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Complex interventions for preventing diabetic foot ulceration

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Abstract

English

Background

Ulceration of the feet, which can lead to the amputation of feet and legs, is a major problem for people with diabetes mellitus, and can cause substantial economic burden. Single preventive strategies have not been shown to reduce the incidence of foot ulceration to a significant extent. Therefore, in clinical practice, preventive interventions directed at patients, healthcare providers and/or the structure of health care are often combined (complex interventions).

Objectives

To assess the effectiveness of complex interventions in the prevention of foot ulcers in people with diabetes mellitus compared with single interventions, usual care or alternative complex interventions. A complex intervention is defined as an integrated care

approach, combining two or more prevention strategies on at least two different levels of care: the patient, the healthcare provider and/or the structure of health care.

Search methods

For the second update we searched the Cochrane Wounds Group Specialised Register (searched 22 May 2015), The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2015, Issue 4), The Database of Abstracts of Reviews of Effects (DARE) (The Cochrane Library 2015, Issue 4), The Health Technology Assessment Database (HTA) (The Cochrane Library 2015, Issue 4), The NHS Economic Evaluation Database (NHS EED) (The Cochrane Library 2015, Issue 4), Ovid MEDLINE (1946 to 22 May 2015), Ovid MEDLINE (In-Process & Other Non-Indexed Citations 21 May, 2015), Ovid EMBASE (1974 to 21 May, 2015) and EBSCO CINAHL (1982 to 22 May, 2015).

Selection criteria

Prospective randomised controlled trials (RCTs) which compared the effectiveness of combinations of preventive strategies, not solely patient education, for the prevention of foot ulcers in people with diabetes mellitus, with single interventions, usual care or alternative complex interventions.

Data collection and analysis

Two review authors were assigned to independently select studies, to extract study data and to assess risk of bias of included studies, using predefined criteria.

Main results

Only six RCTs met the criteria for inclusion. The study characteristics differed substantially in terms of healthcare settings, the nature of the interventions studied and outcome measures reported. In three studies that compared the effect of an education-centred complex intervention with usual care or written instructions, only little evidence of benefit was found. Three studies compared the effect of more intensive and comprehensive complex interventions with usual care. One study found a significant and cost-effective reduction, one of lower extremity amputations (RR 0.30, 95% CI 0.31 to 0.71). One other study found a significant reduction of both amputation and foot ulcers. The last study reported improvement of patients' self care behaviour. All six included RCTs were at high risk of bias, with hardly any of the predefined quality assessment criteria met.

Authors' conclusions

There is no high-quality research evidence evaluating complex interventions for preventing diabetic foot ulceration and insufficient evidence of benefit.

Plain language summary

English

Combined strategies to avoid foot ulcers in patients with diabetes

Foot ulcers (open sores) are common in people with diabetes mellitus (type 1 and type 2), especially those with problems in the nerves (peripheral neuropathy), the blood supply to their legs (peripheral vascular disease) or both. People with ulcers due to diabetes will sometimes need an amputation (surgical removal of part of the limb). Foot ulcers not only lead to physical disability and loss of quality of life, but also to economic burden (healthcare costs, industrial disability). The aim is therefore to prevent foot ulcers occurring, for example, by showing patients with diabetes how to look after their feet or by prompting doctors to check their patients' feet more often. The results of single prevention strategies alone have so far been disappointing, therefore in clinical practice, preventive interventions directed at patients, healthcare providers and/or the structure of health care are often combined. In this review of trials of complex, preventive interventions, we found insufficient evidence that these combined approaches can be effective in reducing foot problems.

Background

Description of the condition

Diabetes mellitus is a serious health issue globally. The worldwide prevalence of diabetes is expected to rise from 2.8% in 2000 to 4.4% in 2030, which means that 366 million people will be affected (Wild 2004). One of the most disabling complications of diabetes is foot ulceration, which is a common outcome of a variety of aetiological pathways that often comprise neuropathy, ischaemia or both (Watkins 2003; Edmonds 2006). A diabetic foot ulcer is defined as a full-thickness wound of any duration, below the ankle, in a person with diabetes. Skin necrosis and gangrene are also classified as ulcers (Schaper 2004). Foot ulceration affects between 15% and 25% of people with diabetes at some point during their life (Singh 2005). Even when immediate and intensive treatment is provided, these wounds may take weeks or months to heal or may not heal at all. This not only leads to physical disability and marked reduction of quality of life (Vileikyte 2001; Nabuurs-Franssen 2005), but also precedes the majority of lower-extremity amputations (Pecoraro 1990; Global Lower Extremity Amputation Study Group 2000). Patients with neuropathic diabetic foot ulceration have a 7% risk of amputation in the next 10 years (Margolis 2005). Moreover, 70% of foot ulcer patients have recurrent lesions within five years after treatment (Apelqvist 1993).

Treatment of diabetic foot ulceration is very challenging and often needs to be of long duration. It requires not only expert attention, orthopaedic appliances and antimicrobial drugs, but also costly topical dressings and inpatient care (Jeffcoate 2003; Boulton 2004; Ragnarson Tennvall 2004; Cavanagh 2005; Singh 2005; Edmonds 2006). Not surprisingly, this leads to substantial economic burden. According to a review of health-economic studies, healing of an infected ulcer not requiring amputation costs approximately USD 17,500 (1998 US Dollars) (Ragnarson Tennvall 2004). In cases where lower extremity amputation is required, health care is even more expensive: USD 30,000 to 33,500 (1998 US Dollars) (Ragnarson Tennvall 2004). These costs do not even represent the total economic burden, since costs related to loss of productivity, preventive efforts, rehabilitation and home care should also be considered. When all this is taken into account, 7% to 20% of total

expenditure on diabetes in North America and Europe might be attributable to diabetic foot ulceration (Boulton 2005).

Description of the intervention

In 1989 the European Declaration of St. Vincent set a target of reducing the incidence of foot amputations by 50% over the next five years (St Vincent Declaration 1989). The benefits that could result from such a reduction were further emphasised by cost-effectiveness evaluations (Ragnarson Tennvall 2001; Ortegon 2004). International guidelines underpinned this drive by outlining foot ulcer prevention strategies, such as optimising metabolic control, identification and screening of people at high risk of diabetic foot ulceration and patient education in order to promote foot self care (IDF clinical guidelines task force 2005; Frykberg 2006; American Diabetes Association 2007).

Recent population-based research suggests that nowadays a meaningful reduction of the incidence of amputations caused by diabetes mellitus has been achieved. Before the European assembly in St. Vincent, the relative risk of a lower extremity amputation was still 15 times higher in people with diabetes mellitus than in people without diabetes mellitus (Most 1983). More recently, one study has suggested that the relative risk of amputation has reduced to 8.8 (7.3 to 10.7) in men and 5.7 (4.3 to 7.6) in women (Icks 2009), whilst another reported a relative risk of 7.7 (5.0 to 12.9) (Canavan 2008). However, it cannot be inferred from these figures that current preventive efforts are (cost)effective, since the reduction in amputation incidence may also have resulted from improvements in ulcer treatment. Moreover, another systematic review has shown that very little evidence is available supporting patient education alone for reducing foot ulceration and amputation incidence effectively (Dorresteijn 2010) and it is now generally agreed that there is no single, magic bullet for long-term prevention of diabetic foot ulceration and amputation (Reiber 2005).

In clinical practice patient education is therefore often combined with a wide variety of other preventive interventions, depending on the availability of expertise and resources. These interventions may, like patient education, aim to improve patients' health outcomes directly (patient level intervention). Examples are: podiatry care, foot ulceration risk assessment and motivational coaching to reinforce foot self care behaviours. However, interventions to prevent foot ulceration may also benefit patients indirectly through improving healthcare professionals' ability to provide adequate care (care provider level intervention) or through improving the health care system (structure of health care level intervention). Examples of the first are healthcare provider education (Khoury 1998), introduction of clear flow sheets for risk assessment and referral or introduction of new screening instruments for foot ulceration risk assessment. Examples of healthcare structural interventions in general are listed in the Cochrane Effective Practice and Organisation of Care (EPOC) Group checklist (McAuley 2002) and may include the introduction of a multidisciplinary team approach (Larsson 1995; Armstrong 1998; Dargis 1999a) or measures to improve regularity of follow-up and continuity of care (Khoury 1998; Renders 2000).

In this systematic review of trials we aim to evaluate the effectiveness of 'complex interventions', defined as an integrated combination of patient level interventions, healthcare provider level interventions and/or structural interventions.

Why it is important to do this review

Despite the fact that preventive interventions are often combined in clinical practice, there is very little scientific evidence demonstrating the effectiveness of such complex interventions. Existing review articles are mainly written from a clinical perspective (Jeffcoate 2003; Watkins 2003; Boulton 2004; Cavanagh 2005; Singh 2005; Edmonds 2006) and frequently lack the essential components of systematic review methodology, such as assessment of the risk of bias of included studies. A systematic review of the evidence of the effectiveness of complex interventions for the prevention of diabetic foot ulcers is therefore needed.

Objectives

To determine the effectiveness of complex interventions for the prevention of diabetes-related foot ulcers compared with single interventions, usual care or alternative complex interventions.

Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), including cluster-randomised controlled trials, evaluating complex intervention programmes for the prevention of foot ulcers in people with diabetes mellitus. We excluded studies that are solely aimed at optimising blood glucose concentration. An explicit focus on foot ulceration was required.

Types of participants

People aged 18 years or older with type 1 or type 2 diabetes mellitus in any healthcare setting.

Types of interventions

Complex interventions aiming to reduce the incidence of foot ulceration in people with diabetes mellitus. A complex intervention is defined as an integrated care approach, combining two or more prevention strategies on at least two different levels of care: the patient, the healthcare provider and/or the structure of health care (for examples of interventions on each level see: Background). Studies solely directed at patient education were not eligible. This topic is addressed in another systematic review (Dorresteijn 2010).

