The Association between Serum Creatinine, HIV-Infection and Metabolic Variables in Patients Living with Diabetes Mellitus

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ABSTRACT

Background: Globally, diabetes mellitus (DM) remains the major aetiological factor for developing end-stage renal disease (ESRD) being characterised by a reduction in glomerular filtration rate (GFR) and a rise in the levels of serum urea and creatinine. No current data is available on the association between creatinine and glycaemic control within the context of HIV infection.

Objectives: To determine an association between serum creatinine and glycaemic control in patients living with DM (DM+) in an HIV endemic area.

Methods: Standardised clinic sheets were used from the DM clinic at Edendale Hospital, Pietermaritzburg, South Africa, from 1 January 2019 to 31 December 2019.

Results: This study had 957 DM+ patients; 622 (69.50%) had creatinine <104umol/l while 273 (30.50%) had creatinine ≥104umol/l (62 with unknown creatinine values). Almost one-sixth of patients had an HIV infection (HIV+) (146, 15.30%). In patients with type 2 DM (DM2+) and HIV+, there was improved glycaemic control (HbA1c 9.03% vs 9.51%, p=0.027). In patients with creatinine <104umol/l, those with CD4 values between 200-499 cells/uL had poorer glycaemic control when compared to those with CD4 ≥500 cells/uL (10.37% vs 8.91%, p=0.019). Patients with HbA1c levels < 7.00% with creatinine ≥ 104umol/l had significantly higher triglyceride levels than those with creatinine < 104umol/l (2.04 vs 1.43, p=0.001).

Conclusion: Serum creatinine is significantly associated with glycaemic control among DM+ patients. Our study suggests elevated creatinine levels place patients into a higher risk category for developing dyslipidaemia and cardiovascular morbidity and mortality, hence screening should form part of the comprehensive management of DM.

Keywords
Diabetes Mellitus, Glycaemic control, Serum creatinine, HbA1c.

Introduction
Diabetes Mellitus (DM) is a major aetiological factor for developing end-stage renal disease (ESRD), the most advanced stage of kidney disease [1]. ESRD is characterised by a reduction in glomerular filtration rate (GFR) of <15ml/minute [2] with an associated elevation in the levels of serum urea and creatinine [3]. Creatinine is a nitrogenous waste product produced by muscle and eliminated via the kidneys [4]. Globally, 463 million patients are living with DM (DM+) with more than 19 million patients living in Africa [5]. Estimates predict that by 2045, there will be approximately 47 million DM+ patients in Africa alone [5].
Limited studies have documented results between glycaemic control and serum creatinine in DM+ patients. This association varies greatly, with Prasetyorini et al. finding no significant correlation [6] (p=0.693) while Kommineni Sai Subramanyam et al. reporting a strong positive correlation (p<0.001) [7]. Bamanikar and colleagues found that higher serum levels of urea and creatinine were found in DM+ patients after excluding those with known kidney disease [8].

In Africa, limited information is available on this topic. Locally, Khoza et al. assessed the effect of HIV on both glycaemia and renal function in patients living with Type 2 DM (DM2) in Soweto, South Africa. However, no mention was made of any relationship between glycaemic control and serum creatinine [9].

Glycaemic control in patients living with DM who are HIV-infected (DM+HIV+) has been shown to be suboptimal [9-11]. This can occur in those who are antiretroviral therapy (ART) naïve, those on ART as well as in those with a lower CD4 level <200 cell/μL [9].

Approximately 15.00% of patients have DM+HIV+ [12]. HIV associated nephropathy (HIVAN), defined on renal biopsy, is the most common cause of chronic kidney disease (CKD) in HIV+ patients [13]. It can cause a rapid rise in creatinine as well as in proteinuria [14]. Without treatment, CKD can progress to ESRD within weeks to months [15]. Although the prevalence of presumed HIVAN is declining since the introduction of cART (combined Antiretroviral Therapy) [16], DM+HIV+ patients are still at greater risk of developing CKD [12] when compared to those DM+ or HIV+ patients or those having no co-morbidities (DM-HIV). Pillay et al. found that DM+HIV+ patients had significantly poorer blood sugar control than those with DM alone [17].

