Non-traumatic lower limb amputation in patients with end-stage renal failure on dialysis: an Australian perspective

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ABSTRACT

Background: End-stage renal failure (ESRF) and dialysis have been identified as a risk factor for lower limb amputations (LLAs). High rate of ESRF amongst the Australian population has been reported, however till date no study has been published identifying magnitude and risk factors of LLA in subjects on renal dialysis.

Objective: The study aims to document trends in the prevalence and identify risk factors of non-traumatic LLA in Australian patients on dialysis.

Methods: A retrospective review of all patients (218) who attended the regional dialysis center between 1st January 2009 and 31st December 2013 was conducted. Demographic, clinical and biochemical data were analyzed.

Results: We identified a high prevalence of 13.3% of LLAs amongst Australian patients with ESRF on dialysis at our center. The associated risk factors were the presence of diabetes (OR 1.67 [1.49–1.88] p < 0.001), history of foot ulceration (OR 81 [18.20–360.48] p < 0.001), peripheral arterial disease (OR 31.29 [9.02–108.56] p < 0.001), peripheral neuropathy (OR 31.29 [9.02–108.56] p < 0.001), foot deformity (OR 23.62 [5.82–95.93] p < 0.001), retinopathy (OR 6.08 [2.64–14.02] p < 0.001), dyslipidemia (OR 4.6 [1.05–20.05] p = 0.049) and indigenous background (OR 3.39 [1.38–8.33] p = 0.01). 75% of the amputees had aboriginal heritage. We also identified higher HbA1c and CRP levels as well as low serum albumin, hemoglobin and vitamin D levels to have a strong association with LLAs (p < 0.05).

Conclusion: There is high prevalence of LLAs amongst Australian indigenous patients with diabetes on dialysis in North Queensland. Other strongly associated risk factors include history of foot ulceration, foot deformity and peripheral neuropathy as well as high HbA1c levels and low serum albumin levels.

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Background

It is estimated that 7.4% of the Australian adult population suffer from Diabetes Mellitus (DM), this is said to be an underestimation as a considerable number of patients go undiagnosed till later stages. DM has both micro- and macro-vascular complications being the leading cause for end-stage renal failure (ESRF), blindness, lower limb amputation (LLA) and cardiovascular disease (CVD). Diabetic foot syndrome is defined as any foot pathology that directly results from DM or its long term complications such as diabetic neuropathy and peripheral artery disease (PAD) manifesting in the form of infections or ulceration. DM patients with infected foot ulcer complicated by macrovascular angiopathy have poor prognosis with high rate of osteomyelitis and LLA. PAD is quite a common complication of DM and in United States it has prevalence between 4 and 12%. Within the dialysis population this prevalence is much higher estimated at 28%. Recently, ESRF which is defined as nonreversible kidney injury requiring renal replacement therapy has been identified as a risk factor for PAD leading to non-healing foot ulcers and LLA. Recent international studies have identified dialysis to be an independent risk factor for foot ulcers. These studies have also identified that LLAs are a frequent event in patients on hemodialysis therapy (HD) and that this risk is further increased with the presence of concurrent DM.

Regarding the prevalence of LLAs in ESRF patients, on dialysis that has been recorded has a wide distribution from as low as 1.72% in Japan to as high as 13.4% in Canada, there is no recorded prevalence from the Australian continent even though Australian data suggests high rates of CVD, DM and ESRF amongst the
Indigenous Australians have been found to have a 38 times higher risk for LLA secondary to DM as compared to their non-indigenous counterparts. However, this data does not account for ESRF or dialysis therapy. In this study, we investigated the prevalence of LLA amongst patient with ESRF on dialysis in North Queensland, Australia and further explore the associated risk factors.

Methods

Study population and procedures

Inclusion criteria

Patients with ESRF who attended the Townsville Dialysis Centre for renal replacement therapy in the form of HD or peritoneal dialysis (PD) between 1st January 2009 and 31st December 2013 were retrospectively studied. All patients were required to be over the age of 18 years and have attended the dialysis for at least 1 month.

Exclusion criteria

Patients who attended the dialysis center for a one off dialysis, patients with traumatic or neoplastic amputations or who had an upper limb amputation were excluded from the analysis.

