INTRODUCTION
Diabetes mellitus is one of the most prevalent metabolic diseases which is characterised by elevated blood sugar levels. Type 2 diabetes mellitus constitutes about 90 percent of this group. Untreated DM leads to many complications which are traditionally classified as acute and chronic. The microvascular complications include retinopathy, nephropathy and peripheral neuropathy. Diabetic nephropathy is the most common cause for dialysis and end-stage renal failure across the world. Diabetic nephropathy usually starts with microalbuminuria (UAE 30-300 mg/dL) followed by macroalbuminuria (UAE > 300 mg/dL) and eventually there is progressive loss of renal function by tissue scarring leading on to end-stage renal disease. However, in type 2 DM, there can be a group of patients who can have impaired renal function without albuminuria (UAE<30 mg/ day).

This is being called as “non-albuminuric renal failure”. Reduced GFR in long duration diabetic patients with normal urine albumin excretion have been reported in increasing frequency. There are very few Indian studies which have been done on this group of type 2 diabetic patients. Hence, this study is aimed to evaluate the clinical profile of non-albuminuric renal insufficiency in type 2 diabetes mellitus.

AIM
To study the clinical profile of non-albuminuric renal insufficiency in type 2 DM.

MATERIALS AND METHODS
The study population included 97 patients with non-albuminuric (urine microalbumin less than 30 mg/day, renal insufficiency (GFR less than 60 mL/min. as per Cockcroft–Gault formula) and are diabetic (type 2) admitted in the Department of General Medicine and Nephrology. Patients with comorbidities other than diabetes which can cause renal insufficiency were excluded from the study.

A detailed history was taken and clinical assessment was done for all patients. All patients underwent a panel of tests which included complete blood count, blood urea nitrogen, serum creatinine, electrolytes (Na, Cl, K, HCO3), LFT, urine routine examination, urine microalbumin, urine culture, USG abdomen, ECG, fundus assessment, calcium, phosphorus, uric acid. GFR was calculated in all the study population with Cockcroft–Gault formula and the study group was divided into different stages of CKD.

STATISTICAL METHODS
Categorical variables were expressed as number (%) and continuous variables expressed as mean (SD, Range). Descriptive statistics (age, gender, comorbid illness,) were explained using bar charts, pie diagrams. Correlation between two variables was checked using the Pearson's correlation coefficient method (HbA1c, GFR, Microalbumin).

RESULTS
In the present study, a total of 97 patients met the inclusion criteria.

Among these 97 patients, 62 are male and 35 are female. The minimum and maximum age of the patient in the study group is 43 & 85. The mean age observed in the present study is 61.85. Among the study group of 97 participants, 68 (70.1 %) had trace proteinuria in routine urine examination, while 29 (29.9 %) had negative proteinuria in routine urine examination. The mean HbA1C value in the trace proteinuria is 9.80, and the mean value of HbA1c in the negative proteinuria group is 10.67. In the study population, 9 patients (9.27%) are under CKD-3 as per KDOQI classification of the stages of CKD, 59 (60.8 %) are under CKD-4, 29 (29.89 %) are under CKD-5. In the study group of 97 patients, 54 had non-proliferative diabetic retinopathy, 43 had proliferative diabetic retinopathy. The minimum and maximum duration of diabetes in years in our study is 5 & 37. The mean value is 13.98.

CONCLUSION
Non-albuminuric renal insufficiency seems to be more prevalent among males more than 60 years of age. In this group, most of them were in CKD stage 4. Severity of the retinopathy correlated with the degree of renal insufficiency. Uncontrolled diabetes mellitus status (larger HbA1c value) correlated with proliferative diabetic retinopathy than the larger duration of diabetes mellitus. Patients with higher HbA1c values had negative proteinuria. Hence non-albuminuric renal insufficiency is a unique clinical entity which should be kept in mind while managing type 2 DM patients.

KEYWORDS
Type 2DM, Noalbuminuric Renal Failure.
INTRODUCTION: Diabetes mellitus is one of the most prevalent metabolic diseases which is characterised by elevated blood sugar levels. Type 2 diabetes mellitus constitutes about 90 percent of this group. Type 2 DM begins with insulin resistance but gradually a state of insulin depletion develops.\(^1,2\)

Untreated DM leads to many complications which are traditionally classified as acute and chronic.