Studies of any comparison intervention were eligible for inclusion, i.e. complex interventions compared with single interventions or with usual care. If the comparison intervention consisted of an alternative complex intervention, foot care had to contrast with the experimental intervention on at least two different levels of care.

Types of outcome measures

Primary outcomes

The primary outcomes of interest were risk of:

- incidence of foot ulceration;
- rates of amputation (partial or total).

Secondary outcomes

Secondary outcomes of interest were:

- callus development (e.g. presence of lesions, or a detailed description of the number, location or diameter of lesions);
- resolution of callus;
- number and duration of hospital admissions for diabetes-related foot problems;
- foot care knowledge scores;
- patients' behaviour assessment scores (e.g. washing, creaming, foot inspection, cutting toe nails, use of pumice stones, foot gymnastics);
- costs;
- adverse events.

Trials were included even if only secondary outcomes were reported.

Search methods for identification of studies

The search methods used in the first update of this review can be found in Appendix 1.

Electronic searches

For this second update we searched the following electronic databases to find reports of relevant RCTs:

- The Cochrane Wounds Group Specialised Register (searched 22 May 2015);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2015, Issue 4);
- The Database of Abstracts of Reviews of Effects (DARE) (The Cochrane Library 2015, Issue 4);
- The Health Technology Assessment Database (HTA) (The Cochrane Library 2015, Issue 4);
- The NHS Economic Evaluation Database (NHS EED) (The Cochrane Library 2015, Issue 4);

- Ovid MEDLINE (1946 to 21 May 2015);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations 21 May, 2015);
- Ovid EMBASE (1974 to 21 May, 2015);
- EBSCO CINAHL (1982 to 22 May, 2015).

We used the following search strategy in the Cochrane Central Register of Controlled Trials (CENTRAL):

#1 MeSH descriptor: [Diabetic Foot] explode all trees
#2 MeSH descriptor: [Foot Ulcer] explode all trees
#3 (diabet* near/3 ulcer*):ti,ab,kw
#4 diabet* near/3 (foot or feet):ti,ab,kw
#5 (diabet* near/3 wound*):ti,ab,kw
#6 (diabet* near/3 amputat*):ti,ab,kw
#7 (diabet* near/3 defect*):ti,ab,kw
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
#9 MeSH descriptor: [Primary Prevention] explode all trees
#10 MeSH descriptor: [Preventive Health Services] explode all trees
#11 (prevent* or avoid* or protect*):ti,ab,kw
#12 (reduc* next risk*):ti,ab,kw
#13 (multidisciplinary or interdisciplinary or collaborat* or complex or integrat*):ti,ab,kw
#14 #9 or #10 or #11 or #12 or #13
#15 #8 and #14

The search strategies for Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL can be found in Appendix 2; Appendix 3 and Appendix 4 respectively. We combined the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision) (**Lefebvre 2011**). We combined the EMBASE search with the Ovid EMBASE filter developed by the UK Cochrane Centre (**Lefebvre 2011**). We combined the CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network (**SIGN 2011**). There were no restrictions with respect to language, date of publication or study setting.

Searching other resources

We searched the bibliographies of all retrieved and relevant publications identified by these strategies for further studies.

Data collection and analysis

Selection of studies

We located potentially eligible studies based on screening of title and abstract by two review authors (DK, GV, JD or RH). We obtained full copies of potentially eligible studies. Two review authors (DK, GV, JD or RH), acting independently, decided on inclusion or exclusion, based on predefined inclusion and exclusion forms. Disagreements were initially resolved by

discussion, but a third review author's opinion was decisive in cases where this did not result in consensus.

Data extraction and management

We extracted details of eligible studies and summarised them using a data extraction sheet. This summary contained the baseline characteristics of study and control group participants, including their number, age, gender, duration of diabetes, type of diabetes, ethnicity, risk of foot ulceration, main outcome measures (e.g. ulcer incidence) and all additional relevant characteristics described. Furthermore, we extracted details of the complex interventions studied, plus the content of the total programme if foot care was merely one component plus details of the control interventions. We also recorded the healthcare setting in which the interventions were executed. In addition, we extracted duration of follow-up and numbers lost to follow-up as well as outcomes.

When a study has resulted in more than one publication, we maximally extracted data from all relevant publications but did not duplicate data. Two review authors (DK, GV, JD or RH) independently extracted all data regarding the included interventions studied. We resolved all disagreements by discussion.

Assessment of risk of bias in included studies

After we included all available eligible studies in the review, we assigned two review authors (DK, GV, JD or RH) to independently assess each study using the Cochrane Collaboration tool for assessing risk of bias (**Higgins 2011**). This tool addresses six specific domains, namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues (e.g. extreme baseline imbalance) (see Appendix 5 for details of criteria on which the judgement was based). Blinding of patients and healthcare providers does not appear to be feasible considering the nature of the interventions studied, therefore judgement was solely based on the information provided about blinding of outcome assessors. We assessed blinding and completeness of outcome data for each outcome separately. We completed a 'Risk of bias' table for each eligible study. We calculated initial disagreement of judgement per domain and expressed it as percentage agreement and Cohen's kappa (**Brennan 1992**). We discussed any disagreements in a consensus meeting.

We assessed risk of bias using a 'Risk of bias' summary figure, which presents all of the judgements in a cross-tabulation of study by entry. This display of internal validity indicates the weight the reader may give to the results of the particular studies.

Measures of treatment effect

We reported separately for each study. Depending on the available data we aimed to present the results for binary outcomes (e.g. ulceration or amputation) as risk ratios (RR) with corresponding 95% confidence intervals (CI) and the results for continuous data (e.g. callus diameter) as mean differences (MD) with corresponding 95% confidence intervals.

Unit of analysis issues

Comparisons that randomise or allocate clusters (e.g. clinics) but do not account for clustering during analysis have potential unit of analysis errors resulting in artificially low P values and over-narrow confidence intervals. We encountered this problem in one of the included studies (Litzelman 1993), but were unable to contact the authors and ask for original outcome data. We therefore reported only point estimates (Donner 2001).

Moreover, we identified another unit of analysis issue in one other study (McMurray 2002). After randomisation of individual patients, subsequent amputations and hospital admissions in one patient were regarded as multiple events. After contacting the study authors we could not ascertain exactly how many patients were involved. We therefore did not calculate risk ratios but only presented the event rates for each study group.

Dealing with missing data

We attempted to contact all authors of the included trials to request additional outcome data, corresponding measures of variability or extra information on study methodology. We succeeded in contacting the authors of Rönnemaa 1997, who replied to all of our questions. We contacted the authors of McMurray 2002 and obtained additional information, but the unit of analysis issue described above was not solved. We did not succeed in contacting any of the other authors.

Assessment of heterogeneity

There was considerable variability between studies on the basis of study sample characteristics (baseline risk of foot ulceration), healthcare setting, the complex interventions studied (two or more components) and the outcome measures reported, therefore we did not attempt pooling of outcome data.

Assessment of reporting biases

We were unable to assess reporting bias graphically by means of a funnel plot, because the number of eligible studies was small and the study methodology was too heterogeneous and at high risk of bias, which also diminishes the value of any funnel plot.

Data synthesis

Substantial statistical heterogeneity between studies was observed, therefore we presented all results in a qualitative summary (O'Rourke 1989).

Subgroup analysis and investigation of heterogeneity

Possible sources of variation among studies that would require subgroup analysis were (Deeks 2011):

1. healthcare setting (e.g. podiatry clinics versus general hospitals versus general practice);
2. type of intervention (e.g. content of complex intervention; brief versus intensive programmes; foot care only versus more comprehensive diabetes care);

3. nature of contrast (e.g. intervention versus control intervention; intervention versus no intervention).

Results

Description of studies

Results of the search

We considered 21 studies for selection after initial screening of titles and abstracts by two review authors. Based on reviewing the full-text articles of these 21 studies, the review authors independently agreed on the inclusion of four RCTs (Rönnemaa 1997; McCabe 1998; McMurray 2002, Liang 2012) and two cluster-RCTs (Litzelman 1993; Donohoe 2000). Additionally there was disagreement between the authors about inclusion of four more RCTs (Kruger 1992; Frank 2003; Plank 2003; Rizzo 2012), based on the exact interpretation of the definition of 'complex interventions' described above. For three of these studies this disagreement was not resolved by discussion and therefore the third author's opinion was decisive. The third author concluded that, although the interventions studied in these three RCTs contained multiple components, they did not comprise more than one level of care. We therefore excluded all these trials from this review.

Included studies

We identified four individually randomised (Rönnemaa 1997; McCabe 1998; McMurray 2002, Liang 2012) and two cluster-randomised controlled trials (RCTs) (Litzelman 1993; Donohoe 2000). The characteristics of these studies are described in the Characteristics of included studies and are summarised below.

Healthcare settings

Two of the included RCTs took place in primary care settings: one in primary care practices in the UK (Donohoe 2000) and the other in an academic primary care outpatient practice in the USA (Litzelman 1993). One study was performed in a community-based care setting as patients were recruited from the national drug imbursement register (Rönnemaa 1997). Finally, three studies were performed in a secondary care setting: one in an academic diabetes outpatient care setting in the UK (McCabe 1998) and one in an outpatient care setting for patients requiring haemodialysis or peritoneal dialysis in the USA (McMurray 2002) and lastly, in one study patients were recruited from an inpatient care setting in China. (Liang 2012).

Participants' risk of foot ulceration

In two of the included studies participants appeared to be at higher risk of foot ulceration than the average population of diabetes patients. First, in Liang 2012 patients were recruited who were at high risk of developing foot ulceration according to 1998 American Diabetes Association (ADA) standards. Second, in McMurray 2002, 18 of the 83 participants had a history of prior amputation and since all participants had end-stage renal disease requiring

dialysis treatment, presumably as a complication of diabetes in most cases. In the remaining four studies participants' baseline foot ulceration risk was medium or low. This includes McCabe 1998 in which the intervention was only applied to individuals identified at high risk. This selection however was performed after randomisation.

