NETSCC, HTA

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Title: Predicting foot ulceration in people with diabetes: A systematic review and meta analysis of individual patient data.

PROJECT DESCRIPTION

Research Objectives

- To systematically review and use individual patient data from cohort studies in a meta analysis to estimate the predictive value of clinical characteristics and diagnostic tests for diabetic foot ulceration (DFU).
- To develop a prognostic model of the risk factors for DFU based on data collected worldwide.
- To test the robustness of the model in different demographic profiles - for example, age, duration of diabetes, control of diabetes (insulin, diet or oral medication).

Research Questions

1. How many cohort studies have IPD for predictive factors for diabetic foot ulceration?
2. What are the most highly predictive factors (symptoms, signs, and diagnostic tests) for foot ulceration in people with diabetes based on IPD analyses?
3. Do multivariable models support the use of the same elements in risk assessment procedures for different populations of patient with diabetes?

Existing Research

Diabetic foot ulceration (DFU) is a complication of diabetes which has an associated risk of infection and gangrene; it precedes 85% of foot amputations. In the USA, diabetes accounts for 70% of all amputations and data produced by the Information Services Division (ISD) of the Scottish Government reveal that one diabetes-related lower limb amputation is carried out every other day in Scotland (annual average n=179). The cost of diabetes-related foot ulcers is high: an analysis of UK inpatient hospital data suggested the cost per admission for DFU was £1451 and the annual national cost likely to be around £17 million. [16] Targeting prevention strategies focused on those at greatest risk of DFU could help reduce amputations and save healthcare provider costs, but current foot screening clinical guidelines are largely based on consensus and the findings from individual studies rather than any systematic integration of all available data. [3,4,5,6] Also of concern is that the accuracy of recommended risk assessment strategies has not been fully explored in different groups of people with diabetes. Specialist foot care strategies have not been found to be cost-effective for those categorised as low risk, and economists have advised that the availability of individual patient data would help the development of more accurate economic models for example by permitting discrete event simulations. [17] Targeting prevention strategies focused on those at greatest risk of DFU could help reduce amputations and save healthcare provider costs by properly integrating data and the accuracy of recommended risk factors as predictors of ulceration in different groups of people with diabetes.

It is recommended that all patients in the UK who have diabetes should be assessed for peripheral neuropathy and absent/present pedal pulses on an annual basis. Risk classifications of 3 or 4 levels (low, moderate and high) are sometimes presented visually as traffic lights however this system is based on individual studies. [3,18] Our systematic review of aggregate data found little evidence of the individual contribution for some of the recommended signs, symptoms and diagnostic tests contained

in guidelines For example absent/ present pedal pulses are recommended in the diagnosis of peripheral vascular disease (PVD) but the value of this sign as a method of assessing vascular insufficiency in people with diabetes can be unreliable because arterial-venous shunts can exist when bounding pedal pulses are present. [19] Furthermore, none of the five cohort studies which have investigated the predictive value of foot pulses have found this clinical sign to be predictive of ulceration. [8,11]

Unfortunately although our systematic review remains the best attempt to integrate the evidence from cohort studies to date, the conclusions are compromised because pooled estimate using conventional meta analytic techniques of aggregate data are not adjusted for confounding and mixtures of adjusted and unadjusted analyses are reported in the primary studies. It is also unclear from the reports whether the adjusted analyses tested the models using the same confounders or effect modifiers. Therefore an IPD analyses is the only way to reliably analyse data from several cohort studies while ensuring a standard approach.

The main advantages of undertaking an individual patient data meta analysis (IPD) are the ability to conduct a more complete analysis of time-to event, to investigate interactions and to undertake a re-analysis of all relevant outcomes. [8] The international collaboration proposed in this application would also confer the benefit of world-wide dissemination of the research findings. [9]

The success of this type of research is crucially dependent on a high level of collaboration, trust and commitment between multi-disciplinary researchers and the authors of the primary studies. [9] The ownership of data from primary studies by the pharmaceutical industry can prevent an IPD analysis being accomplished. However, our background work has found that none of the cohort studies included in the systematic review had industry sponsorship. Moreover, authors who possess the data from all 10 of the 11 cohort studies included in the published aggregate systematic review have agreed to take part in our IPD systematic review and to contribute anonymised data from their primary studies for re-analysis. [7]

The proposed research will make a seminal contribution to the evidence-base in the risk assessment of foot ulcers in people with diabetes because it combines data from more than 9,000 patients worldwide. The international nature of these data will ensure a balanced interpretation and the international profile of the group of an International Steering Committee will lead to wide endorsement and dissemination. Given the increased worldwide prevalence in diabetes the findings may lead to reduced costs for health care providers.

