

SYSTEMATIC REVIEW

How effective are dietary interventions for prevention and management of chronic wounds in individuals with diabetes: a systematic review protocol

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Abstract

Background Adequate nutrition is essential for individuals with diabetes and wounds to optimise both wound healing and blood glucose control. Previous systematic reviews have evaluated the effectiveness of nutrition supplementation for wound healing in individuals with diabetes. However, none have reported comprehensively on the range of dietary interventions utilised in this population, despite these being common within clinical practice. Therefore, the aim of this systematic review is firstly to evaluate the effectiveness of dietary interventions for wound prevention and management in people with diabetes, and secondly to describe intervention characteristics.

Methods Using PRISMA-P to guide the review, five databases will be searched for intervention studies (Medline, Embase, CINAHL, Scopus, Cochrane Library) as well as clinical trials registries. The Rob-2 and ROBINS tools will assess risk of bias. Studies will be described narratively, and a meta-analysis conducted if adequate levels of homogeneity exist between included studies and outcome variables, including study types, and characteristics of the sample including sample size. An appropriate model will be chosen to undertake meta-analysis.

Discussion The systematic review results will inform clinicians on the most effective dietary interventions to optimise wound healing in individuals with diabetes. Study results will inform design and conduct of future nutrition interventions in wound healing.

Keywords diabetes, dietary intake, dietary intervention, systematic review, wounds

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Introduction

Chronic wounds are a silent epidemic – the pooled prevalence of ulcers of various aetiologies is 2.21 per 1000 population, accounting for A\$3.5 billion of economic burden to the Australian healthcare system annually.^{1,2} Chronic wounds are defined as hard-to-heal wounds that do not progress through timely healing despite optimal care in 4–6 weeks,³ and include pressure injuries (PI), venous leg ulcers (VLU), arterial ulceration and diabetes-related foot ulcers (DFU)². DFU is a broad term which encompasses three subtypes of wounds – neuropathic, ischaemic and neuro-ischaemic ulcers.⁴ Diabetes is a major contributor to impaired or

delayed healing of chronic wounds.^{5,6} Currently, 10.5% (537 million) of the world's population aged 20–79 years are living with diabetes.⁷ In 2021, 6.7 million deaths worldwide were estimated to have been attributed to diabetes (all types) and related complications,⁷ with one of the most common complications being chronic wounds.⁸

Individuals with diabetes can develop a variety of different chronic wounds, including DFU, PI and VLU, with an estimated 19–34% of those living with diabetes developing a DFU in their lifetime.⁹ The prevalence of other chronic wound types in individuals with diabetes is less clear.^{9,10} Three

previous systematic reviews demonstrated the increased risk of PI in individuals with diabetes,^{11–13} with one review concluding that a person living with diabetes had a 1.77 times increased likelihood of developing a PI compared to an individual without diabetes.¹² The prevalence of VLU in individuals with diabetes has also not been quantified, with previous research postulating that between 17–21.7% of VLU patients also have a diagnosis of diabetes.^{14,15}

The underlying pathophysiology behind diabetes and wound healing is complex, with a combination of neuropathic, vascular, immune and biochemical factors impairing the wound healing process.^{16,17} Peripheral sensory neuropathy secondary to diabetes is particularly relevant, as reduced innervation is proposed to impact on wound healing.¹⁸ Further, peripheral arterial disease results in a reduction of blood flow to lower extremities, reducing nutrient, oxygen and immune cell delivery to foot and leg wounds, further inhibiting the wound healing processes.¹⁹ Finally, hyperglycaemia can negatively impact wound healing¹⁰ through impairing angiogenesis and endothelial nitric oxide synthesis, decreasing leukocyte function, and the accumulation of advanced glycation end-product in tissues is also detrimental to wound healing as it can result in apoptosis.^{20–22}

In populations with diabetes and chronic wounds (VLU, DFU and PIs), previous studies have identified that poor diet quality, micronutrient deficiencies and malnutrition are highly prevalent.^{23–30} Nutrition is an important factor in wound healing, with inadequate intakes of energy, macronutrients, and specific micronutrients, including protein, zinc, vitamin C and vitamin D, delaying timely tissue repair.^{31–34} Further, nutrition can also influence the prevention of wounds.³⁵ A recent systematic review identified specific nutritional deficiencies associated with development of DFU and further described that the micronutrient status of individuals with diabetes and active foot ulcers was significantly different compared to someone living with diabetes without a foot ulcer.³⁶ Specifically, vitamin E supplementation has been demonstrated to assist in the prevention of wounds in individuals with diabetes, as well as assisting to delay the progression of existing wounds.³⁵

Whilst the relationship between nutrition and wound healing is well established, particularly in PI,^{23,32,37} it is not currently clear as to the best way to clinically intervene, particularly in patients with diabetes who have more complex nutritional needs. One previous randomised control trial which included participants with diabetes demonstrated a positive association between medical nutrition therapy and PI healing³⁷. It is well established that individuals with PI have substantial protein and nitrogen losses due to high levels of wound exudate. Therefore, ensuring adequate intake of these nutrients is important to facilitate timely wound healing processes³².

