Differences in glycemic control and survival predict higher ESRD rates in diabetic first nations adults

Abstract

Purpose: Diabetic First Nations people (FN) have higher ESRD rates than other Canadians but the reasons remain unclear. We sought to better understand this disparity by comparing demographic, laboratory and survival features of diabetic FN and other Saskatchewan residents (OSK) by renal function stage.

Methods: Prevalent diabetes cases in 2005/06 were identified in Saskatchewan’s two largest health regions using administrative databases, and linked with centralized laboratory tests. They were sub-divided into five stages of renal function using estimated glomerular filtration rates (eGFR) that were determined in 992 of 2,321 FN (42.7%) and 14,054 of 21,886 OSK (64.2%). Age, sex, urine microalbumin (MA), glycosylated hemoglobin (A1C), low density lipoprotein cholesterol (LDL-C) and two year mortality risk was compared for all subjects.

Results: Diabetic FN were younger (mean age 52.7 vs. 64.2, p<0.0001), more likely to be female (59.6% vs. 45.4%, p<0.001), had increased MA (56.6% vs. 48.4%, p<0.0001) and displayed higher mean A1C levels (8.16% vs. 7.36%, p<0.0001) than OSK. Despite a larger proportion having eGFR’s >60 ml/min (87.0% vs.77.3%, p<0.001), FN were also more likely to have ESRD (2.3% vs.0.8%, p<0.001). Although FN with eGFR’s ≥30 ml/min experienced higher age/sex adjusted mortality risk than OSK, the trends for both adjusted and unadjusted mortality risks for those with advanced pre-ESRD renal failure were lower for FN than for OSK.

Conclusions: Elevated rates of ESRD experienced by FN with diabetes are related to poorer glycemic control at all levels of renal function, and lower age-related mortality at advanced stages of chronic kidney disease.
Diabetes mellitus is the most common cause of end stage renal disease (ESRD) in Canada [1] but the burden of diabetic ESRD upon indigenous peoples is of particular concern. In 1994, a disproportionate incidence of ESRD was reported among Saskatchewan First Nations (FN) people with diabetes [2] and a recent study shows that such disparities persist [3]. While the mechanisms underlying these observations are incompletely understood, there are two possibilities. First, FN with diabetes may be more prone to the initial development of diabetic glomerulosclerosis, which can lead to ESRD. This is supported by reports that diabetic FN have higher rates of microalbuminuria [4]. Second, FN with early diabetic glomerulosclerosis may progress to ESRD more frequently than others because of a more rapid course and/or lower mortality rates. Although our recent findings that FN are diagnosed at a younger age and experience a longer duration between diabetes and ESRD diagnoses are consistent with a differential mortality effect [5] other studies report lower survival rates among FN with all-cause advanced chronic kidney disease (CKD) [6].

Identifying the mechanisms underlying ethnicity-based differences in diabetic ESRD is important for understanding the pathophysiology of this devastating complication, for optimal planning of prevention/management initiatives and to help reduce health disparities among disadvantaged groups. Accordingly, the objectives of this study were to clarify these mechanisms by comparing demographic characteristics, key laboratory indicators of diabetes care, and survival of diabetic FN and other Saskatchewan (OSK) residents across the complete spectrum of kidney function. This was achieved through linkage of laboratory data with health care system administrative data.

Methods

Study Populations

This population-based cross-sectional study in Saskatchewan’s two largest health regions during 2005/06 compared FN and OSK adults with diabetes by stage of renal function. The study was approved by the University of Saskatchewan, Saskatoon Health Region and Regina/Qu’Appelle Health Region Ethics Review Boards. Study populations were identified from Ministry of Health databases used to administer health insurance benefits to approximately 99% of the total Saskatchewan population [7]. Beneficiaries were sub-divided into FN and OSK, and by age and sex. FN are indigenous to Canada and, for this study, included those registered under Section 6 of the Indian Act [8]. Most OSK are of European origin but include non-registered FN (<0.5%) and Métis (about 5%) [9]. Saskatchewan’s population was approximately one million people during the study period and over 10% were FN. Almost 50% of the provincial population lived in the two Health Regions [10].