Interventions

Three studies compared the effect of educationally-orientated complex interventions with usual care or less intensive programmes (Litzelman 1993; Rönnemaa 1997; Donohoe 2000). In Donohoe 2000, patients received educational leaflets (patient level), healthcare providers were educated and received a Semmes Weinstein monofilament as a new objective means of diagnosing sensory neuropathy and guidelines clarifying responsibilities of professionals and criteria for referral (healthcare provider level). Healthcare providers were educated within their own clinics ('educational outreach visits', structure of health care level). The control group received foot care as usual and an educational intervention on diabetic nephropathy. In the study of Litzelman 1993, the patient level interventions comprised a single patient education session, behavioural contracts and reminders by telephone and postcard to reinforce self care. Healthcare providers received educational folders and flow sheets guiding clinical assessment, treatment and referral. The structure of healthcare interventions included 'distribution of educational materials' and 'reminders' (by clipping the flow sheets to the front of the intervention patients' chart during each visit). Patients in the control group received care as usual. Finally, in Rönnemaa 1997, patients received patient education and foot care by a podiatrist (patient level) and they were also followed up by a podiatrist ('revision of professional roles', structure of health care level). Control group patients received written instruction on foot care only.

Three studies compared more intensive and comprehensive complex interventions with care as usual (McCabe 1998; McMurray 2002; Liang 2012). In McCabe 1998 patient level interventions included a thorough foot ulceration risk assessment and weekly diabetic foot clinic visits, including self care advice, podiatry and provision of support hosiery and protective shoes, for those at high risk of foot ulceration. The structural level interventions were: 'continuity of care' (arrangements for follow-up: reminder letters for patients that did not attend to follow-up visits) and 'changes in scope and nature of benefits and services' (intensified provision of care for high-risk patients). Finally, in McMurray 2002, an individualised plan of care was drawn up for all patients in the intervention group and they received individualised self management education, written educational information, regular foot status monitoring and motivational coaching (patient level). Health care delivery, structural interventions, comprised 'revision of professional roles' (follow-up by a diabetes care-manager), 'clinical multidisciplinary teams' (primary physician, diabetes care manager, podiatrist, wound care specialists), 'continuity of care' (designation of a diabetes care manager and one primary care physician) and 'formal integration of services' (consults with diabetes care manager, podiatrist and dietitian during haemodialysis visits). Additionally, patients received interventions that were not primarily directed at preventing foot ulceration including annual eye examinations, close monitoring of glycaemic control by the care manager and nutritional counselling by renal dietitian. Finally, in Liang 2012 patients received a foot care kit, education focusing on foot care and diabetes self-management every

3-6 months. (patient level) additionally arrangements for follow-up were made (structure of health care level). Control group patients received care as usual according to ADA standards.

Words between the quotation marks refer to structure of healthcare interventions as listed in the Cochrane EPOC Group checklist (McAuley 2002).

Duration of follow-up

The median duration of follow-up was 18 months (Litzelman 1993; McMurray 2002; McCabe 1998; Liang 2012), ranging from six months (Donohoe 2000) to seven years (Rönnemaa 1997).

Excluded studies

We excluded studies because they were not RCTs (Pieber 1995; Dargis 1999b; van Soeren 2003); because participants were care providers rather than people with diabetes (Clay 2007); because the focus was not prevention of diabetic foot ulceration (Pedersen 2003); because the intervention was solely a patient educational one (Bloomgarden 1987; Kruger 1992; Frank 2003; Borges 2008; Lincoln 2008) or because the intervention did not target more than one level (patient, care provider, structure of health care) (Barth 1991; Plank 2003; Armstrong 2007; Lavery 2007; Rizzo 2012).

Risk of bias in included studies

We judged all six studies at high risk of bias. Details are presented in separate 'Risk of bias' tables for each of the five studies and a summary table (Figure 1).

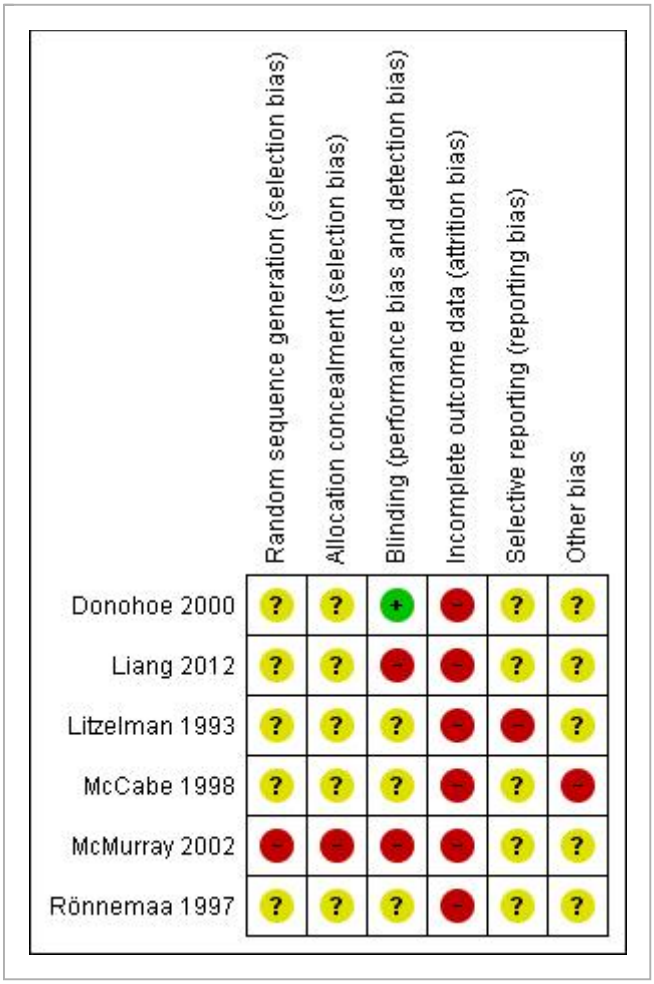

Figure 1.

Open in figure viewer

'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

Two review authors independently made judgements on the six items for each of the six studies. There was initial disagreement on six items (percentage of agreement 83%, Cohen's kappa 0.73). All disagreements were resolved by discussion without needing to consult the third review author. The main reason for disagreement was a difference in the interpretation of the current risk of bias criteria, which provided an opportunity for different interpretations of the study information. When, for example, 'allocation concealment' is not described within a certain article, but unlikely to have been adequate considering the other information that is given about the study methods, it is justifiable to score 'no' instead of 'unclear'. However, in some cases, after extracting similar data from the articles, this led to different judgements. There was no essential disagreement between the review authors on the extracted study characteristics that required the judgement of the third review author.

Allocation

Methods of randomisation and concealment of allocation were only reported in one study (McMurray 2002). In this study a quasi-randomised approach was chosen and adequate concealment of allocation was impossible.

Blinding

Blinding of outcome assessors was reported in only one study (Donohoe 2000); one study clearly did not undertake blinded outcome assessment (McMurray 2002) whilst the other two were unclear.

Incomplete outcome data

Only one study clearly performed and reported undertaking an intention-to-treat (ITT) analysis (McCabe 1998). Moreover, withdrawal rates were higher than acceptable in three studies (Rönnemaa 1997; McCabe 1998; Donohoe 2000).

Selective reporting

Not all outcomes described in the methods section were reported, therefore we concluded that some outcomes may selectively have been omitted from one of the articles and scored this accordingly (Litzelman 1993). Selective outcome reporting might also have occurred in the other studies, but insufficient information was available to permit a definitive judgement.

Other potential sources of bias

Baseline characteristics were only reported for the intervention group and not for the control group in one study (McCabe 1998) precluding the assessment of baseline (im)balance. Moreover, in this study, control group patients crossed over to receive the intervention after a foot ulcer had occurred. This could have influenced the incidence of amputation. In the other four studies insufficient information was provided about the possibility that co-interventions in both the intervention and control group biased the results.

Effects of interventions

The effects of interventions are presented in Table 1 and summarised below.

Table 1. Results from trials

Study ID	Main baseline characteristics	Adherence to the intervention and follow-up	Primary outcomes	Secondary outcomes
Donohoe 2000	Number of clusters: 10 Number of participants: I: 981 C: 958	Compliance with the intervention: Patient compliance not required since intervention is mainly directed at care provider and structure of health care	Not reported	Foot care knowledge scores (mean percentage improvement): I: 1.09 (P = 0.015) C: 1.32 (P = 0.002)

	Mean age: I: 66.7 years (range 18.7 to 95.8) C: 64.8 years (range 18.0 to 93.6) Males: I: 54% C: 53% Mean duration of diabetes: I: 7.6 years (quartiles 3.9 to 14.1) C: 7.4 years (quartiles 3.5 to 13.9) Type 1 diabetes mellitus: I: 18.6% C: 20.6% Mean glycosylated haemoglobin: I : 7.36% (range 3.9 to 14.0) C: 7.27% (range 3.5 to 13.9) Mean foot care knowledge score: I: 65.6% C: 66.0% Mean patients' attitude towards foot care score: I: 81.1% C: 81.9%	Completeness of follow-up: Response rates for foot care knowledge questionnaires: I: 64.6% C: 60.5% Reason for loss to follow-up is non-responding to questionnaires		Costs: Total costs of the intervention programme GBP 4216
Liang 2012	Number of participants: I: 31 C: 31 Mean age: I: 56.2 (range 22-70) C: 55.8 (range 20-68)	Compliance with the intervention: Not explicitly described. Completeness of follow-up: I: n=30 (97%); C: n=29 (94%); Reasons for loss to follow-up for both groups not further investigated.	Amputation: I: 0 (0%) C: 2 (6.90%) (p = 0.46) Foot Ulcers: I: 0 (0%) C: 7 (24.14%) (p = 0.01)	Knowledge (1 year): I: 88.31 (SD 8.15) C: 70.27 (SD 7.92) Foot care behaviour (1 year): I: 86.35 (SD 5.17) C: 75.86 (SD 6.19)