The common acute complications are diabetic ketoacidosis, hyperosmolar non-ketotic coma, and hypoglycaemia.\(^1\)

The chronic complications are further divided into macrovascular and microvascular.

Macrovascular complications include coronary artery disease, cerebrovascular disease and peripheral vascular disease. The microvascular complications include retinopathy, nephropathy and peripheral neuropathy.\(^3\)

Diabetic nephropathy, which is also known as Kimmelstiel–Wilson syndrome is a progressive kidney disease caused by angiopathy of capillaries in the kidney glomeruli.\(^4,5,6\) It is more prevalent among African Americans, Asians, and Native Americans than Caucasians.\(^7\)

Diabetic nephropathy is the most common cause for dialysis and end-stage renal failure across the world.\(^8\)

Diabetic nephropathy usually starts with microalbuminuria (UAE 30-300 mg/dL) followed by macroalbuminuria (UAE > 300 mg/dL) and eventually there is progressive loss of renal function by tissue scarring leading on to end-stage renal disease. In view of this, traditionally screening for diabetes mellitus starts with yearly measurements of urine albumin excretion rate.\(^9,10\) And most often microalbuminuria is associated with reduced renal function defined as (eGFR) <60 mL/min/1.73 m\(^2\),\(^11,12\)

However, in type 2 DM, there can be a group of patients who can have impaired renal function without albuminuria (UAE<30 mg/ day).\(^13\)

This is being called as “non-albuminuric renal failure”. This entity was first highlighted by Lane et al\(^14\) in a group of females. Later on, reduced GFR in long duration diabetic patients with normal urine albumin excretion have been reported in increasing frequency.\(^15,16\)

In fact, its incidence has been reported to be about 20 percent in one study where eGFR <60 mL/min./1.73m\(^2\) was taken as the criteria for reduced renal function.\(^17\)

The possible explanations given for this non-albuminuric renal insufficiency in type 2 DM were treatment with drugs like ACE inhibitors, calcium channel blockers, statins which can reduce urinary albumin excretion, selective parenchymal damage, Renovascular disease, non-diabetic kidney disease, or accelerated ageing of the kidney, either alone or in combination, etc. Still the exact causes are yet to be established.

A lot of research is needed in this particular group of patients who seem to be identified in an increasing manner. There are very few Indian studies which have been done on this group of type 2 diabetic patients.

Hence, this study is aimed to evaluate the clinical profile of non-albuminuric renal insufficiency in type 2 diabetes mellitus.

AIMS & OBJECTIVES: To study the clinical profile of non-albuminuric renal insufficiency in type 2 diabetes mellitus.

MATERIALS AND METHODS:

1. **Source of Data:** Patients admitted in the General Medicine Department and Nephrology Department of Sri Ramachandra Medical College.

2. **Duration of Study:** This study was conducted from August 2012 – September 2014.

3. **Study Design:** To study the clinical profile of Non-albuminuric renal insufficiency in type 2 diabetes mellitus.

4. **Inclusion Criteria:** Type 2 diabetes mellitus patients with non-albuminuric renal insufficiency.

5. **Exclusion Criteria:**
   - Type 1 Diabetes mellitus.
   - Comorbid illness causing renal insufficiency other than diabetes mellitus.
   - Usage of nephrotoxic drugs.
   - Autoimmune diseases.
   - Polycystic kidney disease.
   - Infections.
   - Hereditary renal diseases.

6. **Methods of Study:** Patients who satisfied the study criteria were enrolled after informed consent. Enrolment to study was done for patients who were admitted under Department of Medicine & Nephrology. Institutional Ethics Committee approved the study.

The study population included 97 patients with non-albuminuric (urine microalbumin less than 30 mg/ day), renal insufficiency (GFR less than 60 mL/min as per Cockcroft–Gault formula) and are diabetic (Type 2).

A detailed history was elicited from the patient, relatives, about the type of diabetes mellitus, duration of diabetes, duration of renal disease, excluding the other
causes of renal impairment like hypertension, nephrotoxic drugs intake, polycystic kidney disease, and infections. Details of smoking, alcohol & other substance abuse were obtained. Detailed clinical examination which included general examination, assessment of arterial pulse, blood pressure, respiratory rate, and examination of all major systems were done. The clinical assessment methods were customised to know the characteristics of patients with non-albuminuric renal insufficiency in diabetics.