Diabetic adults aged 20 years and older were identified from databases using a validated algorithm [11] based on National Diabetes Surveillance System case definitions [12]. These required one hospitalization or two physician service claims for diabetes (ICD-9 250.x or ICD-10-CA E10-E14.xxx) within any 730 day period. All diabetes records related to pregnancy were removed to avoid inclusion of gestational diabetes cases. We were not able to distinguish between types 1 and 2 diabetes mellitus but <2% of newly diagnosed diabetes cases in Canada are under age 20 [13], the age group with the highest type 1 diabetes incidence [14].

The Saskatchewan Health Quality Council defines the diabetes incident year as the first fiscal year (April 1 to March 31) in which individuals meet the diabetes case definition when there has been no prior diabetes diagnosis for at least two years [15]. For each year thereafter, individuals covered by Saskatchewan Health are counted as prevalent cases. Only prevalent cases counted on April 1st of the 2005/06 fiscal year were included in this study and the total numbers on that date comprised the core denominators for our analyses.

Laboratory Data Linkage and Definition of Chronic Kidney Disease Sub-Groups

Using encrypted unique identifiers, prevalent diabetes cases in the Saskatoon and Regina/Qu’Appelle Health Regions were

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (%)</th>
<th>First Nations people (%)</th>
<th>Other Saskatchewan people (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic Subjects in Saskatchewan</td>
<td>50,713</td>
<td>6,184</td>
<td>44,529</td>
</tr>
<tr>
<td>Diabetic Subjects in Two Health Regions (%)</td>
<td>24,207 (48)</td>
<td>2,321 (38)</td>
<td>21,886 (49)</td>
</tr>
<tr>
<td>eGFR* Measured (%)</td>
<td>15,046 (62)</td>
<td>992 (43)</td>
<td>14,054 (64)</td>
</tr>
<tr>
<td>Urine MA† Measured (%)</td>
<td>10,128 (42)</td>
<td>867 (37)</td>
<td>9,261 (42)</td>
</tr>
<tr>
<td>Both eGFR and MA Measured (%)</td>
<td>8,071 (33)</td>
<td>488 (21)</td>
<td>7,583 (37)</td>
</tr>
</tbody>
</table>

eGFR = estimated glomerular filtration rate
†MA = microalbumin
linked with nearly 100% of glycosylated hemoglobin (A1C), low density lipoprotein cholesterol (LDL-C) and urine microalbumin (MA) tests performed within centralized laboratories. Individuals tested for at least one of the above were also linked to serum creatinine (CR) tests that differed by <3% between labs using reference samples and are comparable to an isotope dilution mass spectrometry method [16]. Only those who had at least one CR result during the study year were included in the study. When more than one CR was done, the lowest value was used, to avoid CR results possibly associated with acute renal impairment.

Estimated glomerular filtration rates (eGFRs) were calculated in the original Modification of Diet in Renal Disease Study Group (MDRD) equation that uses age, sex, CR, black/white ethnicity [17]. We did not adjust for ethnicity because Saskatchewan has only a small black population and the unadjusted eGFR equation has been preliminarily validated in a North American Indian population [18].

FN and OSK were subdivided by CKD stage using the Kidney Disease Outcomes Quality Initiatives classification (eGFR ≥90 ml/min per 1.73 m² = no CKD and stage 1, 60-89.9 = stage 2, 30-59.9 = stage 3, 15-29.9 = stage 4, <15 = stage 5) [19]. Those with an eGFR ≥90 were further subdivided by the presence or absence of positive MA (spot urine MA ≥ 20 mg/L, 24h urine value ≥ 30 mg/day, urine MA:CR ratio ≥ 2.0 mg/mmol for males or ≥ 2.8 mg/mmol for females) [15] to differentiate between stage 1 and no CKD, respectively. Those with an eGFR <15, and who were not receiving renal replacement therapy (stage 5a), were combined with stage 4 because of small numbers. Finally, people with ESRD (stage 5b) were separately identified using an algorithm based on physician fee-for-service codes for chronic dialysis [20] and modified to include renal transplant recipients [15].

