A systematic review investigating the identification, causes and outcomes of delays in the management of chronic limb threatening ischaemia and diabetic foot ulceration

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Abstract

Objectives

Patients presenting with chronic limb threatening ischaemia (CLTI) and diabetic foot ulceration (DFU) are at high risk of major lower limb amputation. Long-standing concern exists regarding late presentation and delayed management contributing to increased amputation rates. Despite multiple guidelines existing on the management of both conditions, there is currently no accepted timeframe in which to enact specialist care and treatment. This systematic review aims to investigate potential time delays in the identification, referral and management of both CLTI and DFU.

Methodology

A systematic review, conforming to the Preferred Reporting Items for Systematic Review of Meta-Analysis (PRISMA) statement standards, was performed searching MEDLINE, Embase, The Cochrane Library and CINAHL from inception to 14th November 2018. All English language qualitative and quantitative articles investigating or reporting the identification, causes and outcomes of time delays within 'high income' countries (annual gross domestic product per person >$15,000) were included. Data were extracted independently by the investigators. Given the clinical cross-over, both conditions were investigated together. A study protocol was designed and registered at the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42018115286).

Results

A total of 4780 articles were screened, of which 32 articles, involving 71,310 patients and 1,388 healthcare professionals were included. Twenty-three articles focussed predominantly

on DFU. Considerable heterogeneity was noted and only 12 articles were deemed of high quality. Only 4 articles defined a 'delay' however this was not consistent between studies. Median times from symptom onset to specialist healthcare assessment ranged from 15 to 126 days with subsequent median times from assessment to treatment ranging from 1 to 91 days. A number of patient and healthcare factors were consistently reported as potentially causative including, poor patient symptom recognition, inaccurate healthcare assessment and difficulties in accessing specialist services. Twenty articles reported outcomes of delays, namely rates of major amputation, ulcer healing and all-cause mortality. Although results were heterogeneous, they elude to delays being associated with detrimental outcomes for patients.

Conclusions

Time delays exist in all aspects of the management pathway, which are in some cases considerable in length. The causes of these are complex but reflect poor patient health-seeking behaviours, inaccurate healthcare assessment and barriers to referral and treatment within the care pathway. The adoption of standardised limits for referral and treatment times, exploration of missed opportunities for diagnosis and investigation of novel strategies for providing specialist care are required to help reduce delays.

Introduction

Peripheral arterial disease (PAD) is the atherosclerotic disease of arteries, leading to stenotic and occlusive disruption of blood flow to the extremities. Chronic limb threatening ischaemia (CLTI) is the end stage form of the disease, characterised by ischaemic night/rest pain, subsequent limb ulceration and gangrene. Diabetes mellitus is a principle cause of PAD, increasing the risk and severity of symptomatic lower limb PAD.[1, 2] For patients with diabetes, foot ulceration is a leading cause of hospitalisation.[3] The lifetime risk of developing a diabetic foot ulcer (DFU) is 25%, with 5% undergoing a major amputation within 1 year of onset.[4, 5] PAD is an independent risk factor for DFU, occurring in approximately 50% of cases.[6] In patients with diabetes, those who additionally have PAD have almost a 2-fold increased rate of major amputation.[7] Evaluation of peripheral vasculature and revascularisation are therefore key components in managing a DFU. As such, vascular surgeons are now a key component of the multi-disciplinary team (MDT) managing DFUs in many institutions.

There is long-standing anecdotal concern regarding the late presentation and delayed management of patients leading to worse outcomes. As far back as 1991, Mills identified that delays in referral contributed to a patient with a DFU undergoing a more proximal amputation.[8] Whilst multiple guidelines exist on the management of both CLTI and DFU, there is currently no accepted definition of what constitutes a 'delay' nor timeframe in which to enact specialist care and treatment (Table 1).[9-15] The Vascular Society of Great Britain and Ireland's (VSGBI) 2018 Provision of Services report,[16] updated into the 2019 PAD Quality Improvement Framework (PAD-QIF),[17] offers the only guidance which stipulates recommended times for vascular assessment ($\leq$7 days of referral) and revascularisation ($\leq$14 days of referral).

