Intensive versus conventional glycaemic control for treating diabetic foot ulcers (Protocol)

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[Intervention Protocol]

Intensive versus conventional glycaemic control for treating diabetic foot ulcers

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of intensive glycaemic control compared to conventional control on the outcome of foot ulcers in patients with type 1 and type 2 diabetes.

BACKGROUND

Description of the condition

In 2011, 366 million people worldwide (8.3% of adults) were estimated to have diabetes mellitus (IDF 2012). It is expected that this figure will reach 552 million (10% of adults) by 2030 (IDF 2012). Diabetes mellitus is a metabolic disorder characterised by dysregulation in blood glucose levels. Type 1 diabetes (previously known as insulin-dependent, juvenile or childhood-onset) is characterized by deficient insulin production and requires daily administration of insulin (IDF 2012). The cause of type 1 diabetes is not known and it is not preventable with current knowledge (IDF 2012). Type 2 diabetes (formerly known as non-insulin-dependent or adult-onset) results from the body's ineffective use of insulin. Ninety per cent of people with diabetes, worldwide, have type 2 diabetes (IDF 2012). One of the major complications of diabetes is foot ulceration (Boulton 2004). A diabetic foot ulcer has been defined as either a full-thickness wound below the ankle in patients with diabetes, irrespective of duration (Apelqvist 1999), or a lesion of the foot penetrating through the dermis (Schaper 2004). The prevalence of foot ulceration in people diagnosed with diabetes is 4% to 10%; the annual population incidence is 1% to 4%, and the lifetime incidence is as high as 25% (Singh 2005). In

a recent multi-centre study, poor glycaemic control (blood glucose control) was evident in nearly half of the participants who had foot ulcers, with 49% having an HbA1c (glycaemic measure) level above 8.4% (Schaper 2012).

Foot ulceration is caused by the interplay of several factors, most notably diabetic peripheral neuropathy (DPN, i.e. loss of sensation to the foot), peripheral arterial disease (PAD, i.e. lack of blood-flow) and changes in foot structure (Clayton 2009; Shenoy 2012). These factors have been linked to chronic hyperglycaemia (high levels of glucose in the blood) and the altered metabolic state of diabetes (Ikem 2010; Ogbera 2008; Tesfaye 2012).The prevalence of DPN ranges from 16% to 66% in people with diabetes (Cook 2012). The prevalence rates for PAD are as high as 50% in patients with diabetic foot ulcers (Hinchliffe 2012). What is most notable, is that within one year of an ulcer healing, up to 60% of patients will develop another foot ulcer (Wu 2007), and often the end point is lower limb-amputation.

It is currently estimated that there is an amputation every 30 seconds, somewhere in the world, that is due to diabetes (Game 2012). The estimated likelihood of amputation is 10 to 30 times higher amongst people with diabetes compared to those without diabetes and 85% of all amputations in people with diabetes are preceded by a foot ulcer (Boulton 2004; Singh 2005). The five-year mortality rate after the onset of a foot ulcer ranges from 43% to 55%, and is up to 74% for patients with lower limb amputation (Robbins 2008).

Description of the intervention

Chronic hyperglycaemia appears to be one of the most important factors in the development of diabetic foot ulcers, and the potential of ulcers to heal (Christman 2011; Falanga 2005). Current guidelines recommend that treatment should involve a multidisciplinary team, as well as utilising several interventions (Table 1). This review is performed to clarify the effect of intensive glycaemic control on the healing of foot ulcers in people with diabetes.

The management of diabetes includes glycaemic control (Table 2) (Daroux 2010; Geraldes 2010; Giacco 2010; Inzucchi 2012). A common list of glycaemic control medications used in diabetes management is shown in Table 3. Most guidelines have a glycaemic control target of 7% or lower for HbA1c (glycated haemoglobin) (Table 2). The revised guidelines of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend individualisation, with more stringent (6.5% or lower) or less stringent (8% or lower) HbA1c targets as appropriate for individuals (ADA 2012; Cheung 2009; Inzucchi 2012). There is a marked variation in the definition of intensive glycaemic control between guidelines and trials (Hemmingsen 2011a). For the purposes of this review we will include trials where an intervention has been performed with the aim of achieving improved glycaemic control in comparison to a conventional control group.

Most of the current glycaemic targets for diabetes are based on several landmark trials that investigated the effects of intensive glycaemic control compared to conventional treatments (Table 2) (Cheung 2009; Hemmingsen 2011b; Macisaac 2011; Mazzone 2010). The findings from these studies also illustrate the benefits and risks associated with intensive glycaemic control. Therefore, when investigating intensive glycaemic control as a potential intervention for diabetic foot ulcers, it is important to take into account the present literature underpinning current glycaemic management.

Intensive glycaemic control implemented in the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) led to a reduction in the progression and development of microvascular (small vessel) complications including DPN (Mattila 2010). The UKPDS demonstrated a 37% reduction in the risk of microvascular complications for each 1% decrease in HbA1c (95% confidence interval: 33% to 41%) (UKPDS 1998; Stratton 2000). Similarly, the ADVANCE trial found a 14% relative risk reduction for major microvascular events in the intensive control group when compared to the standard control group (9.4% versus 10.9%; hazard ratio (HR) 0.86; 95% CI: 0.77 to 0.97), although mainly in terms of reduced incidence of nephropathy (kidney disease) (ADVANCE 2007).

