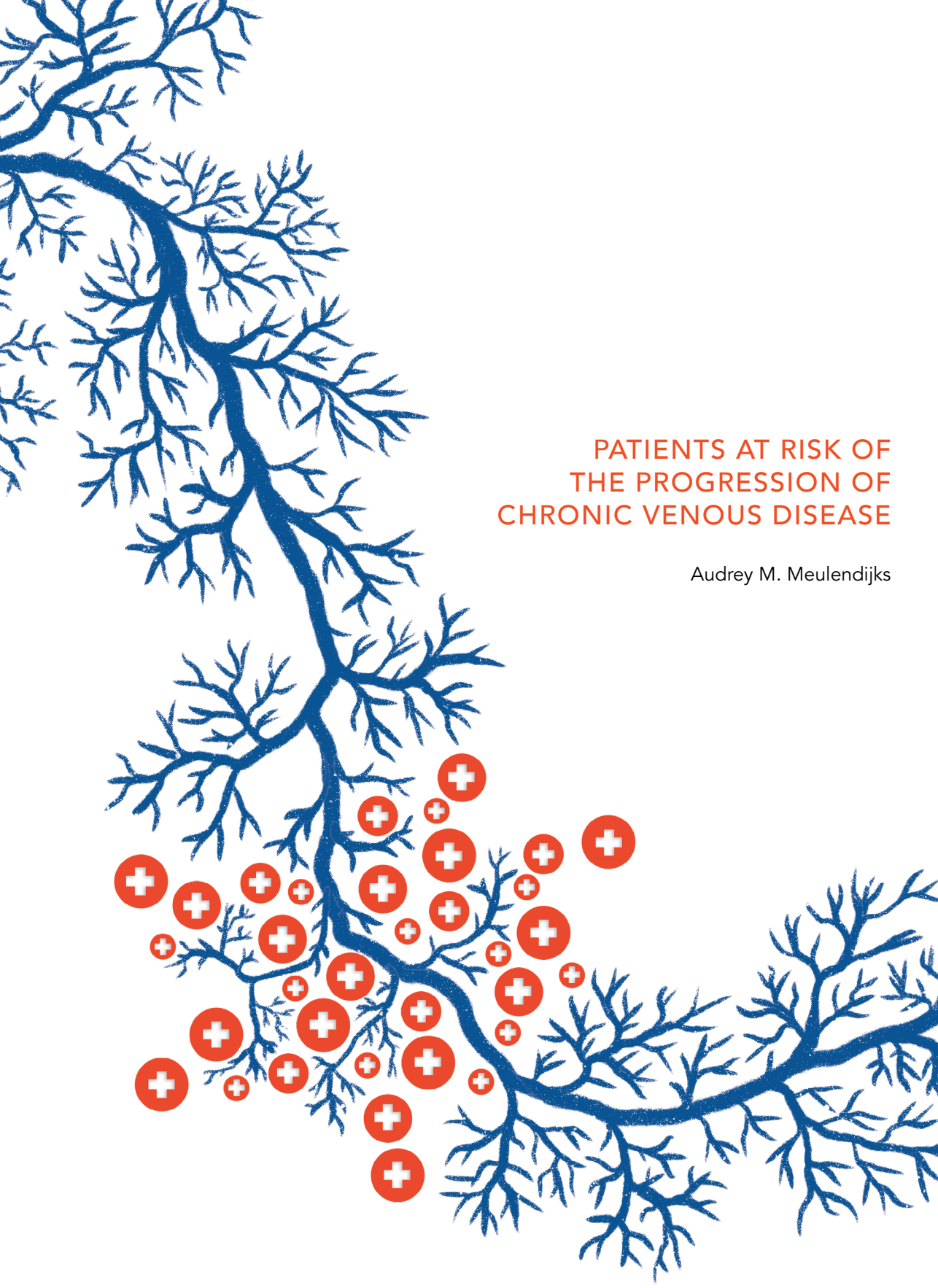

PATIENTS AT RISK OF THE PROGRESSION OF CHRONIC VENOUS DISEASE

Audrey M. Meulendijks

PATIENTS AT RISK OF THE PROGRESSION OF CHRONIC VENOUS DISEASE

Audrey Maria Meulendijks

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PATIËNTEN MET RISICO OP PROGRESSIE VAN
CHRONISCH VENEUZE AANDOENINGEN

(met een samenvatting in het Nederlands)

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"It is more important to know what sort of person has a disease than to know what sort of disease a person has."

- Hippocrates

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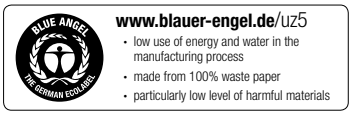

A tree has been planted for every copy of this thesis.

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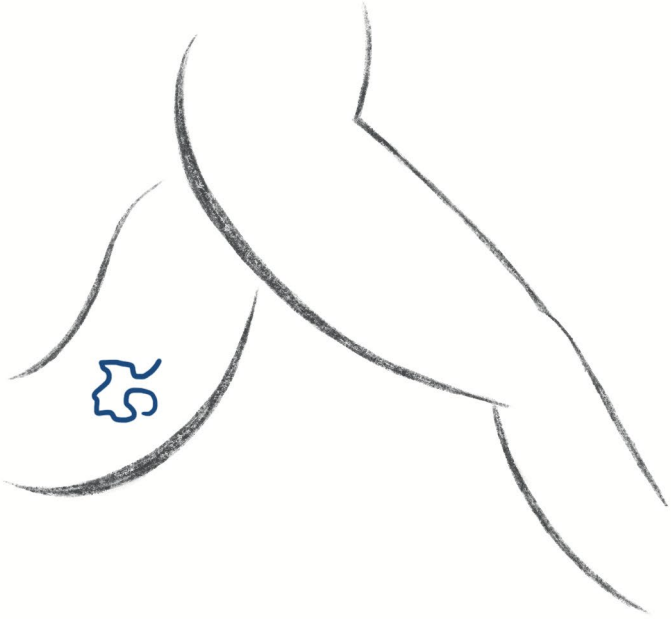
CHAPTER ONE



GENERAL INTRODUCTION

General Introduction

Chronic venous disease: A common inconvenience

Varicose veins are a very common defect of the venous system in the lower extremities, affecting almost a third of the adult population world-wide.(1) The prevalence of varicose veins increases significantly with age; the majority of people who are 60 years old or older experience at least one type of varicose vein.(2) Varicose veins are often left untreated because of their cosmetic reputation. Health insurance companies do not always cover treatment, and there are no fixed healthcare paths for patients with varicose veins. The chronicity and progression of varicose veins is, therefore, often overlooked by patients and by current healthcare providers. However, prolonged varicose veins can progress to chronic venous disease leading to various physical signs like oedema, eczema and a venous leg ulcers. The progression of chronic venous disease often leads to discomfort, disabilities and a reduced quality of life.

Working mechanisms of chronic venous disease

Venous blood in the lower extremities flows from the foot arch into the small saphenous vein (lateral side) or the great saphenous vein (medial side) and then into the upper-located deep veins. The deep veins (femoral vein and popliteal vein) transport venous blood via the iliac veins in the pelvis back to the heart. Due to gravity, the venous pressure in the lower extremities increases in an upright posi-

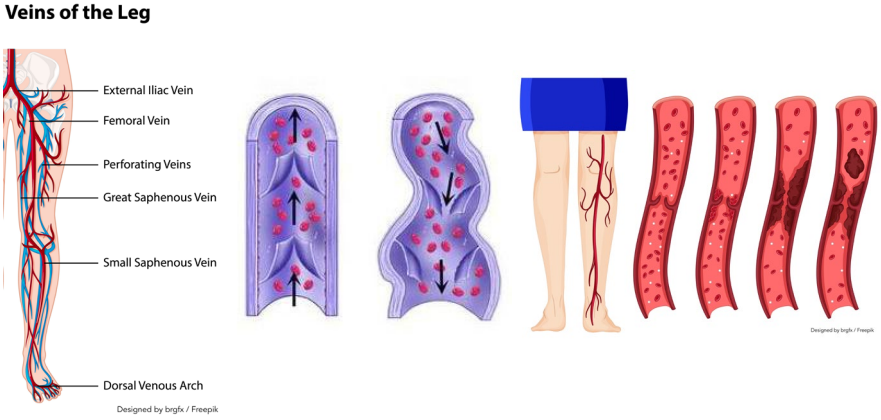


Figure 1: *Venous reflux and obstruction*

tion. Increased venous pressure can lead to a gradual deterioration of the venous system over time, which leads to reflux and obstruction (see Figure 1).

Reflux and obstruction can be a cause or an effect of increased venous pressure in the lower extremities. Venous reflux occurs when the vein walls are weakened and the vein valves malfunction; this leads to a back flow of blood volume to the lower extremities while the person remains in an upright position, and results in less venous return to the heart. Venous obstruction can be caused by a thrombosis obstructing the venous return to the heart. The use of muscle pumps during walking (like the calf muscle pump) play an important role in the venous return to the heart (see Figure 2).

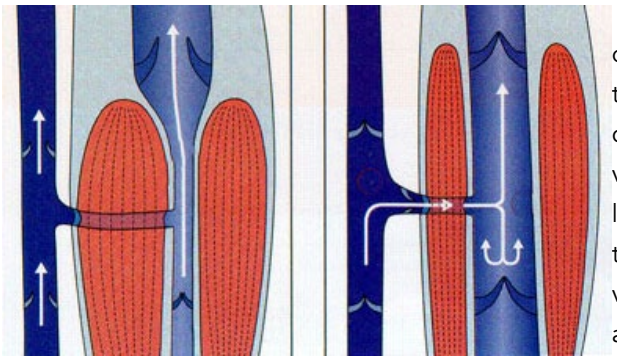


Figure 2: *calf muscle pump function*

However, when the reflux or obstruction in the veins is too large, the muscle pumps cannot compensate for the venous back flow to the lower extremities. This leads to an increased ambulatory venous pressure. Increased ambulatory venous pressure can also occur when reflux or obstruction is not present, but the muscle pumps are impaired and are therefore unable to return enough venous blood volume back to the heart (also referred to as dependency). Age, genetic predisposition, venous thrombosis, immobility and several congenital conditions involving the venous system can be the cause of reflux, obstruction and an increased ambulatory venous pressure (see Figure 3). This is called chronic venous disease. In conclusion, the difference between healthy legs and diseased legs is the amount of lowering of venous pressure during walking. This denotes the importance of walking (muscle pump function) in venous functioning in addition to the function of the veins itself.

Varicose veins: They come with age. No harm done?

Limited reflux or obstruction in small veins or reflux in only one segment of a vein does not always lead to an increased ambulatory venous pressure. However, it does cause a temporal increase in venous pressure when the muscle pumps are not used. Prolonged or temporal increased venous pressure can lead to vein valve dysfunc-

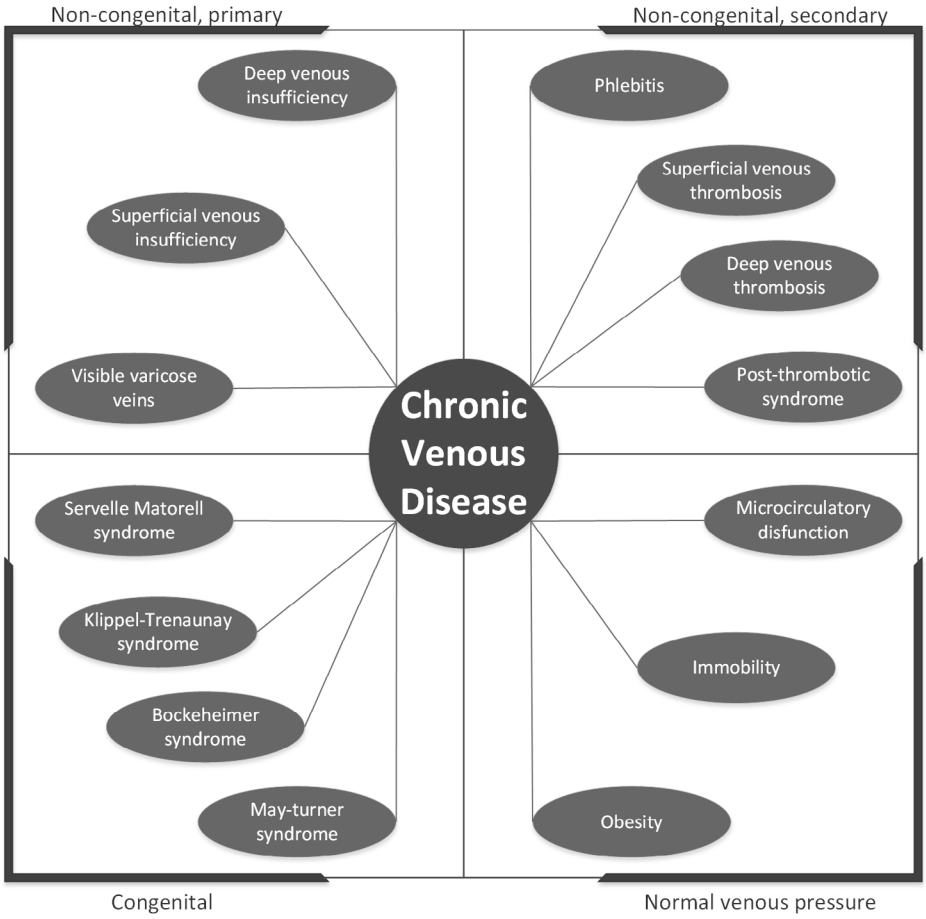


Figure 3: *Causes of venous diseases*

tion and vein wall weakening, which can lead to venous reflux (or vice versa). The increased venous pressure can lead to telangiectasia, reticular veins and varicose veins. These venous deformities are often experienced as cosmetically unsightly. Many people with varicose veins worry about their appearance and feel embarrassed to show their lower extremities.(3) In the general population, reticular and varicose veins are highly prevalent, with 75% of the German population(4) and 86% of the United Kingdom's population(5) suffering from these conditions. In the primary care population, the prevalence of reticular and varicose veins was as high as 62% in Western Europe.(6) The prevalence of varicose veins alone is lower; 31%-35% of the general population(7, 8) and 17% of a primary care population(9) have varicose veins. In the elderly, however, the prevalence of varicose veins is higher; it ranges from 50% in people aged 60-64 years to 69% in people aged 80+ years.(10)

Increasing age is the main risk factor for the development of varicose veins. Other risk factors for varicose vein development are hypertension, obesity, deep vein thrombosis, a positive family history of varicose veins and a standing occupation. (6, 10)

Besides the cosmetic issues, varicose veins can cause a series of physical complaints as well. Heaviness, tightness, muscle cramps, restless legs and itchiness are common symptoms in about 50% of patients with varicose veins.(11, 12) Both the cosmetic and physical complaints lead to a reduction in the quality of life of varicose vein patients, leading to functional and social limitations.(12-14) Patients who experience physical complaints are eligible for varicose vein treatment. Superficial varicose veins can be treated using different techniques to remove the vein. The most common invasive treatments are surgical (stripping, endovascular laser or radiofrequency ablation) and different forms of sclerotherapy.

In the Netherlands, a general practitioner can refer a patient with visible varicose veins and physical complaints to a dermatologist or vascular surgeon for diagnosis and treatment. When the patient does not experience physical complaints, or the varicose veins are not visible, primary care takes no action.(15) Healthcare insurance companies only cover the diagnostics and treatment of varicose veins when a patient experiences physical complaints. This results in a large number of patients with invisible or asymptomatic varicose veins who are left undiagnosed and untreated. No harm done?

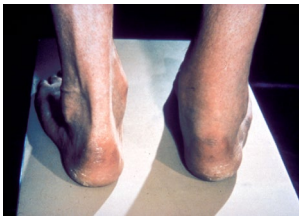
Progression of 'simple' varicose veins to chronic venous disease

Varicose veins can cause real harm. Untreated varicose veins can progress to more severe and complicated varicose veins. However, patients with treated varicose veins or thrombosis can also progress to more severe venous disease. Treated patients can develop neovascularisation, reflux, or obstruction in other veins in the lower extremities. After venous thrombosis, post-thrombotic syndrome can develop, causing signs and symptoms of chronic venous disease such as oedema, hyperpigmentation, feelings of heaviness, muscle cramps, and pain in the lower extremities.

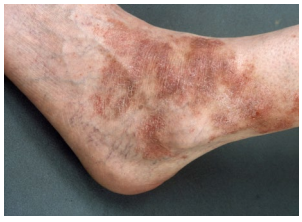
When reflux or obstruction worsens, the ambulatory venous pressure increases. Increased ambulatory venous pressure in the lower extremities can lead to changes in the macro- and microcirculation. When the ambulatory venous pressure is increased, it is also referred to as chronic venous insufficiency. Chronic venous insufficiency is the inability of the venous system in the lower extremities to transport

sufficient blood volume back to the heart. Chronic venous insufficiency often involves reflux or obstruction in the deep or truncal veins. The deep and truncal veins are responsible for the majority of venous return. Chronic venous insufficiency often begins with reticular veins and varicose veins. When varicose veins progress into chronic venous insufficiency, the varicose veins become larger in diameter, include a larger trajectory of the vein, and other symptoms of macro- and microcirculatory dysfunction can occur in the lower extremities. Chronic venous insufficiency can lead to oedema, corona phlebectatica, and trophic skin changes such as 'hyperpigmentation' (iron deposition in the dermis), eczema, lipodermatosclerosis, white atrophy, and eventually a chronic wound known as a venous leg ulcer (See Figure 4). The cosmetic and physical complaints are similar to those of the uncomplicated varicose veins. Embarrassment to show the legs, feelings of heaviness, tightness, muscle cramps, restless legs, itching and pain are common in patients with chronic venous insufficiency.

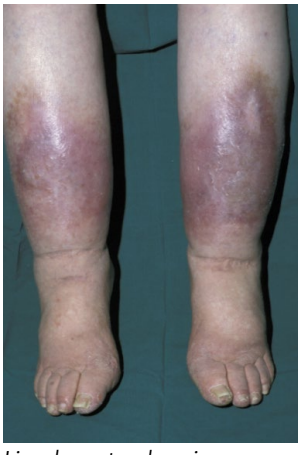
Varicose veins



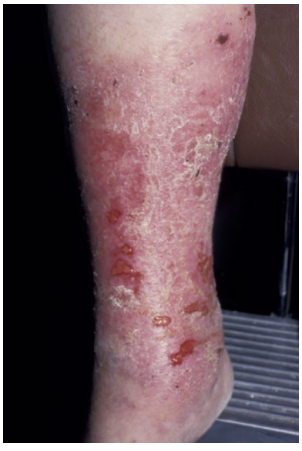
Oedema



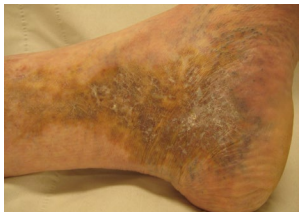
Corona phlebectatica, Hyperpigmentation



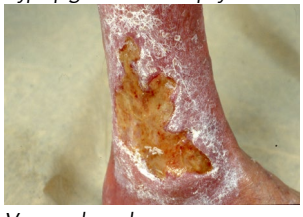
Lipodermatosclerosis



Eczema



Hyperpigmentatie - atrophy blanche



Venous leg ulcer

Figure 4: clinical stages of chronic venous disease

The overarching term for the causes (see Figure 3) and symptoms of varicose veins and chronic venous insufficiency is chronic venous disease. Chronic venous disease is classified according to the Clinical, Etiological, Anatomic and Pathological (CEAP) classification. The CEAP classification is used worldwide to register chronic venous disease in healthcare.(16) The C of the CEAP classification is mostly used to denote the severity of chronic venous disease (see Table 1). However, the clinical classes (C0-C6) do not always occur sequentially in chronic venous disease patients, and not all patients will develop all symptoms. Mild chronic venous disease (C0s-C2) is far more prevalent compared to more severe chronic venous disease (C3-C6). The prevalence of C3-C6 in the general population ranges from 6% of people in the UK(5) in 1989 to 17% in Germany(4) in 2002 and 25% in Western Europe(6) in 2013 in a population recruited by general practitioners. Some patients will develop varicose veins or have a thrombosis and never progress to a more severe stage of chronic venous disease. Some patients will develop a venous leg ulcer without showing any skin changes or oedema. Other patients will develop oedema and skin changes without having varicose veins or a thrombosis but simply from suffering insufficient ambulatory venous return. For example, in patients with permanent immobility who cannot use their muscle pumps in their lower extremities, the venous return is reduced, increasing venous pressure.(17) The reason why clinical signs of chronic venous disease do not always occur sequentially remains unknown. However, the risk factors for chronic venous disease are similar to those of varicose veins alone. Risk factors for chronic venous disease include gender, family history of chronic venous disease, low physical activity, overweight, history of deep vein thrombosis, and a standing occupation.(9, 18, 19)

Clinical Class	Description
C0(s)	No visible or palpable signs of venous disease (symptomatic)
C1	Telangiectasia or reticular veins
C2(r)	Varicose veins, (r) recurrent varicose veins
C3	Oedema
C4a,b,c	Changes in skin and subcutaneous tissue secondary to chronic venous disease: (a) Pigmentation or eczema, (b) Lipodermatosclerosis or white atrophy, (c) corona phlebectatica
C5	Healed venous leg ulcer
C6(r)	Active venous leg ulcer, (r) recurrent active ulcer

Table 1: Revised CEAP classification 2020(16) – the clinical class

CEAP = Clinical, Etiological, Anatomical and Pathological

It is known, however, that age is the main risk factor; the prevalence of chronic venous disease increases in the ageing population.(1, 6, 20) It is also known that when the clinical class increases, the physical complaints increase as well. Heaviness, restless legs, muscle cramps and pain are more common in C3-C6 patients, whereas 73%-94% of chronic venous disease patients experience at least one of these physical complaints. When the C-class increases, the disease-specific quality of life of chronic venous disease patients decreases significantly.(21-23)

Diagnostics and treatment of chronic venous disease

Before chronic venous disease can be treated, full diagnostics must be performed to register the whole CEAP. The gold standard for assessing the severity of chronic venous disease is an invasive measurement where the ambulatory venous pressure is measured inside the veins located in the lower extremities. Because chronic venous disease patients are prone to develop a chronic wound, the invasive ambulatory venous pressure measurement is discouraged in clinical practice. An effective replacement for the ambulatory venous pressure measurement is a duplex ultrasound investigation that measures reflux and obstruction in the deep and superficial veins. With the diagnosis of venous reflux and obstruction, an adequate treatment process can be initiated for chronic venous disease patients. Treatment of chronic venous disease consists of the invasive treatments of varicose veins described above and non-invasive treatments such as ambulatory compression therapy, skin agents, wound dressings, and lifestyle changes. The diagnosis and treatment guidelines for chronic venous disease are collected in one chronic venous disease guideline for secondary care practitioners. In the Netherlands, duplex diagnostics is only performed in secondary care, and patients always need a referral to secondary care from a general practitioner. However, a combined guideline for the diagnosis and treatment (or referral) of chronic venous disease patients in primary care is not yet available. There are separate guidelines for varicose veins, deep vein thrombosis, eczema, and venous leg ulcers.(15, 24-26) The scattered and incomplete guidelines in primary care might lead to an under recognition of chronic venous disease patients, which can lead to inadequate diagnosis and treatment of chronic venous disease in the Dutch primary care system.

And then came the venous leg ulcer

The progression of chronic venous disease takes years. Therefore, a venous leg ulcer develops mostly in people over 40 years of age. A venous leg ulcer is the least

prevalent stage of chronic venous disease and occurs in about 3% of the older population.(27) The incidence of a venous leg ulcer increases with age (similar to the other stages of chronic venous disease). When chronic venous disease progresses, the increased ambulatory venous pressure is transmitted by physical laws (gravity and the law of Laplace) from the macrocirculation to the microcirculation. Deterioration in the microcirculation eventually leads to a venous leg ulcer. The deterioration of the microcirculation progresses as follows: first, the increased intra-capillary pressure leads to capillary leakage (oedema) into the interstitial compartment; The capillary leakage can include small amounts of erythrocytes, which release iron that oxidizes in the dermis ('hyperpigmentation'); Second, increased intra-capillary pressure results in a higher production of collagen IV in the capillary walls, causing thick and non-constrictive capillaries (corona phlebectatica, atrophy blanche); Third, the high pressure in the dermal microcirculation results in the stimulation of an inflammatory process in which cytokine and growth factor release leads to leukocyte migration into the interstitial compartment, triggering further inflammatory events. This process is associated with intense dermal fibrosis and tissue remodelling (lipodermatosclerosis). These skin changes lead to a reduced skin oxygenation, which makes the skin vulnerable for ulceration.(28-30) A venous leg ulcer can also occur without visible skin changes in patients with chronic venous disease clinical classes C2 and C3 (See Figure 5).

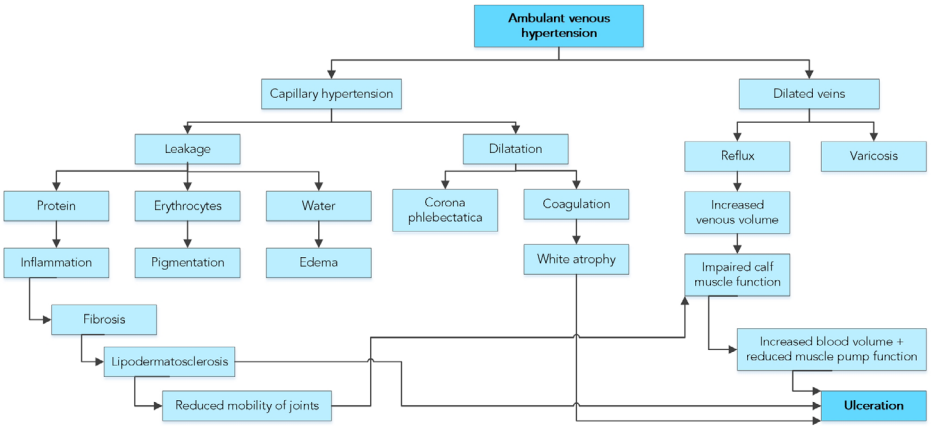


Figure 5: The Rotterdam model(31) of symptom development of chronic venous disease

When a venous leg ulcer is present, it comes with a large amount of physical complaints such as pain, odour, and leakage of wound fluids, in addition to the complaints of heaviness, restless legs and itching. Patients with a venous leg ul-

cer feel insecure, unhappy and restricted in their daily activities.(32) Compared to earlier stages of chronic venous disease, patients with a venous leg ulcer experience significantly lower general and disease-specific health-related quality of life.(33, 34) When the severity of the venous leg ulcer increases, it impacts quality of life even more.(35) When a venous leg ulcer heals, the general and disease-specific health-related quality of life can increase again.(36) However, when a venous leg ulcer heals, patients can experience fear of venous leg ulcer recurrence. The fear of injury and skin tears on the lower extremities can cause non-compliance with directions to wear compression hosiery and engage in physical activity.(37, 38)

Venous leg ulcers can be caused by minor trauma to the lower extremities, but they can also develop on their own. Venous leg ulcers are mostly located at the medial malleoli where the ambulatory venous pressure is the highest. Due to high ambulatory venous pressure and limited venous return, the drainage of waste substances and the supply of oxygen and nutrients are reduced, leading to a slow healing of the venous leg ulcer. The slow healing of over four to six weeks due to chronic venous disease as the underlying pathology classifies the venous leg ulcer as a chronic wound. The average healing of a venous leg ulcer takes about three to six months, or, when the underlying pathology is not treated, it may even take over a year. About 8% of all venous leg ulcers do not heal in five years of treatment. Besides the slow healing, a venous leg ulcer also has a high recurrence rate that increases over the years. A venous leg ulcer recurs in 20%-55% of patients within 12 months and in about 70% of patients within two years.(37, 39, 40) Most patients experience multiple venous leg ulcer episodes over the years.(39, 41) In conclusion, the prevalence of venous leg ulcers may be low, but they are hard to heal, recur often and can have a large impact on a person's quality of life.

How to heal a venous leg ulcer

Patients with a venous leg ulcer need intensive wound care to reduce pain, odour and leakage from the wound. Besides regular wound dressings, some patients might need skin transplants or even amputation of the lower extremity. Therefore, it is important that the underlying chronic venous disease is adequately diagnosed and treated; this prevents the long duration of a venous leg ulcer and its invasive consequences.

There are four phases in the treatment of a venous leg ulcer. First, a duplex diagnosis must be performed to map the venous pathology of the patient. Second, reflux and/or obstruction of the deep and superficial veins in the lower extremities

Diagnostics	Invasive treatment	Non-invasive treatment
Clinical diagnosis	Varicose vein removal	Medication (anticoagulants, antibiotics, venoactive drugs)
Duplex investigation	De-obstruction and venous stenting	Compression Therapy (bandages/ stockings)
Plethysmography	Surgical debridement	Lifestyle advices
Ambulatory Venous Pressure Measurement	Skin transplantation (Vigoni-Schmeller procedure)	Non-invasive debridement (biological, enzymatic, autolytic, mechanical)
Phlebography (magnetic resonance venography)	Decompression of the compartment	Wound dressings (paraffin gauze, foam, hydrofiber)
	Amputation	Skin agents (wound edge, skin care)
		Extra corporeal shock wave therapy
		Hyperbaric oxygen therapy

Table 2: *Diagnostic and treatment options for venous leg ulcers(42)*

should be treated, if possible. Third, appropriate ambulatory compression therapy should be applied to reduce oedema and support the venous return to the heart, thereby stimulating the drainage of waste substances and increasing skin oxygenation. Lastly, the wound must be cleansed and treated. An overview of the diagnostic and treatment options can be found in Table 2.

Because of the underlying pathology, it is important to focus on treating the chronic venous disease and not solely on treating the venous leg ulcer. Studies on wound dressings and other wound treatments (such as extracorporeal shockwave therapy and debridement) show no significant results between various wound dressings, techniques and topical agents.(43-45) Ambulatory compression therapy, on the other hand, is the cornerstone of venous leg ulcer treatment as an intervention on its own or in combination with varicose vein removal.(46, 47) Ambulatory compression therapy increases healing rates of venous leg ulcers and reduces wound days using two-layered (or four-layered) bandaging or graduated compression stockings. When ambulatory compression therapy is provided in combination with varicose vein removal, higher healing rates and a higher reduction in wound days can be accomplished.(48) In the past, invasive treatments were discouraged in patients with an active venous leg ulcer because it was thought to delay venous leg ulcer healing or cause a new venous leg ulcer. Today, however, early invasive treatment of varicose veins is recommended to patients with an active venous leg

ulcer because it leads to faster healing.(42, 49)

In the Netherlands, many healthcare professionals can be involved in the care of venous leg ulcer patients (see Figure 6). The general practitioner is the first stop for all patients with health problems. The general practitioner makes a clinical diagnosis, then can refer for further diagnostics or can treat the venous leg ulcer. For duplex diagnostics, a patient can be referred to either a diagnostic centre (vascular lab technician), a vascular surgeon, or a dermatologist. The vascular surgeon and dermatologist can also perform invasive treatments such as varicose vein removal, vein stenting, surgical debridement and skin transplantation. Compression stockings are tailored by compression therapy specialists and dermal therapists. Wound care of the venous leg ulcer, applying bandages, and aid in taking on and off the compression stockings can be performed by a number of health care professionals such as a doctor's assistant in primary or secondary care, community nurse, specialised wound care nurse, dermal therapist, and nurse practitioners. All previously mentioned healthcare professionals are licensed to perform wound dressing changes and compression therapy bandaging. However, it takes specific training and ex-

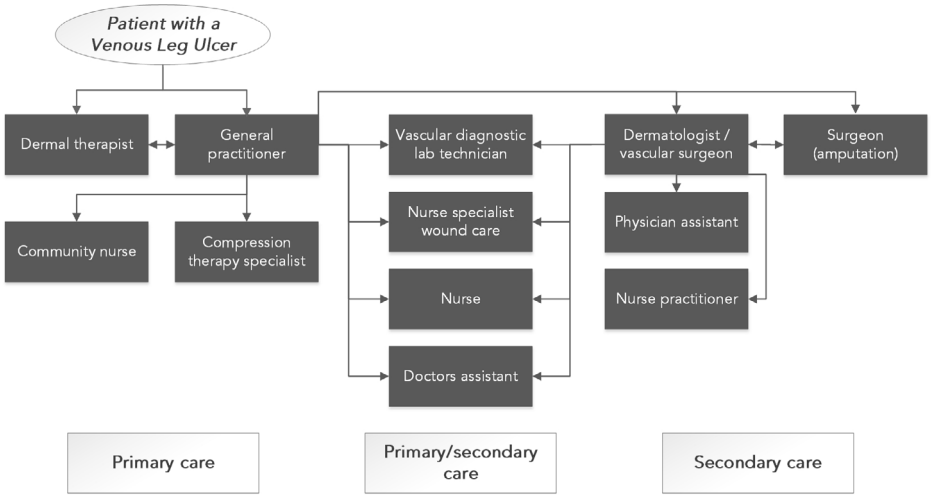


Figure 6: *Healthcare professionals involved in Venous Leg Ulcer management and their referral patterns*

perience to be able to adequately perform compression therapy using bandages. In addition to the different healthcare professionals, there are also different settings in which venous leg ulcer patients can be treated. Patients can be treated in primary care facilities, hospitals, outpatient clinics, wound expertise centres, private clinics and at home.

A patient can be treated in all combinations of these settings; health care professionals each commit to their own guidelines and an overarching quality standard. (24, 50, 51) In conclusion, there are no fixed healthcare paths that ensure adequate diagnostics and treatment for patients with a venous leg ulcer.