The aim of this systematic review is therefore to investigate potential time delays in the identification, referral and management of both CLTI and DFU and to investigate the causes

and outcomes of these delays. Given the recognised clinical cross-over of CLTI and DFU and the substantial overlap in their management pathways within contemporary clinical practice, both conditions will be investigated together within this review.

Methodology

This systematic review was performed in accordance with Preferred Reporting Items for Systematic Review of Meta-Analysis (PRISMA) statement standards.[18] A study protocol was designed conforming to the Preferred Reporting Items for Systematic Review of Meta-Analysis Protocols (PRISMA-P),[19] and registered at the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42018115286).

Search strategy

A search of the MEDLINE, Embase, The Cochrane Library and CINAHL was performed from inception to 14th November 2018. A search strategy was employed using combinations of keywords and thesaurus headings, including: “limb ischaemia”, “diabetic foot”, “foot ulcers”, “delays”, “time factors”, “amputation”, “limb salvage” and “wound healing”. The search strategy was developed in MEDLINE and was adapted accordingly for use with other databases. The full search strategy is shown in Appendix 1. Only English language articles were considered (although no non-English article met the other inclusion criteria). Bibliographic lists were scanned, and additional internet searches were performed, using Google and Google Scholar (Google LLC), for additional articles in particular audits and reports. The searches were developed and performed by reviewer AN and experienced clinical librarian CP.

Types of studies

All observational studies relating to this topic were included. Qualitative research, conference abstracts, policy documents and published audits were also included. Only studies relating to healthcare systems within 'high-income' countries (annual GDP per person >$15,000) were included to minimise heterogeneity.

Types of participants

Articles including adult patients (>18 years) with a presumed or confirmed diagnosis of CLTI and/or DFU were included. Articles which included ulcers of alternative aetiology were excluded unless reported separately from CLTI/DFU.

Outcomes and measures

Figure 1 shows a diagrammatic representation of the management pathway used within this review. This review investigated the identification of delays (timings) throughout this pathway along with patient and healthcare factors leading to delays. Outcomes relating to time delays were investigated, including the rates of major and minor amputation (amputation proximal or at/distal to the ankle), rates amputation-free survival and wound healing, all-cause mortality and other relevant patient outcomes.

For each article baseline data were also extracted including: study setting (country), study design, sample size, authorship, publication date, age of participants (mean or median (years)), sex of participants, predominant focus of the study (CLTI/DFU) and definition of CLTI.

Definition of delays

No universal definition for what length of time constitutes a 'delay' exists in this context. For the purposes of comparison, the VSGBI's recommendations ('non-admitted' pathway) were

used as a baseline standard.[17] The definition of delays reported by individual articles was extracted.

Data extraction

Search results were imported into EndNote™ X9 (Clarivate Analytics®) and duplicates removed. Titles and abstracts were reviewed independently for suitability against the inclusion criteria by AN and BB. The full texts of suitable studies were independently assessed for final inclusion by AN and BB, JH or SN and data extraction from published data was performed independently by the same reviewers. A standardised data extraction form was created and tabulated into Excel™ 2016 (Microsoft®). Disagreement was resolved by discussion and, when required, a third reviewer acted as a final adjudicator.

Where study selection could not be made based upon available information, corresponding authors were contacted via email for clarification. Where no corresponding address was given, messages were sent through ResearchGate™ (Research Gate GmbH) where possible. In the case of no reply, the study was excluded.

Quality assessment

The quality of observational studies was assessed using the Newcastle Ottawa assessment scale for case-control and cohort studies, with studies scoring $\geq$7 stars considered to be high-quality.[20] For cross-sectional studies, a modified version of the scale was employed, with a total of $\geq$6 stars considered as high-quality. For qualitative research, the Critical Appraisal Skills Programme (CASP) qualitative checklist was used.[21] This is designed to give an overall impression of research quality through discussion rather than providing a score. Currently, no tool exists for assessment of audits or conference abstracts.

Quality assessment was performed independently by AN and BB, JH or SN, after data extraction and disagreement was resolved through discussion.

Strategy for data synthesis

A narrative synthesis of results was performed and data tabulated where appropriate. Mean ages were calculated from medians, ranges and interquartile ranges using methodology described by Hozo.[22] Timings were calculated into days and described as medians or means and presented with ranges (high/low or interquartile range (IQR)) or standard deviations (SD) where available. Where categorical data existed, authors were contacted to obtain the continuous data (where possible), otherwise frequencies were described. Given the anticipated heterogeneity of treatment pathways and definitions, it was assumed there was limited scope for data pooling and therefore a meta-analysis was not conducted.

