1

Epidemiology and Economic Impact of Foot Ulcers

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1.1 Introduction

Diabetes mellitus accounts for the majority of nontraumatic lower limb amputations [1], despite affecting a minority (9.4%) of the U.S. population [2]. A systematic review of risk of lower limb amputation in persons with and without diabetes in a defined population yielded 19 publications reporting results from Europe, UK and the US with relative risk of amputation in diabetes ranging from 7.4 to 41.3 [3]. Notably this range of relative risks for amputation exceeds that for diabetes and fatal coronary heart disease of 3.5 (women) and 2.1 (men) from a meta-analysis of 37 prospective studies [4], and is of similar magnitude to that seen for the association between ever smoking and lung cancer [5]. The chief antecedent to diabetic lower limb amputation is the nonhealing foot ulcer [6], which precedes approximately 80% of diabetic amputations, and which has been reported to lead to amputation in 15% of cases [7–9]. The problem of higher amputation risk in diabetes can be traced backwards in the causal chain of events to the development of a diabetic foot ulcer (DFU) [6].

1.2 Diabetic Foot Ulcer (DFU) Definition

Diabetic Foot Ulcer (DFU) is defined as a full thickness skin defect below the ankle that is slow to heal or non-healing. Amongst 1000 patients with DFU enrolled in the Eurodiale Study and followed for up to one year, median time to healing was 147 days for toe (95% CI 135–159 days), 188 days for midfoot (95% CI 158–218 days) and 237 days for heel ulcers (95% CI 205–269 days) [10], with healing success at one year of 79% for plantar and 73% for non-plantar ulcers. The available data demonstrate prolonged healing times for DFU and the frequent occurrence of healing failure.

The study of the epidemiology of DFU or any health condition requires a case definition to identify afflicted persons. There is no established case definition for DFU in general use.

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Definitions of DFU in the published literature may include features such as full thickness skin defect distal to the malleoli, but in some reports no case definition is provided with the identification of DFUs left to the judgement of foot care providers; or through review of podiatry records or electronic medical record data. Although delayed healing is a recognized feature of DFU, there is no established criterion for 'slow to heal' and rarely is a duration criterion included in the ulcer definition. The Seattle Diabetic Foot Study required a healing time greater than 14 days to meet the criteria for a DFU [11], whilst a clinical trial of custom footwear specifically mentioned that duration of ulceration was not be taken into consideration [12]. Consensus on a DFU definition would enable comparisons of the frequency of this complication across populations, regions, and over time.

1.3 DFU Classification

DFU classification systems function as a guide to the best treatment and as a predictor of the probability of wound healing and the need for amputation. The typical components of a wound classification system include wound depth, presence and severity of infection, gangrene, and ischemia. A systematic review of DFU classification systems identified 15 such systems reported in 25 articles [13]. Examples of the systems for which the greatest number of validation studies have been performed are the Meggitt-Wagner (9 validations), and the University of Texas and S(AD)SAD systems (5 validations each). Features of these three systems are seen in Table 1.1.

Comparisons of the ability of different classification systems have generally found them to be predictive of healing and amputation [14, 15].

Little research has been conducted comparing these classification systems using methods commonly employed for other diagnostic modalities such as comparison of area under receiver operating characteristic curves (AUROC), or by comparing test characteristics that alter pre-test probability, such as likelihood ratios [16, 17]. Jeon et al. compared five different DFU classification systems on the ability to predict amputation [18] that included the systems shown in Table 1.1, except that a simplified version of the S(AD)SAD system was used (SINBAD). All systems showed excellent ability to predict amputation with AUROC ranging from 0.85 to 0.89, and positive and negative likelihood ratios ranging from 4 to 18 and 0.21 to 0.41, respectively. Monteiro-Soares et al. compared 11 different prediction models for lower limb amputation in a prospective study of 293 patients with DFU and found positive and negative likelihood ratios ranging from 1.0 to 5.9, and 0.1 to 0.9, respectively, and AUROC curves ranging from 0.53 to 0.83, indicating that considerable diversity exists with some models showing significantly poorer prediction performance [19]. Further research is needed comparing existing classification systems to predict healing and amputation in patients with DFU.