Primary outcome

The main outcome being measured was the prevalence of non-traumatic LLA in this cohort.

Secondary outcomes

The association of demographic, clinical and biochemical risk factors was also being investigated for.

A total of 218 patients met the criteria of inclusion for this study. Demographic factors included in this study were age, gender and cultural background. All patients were screened for DM complications including PAD, neuropathy and retinopathy. Other variables assessed in this study included: presence and type of DM, type of dialysis, arterial hypertension (HPTN), ischemic heart disease (IHD), cerebrovascular event (CVE), and cigarette smoking, together with analytical parameters such as glycated hemoglobin (HbA1c), total cholesterol, triglycerides, hematocrit, urea, creatinine, calcium, phosphate, parathyroid hormone and albumin. A mean of the biochemical values over 5 years was included in the study for analysis.

HPTN diagnosis prior to or after onset of the replacement therapy was considered when the patient was on antihypertensive medication. IHD diagnosis was based on coronary angiogram or by presentation of myocardial infarct diagnosed by means of the clinical picture, serum troponin levels, and electrocardiogram changes. CVE was defined based on the neurological assessment documented in the patients' clinical record indicating presence of rapid neurological deficit that persisted for more than 24 hours. PAD was diagnosed based on absent pedal pulses with ankle brachial index of <0.9 along with a Doppler ultrasound finding consistent with occlusive arterial disease. With regard to cigarette smoking, patients were classified as never-smoked and smoked; the latter comprising both of active smoking and those withdrew from smoking within the last 10 years. Major amputation was defined as at the level of the knee (above, below or through knee).

The study protocol and use of chart reviews were approved by the Townsville District Human Research Ethics Committee, James Cook University External Ethics, Townsville Hospital Site Specific Assessment and the Queensland Government Public Health Act. Clinical history data and demographics were obtained from patients' hospital charts while biochemical and blood results were obtained from the electronic database.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 22.0 software for windows. HbA1c and C-reactive protein (CRP) levels (non-parametric data) were expressed as median and interquartile range. Other continuous variables were expressed as mean ± SD (parametric data). Univariate analyses were done; continuous variables were compared by doing a parametric analysis using Student’s t test or a non-parametric analysis using the Mann–Whitney U test. A $\chi^2$ test was also used to compare categorical variables, obtaining relative risks and 95% confidence intervals. For multivariate analysis, Binary logistic regression was done using the variables with a $p < 0.05$ and odds ratios and 95% confidence internals were obtained to determine independent predictors.

Results

Study population baseline characteristic

The average age of the group was $60.73 \pm 14.48$ years. There were an equal number of males and females and 51.8% was from an indigenous background. The leading causes of ESRF were DM (46.3%) and HPTN (11.9%). Majority of the patients were placed on HD (72.9%) as renal replacement therapy.
Multiple comorbidities observed in patients with ESRF

The most common comorbid conditions (Table 1) were HPTN (93.1%), dyslipidemia (77.1%), DM (65.1%) and IHD (49.5%). The prevalence of foot complications was considerably high, one fourth of the patients had a history of foot ulceration, 28% had peripheral neuropathy and 30.7% were diagnosed with PAD. 5% of the patients were found to have a foot deformity as well. CVE was found to be prevalent in 16.1% of the patients that were included in this study and 29.4% had retinopathy.

Outcome

29 out of the 218 patients (13.3%) included in this study had developed a non-traumatic LLA (Table 1). Amongst the patients who were amputated there were 55.2% males and three quarters were indigenous Australians. Nine out of 29 amputees (31%) had major LLA which was at the level of the knee; one third of these patients with major amputations had had previous minor LLA which had further required more extensive amputation. All patients with LLAs had concurrent DM; however, DM was the cause of the ESRF in only 82.8% of these patients. Foot ulceration was evident in almost all these patients (93.1%); the commonest type of ulcers being neuro-ischemic in nature (44.4%). Other foot complications prevalent amongst the amputees were PAD (89.7%) and neuropathy (82.8%). Majority of these patients had received HD (79.3%) and were found to have HPTN (93.1%) and dyslipidemia (93.1%) as comorbidities (Table 2).