This study aimed to determine a relationship between serum creatinine and glycaemic control in an HIV endemic area within South Africa, a country with the highest prevalence of HIV (13.00%) [18].

Methods
A retrospective, analytical cohort study was performed using data collected from patients who attended a specialised diabetes clinic at Edendale Hospital (EDH), Pietermaritzburg, KwaZulu-Natal. Clinicians used a standardised, comprehensive clinic sheet for all patients consulted in this clinic that has been approved by the University of KwaZulu-Natal Biomedical Research and Ethics Committee BREC – BCA 194/15. The data for this study included all patients 18 years or older who attended the diabetes clinic at EDH between 1 January 2019 to 31 December 2019. The standard operating procedure was for patients to have fasted before coming to the DM clinic.

Patient demographics, serum creatinine, mean HbA1c, random blood glucose, HIV status and the type of DM were recorded, in addition to other variables from the datasheet. Missing, incomplete, or incorrectly completed data were not considered. Good glycaemic control was defined as HbA1c value <7.00% [19]. The Bio-Rad D-10 machine (Bio-Rad, USA) was used for analysing the HbA1c values at the laboratory. Both the laboratory and the machines are NGSP (National Glycohaemoglobin Standardization Program) accredited to maintain standardisation of HbA1c results while the random glucose measurement (mmol/L) was determined using an Accu-Chek® glucometer (Roche, Switzerland). Serum creatinine, as determined by National Health Laboratory Services (NHLS), was classified as high if the level was ≥104μmol/l. Creatinine levels were analysed using the Siemens Dimension EXL which is IDMS-traceable using the Modified Jaffe method. For each patient one test was conducted per year for each investigation.

When estimating the glomerular filtration rate (GFR) values, the CKD-EPI formulae was used as it is more accurate than the MDRD formula for GFR values >60ml/min/1.73m² and can therefore be used to detect patients with mild renal impairment. It can be used to grade severity of renal impairment using the KDIGO 2012 recommendations. The CKD-EPI formula used here does not employ a correction factor for race.

Statistical Analysis
Statistical analysis was conducted with numerical data using the ANOVA (Analysis of Variance) test, whilst categorical data relationships were determined using either Chi-square or Fisher’s exact tests. A p-value <0.05 was used as an indicator of significance. Data were analysed by Statistical Package for Social Science (SPSS) version 25 for Windows (SPSS Inc., Chicago, IL, USA).

The effect of HbA1c on GFR was done using a binary logistic regression. Chi square tests were done for the bivariate data and the significant variables were chosen for the logistic regression. The effect of HbA1c on GFR was adjusted for age, HIV and hypertension.

Results
(A) Epidemiology
Data of 957 DM+ patients were used for this study. Six-hundred and twenty-two (69.50%) participants had creatinine <104μmol/l, while 273 (30.50%) had creatinine ≥104μmol/l (62 were excluded as creatinine (eGFR) values were unavailable). A significant proportion of the patient cohort comprised DM2 (822, 86.20%) while 132 (13.80%) of DM patients had DM1 (3 unknown). Almost one-sixth of the cohort was HIV+ (146, 15.30%). Of this HIV+ cohort with DM, 84 (57.50%) were on a fixed-dose combination (FDC) of antiretroviral treatment (ART).

(B) Age
Age was statistically significant when assessing creatinine levels of patients – elevated levels were more frequently seen in older patients. Patients with creatinine levels of <104μmol/l were significantly younger than those with creatinine ≥104μmol/l (mean age of 49.91 years vs 62.01 years, respectively (p<0.001)). A
similar trend was noted in the urine protein-creatinine ratio (PCR) values (<0.015 versus ≥0.015) with the mean age of 49.05 vs 55.31 years respectively, p=0.003. The duration of being diagnosed with DM showed a similar association with creatinine levels of <104μmol/l versus ≥104μmol/l being 8.74 years vs 14.11 years respectively, p<0.001. DM+ patients with uPCR values <0.015 versus ≥0.015 had a mean duration of DM of 7.66 years vs 10.77 years respectively (p=0.01).

