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Burden of chronic wounds in primary care and impact of diagnostic delays on wound healing

Kirsti Ahmajärvi

ACADEMIC DISSERTATION

Academic dissertation to be publicly discussed, by due permission of the Faculty of Medicine at the University of Helsinki, Unioninkatu 35, in auditorium 116 on May 23, 2025, at 12:00.

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Abstract

The aim of this study was to investigate the pathway of wound care in primary care. Additionally, I examined whether a wound care team led by a general practitioner (GP) is effective for organising wound care and arriving at an early diagnosis and treatment plan for patients with chronic wounds. I also analysed if diagnostic delays affect wound healing.

Methods: A GP-led wound care team was established in a public health centre in Helsinki in 2013. In Study I, I conducted a survey to study the prevalence of wounds in the Helsinki Metropolitan area in 2016 and compared these results with the results of a similar study in 2008. For studies II and III, I collected data from a cohort of 197 patients attending the wound care team for the first visit due to wounds between April 2016 and September 2016. The data consisted of patient and wound characteristics, diagnostic details and information of the clinical pathway within primary and specialist care. The primary endpoint was wound healing. The primary outcome was diagnostic delay, which was categorised into three groups: delays < 4 weeks, between 4—12 weeks and >12 weeks. I studied the diagnostic delay and its effect on wound healing in these three groups, and adjusted the findings for patient characteristics, comorbidities, risk factors and medications. The statistical methods I used were univariate and multivariate analyses, such as the χ^2 test, the Mann-Whitney U test, Kaplan-Meier analysis and Cox regression. The data was analysed using SPSS version 27.0.

Results: According to study I, the prevalence of chronic wounds decreased during the study period from 0.10% to 0.08%. Also, the proportion of wounds with unknown aetiology decreased. According to study II, the diagnostic delay was 57 days (IQR 33-100), the patient-related delay 2 days (IQR0-14) and the delay to specialist care 21 days (IQR 7-52) from referral. Only one in three patients had a diagnostic delay of less than 4 weeks. Study III showed that wounds diagnosed under four weeks healed significantly faster than wounds that were diagnosed later than four weeks. The difference in healing was statistically different also between the groups the diagnostic delay between 4–12 weeks and over 12 weeks.

I conclude that a GP-led wound care team is a proper forum for early wound diagnostics and for managing chronic wounds. Study II suggests that GPs may provide accurate diagnoses, but the organisational delay is still too long than what is recommended. The diagnostic delay affects wound healing and timely recognition of critical wounds (diabetic foot ulcers and arterial ulcers), which is essential for avoiding severe outcomes. My study shows that it is possible to introduce an optimal wound care pathway within primary care and GPs should be considered when wound care pathways are created.

Key words (MeSH): 1. clinical pathway, 2. delayed diagnosis, 3. primary health care, 4. wound, 5. wound healing, 6. patient care team

Abstrakti

Tutkimukseni tavoitteena oli selvittää perusterveydenhuoltoon perustetun lääkärijohtoisen haavavastaanoton toimivuutta haavaa sairastavan potilaan diagnostiikassa ja hoidossa. Tutkimus selvittää lyheneekö hoitoviive, kun keskitytään haavapotilaan diagnostiikkaan varhaisessa vaiheessa, ja kuinka tämä vaikuttaa haavan paranemiseen.

Menetelmät: Helsingin terveysasemalle perustettiin vuonna 2013 yleislääkärijohtoinen haavatiimi. Ennen haavavastaanoton perustamista tehtiin pisteprevalenssitutkimus vuonna 2008 selvittämään kroonisten haavojen esiintyvyyttä. Toistin tämän tutkimuksen vuonna 2016 ja vertasin tuloksia aiemmin tehtyyn tutkimukseen. Osatöiden II ja III aineistoon keräsin 197 huhti-syyskuussa 2016 haavavastaanotolla ensikäynnillä käynyttä peräkkäistä potilaista, ja näiden taustatietoja, haavan diagnoosiin liittyviä tietoja ja käyntejä eri terveydenhuollon yksiköissä. Keräsin tiedot tutkimukseen myös hoitopolusta terveydenhuollon eri yksiköissä ja näissä tehdyt diagnostiset tutkimukset, hoitosuunnitelmat ja viiveen (päivissä) näissä yksiköissä. Poimin tiedot retrospektiivisesti sairauskertomusmerkinnöistä. Päätetapahtumana oli haavan parantuminen ja päämuuttujana oli diagnostinen viive. Viive jaettiin kolmeen ryhmään: viive alle 4 viikkoa, 4—12 viikkoa ja yli 12 viikkoa. Tutkin diagnostista viivettä ja sen vaikutusta haavan paranemiseen näissä kolmessa ryhmässä ja adjustoin tulokset huomioiden potilaiden taustatiedot, liitännäissairaudet, riskitekijät ja lääkitykset. Statistisina testeinä käytin χ^2 testiä, Mann-Whitneyn U-testiä sekä Kaplan-Meier- ja Cox-regressioanalyysejä. Analyysit tehtiin SPSS:n 27.0-versiolla

Tulokset: Osatyön I mukaan haavojen ilmaantuvuus pieneni vuosina 2008-2016 pääkaupunkiseudulla 0.10 %:sta 0.08 %:iin ($p<0.001$). Samoin epäselvien haavaetiologioiden osuus oli vähentynyt. Osatyön II mukaan potilaiden diagnoosiviive oli 57 vuorokautta (IQR 33-100), potilaan viive hoidon piiriin oli 2 vuorokautta (IQR 0-14) ja viive lähetteestä erikoissairaanhoitoon 21 vuorokautta (IQR 7-52). Vain kolmasosalle (n=33) potilaista päädyttiin diagnoosiin suositellussa 4 viikossa. Osatyön III mukaan haavat, jotka diagnosoitiin alle 4 viikossa paranivat nopeammin kuin myöhemmin diagnosoidut haavat. Ero oli tilastollisesti merkitsevä myös ryhmien diagnoosit 4–12 viikossa ja yli 12 viikkoa välillä. Myös haavojen paranemisasteen välinen ero oli merkitsevä näiden ryhmien välillä.

Päätelmät: Perusterveydenhuollossa toimiva yleislääkärivetoinen haavatiimi pystyy tekemään varhaista haavadiagnostiikkaa ja aloittamaan etiologian mukaisen hoidon. Osatyön II mukaan organisaation sisäinen viive on edelleen liian pitkä, vaikka yleislääkäri pystyy tekemään haavadiagnostiikkaa. Varhaisella diagnostiikalla ja hoidolla on vaikutusta haavan parantumiseen, ja tunnistamalla varhain valtimoperäisiä ja diabeettisia jalkahaavoja vältytään vakavilta haavakomplikaatioilta kuten amputaatioilta. Optimaalinen haavanhoitoketju on mahdollista aloittaa jo perusterveydenhuollossa ja haavaa sairastavien potilaiden hoito voidaan koordinoida perusterveydenhuollosta käsin.

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List of abbreviations

ABI	ankle-brachial index
BMI	body mass index
CEAP	classification of venous disorders: Clinical(C), Aetiological(E), Anatomical(A) and Pathophysiological(P)
CTA	computed tomography angiogram
Cu	copper
DFU	diabetic foot ulcer
DSA	digital subtraction angiogram
ECM	extracellular matrix
EPUAP	European Pressure Ulcer Advisory Panel
ER	Emergency room
ESCHAR	*Effect of Surgery and Compression on Healing and Recurrence* – study
EVRA	*Early Venous Reflux Ablation* – study
EWMA	European Wound Management Association
Fe	iron
fP	feasting plasma level
FGF	fibroblastic growth factor
GP	general practitioner
Gluk	glucose
HbA1 c	glycosylated haemoglobin
HIF-1	hypoxia induced factor-1
ICD-10+11	International Classification of Diseases
ICU	intensive care unit
Kol	cholesterol
IL	interleukin
LEA	lower leg amputation
LDL	low-density lipoprotein
M1	macrophage subtype M1
M2	macrophage subtype M1
Mg	magnesium
MMP	matrix metalloproteinase
MRA	magnetic resonance angiogram

MRSA	methicillin resistant *Staphylococcus aureus*
NERDS	Nonhealing, Exudate, Red friable tissue, Debris, Smell
NO	nitric oxide
NSAID	non-steroidal anti-inflammatory drug
pO_2	partial pressure of oxygen
PDGF	platelet derived growth factor
PU	pressure ulcer
Qaly	quality adjusted life year
ROS	reactive oxygen species
RUT	register of ulcer treatment
SINBAD	Site, Ischaemia, Neuropathy, Bacterial infection, Area, Depth
STONEES	Size increasing, Temperature, Probes to bone, New breakdown, Edema/Erythema, Exudate, Smell – infection classification
TGF-α	transforming growth factor alpha
TGF-β	transforming growth factor beta
TIMERS	Tissue, Infection, Moisture, Edge, Repair, Social factors
TNF-α	tumour necrose factor alpha
TNF-β	tumour necrose factor beta
$TcPO_2$	transcutaneous oxygen pressure
TCOM	transcutaneous oxygen measurement
UV LIGHT	ultraviolet light
VEGF	vascular endothelial growth factor
VLU	venous leg ulcer
WIFi	Wound, Ischemia, Foot infection – classification
WHO	World Health Organisation
Zn	zinc

Index

List of original publications

This thesis is based on the following publications:

I Ahmajärvi K, Isoherranen K, Mäkelä A, Venermo M. A change in the prevalence and the etiological factors of chronic wounds in Helsinki metropolitan area during 2008-2016. Int Wound J 2019;16(2):522-526. doi: 10.1111/iwj.13077.

II Ahmajärvi K, Isoherranen K, Venermo M. Cohort study of diagnostic delay in the clinical pathway of patients with chronic wounds in the primary care setting. BMJ Open. 2022 Nov 21;12(11): e062673. doi: 10.1136/bmjopen-2022-062673. PMID: 36410819; PMCID: PMC9680184.

III Ahmajärvi K, Isoherranen K, Pessi T, Venermo M. The Impact of Diagnostic Delay on Wound Healing - A Cohort study in a Primary Care setting. Accepted for publication, International Wound Journal. doi: 10.1111/iwj.70141.

The publications are referred to in the text by their roman numerals.

1 Introduction

The prevalence of chronic wounds has been estimated to be between 0.1 and 4.5% in the general population (Ebbeskog et al., 1996, Graham et al., 2003, Guest et al., 2015). Chronic wounds are a considerable burden for affected individuals and poses significant economic costs to health care systems (Sen, 2021). Delayed wound healing and prolonged treatment decrease the patients' quality of life: pain, stress, social isolation and anxiety are common consequences of chronic wounds (Herber et al., 2007). Management of chronic wounds is expensive. It has been estimated that wound management accounts for 2%–6% of health care costs (Guest et al., 2017b, Phillips et al., 2016, Lindholm and Searle, 2016). Accurate wound diagnosis and diagnosis-related treatment are essential for patients with wounds (Isoherranen et al. 2023).

The definition of a chronic wound is complex, but it has been regarded as a wound for which the normal healing process has failed and the inflammation phase of the wound tends to persist (Kyaw et al., 2018b). The normal healing process lasts for 2–4 weeks. The wound diagnosis presents an aetiology for delayed healing. There are several common types of chronic wounds, *e.g.*, venous leg ulcers, diabetic foot ulcers, pressure ulcers, arterial ulcers, mixed venous and arterial ulcers and atypical ulcers (Nunan et al., 2014).

Patients with wounds are mainly treated in primary care, but GPs tend to consider that it is not their business to contribute to wound management or to diagnose chronic wounds (Friman et al., 2020). If GPs participate in wound management, they are challenged by early identification, timely treatment and referrals (Manu et al., 2018). A diagnostic delay is considered a patient safety issue and constitutes part of a diagnostic error (Singh et al., 2013). Although wound management has been seen as a matter for nursing, the physician's role in wound management is diagnosing and treatment planning. Previous studies have shown that a multidisciplinary team approach, including physicians, is effective in terms of wound healing rate, avoiding hospitalisations and patient-related outcomes (Pruim et al., 2017). Building a team does not always require extra resources but, it does require reorganising of care (Laakso et al., 2017a).

Different team approaches for wound care have been studied: nurse-led teams within public health care (Innes-Walker et al., 2019, Lorimer, 2004, Harrison et al., 2005), diabetic foot ulcer teams (Armstrong et al., 2023, Jeffcoate et al., 2018) and

working groups in secondary or tertiary hospitals for treating hard-to-heal ulcers (Gottrup et al., 2001, Gottrup, 2004), but studies focusing on GP-led wound care teams are lacking. The aim of this cohort study was to examine diagnostic delays related to management of chronic wounds within primary care. I identified gaps in the diagnostic process of patients with wounds. The study was conducted in the Helsinki area, where a special GP-led wound care team was established in 2013 to promote early and timely diagnosis of chronic wounds in primary care.

2 Review of the literature

2.1 Burden of chronic wounds

Chronic wounds are a silent epidemic that affects a large proportion of the world's population. They constitute a financial burden on health care systems and societies (Sen, 2019, Posnett and Franks, 2008) (Nussbaum et al., 2018) (Guest et al., 2017a, Guest et al., 2018). The severity of ulcers, the healing times, and the complications are increasing and raise the economic burden for developed countries (Atkin et al., 2019). Snowballing costs have been reported worldwide (Queen and Harding, 2024). In the Scandinavian countries, the associated costs account for 2–4% of total health care expenses (Gottrup et al., 2001).

Chronic wounds affect many aspects of the lives of patients (Gethin et al., 2020). Wounds are often painful, give rise to anxiety, depression, sleeping disorders, social isolation and dependency on others (Gethin et al., 2020) (Lindholm et al., 1993). Long-term and recurrent ulcerations cause uncertainty, hopelessness and fear that the situation will persist (Cwajda-Białasik et al., 2017). Risk factors and circumstances for recurrence of venous ulcers reflect may coalesce in the same individuals (Eckert et al., 2023). A poor quality of life is associated with chronic wounds (Gorecki et al., 2009) (Olsson et al., 2019, Lindholm et al., 1993).

Prevention of common chronic ulcers is more effective than treatment (Kavola and Laine, 2020). According to Demarré et al., the costs for preventing PUs was 10% of the costs for treatment of PUs. The main costs were labour costs, which accounted for 79-85% of the total costs of prevention (Demarré et al., 2015). Labour costs constitute the major expense also in the management of chronic wounds (Vu et al., 2007, Oien et al., 2000). Öien et al. reported already in 1998 that 13.3% of the resources of the district nurses working in health care centres were allocated to wound management. Ulcers with an unknown aetiology decreased from 30% to 6% when sufficient nurse resourced were dedicated to wound management. Eleven percent of the patients were not consulted by a physician but treated by a nurse (Oien et al., 2000).

According to a study by Abrahamyan et al., the main barriers to effective wound management were shortage of resources (of time, diagnostic tests, wound-specific treatments, infrastructure, and education). A lack of preventive care and supportive devices (off-loading devices, compression-relieving devices, pressure-relieving

devices) and home care products (Abrahamyan et al., 2015). Further limitations were poor patient adherence, limited community support, quick staff burnout, and high staff turnover rate (Abrahamyan et al., 2015).

As written in a Position Document of hard-to-heal ulcers (European Wound Management Association, 2008), the severity of ulcers, healing times, and complications are increasing which raises health care in the developed countries. The mortality related to chronic wounds parallels total mortality and the same has been reported regarding treatment costs for chronic wounds and for cancers. Therefore, management of chronic wounds deserves as much recognition as cancer management (Armstrong et al., 2007).

2.2 Challenging definition of chronic wound

A wound is defined as tissue damage which may influence the skin and/or tissues underlying the skin, *e.g.*, muscle, adipose tissue and bone. Wound healing is a complex process with several phases and interactions on the cellular level. The atmosphere must be optimal if healing is to develop comprehensively (Wilkinson and Hardman, 2020).

A wound is chronic if it has failed to heal within the realms of a normal healing process. The timeframe varies between 2 weeks and 3 months (Nunan et al., 2014, Kyaw et al., 2018a, Leaper and Durani, 2008). Diabetic foot ulcers are considered chronic from the outset due to the underlying mechanisms. On the other hand, leg ulcers may be treated for several months before being thought of as hard-to-heal ulcers (Kyaw et al., 2018a).

The definition of chronic ulcer varies by study and depends on the aetiology of the wound, on the institute where the study is carried out and on the population studied, since studies are conducted both in specialist care and primary care units. A definition of chronic wound is found in the literature since the 1950's but an exact description is still lacking (Kyaw et al., 2018b). This lacks poses challenges for reliable estimation of the prevalence of chronic wounds.

2.3 Prevalence of chronic wounds

Since wounds constitute a heterogeneous entity, prevalence studies have resulted in a variety of outcomes and makes comparisons difficult. The studies include different populations, different wound aetiologies, different locations, different comorbidities and different setting (hospital-based and community-based studies) (Graham et al., 2003). Prevalence studies are susceptible to several biases, such as the following: Usually only patients treated in some specified health care units are included, while the patients treated at home without contact to health care are not included. Furthermore, study methods vary, as do diagnostic assessments and the definition and categorisation of chronic wounds (*e.g.,* leg ulcers and foot ulcers may be counted in same group or in separate groups) (Martinengo et al., 2019). A summary of prevalence studies is presented in Table 1.

Most of the prevalence studies are conducted in developed countries, which makes a challenge to estimate the burden of chronic wounds on a global level (Probst et al., 2023). Although Probst et al. conducted a systematic review and meta-analysis found that the global prevalence of venous leg ulcers was 0.32%. They also noted that the findings were only estimates, since the studies were heterogeneous (Probst et al., 2023). Some other studies suggest that the global prevalence of venous leg ulcers is 1% in the overall population and even higher among the aged, *i.e.,* the population above 65 years of age (3.6%)(Schneider et al., 2021).

To estimate the global prevalence of chronic wounds based on epidemiological studies would demand accurate definitions and diagnostic criteria, including lack off precise ICD-codes, for different wound aetiologies to find the information on the different wounds from patient records. Estimations of the populational prevalence of chronic wounds vary between 0.1 and 4.5% and (Ebbeskog et al., 1996, Graham et al., 2003, Guest et al., 2015, Schneider et al., 2021). Among elderly the prevalence figures are even higher (Margolis et al., 2002, Martinengo et al., 2019, Díaz-Herrera et al., 2021a, Schneider et al., 2021).

Most wounds are located in the lower leg area (Körber et al., 2011) and therefore most of the studies are conducted with patients with leg ulcers (Ebbeskog et al., 1996, Graham et al., 2003, Martinengo et al., 2019, Vowden and Vowden, 2009) It seems that the variation between decades has been quite stable, since according to Martinengo et al. reported the prevalence in the adult population 0.22% for mixed ulcers and 0.15% for leg ulcers (Martinengo et al., 2019) whereas an older point prevalence study from Forssgren et al. reported a reduction in the prevalence of leg ulcers in the Skaraborg area (Sweden) from 0.31% in 1988 to 0.24% in 2022 (Forssgren et al., 2008) and some 30 years ago, Ebbeskog et al. reported a prevalence of 0.12% of leg and foot ulcers (Ebbeskog et al., 1996).

The prevalence of diabetic foot ulcers increases along with the prevalence of diabetes. The annual prevalence of diabetic foot ulcers among patients with diabetes is

2-5 % and the lifetime incidence of ulcers is 20-35 % (Armstrong et al., 2017). In the systematic review of Zhang et al. the prevalence of diabetic foot ulcers was 6.3%. (Zhang et al., 2017).

To evaluate the global prevalence of PUs is even more challenging and is not much helped by the fact that there is an ICD-10 code for PUs. The prevalence varies significantly by health care setting. Li et al. conducted a meta-analysis on the overall prevalence of PU and arrived at an estimate of 12.8% (Li et al., 2020). Prevalence of PUs tend to vary by settings, population and definition (Table 1) (Labeau et al., 2021, Sugathapala et al., 2023, Jackson et al., 2019, Triantafyllou et al., 2021). In Sweden, a survey was conducted during the years 2011–2018 before and after implementation of a national patient safety initiative to prevent PUs. The survey covered all Swedish hospitals. The survey found that the prevalence of PUs had dropped from 17.0% to 11.4% after implementation of the national patient safety initiative (Källman et al., 2022).

Additionally, the awareness of atypical wounds as an important wound category has increased in recent years. Atypical wounds are a heterogenous wound group, and the prevalence of atypical wounds of chronic wounds treated at tertiary wound clinics is around 10%-20 % (Isoherranen et al., 2019, Virkkala et al., 2022, Becker et al., 2024).