	Female: I: 16 C: 10 Type 2 Diabetes Mellitus: I: 28 C: 26 Duration of diabetes I: 11.2 (range 3-26) C: 10.1 (range 5-25) HbA1c I: 9.68 (SD 2.31) C: 9.40 (SD 2.45)			Knowledge (2 years): I: 89.56 (SD 7.00) C: 67.87 (SD 5.26) Foot care behaviour (2 years): I: 87.24 (SD 6.2) C: 71.43 (SD 5.17)
Litzelman 1993	Number of clusters: 4 Number of participants: I: 191 C: 205 Mean age: I: 60.9 years (SD 9.8) C: 59.9 years (SD 9.4) Males: I: 18% C: 20% Ethnicity: I: 75% black C: 77% black Mean duration of diabetes: I: 9.6 years (SD 8.0) C: 10.1 years (SD 8.1) Requiring insulin treatment: I: 52% C: 47% Mean glycosylated haemoglobin:	Serious foot lesions (graded 1.3 or higher on the Seattle Wound Classification System): Odds ratio 0.41*, favouring intervention. *Measures of variability not reported, because cluster-randomisation may have caused over-narrow confidence intervals Compliance with the intervention: Not explicitly described. Presumably all participants received the single education session, a behavioural contract and self care reminders. Completeness of follow-up: 43 patients did not complete follow-up (distribution according to allocation group unknown). Reasons were change of residence (15), death (11), illness (6), transportation problems (3), miscellaneous reasons (8).	Amputation: I: 1 C: 4 *Measures of variability not reported, because cluster-randomisation may have caused over-narrow confidence intervals	Patients' behaviour assessment scores; Means after adjusting for baseline imbalances (lower is more appropriate): I: 1.90* C: 2.12* *Measures of variability not reported, because cluster-randomisation may have caused over-narrow confidence intervals

	I: 10.5% (SD 2.3) C: 10.0% (SD 2.6) Mean fasting plasma glucose: I: 11.48 mmol/L (SD 4.81) C: 11.40 mmol/L (SD 4.41) Mean BMI: I: 34.0 kg/m^2 (SD 7.7) C: 33.4 kg/m^2 (SD 6.9)			
McCabe 1998	Number of participants: I: 1001 C: 1000 Mean age: I: 59.6 years (range 17 to 92.6) C: unknown Males: I: 53% C: unknown Type 1 diabetes mellitus: I: 19.9% C: unknown Neuropathy: I: 21.8% C: unknown Peripheral vascular disease: I: 7.7% C: unknown Neuropathy as well as peripheral vascular disease: I: 4% C: unknown History of smoking: I: 62% C: unknown	Compliance with the intervention: All participants in the intervention group underwent initial screening Of 259 patients identified to be at risk 229 (88%) attended the re screening appointment All 127 patients identified to be at high risk after re screening were provided with protective footwear. 36% of responders to the follow-up questionnaire claimed to have used them at all times Completeness of follow-up: I: 678 patients (68%); reasons for loss to follow-up were non-attendance at the follow-up examination/questionnaires but still to the general diabetes clinic (159), habitual non-attendance (125), death (37) and unknown (2) C: 469 patients (47%); reasons for loss to follow-up not further investigated	Amputation: I: 7 (1 major and 6 minor) C: 23 (12 major and 13 minor) RR 0.30 (95% CI 0.13 to 0.71) Foot ulceration: I: 24 (not counting 4 active at baseline; 29% progressed to amputation) C: 35 (66% progressed to amputation) RR 0.69 (95% CI 0.41 to 1.14)	Costs: Total costs of the intervention programme were GBP 100.372 (1991/1992): this equals GBP 100 for each patient within the intervention group or GBP 9125 for each major amputation that was thought to be prevented by the intervention

	Current smoking: I: 25.3% C: unknown			
McMurray 2002	Number of participants: I: 45 (+ 4 who did not complete baseline assessment) C: 38 (+ 4 who did not complete baseline assessment) Mean age: I: 63 years (SD 13.5) C: 60.9 years (SD 11.7) Males: I: 53% C: 55% Mean duration of diabetes: I: 20.5 years (SD 13.0) C: 22.0 years (SD 11.7) Mean glycosylated haemoglobin: I: 6.9% C:6.9% Type of dialysis: I: 37 haemodialysis, 8 peritoneal dialysis C: 33 haemodialysis, 5 peritoneal dialysis Mean duration of dialysis: I: 32.4 months (SD 22.8) C: 33.2 months (SD 24.2)	Compliance with the intervention: Not explicitly described. Since patients had to attend to concurrent dialysis appointments, compliance was presumably good. Completeness of follow-up: I: 45 (92%) C: 38 (90%) Reasons for loss to follow-up: unwillingness to complete baseline assessments	Amputation: I: 0 C: 5 (subsequent amputations in 1 patient or on the same limb counted as separate events)	Patients' behaviour assessment: Checking feet: I: 60% C: 37% RR 1.63 (95% CI 1.01 to 2.63) Using hydrating lotion: I: 51% C: 5% RR 9.71 (95% CI 2.45 to 38.56) Wearing appropriate shoes and socks: I: 58% C: 13% RR 4.39 (95% CI 1.87 to 10.32) Hospital admissions (for diabetes, peripheral vascular problems, lower extremity infections and amputations): I: 1 C: 10 (subsequent admissions for 1 patient counted as separate events)

	Foot risk score: I: 2.2 C: 2.7 Previous amputations: I: 8 C: 10 Self care behaviour: I: 47% checks feet, 13% uses lotion, 18% wears appropriate shoes and socks C: 74% checks feet, 26% uses lotion, 13% wears appropriate shoes and socks			
Rönnemaa 1997	Number of participants: I: 267 (baseline characteristics for 233) C: 263 (baseline characteristics for 226) Foot care knowledge score: I: 26.7 (SD 11.4) C: 26.1 (SD 11.8) Self care behaviour assessment score: I: 5.4 (SD 2.8) C: 5.3 (SD 2.6) Callus: I: 18.5% calcaneal region, 54.5% other regions C: 16.8% calcaneal region, 51.3% other regions Diameter of greatest callus:	Compliance with the intervention: The intervention group paid a mean of 4.7 visits to the podiatrist in the first year of follow-up After 7 years follow-up 17.7% of patients reported not having seen a podiatrist in the last 6 years. 30.8% visited a podiatrist within the last year of follow-up. It is not clear whether this is due to non-compliance or absence of need for follow-up visits for most patients. Completeness of follow-up: After 1 year: I: 233 (87%), reasons were death (5), unspecified (29) C: 226 (86%), reasons were death (7), unspecified (30) After 7 years: I: 169 (63%), reasons were death (48), unspecified (50) C:163 (62%), reasons were death (44), unspecified (56)	Amputation: 1-year follow-up: I: 0 C: 0 7 years follow-up: I: 1 C:0 Foot ulceration: 1-year follow-up: I: 1 C: 0 7 years follow-up: I: 1 C: 1	Callus development: 1-year follow-up: Calcaneal region: Presence of callus: I :12.0% C: 15.5% RR 0.78 (95% CI 0.49 to 1.23) Mean diameter: I: 25.5 mm (SD 28.8) C: 28.3 mm (SD 26.8) Mean difference in diameter: I: -15 mm (P = 0.001) C: -2.3 mm (P = 0.65) Other regions: Presence of callus: I: 39.5% C: 48.2% RR 0.82 (95% CI 0.66 to 1.01) Mean diameter: I: 11.4 mm (SD 10.3) C: 14.4 mm (SD 9.9) Mean difference in

	I: calcaneal region (n = 49) 40.5 mm (SD 30.8), other regions (n = 141) 16.6 mm (SD 10.2) C: calcaneal region (n = 55) 30.6 mm (SD 28.5), other regions (n = 138) 15.2 mm (SD 9.8) Podiatrist visit: I: 12.4% in previous year, 73.4% never before C: 10.4% in previous year, 76.1% never before Foot examination by physician in previous year: I: 36.7% routinely, 9.5% following complaints C: 46.4% routinely, 12.3% following complaints		diameter: I: -5.2 mm (P < 0.001) C: -0.8 mm (P = 0.39) 7 years follow-up: Calcaneal region: Presence of callus: I: 12.4% C: 12.9% RR 0.96 (95% CI 0.55 to 1.70) Other regions: Presence of callus: I: 23.1% C: 30.1% RR 0.77 (95% CI 0.53 to 1.01) Foot care knowledge scores: 1-year follow-up: Mean scores: I: 32.1 (SD 10.8) C: 29.2 (SD 12.6) Mean differences: I: 5.4 (P < 0.001) C: 3.1 (P < 0.001) 7 years follow-up: Mean scores: I: 33.6 (SD 10.5) C: 33.0 (SD 11.1) Patients' behaviour assessment scores: 1-year follow-up: Mean scores: I: 7.0 (SD 3.2) C: 6.0 (SD 2.5) Mean differences: I: 1.6 (P < 0.001) C: 0.7 (P < 0.001) 7 years follow-up: Mean scores: I: 6.6 (SD 2.7) C: 6.4 (SD 2.7)
Abbreviations: I = intervention group, C = control group, n = number of participants within group, RR = risk ratio, SD = standard deviation, CI = 95% confidence interval, P = P value			

Educationally-focused interventions versus usual care or less intensive programmes

Primary outcomes

Foot ulceration and amputation

In Rönnemaa 1997, participants at low risk of ulceration were individually randomised to receive individual patient education from a podiatrist and podiatric care whilst the organisation of care was amended to introduce follow-up by a podiatrist. People in the control group received written foot care instructions only. Foot ulceration risk at baseline was low (people with a history of foot ulceration or with obvious need for foot care were excluded from the study). Despite seven years follow-up of 267 patients in the intervention group (37% lost to follow-up) and 263 patients (38% lost to follow-up) in the control group few endpoints were observed (one amputation, in the intervention group) and two ulcerations (one in each group) were observed.