**Between-Group Comparisons and Statistical Analyses**

We determined and compared the distribution, sex and mean age of FN and OSK by CKD stage. We also calculated the proportion tested for MA, A1C and LDL-C as well as the proportion with a positive MA and the mean A1C and LDL-C values. All proportions were compared using chi square tests while mean A1C and LDL-C values were compared using two tailed t-tests. Finally, all-cause two year mortality risk was compared between and within ethnic groups by CKD stage. Hazard ratios (both unadjusted and adjusted for age and sex) with 95% confidence limits were first used to compare overall mortality risk between FN and OSK and within each CKD stage. Mortality risk was then compared by CKD stage within each ethnic group using those with an eGFR >90 as the reference group.
analyses were carried out using SAS software version 9.1.3. A value of \( <0.05 \) was considered significant.

### Results

Table 1 shows Saskatchewan’s diabetes populations during 2005/06 by ethnicity and renal testing. The 24,207 prevalent diabetes cases (21,886 OSK and 2,321 FN) in the two health regions represented almost half of the province’s diabetic population. eGFR values were available for 64% of OSK and 43% of FN. Both eGFR and MA results were available in 37% of OSK and 21% of FN.

Table 2 shows the distribution of diabetes cases by CKD stage and ethnicity, and the age, sex and key laboratory findings. Almost 50% of FN had eGFR’s \( \geq 90 \text{ ml/min} \) (no CKD or stage 1) and an additional 37.6% had stage 2 CKD. In contrast, only 24.9% of OSK had eGFR’s \( \geq 90 \text{ ml/min} \) with the majority (52.4%) having stage 2 CKD. Almost twice as many OSK had stage 3 CKD (20.8% versus 10.6% of FN). Despite that, a larger proportion of FN had stages 4/5a CKD and ESRD.

Overall, FN were almost 12 years younger than OSK. Mean ages in both ethnic groups increased progressively from those with eGFR’s \( >90 \text{ ml/min} \) to those with stages 3 and 4/5a CKD. While the mean age of FN with ESRD was about 5 years younger than FN in stages 3 and 4/5a, OSK with ESRD were almost 13 years younger than OSK in stages 3 and 4/5a. There was also a marked difference in gender between ethnic groups. Almost 60% of FN were female in comparison with 45.4% of OSK. While the F:M ratio for FN was elevated regardless of CKD stage, OSK displayed a decreased F:M ratio in those with no CKD and early CKD, but an increased F:M ratio in those with stages 3 and 4/5a CKD. Despite this, only 36.4% of OSK with ESRD were female in comparison with a majority being female in stages 3 and 4/5a. This was associated with a decrease of almost 15 years in mean age (from 75.4 to 61.8 years) between stages 4/5a CKD.

More than 80% of FN and almost 90% of OSK had at least one A1C level measured during the study period. The mean A1C was 8.16% in FN and 7.36% in OSK, and higher values in FN were particularly noteworthy in those with eGFR’s \( >30 \text{ ml/min} \). There were no significant differences in mean LDL levels between FN and OSK, regardless of eGFR.

Table 3 shows the characteristics of FN and OSK with eGFR’s \( >60 \text{ ml/min} \) who were also tested for MA. When compared within each eGFR category (eGFR90+, eGFR 60-<90 and total eGFR 60+) by negative versus positive MA test results, FN were younger, more likely to be female, and had...
significantly higher mean A1C levels than OSK regardless of MA positivity. There were also significant within-ethnic group differences: for both FN and OSK within each eGFR category, the proportion of females was lower, and mean A1C levels higher in those with positive MA.

