Association of HbA1c with Kidney Dysfunction in Diabetes Mellitus and Cardiovascular Diseases

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ABSTRACT

Diabetes mellitus (DM) and cardiovascular diseases (CVD) are some of the known conditions which predispose an individual to develop chronic kidney disease (CKD). Serum Creatinine (SCr) is the most widely used endogenous marker of GFR (Glomerular Filtration Rate), expressed as its serum concentration or renal clearance. Estimated GFR (eGFR) has been devised for more valid estimate of GFR. Association of HbA1c in renal dysfunction in DM and CVD is recently postulated. The study aimed to evaluate the association of HbA1c & eGFR in DM and CVD. Three hundred seventy subjects including 100 healthy controls, 100 diabetic patients, 100 patients with CVD and 70 patients with both DM and CVD were selected. They were analysed for SCr and HbA1c. The eGFR was calculated by four variable Modification of Diet in Renal Disease (MDRD) equation using QxMD nephrology calculator. Variation in SCr levels among the study groups as compared to controls was not statistically significant. Decrease in e-GFR and increase in HbA1c values in study groups as compared to controls was found statistically significant (p<0.01). Statistically significant positive correlation of HbA1c with SCr values and negative correlation of HbA1c with eGFR values is observed in Controls, DM, and DM with CVD, however, it was not statistically significant in CVD patients. Increased HbA1c in monitoring DM raises an attention for complete evaluation of Renal Function Tests. eGFR can be routinely implemented in renal function tests for early diagnosis of preventable renal impairment due to DM or CVD.

KEY WORDS: cardiovascular disease, diabetes mellitus, eGFR, HbA1c, kidney dysfunction

INTRODUCTION:

Diabetes Mellitus (DM) is one of the major risk factors for chronic kidney disease (CKD). GFR (Glomerular Filtration Rate) provides a tool for evaluation of kidney function. Decrease in GFR precedes all forms of kidney failure. Creatinine is freely filtered at the level of glomerulus and its concentration is inversely proportional to GFR. However, a small but significant and variable proportion of creatinine appearing in the urine is derived from tubular secretion. Creatinine concentration in isolation has a complicated nonlinear relationship to kidney function measured as GFR. This filtration may lead to inadequate recognition of CKD in patients with risk factors for CKD. In patients with CKD, extra renal clearance of creatinine blunts the anticipated increase in serum creatinine in response to falling GFR, at early stages of CKD (Table 1) [1].

Though specific, serum creatinine (SCr) may not exceed upper limit of reference range, until Glomerular Filtration Rate or Creatinine Clearance Rate (CCR) is reduced by 60% of normal. Commonly CCR is a more sensitive indicator of early glomerular dysfunction than that of SCr concentration [2]. Diabetic control is not reflected reliably by traditional blood glucose estimations only due to wide fluctuations. HbA1c provides average glycemia over previous 120 days [3]. Glycated hemoglobin (HbA1c) is an important indicator for long-term glucose control and has recently been recommended for use in the diagnosis of diabetes mellitus (DM) by the American Diabetes Association (ADA) [4]. However, the use of HbA1c for identifying pre-diabetics is a controversial topic [5]. In 2015, the ADA suggested that an HbA1c of 5.7–6.4% (39–46 mmol/mol) is reasonable for the diagnosis of pre-diabetes and that patients with HbA1c > 6.0% (>42 mmol/mol) should be considered to be at very high risk for DM [6]. Many studies have reported an
association between HbA1c and Metabolic Syndrome in non-DM patients. Both are recommended to identify early risks for renal impairment at reversible stage.

Estimation of GFR by using Modification of Diet in Renal Disease (MDRD) equation, which is based on SCr, age, sex, ethnicity and body size could improve the GFR prediction from SCr. The MDRD equation predicts GFR over a wide range of values and can be used for identifying renal insufficiency, assessing progression of renal disease and detecting onset of end stage renal disease (ESRD). It does not require collection of timed urine sample, measurement of height and weight, and cause of renal disease. For early detection of CKD, evaluation of eGFR should be performed for all individuals at risk of CKD even if they show no microalbuminuria. Also, by the time microalbuminuria manifests itself almost 25% of nephron function is already lost. Early detection allows enough time for diagnosis and treatment but requires explicit testing strategies for asymptomatic individuals at risk.

This study was designed to evaluate the association of HbA1c & eGFR in Diabetes Mellitus (DM) and Cardiovascular Diseases (CVD).