Where the same cohort is analysed in different publications, the data of the baseline cohort was only recorded once.

Results

On completion of the search strategy 4780 articles were screened with 32 articles[8, 23-53] being included in the final synthesis (Figure 2). The characteristics of the studies are shown in Table 2. Overall, delays were studied in 71,310 patients, with the opinions of 1388 healthcare professionals identified. 56,644 patients were diagnosed with DFU and 18,781 with CLTI (exclusively or with DFU). The pooled mean age of the cohort was 66.3 years. Five articles did not present age statistics.[26, 27, 31, 37, 51] No consistent definition of CLTI was given, with multiple validated scoring systems and criteria described.

The quality assessment of the observational studies is shown in Appendix 2. Six, nine star cohort studies[29, 35, 43, 45, 46, 50] were identified. Overall, 12 observational studies[29, 32, 35, 39-41, 43, 45, 46, 48-50] were deemed of high quality, of which none were cross-sectional studies. Of the three qualitative studies, two were deemed of good quality,[30, 34] with the remaining study of moderate quality.[44]

Twenty-six articles[8, 23-29, 31-33, 35-39, 41-43, 46-50, 52, 53] presented data on the identification of delays. The definition of a 'delay' was only specified within four articles,[8, 31, 48, 53] however the definition of 'delay' varied considerably between studies. The study characteristics are shown in Table 2.

Symptom onset to primary care assessment: Two articles reported median times of 3 days[48] (range 0-243) and 4 days[37] (range 0-247) respectively, however the rate of missing data was up to 37%[37]. Canavan[26] reported a mean of 25 days, whilst Manu[38] reported mean times across 4 different European countries, ranging from 10 days (UK) to 15 days (France). Smith-Strøm[49] presented categorical data, with 69.5% of patients waiting 14 days or greater prior to assessment.

Primary care assessment to specialist healthcare assessment (SHA): Median times ranged from 7 days[48] (range 0-522) to 25 days[24] (1-100). Three articles reported means of 17 days[47] (SD 2 days), 24 days[50] (SD 9 days) and 54 days[26] respectively. A further 2 articles reported that 29%[8] and 24%[49] of patients presented with referral times of 14 days or greater. Normahani[42] reported categorical data on times from podiatric service to vascular assessment based upon a survey of podiatrists, with 40% reporting referral times of greater than 28 days. Furthermore, Krysa[36] identified 58% of patients being inpatients for greater than 7 days prior to referral to a specialist vascular unit.

Symptom onset to SHA: Median times varied from 15 days[37] (range 0-608) to 126 days[23] (range 28-253) with Benotmane[25] presenting a mean of 31 days (range 2-120). A further 7 articles[29, 31, 36, 46, 49, 52, 53] presented categorical data. Four articles[29, 49, 52, 53] reported at least 45% of patients having times over 28 days. Prompers[46] also identified 83% of patients presenting greater than 7 days since symptom onset, with 24.9% presenting over 3 months after symptoms started. Krysa[36] identified times of over 7 days reported in 80% of patients requiring emergency transfer to vascular surgery. Conversely the NHS National Diabetes Foot Care Audit (England and Wales) (NDFCA*)*[31] reported only 9% of patients presenting with symptoms of >61 days duration, although this proportion increased between 2014-15 and 2016-17.

SHA to treatment: Median times ranged from 1 day[27] (range 1-64) to 91 days[41] (range 3-289). Noronen[43] reported longer times in patients undergoing surgical compared to endovascular revascularisation (51 days vs 44 days), however this was not statistically tested.

Other specialty to treatment: Faglia[33] presented a mean time of 6 days (range 1-22) from inpatient referral to urgent debridement.