An inverse relationship was present between HbA1c values and age (p=0.01). The effect of HbA1c on GFR was adjusted for age, HIV and hypertension.

(C) Urine Protein-Creatinine Ratio (uPCR) and Glycaemic Control

HbA1c values were significantly higher in the HIV-uninfected DM2 patients when the uPCR was ≥0.015 versus <0.015 (9.78% vs 9.04%, p=0.025). No significant associations were found between DM1 patients and uPCR values or in those DM+HIV+ patients and uPCR values.

(D) Type 1 vs Type 2 DM

DM1 patients had higher mean HbA1c levels than DM2 patients did. In HIV- patients, the mean HbA1c was higher in DM1 compared to DM2 patients (10.08% vs 9.51%, p=0.011). After adjusting for age, this association became insignificant (p>0.05). Creatinine levels were significantly higher in DM2 patients compared to DM1 patients (109.19μmol/l vs 79.48μmol/l, p<0.001).

(E) HIV status and HbA1c

DM+HIV+ patients had lower mean HbA1c levels compared DM+HIV- patients. In DM1+HIV+ patients with serum creatinine values ≥104 μmol/l vs <104μmol/l, there were lower HbA1c levels of 7.20% vs 10.45% respectively, p=0.002. In DM2+HIV+ patients, significantly lower HbA1c levels were found when compared to those DM2+HIV- patients (9.03% vs 9.51%, p=0.027). In addition, DM2+HIV+ patients with serum creatinine values ≥104μmol/l had significantly lower mean HbA1c levels than DM2+HIV- patients with creatinine values ≥104μmol/l (8.61% vs 9.51%, p=0.025).

Table 1: Association between uPCR and Mean HbA1c in the context of HIV-infection.

<table>
<thead>
<tr>
<th></th>
<th>HIV Uninfected</th>
<th>HIV Infected</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Count</td>
<td>HbA1c (%) ± SD</td>
<td>Count</td>
</tr>
<tr>
<td>Type 1 Urine PCR</td>
<td>&lt; 0.015</td>
<td>10</td>
<td>9.69 (1.57)</td>
</tr>
<tr>
<td></td>
<td>≥ 0.015</td>
<td>14</td>
<td>10.18 (2.10)</td>
</tr>
<tr>
<td>Type 2 Urine PCR</td>
<td>&lt; 0.015</td>
<td>57</td>
<td>9.04 (2.14)</td>
</tr>
<tr>
<td></td>
<td>≥ 0.015</td>
<td>139</td>
<td>9.78 (2.05)</td>
</tr>
<tr>
<td>Overall</td>
<td>T2DM</td>
<td>693</td>
<td>9.51 (2.25)</td>
</tr>
<tr>
<td></td>
<td>T1DM</td>
<td>115</td>
<td>10.08 (2.09)</td>
</tr>
</tbody>
</table>

Table 2: Association between creatinine, type of DM, HIV status and HbA1c level.

<table>
<thead>
<tr>
<th>Creatinine (umol/l)</th>
<th>HIV Status</th>
<th>Uninfected</th>
<th>Infected</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM1+ creatinine &lt; 104</td>
<td>Count</td>
<td>HbA1c (%) ± SD</td>
<td>Count</td>
<td>HbA1c (%) ± SD</td>
</tr>
<tr>
<td>DM1+ creatinine ≥ 104</td>
<td>96</td>
<td>10.05 (1.94)</td>
<td>13</td>
<td>10.45 (1.48)</td>
</tr>
<tr>
<td>DM2+ creatinine &lt; 104</td>
<td>7</td>
<td>9.91 (4.05)</td>
<td>4</td>
<td>7.20 (1.72)</td>
</tr>
<tr>
<td>DM2+ creatinine ≥ 104</td>
<td>432</td>
<td>9.55 (2.19)</td>
<td>81</td>
<td>9.14 (2.21)</td>
</tr>
<tr>
<td>Total DM1+</td>
<td>220</td>
<td>9.51 (2.37)</td>
<td>42</td>
<td>8.61 (2.41)</td>
</tr>
<tr>
<td>Total DM2+</td>
<td>155</td>
<td>10.08 (2.09)</td>
<td>17</td>
<td>9.68 (2.05)</td>
</tr>
</tbody>
</table>

