TITLE: Compression Therapy in Diabetic Foot Ulcer Management: A Review of Clinical Effectiveness, Cost-effectiveness and Guidelines

DATE: 15 October 2014

CONTEXT AND POLICY ISSUES

The rising prevalence of diabetes mellitus (DM) and associated complications represent a global public health care problem and financial burden.[1,2] The estimated prevalence of DM in Canada was 6.8% (2.4 million) in 2009, a 230% increase from estimates in 1998. Increasing prevalence and associated costs to Canada's publically funded healthcare system is projected to continue. As of 2010 the estimated economic burden of DM and its complications in Canada was $12.2 billion.[3] The most common chronic complication of DM is diabetic foot ulcers (DFUs), with a prevalence of four to ten percent among DM patients.[1,4] Several factors predispose DM patients to DFUs including long duration of diabetes, trauma, infection, poor glycemic control, improper footwear, old age, smoking, low socioeconomic status, and psychological factors, however neuropathy and peripheral vascular disease (PVD) may be the most significant causative factors.[1] The presentation of DFUs varies considerably with underlying pathogenesis and with the presence or absence of infection and ischemia. Along with serious complications including wound infection, osteomyelitis, and cellulitis, DFU patients also suffer from complications associated with DM including nephropathy, retinopathy, ischemic heart disease, and cerebrovascular disease. Furthermore, the potentially preventable endpoint of untreated DFU is amputation, which is itself associated with immense social and psychological consequences, in addition to significant morbidity, mortality and financial impact on healthcare.[1,2]

Local circulation is an essential requirement for efficient wound healing, providing sufficient oxygen and nutrient delivery.[5] Therefore it is possible that compression therapies can improve local circulation and improve clinical outcomes for patients with DFUs, as has been demonstrated for other wound types.[5,6] Compression therapies apply controlled external pressure to promote local circulation by simulating vasodilation or reduction of venous congestion and edema.[5,7] The controlled external pressure is applied using bandages, specialized stockings, or inflatable garments. Intermittent pneumatic compression (IPC) is a compression therapy utilizing sleeves that are inflated to a defined pressure before being deflated, simulating the effect of walking and weight-bearing on the venous system.[5] A related treatment called compressed air massage utilizes a stream of compressed air directly on the

affected area and may have similar local circulation effects.[8] However, DFUs are a unique wound type and are often accompanied by contraindications for compression therapy including ischemia and peripheral vascular disease (PVD).[3,6]

The purpose of this report is to retrieve and review existing clinical efficacy evidence for compression therapy in the treatment of DFUs. Additionally this report aims to retrieve and review evidence for compression therapy cost-effectiveness, and to retrieve and review the existing compression therapy guidelines for the treatment of DFUs

RESEARCH QUESTIONS

1. What is the clinical effectiveness of compression therapy for the treatment of diabetic foot ulcers?

2. What is the cost-effectiveness of compression therapy for the treatment of diabetic foot ulcers?

3. What are the evidence-based guidelines regarding compression therapy for the management of diabetic foot ulcers?

KEY FINDINGS

The identified evidence suggests that intermittent compression therapy and compressed air massage may offer superior clinical outcomes for the treatment of diabetic foot ulcers. Conclusions are limited by the available evidence. One good quality randomized clinical trial and one randomized clinical trial with significant methodological limitations are the source of the evidence included in two SRs and one set of guidelines identified in this report. More evidence, including data on the frequency and type of adverse events in this patient population, is required to more accurately evaluate the benefits and harms of compression therapy. No cost-effectiveness evidence was identified for the use of compression therapy treatment of diabetic foot ulcers. One set of guidelines was identified that provided an evidence statement for the efficacy of compression therapy of diabetic foot ulcers but did not formulate an evidence-based recommendation.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014 August, Issue 8), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was limited to English language documents published between Jan 1, 2009 and August 19, 2014.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications for relevancy and then evaluated the full-text publications for inclusion, according to selection criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Adults (18+) with diabetic foot ulceration in a hospital or community care setting.
Intervention	Lower leg compression using bandages, compressed air massage, specialized stockings or inflatable garments (intermittent pneumatic compression).
Comparator	Standard care with no compression.
Outcomes	Foot ulcer healing rate (% healed), time to healing, wound size, formation of granulation tissue, lower limb amputation. Costs, cost-effectiveness Clinical guidelines on management of foot ulcers for people with diabetes.
Study Designs	Health Technology Assessments (HTA)/ Systematic review (SR)/ Meta-analysis (MA); Randomized controlled trials (RCTs); Economic evaluations; and Evidence-based Guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications, or were published prior to 2009. Ulcers of different etiology (e.g. venous leg ulcers) and other lower limb conditions (e.g. chronic edema) were not within the scope of this report, and studies focusing on these conditions were excluded.