Better safe than sorry

As chronic venous disease worsen, the expenses made on an individual, societal and financial level increase. Quality of life decreases significantly with each clinical stage of chronic venous disease on a physical, emotional and social level.(20) Severe stages of chronic venous disease can even lead to loss of work productivity and the need for informal care. The progression of chronic venous disease is accompanied by an increase in health care costs; the venous leg ulcer is the most expensive to treat. However, chronic venous disease is the only chronic disease with the potential to develop into a chronic wound that does not receive regular check-ups to monitor and treat disease progression. For other chronic diseases that carry a risk of the development of a chronic wound (such as diabetes and peripheral arterial disease), prevention of disease progression is imbedded in current healthcare.(52-55) Patients with diabetes receive regular check-ups to monitor and control their glucose levels. Patients with peripheral arterial disease receive regular check-ups for their blood pressure and ankle brachial pressure index. Lastly, patients with (temporal)

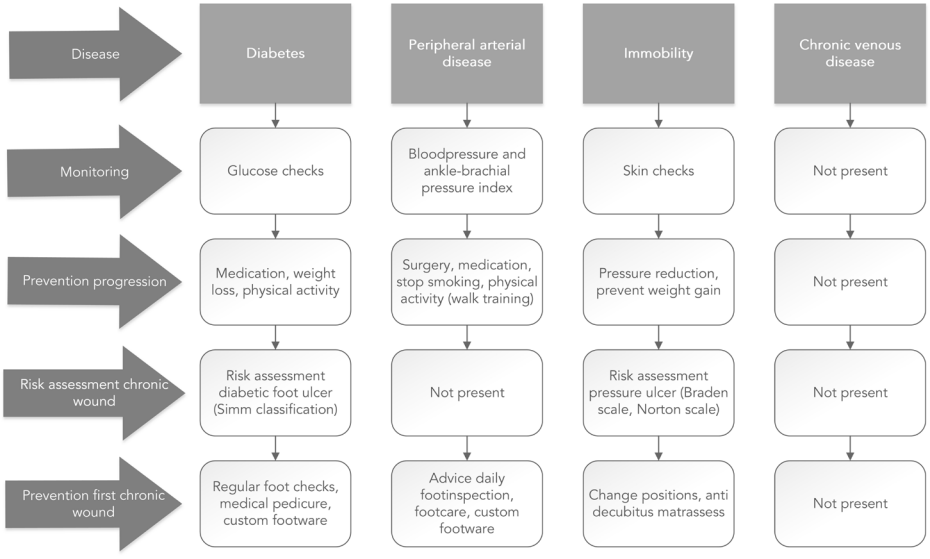


Figure 7: *Prevention of progression for diseases with a risk of a chronic wound*

immobility receive regular skin checks to monitor any signs of pressure injury. In addition to these patients being monitored, they also receive lifestyle advice and the necessary guidance to implement any changes. For example, a dietician is involved in a diabetic's care to monitor weight loss, and a physical therapist is involved in the care for peripheral arterial disease for specific walk training (see Figure 7).

Furthermore, of all chronic wounds on the lower extremities (excluding the feet), the venous leg ulcer is the most prevalent.(56, 57) However, the venous leg ulcer is the only chronic wound for which prevention is not implemented in clinical practice guidelines. The fact that prevention is missing in chronic venous disease care might be explained by the lack of large recent population studies on the risk factors for the progression of chronic venous disease.(58, 59) Besides venous functioning and age, weight and physical activity are possible risk factors.(59, 60) However, how these factors contribute to chronic venous disease progression is not common knowledge. In conclusion, there are several gaps in chronic venous disease care:

- *Not all patients experience/recognise chronic venous disease signs and symptoms.*
- *Not all patients seek healthcare for their chronic venous disease.*
- *Not all healthcare providers recognise signs and symptoms of chronic venous disease.*
- *There are no clear diagnosis and treatment strategies in collaboration with primary and secondary care.*
- *Guidelines on chronic venous disease do not include monitoring and prevention of disease progression.*
- *Risk factors (and their working mechanisms) for chronic venous disease progression are not well known.*

Adequate prevention for the progression of chronic venous disease (and the development of a first venous leg ulcer) is missing due to a poor understanding of its risk factors. How to properly detect patients at risk and prevent disease progression remains unknown.

Objectives of this thesis

The main objective of this thesis is to make a first step towards prevention of the progression of chronic venous disease and the development of a first venous leg ulcer in chronic venous disease patients. The aim is to identify chronic venous disease patients at risk of developing more severe clinical stages, provide insight into the lifestyle risk factors, and provide an overview of current chronic venous disease

care in the Netherlands.

The objectives of this thesis are as follows:

- *To study the patient's perspective on the progression of chronic venous disease and the development of a venous leg ulcer*
- *To identify known risk factors for the development of a first venous leg ulcer*
- *To identify and investigate (known) risk factors in the progression of chronic venous disease*
- *To investigate the current care for chronic venous disease in the Netherlands*

Outline of this thesis

The overall outline of this thesis consists of eight chapters, including the general introduction. Chapter 2 describes a qualitative study on the patient's perspective in the development of a first venous leg ulcer. Chapter 3 describes a systematic review of the risk factors for the development of a first venous leg ulcer. Subsequently, Chapter 4 describes a scoping review on how obesity and physical activity affect the progression of chronic venous disease. Chapters 5, 6and 7 describe the results of the cross-sectional study among patients with chronic venous disease; the risk factors obesity and physical activity are further investigated and the current care for patients with chronic venous disease is presented. Chapter 8 covers the general discussion; the main research findings will be shown and discussed. To finalise the thesis summaries in English and Dutch, the curriculum vitae of the author and the acknowledgements can be found in Chapter 9.

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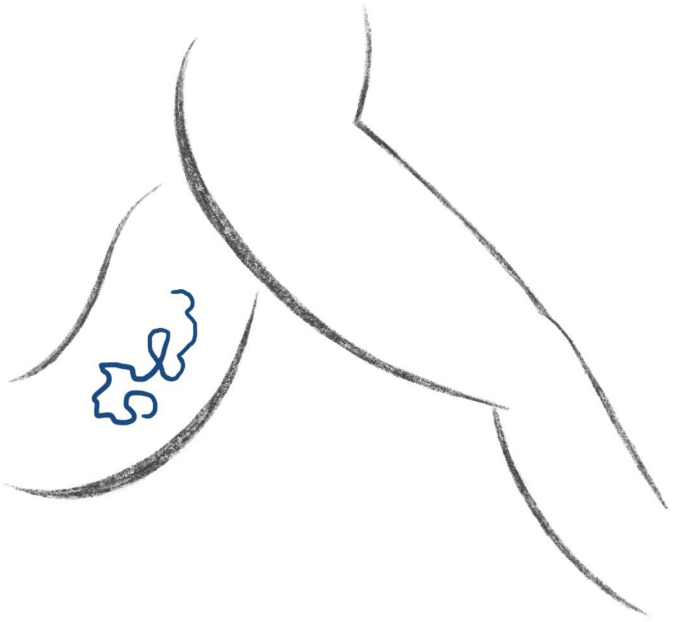
CHAPTER TWO



A QUALITATIVE STUDY ON THE PATIENT'S NARRATIVE IN THE PROGRESSION OF CHRONIC VENOUS DISEASE INTO A FIRST VENOUS LEG ULCER: A SERIES OF EVENTS

SUMMARY

Background A Venous Leg Ulcer (VLU) has a significant negative impact on quality of life. Prevention for a VLU is not yet imbedded in clinical practice because risk factors for developing a first VLU are not well-known.

Objectives The objective was to further explore the progression of Chronic Venous Disease (CVD) into a first VLU from a patients' perspective.

Methods A qualitative study using semi-structured interviews was conducted amongst male and female patients with a VLU. Patients from primary and secondary care, under and over 50 years of age and patients with first and recurrent VLUs were included. The interviews were transcribed and analysed using a narrative approach to a thematic analysis. Transcripts were organised in a chronological order and an iterative process was used to code the transcripts.

Results Four key-themes and the connections made between them emerged from the eleven narratives on the progression of CVD towards a first VLU: 'Comorbidity', 'Mobility', 'Work & Lifestyle', and 'Acknowledgement of CVD'. Comorbidity was linked to a reduced Mobility and a late Acknowledgement of CVD. Comorbidity also affected Work & Lifestyle and vice versa. Work & Lifestyle affected Mobility and was linked to the Acknowledgement of CVD.

Conclusion A reduction in Mobility as a result of Comorbidity and Work & Lifestyle occurred before the VLU developed. Patients did not recognise symptoms of CVD and did not acknowledge the chronicity of CVD. Health Care Professionals should be aware of reductions in mobility and the knowledge deficit in patients with CVD.

As published

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A qualitative study on the patient's narrative in the progression of Chronic Venous Disease into a first Venous Leg Ulcer: a series of events

Introduction

A Venous Leg Ulcer (VLU) as a result of Chronic Venous Disease (CVD) occurs in approximately 0.3% of the western adult population.[1] The incidence might seem low, but the impact of a VLU is high as patients with a VLU have a significant lower quality of life compared to patients with an earlier stage of CVD on generic and disease specific quality of life.[2-5]

Patients with CVD have an increased ambulatory venous pressure and a decreased venous outflow due to obstruction in the veins, weakened vein walls or vein valves, or an impaired function of the calf muscle pump. CVD symptoms start mild with reticular veins and varicose veins however it can progress to more severe symptoms like oedema, skin changes and eventually a VLU.[6] Progression of CVD takes years and a VLU mostly develops in patients over 50 years old as age is an important risk factor for the progression of CVD. Yet, not all patients with CVD will develop aVLU.[7]

Factors which have been associated with the development of a VLU are increased age and BMI, hypertension, lower physical activity, deep vein reflux, deep vein thrombosis, and a family history of VLU. However, these factors were identified from case-control studies in which causality could not be established.[8] A prevention strategy for a VLU is therefore not yet imbedded in the current clinical practice of CVD.[9]

Not only CVD but also the risk factors for developing a VLU can be present some time before the VLU occurs. It remains unclear how these risk factors progress over time since most studies use a cross-sectional design with mostly cross-sectional measurements.[8] The patients' perspective on developing a first VLU could provide insight in the timeline of the progression of CVD into a first VLU. This information can be used for selecting valid and reliable measurements for a quantitative study into the risk factors for a VLU and provides health services with more insight into when to start a prevention strategy. Timely prevention for CVD patients at risk of a VLU should eventually lead to a reduction in the incidence of VLUs and subsequently prevent a decrease in quality of life.

The patients' experience was studied previously amongst patients with a (recur-

rent) VLU focussing on the impact of the current VLU on quality of life. The negative impact on quality of life was caused by pain odour and exudate of the VLU.[10] The patients' perspective on the recurrence of a VLU provided insight in factors that preceded the recurrence. Trauma on the lower extremities and non-adherence to compression therapy were factors that preceded the recurrence of a VLU.[11] However, no studies were found that investigated the patients' perspective towards their first VLU. Therefore, the objective of this study is to further explore the progression of CVD to a first VLU from a patients' perspective to provide insight in the factors that precede a first VLU.

Patients and methods

This study is reported according to the Standards for Reporting Qualitative Research.[12]

Design

We performed a qualitative study using a narrative research approach[13] since not all patients are aware of CVD as the underlying cause of the VLU.[14] A narrative research approach with the oral history of the patients gives them the opportunity to tell their story and reflect on events and the causes and effects of these events from their perspective.[15] The qualitative design is an efficient way to gain first insight in the events preceding a VLU. It provides a different perspective on the progression of CVD into a VLU and therefore might lead to new insights on risk factors.

Researcher characteristics and reflexivity

The first author (A.M., female, background in skin therapy and epidemiology) conducted all the interviews and performed the analysis. The second author (M.W., female, background in physiotherapy and health science) gave feedback on the recorded interviews and transcripts and partially performed the analysis. M.W. and A.M. had no relationship or prior contact with any of the patients. A.M. approached this study from the constructivism research philosophy to give insight in the individual reconstructions and understanding of the participants in the development of a VLU.

Sampling strategy

Male and female patients with an active VLU were recruited in The Netherlands. Patients were asked for participation by their health care professional during a wound

care visit. Patients were included when they spoke the Dutch language and were able to understand and sign the informed consent. We used criterion sampling[16] to include a heterogenic group of patients with a variety of characteristics that might influence their narratives. The sampling criteria were as follows: patients under and over 50 years of age, patients with a first and recurrent VLU and patients from primary and secondary care. Saturation was considered to be reached when we included patients from all of the sampling criteria and reached inductive thematic saturation by not gaining new themes in two consecutive interviews.[17]

Data collection

We performed face-to-face, semi-structured interviews among patients with a VLU to explore the patients' perspective in-depth. The patients were interviewed at their homes. Each interview started with the question 'As mentioned before, I am interested in your experiences concerning the development of the VLU, can you start from the beginning?'. We used an interview guide with the following topics: advice to others at risk for developing a VLU, preventing the VLU, looking back: change of actions in the past with current knowledge, needs before the VLU developed and self-management. The topics are compiled by literature and revised by the co-authors. Interviews with a duration of 24-58 minutes were conducted and recorded digitally in the period of November 2016 until July 2017. After recording an interview A.M. transcribed the interviews verbatim using a transcription protocol[18] and replaced all identifiable information.

Data analysis

We used the narrative approach to thematically analyse the key elements of the events the patients experienced in the development of their VLU. The narratives of the patients were rewritten into a chronological order where we focused on what was said rather than how it was said.[19,20] The thematic analysis was performed in five stages: (i) A.M. and M.W. summarised the interviews highlighting the tentative themes (and check for saturation). (ii) A.M., M.W. and two research assistants used an inductive approach to code the first four transcripts. (iii) A.M. organised the codes and themes and M.W. checked the coding template. (iv) A.M. reconstructed all transcripts in a chronological order and for each patient a timeline of events was created using the patients' wording. (v) The coding template was continued using an iterative process[21] of revising the data (individual narratives, themes and subthemes from all narratives) and discussing the themes and subthemes with M.W. in perspective of the research objective. Finally, the themes and sub-themes were dis-

cussed and revised with all authors. We used MAX-QDA 12© for qualitative data management.

Ethics

The study was approved by the Medical Ethics Committee of the University Medical Centre Utrecht The Netherlands (registration number 16-744/C). Patients were given written and verbal information about participating in the study before they signed informed consent. The patient names were replaced by pseudonyms to ensure anonymity of patient data.

Results

Thirteen patients with a VLU were approached to participate in this study. One participant was not able to participate due to hospitalisation of the spouse, and another participant reported no reason. Eleven patients completed the interviews. Nine patients were over 65 years old. We recruited five males and six females. Most patients had a first VLU and were recruited in primary care. Table 1 shows an overview of the patient characteristics.

Patient*	Age (years)	Gender	Recruited from	Ulcer	Time of the current ulcer in months	Index leg
Leroy	43	Male	Dermatologist	First	2	Right
Agnes	50	Female	Dermatologist	Recurrent	>12	Both
Wilma	68	Female	General Practitioner	First	3	Right
Jack	68	Male	Dermatologist	Recurrent	24	Both
Doris	70	Female	General Practitioner	Recurrent	4 and >12	Both
Irene	72	Female	Dermatologist	Recurrent	>12	Both
Frank	71	Male	Home care	First	>12	Right
Earl	75	Male	Dermatologist	First	24	Right
Henry**	77	Male	General Practitioner	Recurrent	6	Right
Grace	78	Female	Home care	First	5	Right
Rose	89	Female	General Practitioner	First	18	Left

Table 1: Patient characteristics

** Patient names are replaced by pseudonyms to ensure anonymity of patient data. ** the recording device failed to record, so this interview does not contain quotes but notes from the researcher (AM).*

Key-themes

Four key-themes emerged from the narratives of the patients on the progression of CVD towards a first VLU. The key-themes Comorbidity, Mobility, Work & Lifestyle, and Acknowledgement of CVD and the connections the patients made between them are presented in Figure 1. To elaborated on the concepts of the key-themes the coding tree is presented in Appendix 1.

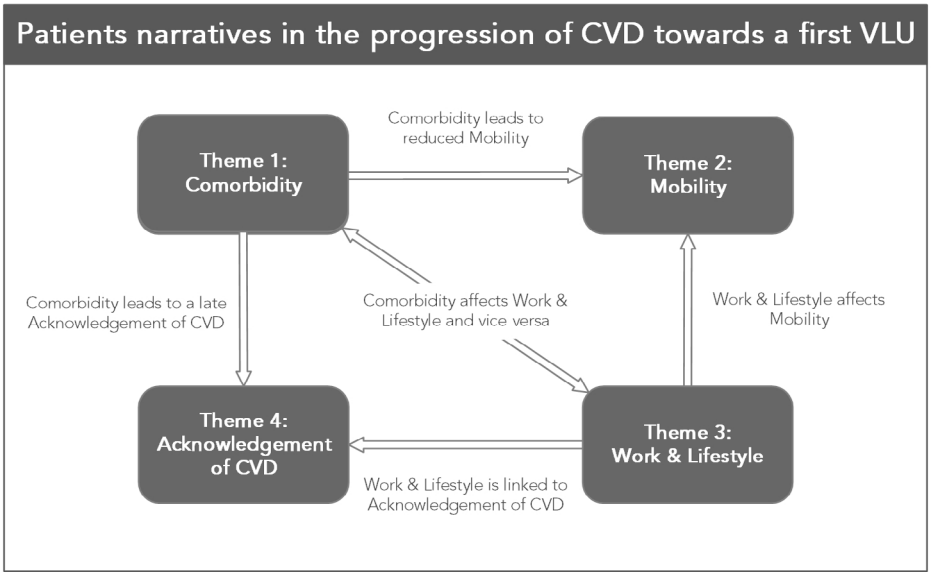

Figure 1: Key-themes

CVD = Chronic Venous Disease, VLU = Venous Leg Ulcer

A series of events

The patients narrated on a series of events in which all themes came forward. Subsequently, patients connected the themes in their narratives to the progression of CVD towards a first VLU. To illustrate the patients' narrative as a whole we present one case which is representative for all of the cases included in this study. Table 2 shows that Leroy started the narrative with an event related to key-theme 3: Work & Lifestyle that started years ago and continued for at least 20 years. He also narrated on several Comorbidities (Theme 1) that led to a reduced Mobility (Theme 2) prior to the development of the VLU. Furthermore, he narrated on the Acknowledgement of CVD (Theme 4) in which he did not act upon recognising the symptoms because he prioritised the Comorbidity (Theme 1). Finally, he had a late response to the actual development of the VLU because of events related to Work & Lifestyle

(Theme 3). After the VLU developed the Acknowledgement of CVD (Theme 4) also affected his Work & Lifestyle (Theme 3). However, this last event is not within the scope of this study as it occurs after the VLU developed.

Year	Events	Theme
1992 – present	Assembly line job - standing all day	Work & Lifestyle – Mobility
2010	Varicose veins - oedema - advice compression stockings – non-adherence to advice	Acknowledgement of CVD
2015 – 2016	Arthritis in the knee – trouble walking	Comorbidity – Mobility
2016	Gout in the ankle – trouble walking	Comorbidity – Mobility
2016	Atrophie blanche – urgent advice take action – comorbidity had priority (so no action taken)	Comorbidity – Acknowledgement of CVD
2017	VLU developed - no action - work had priority	Work & Lifestyle – Acknowledgement of CVD
2017	Incapacitated because of the VLU (outside of the scope of this study)	Acknowledgement CVD – Work & lifestyle

Table 2: The timeline of Leroy showing the different events and corresponding themes, and the connections he made between the themes

Theme 1: Comorbidity

Patients narrated on their comorbidities and sometimes directly linked these co-morbidities to the development of a VLU. In some patients the comorbidity was a recent event like Grace:

> *"No idea, I really have no idea. Because I thought I lived healthy and everything. I exercise and have enough fresh air. So I think it's the stress (few months). That's the only thing I can explain, or eh what I think is the cause."*

While others mentioned comorbidities that happened many years ago, like Rose who suspected the multiple erysipelas infections that happened over 20 years ago to be related to the development of oedema and the VLU. Jack and Wilma also mentioned stress and multiple erysipelas infections, however they did not clearly link these comorbidities to the progression of CVD into a VLU.

Patients also narrated on the connection between comorbidity and the other key-themes. Comorbidity was in some cases the cause of a change in Work & Lifestyle,

mostly as a consequence of reduced Mobility. However, none of the patients linked these events directly to the progression of CVD into a VLU like Jack:

> *"I was a truck driver before yes.. in, let's see, about 30 years ago I ended up in the wheelchair permanently." (after surgery for comorbidity)*

Furthermore, comorbidity was connected to reduced mobility which Henry linked to the progression of CVD to a VLU. He told that since he developed peripheral arterial disease he became less active, but he knows walking is important for the veins and the oedema. Others also mentioned reduced mobility after comorbidity, however they did not directly link the reduction in mobility to the development of the VLU. This varied from comorbidities that happened years ago like the bicycle accident that caused Grace to shuffle instead of walking to more recent events like Wilma:

> *"yes and the trouble with walking they (doctors) suspect it is because it (hip) is worn. … So now since January (6 months ago) they placed the stair elevator."*

In addition, Comorbidity was connected to Acknowledgement of CVD. For Grace and Doris their comorbidity led to a possible incorrect interpretation of CVD symptoms which led to disregarding the symptoms instead of acting upon them. Doris explained she had vitiligo on her arms and that she was unsure whether or not the white spots on her ankles were also vitiligo (possible atrophie blanche). Grace connected the possible lipodermatosclerosis which she had on both lower legs to the hematomas she had on her left leg from the bicycle accident she had nine years ago. Even when the VLU appeared patients did not always linked this wound to CVD like Frank (who had varicose veins and oedema):

> *"The accident caused the large wound, and that wound did not heal because of the piece of bone sticking out. But now there are a few new smaller ones (wounds) that do not heal either, and those are just the skin. And that is eventually the problem that stayed."*

Theme 2: Mobility

Mobility was mentioned by patients as events related to their physical activity (e.g. sports, work, walking aid) and events related to a reduced body function (e.g. limping, shuffling, divergent foot position). Mobility was mentioned by all patients, however they never linked it directly to the progression of CVD towards a first VLU. For example, Rose mentioned she became less active in the past 10 years because of her age, however she did not link this reduced mobility to the development of a VLU. Grace and Frank mentioned their sports career and how they had ended this

over 20 years ago. However, they also did not link this active lifestyle or the subsequent reduction in physical activity to the progression of CVD towards a first VLU. When mobility was linked to the progression of CVD to a VLU the patients always connected Mobility to either Comorbidity or Work & Lifestyle.

Theme 3: Work & Lifestyle

Patients narrated on Work & Lifestyle and linked this directly to the progression of CVD towards a first VLU in some cases. When narrating on Work & Lifestyle events, patients always mentioned events that lasted for over 20 years. For example, Rose speculated on wearing heels all her life and the negative effects on her legs, whereas Earl guessed the long-term use of tobacco and alcohol did not have a positive effect either.

Patients also narrated on the connection of Work & Lifestyle with Mobility and the Acknowledgement of CVD. Doris connected Work & Lifestyle to Mobility in the progression of CVD to a VLU where she mentioned working in a standing occupation for over 50 years and how this could not have been good for her legs. She also mentioned her colleagues having similar complaints. Henry narrated on his length as a possible cause for the progression of CVD towards a first VLU. From his perspective the veins got worse because of his knees being bent all the time when sitting because the chairs at work were never tall enough for him. Earl on the other hand mentioned the connection between Work & Lifestyle and Mobility, but did not directly link this to the progression of CVD to a VLU:

> "*I was never a fan of walking. … and I sat a lot. Because in the weekends, making music, I would sit with my accordion two whole nights from 20:00h till 02:00h in the night. … I always wore it (the accordion) on my right leg (index leg) and the pressure of it, now that annoys me, it hurts.*"

Patients also narrated on how Work & Lifestyle was connected to the acknowledgement of CVD. Patients would reflect on why they were not compliant to compression therapy before the VLU developed like Agnes:

> *"I eh I sometimes skip the stockings when my legs are healed, when I wear pretty cloths you think no way I'm going to wear these stupid stockings."*

Patients also mentioned their body composition or related Comorbidity like diabetes type II in the progression of CVD towards a VLU. Earl and Wilma narrated on how they knew their diabetes was a cause of the slow healing of wounds and therefore also the slow healing of their VLU. Henry also mentioned that his body mass index of 30 was not helpful for his leg complaints.

Theme 4: Acknowledgement of CVD

Acknowledgement of CVD was decreased in all patients in some way. However, Agnes and Irene did acknowledge CVD as the underlying cause of the VLU and Agnes acted upon the symptoms in an early stage.

> ***Irene:*** *"Now we are with the two of us (Irene and Agnes). So you can see that it (CVD, VLU) is hereditary."*
>
> ***Agnes:*** *"Because of the bad circulation and the bad veins. That's what they (doctors) always told us (Irene and Agnes). … I was 15/16 when I got the stockings, that they (doctors) saw it wasn't going well with my legs. I went with my mother at that time."*

Other patients did not understand the underlying pathology of CVD like Jack who was permanently immobile. He was unaware of the importance of the calf muscle pump in venous function:

> *"I don't know, really I don't. Maybe the bacteria had always been in there? … Other wounds heal just fine. Only on this leg (index leg) the wounds keep appearing on the same spot, it's very strange."*

Even when the pathology was explained not all patients were adherent to compression therapy like Wilma who told her doctor she was convinced the VLU would heal just fine without compression therapy. In addition, others had a late response to the symptoms of CVD or the VLU or did not act upon this at all like Earl:

> *"I see them (varicose veins) now, but they don't bother me. … And even if I needed surgery for it I would have never done it in the army. No, I'm not a fan of doctors in general."*

The lack of acknowledgement of the CVD as the underlying cause also led to a late response when the VLU occurred. Wilma and Earl treated the VLU like a regular wound and only consulted a doctor when it kept getting worse or after the advice of others:

> ***Earl:*** *" And that's how it stayed. It had a crust and after I showered I rubbed it open again and it started bleeding again, hop, a bandage on it and done. And later I went to the pedicure and she said to me: 'You have to see a doctor.' I said what am I going to do there?*

Even when the VLU occurred and the underlying cause of CVD was known, not all patients understood the permanent chronicity of CVD and compression therapy in the progression of CVD towards a VLU:

> ***Leroy:*** *"Wish I had done it back then (stockings). Maybe I wouldn't have needed the stockings now anymore, but now I do."*

Discussion

This study shows how patients narrate on the progression of CVD into a first VLU and why, in their opinion, the VLU developed. Each narrative was a series of events that patients directly or indirectly linked to the progression of CVD into first VLU. In a narrative the conscious, subconscious and unconscious mind are involved which could have led to providing information from the sub- or unconscious mind without making a clear link of this information to the progression of CVD towards a first VLU. Patient narratives resulted in four key-themes describing their perspectives on the progression of CVD into a first VLU: (i) Comorbidity (ii) Mobility (iii) Work & Lifestyle and (iv) Acknowledgement of CVD. Most patients started their narrative decades to several years before the VLU developed with events related to the four key-themes.

A systematic review[10] on patients' experiences of living with a VLU showed that pain and compression therapy led to a reduction in mobility after the VLU developed. However, this study shows that the patients had a reduction in Mobility before the VLU developed. Patients narrated on reduced or impaired mobility that lasted for at least a decade or happened within a few years before the first VLU developed. The reduced mobility was perceived to be a result of Comorbidity or Work & Lifestyle. Most of the Comorbidities affected the lower legs like rheumatic arthritis in the knees, gout in the ankle, a divergent foot position, peripheral arterial disease, and trauma leading to a wound to the bone on the lower leg. Furthermore, events related to Work & Lifestyle such as a standing occupation, or not being a fan of walking led to a sedentary lifestyle prior to the development of the first VLU. These Comorbidities and events related to Work & Lifestyle that reduced the Mobility can be related to a reduced range of ankle motion[22] and/or an impaired calf muscle function[23] which leads to an increased ambulatory venous pressure and is therefore a risk factor in the development of a VLU. Obesity can also lead to an increased ambulatory venous pressure whereas people with obesity have a different gait and a reduced range of ankle motion compared to the non-obese.[24] In addition, obesity (BMI>30) is a known risk factor for the development of a VLU.[25-28] However, patients in this study did not directly link obesity to a reduced Mobility. A quantitative study is necessary to investigate the exact association of reduced mobility with the development of a VLU in patients with CVD. This qualitative study shows that it is important to include changes in mobility in the past as well as chronic comorbidities that impact the mobility of the lower legs in future quantitative studies on risk factors for a VLU.

Patients in this study did not acknowledge the importance of the symptoms of

CVD before the first VLU occurred and therefore did not seek medical attention. The low acknowledgement of symptoms in CVD patients was also found in a study investigating knowledge deficits in VLU patients.[14] VLU patients perceived their VLU as an acute event and the knowledge on CVD as the underlying cause of the VLU was limited.[14] The patients in the current study who did recognise their CVD symptoms before the VLU developed did not always follow-up on these symptoms because they prioritised their comorbidity or work. However, the patients were not followed-up by their Health Care Professional (HCP) either despite of the regular visits to several HCPs for their comorbidities. This is in line with research of the National Institute for health Care Excellence (NICE) in the United Kingdom (UK). The publication of the UK NICE clinical guideline for referral of VLU to a vascular specialists did not lead to a significant change in referral from primary care to specialist care.[29] The current study illustrates that there still is a need for more awareness concerning CVD and its consequences. More awareness amongst the public as well as amongst HCPs should lead to an increase in early recognition, timely treatment and possible prevention of a VLU in CVD patients preserving their quality of life. A first start would be to provide easy accessible information and prevention on the progression of CVD (into a VLU) similar to the information and prevention strategies of other chronic wounds like the diabetic foot ulcer[30] and pressure ulcers[31] with medical follow-ups and (guidance in) lifestyle interventions.

Strengths and limitations

We included patients with different characteristics (purposive sampling) to enhance generalisability of the results. The patients with recurrent VLUs narrated more on the periods between the recurrences and the healthcare they received in the past. This made it more difficult to create a timeline and to distinguish their own narrative in the development of the first VLU and the information they received from several healthcare professionals over the years. In one case the recording device failed to record. This interview is analysed based on the notes of the researcher which is less extensive than analysing the full transcript. However, notes were made during and directly after the interview, so most of the narrative of the patient was captured. The narrative approach in the interviews makes the interviewer co-author of the story in the here-and-now.[32] However, A.M. created a safe and non-judgemental environment for patients to speak freely and let the patients lead the conversation by asking open ended questions. All patients were asked how they experienced the interview and they all reflected on the interview as being very pleasant. Finally, to reduce researcher bias, researchers and research assistants from different backgrounds were involved in all stages of the data analysis.

Conclusion

A reduction in Mobility as a result of Comorbidity and Work & Lifestyle occurred before the VLU developed. Patients in this study did not recognise symptoms of CVD and did not acknowledge the chronicity of CVD. Therefore, Health Care Professionals should be aware of reductions in mobility and the knowledge deficit in patients with CVD. Patient education, and follow-up of patients should be imbedded in the care for patients with CVD to prevent or take early action in the development of a first VLU.

Acknowledgement

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Appendix

Coding tree including key-themes, sub-themes and corresponding codes from the patients narratives on the progression of CVD into a first VLU (in no particular order)

Key-theme	Sub-theme	Codes
Theme 1 Comorbidity	Trauma	Wound until bone on lower legs / Surgery lower legs
	Rheumatic diseases	Spondylitis / Rheumatic Arthritis / Gout / Fibromyalgia / Arthroses
	Vascular diseases	Hypertensions / Peripheral arterial disease / Transient Ischemic Attack / Vascular Malformation
	Infection diseases	Polio / Erysipelas
	Other	Vitiligo / Diabetes type II (slow wound healing) / Stress
Theme 2 Mobility	Reduced foot movement	Polio / Orthopaedic shoes
	Permanent immobility	Spondylitis Surgery
	Reduction in mobility (gait, shuffling)	Bicycle accident / Transient Ischemic Attack / Kyphosis
	Physical activity reduction (sports)	Age / Multiple ruptures of ankle ligaments / gastrocnemius muscle / Accident affecting the lower legs
	Low Physical Activity	Work / Hobby / Does not like walking
	Walking aid	Transient Ischemic Attack / Accident affecting lower legs
Theme 3 Work & Lifestyle	Standing occupation	Assembly line / Counter desk
	Sitting occupation	Desk job
	Walking job	Managing function / Catering business
	Retirement	Change in lifestyle / Change in mobility
	Length and weight	Tall / Overweight / Obesity
	Hobbies	Sports / Playing music instrument / Reading
	Attitude	Appearance / Priorities
	Smoking and alcohol	-
	Shoe wear	High heels / no high heals

Theme 4 Acknowledgement of CVD	Recognition of symptoms CVD	Not recognising CVD symptoms / not recognising VLU
	(Late) Response to symptoms CVD	Priority of work / Priority of comorbidity
	Therapy (non) compliance	Need for compression therapy / Compliance only after VLU / No compliance
	Understanding of (chronicity of) CVD	Limited understanding of CVD and Symptoms / Limited understanding of chronicity of CVD

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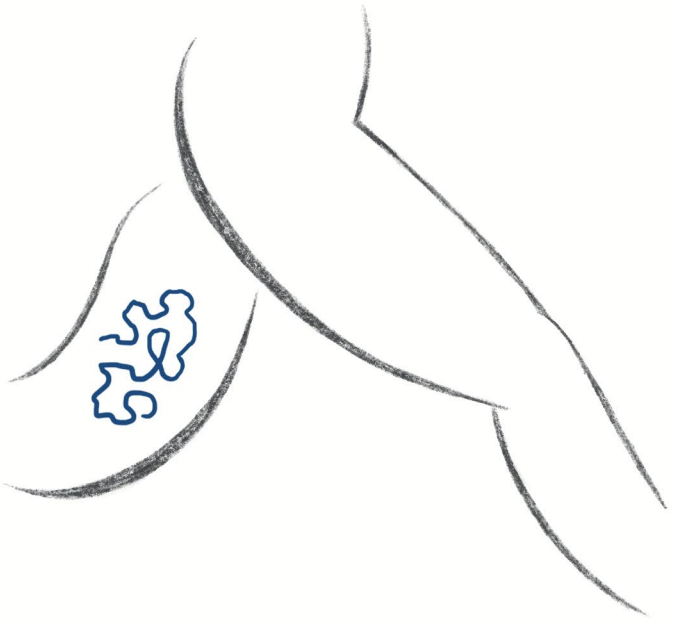
CHAPTER THREE



A SYSTEMATIC REVIEW ON RISK FACTORS IN DEVELOPING A FIRST TIME VENOUS LEG ULCER

SUMMARY

Venous Leg Ulcers (VLU) occur in about 1% of the Western population. A VLU takes three to twelve months to heal, it recurs often, and it has a negative impact on the quality of life. The risk factors for the development of a first VLU are not well-understood and prevention of a first VLU therefore remains underappreciated. The aim of this study is to identify risk factors for developing a first VLU in adults (aged >18 years) by searching the literature. We searched the Cochrane Library, Pubmed, Cinahl, and Narcis to identify studies that investigated risk factors in developing a VLU. The last search was performed in January 2018. Two reviewers independently reviewed the abstracts and full-text articles, and assessed the methodological quality of the included studies. Results of studies using duplex scanning, and comparing participants with and without VLUs were included in the qualitative analysis. Where possible a quantitative meta-analysis was conducted. We found five studies that investigated the relation of several risk factors with VLU development. The methodological differences of the studies made it impossible to perform a quantitative analysis. The risk factors: higher age (four studies), higher Body Mass Index (four studies), low physical activity (four studies), arterial hypertension (four studies), deep vein reflux (three studies), deep venous thrombosis (three studies) and family history of VLU (three studies) were significantly associated with a VLU in the majority of the studies. To what extent they influence the development of a VLU remains unclear because of the limited number of studies that investigated the association of these risk factors with VLU development, and the heterogeneity of these studies. Further studies are needed to confirm the association of these risk factors with the development of a VLU and to explore overweight and low physical activity in more detail.