Research Methods

Prognostic or predictive models are statistical models that combine two or more items of patient data to predict clinical outcome. [13] By using worldwide data collected from people with diabetes our analysis will develop a predictive model which is central to development of an evidence-based screening strategy for diabetic foot disease and robust enough to reliably inform international clinical guidelines.

We will begin by developing a protocol based on the following review methods:

Search strategy

A detailed electronic search strategy has been developed and is included in the submission of our application. Fourteen cohort studies have been identified using a search of MEDLINE (1966-February 2005), Embase (1980-February 2005) and CINAHL (1982-February 2005) databases and contact with authors. New studies (published since February 2005) which have assessed the predictive value of diagnostic tests signs and symptoms or elements from the patient history will be identified and obtained. The reference lists of recent clinical guidelines, review articles will also be searched. There will be no language restrictions.

Two reviewers working independently will apply the IPD review eligibility criteria detailed below to the studies we identify in our new search and also all studies excluded from our aggregate systematic review to ensure we do not miss eligible IPD. For example, cohort studies which recruited patients with prevalent foot ulceration at the time of recruitment were ineligible for inclusion in the aggregate review but if after we make contact it is revealed that those authors possess IPD for patients without prevalent foot ulcers we will seek to include them in the review.

Eligibility Criteria

Types of Participants
The IPD review will only include data from individuals who are free of foot ulceration at the time of study entry and who have a diagnosis of diabetes mellitus (either type 1 or type 2).

Types of exposure variables
All elements from the patient history, symptoms, signs and diagnostic test results will be considered for inclusion in the review. These are collected variously as continuous, binary and multi-categorical data.

Type of outcome variable
The outcome variable will be incident foot ulceration (present/absent) and time to ulceration from initial diagnosis of diabetes as well as from the time of screening.

Types of studies
Cohort studies of people with diabetes who do not have a foot ulcer at the time of study recruitment (prevalent ulcers) will be identified and the corresponding authors of cohorts not previously identified by us will be contacted and invited to share their data. Where we identify studies with a proportion of patients who had prevalent foot ulcers we will seek data from those who were free of ulceration at the time of recruitment. The authors of these studies will also be contacted to determine the nature of the data and if suitable will be invited to share their data.

Quality assessment
Methodological quality assessment (QA) is an important component of an IPD systematic review, but there are no widely agreed quality criteria. However, it has been suggested that similar methodological considerations apply to both diagnostic studies and evaluations of prognostic variables. [20]A QA tool has therefore been developed by the team by combining and adapting items from three different sources of QA criteria.[21,22,23]

Statistical analysis
Acquiring IPD from multiple cohort studies will allow us to construct a prognostic model using data from patients worldwide.

We propose, as a provisional analysis plan, to use a multi-level mixed model, using “study” as one of the levels. Such a model can also allow for the within-patient clustering that occurs if a patient contributes data from both feet, although to aid interpretation, we prefer to use patients rather than feet as the unit of analysis. We will only attempt this analysis if the results of the investigation of heterogeneity do not rule it out and the model diagnostics are acceptable.

As with any meta-analysis, heterogeneity must be considered, both from a clinical and statistical viewpoint. First, clinical expertise will be used to decide if it would be meaningful to combine the studies based on the patient demographics, risk factors (symptoms, signs, elements from patient’s history and diagnostic test results), outcome measures and timing of outcome measures (length of follow-up). We will examine histograms of relevant variables from each dataset to check the spread, mean, median, and skewness, and the consistency of these properties across datasets, before reaching a decision about whether it make clinical or statistical sense to combine the data. We will also consider relationships between variables using tables and scatter plots.

Sources of heterogeneity that particularly concern us are differences between the patient groups with regard to basic demographics and disease spectrum as these may have a strong influence on prognosis and the performance of the tests. Also important are the various methods use to conduct the tests, which again may lead to marked differences in test performance. Another potentially important source of heterogeneity is length of follow-up as this may impact on the proportion of patients who develop ulceration.