A recent Cochrane review concluded that intensive glucose control reduced the risk of amputation by 36% in type 2 diabetes (relative risk (RR) 0.64, 95% CI: 0.43 to 0.95; 6960 participants in eight trials) (Hemmingsen 2011b). In addition there was an 11% relative risk reduction (RR 0.89, 95% CI: 0.83 to 0.95; 25,760 participants in four trials) and a 1% to 2% absolute risk reduction in composite microvascular outcomes in favour of intensive glycaemic control for all included trials (Hemmingsen 2011b). A number of meta-analyses have demonstrated that the incidence of hypoglycaemia (low blood sugar) was increased during intensive glycaemic control, making this a significant adverse outcome (Hemmingsen 2011b; Ma 2009; Mattila 2010). It must be noted that the beneficial effects on microvascular complications from using intensive glycaemic control took more than five years to emerge, and the benefits were less pronounced for people with advanced type 2 diabetes compared to those with new-onset type 2 diabetes (Hemmingsen 2011b; Mattila 2010). Despite this, data on retinopathy (disease of the retina) suggest that people with the advanced stages of type 2 diabetes may also benefit from intensive glycaemic control (Hemmingsen 2011a). The effects of intensive glycaemic control in people with type 1 diabetes demonstrated in the DCCT were still evident after 14 years of follow-up (i.e. long after the intervention was completed), and this phenomenon has been termed 'glycaemic memory' (Giacco 2010). More recent data suggests that glycaemic memory also occurs in people with type 2 diabetes, where it is termed the 'legacy effect', whereby benefits of earlier interventions are evident later on in disease progression (Giacco 2010).

While intensive therapy, with the goal of achieving near normal

HbA1c levels (7%), has altered the clinical course of nephropathy, neuropathy and retinopathy, the majority of studies have not examined the benefits of intensive therapy when implemented after the onset of late diabetes complications, such as diabetic foot ulcers (Nathan 2012).

How the intervention might work

Hyperglycaemia has been associated with delayed healing of foot ulcers (Burakowska 2006; Christman 2011; D'Souza 2009; Falanga 2005; Rafehi 2010). Therefore, interventions that target improvements in glycaemic control are of potential benefit. Delayed healing of foot ulcers appears to be the net result of both microvascular and macrovascular disease (Burakowska 2006; Dinh 2005). Well-orchestrated wound healing is essential for tissue replacement and restoration, and generally involves three main phases: acute inflammation, proliferation, and remodelling (Rafehi 2010). In contrast, diabetic foot ulcers do not follow the orderly process of wound healing and differ at a molecular level in terms of expression of growth factors, cytokines and proteins (Dinh 2005; Rafehi 2010). These processes are known to be affected by hyperglycaemia.

Several proposed pathogenic pathways exist to explain the adverse effects of hyperglycaemia (Geraldes 2010). These include: 1) activation of the polyol pathway; 2) non-enzymatic glycosylation and formation of advanced glycation end products (AGEs); 3) activation of the diacylglycerol- (DAG) protein kinase C pathway; and 4) overactivity of the hexosamine pathway (Brownlee 2004; Geraldes 2010; Giacco 2010; Gupta 2010). All four mechanisms have been linked to a single, unified preceding event, namely mitochondrial overproduction of reactive oxygen species (ROS) (Brownlee 2004). ROS are known to promote cellular dysfunction through damage to DNA synthesis, oxidation of lipids and amino acids and inactivation of key enzymes in metabolic function, which are implicated in the formation of diabetic foot ulcers. Hyperglycaemia also promotes endothelial dysfunction, vascular leakage and impaired angiogenesis (formation of new blood vessels) originating from the above mentioned pathways, and leads to activation of the inflammatory response via activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (D'Souza 2009; Giacco 2010). The incidence of infection is also increased in people with diabetes, and different immunological disturbances, such as deficiencies in polymorphonuclear leukocyte, monocyte and macrophage (types of white blood cell) function have been noted during hyperglycaemia (Delamaire 1997; Stegenga 2008). All these factors, which are a consequence of hyperglycaemia, may play a role in delayed healing of foot ulcers. A recent observational study showed that HbA1c was an important clinical predictor of the rate of wound healing; with each 1% increase in HbA1c level associated with a decrease in the wound healing rate of 0.028 cm² per day (95% CI: 0.003 to 0.054) (Christman 2011). Despite this, the effects of short-term reduction in HbA1c did not appear to have any effect on endothelial function in patients with type 2 diabetes with a history of poor glycaemic control (Bagg 2001). Therefore, there remains a clear need to document benefits associated with improved glycaemic control in the diabetic foot ulcer population (Idris 2005). While chronic complications of diabetes such as DPN and PAD maybe difficult to reverse, it can be postulated that aspects of ulcer healing relating to immunological and connective tissue function may be more amenable to improvement if normoglycaemia (normal level of sugar in blood) is achieved (Jeffcoate 2004).

Why it is important to do this review

Foot ulcers continue to be a significant burden for patients with diabetes, their caregivers and the healthcare system (Schaper 2012). The outcome of a foot ulcer in people with diabetes should not only be viewed from a clinical perspective (e.g. healing and amputation), but also from a patient and socioeconomic perspective. Health-related quality of life (HRQoL) is significantly reduced in patients with diabetes, and further impaired by the presence of foot disease, whilst it is improved with foot ulcer healing (Hogg 2012). Healthcare costs associated with foot ulcers and amputations contribute significantly to the financial burden of diabetes (Jones 2007). In the United States in 2008, the total number of discharges attributed to diabetes-related amputations was 45,000. The average length of stay was 10.1 days and the in-hospital mortality rate was 1.29% (Cook 2012). The mean hospital charges were USD 56,216 per patient and the estimated aggregate cost for the year 2008 was USD 2,548,319,965 (Cook 2012).

Therefore, foot ulceration in people with diabetes has substantial socioeconomic, quality of life, and health care implications, and it is imperative that all efforts be made to prevent and treat the burden of foot ulceration in order to reduce amputation rates - as highlighted by the St Vincent Declaration in 1989 (Game 2012). Optimum healing of a foot ulcer requires a well-orchestrated integration of molecular and biological events including, cell migration, proliferation, extracellular matrix deposition and remodelling, which is hindered by the effects of hyperglycaemia (Falanga 2005; Rafehi 2010).

