A systematic review and individual patient data meta-analysis of prognostic factors for foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulcerations (PODUS)

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Scientific summary

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Background

Clinical and cost-effective health care requires the careful measurement of health outcomes, and the need for an evidence-based approach to foot care services for people with diabetes is well documented. The optimal clinical management of people with diabetes includes annual foot risk assessment. This is recommended in national and international clinical guidelines such as the Quality and Outcomes Framework (QOF) of the General Medical Contract in the UK. At present, the guidelines are mostly consensus based and use only a proportion of the available evidence.

The authors of two systematic reviews found marked variation in the incidence of foot ulcers across different study populations. Independent risk factors and prediction rules derived from high-risk populations might perform differently in the general diabetic (low-risk) population. Also of concern is the fact that the accuracy of some recommended risk factors has not been fully explored in different groups of people with diabetes, and there have been few attempts to validate the statistical models of risk factors from derivation cohort studies.

The purpose of this systematic review and meta-analysis of individual patient data (IPD) was to contribute to the evidence base for the risk assessment for foot ulcers in people with diabetes. It is based on data from more than 16,000 patients worldwide. Given the increased worldwide prevalence in diabetes, the identification of the most predictive risk factors could lead to reduced costs for health-care providers and patients.

Meta-analyses based on the literature estimates—aggregate data—do not permit adjustments for covariates to be performed. The only practicable way to analyse data from several cohort studies with the same adjustments is to use IPD.

Objectives

Our review focused on the following research questions:

1. What are the most highly prognostic factors for foot ulceration (i.e. symptoms, signs, diagnostic tests) in people with diabetes?
2. Can the data from each study be adjusted for the same covariates?
3. Does the model accuracy change when patient populations are stratified according to demographic and/or clinical characteristics?
4. How predictive are the risk assessment recommendations in UK national clinical guidelines?

Methods

We adhered to the highest methodological standards for systematic reviews and meta-analyses of IPD. This included the creation of a three-tier committee structure involving an international group of individuals.

We searched for relevant studies in EMBASE and MEDLINE databases. The electronic search strategies created during the aggregate systematic review of predictive factors for foot ulceration in diabetes were updated and rerun to January 2013.
One reviewer applied the IPD review eligibility criteria to the full-text articles of the studies identified in our literature search and also to all studies excluded from our aggregate systematic review to ensure that we did not miss eligible IPD. A second reviewer applied the eligibility criteria to a 10% random sample of the abstract search yield to check that no relevant material was missed by having only one reviewer assess all the abstracts.

This review includes data only from individuals who were free of foot ulceration at the time of study entry and who had a diagnosis of diabetes mellitus (either type 1 or type 2). When we identified studies with some patients who had prevalent foot ulcers at the time of recruitment, we ascertained whether or not it would be possible to include only patients who were free of ulceration at the time of recruitment. The corresponding authors of all identified cohort studies were contacted and invited to share their data.

The assessment of methodological quality is an important component of an IPD systematic review, but there is complexity in assessing potential threats to the validity of primary studies for this research genre and no widely agreed criteria exist. We therefore compiled a list of items relevant to our IPD review question which we believed likely to distinguish between studies with data that are compromised by threats of validity.

Data extraction was undertaken by two reviewers working independently and disagreements were resolved by discussion. For quality assessment, a two-stage process was used. Our published protocol incorporated a data confidentiality agreement which made clear the need for the data provided to de-identify individual patients. It also includes an assurance that the original investigators are in possession of local ethical approval for their study.

All elements from the patient history, symptoms, signs and diagnostic test results were considered for inclusion in the prognostic model. These were collected variously as continuous, binary and multicategorical data. The outcome variable was incident foot ulceration (present/absent).

Data were stored in password-protected files on a secure University of Edinburgh computer (University of Edinburgh data protection registration number Z6426984) and were only accessible to members of the Data Management Committee.

The methodology of IPD meta-analyses of observational studies is relatively undeveloped compared with that for randomised controlled trials (RCTs). We recognised that reviewers undertaking IPD meta-analyses of observational studies need to proceed with caution, given that guidance is not always available and the methodology somewhat untested. There were, therefore, difficult methodological issues regarding the analysis for this project, some of which were particular to IPD meta-analysis methodology and some of which were more general. We also had a choice between two main methods of meta-analysis commonly known as one-step and two-step methods, respectively. Both these methods have pros and cons.