As published

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A systematic review on risk factors in developing a first time Venous Leg Ulcer

Introduction

Chronic Venous Disease (CVD) is very common in the Western population, with up to 40% of the people showing symptoms.1 CVD patients develop symptoms like: Varicose Veins (VV), oedema, lipodermatosclerosis, atrophy blanche, and eventually a Venous Leg Ulcer (VLU). An open or healed VLU exists in approximately 1% of the general population.2

CVD progresses slowly, and not all patients develop all symptoms in the same order, or end up with a VLU. It might take years or even decades for CVD to progress to a first VLU.3,4 Because of the normally slow progression and the relatively low incidence population studies combine skin changes (C4) and active or healed VLU's (C5-C6) in one category (CEAP-classification5). The Vein Consult Program6 showed that 'severe CVD'(C4-C6) significantly increases with age. Two population studies in Spain7 and in Belgium and Luxembourg8 showed that age, Body Mass Index (BMI), a positive family history of CVD and the number of pregnancies in females are all correlated with the C-class of the CEAP classification. The low Physical Activity (PA) and smoking groups showed a higher percentage of 'severe CVD'. However, a population study on the risk factors involved in developing a VLU (C5-C6) specifically was not found.

Although the incidence of a VLU is relatively low, the burden of this invasive chronic disease is high due to a negative impact on the Quality Of Life (QOL).9 Both generic and disease specific QOL of patients with a VLU is significantly lower compared to other stages of CVD.10,11 This denotes the importance of VLU prevention in CVD patients.

VLUs normally heal within six months in most patients but in some patients healing takes up to a year or longer.12 After healing a VLU recurs within a year in about 20% of the patients. This percentage increases over time, and in some patients the VLU recurs even more than once.13 A systematic review on compression hosiery to prevent recurrence showed that compression hosiery can be a protective factor in the recurrence of a VLU.14 Previous clinical studies showed that risk factors for VLU recurrence are: larger ulcer size, longer ulcer duration and a history of multiple ulceration periods.15-17 However, the risk factors for the development of a first time VLU are not well-understood and prevention of a first VLU in patients with CVD

therefore remains underappreciated in general practice.

The aim of this systematic review is to identify risk factors for developing a first time VLU in adults (aged >18 years) with CVD by searching the literature.

Materials and methods

We report this systematic review according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines for reporting systematic reviews and meta-analysis of observational studies.18

Search strategy. To identify eligible studies on risk factors for developing a VLU we performed systematic searches in four databases: PubMed, Cinahl, The Cochrane Library and Narcis. The last search was performed in January 2018. First, we used the following search words and their synonyms in MeSH terms and free text words: Chronic Venous Disease OR Venous Leg Ulcer AND Prognosis OR Risk Factor. Our full PubMed search is shown in Appendix 1. We screened the references of eligible studies to identify other studies on this topic.

Eligibility. Studies written in English, Dutch or German were considered eligible. The in- and exclusion criteria are presented in Table 1. We included studies that diagnosed participants with duplex scanning (clinical gold standard) or Ambulatory Venous Pressure (AVP) measurement because this is the gold standard to diagnose venous disease and therefore identify VLU. We excluded non-systematic reviews because it is unclear which inclusion and exclusion criteria they used. We also excluded case-studies because of their low level of evidence. We did not apply in- or exclusion criteria on the risk factors in order to create a complete overview of all the factors related to Chronic Venous Disease (CVD) that might play a role in the development of a VLU.

Inclusion criteria	Exclusion criteria
Diagnosis by duplex scan or Ambulatory Venous Pressure	Other diseases (e.g. cardiovascular disease, arterial disease, cerebrovascular disease)
Studies that include risk factors for developing a VLU	Studies that investigate a specific treatment for CVD/VLU
Studies that compare CVD patients without a VLU (in the past) to (healed) VLU patients (aged >18)	Studies focusing on VLU recurrence as an outcome
Experimental studies, observational studies, systematic reviews and meta-analysis	Studies that investigated "severe CVD" as C4-C6 (including skin changes)
	Non-systematic reviews and case-studies

Table 1: In- and exclusion criteria

VLU = Venous Leg Ulcer, CVD = Chronic Venous Disease

Study selection. Refworks© (version 2.0) was used to screen all references. First, the first author (Meulendijks) screened all duplicates on author and title. Second, Meulendijks performed a quick screening of all remaining titles and abstracts using the eligibility criteria as previously described. Then, the first and the second author (Meulendijks and de Vries) independently reviewed in detail the abstracts and full-text articles of the remaining studies. The findings on methodological quality and data extraction were discussed until consensus was reached. Both reviewers resolved any differences of opinion on whether or not to include a particular study by consulting a third reviewer (Neumann).

Data analysis. Characteristics of each included study were extracted using a standard form (author, publication date, disease, design, study population, risk factors studied, outcome tool used, statistics, etc.). Subsequently, data on the association of possible risk factors with developing a VLU were extracted from the included studies e.g. BMI, age, Physical Activity (PA), smoking, arterial hypertension, arthritis, etc. An association was considered statistically significant at $P < 0.05$. When the data in an article were not sufficient for quantitative analysis, the authors of the articles were contacted via e-mail to request additional data. Afterwards, both Meulendijks and de Vries assessed the methodological quality of the included studies using the Newcastle-Ottawa Scale (NOS). Results of studies comparing participants with and without VLUs were included in the qualitative analysis. If a multivariate analysis was conducted in multiple included studies, we performed a quantitative meta-analysis.

Results

The search results are presented in a PRISMA flow diagram (Fig. I)19. The search results included a large number of studies on other diseases or progression of venous insufficiency in general e.g. Cerebro Vascular Disease, Varicose Vein (VV) development and pathophysiology of venous insufficiency. These studies were excluded based on their titles. Amongst the studies excluded on language, only one study might have been eligible based on the title and abstract.20

Eventually, five studies, two case-control21,22 and three cross-sectional studies23-25, were included in the qualitative synthesis. Heterogeneity of the studies prevented us from doing a meta-analysis. We contacted the researchers of some of the included studies to request additional data for the quantitative synthesis, but received no additional data.

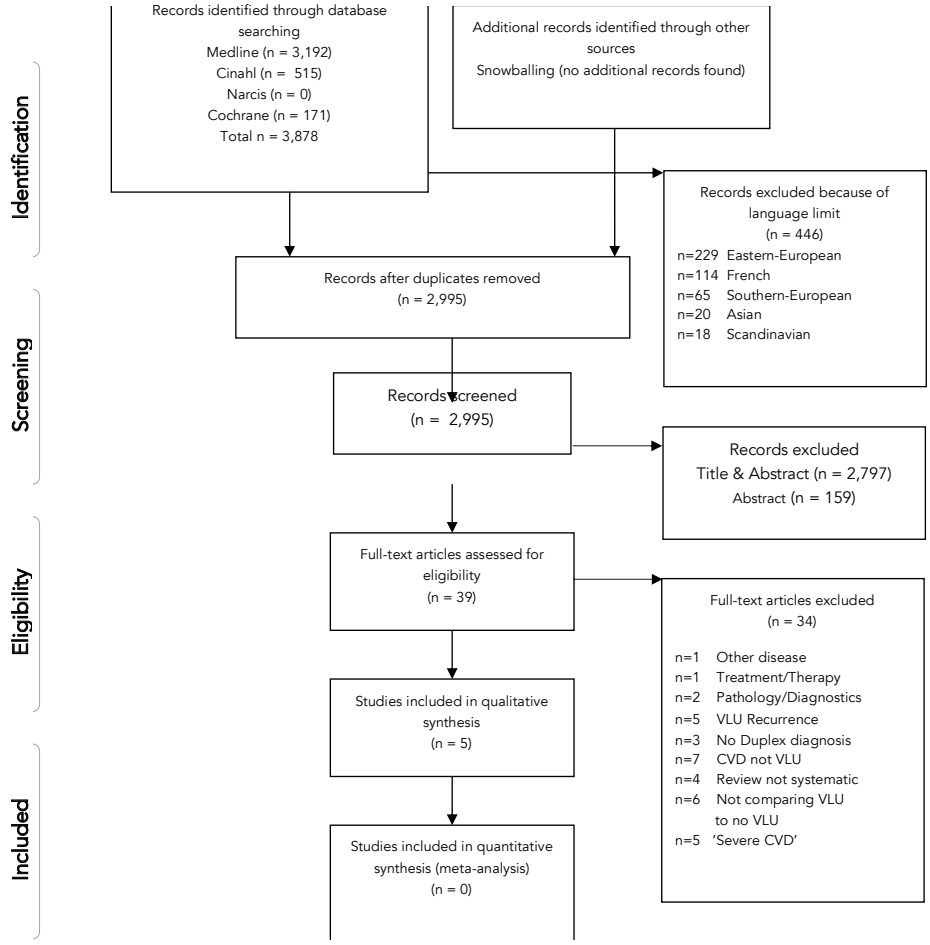

Figure 1: PRISMA flow diagram study selection

CVD = Chronic Venous Disease, VLU = Venous Leg Ulcer, 'severe CVD' includes skin changes and Venous Leg Ulcers as one category (C4-C6)

Study quality.

The characteristics of the included studies are presented in Table 2. All studies recruited their participants from a hospital setting or primary care. In all studies the mean age was >50 years (except for the controls in one study22) and the gender was predominantly female (>50%).

The NOS-score on methodological quality is presented in Table 3. All studies used questionnaires or structured interviews to measure the exposures in the same way for both cases and controls. Only one study mentioned blinding of the researcher for case or control status during the interviews. All studies also had representative cases (all C5-C6 patients) and con-

First Author (year)	Country	Recruitment	Study design	Comparison*	Sample size (N VLU patients)	Statistics
Robertson et al.[19]	Scotland	Vascular Laboratory and various general practitioners	Case-control	C5-C6 vs C2-C4	240 (120)	Stepwise Logistic Regression (BMI and blood pressure continuous)
Dzieciu-chowicz et al.[21]	Poland	Vascular Outpatient Clinic	Cross-sectional	C5-C6 vs C2-C4	466 (114)	Analysis of variance (ANOVA)
Vlajinac et al.[22]	Serbia	Various Venous Specialists	Cross-sectional	C5-C6 vs C0s-C4	1679 (278)	Stepwise Logistic Regression (BMI and blood pressure categorical)
Matic et al.[23]	Serbia	Dermato-venereological clinic	Cross-sectional	C5-C6 vs C1-C4 vs no CVD	162 (55)	Univariates analysis (Multivariate Logistic Regression not shown in article)
Abelyan et al.[20]	Armenia	Tertiary clinic Surgery department	Case-control	C5-C6 vs C1-C4	160 (80)	Logistic Regression based on predetermined hypotheses† (BMI and blood pressure categorical)

Table 2: Study characteristics

**comparison using the C of the CEAP classification – Clinical, Etiological, Anatomical, Pathological classification. † Hypothesis: deep venous reflux, history of leg injury, post-thrombotic syndrome, physical inactivity are risk factors for VLU. BMI = Body Mass Index, CVD = Chronic Venous Disease, VLU = Venous Leg Ulcer*

trols that had no VLU history. Furthermore, all studies used hospital or care-related controls and no population controls. Two studies22,23 did not perform duplex scanning during the study to ascertain the underlying venous pathology. These studies used medical records with data on duplex scanning instead. Moreover, in each of the included studies the comparability of cases and controls differed. Some studies21,22,25 adjusted for age and gender in a multi-

variate analysis, while another study conducted a univariate analysis only23, or did not show the multivariate analysis24. In addition, one study25 did not report a non-response rate, two studies23,24 used medical records only so non-response was not possible; in one study21 there was a rate-difference of 17% in the non-respondents and in one study22 a large amount of cases and controls could not be contacted because of missing phone numbers.

	Case definition	Representativeness of cases	Selection of controls	Definition of controls	Comparability	Ascertainment of exposure	Same ascertainment case-controls	Non-response rate
Robertson et al.19	+	+	-	+	+	+	+	-
Dzieciuwicz et al.21	-	+	-	+	-	?	+	+
Vlajinac et al.22	+	+	-	+	+	?	+	?
Matic et al.23	+	+	-	+	-	?	+	+
Abelyan et al.20	-	+	-	+	+	?	+	+

Table 3: Risk of bias summary - review authors' (Meulendijks, de Vries) judgements on each risk of bias item for the included studies using the NOS-scale.

+ high quality, – low quality, ? not specified in the article

Risk factors

In Table 4 we provide an overview of the risk factors, and whether they were statistically significant or not in a univariate or multivariate analysis. Table 5 shows the possible risk factors that yielded in inconclusive results, and Table 6 shows the possible risk factors that were investigated in only one of the included studies.

Age and gender

In all studies, age and gender were investigated, matched for, or controlled for in VLU patients compared to CVD <C5 patients. In three studies age was significantly higher in the VLU group compared to age in the CVD <C5 group.22,23,25 One

	Robertson et al.19	Vlajinac et al.22	Matic et al.23	Abelyan et al.20	Dzieciuchowicz et al.21
Outcome measure	OR (CI), Group diff. % (VLU / non VLU)	OR (CI) Group diff. % (VLU / non VLU)	OR (CI), Group diff. % (VLU / VV / non VLU)	OR (CI)	Group diff. (VLU / non VLU)
Age	Matched	1.03 (1.02-1.04)†	Age 63 / 59 / 60	1.13 (1.09-1.18)*	Age 64 / 53*
Gender	Matched	M 1.45 (1.07-1.95)†	F 76% / 61% / 62%	F 0.47 (0.21-1.02)	M 22% / 26%
Higher BMI / Overweight	1.08 (1.01-1.15)†	1.44 (1.15-1.81)†	Mean BMI 31 / 28* / 26*	1.26 (1.13-1.40)*	
Blood pressure / Arterial hypertension	1.03 (1.00-1.05)	1.47 (1.07-2.02)†	69% / 60%* / 46%*	5.22 (2.64-10.30)*	
PA: Regular exercise	0.43 (0.20-2.93)			0.26 (0.08-0.90)†	
PA: Regular walking	0.29 (0.11-0.77)*				
PA: Low exercise		2.21 (1.51-3.23)†			
PA: Hours Standing			76% / 65% / 53%*	1.39 (1.17-1.62)*	
PA: Hours Sitting				1.32 (1.08-1.61)†	
Reflux in the deep veins	2.82 (1.03-7.75)†	8.29 (4.60-14.95)†		3.58 (1.23-10.31)†	
DVT / PTS	28% / 8%*	3.17 (2.57-5.26)†		14.90 (3.95-56.19)†	
Family history of VLU		3.68 (2.57-5.26)†	38% / 14%* / 2%*	2.85 (1.04-7.79)*	
Family history of DVT		10% / 7%*		2.34 (1.13-4.86)*	

Table 4: Factors associated with the development of a Venous Leg Ulcer

*OR = Odds Ratio, CI = Confidence Interval, PA = Physical Activity, *significant difference / univariate analysis at P0.05, † significant in multivariate analysis at P0.05, + significantly associated with VLU development, VLU = Venous Leg Ulcer, DVT = Deep Vein Thrombosis, PTS = Post Thrombotic Syndrome, BMI = Body Mass Index, M = Male, F = Female, ---- not studied in this article*

study24 found no significant difference in age between the VLU group and CVD <C5 group. For male gender, one study25 found a significant association with developing a VLU, while in three other studies22-24 there was no significant difference between the number of males in the VLU group compared to the CVD <C5 group.

Reflux

Reflux in the deep veins was significantly associated with VLU development in three studies.21,22,25 Another study21 specifically showed an association of popliteal vein reflux and the development of a VLU.

Deep vein thrombosis

Deep Vein Thrombosis (DVT) or the post-thrombotic syndrome are significantly associated with developing a VLU in three studies.22,24,25 Another study21 showed a significantly higher occurrence of DVT amongst VLU patients compared to CVD <C5 patients, but did not find an association in the multivariate analysis.

BMI

Higher BMI was significantly associated with developing a VLU in three studies.21,22,25 One study25 specifically showed the association of overweight (BMI 25-29) and obesity (BMI>30) with developing a VLU. A fourth study24 showed a significantly higher BMI amongst VLU patients compared to CVD <C5 patients.

Physical Activity (PA)

Regular PA is associated with protecting against VLU development in one study22, and in another study21 regular PA was significantly more present amongst CVD <C5 patients compared to VLU patients. In the latter, the comparison was not significant in the multivariate analysis. In addition, low PA is significantly associated with VLU development in one study.25 Moreover, one study22 also showed an association of increased average standing time and increased average sitting time with the development of a VLU. A fourth study24 showed that a standing occupation was significantly more frequent amongst the VLU patients compared to the CVD <C5 patients.

Arterial hypertension

The impact of arterial hypertension was investigated in four studies.21,22,24,25 One study21 found a significant association of higher blood pressure with developing a VLU, whereas two other studies22,25 found a significant association of

arterial hypertension with developing a VLU (in univariate and multivariate analysis respectively). In the fourth study24 arterial hypertension occurred significantly more frequent amongst VLU patients than in CVD <C5 patients.

Family VLU and family DVT

VLU or DVT in the parents was significantly associated with VLU development in one study.25 Another study22 found a significant association of family VLU and family DVT with VLU development in a univariate analysis. A third study24 found that a VLU in the parents of VLU patients occurred significantly more frequent compared to the parents of CVD <C5 patients.

	Robertson et al.19	Vlajinac et al.22	Matic et al.23	Abelyan et al.20
Outcome measure	OR (CI), Group diff. (VLU / non VLU)	OR (CI) Group diff. (VLU / non VLU)	OR (CI) VV / non VLU Group diff. (VLU / VV / non VLU)	OR (CI)
Ever smoked	1.99 (1.16-3.42)*		22% / 23% / 28%	1.12 (1.01-1.25)*
Skeletal / joint diseases	18% / 11%	1.42 (1.03-1.96)*		2.33 (1.01-5.39)*
Leg injury	40% / 35%			6.66 (3.00-14.77)†
Family VV		49% / 51%	89% / 70% / 30%*	0.51 (0.26-1.00)
Diabetes		1.69 (1.19-2.39)*	11% / 9% / 10%	Ex.
Peripheral Arterial Disease		5% / 2%	2.71 (1.18-6.22)* / 3.38 (1.13 – 10.12)*	Ex.
Number of children			Mean 2 / 2 / 2	2.07 (1.30-3.28)

*Table 5: Factors with contradictory results concerning the risk of developing a Venous Leg Ulcer OR = Odds Ratio, CI = Confidence Interval, VV = Varicose Veins, Ex. = Excluded, *significant difference or univariate analysis at P0.05, † significant in multivariate analysis at P0.05, ---- not studied in this article*

Risk factors with contradictory results.

Contradictory results were found for smoking21,22,24, diabetes24,25, peripheral arterial disease24,25, skeletal / joint diseases21,22,25, leg injury21,22 and the

number of children for women. Moreover, VV in the family was associated with protecting against the development of a VLU in one study22, it was significantly more frequent in VLU-patients compared to CVD <C5 patients in another study24 and it was not significantly associated with developing a VLU in a third study25.

Risk factors investigated in only one of the studies.

The factors Chronic Obstructive Pulmonary Disease (COPD)25 and skin changes (C4)21 were both significantly associated with VLU development. The factor normal ankle range of motion was associated with protecting against developing a VLU.21 Furthermore, the factors phlebitis21, heart disease25, renal disease25, malignant disease25, constipation25 and oral contraceptives24 were not significantly associated with developing a VLU.

	Robertson et al.19	Vlajinac et al.22	Matic et al.23
Outcome measure	OR (CI), Group diff. (VLU / non VLU)	OR (CI) Group diff. (VLU / non VLU)	OR (CI) VV / non VLU Group diff. (VLU / VV / non VLU)
Sufficient venous calf muscle pump	0.96 (0.92-0.99)†		
Sufficient dorsiflexion of index leg	0.88 (0.81-0.97)†		
Lipodermatosclerosis	8.90 (1.44-54.8)†		
Corona Phlebectatica	4.52 (1.81-11.3)†		
Dermatitis	2.87 (1.12-7.07)†		
Phlebitis	37% / 28%		
Family history of oedema		36.7% / 31.5%*	
Heart disease		25.9% / 13.8%	
Renal disease		4.0% / 1.4%	
Malignant disease		4.3% / 3.6%	
Inflammatory bowel disease		1.1% / 1.3%	
Chronic obstructive pulmonary disease		2.56 (1.53-4.28)	
Oral Contraceptives			26% / 29% / 42%

*Table 6: Risk factors for developing a Venous Leg Ulcer studied in only one of the included studies OR = Odds Ratio, CI = Confidence Interval, *significant difference or univariate analysis at P0.05, † significant in multivariate analysis at P0.05, ---- not studied in this article*

Discussion

We aimed to identify risk factors associated with the development of a first VLU in patients with CVD. We identified several risk factors that play a role in developing a first VLU: higher age, deep vein reflux, DVT, higher BMI, low PA, arterial hypertension, and family VLU. However, it remains unclear which role these factors play in developing a VLU and to what extent they influence the development of a VLU due the cross-sectional designs and heterogeneity of the included studies. In addition, four out of five studies are conducted in eastern European countries where the incidence of CVD is higher compared to western European countries.6 Therefore, the results may not be accurate for the whole of Europe or other continents.

The risk factors deep vein reflux and DVT point out the role of CVD as the underlying pathology of the VLU. Two studies comparing patients with and without DVT support this pathway as they show significantly higher percentages of patients with VLUs in the DVT group.26,27 The involvement of CVD would also explain higher age as a risk factor since CVD deteriorates over time according to two large population studies.6,28 Yet, higher BMI and low PA indicate that lifestyle factors are also involved in VLU development.

The included studies investigated different risk factors, made different comparisons, used different measurement tools, or used different statistics. For example, the study of Vlajinac (2014) analysed BMI as a categorical variable, while the study of Robertson (2009) analysed BMI as a continuous variable. The study of Abelyan (2017) added BMI as a confounder in the multivariate analysis and did not show the Odds Ratio of the multivariate association of BMI with VLU development. These differences made it impossible to conduct a meta-analysis or compare the results quantitatively.

However, BMI was significantly associated with having a VLU in all included studies measuring BMI. In addition, three studies comparing participants with overweight (BMI 25-30) and obesity (BMI >30) to participants without overweight (BMI<25) showed significantly higher percentages of VLUs in the overweight/obesity groups.29-31

Another issue regarding the heterogeneity of the included studies involved differences in risk factor definitions. For example, the study of Abelyan (2017) divided Physical Activity (PA) in two categories (regular exercise ≥5 days a week, non-regular exercise) and included sitting and standing time. The study of Robertson (2009) divided PA in four categories (nil, light, moderate and strenuous) and included former PA and daily activity. The study of Vlajinac (2014) included 'sports' and 'walk-

ing' as PA categories. However, all included studies point in the same direction suggesting that inactivity is a risk factor for the development of a VLU and regular PA might protect against VLU development.

Lower PA can lead to an increased venous pressure and a decreased venous outflow because of a decreased calf muscle pump function. Lower PA is therefore an important factor to address in clinical practice, however it is difficult to measure because of the lack of standardised and easy to use measurement tools. In addition, people who are overweight or obese generally have lower levels of PA. Therefore, measuring BMI as standard practice in patients with CVD could be an easy to use and reliable measurement tool to measure the risk of BMI as well as PA.

Theoretically, a prospective cohort is preferable to study the risk factors in VLU development. This cohort should be done to find a causal relationship of the risk factors for VLU development, lasting at least 25 years, and including approximately 320,000 participants, given the prevalence of VLU being 0.3% per year.2 However, this design is not feasible because of the large number of participants and the long duration of the study. Instead, a case-control study using first-time VLU cases and CVD <C5 controls would be more feasible. In such a study cases and controls should be matched on age and gender to exclude these confounders. In addition, duplex scanning or AVP measurement should be used to avoid misclassification of the cases and controls. Finally, the case-control study should use common, validated measurement tools to compare the results to other studies and improve reproducibility (e.g. BMI and hip to waist ratio, accelerometers for PA etc.).

Study limitations.

We excluded studies that combined C4-C6 patients as one category. We also excluded studies which did not use duplex scanning, the gold standard in practice, to diagnose CVD. These exclusion criteria led to exclusion of a few studies that could have been relevant for this review. Nevertheless, the studies which combined C4-C6 would lead to less valid outcomes since C4 has a higher prevalence compared to C5/C6 and not all patients progress from C4 to C5/C6.6 In the studies not using duplex scanning (patient- or physician -reported, based on clinical features only), misclassification could have occurred because some leg ulcers might have other causes than venous insufficiency. In addition, language bias might have occurred due our language search limits, although only one possibly eligible study was identified.

One of the strengths of this review is that we did not predefine risk factors in the search string. This open approach led to a broad search to include studies on all

possible risk factors related to developing a VLU in patients with CVD. In addition, two reviewers selected the studies to prevent selection bias. Furthermore, we applied strict in- and exclusion criteria to only include studies that investigated the risk factors for a VLU (C5-C6). Although the harvest is small, it provides a clear and transparent insight into the actual knowledge on risk factors for a first time VLU and it highlights the complexity of the progression of CVD to the most severe stage.

Conclusion

Only a small number of studies investigated the risk factors involved in the development of a first VLU. The precise relationship of the risk factors in developing a VLU still remains unclear because the quality of the papers in our final selection did not give us the possibility to make more precise conclusions. However, the risk factors: age, higher BMI, arterial hypertension, reflux, DVT, low PA and family VLU play a role in developing a first VLU. Further studies are needed to confirm the association of these risk factors with the development of a VLU and to explore risk factors like higher BMI and low PA in more detail. With more specific knowledge of these risk factors patients with CVD who are at risk of the development of a VLU may be identified earlier. This can lead to more rapid and targeted treatment to prevent a VLU in CVD patients.

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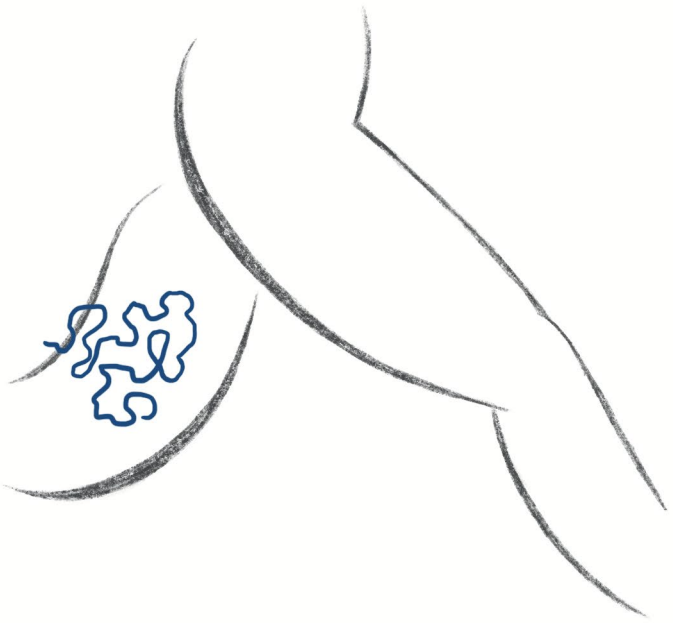
Appendix

Full PubMed Search:
((((((((((“Venous Insufficiency”[Mesh:NoExp]) OR “venous insufficiency”[title/abstract]) OR “chronic venous”[title/abstract]) OR “venous disease”[title/abstract]) OR “venous disorder*”[title/abstract]) OR “venous stasis”[title/abstract]) OR “Varicose Ulcer”[Mesh]) OR “Varicose ulcer*”[Title/abstract]) OR “Venous ulcer*”[Title/Abstract]) OR “Venous Leg ulcer”[Title/Abstract]) AND ((((((((((“Prognosis”[Mesh]) OR prognos*[title/abstract]) OR “Risk Factors”[Mesh]) OR “risk factor*”[title/abstract]) OR “Protective Factors”[Mesh]) OR “protective factor*” [Title/abstract]) OR “disease progression”[Mesh]) OR “disease progress*”[title/abstract]) OR “natural course*”[title/abstract]) OR “severity of Illness Index”[Mesh]) OR “severity of illness”[title/abstract]) OR “severity of disease”[title/abstract]) OR “disease severity”[title/abstract])

Hits: 3192 (Last search: January 2018)

CHAPTER FOUR



THE ROLE OF OBESITY AND PHYSICAL ACTIVITY IN THE PROGRESSION OF CHRONIC VENOUS DISEASE: A SCOPING REVIEW.

SUMMARY

Objective. The risk factors obesity and reduced mobility are not well known in the development of a Venous Leg Ulcer (VLU). The aim of this scoping review is to explore the mechanisms by which obesity and reduced mobility contribute the development of a VLU in patients with Chronic Venous Disease (CVD).

Methods. For this scoping review a search was performed in May 2019 in the Cochrane Library and Pubmed to identify studies on the working mechanisms of obesity and mobility in developing a VLU. Hand searches were performed to find additional studies explaining the working mechanisms (indirectly related to the VLU). Two reviewers independently reviewed the abstracts and full-text articles.

Results. Twenty-eight studies met our eligibility criteria. Disturbed range of ankle motion and gait can lead to a reduced Calf Muscle Pump (CMP) function leading to a venous outflow disorder. Increased abdominal pressure due to obesity can lead to a venous outflow obstruction and increased adipose tissue mass results in an increase in adipokine secretion. The venous outflow disorder, outflow obstruction and increased adipokine secretion can all lead to chronic systemic inflammation, increased endothelial permeability and hence microcirculatory dysfunction. This alone can result in a VLU.

Conclusion. Obesity and reduced mobility can lead to a reduction of the CMP function, an increase in abdominal pressure and an increase in adipose tissue mass. This can simultaneously lead to haemodynamic changes in the macro- and microcirculation of the lower extremities and eventually in a VLU. In patients with obesity and reduced mobility the microcirculation alone can lead to skin changes and eventually a VLU. Therefore, early recognition of CVD symptoms in patients with obesity and reduced mobility is crucial to diagnose and treat CVD to prevent a VLU.

As published

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The role of obesity and physical activity in the progression of Chronic Venous Disease: a Scoping review.

Introduction

Venous Leg Ulcers (VLU) are chronic wounds of the lower extremities caused by Chronic Venous Disease (CVD). The VLU occurs in approximately 0.3% of the Western-population and the incidence increases with age.[1] Risk factors for the development of a VLU include age, family history of VLU, venous insufficiency in the deep veins, obesity and reduced mobility.[2-5] Age and family history cannot be altered and the treatment of deep venous insufficiency is already imbedded in current clinical practice.[6,7] However, screening and prevention of the risk factors obesity and reduced mobility are not fully integrated in current CVD/VLU guidelines.[6,7] Despite studies showing that regular exercise protects against developing a VLU[2,4], weight loss and exercise is only advised when a VLU forms to stimulate the healing process or prevent recurrence.[6-8] Furthermore, obesity and reduced mobility are highly present in the CVD population and even more so in the VLU population.[8-10] As CVD progresses obesity and reduced mobility prevalence increases.[5,11,12] In addition, the prevalence of a VLU is significantly higher in patients with obesity compared to patients with normal weight.[13,14] However, the exact working mechanisms of obesity and reduced mobility in developing a VLU are not well known.

The aim of this scoping review is therefore to explore the mechanisms by which obesity and reduced mobility contribute to VLU development in patients with Chronic Venous Disease (CVD).

Materials and Methods

In this scoping review we first identified the research question and discussed relevant topics with all authors (e.g. definition of obesity, mechanisms related to mobility). We identified relevant studies by performing a search in the Cochrane Library, Pubmed and Embase (see appendix A for the Pubmed searches). The search was performed in May 2019 with the language limits English, Dutch and German. The retrieved titles and abstracts were independently screened by two authors (AM focussing on mobility and WF focussing on obesity) according to predetermined in- and exclusion criteria (see table 1). Studies that prospectively measured mobility in VLU patients were excluded, because a VLU itself can influence mobility.[15] Second, the authors AM and WF discussed the eligibility of the abstracts and the remaining

studies were read independently in full-text by both authors. Third, data explaining the role of obesity or mobility in developing a VLU were extracted using a predefined data-extraction form. WF extracted the data for the obesity related articles and AM extracted the data for the mobility related articles after which both authors verified the results. AM and WF used thematic analysis to explore the extracted data from the studies. For this purpose, statistical references are not relevant and therefore not included in this scoping review. Finally, snowballing and hand searches were performed to find additional articles to include all relevant information on the role of obesity and reduced mobility in the development of a VLU.

Inclusion	Exclusion
Working mechanisms in the development of venous leg ulcers	Studies focussing on chronic venous disease without venous leg ulcers
Body composition	venous leg ulcer recurrence
Mobility	venous leg ulcer healing

Table 1: In- and exclusion criteria

Results

The systematic and hand searches resulted in 570 articles of which 28 articles were eligible for inclusion. Figure 1 shows the Prisma-flowchart[16] of the searches and the reasons of exclusion. Most studies were excluded due to the lack of obesity or mobility related mechanisms or the use of healing of a VLU as the outcome. The included studies dated from 1994 – 2018 of which 18 studies were published in the last 10 years. All but one study included over 40 patients.

Below we will first describe the pathways of the macro- and microcirculation in the development of a VLU and then describe how obesity and mobility influence these pathways.