All patients underwent a panel of tests which included complete blood count, blood urea nitrogen, serum creatinine, electrolytes (Na, Cl, K, HCO3), LFT, urine routine examination, urine microalbumin, urine culture, USG abdomen, ECG, fundus assessment, calcium, phosphorus, uric acid. GFR was calculated in all the study population with Cockcroft–Gault Formula and the study group was divided into different stages of CKD.

**STATISTICAL METHODS:** Categorical variables were expressed as number (%) and continuous variables expressed as mean (SD, Range). Descriptive statistics (age, gender, comorbid illness) were explained using bar charts, pie diagrams. Correlation between two variables was checked using the Pearson’s correlation coefficient method (HbA1c, GFR, Microalbumin).

**RESULTS**

**AGE:** Age of participants ranged from 43-85 (mean 61.85 yrs.). Most were in age group more than 60 yrs. (51.5 %).

Table 1 and figure 1 gives distribution of age among study participants.

The minimum age of the participant in the study group is 43 and the maximum age of the participant is 85.

**SEX**

<table>
<thead>
<tr>
<th>SEX</th>
<th>Frequency</th>
<th>Percent</th>
<th>Valid Percent</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALE</td>
<td>62</td>
<td>63.9</td>
<td>63.9</td>
<td>63.9</td>
</tr>
<tr>
<td>FEMALE</td>
<td>36</td>
<td>36.1</td>
<td>36.1</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>97</td>
<td>100.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: Gender distribution among study participants**

Fig. 2: Out of 97 cases, 62 were Male (63.9 %) and 35 were Female (36.1 %)

32 are male & 15 are female in the age group of 41-60 yrs.
30 are male & 20 are female in the age group of more than 60 yrs.
The largest group of study participants are in the range of 70-10 of the study participants (47.4) are in the range of 7-10.

**Table 4: Showing the HbA1c ranges among the study participants**

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>Frequency</th>
<th>Percent</th>
<th>Valid Percent</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valid</td>
<td>&lt; 7</td>
<td>4</td>
<td>4.1</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>7 - 10</td>
<td>46</td>
<td>47.4</td>
<td>51.5</td>
</tr>
<tr>
<td></td>
<td>10 - 13</td>
<td>38</td>
<td>39.2</td>
<td>90.7</td>
</tr>
<tr>
<td></td>
<td>13 - 16</td>
<td>9</td>
<td>9.3</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>97</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**Fig. 3: Demonstrating the HbA1C ranges among the study participants**

**Table 5: Showing Correlation of HbA1C values with age among the study participants**

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>COUNT</th>
<th>% OF TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>41 - 60 YEARS</td>
<td>22</td>
<td>22.7%</td>
</tr>
<tr>
<td>&gt; 60 YEARS</td>
<td>44</td>
<td>47.4%</td>
</tr>
</tbody>
</table>

**Table 6: Showing Correlation of HbA1C values with sex among the study participants**

<table>
<thead>
<tr>
<th>SEX</th>
<th>HbA1c</th>
<th>COUNT</th>
<th>% OF TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALE</td>
<td>&lt; 7</td>
<td>3</td>
<td>3.1%</td>
</tr>
<tr>
<td></td>
<td>7 - 10</td>
<td>30</td>
<td>30.9%</td>
</tr>
<tr>
<td></td>
<td>10 - 13</td>
<td>26</td>
<td>26.8%</td>
</tr>
<tr>
<td></td>
<td>13 - 16</td>
<td>3</td>
<td>3.1%</td>
</tr>
<tr>
<td>FEMALE</td>
<td>&lt; 7</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td></td>
<td>7 - 10</td>
<td>16</td>
<td>16.5%</td>
</tr>
<tr>
<td></td>
<td>10 - 13</td>
<td>12</td>
<td>12.4%</td>
</tr>
<tr>
<td></td>
<td>13 - 16</td>
<td>6</td>
<td>6.2%</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>47.4%</td>
<td></td>
</tr>
</tbody>
</table>

**Proteinuria:** Table showing proteinuria range among study participants; among 97 patients, 68 had trace proteinuria & 29 had negative proteinuria in urine routine examination.
This table demonstrates patients with uncontrolled diabetes (HbA1c mean 10.67) have negative proteinuria (29).