Table 1 Prevalence studies of wounds

Author(s), year	Wound type	Geographical area; setting	Time period, number of population / reviews included	Prevalence; incidence; comments
Carter et al. (2023)	Chronic wounds; (diabetic foot ulcers and infections; arterial ulcers; skin disorders and infections; surgical wounds and infections; traumatic wounds; venous ulcers and infections; unspecified chronic ulcers; and others)	Medicare USA; Medicare beneficiaries	2014-2019, N=with a wound increased from 8.2 million to 10.5 million	Wound prevalence 14.5% to 16.4%; aged <65 years (males: 12.5% to 16.3%; females: 13.4% to 17.5%). Arterial ulcers (0.4% to 0.8%), skin disorders (2.6% to 5.3%), traumatic wounds (2.7% to 1.6%)
Díaz-Herrera et al. (2021)	Chronic wounds	Point prevalence study in south Barcelona, Spain; nursing homes	16 April and 13 June 2013; included 52 primary care centres: total population 1,217,564	Total prevalence 0.11%, VLUS 0.04%(highest), PU 0.03%, patients over 74 yrs 69.4% of chronic wounds
Ebbeskog et al. (1996)	Leg and foot ulcers	Prospective survey, structured questionnaire for nurses and physicians in area, south Stockholm, Sweden; primary health care and hospitals	6-week study Oct 1993 to Jan 1994; population 241,804	Prevalence 0.12%, n=294 patients, 92% over 65 years. VLU 42% of all. Majority treated in primary health care, compression 86% of all VLU diagnosed. Pain 47%, pain relief 29% of patients
Forssgren et al. (2008).	Leg ulcers	Skaraborg county, Sweden; population-based study (inpatient and outpatient care in hospitals,	Point prevalence study in 1988; population of 254,111	Point prevalence 2.4/1000 population in 2002 *vs.* 3.1/1000 in 1988. 23% decrease in leg ulcer prevalence. VLU highest, although prevalence had decreased 46%, and arterial ulcers decreased 23%. Diabetic and multifactorial ulcers increased.

Author(s), year	Wound type	Geographical area; setting	Time period, number of population / reviews included	Prevalence; incidence; comments
		primary care and community care within Skaraborg)		
Graham et al. (2003).	Leg ulcers	Systematic review	22 reports and 8 population-based studies	Prevalence 0.12% -1.1% in a population; differentiation by study design, ulcer definition, aetiology, assessment method and validation of ulcers difficult when defining prevalence
Gunningberg et al. 201	PUs	National prevalence survey, Sweden; cross-sectional study	Sample of 35,058 persons in hospitals and nursing homes, 2011	Prevalence 16.6% in hospitals, 14.5% in nursing homes.
Herraiz-Adillo et al. (2021)	PUs	Questionnaire sent to all nurses attending primary care centres; Cuenca area, Spain	17th February 2020 (point prevalence study) 152 professionals answered the questionnaire (response rate 98.1%) 131,190 habitants	Overall prevalence 0.389 per 1000 (IC 95%: 0.296-0.511); global prevalence higher in women than men (0.532‰ vs. 0.245‰, p = 0.008, respectively) and increased with age, prevalence in patients ≥ 65 years old 1.982‰ and 1.144‰ for women and men
Källman et al. (2022).	PUs	10-year nationwide survey, Sweden; national; hospitals	2011-2020; n=130.000 patients	PU prevalence decrease, hospitals from 17.0% to 11.4%, hospital-acquired PUs decrease from 8.1% to 6.4% (2018-2020); no decline in device-related PUs
Körber et al. (2011).	Leg ulcers	Questionnaire sent to 100 German wound care professionals	31,619 patients	Aetiologies of leg ulcers: venous insufficiency 47.6 %, arterial insufficiency 14.5 %, mixed 17.6 %. Rarer causes: vasculitis (5.1 %), exogenous factors (3.8 %), pyoderma gangrenosum (3.0 %), infection (1.4 %), neoplasia (1.1 %), calciphylaxis (1.1 %), drug-induced (1.1 %)
Labeau et al.	PUs	Intensive care units (n=1117) in 90 countries; 1-day point-	15th of May 2018; all patients n= 13 254	6747 PUs in 3526 patients, of which 3997 were ICU-related. Overall prevalence of PUs was 26.6% whereas ICU-acquired prevalence was 16.2%(95%cl 15.6 – 16.8)

Author(s), year	Wound type	Geographical area; setting	Time period, number of population / reviews included	Prevalence; incidence; comments
		prevalence study		
Li et al. (2020)	Pressure injuries	Systematic review; hospital-acquired pressure injuries globally	Jan 2008-Dec 2018; 42 studies; 39 were eligible for meta-analysis. Total 2,579,049 patients.	Pooled prevalence 12.8% (95% CI 11.8-13.9%), pooled incidence 5.4 per 10,000 patient-days (95% CI 3.4-7.8), pooled hospital-acquired pressure 8.4% (95% CI 7.6-9.3%). Most common Stage I (43.5%), Stage II (28.0%)
Margolis et al. (2002).	Venous leg ulcers	Retrospective cohort study, NHS General practice research database, United Kingdom; elderly	1988 – 1996; About 50,000 elderly persons were eligible per year	Annual prevalence 1.69%, overall incidence 0.75 male, 1.42 female per 100 person years
Martinengo et al. (2019).	Chronic wounds	Systematic review and meta-analysis	Jan 2000-June 2018; 17 studies/11 of chronic wounds in population	Pooled prevalence, mixed aetiologies (n=3) 2.21 per 1000, chronic leg ulcers(n=9) 1.51 per 1000, mostly leg ulcers
Mäkelä et al. 2010	Chronic wounds	Questionnaire, Helsinki metropolitan area	Point prevalence study in 2008; population 1,013,594	Point prevalence of chronic wounds 0.10%. Following aetiologies among 1029 wound patients: PUs 23%, venous ulcers 13%, diabetic ulcers 11%, unhealed post-surgical 11%, ischemic 7%, multifactorial 21%, unknown aetiology 14%
Probst et al. (2023).	Venous leg ulcers	Systematic review and meta-analysis; international	Up to Nov 2022; 14 studies; 10 reported prevalence	Pooled prevalence 0.32%, pooled incidence 0.17%; extreme study heterogeneity prevents interpretation
Sugathapala et al. (2023).	Pressure injuries	Systematic review and meta-analysis; nursing homes, aged care and long-term care	Incl. 47 studies, 30 studies reported PUs at any stages.	Pooled prevalence 11.6 % (95 % CI 9.6-13.7 %). 15 studies excluded stage I, pooled prev. 7.2% (95 % CI 6.2-8.3 %). Nursing homes 8.55 (95 % CI 4.4-13.5 %)
Triantafyllou et al. (2021).	PUs	Systematic review and meta-analysis; hospital-	March 2020; incl. 21 studies in systematic review and	Overall prevalence 0.47% to 31.2%, cumulative incidence 3.7% to 27%. Pooled prevalence 7.0% (95% CI: 4.3%-10.4%), pooled

Author(s), year	Wound type	Geographical area; setting	Time period, number of population / reviews included	Prevalence; incidence; comments
		acquired PUs, paediatric populations	19 studies in meta-analysis	cumulative incidence 14.9% (95% CI: 7.7%-23.9%). Note: marked variation across different age groups; neonatal, age under 1 year and over 1 year.
Vowden and Vowden (2009).	PUs	Survey in Bradford	Between 16 and 21 March 2007; general population 487,975 inhabitants	Prevalence 0.71 per 1000. If PUs in tertiary hospital included, prevalence 0.74 per 1000 (95%CI 0.6-0.8). 53.7% stage II PU 11% hospitalised for treatment, in postal coded areas with nursing homes prevalence was higher (1.39 per 1000) than in areas with no nursing homes (0.39 per 1000)
Zhang et al. (2017).	Diabetic foot ulcers	Systematic review and meta-analysis	Sept 2015; incl. 67 studies; 801,985 patients	Global prevalence of diabetic foot 6.3% (95%CI: 5.4-7.3%). Prevalence of diabetic foot ulceration in hospital-based studies (7.1%, 95%CI: 5.4–8.8%) and public health centre studies (5.6%, 95%CI: 3.5–7.6%) higher than in population-based (4.6%, 95%CI: 3.7–5.5%) and community-based (2.9%, 95%CI: 1.0–4.7%) studies

2.4 Wound healing process and factors associated with chronic wounds

2.4.1 Normal wound healing

Wound healing is a complex physiological process which includes four phases: haemostasis, inflammation, proliferation, and maturation (Figure 1) (Demidova-Rice et al. (2012), (Patel et al., 2016, Eming et al., 2007). There are many different cell types, cytokines, and growth factors involved in wound healing. The timeframe for normal wound healing is 1-3 weeks (Snyder et al., 2016). Wound healing is normal if the healing process proceeds undisturbed through the healing phases.

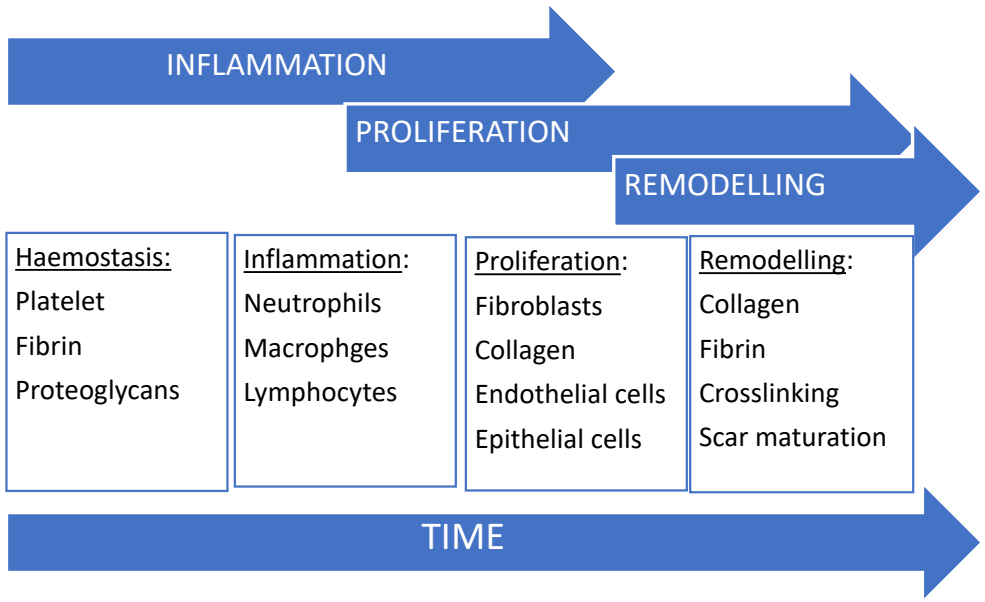

Figure 1 Normal wound healing process and involved cells and bioactive molecules

2.4.1.1 Haemostasis phase

Haemostasis occurs immediately after tissue damage. The coagulation cascade starts within a few seconds from the damage and aims at stopping bleeding and invasion of external pathogens (Young and McNaught, 2011). Thrombocytes release transmitter substances, especially platelet derived growth factor (PDGF), transforming growth factor beta (TGF-β), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) which initiate the wound healing process (Peña and Martin, 2024). The physiological phenomena that follow are blood vessel constriction, platelet aggregation, and blood clot formation (Peña and Martin, 2024, Sorg et al., 2017).

2.4.1.2 Inflammation phase

The second phase of the wound healing process is the inflammation phase, and it runs nearly in parallel to haemostasis. Inflammation starts within a few minutes after wound occurrence. Infiltration of leucocytes is a major event in the inflammatory response. The transmitters released from thrombocytes attract neutrophils, macrophages, and lymphocytes to the wound area.

Neutrophils protect and clean the wounded area from damaged cells and necrotic tissue and kill microbes (Burian et al., 2022b, Bonnici et al., 2023, Snyder et al., 2016). Neutrophils excrete reactive oxygen species (ROS), proteases (*e.g.* leucocyte elastase, protease 3 cathepsin G), and matrix metalloproteases (MMP) 8 and 9. This results in endogenous debridement of the wound and transforms the debris into slough which is phagocytised by macrophages (Diller and Tabor, 2022, Kotwal and Chien, 2017). Additionally, the pro-inflammatory cytokines IL-1α, IL-1β, TNF, and TGF-β activate other mediators which contribute to the inflammation process by activating macrophages (Van Den Eeckhout et al., 2020, Kotwal and Chien, 2017).

Macrophages are considered to have a significant role in the wound healing process (Snyder et al., 2016, Leibovich and Ross, 1975). There are several types of macrophages, and pro-inflammatory subtype M1 macrophages participate in the inflammation phase. They recognise bacteria and fungi by their surface proteins and form phagolysosomes, and also release antibacterial ROS and nitrogen oxides which protect the wound from foreign bodies (Kotwal and Chien, 2017). They clear the wounded area from debris and apoptotic neutrophils (Kotwal and Chien, 2017).

M1 subtypes produce several pro-inflammatory cytokines, *e.g.*, TNF-*α* (tumor necrosis factor-α) and IL-1 (interleukin 1), and they participate in the inflammation phase. Macrophages produce and release chemotactic factors, like TNF-*α,* VEGF, and TGF-β, which leads to neovascularisation and formation of granulation tissue. Debridement of the extracellular matrix in the wounded area requires proteases

(elastase, collagenase, MMPs), and an increased occurrence of matrix metalloproteases (MMP) is typical for the inflammation phase (Patel et al., 2016, Landén et al., 2016) (Schultz and Mast 1998).

Macrophages produce nitric oxide (NO), which has affects wound healing in many ways. NO regulates vessel permeability and vasodilatation, and it is both antithrombotic and anti-atherosclerotic (Witte and Barbul, 2002). NO is antimicrobial and activates keratinocytes, which divide and move (Stallmeyer et al., 1999). It catalyses growth factor and collagen production by fibroblasts (Witte and Barbul, 2002, Schäffer et al., 1997, Stallmeyer et al., 1999). NO is produced by fibroblasts and macrophages and therefore NO is present in the early phase of wound healing (Witte and Barbul, 2002, Schäffer et al., 2004).

The typical clinical signs of inflammation – *rubor, tumor, calor, dolor* – are caused by mediators like cytokines, growth factors, histamine, and prostaglandins in the area (Tracy, 2006). These are the key elements which orchestrate cell and tissue movement and repair injury. The *rubor* is due to vasodilatation and increased vessel permeability caused by transmitters (Hellenthal et al., 2022, Snyder et al., 2016). Oedema is caused by leakage of proteins from vessels to tissues followed by water molecules. Cytokines and prostaglandins contribute to the temperature rise, *calor* (Hellenthal et al., 2022, Netea et al., 2000). *Dolor* is caused by oedema, reduction of oxygen levels (damaged vessels on the area), reduced pH and some transmitters, which cause pain through nerve sensitisation (Zhang et al., 2023).

In the late stage of inflammation phase, T lymphocytes regulate inflammation by producing interferons and enabling progression of the inflammation to the proliferation phase (Bonnici et al., 2023).

2.4.1.3 Proliferation phase

This phase is the mid-phase of healing, characterised by granulation tissue formation. Granulation tissue is richly vascularised and consists of newly regenerated tissue which spreads into the wound bed (Peña and Martin, 2024). This phase starts within 2-4 days of the injury (Kotwal and Chien, 2017).

Macrophage transition from the M1 subtype to the M2 subtype is a key element when inflammation transitions to proliferation (Kotwal and Chien, 2017). M2 macrophages secrete anti-inflammatory mediators and growth factors (Bonnici et al., 2023) and downregulate the pro-inflammatory M1 macrophages (Snyder et al., 2016). It is essential for the wound healing process that macrophages change from the M1 to the M2 subtype (Landén et al., 2016, Murray, 2017). Subtype M2 macrophages release cytokines and growth factors (PDGF, VEGF) and promote therefore angiogenesis and fibroblast proliferation, necessary sequences for granulation tissue formation. Changed M2 macrophages also secrete anti-

inflammatory cytokines to inhibit the inflammation phase and collagen precursors to stimulate fibroblasts (Bonnici et al., 2023, Landén et al., 2016). Indeed, macrophages of the M2 subtype are needed for the formation of granulation tissue and for advancing the wound healing process to tissue regeneration and formation (Bonnici et al., 2023, Sorg et al., 2017).

Fibroblast migration into the wound area from the surrounding tissues is initiated by PDGF produced by macrophages and platelets (Patel et al., 2016). Fibroblasts themselves produce matrix metalloproteases to facilitate cell movement from the matrix of the temporary wound bed (Patel et al., 2016). Fibroblasts produce collagen, and collagen is modified later in the proliferation phase (Patel et al., 2016). Fibroblasts are crucial for extracellular matrix (ECM) formation, which involves collagen, glycosaminoglycans, and proteoglycans (Guo and Dipietro, 2010). New tissue formed in the wound bed requires nutrition and oxygen, the access of which is handled by angiogenesis.

Angiogenesis is initiated by low levels of oxygen, high lactate levels, and low tissue pH, which increase hypoxia-induced factor-1 (HIF-1) production. HIF-1 upregulates VEGF in endothelial cells, and this promotes growth and branching of blood vessels (Bonnici et al., 2023).

New vessels are formed from old vessels. Endothelial cells which move outside the old vessels and through the basal membrane start to divide and to form new vessels outside the old vessels. These endothelial cells form loops and microvascular connections until the new tissue is covered with new vessels (Korablev et al., 2024, Nowak-Sliwinska et al., 2018). Angiogenesis stops when the activating circumstances stop (Korablev et al., 2024, Díaz-Bulnes et al., 2019).

Lucas et al. found out that macrophages stabilise vascular structures. If the macrophages are depleted, more haemorrhaging would occur. Macrophages participate in facilitating the transition of granulation tissue to the scarring phase (Lucas et al., 2010).

Epithelialisation

Granulation tissue is formed without epithelial input, but keratinocytes need stimuli from the wound bed to grow (Lucas et al., 2010). The extracellular matrix (ECM) helps cell adhesion, migration, and proliferation (Lucas et al., 2010). Epithelial cells (keratinocytes) migrate from the edges of the wound over the granulation tissue. Keratinocytes and mesenchymal cells of the granulation tissue form the basement membrane (Landén et al., 2016). Through mitosis and differentiation keratinocytes cover the wound until final closure of the wound (Piipponen et al., 2020). This epithelial barrier is fragile and very sensitive to interruptions, *e.g.,* dressing changes, moisture, or debridement (Coelho et al., 2023).

2.4.1.4 Maturation phase

The maturation phase starts within 3-4 weeks from appearance of the original wound and continues even for months after skin closure. In this phase, the extracellular matrix is remodelled and fibroblasts differentiate into myofibroblasts, which produce type I and III collagen. Collagen fibers crosslink and harden the ECM (Diller and Tabor, 2022, Bonnici et al., 2023). Later in this phase, the MMPs reduce collagen type III which leaves the type I collagen as the main factor for scar tissue formation (Diller and Tabor, 2022, Rohani and Parks, 2015). Macrophages play a role also for scarring, and macrophage depletion decreases the degree of scar formation (Lucas et al., 2010).

2.4.2 Factors associated with chronic wounds

2.4.2.1 Inflammation

Inflammation is essential for normal wound healing. In contrast, chronic wounds tend to remain in the inflammation phase and do not proceed into the proliferation phase (Eming et al., 2007, Guo and Dipietro, 2010). Hyperinflammation is characteristic for chronic wounds for which there are several pathophysiological explanations. Here, macrophages play a major role (Li et al., 2021).

Lucas et al. studied the important role of macrophages by restricting them from the early stage of wound healing. This resulted in a reduction of granulation tissue formation, impaired epithelialisation, and minimised scarring (Lucas et al., 2010). There are several reasons why the wound healing process remains in the inflammation phase. Macrophages may be dysregulated and do not switch from subtype M1 to subtype M2. Pathophysiologies that affect the macrophages include bacterial load and infection, necrotic tissue, obesity, ageing, diabetes, and inflammatory diseases (*e.g.*, vasculitis and pyoderma gangrenosum) (Li et al., 2021, Krzyszczyk et al., 2018, Coelho et al., 2023).

Studies on wound exudates have shown that different bioactive substances are present in acute wounds compared to chronic wounds. MMPs play a role in wound healing but excess MMPs results in non-healing wounds because proteins of healing wounds, necessary for healing, are degraded. There are excess amounts of proteases, *e.g.* MMPs, in the wound fluid from chronic wounds (Caley et al., 2015).

2.4.2.2 Infection

Infection disturbs wound healing by several mechanisms (Coelho et al., 2023). Infections keep the wound healing process in the inflammation phase and prevent initiation of the proliferation phase. Proteolysis is activated and prohibits healthy

cells from growing (Townsend et al., 2024, McCarty and Percival, 2013). Exudate and pus accumulation lowers the oxygen levels in the wound and bacteria begin to inhibit the body's own cells from growing and dividing (Townsend et al., 2024). An infection may generate abscesses and cause mechanical disturbances. Bacteria secrete also toxins which destroy normal cells (Kirchner et al., 2020). There is controversy about the significance of a biofilm for wound healing (Bianchi et al., 2016).

2.4.2.3 Oxygen

Tissues need oxygen for their vitality, biochemical reactions, cellular functions, nutrition, and as a substrate to ROS species which are needed for cleansing wounds from pathogens (Eisenbud, 2012, Tandara and Mustoe, 2004). Angiogenesis and proliferation of new tissue are induced by slight hypoxia in the beginning of the tissue damage process (Li et al., 2021). On the other hand, prolonged hypoxia does not only impair wound healing, but it causes also tissue damage (Sen, 2009). Decreased oxygen levels in tissues weaken the functions of white blood cells and fibroblasts and impair collagen synthesis (Eisenbud, 2012, Sen, 2009, Tandara and Mustoe, 2004). Maturation of collagen is dependent on oxygen (Prockop et al., 1979, Sen, 2009). Sheffield noted that chronic wounds have a cutaneous pO_2 value of 5-10mmHg, when healthy tissues have 35-50mmHg (Sheffield, 1998).

Oxygen reaches the cells through transportation by haemoglobin but also as free oxygen from plasma. Sufficient microvascularisation reduces the distance for oxygen to diffuse from plasma to tissue, and this facilitates wound healing (Tandara and Mustoe, 2004, Sheffield, 1998).