Pathways of the marco- and microcirculation in the development of a Venous Leg Ulcer

Macrocirculatory dysfunction

Venous reflux (varicose veins) or venous obstruction (thrombosis) of the macrocirculation (large veins) in the lower extremities leads to a venous outflow disorder or venous outflow obstruction. These changes in the macrocirculation can lead to an increased Ambulatory Venous Pressure (AVP). Increased AVP can be a cause or a

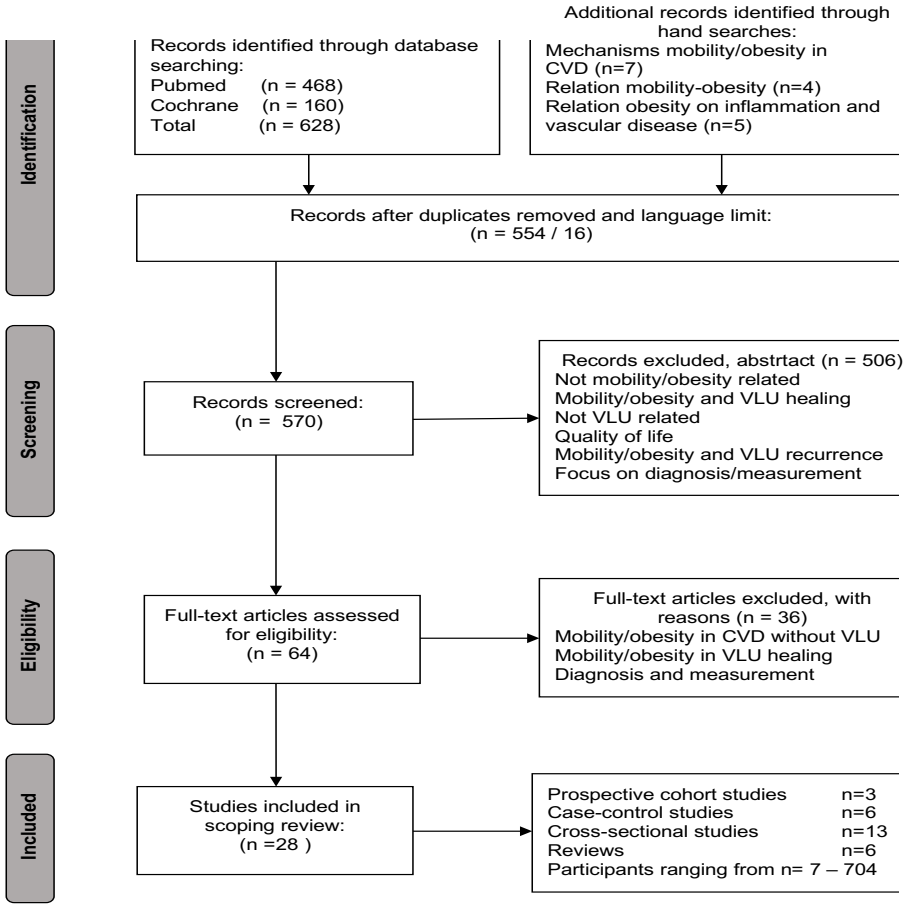

Figure 1: Prisma-flowchart of the searches on obesity and mobility in the development of a venous leg ulcer.

VLU = Venous Leg Ulcer, CVD = Chronic Venous Disease. Image23625.JPGFigure 1: Prisma-flowchart of the searches on obesity and mobility in the development of a venous leg ulcer.VLU = Venous Leg Ulcer, CVD = Chronic Venous Disease.

result of venous reflux or venous obstruction.[6] Both venous reflux and venous obstruction are visible on a duplex ultrasound which is used to diagnose the etiological, anatomical and pathophysiological classification of CVD.[17] Dysfunction in the macrocirculation can eventually lead to a dysfunction in the microcirculation which results in more severe CVD with skin changes and the VLU.[18]

Chronic systemic inflammation

A prolonged increase in AVP because of dilated veins or vein valve dysfunction leads to a reduction in shear stress. Shear stress is the turbulent and therefore slower venous blood flow which results in a reduced stress on the vein wall, hence the endothelium of the veins.[19] Reduced shear stress trigger endothelial dysfunction which promotes chronic systemic inflammation and reduces the antithrombotic effects in patients with CVD.[20-22] Subsequently, biomarkers of chronic systemic inflammation are increased in the lower legs in patients with severe CVD.[23-25]

Endothelial permeability

A prolonged increase in AVP and therefore the chronic systemic inflammation and reduced antithrombotic function are hypothesised to lead to an increase in endothelial permeability in CVD.[26,27] Increased endothelial permeability prevents optimal cellular metabolism of toxins and oxygen in the skin leading to skin changes and the VLU.[27,28]

Microcirculatory dysfunction

A prolonged increase in AVP and therefore increased chronic systemic inflammation and endothelial permeability leads to a dysfunction of the microcirculation.[29] This is not visible on a duplex ultrasound. However, the microcirculatory dysfunction leads to more severe CVD with clinical symptoms such as oedema, hyperpigmentation, lipodermatosclerosis, atrophie blanche and eventually the VLU.[17,18]

Figure 2 shows the pathways of the macro and microcirculation in the development of a VLU. Figure 3 shows the (possible) working mechanisms of obesity and reduced mobility in the development of a VLU and their shared pathway through the Calf Muscle Pump (CMP) function.

Working mechanisms of obesity and reduced mobility in the development of a Venous Leg Ulcer

Obesity: Intra-abdominal pressure and the venous leg ulcer

Although the exact mechanisms explaining the development of a VLU in patients with obesity have not been fully elucidated, potential mechanisms may include haemodynamic alterations and adipose tissue dysfunction leading to increased chronic systemic inflammation, insulin resistance and increased endothelial permeability.

Haemodynamic alterations are thought to be a result of the increased intra-abdominal pressure caused by the increased abdominal adipose tissue mass. This

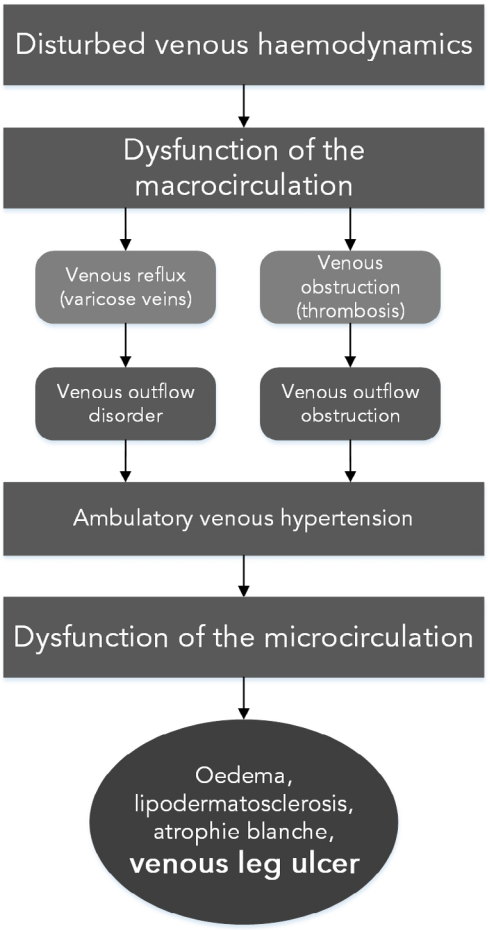

Figure 2: Pathways of the macro- and microcirculation in the development of a venous leg ulcer.

increase in adipose tissue mass can lead to an increased AVP because of an outflow obstruction. It is hypothesised that the elevated intra-abdominal pressure is transmitted to the extremities by the femoral veins, resulting in external venous obstruction. Due to a higher tension on the vein walls in the lower limbs venous elasticity is attenuated and will potentially lead to macrocirculatory problems like venous reflux.[30] In a study comparing patients with overweight and obesity to patients with a normal weight the reflux outcomes were similar. However, the overweight patients had a significantly higher prevalence of skin changes and VLU's compared to patients with normal weight.[13] This implies an additional pathway of overweight/obesity affecting the microcirculation in the development of a VLU.

Increased AVP due to increased intra-abdominal pressure can also lead to a reduction in shear stress.[30] As described before this can lead to microcirculatory dys-

function. Two studies in obese patients with skin changes and VLU's showed no reflux or obstruction on the duplex ultrasound in most of the patients. This suggests a pathway through the microcirculation alone in the development of a VLU in patients with obesity.[31,32]

Obesity: Adipose tissue dysfunction and chronic venous disease

Adipose tissue has long been considered as a non-functional passive depot for lipid storage. Today research has revealed that adipose tissue has to be regarded as an active endocrine organ that secretes a unique profile of adipokines. Adipokines include a wide range of regulatory mediators that exhibit hormone characteristics.[33,34] Several studies have shown that higher levels of adipokines increase the risk of the development of CVD.[35,36]

Increased adipose tissue mass results in an increased adipokine secretion which subsequently leads to adipose tissue mass inflammation.[34,37] Furthermore, the increased adipokine secretion through adipocytes lead to endothelial dysfunction.[38,39] Adipokines therefore probably affect the endothelial function of the venous macro- and microcirculation. Adipokines are found to be increased in patients with CVD[35] however, a direct link to a VLU has not yet been found.

Adipose tissue mass inflammation and an increased secretion of adipokines lead to chronic systemic inflammation because of an increased secretion of pro-inflammatory cytokines.[34] These cytokines are associated with endothelial cell activation and an increased endothelial permeability leading to dysfunction of the microcirculation in patients with CVD.[21] Whereas obesity plays a key role in the development of chronic systemic inflammation it is postulated that obesity contributes to the development of a VLU through adipose tissue mass dysfunction.

The direct effect of increased adipokine secretion and the chronic systemic inflammation also contribute to the development of insulin resistance. Circulating insulin levels affect venous function through vasculoprotective and anti-inflammatory effects and plays a major role in the regulation of endothelial function. An impaired insulin sensitivity in patients with obesity will lead to endothelial dysfunction which in turn probably contributes to the process of CVD and the VLU.[40]

Reduced mobility: Calf muscle pump function and the Venous Leg Ulcer

The function of the Calf Muscle Pump (CMP) is reduced in CVD patients and even more so in patients with a VLU.[41,42] In a study comparing CVD patients with and without a VLU the venous reflux outcomes were similar, whereas patients with a VLU had a significantly reduced function of the CMP.[43] Furthermore, non-functioning of

the CMP in permanent immobility leads to an outflow disorder which may lead to the development of oedema, skin changes and a VLU without evidence of venous reflux or venous obstruction on a duplex ultrasound.[44] It is therefore suggested that the CMP can play a role in the development of a VLU through dysfunction of the microcirculation alone.

Comorbidity in the lower extremities will often lead to a reduction in the Range Of Ankle Motion (ROAM), or directly to a reduced function of the CMP which results in an altered or reduced mobility.[45] Comorbidities resulting in reduced mobility that are associated with the development of a VLU are rheumatic diseases[46], peripheral arterial disease[47], and neuropathy[45]. The reduced mobility in the lower extremities leads to a restriction in optimally utilizing the foot plate. The CMP is therefore not used to its fullest potential leading to a reduced outflow volume and therefore a venous outflow disorder.[48] Reduced ROAM and/or CMP function can result in an increased AVP leading to oedema, skin changes, and a VLU through the path of the microcirculation without a positive diagnosis on a duplex ultrasound.[46,49,50]

A reduced ROAM correlates with a reduced function of the CMP.[51] The CMP is the main factor in venous outflow because it transposes the most blood volume specifically in the body weight transfer manoeuvre.[52] The body weight transfer manoeuvre is comparable to walking. The study of Suehiro, 2016[50] showed that a walking distance <200m per day is a risk factor for the development of a VLU. The study of Robbertson, 2009[4] shows on the other hand that regular walking is protective for the development of a VLU.

Both reduced calf muscle function and reduced ROAM can lead to alterations in walking and more specifically in the gait (speed). A study on gait in (healed) VLU patients showed that (healed) VLU patients had a significantly lower calf muscle endurance, a wider base and slower gait speed compared to healthy controls.[53] A slower gait speed is also found in CVD patients compared to healthy controls.[54] Furthermore, obesity can lead to a reduced ROAM and alterations in gait (speed) because of the increase in adipose tissue mass.[55-58] Obesity and reduced mobility therefore share a pathway in the development of a VLU through gait and the CMP function.

Discussion

This scoping review shows that obesity and reduced mobility are a risk for the development of a VLU through pathways in the macro- and microcirculation. Dysfunction of only the microcirculation results in a negative duplex diagnosis while venous

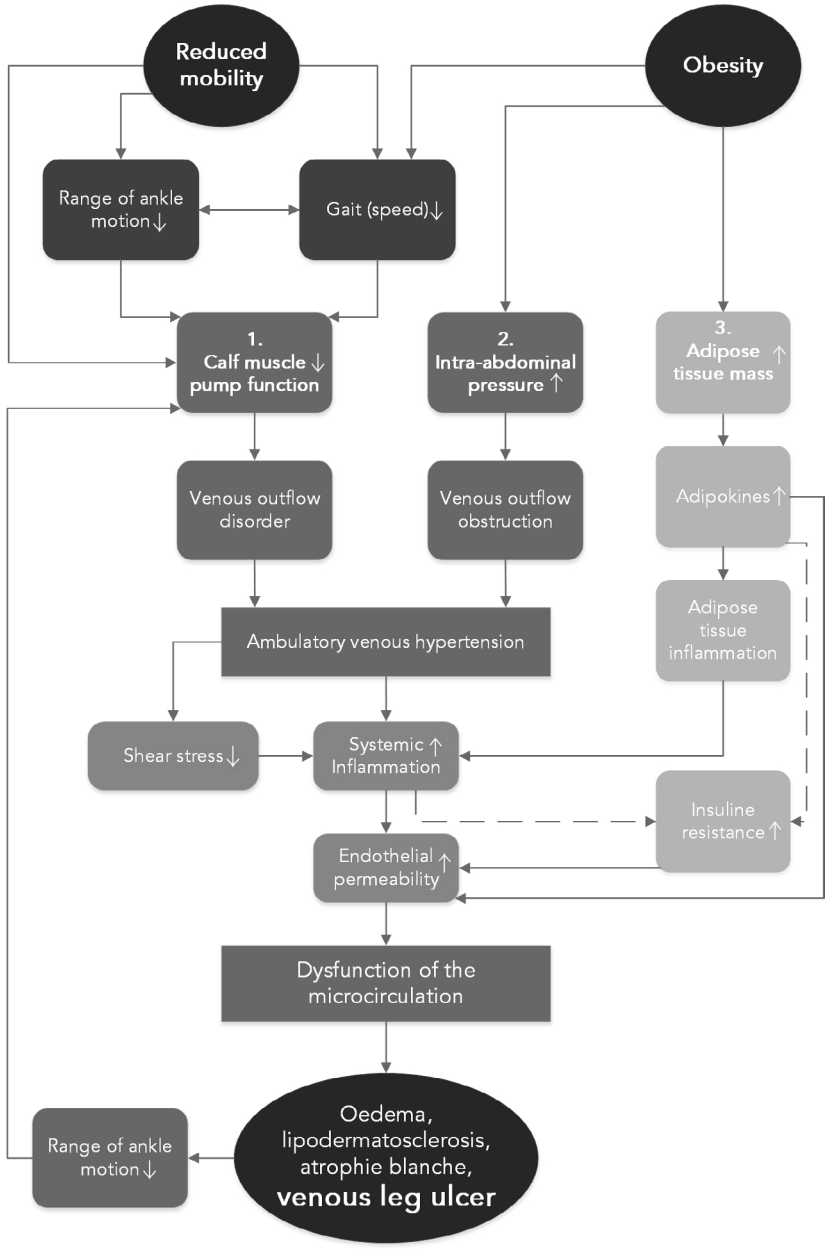

Figure 3: The (possible) working mechanisms of obesity and reduced mobility in the development of a venous leg ulcer

insufficiency can still lead to clinical symptoms of CVD and eventually a VLU. This denotes the importance of the recognition skin changes like oedema, hyperpigmentation, lipodermatosclerosis and atrophie blanche in the prevention of a VLU in

patients with obesity or a reduced mobility.

The scoping review also shows that obesity and reduced mobility share a pathway in the development of a VLU through gait (speed). In addition, the scoping review denotes the joint risk through the different pathways of obesity and reduced mobility which can occur simultaneously. Obesity and reduced mobility can be a result of comorbidity. However, obesity and reduced mobility can also be a result of a sedentary lifestyle. Several studies show that a sedentary lifestyle is related to obesity and obesity on the other hand is related to a sedentary lifestyle.[59-61] In other words, obesity and reduced mobility are often seen as a joint morbidity and should therefore be treated simultaneously in the prevention of a VLU. In addition, the risk of obesity in the development of a VLU is yet another reason to approach obesity as a disease on its own whereas obesity is a risk factor for many more diseases.[62]

When mobility is increased by stimulating the CMP function skin oxygen levels increase in patients with a VLU.[63] However, the dysfunction of the microcirculation in VLU patients can cause skin oxygen levels to stay low during exercise when the outflow disorder/obstruction in the macrocirculation is not compensated.[64] It is therefore important to include weight loss and exercise in the treatment of CVD to be able to treat the outflow disorder/obstruction caused by obesity or reduced mobility. Furthermore, a systematic review on exercise in non-ulcerated CVD showed insufficient evidence for exercise programs and denotes the need for research into frequency, time and intensity of exercise in CVD to restore AVP.[65] However, treatment of CVD to prevent a VLU is multifactorial because of the underlying pathologic pathways and risk factors which can vary in each patient. Prevention should therefore consist of a multifactorial (complex) intervention. Unlike the VLU, prevention for other chronic wounds such as the diabetic foot ulcer and pressure ulcers are studied in complex interventions and the prevention is profoundly imbedded in clinical practice guidelines.[66,67] This denotes the importance of developing a complex intervention for the prevention of a VLU including the risk factors obesity and reduced mobility among others.

Strength and limitations

We used a scoping strategy to be able to include all studies on the working mechanisms of obesity and reduced mobility in the development of a VLU. One of the limitations is that we did not perform a systematic assessment of the methodological quality of the studies and we included all levels of evidence. Studies on working mechanisms are often studies with a low level of evidence. As we aimed to provide insight in the possible working mechanisms of obesity and reduced mobili-

ty in the development of a VLU and identify a research gap concerning these topics, the low level of evidence is not necessarily a problem. However, if we would have included the methodological quality of the studies, we might have been able to give a recommendation on what specific working mechanisms would require further investigation. In addition, we did perform a systematic search in two databases and the included articles were read in full-text and discussed by at least two authors.

Conclusion

This article provided insight in the pathways of obesity and reduced mobility in the progression of CVD into a VLU. A reduction of the CMP function, an increase in abdominal pressure and an increase in adipose tissue mass can lead to haemodynamic changes in the macro- and microcirculation of the lower extremities and eventually in a VLU. These pathways can act simultaneously in the development of a VLU which denotes the importance of treating both obesity and reduced mobility at the same time. Furthermore, obesity and reduced mobility can lead to a dysfunction in the microcirculation alone leading to skin changes and eventually a VLU. Therefore, early recognition of CVD symptoms in patients with obesity and reduced mobility is crucial to diagnose and treat CVD to prevent a VLU. At an early stage health care professionals and patients should be (made) aware of the health consequences of obesity and reduced mobility in the onset and progression of CVD towards a VLU.

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Appendix

Pubmed search

<u>Mobility</u>

((((((((“Varicose Ulcer”[Mesh]) OR “Leg Ulcer”[Mesh]) OR “Varicose Ulcer”[Mesh]) OR “Venous Leg Ulcer”[Title/Abstract]) OR “Venous Ulcer”[Title/Abstract]) OR “Leg Ulcer”[Title/Abstract])) AND Venous[Title/Abstract]))) AND (((“Range of Motion, Articular”[Mesh]) OR “Standing Position”[Mesh]) OR “Sitting position”[Mesh]) OR “Immobility Response, Tonic”[Mesh]) OR “Immobilization”[Mesh]) OR “Mobility Limitation”[Mesh]) OR “Occupations”[Mesh]) OR “Return to Sport”[Mesh]) OR “Fitness Trackers”[Mesh]) OR “Exercise”[Mesh]) OR “Exercise Movement Techniques”[Mesh]) OR “Exercise Therapy”[Mesh]) OR “Muscle, Skeletal”[Mesh]) OR “Range of Motion”[Title/Abstract]) OR “Standing Position”[Title/Abstract]) OR “Sitting position”[Title/Abstract]) OR “Immobility Response”[Title/Abstract]) OR Immobilization) OR “Mobility Limitation”[Title/Abstract]) OR Occupation) OR “Return to Sport”[Title/Abstract]) OR “Fitness Trackers”[Title/Abstract]) OR Exercise[Title/Abstract]) OR “Exercise Movement Techniques”[Title/Abstract]) OR “Exercise Therapy”[Title/Abstract]) OR Muscle[Title/Abstract]) OR “Physical Activity”[Title/Abstract]) OR “Range of Ankle Motion”[Title/Abstract]) OR “Ankle Range of Motion”[Title/Abstract]) OR AROM[Title/Abstract]) OR ROAM[Title/Abstract]) OR ROM[Title/Abstract]) OR Immobility[Title/Abstract]) OR Mobility[Title/Abstract]) OR “Calf Muscle Pump”[Title/Abstract]) OR “Calf Muscle”[Title/Abstract]) OR “Muscle Pump”[Title/Abstract]) OR “Foot Pump”[Title/Abstract]) OR “Calf Muscle Function”[Title/Abstract]) OR Gastrocnemius[Title/Abstract]) OR Gait[Title/Abstract]))))

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<u>Obesity</u>

((“Body Weight”[Mesh]) OR “Weight loss”[Mesh]) OR “Weight gain”[Mesh]) OR “Body Weight Changes”[Mesh]) OR “Body-Weight Trajectory”[Mesh]) OR “Waist-Height Ratio”[Mesh]) OR “Body Mass Index”[Mesh]) OR “Overweight”[Mesh]) OR “Pediatric Obesity”[Mesh]) OR “Obesity”[Mesh]) OR “Obesity, Abdominal”[Mesh]) OR “Obesity, Morbid”[Mesh]) OR “Waist-Hip Ratio”[Mesh]) OR “Waist Circumference”[Mesh]) OR “Body Fat Distribution”[Mesh]) OR “Abdominal Fat”[Mesh]) OR “Intra-Abdominal Fat”[Mesh]) OR “Body Size”[Mesh]) OR “Body Composition”[Mesh]) OR “Body Constitution”[Mesh]) OR “Ideal Body

Weight"[Mesh]) OR "Anthropometry"[Mesh]) OR "Body Weight" [Title/Abstract]) OR "Weight loss"[Title/Abstract]) OR "Weight gain"[Title/Abstract]) OR "Body Weight Changes"[Title/Abstract]) OR "Body-Weight Trajectory"[Title/Abstract]) OR "Waist-Height Ratio"[Title/Abstract]) OR "Body Mass Index"[Title/Abstract]) OR Overweight[Title/Abstract]) OR "Pediatric Obesity"[Title/Abstract]) OR Obesity[Title/Abstract]) OR "Abdominal Obesity"[Title/Abstract]) OR "Morbid Obesity"[Title/Abstract]) OR "Waist-Hip Ratio"[Title/Abstract]) OR "Waist Circumference"[Title/Abstract]) OR "Body Fat Distribution"[Title/Abstract]) OR "Abdominal Fat"[Title/Abstract]) OR "Intra-Abdominal Fat"[Title/Abstract]) OR "Body Size"[Title/Abstract]) OR "Body Composition"[Title/Abstract]) OR "Body Constitution"[Title/Abstract]) OR "Ideal Body Weight"[Title/Abstract]) OR Anthropometry[Title/Abstract]) OR WHR[Title/Abstract]) OR "Waist-to-Hip Ratio"[Title/Abstract]) OR "Lean Body Weight"[Title/Abstract])))) AND (((((((("Varicose Ulcer"[Mesh]) OR "Leg Ulcer"[Mesh]) OR "Varicose Ulcer"[Mesh]) OR "Venous Leg Ulcer"[Title/Abstract]) OR "Venous Ulcer"[Title/Abstract]) OR "Leg Ulcer"[Title/Abstract])) AND Venous[Title/Abstract])

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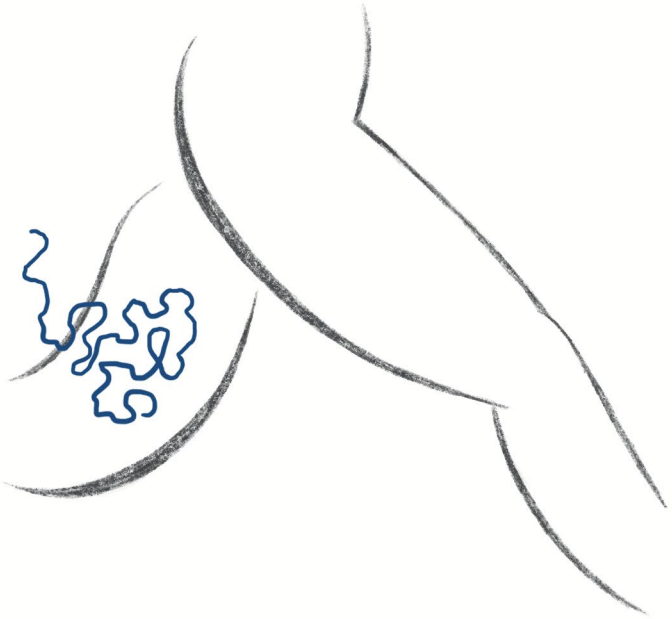
CHAPTER FIVE



RISK FACTORS IN PATIENTS WITH CHRONIC VENOUS DISEASE, THE ROLE OF ABDOMINAL OBESITY AND ANKLE MOBILITY.

SUMMARY

Introduction: Chronic Venous Disease (CVD) is highly prevalent in the Western-population. Varicose veins, oedema, skin changes and a venous leg ulcer are clinical stages of CVD that can lead to a decrease in quality of life. Lifestyle risk factors of CVD are not well-known. The aim of this study is therefore to assess the relation of waist circumference and calf muscle pump related physical activity with the progression of CVD. **Methods:** Data were collected in primary care, secondary care and through convenience sampling in the general population in The Netherlands. In total 74 participants (aged >40 years) with CVD (varicose veins, oedema, skin changes and venous leg ulcers) were recruited (diagnosed with duplex ultrasound). Physical measurements were performed for waist circumference, range of ankle motion, and the number of steps (accelerometer). Data on patient characteristics and physical activity were collected using a questionnaire. **Results:** 29 patients with varicose veins and 43 patients with more severe CVD were included. Patients had a mean age of 68.5 years and were predominantly female. Multivariable logistic regression showed that abdominal obesity (OR 3.9, 95% CI: 1.3-12.3) and reduced dorsal flexion of the ankle (OR 5.9, 95% CI: 1.8-19.4) were independently associated with more severe CVD. **Conclusion:** Both abdominal obesity and dorsal flexion of the ankle <10° were associated with more severe CVD and were likely to be present for over five years which suggests that they are risk factors for the progression of CVD. Measuring and treatment of these risk factors should be implemented in CVD care to improve venous function.

As submitted

Meulendijks AM, Tjin EPM, Schoonhoven L, Neumann HAM. Risk factors in patients with Chronic Venous Disease, the role of waist circumference and mobility.

Risk factors in patients with Chronic Venous Disease, the role of abdominal obesity and ankle mobility.

Introduction

Chronic Venous Disease (CVD) is a group of conditions affecting the venous system of the lower abdomen and primarily the lower extremities causing venous hypertension and disturbed skin microcirculation. Causes of CVD include varicose veins, venous thrombosis, and syndromes like the Klippel-Trenaunay syndrome which lead to insufficient venous return. CVD is an underestimated cardiovascular disease because of its cosmetic reputation and low mortality rate. However, when CVD progresses it significantly reduces a patients quality of life on a physical, emotional and social level.[1,2] In addition to the impact on quality of life, the progression of CVD also leads to increased health care costs leading up to 1%-2% of the annual health care budget in Western Europe and the USA.[3] The high costs might be explained by the insufficient recognition, diagnostics and acknowledgement of CVD in primary care.[4] Inadequate diagnostics and treatment of early signs and symptoms of CVD lead to a progression to more severe clinical stages.[5] CVD can present several clinical stages from reticular veins and (truncal) varicose veins, to oedema, skin changes (lipodermatosclerosis, eczema) and eventually a venous leg ulcer. Common symptoms of CVD are restless legs, heavy feeling in the legs, muscle cramps, pain, and itching.[6,7]

In the Western population CVD occurs in about 40%.[8] CVD can be treated with invasive and non-invasive treatments such as endovascular laser ablation of insufficient veins, anti-coagulation medication for thrombosis, venous stenting, and ambulatory compression therapy to improve venous return.[9] However, varicose veins, venous thrombosis and venous leg ulcers all have high recurrence rates and therefore require ongoing health care.[10-12] A shift in healthcare towards acknowledgement of CVD and preventing progression is therefore required. A few studies investigated the progression of CVD and identified increasing age, obesity and reduced physical activity as its risk factors.[13-15] Both obesity and reduced physical activity, more specific, abdominal fat and impaired calf muscle pump function, play a role in the reduced venous return which leads to an even higher venous hypertension.[16]

In most studies and in clinical practice obesity is measured using the Body Mass Index. The Body Mass Index however, is not a good representative for abdominal fat and an additional measure is advised to assess abdominal fat in assessing car-

diovascular disease risk.[17] The waist circumference is a measure that is a good indicator of total body fat and abdominal fat and it is used in international guidelines to measure abdominal obesity and cardiovascular disease risk.[18,19] Because CVD is a cardiovascular disease waist circumference is a representative measure to assess the risk of the progression of CVD. However, we found no studies including waist circumference as a risk factor in a CVD population.

In addition, physical activity is measured in several ways in CVD research. Mostly it includes measures to assess body position like a standing occupation or a general physical activity questionnaire to assess daily or regular physical activity in general.[20,21] However, physical activity in CVD should be focused on the functioning of the calf muscle pump. Direct measurements such as plethysmography to assess the calf muscle pump function are expensive and time-consuming to use in daily practice. Easy to use and inexpensive measurements can include time spent walking and measuring the Range Of Ankle Motion (ROAM) as walking and ROAM correlate well with the calf muscle pump function and CVD severity.[22-25]

The aim of this study is therefore to assess the association of waist circumference and calf muscle pump related physical activity with the progression of CVD.

Materials and Methods

Study design

This cross-sectional study was conducted in The Netherlands. Patients were recruited in secondary care through six dermatologists, two vascular surgeons and two specialised wound care nurses, and in primary care through two general practitioners and two home care organisations specialised in wound care. Patients were also recruited from the general population through convenience sampling, flyers in healthcare institutions and research invitations in local newspapers.

Participants

Patients >40 years old with clinical signs (C-classification)[26] of varicose veins (C2), oedema (C3), skin changes (C4) and (healed) venous leg ulcers (C5-C6) were included in the study. We included patients with a first venous leg ulcer only in case of CVD C5-C6. We excluded patients with permanent immobility, and patients who were unable to understand and sign the informed consent.

Data collection

Data were collected between November 2018 and February 2020. The researcher

AM performed all measurements for each patient according to a study protocol and registered the outcomes in a Case Report Form. Patients visited the location of their health care provider or one of the study locations close to them for the measurements and to fill out a questionnaire.

Measurements

The following outcomes were measured: weight, height (to calculate Body Mass Index), waist circumference with a measuring tape, blood pressure, Ankle Brachial Pressure Index (ABPI), and Range Of Motion (ROM) of the ankle using a goniometer. Dorsal flexion and plantar flexion of the ankle were measured in a supine non-weight baring position. Active ROM was measured according to the neutral-0-method. Duplex Ultrasound was used to diagnose deep or superficial (truncal) venous insufficiency in each patient. Patients wore an accelerometer (ActiGraph wGT3X-BT) at the waist for 7 executive days to retrieve prospective data on the number of steps per day. The following outcomes were collected using a questionnaire: patient characteristics (age, gender, clinical classification of CVD, education, thrombosis, family history of VV and VLU, smoking, alcohol, and the source of recruitment), medication use, comorbidities, occupation they had the longest (to include a standing occupation), reduced physical activity in the past (with reason), and a Visual Analog Score (1-10) for physical activity before and after a change in physical activity in the past. Multimorbidity was defined as two or more chronic diseases in addition to the CVD including other cardiovascular diseases, diabetes, skeletal- and joint diseases, lung diseases, and neurological diseases among others.

Data analysis

Data were analysed using IBM SPSS statistics version 25. Continuous variables are presented as mean and standard deviations or median and interquartile range when the variable was not normally distributed. The median of the number of steps and ROAM of the total study population was used to create two equal groups and include a possible cut-off value. Categorical variables are presented as the number of patients and percentages. Differences between patients with C2 and C3-C6 were calculated using T-tests and Mann-Whitney U-test (when assumptions were violated) for continuous data and Chi-square test for categorical data. Eventually, univariable and multivariable logistic regression was performed. Abdominal obesity was included in the logistic regression analysis instead of BMI because abdominal obesity plays a role in venous return to the heart.[16] Multivariable logistic regression analysis was performed using a step-wise enter method in the multivariable model

including the risk factors that reached a significance of $p<0.10$ in the univariable logistic regression analysis. Statistical significance for all other analysis was set at $p<0.05$. Risk factors that did not reach significance in the model were excluded from the model because of the small sample size. Age and hypertension were forced in the model because they are known risk factors for the progression of CVD.

Ethics

The study protocol was submitted to the Medical Research Ethics Committee (MREC) of the University Medical Centre (UMC) Utrecht (registration number 17-670/C). The MREC declared that the "Medical Research Involving Human Subjects Act" (WMO) does not apply to this study and official approval of the MREC UMC Utrecht is not required under the WMO. All participants signed a written consent prior to participation.

Results

A total of 74 patients were included in the study. Data of four CVD C2 patients (two males and two females) on one questionnaire and the measurements were lost due to a technical error in the case report forms. The four patients were contacted and asked to fill out the questionnaire again. Repeating the measurements was not possible due to the COVID-19 outbreak. Two patients returned the questionnaire. In addition, the accelerometers were not returned for six patients and therefore data is missing on the average number of steps per day. This explains the variation in the total number of patients of the results.

Patient characteristics

The patient characteristics are shown in Table 1. The study population consisted of predominantly female patients (64%). The mean age was 68.5 years (SD 10.6). The majority of the patients had overweight (BMI≥25). Of all patients 50% had a current venous insufficiency in the truncal veins and again 50% had a bilateral venous insufficiency. Almost 20% of the patients had a venous thrombosis (in the past) and most patients had a family history of varicose veins. Smoking and heavy drinking occurred in 47% and 25% of the patients, respectively. Most patients were recruited from the general population and secondary care. No significant differences of the patient characteristics between C2 and C3-C6 patients were found accept for BMI. BMI was significantly higher in C3-C6 patients compared to C2 patients with a BMI of 30 and 26, respectively.