Causes of delays

Twelve articles[8, 24, 26, 30, 34, 37, 38, 42-44, 48, 53] investigated the causes of delays. Six articles[8, 24, 38, 42, 43, 48] identified causes related to healthcare factors, three articles[30, 37, 53] identified patient related causes and three described both.[26, 34, 44]

Patient factors: Two articles[34, 37] explored the theme of poor symptom recognition by patients as a cause of delays. Feinglass[34], reporting results from patient interviews, identified patient misunderstanding of their condition and confusion about the need for specialist care as factors. Further to this, concurrent retinopathy and neuropathy prevented patients appreciating a deterioration in their symptoms. Macfarlane[37] reported that only 53% of DFUs were first

identified by the patients and poor patient education on the risks of DFUs was identified by Pankhurst[44]. This was also recognised following root cause analysis of delays by Canavan[26].

Furthermore Yan[53] reported statistical associations between 'long delays' (>30 days from symptom onset to SHA) and both: a lack of diabetic foot education (odds ratio (OR) 2·70, 95% confidence interval (CI) 1·03-7·06, P=0·043) and a lack of patient knowledge of foot danger signs (OR 2·14, 95% CI 1·16-3·94, P=0.015). Contradicting this, Delea[30] reported patient perception of their education to be satisfactory, however patients noted they ignored instructions from healthcare professionals.

Healthcare factors: Four articles[8, 24, 34, 44] identified inaccuracy in the assessment of symptoms or urgency of the condition as causative. *Sanders*[48] also identified an association between the number of healthcare professionals in the referral trajectory prior to SHA and 'increased delays' (exponentiation of the β coefficient 7·07, *P*=0·001). Furthermore, Normahani[42] showed that 17% of podiatrists would only refer for a vascular opinion if a DFU remained unhealed after 42 days of conservative management.

After questioning of specialist healthcare professionals, *Pankhurst*[44] identified difficulties in accessing specialist diabetic foot services, citing funding constraints, lack of staffing and centralisation of services. Normahani[42] also cited the difficulties podiatrists experience with the referral process to specialist services, accessing vascular clinics and obtaining vascular advice from a MDT foot clinic as causative for delays. Communication amongst the diabetic foot MDT was also recognised as a root cause of referral delays following analysis by Canavan[26]. Similarly, Noronen[43] identified that waiting for vascular imaging and decisions based upon imaging led to treatment delays. Manu[38] questioned general practitioners throughout 4 European countries, identifying differences in the approach to MDT management,

decision making for when to refer a patient and knowledge of specialist services among respondents.

Outcomes of delays

Twenty articles[8, 24, 29, 31-33, 35, 36, 39-41, 43, 45, 47-53] reported outcomes for delays. No articles reported outcomes for minor amputation or amputation-free survival, however Yan[53] did not differentiate between major and minor amputations. The study characteristics are shown in Table 5.

Rate of major amputation: Two articles[50, 53] investigated time from symptoms onset to primary care assessment. Spanos[50] identified increased odds of major amputation with each additional day to assessment (OR 1·04, 95% CI 1·01-1·06, P=0·01), whilst Yan[53] reported increased odds for those waiting greater than 30 days compared to those waiting less than 7 days (OR 2.·22, 95% CI 1·36-3·64, P=0·002). A further 2 articles[8, 24] reported contradictory results for time from primary care assessment to SHA. Whilst Bailey[24] identified no association between times of greater than 14 days and the rate of major amputation (P>0·1), Mills[8] qualitatively described that a "more proximal amputation" was required in 38% of patients waiting greater than 14 days. Further description of this however was not provided.

Noronen[43] investigated the time from SHA to revascularisation. In patients with diabetes, a wait of greater than 14 days was identified as an independent predictor of major amputation (OR 3·1, 95% CI 1·4-6·9), however this was not identified in patients without diabetes. Faglia[33] described a higher rate of Chopart/above knee amputation in patients referred from another specialty for emergency surgical debridement compared with those directly referred from specialist outpatient clinic (OR 1·61, 95% CI 1·10-2·36, P=0·015). The association between time from symptoms onset to SHA and major amputation was not reported.

Wound healing: Investigating time from symptom onset to primary care assessment, Smith-Strøm[49] reported a 58% reduction in the chances of ulcer healing for patients waiting greater than 52 days.

Five articles[31, 39, 41, 45, 52] reported significantly lower rates of ulcer healing between times from symptom onset to SHA between times ranging from 42 to 91 days[45, 52]. Investigating the same time period the NDFCA[31] identified that times of between 14-61 days were associated with significantly reduced ulcer-free survival at both 12 weeks (84 days) and 24 weeks (168 days) compared with those being assessed within 2 days or less. This effect was greater if times to SHA increased to greater than 61 days. Despite this, Ince[35] identified no association when comparing times for 7 days or greater, to those patients waiting less than 7 days.