In Litzelman 1993, patients were cluster-randomised (at the level of primary care practice) to receive a single patient education session from a nurse, a behavioural contract and reminders (postcard and telephone) to reinforce self care. Control group participants received usual care. Serious foot lesions, defined as grade 1.3 or higher on the Seattle Wound Classification System (Pecoraro 1991), were measured as a surrogate marker for foot ulceration lesions occurred less frequently in the intervention group compared with the usual care group: odds ratio (OR) 0.41, however the confidence interval (CI) (0.16 to 1.00) may be artificially narrow since cluster-randomisation was not accounted for in the analysis. Furthermore, in this study only five amputations were observed during one year follow-up, with no significant difference between the experimental and control group.

Secondary outcomes

Foot care knowledge scores

Significant improvements in foot care knowledge in both the intervention (26.7 to 32.1; $P < 0.001$) and control groups (26.1 to 29.2; $P < 0.001$) were reported in Rönnemaa 1997 after one year of follow-up, however at seven years follow-up there was no difference in foot care knowledge scores between the intervention (33.6; standard deviation (SD) 10.5) and control groups (33.0; SD 11.1). In Donohoe 2000 981 participants in the intervention group received written educational material whilst their care providers received education including in diagnosis of neuropathy, guidelines and educational outreach, and 958 in the control group received education regarding diabetes related kidney disease and usual care. This study also reported that foot care knowledge scores improved in both the intervention group (mean percentage improvement: 1.09 ($P = 0.015$)) and the control group (mean percentage improvement: 1.32 ($P = 0.002$)) after six months of follow-up. It should be noted that only 62.6% of the total study population was followed up for this outcome.

Patients' behaviour assessment scores

Significant improvement in both the intervention (5.4 to 7.0; P < 0.001) and control group (5.3 to 6.0; P < 0.001) was reported in Rönnemaa 1997 after one year of follow-up. After seven years of follow-up, behaviour assessment scores were similar in both groups (intervention group: 6.6; SD 2.7, control group: 6.4; SD 2.7). In Litzelman 1993 the intervention group patients were reported to have more appropriate patient behaviour assessment scores after approximately one year of follow-up. However, in this study no baseline values are presented and the reported measures of variability may have been over-narrow due to cluster-randomisation. Therefore the importance of this finding cannot be inferred from this study report.

Callus development and resolution of callus

In Rönnemaa 1997, a significant reduction in the mean diameter of callus was observed in the intervention group, but not in the control group after one year of follow-up. The mean difference in calcaneal callus diameter was: intervention group -15 mm (P = 0.001); control group -2.3 mm (P = 0.65). The mean difference in callus diameter in other foot regions was: intervention group -5.2 mm (P < 0.001); control group -0.8 mm (P = 0.39). It should be noted that podiatry care, which includes callus removal, was an important component of the intervention in this study. The prevalence of callus after one year of follow-up, however, was not significantly affected by the intervention. Calcaneal callus was present in 12% of participants in the intervention group compared with 15.5% of participants in the control group (risk ratio (RR) 0.78, 95% CI 0.49 to 1.23). Callus was present in non-calcaneal regions in 39.5% of participants in the intervention group compared with 48.2% of participants in the control group (RR 0.82, 95% CI 0.66 to 1.01). Even after seven years of follow-up prevalence of callus lesions was not significantly different between groups.

Costs

Costs were only reported in Donohoe 2000. The total expenses for the education-centred intervention were GBP 4216 (including care time attending educational sessions and the cost of all materials, based on accepted rates for travel, staff cost and resources; price year not reported).

Number and duration of hospital admissions for diabetes-related foot problems

Not reported in these trials.

More intensive and comprehensive complex interventions versus usual care

Primary outcomes

Foot ulceration and amputation

In McCabe 1998, individual patients were randomised to receive a detailed foot ulceration risk assessment, a weekly diabetic foot clinic for high-risk patients, podiatry, support hosiery

and protective footwear. Care was reorganised to ensure continuity of care, appointment reminder letters to patients, and more intensive follow-up of at-risk patients. Meanwhile control group patients received usual care. There were seven amputations in the intervention group during two years of follow-up, compared with 23 amputations in the control group (RR for amputation 0.30, 95% CI 0.13 to 0.71) thus favouring the intervention (Analysis 1.1). The incidence of foot ulceration was not significantly different between groups: the intervention group had 24 events in 1001 patients and the control group had 35 events in 1000 patients; RR of ulceration 0.69, 95% CI 0.41 to 1.14 (Analysis 1.2). This difference was not statistically significant.

In **McMurray 2002**, patients were individually randomised to receive an individualised plan of care, individualised self management education, educational materials, regular foot status monitoring and motivational coaching. The control group received usual care. There were no amputations in the 45 patients of the intervention group compared with five amputations in the 38 patients of the control group. However, subsequent amputations in one patient or on the same limb were counted as separate events. Therefore, the significance of this finding is not clear. Rates of foot ulceration were not reported.

In **Liang 2012**, patients were individually randomised to receive a foot care kit, education focusing on foot care, diabetes self-management every 3 to 6 months and arrangements for follow-up. The control group received care as usual according to ADA standards. There were zero amputations in the 30 patients of the intervention group compared to two in the 29 patients of the control group (p=0.46). Aditionally, there were zero foot ulcers in the intervention group compared to seven in the control group (p=0.01).

Secondary outcomes

Patients' behaviour assessment scores

According to the questionnaires that were completed by the study participants of **McMurray 2002**, intervention group patients were significantly more likely than control group patients to regularly check their feet (RR 1.63, 95% CI 1.01 to 2.63; Analysis 1.3), use hydrating lotion (RR 9.71, 95% CI 2.45 to 38.56; Analysis 1.4) and wear appropriate shoes and socks (RR 4.39, 95% CI 1.87 to 10.32; Analysis 1.5).

The multidisciplinary team from the **Liang 2012** study composed a diabetes knowledge questionnaire which consisted of 20 questions, with 5 points for each question. According to this questionnaire a significant improvement in diabetes knowledge in both the intervention (33.52 ± 5.47 to 87.24 ± 6,2; p < 0.01) and control group (32.73 ± 6,35 to 71.43 ± 5,17; P < 0.01) was seen after the second year of follow-up.

Number and duration of hospital admissions for diabetes-related foot problems

In **McMurray 2002**, 10 hospital admissions were observed in the 38 patients in the control group versus one hospital admission in the 45 patients in the intervention group. However, subsequent admissions of one patient were counted as separate events. Therefore, the significance of this finding is not clear.

Costs

The total costs of the intervention programme of McCabe 1998 were estimated to be GBP 100 (1991/1992) for each participant in the intervention group. In this study prevention of one major amputation cost GBP 9125.

Foot care knowledge scores, callus development and resolution of callus

The multidisciplinary team from the Liang 2012 study also composed a diabetes foot care questionnaire which consisted of 20 questions, with 5 points for each question. According to this questionnaire a significant improvement in foot care knowledge was reported after the second year of follow-up in both the intervention (40.86 ± 4,73 to 89.56 ±7.00; $p < 0.01$) and control group (41.35 ± 5,24 to 67.87 ± 5,26; $P < 0.01$).

Discussion

Summary of main results

In this review we included six randomised trials studying the effect of a wide variety of complex interventions. The results of this review are presented in a study-by-study qualitative synthesis. Pooling of the results was precluded by marked, mainly clinical, heterogeneity, because participants, types of interventions, types of control interventions, outcome measures, outcome assessment tools, duration of follow-up and risk of bias varied widely between studies.

Three studies compared educationally-focused complex interventions with usual care or written foot care instructions only. From these studies, which were all at unclear or high risk of bias, there is no strong evidence that the interventions resulted in fewer ulcers, amputations, less callus or improved knowledge or behaviour. This is a lack of evidence rather than evidence of no effect, however. For example, in the single study that reported amputations and foot ulcerations, there were only three events over seven years of follow-up in 530 participants (one amputation and two foot ulcers) (Rönnemaa 1997). The most probable explanation is that the study population was at very low risk of foot ulceration, because patients with obvious need for podiatry care were excluded. Additionally, in another study, foot lesions were reported as a surrogate marker for foot amputation (Litzelman 1993). The odds ratio was 0.41 favouring intervention, but the 95% confidence interval reported (0.16 to 1.00) may be artificially narrow, because cluster-randomisation was not accounted for. Patients' foot care knowledge scores increased in two studies equally in both the intervention and the control group (Rönnemaa 1997; Donohoe 2000). In one of these studies, similar findings are reported for patients' behaviour assessment scores (Rönnemaa 1997). One other study reported that patients' behaviour assessment scores in the intervention group were more appropriate than in the control group, but essential information was lacking from the study report to assess the significance of this finding (Litzelman 1993). Finally, in one study, the diameter of callus was markedly reduced in the group that received the complex intervention compared to the diameter of callus in the control group. This was not surprising, since the intervention comprised podiatry care.

However, the prevalence of callus at seven years follow-up was unaffected (Rönnemaa 1997).