Characteristic	Total (N=72)	C2 (N=29)	C3-C6 (N=43)
Age (mean, sd) (N=74)	68.5 (10.6)	66.1 (10.1)	70.1 (10.8)
Gender (% female) (N=74)	47 (64%)	20 (65%)	27 (62%)
Education			
Low (primary school)	28 (39%)	12 (41%)	25 (64%)
Medium (intermediate vocational education)	33 (47%)	14 (48%)	8 (21%)
High (higher vocational education/university)	9 (13%)	3 (10%)	6 (15%)
BMI (mean, sd)	29.3 (8.8)	26.4 (3.5)	30.0 (5.9)*
Clinical classification (N=74)			
C2: Varicose Veins	31 (42%)	-	-
C3: Oedema	18 (24%)	-	-
C4: Skin changes	6 (8%)	-	-
C5: Closed venous leg ulcer	9 (12%)	-	-
C6: Active venous leg ulcer	10 (14%)	-	-
Venous insufficiency in the truncal veins (N=70)			
Current insufficiency in the truncal veins	35 (50%)	10 (36%)	25 (60%)
No insufficiency in the truncal veins	14 (20%)	8 (29%)	6 (14%)
Insufficiency in the past (treated)	21 (30%)	10 (36%)	11 (26%)
Bilateral chronic venous disease (N=70)	35 (50%)	14 (50%)	42 (50%)
Thrombosis	14 (19%)	6 (20%)	8 (19%)
Family history of varicose veins	54 (77)%	25 (86%)	28 (70%)
Family history of venous leg ulcers	14 (19%)	7 (24%)	6 (15%)
Smoker (current or in the past)	34 (47%)	14 (47%)	20 (48%)
Alcohol heavy drinker	18 (25%)	7 (23%)	11 (26%)
Recruited from (N=74)			
General population	34 (46%)	22 (71%)	12 (28%)
Primary care	5 (7%)	0 (0%)	5 (12%)
Secondary care	35 (47%)	9 (29%)	26 (61%)

Table 1: *Patient characteristics*

**significantly different in T-test. Sd=standard deviation, N=number of patients.*

Classifying obesity using BMI and waist circumference

Classifying obesity using BMI cut-off values (BMI≥30) resulted in a different classification of 19% of the CVD patients with abdominal obesity according to their waist circumference (male ≥102cm, female ≥88cm) (see Figure 1). Four patients with normal weight according to their BMI had overweight (N=2) and obesity (N=2) according to their waist circumference. Ten patients who were overweight according to their BMI had abdominal obesity according to their waist circumference.

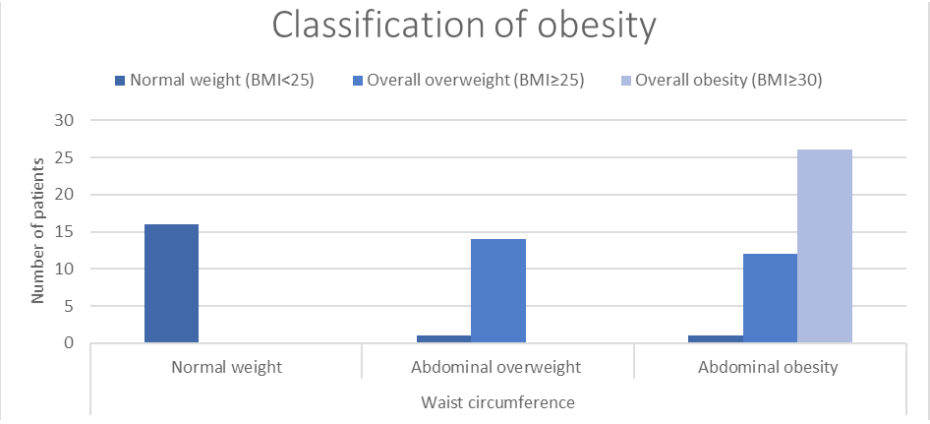


Figure 1: Differences in the classification of obesity using Body Mass Index and Waist Circumference

Differences in possible risk factors in CVD patients

Table 2 shows the differences in the possible risk factors for CVD patients with C2 compared to CVD C3-C6. No significant differences were found between the CVD C2 and CVD C3-C6 patients for type of occupation, reduced physical activity, the ROAM: plantar flexion, visual analogue score for physical activity and foot disorders and/or orthopaedic insoles or shoes. Multimorbidity occurred in the majority of the CVD patients but did not differ between the groups.

The visual analogue score for physical activity is significantly different when comparing the score before and after an event had occurred in the total study population. The median score of 8 before the event dropped to a median score of 7 after the event. Events that led to the reduction in PA were sustained trauma, comorbidity, or retirement. However, in some cases retirement had led to an increase in physical activity (results not shown).

Significant differences between C2 and C3-C6 patients were found for (abdominal) obesity, personal history of hypertension, less than 6000 steps per day, and the ROAM: dorsal flexion. The majority of patients with CVD C3-C6 has abdominal

obesity compared to a minority of patients with CVD C2. These results are similar but not an exact match with overall obesity (BMI). Personal history of hypertension occurred more often in CVD C3-C6 patients compared to C2 patients. Of the CVD C3-C6 patients 64% walked less than 6000 steps per day compared to 31% in CVD C2 patients. Finally, the dorsal flexion of the ankle was more often reduced in patients with CVD C3-C6 compared to patients with C2.

Abdominal obesity and reduced ankle mobility as risk factors for CVD progression

A personal history of hypertension, abdominal obesity, less than 6000 steps per day, and reduced ROAM: dorsal flexion significantly increased the odds of having

Possible risk factor	C2 N=29 (100%)	C3-6 N=43 (100%)
Waist circumference		
Male (median, IQR) (N=25)	101 (97-107)	101 (97-110)
Female (median, IQR) (N=45)	83 (73-91)	93 (85-102)*
Abdominal obesity (N=70)	9 (32%)	29 (69%)*
Overall obesity	5 (17%)	21 (50%)*
Personal history of hypertension	6 (20%)	19 (45%)*
Multimorbidity (excl. CVD)	18 (60%)	32 (76%)
Physical activity		
Standing occupation or heavy work	5 (17%)	12 (28%)
Reduced physical activity total	13 (45%)	26 (60%)
Reduced physical activity ≥5 years	3 (10)%	10 (23%)
VAS PA before event that impacted PA (median, IQR)	8 (7-9)	8 (8-8)
VAS PA after event that impacted PA (median, IQR)	7 (6-8)	7 (6-8)
Number of steps a day ≤6000 (N=68)	9 (31%)	25 (64%)*
ROAM plantar flexion ≤30° (N=70)	12 (43%)	26 (62%)
ROAM dorsal flexion ≤10° (N=70)	6 (21%)	27 (64%)*
Foot disorders or orthopaedic shoes/insoles	12 (40%)	25 (60%)

*Table 2: Differences in possible risk factors between patients with C2, C3 and C4-C6 Chronic Venous Disease. N=number of patients, IQR = Inter Quartile Range, CVD = Chronic Venous Disease, VAS = Visual Analog Score, ROAM = Range Of Ankle Motion. *significantly different between C2 and C3-C6 patients in T-test, Mann-Whitney U-test, or chi-square test (P<0.05).*

Risk factors	C2 (%)	C3-C6 (%)	OR (95% CI)	p-value
Age (N=74) (mean, sd)	66.1 (10.1)	70.1 (10.8)	1.036 (0.989-1.084)	0.133
Personal history of hypertension (N=72)	20%	45%	3.304 (1.121-9.744)	0.030*
Abdominal obesity (N=70)	32%	69%	4.709 (1.685-13.166)	0.003*
Average number of steps per day ≤6000 (N=68)	31%	64%	3.968 (1.426-11.040)	0.008*
Range of ankle motion: Dorsal flexion ≤10˚ (N=70)	21%	64%	6.600 (2.194 -19.857)	0.001*

Table 3: Univariable Logistic Regression analysis of possible risk factors for the progression of CVD from C2 to C3-C6.

N=Number of patients, sd=standard deviation

Risk factor model (N=70)	Odds Ratio (95% CI)	p-value
Personal history of hypertension	3.232 (0.927-3.232)	0.066
Abdominal obesity	3.928 (1.252-12.326)	0.019*
Range of ankle motion: Dorsal flexion ≤10˚	5.910 (1.800-19.402)	0.003*

Table 4: Multivariable logistic regression analysis of obesity and mobility as risk factors for the progression of CVD from C2 to C3-C6

**significant P-value, OR=Odds Ratio, CI= Confidence Interval*

Multivariable model: R squared Hosmer and Lemeshow test = 0.986, Nagelkerke R squared = 0.375, Model chi-squared= 22.733, p<0.001vvvv

CVD C3-C6 in univariable logistic regression analysis (See table 3). Stepwise multivariable logistic regression analyses showed that abdominal obesity (OR 3.8, 95% CI: 1.2-12.0) and reduced dorsal flexion of the ankle (OR 7.9, 95% CI: 1.8-35.2) were independently associated with more severe CVD (C3-C6) (See Table 4). The effect remained the same with or without adjusting for age. Less than 6000 steps per day did not reach significance (p>0.05) in the stepwise approach when abdominal obesity was in the model (results not shown).

Duration of obesity and reduced physical activity

Of the patients with a reduced ROAM: dorsal flexion (<10 ˚, N=33) 88% had experienced an event which led to a reduction in physical activity at least 5 years i.e. trauma of the legs, use of walking aids, foot problems or a standing occupation (see

Table 5). This was significantly lower in patients with a larger ROAM: dorsal flexion (<10˚, N=37) with 68% experiencing an event that led to a reduction in physical activity for at least 5 years. Of the patients with obesity according to BMI (N=34), 87% was obese for at least five years before the measurements (calculated using the patients' self-reported weight of 5 years ago).

Reduced physical activity	Dorsal <10˚ N=33 (100%)	Dorsal >10˚ N=37 (100%)
Trauma on the legs in the past	21 (63.6%)	17 (45.9%)
Less physical activity for at least 5 years	10 (30.3%)	2 (5.4%)*
Walking aids	5 (15.2%)	0 (0.0%)*
Foot problems or orthopaedic aids	20 (60.6%)	16 (43.2%)
Standing occupation or heavy work	11 (33.3%)	5 (13.5%)*
Any of the above	29 (87.9%)	25 (67.6%)*

Table 5: Reduced physical activity in the past

Discussion

In this study we aimed to identify the relationship of abdominal obesity and physical activity with the progression of CVD. The study showed that abdominal obesity and an active dorsal flexion of ≤10˚ of the ankle (measured in a supine non-weight baring position) are significantly associated with more severe CVD (C3-C6).

This is in line with the San Diego Population study which also found an association of waist circumference with CVD.[27] The San Diego population study compared people with no CVD to people with severe CVD (C4-C6). A 10 centimetre increase in waist circumference was associated with an OR of 1.37 (95% CI: 1.15-1.63) for men and an OR of 1.24 (95% CI: 1.11-1.39) for women for severe CVD. Similar results were also found for the dorsiflexion of the ankle. In a case-control study comparing CVD patients with and without ulceration a significant difference (P<0.001) was found in the ROAM dorsiflexion of an average of 13˚ (sd 5.0) in the cases (C5-C6) compared to 17˚ (SD 5.3) in the control population (C2-C4).[28] The case-control study also showed that the RAOM dorsal flexion was slightly lower in patients with active compared to healed VLU. However, both the ROAM dorsal flexion of active and healed VLU were significantly different from the controls (p<0.05). In our study population the mean ROAM dorsiflexion was 12˚ (sd 4.3) in patients with C2 and only 9˚ (sd 5.7) (P=0.021) in patients with C3-C6 which is lower compared to the

study of Robertson (2009).[28] An explanation for this difference can be the age of the study population which was 60 years and 64 years respectively for the controls and cases in the study of Robbertson (2009) compared to 66 years and 70 years for the C2 and C3-C6 patients in our study. Increasing age is known to have a negative influence on the range of motion of the ankle.[29-31] In contrast to the study of Robbertson (2009) we did not exclude patients with peripheral arterial disease. Peripheral arterial disease is known to reduce the range of ankle motion.[32,33] This might be another explanation for the lower degree of ankle range of motion in our study.

The study population consisted of mostly older patients and the majority of the patients was obese. Increasing age and obesity can reduce the range of motion of the ankle.[34,35] A study including CVD patients showed a negative correlation between BMI and range of motion of the ankle.[36] Age and obesity can therefore influence the association of ROAM dorsal flexion with CVD. However, the multivariable analysis adjusted for both age and abdominal obesity showing that reduced ROAM dorsal flexion alone is associated with more severe CVD. In addition, the ROAM dorsal flexion might serve as a risk factor for the progression of CVD. The higher age and high prevalence of obesity in the study population might have led to a prolonged reduction in their ROAM before the development of more severe CVD. Furthermore, the majority of the patients had a reduction in physical activity in the past that might also lead to a reduced ROAM. Moreover, reduced ROAM as a cause or an effect of more severe CVD should in both cases be treated to increase the calf muscle pump function.[23,37] In clinical practice the ROAM dorsal flexion should be measured in all patients with CVD C2-C6 to be able to diagnose and treat reduced ROAM dorsal flexion <10˚. Using goniometry to measure the range of motion of the ankle is cheap and easy and can therefore be easily implemented in clinical practice. Healthcare professionals should also be aware of increasing age, obesity and any reductions in physical activity in patients with CVD that might lead to a reduced ROAM dorsal flexion. This should lead to timely treatment to improve ROAM and therefore calf muscle function in CVD patients.

Causality cannot be measured in a cross-sectional study. However, we can assume that abdominal obesity is a risk factor in the development of more severe CVD. The vast majority of the patients with abdominal obesity were obese for at least five years before they were included in the study. It is therefore likely that abdominal obesity is a risk factor for the development of more severe CVD. This is also in line with the Bonn Vein Study[38] and the Edinburgh Vein Study[39] which prospectively showed that increased BMI is a risk factor for the progression of CVD. Besides obesity as a risk factor for CVD, it can also impact the treatment outcomes

of CVD patients in truncal varicose vein removal. CVD patients with obesity treated for their truncal varicose veins showed significantly less improvement in clinical severity score and quality of life when compared to non-obese CVD patients.[40] In addition, obesity itself can lead to signs and symptoms of CVD without major abnormalities in the venous system.[41] Furthermore, waist circumference is inversely correlated with venous haemodynamic. Venous outflow in obese compared to non-obese patients is reduced leading to an increased risk for venous thrombosis and venous insufficiency.[42,43] This suggests that CVD can also be a complication of obesity. Whether abdominal obesity is a risk factor for CVD or a result of CVD, it should always be measured, followed-up and treated with weight loss interventions in clinical practice.

This study also shows the differences in classification of obesity between BMI and waist circumference. It shows that abdominal obesity (waist circumference) is more prevalent in our study population compared to obesity of total body fat (BMI). This indicates the importance of measuring waist circumference in all patients with CVD in addition to BMI.[44] It also confirms that CVD should be acknowledged as one of the cardiovascular diseases in which abdominal obesity is a risk factor. This means weight loss interventions for CVD patients with abdominal obesity should be standard care similar to other chronic (cardiovascular) diseases like hypertension, high cholesterol, and diabetes mellitus.[45]

Strengths and limitations

This study is the first to assess the relation of abdominal obesity with the progression of CVD in patients with CVD. The study included a small sample that might not be a good representation of the total CVD population. However, the patient characteristics are comparable to those of the larger CVD population with overall older patients, mostly female patients except in the more severe CVD categories, and a high percentage of obesity and comorbidity (references Bonn veins study, VCP). The small sample could also lead to problems performing a multivariable logistic regression. Keeping in mind the minimum of ten events per variable (Peduzzi, 1996) we would be able to include only two variables in the model. We therefore aimed at the most important lifestyle factors waist circumference and physical activity. We also performed a sensitivity analysis removing age and hypertension from the model, and it showed no significant differences in the association of abdominal obesity and dorsal flexion of the ankle with more severe CVD.

Conclusion

Abdominal obesity and a ROAM dorsal flexion <10° are associated with more severe CVD C3-6 compared to CVD C2. Both abdominal obesity and ROAM dorsal flexion <10° were likely to be present for over five years which suggests that they are risk factors for the progression of CVD. Measuring waist circumference and ROAM dorsal flexion should be integrated in CVD care. This should lead to timely weight loss interventions and interventions improving ROAM dorsal flexion in CVD patients to improve their venous function.

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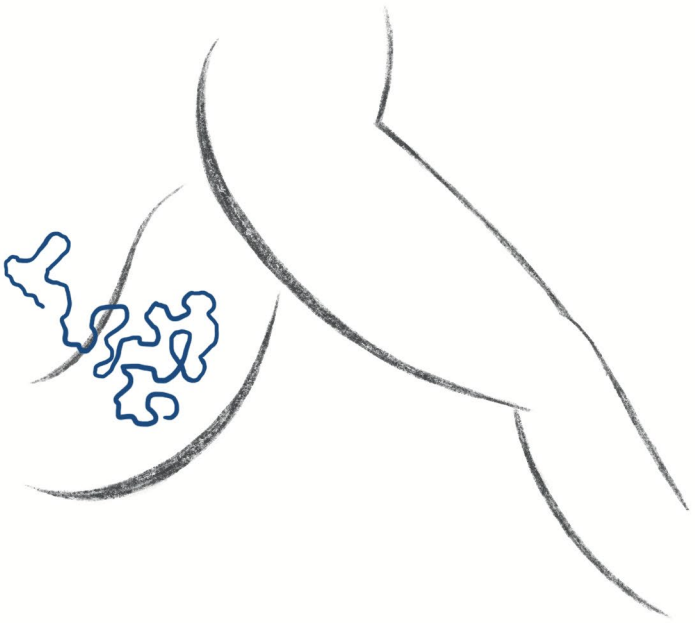
CHAPTER SIX



EXPLORING PHYSICAL ACTIVITY LEVELS IN PATIENTS WITH CHRONIC VENOUS DISEASE

SUMMARY

Introduction: Chronic venous disease (CVD) is a common pathology of the circulatory system and highly prevalent in the older population. One of the risk factors for the progression of CVD is physical inactivity. Signs and symptoms of CVD like ankle oedema, lower leg pain and venous leg ulcers can lead to a reduction in Physical Activity (PA) due to swelling and pain. The aim of this study is to investigate the PA levels of CVD patients with mild to severe CVD and to compare the results with the PA recommendations of the World Health Organisation (WHO).

Methods: A cross-sectional study was conducted on 74 CVD patients with varicose veins, oedema, skin changes or venous leg ulceration. PA was measured using a standardised questionnaire and accelerometers. Sedentary behaviour, light PA and Moderate to Vigorous PA was calculated using Freedson 2011 cut-offs.

Results: Patients had a mean age of 68.5 ±10.4 and were predominantly female (66%), 60% had multimorbidity. Only 34% of the patients met the WHO PA recommendations and 39% of the patients reported walking for 30 minutes on 5 days per week. The accelerometer data showed that 73% of the patients did not engage in an executive of 30 minute MVPA, patients had a median of 85 minutes (Inter Quartile Range [IQR] 21-158) of MVPA in bouts of 10 minutes, and a median of 6 hours (IQR 4.3-7.5) of sedentary behaviour per day. The median number of steps differed significantly between patients with mild and moderate to severe CVD with a difference of 29% (7747 [IQR 5858-9604] vs. 5536 [IQR 4510-8438]).

Conclusion: PA in CVD patients is insufficient and should be treated in CVD healthcare to improve venous outflow and optimise the calf muscle pump function to aim at delaying the onset of more severe CVD. Further research is necessary to investigate the effect of increasing PA levels in CVD patients on disease progression.

As submitted

Meulendijks AM, Franssen WMA, Tjin EPM, Schoonhoven L, Neumann HAM. Exploring physical activity levels in patients with chronic venous disease.

Exploring physical activity levels in patients with chronic venous disease

Introduction

Chronic venous disease (CVD) is a common pathology of the circulatory system and highly prevalent in the older population. CVD is caused by chronic venous insufficiency or venous thrombosis and characterised by signs including varicose veins, venous oedema, skin changes and a venous leg ulcer. CVD occurs in about 40% of the Western population.[1,2] As the severity of CVD increases the prevalence decreases. A (healed) venous leg ulcer is present in approximately 1% of the general population.[3] However, the severity of CVD is related to significantly lower general and disease specific quality of life.[4,5]

The main risk factors for the progression of CVD are age, family history, overweight, and physical inactivity.[6] Furthermore, signs and symptoms of CVD like ankle oedema, lower leg pain and venous leg ulcers can lead to a reduction in Physical Activity (PA) due to swelling and pain.[7-9] This results in a vicious cycle of physical inactivity and CVD severity, therefore, PA is a risk factor and a consequence of CVD at the same time. This implies the need for PA assessment and treatment in all stages of CVD.

PA is shown to increase venous function by using the calf muscle pump to return venous blood to the heart.[10,11] However, in patients with mild to severe CVD there is an increase in ambulatory venous pressure due to venous insufficiency in returning venous blood to the heart (varicose veins or venous thrombosis). A prolonged increase in ambulatory venous pressure leads to the deterioration of CVD, even with an optimal calf muscle pump.[12] Therefore, treatment of insufficient veins, venous obstruction and ambulatory compression therapy are the corner stones of CVD management to restore venous function.[12,13] In addition, when a venous leg ulcer occurs increasing PA in combination with compression therapy has shown to improve ambulatory venous function and wound healing.[5,14,15] However, studies on PA interventions in earlier stages of CVD are scarce.[16,17] Guidelines for PA in CVD patients are therefore limited to the advice of walking and calf muscle exercises.[13]

The World Health Organisation (WHO) has developed general recommendations for PA for a healthy lifestyle and prevention of non-communicable diseases.[18] For adults these recommendations include at least 150 minutes of moderate- to vigorous-intensity aerobic PA throughout the week in combination with muscle-strengthening activities on two or more days per week. The aerobic activity should be per-

formed in bouts of at least 10 minutes. Furthermore, a recommendation to engage in balance exercises on at least three days per week is added for older adults with poor mobility.

Because CVD is a non-communicable disease, the WHO guideline would be suitable for CVD patients. However, to our knowledge there is no study that investigates PA levels in a CVD population and whether these patients achieve the WHO recommendations for PA.

Therefore, the aim of this study is to investigate the PA levels of CVD patients with mild to severe CVD and to compare the results with the PA guidelines of the WHO.

Methods

Study design

A cross-sectional study was conducted on 74 patients with CVD. Patients were recruited from primary and secondary care in the Netherlands. Patients were also recruited from the general population through convenience sampling and research invitations in local newspapers. Data were collected between November 2018 and February 2020. The researcher AM performed all measurements for each patient according to a study protocol and registered the outcomes in a Case Report Form (CRF). Patients visited the location of their health care provider (HCP) or one of the study locations close to them for the measurements.

Participants

Patients(>40 years old) with clinical signs (C-classification, Lurie, 2020) of varicose veins (C2), oedema (C3), skin changes (C4) and (healed) venous leg ulcers (C5-C6) were included in the study. CVD patients with no clinical signs (C0) and only reticular veins (C1) were excluded because these patients have no signs of venous insufficiency (yet). CVD patients with clinical signs C2-C6 mostly experience one or more of the symptoms that might influence their PA or will have progressed to more severe clinical signs because of reduced PA. In case of CVD C5-C6, patients with a first venous leg ulcer were included. Patients with permanent immobility, and patients who were unable to understand and sign the informed consent were excluded.

Patient characteristics

Patient characteristics were measured using a questionnaire including: age, gender,

clinical classification of CVD, education, personal history of thrombosis, the source of recruitment, multimorbidity, use of walking aids, changes in PA in the past and a score on a visual analogue scale (1-10) for PA after a change in PA in the past. Multimorbidity was defined as two or more chronic diseases in addition to the CVD including, among others, other cardiovascular diseases, diabetes, joint diseases, lung diseases, and neurological diseases. The following additional patient characteristics were measured: weight and height (to calculate Body Mass Index), waist circumference with a flexible metric measuring tape (at the midpoint between the lower rib margin and the top of the iliac crest). Duplex Ultrasound was used to diagnose deep or superficial (truncal) venous insufficiency in each patient.

Physical activity measurement

PA was measured using accelerometers (wGT3X, Actigraph LLC, Pensacola, FL, USA) for the objective measurement of physical activity and sedentary behaviour. Patients were instructed to wear the accelerometer at the waist for seven executive days. Measurement of over twelve hours per day on at least three days were used in the analysis. Each minute of activity was categorised using the following intensity threshold values of accelerometer counts per minute (CPM) of the 3-axis of the accelerometer (vector magnitude): sedentary behaviour (<200 vector magnitude CPM in bouts of 30 minutes), light PA (200-2689 vector magnitude CPM in bouts of 10 minutes), and moderate to vigorous PA (>2689 vector magnitude CPM in bouts of 10 minutes).[19] Self-reported PA with a standardised questionnaire is shown to correlate with objective accelerometer data on PA.[20] We therefore used a combination of objective and subjective measurements of PA to gain insight into short (7-days of accelerometer data) and long-term (questionnaire on PA in the past six months) PA including water sports that cannot be measured with the accelerometers.[21] Subjective assessment of PA was measured using a standardised questionnaire for the Dutch Health Monitor developed by the National Institute for Public Health and the Environment.[22] This questionnaire includes: PA from and to work, PA at work, domestic activities, sports and leisure PA (including walking and bicycling).

Data analysis

Data were analysed using IBM SPSS statistics version 25 (IBM SPSS Statistics for Windows, Chicago, IL, USA) and ActiLife 6 version 6.13.4. Freedson Adult Vector Magnitude (3-axis) 2011[19] was used to calculate the CPM of sedentary behaviour, light PA and moderate-to-vigorous PA (MVPA). Using the valid measurement days, daily averages for all PA measurements were calculated. In addition, a week aver-

age for MVPA was calculated. Continuous variables were presented as mean and standard deviations or median and interquartile range when the variable was not normally distributed. Categorical variables were presented as the number of patients and percentages. Meeting the physical activity recommendations was calculated and middle-aged (40-64 years) patients were compared to elderly patients (65 years and older). For all PA data patients with mild CVD (C2) were compared to patients with moderate to severe CVD (C3-C6). Between groups differences of categorical variables were calculated using Chi-Squared test. Between groups differences of continuous variables were calculated using independent sample T-tests for normally distributed data and Mann–Whitney U-tests for abnormally distributed data. Correlations between variables were calculated using Spearman's Rho for abnormally distributed continuous data. Statistical significance was set at $p<0.05$.

Ethics

The study protocol was submitted to the Medical Research Ethics Committee (MREC) of the University Medical Centre (UMC) Utrecht (registration number 17-670/C). The MREC declared that the "Medical Research Involving Human Subjects Act" (WMO) does not apply to this study and official approval of the MREC UMC Utrecht is not required under the WMO. All participants signed a written consent prior to participation. The study was performed according to the Declaration of Helsinki.

Results

A total of 74 patients were included in this study. Data of four CVD C2 patients (two males and two females) were lost due to a technical error in the case report forms. The four patients were contacted and asked to fill out the questionnaire again. Two patients returned the questionnaire and accelerometer data were available off all four patients. In addition, the accelerometers were not returned by six patients and three patients did not wear the accelerometer for a minimum of 12 hours on at least three days. This explains the variation in the total number of patients of the results.

The study included mostly older patients with a mean age of 68.5 ±10.6 years (Table 1). The majority of the patients were female (64%), overweight or obese (75%), and had two or more comorbidities (69%). Half of the patients had a current insufficiency in one of the truncal veins and 19% had a personal history of thrombosis. Seven percent of the CVD patients used walking aids and 55% experienced an event in the past that led to a reduction in their PA. Patients scored their PA a

Variable	Patients with questionnaire data (N=72)	Patients with accelerometer data (N=63)*
Age (mean, SD)	68.5 (10.6)	68.5 (10.4)
Gender (female)	46 (64%)	40 (66%)
Body Mass Index (kg/m2, mean, SD)	29.3 (8.8)	28.2 (5.0)
Normal weight (<25)	18 (25%)	15 (24%)
Overweight (25-30)	28 (39%)	27 (43%)
Obesity (>30)	26 (36%)	19 (30%)
Clinical classification		
C2: Varicose Veins	31 (42%)	28 (44%
C3: Oedema	18 (24%)	14 (22%)
C4: Skin changes	6 (8%)	6 (10%)
C5: Closed venous leg ulcer	9 (12%)	7 (11%)
C6: Active venous leg ulcer	10 (14%)	8 (13%)
Venous insufficiency in the truncal veins (N=70)		
Current insufficiency in the truncal veins	35 (50%)	30 (49%)
No insufficiency in the truncal veins	14 (20%)	12 (20%)
Insufficiency treated in the past	21 (30%)	19 (31%)
Bilateral chronic venous disease (N=70)	35 (50%)	
Thrombosis	14 (19%)	12 (20%)
Recruited from		
General population	34 (46%)	29 (46%)
Primary care	5 (7%)	4 (6%)
Secondary care	35 (47%)	30 (48%)
Walking aids	5 (7%)	4 (7%)
Current VAS-score for physical activity (median, IQR)	7 (5-8)	7 (5-8)
Experienced an event that led to reduced physical activity	39 (55%)	34 (56%)
Multimorbidity (≥2 comorbidities excl. CVD) (%)	50 (69%)	44 (70%)

Table 1: Patient characteristics

Abbreviations: SD=standard deviation, IQR=interquartile range, VAS=Visual Analogue Score, CVD=Chronic Venous Disease.

**Data on BMI measurement and venous insufficiency in the truncal veins were not available off the two patients who did not return the questionnaire for these characteristics N=61.*

median of 7 out of 10 on a VAS. From the patient characteristics only BMI differed significantly between mild and moderate to severe CVD patients (26.5 ±3.5 kg/m2 in mild CVD patients compared to 29.7 ±5.6 kg/m2 in moderate to severe CVD patients, p=0.011).

Physical activity recommendation	40-64 year (N=24)	65-90 year (N=48)
Meets the guideline for PA: 150 minutes of MVPA	12 (50.0%)	15 (31.3%)
Meets the guideline for PA: 150 minutes MVPA including muscle strengthening activities	9 (37.5%)	15 (31.3%)
Muscle strengthening activities	8 (33.3%)	29 (60.4%)
Sports at least 2x per week	7 (29.2%)	18 (37.5%)
Balance exercises	2 (8.3%)	7 (14.6%)

Table 2: Physical activity from the health monitor questionnaire in different age groups

Abbreviations: MVPA=Moderate to Vigorous Physical Activity

Physical activity recommendation	All patients (N=72)	Mild CVD (N=30)	Moderate to severe CVD (N=42)
Meets the guideline for PA: 150 minutes of MVPA	27 (38.0%)	14(48.3%)	13 (31.0%)
Meets the guideline for PA: 150 minutes including muscle and bone strengthening exercises	24 (33.8%)	13 (44.8%)	11 (26.2%)
Muscle strengthening activities	37 (52.1%)	16 (55.2%)	21 (50.0%)
Muscle strengthening activities (sports) at least 2x per week	25 (35%)	11 (37%)	14 (34%)
Balance exercises	9 (12.7%)	7 (24.1%)	2 (4.8%)*
A 30 minute walk on at least 5 days per week	28 (39.4%)	12 (40.0%)	16 (39.0%)
Reported no walking per week	11 (15.3%)	4 (13.3%)	7 (16.7%)

Table 3: Physical activity data from questionnaire for mild and moderate to severe chronic venous disease

Abbreviations: CVD=Crhonic Venous Disease, MVPA=Moderate to Vigorous Physical Activity

**significantly different in Chi-Square test ($p<0.05$)*

of the middle-aged patients reached the 150 minutes of MVPA in a week according to the health monitor questionnaire. For the elderly patients this was only 31.3% but they had higher percentages of muscle strengthening activities (60.4% compared to 33.3% in middle-aged patients). The percentage of patients performing balance exercises were very low in both age groups with only 8.3% and 14.6% of the middle aged and elderly patients (Table 2).

The minority of the patients reached the PA recommendations (<45%) except for the muscle strengthening activities which was performed at least once a week by 50-55% of the CVD patients. No significant differences were found between

reaching the physical activity recommendations in mild CVD patients compared to moderate to severe CVD patients (Table 3). Furthermore, 15% of the CVD patients did not perform weekly walks and only 39% walked at least 30 minutes on at least five days per week.

The data from the accelerometers (Table 4) showed similar results to the questionnaire with 30.2% (compared to 38.0%) of the CVD patients reaching the 150 minute MVPA guideline. However, 55.6% of the CVD patients did engage in any light PA or MVPA for 30 minutes or more on at least five days in the past week. For MVPA only, the majority of the patients (72.6%) did not engage in any MVPA for 30 minutes or more in the past week. Overall, the patients with moderate to severe CVD scored slightly worse compared to the mild CVD patients who engaged in more (extensive) MVPA. However, this difference was not statistically significant.

The median number of steps per day was significantly lower ($p<0.05$) in patients with moderate to severe CVD, compared to mild CVD patients (7747 [5858-9604] vs. 5536 [4510-8438]). There was a 29% difference in the median number of steps between the groups. Mild CVD patients engaged significantly longer in light PA per bout but it differed only by 2 minutes (18 minutes compared to 16 minutes per bout). Overall, moderate to severe CVD patients scored slightly worse compared to the mild CVD patients with an hour more sedentary behaviour per day, 10 minutes less light PA per day and 61 minutes less MVPA per week (9 minutes less per day). However, these findings were not statistically significant.