Table 4 shows the two year all-cause mortality risk for FN:OSK within each CKD stage. Before age/sex adjustment, there were no differences in mortality risk between FN and OSK regardless of CKD stage although there was a trend (exception stage 3 CKD) for lower mortality risk among FN particularly in stages 4/5a. After age/sex adjustment, FN experienced a significantly elevated mortality risk in comparison with OSK overall and within each CKD stage, with the notable exception of those in stages 4/5a.

Table 5 shows the two year mortality risk by CKD stage within each ethnic group. For FN, mortality risk was higher for people in stages 3 and 5b in comparison with those with an eGFR 90+ before age/sex adjustment. After age/sex adjustment, only those with ESRD experienced a higher mortality risk, while those in stage 2 had a lower risk of dying. Among OSK, there was a progressive increase in mortality risk from stages 3 to 5b CKD before adjustment, and from stages 4/5a to 5b CKD after adjustment. In contrast, adjusted mortality risk for OSK with stages 2 and 3 CKD was significantly lower compared to those with an eGFR of 90+.

**Discussion**

Diabetic FN adults with all levels of renal function were younger, more likely female, had higher rates of elevated MA and displayed higher mean A1C levels than diabetic OSK adults. Despite a much larger proportion having normal or mildly impaired renal function, FN with diabetes also experienced higher rates of ESRD. This was associated with a lower risk of death for FN in comparison with OSK in stages 4/5a, although the differences were not significant likely because of the small sample numbers. These findings are consistent with two important mechanisms contributing to ethnicity-based disparities in ESRD rates: FN are more prone to the initial development and progression of diabetic glomerulosclerosis because of poorer glycemic control and, because they are significantly younger, FN with diabetes are more likely to survive long enough to develop ESRD particularly when they reach advanced pre-ESRD stages of CKD.

Although ESRD incidence has stabilized among both FN and OSK with diabetes since the mid 1990s, it was still over three times higher in FN women and over two times higher in FN men compared to their OSK counterparts during 2003-
2005 [5]. The reasons for these disparities remain perplexing. While this and other studies [3,4] demonstrate poorer glycemic control among diabetic FN, they are also more likely to have normal or near normal eGFR’s (Table 2) and experience a longer time from diabetes to ESRD diagnosis than diabetic OSK [5]. These seemingly contradictory findings could be explained by lower pre-ESRD mortality risk among FN, but age/sex adjusted mortality risk is higher for FN with all-cause CKD [6]. Is there a plausible explanation for these disparate findings? We believe that this study helps to answer that question.

Although we have confirmed much higher age/sex adjusted risks of death for FN in comparison with OSK with eGFR’s >60 ml/min, the corresponding unadjusted hazard ratios for FN were not significantly different than those for OSK. These contrasting findings are likely related to the fact that most FN are younger than and most OSK are older than age 50 when they develop diabetes [21] and, as we have now shown, FN are approximately 10 years younger than OSK in each stage of pre-ESRD CKD. Furthermore, both the unadjusted and adjusted hazard ratios (0.33 and 0.72 respectively) for FN in stages 4/5a were much lower compared to OSK although not significantly different likely because of small patient numbers. Finally, within-population findings revealed a much higher mortality risk for OSK in stages 4/5a in comparison with OSK with normal eGFR’s, while mortality for FN in stages 4/5a was similar to FN with normal eGFR’s. All of these findings suggest that diabetic FN with advanced chronic renal insufficiency are more likely than OSK to survive to ESRD. This is further supported by the much larger drop in mean age between OSK in stages 3/4/5a and OSK with ESRD when compared to FN, and an associated reversal in the F:M ratio among OSK (from a higher proportion of females in stages 3/4/5a to a marked predominance of males with ESRD). Thus, it not only appears that OSK are more likely than FN to die before developing diabetic ESRD but that the mortality risk for OSK with advanced pre-ESRD kidney failure may be higher for women than men. The latter is consistent with our recent findings that ESRD incidence among OSK women with diabetes is approximately half that observed in their OSK male counterparts [5]. Once again, this may be due to age-related differential mortality since OSK women in stages 4/5a are substantially older than OSK men, while OSK men and women with ESRD have similar ages.