DFUs are often described without using a classification system, but in reference to likely ulcer aetiology (neuropathic versus ischemic versus both) or foot location [20]. Ulcers usually develop over bony prominences that can be found on the plantar and dorsal foot surfaces especially if a structural deformity has developed resulting in abnormally high arch, prominent metatarsal heads, and clawing of the toes. The most common location for ulcer in the Eurodiale Study was on toes, with nearly equal division between plantar and non-plantar surfaces. Ulcers on the heel took longer and were less likely overall to re-epithelialize

Table 1.1 Diabetic foot ulcer wound classification systems.

Wagner					
Stage					
1	Superficial ulcer of skin or subcutaneous tissue				
2	Ulcers extend into tendon, bone, or capsule				
3	Deep ulcer with osteomyelitis, or abscess				
4	Gangrene of toes or forefoot				
5	Midfoot or hindfoot gangrene				
University of Texas					
Wound description	No infection or ischemia		Infection present	Ischemia present	Infection and ischemia present
Superficial	1A		1B	1C	1D
Penetrates to tendon or capsule	2A		2B	2C	2D
Penetrates to bone or joint	3A		3B	3C	3D
S(AD)SAD – Size (Area, Depth), Sepsis, Arteriopathy, Denervation					
	SIZE				
Grade	Area	Depth	Sepsis	Arterial disease	Neuropathy
0	Skin intact	Skin intact	None	Pulses present	Pin prick intact
1	$< 1\,cm^2$	Skin and subcutaneous	Surface	Pulses diminished or one missing	Pin prick reduced
2	$1–3\,cm^2$	Tendon, joint	Cellulitis	Absence of pedal pulses	Pin prick absent
3	$> 3\,cm^2$	Bone, joint space	Osteomyelitis	Gangrene	Charcot deformity

than other foot locations, but no difference was observed in overall healing success comparing plantar to non-plantar locations [10]. Similar healing success was seen amongst 405 patients with a neuropathic ulcer in plantar (n = 175, 91% healed) and non-plantar (n = 230, 94% healed) locations [21].

1.4 DFU Incidence and Prevalence

A wide range of estimates is available for DFU incidence and prevalence. A recent systematic review of the global literature identified 67 publications from 33 different countries and 5 continents [22]. Foot ulcer prevalence ranged from 1.5 to 16.6% in populations that

included inpatients, outpatients, diabetes clinics, and defined communities. Identification of foot ulcers was based on self-report, examination, medical record review, or electronic diagnostic codes (ICD-9). The report highlights the difficulties in assessing the frequency of this complication worldwide given the inconsistent methodologies employed.

The capture of this complication in a large population or nationally requires use of electronic diagnostic codes. The value of this information depends on the completeness and accuracy of such codes. The sensitivity and specificity of five such methods were recently estimated by comparison to medical record reviews of 512 patients receiving outpatient and inpatient care in the US from the Veterans Health Administration [23]. Sensitivity of all methods was at least 93%, with specificity ranging from 74 to 91%.

Several reviews of large, well-defined populations have been published on the incidence and prevalence of DFU. The Translating Research Into Action for Diabetes (TRIAD) included a random sample of adults with diabetes enrolled in 10 managed care health plans in eight US States that served approximately 180 000 persons with diabetes [24]. Foot ulcer was defined by ICD-9-CM code 707.1x or 707.9 in any inpatient or outpatient encounter. Between 1999 and 2003, 205 patients had at least one DFU (2.9%). A search of electronic health data in diabetic patients 67 years or older receiving care in the US from Veterans Health Administration and Medicare in 1999 identified a lower extremity ulcer or infection prevalence of 13% [25]. A more recent survey of outpatient and inpatient ICD-9 diagnosis codes in national US Medicare fee for service data from 2006 to 2008 revealed a prevalence of 8.0–8.1% and an annual incidence of 6.0% of DFU [26, 27]. A broad range of diagnosis codes were used to define DFU including lower limb ulceration (707), cellulitis (682), osteomyelitis (730), and open wounds (892), but excluding venous leg ulcer (454).