2.4.2.4 Smoking

Smoking inhibits wound healing in several ways. It reduces tissue oxygen levels through vascular constriction, which reduces tissue blood flow (Bechara et al., 2024). Carbon monoxide takes the place of oxygen in the haemoglobin molecule which affects tissue oxygenation. Hydrogen cyanide prevents enzyme functions necessary for oxygen delivery and this causes ischaemia on the tissue level (Silverstein, 1992). Tobacco contains also several toxic ingredients, such as nicotine, hydrogen cyanide, carbon monoxide, formaldehyde, lead, arsenic, and ammonia. Nicotine causes capillary contraction and damages the endothelial cells of the arteries (Morecraft et al., 1994). Vessel damage activates the coagulation cascade, generating microembolisms (Silverstein, 1992, Mosely and Finseth, 1977). It has been known for decades that smoking increases the risk for infections and affects common wound healing as well as post-surgical wound healing (Silverstein, 1992, Goldminz and Bennett, 1991, Sørensen et al., 2002). Nicotine disturbs the immune defence system by affecting the function of macrophages, and a root cause for several pathologies might be the effect of nicotine on polarisation of macrophages (Saranyutanon et al.,

2022). Smoking also delays the division and migration of keratinocytes to the wound area, and interferes with collagen production, which delays the proliferation phase (Wong et al., 2004, Arredondo et al., 2003).

2.4.2.5 Diabetes

Type 2 diabetes is caused by insulin resistance, which leads to decreased insulin-simulated glucose uptake into cells. Insulin resistance is associated with obesity, physical inactivity, and ageing (Donath and Shoelson, 2011, Rohm et al., 2022). Hyperglycaemia, as well obesity, cause chronic inflammation and both of these disorders may be considered inflammatory diseases (Rohm et al., 2022, Donath and Shoelson, 2011). In diabetes, leucocytes recognise only moderately foreign material of the wounded area, immigrate more slowly to the wounded area, and attenuate the inflammation reaction. All these changes increase the risk of infection (Edmonds, et al., 2021, Loots et al., 1998). Neutrophils interact less actively with foreign material, phagocytosis is inadequate, and this increases the risk for severe infections, as well (Berbudi et al., 2020). Hyperglycaemia damages blood vessels, especially microarteries, and reduces angiogenesis and wound healing (Rai et al., 2022, Okonkwo et al., 2020). Hyperglycaemia also affects the functioning of fibroblasts and endothelial cells negatively (Rai et al., 2023, Loots et al., 1998). Thus, it was no surprise when Loots et al. reported that the edges of diabetic foot ulcers have a hyperkeratotic epidermis and necrotic tissue containing an excess of inflammatory cells (Loots et al., 1998).

2.4.2.6 Ageing

Ageing of the skin is a multifaceted phenomenon. The dermis and the epidermis get thinner, cell proliferation diminishes, and the cells become less active. The skin gets fragile and thin, which exposes it to skin tears, PUs and haematomas. The skin becomes also drier, since the production of sebum from the sebaceous glands is reduced, and ceramides, fatty acids, and cholesterol are produced in lower amounts. The pH of the skin rises predisposing the skin to infections. Reduction of collagen and elastane fibers causes skin changes: the subcutis gets thinner and the number of vessels diminishes (Tobin, 2017, Tobin, 2006, Gould and Fulton, 2016).

Dermatoporosis is a term used to describe ageing skin which has lost its crucial properties (Wollina et al., 2019, Kaya and Saurat, 2007): the skin loses its normal elasticity and strength due to a reduction in collagen and other supportive tissues. It is a complex syndrome involving pigmentary, vascular, connective tissue, and adipose tissue aspects (Dyer and Miller, 2018, Kaya and Saurat, 2007). Skin layers are thinner and the subcutis is more or less absent. Keratinocytes are defective and no longer proliferative, and the ECM with collagen and elastin fibers is thinner (Dyer and Miller, 2018, Xia et al., 2001). MMP-1, 2, and 3, being upregulated in ageing skin,

cause breakage of collagen and elastase (Hornebeck, 2003). Hyaluronic acid, produced by fibroblasts, holds collagen fibers together and softens the friction between collagen fibers. Hyaluronic acid synthesis is reduced in dermatoporotic skin, resulting in an elevated risk for skin damage in connection with minor trauma, such as shear forces and skin tears (Dyer and Miller, 2018). Thus, only a slight trauma, such as a light knock to an object or someone grabbing the arm, may cause a wound. Special attention needs to be paid when tapes and adhesives are removed, since they may be attached quite firmly to the dermatoporotic skin, and removal of the skin dressing may peel off the whole skin (Dyer and Miller, 2018, Kaya and Saurat, 2007). UV light affects the skin and causes photodamages which accumulate with age (Cadet et al., 2005, Sellheyer, 2003).

Chronic wounds tend to relate to advanced age (Díaz-Herrera et al., 2021a, Gould et al., 2015, Martinengo et al., 2019). The mean age in the prevalence study of Martinengo et al. was 70-80 years, and since other studies corroborate this finding, we may conclude that chronic wounds pose "a geriatric time bomb"(Martinengo et al., 2019). One aspect to remember is that elderly patients may adhere less well to treatment, *e.g.*, it may be difficult to understand the full value of compression therapy. Further challenges for elderly patients may be cost (to pay, *e.g.*, for bandages, compression materials, and assistance equipment), overestimation of the individual's capability carry out self-treatment, patient's false understanding of the consequences of chronic ulcers etc. (Weller et al., 2021, Harris and Fraser, 2004).

Although age has been considered to be as a risk factor for chronic wounds, comorbidities of the elderly affect wound healing even more than age alone. Inflammatory diseases and anti-inflammatory treatments that effect on wound healing are much more common among the elderly and may well contribute to the presence and prevalence of chronic wounds (Kremer and Burkemper, 2024, Graham et al., 2006, Gould et al., 2015, Gould and Fulton, 2016).

2.4.2.7 Oedema

Oedema delays the wound healing by restricting blood flow, oxygen, and delivery of nutrients to the wounded area. There is also an increased risk for infections due to the moist environment of wound and the reduced immune response (Burian et al., 2022a).

There are different causes for oedema (Table 2). If caused by inflammation or infection it may occur locally at the wound area. Inflammation and infection increase the permeability of the vessels, which leads to leakage of water molecules, followed by leakage of bigger molecules, *e.g.,* proteins, into the extravascular space of tissues. Venous insufficiency, disorders of the lymphatic system, dysfunctional ankle movement, poor calf muscle pump function, and obesity are the underlying causes of leg oedema. Also, systemic diseases, such as heart failure, kidney and liver

malfunctions, and malignancies cause fluid retention and oedema of the tissues, including the tissues of the legs (Burian et al., 2022a). Also, adverse events of some medications, *e.g.,* calcium channel blockers, glucocorticosteroids, and NSAIDs, include leg oedema (Leonetti et al., 2002, Messerli, 2002, Sinnathamby et al., 2024).

Table 2 Other reasons for leg oedema (modified from Korhonen and Laine, Duodecim, 2021)

Unilateral	**Bilateral**
Acute	**Acute**
Deep vein thrombosis	Cardiac failure
Cellulitis	Kidney failure
Gout	Cushing syndrome
Trauma (cave elderly, diabetics)	Liver failure
Charcot foot syndrome	
Chronic	**Chronic**
Venous insufficiency	Hypoalbunaemia
Bakers' cyst	Pregnancy
Lymphoedema	Obesity
Post thrombotic	Medication (Calcium channel blocker)
Post cellulitis	Excess of salt
Infection(filariasis)	Excess of liquorice
Cancer (sarcoma, melanoma, cancer in the pelvic area) which is causing venous compression	Bilateral lymphoedema
Cancer surgery incl. removal of lymph nodes	
Post radiation therapy	
Injuries or accidents	
Dysfunction of calf muscle pumps	
Immobility	
Disease of joints (*e.g.* rheumatoid arthritis, arthrosis, diabetic neuropathy, lumbal causes)	
Post-traumatic dysfunction of the ankle joint	
Neurological conditions	

2.4.2.8 Nutrition

Nutritional deficit is a risk factor for delayed wound healing, and therefore assessing the adequacy of the patient's nutrition is an essential part of wound management (Seth et al., 2024, Ghaly et al., 2021).

Maintaining the functions of the body – cell division, protein synthesis, enzyme synthesis etc. – requires energy and certain chemical compounds. An open wound may cause catabolism when the wound exudes water, proteins, blood cells, and other biologically important substances. In this situation the body is breaking down tissues and cells, and if the tissue damage is substantial, the catabolic situation is worse (Molnar et al., 2014). The body tries to repair the damage, and, for this, energy and certain substances are needed (Barchitta et al., 2019). Carbohydrates are a source of

energy and there should be enough of these in the diet (Danby, 2010, Barchitta et al., 2019). Proteins are essential for wound healing, especially if the patient's intake of protein is reduced as the proteins are not stored to any great extent by the body to be used when needed. Indeed, low protein levels inhibit wound healing and increase the risk for infections (Wu et al., 2009, Harris and Fraser, 2004).

Vitamins essential for wound healing are vitamins A, C, D, K, and E; vitamin B supports the immunological response of the body (Molnar et al., 2014, Bechara et al., 2022, Burkievcz et al., 2012, Lin et al., 2023, Barchitta et al., 2019). Zinc (Zn^{+}) is a cofactor in the metabolism of enzymes, *e.g.,* MMP synthesis, and is essential for collagen synthesis and cell proliferation. Zinc also participates in the immunological process (Lansdown et al., 2007, Agren et al., 1991). Iron (Fe^{2+}) is needed for oxygen transportation in haemoglobin. Copper (Cu^{2+}) is involved in all stages of wound healing, from modulation of cytokines and growth factors to collagen and elastin production (Kornblatt et al., 2016, Seth et al., 2024). Magnesium (Mg^{2+}) is a cofactor for enzymatic functions involved in collagen and protein synthesis, and especially in energy production (Razzaghi et al., 2018).

2.4.2.9 Medication

Some medicines affect wound healing (Khalil et al., 2017). Anticoagulants affect blood clot formation early in the healing process (Galvan, 1996). Acetylsalicylic acid and NSAIDs have a similar effect on coagulation, they influence the synthesis and the number of fibroblasts, and they diminish re-epithelialisation and angiogenesis (Dong et al., 1993, Khalil et al., 2017). Glucocorticosteroids inhibit inflammation and affect macrophage function and leucocyte phagocytosis; both of these phenomena increase of risk for infection (Barnes, 2006). Glucocorticoid medication may also inhibit keratinocyte proliferation, leading to dysfunctional keratinocytes and thinning of the skin. Hydroxyurea is associated with poor wound healing (Dissemond et al., 2006). Cytostatic drugs interfere with cell proliferation and cell function; leucocytes are especially vulnerable to the effect of cytostatics, and this causes a higher risk for infections (Khalil et al., 2017).

2.4.2.10 Local factors

Wound bed preparation is a prerequisite for wound management and healing (Sibbald et al., 2021). Keeping a good moisture balance and exudate control are necessary alongside proper debridement of the wound from slough, debris, foreign substances, necrotic tissue, and non-vital tissue. Debridement inhibits the persisting inflammatory reaction and decreases the bacterial load. These circumstances prolong the inflammatory phase and delay progression of the wound healing process to the proliferative phase (Sibbald et al., 2021). Pain management is crucial in wound management; pain increases immunological stress and has been shown to associate

with wound healing (Woo, 2012). And, of course, proper analgesia is also a basic patient right.

2.4.2.11 Psychosocial factors

Stress affects the body in several ways and involves the neural, humoral, and immunological systems of the body (Woo, 2012, Segerstrom and Miller, 2004). The direct pathological process is effectuated through involvement of the hypothalamus, pituitary, and adrenals; this is known as the sympathetic-adrenomedullary axis. There is also an indirect pathological process through negative psychological feedback: anxiety, depression, and social isolation (Basu et al., 2022, Broadbent and Koschwanez, 2012). Gouin et al. have proposed that there is a relation between social support, vasopressin, oxytocin, and wound healing. Patients with high oxytocin levels and who experienced supportive and positive interactions with friends and companions had better wound healing (Gouin et al., 2010, Detillion et al., 2004) than those who did not. In agreement with these observations, Vedhara et al. reported that diabetic foot ulcer healing was associated with depression and poor coping methods (Vedhara et al., 2010, Gonzalez et al., 2011).

Extended immunological activation leads to a substantial inflammatory response, driven mainly by cortisol. High cortisol secretion leads to poor wound healing, since cortisol decreases the immunological response by downregulating cellular differentiation and proliferation and by reducing cell adhesion required for cell migration (Woo, 2012). T-cells react poorly to interleukin-1, which leads to poor secretion of growth factors and poor wound healing (Woo, 2012, Basu et al., 2022). High levels of epinephrine inhibit also wound healing. Epinephrine activates β-adrenergic receptors of keratinocytes, but there is controversary understanding of the role of these receptors in keratinocyte migration in the wound bed. Sivamani et al., Steenhuis et al. and Romana-Souza et al. suggests that keratinocyte behavior is context-dependent, but complete understanding of these receptors needs further research. Fibroblast function was also found to be reduced (Sivamani et al., 2009, Steenhuis et al., 2011, Romana-Souza et al., 2011, Romana-Souza et al., 2010).

2.5 Aetiologies of chronic wounds

Chronic wounds are categorised into several diagnostic groups according to their aetiology. The wound types are differentiated from each other by different diagnostic methods, and the wound aetiologies are called wound diagnoses despite the fact that there are no specific ICD-10 nor ICD-11 codes for the different diagnoses covering chronic wounds. There are five common aetiologies: venous, arterial, mixed venous and arterial, diabetic, and pressure (PUs). A sixth group is called atypical wounds, and it comprises about 10-20 % of all wounds treated at tertiary wound care clinics (Becker et al., 2024). Venous leg ulcers are the most common of leg ulcers, but there are several other causes for leg oedema and therefore oedema-related wounds are separated into a category of their own. Although the present thesis does not focus on acute wounds or burns, there is a category comprising post-traumatic ulcers at risk for becoming chronic, due to various mechanisms. Table 3 summarises wounds by aetiology, their risk factors, pathophysiology, clinical symptoms, diagnostics, and treatment.

2.5.1 Venous leg ulcers (VLU)

Chronic vein insufficiency is the most common aetiology of leg ulcers (Nelzén et al., 1996, Raffetto et al., 2020, Jockenhöfer et al., 2016). Some 50- 70% of all leg ulcers are venous ulcers (Alavi et al., 2016).

Venous insufficiency is a condition where the venous blood flow is impaired due to dysfunctional venous valves. Many factors seem to cause venous dilatation, venous reflux, and decompensated valvular function (Comerota and Lurie, 2015). These factors are related to endothelial cell injury and to permeability, inflammatory reactions such as macrophage and leucocyte infiltration, sustained hypercytokinaemia, MMPs, reactive oxygen and nitrogen species, iron, and to other tissue metabolites. Venous ulceration results from the activity of several complex biomolecules (Raffetto et al., 2020).

Venous hypertension in the lower extremities causes the symptoms of venous insufficiency (Comerota and Lurie, 2015). Suspicion of a venous aetiology should arise from the typical clinical picture, but eventually the diagnosis must be verified with duplex ultrasound. The CEAP classification is used for defining the severity of the disease (Table 3)(Chaudhry and Lee, 2024, Lurie et al., 2020, O'Donnell and Passman, 2014). The risk factors for venous insufficiency and the underlying conditions are presented in Table 4. Poor functionality of the calf muscle pumps worsens venous hypertension and may in some cases be the direct cause of venous ulceration (Comerota and Lurie, 2015).

With the correct treatment, 75% of VLUs heal within 4 to 6 months. If a wound has not improved with correct treatment, a vascular surgeon should be consulted for

a vascular procedure (Gohel et al. 2018). The golden treatment standard of VLUs is surgical treatment aiming to eliminate the venous reflux, *e.g.,* endovenous laser ablation sclerotherapy or surgical ligation (Marsden et al., 2013). In Early Venous Reflux Ablation (EVRA) ulcer trial Gohel at al. concluded that early surgical venous ablation together with compression therapy shortens the healing times of venous ulcers significantly compared to compression therapy alone (Gohel et al., 2018). The Effect of Surgery and Compression on Healing and Recurrence (ESCHAR) study found that adding superficial venous surgery to compression therapy significantly reduced the recurrence of ulcers compared to using compression alone (Barwell et al., 2004, Gohel et al., 2007). All treatment methods of VLUs are presented in Table 4.

Table 3 CEAP (Clinical, Etiological, Anatomical, and Pathophysiological) classification of venous insufficiency (Lurie et al., 2020, Eklöf et al., 2004)

CEAP	Clinical features and patient history
C1	Telangiectasias, reticular veins
C2	Varicose veins
C3	Leg oedema
C4	Venous insufficiency and dermatological changes; pigmentation, eczema, lipodermatosclerosis, atrophy blanche
C5	Previous venous ulcer (healed)
C6	Venous ulcer (unhealed or recurrent)

C1-3 are considered mild symptoms and C4-6 severe symptoms

2.5.2 Ulcers due to other causes of oedema

There are also other reasons for leg oedema than venous insufficiency (Table 1), although the underlying reason for ulceration is the same in all oedema types. The basis of treatment is compression therapy in addition to treatment of the aetiology of the oedema are presented in Table 4 (Moffatt et al., 2019).

2.5.2.1 Lymphatic ulcers

The function of the lymphatic system is to drain excess fluid from tissue. The lymph fluid is similar to plasma. It contains different substances and particles, like water, proteins, and leucocytes. Lymphatic vessels run near the vascular system. Lymphoedema is caused by dysfunctional lymph vessels (Dean et al., 2020). It is a chronic condition, where lymphatic fluid cumulates in tissues and causes swelling.

Lymphatic disorders can be divided into two categories: primary and secondary. The primary category includes genetic malformations of lymph vessels, while the secondary category includes traumatic causes for destroyed lymph vessels, oncological surgery, scar tissue after surgery, and blocked lymph vessels due to malignancy (Radhakrishnan and Rockson, 2008, Dean et al., 2020). Other causes for lymphoedema include infections, *e.g.* cellulitis and filariasis, deep vein thrombosis,

chronic venous insufficiency (phlebolymphoedema) (Radhakrishnan and Rockson, 2008, Burian et al., 2021, Moffatt et al., 2019), vascular conditions that affect lymph vessels like deep vein thrombosis (DVT) and, as mentioned above, chronic venous insufficiency (Farrow, 2010).

Treatment of lymphatic leg ulcers is primarily compression therapy, but in severe cases lymphatic therapy or lymphatic massage may improve lymph drainage. Lymph vessel surgery, such as liposuction and microsurgical reconstructive procedures, is employed for treating primary or secondary lymphoedema (Farrow, 2010).

2.5.2.2 Obesity

Obesity impairs both venous and lymphatic circulation and leads to leg oedema. The impairment is mechanical and related to increased abdominal fat. Intra-abdominal pressure increases, leading to interruption of the venous flow towards the heart. This causes malfunction of the venous system and leads to leg oedema. (Danielsson et al., 2002, Meulendijks et al., 2020, Nelzén et al., 1994).

Treatment of wounds caused by obesity is complex, and mainly based on conservative approaches, such as compression therapy, exercise, local wound treatment, and weight control. Psychological intervention may be needed for the holistic treatment of the patient (Tapking et al., 2019, Haywood and Sumithran, 2019).

2.5.2.3 Immobility and insufficient ankle movement

The calf pump is considered to be the “heart of the legs “ (Bolton, 2019). The calf muscles pump venous blood towards heart, and the calf muscle pump is needed to maintain sufficient venous. If this mechanism fails for some reason, venous insufficiency and swelling of the legs ensues. This may occur for immobile patients and for patients with poor ankle movement, dysfunction of the Achilles tendon, neuropathy, ankle or foot fractures, or other conditions that affect the functions of the entire lower leg (calf muscles, ankle joint, and feet) (Meulendijks et al., 2020).

Treatment is based on local wound management, compression therapy, physiotherapy to activate the lower leg muscles, and in specific situations consultation of a lower leg orthopaedic surgeon for surgical treatment (Bus et al., 2024).

2.5.2.4 Cardiac, kidney, or liver failure

Our body functions are in homeostasis under normal circumstances. If some organs fail, homeostasis changes. Oedema is one symptom of cardiac, liver, and/or kidney failure. There are several pathophysiological mechanisms for the oedema in this

condition, but physicians must keep in mind that these conditions may affect the wound healing. If possible, the oedema should be treated with compression therapy alongside the treatment of the comorbidities (Maroz and Simman, 2013, Lin et al., 2024, Rhou et al., 2015).

2.5.3 Arterial ulcers

In atherosclerosis, arteries are subjected to the consequences of the metabolic syndrome, which is characterised by high blood pressure and hypercholesterolaemia and accumulation in the walls of the arteries. This leads to chronic tissue ischaemia in areas supplied by small peripheral arteries (Farber and Eberhardt, 2016). The pathophysiology of arterial atherosclerosis is presented in Table 3 (Farber and Eberhardt, 2016). Atherosclerosis of the bigger arteries, if grave, leads to limb-threatening acute ischaemia when an atherosclerotic plaque ruptures leading to thrombosis. This causes extreme pain for the patient, the ischemic limb is pale and may exhibit motor and neuropathic symptoms (McNally and Univers, 2018, Rutherford, 2009).