Advances in the treatment of diabetic foot ulcers are promising, however the intrinsic pathophysiological abnormalities of hyperglycaemia that lead to ulceration and delayed ulcer healing cannot be ignored (Falanga 2005). Recent changes to glycaemic targets and current emphasis on individualisation of glycaemic targets seems to open a new era in diabetes management. The review authors believe that this systematic review and meta-analysis will assess the effectiveness of intensive glycaemic control in the management of diabetic foot ulcers.

OBJECTIVES

To assess the effects of intensive glycaemic control compared to conventional control on the outcome of foot ulcers in patients with type 1 and type 2 diabetes.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished randomised controlled trials (RCTs) will be considered for inclusion where they investigate the effects of intensive glycaemic control on the outcome of active foot ulcers (either as a primary or secondary outcome). Non randomised and quasi-randomised trials will be excluded.

Types of participants

Men and women (over 18 years) diagnosed with type 1 or type 2 diabetes by clearly-defined, accepted standards relevant to the time of the study, with an active foot ulcer that has any of the following aetiologies (causes):

- neuropathic, or
- neuro-ischaemic, or
- ischaemic, with or without
- infection (as clinically or diagnostically documented by laboratory analysis).

For the purposes of this review, venous ulcers, malignant ulcers and post-surgical ulcers will be excluded.

Types of interventions

We will include trials that have assessed any intervention that aims to achieve a lower glycaemic target in a diabetes group (i.e. near normal glycaemic levels) when compared to a control group with a higher glycaemic target. The latter group is then defined as a 'conventional' group. Therefore the intensive group will have a lower glycaemic target level compared to the conventional group in the trial. Trials will be included where the reported level of glycaemia is lower in the intensive group.

Therefore, we will include any intervention that has:

1) attempted to maintain or control blood glucose levels and measured changes in markers of glycaemic control (HbA1c or fasting, random, mean, home capillary or urine glucose), and

2) documented the effect of these interventions on active foot ulcer outcomes.

Interventions may include more frequent subcutaneous insulin administration, continuous insulin infusion or oral anti-diabetic agents - or both - as well as any lifestyle interventions (Table 4).

The definition of the conventional (comparison) group is that it should have a higher glycaemic target than the intervention group. Pharmaceutical treatment may include any route of administration, dose, duration or frequency of insulin and/or other pharmaceutical agents.

Types of outcome measures

Primary outcomes

- Number of ulcers healed
- Time to complete healing.
- Change in ulcer severity reported as a change in an ulcer grading score using a well-defined validated ulcer grading scale; e.g. University of Texas Wound Classification System (UTWCS) that measures the depth, presence of infection and ischaemia of an ulcer (Armstrong 1998).
- Incidence of amputation (identified on International Classification of Disease (ICD) codes (NCCH 2006).

Secondary outcomes

- New ulcer development (re-occurrence of an ulcer or initiation of a new ulcer).
- Proportion of infected ulcers at study completion.
- Adverse events: adverse events will be noted from each individual trial, and, where trial reports are based on a sound methodology with standardised approach to detect and assess adverse events, these will be included in any potential analysis and judged on a case by case basis. Treatment-focused examples include: adverse drug reaction requiring hospitalisation; weight gain; and hypoglycaemia. Disease-focused examples include: worsening of neuropathy (clinically or using a validated neuropathy score); development or worsening of PAD (clinically or by diagnostic measurement such as ankle brachial index (ABI); gangrene; congestive heart failure; chronic kidney disease (CKD) (stages 1-5); dialysis; retinopathy and documented diabetic ketoacidosis (DKA); hyperosmolar nonketotic (HONK) hyperglycaemia; and lactic acidosis).
- Effect on HRQOL: as measured by a validated quality of life (QOL) measurement tool that is disease-specific to foot ulcers or generic to QOL - or both.
- Cost of intervention compared to conventional treatment, including: direct medical costs; direct non-medical costs (e.g. transport, assistive devices); indirect costs (e.g. sick leave, reduced productivity, early retirement and premature death); disability-adjusted life years (DALY) and years of life lost (YLL).
- All cause mortality.

Search methods for identification of studies

Electronic searches

We will search the following electronic databases to identify reports of relevant randomised clinical trials:

- The Cochrane Wounds Group Specialised Register;
- The Cochrane Central Register of Controlled Trials (CENTRAL) (latest issue);
- EMBASE via Ovid (1980 to present);
- MEDLINE via Ovid (1946 to present);
- CINAHL plus via EBSCOHost (1981 to present);
- SCOPUS (1960 to present);
- Web of Science via ISI Web of Knowledge (1965 to present);
- BioMed Central (1997 to present);
- LILACS (1995 to present).

We will search The Cochrane Central Register of Controlled Trials (CENTRAL) using the following exploded MeSH headings and keywords:

#1 MeSH descriptor: [Blood Glucose] explode all trees
#2 MeSH descriptor: [Hypoglycemic Agents] explode all trees
#3 MeSH descriptor: [Hyperglycemia] explode all trees
#4 MeSH descriptor: [Hypoglycemia] explode all trees
#5 MeSH descriptor: [Insulin] explode all trees
#6 MeSH descriptor: [Metformin] explode all trees
#7 MeSH descriptor: [Thiazolidinediones] explode all trees
#8 MeSH descriptor: [alpha-Glucosidases] explode all trees
#9 MeSH descriptor: [Glucagon-Like Peptide 1] explode all trees
#10 MeSH descriptor: [Acarbose] explode all trees
#11 (blood glucose):ti,ab,kw
#12 (((glycaemic or glycemic) next control) or "intensive glucose control"):ti,ab,kw
#13 ((hypoglycaemi* or hypoglycemi*) next (agent* or drug*)):ti,ab,kw
#14 (oral next (hypoglycaemi* or hypoglycemi*)):ti,ab,kw
#15 ("fasting glucose" or "glucose target"):ti,ab,kw
#16 ((anti-diabetes next medication*) or (diabetes next medication*) or insulin* or sulphonyureas or metformin or thiazolidinedione* or DPP-4 inhibitor* or glitinide or (glucosidase next inhibitor*) or biguinide or "GLP-1 agonist" or acarbose or (incretin next enhancer*) or (incretin next mimetic*) or HbA1c):ti,ab,kw
#17 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #13 or #14 or #15 or #16
#18 MeSH descriptor: [Foot Ulcer] explode all trees
#19 MeSH descriptor: [Diabetic Foot] explode all trees
#20 (diabet* near/3 ulcer*):ti,ab,kw
#21 (diabet* near/3 (foot or feet)):ti,ab,kw
#22 (diabet* near/3 wound*):ti,ab,kw
#23 (diabet* near/3 defect*):ti,ab,kw
#24 ("foot gangrene" or amputat*):ti,ab,kw
#25 #18 or #19 or #20 or #21 or #22 or #23 or #24
#26 #17 and #25

The MEDLINE search will be combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format - which is outlined in Chapter 6 of the Cochrane Handbook for Systematic Reviews of Interventions (Lefebvre 2011). The EMBASE search will be combined with the Ovid EMBASE filter developed by the UK Cochrane Centre, which is also cited in the Handbook (Lefebvre 2011). The CINAHL searches will be combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (SIGN 2012). We will not restrict studies with respect to language, date of publication or study setting.

Searches of the Cochrane Wounds Group Specialised Register, CENTRAL, MEDLINE, EMBASE and CINAHL will be carried out at the Cochrane Wounds Group editorial base. We will modify the original search strategy shown above to search the SCOPUS, Biomed Central, Web of Science and LILACS databases. We will seek additional support from an institutional librarian to conduct these searches.

We will search the following ongoing trial databases for relevant published, non-published, ongoing and terminated clinical trials:

- EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/index.html);
- ClinicalTrials.gov (http://www.clinicaltrials.gov/);
- WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/);
- Current Controlled Trials (http://www.controlled-trials.com)

We will also search the pharmaceutical trials databases listed below (known pharmaceutical companies involved in manufacture of diabetes medication) for relevant published, non-published, ongoing and terminated clinical trials:

- AstraZeneca Clinical Trials web site (www.astrazenecaclinicaltrials.com);
- Eli Lilly and Company Clinical Trial Registry (www.lillytrials.com);
- Novartis (www.novartisclinicaltrials.com/webapp/etrials/home.do);
- Novo Nordrik (http://www.novonordisk-trials.com/WebSite/Content/Default.aspx);
- MSD (http://www.msd-australia.com.au/research/clinical-development/home.html);
- Servier (http://www.servier.co.uk/clinical-trials/).

We will search guidelines produce by the Joanna Briggs Institute, the National Institute for Health and Care Excellence (NICE), the National Health Service (NHS), the National Health and Medical Research Council (NHMRC), the Scottish Intercollegiate Guidelines Network (SIGN), National Clearinghouse and the International Working Group on the Diabetic Foot for any studies or publications of relevance that have not been identified through

other search options.
Where translation(s) is required, we will contact the original authors first to acquire an English-language version of the manuscript. If the authors are not able to provide an English version, then the articles will be translated to English using translation services from the local hospital or through the Cochrane Wounds Group.

Searching other resources

We will check the reference lists of all included and excluded studies for any further studies of relevance.We will also contact key local and international pharmaceutical groups regarding any unpublished trials. All international and national clinical guidelines in the management of diabetic foot ulcers will be screened for any additional studies. We will also contact leading academics,clinicians and researchers in the area of diabetes management and management of diabetic complications, for information about any prospective or past studies not identified by the literature searches.

Data collection and analysis

Selection of studies

Two review authors (MF and RS) will retrieve and assess articles for inclusion independently using these selection criteria; the title, abstract or key-words - or both - of a potentially-relevant study to assess whether the study investigated:
1) changes in glycaemic state of participants with type 1 or type 2 diabetes via changes in markers of glycaemic control (HbA1c or fasting, random, mean, home capillary or urine glucose), and
2) foot ulcer outcomes.
Full text publications of all articles meeting these selection criteria will be assessed. Any articles that are deemed not to be suitable will be excluded (exclusion after screening of full-text). Differences in opinion regarding whether to include or exclude a study will be resolved by three third parties (JG, KS, YT). If no resolution is achieved, or possible, the original authors of the study will be contacted for further clarification, so that we know whether to include the study, or not. The selection process will be plotted as a PRISMA flow diagram (Moher 2009). All citations will be managed using Endnote version 5.1 (Thomson Reuters 2012). A table demonstrating the reasons for exclusion for all excluded trials will be constructed.

Data extraction and management

Data extraction will be conducted independently by two review authors (MF and RS) and entered into a structured electronic data format using the Cochrane Wounds Group extraction form to collect and organise data.This will include information concerning:

- general information about the study (i.e. location, setting, aims);
- study eligibility;
- characteristics of study methods;
- participants;
- intervention groups;
- outcomes;
- 'Risk of bias' assessment;
- areas for sub-group analysis areas.

The data will include information on participant characteristics, study design, interventions utilised, outcomes assessed, and adverse events.
Disagreements between the two review authors will be resolved by a third (MC) and fourth review author (PB).
Meta-analysis will be conducted on reported outcomes only (i.e. where outcome data on ulcer reduction are provided, but not on amputation; meta-analysis can be done for ulcer reduction but not for amputation). All studies meeting inclusion criteria and reporting outcome variables of interest will be included in the review; where possible, all studies meeting eligibility for meta-analysis will be included in meta-analysis.