Practical constraints led us to select the two-step approach, which is also simpler and more transparent because it uses methods that have been much used and are well understood by the systematic review community. For the two-step method, each data set is analysed in turn by the meta-analysts, using ordinary methods of analysis such as logistic regression, and then the estimates from each analyses are combined using established meta-analysis methods. The advantage of the two-step method over a meta-analysis of published studies is that the meta-analysts have some flexibility in the estimates they can obtain from each study. If, for example, they require all estimates to be adjusted for age, and all the data sets have the patients’ ages, it is simple to get age-adjusted estimates.

The data sets contributing IPD covered a range of temporal, geographical and clinical settings. It was, therefore, only reasonable to expect some degree of heterogeneity between the studies. We chose to use random-effects meta-analysis, which does not assume that all the estimates from each study are estimates of the same underlying true value, but rather that the estimates belong to the same distribution.
Before undertaking any meta-analysis, we assessed the extent of heterogeneity. We employed standard methods of assessing heterogeneity, by examining forest plots of estimates and calculating $I^2$ and $\tau$-statistics, but also used the IPD to look at histograms and data summaries for each study.

The methodology of handling systematically missing data in IPD meta-analysis is still very much in development. We felt it would be useful, therefore, to present the results of a complete case, because complete case analyses are known not to be biased providing the missing data are missing at random (MAR), although we also used multiple imputation in a secondary analysis.

The studies contributing data to this IPD analysis collected data on hundreds of variables. It would not have been statistically rigorous or clinically relevant to perform meta-analyses for all these variables. We therefore needed a method to select candidate variables for meta-analysis. We used the following criteria:

- Variables had to have been collected in at least three studies, with $< 60\%$ missing.
- Variables needed to have been coded in such a way to allow standardisation across data sets. For example, we were unable to use eye data, as in some data sets this had been defined as retinopathy and in others as requiring glasses.
- The extent of heterogeneity did not preclude meta-analysis.

We did not choose variables for the multivariable model on the basis of univariate results, as we believe this to be a flawed method.

We also undertook secondary meta-analyses to compare the contribution of individual predictive factors with that of the risk categories contained in UK clinical guidelines.

Our search identified 16 cohort studies and we obtained IPD for 10. These data were collected from more than 16,000 people with diabetes worldwide and reanalysed by us. We were unable to obtain IPD from six of these because either we could not make contact with the authors or the authors were no longer in possession of the data.

One data set was not used in the primary meta-analyses and kept for independent validation. Anonymised data from each of the collaborators of the primary cohort studies were accepted in the way deemed most convenient to the original study investigators.

All data sets were prepared for meta-analysis the same way, following a list of rules, exclusion criteria and for a selected number of variables. A few data sets contained more patients than presented in the corresponding manuscript owing to multipurpose collection. We focused on the data collected to assess an ulcer or amputation outcomes in diabetic patients.

Each author provided information on the reason for the data being missing when available. This information was essential to confirm the patterns of missing data.

Univariate analyses of common variables are presented on forest plots to display the degree of heterogeneity between studies. All variables common to the original studies were identified and those that met the following criteria, collected in at least three data sets and having consistent definitions, were:

- age
- sex
- body mass index (BMI)
- smoking
- height
- weight
- alcohol
• glycated haemoglobin (HbA1c)
• insulin regime
• duration of diabetes
• eye problems
• kidney problems
• monofilament
• pulses
• tuning fork
• biothesiometer
• ankle reflexes
• ankle–brachial index (ABI)
• peak plantar pressure
• prior ulcer
• prior amputation
• foot deformity.

A univariate meta-analysis was performed for each of these variables and the results discussed by members of the review international steering committee. The most important clinical predictors identified by them for inclusion in the primary, multivariable meta-analysis were age, sex, duration of diabetes, monofilaments and pulses.

The analysis was repeated twice, once for patients with no previous history of amputation or ulceration and again for all patients regardless of previous history. In the second analysis, previous history was also used as a predictor.