Arterial dysfunction is examined in primary care by palpation of peripheral pulses and by measuring the ankle-brachial index. In specialised care further investigations may include, *e.g.,* toe pressure and transcutaneous oxygen measurements (Fife et al., 2009). If arterial insufficiency is detected, imaging studies of the lower limb arteries are needed.

The primary treatment is revascularisation, *i.e.,* peripheral angioplasty and/or arterial bypass performed by a vascular surgeon. Non-surgical treatment is based on the treatment of cardiovascular risks in general: hypertension, hyperlipidaemia, and diabetes. The treatment regimen includes also anti-platelet treatment, weight control, stopping smoking, and exercise (Jones and Farber, 2020).

2.5.4 Diabetic foot ulcers

Diabetic foot problems constitute a severe category of diabetic complications. Half of diabetic foot ulcers are infected and 20% of them require hospitalisation (Vuorisalo et al., 2009, Armstrong et al., 2020). In patients with diabetes, the lifetime risk for developing a foot ulcer is 25% (Singh et al., 2005) and half of these patient will develop an infection (Armstrong et al., 2023, Cortes-Penfield et al., 2023, Prompers et al., 2007). Diabetic foot ulcers are of neuropathic or angiopathic origin, or both, and some minor trauma is required for clinical exacerbation of the symptoms. The most common foot ulcers are the neuropathic foot ulcers. Peripheral atherosclerosis is present in 50% of diabetic ulcers and, of these, neuroischemic and infected ulcers pose a major risk for a severe foot infection and possibly amputation (Armstrong et al., 2023, Prompers et al., 2007).

The mortality of patients with diabetic foot complications has been compared with the mortality of patients with some types of cancer. The 5-year mortality of patients with Charcot foot, DFU, after minor amputation, and after major amputation was 29.0%, 30.5%, 46.2% and 56.6%, respectively, whereas the corresponding figure for patients with breast cancer was 9.0% and lung cancer 80.0%. The pooled 5-year mortality rate for patients with any form of cancer was 31.0% (Armstrong et al., 2020).

Glycosylation of the nervous and inflammatory system cause diabetic sensomotor neuropathy which causes pain, paraesthesia, and numbness of the distal parts of the lower extremities. Autonomic neuropathy causes dryness of the skin which results in the loss of protective sensations and increases the risk for microtraumas and ulceration in the lower extremities. The neuropathy-induced macroscopic changes are hyperkeratosis, clavi, deformation of joints and tendons causing mallet toes, and stiffness of Achilles tendon with resulting dysfunction of the ankle movement. Poor joint movement of the lower leg results in abnormal pressure areas of the forefoot and an increased risk for ulcers (Lavery et al., 2002, Vuorisalo et al., 2009). Charcot foot develops in a neuropathic foot and is at risk for ulceration (Wukich et al., 2024). Therefore, screening for neuropathy and examination of the feet of diabetics is essential for detection and prevention of diabetic foot ulcers (Kanji et al., 2010).

Glycosylation causes angiopathy and comorbidities related to diabetes. These complications are related to glycaemic control (Armstrong et al., 2023, Lane et al., 2020). The treatment of diabetic foot ulcers is off-loading of the foot under the guidance of a podiatrist, good diabetes balance, proper local wound care, prevention of infections, and treatment of peripheral arterial disease if present and if treatable (Luo et al., 2022, Lane et al., 2020, Chen et al., 2024).

2.5.5 Mixed venous and arterial ulcers

It is not rare to encounter patients with both venous and arterial insufficiency in the same leg. The prevalence of foot ulcers with a mixed aetiology is increasing in pace with ageing of the population. Several comorbidities are common (Hedayati et al., 2015). These facts should be considered when examining patients, if concomitant arterial insufficiency in a leg with venous insufficiency is to be identified. Before introducing compression therapy, the blood flow of the leg must be assessed and treated, if necessary (Hedayati et al., 2015). Mosti et al. claims that it is safe to use inelastic compression bandages if the ABI of the leg is above 0.5 and the total ankle pressure is above 60mmHg (Mosti et al., 2012). Hard-to-heal ulcers have often mixed pathophysiologies and patients have several comorbidities. Obviously, a multidisciplinary approach is essential for optimal management of these patients (Atkin et al., 2019, Harding and Hedayati, 2021).

2.5.6 Pressure ulcers

Pressure ulcers (PU) are common chronic ulcers, especially among the elderly (Källman et al., 2022). The biomechanism of the ulceration of PUs is related to cell deformation under pressure. The skeleton of the deformed cells breaks, leading to cell destruction and release of proinflammatory substances and initiation of an inflammatory process. Cell deformation is therefore the fundamental cause for ulceration and for upholding the vicious cycle of PUs (Gefen et al., 2022, Gefen, 2024).

PUs occurs in areas close to bone processes of the body in immobilised individuals. Patients at risk are immobile in different situations throughout their life: at emergency services, in operation theatres, at wards, in elderly care, in home care, and in 24-hour care. The risk varies also by circumstances like medical devices (Jackson et al., 2019), patient transportation, especially long-distance transportation, medical examinations that take a long time, and use of casts or other tools of immobilisation (Lima Serrano et al., 2017, Özdemir et al., 2023, Kottner et al., 2020, Jackson et al., 2019).

The treatment of PUs aims at reducing the pressure against the affected body area by repositioning and with the use of assistance devices, *e.g.*, mattresses and cushions, or other equipment that has the property to distribute pressure over a wider body area. Other important elements of PU treatment are local wound management, assessment of the patient's skin and nutritional state, vascular assessment, and consultation of a vascular surgeon regarding the findings, and, possibly, plastic and reconstructive surgical treatment, *e.g.*, flap surgery and skin substitutions techniques (Kottner et al., 2020).

Foot malformations

Foot malformations are a risk for PUs. The aetiologies of foot malformations vary, but the cause of the wound is pressure. Rheumatoid arthritis, gout, arthrosis, post-fracture deformities, mallet toe, claw toe, and hammer toe are examples of foot malformations that may cause ulceration. Diabetic foot malformations are discussed in a separate paragraph (See Chapter 2.4.4.).

Treatment requires both podiatric expertise for treatment, choice of proper footwear, and pressure off-loading. If surgical methods are needed, a foot orthopaedic surgeon must be consulted (Meshkin et al., 2020).

2.5.7 Atypical wounds

Atypical wounds are a heterogenous group of wounds – not categorised in the main wound groups – with different aetiologies. These wounds may be categorised as inflammatory or non-inflammatory wounds. Atypical wounds represent 10-20% of all

chronic ulcers (Ansert et al., 2022, Becker et al., 2024). Several comorbidities associate with these wounds and it is precisely this fact that gives a hint to a correct, underlying diagnosis (Becker et al., 2024). Usually these wounds are diagnosed and treated by dermatologists; timely referral to specialist care is essential (Jockenhöfer et al., 2019, Lima Pinto et al., 2015, Oliveira and Frazão, 2015). The golden standard for treatment is to treat the underlying condition and the local wound according to guidelines (Becker et al., 2024, Virkkala et al., 2022).

2.5.8 Infectious wounds

All chronic wounds are contaminated, but not all are infected (Tomic-Canic et al., 2020). Still, all types of wounds have the potential to become infected. There is a lack of consensus regarding the critical bacterial amount: when is bacterial colonisation becoming bacterial infection (Haesler et al., 2022)? The actual diagnosis of wound infection is clinical, and findings like erythema, local oedema, purulent exudate, increased exudation, hypergranulation, increasing pain and delayed healing are critical for diagnosis (Haesler et al., 2022). Indeed, some infectious diseases, such as leishmaniasis and tuberculosis, may cause ulceration (Table 3).

2.5.9 Post-traumatic ulcers

Traumatic wounds are acute wounds treated in emergency or trauma departments or surgical theatres. Traumas occur regardless of age and circumstances. Some wounds related to injuries, acute at the outset, become chronic due to the same aetiological factors as chronic wounds (Strazzieri-Pulido et al., 2017) (see chapter 2.3).

It is necessary to assess patients with traumatic wounds carefully if the wounds tend to become chronic. When traumatic leg ulcers are treated in acute and primary care, it is important to recognise if the patient has diabetes or peripheral arterial disease, as traumatic ulcers arising in these circumstances need more intensive care and control. Also, the presence of oedema should be recognised and compression therapy initiated, if arterial circulation allows compression. Compression therapy should be initiated to treat all chronic wounds, and should highly prioritised for treating acute traumatic wounds which healing slowly (Shavit and Alavi, 2019).

2.5.9.1 Pretibial injuries

Haematomas which have not been evacuated primarily after trauma, cause delayed healing (Cole et al., 2022). There are several underlying mechanisms to consider: oedema, haemorrhage and dissecting haematomas, persisting inflammation, dermatoporosis (occasionally among elderly patients), certain medications (*e.g.,* anticoagulants, NSAIDs, and glucocorticosteroids), and comorbidities (Seppälä et al., 2023, Strazzieri-Pulido et al., 2017, Seppälä et al., 2021).

2.5.9.2 Skin tears

Skin tears are of traumatic origin (LeBlanc et al., 2018). They occur in premature skin, as in neonates and childhood, in elderly osteoporotic skin, and among critically ill and multimorbid patients. The International Skin Tear Advisory Panel (ISTAP) defines a skin tear as separation of skin layers due to minor traumas, such as shear, friction, or blunt force. The separation of skin layers may be complete or partial thickness separation of underlying tissue (Van Tiggelen et al., 2020b). Skin tears may give rise to chronic wounds if not treated properly from the beginning. (LeBlanc et al., 2018)

Table 4 Chronic wounds: aetiologies, risk factors, pathophysiology, clinical features, diagnostics and treatment (Isoherranen et al., 2023).

Aetiologies	Wound types	Prevalence (estimation)	Risk factors	Pathophysiology	Clinical features	Location	Diagnostics	Treatment
Venous leg ulcers	Wounds with venous insufficiency	0.32% pooled prevalence (Probst et al., 2023), 45-70% of leg ulcers are venous. (Forssgren et al. 2008; Diaz-Herrera et al. 2021)	Chronic venous insufficiency, deep vein thrombosis, immobilisation, obesity, high age, female sex, family history of venous insufficiency, prolonged sitting, pregnancy (2 or more)	Dysfunction of venous valves leading to venous reflux and thereafter venous hypertension	Leg oedema, prominent superficial veins, stasis dermatitis, erythema, hyperpigmentation, lipodermatosclerosis, pain and/or heaviness of the legs, atrophie blanche	Lower leg, often gaiter region	Clinical assessment. Venous duplex ultrasound.	Firstly, surgical treatment *e.g.*, endovenous laser ablation sclerotherapy or surgical ligation methods. Secondly, compression therapy, good local wound care, moisture balance and surrounding skin care.
Ulcers due to other reasons for leg oedema	Lymphatic ulcers, obesity, immobility or insufficient ankle movement, cardiac/liver/kidney failure		Obesity, lymphoedema, history of cellulitis/erysipelas, immobility, post-traumatic deformities of lower extremities and joints (*e.g.* ankle, feet), cardiac/renal/hepatic insufficiency, cancer and cancer surgery and radiation therapy	Related to aetiology	Presence of oedema (especially in the feet), lipodermatosclerosis, elephantiasis of the legs, leakage of lymphatic fluid from the wound, symptoms of organ failure	Lower leg, gaiter, feet	Clinical assessment: presence of oedema, lipoedema, presence of lipodermatosclerosis differential diagnostics (vena insufficiency, venous duplex ultrasound, Stemmer´s sign (pinching a fold of skin of second toe or finger and if the skin is lifted, result is negative. On the contrary the positive result is when the skin can't be lifted and this may predict lymphoedema) Measuring lymphoedema: the Bioimpedance spectroscope (BIS), water volumetry, tape	Treatment of underlying condition for oedema, compression therapy, common local wound care, exercise, surgery for selected cases in lymphoedema

Aetiologies	Wound types	Prevalence (estimation)	Risk factors	Pathophysiology	Clinical features	Location	Diagnostics	Treatment
							measurement and perometry to detect alterations of the fluid balance in the tissue. Magnetic resonance lymphology (MRL) can be used for measuring lymphatic vessels.	
Arterial ulcers	Arterial ulcers in the extremities	0.8 % in a population (Carter et al. 2023), 10–20 % of leg ulcers (Mekkes et al. 2003)	Diabetes, smoking, hypertonia, hypercholesterolemia, obesity, low physical activity/absence of exercise	Fatty material, primarily low-density lipoprotein (LDL) infiltrates to the endothelium of the arterial wall. Human body immune cells (macrophages) try to scavenge fatty materials and when filled with lipids, the macrophages become “foam cells”. Endothelium is injured, and the small lesion thicken and enlarge, develop fist to atheroma and thereafter to atherosclerotic plaque. Inflammation is part of the cascade which leads to dysfunction of arteries. Furthermore, atherosclerotic plaque may rupture, causing acute thrombosis and occlusion of the artery.	Pain in lower legs muscles claudication (during exercise, walking, climbing stairs. In severe cases pain at rest, which reliefs when putting legs downwards). Muscle atrophy decreased or absent lower leg pulses (a. femoralis, a. popliteal, a. dorsalis pedis and/or a. tibialis posterior), numbness of feet and legs, loss of hair and slow-growing nails. Ulcers are extremely painful, non-viable or necrotic tissue in the wound or the edges.	Lower leg ulcer, malleolus, feet, toes	Clinical assessment. Arterial pulse palpation, Ankle brachial index (ABI), toe pressure (TP), transcutaneous oxygen measurement ($TcpO_2$). And if these detect arterial insufficiency imaging of the lower limb arteries. The first line imaging method varies among centres, but currently the most common imaging method is computed tomography angiography (CTA) and magnetic resonance angiography (MRA). Digital subtraction angiogram (DSA) is used when there is a plan to do endovascular revascularisation in connection with the study.	Firstly, surgical treatment methods are peripheral angioplasty and/or arterial bypass. Secondly, non-surgical treatment methods are based on cardio-vascular risks in general and the treatment of hypertension, hyperlipidaemia, diabetes, anti-platelet treatment, weight control and exercise.

Aetiologies	Wound types	Prevalence (estimation)	Risk factors	Pathophysiology	Clinical features	Location	Diagnostics	Treatment
Mixed leg ulcers	Arterial and venous ulcers	26 % of leg ulcers (Hedayati et al. 2015)	Risk factors as venous and arterial ulcers, additionally high age and many comorbidities	The same underlying mechanisms as venous ulcers with venous hypertension and leg oedema additionally, presence of atherosclerosis and peripheral arterial disease in the lower extremities.	Clinically similar to venous leg ulceration with poor pulses and features of arterial ulceration.	Lower leg, often gaiter region	Diagnostic methods include both arterial and venous investigation and clinical assessment.	Treatment follows the treatment protocols for arterial and venous ulcers *e.g.*, revascularisation and endovenous venous ablation. Additional compression therapy, which is individually planned according to arterial supply, and general wound management.
Diabetic foot ulcers	Neuropathic diabetic foot ulcer, vascular ulcers, Charcot foot syndrome	Global prevalence 6.3 % (Zhang et al. 2017), 15 %-25 % of lower leg ulcers (Armstrong et al. 2020)	Diabetes with complications; Neuropathy, Angiopathy	Diabetic foot ulcers are neuropathic and/or angiopathic of origin. Glycosylation of nervous and inflammatory system cause peripheral neuropathy, which is mainly sensorimotor, leading to pain, paraesthesia and skin changes such as hyperkeratosis, dryness, loss of sensation and deformities in the foot area. Pathology of angiopathy has been explained in the section arterial ulcers. Also, a minor trauma occurs prior ulceration.	Neuropathy, an ulceration of pressure area of the foot, toe deformity, presence of callus, "probe to bone" as a sign for osteomyelitis. Presence of infection, detection of severe, deep infection *e.g.* in the fore foot, with mild sign of an infection. Angiopathy of peripheral arteries is common in diabetic foot problems and vascular assessment is required	Achilles tendon, heels, ankles, feet, toes	Glucose profile, clinical assessment (pressure areas, deformities, 'Charcot foot', joint mobilisation, wound assessment), clinical assessment of infection, monofilament and vibration test, sense of temperature and sensitivity, vascular assessment (pulse palpation, ABI, toe pressure, transcutaneous oxygen measurement, angiography)	Off-loading, revascularisation, infection management, optimisation of diabetes care, plastic surgical debridement or procedures, orthopaedical procedures if needed (surgical treatment of deformities)

Aetiologies	Wound types	Prevalence (estimation)	Risk factors	Pathophysiology	Clinical features	Location	Diagnostics	Treatment
PUs	PUs in the bony areas (*e.g.* sacrum, hips), also related to deformities of the extremities caused by rheumatoid arthritis, gout, Charcot foot, neuropathic feet etc.	12.8% (Li et al, 2020), and in hospitals 11.4 %-16.6 % (Källman et al. 2022) (Gunningberg et al. 2013)	Immobility; bed-ridden patients or patients with an acute condition (*e.g.* trauma, surgery, unconsciousness), use of medical devices, immature skin in babies, skin fragility in the elderly	Deformation of cells caused by pressure and/or shear force. This leads to cell destruction and inflammation, continues as a circle and leads to chronic inflammation and ulceration of the tissue.	Graded into 4 categories. 1. degree PU is redness of the skin. 2. -4. degree PUs are ulcerations from superficial grade to deep ulcers until bones.	Bony prominences, most frequently in the sacrum, hips and heels. Skin area under medical devices.	Risk assessment to detect patients at PU risk and assessment of the patient, the skin and the wound. Diagnosis is clinical.	Off-loading with various methods repositioning and with the use of devices, optimizing nutrition and diabetes care, debridement, local wound care, NPWT, surgery
Infected wound	Infection in an ulcer due to other aetiology, infectious ulcers (*e.g.* Leishmaniasis, tuberculosis)		Diabetes, older age, large and open wounds, dirty wounds of origin, calciphylaxis, travel and immigrant history	Bacterial/fungal invasion causing infection	Rubor, tumor, dolor, calor, atypical appearance	Various locations	Clinical signs of infection, blood tests (leucocytes, crp, blood cultivation) or bacterial/fungal swab, PCR	Antimicrobial treatment; local or systemic, surgical debridement
Post-traumatic	Deep dissecting haematomas, skin tears, acute post-traumatic	1.6 % in a population (Carter et al. 2023)	Age, dermatoporosis, fragile patient, obese, immobility	Several underlying conditions, foreign materials, infection, dissecting haematomas, dermatoporosis, arteriolosclerosis,	Primarily traumatic wound of origin. Traumatic wound which has been treated conservatively, infection, persisting	Various	Clinical, imaging if needed	Surgery, debridement, treatment of infection, compression therapy, local wound care.

Aetiologies	Wound types	Prevalence (estimation)	Risk factors	Pathophysiology	Clinical features	Location	Diagnostics	Treatment
	wounds that develop into chronic wounds			chronic oedema, diabetes	ulceration, haematoma which has not been evacuated or dissecting the skin layers, persisting oedema, especially in the lower leg traumas, dermatoporotic skin tears, arterial insufficiency which complicates posttraumatic healing			
Atypical wounds		10 %-20 % of all ulcers (Becker et al., 2024)						
Vasculitis		5.1% of leg ulcers (Körber et al. 2011)	Auto-immune disorders (*e.g.* rheumatoid arthritis, scleroderma, lymphoma), medication, infection	Vasculitis is an autoimmune and inflammatory disorder of the blood vessels, leading to destruction of the vessels and necrosis	Symmetrical palpable purpura, livedo racemosa and haemorrhagic ulcers	Lower legs, or anywhere in the body	Clinical picture, biopsy and immunofluorescence specimen, laboratory tests including ANCA-antibodies (Antineutrophilic cytoplasmic antibodies)	Immunosuppressive treatment, treatment of pain, local wound care, compression therapy
Pyoderma gangrenosum		3.0 % of leg ulcers (Körber et al. 2011)	Inflammatory bowel disease, haematologic malignancies, rheumatoid arthritis, connective tissue disease	Neutrophilic dermatosis	Erythematous papules, nodules, or pustules and painful ulcerations with violaceous borders	Lower legs, or anywhere in the body	Diagnostic criteria are clinical, but skin biopsy is needed for exclusion of other causes	Immunosuppressive treatment, NPWT and surgery once the inflammatory reaction has been reduced

Aetiologies	Wound types	Prevalence (estimation)	Risk factors	Pathophysiology	Clinical features	Location	Diagnostics	Treatment
Martorell HYTILU ulcers			Hypertension, diabetes (type II)	Arteriolosclerosis leading to skin infarctions	Painful, necrotic ulcers, livedo racemosa, "red lipstick sign"	Latero-dorsally aspect of the leg, Achilles tendon	Clinical and histopathological	Surgery, treatment of hypertension and pain, sodium thiosulphate
Calciphylaxis		1.1% of leg ulcers (Körber et al. 2011)	End-stage kidney disease, diabetes, obesity, medications (*e.g.* warfarin, glucocorticosteroids, iron)	Subcutaneous obliterating arteriolosclerosis, with and without medial calcification, adjacent dermal necrosis	Painful necrotic skin ulcers, livedo racemosa	Lower legs, thighs, abdomen	Clinical and histopathological	Sodium thiosulphate, bisphosphonates, treatment of infection, pain and local treatment of the wound
Livedoid vasculopathy and other ulcers due to vasculopathy			Venous insufficiency, prothrombotic conditions	Thrombosis of the small arteries	Painful purpuric ulcers with reticular pattern, white stellate scars (atrophie blanche)	Bilaterally in the lower legs, around the ankles and feet	Clinical and histopathological	Anticoagulant/antithrombotic therapy, compression therapy
Malignant ulcers	Primary and secondary malignant ulcers	1.1% of leg ulcers (Körber et al. 2011)	Expose to UV-radiation, age, immunosuppressive therapy, chronic inflammation in a chronic wound	Cells turn malignant, where mitosis is increased, for various reasons. Invasion of malignant cells.	Hypergranulation, atypical pigmentation, rolled edges, bleeding, verrucous papules, no treatment response	Various locations	Clinical suspicion. Biopsy is required.	Main treatment is surgical. Principals of palliative wound care are treatment methods of the symptoms *e.g.*, pain, odour, exudation, infection, oedema, off-loading and pressure relieving treatment.