More recent evidence suggests that DFU incidence is declining in several developed countries. In a review of electronic patient records, the incidence in persons with both type 1 and 2 diabetes dropped between 2002 and 2014 at a large specialized diabetes hospital in Denmark, 8.1 per 1000 patient-years to 2.6 per 1000 patient-years, and 17.0 per 1000 patient-years to 8.7 per 1000 patient-years, respectively [28]. The incidence of foot ulcer in a primary care practice database in the Netherlands that included over 1.5 million patients from about 500 practices was 0.34% between 2010 and 2013 [29], considerably lower than an incidence ranging from 1.2 to 3.0% in an earlier Dutch study in a primary care practice from 1993 to 1998 [30]. The U.S. Diabetes Surveillance System maintained by the Division of Diabetes Translation at the Centres for Disease Control and Prevention provides estimates over time of the incidence of diabetes and its complications. Figure 1.1 displays the trend over time in hospitalization for lower extremity ulcer, inflammation, or infection. The U.S. National Inpatient Sample (NIS) that includes data from more than seven million hospital stays per year was searched for lower limb ICD-9 codes in persons with diabetes, including ulcer (707), carbuncle (680), cellulitis (681–682), pyogenic arthritis (711), osteomyelitis (730), gangrene (785), and venous ulcer (454). The trend since 1993 shows a fall in the age-adjusted hospitalization rate for this composite outcome when first-listed, with perhaps a levelling-off since 2009, whilst the trend for any-listed outcome is less clear. Given the broad definition of the outcome, whether the figure reflects a fall in hospitalizations for first-listed ulceration or the other conditions included in the outcome is not known. When assessing whether a change in incidence has occurred, it is important to consider that a decline might

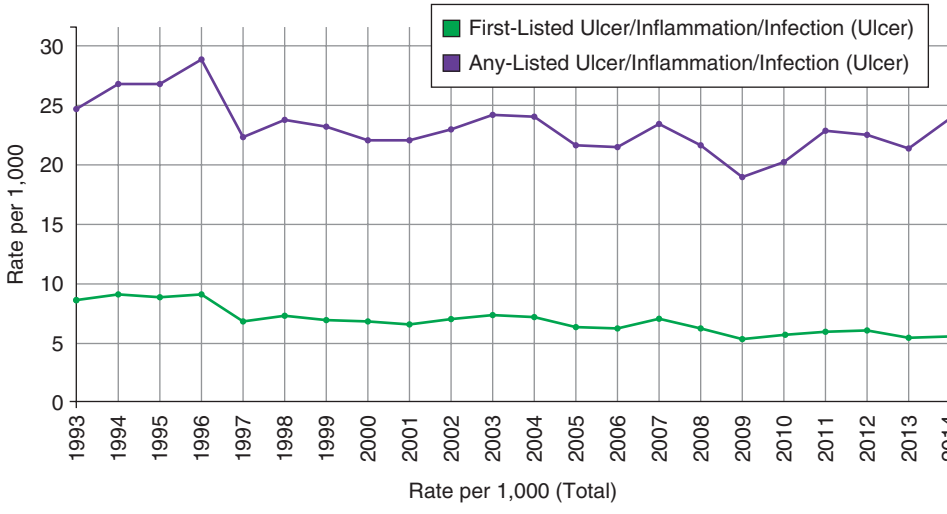

Figure 1.1 Age-adjusted hospitalization rate per 1000 for lower extremity ulcer, inflammation, or infection among the United States diabetic population, including all ages.

be due not only to fewer ulcers occurring but also enlargement of the denominator, which might occur due to improvements in diabetes screening and case detection.

Given the evidence that the rate of foot ulceration may be on the decline in some developed countries, it may no longer be the case that the estimated cumulative lifetime DFU risk is 15–25% [31].