Dietitian intervention, nutrition counselling and nutrition education are commonly employed in practice to help individuals optimise their dietary intakes, with multiple

studies demonstrating effectiveness.^{24,37–41} Previous systematic reviews and meta-analyses have investigated the effectiveness of specific nutrition supplementation approaches for wound healing in DFU.^{23,42–50} However, none to date have explored the effectiveness of different dietary interventions (behavioural and/or supplementation) for either the prevention and/or management of a range of chronic wound aetiologies (VLU, DFU, PI) in individuals with diabetes.

Objectives

Therefore, this systematic review aims to:

- Evaluate the effectiveness of dietary interventions for wound prevention and management in the healing and incidence of wounds in individuals with diabetes.
- Describe the characteristics of dietary interventions used for the prevention and management of wounds in those living with diabetes.

Methods

This systemic review protocol will be reported in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols checklist (PRISMA-P).⁵¹

Participants/setting

Studies will be included:

- That include individuals of any age, sex and ethnicity, in any healthcare setting (i.e., hospital, community, residential aged care), with any co-morbidities, with type 1 or 2 diabetes with a wound will be included.
- If wounds include DFU, pressure ulcerations/PIs, arterial/ ischaemic ulcers, VLU or mixed leg ulcerations.
- If wound classification systems include Texas Wound Classification System, Wifl Classification System or Wagner's Classification.^{52–54} Acute surgical wounds will be excluded.
- If all participants have diabetes, or if studies which are not specifically in a diabetes cohort report outcomes of those with diabetes separately.

Intervention(s)

Studies will be included:

- That test a dietary intervention for the prevention and/or treatment of wounds in people living with diabetes.
- If dietary interventions include: supplementation (oral, enteral or parenteral) of any type (food pattern, macronutrient, vitamin, mineral or multi-nutrient), dose, mode, duration; any special diet; nutrition education; dietitian intervention; and/or nutrition counselling.
- If preventative dietary interventions target preventing wounds in those living with diabetes who are at risk of ulceration and who are currently without an active wound.

Studies will not be included:

- If the participants with diabetes are part of a larger group and are not able to be evaluated as a sub-group.

- If the dietary intervention is a part of a multi-component intervention or bundle of care, where the results of the dietary intervention cannot be evaluated individually.

Comparator(s)

- Control group with no dietary intervention OR
- Standard care/diet OR
- Comparison of two or more types of wound prevention/ treatment dietary interventions.

Outcome measures for wound prevention studies

Primary outcomes:

- Incidence of ulcers/wounds during the study intervention.

Secondary outcomes:

- Changes to eating behaviours, diet quality, food and/or nutrient intake.
- Any biochemistry assessed but not limited to: HbA1c, fasting glucose, inflammatory markers (e.g., CRP, IL-6, TNF- α), vitamin/mineral status, cholesterol levels, urinalysis or any other objective measures reported.
- Acceptability/satisfaction with intervention.
- Cost of intervention.
- Quality of life – validated scale.
- Adherence/dropout rate.
- Physical activity levels.

Outcome measures for wound management studies

Primary outcomes:

- Measures of wound healing, including time to healing, changes in healing rate, changes in wound length, width and depth, total number of wounds, time to complete healing, or proportion of wounds healed at completion of study.

Secondary outcomes:

- Changes to eating behaviours, diet quality, food and/or nutrient intake.
- Any biochemistry assessed but not limited to: HbA1c, fasting glucose, inflammatory markers (e.g., CRP, IL-6, TNF- α), vitamin/mineral status, cholesterol levels, urinalysis or any other objective measures reported.
- Acceptability/satisfaction with intervention.
- Cost of intervention.
- Quality of life – validated scale.
- Adherence/dropout rate.
- Physical activity levels.
- Admission and length of stay (if in hospital).
- Development of new ulcers.
- Amputation rate.
- Surgical interventions.

Studies will also be included if wound healing is included as a secondary outcome.

Study design

Randomised control trials, pseudo-randomised control trials, quasi-experimental studies and pre- and post-studies of any timeframe, in English and any publication year will be included.