Aetiologies	Wound types	Prevalence (estimation)	Risk factors	Pathophysiology	Clinical features	Location	Diagnostics	Treatment
			(Marjolin`s ulcer)					Local wound management.
Factitious ulcers			Personality disorder	Ulcer due to self-conflicted trauma	"Hollow" history of the wound, geometrical shapes, unusual location	Various locations	Diagnosis of exclusion, the patient must not be confronted	Psychological/psychiatric consultation, medication *e.g.* antidepressants
Miscellaneous	Medication-induced, gout, sarcoidosis, trigeminal trophic syndrome, sickle cell disease							

2.6 Assessment and diagnostics of wound patients

2.6.1 Patient assessment

Patient assessment is building a relation with the patient. Patient-centredness is important, because healing requires the patient to adhere to treatment and adherence tends to improve by increasing the patient's understanding, knowledge, and education (Callender et al., 2021, Gethin et al., 2020).

The physician's primary aim is to set an accurate diagnosis of the patient's health condition and to design a treatment plan (Croskerry, 2009, Albert et al., 2024). Comprehensive and systematic exploring of factors that associate with the patient's skin problems and ulceration is key to diagnostics (Table 5). Different medical conditions may affect the appearance of the wound or delay healing (Table 6). Clinical reasoning is an intuitive or analytical process that aims at one diagnosis and involves excluding discrepant conditions based on available information (Norman et al., 2017). Algorithms, such as check-lists and mnemonic tools, help the clinician to wander through the diagnostic process by preparing the clinician mentally through the patient assessment process. This is especially valuable, if the physician is unexperienced and the features of the phenomenon are unusual (Snyder et al., 2019, Kaari et al., 2022, Thomas Hess, 2011) (Isoherranen et al. 2023).

Table 5 Patient and wound history (Sibbald et al., 2021)

Patient and wound history
Comorbidities
Medications
Previous wounds
Previous deep vein thromboses or erysipelas
Previous surgical procedures (vascular, plastic surgical etc.)
Previous test results (laboratory, radiological)
Allergies
Living status
Mobility - walking with/without devices, walking outdoors also, wheelchair, bedridden
Psychosocial status
Smoking, alcohol, or drug abuse

Patient and wound history
Nutritional status
Travelling history
Wound history
Occurrence of the wound - date
Cause of the wound
Previous treatment of the wound - local treatment, compression therapy, off-loading, skin care
Previous wounds at the area, wound recurrence
Previous surgical procedures
Impact on daily living

Table 6 Comorbidities related to chronic wounds (Isoherranen et al., 2023)

Comorbidity	**Associated ulceration**
Diabetes	DFU, arterial ulcers, venous ulcers, infection, PUs
Cardiovascular diseases	Arterial ulcers, DFUs
Hypertension	Martorelli hypertensive ischemic leg ulcer (HYTILU)
Hyperlipidaemia	Arterial ulcers, DFUs
Inflammatory diseases	Vasculitis, pyoderma gangrenosum, rheumatoid ulcers, Infection, PUs
Obesity	Ulcers due to leg oedema, venous insufficiency, lymphatic ulcers, arterial ulcers DFUs
Kidney failure	Calciphylaxis
Gout	Gout ulcers
Cancer	Skin metastases, skin cancers
Dementia, mental condition	Mental conditions affect a person's ability to take care of oneself. Adherence to treatment is important for wound healing.
Obesity, immobility, drug and alcohol use	Lifestyle components affect wound appearance and healing
Neuropathies; spinal stenosis, sciatica, alcohol neuropathy, post-traumatic situations, polyneuropathy (several reasons)	DFU, Charcot foot, PUs

2.6.2 Physical examination

A systematic physical examination is the basis of the assessment of wound patients (Table 7). Evaluation of the patient's general condition, *e.g.* detection of septichemia, involves also deciding whether the patient is in need of hospitalisation or can be treated as an outpatient. It is important to note that elderly patients with diabetes might not have these dramatic signs due to a weak inflammatory responses and still require hospital care (Lavery et al., 2006). If the diagnosis is necrotizing fasciitis or acute vascular embolism, immediate evaluation, diagnosis, and treatment are required. Symptoms include acute, intense pain, motor and neurological defects of the leg, and absence of peripheral pulses (Conte et al., 2019).

The diagnosis of wound infection is clinical, therefore assessment of wounds for the presence of infection is essential. Bacterial cultures of the wound without clinical evaluation are not routinely recommended. Woo and Sibbald validated two mnemonics for detecting infection in an open wound, NERDS (Nonhealing, Exudate, Red friable tissue, Debris, Smell) and the STONEES (Size increasing, Temperature, Probes to bone, New breakdown, Edema/Erythema, Exudate, Smell) (Woo and Sibbald, 2009).

Assessment of the vascular system of every wound patient should be conducted within two weeks of presentation (Conte et al., 2019) Since pulse palpation is an unreliable method, objective haemodynamic measures are recommended, unless ADP and ATP are palpable without any doubt (Conte et al., 2019). The ankle-brachial index (ABI) is easy to measure also in primary care. The normal ABI is over 0.9 (Peltonen et al., 2022, Potier et al., 2015, Hafner et al., 2000), but the value measured of elderly patients or diabetics must be viewed critically, since ABI might be falsely too high due to mediasclerosis (Laivuori et al., 2024). Toe pressure is a measurement of small artery blood pressure, and it might be more reliable than the ABI, especially in diabetics (Laivuori et al., 2024, Laivuori et al., 2021, Linton et al., 2020, Tay et al., 2019). Transcutaneous oxygen measurement (TCOM or $TcPO_2$) relates to tissue blood flow. If there is any suspicion of ischaemia, referral to vascular surgeon and imaging of the arteries is recommended. (Godavarty et al., 2023)(Tables 4 and 7).

Venous doppler ultrasound is a method to detect and diagnose venous insufficiency. It is mainly used in specialist care, but in primary care the presence of oedema and other clinical findings can be evaluated (Table 3) (Eklöf et al., 2004)

Assessment of the foot includes evaluation of deformities of the feet and toes, of pressure areas, of joint mobility, of the length of the Achilles tendon, and of the presence of as well neuropathy (measurement of pressure and vibration threshold) (McDermott et al., 2023).

Table 7 Patient assessment (Sibbald et al., 2021)

Patient assessment
General condition
Vital signs — blood pressure, heart rate, oxygenation, skin colour and warmth, fever
Acute situations — necrotizing fasciitis, acute severe embolism
Laboratory tests — infection parameters, blood glucose, lipids, kidney and liver functions, and if suspected atypical wounds immunological tests
Infection — severe infection, sepsis, clinical feature (bacterial swab indicated to guide the treatment)
Vascular status — pulse palpation of extremities, ABI, toe pressure, transcutaneous oxygen measurement
Vascular status — radiological imaging: CTA, MRA, DSA (Table 4)
Venous doppler
Presence of oedema
Skin assessment (Table 8)
Foot assessment — deformities of the feet and toes, pressure areas, joints, Achilles tendon
Neuropathy — monofilament test, vibration test
Biopsy of the wound

ABI = ankle brachial index, CTA = computer tomography angiogram, MRA = magnetic resonance angiogram, DSA = digital subtraction angiogram

2.6.3 Skin assessment

Assessment of the affected skin and the perilesional is necessary for successful wound management. The assessment includes identification of infections, of oedema, and of venous insufficiency (Sibbald et al., 2021). Guidelines also emphasise that prevention of PUs is initiated by checking bony prominences and the skin underneath medical devices. (Table 4 and 8) (Gefen et al., 2013, Kottner et al., 2019).

Table 8 Skin assessment (Sibbald et al., 2021)

Skin assessment
Colour
Temperature
Dryness
Itching
Eczema
Bruising/haematomas
Thickness
Oedema
Pigmentation
Perilesional skin condition
Edges of the wound

Skin assessment
Maceration
Atrophie blanche
Necrosis
Infection
Nails
Pain

2.6.4 Laboratory tests and radiology

Infection, especially severe, systemic infection, raises the C-reactive protein level and causes leucocytosis. The inflammatory system is interrupted by high levels of glucose which affects the risk of severe infections (Polk et al., 2021). High levels of blood sugar affect cellular function and wound healing, and the glucose profile should be checked for every patient with a wound, unless done within the six previous months (McDermott et al., 2023, Polk et al., 2021) (Isoherranen et al. 2023). The diagnosis of wound infection is clinical, but bone or blood should be sampled for bacterial culture if the infection is severe and especially if the patient has a diabetic foot infection (Aragón-Sánchez et al., 2011, Gariani et al., 2021, Butalia et al., 2008). Radiograms or MRIs are needed when osteomyelitis or foreign body infections are suspected (Aragón-Sánchez et al., 2011, Lauri et al., 2017, Butalia et al., 2008).

When an inflammatory ulcer is suspected, there are several immunological tests to check (Isoherranen et al., 2019, Becker et al., 2024).

In addition, the nutritional status of the patient should be assessed. The signs of malnutrition are weight loss and reduced muscles mass and strength. Laboratory test, *e.g.*, albumin and prealbumin levels and the transferrin level may indicate if the protein intake of the patient is sufficient for wound healing (Demarest-Litchford et al., 2024).

2.6.5 Wound assessment

There is no established standard for wound assessment, but a useful approach is provided by the mnemonic TIMERS (Tissue, Infection, Moisture, Edge, Repair, Social factors) (Atkin et al., 2019, Leaper et al., 2012, Schultz et al., 2004), which combines different aspects of wound assessment and management.

Comprehensive wound assessment is a multifaced process (Table 9). There is consensus that different wound types require different emphases on wound management, *e.g.*, diabetic wounds require removal of callus and infection control. In contrast, venous wounds or wounds due to leg oedema need primarily moisture control (Sibbald et al., 2021). The recommendations for debridement of different wound types vary: sharp debridement is more suitable for DFU than enzymatic,

ultrasonic, or hydrosurgical debridement (Sibbald et al., 2021). In general, management of the wound bed includes removal of slough which has been thought to be dead tissue in the surface of the wound (McGuire and Nasser, 2021).

Different international classification systems have been developed to help assessment of different wound types: For PU diagnostics there is the EPUAP Guideline (Kottner et al., 2019), for DFU diagnostics and classification the SINDBAD mnemonic (site, ischemia, neuropathy, bacterial infection, area, depth) (McDermott et al., 2023, Schaper et al., 2024), (Ince et al., 2008), and for wound infections and vascular assessment the WIFi guidelines (Wound Ischaemia and Foot Infection) (McDermott et al., 2023) (Zhan et al., 2015). NERDS and STONEES have been designed for assessment of clinical infections (Woo and Sibbald, 2009), and there is a guideline created by a Global Wound Biofilm Expert Panel for identification of the biofilm, as well (Schultz et al., 2017).

Table 9 Wound assessment (Sibbald et al., 2021)

Wound assessment
Size of the wound
Depth of the wound, which tissue (**T**issue)
Pockets, fistulas, other structures of the wound bed
Wound exudate —excess exudate or dryness (**M**oisture)
Wound edges — color, necrosis and devitalised edge, moisture damage, haematomas
Infection — rubor, tumor, dolor, calor - signs of infection or inflammation (**I**nfection)
Odour
Oedema
Pain — different assessment tools
Wound bed — yellow - fibrin, red - granulation tissue, black - necrotic tissue, pink - epithelialisation
Perilesional area (**E**dge)

2.7 Diagnostic delay of chronic wounds – challenges of early diagnosis

Every chronic wound should have a diagnosis on which the treatment is based on. Diagnostics is a process over time: there is a first assessment, then tests are carried out and interpreted, there is follow-up information, concluding diagnostic information, referrals for consultations, and coordination of care. Throughout all this, patient adherence and patient centredness are focal (Singh et al., 2013, Kostopoulou et al., 2008). A diagnostic error occurs when a diagnosis is missed, inappropriately delayed, or is wrong (Graber et al., 2005). Early diagnosis is essential

for wound healing and in avoiding amputations (Laakso et al. (2017a), (Mooij and Huisman, 2016, Noronen et al., 2017).

Implementation of evidence-based wound care is unsatisfactory. Weller et al. conducted a survey among GPs who treated venous leg ulcers (VLU) and found that of 972,100 encounters with GPs 0.34% were involved in managing VLUs. The major treatment strategies were dressings (76%) and medication (25.7%). Only a minority of the patients received treatment following best practices, such as compression therapy (2.1%) or referral to specialist consultations (4.9%) (Weller et al., 2020).

Optimal wound patient treatment pathways include early detection of wound healing problems. Ghauri et al. reported inertia among the public GPs in generating referrals to specialist care, although they had the possibilities to refer all their leg ulcer patients (Ghauri et al., 2000). The Weller study found also that it was more likely to refer hard-to-heal ulcers than common ulcers to specialist clinics, but the common ulcers were not diagnosed very effectively. Proper assessment, management, and follow-up tended to be unsatisfactory (Ghauri et al., 2000).

2.8 Team approach for wound care

2.8.1 Holistic team-based wound care

The holistic, team-based approach is essential for successful wound management (Moore et al., 2014). There are several ways to organise such wound care:

1. A multidisciplinary team consists of different professions focusing on their own specialties regarding the patient's needs (Choi and Pak, 2006). The multidisciplinary team concept in wound care has been developed globally since 1990's (Stevens et al., 1997, Dorman et al., 1995).

2. An interdisciplinary team is defined as a team with a dedicated group of professionals and the patient, who together according to defined processes and functions for the individual team members (Choi and Pak, 2006).

3.Transdisciplinary team has the highest level of expertise. The professionals in the team may include scientists, non-scientists, and other stakeholders. All work across the boundaries of their professional roles and bring new insight and knowledge to the existing team work (Moore et al., 2014), (Choi and Pak, 2006).

Multidisciplinary wound care, or interdisciplinary levels of care, is organised in teams in different settings: hospital-based wound centres or outpatient clinics and community-based wound clinics are characterised by collaboration between specialists, surgical and medical specialties, primary and secondary levels of care, inpatient and outpatient care, and home care setting (Gottrup et al., 2018) (Table 10).

The team approach has evolved during the recent decades from nurse-led public special clinics with options to refer patients to hospital specialists to secondary or tertiary level teams in interdisciplinary wound centres (Moore et al., 2014, Gottrup et al., 2018).

Table 10 Professionals and their contributions to multidisciplinary teams (Modified from Kim et al., 2013; Pruim et al., 2017)

Team member	Contribution
Physician or specialist in charge	Patient assessment, diagnostics and treatment plan with referrals
Dermatologist	Diagnostics and treatment of chronic hard-to-heal ulcers and consultation, *e.g.* atypical wounds
Vascular surgeon	Vascular assessment and revascularisation, surgical treatment of venous insufficiency
Plastic surgeon	Soft tissue revision, construction and coverage
Endocrinologist	Consulting for diabetes treatment or other endocrinological diseases
Infectious diseases specialist	Consulting for infection management
Internist	Consulting/management of comorbidities
Orthopaedic surgeon	Lower extremity orthopaedic reconstruction
Rheumatologist	Autoimmune processes and/or medications
Haematologist	Blood coagulation problems
Hospitalist	Holistic inpatient management
Radiologist	Medical imaging and *e.g.* vascular procedure
Wound care nurse	Wound care and patient education, cooperation with other specialists
District nurse	Wound care and patient education
Public health care nurse	Wound care
Home care nurse	Wound care and patient education
Podiatrist	Off-loading of feet
Physiotherapist	Rehabilitation and mobility training
Occupational therapist	Rehabilitation and assistant devices for daily living
Social worker	Guidance in social and financial matters
Nutritionist	Optimising nutritional supplementation and patient education
Psychologist	Psychological assessment and non-pharmacological psychological support
Pain specialist	Non-pharmacological treatment of pain, pain education
Orthotist/prosthetist	Orthotics, prosthetics
Medical assistant	Casting, assistance devices

2.8.2 Benefits to wound care of holistic teams in primary care

The benefits of holistic team-based wound care are well documented. Seaton et al. included 18 studies carried out in public wound care centres in 2007-2018. Different types of care models globally were included. They reported a variety of settings from hospital to outpatient teams, public primary care clinics, home care services, and independent clinics. All settings included the idea of multidisciplinary, evidence-based care and standardised protocols across the care pathways. Among the reported benefits of team-based models, were improved healing rates in 3-months, lower recurrence rates, longer ulcer-free times, improved health-related quality of life, reduced amputation rates, and better use of resources (Seaton et al., 2020).

Abrahamyan et al. studied and described multidisciplinary wound care teams in Ontario, Canada (Abrahamyan et al., 2015). They identified all wound care teams in the area with a 90% (n=44) response rate to survey. The majority of the teams were outpatient teams in hospitals (n=32); they were heterogenous regarding team size and possibilities to diagnose and manage chronic wounds. Hospital-based teams had better access to diagnostic tests, *e.g.*, radiological examinations (CT scan, radiography), microbiological tests (bacterial cultures from bone and blood samples), and surgical treatments. Two-thirds of the teams had three or more disciplines. The most common combination was a physician (GP or specialist) and a nurse (n=30 teams), or a team which consisted of a physician, a nurse, and a chiropodist (n=9 teams). The team leaders were a family physician (20% of the teams), an internist (18%), or a registered nurse (16%). The benefits of the team model were team support, advanced education, in wound care, and introduction of the holistic aspect of wound management. Important findings associated with an effective care process were early detection of the wounds, rapid referrals, and brief waiting times to specialists. (Abrahamyan et al., 2015).

Despite the establishment of wound care teams on the grass-root level, there is a global lack of centralised co-ordination of wound care services at the public (community) level. The existing wound care teams and centres are single centres in specific countries (Gottrup, 2004, Vu et al., 2007, Steed et al., 1993). There is no recommendation for how many wound care teams are optimal to serve a population (Gottrup et al., 2018). Globally, primary health care is organised in different ways: there are health care centres, primary care practices, and primary care clinics, and there are community-driven, insurance-driven, and private clinics and, further, various home care units and organisations to serve the elderly. The diverse organisational structurers pose a challenge with regard to practical recommendations and implementation of physician-led wound care teams in primary care (WHO, 2015). Since most of wounds are treated by publicly funded organisations there is an obvious need for public (community) wound care teams. (Oien et al., 2000).

2.8.3 Nurse-led teams

Globally, nurse-led wound clinics in the public setting have been established. There are studies on their impact on outcomes, *e.g.,* wound healing rates, number of visits to the units, and costs related to supplies (Innes-Walker et al., 2019, Lorimer, 2004) (Harrison et al., 2005). Lorimer et al. concluded that if a nurse was specialised on wound management, the healing rates increased, appointments to the nurse decreased, and the supply cost declined (Lorimer, 2004).

In a study by Innes-Walker et al., nurse-led wound clinics across three Australian states resulted in increased confidence by the personnel on wound management, more empowered decision-making, better assessment of different wound types, a positive impact on patient wellbeing, and better wound healing rates (Innes-Walker et al., 2019).

Ghauri et al. introduced a leg ulcer clinic focused on accurate diagnosis and management of leg ulcers accordingly. The 12-week healing rates increased from 12% to 22% and the 12-month recurrence rate decreased from 50% to 41%-17% (Ghauri et al., 2000).

Harrison et al. studied a nurse-led team model based on registered nurses trained in wound management and consulting within primary care. The number of nursing visits declined from 37 (IQR 24-42) to 25 (IQR15-35) per 3 months. Also, the supply costs per patient decreased from a median of $1923 (IQR 395-1931) to $406 (IQR 219-920) (p=0.005). Also, wound healing outcomes and healing rates improved (Harrison et al., 2005).

There are references to suggest that community-based wound care centres could be an appropriate way to organise wound care, but the results to date show positive impacts mainly by nurse-led teams. Thus far, GP-led teams have not been studied.

2.8.4 Diabetic foot ulcer – clinics

A study by Jeffcoate et al. reported poor implementation of existing guidelines for diabetic foot problems and variation in the design of care pathways. They recommended a change favouring clearer care pathways, evidence-based guidance, and better continuity of care. This included early assessment of diabetic foot ulcers (DFU) by a specialist, multidisciplinary service, and organised follow-up and care for patients with a history of DFU and are in remission (Jeffcoate et al., 2018).

Diabetic foot teams aim at early detection and treatment of foot problems, and multidisciplinary teams are associated with a lowered rate of major amputations compared with usual care (Armstrong et al., 2023) (Musuuza et al., 2020, Monteiro-Soares et al., 2021). Laakso et al. studied diabetic foot infections treated by a multidisciplinary team in a tertiary hospital. After re-organising the treatment of

chronic wounds by specialised teams lower extremity amputations (LEA) of the lower extremity with an infected DFUs sank significantly, from 25.8% to 9.5% (Laakso et al., 2017.) The hospitalisation time decreased as well as the median time from admission to surgery (Laakso et al., 2017b). Krishnan et al. concluded that – following the introduction of multidisciplinary team-based care – the rate per 10,000 diabetics of total amputations decreased from 53.2% to 16.0%, and major amputations decreased from 36.4% to 6.7% (Krishnan et al., 2008, Trautner et al., 2007). The same finding was reported in Denmark, where diabetic foot ulcers treated by a multidisciplinary team reduced costs and amputation rates (Apelqvist et al., 1994). Re-organising current care pathways does not always require extra resources (Gottrup et al., 2018) (Laakso et al., 2017a, Laakso et al., 2017b).