Rasmussen et al[47] reported a small positive correlation between times from primary care assessment to SHA (r=0·2, *P*=0·01). Investigating times from SHA to treatment, Elgzyri[32] identified a significant increase in the rate wound healing without amputation for patients undergoing revascularisation within 56 days compared to those with longer times (HR 1·96, 95% CI 1·52-2·52, P<0·001). Investigating all 3 steps from symptom onset to SHA, Sanders[48] established no association between waiting time and time to ulcer healing.

All-cause mortality: Yan[53] identified a significantly higher rate of mortality in patients waiting greater than 28 days from symptom onset to SHA compared to those waiting less than 7 days (OR 2·69, 95% CI 1·35-5·33, P=0·005). Kyrsa[36] also identified a 50% post-amputation mortality rate in patients waiting greater than 7 days, compared with 7·2% in those with shorter delay, however this was not statistically tested. Contradicting this, Bailey[24] found no association between mortality and time from primary care assessment to SHA

Moxey[40] identified an increased in-hospital mortality for each day elapsed between SHA and definitive treatment (major amputation) (OR 1·02, 95% CI 1·01-1·02, P<0·0001), although this effect was only identified in men. No articles reported both time from symptoms onset to primary care assessment and mortality.

Other outcomes: Sanders[48], identified small correlations between the duration of specialist treatment and the time from symptoms onset and primary care assessment to SHA(r^2=0·116, P=0·05). Moxey[40] also reported a small association between each additional day from SHA to major amputation and increased post-operative recovery time for both men (exponential estimated (EE) 1·01, 95% CI 1·01-1·02, *P*<0·0001) and women (EE 1·02, 95% CI 1·01-1·02, *P*<0·0001)

Faglia[33] reporting that patients referred from another speciality prior to urgent debridement had a higher proportion of deep space infection extending to the hind foot compared to patients directly referred (P=0·005). Tshomba[51] investigated times from symptom onset to the insertion of a sacral nerve stimulator for CLTI. Here, time from symptom onset to treatment was identified as an independent predictor of functional success ((30m pain free walking distance) (P<0·001). Furthermore for every 30 days elapsed prior to insertion, the rate of functional success decreased by 41%.

Discussion

It is a widely held opinion that time delays in managing both conditions have a direct and detrimental impact on the outcome for patient. Whilst natural time interruptions will occur in even the most efficient care pathway, it is not accepted as to when a wait becomes a 'delay'. This is demonstrated by only 4 articles providing a definition for delays, all of which were different. Current guidelines provide little clarity and at worst serve to provide confusion,

especially to professionals not specialised in managing these conditions.[9-15] Agreeing on a definition of delays is particularly challenging given the differences between healthcare systems and lack of standardisation to managing both conditions.

In the case of diabetes, evidence has shown that major amputations, adverse cardiovascular outcomes and mortality can be reduced with targeted risk factor modifications and improved clinical-decision making tools.[54-56] It therefore stands to reason that the creation of universal and coherent target timeframes within the management pathway is a key step to further improving outcomes. These timeframes could also be used by healthcare commissioners to incentivise professionals and healthcare systems to delivery more timely care to patients.

The VSGBI's 2019 recommendations help provide a sound foundation for this definition, however taking a universal prescriptive approach may not be possible given the diversity of healthcare systems.[17] The recommendations are also currently ambitious, especially given a significant proportion of patients within this review did these meet the target times. Forming national consensus statements are one method of achieving this, allowing for differences in individuals systems to be acknowledged. Whilst challenging, creating a recognised definition for a 'delay' would not only provide a treatment standard, but also allow for a greater standardisation of guidelines and research into this field.

The reasons for the observed time delays are complex, involving both patient and healthcare factors. Difficulties for patients identifying signs and symptoms was consistently reported, in addition to inaccurate healthcare assessment and barriers to accessing specialist services.