Demographic and comorbid risk factors

LLA was associated with an 81-fold higher prevalence of history of foot ulceration, 31-fold higher prevalence of PAD and a 23-fold higher prevalence of foot deformity. It was also found to be associated with 19-fold higher prevalence of peripheral neuropathy and a six-fold increased prevalence of retinopathy. Having concurrent DM with dyslipidemia and being from an aboriginal heritage were also found to be strongly associated with LLAs (Table 3). A binary logistic regression showed that history of foot ulceration significantly played majority of the role (OR 12.408 [2.23–69.04] p = 0.004) in LLA. Other factors playing a significant role were indigenous background, PAD and foot deformity (Table 4).

Biochemical risk factors

The mean 5-year serum albumin, vitamin D and hemoglobin levels were significantly lower in the group of

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| Table 1. Baseline characteristics. |
|-----------------------------------|
| N  | 218 |
| Age (years) | 60.73 ± 14.48 |
| Male | 109 (50%) |
| Indigenous | 113 (51.8%) |
| HD | 159 (72.9%) |
| DM | 142 (65.1%) |
| Type I | 5 (3.5%) |
| Cause of ESRF |  |
| Diabetes Mellitus | 101 (46.3%) |
| Hypertension | 26 (11.9%) |
| Other/unknown | 91 (41.8%) |
| Ulceration | 54 (24.8%) |
| PAD | 67 (30.7%) |
| Retinopathy | 64 (29.4%) |
| Neuropathy | 61 (28%) |
| Foot deformity | 11 (5%) |
| IHD | 108 (49.5%) |
| CVE | 35 (16.1%) |
| HPTN | 203 (93.1%) |
| Dyslipidemia | 168 (77.1%) |
| Amputation | 29 (13.3%) |
| Notes: Continuous variable expressed as mean ± SD, nominal variable expressed as n (%). |

| Table 2. Characteristics of group of patients with non-traumatic LLA. |
|--------------------------|
| N | 29 |
| Male | 16 (55.2%) |
| Indigenous | 22 (75.9%) |
| Diabetic nephropathy as cause of ESRF | 24 (82.8%) |
| Diabetes Mellitus | 29 (100%) |
| Type I | 1 (3.4%) |
| Major amputation | 9 (31%) |
| Previous multiple minor amputations | 3 (33.3%) |
| Ulceration | 27 (93.1%) |
| Neuro-ischemic ulcers | 12 (44.4%) |
| Ischemic heart disease | 17 (58.6%) |
| Cerebrovascular event | 6 (20.7%) |
| Peripheral arterial disease | 26 (89.7%) |
| Retinopathy | 19 (65.5%) |
| Neuropathy | 24 (82.8%) |
| Foot deformity | 8 (27.6%) |
| Hypertension | 27 (93.1%) |
| Dyslipidemia | 27 (93.1%) |
| Note: Nominal variables expressed as n (%). |

| Table 3. Demographic and comorbid risk factors for LLA. |
|-----------------------------------|
| Association | OR [95%CI] |
| Pearson’s Chi Squared with continuity correction |
| Ulceration | 81 [18.20–360.48] | <0.001 |
| PAD | 31.29 [9.02–108.56] | <0.001 |
| Neuropathy | 19.72 [7.05–55.14] | <0.001 |
| Dyslipidemia | 4.6 [1.05–20.05] | 0.049 |
| Indigenous | 3.39 [1.38–8.33] | 0.011 |
| Male | 1.3 [0.59–2.85] | 0.651 |
| DM present | 1.67 [1.49–1.88] | <0.001 |
| HD | 1.49 [0.58–3.87] | 0.545 |
| IHD | 1.53 [0.69–3.37] | 0.395 |
| CVE | 1.44 [0.54–3.84] | 0.647 |
| Foot deformity | 6.08 [2.64–14.02] | <0.001 |
| HPTN | 0.99 [0.21–4.67] | <0.001 |