It is possible to use conventional methods of investigating heterogeneity on aggregate data generated from the datasets. We shall therefore generate summary measures and use these to create forest plots and compute I^2, statistics.[15] I^2 values of 50% and 75% have been used to denote moderate and high levels of variation between studies that are not explainable by chance. We shall use these figures as a guide only, together with the results from the IPD. We are aware that a consensus has not yet been reached about the investigation of heterogeneity in IPD systematic reviews. [15]

As the datasets should contain the date of initial diagnosis of diabetes and the date, if any, of foot ulceration, we propose to use survival analysis. Covariates will be added to the model based on clinical relevance, if there are many possible covariates that could be added given the number of events and patients and there is a danger of model overfitting, the clinicians will be asked to choose a subset of covariates based on their expertise and experience. We shall not use data-derived methods as these lead to overly optimistic estimates of model performance. Model performance will be assessed graphically and with chi-square statistics.

Where possible, we shall use the patient, rather than the foot, as the unit-of-analysis. This means we can use a simpler model that will be easier to interpret. It is also important from the view of patient outcomes – an amputation affects the patient as a whole and not just the foot. One approach to construct the model is to use the most badly affected foot from each patient. However, if the model performance merits an analysis using the foot as the unit-of-analysis, and of course allowing for the correlation between feet belonging to the same patient, we shall conduct such an analysis.

To avoid a loss of information, wherever possible we shall keep continuous variables as continuous and not dichotomise or otherwise categorised variables. E.g. we shall use BMI, rather than subdivide patients into “underweight”, “normal weight”, “overweight”, and “obese”. Sometimes the relationship between a continuous covariate and the outcome is not linear, and in such cases we will investigate the use of fractional polynomials and similar.

The analysis will determine whether the following variables are independently predictive of foot ulceration.[24,25]

Continuous variables

1. BMI

2. HbA1c

3. ABI*

4. Peak plantar pressure

5. Duration of diabetes

Binary and other categorical variables

1. Age

2. Gender

3. Cutaneous sensation (monofilaments)

4. Vibration Perception Thresholds (VPT (tuning forks and neuro or biothesiometers))

5. Absent pedal pulses*

6. Insulin use

* indicates the unit of analysis is the foot as opposed to the individual patient

Outcome variable; Incident foot ulceration (present/absent) and time to ulceration

Confounding variables; duration of diabetes, age, sex, HbA1c, previous ulceration, deformity (PPP), neuropathy (monofilaments) neuropathy (VPT).

Effect modifying variables (interactions); Socio economic status, access to health care (podiatry, duration of diabetes, age, HbA1c).

Specifying variables for analysis

Table 2 below shows the common dataset from the largest studies and an update of the search might identify additional common data.

The authors of the cohort studies will be able to supply data in the way that is most convenient to them and these data will then be converted into suitable categories. A single individual will be identified for each study to whom all queries about the data will be addressed.

Where possible we will seek the outcome variable (foot ulcer) with the foot as the unit of analysis, but if these data are not available we will conduct the analysis using the person as the unit of analysis. As most of the variables effect both feet this makes clinical sense.

For each of the exposure variables, individuals will be divided into two groups; those with foot ulceration and those without. The distributions for the exposure variables will be re-examined within each group both as a final check that corrections have been made and to fulfil the assumptions of the regression analysis. All demographic, numerical data (age at consultation, duration of diabetes, types of diabetes) will be presented as means for each group.

Ethics and governance

The ethics of obtaining data collected from a number of sources which cross international boundaries and different legal systems have been carefully considered and advice sought from the National Research Ethics Service. The original studies were conducted in Europe and the USA and because the investigators of each of the original studies obtained local ethical committee approval and written, informed patient consent no further ethical approval is required.

This research relies entirely on a combination of existing data sets and no new data will be collected. The value of the IPD analysis will be the production of a global dataset of predictive factors for diabetic foot disease and the opportunities for new uses will be maximised. Anonymised data from each of the collaborators of the primary cohort studies will be transported using encrypted USB drives for safe transportation. Data will be formatted in a consistent way to permit a re-analysis. This will be

stored on a secure University of Edinburgh computer [University of Edinburgh Data protection registration number: Z6426984].

Expertise

The multidisciplinary team has extensive experience in matters relating to evidence based health care, individual patient data analyses, qualitative research methods, diabetes, peripheral vascular disease podiatric and primary as well as secondary care. The applicants will act as the project secretariat and will be collectively responsible for the day-to-day running of the project.

The Applicants

Dr Fay Crawford is a senior health services researcher and a state registered podiatrist. She has recently published a cohort study of predictive factors for foot ulceration in diabetes and has undertaken many systematic reviews of interventions, prognostic and diagnostic tests. She is the Principal Investigator and will be responsible for all aspects of project management and research outputs.