Dealing with duplicate publications

When more than one publication is found for a study, we will evaluate all publications together to extract the maximum amount of relevant information. Any discrepancies between the studies will be resolved by contacting the study authors. If there are repeated observations of the same participants, the longest follow-up period will be used for defining outcome measures of this study.

Assessment of risk of bias in included studies

The risk of bias will be assessed using the guidelines provided in the Cochrane Handbook of Systematic Reviews of Interventions (Higgins 2011a). Risk of bias will be rated as low, high or unclear in nature (Higgins 2011b), and a 'Risk of bias' graph and 'Risk of bias' summary will be included. Two review authors (MF and RS) will assess each study independently.
We will use the following bias criteria:

- sequence generation (selection bias);
- allocation concealment (selection bias): a summary of how allocation sequences were generated and attempts to conceal allocation of assigned intervention will be reported, along with any judgements concerning the risk of bias that may arise from the methods used;
- blinding for participants, personnel and outcome assessment (performance and detection bias): a brief summary of who was blinded or masked during the conduct and analysis of the studies will be reported. Implications regarding blinding of outcome assessment may vary for different outcomes, so these

may need to be addressed separately. Judgements concerning the risk of bias associated with blinding will be summarised;

- incomplete outcome data (attrition bias): review authors' concerns over exclusion of participants and excessive (or differential) drop-out rates will be reported;
- selective reporting (reporting bias): concerns over the selective availability of data may be summarised, including evidence of selective reporting of outcomes, time-points, subgroups or analyses;
- other bias(es) identified.

We will present our assessments using a 'Risk of bias' summary figure, which will present all bias assessment points in a table format.

Measures of treatment effect

For dichotomous data, we will present results as summary risk ratios with 95% confidence intervals. For continuous data, when outcomes were measured the same way between trials, we will use the mean difference. We will use the standardised mean difference to combine trials that measured the same outcome, but used different methods of measurement. Time to complete wound healing is time-to-event data; the most appropriate way of summarising it is to use methods of survival analysis and to express the intervention effect as a hazard ratio. It is not appropriate to analyse time-to-event data using methods used for continuous outcomes (e.g. using mean times-to-event), as the relevant times are only known for the subset of participants who have had the event. Censored participants must be excluded, which, almost certainly, will introduce bias. Time-to-event data that were presented incorrectly as continuous data will not be analysed, but will be presented in a narrative format in the review (Higgins 2011a).

Unit of analysis issues

The unit of analysis used in each individual study will be identified in relation to a wound, a foot, a participant or as multiple wounds on the same participant. Where studies have incorrectly treated multiple wounds on a participant as being independent, rather than using within-patient analysis methods, this will be recorded in the 'Risk of bias' assessment. For wound healing and amputation, unless otherwise stated, where the number of wounds appears to equal the number of participants, the wound will be treated as the unit of analysis. We will treat these studies with caution; we will include them in the systematic review, but conduct any potential meta-analysis with, and without, them in sensitivity analyses, to assess the effect they have on the results. The level of randomisation of each trial will also be assessed; the number of observations should match the number of units randomised. Where the unit of analysis is unclear, the trial author will be contacted for results per person.

For adverse event data, the unit of analysis will be assessed on a trial by trial basis to establish whether the data were at participant level, or whether multiple events per participant were possible. Where the latter is the case, although the data can be reported on a trial by trial basis, they cannot be analysed further without violating assumptions of independence. The method of data collection, and potential risks of measurement and performance biases, as well as the unit of analysis of adverse event data will be discussed in detail in the review.

If multiple treatment arms are reported, we will carry out multiple meta analyses using one treatment arm respectively. If more than one control group is used or where a single 'conventional' control group is not recognisable, we will combine all control group results and carry out a pooled analyses of all control groups against the intervention group.

In relation to the inclusion of cluster RCTs, we will attempt analysis where relevant information is available (i.e. the number, or mean size, of clusters, outcome data for total individuals with events, and an estimate of the intra-cluster/intra-class correlation coefficient (ICC). A more reliable analysis will then be conducted by reducing the size of each trial to its effective sample size using the design effect of a cluster RCT, and the standard error will be obtained from confidence intervals, as recommended by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011a). Then any potential meta-analysis can be performed using the inflated variances.

Dealing with missing data

Missing information will be sought from the original authors by emailing the contact person for the published studies. In particular, where the reported findings of a study extend beyond foot ulcers and it is difficult to determine the data relating to foot ulcers, the authors will be contacted for the relevant data. When responses are not received, we will contact additional authors from the publication. To avoid overly positive answers and the risk of false information, open-ended questions will be used for contacting authors (Higgins 2011a). If information relating to outcomes (according to outcome measures) is missing, then the article will not be included in this review.

Therefore, multiple efforts will be made to acquire any missing data from authors. We will inspect factors such as attrition rates, drop-out rates, randomised and included subject numbers, as well as numbers for intention to treat, treated per protocol and losses to follow-up carefully. These will be appraised critically and their impact on the data will be assessed in the light of the results of the review.

Sometimes measures of dispersion are not recorded. Where the standard error (SE) or the t-statistic is reported, standard deviations will be calculated with statistical assistance from PB. If the authors did not report the aetiology of ulcers, they will be contacted for details. If the authors are unable to confirm aetiology, the study

will be excluded.

Assessment of heterogeneity

Clinical heterogeneity

We will determine potential reasons for heterogeneity by exploring individual study and sub-group characteristics such as age and gender of participants, risk factors for foot ulceration, duration of disease, initial size of ulcer, type of treatment, duration of follow-up, presence or absence of infection, history of ulceration, history of significant cardiovascular events, presence or absence of PAD, type of ulcer, location of ulcer, time to ulcer healing, type of medication used, as well as how ulcer healing was defined within the context of the study.