| Pearson’s Chi Squared with continuity correction | 1 |
of Townsville region is represented by people with an indigenous background.23 Thus the prevalence of indigenous patients amongst our sample size was much higher than the general population. This suggests that there are very high rate of chronic kidney disease and ESRF amongst indigenous Australian patients in the region. We were also able to identify associated demographic, comorbid as well as biochemical risk factors. LLA was higher in patients with DM, past history of foot ulceration, PAD, peripheral neuropathy, dyslipidemia, retinopathy and foot deformity. Our study’s findings are consistent with other studies done internationally. Speckman et al. identified DM as the strongest risk factor for lower extremity amputation in new hemodialysis patients.24 Interestingly, our study found that all amputees had concurrent DM. Locking-Custolito et al., Combe et al., Plantinga et al. and Ishii and colleagues, also found positive association between presence of DM and LLAs.15–17,21 The strongest association with LLAs, that our study found, was that of history of ulceration. In contrast, previous studies do not associate this as the strongest risk factor. This could be true in the case of our study as all the subjects with LLA had concurrent DM which is strongly associated with foot ulceration.12,25 On the other hand, the strong association between PAD and LLAs in the current study was identified however only in patient with DM amongst ethnic minorities but not in patients with ESRF on

patients who had LLA. The mean 5-year levels for serum albumin, vitamin D and hemoglobin when comparing amputees to non-amputees were 29.32 g/L to 32.81 g/L (p < 0.001), 44.11 nmol/L to 65.45 nmol/L (p < 0.05) and 104.32 g/L to 108.53 g/L (p < 0.05), respectively. The group of amputees was found to have a higher median 5-year CRP level (59.75 mg/L vs. 36.49 mg/L (p < 0.01) as well as higher median 5-year HbA1c level (7.1% vs. 5.72%) (Table 5). A multivariate analysis using the binary logistic regression showed that majority of the role in LLA amongst biochemical factors was played by higher HbA1c levels (OR 2.94 [1.35–6.4] as p = 0.007). The other factor that played a role was low albumin levels (Table 6).

Discussion

We have reported our experience evaluating 218 Australian patients with ESRF attending the Townsville Dialysis Centre. High prevalence of non-traumatic LLA was observed in this study where 13.3% of these patients had LLA. This prevalence is similar and comparable to that in the United States and Canada.17,21,22 however, is much higher than other parts of the world, such as Japan.24 A closer look at our data revealed that half of the patients attending to the dialysis center were from an aboriginal heritage; however as per the 2011 census only 6.13% of the population of Townsville region is represented by people with an indigenous background.23 Thus the prevalence of indigenous patients amongst our sample size was much higher than the general population. This suggests that there are very high rate of chronic kidney disease and ESRF amongst indigenous Australian patients in the region.

Table 4. Multivariate analysis—binary logistic regression for demographic and comorbid risk factors.

| Association     | B   | S.E  | Significance | OR   | Lower | Higher |
|-----------------|-----|------|--------------|------|-------|--------|
| Ulceration      | 2.52| 0.88 | 0.004        | 12.41| 2.23  | 69.04  |
| PAD             | 2.005| 0.87 | 0.02         | 7.43 | 1.36  | 40.45  |
| Retinopathy     | 0.62| 0.64 | 0.337        | 1.85 | 0.53  | 6.52   |
| Neuropathy      | 0.97| 0.73 | 0.182        | 2.64 | 0.64  | 10.99  |
| Foot deformity  | 2.02| 1.01 | 0.045        | 7.51 | 1.05  | 53.86  |
| Dyslipidemia    | 1.57| 1.16 | 0.175        | 4.808| 0.49  | 46.39  |
| Indigenous      | 1.61| 0.69 | 0.019        | 4.98 | 1.3   | 19.23  |
| Constant        | −1.62| 1.03 | 2.46         | 0.117| 0.2   |        |

Table 5. Biochemical risk factors.