Improving a patient's knowledge of their conditions provides a logical method of helping to reduce delays. This is particularly germane in those with diabetes, where awareness of symptoms may be limited and ulcers are at a high risk of recurrence.[57] Whilst attempts have

been made to help improve understanding, isolated education programmes have demonstrated only limited success and have not been proven to translate into better outcomes.[58-62] Given the results of this review, further work is clearly required to develop education programmes which produce sustained benefits. Placing emphasis on continuous education throughout a patient's care, with teaching being reinforced at each clinical encounter is a potential solution which could be evaluated.[57]

Issues regarding inaccurate clinical assessment by healthcare professionals represent a more challenging problem. Knowledge of PAD, CLTI and DFU has been shown to be inadequate amongst non-specialists professionals and more worryingly, this trend is observed to start during training.[63-65] Whilst placing a greater focus on education is essential (especially in the undergraduate phase) accurate clinical assessment is a complex process formed on many facets, of which education is only one.

The theme of 'missed opportunities' involving patient interactions with non-specialist practitioners has been explored within the field of cancer diagnosis. Two models for 'missed opportunities' have been hypothesised: 'competing demands', whereby competing medical complaints make exploration and recognition of signs and symptoms more difficult within a consultation, and 'alternative explanations', whereby symptoms are incorrectly attributed to existing conditions.[66] These ideas are highly relevant to CLTI and DFU, where concurrent comorbidities are prevalent. To date these themes have received little attention within the management of both conditions. Further investigation of primary and secondary care consultations prior to a diagnosis of CLTI/DFU may establish whether the issue of 'missed opportunities' exists and could stimulate the development of strategies to help shorten the time to SHA.

This review also indicates difficulties accessing specialist services remain an on-going issue. Whilst the nature of these barriers will vary between healthcare systems, the themes of delays accessing vascular imaging and difficulties obtaining assessment were universally recognised. Normahani demonstrated that 11·3% of podiatrists treating DFUs within the UK could obtain non-invasive vascular imaging within one week of referral.[42] Within systems similar to the UK, key professionals such as podiatrists often have no direct access to these services and considerable time can be spent in referral.

Both Normahani and Pankhurst also identified problems accessing vascular advice and assessment, partly due to complex referral pathways, even between complementary specialities.[42, 44] This is interesting given the move towards multidisciplinary DFU services and centralisation within vascular centres. Despite vascular surgery being an integral part of a MDT service, few centres report providing direct access to vascular imaging and treatment without onward referral.[67-70] Whilst taking a 'monolithic' approach (whereby one specialty direct all the care provided to a patient) could potentially reduce delays between specialities, it would undermine the substantial benefits which are brought about through MDT working.[71]

Specialist limb salvage services present a potential solution, providing rapid-access to both multidisciplinary specialist assessment, vascular imaging, debridement and decision-making regarding intervention to all patients with DFUs or suspected limb ischaemia. Variations of these services exist, usually based around 'toe-and-flow' model, which build on collaborative working and helps bridge the gap between vascular services and other providers managing ischaemia and DFUs.[72] Evidence is promising however these clinics are not yet widely established.[68, 73-75] Given the barriers to treatment identified within this review, an essential component of these services is to have an 'open-access' policy, providing a single referral target and source of advice for any healthcare professionals managing a patient with suspected

ischaemia or DFU. Not only could this help to reduce delays in accessing specialist assessment but also improve communication between specialist and non-specialist healthcare professionals. Whilst forming these services remains aspirational, adopting some of the key principles of these, namely creating greater collaboration to reduce unnecessary referrals and minimising the complexity of referral pathways, could be implemented without major service changes.

Lastly, 'cultural' and financial aspects of healthcare systems are of worthwhile mention. As described by Manu,[38] variation between countries exists in the management of DFUs, especially in the context of MDT working and decision making regarding ischaemia. This is further evidenced by the lack of standardisation in the classification systems used to grade the severity of ulceration and ischaemia. This 'cultural' difference in the approach to treating patients undoubtedly leads inconsistencies and delays in care, something which is not helped by the complexity of established guidelines. The publication of the Global Vascular Guidelines and the universal adoption both of the SVS Wifi (wound, ischaemia, foot infection) score and an agreed definition of 'delay' will hopefully go some way to addressing this by providing greater standardisation in care.[15]