Critical Appraisal of Individual Studies

The quality of the included systematic reviews (SR) were assessed using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool.[9] Critical appraisal of the included guideline used the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument,[10] and was also examined using the AMSTAR tool as the guidelines contained a comprehensive SR.[11] Instead of assigning a numerical score, strengths and limitations were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

Following the literature search, as outlined in the literature search strategy, 94 citations were initially identified. Titles and abstracts were screened for potential relevance and 88 citations were excluded. Full text of the remaining six articles were retrieved along with nine articles that were identified and retrieved from grey literature. Of the 15 full-text articles examined 12 were excluded; eight studies examined an irrelevant population, and four studies examined an irrelevant intervention.

After this selection, two systematic reviews and one set of guidelines met the inclusion criteria for this report. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart describes the section procedure of the studies included in this review

(Appendix 1).[12] Each SR identified one different relevant RCT.[5,13] The guidelines identified both of these RCTs examining the use of compression to treat DFU.[11] No evidence for the cost-effectiveness of compression therapy for the treatment of DFU was identified.

Summary of Study Characteristics

Clinical Effectiveness

Characteristics of the included SRs are tabulated in Appendix 2, Table A2.1

Study design

The identified SRs both include an examination of the use of compression therapy for DFU but have a different overall focus. The most recent SR, published in 2012, focuses on the different treatment options available for DFU.[13] This SR identified one relevant open-label RCT conducted in Durban, South Africa.[8] The other SR was published in 2009 and focuses on pneumatic compression therapy for the treatment of chronic ulcers.[5] This SR identified a different relevant trial, a double-blinded RCT, conducted in Texas, USA.[7]

Population

Patients in the relevant RCT included in the SR that focused on DFU had post-operative DFU over 2500 mm^2.[13] There were 60 patients in this trial with infected, non-ischemic foot ulcers with at least one pedal pulse palpable.[8] The other SR examined the clinical evidence for IPC therapy of venous ulcers, chronic arterial ulcers, and DFU.[5] The relevant RCT included in this SR examined 97 patients with foot infections requiring incision and debridement. Descriptive trial participant characteristics were tabulated in this study and included age, sex, ethnicity, duration of diabetes, glycosylated hemoglobin level (HbA1C), vibration perception threshold, transcutaneous oxygen tension, and wound size. HbA1C levels averaged over 9% in both treatment groups. Inclusion criteria did not mention PVD or relevant characteristics, such as ankle-brachial index (ABI). Average transcutaneous oxygen tension measurements were presented, the intervention group had 42.0 ± 13.9 mm Hg while the placebo group had 50.8 ± 23.2 mm Hg, however the significance or relevance of this data was not mentioned.[7]

Interventions and Comparators

In addition to the RCT on compression therapy, the SR focused on DFU[13] also examined studies of other interventions including debridement, wound bed preparation, resection of the chronic wound, hyperbaric oxygen therapy, negative pressure therapy, hydrogels, cells, skin grafts, lasers, shockwaves, and ultrasound. The specific intervention of the RCT on compression therapy consisted of compressed air massage at 100kPa for 15-20min for five days per week along with standard wound care (SWC). The compressed air stream was stroked over an affected area through an applicator head providing a superficial effleurage massage. The comparator group received only SWC which included antibiotics, appropriate insulin infusion, strict bed rest, daily lavage of the wounds with saline, and antiseptic cream dressings.[8] The other SR examined IPC in the relevant RCT, however it also identified evidence for sequential pneumatic compression, and cardiosynchronous intermittent pneumatic compression in other patient populations.[5] The intervention of the relevant RCT included in this SR was a pulsatile pneumatic foot compression system (Kinetic Concepts Inc., San Antonio TX). This system rapidly inflates a bladder to 160mm Hg for two seconds to empty the veins of the foot,

and the cycles is repeated every 20 seconds for eight hours a day. A nonfunctioning device was used as a comparator with all lights, audible alerts, and programming indicators identical to the functional device. The comparator foot wrap was fenestrated as to not impart compression. The authors stated that the patients had moderate to severe peripheral neuropathy and were not generally able to feel whether they were receiving the intervention.[7]

Outcomes

Both SRs specified primary clinical outcomes in their inclusion criteria. Both SR included healing, time to healing, or amputation.[5,13] The most recent SR also specified that reduction in ulcer area outcomes were part of the inclusion criteria.[13] The relevant randomized controlled trial (RCT) from this SR reported time to heal, the number receiving skin grafts, and amputation outcomes.[13] The relevant RCT included in the SR from 2009 reported healing efficacy, edema reduction, compliance, and compliance related efficacy.[5]

Guidelines and Recommendations

Included guideline characteristics are tabulated in Appendix 2, Table A2.2

Origin of Guidelines

The identified guidelines originated from the School of Population Health and Clinical Practice, University of Adelaide, Australia in 2011.

Interventions

These guidelines also included an SR and had a very broad focus on diabetic foot complications including prevention, identification, and treatment of DFU. This SR examined a large number of intervention categories including systemic therapeutic drugs, drugs that improve immune function, surgical interventions, human growth factors, hyperbaric oxygen therapy, negative pressure wound therapy, nutritional supplements, debridement, skin replacement therapies, radiowave or electric therapy, orthotics, topical treatments, and prevention.[11] The RCTs identified in these guidelines were also identified by the SRs included in this report.[5,7,8,11,13] The interventions examined in these RCTs were a pulsatile pneumatic foot compression system (Kinetic Concepts Inc., San Antonia, TX) and compressed air massage.[7,8]

Grading of Recommendations and Levels of Evidence

The University of Adelaide guidelines grade recommendations from A to D with supporting levels of evidence ranked I to IV. More detail on the scheme used to assign levels of evidence and grades of recommendations for the included guideline is provided in Appendix 3, Table A3.1.

Summary of Critical Appraisal

Neither of the included SRs assessed publication bias, had a list of excluded studies, reported potential conflicts of interest (COIs) of included studies, or mentioned adverse events of compression. The strengths of both SRs were a description of a comprehensive literature search strategy with explicit inclusion and exclusion criteria, and tabulated study characteristics including aspects of trial quality.[5,13] The most recent SR also had a statement of no COI, a

quantitative assessment of study quality, an examination of the risk of bias, and also searched Russian, Chinese, and Spanish language literature.[13] The SR from 2009 did not include a COI statement, or mention patient characteristics of the included studies.[5] Each SR identified one relevant RCT. Neither identified both RCTs because of the defined date limitations of each SR literature search. A summary of the critical appraisal of the included SRs using the AMSTAR tool is available in Appendix 4, Table A4.1.[9]

The most recent SR, Game et al. (2012),[13] identified an RCT published in 2008 by Mars et al.[8] The methodological quality of this RCT was evaluated and the study was translated into a level of evidence designated as 1- using the Scottish Intercollegiate Guidelines Network instrument. The tabulated quality descriptions relevant to the quality of the RCT were that it was an open label trial, did not include the method of randomization, there was no data on the actual healing incidence, there was no baseline data on neuropathy or arteriopathy, and results were reported for 57 of 60 patients.[13] One patient in each group died of a myocardial event during the trial and one patient in the treatment group was lost to follow-up after discharge.[8] Methodological quality descriptions, were also given for the RCT included in the other SR.[5,7] The RCT was described as having allocation by computer generated table, being double-blinded, and not using intention to treat (ITT) analysis.[5]

The included guidelines were comprehensive despite a broad focus on DFU and comprise a document of over 1700 pages. Recommendations were graded and associated with a supporting level of evidence. The methodology was described including guideline development, guideline implementation, statistical methods, database and grey literature searching, and literature selection. Additionally, publication bias was assessed for a variety of interventions, a meta-analyses was provided, statistical heterogeneity was tested, risk of study bias was assessed, a list of excluded studies with reasons for exclusion was provided, and adverse events were examined. Despite the length of the guideline document, extracting information of interest was facilitated by providing a literature selection flowchart, and predefined questions using PICO to structure the guidelines.[11]

The guidelines also provide a critical appraisal of the two included relevant RCTs.[7,8,11] The RCT by Armstrong et al., published in 2000 was described as an RCT that used computer generated randomization, found no statistically significant differences in patient characteristics between study arms, and blinding methods were described and appropriate. The guidelines reported that patients were lost to follow-up and an ITT analysis was used, however examination of the RCT indicated that, as described in the SR reviewing this study, no ITT analysis was conducted.[5,7] The guideline authors describe the trial as “A well designed and conducted study.” (pp. 1590) The RCT by Mars et al.,[8] published in 2008 was not evaluated as positively. The guideline authors noted that there was no patient exclusion criteria, the method of randomization was not given, it was not a blinded trial, and ITT analysis was not applied. This RCT was rated as poor to moderate external applicability due to the lack of exclusion criteria and general inclusion criteria without a description of the recruitment process.[11]

Summary of Findings

Major findings and author’s conclusions regarding the clinical effectiveness evidence of compression therapy for DFUs are summarized in Appendix 5, Table A5.1.

Evidence from two RCTs, examined by two SRs and one set of guidelines included in this report, suggest that IPC and compressed air massage improve clinical outcomes for DFU

patients. One RCT, examining compressed air massage, found a significant reduction in the time to healing, but not in numbers receiving skin grafts or amputation rates. The average time to DFU healing was 58.1 days in those patients receiving compressed air massage, while those patients receiving only standard wound care averaged 82.7 days until ulcer healing.[11,13] Time to healing was also significantly faster in treated patients who underwent skin grafting or amputation compared to untreated patients in these subgroups.[8] The other RCT found a significant increase in healing efficacy and that this efficacy also had a statistically significant dependence on patient compliance with IPC therapy. After 12 weeks of therapy, 75% of patients receiving IPC had healed DFUs whereas only 51% of patients receiving the sham treatment were healed. In patients defined as compliant, (patients undergoing 50+ hours of compression therapy weekly), 100% of patients had healed DFUs at 12 weeks. There was no statistically significant difference in compliance, as defined previously, between treatment and placebo groups and averaged 20%.[7] This RCT also found that significant edema reduction was achieved in the study arm receiving IPC therapy.[5,11]

No relevant cost-effectiveness evidence was identified.

While the identified guidelines included an SR to examine the clinical effectiveness of compression therapy of DFU no relevant evidence-based guidelines were formulated.[11] Although not an evidence-based recommendation, an evidence of Grade C was given to the statement, "The evidence suggests that foot compression in addition to standard wound care is more effective for healing of infected diabetic foot ulcers than standard care alone." These guidelines identified the same evidence, from two RCTs, as identified in the two SRs. In these guidelines, the RCT also included in the most recent SR was noted as not observing any benefits of compression massage in the rate of amputation, only the time to healing without considering those patients lost to follow-up. This study was not used to support the evidence statement due to insufficient quality. The other RCT was of higher quality and used to support the evidence statement. The guidelines states that this trial demonstrated good external validity and that IPC is shown to have a significant and clinically important advantage over the non-functioning placebo device.[11]

Limitations

No convincing consensus on the clinical effectiveness of compression therapy for the treatment of DFUs was identified because only data from one good quality trial was identified. This trial did not quantify or mention any adverse event outcomes.[6] Identified evidence was limited to IPC therapy and compressed air massage, no evidence was available on other compression therapy interventions for DFU treatment. No cost-effectiveness data or evidence-based recommendations were identified for compression therapy of DFUs.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

All identified evidence suggests that compression therapy may improve clinical outcomes for DFUs. Statistically significant improvements in clinical efficacy outcomes were observed in DFU patients receiving compressed air massage or IPC therapies over standard care or sham compression, respectively.[5,13] This evidence was from one good quality RCT, examining IPC, and one RCT with significant limitations that examined compressed air massage. IPC was observed to increase DFU healing efficacy and reduce edema, however patient compliance was approximately 20%.[7] Compressed air massage demonstrated a statistically significant reduction in time to heal as compared to SWC.[8] PVD is a common co-morbid condition of DFU patients,

and is also a contraindication for compression therapy.[6,11] None of the identified evidence examines PVD in trial participants. The good quality RCT did not report any data on adverse events. These disadvantages of the included evidence limit the ability to weigh the balance of benefits and harms for this DFU treatment option. Additional trials examining the use of compression therapy, and its safety profile, for the treatment of DFUs are warranted as the limited evidence suggests it may provide significant clinical benefits.

No cost-effectiveness data was identified for the use of compression therapy treatment of DFUs.

The identified guidelines found grade C evidence to support compression therapy as providing superior clinical effectiveness outcomes for DFU patients. The guidelines do not provide any evidence-based recommendations for compression therapy treatment of DFUs, however the identified guidelines state that the evidence suggests that foot compression with SWC is more effective for healing DFU than SWC alone.[11]

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LIST OF ABBREVIATIONS

AGREE II	Appraisal of Guidelines for Research and Evaluation
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
COI	conflict of interest
DFU	diabetic foot ulcer
DM	diabetes mellitus
IPC	intermittent pneumatic compression
NR	not reported
PICO	population, intervention, comparator, outcomes
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PVD	peripheral vascular disease
RCT	randomized controlled trial
SD	standard deviation
SR	systematic review
SSD	statistically significant difference
SWC	standard wound care

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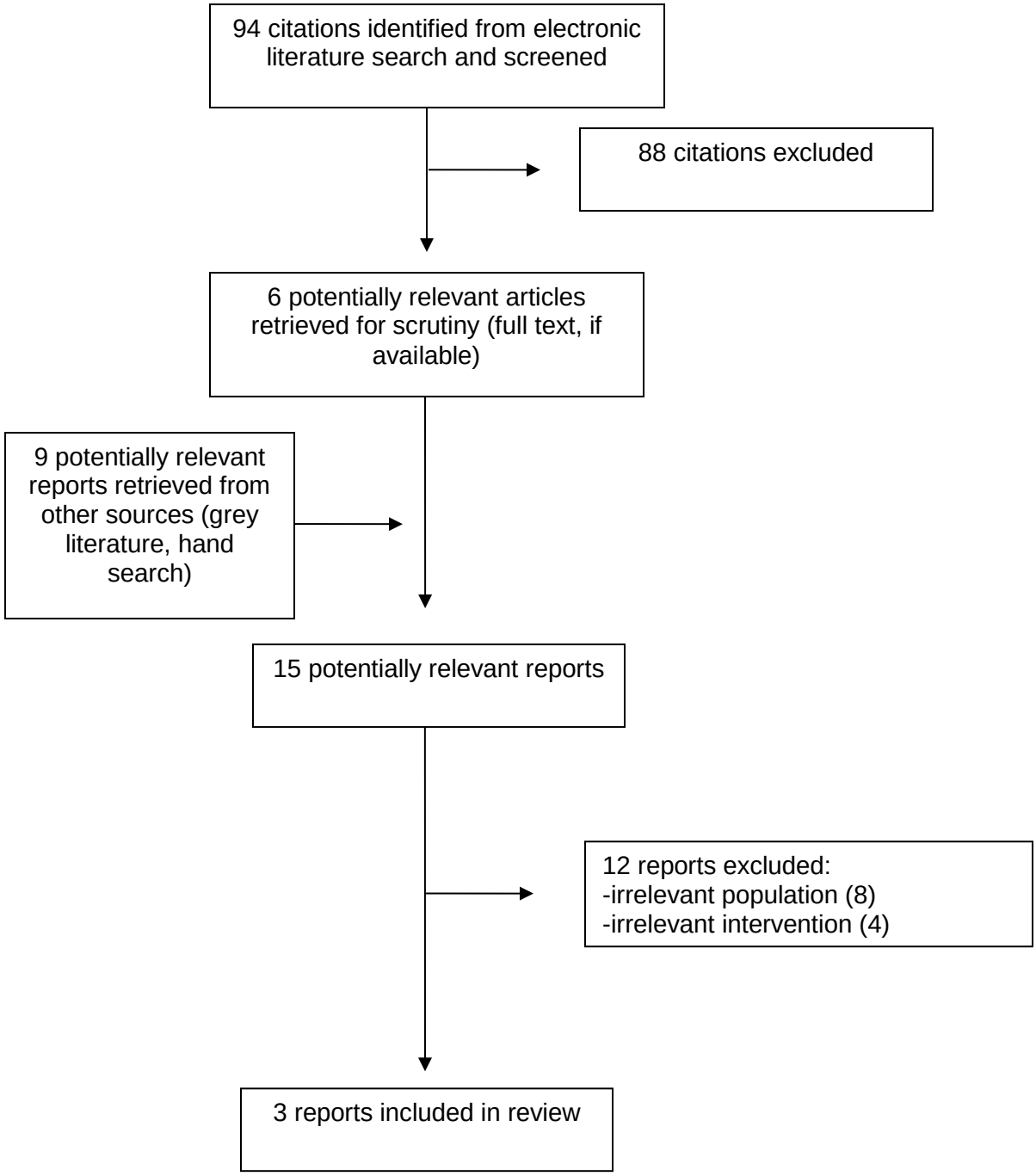
APPENDIX 1: Selection of Included Studies



APPENDIX 2: SUMMARY OF STUDY CHARACTERISTICS

Table A2.1: Summary of Study Characteristics of Included SRs

Study Design	Population (sample size of RCT)	Intervention (of RCT)	Comparator(s) (of RCT)	Outcomes
Game et al., 2012[13]				
SR: DFU (1 open label RCT[8])	DFU (n = 60)	Compressed air massage at 100kPa for 15-20min, 5 days/week. Other treatment as per comparator	SWC with antibiotics and insulin infusion.	• Time to healing • Number receiving skin grafts • Amputations
O'Sullivan-Drombolis et al., 2009[5]				
SR: Pneumatic compression (1 double-blind RCT[7])	DFU (n=97)	IPC 160mm Hg max over 2 seconds, 8 hours per day	IPC sham	• Healing efficacy • Edema reduction • Compliance (defined as 50+ hours weekly)

DFU=diabetic foot ulcer; **IPC**=intermittent pneumatic compression; **RCT**=randomized clinical trial; **SR**=systematic review; **SWC**=standard wound care

Table A2.2: Summary of Study Characteristics of Included Guideline

Origin, Publication Year	Interventions of Interest	Grading (See Appendix 3)	Target Users
University of Adelaide, 2011[11]			
School of Population Health and Clinical Practice, University of Adelaide, Australia, 2011	Compression	Levels of Evidence I – IV Recommendations Graded A -D	NR
NR=not reported			

APPENDIX 3: Summary of Guideline Grading and Recommendations and Levels of Evidence

Table A3: Guideline Grading of Recommendations and Levels of Evidence

Recommendation	Levels of Evidence
University of Adelaide, 2011[11]	
A Level **I** (n≥1) or Level **II** (n≥2) with a low risk of bias **B** Level **II** (n≤2) with a low risk of bias or SR or several level **III** studies with low bias risk **C** Level **III** (n≤2) with low bias risk or Level **I** or **II** studies with moderate bias risk **D** Level **IV** (n≥1) or Level **I** – **III**, SRs with high bias risk **EO** Expert Opinion	**I** SR of Level **II** studies **II** RCT **III-1** pseudo-randomized controlled trial **III-2** non-RCT, cohort study, case-control study, interrupted time series with control group **III-3** historical control study, two or more single arm studies, or interrupted time series without parallel control group **IV** Case series
RCT=randomized clinical trial; **SR**=systematic review	

APPENDIX 4: Summary of Critical Appraisal

Table A4.1: Critical Appraisal Summary for the included SR using AMSTAR tool[9]

Strengths	Limitations
Game et al., 2012[13]	
• Statement of no COI • Literature search selection/inclusion/exclusion methodology described • Study quality assessed quantitatively • Study heterogeneity mentioned • Detailed tabulated study characteristics and results • Patient characteristics of included studies discussed in context • Risk of bias examined • Searched Russian, Chinese and Spanish language literature	• No mention of potential COI of included studies • No assessment of publication bias • No list of excluded studies • No mention of adverse events • Only one relevant RCT identified
O'Sullivan-Drombolis et al., 2009[5]	
• Literature search selection/inclusion/exclusion methodology described • Tabulated study characteristics and results • Aspects of methods tabulated indicating quality and potential for bias	• No COI statement • No mention of potential COI of included studies • No assessment of publication bias • No list of excluded studies • No mention of adverse events • Only one relevant RCT identified • No mention of patient characteristics
COI=conflict of interest; **RCT**=randomized controlled trial;	

Table A4.2: Critical Appraisal Summary for Guidelines using the AGREE II tool[10] and the AMSTAR tool[9]

Strengths	Limitations
University of Adelaide, 2011[11]	
• Graded recommendations • Grades of recommendations associated with a level of evidence • Guideline development methodology described • Recommendation implementation discussed • Literature search selection/inclusion and exclusion methodology detailed • Publication bias statistically examined • PRISMA flowchart • List of excluded studies and reason for exclusion • Predefined questions and PICO • Risk of bias of included studies assessed • Statistical methods described • Meta-analyses provided, statistical heterogeneity tested • Examination of adverse events	• Very broad scope and with broad research questions • No COI statement • Only two relevant RCTs identified
COI=conflict of interest; **PICO**=population, intervention, comparator, outcomes; **PRISMA**=Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **RCT**=randomized controlled trial;	

APPENDIX 5: Summary of Findings

Table A5.1: Summary of Main Findings and Author's Conclusions of the SR

Main Findings		Author's Conclusions
Game et al., 2012[13]		
From Mars et al., 2008[8]		"The results suggested a significant reduction in time to healing in the intervention group, but the study was non-blinded and of low methodological quality." (pp. 122)
Time to healing (p = 0.001)	
Compressed air massage	58.1 ± 22.3 days
SWC	82.7 ± 30.7 days
Numbers receiving skin grafts - no SSD	
Compressed air massage	9/28
SWC	10/29
Amputations - no SSD	
Compressed air massage	14/28
SWC	15/29
O'Sullivan-Drombolis et al., 2009[5]		
From Armstrong et al., 2000[7]		"A well designed RCT also demonstrated greater oedema reduction and faster healing of diabetic foot ulcers compared to sham controls." (pp. 81)
Healing Efficacy at 12 weeks (p < 0.005)	
IPC	39/52 (75%)
IPC sham	23/45 (51%)
Edema Reduction (foot circumference ± SD) (p < 0.001)	
IPC	from: 28.3 ± 3.2 cm to: 23.8 ± 1.9 cm
IPC sham	from: 28.1 ± 4.3 cm to: 25.7 ± 2.7 cm
Compliance defined as 50+ hrs weekly (n/N (% healed at 12 weeks)	
IPC compliant	11/52 (100%)
IPC noncompliant	41/52 (68%)
IPC sham compliant	9/45 (56%)
IPC sham noncompliant	36/45 (50%)
SSD: IPC compliant vs IPC noncompliant (p < 0.005)	
SD=standard deviation; **SSD**=statistically significant difference; **SWC**=standard wound care		

Table A5.2: Summary of Recommendations by Source (see Appendix 3 for grading schemes).

University of Adelaide, 2011[11]
No relevant evidence based recommendations were formulated Evidence Grade C "The evidence suggests that foot compression in addition to standard wound care is more effective for healing of infected diabetic foot ulcers than standard care alone." (pp. xxxii)