| Association         | Amputees | Non-amputees | Significant value |
|---------------------|----------|--------------|-------------------|
| Vitamin D           | 44.11 ± 17.07 | 65.45 ± 33.64 | 0.037             |
| Calcium             | 2.04 ± 0.41  | 2.08 ± 0.41   | 0.579             |
| Corrected calcium   | 2.25 ± 0.45  | 2.22 ± 0.43   | 0.761             |
| Phosphate           | 1.64 ± 0.32  | 1.63 ± 0.58   | 0.894             |
| Albumin             | 29.32 ± 4.70 | 32.81 ± 4.00  | <0.001            |
| Cholesterol         | 3.93 ± 0.93  | 4.04 ± 1.09   | 0.626             |
| Triglycerides       | 1.72 ± 1.33  | 1.98 ± 1.24   | 0.295             |
| HDL                 | 0.70 ± 0.43  | 0.84 ± 0.43   | 0.095             |
| Hemoglobin          | 104.32 ± 10.13 | 108.53 ± 10.07 | 0.041             |
| Hematocrit          | 0.32 ± 0.03  | 0.48 ± 1.96   | 0.673             |
| Urea                | 18.42 ± 5.26 | 19.83 ± 5.48  | 0.041             |
| Creatinine          | 573.90 ± 226.58 | 626.83 ± 212.38 | 0.224             |
| Parathyroid hormone | 46.72 (5.10–121.78) | 47.64 (4.00–14.86) | 0.291             |
| C-reactive protein  | 59.75 (0.00–133.48) | 36.49 (0.03–257.00) | 0.008             |
| Bilirubin           | 10.48 (6.17–27.64) | 10.75 (4.00–43.32) | 0.080             |
| Direct bilirubin    | 4.44 (4.00–18.46) | 4.00 (4.00–27.80) | 0.116             |
| LDL                 | 2.08 (0.99–3.80) | 2.00 (0.60–4.42) | 0.401             |
| HbA1c               | 7.10 (5.17–9.22) | 5.72 (3.90–10.80) | <0.001            |

Note: Values expressed as mean ± SD or median (interquartile range).
Our findings are in line with another report from United States which identified the Pima Indian population at a higher risk of amputations although Ndip et al. did not find such association. Similarly, patients from an African American background have also been found to be at five-times higher risk of diabetic LLA, this has primarily been attributed to lifestyle factors and genetic makeup. At the same time, Canadian aboriginal peoples have been found to have high rates of foot complications that places them at high risk of ulceration at a younger age. Studies have found aboriginal subjects to be younger than non-aboriginal counterparts at the time of diabetes diagnosis as well as first major LLA. This has been attributed to poor health care seeking behavior and low level of foot care.

Another interesting finding in this report was the link between low hemoglobin, vitamin D and albumin levels in subjects with LLA. This group also had a higher level of HbA1c and CRP. After adjusting for potential confounding factors, the strong association between uncontrolled DM and LLA was still significant; where the group who had LLA had almost three-fold higher prevalence. The reason for the high rate of LLA in patients with hypovitaminosis D is not known. However, it is proposed that low vitamin D levels are linked to various immunological alterations in the human body which put the individual at a higher susceptibility towards infections. In its active form, vitamin D has been proven to stimulate macrophages and phagocytosis. It stimulated T helper 2 cells which primarily are responsible for combattting extracellular pathogens (bacteria). Therefore, along with hyperglycemia, vitamin D deficiency could be involved in susceptibility of foot ulcers towards infection. In support of this, Chua et al. investigated the link between vitamin D and PAD and found that vitamin D deficiency could be an independent risk factor for the development of PAD. It also found higher amputation rates among PAD patients with lower vitamin D levels.

