Risk assessments and structured care interventions for prevention of foot ulceration in diabetes: development and validation of a prognostic model

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Scientific summary

Prevention of foot ulceration in diabetes

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Scientific summary

Background

Diabetes-related foot ulcers give rise to considerable morbidity, generate a high monetary cost for health and social care services and are known to precede the majority of diabetes-related lower extremity amputations. Identifying those at risk of developing a foot ulcer and providing an effective intervention to prevent these wounds developing has been a long-time goal of many working in the field.

There are many clinical prediction rules in existence to assess the risk of foot ulceration in diabetes mellitus, but few have been subject to validation. In the UK, two diabetes clinical guidelines make recommendations about the management of the foot and risk assessment procedures, and preventative interventions for those found to be at risk. However, the recommendations in these influential documents are based predominantly on clinical consensus, and robust evidence that routine monitoring reduces the number of diabetes-related foot ulcers or lower extremity amputations is scarce.

Current clinical guidelines for the management of the diabetic foot from the National Institute for Health and Care Excellence recommend that people with diabetes mellitus have a foot examination involving several elements and a vascular assessment with an ankle–brachial pressure index test every year. For those judged to be at moderate or high risk, monitoring is escalated to 6-monthly intervals and up to a maximum frequency of once per week. As peripheral neuropathy, the most common foot complication of diabetes mellitus, is irreversible, these intensive monitoring intervals are unlikely to positively influence patient outcomes. The recommendations of the diabetes guideline from the Scottish Intercollegiate Guidelines Network (synonymous with the Scottish Care Information – Diabetes Collaboration SCI-Diabetes, a computerised decision support tool) include a foot examination involving five risk factors and advocate the use of some expensive equipment not readily available outside specialist care settings. The Scottish Intercollegiate Guidelines Network diabetes guideline states that monitoring should take place at least annually but concedes that the optimal frequency is unknown, citing evidence from one cohort study in which low-risk patients had a 99.6% (95% confidence interval 99.5% to 99.7%) chance of being ulcer free at 1.7 years.

Both UK national diabetes guidelines (from the Scottish Intercollegiate Guidelines Network and the National Institute for Health and Care Excellence) advise that patients in higher-risk categories be referred to a multidisciplinary foot clinic for specialist care, but there is a lack of evidence to show whether or not these expensive teams of clinicians and resource-intense arrangements result in fewer lesions.

Objectives

The objective was to undertake an evidence-based evaluation of the clinical effectiveness and cost-effectiveness of the foot ulcer risk assessments and structured care interventions for people with diabetes mellitus.

Our research questions were:

- What is the estimated clinical effectiveness and cost-effectiveness of the use of a validated clinical prediction rule as part of structured care to reduce the incidence of diabetes-related foot ulcers?
- What is the likely clinical effectiveness and cost-effectiveness of alternative strategies including monitoring intervals?
- Is there potential worth in undertaking further research, particularly a randomised controlled trial of preventative interventions?

Our research objectives were to produce an evidence clinical pathway by:

- extending (developing) our existing prognostic model into a clinical prediction rule and conducting its external validation
- undertaking a survival analysis of the time to ulceration and analysing routinely collected data from people with diabetes mellitus to calculate the transitional probability of an individual moving from one risk state to another over time to inform the economic model
- conducting a systematic overview of the evidence of preventative effects of interventions for foot ulceration in diabetes mellitus that have been evaluated in systematic reviews and randomised controlled trials.

And then:

- combining the evidence from these three objectives in a cost-effectiveness decision model framework and analyse alternative clinically effective and cost-effective regimens at different monitoring intervals
- performing a value-of-information analysis.

Methods

The clinical prediction rule

Our previous research developed a predictive model with three risk factors for foot ulceration in diabetes mellitus (inability to feel a 10-g monofilament, absent pulses and history) using data from 16,385 people with diabetes mellitus worldwide. Four studies, two in the community in the UK and two in hospitals in mainland Europe and the USA, were used to develop the clinical prediction rule. The outcome was defined as a binary outcome of foot ulceration within 2 years.