Table 3: Associations between Creatinine, FDC, CD4 and HbA1c.

<table>
<thead>
<tr>
<th>Creatinine &lt; 104 umol/l</th>
<th>Creatinine ≥ 104 umol/l</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
<td>HbA1c (%) ± SD</td>
<td>Count</td>
</tr>
<tr>
<td>HIV-infected Not on FDC</td>
<td>21</td>
<td>9.53 (2.29)</td>
</tr>
<tr>
<td>On FDC</td>
<td>63</td>
<td>9.24 (2.17)</td>
</tr>
<tr>
<td>CD4&lt;100</td>
<td>1</td>
<td>8.70 (0)</td>
</tr>
<tr>
<td>CD4: 100–199</td>
<td>4</td>
<td>7.47 (2.51)</td>
</tr>
<tr>
<td>CD4: 200–499</td>
<td>17</td>
<td>10.37 (1.65)</td>
</tr>
<tr>
<td>CD4: 500+</td>
<td>29</td>
<td>8.91 (2.13)</td>
</tr>
<tr>
<td>HIV uninfected</td>
<td>530</td>
<td>9.64 (2.15)</td>
</tr>
</tbody>
</table>
control than those with CD4 ≥500 cells/μL (10.37% vs 8.91%, p=0.019). Among DM+HIV- patients, no significant differences in HbA1c levels were seen between those with creatinine levels <104 μmol/l or ≥104 μmol/l (9.64% vs 9.52%, respectively, p=0.499).

An odds ratio (OR) analysis illustrated that in DM+HIV+ patients between 61-70 years is 1.92 times more likely than ≤30 years to have abnormal HbA1c. Moreover, DM+HIV+ patients between 41-50 years are 2.99 times more likely than ≤30 years to have abnormal HbA1c.

In DM+HIV+ patients on ART for <5 years, those with creatinine levels <104 μmol/l, had lower HbA1c levels than those with creatinine ≥104 μmol/l (9.78% vs 7.39%, p=0.001). No such significance was found for those on ART between 6-10 years, 11-15 years and 15+ years. The DM+HIV- patients had a significantly shorter DM duration than the DM+HIV+ patients (7.54 years vs 10.69 years, p<0.001).

### F Serum Creatinine and lipids

DM+ patients with HbA1c levels <7.00% and creatinine <104 μmol/l, had significantly lower triglyceride levels than those with a creatinine ≥104 μmol/l (1.43 vs 2.04, p=0.001). Furthermore, in those with creatinine <104 μmol/l, those with HbA1c levels <7% had significantly lower triglyceride levels than those with HbA1c levels ≥7% (1.43 vs 1.80, p=0.013). DM+ patients with HbA1c levels ≥7% with a creatinine <104 μmol/l had a significantly higher high-density lipoproteins (HDL) level compared to those with creatinine levels ≥104 μmol/l (1.26 vs 1.18, p=0.011). We found no association between low-density lipoproteins (LDL) to HbA1c levels or creatinine in our study (Table 4).

### G Body Mass Index (BMI)

In the cohort with HbA1c <7%, those with a creatinine level of <104 μmol/l compared to ≥104 μmol/l had a mean BMI of 34.63 vs 31.77 respectively, p=0.083. Similarly, in the HbA1c ≥7% cohort, no significance between BMI and HbA1c was found (p=0.098).