A large retrospective study done in Tennessee also supports this claim. It found that individuals who were vitamin D deficient had higher amputation rates when compared to individuals who were non-deficient. Along with vitamin D deficiency, low hemoglobin levels have been linked with poorer outcomes for patients with IHD as well as heart failure. In IHD patients, anemia is an independent predictor of both short and long term mortality. A 1-year follow up, multicenter study, done in three university hospitals in France which included 925 consecutive patients being admitted with PAD found that anemia was significantly and independently associated with death and amputation (HR 1.44 (1.15–1.80) p < 0.001). We also found that if these patients have a lower serum albumin level their risk for LLAs is higher. Serum albumin is a negative acute phase reactant. It is a marker of inflammation; however, being a negative acute phase reactant, its level drop down during states of inflammation. This is a plausible explanation to our finding of low serum albumin level associated with LLAs. Long term inflammation resulting from non-healing ulcers could result in LLAs. Another explanation to this finding could be the link between nutritional state and healing. Nutrition is essential for wound healing. Nutritional deficiencies impede the normal stages of wound healing, reducing wound tensile strength and increasing rates of infection. This results in chronic non-healing ulcers and hence requiring LLAs. Serum albumin levels are a marker of nutritional state, where hypoalbuminemia (low levels of albumin) suggests malnutrition. We also identified an association between high CRP levels and LLAs. CRP is an acute phase reactant, however, in contrast to albumin, its levels rise with inflammation and infection. This explains the association of high CRP levels amongst amputees, suggesting long term infection or inflammation possibly associated with non-healing foot ulcers. Literature suggests that CRP has also been associated with CVD; it constitutes an independent risk factor. It is hypothesized that CRP directly interacts with atherosclerotic vessels leading to activation of complement and further promoting inflammation thereby also leading to thrombosis. This same hypothesis could also be applied in the case of PAD, where atherosclerotic peripheral vessels undergo a process of inflammation and lead to ischemic lower limbs worsening preexisting foot complications leading to LLAs. Along with low serum albumin levels and high CRP, we found higher HbA1c levels to be associated with LLAs, suggesting, uncontrolled DM as a risk factor. As previously discussed that DM predisposes to micro- and macro-vascular complications, development of diabetic foot syndrome and also infections, it would be ideal for these patients to have a tighter control of their blood sugar levels hence preventing worsening prognosis of foot complications which require LLAs. Our findings are consistent with other studies done previously; Plantinga et al. and Ishii et al. also found the association between high CRP levels while Plantinga et al.’s study along with Speckman et al. also reported the low levels of albumin amongst amputees, while Locking-Custolito et al. found that elevated HbA1c was associated with LLAs.

Our study was a retrospective chart audit and we were relying on the health professional’s accuracy of
information documented in patient medical records as well as biochemical pathology data base for our data collection. This posed a significant limitation to this study particularly regarding availability and reliability of data. In order to overcome this limitation, we accessed data from various sections of patient medical charts including clinical appointments, dialysis notes, high risk foot forms as well as anesthetic records. Only one member from the research team performed the data collection in order to maintain standard and continuity of methods of data collection. Being a retrospective audit, the other limitation that was faced was of missing data in the patient records. This was particularly evident for record of smoking status. In order to be able to overcome as much of this limitation as possible, we included the largest possible number of patients, hence including patients attending the Townville Dialysis Centre over a period of 5 years in order to have a true representation of the demographics as well as risk factors. Smoking status as a risk factor was excluded from the analysis due to the fact that there was missing data in the patient records.

Our findings have important clinical implications as they alert health care professionals that patients on dialysis therapy are at a risk of lower limb complications. This study would give health care providers the ability to easily identify the “at risk” subjects within this population at an earlier stage and accordingly provide them with improved quality of clinical care. There are DM guidelines and recommendations in place for management of foot ulcerations however, these guidelines do not account for the patient population on dialysis therapy and the risks they face. Based on the findings of the current study, we suggest that patients attending dialysis centers get optimal education regarding foot complications and care, before starting dialysis therapy as well as throughout it. There should be sufficient opportunities taken by the health care provider to do regular foot checks for this patient population as such activities have proven to be beneficial in limb salvage.

In summary, this current study reports a high prevalence of LLA in Australia’s North Queensland patients with ESRF on dialysis. The LLA occurred predominantly amongst indigenous Australians. Other risk factors identified were DM, past history of foot ulceration, foot deformity, peripheral neuropathy and retinopathy. From the findings of this study, it is suggested that certain biochemical factors may be used to identify “at risk” patients in this population: high HbA1c and CRP levels as well as low vitamin D, hemoglobin and albumin levels. Further prospective research on a larger population is needed to verify our findings.

Disclosure statement
The authors declare that they have no competing interests.

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Authors’ contributions
RG was responsible for design of the study, carrying out the data collection and analysis along with writing of the manuscript, BR participated in the data collection process along with GK and DP’s support. VV has been providing statistics and analytical support along with supervision of the project. KS has provided research assistance throughout the project. UM has been the primary supervisor who conceived of the study along with RG and participated in its design and coordination and helped to draft the manuscript.

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