Methodological heterogeneity

The formal assessment of bias of each study, as described above, will help identify methodological heterogeneity between studies.

Statistical heterogeneity

Forest plots, Q and I^2 statistics will be used to indicate heterogeneity. If heterogeneity is present, then we aim to identify the studies that produce it, and to conduct an analysis without them. With the I^2 statistic, values of 75% or more will be taken as indicative of high levels of heterogeneity (Higgins 2011a), and will be used to assess further the heterogeneity of studies.

Only those studies that are clinically, methodologically and statistically homogenous will be pooled for meta-analysis effect-size calculations. Sub-group analysis will be defined by the factors we identify as being responsible for heterogeneity, as mentioned above.

Assessment of reporting biases

Funnel plots will be used to assess publication bias, if there are a sufficient number of studies (10 or more) available. If there are not enough studies in the meta-analysis for constructing a meaningful funnel plot, then the potential for publication bias will only be discussed.

Data synthesis

We have consulted the Cochrane Collaboration recommendations and decided to conduct both random-effects and fixed-effect models where appropriate for any potential meta-analysis. For example where clinical, methodological and statistical heterogeneity are not apparent, similar studies will be pooled in a fixed-effect model. Where any of the above mentioned heterogeneity is evident, or whereby I^2 values which demonstrate heterogeneity are significant, a random-effect model will be utilised. Where heterogeneity levels are insignificant and no other forms of heterogeneity are evident, both random effect and fixed effect models will be used for comparison. We will attempt to investigate any significant differences in results and heterogeneity of studies through use of these two statistical models. If there are any vast differences between the two methods, we will explore these differences. If fixed-effect and random-effects meta-analyses give identical results, then it is unlikely that there is important statistical heterogeneity, and we believe either method will be appropriate for reporting. All studies meeting inclusion criteria and reporting outcome variables of interest will be included in the review. All studies meeting eligibility for meta-analysis will be included in a meta-analysis. Meta-analysis will be conducted separately on provided and published data, and also on results from intention-to-treat trials. We will use Review Manager for data analysis. 'Summary of findings' tables will be used to report each of the primary outcome variables with comparative risk ratios (RR) and relative effects with 95% confidence intervals, number of participants and the GRADE score along with a comment about each different outcome. As mentioned previously, if quantitative synthesis is not appropriate, findings from individual studies will be included and discussed in the review.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be attempted at several levels in the meta-analysis. The sub-groups will be decided after consideration of a number of factors, and will be based on:

1. follow-up time: studies will be stratified as short-, medium- and long-term, where less than one year of follow-up will be considered as short-term, one to three years will be considered as medium-term, and more than three years will be considered to be long-term;
2. variation in the intervention and control group (e.g. groups who received lifestyle interventions versus anti-diabetic medication versus insulin).

Sensitivity analysis

Sensitivity analysis will be done by excluding and including studies that cause heterogeneity in the data. Sensitivity analysis will also be conducted by excluding and including studies that are deemed to be of lower quality (high risk of bias). The results of sensitivity analyses will be discussed.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Diabetic foot management guidelines and levels of evidence

Guideline and management recommendations	Level of evidence (According to Oxford Centre for Evidence-based Medicine - Levels of Evidence (March 2009))	Glycaemic target
National Health and Medical Research Council (NHMRC): Prevention, identification and management of foot com-	Expert opinion Grade B	Not reported

Table 1. Diabetic foot management guidelines and levels of evidence (*Continued*)

plications in diabetes mellitus 2011 • Local sharp debridement • Topical hydrogel dressings • Pressure reduction • Offloading • Removable offloading • Multidisciplinary care management • Negative pressure therapy • Hyperbaric oxygen • Larval therapy • Cultured skin equivalents • Skin grafting Note: as per NHMRC levels of evidence	Grade B Grade B Expert opinion Grade C Grade B Grade B Grade C Grade B Grade D	
National Clearinghouse Guidelines 2011 • Debridement with multidisciplinary team • Off-loading of foot ulcers • Pressure relieving support surfaces • Negative pressure wound therapy • Avoid the use of: ○ dermal or skin substitutes ○ electrical stimulation therapy ○ autologous platelet-rich plasma gel ○ regenerative wound matrices and dalteparin ○ growth factors ○ hyperbaric oxygen therapy	Not reported	HbA1c < 7% Level B
National Clearinghouse guidelines 2012 (treatment of neuropathic wounds) Assessment by a wound expert	Grade C	
National Health Service (NHS): Type 2 diabetes: prevention and management of foot problems 2004 • Urgent attention within 24 hours • Multidisciplinary treatment • Multidisciplinary team comprising of a podiatrist, orthotists, specialised nurse, diabetologist; with unhindered access to suites for managing major wounds, antibiotic administration, urgent inpatient facilities, community nursing, microbiology and diabetic services • Prompt Revascularisation • Intensive systemic antibiotic therapy	Grade D Grade D Grade D Grade D Grade C Grade D Grade D Grade B Grade B Grade D Grade B	Not reported

Table 1. Diabetic foot management guidelines and levels of evidence (*Continued*)

• Appropriate wound dressing • Close monitoring and regular wound dressing changes • Debridement of dead tissue • Total contact casting • Hyperbaric oxygen, cultured human dermis, topical ketanserin or growth factors • Foot care reminders		
National Health Service (NHS): 2011 National Institute for Health and Care Excellence (NICE) clinical guideline. Developed by the Centre for Clinical Practice at NICE: Diabetic foot problems: inpatient management of diabetic foot problems • Debridement • Wound dressings • Offloading • Antibiotics for infection • Timing for surgical management.	Not reported	Not reported
2012 International Working Group on Diabetic Foot (IWGDF): Global guideline for type 2 diabetes • Local wound care • Relief of pressure • Treatment of infection • Metabolic control • Restoration of skin perfusion	Not reported	< 8 mmol/l
Australian Diabetes Foot Network: Management of diabetes related foot ulceration - a clinical update • Debridement • Dressing selection • Pressure offloading • Management of infection • Glycaemic control • Multidisciplinary care	Not reported	Not reported
American College of Foot and Ankle surgeons 2006 (revision): Diabetic foot disorders - a clinical practice guideline • Debridement • Pressure offloading • Treatment of infection • Optimise metabolic perturbations	Not reported	Not reported