<table>
<thead>
<tr>
<th>PROTEINURIA</th>
<th>N</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Std. Error Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c TRACE</td>
<td>68</td>
<td>9.80</td>
<td>1.817</td>
<td>.220</td>
</tr>
<tr>
<td>NEGATIVE</td>
<td>29</td>
<td>10.67</td>
<td>2.561</td>
<td>.476</td>
</tr>
</tbody>
</table>

This table showing comparison between HbA1C values and proteinuria

Among the study participants, in the group of HbA1c less than 7, 3.1% have trace & 1% have negative proteinuria.

In the group of HbA1c (7-10), 34% have trace & 13.4% have negative proteinuria.

In the group of HbA1c (10-13), 30.9% have trace & 8.2% have negative proteinuria.

In the group of HbA1c (13-16), 2.1% have trace & 7.2% have negative proteinuria.

**Retinopathy:** Table showing distribution of proliferative & non-proliferative diabetic retinopathy among study participants.

<table>
<thead>
<tr>
<th>PROTEINURIA</th>
<th>Count</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRACE</td>
<td>3</td>
<td>3.1%</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>34.0%</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>30.9%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2.1%</td>
</tr>
<tr>
<td></td>
<td>68</td>
<td>70.1%</td>
</tr>
<tr>
<td>NEGATIVE</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>13.4%</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>6.2%</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>7.2%</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>29.9%</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>4.1%</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>47.4%</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>39.2%</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>9.3%</td>
</tr>
<tr>
<td></td>
<td>97</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

This table showing comparison between HbA1C levels with occurrence of proteinuria

Among 97 patients, 43 had proliferative DR, (44.3 %), 54 had non-proliferative DR (55.7 %)
Among the study group of 97 patients, 9 are in CKD-3 (e GFR 30-60 mL/min) (9%). 59 are in CKD-4 (e GFR 15- 30 mL/min) (61%). 29 are in CKD-5 (e GFR < 15 mL/min) (30%).

Prevalence of non-proliferative diabetic retinopathy in different stages of CKD patients

Prevalence of non-proliferative diabetic retinopathy in CKD-3 is 13%.
Prevalence of non-proliferative diabetic retinopathy in CKD-4 is 80%.
Prevalence of non-proliferative diabetic retinopathy in CKD-5 is 7%.
Total number of non-proliferative diabetic retinopathy in the study group is 54.
Prevalence of proliferative diabetic retinopathy in CKD-3 is 7%.
Prevalence of proliferative diabetic retinopathy in CKD-4 is 37%.
Prevalence of proliferative diabetic retinopathy in CKD-5 is 56%.
Total number of proliferative diabetic retinopathy in the study group is 43.
The minimum and maximum of age in the study group was 43 & 85.
The minimum and maximum of FBS in the study group was 103 & 434.
The minimum and maximum of PPBS in the study group was 154 & 606.
The minimum and maximum of HbA1c in the study group was 5.1 & 48.6.
The minimum and maximum of duration of DM in the study group was 5 & 27.
The minimum and maximum of microalbumin in the study group was 6 & 20.

**DISCUSSION:** Diabetic nephropathy is the most dreadful microvascular complication of type 2 diabetes mellitus. It is known that in diabetic patients, renal injury starts as microalbuminuria and subsequently progresses to macroalbuminuria which often predicts the subsequent decline in renal function (GFR).\(^{(21,22,23,24,25)}\) However, many recent studies have shown that renal failure can develop in type 2 DM patients without albuminuria.\(^{(26,27,28)}\)

Renal insufficiency in the absence of both retinopathy and albuminuria has been studied too.\(^{(18)}\)

Based on the recent data, it is increasingly evident that this particular group is growing in volume.\(^{(26,27,29,30)}\)

In spite of rapidly accumulating data, the cause for non-albuminuric renal failure is still not clear.

In the present study, we studied the relevant clinical and biochemical characteristics of non-albuminuric renal insufficiency in type 2 diabetes mellitus presented to our hospital. We took the cut-off value of microalbumin level as less than 30 mg/day for defining non-albuminuria.