### Discussion

Glycaemic control varies among DM patients, while serum creatinine concentrations vary with age. Available literature reports that serum creatinine may increase steadily with age [21] or remain constant for average healthy patients between 20 and 70 years of age, thereafter increasing slowly after 70 years [22]. In the elderly, those with higher creatinine levels are associated with functional limitation [23]. In this group, the association of a low creatinine level with functional limitation suggests that creatinine levels are influenced by factors other than kidney function and muscle mass in the elderly [23]. Our study found that increasing age was associated with higher creatinine levels and found that those with elevated creatinine levels of greater than 104 μmol/l was associated with a longer duration of DM. We postulate that this is due to CKD secondary to diabetic kidney disease, especially in an environment where most patients have poorer glycaemic control. Our study also found that those DM2 patients have significantly higher creatinine levels than in DM1 patients. We postulate that the reason for the elevated creatinine levels in DM2 is due to the increased duration of DM.

In our study DM1 patients were found to have significantly poorer HbA1c levels than DM2. When assessing BMI and HbA1c, we found no statistically significant relationship. This contrasted with other studies, which found that HbA1c was significantly associated with BMI levels [24]. Chetty et al. suggested that genes and a positive family history of DM affected glycaemia in DM1 patients as significantly, if not more, than in DM2 patients [19]. It was also found that both DM1 patients and DM2 patients with creatinine ≥104 had lower HbA1c levels. This was possibly due to renal impairment which led to decreased insulin catabolism by the kidneys which play an essential role in the clearance and degradation of circulating insulin [25]. When assessing proteinuria (through urine PCR levels), poorer glycaemic control was found in those with uPCR values ≥0.015. Although we expected that the patients with proteinuria would have renal impairment and have a lower HbA1c level due to this decreased insulin catabolism, higher HbA1c levels were found in our study. Mohan et al found a similar finding that higher HbA1c levels were found in patients who had proteinuria [26]. He emphasised the need to optimise glycaemic control to prevent further nephropathy [26]. This explains how higher glycaemia may cause renal dysfunction, leading to proteinuria and a rise in creatinine levels, while lower glycaemia may occur secondary to renal dysfunction due to decreased insulin catabolism. This highlights the variation in glycaemic control which may arise in DM patients based on the underlying mechanism.
HIV played a significant role on HbA1c levels. Although glycaemic control has been found to be sub-optimal in DM+HIV+ patients [9-11], our study found that those DM+HIV+ patients, had lower HbA1c levels than DM+HIV- patients, suggesting improved glycaemic control. A possible reason for this can be attributed to the duration of DM. In the DM+HIV+ cohort, DM1 and DM2 patients with elevated creatinine levels had substantially lower HbA1c levels (being statistically significant in DM1 patients). In the DM+HIV- cohort, fewer discrepancies in HbA1c levels were found when comparing elevated creatinine levels and the type of DM. Avari et al. recommended that HbA1c should NOT be used in the diagnosis of DM+HIV+ patients as it may underestimate the actual value of HbA1c due to a greater HbA1c-glucose discordance which is possibly related to faster turnover time of red blood cells [27]. This would promote the idea that the values reported may be markedly underestimating the real glycaemic status of the HIV-infected patients, suggesting that caution should always be exercised in HIV+ patients. However, newer evidence emerging from a local South Africa study in 2021 by Hird et al. shows that HIV is unlikely to affect HbA1c values in a South African context [28]. Another reason for this improved glycaemic control in DM+HIV+ may be due to the multifaceted interventions implemented at the DM Clinic at Edendale Hospital since the previous study done in 2012-2013. This would suggest that patients who have multiple co-morbidities are more concerned about their health, leading to more significant efforts to manage their chronic conditions.