Three studies compared more comprehensive (more than education) and intensive approaches with usual care. In one of these studies there was a statistically significant reduction of amputations (seven amputations amongst 1001 intervention group participants compared with 23 amputations amongst 1000 control group participants; RR 0.30 (95% CI 0.13 to 0.71)). There were also fewer foot ulcers developing in the intervention group, however this difference was not statistically significant (24 ulcers in 1001 intervention group patients compared with 35 ulcers in 1000 control group patients; RR 0.69 (95% CI 0.41 to 1.14) (McCabe 1998). Furthermore this study was at unclear or high risk of bias and therefore this promising finding requires confirmation in other studies. In the second study of comprehensive, intensive interventions, only amputations were reported (five events in 38 control group patients versus no events in 45 intervention group patients), but the significance of the findings remains uncertain since subsequent amputations in one patient were counted as separate events (McMurray 2002). However, in this study, convincing improvements in patient behaviour were observed. Patients in the intervention group were more likely to regularly check their feet, use hydrating lotion and wear appropriate shoes and socks. In the third study (Liang 2012), a reduction of amputations and foot ulcers was found; no amputations and foot ulcers were reported among those receiving the intervention compared with two amputations and seven foot ulcers amongst the control group. However, this study is at high risk of bias, it is unclear whether there was blinding of outcome assessors. Moreover, the study may not be representative for healthcare in western countries as many diabetes complications were treated on an inpatient basis. In addition the trial reported that some people (allocated to the control group) were subject to delays of more than four weeks after the development of a foot ulcer before going to the hospital, they required minor foot amputations. Whilst being aware of the study limitations, there is some evidence that complex interventions can improve foot care behaviour and reduce complications of diabetes.

Overall completeness and applicability of evidence

Despite the fact that complex interventions for preventing diabetic foot ulceration are widely used in clinical practice worldwide, only six randomised trials evaluating the effectiveness of these types of interventions were eligible for inclusion in this review. Two of these trials reported a significant effect on primary endpoints (amputation and foot ulceration incidence) and that study was at unclear or high risk of bias; the results should therefore be viewed with caution and require confirmation in future research (McCabe 1998; Liang 2012). The other four trials do not share a common set of characteristics (interventions, control interventions, outcome measures etc.), thereby hindering present and future pooling. The trials covered by this review were performed in different healthcare settings and different healthcare systems. Indeed, the scarcity and quality of the evidence and the heterogeneity of provision of health care worldwide necessitate caution when applying the results to current clinical practice.

Quality of the evidence

In general, we judged the six included trials to be at high or unclear risk of bias, caused mainly by lack of information in the trial reports. Despite our efforts to contact all authors of the included trials to request additional outcome data, hardly any of the criteria of our risk of bias assessment were sufficiently met. Therefore the results of all these trials should be interpreted with caution.

Potential biases in the review process

Preceding the development of this review two of the review authors (GV and DK) were already familiar with the results of most of the studies eligible for inclusion. However both other review authors (JD and RH) had no foreknowledge and were independently involved in all decisions and judgements. JD was the principal designer of the concept protocol. Furthermore the review protocol was strictly adhered to.

It is not likely that publication bias has greatly affected the results of this review. Apart from searching electronic databases (MEDLINE, EMBASE, CINAHL), we also attempted to reveal unpublished studies by searching the Cochrane Central Register of Controlled Trials (CENTRAL) and the Wounds Group Specialised Register, The Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment Database (HTA) and The NHS Economic Evaluation Database (NHS EED). Due to heterogeneity and the limited number of included studies we were unable to compose a funnel plot graph. However, since most included studies did not show significant findings, it is unlikely that we overestimated any of the effects.

Agreements and disagreements with other studies or reviews

This review was written in close conjunction with another review on the effectiveness of patient education for preventing diabetic foot ulceration (**Dorresteijn 2010**). That review shows that brief educational interventions alone are not sufficiently effective to achieve a clinically relevant reduction of ulcer and amputation incidence. This conclusion contributes to the thought that reducing ulcer incidence in patients with diabetes remains very challenging and requires an intensive integrated approach, combining more than one preventive strategy, especially in patients at high risk of foot ulceration.

Authors' conclusions

Implications for practice

There is insufficient evidence to support the effectiveness of complex interventions for preventing or reducing diabetic foot ulceration. This should be interpreted, however, as a lack of evidence rather than evidence of no effect. There were very few studies and those that exist were at unclear or high risk of

bias. It may be advisable to concentrate preventive efforts on those who appear to be at highest risk of foot ulceration after careful screening and selection.

Implications for research

More randomised trials that evaluate the effect of intensive comprehensive complex interventions are urgently needed. As discussed above, the evidence in this field is still scarce and does not allow us to draw firm conclusions. The main shortcomings of the studies included in this review are: (1) insufficient power and duration of follow-up to detect clinically relevant improvements in foot ulceration and amputation incidence, (2) marked clinical heterogeneity and (3) high risk of bias.

First, the ultimate aim of preventive strategies is to reduce the incidence of foot ulceration. This means that randomised trials that include diabetes patients at average risk of foot ulceration, need at least 430 to 870 patients per treatment arm in order to detect a 50% reduction in the incidence of foot ulceration (based on an annual incidence of foot ulceration in the general diabetes population of 2% to 4% per year or 4% to 8% over two years) (Reenders 1993; De Sonnaville 1997). Five of the randomised controlled trials (RCTs) included in this systematic review reported amputation or foot ulceration incidence, or both, but only one of these was sufficiently powered (McCabe 1998).

Secondly, in order to facilitate proper analysis and future comparison of the results of studies evaluating the effects of complex interventions, more homogeneity of study characteristics and study reporting is needed. To begin with, particular consideration should be given to adequate reporting of baseline values and criteria for exclusion and inclusion (Reed 2005). Also, it is important that studies report the content of the 'usual care' that is provided to the control group, because this differs between countries and health care settings and has evolved over time. One of the intervention components that could be standardised in the future is (patient) education. This can be achieved by developing clear and commonly accepted learning objectives (Colagiuri 2009). Furthermore, all future RCTs studying the effect of complex interventions for preventing diabetic foot ulceration should at least report the incidence of foot ulceration and amputation. Also, an outline of the costs that were associated with each intervention is vital to assess cost-effectiveness. If changes in patients' foot care knowledge and self care behaviour are reported, these should be measured with standardised and validated tools. However, such standard sets of

outcomes, like available in rheumatology (OMERACT) and low back pain research (Deyo 1998), still need to be developed for research on the diabetic foot.

Thirdly, efforts must be made to reduce risk of bias and poor reporting of future studies. Patients should be randomised properly with concealed allocation. Blinding of patients and healthcare providers is often not possible due to the nature of the intervention, but blinding of outcome assessors must be ensured. Also, more pragmatic study design options like the Zelen's design, in which the control group is not informed, might be an option (Schellings 2005). Co-interventions need to be registered and reported accurately. Furthermore, loss to follow-up should be avoided, because this may lead to underestimation of the intervention results. If loss to follow-up is notable, reasons for study withdrawal should be reported in order to reveal any causality. Finally, RCTs must be reported in accordance with the CONSORT guidelines (Moher 2005) and their extension to cluster-randomised trials (Campbell 2004).

We realise that trials of this magnitude are costly, but the benefits in terms of the potential reduction in costs associated with effective treatment are potentially significant.

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Data and analyses

Download statistical data

Comparison 1. Effects of more comprehensive complex interventions versus care as usual

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Amputation incidence (2 years follow-up)	1	2001	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.13, 0.71]
2 Foot ulcer incidence (2 years follow-up)	1	2001	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.41, 1.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Patients' self care behaviour (after 12 months of follow-up): regularly checking the feet	1	83	Risk Ratio (M-H, Random, 95% CI)	1.63 [1.01, 2.63]
4 Patients' self care behaviour (after 12 months of follow-up): using hydrating lotion	1	83	Risk Ratio (M-H, Random, 95% CI)	9.71 [2.45, 38.56]
5 Patients' self care behaviour (after 12 months of follow-up): wearing appropriate shoes and socks	1	83	Risk Ratio (M-H, Random, 95% CI)	4.39 [1.87, 10.32]

Appendices

Appendix 1. Search methods used in the first update of the review

For this first update we searched the following electronic databases to find reports of relevant RCTs:

- the Cochrane Wounds Group Specialised Register (searched 16 June 2011);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 2);
- Ovid MEDLINE (2008 to June Week 2 2011);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations, 15 June 2011);
- Ovid EMBASE (2008 to 2011 Week 16); and
- EBSCO CINAHL (2008 to 17 June 2011).

Searching other resources

The bibliographies of all retrieved and relevant publications identified by these strategies were searched for further studies.

Appendix 2. Search strategy Ovid MEDLINE

1 exp Foot Ulcer/
2 exp Diabetic Foot/
3 (diabet* adj3 ulcer*).tw.
4 (diabet* adj3 (foot or feet)).tw.
5 (diabet* adj3 wound*).tw.
6 (diabet* and defect*).tw.
7 or/1-6
8 exp Primary Prevention/

9 exp Preventive Health Services/
10 (prevent* or avoid* or protect*).ti,ab.
11 (reduc* adj risk*).ti,ab.
12 (multidisciplinary or interdisciplinary or collaborat* or complex or integrat*).ti,ab.
13 or/8-12
14 7 and 13
15 randomized controlled trial.pt.
16 controlled clinical trial.pt.
17 randomi?ed.ab.
18 placebo.ab.
19 clinical trials as topic.sh.
20 randomly.ab.
21 trial.ti.
22 or/15-21
23 exp animals/ not humans.sh.
24 22 not 23
25 14 and 24
26 (2013* or 2014*).ed.
27 25 and 26

Appendix 3. Search strategy Ovid EMBASE

1 exp Foot Ulcer/
2 exp Diabetic Foot/
3 (diabet* adj3 ulcer*).tw.
4 (diabet* adj3 (foot or feet)).tw.
5 (diabet* adj3 wound*).tw.
6 (diabet* adj3 defect*).tw.
7 or/1-6
8 exp Prevention/
9 exp Preventive Health Service/
10 (prevent* or avoid* or protect*).tw.
11 (reduc* adj risk*).tw.
12 (multidisciplinary or interdisciplinary or collaborat* or complex or integrat*).tw.
13 or/8-12
14 7 and 13
15 Randomized controlled trials/
16 Single-Blind Method/
17 Double-Blind Method/
18 Crossover Procedure/
19 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or assign$ or allocat$ or volunteer$).ti,ab.
20 (doubl$ adj blind$).ti,ab.
21 (singl$ adj blind$).ti,ab.
22 or/15-21
23 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal

tissue/ or animal cell/ or nonhuman/
24 human/ or human cell/
25 and/23-24
26 23 not 25
27 22 not 26
28 14 and 27
29 (2013* or 2014*).em.
30 28 and 29