Accelerometer variable	All patients (N=63)	Mild CVD (N=28)	Moderate to severe CVD (N=35)
150 minutes MVPA in bouts of 10 minutes	19 (30.2%)	11 (39.3%)	8 (22.9%)
No physical activity of 10 executive minutes of MVPA	13 (20.6%)	4 (14.3%)	9 (25.7%)
No physical activity of 30 executive minutes of MVPA	45 (72.6%)	18 (64.3%)	27 (79.4%)
At least 5 days of at least 30 minutes executive light or moderate to vigorous physical activity	28 (55.6%)	13 (53.6%)	15 (57.1%)

Table 4: Physical activity data from accelerometers for mild and moderate to severe chronic venous disease

**MVPA = Moderate to Vigorous Physical Activity*

Accelerometer variable	All patients (N=63) (Median, IQR)	Mild CVD (N=28) (Median, IQR)	Moderate to severe CVD (N=35) (Median, IQR)
Steps per day	6427 (4989-8834)	7747 (5858-9604)	5536 (4510-8438)*
Sedentary behaviour			
Hours per day	6.0 (4.3-7.5)	5.5 (3.9-7.1)	6.5 (4.7-7.6)
Minutes per 30 minute bout	53.6 (46.7-60.8)	50 (44-60)	56 (48-62)
Number of 30 minute bouts per day	6.7 (5.0-8.4)	6.0 (5-8)	7.0 (5-8)
Light Physical Activity			
Minutes per day	245 (192-331)	254 (190-290)	244 (192-340)
Minutes per 10 minute bout	17.2 (16.1-19.8)	16.2 (15-18)	17.8 (17-21)*
Number of 10 minute bouts per day	13.6 (11.1-17.5)	14.7 (12-18)	13.3 (11-17)
Moderate to vigorous Physical Activity			
Minutes per week in 10 minute bouts	85 (21-158)	115 (35-180)	56 (13-142)
Minutes per day in 10 min bouts	12 (3-23)	16.6 (5-25)	8.0 (2-20)
Minutes per 10 minute bout	13.0 (10.4-18.8)	13.4 (11-20)	12.8 (3-19)
Number of 10 minute bouts per day	0.71 (0.2-1.3)	0.86 (0.4-1.6)	0.50 (0.1-1.3)

Table 5: Physical activity data on sedentary behaviour, light and moderate to vigorous physical activity for uncomplicated and complicated chronic venous disease

Abbreviations: CVD=Chronic Venous Disease, IQR = inter quartile range.

**significantly different (p<0.05) in Mann-Whitney U test.*

Risk factors for CVD: age and excess weight

Age has a significant but weak negative correlation (r=-0.318; p=0.013) with the average number of steps per day. BMI has a significant but weak negative correlation (r=-0.493; p<0.001) with the minutes per MVPA bout and the minutes of MVPA per week. Waist circumference in females shows a weak but significant negative correlation (-0.417; p=0.008) with the number of steps per day, and a weak signif-

icant positive correlation with hours of sedentary behaviour (r=0.341; p=0.034). In addition, waist circumference shows a moderate negative correlation with minutes of MVPA per week (r=-0.513; p=0.001) and minutes per MVPA bout (r=-0.632; p<0.001).

Age, BMI and waist circumference	Physical activity measure	Spearman's Rho	P-value
Age	Number of steps per day	-0.318	0.013
BMI	Minutes per MVPA bout	-0.493	<0.001
BMI	Minutes of MVPA per week	-0.300	0.019
Waist circumference (female)	Steps per day	-0.417	0.008
Waist circumference (female)	Hours of sedentary per day	0.341	0.034
Waist circumference (female)	Minutes of MVPA per week	-0.513	0.001
Waist circumference (female)	Minutes per MVPA bout	-0.632	<0.001

Table 6: correlations of age and weight with physical activity measures

Abbreviations: BMI= Body Mass Index, MVPA= Moderate to Vigorous Activity

Discussion

The aim of this study is to investigate the PA levels of CVD patients with mild to severe CVD and to compare the results with the PA recommendations of the WHO. We found that a minority of the CVD patients engaged in sufficient PA according to the recommendations of the WHO. The number of steps per day was significantly lower in patients with moderate to severe CVD compared to patients with mild CVD with a difference of 2,000 (29%) steps per day. In addition, weak to moderate significant correlations were found showing a decrease in PA the CVD patients when age, BMI or waist circumference increased. Furthermore, patients with moderate to severe CVD had slightly lower light PA and MVPA, and an hour more sedentary behaviour per day compared to patients with mild CVD. However, this difference was not statistically significant.

The significantly lower number of steps per day in CVD patients was also found in a study comparing 75 CVD and non-CVD patients (23 C2-C3 patients, 24 C4 patients, 24 C5-C6 patients, and 15 controls).[23] However, the CVD C5-C6 patients showed a higher number of continuous steps per day compared to the other stages

of CVD. This might have been the result of treatment strategies, because exercise like walking is advised in case of a venous leg ulcer.[13] In addition, the number of steps per day in the study of Eiffel et al. (2006) was considerably higher, with 15,716-20,433 steps per day. This can be explained by the exclusion of patients with impaired mobility, current musculoskeletal disease or other diseases limiting PA. The much lower average of daily steps in our study might be explained by the inclusion of patients with comorbidity impairing PA and the higher average age of 68.5 ±10.6 years compared to the average age of 50 years in the study of Eiffel et al. (2006). Increasing age is associated with lower levels of PA and therefore less steps per day. A study with 554 healthy older adults (aged 60-79) in Germany found a step average of approximately 7500 steps per day.[24] This is in line with our findings in the patients with mild CVD.

A review of studies including older adults and populations with chronic diseases found that 7,100 steps per day should be feasible for older adults.[25] This number included 5,000 daily steps and at least 5 times per week a walk of 30 minutes (MVPA) equalling 3,000 steps. Our study shows that at least 25% of the patients with moderate to severe CVD did not even reach the 5,000 steps per day (4,500 steps as maximum of the first quartile). However, we found that 40% of the CVD patients walked for 30 minutes or more on at least 5 days a week. This percentage is much higher compared to the 13% found in a study among Dutch venous leg ulcer patients.[26] This can be explained, because patients with venous leg ulceration experience the most severe lower leg complaints, like pain, and the highest impact on their daily living.[4,27] In addition, patients with (healed) venous leg ulceration might avoid PA because of a fear of injury.[28]

Furthermore, a study including 150 Dutch patients with venous leg ulcers found that 26% of the patients did not have any MVPA during the week.[26] This is comparable to the 25% we found in the moderate to severe CVD patients. In addition, the venous leg ulcer study found a slightly higher percentage of 44% of patients who reached 150 minutes of MVPA in one week compared to the 38% in our study.[26] Venous leg ulcer patients are expected to have lower PA levels due to pain and bandaging of the lower legs that can lead to a reduced range of ankle motion.[29] However, venous leg ulcer patients often receive exercise interventions and the advice to walk more often according to venous leg ulcer guidelines.[13,30] This might explain the higher percentage of patients reaching the 150 minutes MVPA in the study of Heinen et al. (2007) and the higher number of steps per day in the study of Eiffel et al. (2006) in venous leg ulcer patients.

Overall the total study population had insufficient PA levels with only 38% of

<65 year old CVD patients and 31% of ≥65 years old CVD patients reaching the PA recommendation of the WHO. In the general Dutch population this percentage is higher with 52% of the <65 year olds and 40% of the ≥65 year olds reaching the PA recommendations. A study including 409 older (65-75 year old) Dutch patients showed an even higher prevalence of sufficient PA in 48% in males to 40% in females.[31] However, in the study of Lubs et al. (2018) sufficient PA was defined as vigorous activity at least once a week. Our study shows that the CVD patients are less physically active compared to the general Dutch population. This indicates the need for PA measurement and interventions in CVD patients with earlier stages of CVD and not just in patients with a venous leg ulcer. The RIVM questionnaire is a standardised, accessible and easy to use tool to implement in Dutch clinical practice for CVD care. It provides a complete view on a patient's PA pattern and can help improve PA to possibly delay the progression of CVD.

In this study we focused on the recommendations of the WHO for PA to maintain a healthy lifestyle including 150 minutes of MVPA. In addition, a large PA study in 13 European countries including older adults showed that participating in light PA to moderate PA more than once a week is associated with lower odds of developing chronic disease.[32] This might implicate that light PA is equally important in older adults to achieve sufficient PA levels. However, most studies including our study use the standardised threshold values for MVPA of 2690 CPM. This threshold represents a metabolic equivalent of three or more indicating an increase in heart rate. Other studies among older adults and older adults with chronic diseases like diabetes mellitus have found that the threshold for reaching MVPA (metabolic equivalent of three or more) might be lower for these patient populations.[33-35] Older adults and patients with chronic diseases might reach higher heart rates compared to healthy adults (reaching a higher metabolic equivalent value) when engaging in the same PA. In other words, light PA in older adults might be comparable to MVPA in younger adults using the threshold values of 2690 CPM. The results of MVPA might therefore be underestimated in our study. In future research using accelerometers to measure PA levels, the heart rate should be measured as well to gain a better insight in the actual MVPA in older adults with CVD. Thresholds for MVPA should be recalculated for different age groups to include age-appropriate thresholds in future PA research.

In addition, we found that age, BMI and waist circumference in women had a weak but significant correlation with several PA outcomes. This is in line with a study that investigated the influence of BMI and waist circumference on physical performance in 1076 older patients (57-70 years). The study showed that increased BMI

and waist circumference after 10 years was significantly associated with poor physical performance on several fitness tests like the 6 minute walking test and timed up and go test.[36] In addition, it is known that age and chronic diseases in can negatively affect PA levels.[25] This indicates that in patients with CVD, where the prevalence increases with age and overweight and comorbidity is common, multiple factors might play a role in their PA levels. We might therefore conclude that measuring and treating PA problems should be an ongoing process in healthcare for CVD patients to increase current PA and prevent further reduction of PA. Furthermore, the interplay between age, excess weight, comorbidity and PA in CVD patients points to the importance of assessing the CVD patient as a whole and not just focus on the treatment of the individual signs and symptoms. The next step towards improving CVD care is to investigate PA interventions focused on improving insufficient PA levels in the prevention (and delayed onset) of disease progression in CVD patients.

Strengths and limitations

The use of objective and subjective measurements of PA made it possible to provide a complete overview of the patients' PA levels. The accelerometer offers a reliable measurement, however it does not account for temporal changes in PA in the short period of measurement. The questionnaire was, therefore, a valuable addition to gain insight into PA levels in the past six months and specific activities such as walking. In addition, the sedentary time might be underestimated using the accelerometers. Patients were instructed to wear the accelerometer from getting up to going to bed because we did not collect sleep data. The accelerometers often stopped measuring around 8 or 9 p.m. leading to measurement days of less than 16 hours (24 hours – 8 hours of sleep). It is possible that patients took of the accelerometer early. Because patients knew the accelerometers were for PA measurement it is unlikely that the patients would engage in PA after taking off the accelerometer. We therefore assume the measurement days of at least 12 hours are reliable to include all PA data.

Conclusion

PA in CVD patients is insufficient and should be treated in CVD healthcare to improve venous outflow and optimise the calf muscle pump function to aim at delaying the onset of more severe CVD. Patients with moderate to severe CVD had significantly less steps per day compared to patients with mild CVD. Overall, CVD patients were mostly older, overweight, and did not meet the international PA recommendations for a healthy lifestyle. Further research is necessary to investigate

the effect of increasing PA levels in CVD patients on disease progression.

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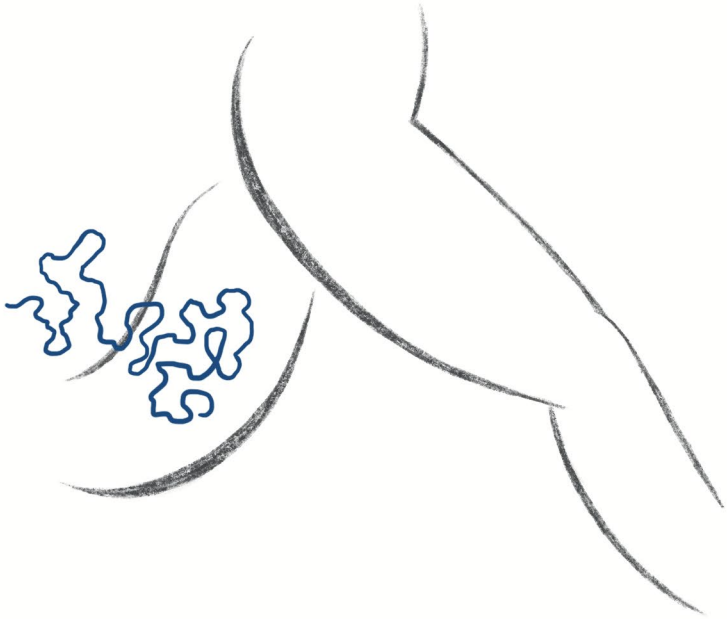
CHAPTER SEVEN



CURRENT CARE FOR CHRONIC VENOUS DISEASE PATIENTS IN THE NETHERLANDS: WHAT IS MISSING?

SUMMARY

Background: Chronic Venous Disease (CVD) is a progressive disease. The progression of the clinical signs of CVD lead to a significant decrease in disease specific quality of life. Healthcare for CVD includes duplex diagnostics, invasive and non-invasive treatments. Several healthcare providers (HCP) are involved in the treatment of CVD but clear, consistent guidelines on referral, treatment and follow-up of patients is lacking. The aim of this study is to investigate the current care for patients with CVD in The Netherlands.

Methods: Data were collected in primary care, secondary care and through convenience sampling in the general population in The Netherlands. In total 74 participants (aged >40 years) with CVD (varicose veins, oedema, skin changes and venous leg ulcers) were recruited. Data on quality of life, treatment and follow-up were collected using questionnaires and duplex ultrasound was used for CVD diagnostics.

Results: Patients had a mean age of 68.5±10.6 and 64% was female. The majority of the patients experienced one or several physical complaints that led to a reduction in quality of life. Over 30% of the patients did not receive invasive treatment at the time of the measurements. Half of the patients with a current venous insufficiency were treated for one of the truncal veins in the past. Non-invasive treatments such as calf muscle exercises, and advice for walking was mentioned by 4%-23% of the patients. Non-compliance to wearing compression stockings was 90%.

Conclusion: Healthcare for CVD patients in the Netherlands is insufficient. A collaboration between primary and secondary care HCPs is crucial in the management of this seemingly harmless yet complex disease.

As submitted

Meulendijks AM, Tjin EPM, Schoonhoven L, Neumann HAM. Current care for Chronic Venous Disease patients in The Netherlands: what is missing?

Current care for Chronic Venous Disease patients in The Netherlands: what is missing?

Introduction

Chronic Venous Disease (CVD) appears in about 40% of the Western population.[1] CVD can present several clinical signs from reticular veins and Varicose Veins (VV) to oedema, trophic skin changes and eventually a venous leg ulcer. Whereas reticular veins are mostly experienced as a cosmetic problem, larger VV, oedema, and more severe stages of CVD can cause serious complaints that have a negative impact on daily living. The progression of the clinical signs and symptoms of CVD therefore lead to a significantly decreased disease specific Quality of Life (QoL).[2]

However, not all CVD patients recognise the signs of CVD or experience the CVD symptoms as 'complaints'. A population study in Germany showed that about 6-38% of CVD patients with VV to venous leg ulcers do not experience any complaints such as a feeling of heaviness in the legs, swelling, pain or muscle cramps.[3] Patients without CVD complaints are less likely to seek healthcare for their CVD. Healthcare seeking behaviour also differs between men and women. Men have a significantly higher clinical class (C-class) compared to women when they are treated for their varicose veins.[4] However, even when CVD is diagnosed and treated the disease can still progress into more severe clinical stages. The Edinburgh vein study showed that 58% of the patients with VV, oedema or skin changes progressed to a more severe clinical stage in a period of 13 years.[5] A healthcare follow-up to monitor, treat and prevent progression of CVD is therefore indicated.

When patients do seek healthcare for their CVD signs and symptoms a diagnosis must be made. To diagnose CVD, ambulatory venous pressure measurement is the gold standard. However, this measurement is too invasive and expensive for use in daily practice. International CVD guidelines for dermatologists and vascular surgeons therefore recommend the use of a duplex ultrasound to diagnose and locate the CVD.[9] When duplex diagnostics is not feasible, for example in primary care, the clinical-class (C-class) of the CEAP (clinical, etiological, anatomical and pathological) classification[6] should be registered.[9] A study including 89 patients with CVD showed that the C-class of the CEAP classification correlates well with ambulatory venous pressure measurement. However, the patients in this study were assessed by a dermatologist and a phlebologist.[8] Both dermatologists and phlebologists are Healthcare Providers (HCP) trained to recognise signs and symptoms of CVD. HCPs in primary care are not trained in this field of expertise. A large study among

general practitioners in Belgium and Luxemburg showed that general practitioners recognised only 46% of the 6009 CVD patients. The underestimation of CVD patients in primary care can lead to restrained referral patterns for adequate diagnostics and treatment. A study investigating the Dutch healthcare for CVD patients was not found.

After diagnosing CVD, treatment consists of invasive treatments like VV removal, vein stenting and anticoagulants for venous thrombosis, and non-invasive treatments like compression therapy and lifestyle advices to support the venous outflow.[7] In the Netherlands HCPs in primary care can provide compression therapy and lifestyle advice. HCPs in secondary care provide the duplex diagnostics and invasive treatments. The general practitioner is the gatekeeper for healthcare in the Netherlands and therefore the first HCP any patient with healthcare problems visits. However, there are no clear primary care guidelines on how to diagnose or register CVD patients and when to refer a patient with CVD for duplex diagnosis and possible invasive treatment.[10,11] There are also no clear international and national guidelines for primary and secondary care on the (frequency of) follow-up of a patient with CVD.[7,9-12] Current care for patients with CVD in the Netherlands therefore remains unknown.

The aim of this study is to investigate current care for patients with CVD from VV to a venous leg ulcer in the Netherlands.

Methods

Study design

This cross-sectional study was conducted in the Netherlands. Patients were recruited in secondary care through six dermatologists, two vascular surgeons and two specialised wound care nurses, and in primary care through two general practitioners and two home care organisations specialised in wound care. Patients were also recruited from the general population through convenience sampling, flyers in healthcare institutions and research invitations in local newspapers.

Participants

Patients >40 years old with a CVD classification C2-C6 (see Table 1) were included in the study. CVD C0 and C1 patients were excluded because treatment is not always indicated in these clinical stages. We included patients with a first venous leg ulcer only in case of CVD C5-C6. We excluded patients with permanent immobility, and patients who were unable to understand and sign the informed consent.

Clinical class	Clinical sings
C0	No clinical signs
C1	Reticular veins
C2	Varicose veins
C3	Oedema
C4	Skin changes (pigmentation, eczema, lipodermatosclerosis, atrophie blanche, corona phlebectatica)
C5	Healed venous ulcer
C6	(Recurrent) Active venous ulcer

Table 1: Clinical classification of Chronic Venous Disease (Lurie, 2020)

Data collection

Data were collected between November 2018 and February 2020. The researcher AM performed the measurements for each patient and registered the outcomes in a Case Report Form (CRF). Patients visited the location of their healthcare provider (HCP) or one of the study locations close to them for the measurements and to fill out three questionnaires.

Outcomes

The following outcomes were measured: weight, height (to calculate Body Mass Index), waist circumference, blood pressure and Ankle Brachial Pressure Index (ABPI). Duplex Ultrasound was used to diagnose deep or superficial (truncal) venous insufficiency in each patient. The researcher (AM) measured obstruction and reflux in the femoral vein (FV), saphenofemoral junction, the great saphenous vein (GSV) (three centimetre below the junction, halfway of the thigh and at the knee), the popliteal vein (PV), and the small saphenous vein (SSV) (below the knee and mid-calf). The following outcomes were collected using a questionnaire: patient characteristics (age, gender, clinical classification of CVD, the source of recruitment, education, comorbidities, smoking, alcohol, and minutes walking per week), age of onset and first treatment of CVD, follow-up by any HCP, the patients knowledge on the progression of CVD into a venous leg ulcer, and CVD treatment (invasive and non-invasive treatments as mentioned in the Dutch guidelines[7-10,11]). Quality of life was measured using the self-administered versions of the general European Quality of Life 5 dimensions 5 levels (EQ-5D-5L) and the disease specific ChronIc Venous Insufficiency Questionnaire (CIVIQ-14)[13]

Data analysis

We analysed the data using IBM SPSS statistics version 25. Continuous variables with a normal distribution are presented as mean and standard deviations. Median and interquartile ranges are presented when the variable was not normally distributed. Categorical variables are presented as number of patients and percentages. No statistical references are made in this study.

Ethics

The study protocol was submitted to the Medical Research Ethics Committee (MREC) of the University Medical Centre (UMC) Utrecht (registration number 17-670/C). The MREC declared that the "Medical Research Involving Human Subjects Act" (WMO) does not apply to this study and official approval of the MREC UMC Utrecht is not required under the WMO. All participants signed a written consent prior to participation.

Results

A total of 74 patients were included in the study. Data of four CVD C2 patients (two males and two females) on one questionnaire and the measurements were lost due to a technical error in the case report forms. The four patients were contacted and asked to fill out the questionnaire again. Repeating the measurements was not possible due to the COVID-19 outbreak. Two patients returned the questionnaire. This explains the variation in the total number of patients in the results.

Patient characteristics

Patient characteristics are shown in Table 2. The study population had a mean age of 68.5 years (SD 10.6) and consisted predominantly of female patients (64%). Most patients had CVD C2 (42%) and were recruited from the general population and secondary care. More than half of the patients had a high risk of developing cardiovascular disease and had multimorbidity with two or more chronic diseases in addition to the CVD (i.e. pulmonary diseases, joint diseases, neurological diseases etc.). More than a third of the patients had hypertension, obesity and were current or past smokers (see Table 1). Patients reported walking with a median of 165 minutes per week.

Chronic Venous Disease and healthcare

The total scores of the general and disease specific QoL were similar with a median

of 0.87 and 89.5 respectively which indicates a reduced QoL (see Table 3). In addition, 65% and 90.5% of the patients currently experienced complaints regarding to general and disease specific QoL respectively. The majority of the patients had trouble sleeping, experienced pain, had trouble bending and kneeling, and/or experienced problems with their daily activities because of their CVD.

Fifty percent of the patients reported the onset of the first symptoms of CVD before 40 years of age (see Table 4). Patients who had their VV removed after the age of 40 were more prevalent compared to patients with VV removal before the age of 40 (44% vs 27%). Eight percent of the patients never sought any healthcare for their CVD and only 30% of the patients knew that CVD can lead to a chronic wound. A total of 13% of the patients had a follow-up planned with a HCP. Five out of nineteen patients with a VLU did not receive a duplex diagnostics (yet). The average duration of the wound of these five patients was 16 weeks (data not shown).

Invasive treatment and non-invasive treatment

Any invasive treatment occurred in 68% of the patients at the time of the measurements. Invasive treatment in the truncal veins (GSV, SSV) occurred in 37 (51%) patients (see Table 5). Of those patients 70% had a recurrent insufficiency in at least one of the truncal veins. Of the 26 patients who were treated in the past and had a recurrent insufficiency 62% was treated over 10 years ago. In addition, 80% of the patients who did not receive invasive treatment (yet) had an insufficiency in one of the truncal veins.

Of the non-invasive treatments Ambulatory Compression Therapy (ACT) is the most frequent therapy with 32% for bandages and 78% for stockings (ACTS). The compliance to wearing the ACTS however is very low. Only 7% of the study population would wear the ACTS on a daily basis. This included mostly the patients with an active VLU (data not shown). In addition, in patients with more severe CVD (C3-C6) 24% had no experience with ACTS (yet) and 21% has not worn the ACT for at least six months.

Whereas invasive treatment and ACTS was present for the majority of the patients, other non-invasive treatments occurred less frequently (see Table 6). Lifestyle advice such as calf muscle exercises, putting the legs high when resting, avoid standing, and walking more frequently was mentioned by 4%-23% of the patients. The advice for weight loss was mentioned by 1 patient only.

Characteristics	N=74 (%)
Age (mean, sd)	68.5 (10.6)
Gender (female)	47 (64%)
Clinical classification	
C2	31 (42%)
C3	18 (24%)
C4	6 (8%)
C5	9 (12%)
C6	10 (14%)
Recruited from	
General population	34 (56%)
Primary care	5 (7%)
Secondary care	35 (47%)
Education	
Low (primary school)	28 (39%)
Medium (intermediate vocational education)	33 (47%)
High (higher vocational education/university)	9 (13%)
Hypertension (diastolic blood pressure of ≥90 mm/Hg)	N=72 (100%)
Current hypertension	7 (10%)
No current hypertension because of medication use	20 (27%)
Cardiovascular disease risk*	40 (57%)
Body Mass Index	
≤24.9 (normal weight)	18 (25%)
25.0-29.9 (overweight)	28 (39%)
≥30 (obesity)	26 (36%)
Peripheral arterial disease (ABPI <0.8)	2 (2.8%)
Personal history of thrombosis	14 (20%)
Post-thrombotic syndrome	3 (4%)
Multimorbidity (≥2 chronic diseases excl. obesity and CVD)	50 (69%)
Polypharmacy (≥5 drugs)	18 (25%)
Smoking (current or past)	34 (48%)
No or normal alcohol use	51 (73%)
Minutes reported walking per week (median, IQR)	180 (60-360)
Days reported walking per week (median, IQR)	3.5 (1-7)
Patients that reported walking of at least 30 minutes per day	30 (42%)

Table 2: Patient characteristics

*Sd = standard deviation, ABPI = Ankle Brachial Pressure Index, CVD = Chronic Venous Disease, IQR = Inter Quartile Range, *measured by waist circumference male >102 centimetre, female >88 centimetre*

Quality of life (QoL) scores	N=74 (100%) / Median (IQR)
General QoL: EQ5D5L index	0.87 (0.81-1.00)
EQ5D5L VAS score	89.5 (75.0-100)
Disease specific QoL: CIVIQ-14 index score	91.1 (73.2-96.4)
Experiencing any reduction in general QoL (index <1.00)	48 (65%)
Experiencing any reduction in disease specific QoL (index <100)	67 (90.5%)
EQ-5D-5L score >1*	
Pain	45 (61%)
CIVIQ-14 score >1*	
Sleeping poorly	43 (58%)
Pain	42 (57%)
Problems squatting / kneeling	39 (53%)
Impairment with daily activities	36 (49%)

Table 3: General and disease specific quality of life

*IQR = Inter Quartile Range, EQ-5D-5L = European Quality of Life, 5 dimensions, 5 levels, CIVIQ-14 = ChronIc Venous Insufficiency quality of life Questionnaire 14 questions, >1 = slight to severe problems. The full overview of the quality of life questionnaires can be found in appendix 1. *Only the questions where approximately half of the patients experienced problems are presented.*

CVD onset & Healthcare	N= 72 (100%)
Age of CVD onset	
<40 years	36 (50%)
>40 years	36 (50%)
Age of first treatment of varicose veins	
<40 years	19 (27%)
>40 years	32 (44%)
No treatment	21 (30%)
Healthcare	
Never had any treatments	6 (8%)
Follow-up by any health care professional	9 (13%)
Patient's knowledge on CVD as the underlying cause of a chronic wound	19 (30%)

Table 4: Onset of Chronic Venous Disease and healthcare

CVD: Chronic Venous Disease

Treatment	N=72 (100%)
Removal of small veins (reticular)	7 (10%)
Varicose vein removal (any varicosities) including duplex diagnostics	48 (68%)
Current insufficiency in the GSV or SSV	54 (76%)
No invasive treatment of the GSV or SSV	**35 (100%)**
Not treated and no current insufficiency in GSV or SSV	7 (20%)
Not treated and current insufficiency in GSV or SSV	28 (80%)
Invasive treatment of the GSV or SSV	**37 (100%)**
Treated and no current insufficiency in GSV or SSV	11 (30%)
Treated and current insufficiency in GSV or SSV	26 (70%)
Invasive treatment in the past and current insufficiency in the GSV or SSV	**26 (100%)**
Less than 10 years between treatment and new insufficiency	7 (27%)
More than 10 years between treatment and new insufficiency	16 (62%)
I do not remember	3 (12%)

Table 5: Invasive treatments for varicose veins

GSV: Great Saphenous Vein (junction to knee), SSV: Small Saphenous Vein (knee to mid-calf)

Treatment	N=72 (100%)	
Received one of the following treatments		
Calf muscle exercises	7 (10%)	
Putting legs high	16 (23%)	
Advice for weight loss	1 (1%)	
Advice for walking more frequently	13 (18%)	
Avoid standing for long periods	3 (4%)	
Bandages	23 (32%)	
Medical compression stockings	55 (78%)	
Current medical compression stockings	**72 (100%)**	**42 (C3-C6) (100%)**
No experience yet*	23 (32%)	10 (24%)
Wearing stockings every day (including taking off earlier)	5 (7%)	4 (10%)
Not wearing stockings for a minimum of 1 day per week	30 (42%)	19 (45%)
Not worn the stockings in the past 6 months	14 (19%)	9 (21%)

Table 6: Non-invasive treatment for Chronic Venous Disease

**Three C6 patients had bandages at the time of the measurements*

Discussion

The aim of this study was to investigate the current care for patients with CVD clinical class C2-C6 in the Netherlands. CVD patients are often treated later than the onset of their 'complaints' and there is almost no follow-up, although it is a slow progressive disease. The majority had invasive treatment in the past but this was not always sufficient. The minority of patients reported non-invasive treatments. Except for compression therapy, which was the most reported treatment but with a low compliance.

Recruiting from the general population resulted in the inclusion of patients with CVD who never, or not recently had seen a HCP for their CVD. Most patients did not experience their current signs and symptoms of CVD as 'complaints' and therefore had no follow-up planned with a HCP. This study also showed that only a third of the patients knew that CVD could progress into a Venous Leg Ulcer (VLU). A qualitative study among Dutch patients with a VLU shows that patients often see the VLU as a skin problem and do not understand the underlying venous pathology when the VLU develops.[14] Another qualitative study among Dutch patients with a VLU shows that patients also did not recognise (the severity of) earlier symptoms of CVD.[15] We can therefore assume that the patients' knowledge on CVD and its progression is insufficient. The patients' awareness of CVD signs and symptoms should be raised in current care in the Netherlands to stimulate healthcare seeking behaviour. Common knowledge on CVD as a chronic progressive disease should also be raised in the general population to increase healthcare seeking behaviour in early stages of CVD.

Almost half of the patients did not receive invasive treatment for their CVD. A large cohort study in North America shows that invasive treatment is a protective factor for the progression of CVD into a VLU with a hazard ratio of 0.187 (CI: 0.182-0.193).[21] However, invasive treatment is only possible with diagnostics using a duplex ultrasound to register the CEAP classification.[7,9,12] More than a third of the patients never had a duplex diagnosis. This might be explained by the guidelines in primary care in the Netherlands. The general practitioner is the first HCP a patient consults when they experience healthcare problems. However, the general practitioners in the Netherlands do not perform duplex diagnostics and therefore cannot register the full CEAP classification. In the VV guideline[10] for general practitioners it is described that a patient should be referred for further diagnostics and treatment: 1) when a patient wishes to be referred and is well-informed, 2) when there are truncal VV or oedema and compression therapy is not sufficient, and 3) when the

patient has an active or healed VLU or trophic skin changes that might benefit from invasive treatment.[11] However, truncal varicose veins in the calf or upper legs are rarely visible, invasive treatment is almost always indicated in C3-C6 patients, and a chronic wound should always be diagnosed to be able to treat the underlying pathology. In addition, when oedema (C3) and skin changes (C4) are present invasive treatment can lead to more additional invasive treatment and a higher recurrence of VV compared to invasive treatment in C2 patients.[22] Therefore, optimising referral criteria in primary care should ensure early duplex diagnostics and invasive treatment for patients with 'only' CVD C2. Furthermore, specific questions on the signs and symptoms of CVD and a thorough examination of the lower extremities is crucial to recognise CVD in primary care.

However, even after duplex diagnostics and invasive treatment CVD is still a chronic condition. The majority of the patients had a recurrence of truncal VV. Studies on truncal VV removal (GSV/SSV) show recurrence rates of about 22% in 2 years[16-18] to 18.5%-40% in 5-10 years[17,19]. In the study of Lam[20] (2018) the recurrence rates were comparable to recurrence reported by patients in the current study. Lam (2018) reported a recurrence rate in the truncal veins of 50%-67% after eight years amongst 223 Dutch patients with invasive treatment of the GSV. In addition, almost a third of the patients in this study developed a recurrence within 10 years. This might be underestimated because we registered the patients' *first* invasive treatment. We did not register whether they had a truncal VV removed at their first treatment. This leads to possible misclassification of the patients that are now registered as 'more than ten years between treatment and recurrent insufficiency'. The time to recurrence of a truncal VV might have been shorter than ten years. A follow-up of CVD patients including duplex investigation is therefore preferred within ten years after treatment of a truncal VV.

Lastly, non-invasive treatments or compliance to compression therapy was mentioned by the minority of the patients. Even though non-invasive treatments are recommended by national and international CVD guidelines (i.e. compression therapy and lifestyle advices such as weight loss, walking more often and calf muscle exercises).[7,9,12] However, not all patients received healthcare at the time of the measurements. The low numbers of non-invasive treatments might therefore be explained by recall bias. In addition, lifestyle advices and wearing ACTS require a behavioural change which can only be accomplished with the active involvement and guidance of a HCP.[23,24] This again denotes the importance of a follow-up for CVD patients. Not only to monitor progression but also to increase adherence to lifestyle advices and wearing ACTS. A collaboration with HCPs involved in weight loss, physical

activity, or compression therapy such a dieticians, physical therapists, and dermal therapists should be implemented in primary and secondary care guidelines to increase compliance.

We specifically recruited patients with a first VLU among other CVD patients. This resulted in a sample that is less representative to the general population because of the overrepresentation of C5-C6 patients our study population. In the general population in Western Europe CVD C5-C6 is the least prevalent of all CVD clinical classes.[25] In the current study 26% of the CVD C2-C6 patients had an active or healed VLU which is higher than the percentages of C3 patients and C4 patients. VLU patients require more frequent healthcare compared to earlier stages of CVD. The overrepresentation of VLU patients should therefore have led to a higher percentage of follow-up. However, the percentage of follow-up we found is similar to that of the Vein Consult Program which included a more representative sample of CVD patients from four countries in Western-Europe.[26] Moreover, we recruited patients from different healthcare and non-healthcare settings to provide more insight in the actual current care in the Netherlands. The recruitment strategy led to the inclusion of patients who currently received no healthcare and no follow-up for their CVD. This might explain the low numbers of follow-up in our study and denotes the problem of the under-recognition of the chronicity of CVD in healthcare.