Pankhurst also identified financial and resource constraints as further contributing to delays.[44] This problem is highly relevant to healthcare systems which provide healthcare through a central taxation model. Within the UK, examples exists of financial incentives being used to reduce referral rates from general practice.[76] Austerity in healthcare funding can also lead to the delaying or even the denial of treatment due to lack of resources and man-power.[77] Whilst within a 'self-pay', privatised healthcare system the substantial cost to the individual of managing CLTI/DFUs acts as a potential deterrent from seeking treatment.[78] This is particularly relevant as the financial cost to patients and healthcare systems as a result of a

major lower limb amputation is considerable and increasing.[79-81] Confronting the increasing challenges of diabetes is imperative, as the cost of managing these conditions may become unmanageable for many economies.[82] Whilst this goes beyond the scope of this review, it highlights the need to prioritise spending on the prevention and early treatment of diabetes and cardiovascular-related diseases at a national level.

Although this is the first systematic review of this topic, there are a number of limitations which affect the quality of the conclusions. Firstly, the articles analysed were heterogeneous in nature, describing different methods, healthcare settings and treatments. This prevented a formal meta-analysis of the results and makes drawing definitive conclusions regarding the outcomes of delays challenging. In part this heterogeneity is inherent given the nature of this review, however focussing on a single condition could potentially have helped limit this. Despite this, it was felt the increasingly recognised clinical cross-over of both conditions justified their inclusion and considering either condition alone is unlikely to significantly reduce the heterogeneity. Furthermore, the intention of this review was to use a systematic methodology to provide a broad and complete overview of the current evidence regarding delays and as such, the observed heterogeneity does not prevent meaningful conclusions being drawn.

Secondly although 12 studies were deemed of high quality, the majority of studies were retrospective in nature and therefore open to selection and performance bias. The cross-sectional evidence used was of poor quality and results from four articles were reported only in conference abstracts. The inclusion of conference abstracts is contentious. Many abstracts undergo little or no peer review and limited judgement on methodology can be made. Furthermore, comparing outcomes from abstracts with full-text publications is challenging given the limited data presented and, in the case of this review, the limited description of the healthcare systems. Whilst removing these would have improved the overall quality of the

articles, this would have been detriment the breadth of the review, which was intended to be broad in scope. Attempts were made to mitigate this by contacting the authors for further data and to enquire about full-text publication, however the response rate was low (25%) and not all authors were contactable.

Another limitation of this review regards the possibility of lead-time bias. This concept is widely discussed in the outcomes from screening programmes (e.g. survival following cancer screening), however is not mentioned by any of the included articles. It is possible that benefits in terms of outcomes, such as ulcer-free survival, are a result of the 'lead time' rather than any actual benefit of early diagnosis and treatment. Evaluating the effect of this within this review is challenging, however given the nature of the outcome measured used in the included articles, any bias is likely to be small.

Finally, this review could also be affected by publication bias, which is inherent when relying of the results of published research. It is possible that articles which failed to identify delays or found no significant association of delays with outcomes were not published leading to this study overstating the recorded delays and outcomes of these. This is pertinent given the small number of included articles, however it is difficult to assess the magnitude of this effect.

Conclusion

Time delays exist in all aspects of the management pathways for both CLTI and DFU, which in some cases are extensive in length. The causes of these delays are complex and reflect poor patient health-seeking behaviours and symptom recognition, inaccurate healthcare assessment and appreciation of clinical urgency and structural barriers which hinder referral, timely assessment and treatment in care pathways. When delays occur, the results of this study elude to a detrimental effect on outcomes, particularly for patients with diabetes. High-quality, multi-

centre, prospective research is required to fully investigate the impact of delays on the management and prognosis of CLTI and DFU.

The adoption of standardised limits for referral and treatment times could help reduce delays. The aim of providing specialist assessment within 7 days of referral (which itself occurs immediately) and enacting definitive treatment within a total of 14 days, provides sound and ambitious targets for these limits. Whilst these may not be immediately achievable for all, developing national consensus statements would help create targets that take account of the provision of individual healthcare systems. Further investigation is also required of 'missed opportunities' for diagnosis in primary care and development of improved patient/professional education. Rapid-access limb salvage service, providing multidisciplinary specialist assessment and vascular imaging may also reduce barriers to treatment and reduce treatment times, although further research is required to establish their role.

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