We used the prediction model with the three risk factor predictors and the corresponding coefficients to show how much the log-odds change when monofilaments, pulses or history change from test negative to test positive and an individual's estimate change given baseline risk. A random-effects meta-analysis of the three intercepts from the Prediction Of Diabetic foot UlcerationS (PODUS) studies with 2 years of follow-up to produce a single average intercept was used. We used this and the log-odds coefficients for the three predictors to calculate the probability of ulcer for each possible predictor combination and to produce a clinical prediction rule scoring scheme. Finally, we calculated the probability of ulcer for each score using a population average method. The clinical prediction rule's internal validity was calculated by examining its discrimination and calibration; its external validity was then assessed in a fifth data set.

The reviews

We searched for eligible systematic reviews and randomised controlled trials of interventions using search strategies created for Ovid® (Wolters Kluwer, Alphen aan den Rijn, the Netherlands) MEDLINE, Ovid EMBASE and the Cochrane Central Register of Controlled Trials. Randomised controlled trials in progress were identified via the International Standard Randomised Controlled Trial Number Registry.

People of any age with a diagnosis of diabetes mellitus, either type 1 or type 2, who participated in randomised controlled trials of interventions to prevent foot ulceration in diabetes mellitus were eligible for inclusion. Eligible interventions could be either simple or complex, that is comprising several interacting components. We included randomised controlled trials that compared the effects of interventions with those of standard care or active comparators. The primary outcome was incident (new) and recurrent foot ulcers reported as binary outcomes (present/absent).

One reviewer screened all titles and abstracts to identify potentially relevant systematic reviews and randomised controlled trials. A second reviewer screened a 10% random sample of the yield.

The two reviewers working independently screened the full text of papers, and data were extracted into review-specific data extraction tools by two reviewers working independently. For the overview we used the risk of bias in systematic reviews tool to assess the risk of bias, and for randomised controlled trials we used the items recommended in the Cochrane handbook. [Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011)*. 2018. URL: www.handbook.cochrane.org.]

For the review of randomised controlled trials, we calculated pooled relative risks of effects and 95% confidence intervals using a frequentist meta-analytical approach with data analysed on an intention-to-treat basis. Trials were weighted in accordance with the inverse variance method for the dichotomous primary outcome of the overview: foot ulceration. Heterogeneity was assessed using the I^2 statistic.

Economic evaluation

Our economic evaluation was undertaken from the perspective of the UK NHS and Personal Social Services; that is, the costs relevant to the economic analysis were those incurred by the NHS and Personal Social Services. Our search returned 15 relevant papers to be reviewed.

We investigated the costs and health outcomes associated with each clinical pathway over a 20-year time horizon. We created a new conceptual semi-Markov model to visually represent the events that we sought to capture and how these events relate to costs and quality-adjusted life-year outcomes. To calculate the monitoring interval for risk assessment, we used data from an electronic health record (Scottish Care Information – Diabetes Collaboration), which is used in the routine management of NHS patients with diabetes mellitus in Scotland. Transition probabilities (of moving from one risk category to another) that are required for the model were then estimated based on a set of parametric survival models.

The project researchers received advice from an independent Study Steering Committee.

Results

The clinical prediction rule

We produced a clinical prediction rule that gives scores from 0 to 4. The study-specific estimates have a calibration slope of 1 and an intercept of 0, and the model has ideal calibration in the data set in which it was developed. The discrimination and calibration plots generated by the clinical prediction rule in the validation data set produced very similar results to those obtained in the internal validation. The calibration results suggest that calibration is good in low-risk patients, but the clinical prediction rule can over-estimate risk in high-risk groups.

The reviews

We identified 20 systematic reviews that aimed to evaluate interventions to prevent foot ulceration in participants with diabetes mellitus. Nine included only randomised controlled trials and 10 included randomised controlled trials and observational studies. Our separate search for randomised controlled trials found 22 that met the eligibility criteria. We identified eight separate interventions and evidence of effectiveness from three. Digital infrared thermometry, complex interventions such as specialist foot clinics, and therapeutic footwear with offloading devices appear to be effective in preventing foot ulceration in people with diabetes mellitus.

The pooled effect from trials of digital skin thermometry indicates this to be a potentially promising preventative intervention that deserves further evaluation in larger trials; however, advising patients to abstain from all weight-bearing activities when their foot temperature rises by > 4 °C may prove challenging, and an inability to abstain could diminish any beneficial effects. A benefit from specialist foot care for those at high risk of ulceration became apparent only in our pooled analysis, and this effect was not evident in the individual trials. Education by itself appears to be ineffective in reducing the incidence of foot ulcers, and the small trials of antifungal nail lacquer, elastic stockings and podiatric care did not show evidence of effect.