1.5 DFU Recurrence

The epidemiology of DFU clearly demonstrates that it is not an isolated occurrence, as approximately 40% develop recurrent ulceration within one year after healing [32]. This fact supports the opinion that patients with DFU who heal should be viewed as being in remission from active ulceration and not cured. What is not clear from the literature on ulcer recurrence is whether the new ulcer is at the healed site or a new location. A study based in Malta specifically addressed the location of recurrent DFU [33]. Of 66 diabetic patients presenting with ulcer, 32 presented with a recurrent ulcer, with 27 (84%) experiencing the recurrence on the same foot, and 11 (34%) presenting at the same site as the previous ulcer. Although this is a small study, it suggests that the majority of recurrent DFUs develop at a site different from the original ulcer. A recently published study from Egypt of 93 diabetic patients with a healed foot ulcer who were followed for two years noted a recurrence in 61%, with 67% of recurrences in the same foot, and 37% of recurrences at the previous healed ulcer site, therefore supporting the results of the Malta study that recurrences were more likely to be located at sites other than that of the healed ulcer [34]. Given that most 'recurrences' are actually ulcers in different locations and not at the site of the previously healed ulcer, the problem of recurrence is more likely due to the same factors that led to the initial ulcer than defective wound re-epithelialization.

1.6 Risk Factors for Diabetic Foot Ulcers and Lower Extremity Amputation

A number of investigators have examined risk factors for **DFU development** or recurrence. The most commonly identified factors associated with higher risk of DFU development are diabetic peripheral neuropathy, peripheral arterial disease (PAD), foot deformity and previous foot complications. These variables were consistently associated with DFU development [35].

There are several classifications that can be used to stratify subjects by their risk of developing a DFU. At least five classification systems exist, with different structures, but that most commonly include diabetic peripheral neuropathy, foot deformity, PAD, and previous DFU or lower extremity amputation (LEA) [36]. These classifications presented similar prognostic accuracy when validated in the same cohort [36, 37].

In a cohort of subjects with healed DFU from the Eurodiale consortium, independent predictors of **DFU recurrence** were initial DFU plantar location, presence of osteomyelitis, glycated haemoglobin greater than 7.5%, and C-reactive protein greater than 5 mg/l [38].

In investigations of clinical tests that can help predict **DFU healing**, only transcutaneous oxygen measurement and ankle brachial index (ABI) proved of benefit [39].

Higher **minor LEA** risk was linked with male sex, greater DFU depth, presence of infection, and PAD in the Eurodiale consortium study [40]. Hypertension, ischemic heart disease, cerebrovascular disease, and PAD were found to be associated with higher **major LEA** rate [41]. In addition to these factors, different systematic reviews, including from 7 to 101 studies, concluded that being male [42, 43], smoking [43] and presence of depression [44] increased the risk of **LEA**. Regarding laboratory findings, higher fasting blood glucose, white blood cell count, C-reactive protein, and erythrocyte sedimentation rate were predisposing factors for LEA [45]. Two reviews concluded that the risk of LEA increased with higher glycated haemoglobin levels [45, 46]. A systematic review found that intensive glycaemic control significantly decreased the risk of LEA and sensory vibration perception impairment [47].

Self-care practices were also related to risk of both DFU and LEA. In a study, when the general practitioner indicated in the health registry he/she had good influence of the patient's own effort in diabetes treatment and that the patient had very good motivation for diabetes management, it was associated with a lower risk of both DFU and LEA during six years of follow up [48].

There are at least 16 classification systems that can be used for DFU prognosis assessment/LEA prediction [13, 49]. The Meggitt–Wagner, S(AD)SAD and Texas University Classification systems were the most extensively validated. When comparing all the systems they presented similar accuracy values [19, 49]. The most commonly included variables were DFU's area, depth and infection and presence of PAD, diabetic peripheral neuropathy, and foot deformity.