2.8.5 Team approach in wound care in specialised care – wound centres

The trend in secondary or tertiary care is towards wound centres. The wound centres focus on complex wounds, while the common wounds are treated in wound clinics in primary care (Pruim et al., 2017). Recent decades have seen the establishment of wound centres in many countries globally, *e.g.,* in Denmark (Gottrup et al., 2001) (Gottrup, 2004), the United Kingdom (Davies et al., 2018) (Gray et al., 2018), the Netherlands (Pruim et al., 2017), Finland (Laakso et al., 2017a), USA (Fife and Carter, 2012) (Fife and Carter, 2012), Canada (2009) (Health care Toronto, 2009), and Australia (Cheng et al., 2018, Innes-Walker et al., 2019).

Boersema et al. conducted a systematic review of non-healing or hard-to-heal ulcers categorised into four wound types by healability: healable, hard-to-heal, maintenance wounds, and non-healable wounds. Identifying these types of chronic wounds is necessary for successful timely referrals to interdisciplinary wound centres (Boersema et al., 2021).

Pruim et al. studied the effectiveness and quality of wound care centres in the Netherlands (Pruim et al., 2017). The effectiveness variables of the wound centres consisted of costs, healing rate, recurrence rate, duration of wound, and number of visits. The study registered also the types of wound centres, sample sizes, and the study designs (Pruim et al., 2017). They divided the results into three categories: multidisciplinary collaboration, standardisation, and effectiveness. Multidisciplinary collaboration was characterised as collaboration among various specialties, support to primary care providers, and professionals in the care pathway. Standardisation included wound care pathways, treatment protocols, and staff education policies. The study recommended the use of international guidelines, treatment algorithms, and coordinated follow-ups (Pruim et al., 2017). Effectiveness lacked significant outcomes. Healing and recurrence rates were the measures of effectiveness (Pruim et al., 2017).

Rondas et al. reported that wound centres had lower costs than standard methods used for wound management. This was due to decreased hospital costs; these costs sank by 34.7% when an outpatient clinic was established (Rondas et al., 2015).

The cost-effectiveness analysis of Edwards et al. concluded that costs decreased because the total number of visits per week decreased. After admission to the centre, the care of the patients was assessed once per week for 12 weeks instead of 2-3 times per week (Edwards et al., 2013) and hospital visits decreased from 29.0 to 16.3 visits per 24 weeks. Naturally, when the frequency of treatment visits decreased, the wound centres were able to treat more patients (Edwards et al., 2013).

Full-time, service-providing wound care clinics are not common, and they are located in tertiary hospitals, *i.e.,* university hospitals with multiprofessional competencies and with facilities to treat complex wounds. The benefits of having a wound centre in a tertiary hospital are that all actors are co-located, and the patients have easier access to investigations and procedures. High-quality wound centres are especially beneficial for patients in need of revascularisation, limb salvage, soft tissue replacement and reconstruction, and correction of biomechanical issues of the lower extremities (Kim et al., 2013).

There are several models of multidisciplinary teams in the literature, but there is no standardisation. Due to lack of quality standards, the European Wound Management Association (EWMA) proposed a wound centre concept model (EWMA Wound Centre Endorsement Project). The model focuses on the minimum requirements for wound centre services and to on supporting the establishment of multidisciplinary teams within organisations (Gottrup et al., 2018). The project supports collaboration and sharing of knowledge to establish, develop and maintain high-quality wound care centres globally (Gottrup et al., 2018).

3 Aims of the study

This thesis includes one study on the prevalence of wounds and two studies on the diagnostic delay associated with the diagnostics of chronic wounds.

The specific aims are:

1) to analyse the prevalence of wounds among patients in health care and to examine if the prevalence has changed during the last decade (Study I).

2) to study the delay in diagnosing wounds and in starting treatment based on the correct aetiology of the wounds within primary health care (Study II).

3) to study the impact of the diagnostic delay on the time for chronic wounds to heal, and to analyse the impact of a specialised wound care team within primary health care on the diagnostic delay and wound healing (Study III).

4 Patients and methods

4.1 Patients and description of the data

4.1.1 Study I

Study I was a point prevalence study which was implemented as a survey to health care units. The questionnaire was delivered by supervisors to the staff responsible for wound care or other care of the patients, *i.e.,* the responders were health care professionals rather than patients. The methodology is presented in detail in chapter 4.2.1.

4.1.2 Study II and Study III

A GP-led wound care team was established in primary care in Helsinki in 2013. The team consisted of a GP specialised in general medicine and educated in the management of chronic wounds, three wound care nurses, and a part-time podiatrist. The team could consult a vascular surgeon who visited the unit for a half day every 2-3 weeks and had 4-5 patient appointments. This unit was organisationally part of the primary care health centre network of the City of Helsinki and located in one large health care centre in southern Helsinki. The team focused on early diagnosis of chronic wounds and specialist consultations were provided to all the primary care units in the Helsinki area. The team served the whole primary care sector, including health centres, home care services, and nursing homes, both public and private.

Patients and data for the cohort studies II and III were recruited prospectively and comprised 197 consecutive patients who visited the primary care wound care team for the first time between 1 April 2016 and 30 September 2016. Electronic patient records were used to collect patient data, which included background information (age, sex, mobility, and living conditions, need of assistance or home care, smoking, comorbidities, medication, lipids, and blood sugar levels). The wound history was recorded from appearance to evaluation in different health care units, starting from the very first contact to health services, visits to primary care physicians, visits to the wound care team, and, if pertinent, referrals to and appointment with specialised care.

Additional data of the diagnostics and treatment were collected as follows:

1. Patient assessment in primary care: body mass index (BMI), ABI-index, pulse palpation, presence of oedema, clinical signs of infection, bacterial swab, wound biopsy, monofilament test

2. Basic treatment methods in primary care: included sharp debridement, negative pressure wound care (NPWT), treatment of infection with antimicrobials or local antimicrobials, compression therapy, pressure-relieving treatment and foot offloading planned and followed up by a podiatrist, and patient education.

3. Specialist care investigations (requiring a referral): radiological imaging, Duplex ultrasound, ABI, tpcO2, toe pressure, angiography or MRI, biopsy of the wound, laboratory tests (especially when an atypical aetiology was suspected).

4. Specialist care treatment methods: revascularisation with bypass surgery and / or angioplasty or both, excision of the wound and coverage with a surgical flap reconstruction, skin substitute or skin grafting, venous ablation, orthopaedic surgical reconstruction of lower leg deformities, compression therapy, off-loading, antimicrobial treatment, nutritionist consultation, conservative treatment.

When the impact of delay was studied, we excluded patients (n=15) who had had the wound more than 365 days prior to the first appointment at the wound care team.

4.2 Methodology

4.2.1 Study I

As described in chapter 4.1.2., a GP-led wound care team was established in 2013. Mäkelä et al. conducted a survey of the prevalence of chronic wounds in the Helsinki Metropolitan area in 2008 (Mäkelä et al., 2010) and Study I was a follow-up to that survey with the same methodology. The aim of the Study I was to compare the prevalence of chronic wounds before and after (year 2008 vs year 2016) the establishment of the primary care wound care team.

A one-day electronic prevalence questionnaire (Figure 2) was sent to all social and health care units in the Helsinki metropolitan area via email: public health care centres, home care units, public and private nursing homes, specialist-care outpatient clinics, and inpatient hospital wards.

Läpileikkaustutkimus Helsingin alueella kroonisten haavojen esiintyvyydestä

Tarkoituksena on kartoittaa kaikki pitkittyneet ja kroonistuneet haavat, jotka eivät ole parantuneet **4 viikon aikana**
Kartoitus koskee kaikkia Helsingin terveydenhuollon yksiköitä; terveysasemia, kotihoitoa, kotisairaalaa, kaupungin sairaaloita, erikoissairaanhoidon vuodeosastoja ja poliklinikoita.

Paljonko on tänään hoidettu potilaita yksikössäsi
Paljonko on tänään hoidettu haavoja yksikössäsi

Kaupungin yksikkö									
Haavan sijainti	Painehaava	Diabeettinen haava	Iskeeminen haava	Laskimo-insuffisienssi	Traumahaava	Post-operatiivinen haava	Monitekijäinen haava	Vaskuliittihaava	Ilman etiologiaa
Jalkaterä/nilkka									
Sääri									
Reisi									
Polvi									
Selkä/lantio/vartalo									
Muu									
Ei mainintaa									
Yhteensä									

Figure 2 Electronic prevalence questionnaire formula

The date for data collection was 30 November 2016, with the exception in the City of Vantaa, where the date was postponed to 23 January 2017 due to organisational matters. To increase the response rate, the questionnaire was re-sent to those health care centres in Helsinki, which had not responded to the survey by the original date, 3 April 2017.

The survey collected answers to the following questions: 1) number of all patients visiting the unit on that day, *i.e.*, outpatients as well as and in-patients (ward patients) and 2) how many out of these patients had a wound. I also asked for information on the aetiology and location and of the wounds. The aetiology was reported by the personnel of the units and no further questions concerning the diagnostic criteria, or the diagnostic process were asked. The respondents, who were mainly nurses (307 nurses or head nurses, 2 physicians and 13 podiatrists), reported the diagnosis (ICD-10 code) used in the patient records or defined the aetiology of the wound themselves.

4.2.2 Study II

4.2.2.1 Details of diagnostics and grouping

To evaluate the diagnostic delay, we collected detailed information on the diagnostic process: details on the assessment, investigations, ICD-10 codes, and treatment plans and treatment methods. Based on this information, we investigated the date when the correct diagnosis was set.

Since adequate ICD-10 codes do not exist for all types of chronic wounds, I categorised the diagnoses into ten groups (Table 11). The grouping included more than only an ICD-10 code: information on how the wounds appeared, which diagnostic methods were used, and the final treatment plan according to conclusion of the final diagnosis was also collected.

Table 11 Categorisation and diagnostic variation in the clinical pathway of wound patients. (Modified from Ahmajärvi et al., BMJ Open, 2022)

Diagnostic categories	Primary care physician (n=155)	Wound care team physician (n= 197)	Specialist care physician (n=111)
Venous or oedematous ulcer	15	57	17
Diabetic foot ulcer	4	24	15
Arterial ulcer	4	16	26
Mixed-aetiology ulcer	0	7	3
Pressure ulcer	12	29	9
Infectious wound	42	11	10
Post-traumatic ulcer	16	23	3
Foot malformation or foot pressure ulcer	0	7	1
Wound without a specific aetiology	36	13	19
No diagnostic code*	26	2	1

*This category was used for patients who had been seen by a physician but there was no ICD-10-coded diagnosis in the patient records.

4.2.2.2 Delays

Delays in the pathway of treatment were calculated as the number of days from wound occurrence to appointments at health care services.

The delays were categorised as: 1) patient-related delay (time from wound occurrence to the patient's first contact with health care providers), 2) diagnostic delay (time from the appearance of the wound to the first physician's appointment where the initial diagnosis was made), and 3) organisational delays within primary care before the correct diagnosis was made and treatment was started (time from the first contact with the primary health care unit to the wound care team consultation). For patients who needed a referral to a specialist consultation, this delay was also considered.

The outcome measures were overall wound healing rate, wound healing rate at 356 days, amputation rate, and survival. Wound healing was described in patient records as healed, epithelialised, or otherwise described by a health care professional, usually nurse.

I also examined diagnostic delays in different subgroups to examine if there are differences between the sexes, age groups, diabetics *vs.* non-diabetics, mobilised *vs.* immobilised, and diagnostic delay groups (delay less than four weeks *vs.* more than four weeks).

4.2.3 Study III

4.2.3.1 Delays and wound healing

To study the effect of delay and other possible risk factors on wound healing impairment, I collected data on basic demographics, comorbidities, medications, and risk factors. Information on the diagnostic and treatment pathways, as well as on the delay in setting the diagnosis are presented in Study II. The data includes also details on the treatments provided in primary care and specialist care (see chapter 4.1.2).

The primary outcome measure was the time to wound diagnosis and the association of this time with wound healing.

When the impact of delay was studied, I excluded patients (n=15) who had had the wound for longer than 365 days prior to the first appointment with the wound care team.

The diagnostic delays were divided into three groups according to the duration of the delay: 1) delay < 4 weeks, 2) delay 4–12 weeks, and 3) delay > 12 weeks. Then I analysed the wound healing time in each delay group. I conducted univariant analyses of all parameters (patient characteristics, comorbidities, risk factors, medication, tests and investigations, treatment methods, and referrals) to select the variables for multivariate analysis which we performed with Cox regression analysis to find the factors independently associated with wound healing.

I also analysed the variation of the diagnoses in the three delay groups to understand whether there were any specific types of wounds that were diagnosed within the recommended four weeks, and which aetiologies were diagnosed before and after three months (Table 10). The healing rates were compared between these three different subgroups of diagnostic delay.

4.3 Statistical analysis

4.3.1 Study I

Proportions are presented as percentages. Prevalence of the wounds was calculated by dividing the total number of wounds in the questionnaire with the population of the area where the questionnaires were sent, *i.e.,* the Helsinki Metropolitan area.

4.3.2 Study II

For the statistical analyses, the SPSS version 27.0 was used for Studies II and III. The delays were presented as medians, interquartile ranges, and minimum—maximum. Subgroups were compared with the χ^2-square and Mann-Whitney U test for significant differences between the groups.

4.3.3 Study III

To determine whether delays, sex, age, mobility, living conditions, risk factors, medications, or comorbidities affected wound healing we used Cox regression analysis.

Kaplan–Meier survival rates were used to describe wound healing rates at the time points 6 months, one year, 18 months, and 2 years.

5 Results

5.1 Prevalence of wounds (Study I)

The questionnaire was sent to 797 units in the Helsinki Metropolitan area; 322 (40.4%) responded. The highest response rate (77.7%) was achieved in the units of the City of Helsinki, and the different units within Helsinki responded as follows: home care 73.6%, nursing homes 90.9%, Helsinki city hospitals 80.0%, and health care centres 84.0%. Private clinics or private hospitals in the area did not respond to this survey.

Of the 12,051 patients visiting the health care units for any reason, 911 (7.6%) had a total of 1021 wounds. In 2016, the population in the Helsinki Metropolitan Area (Helsinki, Espoo, Vantaa) was 1,112,615. Thus, the prevalence of wounds was 0.08%. In comparison to a similar study-in 2008,-1,029 patients had a total of 1,192 wounds and the prevalence was 0.10% ($p<0.001$).

The aetiological variance of the wounds in 2008 and 2016 are presented in Figure 3. In 2016 most of the wounds were located in the lower legs (60%) (Table12).

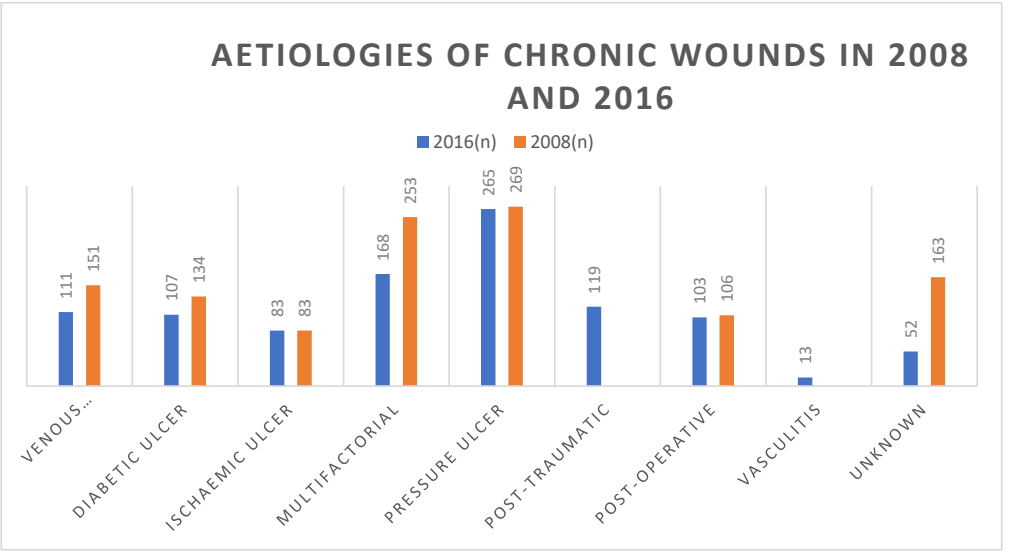

Figure 3 Aetiological variation of chronic ulcers 2008-2016

Table 12 Locations of wounds in 2016 (Modified from Ahmajärvi et al. Int Wound J., 2019)

Locations of wounds in 2016	% (n)
Body	19.1 (195)
Thigh/knee	6.5 (66)
Leg	22.6 (231)
Foot/ankle	37.0 (378)
Other	12.2 (125)
Unknown	2.5 (26)
Total	100.0 (1021)

The patients were treated mainly by primary care providers (73.9%) (Table 13). Over half of them were treated as outpatients (53.1%), 21.0 % were hospitalised, and 25.9% were living in a nursing home. The prevalence of wounds among hospitalised patients was higher (17.9%) than among patients treated at health care centres (10.9%) or by home care (5.8%) (Table 13).

Table 13 Variation of patients by setting (Modified from Ahmajärvi et al. Int Wound J, 2019)

Setting	All patients in the units of the City of Helsinki	Wound patients	%	All the patients in the units of the Metropolitan Area	Wound patients	%
Outpatient	4304	333	56.6	6664	484	53.1
In-patient	725	127	21.6	1156	191	21.0
Nursing homes	3138	128	21.8	4275	236	25.9
Total	8167	588	100.0	12051	911	100.0

5.2 Characteristics of patients visiting wound care team (Study II and III)

The mean age of the 197 patients was 71 years, 53.5% (106) of the patients were female. The demographics and risk factors are shown in Tables 14-15. Most of the patients were living at home (n=172, 86.9%), some of these needed support from home care (n=42).

The patients had several comorbidities (Tables 16-16) of which hypertension (55.8%), diabetes (39.1%) and atrial fibrillation (31%) were the three most common diseases. Other common risk factors were obesity (27.9%) and overweight (61.4%),

neuropathy (43.4%) and high cholesterol (22.8%) and smoking (20.8%). Almost half of the patients had had previous wounds (48.7%). Venous insufficiency had been diagnosed earlier in 8.1% and deep vein thrombosis in 5.1% (Table 16).

The use of analgesics occurred in 44.7% of patients when 15.2% used additionally opioids (Table 17).