Dr Francesca Chappell is a medical statistician. Her PhD thesis develops meta analytical techniques for systematic reviews of test accuracy. She has also published an IPD analysis within a Health Technology Assessment monograph.

Dr Jackie Price is a clinical senior lecturer in epidemiology, honorary consultant in public health medicine and a co-ordinating editor of the Cochrane Collaboration PVD review group. She has extensive experience in the design and interpretation of epidemiological studies, including prospective cohort studies, clinical trials, systematic reviews and meta-analysis. She recently participated in an international IPD analysis of ABI as a predictor of cardiovascular disease and has published widely in the fields of both peripheral vascular disease and diabetes.

Professor Gordon Murray is The Professor of Statistics in Public Health at the Centre for population Health Sciences at The University of Edinburgh and the Director of the Edinburgh Trials Unit.

Professor Aziz Sheikh is Professor of primary care research and development. He is an experienced systematic reviewer with established interests in the secondary uses of data and the development of risk prediction rules.

Dr Colin Simpson is a CSO-supported National Post-Doctoral Research Fellow, with expertise in the use of primary care data and data linkage for epidemiological research.

Professor Gerard Stansby is Professor of vascular surgery and a consultant vascular surgeon who regularly deals with diabetic foot problems and has an interest in assessment of arterial disease. He is a co-ordinating editor of the Cochrane PVD group with Dr Price, and director of the North East England aneurysm screening programme.

Dr Matthew Young is a consultant diabetologist who has conducted 2 cohort studies of predictive factors for foot ulceration.

International Steering Group members

The following principal investigators of cohort studies have agreed to take part and contribute the data from their cohort study and letters of collaboration accompany our application. Together they possess more than 95% of data included in the aggregate systematic review of predictive factors for DFU.

David G. Armstrong, is a professor of surgery and associate dean of the Scholl College of podiatric medicine at the Rosalind Franklin University of Medicine and Science in North Chicago, USA

Edward J. Boyko, is a professor of medicine at the University of Washington, USA

Thomas Kastenbauer is a biologist working on metabolic illness and nephrology at the Karl Landsteiner Institute in Vienna, Austria.

Lawrence Lavery is a podiatric surgeon based at the A&M Health Science Centre in Texas.

Graham Leese is a consultant diabetologist at Ninewells Hospital, NHS Tayside Scotland.

Steve Rith-Najarian is a family medicine physician and a Bemidji Area diabetes consultant at the Cass Lake Indian Hospital.

Aristidis Veves is the research director of microcirculation at Joslin-Beth Deaconess Foot Centre and an associate professor at Harvard Medical School, USA.

Additional Collaborators

We also now have clinical input from four clinicians, three of whom who provide care for people with diabetes in the NHS in England and have a special interest in foot disease and one who has expertise in primary care and clinical prediction rules. They are;

Dr Nicola Leech: a consultant in Diabetes and Metabolic Medicine and Clinical Lead for Diabetes Newcastle upon Tyne Hospitals Foundation Trust.

Ms Nikki Coates: the Lead Diabetes Podiatrist. Newcastle Hospitals, Community Health.

Ms Coates and Dr Leech are responsible for the foot clinic in the Newcastle Diabetes Centre. Patient reviews are attended by multidisciplinary teams including podiatrists, diabetologists, diabetes specialist nurses and vascular surgeons from the Newcastle upon Tyne Hospitals in regular meetings.

Professor William Jeffcoate: a Consultant in Diabetes and Endocrinology and co-founder of the Foot Ulcer Trials Unit at the University of Nottingham. His main research interest lies in collating evidence to underpin protocols for the clinical care of foot disease.

Professor Tom Fahey: Head of the department of General Practice at Royal College of Surgeons, Ireland is a practicing general practitioner who has extensively researched the development and validation of clinical prediction rules.

The collaboration of these clinical experts with our international steering committee will help ensure the analysis is relevant to routine clinical practice in a variety of health care settings. The collaborators will contribute to the development of the protocol and to the discussion during the face to face meeting with the study authors (Principal Investigators) and the applicants. Importantly they will also help the dissemination of the research findings into routine NHS clinical practice.

Collaborators meeting

Once the initial analysis has been performed a face-to-face meeting of all collaborators (the applicants the steering committee and the additional collaborators) will be convened. The purpose of the meeting is to allow everyone to know the results of the review and meta analysis first and to have the opportunity to interpret the data and question the findings. The cost of a face to face meeting in Edinburgh is included in the costs.