A systematic review [50] reported that, in subjects with DM, the most common risk factors associated with a higher risk of **death** were being older, male, with nephropathy, DFU and/or LEA presence or history, PAD, longer diabetes duration, and poor glycaemic control. However, results were not consistent across studies. In a study from Thailand [51], including subjects with and without DFU, DFU history, type 1 diabetes, high low-density

lipoprotein, and being male was linked to a higher risk of mortality. One study, conducted in Brazil, concluded that the risk of dying after a DFU was increased in older people, and in those with low haemoglobin values and a major LEA [52].

In veterans following DFU development, an increased risk of mortality was observed in older, male, married subjects, with peripheral neuropathy, coronary heart disease, PAD, history of stroke, foot deformity, nephropathy, gangrene and osteomyelitis, more outpatient or emergency room visits, more hospitalizations, and absence of statin use at baseline [53]. In the Eurodiale study, health-related quality of life (HRQoL) low global and domain specific values, measured by the EQ-5D, were highly associated with risk of dying [54]. In the same way, identity (How much do you experience symptoms?) and coherence (How well do you feel you understand your ulcer?) beliefs had a significant impact on mortality in another study [55].

1.7 Diabetic Foot Ulcer Outcomes

1.7.1 Health Centred Outcomes

In a systematic review assessing predictive factors for DFU occurrence, DFU development (including exclusively patients with no active, recently healed or past DFU history) ranged from 5.0 (after a mean follow up of 43 months) to 7.2% (after a mean follow up of 12 months) and recurrence from 15.5 to 60.5%, after a mean follow up of 24 and 32 months [35]. In Denmark, after six years of DM diagnosis, 2.93% of the individuals developed their first DFU [48].

In a cohort of subjects with a healed plantar forefoot DFU, 42% had **another DFU** over two years of follow-up [56]. During a three year follow-up, 57.5% of subjects with a healed DFU recurred in the Eurodiale cohort [38]. In a cohort of individuals with a minor LEA history (defined as below the ankle), re-ulceration-free survival time was merely eight months after LEA [57].

In one study, 30 days after a hospitalization for treatment of a DFU, 21.5% of individuals required a **re-admission**. The majority of the re-admissions were unplanned (81.8%) and related to the wound and vascular status (67.7%) [58]. In a retrospective cohort study from Brazil, conducted between 2007 and 2012, after a hospitalization, in a vascular surgery unit, for treatment of DFUs and/or infections, 21% of patients were readmitted once and 18% two or more times [59].

LEA incidence and prevalence is highly variable. In England, one study reported that it could vary 10-fold for both minor (0.22–2.20 per 1000 person-years) and major LEA (0.30–3.25 per 1000 person-years) [60]. The Eurodiale consortium observed that the minor LEA rate in people with an active DFU, treated in 14 European Centres in 2003 and 2004, at one year of follow-up, ranged from 2.4 to 34% in the different centres [40]. A review assessing the global variability of annual LEA incidence reported that it ranged from 46.1 to 9600 per 10^5 persons [61]. Major LEA varied from 5.6 to 600 per 10^5 individuals [61].

Having a DFU and/or LEA, especially major, are linked with remarkably high **mortality** rates. A 2.4-fold higher risk of death amongst patients with DFU was first reported in 1996 [62]. One study concluded that having a DFU significantly increased the mortality risk, inde-

pendently of age and number of diabetes-related complications [63]. These results are in line with the ones reported in the largest cohort conducted until now evaluating the association between DFU and death in individuals with DM [64]. The higher risk of dying in people with DFU was addressed in several studies. A meta-analysis showed higher pooled relative risk of all-cause mortality and of fatal myocardial infarction for those subjects that had a DFU [65]. This higher risk was also reported for Asian patients [51]. Subjects with a neuropathic DFU may have a greater risk of dying due to ischemic heart disease [66]. These results were not substantiated by other studies for which no differences in mortality were found [67].