Table 14 Patient demographics (modified from Ahmajärvi et al. BMJ Open, 2022)

	Male (n)	%	Female (n)	%	Total (n)	%
Gender	91	46.2	106	53.8	197	100.0
Age (years), mean	69	97.2	78	39.6	71	36.0
Age (years), median	73	37.1	80	40.6	41	20.8
Mobility (n)						
walking	56	28.4	38	19.3	94	47.7
walking with assistance device	20	10.2	33	16.8	53	26.9
walking with device only indoors	5	2.5	16	8.1	21	10.7
wheelchair	8	4.1	11	5.6	19	9.6
bedridden	2	1.0	8	4.1	10	5.1
Residence (n)						
home	73	37.1	57	28.9	130	66.0
home, homecare	12	6.1	30	15.2	42	21.3
nursing home with home care aid	5	2.5	14	7.1	19	9.6
24/7 nursery unit	1	0.5	5	2.5	6	3.0

Table 15 Comorbidities and risk factors in order of frequency (Modified from Ahmajärvi et al. BMJ Open, 2022)

Comorbidities	Male (n)	% (of 197)	Female (n)	% (of 197)	Total (n)	%
Hypertension	50	25.4	60	30.5	110	55.8
Diabetes	47	23.9	30	15.2	77	39.1
Atrial fibrillation	24	12.2	37	18.8	61	31.0
Peripheral arterial disease	24	12.2	16	8.1	40	20.3
Respiratory condition	11	5.6	27	13.7	38	19.3
Heart failure	11	5.6	25	12.7	36	18.3
Dementia/memory disorder	9	4.6	25	12.7	34	17.3
Cancer	14	7.1	14	7.1	28	14.2
Cerebrovascular disorder	13	6.6	15	7.6	28	14.2
Musculoskeletal disorder	7	3.6	21	10.7	28	14.2
Kidney malfunction	15	7.6	12	6.1	27	13.7
Ischaemic cardiac disease	10	5.1	13	6.6	23	11.7
Rheumatoid arthritis	6	3.0	15	7.6	21	10.7
Mental health condition	9	4.6	9	4.6	18	9.1
Urinary condition	10	5.1	4	2.0	14	7.1
Gout	8	4.1	3	1.5	11	5.6
Haematological condition	6	3.0	5	2.5	11	5.6
No comorbidities	4	2.0	3	1.5	7	3.6
Risk factors	**Male**	**%**	**Female**	**%**	**Total**	**%**
Overweight (BMI 24-30)	62	31.5	59	29.9	121	61.4
Previous wounds	50	25.4	46	23.4	96	48.7
Neuropathy (monofilament tested positive)	54	27.4	32	16.2	86	43.7
Obesity (BMI over 30)	29	14.7	26	13.2	55	27.9
High cholesterol (diagnosed)	23	11.7	22	11.2	45	22.8
Smoking	28	14.2	13	6.6	41	20.8
Neuropathy (coded diagnosis)	18	9.1	8	4.1	26	13.2
Venous insufficiency	7	3.6	9	4.6	16	8.1
Chronic cellulitis	5	2.5	10	5.1	15	7.6
Alcohol abuse	11	5.6	3	1.5	14	7.1
Joint malformation	3	1.5	8	4.1	11	5.6
Previous deep vein thrombosis	1	0.5	9	4.6	10	5.1
MRSA	6	3.0	2	1.0	8	4.1
HbA1c						

Comorbidities	Male (n)	% (of 197)	Female (n)	% (of 197)	Total (n)	%
Mean (SD)	49 (16.8)		43 (12.9)		46 (15.1)	
Median (IQR)	43		40		41 (37-52	
fP-Kol-LDL						
Mean (SD)	2.4 (0.86)		2.5 (0.83)		2-5 (0.84)	
Median (IQR)	2.3		2.4		2.4 (1.8-3.0)	
fP-Gluk						
Mean (SD)	7.3 (3.4)		6.0 (1.8)		6.6 (2.7)	
Median (IQR)	6.7		5.8		5.9 (5.3-6.9)	
BMI						
Mean (SD)	29.0(6.2)		27.4 (8.2)		28.0 (7.4)	
Median (IQR)	28		26		26 (23.32)	

Table 16 Number of comorbidities (Ahmajärvi et al. unpublished)

Number of comorbidities	Number of patients
1	11
2	16
3	22
4	39
5	36
6	24
7	16
8	15
9	8
10	2
0	7

Table 17 Medications (Modified from Ahmajärvi et al. BMJ Open, 2022)

Medication	Male (n)	%	Female (n)	%	Total (n)	%
Beta blockers	41	20.8	57	28.9	98	49.7
ACE inhibitors	47	23.9	38	20.3	85	43.1
Diuretics	32	16.2	45	22.8	77	39.1
Statins	35	17.8	40	20.3	75	38.1
Anticoagulants	26	13.2	41	20.8	67	34.0
Calcium channel blockers	31	15.7	27	13.7	58	29.4
Antithrombotic	26	13.2	41	20.8	57	28.9
Diabetes medication						
Oral medication	21	10.7	16	8.1	37	18.8
Insulin	30	15.2	12	6.1	42	21.3
Dementia medication	6	3.0	16	8.1	22	11.2
Antidepressant	11	5.6	14	7.1	25	12.7
Benzodiazepines	10	5.1	13	6.6	23	11.7
Sleeping medication	12	6.1	23	11.7	35	17.8
Analgesia (mild)	31	15.7	57	28.9	88	44.7
Opiates	12	6.1	18	9.1	30	15.2
Cancer medication	3	1.5	2	1.0	5	2.5
Immunosuppressives	4	2.0	11	5.6	15	7.6
Glucocorticosteroids by mouth	4	2.0	12	6.1	16	8.1
Thyroxin	3	1.5	16	8.1	19	9.6
Calcium suppl.	16	8.1	46	23.4	62	31.5
Folic acid	3	1.5	7	3.6	10	5.1
B12 vitamin suppl.	12	6.1	11	5.6	23	11.7
D vitamin suppl.	22	11.2	44	22.3	66	33.5
Nutrition suppl.	2	1.0	6	3.0	8	4.1
Magnesium suppl.	4	2.0	7	3.6	11	5.6
Potassium suppl.	9	4.6	11	5.6	20	10.2
Inhaler/nebulisator	16	8.1	26	13.2	42	21.3
Proton pump inhibitor	20	10.2	39	19.8	59	29.9
Urine medication	12	6.1	8	4.1	20	10.2
Skin cream	10	5.1	19	9.6	20	10.2
Glucocorticoid creams	0	0.0	4	2.0	4	2.0

5.3 Diagnostic delays (Study II)

5.3.1 Grouping of the diagnosis and definition of diagnostic delay

The wound care team made the diagnosis for all 197 patients included in the study at the first patient visit. 155 patients had met a primary care physician earlier and, of them, 129 were ICD-10 coded before the first contact with the wound care team. Most diagnoses (60%) were either ICD-10 code L97 (Ulcer of lower limb, not elsewhere classified) (n=36) or infectious wounds (n=42). Out of 155 patients 94 were treated with antimicrobials (Table 11).

The most common leg ulcer type was venous and/or oedematous ulcer, where compression therapy is the treatment of choice. The primary care physician identified 15 of these cases, while the wound care team made this diagnosis for a total of 57 patients.

Aetiologies, which preferably require rapid evaluation, treatment, and referral to specialist care (arterial disease, diabetic foot ulcer) were seldomly diagnosed during the first visit; only 4/155 patients had the correct diagnosis set after the first evaluation by the primary care physician. (Table 11) This was the case despite the fact that both arterial disease and diabetic foot ulcer were not rare, 13.1% (n=26) and 12.2% (n=24) respectively. Infectious wounds were diagnosed primarily by the primary care physician early in the treatment pathway. (Table 11).

After assessment of the correct diagnosis and the date when it was recorded, I compared all diagnoses that had been set by different physician (physicians in primary care health centres, in primary care wound care teams, and in specialist care). The initial diagnosis was the diagnosis recorded by the physician who assessed the wound on the very first visit. For 34.5% of the patients, a diagnosis was not set at this phase, but later by the wound care team physician.

Evaluation of the diagnostic details revealed that the diagnosis varied throughout the treatment pathway. Only 24 patients had an unchanged diagnosis through the whole pathway. Accordingly, I could not assume that a diagnosis was made at the first physician's appointment. For addressing this question in detail, I compared the diagnostic assessments, treatments, further planning, and referrals to establish the correct time when the diagnosis was made (Table 18).

Therefore, I assumed after detailed investigation of the process of diagnostic methods and codes and treatment according to it, that the date for diagnosis occurred at the first visit to the wound care team.

Table 18 Diagnostic differentiation through the treatment pathway (Modified from Ahmajärvi et al., BMJ Open, 2022)

	Same diagnosis throughout entire treatment pathway~	Same diagnosis within primary care~~	Same diagnosis by wound care team and specialist
1 = the same	24	60	83
0 = different	47	67	27
total	71	127	110
% of diagnosed*^ patients	21.8	47.2	75.5
% of 197 (whole sample)	12.2	30.5	42.1

~ treatment pathway: primary care physician, wound care team (physician) and specialist care.

~~primary care physician and wound care team (physician)

*155 patients visited a primary care physician before the appointment with the wound care team, but only 129 patients were diagnosed.

^110 patients were diagnosed in specialist care.

5.2.2 Diagnostic delay in subgroups

To analyse diagnostic delays, I included the patients who had had the wound for one year or less before visiting the wound care team (n=182). The mean delay was 57 days (IQR 33-101). There were no statistically significant differences in mean delays between patients who had diabetes and non-diabetic patients, between patients living at home and those living at an institution and between mobilised and non-mobilised patients (Table 19). When the diagnosis was made within 28 days, the median delay (IQR) was 26 days (19-41) and when the delay was more than 28 days, the median was 73 days (29-338).

Table 19 Diagnostic delays by subgroup (modified from Ahmajärvi et al. BMJ Open, 2022). Figures are medians (IQR; Min–Max; Range)

Diagnostic delay; Subgroups	n	Wound appearance -first contact to health care	Wound appearance to first physicians' evaluation	Wound appearance to wound care team (considered as a diagnostic point)	Delay from first contact to wound care team (organisational delay within primary care)	Delay Wound care team to specialist care	Mann-Whitney-U
All patients	182	2 (0-14;0-351;351)	8(1-32;0-314;314)	57(33-101;2-358;356)	42(22-80;1-484;483)	21(7-52;414)	
Male	81	3 (0-24;0-351;351)	9(1-37;0-314;314)	69(37-111;2-358;356) *	44(23-85;2-484;482)	23(3-48; -58-235;293)	*p=0.058
Female	101	1 (0-8;0-295;295)	8(1-24;0-295;295)	54(30-96;2-306;304) *	41(22-76;1-264;263)	20(8-58;0-176;176)	
Age under 65 y	46	6 (1-27;0-298;298) *	9(3-30;0-142;142)	62(36-100;11-320;309)	37(22-76;6-382;376)	28(14-48;1-182;181)	*Cat 1 vs 2, p=0.005
Age 65-80 y	62	0 (0-14;0-258;258) *	10(0-38;0-314;314)	61(41-106;10-337;327)	49(25-88;4-264;260)	16(2-50;0-235;235)	*1 vs 3, p=0.003
Age over 80 y	74	1 (0-8;0-351;351) *	7(1-32;0-295;295)	53,5(30-98;2-358;356)	40(22-78;1-484;483)	16(6-56; -58-167;225)	
DM+	72	1 (0-15;0-142;142)	10(1-37;0-142;142)	59(36-102;2-324;322)	45(26-75;2-245;243)	14(3-48;0-235;235)	no statistical difference
DM-	110	2 (0-13;0-351;351)	7(1-32;0-314;314)	56(31-101;4-358;354)	40(22-84;1-482;483)	26(8-56; -58-167;225)	
Living at home	160	2 (0-15;0-351;351)	9(1-33;0-314;314)	57(33-102;2-358;356)	42(22-83;1-382;381)	20(5-48;0-235;235) *	*p=0.010
Living in institution	22	1 (0-8;0-295;295)	3(0-14;0-295;295)	55(34-86;7-306;299)	43(24-72;7-484;477)	56(16-143; -58-176;234) *	
Walking outdoors	134	3 (0-15;0-351;351) *	8(1-27;0-246;246)	56(33-97;4-358;354)	40(22-76;1-382;381)	22(6-56-58-235;293)	*p=0.047
Not walking, staying indoors	48	0 (0-5;0-298;298)	9(1-55;0-314;314)	71(33-108;2-337;335)	54(24-94;2-484;482)	16(7-46;0-182;182)	
Delay to wound care team under 28 days	61	6 (0-20;0-351;351) *	7(3-24;0-295;295)	26(19-41;2-358;356) *	18(12-22;1-28;27)	22(4-42;0-167;167)	*p<0.001
Delay to wound care team over 28 days	121	0 (0-8;0-258;258)	9(0-34;0-314;314)	73(51-112;29-337;308)	70(42-101;29-484;455)	20(7-55;-58-235;293)	

5.4 Categorisation of the diagnostic delay (Study III)

Of the 182 included individuals only 33 (18.1%) achieved the diagnosis in the recommended 4 weeks. Half of the patients were diagnosed between 4-12 weeks (n=94, 51.6%) and in 55 patients the diagnostic delay was over 12 weeks.

Diagnoses were categorised into groups according to the delays (Table 20). The majority of the wounds were post-traumatic ulcers (n=12) in the diagnostic delay group of under 4 weeks, the following were venous leg ulcers (n=5) and diabetic foot ulcers(n=5). Most of the diabetic foot ulcers (n=11) and arterial ulcers (n=10) were diagnosed in the delay group between 4 to 12 weeks, which is opposite of the recommendations of the guidelines. The biggest aetiological group in this delay group were venous leg ulcers(n=26), whereas over the half of the venous leg ulcers were diagnosed under 3 months of time (54.2%) (Table 20).

Table 20 Aetiological variation between the three diagnostic groups (modified from Ahmajärvi et al. Int Wound J., 2024)

Diagnostic delay	n	No diagnosis**	Arterial ulcer	Venous ulcer	Diabetic foot ulcer	Pressure ulcer	Post-traumatic ulcer	Atypical wound	Mixed ulcer	Infectious wound	Ulcer related to foot malformation	A wound without spesific aetiology^
> 4 weeks	33	1	1	5	5	4	12	0	0	1	3	1
4–12 weeks	94	1	10	26	11	12	13	2	2	6	3	8
< 12 weeks	55	0	5	17	7	11	4	2	4	2	1	2

* Diagnosis done by the wound care team physician,

** Not used any ICD-10 code by a physician,

^ Unspecific ICD-10 code used for a leg ulcer, S81 or L97

The healing rates of different delay categories at different timepoints are presented in Figure 4. Most of the wounds which had been diagnosed before 4 weeks were healed within a year whereas most of the wounds diagnosed between 4 to 12 weeks had healed in 18 months. In the latest diagnosis group the healing rates were also delayed.

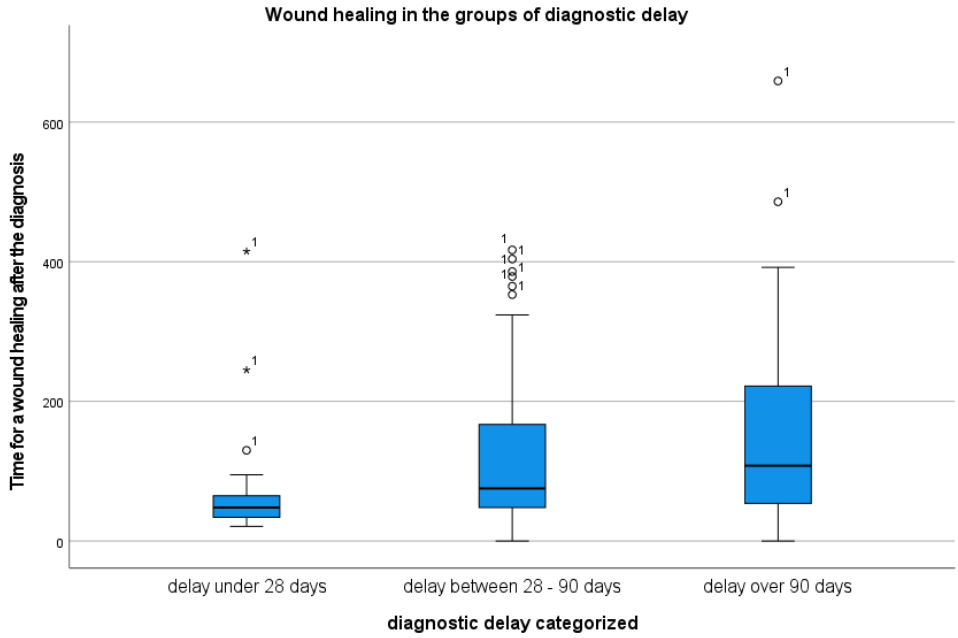

Figure 4 Wound healing in the three groups of the diagnostic delay. (Kirsti Ahmajärvi, unpublished data)

In Table 21 is presented time of wound healing after the diagnosis in different categories and according to the delayed diagnosis the healing thereafter is delayed: in the delay group of over 12 weeks the mean time in days were 167, whereas diagnose between 4 to 12 weeks was mean 128 days an in an early diagnosis group 25 days.

Table 21 Wound healing time after the diagnosis in different categories (Modified from Ahmajärvi et al. Int Wound J, 2024)

Diagnostic delay in groups	Healed wounds(n)	Wound healing (days)			
		Mean (SD)	95% CI for Mean	Median (IQR)	Range
< 4 weeks	25	73 (85)	38–108	48 (28.5 – 67.5)	21–415
4–12 weeks	74	128 (134)	97–159	75.5 (14 – 137)	0–825
> 12 weeks	40	167(186)	107–226	108 (23 – 193)	0–927

SD= standard deviation, IQR= interquartile range, CI= confidential interval

5.5 The factors associated with wound healing (Study III)

There was a significant difference in wound healing between different delay categories; wounds diagnosed < 4 weeks, between 4 — 12 weeks and > 12 weeks categorised (log rank-test between the groups p<0.001) (Figure 5).

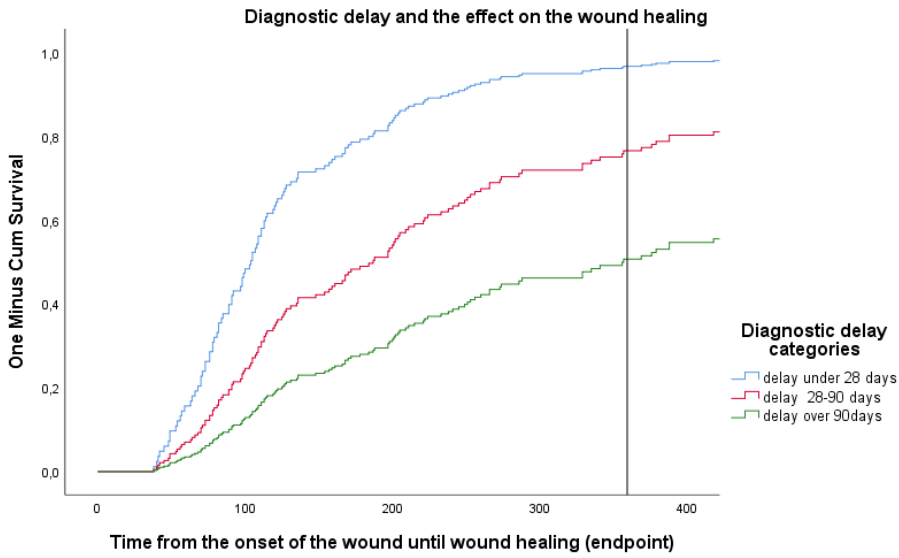

Figure 5 Diagnostic delay and its effect on wound healing in three different delay categories. Grey column presents one year. (Modified from Ahmajärvi et al, Int Wound J, 2024)

Factors affecting wound healing according to the multivariate analysis were as follows (Table 22): diagnostic delay between 4 to 12 weeks (HR 0.31), diagnostic delay between over 12 weeks (HR 0.17), anti-incontinence medication (HR 1,93), ACE inhibitor (1.73), specialist care physician appointment (0.51) and NSAIDs (0.42).

Table 22 Factors affecting wound healing according to multivariant analysis (Cox regression) (Modified from Ahmajärvi et al. Int Wound J., 2024)

Factor	B(exp)	Adjusted HR (95% CI)	p	n
Diagnostic delay				
> 4 weeks		ref	<0.001	33
4–12 weeks	-1.18	0.31(0.18–0.52)	<0.001	94
< 12 weeks	-1.78	0.17(0.10–0.30)	<0.001	55
Specialist appointment	-0.67	0.51(0.36–0.74)	<0.001	96
ACE inhibitor	0.55	1.73(1.23–2.42)	0.002	78
Analgesia	-0.86	0.42(0.29–0.62)	<0.001	82
Anti-incontinence medication	0.66	1.93(1.09–3.41)	0.024	16

In univariate analysis, ability to live and walk independently, compression therapy, per oral glucocorticosteroids and wound early wound revision in primary care were associated with faster wound healing. When in turn, revascularisation, cancer, atrial fibrillation and dementia or memory disorder were associated with delayed wound healing.

6 Discussion

6.1 The prevalence of chronic wounds – challenges in epidemiological research (Study I)

In the early 21st century, a taskforce was created in the Helsinki University Hospital area to clarify the wound care pathway from the onset of the wound, and treatment in primary care to the tertiary care hospital. The aim was to build bridges and ease collaboration between Helsinki City health care centres and their care providers and the specialist care in the Helsinki University Hospital.

Before the establishment of a wound care team, a survey to investigate the prevalence of the chronic wounds at the whole capital area was conducted (Mäkelä et al., 2010). Therefore, I performed a similar survey in 2016, three years after the wound care team had been settled in 2013.

According to the findings of this study, the prevalence of chronic wounds in this population had diminished significantly from 0.10% to 0.08% within the period 2008-2016. Even though the prevalence of chronic wounds is difficult to study, result is concordant with other studies at a populational level. However, the settings, populations and aetiologies of chronic wounds were different in these studies. Díaz-Herrera et al. reported in a similar setting the total prevalence of chronic wounds being 0.11% in the community setting. The majority of these wounds were venous leg ulcers (0.04%) and PUs (0.03%) (Díaz-Herrera et al., 2021b). Whereas Martinengo et al. reported the pooled prevalence of the chronic wounds 2.21 per 1000 individuals and the patients in the included studies had mainly leg ulcers (Martinengo et al., 2019).

Previous studies also support my finding where over half of patients had lower leg ulcers (59.6%). My finding, that the proportion of wounds with no specific aetiology had diminished, which I feel could attributed to the increased knowledge of wound aetiologies. Guest et al. had similarities with my results in a retrospective study in the UK from the database of patient records created by GPs (Guest et al., 2015). They reported the annual prevalence of chronic wounds in the UK: unknown aetiology leg ulcers 19%, venous of origin ulcers 13%, chronic post-operative ulcers 11%, DFUs 8%, PUs 7%, post-traumatic ulcers 7% and arterial ulcers 1% (Guest et al., 2015).

I found that the number of diabetic and arterial ulcers had decreased whereas the proportion of mixed aetiology ulcers had increased (Table 12). The same finding was

verified by Hedayati et al. They reported that up to 26% of leg ulcers are mixed arterial and venous ulcers. The management of mixed arterial and venous aetiologies, whether to choose surgical or conservative or both, is under discussion, and requires multiprofessional aspect in the treatment strategy (Hedayati et al., 2015).

In my study, despite the awareness and existing guidelines regarding the most common chronic ulcers, the PUs had increased from 22.6% up to over a quarter of all wounds (26.0%) and among patients in nursing homes the PU prevalence was even higher (42.8%). PUs presented also the most common ulcer types in this study. Gunninberg et al. studied PUs in the Swedish population and interestingly found out, that PU prevalence was higher in hospitals (16.6%) than nursing homes was 14.5%. (Gunningberg et al., 2013). PUs are associated with immobility which may explain that they are common in nursing homes. There is also an argument that age influences wound healing (Wicke et al., 2009, Gould et al., 2015). Additionally, comorbidities, that are more prevalent in aged population, have an impact on wound healing (Kremer and Burkemper, 2024).