The following study designs will be excluded – cross-sectional studies, cohort studies, case studies, case series, systematic reviews and meta-analysis, and conference abstracts.

Information sources

We will utilise five databases to maximise the inclusion of all studies relevant to the review aims. The databases to be searched are Medline, Embase, CINAHL, Scopus and Cochrane Library. Reference lists of included studies will also be searched for articles relevant to the aims of this study. Study authors will be contacted if key data is not presented in the relevant format. Experts in the field will be contacted to confirm all relevant studies are included in this review. Moreover, the clinical trials registries (Europe, Australia and New Zealand, the World Health Organization and the United States of America trials database) will be searched for relevant registered studies. Trial full texts will be sought after on other databases. If trials have not been published, authors will be contacted so see if there has been any progress.

Search strategy

The search strategy was developed within the research team and assistance from an experienced senior health and medical research librarian. An initial search was conducted on Medline to confirm the search strategy identifies relevant articles. The Medline search strategy is presented in Table 1. Potentially eligible articles identified in the initial search will be screened for key words that can be used to strengthen the search strategy. The search will be limited to human subjects and studies published in English. To identify articles eligible for inclusion in the systematic review, search terms with appropriate truncation and indexing will be utilised. The search strategy will be modified to suit each database used. The search strategy aims to identify experimental studies investigating the effectiveness of dietary interventions on wound healing in those living with diabetes.

Study records

Data management

For consistency and efficiency, the Covidence® systematic review software (Veritas Health Innovation, Melbourne, Australia) will be used to store eligible studies and facilitate research team-based screening of titles and abstracts, full texts and data extraction. The literature search, uploading of studies to Covidence® and removal of duplicates will be conducted by one author (HD).

Selection process

Three researchers will utilise Covidence® to independently screen titles and abstracts of all studies identified in the search, with two researchers assessing each title and abstract. A third researcher will resolve conflicts in title and abstract screening. For studies that are considered potentially relevant, full text records will be retrieved and independently assessed by two researchers for inclusion. For studies excluded during the full text screening, a reason for exclusion will be recorded. If there is conflict between the two researchers for inclusion or exclusion of a study during full text screening, this will be resolved by discussion. Studies deemed to meet inclusion criteria will be included.

Data collection process

Data will be extracted from eligible studies independently by a single researcher using a standardised data extraction criterion developed by the research team (Table 2). A 10% check of data extraction will be completed by an independent person (second reviewer). Data will be extracted

Table 1. Medline search strategy

#	Searches
1	Diet/ or diet*.mp. or Diet Therapy/
2	nutrition* counsel*.mp.
3	dieti?ian.mp. or Nutritionists/
4	Parenteral Nutrition/ or Nutrition Therapy/ or Enteral Nutrition/ or nutri* therapy.mp. or Nutritional Support/
5	feeding.mp.
6	food.mp.
7	nutri* education.mp.
8	energy intake.mp.
9	diet* supplement*.mp. or dietary carbohydrates/ or dietary fats/ or dietary proteins/ or dietary supplements/
10	supplement*.mp.
11	nutri* supplement*.mp.
12	nutrition*.mp.
13	diet* intervention.mp.
14	nutri* intervention.mp.
15	nutrients/ or micronutrients/
16	((micronutrient* or "micro-nutrient*" or vitamin* or multivitamin* or mineral* or "trace next element*" or zinc or iodine or iron or cobalt or chromium or copper or manganese or magnesium or fluoride or sodium or selenium or molybdenum or "vitamin A" or "vitamin B9" or "vitamin C" or "ascorbic acid" or "vitamin D" or "vitamin E" or "folic acid") adj3 (supplement* or fortification or capsule* or tablet* or liquid*).mp.
17	(nutrient* adj3 (supplement* or fortification or capsule* or tablet* or liquid*).mp.
18	((macronutrient* or "macro-nutrient*" or protein* or "amino next acid*" or carbohydrate* or calorie* or energy* or fat* or lipid*) adj3 (supplement* or fortification or capsule* or tablet* or liquid*).mp.
19	((arginine or glutamine or "b-hydroxy-b-methylbutyrate" or "omega-3" or "omega-3 fatty acid*" or probiotic* or antioxidant) adj3 (supplement* or fortification or capsule* or tablet* or liquid*).mp.

using Covidence® software. The data extraction criterion will be pilot tested with five studies randomly selected. Included studies that contain missing data or unclear information will be contacted (where available).

Risk of bias in individual studies

We will assess the risk of bias in the individual studies included by using Rob-2 and ROBINS Tools.^{55,56} The tool will be utilised by two independent reviewers (HD, PT), and a third reviewer will address any disagreements that arise (EC).