We also found differences in laboratory findings between the two populations. First, more FN had positive MA results and differences were largest in those with stages 2 and 3 CKD. For those with eGFR’s >90, both FN and OSK with positive MA were more likely to be male and had higher mean A1C’s than those with negative MA. This suggests that, despite the limitations of eGFR measurements [22], the presence or absence of MA in those with normal eGFR’s can identify distinct groups more likely to have early diabetic glomerulosclerosis.

Second, as far as we are aware, this is the first study to compare key laboratory indicators of quality of diabetes care between FN and others by CKD stage. Despite a recommended target A1C of <7.0% [23], mean A1C’s were significantly higher among FN in all stages except 4/5a/5b. Since poor glycemic control is a major risk factor for the development and progression of microvascular complications [24] including incident CKD [25], the marked differences in A1C levels between FN and OSK likely contribute to the disparities in diabetic ESRD rates.

An unexpected finding was that FN experienced similar mean LDL-C levels compared to OSK. In the context of A1C evidence for poorer quality of diabetes care, this observation suggests that there may be underlying differences in lipid metabolism between FN and OSK [26].

Strengths of this study included use of a validated algorithm to identify diabetes cases [11], inclusion of almost half of Saskatchewan’s diabetes populations (although a larger urban component may differ in some ways from the province’s total diabetes populations), and the ability to carry out a linkage between laboratory and health care system administrative data. Limitations included an inability to evaluate important health determinants such as smoking, hypertension, obesity and the impact of acculturation. We could not identify people of Aboriginal heritage other than FN, but this limitation would tend to reduce the true differences between FN and OSK. Similarly, while Saskatchewan laboratories were still reporting random urine MA concentrations without adjusting for urine creatinine in 2005/06, the resulting small proportion of false positive and negative results would also tend to reduce the true differences between FN and OSK. Although we were unable to differentiate between types 1 and 2 diabetes, most diabetic adults have type 2 [13]. While there are limitations to the use of the MDRD eGFR equation that are more pronounced at eGFR’s >60 ml/min [22,27,28], they should equally affect FN and OSK. Nonetheless, because of these concerns we have provided both overall data for those with eGFR’s >60 ml/min as well as sub-group information for those with eGFR’s >90 and 60-90 ml/min. Finally, the cross-sectional design has significant limitations in reflecting the longitudinal progression of a cohort from the time of diabetes diagnosis through the CKD stages. For example, we could not evaluate the impact of time from diabetes diagnosis on mortality risk, which was also lim-
ited by a short two year follow-up and associated small numbers of deaths. This may have accounted for the inability of the analysis to show significant differences between groups when there appeared to be a difference in trends.

Results from this study suggest that marked differences in age between FN and OSK populations and poorer diabetes management among FN contribute significantly to ethnicity-based disparities in ESRD rates. FN with diabetes are much younger when they develop diabetes and appear more likely to survive long enough to experience the metabolic consequences of prolonged, sub-optimal glycemic control. Our findings require confirmation using longitudinal studies that analyze the competing risks of ESRD versus death from the age of diabetes diagnosis. Because of the complex nature of the interactions between important variables, we believe that additional insights could also result from the use of simulation modeling to examine the relative contributions of these variables [29]. If confirmed, our findings suggest that not only preventing but even delaying the onset of diabetes among FN, as well as improving glycemic control after diabetes diagnosis, are key elements in reducing ethnicity-based disparities in rates of diabetic ESRD. To be most effective, such initiatives must be focused on the young.

Acknowledgments

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Disclaimer

This study is based in part on non-identifiable data provided by the Saskatchewan Ministry of Health. The interpretations and conclusions contained herein are not intended to represent those of the Government of Saskatchewan or the Saskatchewan Ministry of Health.

References