In this study most of the patients were treated in outpatient clinics (53.1%) and in primary care (75.5%). This finding is supported by existing literature (Friman et al., 2021). Guest et al. published a study of the burden of different wound types in the national health system and reported that the 2.2 million patients with a wound during 2012-2013 were mainly treated by communal care providers, nurses and GPs (Guest et al., 2017b). Since primary care units are responsible for organising the treatment for patients with wounds the question remains how to implement evidence-based wound care according to existing guidelines in the prevention and management of common chronic wounds (Van Tiggelen et al., 2020a, Schaper et al., 2024, Haesler et al., 2022). Poor implementation practices of the present guidelines are also under investigations, which must be addressed (Lloyd-Vossen, 2009, Haavisto et al., 2022).

Consequently, finding that the responders were practically all nurses (n=307; 95.3%) brings up the question whether the physicians participate in the management and diagnostic process of the wounds. There is a gap between nurses and GPs regarding the management of wounds even though most of the wounds are treated in primary care units. This problem of setting an accurate diagnosis at the early stage of the wound care pathway was one of the aims of the newly established GP-led wound care team.

6.2 The importance of delayed diagnosis of the wounds (Study II)

I studied the diagnostics and diagnostic delay in a process of wound management in Helsinki City health centres. The delays were categorised as patient-related, organisational, diagnostic delays and referral delays. Patient-related delay was punctual since the median delay was only 2 days. In contrast the diagnostic delay was 57 days which was two times longer than the four weeks, which was recommended for consultation of the wound care team if the wound is not progressing without a diagnosis. Within four weeks only one third (31.0%) of the patients had their first visit to the wound care team.

Diagnostic process is vulnerable to diagnostic errors, where a diagnostic delay is one type of diagnostic error, and it has been suggested that the most frequent diagnostic error is "premature closing" where the physician has the inclination to remain in the first reached diagnosis and stop considering other possible diagnoses (Norman and Eva, 2010, Graber et al., 2005). The differential diagnostics play a key role in diagnosing chronic wounds and there is a possibility in performing a diagnostic error if the ability for differential diagnostics is lacking (Eliassen et al., 2013, Sheikh et al., 2016).

6.2.1 Inaccuracy of the diagnosis of chronic wounds

Conversely, the delay for a first physician in health care services was median 8 days (IQR 1-32), which proposes that these patients had a possibility to have a diagnosis earlier but only 65.5% of these patients had a wound diagnosis before the first visit to the wound care team and only half of the patients (50%) had a coherent diagnosis with the aetiology of the wound. Accordingly, the delays in DFU diagnostics in the four European countries were in 21-34% of the cases over three weeks, where the shortest and mean time for a diagnosis was 10 days in the UK and 14 days in France and Spain, and 20 days in Germany (Sánchez-Ríos et al., 2019). An early diagnosis of arterial insufficiency and diabetic foot problems is essential in avoiding amputations and mortality (Laakso et al., 2017a, Mooij and Huisman, 2016, Noronen et al., 2017).

However, there are scarcely any studies of the effects of the diagnostic delays in wound management, especially in primary care setting (Walker et al., 2015, Eliassen et al., 2013, Janowska et al., 2018).

6.2.2 Professionals participating in wound care

The health care professionals participating in wound management in different countries differ substantially. In Finland, patients with chronic wounds are evaluated and managed mainly in health care centres and in home care units or nursing homes

by primary care professionals (Mäkelä et al., 2010). Often these professionals are nurses, whereas physician's role is mainly consulting, and this is occurring only if the nurse is requiring for it. I propose that physicians should take part of the wound care process, and especially diagnostics more. There is an existing legislation in Finland for doctors to have a right to make a diagnosis and prescribe medicines (Health Care Professionals Act N0 559/1994 Section 22). According to a study conducted in four European countries, Germany, France, Spain and UK, the management of DFU´s was mostly performed by the multidisciplinary approach (Sánchez-Ríos et al., 2019). Accordingly, in the UK, the district nurses performed most of the DFU diagnoses, whereas GPs participated in the diagnostic process less than half of the cases (45%). Additionally, most of the GPs (94%) thought that it is not their responsibility to diagnose diabetic foot ulcers, but they rather referred diabetics with foot ulcers to a podiatrist than proceeded the diagnosis themselves (Sánchez-Ríos et al., 2019). I could discuss this finding since successful wound management pathways include an early detection of healing problems, especially in avoiding fatal errors in diabetic foot ulcers, which may lead in delays of treatment which in turn increases risks for amputations (Noronen et al., 2017).

I found also that the diagnostic codes varied greatly in the treatment pathway between the first physician, wound care team physician and tertiary care physician. Only 12.2% of the diagnosis being the same throughout the whole treatment pathway and these were mainly infectious by aetiology. Accordingly, the diagnosis by the wound care team and the patients who were referred to a specialist had in 75.5% of the cases the same diagnoses suggesting that the diagnostic process was close enough to the correct diagnosis. The remaining diagnoses (24.5%) that were diagnosed in specialist care with more accurate diagnostic methods had a diagnostic prognosis in referrals and this was confirmed in specialist care. According to this finding I could assume that infection as aetiological reason for delayed healing occurred to physician but if a GP was educated on wound care the possible differential diagnostics were more comprehensive than at quick consultation or at emergency room (ER).

6.2.3 The diagnosis of wound infection

This data suggests that the infective wounds had an early diagnosis in the first contact to health services, but whereas clinical signs of infection were detected in only 32.6% of the cases, yet the antimicrobials were used in 63.2% of the cases. This poses a question whether infection was over-diagnosed in primary care. According to a study conducted in Sweden, the use of antimicrobials was reduced with systematic and comprehensive use of the Swedish Wound Registry (Oien and Forssell, 2013). Additionally, Woo et al. studied GPs ability to recognise and manage wound infections and reported about a gap in GPs knowledge and desire for further educations of the topics when to use antimicrobials (82%-95%), how long to treat the infection with antimicrobials (81%-82%), and the use of local antimicrobials (80%-

68%)(Woo and Sibbald, 2009). Diagnostics of the wound infection requires comprehensive assessment, which should not be limited to emergency settings. A literature review suggests that increase of wound pain could be a sign of an infection (Reddy et al., 2012), even though the clinical based diagnosis of the infection poses a challenge an relies on the experience of the physician (Haesler et al., 2022). These results indicate that further education on detecting and managing wound infection is needed.

6.2.4 Wound management and prevention according to diagnosis

According to the findings of study II, compression therapy was the most common treatment not only for venous leg ulcers, but also for the treatment of the ulcers due to leg oedema and prolonged post-traumatic ulcers, which represented 40.6% of the total ulcers. Compression therapy is recommended for different types of ulcers, after arterial insufficiency and severe cardiac insufficiency have been ruled out (Isoherranen et al. 2023).

One finding in this study II was that almost half of the patients had had previous wounds. This poses a question whether the same patients require repeatedly wound care. This phenomenon has been observed in the use of health services in general, since it has been estimated that 3 – 10% of the population is using up to 70 – 80% of the resources of the wellbeing counties. (Sosiaali- ja terveysministeriö Tarkastuskertomus 11/2017 viitattu 26.1.2025) The question arises whether preventive actions fail even if there is awareness of the elevated risk for relapses among patients with previous wounds, and if so, why it happens and are there actions to prevent relapses.

6.2.5 Value of timely referral and consultation

Referrals were made when an arterial ulcer was suspected, or when the wound required plastic or orthopaedic surgery, to tertiary diabetic foot care clinic or dermatological department. The median delay for tertiary care was 21 days. It has been discussed in previous studies that the delay from a referral to a revascularisation in diabetic foot ulcers should be less than two weeks to avoid amputations (Noronen et al., 2017). Additionally, delayed diagnosis of Charcot foot problems may influence the patient-related outcome. Korst et al. reported in their study, that 53.2% of all Charcot foot cases experienced a delay in diagnosis (Korst et al., 2022).

Also, Heatley et al. surveyed the referral pathways of patients with venous leg ulcer in primary care after the EVRA study had been published (Gohel et al., 2018). They got 634 responses, only 1.1% from GPs. most were either from district nurses (48,4%) or community nurses (38,3%). The majority of responders stated that the

referral should be made by a GP (69%). 25% of the nurses could make the referrals to a specialised leg ulcer service themselves. After the EVRA trial, nearly half (45%) of the responders thought that GPs are responsible for the referrals. On the other hand, GPs may act as barriers as well – if patients are not referred to vascular surgeons if needed. (Heatley et al., 2021).

6.2.6 Benefit of a GP led wound care team on wound diagnosis

The finding of the delayed diagnosis in diabetic foot ulcers and arterial ulcers in primary care was also problematic, since only one arterial insufficiency and four diabetic foot ulcers were diagnosed before the wound care team consultation. Whereas the wound care team diagnosed 54 diabetic foot ulcers and suspected an arterial ulcer in 26 patients. This highlights the value of educated primary care physician, GP, who has an ability to provide accurate and timely assessments (triage) of the wounds and comprehensive treatment. These patients were referred to a tertiary hospital for final investigations and diagnosis. These findings aligned with a study by Garcia-Klepzig et al. where they reported that even if GPs were aware of the peripheral arterial disease and neuropathy associated in diabetic foot problems, they further investigated further the diabetic feet only in half of the patients, and of those pulse palpation or ABI-index measurement was conducted in 78%-90% of the patients and monofilament test in 21%-43% of the cases (Garcia-Klepzig et al., 2018).

6.2.7 Diagnostic delay

According to Study II there was an organisational delay for accurate wound diagnosis. This means that the wound patients were evaluated for the first time mostly in the acute care setting at the emergencies or quick nurses' appointments consultation in primary health care units. My study reports that the physician's assessment of the patient or the wound does not conclude a correct diagnosis of the wound in most of the cases. Therefore, especially in emergencies, the assessment of wound patients requires systematic approach and the evaluation of the three acute aetiologies such as ischemia, infection and diabetes (Salava and Isoherranen, 2021). The wound assessment requires time and resources, which are not provided at the emergencies but at the other health care units (Friman et al., 2020).

Practical instruments or checklists has been developed to avoid diagnostic errors in wound management (Snyder et al., 2019, Kaari et al., 2022). A study about check-list by Ely et al. propose that the use of a check-list in emergency setting does not eliminate diagnostic errors but the physicians had a broader differential diagnostic range with the use of check-lists (Ely et al., 2011). Also, the atypical wounds which require specialist care referral and treatment were identified with the use of coherent approach and the use of checklists (Yin et al., 2013, Tuffaha et al., 2016). The diagnostic process may also be memorised with mnemonic rules, such as the 3 I´s

and the ADP developed by Salava and Isoherranen (Salava and Isoherranen, 2021, Salava and Isoherranen, 2023). These letters suggest that ischemia, infection, diabetes, atypical causes, leg oedema and pressure-related injuries should be detected in early phase of a wound management (Salava and Isoherranen, 2021, Salava and Isoherranen, 2023).

Study II highlights the importance of an early diagnosis and coherent treatment pathway of chronic wounds and the importance of the role of primary care and especially team approach in wound care.

6.3 The effect of delayed diagnosis on wound healing (Study III)

This study aimed to investigate the GP-led team model in primary care focusing on early assessment and diagnostics of unhealed wounds. The recommendations of the Helsinki City Officials were for an early consultation of the team, within two to four weeks, if the wound showed no progress. The results indicate that the earlier the diagnosis and the earlier aetiology-based treatment of the wound is achieved, the healing time is decreased. This study also concludes that if the primary care providers are thoroughly educated in wound care and related differential diagnostics, providers can make an early diagnosis and prevent diagnostic and treatment delays and refer the most of the hard to heal ulcers to wound centres in the tertiary care. The European Wound Management Association (EWMA) has also published recently a document which highlights the importance of correct diagnosis of leg ulcers (Isoherranen et al. 2023). There is paucity of studies of the effect of diagnostics on wound healing, thus chronic wounds pose a burden for individuals and societies.

Friman et al. conducted a quantitative study where they interviewed GPs (n=16) about their role in wound management. The answers were categorised into different themes: ‘physicians’ responsibilities for diagnoses’, ‘GPs role as a consultant for district nurse’, ‘collaboration within the organisation’ and ‘continuity in wound care’. They discussed challenges related to late consultations since the consultation did not occur at an early stage of the wound but later when the wound management had already failed. Furthermore, the result showed that the diagnostic process was unclear, and GPs were unaware of the patient's with wounds if they were acceptably diagnosed and most of the diagnoses were set in the emergency setting (Friman et al., 2020).

Previously, it has been recognised that physicians, especially GPs, have an important role and responsibility as part of a team in diagnosing and treating chronic wounds.

According to my study the factors associated with delayed wound healing were appointments in specialist care and there was an assumption that these wounds were

hard-to-heal-wounds of origin. In a recent study, Zorge et al. reported that hard-to-heal ulcers were in academic hospitals more frequent than in home care units or community hospitals and hence wound healing was longer in tertiary hospitals, the median 9 months compared to 2 months in communal units (Zorge et al., 2023). A Swedish study showed decreased healing time of the hard-to-heal ulcers after the implementation of national wound registry (Registry of Ulcer Treatment; RUT) and suggests that structured assessment and patient recording followed by the accurate diagnostics is key to decrease wound healing time (Oien and Forssell, 2013).

In my data, ulcers that should preferably be diagnosed early, within 2 to 4 weeks, i.e. arterial (n=1; 21% of the DFUs) and diabetic ulcers (n=5; 6% of the arterial ulcers), were actually diagnosed between 4 to 12 weeks. Importantly, there were 21 amputations performed on these patients. (Study II). Aguirra et al. concluded that an early ABI index measurement was related to an early referral and revascularisation and had an impact on wound healing respectively (Aguirre et al., 2022).

Lecouturier et al. reported difficulties in accessing to a GP as well as when seeing a GP for other reasons, the GP's poor abilities to interpret the symptoms of peripheral arterial disease a leading to a delay to ABI measurement (Lecouturier et al., 2019). These reasons delay on the diagnostics of common chronic wounds. However, if the patients with wounds have no access to health service and are not properly assessed from the onset of the wound there will be extensive delays in the treatment pathway and this may lead to severe complications such as limb amputation, or infection that may lead to septicaemia (Lecouturier et al., 2019, Noronen et al., 2017).

Another study conducted by Gray et al. studied complex wounds in the community and found that these were not properly assessed. For instance, ABI measurement was not accomplished in 40% of the patients, 31% of venous leg ulcers didn't have concordant compression therapy, 39% of the patients with PUs were lacking pressure-relieving cushion or mattress and antimicrobial dressing were the first line dressings in 36% of the patients. These results revealed the lack of implementation of the evidence-based wound care practices in daily wound care (Gray et al., 2018).

Medications that associated with wound healing

Interestingly, as secondary results for factors affecting on wound healing, we found certain medications having an influence on wound healing: ACE inhibitors, NSAIDs, paracetamol and anti-incontinence medication.

In previous molecular studies with animals, the ACE inhibitors which affect the renin-angiotensin-system (RAS) influence the inflammation process. This effect is regulated by angiotensin receptors 1 and 2. Medications that affect RAS system have been studied in scarring formation and wound healing. According to the studies the use of enalapril is stimulating the proteases of extracellular matrix and diminishing scarring (Maranduca et al., 2023, Iannello et al., 2006, Aleksiejczuk et al., 2019).

The effect of RAS affecting medication has been discussed in several studies, but we found no research conducted in humans (Maranduca et al., 2023, Hedayatyanfard et al., 2023). The benefits of ACE inhibitors on wound healing need further investigation.

Studies of NSAIDs suggest that these drugs affect wound healing by the inflammation process by delaying angiogenesis, fibroblast proliferation, epithelialisation and by reducing wound contraction (Guo and Dipietro, 2010, Krischak et al., 2007). These drugs have additionally antiplatelet effects and are prohibited prior to surgery. Additionally, the studies of NSAIDs propose that they inhibit the healing of the soft tissue (Ghosh et al., 2019). I also suggest that when pain is delaying wound healing, the use of analgesics is decreased according to wound healing. On the contrary the need for NSAIDs remains in the inflammation phase of normal wound healing process (Goto and Saligan, 2020, Kim et al., 2021, Woo and Sibbald, 2008). Opiates were not related to wound healing according to this study.

Anti-incontinence drugs could affect optimal moisture condition of the skin and therefore improve patients skin condition in the surrounding area of the wound, thus affecting the healing.

6.4 Strengths and limitations of the study

Strengths of the prevalence study were that the same study protocol existed from the year 2008, and I sent the questionnaire to the same units as were sent 8 years prior the study. The units of Helsinki city area responded with a reasonable response rate, and I could conduct a perspective of the prevalence of the chronic wounds in this area. This was meaningful since the wound care team served all units in Helsinki city health services. The strengths of Studies II and III was that the collected data were systematic and detailed and there were practically no lost to follow-ups. The wound care team used a systematic approach and therefore the patient records provided systematic information of the treatment pathway. This is a study with a unique data from primary care patients having chronic wound problems.

The limitation of the Study I was that the response rate was very low, in the whole study area (n=322 responded units, 40.4%) whereas, in 2008 the response rate was 60.9% (n=466 responded units), even though other published prevalence studies rarely report any response rate (*e.g.* Vowden et al., 2008, Moffat et al. 2004, Vuylsteke et al. 2018, Probst et al., 2023, Martinengo et al., 2019). However, the primary care response rate was fairly high, in Helsinki city area was 78% and in 2008 79%-100% and the numbers of wounds reported were quite similar to those reported in 2008 (1021 wounds in 2016 vs. 1029 in 2008) and since most of the wounds are treated in primary care we could assume that this survey found most of the wounds in these primary care units. The response rate was lower for those units that had no wound patients. The response rate was 25% in 2016 compared to 39% in 2008, the

non-responders therefore lowering the response rate for the entire study area. In the City of Helsinki units, the response rate was high at 78%. There was no age-adjusted prevalence counted, but the prevalence was compared to the whole population in the area.

Another limitation of the Study I is that I had data only on the number of patients, wound location, and aetiology, but no information on the patients' age. Therefore, I was unable to calculate the age-adjusted prevalence.

The main limitation of the Studies II and III was limitation was the retrospective nature. All the information was in the patient records and there was no intervention other than diagnostics by the wound care team available. Also, at the very beginning there was a question of timing of a correct diagnosis especially in a situation where there were none existing ICD-10 codes for different wound types which could be found from the patient records. I solved this problem as it is presented in Study II.

The variety of aetiologies of wounds caused also limitations for the study design and I had to analyse all the wounds as a same group, since the numbers of each aetiological groups were so small I couldn't analyse the data in subgroups of main common aetiologies. It could have been interesting to analyse these aetiological subgroups, since different wound aetiologies have different tendencies to heal.

Also, I did not take socio-economic status or psycho-social factors into account, although it has been discussed that they affect wound healing.

Finally, there was no patient and public involvement in the study design.

6.5 Future perspectives

Involvement of primary care physicians is essential in future wound care. According to this study I could assume that it is possible to make accurate diagnostics in primary care, but further investigations are needed regarding different wound types to find out if there are differences between diagnostic groups in timely treatment. There is an urgent need of GP´s to be interested in wound management and development of multiprofessional wound care pathways within a primary care, and in collaboration with secondary and tertiary care, since wound care is costly and resource consuming.

There are studies about total costs of chronic wounds or costs of different wound types, *e.g*. DFUs and PUs, to societies, but this study highlights a need for further investigation of the cost-effectiveness of a primary care wound care team and of an early diagnosis.

Additionally, accurate concern in wound care is implementation of best practices. If the principals of wound care in assessment, diagnostics and treatment are lacking, e.g. proper wound assessment and debridement, compression therapy, off-loading and vascular assessment and timely referrals, it may become meaningless to invest to high-

level and intelligent wound therapies. Investigations are needed about wound types that are totally curable in primary care and which wounds require tertiary care evaluation.

There is a need for commonly accepted outcome measures in wound research. Lack of definition of a chronic wound and related ICD-10 (or ICD-11) codes has an impact on systematic and comparable research. Creation of national wound registries would increase systematic assessment, diagnostics and defined outcomes, and therefore facilitating wound research.

This study is highlighting organisational aspects of wound care, but there is a need of further investigations within primary care, *e.g.* studies of differential diagnostics, knowledge and education of primary care physicians, aspects of prevention in wound care. Also, Universities and Medical faculties have an important role in educating professionals also in wound management.

Finally, in holistic wound management the patient's perspective, psycho-social factors, socio-economic status, quality of life and patient involvement in wound pathways are important topics to investigate.

7 Conclusion

This thesis concludes:

1) It seems to be that the prevalence of wounds among patients in the Helsinki Metropolitan area's health care services has decreased during the years 2008-2016, after the establishment of a GP-led wound care team.

2) In primary care, the diagnostic delay of chronic wounds was two times longer than the recommended four weeks. The initial patient-related delay was short, however, the first physician contacts seldomly led to a correct diagnosis. Based on our results, a specialised primary care physician in wound care can reduce the diagnostic delays.

3) Early diagnosis is essential in wound care pathways as it has a direct impact on the wound healing rate. The delay in diagnostics of chronic wounds increases healing time. The timely diagnosis (less than 4 weeks) leads to significantly shorter healing time.

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