Appendix 4. Search strategy EBSCO CINAHL

S26 S13 and S25
S25 S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24
S24 MH "Quantitative Studies"
S23 TI placebo* or AB placebo*
S22 MH "Placebos"
S21 TI random* allocat* or AB random* allocat*
S20 MH "Random Assignment"
S19 TI randomi?ed control* trial* or AB randomi?ed control* trial*
S18 AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)
S17 TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)
S16 TI clinic* N1 trial* or AB clinic* N1 trial*
S15 PT Clinical trial
S14 MH "Clinical Trials+"
S13 S7 and S12
S12 S8 or S9 or S10 or S11
S11 TI (multidisciplinary or interdisciplinary or collaborat* or complex or integrat*) or AB (multidisciplinary or interdisciplinary or collaborat* or complex or integrat*)
S10 TI reduc* N3 risk* or AB reduc* N3 risk*
S9 TI (prevent* or avoid* or protect*) or AB (prevent* or avoid* or protect*)
S8 (MH "Preventive Health Care+")
S7 S1 or S2 or S3 or S4 or S5 or S6
S6 TI diabet* N3 amputat* or AB diabet* N3 amputat*
S5 TI diabet* N3 wound* or AB diabet* N3 wound*
S4 TI (diabet* N3 foot or diabet* N3 feet) or AB (diabet* N3 foot or diabet* N3 feet)
S3 TI diabet* N3 ulcer* or AB diabet* N3 ulcer*
S2 (MH "Foot Ulcer+")
S1 (MH "Diabetic Foot")

Appendix 5. 'Risk of bias' table judgement criteria

Criteria for a judgement of 'yes' for the sources of bias.

1.Was the allocation sequence randomly generated?

Yes, low risk of bias

A random (unpredictable) assignment sequence. Examples of adequate methods of sequence generation are computer-generated random sequence, pre-ordered sealed envelops, telephone call to a central office, coin toss (for studies with two groups), rolling a dice (for studies with two or more groups), drawing of balls of different colours.

No, high risk of bias

- Quasi-randomised approach: examples of inadequate methods are: alternation, birth date, social insurance/security number, date in which they are invited to participate in the study and hospital registration number.
- Non-random approaches: allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.

Unclear

Insufficient information about the sequence generation process to permit judgement.

2. Was the treatment allocation adequately concealed?

Yes, low risk of bias

Assignment is generated independently by a person not responsible for determining the eligibility of the participants. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about whether the person is eligible to enter the trial. Examples of adequate methods of allocation concealment are: central allocation, including telephone, web-based and pharmacy-controlled, randomisation; sequentially-numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.

No, high risk of bias

Examples of inadequate methods of allocation concealment are: alternate medical record numbers, unsealed envelopes, date of birth, case record number, alternation or rotation, an open list of random numbers or any information in the study that indicated that investigators or participants could influence the intervention group.

Unclear

Randomisation stated but no information on method of allocation used is available.

3. Blinding - was knowledge of the allocated interventions adequately prevented during the study?

Was the participant blinded to the intervention?

Yes, low risk of bias

The treatment and control groups were indistinguishable for the participants or if the participant is described as blinded and the method of blinding is described.

No, high risk of bias

- Blinding of study participants is attempted, but likely that the blinding could have been broken.

- Participants were not blinded.
- The non-blinding of others was likely to introduce bias.

Unclear

Was the care provider blinded to the intervention?

Yes, low risk of bias

- The treatment and control groups were indistinguishable for the care/treatment providers.
- The care provider is described as blinded and the method of blinding is described too.

No, high risk of bias

- Blinding of care/treatment providers was attempted, but likely that the blinding could have been broken.
- Care/treatment providers were not blinded.
- The non-blinding of others was likely to introduce bias.

Unclear

Was the outcome assessor blinded to the intervention?

Yes, low risk of bias

The outcome assessor (of the primary outcomes) is described as blinded and the method of blinding is described.

No, high risk of bias

- No blinding.
- Incomplete blinding: the outcome or outcome measurement is likely to be influenced by lack of blinding.

Unclear

4. Were incomplete outcome data adequately addressed?

Was the drop-out rate described and acceptable?

Yes, low risk of bias

- No missing outcome data.
- The percentage of withdrawals and drop-outs is described and does not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead

to substantial bias. Reasons for missing outcome data are described and unlikely to be related to true outcome.

- The percentage of withdrawals and drop-outs is described and balanced in numbers across intervention groups, with similar reasons for missing data across groups.
- The percentage of withdrawals and drop-outs is described and missing data have been imputed using appropriate methods. Reasons for missing outcome data are described and unlikely to be related to true outcome.

No, high risk of bias

Reasons for missing outcome data are likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups.

Unclear

Were all randomised participants analysed in the group to which they were allocated (ITT analysis)?

Yes, low risk of bias

- Specifically reported that ITT was undertaken and this was confirmed on study assessment.
- Not stated but evident from study assessment that all randomised participants are reported/analysed in the group they were allocated to for the most important time point of outcome measurement (minus missing values) irrespective of non-compliance and co-interventions.

No, high risk of bias

- Lack of ITT confirmed on study assessment regardless of whether ITT reported or not: patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation.
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
- Potentially inappropriate application of simple imputation.

Unclear

- Described as ITT analysis, but unable to confirm on study assessment.
- Not reported and unable to confirm by study assessment.

5. Are reports of the study free of suggestion of selective outcome reporting?

Yes, low risk of bias

All the results from all pre-specified outcomes have been adequately reported in the published report of the trial. This information is either obtained by comparing the protocol and the final trial report, or in the absence of the protocol, assessing that the published report includes enough information to make this judgement. Alternatively a judgement could be made if the trial report lists the outcomes of interest in the methods of the trial and then reports all these outcomes in the results section of the trial report.

No, high risk of bias

- Not all of the study's pre-specified primary outcomes have been reported.
- One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not prespecified.
- One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).
- One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis.
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear

6. Other sources of potential bias

Were the groups similar at baseline regarding the most important prognostic indicators?

- Groups were similar at baseline regarding demographic factors, duration and severity of complaints, for example size and duration of ulcer.
- Imbalances at baseline have been accounted for in the analysis of the study.

Were co-interventions avoided or similar?

- There were no co-interventions.
- There were co-interventions, but they were similar between the treatment and control groups.

What's new

Date	Event	Description
22 May 2015	New citation required but conclusions have not changed	no change to conclusions

Date	Event	Description
22 May 2015	New search has been performed	Second update, new search, one new trial included (Liang 2012)

History

Date	Event	Description
29 July 2011	New search has been performed	First update, new search, conclusions unchanged.
16 March 2010	Amended	Reference corrected

Contributions of authors

RH Hoogeveen: contributed to the selection of the eligible articles for the second update, performed assessment of characteristics, methodology and results of included articles, performed data analyses and wrote the second update of the review.

JAN Dorresteijn: developed the review protocol, completed the first draft, contributed to and edited the protocol and approved the final version of the protocol prior to submission. Contributed to the selection of the eligible articles, performed assessment of characteristics, methodology and results of included articles, performed data analyses, wrote the original and first update of this review and contributed to and edited to the second update.

GD Valk: conceived the review question, contributed to and edited the review protocol and approved the final version of the protocol prior to submission. Contributed to selection of one-half of the eligible articles, performed assessment of characteristics, methodology and results of one-half of the included articles, supervised the analyses, contributed to and edited the review.

DMW Kriegsman: contributed to and edited the review protocol, contributed to selection of one-half of the eligible articles, performed assessment of characteristics, methodology and results of one-half of the included articles, contributed to the analyses process, contributed to and edited the review text.

Contributions of editorial base:

Nicky Cullum: edited the protocol and review; advised on methodology, interpretation and content. Approved the final review prior to submission.
Sally Bell-Syer: co-ordinated the editorial process. Advised on methodology, interpretation and content. Edited and the protocol and review updates.
Rocio Lopez: designed the search strategy, ran the searches and edited the search methods section.

Declarations of interest

RH Hoogeveen: none known.
JAN Dorresteijn: none known.
GD Valk: none known.
DMW Kriegsman: none known.

Sources of support

Internal sources

- No sources of support supplied

External sources

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Differences between protocol and review

Blinding of patients and healthcare providers does not appear to be feasible considering the nature of the interventions studied in the RCTs included in this review, therefore it was later added to the protocol that judgement for risk of bias was solely based on the information provided about blinding of outcome assessors. Also, erroneously, 'compliance' was predefined in our protocol as a potential source of bias.