Conclusion

In conclusion, healthcare for CVD patients in the Netherlands is insufficient. The study shows that the majority of the CVD patients did not receive adequate care, patients were not compliant to care, and a regular follow-up of patients with CVD is not imbedded in current care. This might be a result of the lack of common knowledge amongst patients and HCP on CVD signs and symptoms, and the progression of CVD. HCPs in current care should focus more on the clinical signs and symptoms of CVD and referral of CVD patients so they can receive adequate diagnostics (duplex ultrasound), (invasive) treatment and follow-up. A collaboration between primary and secondary care HCPs is crucial in the management of this seemingly harmless yet complex disease.

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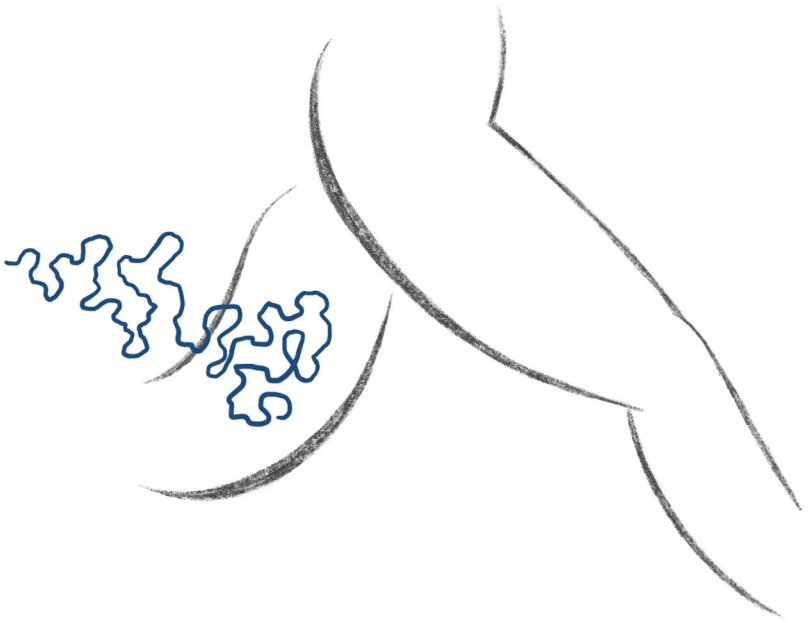
Appendix

Quality of life N=74 (100%)	%	%	%	%	%
EQ-5D-5L >1	1	2	3	4	5
Pain / discomfort	39%	34%	26%	1%	0%
Mobility	66%	15%	16%	3%	0%
Usual activities	74%	19%	5%	1%	0%
Anxiety / depression	88%	5%	4%	2%	0%
Self-care	89%	4%	4%	1%	1%
CIVIQ-14 >1	1	2	3	4	5
Sleeping poorly	42%	30%	20%	4%	4%
Pain	43%	24%	19%	12%	1%
Problems squatting / kneeling	47%	23%	11%	10%	9%
Impairment with daily activities	51%	23%	20%	4%	1%
Problems walking at a good pace	53%	20%	10%	7%	9%
Problems climbing stairs	62%	22%	5%	8%	3%
Problems performing athletic activities	61%	15%	11%	8%	4%
Being embarrassed to show legs	61%	23%	7%	4%	4%
Problems going to parties	65%	16%	8%	4%	5%
Becoming irritable easily	65%	26%	4%	4%	0%
Feeling nervous	70%	23%	3%	3%	0%
Having the impression of being disabled	81%	10%	4%	3%	1%
Having the impression of being a burden	81%	8%	5%	3%	0%
Having no desire to go out	85%	8%	4%	1%	0%

Table 1: General and disease specific quality of life

1=no complaints, 2= slight complaints, 3=moderate complaints, 4=severe complaints, 5=very severe complaints/impossible.

CHAPTER EIGHT



GENERAL DISCUSSION

General discussion

In this chapter, the main findings will be summarised and their implications for improving chronic venous disease care will be further discussed. Reflections will be made on the methodology of the studies. In addition, an ideal healthcare path for improving the recognition of chronic venous disease and its risk factors, as well as a recommended approach to prevent the progression of chronic venous disease will be described. The chapter will end with recommendations for future research, education and clinical practice.

Summary of the main findings

The aim of this thesis was to identify chronic venous disease patients at risk of developing more severe clinical stages, to provide insight in the risk factors, and to provide an overview of current chronic venous disease care in the Netherlands. Arterial hypertension, family history of venous leg ulcers, low physical activity, and being overweight were identified as known risk factors for the development of a venous leg ulcer. Furthermore, calf muscle pump function, range of ankle motion, abdominal fat, and inflammatory factors play a role in the reduction of venous outflow and, therefore, the progression of chronic venous disease. Reduced range of ankle motion and abdominal obesity are found to be associated with more severe chronic venous disease. Physical activity was low, and a reduction in mobility occurred often in chronic venous disease patients. The reduction in mobility was mostly present before the venous leg ulcer developed, and was often caused by other comorbidities. In addition, not all chronic venous disease patients in the studies experienced signs and symptoms as 'complaints'. Moreover, when patients did have complaints, they often did not assign the signs and symptoms to the chronic venous disease; therefore, they did not seek healthcare. Finally, not all chronic venous disease patients in the studies received diagnostics or treatment for their venous insufficiency, and follow-up of chronic venous disease patients was very low.

Risk factors for chronic venous disease

Some risk factors like age and venous thrombosis are already known and treated in chronic venous disease progression. In addition, not all risk factors can be treated. In this section, risk factors for chronic venous disease will be discussed. The risk

factors are divided in three categories: etiological risk factors, non-modifiable risk factors and modifiable risk factors.

The patients at risk of developing and progressing in chronic venous disease are evidently the patients with ambulatory venous hypertension. Known etiological risk factors for chronic venous disease progression are reflux and obstruction in the (deep) veins.(1) In addition, skin changes like lipodermatosclerosis, atrophy blanche, hyperpigmentation and corona phlebectatica are clear clinical signs of severe chronic venous disease and increase the risk of developing a venous leg ulcer.(2, 3) The same progression is found in arteriovenous shunts leading to venous hypertension of the hand, causing similar skin changes and ulceration.(4, 5) This indicates that venous hypertension can be caused by factors other than reflux and obstruction of the veins like obesity and immobility. Furthermore, permanent immobility can be an etiological risk factor as well as a non-modifiable risk factor. Treatment with ambulatory compression therapy is the cornerstone of chronic venous disease care in combination with varicose vein removal and anti-coagulant treatment in case of venous thrombosis.(6) However, in immobile patients, there might not be an anatomical abnormality to treat, and ambulatory compression therapy is not feasible.(7) The immobile patient with clinical signs and symptoms of chronic venous disease is, therefore, a challenge for clinical practice. However, the population with immobility or severely impaired physical activity should not be overlooked in chronic venous disease care. Further research is necessary to investigate the prevalence of patients with immobility (or severely impaired physical activity) and clinical signs and symptoms of chronic venous disease to identify the magnitude of this problem and find possible solutions, such as passive stimulation of the calf muscle pump.

In addition to the etiological risks, there are non-modifiable risk factors for the progression of chronic venous disease, such as age and family history of chronic venous disease. These risk factors can identify chronic venous disease patients at risk of disease progression. However, there is no treatment involved.

The modifiable risk factors for chronic venous disease we found in our studies described in Chapter 3 and 5 are hypertension, excessive weight, and reduced physical activity. These risk factors can be treated in clinical practice and should have a prominent place in the management of chronic venous disease. The same risk factors already have a prominent place in national and international guidelines for cardiovascular disease and diabetes mellitus type II.(8-10) Obesity, hypertension and physical activity are screened, monitored and treated simultaneously to prevent disease progression of cardiovascular disease and diabetes mellitus type

II (into a diabetic foot ulcer). Obesity even has its own guideline. In this guideline hypertension, screening, monitoring and treatment of cardiovascular disease and diabetes mellitus type II are included as a result of obesity.(11)

Overall, overweight and low physical activity have a negative impact on a patient's health and should, therefore, be screened, monitored and treated. It is partially the government's task to stimulate and provide information on healthy behaviour. Stimulating healthy behaviour by government-led public health initiatives is in line with other public health initiatives, such as 'stop smoking' campaigns and 'use sunscreen to prevent skin cancer' campaigns. Stimulating healthy behaviour to target obesity and insufficient physical activity should start at an early age, because childhood obesity and insufficient physical activity in children is a growing problem in Europe.(12, 13) These increases in obesity and insufficient physical activity in children may lead to an increase in the incidence of chronic venous disease in the future. This denotes the need for screening, monitoring and treating chronic venous disease and its risk factors.

Obesity and mobility as risk factors for chronic venous disease

Current chronic venous disease guidelines provide only a short piece of advice on weight loss and improving physical activity.(14, 15) Furthermore, the guidelines do not mention how these lifestyle factors should be measured and monitored. In this section, the different measurements of obesity and mobility we used to identify these factors as risk factors for the progression of chronic venous disease in our studies and in clinical practice will be discussed.

The systematic review, scoping review and qualitative study revealed that the weight and mobility risk factors remained partially unexplained in most risk factor studies. The specific risk for chronic venous disease lies in abdominal pressure and calf muscle pump function. However, studies mostly measure Body Mass Index (BMI), which is not a good representation of abdominal fat.(16) Physical activity was measured in many ways in the literature that do not always link directly to the calf muscle pump function, like the amount of hours spent participating in sports each week. The weight and mobility risk factors, therefore, required more elaborated measurements to assess their association with the progression of chronic venous disease. We made an informed decision for the risk measurements in the cross-sectional study. First, we searched for measurements that include abdominal obesity and physical activity related to the calf muscle pump (objective and subjective measurements). Second, we assessed whether these measurements would be easy

to implement in clinical practice (ease of use, reliability, costs). Finally, we added retrospective questions about weight and calf muscle related factors to assess the presence of these factors in the past (denoting a risk). The retrospective questions were added because chronic venous disease progresses over the years, and obesity and calf muscle function can be influenced by chronic venous disease signs and symptoms. For example, physical activity can either decrease because of chronic venous disease signs and symptoms (like pain and lipodermatosclerosis in the ankle area), or it can increase because of specific therapies focused on exercise in venous leg ulcer treatment.(17-20) In clinical practice, it should be assessed if and why a chronic venous disease patient has changes in weight or mobility to provide adequate treatment and follow-up. This denotes the importance of examining the patient as a whole in addition to the signs and symptoms of chronic venous disease.

In addition, the obesity and physical activity risk factors might be overestimated in the cross-sectional study because of the high percentage (26%) of venous leg ulcer patients. However, in severe chronic venous disease, the clinical classes C4-C6 are often combined in research because of the increased risk of C4 to progress to a venous leg ulcer.(2, 3) Damage in the microcirculation of the skin is already present en possibly irreversible in the case of a chronic venous disease C4 classification.(17) When clinical classes C4-C6 are combined, the percentages of the patients in our study population is comparable to that of a large primary care population in Belgium and Luxembourg.(21) In Belgium and Luxembourg the prevalence of chronic venous disease in primary care was 39%, 32%, and 29% of patients with clinical class C2, C3 and C4-C6 respectively. In the cross-sectional study we found similar percentages: 42%, 24%, and 34% for clinical class C2, C3, and C4-C6 respectively. It is, therefore, unlikely that the prevalence of obesity and low physical activity are overestimated in our study population compared to the chronic venous disease population as a whole.

Obesity

To measure the influence of obesity, we included multiple measurements and control questions. We measured length and weight to calculate BMI, but we also measured waist circumference to measure abdominal obesity. To include obesity as a risk factor, we asked patients how much they weighed one year ago (before the venous leg ulcer appeared) and five years ago. Additionally, we asked how many clothing sizes they had changed in the past five years. These questions provided more insight into the duration of their obesity and, therefore, the impact obesity has on the progression of chronic venous disease (instead of the impact the progression of

chronic venous disease has on obesity). In clinical practice, BMI and waist circumference can easily be measured using the primary care protocol.(22)

Mobility

In addition to the various measurements of weight, we also included multiple measurements of physical activity that were related to the calf muscle pump function. We objectively measured the number of steps, intensity of activity as well as sedentary behaviour by using accelerometers. In addition, we used a standardised physical activity questionnaire developed and used by the Dutch National Institute for Public Health and Environment (RIVM) for the annual national health and lifestyle monitors.(23) The RIVM questionnaire was a valuable addition to the accelerometers, because it assesses a person's physical activity over the past six months (in contrast to the accelerometers, which provide a snapshot of only one week). Furthermore, the questionnaire also includes sports. Sports like swimming and aqua gym could not be measured with the accelerometers, as the accelerometers were not waterproof. The questionnaire also provided more insight into the frequency and duration of walking per week over the past six months. Data on the number and duration of walks is relevant because the use of the calf muscle pump in walking is higher than its use in bicycling or swimming, for example. The combined data on physical activity provided insight into the patients' patterns and made it possible to calculate the patients' amount of physical activity and compare this to the amount of physical activity necessary for a healthy lifestyle.(24) The use of the RIVM questionnaire also allowed us to compare the physical activity of the study population to that of the general population in the Netherlands.

To gain insight into patients' past physical activity levels, we also asked them if their daily activities had changed; we asked if they had become more or less physically active, or physically active in different ways, and why. To gain insight into lower leg problems that might influence gait patterns and calf muscle pump function in chronic venous disease progression, we specifically asked about trauma on the lower legs in the past, foot disorders (flat feet, hollow feet, hallux valgus) and if they used insoles, orthopaedic shoes or walking aids.(25-27) The reduction in mobility in the past provided insight into the duration of the reduction and its influence on chronic venous disease, instead of the influence of chronic venous disease on mobility. In addition, we asked the patients about their current occupation and the occupation they held for the longest time in the past (and how many years they worked in each occupation). Insight into current and past occupations made it possible to assess the risk of standing occupations on chronic venous disease,

because most patients were already retired at the time of the measurements. All the physical activity questions combined made it possible to create a full overview of the physical activity patterns of patients with chronic venous disease. The physical activity patterns provided insights into restrictions in physical activity and mobility that can lead to the insufficient function of the calf muscle pump in chronic venous disease patients. These restrictions (such as reduced range of ankle motion, insufficient walking, leg injury, sudden reduction in physical activity, and foot disorders) should be addressed in clinical practice to be able to restore the calf muscle pump function and increase venous outflow. The RIVM questionnaire could be used in clinical practice to provide insight into a patient's physical activity. In addition, a goniometer can be used following the Neutral-0-Method.(28) Both the questionnaire and the goniometer provide easy and reliable measurements using the protocols and can be used at low costs in clinical practice.

Obesity and mobility: a combined risk

Obesity and reduced mobility can occur as individual risk factors. However, obesity and reduced mobility often occur simultaneously in an ageing population. In this section we discuss the combined effect of obesity and reduced mobility on chronic venous disease progression (and vice versa), and on chronic venous disease treatment.

Muscle decline, also known as sarcopenia, naturally occurs during ageing and increased immobility. When muscle decline occurs simultaneously with obesity, it is called sarcopenic obesity.(29) Specifically, abdominal obesity is shown to be associated with a loss of muscle strength in older men.(30) In sarcopenic obesity, the loss of muscle strength might play a larger role than the loss of muscle mass in the risk of cardiovascular disease.(31) This is comparable to chronic venous disease; muscle strength was found to be significantly impaired when the chronic venous disease clinical class increased.(32) The combination of obesity and muscle decline can increase the risk of chronic venous disease progression because both obesity and a reduced calf muscle pump function play a role in reduced venous return to the heart. Therefore, it is important to focus not only on weight loss in clinical practice, but on the combination of weight loss and exercise to prevent muscle decline. Exercise focused on strengthening the calf muscle to increase the calf muscle pump function is especially important in chronic venous disease; this increases venous return to the heart, thereby decreasing ambulatory venous pressure.(33)

In addition, it is common knowledge that obesity can lead to less physical ac-

tivity (and vice versa). Obesity is associated with slower gait speed and increased sedentary behaviour.(34) Alternatively, higher physical activity is associated with a lower risk on developing obesity.(35) Overall, when there is an imbalance of energy intake and energy uptake, weight gain is the result. The amount of visceral fat tissue and subcutaneous fat tissue will increase. Being overweight or obese can also lead to intramuscular adipose tissue. Intramuscular adipose tissue in the calf muscle is shown to reduce physical performance of the muscle.(36, 37) Intramuscular adipose tissue in the calf muscle is also associated with a reduced gait speed and greater step width.(38, 39) Both gait speed and step width are important in utilizing the foot plate to its fullest potential for the optimal use of the calf muscle pump in achieving venous return to the heart and lowering ambulatory venous pressure. A study among patients with chronic venous disease showed that chronic venous disease patients had a greater step width, slower gait speed and impaired calf muscle endurance compared to healthy controls.(40) This could indicate that even when obese chronic venous disease patients engage in physical activity, the calf muscle pump function can still be suboptimal. This is yet another reason why obesity and reduced physical activity should be seen and treated as a combined risk in chronic venous disease progression.

Impact of obesity and mobility on chronic venous disease treatment

Obesity, in combination with reduced physical activity, is not only a risk for chronic venous disease, but also a risk for the successful treatment of chronic venous disease. As mentioned before, obesity negatively impacts treatment outcomes of varicose vein removal, leading to less improvement in venous clinical score and quality of life when compared to non-obese varicose vein patients.(41) Obesity is also associated with a higher recurrence of varicose veins.(42) In addition, obesity and reduced physical activity impact the treatment outcomes of ambulatory compression therapy. Ambulatory compression therapy is shown to reduced oedema and chronic venous disease symptoms while walking.(43) The most eminent problem with compression therapy in obese patients is the conical shape of the legs. During the qualitative and cross-sectional study, patients complained about bandages and compression hosiery that tended to slip down when the patient engaged in physical activity. This might be an explanation for the significantly lower compliance with compression therapy found in a study among chronic venous disease patients with obesity compared to patients without obesity.(44) In addition, patients with obesity might experience more trouble putting the compression hosiery on and taking it off, because they can experience difficulty in reaching their feet. Chapter 7 showed

that the compliance with compression therapy in general is low in the chronic venous disease population. In clinical practice, attention should be given to the practical issues involved in ambulatory compression therapy. These practical issues can vary over time as changes in weight or mobility can occur. It is, therefore, important to include regular follow-up appointments addressing the barriers in ambulatory compression therapy and providing tailored solutions to increase compliance to ambulatory compression therapy.

In addition, the most important function of ambulatory compression therapy is the support of the calf muscle pump function, which increases venous return to the heart. An increase in physical activity combined with compression therapy is more effective than compression therapy alone.(45) Furthermore, including specific exercises in combination with compression therapy is important, because bandages can lead to a reduced range of ankle motion.(46) As the results in Chapter 5 show, a restriction of the range of ankle motion is associated with more severe chronic venous disease and is, therefore, an important factor to take into consideration while managing the progression of chronic venous disease.

Risk or result: treatment is required

The studies in this thesis show that obesity and reduced mobility can be an etiological and a modifiable risk factor for chronic venous disease. They can cause venous hypertension, lead to reflux or obstruction in the veins of the lower extremities and decrease venous return to the heart. They often occur simultaneously, and they negatively impact chronic venous disease treatment. However, these risk factors receive little attention in current management for chronic venous disease. Whether or not obesity and reduced mobility are a risk for or a result of chronic venous disease, they are as important as, if not more important than, venous insufficiency in the disease management.

Abdominal obesity and reduced physical activity should be measured and treated in clinical practice to optimise ambulatory venous function, whether they are a risk or a result of chronic venous disease. In both scenarios (risk and result), treatment of abdominal obesity and reduced physical activity can lead to an increase in venous outflow to the heart. In addition, treatment of obesity and reduced physical activity can be easily implemented; there is no need for the development of new interventions. Weight loss and exercise interventions for obesity and improving range of ankle motion are widely implemented in clinical practice.(11, 47, 48) In the treatment of obesity, interventions that combine weight loss and exercise are preferred over interventions that involve weight loss alone to prevent muscle decline.(49)

Many studies have been performed on weight loss and exercise programs in obese patients, and two meta-analyses show that the combination of weight loss interventions with exercise is effective in fat reduction and preventing muscle decline.(50, 51) The only addition for chronic venous disease patients would be physical therapy to improve the range of motion of the ankle in order to optimise calf muscle pump function. Simply treating venous reflux and obstruction might be of lesser importance in managing chronic venous disease when obesity and reduced mobility are left untreated. The role of treating obesity and reduced mobility in restoring venous return to the heart should not be underestimated.

Furthermore, reducing obesity and increasing physical activity requires a change in lifestyle. It is known that changes in lifestyle require more intensive healthcare and guidance when compared to invasive treatments of chronic venous disease. In line with smoking and sunbathing, patients should be made aware of the risks of obesity and low physical activity. In the case of smoking and sunbathing, the healthcare professionals and government public health initiatives took action and achieved widespread awareness of the health risks. However, awareness of health risks alone is insufficient to achieve a lifestyle change. Measuring the risks, monitoring these risks and guiding a patient to change these lifestyle risk factors is necessary to increase compliance.(52, 53) In diabetes care, multiple initiatives have been found to help patients reach healthy lifestyles, including reducing weight and increasing physical activity.(54-56) However, healthcare professionals need to guide and monitor patients in order to maintain these changes and treat the progression of chronic venous disease signs and symptoms. In venous leg ulcer care, it is already shown that therapy guidance leads to a better understanding of the disease and compliance to lifestyle changes, including ambulatory compression therapy.(57, 58)

The indirect evidence suggests that the screening, monitoring and treatment of obesity and reduced mobility can improve treatment outcomes and reduce disease progression. However, further research is required to assess whether or not the screening, monitoring and treatment of lifestyle risk factors significantly reduces chronic venous disease progression and further improves chronic venous disease signs, symptoms and treatment outcomes.

Methodological reflections

During the execution of the studies included in this thesis, we encountered a few barriers in the recruitment of patients with chronic venous disease. These barriers provided more insight into the current care for chronic venous disease patients. In

this section, we reflect on the diagnosis of chronic venous disease patients, and recruitment of patients for the studies in this thesis.

Diagnosis of chronic venous disease patients

For the literature review and cross-sectional study, we focused on venous leg ulcer patients with a first (healed) venous leg ulcer. We included patients with a first venous leg ulcer because patients with venous leg ulcer recurrences might experience more severe disease characteristics and possibly more severe risk factors. Including patients with venous leg ulcer recurrence would, therefore, influence the data by increasing the differences in risk factors between patients with mild and more severe chronic venous disease. In addition, the retrospective questions on the risk factors would have had an increased recall bias in patients with a recurrent venous leg ulcer because we included questions on their situation before the first venous leg ulcer was present. The focus in studying the risk factors and current care of chronic venous disease was to make discoveries that could prevent a first venous leg ulcer, not venous leg ulcer recurrence.

In this thesis, we specifically included patients whose diagnosis of chronic venous disease was confirmed by clinical signs and symptoms of chronic venous disease in combination with duplex diagnostics. This way, we ensured the inclusion of chronic venous disease patients and excluded other diseases that can be a cause of oedema and lower leg ulcers on their own (i.e. congestive heart failure and diabetes mellitus). The duplex diagnostics also allowed us to include patients with mixed ulcers caused by multiple underlying pathologies, such as diabetes and peripheral arterial disease, in addition to chronic venous disease. Patients with mixed pathology of oedema and leg ulcers are very common. About 20% of venous leg ulcers have a mixed pathology of arterial-venous origin.(59, 60) However, comorbidities (like diabetes mellitus and peripheral arterial disease) are often excluded in chronic venous disease research to ensure the venous cause of the oedema or the leg ulcer. (61-64) The inclusion of duplex diagnostics allowed us to include chronic venous disease patients with comorbidities in the qualitative and cross-sectional study. This led to a sample that better represents the chronic venous disease patients in the general population.

Recruitment

Patients with chronic venous disease were recruited from healthcare settings and the general population so that our study sample would representative for the Dutch population in the qualitative and cross-sectional study. During the recruitment of

chronic venous disease patients in the different healthcare settings, a few barriers arose:

- *In secondary care, patients with a venous leg ulcer were mostly patients with recurrent venous leg ulcers, which were excluded from our studies.*
- *In home care and nursing homes, patients were often permanently immobile or suffered from cognitive dysfunction, which were exclusion criteria in our studies.*
- *In primary care, the use of ICPC codes (International Classification in Primary Care) appeared to be a challenge in selecting patients with chronic venous disease clinical class C2-C6. The ICPC codes to register diagnostics in primary care did not define the venous origin of chronic venous disease signs like oedema or leg ulceration. The diagnose codes for varicose veins and venous thrombosis also include patients with reticular veins and minor superficial thrombosis who do not necessarily have insufficient veins and increased venous hypertension. Therefore, it was impossible to recruit patients from the primary care research networks who use the ICPC codes to select and recruit patients for research purposes. The lack of registration of the venous origin or severity of chronic venous disease makes the ICPC codes not only a barrier for research purposes, but mainly for the recognition and registration of chronic venous disease in clinical practice.*

Overall, recruiting patients with a first venous leg ulcer or patients with a chronic venous disease diagnosis was a challenge. The lack of registration of the venous origin of signs and symptoms of chronic venous disease and the absence of duplex diagnostics in primary care can hinder the correct diagnosis of chronic venous disease in clinical practice. The Vein Consult Program(65) in Belgium and Luxemburg, reported that only 17% of the patients were referred to secondary care while 43% had chronic venous disease clinical class C2-C6. Patients with clinical class C2-C6 should be diagnosed with a duplex ultrasound, and would most likely require invasive treatment according to secondary care chronic venous disease guidelines.(66) The referral of chronic venous disease patients for diagnostics and treatment of chronic venous disease might have been increased after training the general practitioners in the Vein Consult Program, but it was still insufficient. Furthermore, a study on the release of a venous leg ulcer guideline in the United Kingdom led to an increase in referrals from general practitioners to specialist care for the diagnosis and treatment of active venous leg ulcers.(67) However, the time between seeking primary healthcare and the referral for venous leg ulcer patients to secondary care

was still 16 weeks. In addition, the study did not include the preventative referral of patients in earlier stages of chronic venous disease. The international studies, the recruitment of patients for our studies and the results from Chapter 2 and Chapter 7 show that awareness of chronic venous disease among healthcare professionals is low. Awareness of healthcare professionals should be raised to increase recognition of chronic venous disease and improve early diagnostics, treatment and follow-up for chronic venous disease patients.

Awareness of signs and symptoms of chronic venous disease

Widespread awareness of chronic venous disease signs and symptoms is still lacking among the general population and in healthcare. In the general population not all chronic venous disease patients have (visible) varicose veins or recognise their oedema or skin changes, and not all patients complain of symptoms like calf muscle cramps, pain, heaviness and itching.(68) These patients are unlikely to seek healthcare for these chronic venous disease signs and symptoms. In this section we discuss the awareness of chronic venous disease signs and symptoms and how to improve awareness in clinical practice.

Not recognising the signs and not experiencing the symptoms as 'complaints' was one of the reasons in the cross-sectional study why patients did not seek healthcare or follow-up for their chronic venous disease. On the other hand, an Italian study showed that the under-recognition of chronic venous disease symptoms led to 6.6% of emergency care calls by chronic venous disease patients.(69) Chronic venous disease usually does not require acute emergency care. In addition, the under-recognition of chronic venous disease is a worldwide problem. Researchers all over the world write articles to raise awareness of chronic venous disease in the general population and healthcare to increase early recognition and rapid diagnostics and treatment for chronic venous disease.(70-73) However, these articles are published in scientific journals mostly read by other researchers and healthcare professionals who are searching for specific information on chronic venous disease and have access to these scientific journals. Articles to raise awareness of chronic venous disease should be published in national professional journals to be able to reach all healthcare professionals that encounter patients with chronic venous disease. These professional journals are easily accessible for healthcare professionals and have a wider reach within clinical practice.

Mortality of chronic venous disease

Another reason for the low awareness of chronic venous disease in healthcare might be the fact that chronic venous disease is considered a non-life-threatening condition. Varicose veins, oedema, skin changes and post-thrombotic syndrome are not a direct cause of death. However, a recent study in Germany showed an increased mortality rate of 35% and 23% over a period of 10 years for people with deep vein thrombosis in the femoral veins and venous leg ulcers respectively.(74) Other pathologies causing chronic wounds (like diabetes mellitus and peripheral arterial disease) are more life-threatening. Two meta-analyses and a systematic review show that diabetic foot ulcers and critical limb ischemia (peripheral arterial disease) increase mortality by 30%(75) and 50%(76) respectively within 5 years, and pressure ulcers lead to an increased hazard ratio of 1.78 (95% CI 1.46-2.16) in 0.5-3.0 years. (77) Furthermore, the mortality rates of chronic diseases naturally play a major role in prioritising diseases in healthcare and in research. Next to mortality, incidence and impact on quality of life also play a role in prioritising a disease. Today, for chronic venous disease, little is done to increase the awareness among the general population and healthcare professionals, despite its high prevalence and negative impact on quality of life.(78, 79) As chronic venous disease is a part of cardiovascular disease, knowledge distribution and awareness could be increased by the national cardiovascular associations. Moreover, the modifiable risk factors (hypertension, obesity and insufficient physical activity) for chronic venous disease are also risk factors for cardiovascular disease in general. Chronic venous disease, therefore, deserves a more prominent place in cardiovascular disease management. It is time to move past the cosmetic reputation of varicose veins and acknowledge chronic venous disease as a cardiovascular disease that can progress to severe and disabling clinical stages with an increased mortality.

Possible prevention strategy: screening, diagnostics and monitoring of chronic venous disease and its risk factors

We now know how to make the first step in being safe rather than sorry in chronic venous disease healthcare. The results of this thesis show that we should examine the chronic venous disease patient as a whole, including disease signs, symptoms, comorbidities, and risk factors. In this section, we present a possible prevention strategy for chronic venous disease progression.

The general practitioner plays a key role in the recognition and diagnosis of a disease; this includes the recognition and diagnosis of chronic venous disease. As pre-

viously mentioned, in the Netherlands, the general practitioner is the first stop for every health issue and the centre piece in referrals and the management of healthcare for all patients. Due to the large number of patients per general practitioner in the Netherlands, most general practitioner practices are supported by practice nurses who screen, diagnose and monitor patients with specific conditions (like diabetes, lung disease and cardiovascular disease). Screening patients for signs and symptoms of chronic venous disease would fit into the general practitioner practice; these screenings could be performed by either the general practitioner or a practice nurse specialised in cardiovascular risk management.

Screening for chronic venous disease and its risk factors

Ideally, screening should take place in an older population, since the prevalence of chronic venous disease increases with age. Older patients with risk factors for the development of more severe chronic venous disease would be eligible for chronic venous disease screening. The risk factors for the progression of chronic venous disease do not differ much from other cardiovascular diseases or chronic diseases that lead to a chronic wound. Hypertension, obesity and low physical activity or reduced mobility are risk factors for cardiovascular diseases (like peripheral arterial disease), diabetes mellitus, and pressure ulcers(8, 9, 80, 81). Therefore, a new intervention is not needed. Screening and prevention programs for cardiovascular diseases and diabetes have already been proven effective and interchangeable. (10) Acknowledging chronic venous disease as a cardiovascular disease can lead to a direct implementation of chronic venous disease screening in the cardiovascular risk management program.

In the Netherlands, a screening program has been developed for the early recognition, treatment and follow-up of patients at risk for cardiovascular disease. This cardiovascular risk management program(8) has been implemented in all general practitioner practices. During this cardiovascular risk management program, several risk measurements are performed:

- *Blood pressure*
- *Blood workup for cholesterol and glucose levels*
- *Height and weight (to calculate BMI)*
- *Waist circumference*
- *Smoking and alcohol use*
- *Physical activity assessment*
- *Comorbidities*

In this cardiovascular risk management program, a large older population (men >55 years old and women >60 years old) is screened for cardiovascular disease risk. With only a minor addition, the cardiovascular risk management program can screen for chronic venous disease as well. A visual check of the lower extremities and a few questions regarding the symptoms of chronic venous disease would be all that is needed to include chronic venous disease into the cardiovascular risk screening. Table 1 shows a checklist that could be implemented to recognise chronic venous disease in the risk assessment for cardiovascular diseases. Patients could be given the opportunity to check the symptoms themselves prior to the cardiovascular risk measurements (as described above). It should be kept in mind that the signs of chronic venous disease do not necessarily occur in a particular order, and that, for example, skin changes can be present without visible varicose veins or oedema.

Any of the following symptoms of the lower leg in the past 4 weeks*	Clinical classification according to the CEAP classification*	
	C0	No visible or palpable signs of venous
Pain	C1	disease
Sensation of swelling or burning	C2	Telangiectasia or reticular veins
Night cramps in the calf muscle	C3	(Recurrent) Varicose veins
Sensation of pins and needles	C4a	Oedema
Itching	C4b	Pigmentation or eczema
Heaviness	C4c	Lipodermatosclerosis or atrophie blanche
	C5	Corona phlebectatica
	C6	Healed venous ulcer
		(Recurrent) Active venous ulcer

Table 1: signs and symptoms of chronic venous disease for risk assessment in primary care

**As described in the Vein Consult Program protocol(83), CEAP = Clinical, Etiological, Anatomical and Pathological classification(82)*

Diagnostics and monitoring of chronic venous disease and its risk factors

When a general practitioner or the practice nurse has registered a clinical stage of C2 or higher with one of the symptoms, or a clinical stage of C0-C1 with two or more symptoms in the past four weeks, further diagnostics are required. According to international secondary care chronic venous disease guidelines a patient with varicose veins, more advanced clinical stage of chronic venous disease, and/or several symptoms of chronic venous disease should be investigated with duplex diagnostics.

For monitoring patients at risk (elderly, high blood pressure, obese, reduced ankle mobility, family history of venous leg ulcers), there are several options, de-

pending on the severity of disease and its risk factors. Overall, the screening and diagnosing of patients with chronic venous disease should be aimed at preventing a venous leg ulcer. Today, there is no fixed strategy for preventing a venous leg ulcer, as shown in Figure 7 in the general introduction (Chapter 1). Following the results of this thesis, Figure 1 shows an optional strategy aimed at preventing a venous leg ulcer. This strategy partially fits the screening of cardiovascular disease as described previously. For the follow-up of patients at risk, the following guidelines might adequately help prevent a venous leg ulcer:

First, always follow-up with a patient when they experience new signs or symptoms of chronic venous disease or their current signs and symptoms worsen.