Table 1. Diabetic foot management guidelines and levels of evidence (*Continued*)

Scottish Intercollegiate Guidelines Network (SIGN) Guidelines 2010 • Referral to a multidisciplinary care team • Total contact casts for unilateral ulcers • Irremovable walkers • Negative pressure wound therapy • Arterial reconstruction for those who require it	 Grade C Grade B Grade B Grade B Grade B	Not reported
American Diabetes Association Standards of Medical Care in Diabetes 2012 Multidisciplinary approach Foot ulcers and wound care may require care by a podiatrist, orthopedic or vascular surgeon, or rehabilitation specialist experienced in the management of individuals with diabetes	Grade B Not reported	As per position Statement for optimal Control

Table 2. HbA1c targets recommended by different international guidelines [a]

Country	Guideline	Year	Hba1c targets in adults	Level of Evidence (According to Oxford Centre for Evidence-based Medicine - Levels of Evidence (March 2009))
Australia	National Health and Medical Research Council/Diabetes Australia	2009	≤ 7%	Grade A
	Australian Paediatric Endocrine Group/ Australian Diabetes Society	2011	≤ 7%	Grade D
UK	National Institute for Health and Care Excellence (NICE) - Managing type 1 DM diabetes in adults - Blood glucose lowering therapy for type 2 DM	 2012 2012	 ≤ 7.5% if increased arterial risk ≤ 6.5% Between 6.5% and 7.5%	Grade B Not reported Not reported

Table 2. HbA1c targets recommended by different international guidelines [a] (*Continued*)

	Scottish Intercollegiate Guidelines Network (SIGN) - Type 1 Diabetes - Type 2 Diabetes	2010	No set figure < 7%	Not reported Grade A
USA	National Clearinghouse	2012	< 7% or individualize to a goal of < 8%	Grade B
	American Diabetes Association	2012	≤ 7% or individualise to a goal: < 6.5% < 8%	Grade B Grade C Grade B
	American Association of Clinical Endocrinologists	2011	≤ 6.5%	Grade D
International Diabetes Federation (IDF)	International Diabetes Federation- Global Guideline for type 2 Diabetes	2012	< 7.0%	U/K
Canada	Canadian Diabetes Association	2008	≤ 7% ≤ 6.5% (may be considered to lower risk of nephropathy further)	Grade C, Level 3 Grade A, Level 1A
Europe	European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA)	2012	< 7% or individualise to a goal of: 6-6.5% (patients with short disease, duration, long life expectancy, no significant CVD) 7.5-8.0% (history of severe hypoglycaemia, limited life expectancy, advanced complications, extensive comorbid conditions and those in whom the target is difficult to attain)	Not reported
New Zealand	New Zealand Group Guidelines	2003	≤ 7%	Grade D

[a] Adapted from Australian Electronic Therapeutic Guidelines (Electronic Therapeutic Guidelines Australia 2012)

Abbreviations

CVD = cerebrovascular disease

DM = diabetes mellitus

U/K = unknown

Table 3. Commonly used medications in diabetes mellitus (type 1 and type 2) for the management of hyperglycaemia.

Class/Drug	Expected decrease in HbA1c
ORAL ANTIDIABETIC THERAPY	
Metformin	1-2%
Sulfonylureas 1. glibenclamide 2. gliclazide 3. glimepiride 4. glipizide	1-2%
DPP-4-inhibitors 1. sitagliptin 2. vildagliptin, 3. axagliptin 4. linagliptin	0.5-0.8%
Acarbose	0.5-0.8%
Thiazolidinedione (glitazones) 1. pioglitazone 2. rosglitazone	0.5-1.4%
PARENTERAL THERAPY	
GLP-analogues exenatide liraglutide lixisenatide	0.5-1.0%
Insulin	1.5-3.5%
Insulin	**Generic name**
Very-short-acting (rapid)	Aspart Glulisine Lispro
Short-acting	Neutral
Intermediate-acting	Isophane (protamine suspension)
Long-acting	Determir Glargine
Biphasic	Neutral/isophane Lispro/lispro protamine

Table 3. Commonly used medications in diabetes mellitus (type 1 and type 2) for the management of hyperglycaemia. (*Continued*)

	Aspart/aspart protamine
Methods of insulin delivery	
1. Syringe 2. Pen injector 3. Pump/continuous subcutaneous insulin infusion	

Table 4. Alternative treatments for lowering blood glucose in people with diabetic foot ulcers

Nature of intervention		
Exercise	**Psychological and behavioural**	**Dietary**
Any exercise intervention that has the primary aim of improving glycaemic control in people with diabetes, where the impact of the intervention on glycaemic control and changes in an active foot ulcer has been documented	Any psychological or behavioural intervention that has the primary aim of improving glycaemic control in people with diabetes, where the impact of the intervention on glycaemic control and the resultant changes in a foot ulcer has been documented	Any dietary or nutritional intervention that has the primary aim of improving glycaemic control in people with diabetes, where the changes in glycaemic control have been correlated with changes in active foot ulcer outcome
Examples		
Exercise programs of any intensity and duration that had the primary aim of improvement in glycaemic control	Frequent checking of blood glucose levels, interventions aimed at good pharmaceutical practice (i.e. improving compliance with medication)	Healthy eating programs, dietary or nutritional supplements

APPENDICES

Appendix 1. Glossary of Terms

Diabetes: a disease caused by reduced production of the hormone insulin, or a reduced response of the liver, muscle, and fat cells to insulin. This affects the body's ability to use and regulate sugars effectively.

