Temporal association between the incidence of foot ulceration and the start of dialysis in diabetes mellitus

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Abstract
Background. The aim of this study was to seek a temporal association between the start of renal replacement therapy (RRT) and the first recorded foot ulcer in diabetes.

Methods. Details of all patients with diabetes who had received RRT were extracted from the renal database and were cross-checked with the database held in the specialist foot clinic. The date of onset of first registered foot ulcer was taken and compared with the date of onset of RRT. The self-controlled case-series method was used to establish any significant temporal association between the start of RRT and first recorded foot ulcer in diabetes.

Results. Of 466 patients with diabetes dialysed at our hospital since 1976, 94 (20.2%) were recorded as having at least one foot ulcer, with 15 of these undergoing major amputation. Incidence ratios (IRs) were calculated for 90 patients in whom complete data were available. A close temporal association was observed between the start of RRT and the first recorded foot ulceration: IR (95% CI) in the first and between the second and fifth years of dialysis were 3.35 (95% CI: 1.59–7.04), and 4.56 (2.19–9.50), respectively, relative to the time before dialysis. The IR for major amputation was 31.98 (2.09–490.3) in the first year and 34.01 (1.74–666.2) in the second to fifth years.

Conclusion. These results reveal a close relationship between the onset of RRT in diabetes and the onset of foot ulceration, and confirm the high incidence of amputation in those on dialysis. Urgent steps should be taken to coordinate all aspects of diabetes foot care before and after the start of RRT.

Keywords: amputation; diabetes; dialysis; foot ulcer; nephropathy; renal failure

Introduction

Renal replacement therapy (RRT) is associated with a high mortality, especially in people with diabetes [1,2]. Critical limb ischaemia is a major contributory factor [3] and there is evidence that this is accelerated soon after the start of RRT [4], with the incidence of major amputation reported to approach 6% in the first year of dialysis [5]. There are no data, however, on the relationship of established renal failure (ERF) to foot ulceration even though such ulceration nearly always precedes amputation. In addition, foot ulceration in patients with diabetes is by itself a major cause of morbidity and utilization of health care resources [6]. We have, therefore, analysed the databases kept by the Departments of Renal Medicine and of Diabetes and Endocrinology at our hospital since 1976 and 1982, respectively, to explore this relationship.

Methods

Details of all patients with diabetes who had received RRT were extracted from the database held by the Department of Renal Medicine. Those who received RRT for <90 days were excluded. Names were cross-checked with the database held in the specialist foot clinic in order to identify those on RRT who had also had a foot ulcer managed at the same hospital. Details of all new foot ulcers occurring in patients attending the specialist foot clinic in order to identify those on RRT who had also had a foot ulcer managed at the same hospital. Details of all new foot ulcers occurring in patients attending the specialist multidisciplinary out-patient clinic are entered on a departmental database which was first established in 1982. The term ‘foot ulcer’ is taken to refer to all ulcers (interruption of the epithelium) and limb-threatening lesions (including soft tissue infection without an ulcer, gangrene and acute Charcot arthropathy) which occur on or below the malleoli. Because of the inherent imprecision of the data, the date of onset is recorded only by month. The date of onset of first registered foot ulcer was taken and compared with the date of onset of RRT. Both the database maintained in the Department of Renal Medicine and that maintained in the specialist diabetic foot clinic are approved by Nottingham City Hospital.
To analyse our data, we used the self-controlled case-series method [7]. This is derived from the cohort method and uses conditional Poisson regression to analyse data only from exposed cases being based on the comparison of the incidence of the chosen outcome during periods with and without the exposure of interest. The model was adjusted to allow for the impact of age (coded in 5 year age bands), but as the data are based on within-subject comparison, information on additional fixed confounder variables, such as gender, are not required. The chosen outcome was the date of the first recorded foot ulceration and the exposure was the date of onset of RRT. The time from the diagnosis of diabetes up to the start of dialysis was used as the baseline reference period and the time after dialysis was considered as the period of high risk. The period of high risk was subdivided into the first year following exposure, the second to fifth year following exposure and all the subsequent years. To determine whether the mode of RRT [haemodialysis (HD) or ambulatory peritoneal dialysis (PD)] modified the temporal relationship between the onset of dialysis and foot ulcer, we repeated the analysis while stratifying by this variable. No patient had a transplant either before dialysis or within the first 90 days. The mode of RRT was defined as that being used on day 90.

Results

Of 2626 patients who started RRT for ERF at the City Hospital since 1976, 466 (17.7%) had diabetes and 94 (20.2%) were documented as having at least one foot ulcer. Data on four were excluded because the date of diabetes diagnosis was not recorded and all the subsequent analyses were based on data from the remaining 90. There were 47 men (52.2%) and the mean age of exposed patients at the time of starting dialysis was 53.3 (15.2 SD) years. Patients treated with HD (n = 45) tended to be older (57 vs 49 years, P = 0.009, two-sample t-test t = 2.67, df = 88) and were more likely to have type 2 diabetes than those on PD (64 vs 29%, χ² = 11.43, P = 0.001). The date of ulcer onset was not recorded in 11 (12.2%) patients and in these cases, the date used for the purposes of analysis was that of first attendance at the diabetic foot clinic.