Reporting

In the final report we will clearly present the methods of the review including tabulated characteristics of includes studies and details of study designs. The report will conform to recommendations in the PRISMA checklist.[26] Formal synthesis of the results and formal assessments of study quality will also be presented.

Exploitation and dissemination

Dissemination of the findings from these projects will occur in several different ways. The findings of both studies will be;

A. published in peer-reviewed journals and presented at national and international conferences to inform the academic bio medical community of the results;

B. the Press Offices of the Newcastle NHS Foundation Trust and the University of Edinburgh will inform the public via press releases;

C. members of the International Steering Committee and the named collaborators are internationally recognised group of experts who will be able to disseminate the findings to international policy makers as well as academic course syllabuses in institutions training health care professionals who provide podiatric and medical care to people with diabetes

Service users

Consumer involvement in the underpinning DH/CSO funded derivation cohort study came from volunteers from Diabetes UK in Tayside. These volunteers' perspectives allowed researchers to adapt the study documentation and data collection processes in ways acceptable to the general diabetic population. Similar input will be sought in the proposed research by inviting two volunteers from Diabetes UK in Lothian to join the International Steering Committee.

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Table 1. Predictive factors and incidence of foot ulcers

Author (year)	Sample size (n=)	Predictive factors	Controlled for confounding (yes/no)	Incidence of foot ulceration % (n)
Armstrong (2004)	100	Peak plantar pressure.	No	8% (8)
Boyko (1999)	900	Monofilaments, previous foot ulceration, previous amputation, use of insulin, ABI, Charcot foot, vision <20/40.	Yes	UC (162 ulcers over 5442.6 cumulative person years)
Boyko (2006)	1285	Vision, HbA1c, previous foot ulcer, previous amputation, Monofilaments, onychomycosis (fungally infected toe nails).	Yes	16.8% (216)
Crawford (2010)	1192	Previous amputation, Thermal sensation, Monofilaments.	Yes	1.93% (23)
Kastenbauer (2001)	187	Vibration Perception Threshold, Mean Plantar Pressure, alcohol consumption, medial sclerosis.	Yes	5.3% (18)
Lavery (2003)	1666	Peak Plantar Pressure.	Yes	15.8% (263)
Leese (2006)	3526	Risk classification scores; Low/Moderate/High based on groups of test results and symptoms and signs.	No	4.7% (166)
Litzelman (1994)	152	Thermal sensitivity, Monofilaments, HDL (cholesterol),.	No	8.9% (63)
Murray (1992)	63	Previous ulceration, callus, pressure.	No	9.5% (6)
Peters (2001)	213	Previous ulceration.	Yes	25% (54)
Pham (2000)	248	Neuropathy Diabetes Score, Vibration Perception Threshold, Monofilaments, Peak Plantar Pressure.	Yes	29% (84)
Rith Najarian (1992)	358	Monofilaments.	Yes	11.5% (41)
Veves (1992)	86	Peak Plantar Pressure.	No	17.4% (15)
Young (1994)	469	Vibration Perception Threshold	Yes	10.2% (48)

Table 2. Common variables among identified cohort studies

	Armstrong 2004	Boyko 2006	Boyko 1999 n=900	Crawford N =1193	Kastenbauer N=187	Lavery 2003 N=1666	Leese 2006 N=3526	Litzleman 1997	Murray 1996	Peters N=213	Pham N=248	Rith Majarian 1992	Veves 1992	Young 1994
SWF		X	X	X	X	X	X	X		X	X	X		
VPT	X		X	X	X	X	X			X	X		X	X
PPP		X		X		X			X	X	X		X	
ABI	X	X	X	X	X					X		X		
HbA1c		X	X	X	X		X	X		X	X			X
Pulse	X		X	X	X	X	X			X	X			X
Age		X	X	X	X	X	X	X	X	X	X	X	X	X
Sex		X	X	X	X	X	X	X	X	X	X	X	X	X
DD		X	X	X	X	X	X	X	X	X	X	X	X	X
BMI		X		X	X	X	X	X		X	X		X	
Insulin		X	X	X	X		X	X						

SWF =Semmes Weinstein Monofilament; VPT = Vibration Perception Threshold; PPP = Peak Plantar Pressure; ABI = Ankle Brachial Indices; HbA1C = blood glucose; DD =Duration of Diabetes; BMI =Body Mass Index; Insuln = Insulin use.