MATERIALS AND METHODS:
Ethical approval for the present study was obtained from the Institutional Review Board. The study sample consisted of 370 individuals in age group 40-60 years. The study subjects comprised of 100 healthy controls, 100 pre-diagnosed patients with DM, 100 patients with CVD and 70 patients having both DM and CVD. From each study subject 5 mL of fasting venous blood was drawn by disposable syringe with full aseptic precaution. 1 mL was transferred to an Eppendorf tube with EDTA for HbA1c analysis and 4 ml of collected blood was taken in a properly cleaned & dried test tube without anticoagulant for serum creatinine.

Scr estimation was done on Olympus AU 680 Clinical Chemistry Analyzer with Modified Jaffe's Method. GFR was estimated by the 4 variables Modification of Diet in Renal Disease (MDRD) equation using QxMD nephrology calculator. Low eGFR was defined as eGFR<60 mL/min/1.73 m2. MDRD Formula is given below:

\[
\text{eGFR} = 186 \times (\text{SCr})^{-1.154} \times (\text{Age in years})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if Black})
\]

HbA1c estimation was done on Chem-7 Semiautomatic analyser with Ion Exchange Resin, Binding Method. Patients were studied by categorizing them depending on HbA1c<6.5% and 6.5%. Individuals with HbA1c <6.5% were considered with good glycaemic control.

Results were expressed as Mean ± SEM. Data were analysed with SPSS Statistical Software (v22.0). Unpaired t-test & Pearson's Correlation test were done for the comparison and correlation with each other among the study groups. p <0.05 was considered as significant.

RESULTS:
The study population comprising of 370 subjects was investigated for serum creatinine and HbA1c values. The eGFR was calculated using MDRD formula. Gender distribution in the study population is given in Table 1.

Table 1: Gender distribution: Study Population.

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>54 (54%)</td>
<td>46 (46%)</td>
</tr>
<tr>
<td>DM</td>
<td>48 (48%)</td>
<td>52 (52%)</td>
</tr>
<tr>
<td>CVD</td>
<td>49 (49%)</td>
<td>51 (51%)</td>
</tr>
<tr>
<td>DM + CVD</td>
<td>36 (51.42%)</td>
<td>34 (84.58%)</td>
</tr>
<tr>
<td>Total</td>
<td>187 (50.54%)</td>
<td>183 (49.46%)</td>
</tr>
</tbody>
</table>

Table 2: Serum Creatinine among Study Groups.

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>Mean (SEM)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>1.14 (0.06)</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>1.20 (0.04)</td>
<td>0.5420</td>
</tr>
<tr>
<td>CVD</td>
<td>1.04 (0.03)</td>
<td>0.1271</td>
</tr>
<tr>
<td>DM + CVD</td>
<td>1.07 (0.04)</td>
<td>0.3384</td>
</tr>
</tbody>
</table>

21.9% (81/370) of the subjects had decreased eGFR (<60 ml/min/1.73 m2) indicative of CKD. 22.22% (18/81) subjects with decreased eGFR had SCr values within the reference range (0.6-1.2 mg/dl). 77.78% (63/81) subjects with decreased eGFR, had high SCr values.

Among subjects with decreased eGFR, 50.61% were suffering from diabetes mellitus, 8.64% were suffering from CVD and 23.46% were suffering from DM and CVD. Frequency of decreased eGFR in diabetic subjects was 43%, in CVD subjects was 7.00%, in control subjects was 14% and that in subjects suffering from DM as well as CVD was 19%.

Levels of SCr, e-GFR and HbA1c were compared among the study groups as given in Table II, III and IV respectively. Variations in SCr levels among the study
groups i.e. DM (n=100, p>0.05), CVD (n=100, p>0.05) and DM with CVD (n=70, p>0.05) as compared to controls (n=100) was not statistically significant (Table 2).

Decrease in e-GFR in study groups i.e. DM (n=100, p<0.0001), CVD (n=100, p<0.01) and DM with CVD (n=70, p<0.001) as compared to controls (n=100) was found statistically significant (Table 3). HbA1c levels in study groups i.e. DM (n=100, p<0.0001), CVD (n=100, p<0.0001) and DM with CVD (n=70, p<0.0001) compared to controls (n=100) are found to be significantly increased (Table 4).

Correlation of SCr and eGFR values with HbA1c levels among the study groups was studied with Pearson's correlation test, as given in Table 5.

Statistically significant positive correlation of HbA1c with SCr values is observed in Controls (n=100, p<0.05) (Figure 1), DM (n=100, p<0.001) (Figure 2), and DM with CVD (n=70, p<0.001) (Figure 3), but it was not statistically significant in CVD patients (n=100, p>0.05).