Furthermore, our study also found that those patients with lower CD4 counts between 200-499 had higher HbA1c levels when compared to those with CD4 values of greater than 500. This could be attributed to adherence issues, especially in a developing world setting, where those who take their ART would be the ones who are most likely also taking their medication for DM. Another reason for this phenomenon is that there is greater inflammatory milieu associated with lower CD4 count, and this could account for poorer glycaemic control achieved [29]. In addition to these findings, those D+H+ on ART had increased HbA1c levels with creatinine levels <104umol/l compared to creatinine ≥104umol/l. This was a surprising finding, as we would expect increased HbA1c levels to occur in patients with creatinine ≥104umol/l. We postulate that this is due to HbA1c discordance with actual blood glucose levels. Slama et al. supports this idea as he found significant discrepancies between fasting glucose levels and HbA1c levels [28]. Diop et al. postulated that the inappropriately low HbA1c in HIV-infected patients could be due to antiretroviral-induced subclinical haemolsysis [30].

When assessing lipid profiles, we found that those with higher creatinine values had substantially higher triglyceride levels. In addition to this, lower creatinine levels were associated with higher HDL levels. The mechanisms leading to hypertriglycerideremia directly relate to insulin resistance and hyperglycaemia [31]. Both factors lead to overproduction and decreased clearance of triglyceride-rich lipoproteins from the liver, and, occasionally, an altered postprandial lipoprotein metabolism [32]. Hyperglycaemia can also contribute to higher creatinine levels as renal function declines [33]. Our study found that poorer glycaemic control linked with raised creatinine levels was associated with lower HDL levels. A low HDL has been associated with the onset and progression of CKD [34] and is associated with increased risk for cardiovascular disease (CVD) [35]. In 2020, a meta-analysis showed that HDL level is associated with increased mortality risk from all causes, cardiovascular disease and even cancer in extremely low HDL levels (and extremely high levels) [36]. Furthermore, in our study, we found that those patients with HbA1c levels <7% with a raised creatinine level had elevated triglyceride levels. These increased triglyceride levels in renal disease are due to delayed catabolism of triglyceride-rich lipoproteins, with no differences in production rate [37]. A John Hopkins study has reported that higher triglyceride levels are associated with a greater risk of increased creatinine levels [38]. This underscores the importance of monitoring kidney function, as worsening renal function (seen through raising creatinine), may be responsible for precipitating dyslipidaemia. This would further compromise the vascular system in both patients living with DM and HIV infection. Ye et al. determined that in DM2 patients higher serum triglyceride levels are associated with increased risks of cardiovascular disease [39]. Moreover, it has been reported that elevated triglyceride levels increased the risk for sensory neuropathy secondary to HIV+ patients, independently of other risk factors, in those in the highest tertile compared to the lowest tertile [40], independent of other known risk factors such as DM. In addition to these, hypertriglycerideremia also poses an increased risk of strokes, pancreatitis, fatty liver disease [41], and an increased risk of developing proteinuria [42]. These illustrate various complications that arise from abnormal lipid profiles and highlight the importance of maintaining lower creatinine levels, thereby promoting improved lipid profile levels.

Limitations
- Not all patients had all results filled in their datasheets.
- As this was a retrospective study, no causal relationships could be determined; rather, associations were defined.
- Early cases of diabetes are often associated with hyper filtration - so they may not find an association with poor control.

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Conclusion
Serum creatinine is significantly associated with glycaemic control among DM+ patients. DM2+ patients have considerably higher creatinine levels than DM1+ patients, likely due to the longer duration of DM. In DM+HIV+, HbA1c levels should be used with caution due to a likely underestimation of the true glycaemic control. In this same cohort, those with CD4 counts between 200-499 have higher HbA1c levels than those with CD4 values of greater than 500, suggesting that those who take their ART are more likely to also take their medication for DM or the greater inflammation associated with lower CD4 levels. We also found
a significant association between elevated creatinine levels and elevated triglyceride levels, highlighting the usefulness of serum creatinine values. Our study suggests that all patients with elevated creatinine levels should be regarded as being in a higher risk category for the development of dyslipidaemia and screening for it should always be included in the comprehensive management of DM.

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