Diabetic Peripheral Neuropathy (DPN): damage to the peripheral nerves that is characterised by numbness, tingling, pain, or sometimes muscle weakness, particularly in the extremities.

Peripheral Arterial Disease (PAD): narrowing or obstruction of the arteries supplying the legs that is characterised by intermittent claudication (numbness, tingling and pain in the legs that occurs on walking, but is relieved by a short rest)

Hyperglycaemia: excessive glucose (sugar) in the blood.

HbA1c (glycated haemoglobin): a commonly used laboratory measurement that measures average blood glucose levels over the previous two to three months.

Microvascular: small blood vessels.

Macrovascular: large blood vessel.

Nephropathy: disorder of the kidney that includes inflammatory, degenerative and sclerotic (scar forming) conditions.
Retinopathy: disease of the small retinal blood vessels in the eye.
Growth factors: chemical messengers that induce cell growth.
Glycation: binding of a sugar molecule to an amino-acid. In hyperglycaemia, sugar molecules become attached to cell surface proteins throughout the body; this sugar coating leads to small blood vessel damage in nerves, kidney, and the retina.
Polyol pathway: metabolic pathway involved in breakdown of excess glucose.
Advanced Glycation End products (AGEs): proteins that have been non-enzymatically modified by the addition of sugar residues.
Reactive Oxygen Species (ROS): molecules and ions of oxygen that have an unpaired electron, which makes them extremely reactive. Many cellular structures are susceptible to damage by reactive oxygen species.
DAG-protein kinase C pathway: metabolic pathway involved in diabetes-related complications.
Hexosamine pathway: metabolic pathway involved in diabetes-related complications.
Mitochondria: involved in respiration and adenosine tri-phosphate (ATP; energy) production.
Endothelial: cells lining the heart, blood vessels and lymph vessels.
Angiogenesis: process of forming new blood vessels.
NF-κB: transcription factor involved in activation of genes involved in the inflammatory response.
Ulcer grading scale: an ulcer grading system implies any system where the dimensional change in an ulcer has been documented - e.g. the University of Texas Wound Classification System (UTWS), PEDIS system or another.

CONTRIBUTIONS OF AUTHORS

Malindu Fernando: designed and drafted the protocol. Approved the final manuscript for submission to the Wounds Group. Searched background information for protocol, organised group meetings to discuss and co-ordinate protocol development, and wrote the protocol.

Ridmee Seneviratne: drafted the protocol, approved the final document for review, assisted in organising group-meetings to discuss the protocol. Searched background information, assisted in retrieval of papers, and wrote the protocol. Approved the final manuscript for submission to the Wounds Group.

Margaret Cunningham: edited, developed and made an intellectual contribution to the protocol, as well as writing parts of it and providing advice on certain aspects. Approved the final manuscript for submission to the Wounds Group.

Peter Lazzarini: edited, developed and made an intellectual contribution to the protocol, as well as providing advice on certain aspects of it and providing content-related expertise. Approved the final manuscript for submission to the Wounds Group.

Kunwarjit Sangla: developed and edited the protocol and provided intellectual contributions, advice, and content-related expertise. Approved the final manuscript for submission to the Wounds Group.

Yong Mong Tan: developed and edited the protocol and provided intellectual contributions, advice, and content-related expertise. Approved the final manuscript for submission to the Wounds Group.

Petra Buttner: developed and edited the protocol and provided intellectual contributions and statistical methodological advice. Approved the final manuscript for submission to the Wounds Group.

Jonathan Golledge: developed and edited the protocol, and assisted significantly with the final version for submission. Provided methodological and clinical guidance on the topic. Approved the final manuscript for submission to the Wounds Group.

Contributions of editorial base

Liz McInnes, Editor: advised on methodology, interpretation and protocol content. Approved the final protocol prior to submission.
Sally Bell-Syer: co-ordinated the editorial process. Advised on methodology, interpretation and content. Edited the protocol.
Ruth Foxlee: designed the search strategy and edited the search methods section.
Rachel Richardson: undertook editorial checks.

DECLARATIONS OF INTEREST

Malindu Fernando: none known.

Ridmee Seneviratne: none known.

Margaret Cunningham: none known.

Peter Lazzarini: The author declares that he is a former board member of the Australasian Podiatry Council that received sponsorship money for footwear companies (New Balance, Clarks and Steel Blue) and a pharmaceutical company (Novartis). He also received payment from a pharmaceutical company (AstraZeneca) to provide lectures to General Practitioners on diabetes foot care.

Kunwarjit Sangla: I have received a number of pharmaceutical and non pharmaceutical grants as the principal investigator over the years for research in the field of Diabetes and Endocrinology. But this was always as member of a group. No money ever has been paid to me as part of the grants for services rendered. I have received speaker honorarium from pharmaceutical companies over the years for topics unrelated to this Cochrane review.

Yong Mong Tan: none known.

Petra Buttner: Although I am a director of a company (Tropical Health Solutions), my involvement with this company has nothing to do with this review. I am involved in this review because of my position as Associate Professor at James Cook University and my expertise in statistics and epidemiology. Neither I nor THS will have any financial gain from this review.

I am chief investigator on two current grants. Their topics are unrelated to this review.

Jonathan Golledge: I have received support to speak at a number of meetings not related to this project.

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Institutional resources and support

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NOTES

The review authors agreed to change the title to 'Intensive versus conventional glycaemic control for treating diabetes foot ulcers', because of the wider use of the term 'intensive glycaemic control' over 'strict glycaemic control' within the literature, and also because of external reviewers' comments.