There was statistically significant negative correlation of HbA1c with eGFR values in Controls (n=100, p<0.001) (Figure 4), DM (n=100, p<0.001) (Figure 5), and DM with CVD (n=70, p<0.001) (Figure 6), but it was not statistically significant in CVD patients (n=100, p>0.05).

**DISCUSSION:**

Diabetic nephropathy is a chronic microvascular complication in uncontrolled DM. In early renal impairment, classical markers (Urea & Creatinine) may be normal, but there are early glomerular changes like thickening of basement membrane, accumulation of matrix material in the mesangium, subsequently nodular deposits with
consequent microalbuminuria. At this stage, glomerular pathological changes can be reversed by pharmacological intervention. So, newly detected or known DM patients need monitoring for glycemic control, with simultaneous monitoring for early reversible nephropathy.

100 known DM patients were taken in the study in the age group of 40-60 years. Age distribution was similar to Sheikh et al. and Mogensen et al. In contrast to Venugopal & Lyer where majority of subjects were overweight or obese, majority of subjects in our study were with normal BMI.

On comparison, the variation in mean SCr values in the study subjects compared to controls was not statistically significant. But the decrease in eGFR in patients of DM, CVD and DM with CVD was statistically significant as compared to controls. This clearly shows that the early onset of kidney dysfunction in DM and CVD was failed to be indicated by the changes in SCr values. But eGFR detects it at a very early stage even when SCr levels were in the normal reference range. These finding in the study were consistent with our hypothesis.

The extent of decrease in mean eGFR values in DM and DM with CVD patients was more as compared to the mean eGFR values in CVD group in our study. This may be attributed to the accelerated renal damage caused by damage to the glomerular basement membrane in diabetic nephropathy.

22.22% (18/81) subjects with decreased eGFR had serum creatinine values within the reference range (0.6-1.2 mg/dl). This observation in our study signifies the importance of eGFR in detecting renal dysfunction at the early stage even with normal SCr values. Moreover, amongst the
apparently healthy controls with no recorded disease or related symptomatology, the eGFR values were below the recommended range with normal SCr values in 14% of controls. This was the unique finding in our study insisting implementation of eGFR estimation in routine health check-ups along with SCr, so that the impending renal dysfunction can be detected even in normal individuals or pre-diabetic population.

In the present study, the rise in HbA1c levels in DM, CVD and DM with CVD was statistically significant compared to that in controls. Mean HbA1c levels in DM and DM with CVD were higher than those in CVD patients. This can be credited to the deranged glycaemic control in DM and DM related complications.

Seven percent of the controls showed higher HbA1c values more than the recommended range (>6.5%) indicating the borderline derangement of glycaemic control. Those individuals may be pre-diabetic, and have not been assessed for the same due to absence of significant symptomology. This observation was also encountered by Arnold et al[16] where they found over half of all nondiabetic participants at high risk of developing diabetes according to the ADA specifications (5.7–6.4%)[16]. This finding suggest incorporation of HbA1c in screening of individuals for risk of diabetes so as to capture a high proportion of high risk individuals.

In previous studies, higher HbA1c levels has found to be been associated with CKD in patients with diabetes, even in the absence of albuminuria and retinopathy[17,18]. Some studies have stated that HbA1c served as a powerful predictor of CVD and all-cause mortality in their study population with and without diabetes[17,19-21]. Very few studies have explored the association of HbA1c with CKD in the general population, regardless of the diabetic status[22,23].

In the present study, statistically significant positive correlation of HbA1c with SCr values is observed in Controls, DM, and DM with CVD, but it was not statistically significant in CVD patients. Sheik et al[19] found significant positive correlation of HbA1c with SCr in diabetic patients.

There was statistically significant negative correlation of HbA1c with eGFR values in Controls, DM, and DM with CVD, but it was not statistically significant in CVD patients. It proved that HbA1c is equally effective as eGFR, in accessing the predisposition to renal dysfunction. Some studies reported that A1c is a reflection of long-term glycemic fluctuation, were found to increase the risk of chronic kidney disease in type 2 diabetic patients when eGFR decreased<60 ml/ min1.73 m2[24-26]. In our study it is proved that, HbA1c is strongly associated with kidney dysfunction as evident by the significant decrease in eGFR and increased HbA1c levels in DM and CVD.

CONCLUSION:

It can be concluded that, raised HbA1c in monitoring Diabetes Mellitus raises an attention for complete evaluation of Renal Function Tests. For early diagnosis of preventable renal impairment due to DM or CVD, eGFR can be routinely implemented in renal function tests.

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