients new anti-diabetic agents are needed. Empagliflozin, a sodium-glucose co-transporter II (SGLT2) inhibitor, has been approved by FDA. SGLT-2 inhibitor Empagliflozin has been associated with HbA1c reduction and weight loss in a broad range of patients with type 2 diabetes mellitus (T2DM) inadequately controlled on triple drug therapy and are reluctant to insulin therapy.

Methods:

Changes in glycemic parameters on 120 patients who were inadequately controlled on three oral hypoglycaemic agents and reluctant to take insulin therapy. Empagliflozin 25 mg once a day was added to ongoing triple drug therapy. Study was conducted at MGM medical college and hospital, Aurangabad in collaboration with Department of Medicine. Changes in glycemic parameters were evaluated at baseline, three months and sixth months. Study was conducted at MGM medical college and hospital, Aurangabad in collaboration with Department of Medicine. Safety profile were assessed at baseline, three months and sixth months. Study was conducted at MGM medical college and hospital, Aurangabad in collaboration with Department of Medicine.

Conclusions:

Empagliflozin 25 mg once a day on to ongoing triple drug therapy has shown 3.02% reduction in HbA1c and 3.83 kg reduction in bodyweight.

Abstract

Type II Diabetes Mellitus (DM) inadequately controlled on triple drug therapy has shown 3.02% reduction in HbA1c and 3.83 kg reduction in body weight.

Conclusion:

Empagliflozin 25 mg once a day on to ongoing triple drug therapy has shown 3.02% reduction in HbA1c and 3.83 kg reduction in body weight.

Appendix

References:


