

# **Part 6**

## **Identification & Management of Diabetic Foot Disease**

## 6.0 Foot Disease Expert Working Group

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# 6.1 Guideline for the Identification & Management of Diabetic Foot Disease in Type 2 Diabetes

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## 6.1.1 Introduction

### **Aim of the guideline**

This guideline covers issues relating to how diabetic foot disease should be defined, assessed and managed in people with Type 2 diabetes. Its aim is to inform all categories of health professionals of the problems associated with diabetic foot disease and to specifically target general practitioners with this information.

### **Quality Assurance**

In addition to the methods used to identify and critically appraise the evidence to formulate the guideline recommendations which are described in detail in *Part 1* of this document, the Project Management Team reviewed and checked each step of the methods process and:

- repeated a selection of the searches
- double culled the yield from a selection of the database searches
- double reviewed all articles used as evidence references
- checked all recommendations, evidence statements, evidence tables and search strategy and yield tables

The draft document was reviewed by an independent clinical diabetologist and, as a further quality measure the Medical Adviser reviewed the entire final draft in detail.

### **Guideline Format**

Issues identified by the EWG and from the literature as critical to the impact of diabetic foot disease in Type 2 diabetes are shown in point 6.1.2 (next page).

*Each of these issues* is addressed in a separate section in a format presenting:

- **Recommendation(s)**
- **Evidence Statements** - supporting the recommendations
- **Background** - to issues for the guideline
- **Evidence** - detailing and interpreting the key findings
- **Summary** - of major evidence found
- **Evidence tables** - summarising the evidence ratings for the articles reviewed

*For all issues combined*, supporting material appears at the end of the guideline and includes:

- **Evidence references**
- **General references**
- **Other references identified**
- **Search Strategy and Yield Tables** documenting the identification of the evidence sources

## 6.1.2 Issues for Diabetic Foot Disease in Type 2 Diabetes

- Is peripheral neuropathy a risk factor for ulceration or amputation?
- Is peripheral vascular disease a risk factor for ulceration or amputation?
- Is deformity, including a previous amputation, a risk factor for ulceration or amputation?
- Is previous or current ulceration a risk factor for amputation?
- What is the most practical method for detecting loss of protective foot sensation in the primary care setting?
- How should peripheral vascular disease be assessed clinically?
- What should be the frequency of foot examination?
- Does patient education improve footcare and outcomes?
- Does improved glycaemic control decrease the incidence of peripheral neuropathy?
- Does appropriate footwear reduce ulceration and amputation?
- Do specialist foot clinics and multi-disciplinary teams decrease amputation?

### 6.1.3 Summary of Recommendations

| <b>Recommendations</b>  |
|---|
| <ul style="list-style-type: none"><li>• People with Type 2 diabetes who have peripheral neuropathy should be identified because they are at risk of subsequent foot ulceration and amputation</li></ul>   |
| <ul style="list-style-type: none"><li>• People with diabetes should be assessed regularly for peripheral vascular disease</li></ul>   |
| <ul style="list-style-type: none"><li>• People with diabetes should be assessed regularly to detect foot deformities including:<ul style="list-style-type: none"><li>• Hallux deformities</li><li>• Hammer or claw toes</li><li>• Callus</li><li>• Charcot's foot</li><li>• Previous minor amputation</li></ul></li></ul> <p>People with diabetic neuropathy and foot deformities should employ measures to reduce excessive foot pressures (eg podiatry treatment, therapeutic footwear) to prevent ulceration and amputation.</p> |
| <ul style="list-style-type: none"><li>• Diabetic people with a current foot ulcer should be identified as a high risk group for possible amputation: more regular monitoring and preventative interventions to lower that risk should be instituted promptly in this group</li><li>• The history of a healed previous diabetic foot ulcer should be recognised as an indicator of life long increase in risk of recurrent ulceration and amputation</li></ul>   |
| <ul style="list-style-type: none"><li>• People with Type 2 diabetes should be regularly assessed with the 10g Semmes-Weinstein monofilament to detect loss of protective foot sensation</li></ul>   |
| <ul style="list-style-type: none"><li>• People with diabetes should be assessed for peripheral vascular disease by:<ul style="list-style-type: none"><li>• enquiring about symptoms of intermittent claudication</li><li>• palpation of pedal pulses</li></ul></li></ul>  |
| <ul style="list-style-type: none"><li>• The routine surveillance for foot problems in people with diabetes should be performed in the following way:<ul style="list-style-type: none"><li>• in people where no foot complications have previously been found, the minimum frequency of foot examination should be once a year</li><li>• in people with at risk feet but without a current active problem, foot examination should be performed every 3 to 6 months</li></ul></li></ul>  |

- People with diabetes at increased risk of foot problems should receive specific footcare education

- Aim to achieve the best possible glycaemic control in people with Type 2 diabetes in order to prevent or reduce the development of peripheral neuropathy which is a major risk factor for foot ulceration and amputation

- People with diabetes should be encouraged to wear properly fitted, cushioned footwear and padded socks
- People with diabetes and high risk feet require special attention to footwear

- People with diabetes who have foot ulcers or with high risk feet should be cared for by a multi-disciplinary service which should include at least a physician and podiatrist and have ready access to a specialist nurse, orthotist and surgeon

## 6.1.4 Overview of Foot Problems in Diabetes

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The most common reason for hospital admission for diabetes is a diabetic foot complication (Young et al, 1993). People with diabetes are more likely to have an amputation than those without diabetes: 3-fold more likely at age 45-74 and 7-fold for people aged over 75 (Reiber, 1993). About half those having a leg amputation will have a subsequent amputation one on the other side (Apelqvist et al, 1993). Half of all non-traumatic amputations are performed in people with diabetes (Pecoraro et al, 1990). Almost all amputations are preceded by an ulcer. Peripheral neuropathy, with or without peripheral vascular disease, is a major underlying risk factor in people with diabetes developing a foot ulcer. About half of the lower extremity amputations are “major” (below or above knee), while the other half involving the foot or toes are designated “minor”. In Australia there are at least 2600 diabetes-related lower limb amputations each year (Payne, 2000). The Australian National Diabetes Information Audit and Benchmarking (ANDIAB) 2000 survey showed that 24% of people with diabetes attending specialist diabetes centres had peripheral neuropathy, 13% had peripheral vascular disease, 3% had a foot ulcer, 2% had had an amputation in the past and the annual incidence of lower limb amputation was 0.7% (NADC, 2000).

The St Vincent Declaration called for a 50% reduction in amputation from diabetic gangrene (Krans et al, 1992) and a similar target has been advocated for Australia (Colagiuri S et al, 1998). To achieve this goal, the identification of diabetic people who are at increased risk of subsequent amputation is a major priority. Health professionals require adequate knowledge and resources to identify those at risk and to implement those strategies which have been shown to prevent subsequent morbidity in this population. While the impact of education of the “at risk” person with diabetes in preventing amputation has not been fully evaluated, it is clearly time for application of current knowledge about patient empowerment regarding self care and for further research to be implemented. With the rapid increase in the incidence of diabetes in Australia and a finite supply of trained personnel it is appropriate to appreciate the current status of evidence regarding the role of a multi-disciplinary team as a basis to make recommendations for future practice in these areas. The need for further work to answer questions such as what are the minimum resources needed to provide an effective diabetic foot service, is highlighted. There is also a major need to assess and compare the outcomes in an Australian setting of implementing differing approaches to making knowledge, trained personnel and adequate resources available to all those who are at risk of diabetic foot complications.

This guideline has adopted the following definitions to describe risk categories for diabetic foot problems:

- “at risk” – people with
- neuropathy or
  - peripheral vascular disease or
  - foot deformity
- ‘high risk’ – people with
- foot deformity with neuropathy or peripheral vascular disease
  - previous ulcer
  - previous amputation

## 6.1.5 Recommendations

# Section 1: Diabetic Foot Disease

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### Issue

Is peripheral neuropathy a risk factor for ulceration or amputation?

### Recommendation

People with Type 2 diabetes who have peripheral neuropathy should be identified because they are at risk of subsequent foot ulceration and amputation.

### Evidence Statements

- Peripheral neuropathy precedes diabetic foot ulceration  
*Evidence Level II<sup>#</sup>*
- Peripheral neuropathy predicts diabetic foot ulceration and amputation  
*Evidence Level III<sup>#</sup>*
- Other factors contribute to the increased risk of ulceration and amputation in diabetic people with peripheral neuropathy  
*Evidence Level III<sup>#</sup>*

<sup>#</sup>Studies with no intervention

## Background – Peripheral Neuropathy as a Risk Factor

Fifteen percent of people with diabetes will develop a foot ulcer during their lifetime (Reiber et al, 1998). Half of all non-traumatic amputations are performed in people with diabetes (Pecoraro et al, 1990). Foot ulcers precede 84% of all lower limb amputations in diabetic people in the United States (Pecoraro et al, 1990). While the cause of ulceration is multifactorial, understanding the primary factors in aetiology of the ulcer will enable reduction in ulceration and amputation despite the rising incidence of diabetes.

In the UKPDS study damage to the peripheral nerves from prolonged hyperglycaemia and its metabolic consequences were present in 12.3% at diagnosis and in 30% after 12 years of diabetes (UKPDS 33, 1998). The commonest form is a distal symmetrical polyneuropathy with a glove and stocking distribution of loss of sensation. It is the loss of protective sensation that is postulated to be the major factor in subsequent ulceration. Coexistence of autonomic neuropathy can contribute partly by inducing dry skin and foot oedema (Boyko et al, 1999). Muscle wasting and foot deformity resulting from peripheral neuropathy are also thought to contribute to the risk of ulceration. Severe peripheral neuropathy can lead to joint disorganisation from repeated trauma with loss of protective sensation resulting in a Charcot joint (most frequently the tarsometatarsal joint). The resulting foot disorganisation and deformity contribute to recurrent ulceration (Sims et al, 1988). However it is also clear that there are other precipitating factors resulting in diabetic foot ulcers and it is necessary to clarify the relative contribution of different risk factors. Knowing the relative risk of peripheral neuropathy as an underlying risk factor for ulceration and amputation can help in targeting those diabetic subjects who are at risk and implementing preventative interventions to reduce subsequent ulceration and amputation (Shaw & Boulton, 1997).

## Evidence – Peripheral Neuropathy as a Risk Factor

### **Peripheral neuropathy precedes diabetic foot ulceration**

Mason and coworkers (1999) published a systematic review of diabetic foot ulcer prevention including 3 prospective studies which relate sensory loss at baseline to subsequent ulceration or amputation. In a study of 406 Native American Indians, subjects were categorised using a 5.07 Semmes-Weinstein monofilament on 8 points on the plantar surface of each foot (Rith-Najarian et al, 1992). Those failing to sense the monofilament at one or more locations were retested twice before being classified as insensate. In a follow up of the cohort for 32 months, an ulcer was five times as likely to occur in a person with either a history of ulceration or amputation or loss of sensation, than in a person without. Comparing those with sensory loss to those without provided a test sensitivity of 90% and specificity of 86% for predicting ulceration with likelihood ratios for a positive test of 5.2 (95% confidence interval (CI) 4.0-6.7) and 0.12 (CI 0.05-0.27) for a negative test. Amputation risk was increased 17 times (CI 4.5-9.5).

A diabetes foot clinic in Manchester used a biothesiometer to categorise subjects without previous ulcer or significant ischaemia at enrolment (Young et al, 1994). In up to 4 years of follow up, using a biothesiometer threshold of > 25 V, the test sensitivity for developing a first ulcer was 83% with a specificity of 62% with likelihood ratio for a positive test of 2.2 (CI 1.8-2.5) and for a negative test of 0.27 (CI 0.14-0.48). In these 469 subjects with both Type 1 and Type 2 diabetes without previous ulceration, a vibration perception threshold (VPT) > 25V increased ulceration by 7.99 times (CI 3.65-17.5;  $p < 0.01$ ) compared with people who had a

VPT < 15V. Recurrent ulceration only occurred in those with VPT > 25V, who had a cumulative 4-year ulcer incidence of 19.8% or 8.3% per year (Young et al, 1994).

Abbott et al (1998) prospectively investigated the incidence of foot ulcer over one year in 1033 people with Type 1 or Type 2 diabetes with established neuropathy (VPT  $\geq$  25 V on at least one foot and VPT  $\geq$  50 V on both feet). For each 1 unit increase in VPT at baseline the risk of ulcer increased by 5.6% and a VPT > 25 V carried a sevenfold risk of ulceration over 4 years. Abnormal VPT carried a 7% annual risk of foot ulcer (Abbott et al, 1998).

In addition to the evidence from the prospective studies, other studies have also shown that peripheral neuropathy is an independent risk factor for ulceration. Coppini et al (1998) reported the incidence of foot ulcers or amputations in 405 subjects attending St Thomas' Diabetic Clinic without prior amputation. The records were examined retrospectively, and 20 people who developed foot ulcer or amputation over the 14 year follow-up period were each matched with 3 people without ulcers. A raised vibration perception threshold at baseline was a predictor of foot complications developing with OR 4.38 (CI 1.1-17.26,  $p=0.01$ ) while abnormal clinical neurological findings gave an OR 2.3 (CI 1-5.2,  $p<0.01$ ). The sensitivity of VPT (70%) was better than that for clinical examination (55%), although there was similar specificity (70-27%) (Coppini et al, 1998).

In 811 people with Type 2 in a community based study from 37 UK general practices, neuropathy was diagnosed by clinical scoring. Those with neuropathy were significantly more likely to have a current or past ulcer than those without (9.8% versus 2.1%  $p < 0.01$ ). However, only 48% of eligible patients were included in the study and some bias may be present (Kumar et al, 1994). A United States case control study enrolled 76 diabetic subjects with ulceration and 149 control diabetic subjects who had never had a foot ulcer. In multivariate analysis loss of protective sensation (VPT  $\geq$  25 V) had an OR of 32.5,  $p < 0.001$  for ulceration. (Lavery et al, 1998). In a study confined to people with Type 2 diabetes, 352 had foot lesions assessed using the Seattle wound classification system. Monofilament testing and thermal sensitivity testing were used to identify neuropathy. In this predominantly African-American female group, in multivariate modelling, neuropathy predicted both minor wounds and major ulceration, OR 5.23 (CI 2.26-12.13)  $p < 0.001$  (Litzelman et al, 1997).

In an American mixed racial group of blacks, Hispanics, and Caucasians, Frykberg and coworkers (1998) found peripheral sensory neuropathy (by VPT or monofilament) independently predicted current or past ulceration, OR 4.1-4.4 respectively,  $p<0.001$ . However this study of consecutive clinic patients found racial differences in ulceration, which in other studies have been explained by socio-economic differences rather than race. (Frykberg et al, 1998). In another analysis from the Seattle Veterans Study, 46 subjects having an ulcer between 1987 and 1992 were compared with 322 diabetic subjects from medical clinic not having an ulcer. Both vibration sense and monofilament sensation were tested together with ankle-arm blood pressure index and transcutaneous oxygen tension (TcPO<sub>2</sub>) to assess circulation. Being insensate to the monofilament gave an adjusted OR of 18.42 (CI 3.83-88.47) for ulceration. There were two other independent predictors: the absence of Achilles tendon reflex and a low TcPO<sub>2</sub> (McNeeley et al, 1995). In a US study of 86 diabetic people with an ulcer presenting to a foot clinic in the United States were compared to 49 control patients referred to general medical clinics who had diabetes but did not have an ulcer. Abnormal vibratory perception was strongly related to diabetic foot ulceration (OR = 10.77,  $p<0.001$ ). There was a pattern of increasing odds ratio for ulceration with increasing vibration perception abnormality ( $p<0.001$  for trend). The association remained after adjustment for

confounding variables (Boulton et al, 1986). A less rigorous assessment of neuropathy was also performed in another analysis of the Seattle Veterans Study which examined patients at admission for first amputation. Again neuropathy was proposed as responsible in 61% of cases but neuropathy was estimated clinically without VPT or monofilament (Pecoraro et al, 1990).

### **Peripheral neuropathy predicts diabetic foot ulceration and amputation**

In a study of 406 Native American Indians, subjects were categorised using a 5.07 Semmes-Weinstein monofilament on 8 points on the plantar surface of each foot (Rith-Najarian et al, 1992). Those failing to sense the monofilament at one or more locations were retested twice before being classified as insensate. In a follow up of this group for 32 months, Amputation risk was increased 17 times (CI 4.5-95.0).

A prospective study in Seattle followed 776 US veterans with diabetes until first lower extremity amputation. The subjects were white males with a median age of 65, the majority had Type 2 diabetes and follow up was for a median of 3.3 years. Neuropathy assessed by insensitivity to monofilament was associated with an increased relative risk (RR) of amputation of 2.9 (odds ratio (OR) = 1.1-7.8). This study also found that peripheral vascular disease, foot ulcers, former amputation and treatment with insulin were independent risk factors (Adler et al, 1999). In this ongoing Seattle Foot Study 749 subjects have been followed with monofilament testing for a median of 3.7 years. Insensitivity to the monofilament remained an independent risk factor for foot ulcer (RR 2.2 [CI 1.5-3.1]) (Boyko et al, 1999).

A case control study in Pima Indians by Mayfield and coworkers (1996) compared the medical records of 61 subjects with amputations over a 9 year period with 183 controls having no amputation over that period. Peripheral neuropathy was one of the four major contributing risk factors (including peripheral vascular disease, bone deformity and a history of foot ulcers.) Each risk factor conveyed an OR for amputation of 2.1 (CI 1.4-3.3) (Mayfield et al, 1996).

As described above Coppini et al (1998) showed that a raised vibration perception threshold at baseline predicted foot ulceration or amputation (OR 4.38 [CI 1.1-17.26], p=0.01).

### **Other factors contribute to the increased risk of ulceration and amputation in diabetic people with peripheral neuropathy**

While peripheral neuropathy precedes, and is a major independent predictor, of diabetic foot ulceration and amputation, the path to ulceration and amputation is variable. The role of vascular insufficiency, deformity, inadequate patient education and use of inappropriate footwear are all dealt with in subsequent Sections. There are also important precipitating factors such as injury.

Some have attempted to analyse the causal pathways responsible for ulceration by mathematical methods. Reiber et al (1999) used the Rossman model of causation to examine the histories of individuals with incident foot ulcers in Manchester and Seattle between 1990 and 1994. A multi-disciplinary team examined the patient data blinded to patient identity. Peripheral neuropathy assessed by VPT or monofilament was present in 78% (Reiber et al, 1999). In 63% of cases of foot ulceration, a critical triad was present including peripheral neuropathy, foot deformity and minor foot trauma but 32 unique causal pathways were identified! Another analysis from the Seattle study by Reiber et al (1992) studied 80 consecutive diabetic male veterans in Seattle admitted for amputation where it was found that loss of vibration sense resulted in an OR for amputation of 15.5 (CI 8.3-28.7). Loss of distal

touch sensation in the 316 males, with both types of diabetes, gave a risk of amputation OR 5.1 (CI 2.6-10.2) compared with 236 diabetic male case control subjects. While pointing out multiple statistically significant risk factors for amputation from the analysis, the authors comment that while there are important underlying conditions such as sensory neuropathy, other risk factors also contribute, including the events following a minor injury to a neuropathic foot (Reiber et al, 1992).

The recurrence of foot ulceration is also associated with peripheral neuropathy in a study from the United Kingdom in which 26 diabetic subjects with relapsing ulcers had a significantly higher vibration threshold compared with 25 diabetes subjects without relapse of ulcer (VPT 38 versus 25,  $p=0.003$ ) (Mantey et al, 1999). A similar conclusion was reached in a study of 314 consecutive diabetic people referred to a Swedish department of medicine because of foot ulcers (Apelqvist et al 1990). Of these 96% had sensory and muscular disturbances of neuropathy. Neuropathy was more common in those progressing to amputation than in those not. However, consistently, as with most other studies, additional precipitating factors were again found in 84% of subjects, such as wearing ill fitting shoes or acute mechanical trauma (Apelqvist et al, 1990).

## Summary – Peripheral Neuropathy as a Risk Factor

- Prospective studies show a strong relationship between the presence of peripheral neuropathy (assessed by a biothesiometer or Semmes-Weinstein monofilament) and subsequent ulceration
- There is a similarly strong relationship between peripheral neuropathy and subsequent amputation
- Cross-sectional studies have consistently demonstrated that peripheral neuropathy is an independent risk factor for foot ulceration and amputation in people with diabetes
- The presence of peripheral neuropathy requires other permissive factors and/or a series of events (some of which may be preventable or reversible) to culminate in an ulcer or amputation
- More research is required to clarify the factors which influence the different pathways from peripheral neuropathy to ulceration and amputation

## Evidence Table: Section 1

### Peripheral neuropathy as a risk factor for ulceration and amputation

| Author   | Evidence          |        |                   |                |                  |                  |
|--|-------------------|--------|-------------------|----------------|------------------|------------------|
|  | Level of Evidence |        |                   | Quality Rating | Magnitude Rating | Relevance Rating |
|  | Level             | Rating | Study Type        |                |                  |                  |
| <b>Abbott C (1998)</b><br>(Adults – Canada; UK; US)                        | II <sup>#</sup>   | High   | Cohort            | High           | High             | High             |
| <b>Adler AI (1999)</b><br>(Adults – US)                                    | III <sup>#</sup>  | Medium | Cohort            | High           | High             | High             |
| <b>Apelqvist J (1990)</b><br>(Adults – UK)                                 | III <sup>#</sup>  | Medium | Cohort            | Medium         | High             | High             |
| <b>Boulton AJM (1986)</b><br>(Adults – US)                                 | III <sup>#</sup>  | Medium | Case-control      | Medium         | High             | High             |
| <b>Boyko EJ (1999)</b><br>(Adults – US)                                    | III <sup>#</sup>  | Medium | Cohort            | High           | High             | High             |
| <b>Coppini DV (1998)</b><br>(Adults – UK)                                  | III <sup>#</sup>  | Medium | Case-control      | Medium         | High             | High             |
| <b>Frykberg RG (1998)</b><br>(Adults – US)                                 | III <sup>#</sup>  | Medium | Cross-sectional   | High           | High             | High             |
| <b>Kumar S (1994)</b> (Adults – UK)  | III <sup>#</sup>  | Medium | Cross-sectional   | Medium         | High             | High             |
| <b>Lavery LA (1998)</b><br>(Adults – US)                                   | III <sup>#</sup>  | Medium | Case-control      | High           | High             | High             |
| <b>Litzelman DK (1997)</b><br>(Adults – US: African American, Multiethnic) | III <sup>#</sup>  | Medium | Cohort            | Low            | High             | Low              |
| <b>Mantey I (1999)</b> (Adults – UK)                                       | III <sup>#</sup>  | Medium | Cohort            | High           | High             | High             |
| <b>Mason J (1999)</b>  | I                 | High   | Systematic Review | High           | High             | High             |
| <b>Mayfield JA (1996)</b><br>(Adults – US: Gila River Indians)             | III <sup>#</sup>  | Medium | Case-control      | High           | High             | Low              |
| <b>McNeely MJ (1995)</b><br>(Adults – US)                                  | III <sup>#</sup>  | Medium | Case-control      | High           | High             | High             |
| <b>Pecoraro RE (1990)</b><br>(Adult males – US)                            | III <sup>#</sup>  | Medium | Case-control      | High           | High             | High             |
| <b>Reiber GE (1992)</b><br>(Adult male – US)                               | III <sup>#</sup>  | Medium | Case-control      | High           | High             | High             |
| <b>Reiber GE (1999)</b><br>(Adults – UK; US)                               | II <sup>#</sup>   | High   | Cohort            | Medium         | Low              | High             |
| <b>Rith-Najarian S (1992)</b><br>(Adults – US: Red Lake Chippewa Indians)  | II <sup>#</sup>   | High   | Cohort            | High           | High             | Low              |

<sup>#</sup>Studies with no intervention

## Section 2: Diabetic Foot Disease

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### Issue

Is peripheral vascular disease a risk factor for ulceration or amputation?

### Recommendation

People with diabetes should be assessed regularly for peripheral vascular disease.

### Evidence Statements

- Peripheral vascular disease is a risk factor for amputation  
*Evidence Level III<sup>#</sup>*
- Studies on the relationship between peripheral vascular disease and foot ulcers have given variable results  
*Evidence Level III<sup>#</sup>*

<sup>#</sup>Studies with no intervention

## Background – Peripheral Vascular Disease as a Risk Factor

Peripheral vascular disease (PVD) is common in people with Type 2 diabetes being present in 8% at the time of diagnosis and in 45% of people who have had diabetes for 20 years (Hiatt & Sussman, 1994). The prevalence of PVD at diagnosis of diabetes and the risk of developing PVD over time increase with increasing age (Davis et al, 1997).

PVD is considered to be the most important factor related to outcome of a diabetic foot ulcer (International Working Group on the Diabetic Foot, 1999) and is a major contributor to the high rates of amputation in people with diabetes as well as predicting increased risk of cardiovascular mortality (Orchard & Strandness, 1993).

Vascular assessment in the general practice setting is, by necessity, based on history and clinical examination. More sophisticated bedside investigations are available and have been shown to predict ulceration and amputation. The ankle-arm index (AAI) or ankle-brachial index (ABI), is a ratio of blood pressure measured in the arm and in the ankle by a hand-held ultrasound doppler. A ratio of less than 0.50 indicates severe PVD. Calcification of pedal arteries which is common in people with diabetes leads to a falsely high blood pressure reading in the feet and consequently a falsely high ratio. In addition, the repeatability of the AAI/ABI measure has a coefficient of variation of 10 to 15% and therefore requires duplicate readings. In view of the equipment and time required to perform the examination, AAI/ABI may be used in a specialist practice but has limited application in a busy general practice.

Transcutaneous oximetry (TcPO<sub>2</sub>) is a measurement of partial pressure of oxygen at the skin surface. Levels less than 50mmHg are associated with PVD and a reduced healing ability (McNeely et al, 1995).

Invasive techniques such as angiography is more specific in demonstrating PVD but is also associated with significant morbidity. In a study of 104 patients both a score based on the results of an angiogram (OR 2.32 [CI 1.40-3.84]) and the ABI (OR 1.84 [CI 1.10-3.06]) were predictive of major amputation (Fagila et al, 1998).

## Evidence – Peripheral Vascular Disease as a Risk Factor

### **Peripheral vascular disease is a risk factor for amputation**

The prospective Seattle Diabetic Foot Study of 776 veterans with diabetes has shown PVD to be an independent risk factor for amputation (RR 3.0, CI 1.3-7.1) (Adler, et al, 1999). In a multivariate model relative to a reference hazard ratio (HR) of 1 for an individual with neither PVD nor neuropathy, individuals with PVD as indicated by absent or diminished pulses but without neuropathy had an HR for amputation of 20.5 compared with an HR of 9.3 for neuropathy alone and 19.0 when both PVD and neuropathy were present (Adler, et al, 1999). Interestingly all assessments of PVD (AAI, TcPO<sub>2</sub> and absence/diminished peripheral pulses) gave a similar HR for predicting risk of amputation (each HR approximately 3) (Adler, et al, 1999).

Lehto et al (1996) prospectively followed for 7 years 1044 people aged 45 to 64 years with Type 2 diabetes. The incidence of amputation was 5.6% in men and 5.3% in women. The age and sex adjusted RR of amputation in people with 2 absent peripheral pulses was 3.9 (CI

2.3-6.8). Boyko et al (1999) reported in a case control study that the OR for amputation in their diabetic cohort was 2.6 (CI 1.5-4.5) in people in whom PVD was diagnosed clinically.

In a case control study of diabetic Pima Indians which included 61 amputees and 183 controls, the OR for first amputation for people with PVD was 6.9 (CI 2.6-18.3) and this decreased to an OR of 3.4 (CI 1.2-9.4) after adjustment for demographic factors and diabetes severity (Mayfield et al, 1996).

### **Studies on the relationship between peripheral vascular disease and foot ulcers have given variable results**

In a model developed to clarify causal pathways for incident foot ulcers, lower limb ischaemia was a component cause in 35% of study pathways, but not a sufficient cause of ulceration for any of the 147 patients (Reiber et al, 1999). There were no significant multivariate associations between ulceration and vascular disease as measured by ABI, pedal pulses or transcutaneous oxygen tension < 30mm Hg in a Texan study of 76 cases and 149 controls (Lavery et al, 1998). Pham et al (2000) prospective study of foot ulceration in 248 people with diabetes followed for mean a 30 months, PVD assessed by absent pedal pulses was not an independent risk factor for foot ulceration.

However other studies have reported an association with some measures of PVD. A case-control study in the Seattle Veterans population failed to demonstrate a risk of ulceration with low AAI, but reported increased risk with low TcPO<sub>2</sub> (OR 57.87, CI 5.08 – 658.96) after adjusting for age, sex, serum glucose levels, marital status, history of treatment for alcohol abuse, prior LEA and prior revascularisation (McNeely et al, 1995). In a more recent publication from this group in a prospective study of 749 people, both diminished large vessel perfusion as measured by AAI, and tissue oxygen perfusion were associated with increased risk for ulceration [AAI<0.5, RR 1.94 (1.07-3.52); TcPO<sub>2</sub> RR 0.80 (0.69-0.93)] (Boyko et al, 1999). In a prospective cohort of 358 American-Indians, the incidence of plantar ulceration was related to ABI but in all ranges of vascular indices, ulceration rates were significantly higher among people who had lost protective sensation (Rith-Najarian et al, 1992).

## **Summary – Peripheral Vascular Disease as a Risk Factor**

- Peripheral vascular disease is common in people with Type 2 diabetes
- Peripheral vascular disease is associated with a 2-4 fold increase of amputation
- The assessment for peripheral vascular disease includes a history of claudication, palpation of pedal pulses, bedside Doppler studies with calculation of arm (brachial)/ ankle index, transcutaneous oximetry and invasive techniques such as angiography.
- The role of peripheral vascular disease as a independent risk factor for foot ulceration remains uncertain
- Measurement of arm (brachial)/ankle index and tissue oxygen availability predict amputation but are difficult to perform in a routine practice setting

## Evidence Table: Section 2

### Peripheral vascular disease as a risk factor

| Author  | Evidence          |        |              |                |                  |                  |
|---|-------------------|--------|--------------|----------------|------------------|------------------|
|   | Level of Evidence |        |              | Quality Rating | Magnitude Rating | Relevance Rating |
|   | Level             | Rating | Study Type   |                |                  |                  |
| <b>Alder AI (1999)</b><br>(Adults – US)                                 | III <sup>#</sup>  | Medium | Cohort       | High           | High             | High             |
| <b>Boyko EJ (1999)</b><br>(Adults – US)                                 | III <sup>#</sup>  | Medium | Cohort       | High           | High             | High             |
| <b>Lavery LA (1998)</b><br>(Adults – US)                                | III <sup>#</sup>  | Medium | Case-control | High           | High             | High             |
| <b>Lehto S (1996)</b><br>(Adults – Finland)                             | II <sup>#</sup>   | High   | Cohort       | High           | High             | High             |
| <b>Mayfield JA (1996)</b><br>(Adults – US: Gila River Indians)          | III <sup>#</sup>  | Medium | Case-control | High           | High             | Low              |
| <b>McNeely MJ (1995)</b><br>(Adults – US)                               | III <sup>#</sup>  | Medium | Case-control | High           | High             | High             |
| <b>Pham H (2000)</b><br>(Adults – US)                                   | II <sup>#</sup>   | High   | Cohort       | High           | High             | High             |
| <b>Reiber GE (1999)</b><br>(Adults – US; UK)                            | III <sup>#</sup>  | Medium | Cohort       | Medium         | Low              | High             |
| <b>Rith-Najarian S (1992)</b><br>Adults - US: Red Lake Chippewa Indians | II <sup>#</sup>   | High   | Cohort       | High           | High             | Low              |

<sup>#</sup>Studies with no intervention

## Section 3: Diabetic Foot Disease

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### Issue

Is deformity, including a previous amputation, a risk factor for ulceration or amputation?

### Recommendation

People with diabetes should be assessed regularly to detect foot deformities including:

- Hallux deformities
- Hammer or claw toes
- Callus
- Charcot's foot
- Previous minor amputation

People with diabetic neuropathy and foot deformities should have measures to reduce excessive foot pressures (eg podiatry treatment, therapeutic footwear) to prevent ulceration and amputation.

### Evidence Statements

- A previous amputation is a risk factor for ulceration and further amputation  
*Evidence Level III<sup>#</sup>*
- Foot deformity is a risk factor for ulceration, especially in people with neuropathy  
*Evidence Level I<sup>#</sup>*
- Callus is a risk factor for ulceration, especially in people with neuropathy  
*Evidence Level III<sup>#</sup>*
- Measures to reduce elevated foot pressures improve outcomes  
*Evidence Level III-2*

<sup>#</sup>Studies with no intervention

## Background – Deformity as a Risk Factor for Ulceration and Amputation

Mechanical factors play a critical role in the aetiology of neuropathic foot ulcers (Cavanagh et al, 1996; Mayfield et al, 1998). Alterations in the normal biomechanics of the foot result from alterations in foot structure and non-enzymatic glycosylation which alters foot tissue properties. These combine to increase plantar pressure, a consistent finding in people with diabetes which has been associated with increased risk of ulceration (Veves et al, 1992). Plantar pressures are difficult to measure in a general practice setting as sophisticated technology is required, however callus, a sign of increased foot pressure, is more predictive of ulceration than increased plantar pressure alone (Mayfield et al, 1998).

Plantar pressures during walking and standing in the normal foot are sufficient to occlude capillary blood flow and it has been suggested that local reflexes including the hyperaemic response are abnormal in people with neuropathy and that capillary fragility may be greater in people with diabetes (Cavanagh et al, 1996). People who have lost protective sensation may not appreciate increasing damage to the foot due to increased pressure and continue to traumatise the same tissue (Mayfield et al, 1998).

Causes of increased plantar pressures in people with diabetes include increased body mass, (which however contributes less than 14% of variance in peak plantar pressure), changes in posture, gait, soft tissues and bone structure. Limited joint mobility occurs in the absence of neuropathy but only becomes a risk for ulceration with the loss of protective sensation. Glycosylation of soft tissues is thought to predispose to the excess callus formation seen in people with diabetes in response to abnormal plantar pressures. Bony deformities caused by motor neuropathy, hammer toe or claw toe deformity, are present in up to half of all people with diabetes (Mayfield et al, 1998).

Foot deformity is a major contributor to increasing foot pressures. Foot deformities in people with diabetes range from minor abnormalities in joint mobility to the severe deformity seen in advanced Charcot's foot. A previous amputation, particularly a minor amputation, frequently results in abnormal plantar pressures and increases the risk of subsequent amputation.

## Evidence – Deformity as a Risk Factor for Ulceration and Amputation

### **Previous amputation is a risk factor for ulceration and further amputation**

A history of previous lower extremity event (ulceration or amputation) determined by interview, medical record review and examination, was used to classify risk in a prospective study of 358 American Indians (Rith-Najarian et al, 1992). People in the risk category which included previous amputation had the highest level of risk for ulceration (OR 78) and further amputation (rate 180/1000 diabetic person-year). The trend for increasing risk of amputation and ulceration with the risk category which included neuropathy, deformity and a history of ulceration or amputation, was highly significant ( $p < 0.00001$ ). Increased risk associated with a history of amputation was also confirmed in the Seattle Veterans study (RR 2.8, CI 1.84-7.29  $p < 0.001$ ) (Boyko et al, 1999). People who experienced a lower extremity amputation during follow-up were more likely to have had a history of previous amputation (Adler et al, 1999).

In a 5 year prospective study of 189 people with diabetes who had achieved healing after an index amputation (93 with an index minor amputation and 96 with an index major amputation), there were 72 new amputations with 48 occurring in people who had an index minor amputation and 24 in those who had an index major amputation (Larsson et al, 1998). The rates of new major amputations after 1, 3 and 5 years were 9%, 13% and 23% respectively and the rates for mortality were 15%, 38%, and 68% respectively.

A group of 25 patients with an amputation of the great toe were assessed for deformity, using the contralateral extremity as the control. Deformity of the second and third toes were more common ( $p=0.012$ ,  $p=0.002$ ) as were new ulcers in feet that had had an amputation ( $p=0.002$ ) (Quebedeaux et al, 1996). A history of amputation was significantly associated with foot ulceration in a case-control study of 225 people with diabetes (OR 10.0,  $p<0.02$ ) (Lavery et al, 1998). Previous amputation increased the risk of ulceration (OR 12.7,  $p<0.01$ ) in a population based cross sectional study of 811 people with diabetes (representing 48% of eligible people with diabetes on general practice registers in three UK cities) (Kumar et al, 1994).

### **Foot deformity is a risk factor for ulceration, especially in people with neuropathy**

The combination of peripheral neuropathy and foot deformity which results in altered biomechanics of the foot places a person at increased risk of ulceration (Mayfield et al, 1998). The importance of the combined effects of neuropathy and deformity is illustrated by a study which compared people with diabetes and people with rheumatoid arthritis. Both groups had similar rates of deformity but there were no ulcers in people with rheumatoid arthritis while 32% of people with diabetic neuropathy had a history of foot ulcers (Masson et al, 1989). Similarly, in people with limited joint mobility, those with a history of ulcers also had peripheral neuropathy (Fernando et al, 1991).

Deformity, including hallux varus or valgus, claw and hammer-toes, bony prominence, and Charcot foot, was assessed in a cohort of diabetic American Indians. In the presence of peripheral neuropathy in which protective sensation was lost, the rate of ulceration in people with deformed feet was twice that of people without deformity (OR 32) (Rith-Najarian et al, 1992).

Foot deformity, defined as hallux rigidus, hallux valgus, or toe deformities, was significantly associated with foot ulceration in a Texan study of 76 people with diabetes and 149 controls (OR 3.3,  $p<0.03$ ) (Lavery et al, 1998). In a cohort of Veterans in Seattle followed for over 3 years, Charcot's deformity was associated with an increased risk of foot ulceration (RR 3.49 CI 1.22-9.92,  $P=0.019$ ). A weaker association was found with hammer/claw toes and hallux limitus. There was no statistically significant association with other deformities, prominent metatarsal heads, hallus valgus, or bony prominences in this population (Boyko et al, 1999).

Data on foot deformity and risk of amputation are limited. In one study foot deformity was found to have a risk equal to neuropathy and peripheral vascular disease in predicting amputation but the risk increased with increasing number of risk factors (Mayfield et al, 1996). After adjusting for demographic factors and disease severity, and independent of other risk factors, there was a significant association between foot deformity and first amputation in a Native American Indian population (OR 3.0, CI 1.02-8.7) (Mayfield et al, 1996). This study was a retrospective review of medical records, which could have underestimated the prevalence of significant peripheral neuropathy in the control group.

## **Callus is a risk factor for ulceration, especially in people with neuropathy**

Callus is a diffuse hyperkeratotic area which develops in response to shear stresses, usually in proximity to a bony prominence (Reiber et al, 1999). Callus is not only a sign of increased foot pressures but also contributes to further increase plantar foot pressures by acting as a foreign body and predispose to the formation of ulcers beneath such lesions. Furthermore the redistribution of plantar pressure in response to a callus is diminished in people with diabetic neuropathy (Uhlenbruck & Chantelau, 1998) The prevalence of callus has been reported to be similar in diabetic people with and without the ability to detect the 5.07g monofilament (approximately 30%) (Collier et al, 1993).

In a prospective study of 63 people with diabetes and neuropathy assessed on the basis of vibration perception threshold, the presence of plantar callus was highly predictive of ulceration in a callused area (RR 11.0, CI 2.8-43.2, p=0.004). This compares with a relative risk for ulceration in an area of elevated plantar pressure but without callus of 4.7 (1.2-18.9, p=0.04) (Murray et al, 1996). The authors concluded that callus should be recognised as a risk factor for foot ulceration.

In retrospective review of 238 neuropathic ulcers, Edmonds et al, (1986) observed that neuropathic ulcers were invariably associated with callus.

Reiber et al (1999) in a study of causal pathways of incident foot ulcers in 146 people with diabetes from Manchester, UK and Seattle, US concluded that callus was a component cause in 30% of incident foot ulcers.

## **Measures to reduce elevated foot pressures improve outcomes**

Several measures have been shown to reduce abnormal pressures, protect the foot from external trauma and reduce the formation of callus and ulcers. Conservative management of increased plantar pressures involves debridement of callus and footwear modification. Reducing plantar pressures is the basis of treating foot ulcers and preventing ulceration in at risk feet (Cavanagh et al, 1996).

Podiatric treatment of callus is associated with a significant fall in foot pressure. In a study of 17 people with diabetes, Young et al (1992) demonstrated a 26% (p<0.001) reduction in plantar pressures by removal of callus. The rate of plantar callus formation and the need for debridement can be reduced by athletic running shoes (Soulier et al, 1987) and by orthotic devices (Colagiuri et al, 1995).

Several other measures have been shown to reduce plantar pressures. Veves et al (1990) reported that the use of padded socks reduced plantar pressures. Inexpensive running shoes were found to halve plantar pressures at the metatarsal heads (Kastenbauer et al, 1998; Perry et al, 1995). and the use of custom-made insoles reduced pressures at the metatarsal heads by a similar amount (Kastenbauer et al, 1998).

Reduction of weight bearing pressures by the use of total contact casts has been shown in a controlled trial of the treatment of foot ulcers to improve healing rates with 90.5% of ulcers healing in  $42 \pm 29$  days compared with 31.3% in  $65 \pm 29$  days with usual care (Mueller et al, 1989). Rocker and wedge sole modifications can also reduce the pressure under the metatarsal heads by up to 30% and have been used to promote ulcer healing (Perry et al, 1995, Rose et al, 1992).

Therapeutic footwear can prevent ulceration in people at high risk. In the Kings College Hospital study, foot ulcers developed in 26% of people with specially fitted shoes compared with 83% in those wearing regular shoes (Edmonds et al 1986). In another study, Uccioli et al (1995) showed that specially padded shoes reduced the recurrence of ulceration over a 1 year period to 28% compared with 58% in people wearing their usual footwear.

## Summary – Deformity as a Risk Factor for Ulceration and Amputation

- Previous amputation is a risk factor for ulceration and further amputation and is associated with a 68% mortality rate after 5 years
- In the presence of diabetic neuropathy, limited joint mobility and bony deformities increase the risk of ulceration
- Deformity increases the risk of ulceration by at least 3 fold
- The deformity caused by previous amputation also increases the risk of ulceration by at least 3 fold and greatly increased the risk of further amputation
- Callus is common in people with diabetes and in the presence of neuropathy increases the risk of ulceration
- Reducing plantar pressures is the basis for treating foot ulcers and preventing ulceration in at risk feet
- Measures to reduce foot pressures including callus debridement, orthoses and specialised footwear improve outcomes and reduce ulceration

## Evidence Table: Section 3

### Deformity as a risk factor for ulceration and amputation

| Author   | Evidence          |        |                      |                |                  |                  |
|--|-------------------|--------|----------------------|----------------|------------------|------------------|
|  | Level of Evidence |        |                      | Quality Rating | Magnitude Rating | Relevance Rating |
|  | Level             | Rating | Study Type           |                |                  |                  |
| Alder AI (1999)<br>(Adults – US)                                     | III <sup>#</sup>  | Medium | Cohort               | High           | High             | High             |
| Boyko EJ (1999)<br>(Adults – US)                                     | III <sup>#</sup>  | Medium | Cohort               | High           | High             | High             |
| Colagiuri S (1995)<br>(Adults – Australia)                           | II                | High   | RCT                  | High           | High             | High             |
| Collier J (1993)<br>(Adults – US)                                    | III <sup>#</sup>  | Medium | Cohort               | Medium         | Low              | High             |
| Edmonds ME (1986)<br>Adults – UK)                                    | III-2             | Medium | Cohort               | Low            | Medium           | High             |
| Fernando JS (1991)<br>(Adults – UK)                                  | III <sup>#</sup>  | Medium | Cross-sectional      | Medium         | High             | High             |
| Kastenbauer T (1998)<br>(Adults – Austria)                           | III-2             | Medium | Case-control         | High           | High             | High             |
| Kumar S (1994) (Adults<br>– UK)                                      | III <sup>#</sup>  | Medium | Cross-sectional      | Medium         | High             | High             |
| Larsson J (1998)<br>(Adults – Sweden)                                | III <sup>#</sup>  | Medium | Cohort               | High           | High             | High             |
| Lavery LA (1998)<br>(Adults – US)                                    | III <sup>#</sup>  | Medium | Case-control         | High           | High             | High             |
| Masson EA (1989)<br>(Adults – UK)                                    | III <sup>#</sup>  | Medium | Case-control         | High           | High             | High             |
| Mayfield JA (1996)<br>(Adults – US: Gila River<br>Indians)           | III <sup>#</sup>  | Medium | Case-control         | High           | High             | Low              |
| Mayfield JA (1998)   | I <sup>#</sup>    | High   | Systematic<br>Review | High           | High             | High             |
| Mueller MJ (1989)<br>(Adults – US)                                   | III <sup>#</sup>  | Medium | Cross-sectional      | Medium         | High             | High             |
| Murray HJ (1996)<br>(Adults – UK)                                    | III <sup>#</sup>  | Medium | Cohort               | Medium         | High             | High             |
| Perry JE (1995) (Adults<br>– US)                                     | III-2             | Medium | Case-control         | Medium         | High             | High             |
| Quebedeaux TL (1996)<br>(Adults – US)                                | III <sup>#</sup>  | Medium | Cohort               | High           | High             | High             |
| Rith-Najarian S (1992)<br>(Adults -US: Red Lake<br>Chippewa Indians) | II <sup>#</sup>   | High   | Cohort               | High           | High             | Low              |
| Rose NE (1992)<br>(Adults – US)                                      | III <sup>#</sup>  | Medium | Cohort               | Low            | High             | Low              |
| Soulier S (1987)<br>(Adults – US)                                    | III-2             | Medium | Cohort               | Medium         | High             | High             |
| Young MJ (1992)<br>(Adults – UK)                                     | IV                | Low    | Pre & Post           | Medium         | High             | High             |
| Uccioli L (1995)<br>(Adults – Italy)                                 | II                | High   | RCT                  | High           | High             | High             |
| Uhlenbruck C (1998)<br>(Adults – Germany)                            | III <sup>#</sup>  | Medium | Case-control         | Medium         | High             | High             |
| Veves A (1990)<br>(Adults – UK)                                      | III-2             | High   | Cohort               | Medium         | High             | High             |

<sup>#</sup>Studies with no intervention

## Section 4: Diabetic Foot Disease

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### Issue

Is previous or current ulcer a risk factor for amputation?

### Recommendation

Diabetic people with a current foot ulcer should be identified as a high risk group for possible amputation: more frequent monitoring and preventative interventions to lower that risk should be instituted promptly in this group.

The history of a healed previous diabetic foot ulcer should be recognised as an indicator of life long increase in risk of recurrent ulceration and amputation.

### Evidence Statements

- A healed past diabetic foot ulcer is an indicator of high risk for recurrent ulcer and possible eventual amputation  
*Evidence Level III<sup>#</sup>*
- A current ulcer is a high risk condition for amputation and 85% of first and second amputations are preceded by an ulcer  
*Evidence Level III<sup>#</sup>*

<sup>#</sup>Studies with no intervention

## Background – Ulcer as a Risk Factor for Amputation

Observational studies suggest that 6–43% of patients with diabetes and who have a foot ulcer eventually progress to amputation (Moss et al, 1996; Bild et al, 1989; Apelqvist et al, 1994; Larsson et al, 1995). Retrospective studies suggest that lower extremity ulcers precede 71–85% of amputations in this population (Moss et al, 1996; Reiber et al, 1992; Larsson et al, 1995) even in the case of second amputation (Larsson et al, 1998). While the presence of a current ulcer must clearly lead to an increase in risk of amputation, it is important to know what degree of risk is involved and whether a healed ulcer is also a strong risk factor in the assessment of a diabetic patient's feet for future monitoring and preventative intervention. It has been observed that the most likely site for plantar ulceration in neuropathic feet is at the location of a previous ulcer (Sims et al, 1988).

While several studies utilise sophisticated measurements to assess the high risk foot, the history of an ulcer or the detection of a current ulcer by physical examination are both risk factors capable of detection by everyone in primary care. Preventative action can then be instituted in an easily identified high risk group (Apelqvist et al, 1993).

## Evidence – Ulcer as a Risk Factor for Amputation

### **A healed past diabetic foot ulcer is an indicator of high risk for recurrent ulcer and possible eventual amputation**

A UK prospective study of 63 neuropathic patients with callus on their feet and high plantar foot pressure followed diabetic subjects for up to 22 months from baseline while they received treatment for their callus. Previous ulceration proved to be the highest risk factor for the development of a foot ulcer with an RR of 56.8,  $p=0.00001$ . The presence of callus itself was predictive of ulceration with an RR of 11.0,  $p=0.004$  (Murray et al, 1996).

In a 14 year prospective follow up of the 984 older onset diabetic individuals from a population based cohort from Wisconsin, USA, a history of foot ulceration gave the highest OR of 3.56 (CI 1.84-6.89,  $p=0.0005$ ) for amputation in multivariate logistic regression. Male gender was also a risk factor of 2.66 (CI 1.49-4.76,  $p<0.001$ ), as is commonly found (Moss et al, 1999). In the continuing Seattle Diabetic Foot Study of outpatients in a Veterans Affairs medical clinic, 1040 patients with diabetes were followed for a median of 3.3 years. All patients who had an amputation, but only 27% of patients who did not, had a preceding ulcer at some time before or during the study ( $p<0.001$ ) (Adler et al, 1999). A paired case control analysis included 20 patients without amputation before study entry who had an amputation during follow up. Of these 20, 17 had an ipsilateral LEA and 3 had a contra lateral one. The odds ratio associated with first ulcer for subsequent ipsilateral amputation was 5.7 (CI 1.6-30.2) (Adler et al, 1999). Also in the Seattle study, 67 diabetic patients presenting for initial non-traumatic amputation between 1984 and 1987 were compared with 236 consecutive diabetic subjects seen for other unrelated surgery. Presence of prior foot ulcer was independently associated with risk of lower extremity amputation (OR 10.9, CI 4.6-25.5). Interestingly, health care provider awareness of a prior foot ulcer led to significantly more podiatry visits and footcare advice, but awareness of other risk factors did not affect care (del Aguila et al, 1994). In a population based case control study, Pima Indians aged 25-85 years having amputations between 1983 and 1992 were compared with those not having an

amputation by 1992. There was an equal risk for amputation with each of: peripheral neuropathy, peripheral vascular disease, bone deformity and a history of foot ulcer (OR 5.5, CI 2.4-12.5) (Mayfield et al, 1996). In 875 Oklahoma Indians with no prior amputation at initial examination, the history of ulcer was a strong risk factor for amputation when reviewed 10 years later (2.96 in men rate ratio 7.08 in women. (Lee et al, 1993).

Poor wound healing and osteomyelitis may play a part in amputation after foot ulcer. In the Seattle Foot Study 80 diabetic first amputees were compared with 236 diabetic veterans not having amputation, to determine causal pathways using both objective and subjective data from each patient. While 23 causal pathways were identified, a critical triad of injury leading to ulceration and poor wound healing was said to be responsible for 73% of cases. Overall 84% of amputations in this paper were attributed to ulceration (Pecoraro et al, 1990).

In another approach a database analysis was done of 8905 patients with Type 1 and Type 2 diabetes in a large health maintenance organisation from 1993-1995 (Ramsey et al, 1999). The recorded incidence of foot ulcers over 3 years showed a cumulative incidence of 5.8%. Of these 15.6% required amputation, and a similar proportion (15%) developed osteomyelitis, of whom 36% had a lower extremity amputation during the follow up. This suggested osteomyelitis played a part in some, but by no means all, amputations following ulcers. However in research from a database alone it is not possible to conclude that the ulcer was the causal factor in the osteomyelitis or amputation as time incidence was underestimated, the side of the lesions was not recorded and subsequent ulcers were to distinguished. This study was predominantly a cost analysis showing an attributable cost in the USA for foot ulcer of US\$28,000 in the 2 years after diagnosis (Ramsey et al, 1999).

### **A current ulcer is a high risk condition for amputation and 85% of first and second amputations are preceded by an ulcer**

A prospective Swedish study followed 108 men and 81 women diabetic patients aged between 32 and 94 years, who had achieved healing after amputation. It showed that in the mean 6.3 years of follow up, 85% of new amputations were preceded by a foot ulcer. At 5 years there was a 49% recurrence of amputation. Some ischaemia was noted in most (Larsson et al, 1998).

## **Summary – Ulcer as a Risk Factor for Amputation**

- History of past diabetic foot ulcer indicates a life long risk of recurrent foot ulceration or amputation
- A current diabetic foot ulcer puts a patient at high risk for amputation. Close monitoring is necessary as infection, ischaemia and poor wound healing may all play a part
- A second amputation after either a major or minor amputation has occurred is preceded by an ulcer in 85% of cases

## Evidence Table: Section 4

### Ulcer as a risk factor for amputation

| Author   | Evidence          |        |              |                |                  |                  |
|--|-------------------|--------|--------------|----------------|------------------|------------------|
|  | Level of Evidence |        |              | Quality Rating | Magnitude Rating | Relevance Rating |
|  | Level             | Rating | Study Type   |                |                  |                  |
| <b>Adler AI (1999)</b><br>(Adult men – US)                     | III <sup>#</sup>  | Medium | Cohort       | High           | High             | High             |
| <b>del Aguila MA (1994)</b><br>(Adult men – US)                | III <sup>#</sup>  | Medium | Case-control | Medium         | High             | High             |
| <b>Larsson J (1998)</b><br>(Adults – Sweden)                   | III <sup>#</sup>  | Medium | Cohort       | High           | High             | High             |
| <b>Lee JS (1993)</b><br>(Adults – US: Oklahoma Indians)        | III <sup>#</sup>  | Medium | Cohort       | Medium         | High             | Low              |
| <b>Mayfield JA (1996)</b><br>(Adults – US: Gila River Indians) | III <sup>#</sup>  | Medium | Case-control | High           | High             | Low              |
| <b>Moss SE (1999)</b><br>(Adults – US)                         | II <sup>#</sup>   | High   | Cohort       | High           | High             | High             |
| <b>Murray HJ (1996)</b><br>(Adults – UK)                       | III <sup>#</sup>  | Medium | Cohort       | Medium         | High             | High             |
| <b>Pecoraro RE (1990)</b><br>(Adult men – US)                  | III <sup>#</sup>  | Medium | Case-control | High           | High             | High             |
| <b>Ramsey SD (1999)</b><br>(Adults – US)                       | III <sup>#</sup>  | Medium | Case-control | High           | High             | High             |

<sup>#</sup>Studies with no intervention

## Section 5: Diabetic Foot Disease

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### Issue

What is the most practical method for detecting loss of protective foot sensation in the primary care setting?

### Recommendation

People with Type diabetes should be routinely assessed with the 10g Semmes-Weinstein monofilament to detect loss of protective foot sensation.

### Evidence Statements

- Loss of sensation to the 10g Semmes-Weinstein monofilament predicts foot ulceration  
*Evidence Level III<sup>#</sup>*
- The 10 g Semmes-Weinstein monofilament is clinically reliable and practical  
*Evidence Level III<sup>#</sup>*

<sup>#</sup>Studies with no intervention

## Background – Detection of Loss of Protective Foot Sensation

Peripheral neuropathy is common in people with Type 2 diabetes and was present in 12.3% of people participating in the United Kingdom Prospective Study at diagnosis and in approximately 30% after 12 years (UKPDS 33, 1998). As reviewed in Section 1 peripheral neuropathy is a major risk factor for both foot ulceration and amputation. Therefore its clinical detection is important in identifying feet at risk of ulceration and is pivotal for effective strategies to prevent foot ulceration and subsequent amputation.

The objective of foot screening in the primary care setting is to detect a level of peripheral neuropathy sufficient to contribute to the development of foot wounds defined as 'loss of protective sensation'. This is one of the most important criteria in identifying people at high-risk of foot complications and is paramount when instituting a structured management plan to prevent lower extremity complications (Armstrong et al, 1998). The detection of loss of protective sensation is an important indication to both the person with diabetes and the primary carer that more frequent review and suitable preventative actions should be instituted and necessitates behavioural change in both the patient and the doctor.

Several methods of testing to identify loss of protective sensation along the spectrum of neuropathy. The most commonly reported methods used to assess peripheral neuropathy in clinical studies are:

- 5.07 10g Semmes-Weinstein monofilament (10g SW)
- vibration perception threshold (VPT) measured using a biothesiometer or 128Hz tuning fork
- calculation of a neuropathy score based on:
  - symptoms - the University of Texas Subjective Peripheral Neuropathy questionnaire which relies on 4 questions of symptoms of neuropathy (Dyck, 1988) or
  - clinical examination - the neuropathy disability score derived from a combination of testing for pain, temperature and vibration threshold with the presence or absence of ankle reflexes (Young et al, 1993).

Symptoms alone are not considered reliable because a significant proportion of people with diabetes who have neuropathy are asymptomatic (Young & Matthews, 1998). Similarly testing of ankle jerks alone is of little value since they are frequently absent in the elderly population, with or without diabetes (de Hens-Van Putten, et al, 1996) and has not been as successful as the more objective measures (eg vibration perception threshold) in predicting ulceration or amputation in diabetic populations.

The primary care setting requires a simple, cheap and reliable means of identification of the foot which has lost protective sensation (the insensate foot) and has led to the increasing popularity of the 10g Semmes-Weinstein monofilament. The monofilament consists of a pressure sensitive nylon filament attached to a lucite rod. The monofilament buckles at a reproducible pressure of 10g force which has been identified as the level of sensation protective against foot ulceration, initially in leprosy (Birke & Sims, 1986; Halar et al, 1987). The loss of this protective sensation at one site is usually taken as indicating an abnormal monofilament test. The test must be performed in areas free of callus which impairs the ability to feel the monofilament.

The other frequently reported method is the biothesiometer. This is a handheld device which vibrates at 100Hz and connects by an electrical cord to a base unit which allows the voltage to be increased by the operator through a range of 0 to 50V which is displayed on a scale. This instrument is popular in specialist diabetes units but is infrequently used in the primary care setting.

Foot examination is often inadequate as documented in one study of people admitted to a teaching hospital with diabetic foot disease in which it was reported that less than 15% had received a minimally competent lower limb examination as part of their routine care (Armstrong et al, 1998).

## Evidence – Detection of Loss of Protective Foot Sensation

### **Loss of sensation to the 10g Semmes-Weinstein monofilament predicts foot ulceration**

In prospective studies, the 10g monofilament has emerged as the test for peripheral neuropathy most predictive of foot ulcer risk. Boyko and coworkers (1999) studied 749 US veterans with diabetes who were followed up for a mean of 3.7 years. The risk of developing foot ulceration during the course of the study was significant for inability to perceive the 10g SW monofilament at one or more of 9 sites (RR 3.37, CI 2.45-4.63,  $p < 0.001$ ), loss of vibration sensation with the 128 Hz tuning fork (RR 2.33, CI 1.66-3.28,  $p < 0.001$ ) and absence of Achilles tendon reflex (RR 1.40, CI 1.03-1.90,  $p = 0.030$ ). However in multivariate logistic regression analysis, only the 10g SW monofilament was an independent predictor of future foot ulceration (RR 2.2, CI 1.5-3.1).

McNeely et al (1995), in a prospective case control study in the Seattle Veterans Affairs Medical Centre, compared 46 diabetic people with foot ulcers with 322 control subjects without foot ulcers. Neuropathy was determined by vibration sensation with 128Hz tuning fork, a 10g SW monofilament and Achilles tendon reflexes. Vascular indices included ankle/arm blood pressure and transcutaneous oxygen tension on the dorsal foot. From multivariate logistic regression analysis the authors conclude that the 10g SW monofilament was the single most practical measure of risk assessment. The adjusted OR for the monofilament was 18.42 (CI 3.83-88.47) compared with absence of Achilles tendon reflexes (OR 6.48, CI 2.37–18.06), while absent vibration sensation was not a significant independent risk factor (McNeely et al, 1995).

In another prospective study of native American Indians, sensory status was determined by the 10g SW monofilament applied to 8 points on the plantar surface of each foot. The subjects were blindfolded and retested twice before being classified as insensate (if they consistently failed to feel the filament at one or more locations). Lack of sensation gave a greater risk of an ulcer than retained sensation, and combined with deformity and history of prior lower extremity disease there was a 93% sensitivity and an 86% specificity for predicting ulceration with likelihood ratios for a positive test 5.2 (CI 4-6.7) and for a negative test 0.12 (CI 0.05-0.27) (Rith-Najarian et al, 1992).

In a case control study in Type 2 diabetes, assessing 14 ulcer patients and 168 without ulcer history, Olmos and coworkers (1995) found the 10g SW monofilament was superior to vibratory and tendon reflex testing in predicting the risk of having a foot ulcer. The study used three points to examine both feet with the monofilament: the tip of the great toe and the plantar surface of the first and fifth metatarsal heads. Missing one site was sufficient for a

positive test for sensory loss. This test yielded a sensitivity of 86% and a false positive rate of 16% for no ulcer in the past year (Olmos et al, 1995).

In a further case control study, 30 people with recent or current foot ulceration were compared with 85 controls without a history of foot ulcer. (Armstrong et al, 1998). The sensitivity and specificity of vibration perception threshold testing (VPT) assessed using a biothesiometer, the 10g SW monofilament and a four question verbal neuropathy score were compared. Overall, VPT > 25V or 4 or more of eight imperceptible monofilament sites had higher sensitivity (100%) and specificity (76.5%) than the symptom score. However combining the modalities increased specificity (88.2%) but sensitivity decreased to 88.2%. They say the monofilament as described in their paper offers an inexpensive and reliable method for use in primary care, nursing or specialist practice.

A study in 72 people with leprosy and 28 people with diabetes with previous or current ulceration over a one year period the 10g SW monofilament to be the best indicator of subjects who had retained protective sensation and could therefore protect themselves against foot injury (Birke & Sims, 1986).

### **The 10g Semmes-Weinstein monofilament is clinically reliable and practical**

In 1001 people attending a UK diabetes clinic, foot screening was performed with the 10g SW monofilament, biothesiometer and pulse palpation (Klenerman et al, 1996). People with an initial abnormal test were invited to reattend and repeat testing was performed in 229 people. The reproducibility study was carried out in both Type 1 and Type 2 people with diabetes of both genders with a mean age of 59.6 years. The study report does not state whether the same investigator(s) had performed both examinations and whether the repeat examination was blinded. 21.8% had loss of protective sensation as judged by absence of some or all protective sensation to the monofilament. 7.7% had absent pedal pulses, 4% had combined vascular and sensory loss. Between the two testings the biothesiometer variation was considered clinically unacceptable. The same result for palpation of pedal pulses ranged from 68-82% while the same result was obtained in 85-88% with the monofilament. The stability of testing with the monofilament prompted the authors to recommend its routine use in screening for at risk feet.

There is no universal consensus on the optimal testing sites for the 10g SW monofilament with various studies recommending between 1 and 10 different sites. McGill et al (1999) addressed this question in a study of 132 randomly selected Australian diabetic subjects by calculating the sensitivity and specificity of the 10g SW monofilament assessed at 5 different sites in identifying people with a vibration perception threshold (VPT) >40V using the biothesiometer. Inability to detect the monofilament at either of the sites over the first and fifth metatarsal heads gave a sensitivity and specificity of 80 and 86% respectively for a VPT > 40V. While providing a practical approach to screening large numbers of people with diabetes it should be noted that in this study the choice of a VPT >40V was arbitrary and that ulceration was not a study endpoint (McGill et al, 1999).

## Summary – The Semmes-Weinstein Monofilament to Predict Ulceration

- A loss of sensation to the 5.07 monofilament which exerts 10g pressure at buckling point indicates loss of protective foot sensation
- Failure to feel the 10g Semmes-Weinstein monofilament at one uncallused plantar site is predictive of future foot ulceration
- The 10g Semmes-Weinstein monofilament is equivalent to or better than other simple tests of neuropathy for the primary care setting
- The Semmes-Weinstein monofilament test is simple and cheap and its reliability is clinically acceptable

## Evidence Table: Section 5

### The Semmes-Weinstein monofilament to predict foot ulceration

| Author  | Evidence          |        |                 |                |                  |                  |
|---|-------------------|--------|-----------------|----------------|------------------|------------------|
|   | Level of Evidence |        |                 | Quality Rating | Magnitude Rating | Relevance Rating |
|   | Level             | Rating | Study Type      |                |                  |                  |
| <b>Armstrong DG (1998)</b><br>(Adults – US)                             | III <sup>#</sup>  | Medium | Case-control    | Medium         | High             | High             |
| <b>Birke JA (1986)</b><br>(Adults – US)                                 | III <sup>#</sup>  | Medium | Cross-sectional | Medium         | High             | High             |
| <b>Boyko EJ (1999)</b><br>(Adults – US)                                 | III <sup>#</sup>  | Medium | Cohort          | High           | High             | High             |
| <b>Klenerman L (1996)</b><br>(Adults – UK)                              | III <sup>#</sup>  | Medium | Cross-sectional | High           | High             | High             |
| <b>McGill M (1999)</b><br>(Adults – Australia)                          | III <sup>#</sup>  | Medium | Cross-sectional | Medium         | High             | High             |
| <b>McNeely MJ (1995)</b><br>(Adults – US)                               | III <sup>#</sup>  | Medium | Case control    | High           | High             | High             |
| <b>Olmos PR (1995)</b><br>(Adults – US)                                 | III <sup>#</sup>  | Medium | Case-control    | High           | High             | High             |
| <b>Rith-Najarian S (1992)</b><br>(Adults- Red Lake<br>Chippewa Indians) | II <sup>#</sup>   | High   | Cohort          | High           | High             | Low              |

<sup>#</sup>Studies with no intervention

## Section 6: Diabetic Foot Disease

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### Issue

How should peripheral vascular disease be assessed clinically?

### Recommendation

People with diabetes should be assessed for peripheral vascular disease by:

- Enquiring about symptoms of intermittent claudication
- palpation of pedal pulses

### Evidence Statements

- The presence of intermittent claudication in people with diabetes strongly suggests the presence of peripheral vascular disease  
*Evidence Level III<sup>#</sup>*
- The absence of intermittent claudication does not exclude peripheral vascular disease  
*Evidence Level III<sup>#</sup>*
- Palpable foot pulses in people with diabetes make significant peripheral vascular disease unlikely  
*Evidence Level III<sup>#</sup>*
- The absence of foot pulses increases the likelihood of amputation  
*Evidence Level II<sup>#</sup>*

<sup>#</sup>Studies with no intervention

## Background – Clinical Detection of Peripheral Vascular Disease

Peripheral vascular disease (PVD) is common in people with Type 2 diabetes being present in 8% at the time of diagnosis and in 45% of people who have had diabetes for 20 years (Hiatt & Sussman, 1994). The prevalence of PVD at diagnosis of diabetes and the risk of developing PVD over time increase with increasing age (Davis et al, 1997). As reviewed in Section 2, peripheral vascular disease is an important risk factor for amputation. Although various factors predict the outcome of foot ulcers in diabetic subjects, the severity of existing lower extremity arterial disease is considered to be the main independent risk factor for major amputation (Pecoraro et al, 1990).

While sophisticated and invasive tests are now available to quantify the extent of peripheral vascular disease in people with diabetes, clinical means of identifying those with PVD remains important in the primary care setting. A history of intermittent claudication is a well recognised feature of PVD. Claudication pain arises in an exercising muscle when the perfusion pressure of the blood during exercise is insufficient to remove anaerobic metabolites and maintain muscle function. In contrast to those without diabetes, the arteries below the knee are more severely affected in people with diabetes (LoGerfo & Coffman, 1984). Exercise-induced leg pain most commonly begins in the calf but can extend to the thigh or buttocks if exercise is continued. Severe claudication is most often the result of multilevel arterial disease.

Palpation of foot pulses is a routine part of the assessment of the peripheral circulation in people with diabetes. Pedal pulse palpation is reported to be a simple and adequately reliable clinical method (Meade et al, 1968). Other clinical signs which may be useful include atrophic skin and loss of hair, pallor on elevation followed by dusky colour on dependency and a prolonged capillary filling time.

Several studies have reported that clinical signs of PVD correlate well with future risk of amputation although it should be remembered that the absence of claudication does not exclude a diagnosis of PVD since pain may not be a feature if peripheral neuropathy is also present. Also some of the controversy about the usefulness of routine clinical examination of peripheral pulses is in part related to inter-observer variation and a relatively high false-positive rate for the presence of PVD.

## Evidence – Clinical Detection of Peripheral Vascular Disease

### **The presence of intermittent claudication in people with diabetes strongly suggests the presence of peripheral vascular disease**

A cross-sectional study in 631 predominantly male diabetic veterans in a general medical clinic compared data obtained from history and clinical evaluation with the presence of severe PVD measured by an ankle-arm index (AAI)  $\leq 0.5$  using Doppler blood pressure measurements (Boyko et al, 1997). This study identified 92 limbs with AAI  $\leq 0.5$ . Claudication symptoms at less than one block gave a sensitivity of 50% and a specificity of 87% for PVD by AAI, while the self-reported history of prior physician diagnosis of PVD gave a sensitivity of 80% and specificity of 70%. Substitution of the symptom of claudication for a history of PVD in a multivariate model resulted in only a small reduction in model accuracy. The authors concluded that most information related to the probability of having PVD could be obtained from the person's age, self reported history of prior physician diagnosis of PVD (or less than

one block claudication), peripheral pulse palpation and venous filling time. The study used only AAI which can be limited by falsely high ankle pressure measurements due to arterial calcification, however a low cutoff of 0.5 was used to diagnose PVD (Boyko et al, 1997).

Walters et al (1992) studied the predictive values of a history of claudication or the absence of 2 or more pedal pulses in identifying PVD defined in terms of an ABI  $\leq 0.9$ . In 1058 diabetic people, claudication gave a sensitivity of 34%, specificity of 97% and positive predictive value of 72% for PVD.

### **The absence of intermittent claudication does not exclude peripheral vascular disease**

In a study of 104 people with diabetes admitted for current foot ulcers from 1993 to 1995, PVD was assessed by digital subtraction angiography (DSA) (Faglia et al, 1998). Of the 103 subjects in whom DSA detected a haemodynamically significant vascular stenosis, ischaemic pain was present in only 26.2% and in 73.8% pain was completely absent.

Asymptomatic PVD is common in people with diabetes. Elhadd et al (1999) studied 159 British diabetic subjects with both types of diabetes who had no history of cardiovascular disease or symptom of claudication but had absent arterial foot pulses. PVD was assessed by ankle brachial pressure index (ABI) with a value of  $\geq 0.9$  being considered normal. 33% of these asymptomatic individuals were found to have PVD. Walters et al (1992) found a prevalence of asymptomatic PVD of 23.2% in people with Type 2 diabetes. These results contrast with a prevalence of 16.6% in the general population (Fowkes et al, 1991) approximately half the rate in people with diabetes.

### **Palpable foot pulses in people with diabetes make significant peripheral vascular disease unlikely**

Contrary to widely held clinical impressions, congenital absence of the posterior tibial pulse is very infrequent (0.18% of healthy young people) whilst the dorsalis pedis pulse is bilaterally absent in only 1.8% and unilaterally absent in 3.0% (Robertson et al, 1990).

McGee and Boyko (1998) reviewed papers published between 1966 and 1997 regarding bedside diagnosis of peripheral vascular disease. The majority of the 17 studies identified concerned non-diabetic subjects. The authors concluded that the following positive findings were helpful in diagnosing PVD: abnormal pedal pulses, a unilateral cold extremity, prolonged venous filling time and a femoral bruit. In deciding whether a pulse is present or absent, clinicians demonstrated fair to almost perfect agreement (McGee & Boyko, 1998).

A prospective study in Denmark analysed the relationship between the presence of pedal pulses and distal systolic measurements in a group of 132 non-diabetic men and women suspected of having PVD in order to see how much diagnostic information could be gained from the pedal pulse alone (Christensen et al, 1989). The group were aged 62 years, half were men and they had claudication, rest pain or ulcers of presumed arteriosclerotic origin. In general, the presence of palpable pedal pulses is usually associated with an ankle systolic pressure  $> 50\%$  (as a percentage of systemic systolic pressure) and toe systolic pressure  $> 40$  mmHg (Christensen et al, 1989), signs usually conferring good prognostic information. Where pulses were absent in both feet the ankle pressure was below 90% (median 50%). Repeated assessment of the pulses in the feet over time was found to be useful in following the progress of peripheral arterial disease as well as healing of any ulcer present (Christensen et al, 1989). Elhadd et al (1999) demonstrated that in a hospital clinic population with no symptoms of any

macrovascular disease, palpation of peripheral pulses is useful to exclude significant vascular disease whilst the absence of pulses is indicative of a reduced ABI (<0.9) in only half the patients. Walters et al (1992) studied the predictive values of a history of claudication or the absence of 2 or more pedal pulses in identifying PVD defined in terms of an ABI  $\leq$  0.9. In 1058 diabetic people, absent pedal pulses gave a sensitivity of 70%, specificity of 93% and positive predictive value of 72% for PVD.

In a cross-sectional study, 631 diabetic veterans in a general medical clinic in the US had a history and clinical evaluation for the presence of PVD (Boyko et al, 1997). The criterion for the presence of PVD was an ankle brachial pressure index (ABI)  $\leq$  0.5, derived from Doppler blood pressure measurements of ankle and brachial systolic pressures. Pulses were recorded as absent in one foot only if both pulses were absent. Absent peripheral foot pulses had a sensitivity of 65% and a specificity of 78% for detecting an ABI with  $\leq$  0.5. Diminished foot pulses and delayed venous filling were associated with the highest positive likelihood ratios. Classical signs such as decreased hair, or skin or atrophy were not clinically useful. Diminished or absent peripheral pulses in a leg gave a sensitivity of 65.2% and a specificity of 78.3% with a positive likelihood ratio of 3 (CI 2.3-3.9) and a negative likelihood ratio of 0.4 (CI 0.3-0.7). In multivariate analysis the authors found that a negative history of peripheral vascular disease and palpable peripheral pulses effectively ruled out the presence of a critical reduction in lower limb perfusion (Boyko et al, 1997).

### **The absence of foot pulses increases the likelihood of amputation**

The absence of peripheral pulses has prognostic significance. In a study of 314 mainly Type 2 diabetic people with foot ulceration who were followed prospectively, feet requiring amputation were more likely to have absent pedal pulses (77% of feet requiring amputation compared with 44% not requiring amputation,  $p < 0.001$ ) (Apelqvist et al, 1990).

In another study, the absence of palpable peripheral pulses predicted amputation (which occurred in 5.6% of men and 5.3% in women) in a Finnish cohort study of people with Type 2 diabetes aged 45-64 during seven years follow-up RR 3.9,  $p < 0.001$ ) (Lehto et al, 1996).

## Summary – Clinical Detection of Peripheral Vascular Disease

- Peripheral vascular disease is common in people with Type 2 diabetes and is an important risk factor for amputation
- The presence of symptoms of intermittent claudication has a sensitivity of 50% and a specificity of 87% for peripheral vascular disease determined by an ankle arm index  $> 0.5$
- Approximately 30% of people with diabetes and peripheral vascular disease experience intermittent claudication
- The presence of palpable pedal pulses is a good predictor of adequate peripheral circulation but their absence is only a moderate predictor of peripheral vascular disease.
- Both dorsalis pedis and posterior tibial pulses should be to be impalpable for the designation “absent foot pulses”
- A negative history of peripheral vascular disease together with palpable peripheral pulses usually excludes a critical reduction in limb perfusion
- History of claudication and palpation of peripheral pulses are reliable in detecting peripheral vascular disease in a routine practice setting
- The absence of peripheral pulses has prognostic significance for future amputation in people with diabetes with and without foot ulceration

## Evidence Table: Section 6

### Clinical detection of peripheral vascular disease

| Author   | Evidence          |        |                   |                |                  |                  |
|--|-------------------|--------|-------------------|----------------|------------------|------------------|
|  | Level of Evidence |        |                   | Quality Rating | Magnitude Rating | Relevance Rating |
|  | Level             | Rating | Study Type        |                |                  |                  |
| <b>Apelqvist J (1990)</b><br>(Adults – Sweden)             | II <sup>#</sup>   | High   | Cohort            | Medium         | High             | High             |
| <b>Boyko EJ (1997)</b><br>(Adults – US)                    | III <sup>#</sup>  | Medium | Cross-sectional   | Medium         | High             | High             |
| <b>Christensen JH (1989)</b><br>(Adults – Denmark)         | III <sup>#</sup>  | Medium | Cross-sectional   | Medium         | Low              | Low              |
| <b>Elhadd TA (1999)</b><br>(Adults - UK)                   | III <sup>#</sup>  | Medium | Cross-sectional   | High           | High             | High             |
| <b>Faglia E (1998)</b><br>(Adults - Italy)                 | III <sup>#</sup>  | Medium | Cross-sectional   | Medium         | High             | High             |
| <b>Fowkes FG (1991)</b><br>(Adults – UK)                   | III <sup>#</sup>  | Medium | Cross-sectional   | High           | High             | High             |
| <b>Lehto S (1996)</b><br>(Adults – Finland)                | II <sup>#</sup>   | High   | Cohort            | High           | High             | High             |
| <b>McGee SR (1998)</b>                                     | I <sup>#</sup>    | High   | Systematic review | High           | High             | Low              |
| <b>Robertson GSM (1990)</b><br>(Adults & Adolescents – UK) | III <sup>#</sup>  | Medium | Cross-sectional   | Low            | High             | Low              |
| <b>Walters DP (1992)</b><br>(Adults –UK)                   | III <sup>#</sup>  | Medium | Cross-sectional   | High           | High             | High             |

<sup>#</sup>Studies with no intervention

## Section 7: Diabetic Foot Disease

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### Issue

What should be the frequency of foot examination?

### Recommendation

The routine surveillance for foot problems in people with diabetes should be performed in the following way:

- in people where no foot complications have previously been found, the minimum frequency of foot examination should be once a year
- in people with at risk feet but without a current active problem, foot examination should be performed every 3 to 6 months

## Background – Frequency of Foot Examination

While people with diabetes who have peripheral neuropathy, foot deformity, history of previous ulceration or amputation and/or PVD are a group at increased risk of ulceration and amputation, no studies have been done to assess the impact of the frequency of examination on outcomes. It is generally accepted that regular surveillance for foot problems is good clinical practice. The benefits of monitoring people with diabetes arise from the ability to detect feet at increased risk and from the identification of specific foot problems which can be treated early which has the potential to reduce subsequent morbidity.

The lack of routine foot examination is a major issue in the care of people with diabetes. In the UK 47% of people undergoing amputation had an incomplete foot examination on admission to hospital (Deerochanawong et al, 1992). In a New Zealand survey 40% of people with diabetes reported they had not had their feet examined in the previous year (Simmons et al, 1995) and 56% of people with diabetes in the US in urban primary care had not had their feet examined in the past two years (Whyle Rossett et al, 1995).

## Evidence – Frequency of Foot Examination

No studies were found which directly addressed the optimal frequency of foot examination in people with diabetes. However recommendations about frequency of foot examination have been made in several guidelines in Australia and overseas.

The Australian guidelines include:

- the New South Wales Department of Health ‘Guidelines for the Clinical Management of Diabetes Mellitus’ (1996) which suggests six monthly foot review of people with diabetes or at every visit if in the “high risk foot” category
- the ‘Systematic Review of Existing Evidence and Primary Care Guidelines on the Management of Non-Insulin-Dependent Diabetes in Aboriginal and Torres Strait Islander Populations’ (Couzos et al, 1998) proposes that feet should be inspected at every clinic visit, but more comprehensive (vascular and neurological) examination should be performed annually
- the position statement of the Australian Diabetes Society on the Lower Limb in People with Diabetes (Campbell et al, 2000) states that all people should have annual routine foot screening and people with ‘at risk’ feet should be inspected at each clinical visit.

The following guidelines were formulated by overseas groups:

- The US Veterans Health Administration ‘Clinical Guidelines for Management of Patients with Diabetes Mellitus’ (1997) recommend that foot examination should be performed at least annually in all people with diabetes who are over 15 years of age and at more frequent intervals for those at high risk.
- The Scottish National Clinical Guidelines (The Scottish Intercollegiate Guidelines Network, 1997) recommend annual screening examination of feet with more frequent review of people with identified risk factors.
- The European Diabetes Policy Group (1999) states that surveillance for foot problems should be a routine part of the annual review
- International Consensus on the Diabetic Foot (1999) – all people with diabetes should be examined at least once a year for potential foot problems and all people with demonstrated risk factor(s) should be examined more often (every 1-6 months).

- The UK Clinical Guidelines for Type 2 Diabetes – prevention and management of foot problems recommend annual routine screening for foot problems
- The American Diabetes Association (2001) suggests at least annual review with more frequent evaluation once risk factors are detected. People with neuropathy should have a visual inspection of their feet at every visit.

There is therefore general agreement that good clinical practice in the management of people with diabetes includes the following routine surveillance for foot problems:

- in people where no foot complications have previously been found, the minimum frequency of foot examination should be once a year as part of the annual review
- in people with at risk feet but without a current active problem, a foot examination should be performed every 3 to 6 months

## Summary – Frequency of Foot Examination

- No studies have examined the impact of frequency of foot examination on clinical outcomes in people with diabetes
- There is general agreement that people with diabetes should have their feet examined every year for risk factors and if risk factors are identified feet should be examined more frequently

## Summary Table: Section 7

### Frequency of foot examination

| Author   | Evidence                   |        |                               |                |                  |                  |
|--|----------------------------|--------|-------------------------------|----------------|------------------|------------------|
|  | Level of Evidence          |        |                               | Quality Rating | Magnitude Rating | Relevance Rating |
|  | Level                      | Rating | Study Type                    |                |                  |                  |
| American Diabetes Association (2001)                                 | Not Appropriate for Review |        | Position Statement            |                |                  |                  |
| Australian Diabetes Society (2000)                                   | Not Appropriate for Review |        | Position Statement            |                |                  |                  |
| Couzos S (1998)<br>(Australia: Aboriginal & Torres Strait Islanders) | I                          | High   | Systematic Review             | High           | High             | High             |
| European Diabetes Policy Group (1999)                                | Not Appropriate for Review |        | Consensus Guidelines          |                |                  |                  |
| New South Wales Dept Health (1996)                                   | Not Appropriate for Review |        | Evidence/Consensus Guidelines |                |                  |                  |
| Scottish Intercollegiate Guidelines Network (1997)                   | I                          | High   | Systematic Review             | High           | High             | High             |
| UK Guidelines (1999)   | I                          | High   | Systematic Review             | High           | High             | High             |
| Veterans Health Administration (1997)                                | I                          | High   | Systematic Review             | High           | High             | High             |

## Section 8: Diabetic Foot Disease

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### Issue

Does patient education improve foot self care and outcomes?

### Recommendation

People with diabetes at increased risk of foot problems should receive specific footcare education.

### Evidence Statements

- Footcare education for people with diabetes improves knowledge and may improve self care behaviour  
*Evidence Level II*
- Footcare education for people with diabetes may prevent serious foot lesions and amputation  
*Evidence Level II*

\*Studies with no intervention

## Background – Patient Education and Foot Disease

An integral part of any strategy to reduce diabetes foot problems requires people with diabetes to have adequate knowledge to be able to take appropriate action to minimise their risk of developing foot complications (Levin, 1995). There is clear evidence that this does not always occur despite activities involved in self care and podiatry attendance being in themselves simple procedures. Deficiencies in self care of feet can occur because people with diabetes have received inadequate information or are not aware of the importance of, or are unable to perform, foot self care behaviour. Studies have shown that 89% of people with diabetes whose feet are at increased risk are making multiple errors in their foot self care behaviour (Plummer & Albert, 1995). Unfortunately the healthcare system does not currently provide easily accessible education or podiatry services for people with diabetes whose feet are “at risk” (Fletton et al, 1995). Those who are physically unable to practice self footcare due to age or a disability, like visual impairment, are often dependent on family or carers who must also be involved in the educational process. Also people with a lower socio-economic status have increased risk of foot ulceration and poorly fitting (or lack of) footwear (Day & Harkless, 1997).

The extent and nature of the education necessary to prevent the development of diabetic foot complications and the means of selection of appropriate education for each patient is another important issue. There is a general lack of consistency of educational interventions which have used different methods and a variety of target populations, settings and methods of follow-up which complicates interpretation of educational studies because patients may be at different phase of the disease process and therefore may respond differently to education (Mason et al, 1999).

Even the most successful footcare education programs whose results have been published have not necessarily continued to be used in the institutions where they were conducted (Pichert & Penha, 1993). Footcare education programs seem to need to be part of a coordinated approach to footcare where staff also receive education and prompting to perform routine footcare tasks.

## Evidence – Patient Education and Foot Disease

### **Footcare education for people with diabetes improves knowledge and may improve self care behaviour**

Mason et al (1999) reviewed 5 randomised footcare educational studies which included people with Type 2 diabetes and concluded that since there were no consistent patterns in study methods or findings that it was necessary to interpret the results of each study individually.

Rettig et al (1986) evaluated the effectiveness of a general diabetes and footcare home education provided by a nurse in 228 people with Type 2 diabetes and 243 matched controls who did not receive home education. After 6 months foot knowledge score was significantly higher in the intervention group but there were no differences in footcare skill scores or foot appearance scores. At 12 months there no differences in hospitalisations between the 2 groups.

Bloomgarden et al (1987) evaluated a diabetes clinic education (general and footcare) program in 266 people with insulin treated diabetes (127 intervention and 139 controls). Knowledge

score (which did not include any question related to feet) and behaviour score (which included 1 question about frequency of foot inspection) improved significantly in the intervention group but there were no differences in the development of minor or severe foot lesions over an 18 month period.

Barth et al (1991) compared a conventional group education program with a similar program which included 4 additional footcare sessions based on a cognitive motivational technique in 70 Australian people with Type 2 diabetes with sub-optimal glucose control and who had not attended a diabetes education program in the past six months. The intensive footcare program resulted in better compliance with footcare, better footcare knowledge and more frequent compliance with advice to consult a podiatrist at 1 month but these effects were no longer significant after 6 months.

Kruger et al (1992) evaluated a conventional education program in 50 people with diabetes which included in the intervention group, participatory hands-on footcare teaching and learning sessions and provision of a footcare kit. After 6 months there were no differences in knowledge score or self reported foot inspection behaviour, daily foot washing or trimming toenails.

In 395 people with Type 2 diabetes having footcare education in groups of 1-4 by nurse clinicians in a general practice setting were evaluated (Litzelman et al, 1993). The study was a blinded randomised controlled trial in an academic practice providing care predominantly to poorly educated black women. Participants entered into a behavioural contract regarding footcare which included reminders, and healthcare providers of people in the intervention group were given guidelines and flow sheets with prompting in the notes for foot examination and education. People receiving the intervention reported significantly more appropriate self care behaviours, foot examinations and footcare education during regular office visits, more frequent but still low rates of podiatry referral (10.6% compared to 5%  $p=0.04$ ), less serious foot lesions at 1 year but no difference in any foot lesion or amputations.

In a prospective case control study in a rural general practice setting, footcare education was provided to 53 people with Type 2 diabetes as part of a treatment and teaching program by trained general practitioners (Pieber et al, 1995) and compared with 55 people who did not receive any specific instruction. Intervention resulted in a significantly higher knowledge score, less callus, less interdigital problems and better toenail care at 6 months.

Ronnemaa et al (1997) randomised 530 people with both Type 1 and Type 2 diabetes who had not visited a podiatrist in the previous 6 months and who were not in obvious need of podiatry care to received education and primary preventative care from a podiatrist or to receiving only written instructions. After 1 year knowledge of footcare and self care of feet had improved significantly more in the podiatrist group compared with the control group.

In summary, available studies on the effects of footcare education provide inconsistent results about the value of foot education and their interpretation is hampered by inconsistent interventions, major differences in populations studied, the use of different endpoints and the generally short duration of follow up. The results of the 7 studies reviewed in this section show the following results 6 to 18 months after various educational interventions:

- Significantly improved knowledge in 4, no difference in 2, while 1 study did not report on this parameter

- Significantly improved foot self care 3, no difference in 3, while 1 study did not report on this parameter
- Significant improvements in some objective signs of foot outcomes in 2, no difference in 2 while this was not assessed in 3 studies

These studies suggest that education can improve knowledge and may improve self care behaviour but also clearly indicate that more research is required to address this question.

### **Footcare education for people with diabetes may prevent serious foot lesions and amputation**

Relatively few studies have addressed the issue of footcare education in the prevention of ulceration or amputation. As reviewed above, Litzelman et al (1993) observed a borderline significantly lower number of serious foot lesions including ulcer (OR 0.41, CI 0.16-1;  $p=0.05$ ) over 12 months in people with Type 2 diabetes who received footcare education by a nurse clinician. There were no differences in rates of amputation. Although not fully described in the publication, these subjects did not appear to be at particularly increased risk of foot problems.

Malone et al (1989) performed a prospective randomised study of footcare education compared with no footcare education in 203 people with diabetes who had foot ulcers or had had a previous amputation. The education intervention consisted of viewing slides of infected feet and amputated limbs and the provision of simple foot self care instructions. There were significantly more ulcers (15% v 5%,  $p<0.005$ ) and amputations (12% v 4%,  $p<0.025$ ) in the group which did not receive education compared with the education group during a 1-26 month follow up period. The study report does not provide demographic data of the study population or data about baseline comparability of the 2 groups.

## **Summary – Patient Education and Foot Disease**

- Available studies on the effects of footcare education provide inconsistent results about the value of foot education and their interpretation is hampered by inconsistent interventions, major differences in populations studied, the use of different endpoints and the generally short duration of follow up
- Overall studies suggest that education can improve knowledge and may improve self care behaviour and some foot outcomes but also indicate that more research is required to address this question
- One randomised study reported a borderline significantly lower number of serious foot lesions including ulcer over 12 months in people with Type 2 diabetes who received footcare education by a nurse clinician
- One randomised study of footcare education in people with high risk feet reported significantly less ulcers and amputations during a 1-26 month follow up period
- The ideal content, nature and frequency of education necessary to achieve improved outcomes is unknown

## Evidence Table: Section 8

### Effect of patient education

| Author  | Evidence          |        |                   |                |                  |                  |
|---|-------------------|--------|-------------------|----------------|------------------|------------------|
|   | Level of Evidence |        |                   | Quality Rating | Magnitude Rating | Relevance Rating |
|   | Level             | Rating | Study Type        |                |                  |                  |
| <b>Barth R (1991)</b><br>(Adults – Australia)   | II                | High   | RCT               | Medium         | Medium           | High             |
| <b>Bloomgarden ZT (1987)</b><br>(Adults – US: majority African American and Hispanic) | II                | High   | RCT               | Medium         | Medium           | Low              |
| <b>Kruger S (1992)</b><br>(Adults – US)   | II                | High   | RCT               | Medium         | Low              | High             |
| <b>Litzelman DK (1993)</b><br>(Adults – US)   | II                | High   | RCT               | High           | High             | High             |
| <b>Malone JM (1989)</b><br>(Adults – US)  | II                | High   | RCT               | Medium         | High             | High             |
| <b>Mason J (1990)</b>   | I                 | High   | Systematic review | High           | High             | High             |
| <b>Pieber TR (1995)</b><br>(Adults – Austria)   | III-2             | Medium | Cohort            | Medium         | High             | High             |
| <b>Rettig BA (1986)</b><br>(Adults – US)  | II                | High   | RCT               | Low            | High             | High             |
| <b>Ronnemaa T (1997)</b><br>(Adults & children – Finland)                             | II                | High   | RCT               | High           | High             | High             |

<sup>#</sup>Studies with no intervention

## Section 9: Diabetic Foot Disease

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### Issue

Does improved glycaemic control decrease the incidence of peripheral neuropathy?

### Recommendation

Aim to achieve the best possible glycaemic control in people with Type 2 diabetes in order to prevent or reduce the development of peripheral neuropathy which is a major risk factor for foot ulceration and amputation.

### Evidence Statements

- The incidence of peripheral neuropathy in Type 2 diabetes is related to the long-term glycaemic control  
*Evidence Level I*
- Improved glycaemic control can prevent or reduce the development of peripheral neuropathy in people with Type 2 diabetes  
*Evidence Level II*

<sup>a</sup>Studies with no intervention

## Background – Glycaemic Control and Peripheral Neuropathy

The strong correlation between better glycaemic control and a lower incidence of diabetic complications has been known for a long time (Pirart, 1978). There is also a strong relationship between the level of impaired glycaemic control and the severity of diabetic peripheral sensorimotor polyneuropathy (Tkac & Bril, 1998).

As reviewed in Section 1, peripheral neuropathy is a major predisposing condition for ulceration and amputation in people with diabetes. The question therefore arises as to whether achievement of near normal blood glucose levels prevents or reduces the development of peripheral neuropathy as is observed with other microvascular complications. Clinical peripheral neuropathy may be more difficult to quantitate accurately compared with the microvascular complications of nephropathy (albuminuria) and retinopathy. Studies have utilised different methodologies including nerve conduction studies, vibration perception threshold, monofilament perception and clinical scoring systems.

The Diabetes Control and Complications Trial (DCCT) in people with Type 1 diabetes clearly demonstrated that intensive treatment which improved diabetes control could delay the onset or slow the progression of peripheral neuropathy compared with conventional therapy (DCCT, 1993). The risk of developing peripheral neuropathy was reduced by 69% in those without neuropathy and progression was reduced by 67% in those who already had other microvascular complications.

This Section addresses the question of whether a similar effect can be achieved in people with Type 2 diabetes with improved diabetes control.

## Evidence – Glycaemic Control and Peripheral Neuropathy

### **The incidence of peripheral neuropathy in Type 2 diabetes is related to the long-term glycaemic control**

In 1998, prior to the United Kingdom Prospective Diabetes Study (UKPDS) study, Gaster & Hirsh (1998) reported the results of a systematic review of 20 prospective observational English language studies published since 1970 which examined the association between hyperglycaemia and microvascular complications and neuropathy. This review pointed out the similarity of microvascular and neuropathic complications in both Type 1 and Type 2 diabetes when adjusted for level of hyperglycaemia and identified a strong association between hyperglycaemia and complication rate, although only 2 studies included measurements for neuropathy (Gaster & Hirsh, 1998).

The Wisconsin Epidemiological Study of Diabetic Retinopathy studied all insulin requiring people in an 11 county area of southern Wisconsin and a sample of 1780 older onset people with diabetes (Klein et al, 1996). After 10 years, data were available for 85% of the original cohort and showed an exponential relationship between the extent of complications and worsening glycaemic control (Klein et al, 1996). There was a similar relationship between young and mature onset people with diabetes for any given level of hyperglycaemia. This relationship was remarkably similar to that of the DCCT trial for retinopathy, proteinuria and neuropathy (Klein et al, 1996; Klein & Moss, 1995).

## **Improved glycaemic control can prevent or reduce the development of peripheral neuropathy in people with Type 2 diabetes**

The Kumamoto study randomised 110 Japanese people with Type 2 diabetes who were non-obese (body mass index 16.4-23.5 kg/m<sup>2</sup>) (Ohkubo et al, 1995) to receive intensive therapy with multiple insulin injections or conventional insulin therapy. The study included both primary and secondary prevention groups. After 6 years HbA<sub>1c</sub> levels were 7.1% in the intensively treated group which was significantly lower than the 9.4% in conventionally treated group. Neuropathy, assessed by lower extremity vibration threshold was observed in 12.8% of the intensively treated group compared with 64% in the conventionally treated group (p<0.05). This relevance of these findings to obese Caucasian people with Type 2 has been questioned.

In a previous Japanese randomised study of intensified glycaemic control with multiple insulin injections in 50 people, 9 with Type 1 and 41 with Type 2 diabetes, Hotta et al (1993), demonstrated that improving HbA<sub>1c</sub> from approximately 10% to 8% with multiple insulin injections achieved a significant difference in ulnar nerve conduction velocity over a 4 year period. However there was no direct evidence of an effect on clinical neuropathy since vibration perception threshold did not change in either group.

The UKPDS study compared intensive treatment with diet or medications and less intensive control in 5102 people with newly diagnosed Type 2 diabetes who were followed for at least 10 years. The percentage of subjects at entry to the study with a vibration perception threshold over 25 volts assessed with the biothesiometer was similar in the conventional and intensive group (11.4% and 11.8% respectively). The median HbA<sub>1c</sub> over 10 years in the intensive policy group was 7% compared with 7.9% in the conventionally treated group. Significantly less people in the intensive policy group had an impaired vibration sensory threshold (31.2% vs 51.7%, p<0.005) at the end of the study period (UKPDS 33, 1998).

There are little data on whether diabetic neuropathy can be reversed by improving glycaemic control in people with Type 2 diabetes. In a one year intervention 34 elderly Swedish people with Type 2 diabetes (mean age 75.2 years) were randomised to treatment with insulin or sulphonylureas. Neuropathy was present in 56% at entry to the study and did not alter over one year despite a reduction in HbA<sub>1c</sub> from 9.2 ± 1.4% to 7.3 ± 1.1% (p<0.001) in the insulin treated group (n=18). The sulphonylurea treated group (n=16) had an initial HbA<sub>1c</sub> of 9.1 ± 1.2% and did not change significantly throughout the study period. The one year duration of study could be inadequate to detect any significant change of neuropathy (Tovi et al, 1998). The answer to this question may be provided by a sub-analysis of data collected during the UKPDS study.

## Summary – Glycaemic Control and Peripheral Neuropathy

- There is a direct relationship between worsening glycaemic control and the incidence of peripheral neuropathy in people with Type 2 diabetes
- There is strong evidence that improvement in glycaemic control is effective in reducing the risk of the development and progression of neuropathy in Type 2 diabetes
- There is no evidence that established neuropathy can be reversed by improving diabetes control

## Evidence Table: Section 9

### Glycaemic Control and Peripheral Neuropathy

| <b>Author</b>                              | <b>Evidence</b>          |               |                   |                       |                         |                         |
|--|--------------------------|---------------|-------------------|-----------------------|-------------------------|-------------------------|
|  | <i>Level of Evidence</i> |               |                   | <i>Quality Rating</i> | <i>Magnitude Rating</i> | <i>Relevance Rating</i> |
|  | <i>Level</i>             | <i>Rating</i> | <i>Study Type</i> |                       |                         |                         |
| <b>Gaster B (1998)</b>                     | I                        | High          | Systematic Review | High                  | High                    | High                    |
| <b>Hotta N (1993)</b><br>(Adults – Japan)  | II                       | High          | RCT               | Medium                | High                    | Medium                  |
| <b>Klein R 1996)</b><br>(Adults – US)      | #<br>II                  | High          | Cohort            | High                  | High                    | High                    |
| <b>Ohkubo Y (1995)</b><br>(Adults – Japan) | II                       | High          | RCT               | Medium                | High                    | Medium                  |
| <b>Tovi J (1998)</b><br>(Adults – Sweden)  | II                       | High          | RCT               | Medium                | High                    | High                    |
| <b>UKPDS 33 (1998)</b><br>(Adults – UK)    | II                       | High          | RCT               | High                  | High                    | High                    |

<sup>#</sup>Studies with no intervention

# Section 10: Diabetic Foot Disease

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## Issue

Does appropriate footwear reduce ulceration and amputation?

## Recommendations

People with diabetes should be encouraged to wear properly fitted, cushioned footwear and padded socks.

People with diabetes with high risk feet require special attention to footwear.

## Evidence Statements

- Therapeutic footwear reduces the risk of ulcer recurrence  
*Evidence Level I*
- Therapeutic footwear combined with podiatry care reduces the risk of amputation in high risk individuals  
*Evidence Level II*
- Plantar foot pressures are influenced by footwear  
*Evidence Level III-2*
- Callus formation can be reduced by certain footwear  
*Evidence Level II*
- Padded socks reduce plantar pressure  
*Evidence Level III-2*

\*Studies with no intervention

## Background – Footwear to Reduce Ulceration and Amputation

A pivotal or initiating event commonly precedes the development of a foot ulcer or leads to an amputation (Pecoraro et al, 1990). This may be an acute traumatic event, such as stepping on a tack, or the result of abnormal pressure on the foot, such as wearing new or ill fitting shoes or socks. Pressure ulcers, also called stress ulcers or mal perforans, frequently result from repetitive low-pressure stress of walking on an unprotected neuropathic foot, resulting in repeated friction over prominences such as a plantar callus. In addition they may result from ingrown toenails or from immobilisation in a bed or chair. This initiating event superimposed on an at risk foot (eg insensate or with vascular insufficiency) is often the critical factor which may ultimately lead to amputation (Mayfield et al, 1996).

Apelqvist et al (1990) studies 314 consecutive people with diabetes and a foot ulcer and identified an acute traumatic precipitating event in 18%, ill fitting shoes or socks in 39%, mal perforans in 12%, paronychia in 6%, decubitus pressure in 4.5%, and no obvious precipitating event in 16%. In another study shoe trauma preceded ulceration in 47% of 386 ulcers in 239 patients (Edmonds et al, 1986).

Mayfield et al (1996) in a retrospective study of 61 diabetic Pima Indians who underwent an amputation identified trauma as the pivotal event in 44% (shoe trauma 8% of total) and new onset ulcer without trauma, many of which were probably mal perforans, in 39%.

Elevated plantar pressure is causally related to the occurrence of foot ulcers in people with diabetes with neuropathy (Veves et al, 1992). As well as exposing the foot to injury, barefoot walking is associated with higher foot pressures than wearing shoes. In addition the type of footwear also has a significant influence on plantar pressures (Lavery et al, 1997; Kastenbauer et al, 1998).

Tovey (1984) has detailed the desirable characteristics of appropriate diabetic footwear aiming to reduce shock and shear, and accommodate, stabilise and support deformities.

- width to accommodate the first metatarsophalangeal joint
- length should allow about 1cm between the end of the shoe and the longest toe
- depth to allow sufficient room in the toe area and instep
- laces to adjust for oedema and deformities
- snug fit of heel without undue motion
- wide low heels to improve stability.

Most people at risk of ulceration can be protected with the use of manufactured, extra depth, cushioned footwear. Those with previous ulceration, significant deformity or amputation will require custom made insoles and in some cases, custom made footwear. Custom made orthopaedic footwear is expensive, costing considerably more than manufactured footwear.

In addition, acceptance and use of custom made orthopedic footwear is poor. A survey of 62,170 people with diabetes who were Medicare beneficiaries in 3 American states found low utilisation of therapeutic footwear. Of the 13% who fell into the “high risk” group, only 2.9% claimed for footwear and of the 14% with possibly increased risk, claims were made by only 0.7% (Sugarman et al, 1998). Other authors also report low levels of compliance with therapeutic footwear, often related to the appearance of the footwear (Chantelau & Haage, 1994; McCabe et al, 1998). In contrast, specially designed, extra depth, extra width, shoes

with a rocker bottom were well accepted by 24 male Veterans with 88% compliance (Reiber et al, 1997).

Attention to footwear provides an opportunity to improve outcomes for people with at high risk feet.

## Evidence – Footwear to Reduce Ulceration and Amputation

### **Therapeutic footwear reduces the risk of ulcer recurrence**

Mason et al (1999) performed a systematic review of diabetic foot ulcer prevention strategies and identified two randomised trials (Colagiuri et al, 1995; Uccioli et al, 1995) on the effect of therapeutic footwear. Although these showed a beneficial effect, Mason et al recommended confirmatory studies on larger numbers of people with diabetes with comparisons of 'optimised' normal shoes and special therapeutic shoes to confirm the relative effectiveness and cost-effectiveness of wearing therapeutic shoes.

A multicentre, randomised controlled trial assessed therapeutic footwear and ulcer recurrence in people with previous foot ulcers (Uccioli et al, 1995). Manufactured therapeutic shoes were designed according to Tovey's guidelines (1984) as previously described. Customised insoles were also provided. Foot ulcer relapses were significantly lower in the group of 33 wearing therapeutic shoes compared with the control group of 36 wearing their own shoes (27.7% v 58.3%, OR 0.26, CI 0.2-1.54;  $p=0.0009$ ). In multiple regression analysis adjusted for severity of disease, age and sex, the use of therapeutic shoes was negatively associated with foot ulcer relapse (coefficient of variation - 0.315, CI -0.54 to -0.08;  $p=0.009$ ).

A cohort of 51 people with diabetes were provided with protective footwear, cushioned with insoles after healing of a neuropathic foot ulcer and followed up for up to 4 years (Chantelau & Haage, 1994). In those who wore the protective footwear for >60% of daytime hours, ulcer recurrence was reduced by 50% ( $p=0.0002$ ) compared with those who wore their footwear less frequently. After 2 years, the protective effect wore off, suggesting that footwear needed adaptation and renewal within this time period. In addition people without ulcer relapses had a significantly increased frequency of attending for foot-care including callus removal and nail cutting ( $p<0.05$ ).

A cohort of 352 people with Type 2 diabetes were followed over 12 months to assess the impact of footwear on the development of foot wounds (Litzelman et al, 1997). At examination at 12 months 63 feet (53 people) had either a blister or wound. Contrary to expectation, a recommendation to wear special footwear was associated with increased risk of foot wounds at follow up (OR 2.19, CI 1.07-4.49;  $p=0.03$ ). However the study group was not provided with therapeutic footwear or better access to therapeutic footwear and in fact only one person actually wore the special footwear.

Mayfield (1998) offers practical advice about shoe shopping recommending that the person with diabetes stand on a piece of paper and draw an outline of the foot and use this for comparison with the prospective shoe. In addition, people with evidence of elevated pressure (callus), neuropathy, bony deformities, or a previous ulcer should have their footwear fitted by a professional (Mayfield et al, 1998).

## **Therapeutic footwear combined with podiatry care reduces the risk of amputation in high risk individuals**

Protective footwear was offered to a group of high risk patients with neuropathy, previous ulceration, vascular insufficiency ( $ABI \leq 0.75$ ) and/or foot deformity, in a randomised controlled trial of a diabetic foot screening and protection program (McCabe et al, 1998). Although compliance with attendance for podiatry care and wearing protective footwear consistently was poor (46% and 36% respectively), major amputations were reduced - 1 in the intervention group compared with 12 in the control group ( $p < 0.01$ ). Greater compliance with the program may have achieved greater differences in outcomes.

## **Plantar foot pressures are influenced by footwear**

Comparisons of in-shoe foot pressure were made between 44 people with Type 1 or 2 diabetes and 65 health controls (Sarnow et al, 1994). In those with diabetes, pressures were significantly higher than controls when only socks were worn ( $p < 0.02$ ) as would be expected since 50% had peripheral neuropathy. All but two of the diabetic subjects wore comfortable shoes with insole prosthesis when needed compared to the controls who all wore ordinary shoes. In-shoe foot pressures were significantly lower in both groups than those measured when walking only in socks. There were no differences in foot pressures between the two groups when wearing shoes indicating that the wearing of shoes resulted in a greater degree of pressure reduction in people with diabetes, probably due to differences in the footwear between the groups. This study confirms that well fitting shoes have a cushioning effect and reduce foot pressures in people with diabetes.

Moderately priced running shoes were tested in a group of 13 non diabetic controls, 13 people with diabetes but no neuropathy and 13 people with diabetic neuropathy (Perry et al, 1995). Plantar pressures were reduced while wearing running shoes by  $31 \pm 9.1\%$  at the forefoot and heel regions and 44% at the second metatarsal head, the commonest site for diabetic ulceration (percentage reduction,  $r = -0.77$ ). Pressure reduction was similar in all groups although people with diabetic neuropathy had higher pressures at the metatarsal heads initially ( $p = 0.008$ ).

The effectiveness in reducing plantar pressures of commercially available shoes, comfort and cross trainers, were compared with traditional extra-depth therapeutic (Lavery et al, 1997). Each shoe was tested in 32 diabetic people with current or recently healed neuropathic foot ulcers. All shoes reduced pressures compared to a standard inexpensive, rubber-soled, canvas Oxford shoe. ( $p < 0.05$ ). The comfort shoes provided significantly lower pressures than cross trainers and extra-depth therapeutic shoes ( $p < 0.05$ ). For each shoe the addition of a visceroplastic insole provided a further significant reduction in plantar pressures compared with pressures without this insole and compared with a standard insole.

In-shoe plantar pressures were measured in 13 people with diabetes, comparing a leather-soled Oxford shoe, a custom-made insole in an extra depth shoe and a specially designed running shoe (Kastenbauer et al, 1998). The running shoe was designed for maximal pressure relief at the forefoot area. Compared with the Oxford shoe, the running shoe reduced pressures by 29% at the first metatarsal head ( $p < 0.05$ ) and 47% at the second and third metatarsal heads ( $p < 0.01$ ). The extra depth shoe with the custom made insole resulted in the greatest pressure reduction - 50% at the metatarsal heads ( $p < 0.01$ ).

### **Callus formation can be reduced by certain footwear**

A randomised controlled trial assessed the effectiveness of orthotics in reducing callus compared with routine debridement by a podiatrist performed every 3 months (Colagiuri et al, 1995). The orthotic was a custom-made rigid plastic insert worn inside running shoes. At 1 year, those wearing the orthotic (n=9) had less callus compared with the podiatry treated group (n=11) (p=0.02).

Soulier et al (1987) studied the effect of wearing running shoes on callus size. 78 people with diabetes wore the running shoes for at 80% of the time for 6 months. Compared with an observation period before the wearing of the running shoes, callus size was significantly reduced and the need to have calluses trimmed was also decreased. .

### **Padded socks reduce plantar pressure**

Plantar pressures can also be influenced by socks. The effects of experimental padded hosiery was studied in 10 people with diabetes and clinical neuropathy and compared to commercially available sports socks in another 16 diabetic people. Experimental padded hosiery reduced plantar pressures by 31.3% at baseline and 17.6% at 6 months, confirming that the protective effect can be maintained over time (Veves et al, 1990). This compared to reductions of 10.4% and 17.4% for medium and high density padded, commercially available sports socks.

## **Summary – Footwear to Reduce Ulceration and Amputation**

- Shoe trauma is frequently the pivotal event which precedes ulceration or amputation
- Therapeutic shoes and customised insoles have been shown to reduce ulcer recurrence and the severity of callus
- Therapeutic shoes in combination with podiatry care decrease amputation
- Plantar pressures are influenced by barefoot walking and type of footwear
- Plantar pressure can be reduced with moderately priced commercially available running shoes and cross trainers
- Plantar pressures can be further reduced by insoles, especially if custom-made
- Padded experimental hosiery has been shown to reduce plantar pressures
- Diabetic people with high risk feet require special attention to footwear which should be professionally fitted

### **Evidence Table: Section 10**

#### **Foot wear and effect on ulceration and amputation**

| <b>Author</b> | <b>Evidence</b> |
|---------------|-----------------|
|---------------|-----------------|

|   | <i>Level of Evidence</i> |               |                   | <i>Quality Rating</i> | <i>Magnitude Rating</i> | <i>Relevance Rating</i> |
|---|--------------------------|---------------|-------------------|-----------------------|-------------------------|-------------------------|
|   | <i>Level</i>             | <i>Rating</i> | <i>Study Type</i> |                       |                         |                         |
| <b>Colagiuri S (1995)</b><br>(Adults – Australia)             | II                       | High          | RCT               | High                  | High                    | High                    |
| <b>Chantelau E (1994)</b><br>(Adults – Germany)               | III-2                    | Medium        | Cohort            | Low                   | High                    | High                    |
| <b>Kastenbauer T (1998)</b><br>(Adults – Austria)             | III-2                    | Medium        | Case-control      | High                  | High                    | High                    |
| <b>Lavery LA (1997)</b><br>(Adults –US)                       | III-2                    | Medium        | Case-control      | High                  | High                    | High                    |
| <b>Litzelman DK (1997)</b><br>(Adults – US, African American) | III-2                    | Medium        | Cohort            | Low                   | Medium                  | Low                     |
| <b>McCabe CJ (1998)</b><br>(Adults – UK)                      | II                       | High          | RCT               | High                  | High                    | High                    |
| <b>Mason J (1999)</b>   | I                        | High          | Systematic review | High                  | High                    | High                    |
| <b>Mayfield JA (1998)</b>                                     | I <sup>#</sup>           | High          | Systematic review | High                  | High                    | High                    |
| <b>Perry JE (1995)</b> (Adults – US)                          | III-2                    | Medium        | Case-control      | Medium                | High                    | High                    |
| <b>Sarnow MR (1994)</b><br>(Adults – US)                      | III-2                    | Medium        | Case-control      | High                  | High                    | High                    |
| <b>Soulier et al (1987)</b><br>(Adults- US)                   | III-2                    | Medium        | Cohort            | Medium                | High                    | High                    |
| <b>Uccioli L (1995)</b> (Adults – Italy)                      | II                       | High          | RCT               | High                  | High                    | High                    |
| <b>Veves A (1990)</b><br>(Adults – UK)                        | III-2                    | High          | Cohort            | Medium                | High                    | High                    |

<sup>#</sup>Studies with no intervention

# Section 11: Diabetic Foot Disease

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## Issue

Do specialist foot clinics and multi-disciplinary teams decrease amputation?

## Recommendation

People with diabetes who have foot ulcers or with high risk feet should be cared for by a multi-disciplinary service which should include at least a physician and podiatrist and have ready access to a specialist nurse, orthotist and surgeon.

## Evidence Statements

- A multi-disciplinary specialist footcare team can reduce ulceration and amputation in people with high risk feet  
*Evidence Level III-2*
- The multi-disciplinary footcare team commonly includes a physician, podiatrist, specialist nurse, orthotist and surgeon  
*Evidence Level III-2*

<sup>†</sup>Studies with no intervention

## Background – Foot Clinics and Multi-disciplinary Teams

Recommendations to prevention amputation in people with diabetes with high risk feet include regular foot examination, education, suitable footwear and orthotics, podiatry services, and early ulcer treatment including surgery where indicated (Mason et al, 1999). Implementation of these recommendations cannot be achieved easily by one category of health provider and are best achieved with a multi-disciplinary team approach. Providing this recommended care requires the services of a physician, podiatrist, diabetes educator and vascular or orthopaedic surgeon (Bild et al, 1989). Unfortunately multi-disciplinary diabetes foot clinics are not common in Australia and most people receive their care in different sites and some have geographical difficulty in accessing a complete range of services.

Because of cost implications and geographic considerations it is important to evaluate whether a multi-disciplinary team approach can reduce amputation in high risk subjects. Even if this can be demonstrated, the provision of such services will still remain a challenge in many parts of Australia.

## Evidence – Foot Clinics and Multi-disciplinary Teams

### **A multi-disciplinary footcare team can reduce ulceration and amputation in people with high risk feet**

The studies identified are difficult to compare because there is no universal definition of multi-disciplinary care and the settings in which such care is offered vary from primary care to hospital specialist referral clinics. Studies are either retrospective or prospective cohort studies and true randomisation of high risk subjects to routine care or specialised clinic is virtually impossible and probably unethical.

In Manchester, UK, a weekly diabetic foot clinic with a multi-disciplinary team was established at the district hospital to which diabetic people with foot lesions were referred from a wide range of sources, assessed and treated (Thomson et al, 1991). They were discharged from the clinic once adequate provision for follow up podiatry had been made. Type 2 diabetes was present in 73% of people and only 7% of ulcers were purely ischaemic. Ulcer healing was obtained in 81% of cases and the annual amputations in the subsequent 3 years were reduced by 40% compared to prior years (Thomson et al, 1991).

A predominantly descriptive report from Italy detailed the effects of setting up of a multi-disciplinary hospital foot clinic which provided intensive management of ulcers with patient education, surgery and detailed follow up of foot lesions (Ghirlanda et al, 1997). People attending the clinic had underlying neuropathy and presented with ulcers (66%), soft tissue infections (30%), necrosis of at least one toe (24%) and osteomyelitis (10%). In the 250 people evaluated over the initial three year period, no amputation was necessary. 98% of people with neuropathy had healing of their lesion, 10% had ulcer recurrence at the primary site, 4% at a different site and 5% had osteomyelitis at other locations (Ghirlanda et al, 1997).

A Swedish retrospective study reported the changes in diabetes related amputation following the implementation in 1983 of a multi-disciplinary footcare team program for prevention and treatment of diabetic foot ulcers (Larsson et al, 1995). The team consisted of a diabetologist,

orthopaedic surgeon, diabetes nurse, podiatrist and orthotist. From 1982 to 1993 294 people with diabetes (mean age 77 years) had 387 amputations. During this period the total annual number of amputations decreased from 38 to 21 and the total annual incidence of primary amputations decreased by 49%. Per 1000 people with diabetes the total incidence of amputation decreased from 7.9 to 4.1 and of major amputation from 6.7 to 1.5. Reamputation rate decreased from 36 to 22%. These findings indicate that a multi-disciplinary approach plays an important role in reducing major amputations in people with diabetes (Larsson et al, 1995).

Edmonds et al (1986) reported the 3 year outcomes of a specialised foot clinic for diabetic people with foot ulcers which was attended by a podiatrist, shoe-fitter, nurse, physician and surgeon. This multi-disciplinary approach achieved an 86% healing rate in neuropathic ulcers and a 72% healing in ischaemic ulcers. They also observed that ulcer relapse rate in those with special shoes was 25% compared with 83% in those who wore their own shoes. There were 19 amputations over the 3 years compared with 23 in 2 years before the establishment of the clinic (Edmonds et al, 1986).

A further prospective cohort study highlighted the importance of podiatry and vascular surgery collaboration in managing risk foot ulceration in a mixed group with and without diabetes who attended an urban hospital clinic in Arizona, US (Van Gils et al, 1999). Of the 124 high risk subjects of whom 90 had diabetes, there was an 85% limb salvage rate after primary ulcer and a 93% salvage rate over a 5 year follow up (Van Gils et al, 1999).

A 4 year prospective study in a diabetic foot clinic in London examined people who had had renal transplantation (Foster et al, 1995). The study included 50 people with Type 1 or Type 2 diabetes (mean age  $49.2 \pm 11$  years). Foot lesions were treated early in a standardised way with debridement of callus, antibiotics and special footwear with admission and surgery for non-healing lesions or where cellulitis or necrosis was present. 47 classic neuropathic ulcers and 6 ischaemic ulcers developed over the 4 years. There was 94% healing of neuropathic ulcers with a mean healing time of  $11.1 \pm 16.3$  weeks and 50% healing of ischaemic ulcers with a healing time of  $32.7 \pm 24$  weeks. 4 out of the 50 subjects developed digital gangrene compared with 9 of 56 people attending the renal transplant clinic in the 4 years before the clinic was established ( $p < 0.05$ ) (Foster et al, 1995).

In a rural primary care setting a prospective study of American Indians compared 3 time periods, one of standard care at the discretion of the primary care provider, a second phase which included screening and education together with protective footwear, and a third phase during which comprehensive guidelines for foot management were adapted by the primary care clinicians for their practices (Rith-Najarian et al, 1998). 639 individuals (mean age 54 years and duration of diabetes 8-9 years) were involved in the 3 periods of observation. During the first phase the incidence of amputation was 29 per 1000 diabetic person years, 21 per 1000 during the second phase and 15 per 1000 during the final period: an overall 48% reduction ( $p = 0.16$ ). Overall the incidence of a first amputation declined from 21 per 1000 to 6 per 1000 ( $p < 0.001$ ). The provision of education, footwear and the implementation of customised practice guidelines with a footcare team reduced amputation in a rural primary care setting. (Rith-Najarian et al, 1998).

A prospective non randomised controlled study from Lithuania has assessed a multi-disciplinary approach to diabetic footcare on recurrent ulceration and amputation (Dargis et al, 1999). 145 diabetic people with a past history of neuropathic foot ulcers but no evidence of peripheral vascular disease were studied. All received baseline assessment and footcare education. People in the intervention group ( $n = 56$ ) were followed in a special clinic by a multi-

disciplinary team of physicians, nurses and podiatrists and received regular podiatry and reeducation every 3 months and provision of special footwear as required. Scotch casting was also available to aid ulcer healing. The standard treatment group was followed in their local clinic every 3 months for routine care. Subjects in the two groups had a similar mean age of 59 and had similar incidence of neuropathy. Two of the intervention group and 8 of the standard treatment group were hospitalised with ulcers. The intervention group had significantly fewer recurrent ulcers during the two years than the standard group (30.4% v 58.4% respectively; OR 0.31, CI 0.14-0.67;  $p < .0001$ ) and fewer amputations (7% [3 minor, 1 major] v 13.7% [8 minor, 4 major]; NS) (Dargis et al, 1999).

**The multi-disciplinary specialist footcare team commonly includes a physician, podiatrist, specialist nurse, orthotist and surgeon**

The studies reviewed above have used different combinations of personnel in their multi-disciplinary teams. In Manchester the multi-disciplinary team comprised a diabetologist, podiatrist, specialist nurse and orthotist and had ready access to vascular and orthopedic surgeons (Thomson et al, 1991). In the Italian study the team included a diabetologist, nurse specialist, orthopedic surgeon, podiatrist, vascular surgeon and radiologist (Ghirlanda et al, 1997). In the Swedish study the team comprised a diabetologist, orthopaedic surgeon, diabetes nurse, podiatrist and orthotist (Larsson et al, 1995). In the London specialised foot clinic the team included a podiatrist, shoe-fitter, nurse, physician and surgeon (Edmonds et al, 1986). In the prospective Lithuanian study they consisted of a diabetologist, rehabilitation physician, podiatrist, orthopedic surgeon and shoe makers (Dargis et al, 1999).

In summary, the common components of the specialist multi-disciplinary team have been a physician and podiatrist. Most have also included a specialist nurse and orthotist and all have involved or had ready access to a surgeon.

The essential role of the podiatrist as a member of the multi-disciplinary team caring for high risk people with diabetes has been summarised in a non-systematic review by Wormald et al (1995). The podiatrist not only provides preventative footcare treatment including removal of callus, but also provides education and assessment and advice about foot wear.

Further research is required to define the core services in multi-disciplinary care which are essential in improving outcomes by reducing the incidence of ulcer or amputation in people with diabetes with high risk feet (Pinzur et al, 1996).

## Summary – Foot Clinics and Multi-disciplinary Teams

- A multi-disciplinary footcare team can improve the rate of ulcer healing and reduce ulcer recurrence rate and the rate of amputation in diabetic people with high risk feet
- The common components of the specialist multi-disciplinary team have been a physician and podiatrist. Most have also included a specialist nurse and orthotist and have involved or had ready access to a surgeon
- Further research is required to define the core services in multi-disciplinary care which are essential in improving outcomes by reducing the incidence of ulcer or amputation in people with diabetes with high risk feet

## Evidence Table: Section 11

### Foot clinics and multi-disciplinary teams

| Author   | Evidence          |        |              |                |                  |                  |
|--|-------------------|--------|--------------|----------------|------------------|------------------|
|  | Level of Evidence |        |              | Quality Rating | Magnitude Rating | Relevance Rating |
|  | Level             | Rating | Study Type   |                |                  |                  |
| <b>Dargis V (1999)</b><br>(Adults – Lithuania)                   | III-2             | Medium | Case-control | Medium         | High             | High             |
| <b>Edmonds ME (1986)</b><br>(Adults – UK)                        | III-2             | Medium | Cohort       | Low            | Medium           | High             |
| <b>Foster AVM (1995)</b><br>(Adults – UK)                        | III-2             | Medium | Cohort       | Medium         | Medium           | High             |
| <b>Ghirlanda G (1997)</b><br>(Adults – US)                       | III-2             | Medium | Cohort       | Low            | Low              | High             |
| <b>Larsson J (1995)</b><br>(Adults – Sweden)                     | III-2             | Medium | Cohort       | Medium         | High             | High             |
| <b>Pinzur MS (1996)</b><br>(Adults- US)                          | III-3             | Medium | Cohort       | Medium         | Low              | Medium           |
| <b>Rith-Najarian S (1998)</b><br>(Adults – US: Chippewa Indians) | III-2             | Medium | Cohort       | Medium         | High             | High             |
| <b>Thomson FJ (1991)</b><br>(Adults – UK)                        | III-2             | Medium | Cohort       | Low            | High             | High             |
| <b>Van Gils CC (1999)</b><br>(Adults – US)                       | III-2             | Medium | Cohort       | Medium         | High             | High             |

<sup>#</sup>Studies with no intervention

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