Effects measures

The effect measure of mean difference will be utilised in the result synthesis.

Data synthesis

Studies included in data synthesis will be characterised by the intervention type and outcome measures. The synthesising of the data will be guided by the research aims. Extracted findings will be presented in tables. The findings will be

#	Searches
20	oral supplement*.mp.
21	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	wound*.mp. or Wound Healing/
23	pressure ulcer*.mp. or Pressure Ulcer/
24	pressure injury.mp.
25	foot ulcer*.mp. or Foot Ulcer/
26	diabetic foot.mp. or Diabetic Foot/
27	Leg Ulcer/ or arterial ulcer*.mp. or Varicose Ulcer/
28	(venous leg ulcer* or varicose ulcer* or stasis ulcer* or crural ulcer* or ulcus cruris).mp.
29	((arterial or ischaemic or ischemic) adj (wound* or ulcer*)).mp.
30	chronic foot ulcer*.mp.
31	diabetic foot ulcer*.mp.
32	(diabet* adj3 ulcer*).mp.
33	(diabet* adj3 (foot or feet)).mp.
34	(diabet* adj3 wound*).mp.
35	(diabet* adj3 defect*).mp.
36	decubitus*.mp.
37	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38	Diabetes Mellitus, Type 2/ or diabetes.mp. or Diabetes Mellitus, Type 1/ or Diabetes Mellitus/
39	diabet*.mp.
40	diabetes mellitus.mp.
41	38 or 39 or 40
42	21 and 37 and 41
43	limit 42 to (english language)
44	animals/ not humans/
45	43 not 44

Table 2. Data items. Data to be extracted from eligible studies will include authors, year of publication, journal title and country of study as well as the following data

Data items
Participants <ul style="list-style-type: none"> Participant inclusion/exclusion criteria Summary of participant characteristics (e.g., number of participants, age, ethnicity, socio-demographic, diabetes type, diabetes duration, wound duration, previous ulceration, previous amputation, etc), wound classification (e.g., Texas Wound Classification System or the Wifl Classification System, etc)^{52,54} Recruitment methods
Intervention(s) <ul style="list-style-type: none"> Type (oral/enteral/parenteral supplementation, nutrition education, nutrition counselling, dietitian consultation) Dose (for supplementation) Delivery (e.g., face-to-face, online, in a group, one-on-one) Clinician (dietitian, nurse, diabetes educator, etc) Setting (e.g., hospital, residential aged care, clinic, telehealth, online, community) Duration (e.g., hours or days in a row) Length (e.g., 6 months) Frequency (single day, once a week, once a month)
Comparator <ul style="list-style-type: none"> Any comparator (standard care, standard diet, hospital diet, another dietary intervention)
Outcomes <ul style="list-style-type: none"> Outcome types reported and how they were measured Results for the outcome measures (total study population, or if not diabetes specific study, the diabetes population)
Study design <ul style="list-style-type: none"> Type of study design (e.g., randomised controlled trial, pseudo-randomised control trials, quasi-experimental studies and pre- and post-studies.) Sampling strategy Treatment assignment strategy Adherence Length of follow-up

discussed in relation to the current literature and implications for research, policy and practice. Descriptive data will be reported for the number of studies and reported in a table.

If there is sufficient homogeneity amongst included studies, a meta-analysis will be performed. Depending on the number of included studies, the study types and characteristics of the sample, including sample size, an appropriate model will be chosen to undertake meta-analysis.

Reporting bias assessment

Data will only be obtained from the publication, and authors will be contacted for missing data.

Confidence in cumulative evidence

The Grading of Recommendations Assessment, Development and Evaluations (GRADE) system will be used to assess the certainty and strength of the body of evidence.⁵⁷

Discussion

This systematic review and meta-analysis will summarise the scientific literature and determine the overall effectiveness of dietary interventions for the prevention and treatment of

wounds in those living with diabetes. The findings from this systematic review will help inform clinicians and healthcare services on the most effective dietary interventions to optimise wound healing in those with diabetes, whilst emphasising the importance of dietetic input in the care cycle for this population. The results also have the potential to influence wound clinicians' practice for this population and the need to consider nutrition in clinical assessment and subsequent dietitian referral. The findings will postulate appropriate design for future trial designs in this field. Moreover, this systematic review may also highlight the paucity of dietary interventions in those living with a DFU, and emphasise the need for more high quality research in this critical area of patient care.

Conflict of interest

The authors declare no conflicts of interest.

Ethics statement

An ethics statement is not applicable.

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Author contribution

HRD, PET and CEC designed the systematic review protocol. The search strategy was developed within the research team and with assistance from a senior research librarian with experience in health and medical research.

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