The KDOQI classification < CKD stage 3 (eGFR less than 60 mL/min.) was taken as renal insufficiency.

Hence, patients with eGFR <60 mL/min. and having UAE <30 mg/day were included in the study. In the present study, a total of 97 patients met the inclusion criteria.

Among these 97 patients, 62 are male and 35 are female. The minimum and maximum age of the patient in the study group is 43 & 85. The mean age observed in the present study is 61.85. The mean age observed in the study is lesser than that observed by Vincent Rigalleau et al.\(^{(29)}\) which is 68 years. In the study by Giuseppe Penno et al.\(^{(28)}\) the mean age was 73. In our study, 48.5% (47 patients) are in 41-60 years of age & 51.5% (31 Patients) are above 60 years.

In the study group of 97 patients, 62 are male (63.9%), 35 are female (39.1%). In the study by Vincent Rigalleau et al.,\(^{(29)}\) the female patients were 46% while in the study by Richard J. Macisaac et al.,\(^{(30)}\) the females were 56%.

Among the study group of 97 participants, 68 (70.1%) had trace proteinuria in routine urine examination, 29 (29.9%) had negative proteinuria in routine urine examination.

The mean HbA1c value in the trace proteinuria is 9.80, and the mean value of HbA1c in the negative proteinuria group is 10.67.

In the study population, 9 patients (9.27%) are under CKD-3 as per KDOQI classification of the stages of CKD, 59 (60.8%) are under CKD-4, 29 (29.89%) are under CKD-5.

As per the study conducted by Giuseppe Penno et al.\(^{(28)}\), normoalbuminuric CKD 4 is 63%, and CKD-5 is 27%.

In the study group of 97 patients, 54 had non-proliferative diabetic retinopathy, 43 had proliferative diabetic retinopathy.

In the non-proliferative DR group, 7 patients (12.9%) are in CKD-3, 43 (79.6%) are in CKD-4, 4 (7.4 %) are in CKD-5.

In the proliferative DR group, 3 (6.9%) are in CKD-3, 16 (37.2 %) are in CKD -4, 24 (55.8 %) are in CKD-5.

The HbA1c value minimum and maximum values are 6 & 16, the mean value is 10.06. In the study by Vincent Rigalleau et al.,\(^{(29)}\) the mean value of HbA1c was (9+1.3). In the study by Richard. j. Macisaac et al.,\(^{(30)}\) it is (7.3+0.3).

The minimum and maximum duration of diabetes in years in our study is 5 & 37. The mean value is 13.98. In the study by Richard. J. Macisaac et al, the mean value of duration of diabetes is 14+1. In the study by Giuseppe Penno et al.\(^{(28)}\) it was 14 years.

**CONCLUSION:** The combination of impaired renal function characterised by micro, albuminuric in patients with type 2 diabetes mellitus is known.

There are certain group of patients, in which impaired renal function won’t be characterised by proteinuria, instead manifests as normoalbuminuric or non-albuminuric (urine microalbumin < 30 mg/ day).

This study was done to know the characteristics of non-albuminuric renal insufficiency patients.

We had the study population of 97 patients.

Among the study population of non-albuminuric renal insufficiency in type 2 diabetes mellitus:

- 62 are male (63.1%) and 35 (36.1 %) are female. Majority of the population are males.
- More than half of the patients 50 (51. 5 %) are more than 60 years of age group.
- Majority of the patients have trace proteinuria 68 (70.1 %) than the other group of negative proteinuria 29 (29.9 %) in routine urine examination.
- Patients with higher HbA1c values had negative proteinuria.
- 54 patients (55.7%) had non-proliferative diabetic retinopathy and (44.3%) patients had proliferative diabetic retinopathy.
- Proliferative retinopathy correlated with the severity of CKD.
- Uncontrolled diabetes mellitus status (larger HbA1c value) correlated with proliferative diabetic retinopathy than the larger duration of diabetes mellitus.
Among the study population, majority of them (59 patients) are in CKD-4 (61%), than the 29 patients of CKD-5 (30%), 9 are CKD-3 patients (9%).

Average duration of diabetes mellitus is 13.98 years in the study group.

The study indicates that non-albuminuric renal failure is an important entity with unique clinical profile which should be kept in mind while managing type 2 DM patients.

REFERENCES