Survival rates after an incident DFU were reported to be as low as 69% at 2 years and 29% at 5 years [53]. One systematic review concluded that the five-year mortality rate after a DFU was around 40%, rising to 63% if the limb was amputated [50]. In another systematic review, authors reported a five-year mortality rate that varied from 53 to 100% in subjects with a previous LEA [68]. In a more recent cohort of patients with a minor or major LEA [67], survival rates at three and five years were 78 and 44% respectively. The median survival was 50 months. This value is comparable to those with a metastatic cancer. In subjects with a cardiovascular event history median survival dropped to 40 months and in those with nephropathy to 27 months.

1.7.2 Patient Centred Outcomes

Diabetic foot disease has an immense impact on patients' lives by causing pain, impaired mobility, limited social activities, and interference with relationships. However, when it comes to patient-centred outcomes, available evidence is still very scarce.

In 2012, a systematic review [69] was conducted to ascertain the value of patient-reported outcome measures to assess HRQoL. The SF-36 was the most commonly used tool for quality of life (QoL) assessment, although several diabetic foot disease specific tools exist, such as the Diabetic Foot Scale, NeuroQoL, and Norfolk QoL-DN. HRQoL values were lower in subjects with diabetes when compared to healthy subjects, but even lower when foot disease occurs. When a DFU healed, HRQoL values improved. However, HRQoL values in subjects with an active DFU were lower than those reported by individuals after a successful minor LEA. Another systematic review [70] that included research from Spain, Italy, France, England, and Germany identified only six studies assessing QoL in individuals with several diabetic foot complications (namely, foot ulcers, and amputations). Subjects with DFU presented a lower mean score on all SF-36 domains, but particularly in physical capacity. Those with non-healed and recurrent DFU presented lower values than those with healed DFU, and those that underwent a LEA reported lower values when compared to those that did not.

The Eurodiale consortium stated that individuals with active DFU reported low EQ-5D values, with the mobility and pain/discomfort domains the most affected [54]. The inability to stand or walk without help was considered the most important predictor of diminished QoL. Using propensity score matching techniques, investigators found that there were no differences in HRQoL between individuals with active DFU being treated conservatively compared to those undergoing minor LEA [71]. A multi-hospital study of the QoL of Portuguese patients with diabetic foot concluded that, in subjects undergoing a LEA, HRQoL after surgery could be predicted by HRQoL before surgery, the number of diabetes

complications, and a previous LEA [72]. Although physical function HRQoL values diminished after surgery, no changes were found in the mental domain. Physical function HRQoL after LEA was predicted by pain, having a first LEA, depression symptoms, and functionality (measured using the Barthel Index) [73]. Mental HRQoL predictors were anxiety, depression symptoms, and functionality.

Another study [74] concluded that amongst individuals with diabetic foot pathology, having a LEA is the most feared diabetes-related complication, surpassing blindness, infection, dialysis, or even death. However, these results were different in subjects without diabetic foot pathology who ranked their fear for this specific complication after blindness and death.

1.8 Economic Considerations

Diabetic foot complications represent a major burden for healthcare systems, due to both direct and indirect costs. For example, from 2006 to 2010 and according to national emergency department discharge data from the Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP) Nationwide Emergency Department Sample (NEDS), more than 1 million cases of diabetic foot complications presented to emergency departments in the United States of America, incurring estimated costs of 1.9 billion US$ per year [75].

In Brazil, it was estimated that the annual direct medical costs of diabetic foot disease in 2014 was 361 million Int$ (International Dollars) [76]. In 2001, in the United Kingdom (UK) the estimated total costs were 509 million € and in Germany 551 € per patient to manage diabetic foot complications [70]. In 2010–2011, the estimated cost in the UK increased to 580 million € [77]. More than half of this amount was spent on DFU care conducted in primary care and community settings. In Canada, DFU related care was estimated at 547 million $ in 2011 [78].