The temporal relationship between the start of dialysis and the onset of the first recorded ulcer is shown in Figure 1; there was no difference in the pattern of incidence in those 11 patients in whom the date of first attendance was used instead of the date of the onset of ulcer. The results of the case-series analysis were relative to the time before dialysis, the incidence of having a first foot ulcer in the first, second to fifth and later years of treatment were 3.35 (95% CI: 1.59–7.04), 4.56 (2.19–9.50) and 1.66 (0.46–5.95), respectively. The equivalent incidence ratios (IRs) following the start of HD were 4.57 (1.65–12.64), 3.57 (1.09–11.76) and 1.74 (0.20–15.40), while those on PD were 2.10 (0.59–7.52), 6.78 (2.47–18.56) and 1.78 (0.31–10.25). The difference in IRs between PD and HD was not significant when a specific multiplicative interaction term was added to the model.

In the selected cohort of 90 patients, 15 (16.7%) underwent major amputation and the temporal relationship to the start of dialysis is shown in Figure 2. The IR for major amputation was 31.98 (2.09–490.3) in the first year and 34.01 (1.74–666.2) in the second to fifth years. Three- and five-year survival of those with a foot ulcer in the present series was 63 and 47%, respectively, and was very similar to those without an ulcer (63 and 48%; P = 0.54 log rank).

Fig. 1. Cumulative incidence of first recorded foot ulcer and the start of RRT (vertical line) in 90 patients with diabetes. In 11 patients in whom the date of onset was not recorded, the date of first clinic attendance was used (shaded symbols). Open symbols denote those recorded as being under continual review in the diabetes unit at the City Hospital in the 2 years before the onset of RRT.
Discussion

These results illustrate the strength of the relationship between RRT in diabetes and the onset of foot ulceration, and confirm the high incidence of amputation in those on dialysis.

The data are limited by being retrospective and will be affected by under-ascertainment of both foot ulcers and amputations. Many patients may have been treated for ulcers at other hospitals or in the community and may not have been referred to the specialist foot clinic—especially in the early years after its establishment. Moreover, entry of data in the foot register takes place only in the specialist out-patient clinic and this would have excluded some whose foot problems were managed exclusively as in-patients. This is most likely to have led to under-ascertainment of amputations—because of the high peri-operative mortality in this population. However, we believe that the inclusion of any missing cases would simply serve to magnify the extent of an association which is already apparent.

It is also important to note that this analysis assumes that the first recorded ulcer was synonymous with the first ever ulcer, and this may not always have been the case—especially in those patients whose diabetes was managed by others before being transferred to the City Hospital because of renal disease. There was, however, no discernible difference in the pattern of incidence between those who were and those who were not under follow-up by our unit for 2 or more years prior to the date of the first recorded ulcer (Figure 1). Even for allowing these factors, our findings suggest that the start of RRT is associated with a steep increase in the incidence of foot ulceration and that relative to the total pre-dialysis period, there is a more than 3-fold risk of new ulceration in the first year. Our data also confirm the suggestion made by others that the start of RRT in diabetes is associated with a rapid rise in incidence of major amputation [4,5]. The number recorded as undergoing major amputation in this cohort was lower than in other reports [4,8], but was six times higher than in our practice overall (2.6%) [9]. However, the inspection of Figure 1 suggests that the start of the increase in incidence of new ulceration predates the onset of RRT and that it is likely to be related to complications of advanced renal failure in diabetes including accelerated vascular calcification and atherogenesis, anaemia, tissue oedema, general ill-health, poor nutrition and infection. The foot is also at a greater risk of injury from associated complications of diabetes, including poor vision and peripheral neuropathy. Nevertheless, there is reason to believe that the changes which occur in the process of dialysis may also play a part.

Although there are no equivalent data on PD, there is evidence that HD is associated with generalized hypoxaemia, and this may persist for some time after a treatment finishes [10]. It is also possible that the effect of such hypoxaemia may be exaggerated in the periphery as a result of the fluid shifts inherent in dialysis, together with the associated changes in circulating volume and blood pressure and the resultant attempt to conserve central circulation. We have recently demonstrated in a pilot study that tissue oxygenation, measured as transcutaneous oxygen tension (TcpO₂) may fall during the course of dialysis to critically low levels, and these low levels may be maintained for at least 4 h after the end of the treatment [11]. Such changes could lead to critical ischaemia in those with worse macrovascular diseases. If confirmed, these observations suggest that
consideration should be given to interventions which may serve to offset such changes.

Of equal, or greater, importance is the fact that the start of RRT is associated with a major change in the emphasis of care. The process of dialysis dominates the patient’s time as well as the attention of those caring for them and other aspects of diabetes management can become relatively neglected. Whatever the mechanism for the increase in risk of new ulceration, and it is not impossible that the association with the start of dialysis is mainly coincidental and merely reflects the cumulative effect of severe metabolic disease and of other complications of diabetes, the clinical significance of the association is undeniable. These data indicate that those approaching ERF are at enormous risk of foot ulcers which pose a risk both to limb and life. The extent and the significance of this risk may currently be underestimated by the majority of those involved in the management of RRT and urgent attention should be given to improving the integration of all aspects of diabetes care at this time. There is evidence that the incidence of amputation may be substantially improved by the provision of either an integrated programme for those going onto dialysis [12–14] or a programme of education and surveillance by a podiatrist [15] and the consideration of the introduction of such services should become an urgent priority in all units.

Conflict of interest statement. None declared.

References
5. Speckman RA, Frankenfield DL, Roman SH et al. Diabetes is the strongest risk factor for lower-extremity amputation in new hemodialysis patients. Diab Care 2004; 27: 2198–2203
8. McGrath NM, Curran BA. Recent commencement of dialysis is a risk factor for lower-extremity amputation in a high-risk diabetic population. Diab Care 2000; 23: 432–433

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