Characteristics of studies

Characteristics of included studies [ordered by study ID]

Donohoe 2000

Methods	Cluster-randomised RCT, cluster-randomisation by practice
Participants	Study setting: primary care practices in Devon, United Kingdom Inclusion criteria: diabetes mellitus, > 18 years of age, capable of completing a questionnaire
Interventions	Intervention group: - Patient level: provision of educational leaflets - Care provider level: education of the primary care team (general practitioners, practice and district nurses and podiatrists), introduction of the Semmes Weinstein monofilament as a new objective means of diagnosing sensory

	neuropathy, introduction of guidelines clarifying responsibilities of professionals and criteria for referral - Structure of health care level: educational outreach visits Control group: - Educational intervention on diabetic nephropathy - Foot care as usual
Outcomes	Primary outcomes: not reported Secondary outcomes: foot care knowledge scores, costs Outcomes not included in this review: patients' attitudes regarding the value and importance of foot care, healthcare professionals' foot care knowledge, appropriateness of service utilisation
Duration of follow-up	6 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods of randomisation not described
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Low risk	The outcome assessors were blinded to the codes of the computer-coded questionnaires
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up was completed by only 68% of patients in the intervention group and 65% of patients in the control group. No ITT analysis undertaken.
Selective reporting (reporting bias)	Unclear risk	Insufficient information on study protocol available
Other bias	Unclear risk	Baseline characteristics: sufficiently similar Co-interventions: no information provided

Liang 2012

Methods	RCT

Participants	Study setting: the inpatient department of Guangxi Medical University, China (secondary care) Inclusion criteria: The Zhuang tribe, diabetes mellitus, between 20 and 70 years of age, high risk of foot ulcers with no previous history of foot ulcers and not living in a rural area.
Interventions	Intervention group - Patient level: A take home foot care kit, which contained nail clippers, foot care cream, a monofilament, a thermometer to measure the temperature of the water for washing feet, alcohol cotton pieces and a mirror. Patient education: foot care demonstration test, hands on workshops, diabetes education class every 3 to 6 months. -Care provider level: no care provider level intervention -Structure of health care level: arrangements for monthly follow-up were made Control group: - Conventional care according to ADA standards
Outcomes	Primary: incidence of foot ulcers and amputation Secondary: foot care knowledge scores; patients' behaviour assessment scores
Duration of follow-up	2 years
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not attempted
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-out rate The drop-out rate was 3% in the intervention group and 6% in the control group. The reason for drop-out was not specified. No ITT analysis

Selective reporting (reporting bias)	Unclear risk	Insufficient information on study protocol available
Other bias	Unclear risk	Baseline characteristics: no significant differences Co-interventions: no information provided. However, co-interventions are likely to have happened. For example: there was a large HbA1c-level difference during follow-up, but no information about medication use has been provided. Compliance: no specific information provided

Litzelman 1993

Methods	Cluster-randomised RCT, cluster-randomisation by practice
Participants	Study setting: academic primary care outpatient practice in Indianapolis, United States of America Inclusion criteria: type 2 diabetes mellitus, > 40 years of age, diagnosed with diabetes after 30 years of age, no terminal illness, no history of bilateral lower extremity amputation, ability to perform self care, body weight ideal or heavier that ideal, not pregnant, no major psychiatric illness, no renal failure, not involved in the protocol formation, seen at least 2 times in the preceding year by the same care provider
Interventions	Intervention group: - Patient level: single patient education session by a nurse-clinician, behavioural contracts, telephone reminders and postcard reminders to reinforce self-care - Care provider level: provision of educational folders and flow sheets guiding clinical assessment, treatment and referral. - Structure of health care level: distribution of educational materials, reminders (clipping flow sheets to the front of the intervention patients' chart during each visit) Control group: - Care as usual
Outcomes	Primary outcomes: foot ulceration, amputation Secondary outcomes: patients' behaviour assessment scores Outcomes not included in this review: number of referrals to specialty clinics, frequency of foot examinations by healthcare providers and documentation of risk factors, skin and nail condition
Duration of follow-up	Mean 11.8 months +/- 1.5 months
Notes	
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

Random sequence generation (selection bias)	Unclear risk	Methods of randomisation not described
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information provided to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	The drop-out rate was 11% in the total study population. Reasons for loss to follow-up and distribution over the allocation groups are not described. No ITT analysis undertaken.
Selective reporting (reporting bias)	High risk	The methods state that data on the self reported foot care behaviours and the quality of the patients' examination were obtained as well as the presence of neuropathy, peripheral vascular disease and thermal sensitivity. These outcomes were not reported.
Other bias	Unclear risk	Baseline characteristics: the characteristics described are sufficiently similar. However, in the results section it is mentioned that patients' behaviour assessment scores had to be corrected for baseline imbalances, which have not been reported. Co-interventions: no information provided

McCabe 1998

Methods	RCT
Participants	Setting: secondary care, academic diabetes outpatient clinic in Liverpool, United Kingdom Inclusion criteria: diabetes mellitus
Interventions	Intervention group: - Patient level: foot ulceration risk assessment (based on initial assessment with a Semmes-Weinstein monofilament, biothesiometer and palpation of pedal pulses, and in case of positive findings completed by assessment of foot pressures, subcutaneous oxygen levels, ankle-brachial indexes and X-rays), weekly diabetic foot clinic for high-risk patients (including self care advice, chiropody and provision of support hosiery and protective shoes) - Care provider level: no care provider level intervention - Structure of health care level: continuity of care (arrangements for follow-up: reminder letters for patients that did not attend follow-up visits), changes in

	scope and nature of benefits and services (intensified provision of care for high-risk patients). Control group: - Care as usual
Outcomes	Primary outcomes: foot ulceration, amputation Secondary outcomes: costs
Duration of follow-up	2 years
Notes	Process outcomes, like compliance with screening, podiatry services and footwear are also described, but were only measured in the intervention group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods of randomisation not described. Four patients presenting with an active ulcer were assigned to the index group without randomisation.
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up was completed by only 68% of patients in the intervention group and 47% of patients in the control group. No ITT analysis.
Selective reporting (reporting bias)	Unclear risk	Insufficient information on study protocol available
Other bias	High risk	Baseline characteristics: not provided Co-interventions: patients that presented with an ulcer in the control group (35) automatically crossed over to the intervention

McMurray 2002

Methods	RCT
Participants	Setting: secondary care, haemodialysis unit and outpatient clinic for patients undergoing peritoneal dialysis in Indiana, United States of America Inclusion criteria: diabetes mellitus and end stage renal disease, requiring renal replacement therapy
Interventions	Intervention group: - Patient level: individualised plan of care, individualised self management education, written educational materials, regular foot status monitoring and motivational coaching: all provided by a personal diabetes care manager - Care provider level: no care provider level intervention - Structure of health care level: revision of professional roles (follow-up by a diabetes care manager), clinical multidisciplinary teams (primary physician, diabetes care manager, podiatrist, wound care specialists), continuity of care (designation of a diabetes care manager and one primary care physician), formal integration of services (consults with diabetes care manager, podiatrist and dietitian during haemodialysis visits) - Other interventions not primarily directed at preventing foot ulceration: annual eye examinations, close monitoring of glycaemic control by the care manager, nutritional counselling by renal dietitian Control group: - Care as usual
Outcomes	Primary outcomes: amputation Secondary outcomes: patients' behaviour assessment scores, number of diabetes related hospital admissions Outcomes not included in this review: foot ulceration risk scores, diabetes care knowledge scores (not including foot care)
Duration of follow-up	12 months
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	A quasi-randomised approach was used: patients undergoing haemodialysis were allocated according to the day of treatment in the clinic. Patients undergoing peritoneal dialysis were allocated numerically.
Allocation concealment (selection bias)	High risk	No explicit information provided, but allocation concealment seems very unlikely since care providers cared for patients of either the intervention or the control group. If allocation was strictly concealed, many participating patients would have to be referred to another doctor than the one they usually saw.
	High risk	Blinding was not attempted

Blinding (performance bias and detection bias) All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	All patients receiving the intervention completed follow-up. Four patients in each allocation group left the study before completing all baseline assessments. Since these patients were left out of the analysis, no ITT analysis was undertaken.
Selective reporting (reporting bias)	Unclear risk	Insufficient information on study protocol available
Other bias	Unclear risk	Baseline characteristics: sufficiently similar Co-interventions: no information provided

Rönnemaa 1997

Methods	RCT
Participants	Setting: community-based care: unselected patients with diabetes, living in the vicinity of Turku, Finland Inclusion criteria: included in the national drug reimbursement register for receiving antidiabetic treatment, between 10 and 79 years of age, no history of foot ulceration, no obvious need for foot care, no podiatry visit in the preceding 6 months
Interventions	Intervention group: - Patient level: individual patient education by a podiatrist, foot care by a podiatrist - Care provider level: no care provider level intervention - Structure of health care level: revision of professional roles (follow-up by podiatrist) Control group: - Written foot care instructions only
Outcomes	Primary outcomes: foot ulceration, amputation Secondary outcomes: callus development, resolution of callus, foot care knowledge scores, patients' behaviour assessment scores Outcomes not included in this review: skin and nail condition
Duration of follow-up	1 year and 7 years
Notes	
[a] ITT: intention-to-treat RCT: randomised controlled trial	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation was performed separately for men and women and for patients below and above 20 years of age. Methods for randomisation not described.
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The outcome assessor was blinded to the baseline characteristics, but no further information on blinding to the group allocation is provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up was completed by only 63% of patients in the intervention group and 62% of patients in the control group at 7 years. No ITT analysis undertaken.
Selective reporting (reporting bias)	Unclear risk	Insufficient information on study protocol available
Other bias	Unclear risk	Baseline characteristics: sufficiently similar Co-interventions: no information provided

[a] ITT: intention-to-treat
RCT: randomised controlled trial

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Armstrong 2007	Intervention only comprises patient level
Barth 1991	Intervention only comprises patient level
Bloomgarden 1987	Solely directed at patient education
Borges 2008	Solely directed at patient education
Clay 2007	Participants are ward nurses, not adult patients with diabetes

[a] RCT: randomised controlled trial

Study	Reason for exclusion
Dargis 1999b	Not a RCT
Frank 2003	Solely directed at patient education
Kruger 1992	Solely directed at patient education
Lavery 2007	Intervention only comprises patient level
Lincoln 2008	Solely directed at patient education
Pedersen 2003	No relevant outcomes reported. Interventions solely aimed at optimising blood glucose concentration and not primarily at preventing foot ulceration.
Pieber 1995	Not a RCT
Plank 2003	Intervention only comprises patient level
Rizzo 2012	Intervention only comprises patient level
van Soeren 2003	Commentary on other trials on integrated care approaches

[a] RCT: randomised controlled trial

References

Version History

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