Treatment of DFU generates excess cost when compared to the treatment of people without DFU, with such costs persisting beyond the time of ulcer healing and showing high variability. Attributable cost of DFU care, during the two years after diagnosis, amounted to 28 000 US$ [9]. Greater DFU severity leads to higher cost of care and more proximal LEA associated with greater costs compared to a minor LEA. One study reported that the mean healthcare cost per patient with an active DFU without hospitalization is 730 €, increasing to 2260 € when hospitalization is required [79]. Individuals with a DFU treated in the outpatient setting represented a mean cost per month that ranged from 582 €, for those classified as Wagner grade 1, up to 742 €, for those classified as Wagner grade 4/5. Hospitalization increased these amounts to 735 € and 3590 €, respectively. Other estimates are available from a study in Russia, where treating a patient admitted due to a DFU categorized by Wagner grade generated the following mean costs: grade 1–2450 €, grade 2–2821 €, grade 3–3937 €, and grade 4–5340 € [80]. Length of hospital stay, foot surgery, and vascular surgery were the variables having the greatest impact on cost escalation.

Costs of treatment of DFU based on a different wound classification system have also been reported. An Austrian study [81] reported the average cost to heal a DFU categorized according to the San Antonio Wound Classification as follows: stage A – 1071 € (no infection or PAD), stage B – 5093 € (with PAD), stage C – 3467 € (infected DFU) and stage D – 7844 €

(infected DFU with PAD). Also, in this study, undergoing a major LEA precipitously increased the range of the costs of care. For example, a DFU classified as grade B may generate treatment costs ranging from 213 € to 29 585 € for those leading to a major LEA, a grade C DFU from 55 to 8000 € to 22 498 €, and a grade D DFU from 5550 € to 13 900 €. In the Eurodiale consortium study [82], costs ranged from 4214 € for a stage A DFU, up to 16 835 € for a stage D DFU. In the same way, a healed DFU cost 7722 €, a non-healed DFU after 12 months of care cost 20 064 €, and a major LEA 25 222 €.

The role of infection with regard to affecting costs of care was assessed in one UK investigation, where the estimated cost over the first 12 months from initial presentation of a healed DFU was 2138 £, an unhealed DFU 8786 £ and an amputated DFU 16941£ [83]. Presence of infection greatly increased the costs of DFU treatment, ranging from 2604 £ for a non-infected DFU, up to 12 995 £ for an infected DFU.

Research has also been conducted on the cost-effectiveness of several strategies to prevent DFU and LEA. One report [84] found that it was more than 90% likely for primary prevention to be cost-effective if annual prevention costs are inferior to 50 US$ per person and/or reduces the incidence of DFU by at least 25% in people with diabetes; and in subjects at moderate or high risk of DFU if costs are inferior to 150 US$ per person and/or the incidence of DFU decreases at least 10%. Another study from Ireland concluded that the creation of a dedicated bi-weekly multi-disciplinary foot protection clinic was effective in reducing major LEA and saved 114 063€ per year [85]. In Australia, it was found that at five years, implementing optimal care for patients at high risk of DFU would be cost-saving and improve health benefits, measured in quality-adjusted life years, when compared to usual care [86].

For secondary prevention and including direct and indirect costs in Peru, standard care (following the International Diabetes Federation guidelines) prevented 791 deaths and was cost-saving when compared to sub-optimal care (consisting in annual medical visit without appropriate education or footwear provided); and standard care plus temperature monitoring represented an incremental cost ratio (defined as the difference in cost between two possible interventions, divided by the difference in their effect) of 9405 US$, meaning that the increase in efficacy represented an extra cost of merely 9405 US$ and prevented 1385 deaths when compared to sub-optimal care [87]. In Thailand, continuing treatment of individuals following DFU healing by a multidisciplinary diabetic foot protocol resulted in a significantly lower average cost and greater QoL as reflected by higher SF-36 values when compared to standard care [88]. An intensified (specialized diabetic foot clinic) versus standard DFU treatment (general practitioners' clinics) reduced the annual direct costs by 28.9% per patient in grade A DFU and up to 49.7% in grade D by diminishing LEA rates [81]. In addition, the average life expectancy for patients treated intensively was greater than with standard treatment, independent of DFU severity. Multidisciplinary DFU treatment has been found in several studies to be cost-effective [89].

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