Results

In general, the cohort studies included in the review were of a high methodological quality; of the four items used to assess the quality of the conduct of the studies, three indicated a low risk of bias. Patients were recruited consecutively in all but one study. Follow-ups were conducted at least 1 month after the data collection of risk factors, allowing enough time for an ulcer to develop, and all reports provided enough detail for the tests to be replicated.

Meta-analyses of estimates from multivariable logistic regression analyses based on data from the entire population found that a previous history of ulceration [odds ratio (OR) 6.589, 95% confidence interval (CI) 2.488 to 17.45], an inability to feel a 10-g monofilament test (OR 3.184, 95% CI 2.654 to 3.82), at least one absent pedal pulse (OR 1.968, 95% CI 1.624 to 2.386), a longer duration with a diagnosis of diabetes (OR 1.024, 95% CI 1.011 to 1.036), female sex was protective (OR 0.743, 95% CI 0.598 to 0.922) were all predictive of an increased risk of foot ulceration. The absence of heterogeneity in the pooled analyses for the 10-g monofilament test is remarkable.

In people with no previous history of ulceration or amputation, the predictive factors were inability to feel a 10-g monofilament test (OR 3.438, 95% CI 2.772 to 4.264); at least one absent pedal pulse (OR 2.605, 95% CI 1.808 to 3.754); and a longer duration with a diagnosis of diabetes (OR 1.029, 95% CI 1.017 to 1.04).

Receiver operating characteristic curve analyses of data from five individual studies were also performed to compare the prognostic utility of 10-g monofilament and absent pedal pulses. Data from the largest studies showed almost identical estimates of prognostic utility for these two tests, but the consistency of the results for the 10-g monofilament test does favour its use. The results of the meta-analyses for absent pedal pulses are also consistent in the two meta-analyses and show the absence of at least one pedal pulse to be independently predictive of risk. However, adding the palpation of pedal pulses to the risk assessment examination appears to confer no additional prognostic utility over and above the use of 10-g monofilaments alone.
Discussion

We found that the inability to feel a 10-g monofilament and the absence of at least one pedal pulse was at least as predictive as the classification systems for moderate (increased) risk of foot ulceration. Inability to feel a 10-g monofilament, an absent pedal pulse and a previous history of ulceration were at least as accurate as the classification system used to identify people at high risk of foot ulceration.

The most consistent results were from the 10-g monofilament test and clearly show this quick, simple and relatively cheap test to be predictive of foot ulceration for everyone with diabetes. The almost complete absence of heterogeneity in the primary meta-analyses is remarkable given that the pooled estimate is based on data from five different studies and 11,522 people from three different countries. It is important that the predictiveness of the test did not appear to be influenced by the fact that the monofilament was used on different sites of the foot in each of the cohorts.

The results of the meta-analyses for absent pedal pulses were also consistent in the two meta-analyses and show the absence of at least one pedal pulse to be independently predictive of risk. However, adding the palpation of pedal pulses to the risk assessment examination appears to confer no additional prognostic utility over and above the use of 10-g monofilaments alone. This observed effect may be attributable to the underlying pathophysiology of the majority of foot ulcers in these derivation cohorts being neurological rather than vascular in nature.

This review makes a unique and fundamental contribution to the global evidence base for the risk assessment for diabetes-related foot ulcers. We have justified the predictive factors included in the model and presented all univariate and multivariable analyses for inspection by readers who may wonder about the exclusion of particular tests.

We derived and independently validated a prognostic model for common symptoms, signs and diagnostic tests. The absence of data pertaining to elements of patients’ general health prevented the identification of risk factors of a more systemic nature.

We suggest that these findings are carefully considered by diabetes clinical guideline developers. In the UK, the QOF should be refined to reflect the strong evidence from this research to support the use of a 10-g monofilament and one absent pulse to identify those at moderate or intermediate risk of foot ulceration and the addition of a history of foot ulcers or lower-extremity amputation to identify those at high risk.

The effectiveness and cost-effectiveness of the therapeutic impact of the proposed predictors should be evaluated in large well-designed RCTs across different health-care settings.

Future research using cohort designs investigating the prognostic factors for foot ulceration in diabetes should evaluate elements from the patients’ systemic medical history such as cerebral, cardiovascular and renal events rather than signs, symptoms and tests used at the periphery.

Study registration

This study is registered as PROSPERO number CRD42011001841.

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This report

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