Economic evaluation

Our review of published cost–utility analyses of the prevention of diabetes-related foot ulcer revealed considerable heterogeneity in the way that the clinical and cost consequences of treatments have been modelled in the literature, and that risk monitoring frequency has not been considered.

Our cost-effectiveness acceptability curves show considerable uncertainty surrounding which intervention is most likely to be deemed cost-effective, with no clear strategy producing the greatest probability at a willingness to pay of £20,000 per quality-adjusted life-year gained. Only in the case of infrared digital thermometry does the treat-all strategy come out as providing the greatest probability of cost-effectiveness, although, even for this intervention, the cost-effectiveness acceptability curve suggests just over 30% probability that this strategy is likely to be the most cost-effective at a willingness to pay of £20,000 per quality-adjusted life-year.

Our analysis of data from the NHS Fife population who attend foot clinics suggests that patients' diabetes-related foot ulcer risk does not readily change over time. Despite the significant uncertainty, our health economic model suggests that preventative diabetes-related foot ulcer interventions have the potential to be considered cost-effective.

Discussion

For risk assessment programmes to be effective, simple clinical assessment procedures available for use by health-care staff with varying degrees of skill are needed. The clinical prediction rule developed and validated by our group is based on only three risk factors, which are cheap, easy to obtain and accurate in identifying those at risk, especially those at low risk, who constitute the vast majority of people with diabetes mellitus. Its use in clinical practice could simplify current approaches to risk assessment, which could reduce the time spent testing, the costs associated with expensive tests and the time needed to train staff to carry out more complex diagnostic procedures.

To our knowledge, the time interval for foot risk assessments has not been subject to evaluation before. By using data from the electronic health record of people with diabetes mellitus in one health board in Scotland, we are able to show that, in the majority of people with diabetes mellitus, foot ulcer risk status does not change much over time, and a move towards less frequent risk assessment is indicated for the majority of people. This finding suggests that a move towards less frequent risk monitoring of patients would be acceptable.

The majority of systematic reviews aiming to identify effective interventions to prevent foot ulceration did not reach clear, reproducible conclusions about the effect of treatments. As most of the researchers undertaking these summaries lacked sources of funding, this is possibly unsurprising. The absence of meta-analyses of data in the systematic reviews may also have contributed to the opacity, and by pooling data we detected effective interventions for reducing the incidence of foot ulcers.

Trials have shown that the use of digital infrared thermometers can reduce foot ulcers if foot temperature increase leads to a subsequent reduction in activity; however, assessing the levels of compliance with advice to rest in the trial populations will be important.

The markedly different effect in the subgroup analyses of data from two trials of footwear and offloading devices that involved people with no history of ulcers compared with four trials that included only people with a history of ulceration is interesting. If an agreement to share data among the investigators of trials of footwear and offloading was reached, comparing outcomes from subgroups of people in trials already completed or ongoing in an individual patient data meta-analysis could clarify effectiveness without incurring the high cost of a new trial.

The failure of individual trials of complex interventions to show beneficial effects until data were pooled in a meta-analysis supports the opinion of others that trials of specialist foot care in diabetes mellitus need to recruit very large samples of patients. Education by itself appears to be ineffective in reducing the incidence of foot ulcers, and the small trials of antifungal nail lacquer, elastic stockings and podiatric care lacked evidence of effectiveness.

The economic evaluation showed that there is potential for the diabetes-related foot ulcer treatments identified by the systematic review to be cost-effective but uncertainty in the model parameters and other elements (e.g. patient acceptability and adherence to interventions) prohibits a strong conclusion. A better understanding of what constitutes 'current practice' in foot care programmes across the UK, in terms of risk assessment methods (risk factors and how they are assessed), interventions offered and the level of adherence to clinical guidelines, would be helpful. There is a need for further research into the effectiveness and acceptability of and adherence to potentially preventative diabetes-related foot ulcer interventions. Improving the recording of patients' test results and the number of important events in the Scottish Care Information – Diabetes Collaboration computerised support tool and in electronic health records more generally would be of value.

Study registration

This study is registered as PROSPERO CRD42016052324.

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This report

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