- *Ten-year follow-up (risk assessment)*
  - *chronic venous disease C0-C1 with minor symptoms*
  - *chronic venous disease C2, which is diagnosed and treated invasively*
- *Five-year follow-up (risk assessment)*
  - *chronic venous disease C0-C1, with at least 2 symptoms and at least 1 of the risk factors (excluding age)*
  - *chronic venous disease C2, which is treated invasively, and at least 1 of the risk factors (excluding age)*
- *Two-year follow-up (risk assessment)*
  - *chronic venous disease C3-C6, with invasive treatment of the varicose veins or venous thrombosis*

The monitoring and following-up can be performed by the general practitioner or the practice nurse. The diagnostics and invasive treatment of varicose veins or venous thrombosis are performed by a specialist in secondary care, according to existing guidelines. Most risk factors (except for age and family history) can be treated and monitored in primary care, according to existing guidelines for obesity, ankle mobility and hypertension. In addition, the results of Chapters 2 and 7 show that compliance to compression therapy is low, and patients experience barriers in wearing compression hosiery. Regular follow-ups are, therefore, required to address these barriers and aim at increasing adherence to compression therapy. For treatment of chronic venous disease C3-C6 with compression therapy, time to follow-up depends on the patients' self-reliance and intensity of venous leg ulcer care.

In conclusion, in clinical practice, chronic venous disease should be acknowledged as a chronic condition that requires ongoing healthcare, including risk assessment, timely follow-ups for monitoring chronic venous disease progression and

personalised guidance to increase adherence to lifestyle interventions, including compression therapy.

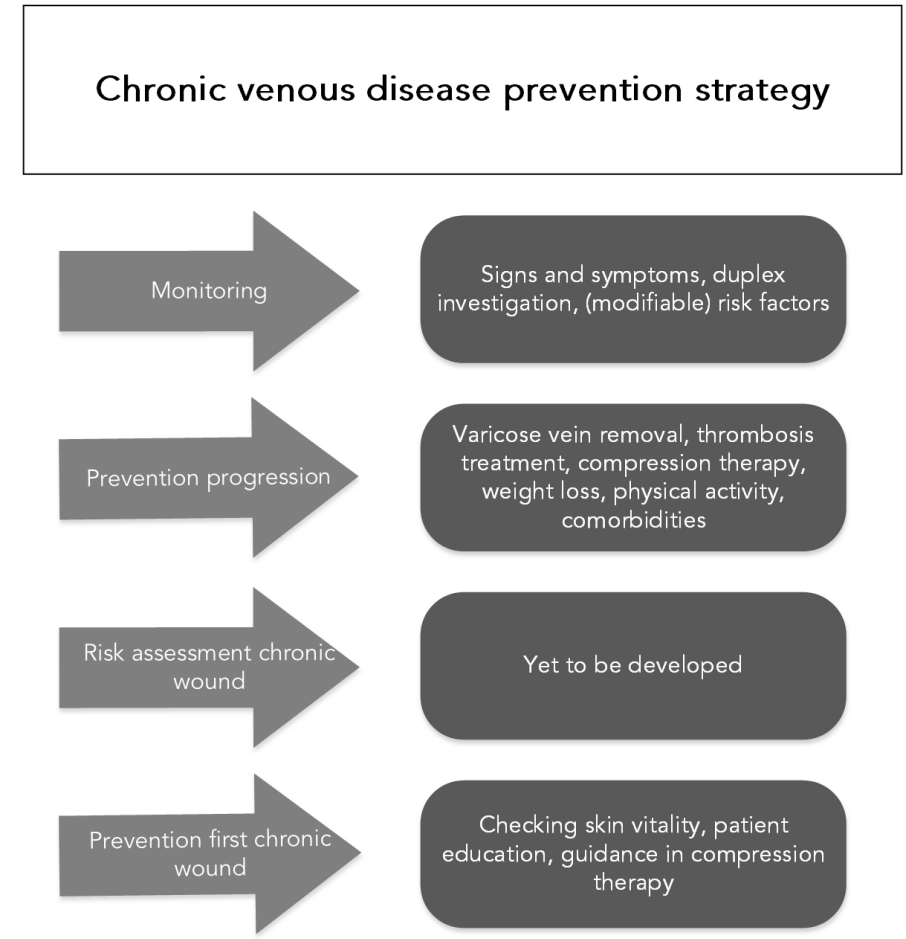


Figure 1: Possible prevention strategy for chronic venous disease progression

Screening for Chronic Venous Disease and its risk factors: can it be cost-effective?

The current organisation of care provides an under-recognition of chronic venous disease patients, scattered care and late diagnostics that can lead to costly and severe chronic venous disease and venous leg ulcers. Roughly 1%-2% of the annual healthcare budget goes to chronic venous disease care. Moreover, healthcare costs increase as disease severity increases.(84) The costs for screening and prevention of chronic venous disease can be low. Embedding the screening within the already existing cardiovascular risk management program comes with no additional costs. Most risk factors are also risk factors for cardiovascular disease. Due to the risks involved in cardiovascular disease, follow-ups would be planned frequently, which is ideal for detecting and treating chronic venous disease. Screening for chronic venous disease specifically can, however, lead to an increase in the prevalence of early diagnosis and invasive treatments that come with higher costs. However, the adequate screening, diagnosing and monitoring of chronic venous disease might also lead to the prevention of more severe chronic venous disease and venous leg ulcers, which can conserve costs and definitely save the patients from a decrease in quality of life.

It is known that ambulatory venous function can be restored when the obstruction or insufficient veins are removed. Treatment of varicose veins today is minimally invasive, with lower costs and a low impact on quality of life compared to 20 years ago.(85) In addition, it is shown that timely treatment of varicose veins is important because a delayed treatment of over six months can lead to progression of the venous insufficiency and chronic venous disease.(86, 87) In the treatment of venous leg ulcers, it is shown that implementing guidelines to ensure an adequate healthcare path (including timely chronic venous disease diagnostics and treatment) can increase positive treatment outcomes and reduce costs.(88-90) Furthermore, varicose veins have a high recurrence rate of about 50% in 8 years. However, the other 50% of varicose vein patients did not experience a recurrence, and possible disease progression was prevented.

For the obesity risk factor, weight loss and exercise interventions are effective treatments.(50) However, treatment of risk factors such as obesity and mobility are challenging, as they require lifestyle changes. Obesity and physical activity interventions require personalised guidance and behavioural interventions, which is a continuous healthcare process stimulating a patient's self-reliance.(91) Yet, these interventions are widely accepted in diabetes care to prevent disease progression

and a chronic wound. This also accounts for physical therapy (walking therapy) for peripheral arterial disease patients to prevent disease progression and chronic wounds. Physical therapy is given at a high frequency, and stimulates a patient's self-reliance (guideline claudication intermittent). Treatment of obesity and the use of physical therapy for improving the range of ankle motion should, therefore, be accepted as a treatment strategy in chronic venous disease to prevent disease progression and chronic wounds. Compared to invasive therapies and hospitalisation, these lifestyle interventions are easily accessible to patients; they are mostly reimbursed and at relatively low costs.

Additionally, treatment for obesity and reduced mobility in chronic venous disease patients might benefit their other comorbidities. Other cardiovascular diseases, rheumatic arthritis, diabetes and COPD are comorbidities that occur often in chronic venous disease patients; each condition would benefit from weight loss and increased physical activity. No solid evidence exists (yet) for the cost-effectiveness of implementing a prevention strategy for chronic venous disease progression in clinical practice. However, this study denotes the need for a prevention strategy, and the indirect evidence (as described above) suggests that it can be cost-effective. Moreover, most of the screening, monitoring and risk factors treatment is already embedded in healthcare for other chronic venous diseases. Chronic venous disease has to be acknowledged as a cardiovascular disease to be included in the pre-existing cardiovascular risk management program.

Research recommendations, education and clinical implications

In this section research recommendations, implications for education, and the clinical implications of this thesis are described.

Research recommendations

The Vein Consult Program (VCP) was developed to raise awareness of chronic venous disease in primary care world-wide. The VCP included approximately 90,000 chronic venous disease patients from over 400 general practitioners world-wide. The VCP invested in training the general practitioners in chronic venous disease recognition and provided tools to assess, recognise, and register chronic venous disease. One of the goals of this program was to raise awareness about chronic venous disease among patients, HCP and health authorities.(92) The VCP was performed in 2010 and 2011 worldwide, and publications followed until 2018, when the final results were published (no results on raising awareness were published).

(93) However, the Netherlands was not one of the participating countries. Implementing the Vein Consult Program in the Netherlands will provide insight in the prevalence of chronic venous disease in primary care. A large prevalence study according to the VCP will most likely raise awareness among the public and general practitioners. The VCP designed protocols for the execution of the study and successfully executed this prevalence study in many countries. The VCP is, therefore, a feasible study design that should be executed in the Dutch primary care to provide insight into chronic venous disease prevalence and increase awareness about chronic venous disease in the Netherlands.

In addition, a long term cohort (such as the Bonn Vein study(94) or the Edinburgh Vein study(95)) would be ideal to investigate the causality of risk factors such as obesity and changes in physical activity. Both the Bonn Vein Study and the Edinburgh Vein Study included only BMI as a weight measurement and did not include physical activity or mobility measurements. A long-term cohort should measure waist circumference, range of ankle motion, level of physical activity and change in physical activity in order to confirm a causal relationship between abdominal obesity and ankle mobility, and calf muscle pump function and chronic venous disease progression.

Finally, the proposed prevention strategy for the progression of chronic venous disease should be studied in the Dutch clinical practice for its cost-utility. Performing a study on a complex intervention, like the prevention strategy in clinical practice, would provide insight into the actual effectiveness of the screenings and risk-factor interventions in chronic venous disease patients representative of the Dutch population. In an intervention study, more information can be gathered on the effectiveness of varicose vein removal, risk-factor management and increased compliance with compression therapy to prevent chronic venous disease progression.

Education

A body of knowledge on chronic venous disease should be implemented in primary and secondary healthcare education to increase recognition of chronic venous disease as a whole and not just its separate clinical signs. In healthcare education, chronic venous disease should be presented as a chronic cardiovascular disease with its different causes (venous thrombosis, venous syndromes, and venous insufficiency), signs, symptoms, and risk factors (increasing age, abdominal obesity, hypertension, ankle mobility and family history of venous leg ulcers). Implementing a body of knowledge on chronic venous disease in healthcare education is the first step towards improving future early recognition of chronic venous disease in clinical practice.

Clinical implications

The main objective of this thesis was to take a first step towards the prevention of the progression of chronic venous disease and the development of a first venous leg ulcer in chronic venous disease patients. This thesis shows that current care for chronic venous disease is insufficient, and a strategy for the prevention of chronic venous disease progression is required. Chronic venous disease guidelines should be updated, including the collaboration of primary and secondary care in the adequate screening, diagnosing, and monitoring of chronic venous disease risk factors in patients. These guidelines could increase the awareness of chronic venous disease primary care. This thesis also identifies several risk factors for the progression of chronic venous disease, and specifically for the development of a venous leg ulcer. Healthcare providers in primary and secondary care should be aware of risk factors like hypertension, abdominal obesity and reduced (ankle) mobility, and they should measure these factors in patients with chronic venous disease. In case of abdominal obesity and a reduced range of ankle motion, dieticians and physical therapists should be consulted for the treatment of these risk factors. The framework for the screening, diagnosing and monitoring of chronic venous disease and the associated risk factors is already proven to be effective in diabetes care.(10) The only difference in chronic venous disease care is the focus on the calf muscle pump function by increasing physical activity and increasing compliance to compression therapy instead of insulin therapy.

Today, there is an excess of demand for general practitioners in the Netherlands. More and more tasks are passed on to other healthcare professionals in primary care to support the general practitioners. For chronic venous disease patients, a practice nurse or dermal therapist could be asked to perform the follow-ups to monitor the disease, assess risks, provide and increase compliance to compression therapy, and coordinate the healthcare of chronic venous disease patients in collaboration with the general practitioner, dietician, physical therapist, and dermatologist or vascular surgeon.

The Dutch population is ageing, and the life expectancy increased over the last decades. In 2000, the average life expectancy was 78.1 years; in 2018, it was 81.8 years.(96) As ageing is the most important risk factor for chronic venous disease, it is likely that the prevalence of chronic venous disease will increase over the years. In addition, the prevalence of obesity has increased in the past two decades. In 2000, the prevalence of obesity among adults in the Netherlands was 9.1% ; in 2018, it was up to 14.8%. For people over 50 years old, the prevalence of obesity was even higher: 17.8% in 2018.(97) The ageing population and the increase in the

prevalence of obesity might lead to even more chronic venous disease patients in the future.(98, 99) This denotes the importance of taking action today.

It is now up to networks of healthcare providers to update their clinical guidelines to improve the recognition of chronic venous disease and its risk factors. Guidelines should include adequate screening, diagnostics, treatment, and monitoring of chronic venous disease and its risk factors. The clinical guidelines should be developed in collaboration with venous specialist, general practitioners, practice nurses, dermal therapists, dieticians, and physical therapists. The time to acknowledge chronic venous disease as a chronic cardiovascular disease is now.

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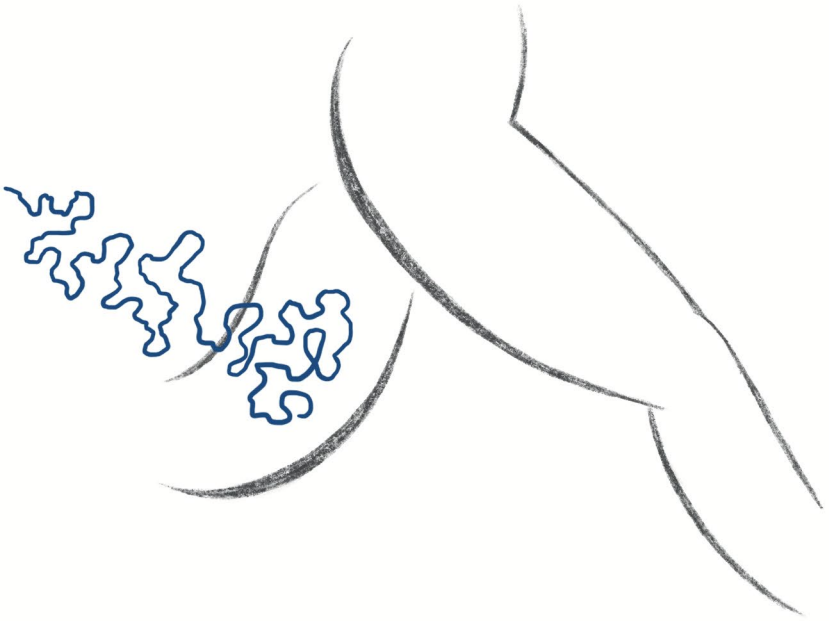
CHAPTER NINE



SUMMARY
SAMENVATTING

Summary

Varicose veins are a very common defect of the venous system in the lower extremities, affecting almost a third of the adult population world-wide. The prevalence ranges from 50% in people aged 60-64 years to 69% in people aged 80+ years. Varicose veins are often left untreated because of their cosmetic reputation. Health insurance companies do not always cover treatment, and there are no fixed healthcare paths for patients with varicose veins. Chronicity and progression of varicose veins is, therefore, often overlooked by patients and by healthcare providers.

Chronic venous disease includes various physical signs like varicose veins, oedema, eczema, skin discolouration, and a venous leg ulcer. A venous leg ulcer occurs when the ambulatory venous pressure is increased for several years. The prevalence of venous leg ulcers is approximately 0.3%, but they are hard to heal, recur often and can have a large impact on a person's quality of life and activities of daily living. Even when a venous leg ulcer heals, patients can experience fear of venous leg ulcer recurrence. The fear of injury and skin tears on the lower extremities can cause non-compliance with common therapies like wearing compression hosiery and engage in physical activity.

The progression of chronic venous disease is accompanied by an increase in health care costs; the venous leg ulcer is the most expensive to treat. The scattered and incomplete guidelines in primary care might lead to an under recognition of chronic venous disease patients, which can lead to inadequate diagnosis and treatment of chronic venous disease in the Dutch primary care system. Chronic venous disease is the only chronic disease with the potential to develop into a chronic wound that does not receive regular check-ups to monitor and treat disease progression. For other chronic diseases that carry a risk of the development of a chronic wound (such as diabetes and peripheral arterial disease), prevention of disease progression is imbedded in current healthcare. Adequate prevention for the progression of chronic venous disease (and the development of a first venous leg ulcer) is also missing due to a poor understanding of its risk factors.

The objective of this thesis, as described in **Chapter 1**, is to make a first step towards prevention of the progression of chronic venous disease and the development of a first venous leg ulcer in chronic venous disease patients. The aim is to identify chronic venous disease patients at risk of developing more severe clinical stages, provide insight into the lifestyle related risk factors, and provide an overview of current chronic venous disease care in the Netherlands.

In **Chapter 2** we further explored the progression of chronic venous disease into a first venous leg ulcer from a patients' perspective. We conducted a qualitative study using semi-structured interviews amongst male and female patients with a venous leg ulcer. Eleven patients (age 43-89 years old) with first and recurrent venous leg ulcers where included. The interviews were transcribed and analysed using a narrative approach to a thematic analysis. Transcripts where organised in a chronological order and an iterative process was used to code the transcripts. Four key-themes and the connections made between them emerged from the eleven narratives on the progression of chronic venous disease towards a first venous leg ulcer: 'Comorbidity', 'Mobility', 'Work & Lifestyle', and 'Acknowledgement of chronic venous disease'. Comorbidity was linked to reduced Mobility and a late Acknowledgement of chronic venous disease. Comorbidity also affected Work & Lifestyle and vice versa. Work & Lifestyle affected Mobility and was linked to the Acknowledgement of chronic venous disease. In conclusion, a reduction in Mobility as a result of Comorbidity and Work & Lifestyle occurred before the venous leg ulcer developed. Patients did not recognise symptoms of chronic venous disease and did not acknowledge the chronicity of chronic venous disease. Health care professionals should be aware of reductions in mobility and the knowledge deficit in patients with chronic venous disease.

In addition to the patient narratives we identified known risk factors for developing a first venous leg ulcer from the literature. In **Chapter 3** we describe the systematic literature review. We searched the Cochrane Library, Pubmed, Cinahl, and Narcis to identify studies that investigated risk factors in developing a venous leg ulcer. The last search was performed in January 2018. Two reviewers independently reviewed the abstracts and full-text articles, and assessed the methodological quality of the included studies. Results of studies using duplex scanning, and comparing participants with and without venous leg ulcers were included in the qualitative analysis. We found five studies that investigated the relation of several risk factors with venous leg ulcer development. The methodological differences of the studies made it impossible to perform a quantitative analysis. The risk factors: higher age, higher Body Mass Index, low physical activity, arterial hypertension, deep vein reflux, deep venous thrombosis and family history of venous leg ulcers were significantly associated with the development of a first venous leg ulcer in the majority of the studies. To what extent they influence the development of a venous leg ulcer remains unclear because of the limited number of studies that investigated the association of these risk factors with venous leg ulcer development, and the heterogeneity of these studies. Further studies are needed to confirm the association of

these risk factors with the development of a venous leg ulcer and to explore body mass and low physical activity in more detail.

To explore the mechanisms of obesity and mobility in the development of an venous leg ulcer we conducted a scoping review as described in **Chapter 4.** We searched the Cochrane library and Pubmed in May 2019 to identify studies on the working mechanisms of obesity and mobility in developing a venous leg ulcer. Hand searches were performed to find additional studies explaining the working mechanisms (indirectly related to the venous leg ulcer). Two reviewers independently reviewed the abstracts and full-text articles. As a result twenty-eight studies met our eligibility criteria. We found that disturbed range of ankle motion and gait can lead to a reduced calf muscle pump function leading to a venous outflow disorder. Increased abdominal pressure due to obesity can lead to a venous outflow obstruction and increased adipose tissue mass results in an increase in adipokine secretion. The venous outflow disorder, outflow obstruction and increased adipokine secretion can all lead to chronic systemic inflammation, increased endothelial permeability and hence microcirculatory dysfunction. Concluding, obesity and reduced mobility can simultaneously lead to haemodynamic changes in the macro- and microcirculation of the lower extremities and eventually in result in a venous leg ulcer. In patients with obesity and reduced mobility the changes in microcirculation alone can lead to skin changes and eventually a venous leg ulcer. Therefore, early recognition of chronic venous disease symptoms in patients with obesity and reduced mobility is crucial for an early diagnosis and treatment of chronic venous disease to prevent a venous leg ulcer.

With the knowledge on the working mechanisms of obesity and reduced mobility from the scoping review we further investigated these factors in relation to the progression of chronic venous disease**.** In **Chapter 5** we assessed the relation of waist circumference and calf muscle pump related physical activity with the progression of chronic venous disease. We collected data from patients in primary care, secondary care and through convenience sampling in the general population in The Netherlands. In total 74 participants (aged >40 years) with chronic venous disease (varicose veins, oedema, skin changes and venous leg ulcers) were recruited and diagnosed with duplex ultrasound. Physical measurements were performed for waist circumference, range of ankle motion, and the number of steps per day (accelerometer). Data on patient characteristics and physical activity were collected using a questionnaire. We included 29 patients with varicose veins and 43 patients with more severe stages of chronic venous disease. Patients had a mean age of 68.5 years and were predominantly female. Multivariable logistic regression showed that

abdominal obesity (OR 3.9, 95% CI: 1.3-12.3) and reduced dorsal flexion of the ankle (OR 5.9, 95% CI: 1.8-19.4) were independently associated with more severe chronic venous disease. Both abdominal obesity and dorsal flexion of the ankle <10° were associated with more severe chronic venous disease and were likely to be present for over five years which suggests that they are risk factors for the progression of chronic venous disease. Measurement and treatment of these risk factors should be implemented in chronic venous disease care to improve venous function.

The cross-sectional study in Chapter 5 showed that the number of steps per day were not associated with more severe chronic venous disease. We therefore further investigated physical activity levels from patients in the cross-sectional study**.** The aim of the study in **Chapter 6** was to investigate the physical activity levels and to compare the results with the physical activity recommendations of the World Health Organisation (WHO). Physical activity was measured using a standardised questionnaire and accelerometers. The accelerometers were used to measure sedentary behaviour, light physical activity and moderate to vigorous physical activity. Sixty percent of the study population had multimorbidity that might influence physical activity. Only 34% of the patients met the WHO physical activity recommendations and 39% of the patients reported walking for at least 30 minutes on 5 days per week. The accelerometer data showed that 73% of the patients did not engage in 30 minutes of continuous moderate to vigorous physical activity. Patients had a median 82 (21-158) minutes of moderate to vigorous activity measured in 10 minute bouts, and a median of 6 hours (4.3-7.5) of sedentary behaviour per day. The median number of steps differed significantly between patients with varicose veins and more severe chronic venous disease with a difference of 29% (7747 [5858-9604] vs. 5536 [4510-8438]). In conclusion, physical activity in chronic venous disease patients is insufficient and should be treated in chronic venous disease healthcare to improve venous outflow and optimise the calf muscle pump function. Further research is necessary to investigate the effect of increasing physical activity levels on disease progression in chronic venous disease patients.

In **Chapter 7** we investigated the current care for chronic venous disease patients in the Netherlands. In the cross-sectional study data on quality of life, treatment and follow-up were collected using questionnaires. The majority of the patients experienced one or several physical complaints that led to a reduction in quality of life. In addition, over 30% of the patients did not receive invasive treatment at the time of the measurements. Half of the patients with a current venous insufficiency were treated for one of the truncal veins in the past. Non-invasive treatments such as calf

muscle exercises, and advice for walking was mentioned by 4%-23% of the patients and non-compliance to wearing compression stockings was 90%. This shows that healthcare for chronic venous disease patients in the Netherlands is insufficient. A collaboration between primary and secondary care health care professionals is crucial in the management of this seemingly harmless yet complex disease.

In **Chapter 8** we discuss our findings and the clinical implications of this thesis. The aim of this thesis was to identify chronic venous disease patients at risk of developing more severe clinical stages, to provide insight in the risk factors, and to provide an overview of current chronic venous disease care in the Netherlands.

Reduced range of ankle motion and abdominal obesity are found to be associated with more severe chronic venous disease. Other literature supports the hypotheses that obesity and reduced mobility can have a solitary and combined effect on chronic venous disease progression (and vice versa). Obesity and reduced mobility can also negatively affect chronic venous disease treatment outcomes such as varicose vein removal and ambulatory compression therapy. The indirect evidence from this study and other literature suggests that the screening, monitoring and treatment of obesity and reduced mobility can improve treatment outcomes and reduce disease progression. However, further research is required to assess whether or not the screening, monitoring and treatment of lifestyle related risk factors significantly reduces chronic venous disease progression and further improves chronic venous disease signs, symptoms and treatment outcomes.

Physical activity was low, and a reduction in mobility occurred often in chronic venous disease patients. The reduction in mobility was mostly present before the venous leg ulcer developed, and was often caused by other comorbidities. In clinical practice obesity and reduced physical activity should be measured, monitored and treated in chronic venous disease patients. The ageing population, reduced physical activity and increase in overweight and obesity in the Netherlands calls for action now.

The modifiable risk factors (arterial hypertension, obesity and insufficient physical activity) for chronic venous disease are also risk factors for cardiovascular disease in general. Chronic venous disease, therefore, deserves a more prominent place in cardiovascular disease management. It is time to move past the cosmetic reputation of varicose veins and acknowledge chronic venous disease as a cardiovascular disease that can progress to severe and disabling clinical stages with an increased mortality.

In addition, not all chronic venous disease patients in the studies experienced signs and symptoms as ‘complaints’. Moreover, when patients did have complaints,

they often did not assign the signs and symptoms to the chronic venous disease; therefore, they did not seek healthcare. Finally, not all chronic venous disease patients in the studies received diagnostics or treatment for their venous insufficiency, and follow-up of chronic venous disease patients was very low. Implementing a body of knowledge on chronic venous disease in healthcare education is the first step towards improving future early recognition of chronic venous disease in clinical practice.

In conclusion, this thesis shows that it is important to not only look at a patients' chronic venous disease alone. The patient should be assessed as a whole to identify the chronic venous disease and all possible risk factors that are associated with the progression of chronic venous disease. It is now up to networks of healthcare providers to update their clinical guidelines to improve the recognition of chronic venous disease and its risk factors. Guidelines should include adequate screening, diagnostics, treatment, and monitoring of chronic venous disease and its risk factors. The clinical guidelines should be developed in collaboration with venous specialist, general practitioners, practice nurses, dermal therapists, dieticians, and physical therapists.

Samenvatting

Varices zijn een veelvoorkomende aandoening van het veneuze system van de onderste extremiteiten. Ongeveer een derde van de volwassen populatie wereldwijd heeft een vorm van varices. De prevalentie varieert van 50% in volwassenen van 60-64 jaar tot 69% in ouderen van 80+. Varices hebben een cosmetische reputatie en blijven daardoor vaak onbehandeld. Verzekeringsmaatschappijen vergoeden de behandeling vaak niet en er zijn geen gereguleerde zorgpaden voor patiënten met varices. Om deze redenen wordt de chroniciteit en progressie van varices vaak over het hoofd gezien door zowel patiënten als zorgverleners. Chronische veneuze aandoeningen typeren zich door fysieke kenmerken als varices, oedeem, huidverkleuringen en uiteindelijk een veneus ulcus cruris. Een veneus ulcus cruris ontstaat wanneer de ambulante veneuze druk langdurig (enkele jaren) is verhoogd. De prevalentie van veneuze ulcera is ongeveer 0.3%, maar deze ulcera zijn moeilijk te genezen en keren vaak terug. Ook hebben veneuze ulcera een grote impact op de kwaliteit van leven en dagelijkse activiteiten van patiënten. Zelfs wanneer een veneus ulcus cruris is genezen behouden patiënten de angst voor een nieuw ulcus. De angst voor verwondingen aan de onderste extremiteiten kan leiden tot minder fysieke activiteit en het niet dragen van ambulante compressie therapie; beide belangrijke therapieën voor patiënten met veneuze ulcera.

De progressie van chronische veneuze aandoeningen gaat gepaard met een verhoging in zorgkosten waarbij een veneus ulcus de meeste zorgkosten met zich mee brengt. De verdeelde en incomplete richtlijnen in de eerstelijnszorg leiden tot onvoldoende herkenning van chronische veneuze aandoeningen bij patiënten. De onvoldoende herkenning van chronische veneuze aandoeningen leidt weer tot inadequate diagnostisering en behandeling van deze aandoeningen in de Nederlandse eerstelijnszorg.

Chronische veneuze aandoeningen zijn de enige chronische aandoening die kunnen leiden tot een chronische wond waarbij geen regelmatige follow-up plaatsvind voor het monitoren en behandelen van de onderliggende chronische aandoening. Voor andere chronische aandoeningen met risico op het ontwikkelen van een chronische wond, zoals diabetes en perifeer arterieel vaatlijden, is preventie van ziekteprogressie volledig ingebed in de huidige zorg. De afwezigheid van adequate preventie voor de progressie van chronische veneuze aandoeningen (en het ontwikkelen van een eerste veneus ulcus cruris) kan mede verklaard worden door gebrekkige kennis over de risicofactoren voor de progressie van chronische ve-

neuze aandoeningen.

De doelstelling van dit promotieonderzoek, zoals beschreven in **Hoofdstuk 1**, is het maken van een eerste stap in de richting van het voorkómen van progressie van chronische veneuze aandoeningen en preventie voor de ontwikkeling van een eerste veneus ulcus cruris. Hierbij streven wij naar het identificeren van patiënten die risico lopen op het ontwikkelen van een ernstiger stadium van chronische veneuze aandoeningen, het verkrijgen van inzichten in leefstijlfactoren als risicofactor en het verkrijgen van een overzicht van de huidige zorg voor chronische veneuze aandoeningen in Nederland.

In **Hoofdstuk 2** gaan we dieper in op het patiënten perspectief op de progressie van chronische veneuze aandoeningen naar een eerste veneus ulcus cruris. Hiervoor gebruikten we semigestructureerde interviews bij mannelijke en vrouwelijke patiënten met een veneus ulcus cruris. Elf patiënten (leeftijd 43-89 jaar) met eerste en herhaaldelijke veneuze ulcera werden geïncludeerd. De interviews werden getranscribeerd en geanalyseerd volgens een narratieve benadering met een thematische analyse. De transcripten werden in chronologische volgorde gezet en met een iteratief proces gecodeerd. Uit de elf verhalen over de progressie van chronische veneuze aandoeningen naar een eerste veneus ulcus cruris kwamen vier hoofdthema's en hun onderlinge samenhang naar voren. De thema's waren 'Comorbiditeit', 'Mobiliteit', 'Werk & Levensstijl' en '(H)erkenning' van chronische veneuze aandoeningen. Comorbiditeit werd gerelateerd aan mobiliteit en vice versa. Werk & Levensstijl had invloed op Mobiliteit en werd gelinkt aan de (H)erkenning van chronische veneuze aandoeningen. Een reductie in Mobiliteit door Comorbiditeit of Werk & Levensstijl vond plaats nog voordat het veneus ulcus cruris ontstond. Patiënten herkenden de symptomen van chronische veneuze aandoeningen niet en erkenden ook de chroniciteit niet. Zorgprofessionals moeten rekening houden met reducties in mobiliteit en het gebrek aan ziekte specifieke kennis van patiënten met chronische veneuze aandoeningen.

Ter aanvulling op de patiënt verhalen hebben we bekende risicofactoren voor het ontwikkelen van een eerste veneus ulcus cruris uit de literatuur geïdentificeerd. In **Hoofdstuk 3** beschrijven we een systematisch literatuur onderzoek. Twee onderzoekers hebben de literatuur onafhankelijk van elkaar beoordeeld. Vijf studies werden geïncludeerd die duplex onderzoek gebruikte voor de diagnose van chronische veneuze aandoeningen en studies die patiënten met en zonder een veneus ulcus cruris vergeleken. De methodologische verschillen maakte het onmogelijk om een meta-analyse uit te voeren. De volgende risicofactoren waren significant geassocieerd met de ontwikkeling van een veneus ulcus cruris bij patiënten met

chronische veneuze insufficiëntie: Hogere leeftijd, hogere body mass index, lage fysieke activiteit, arteriële hypertensie, diep veneuze reflux, diep veneuze trombose en veneuze ulcera in de familie. Tot op welke hoogte deze factoren invloed hebben op de ontwikkeling van een veneus ulcus cruris blijft onbekend. De reden hiervoor is het lage aantal geïncludeerde studies en de heterogeniteit van de studies. Verder onderzoek is nodig om deze risicofactoren te bevestigen en om de invloed van overgewicht en lage fysieke activiteit in meer detail te onderzoeken.

Om de werkingsmechanismen van obesitas en mobiliteit op het ontwikkelen van een veneus ulcus te onderzoeken hebben wij een scoping review uitgevoerd. De scoping review staat beschreven in **Hoofdstuk 4.** Studies die de werkingsmechanismen van obesitas of mobiliteit in relatie tot het ontwikkelen van een veneus ulcus cruris onderzochten werden geïncludeerd. Twee onderzoekers hebben de literatuur onafhankelijk van elkaar beoordeeld. In totaal voldeden 28 studies aan de inclusiecriteria. Verstoorde mobiliteit van de enkel en een alternatieve loopcyclus kunnen leiden tot een verminderde kuitspierpomp functie dat weer kan leiden tot een verstoring in de veneuze uitstroom van de onderste extremiteiten. Verhoogde abdominale druk door obesitas kan leiden tot een obstructie van de veneuze uitstroom. Daarnaast kan abdominale obesitas leiden tot een verhoogde adipokine secretie. Dit alles kan leiden tot chronische systemische inflammatie, verhoogde endothele permeabiliteit en dus een verstoring in de microcirculatie. Samenvattend, obesitas en verminderde mobiliteit kunnen gezamenlijk leiden tot hemodynamische veranderingen in de macro- en microcirculatie van de onderste extremiteiten en zo uiteindelijk resulteren in een veneus ulcus cruris. Bij patiënten met obesitas en verminderde mobiliteit kunnen de veranderingen in microcirculatie alleen leiden tot huidveranderingen en uiteindelijk een veneus ulcus cruris. Vroege signalering van symptomen van chronische veneuze aandoeningen bij patiënten met obesitas en verminderde mobiliteit zijn cruciaal voor een vroege diagnostiek en behandeling van chronische veneuze aandoeningen om mogelijk een veneus ulcus cruris te voorkomen.

Met de kennis van de werkingsmechanismen van obesitas en verminderde mobiliteit uit de scoping review hebben we deze factoren verder onderzocht in relatie tot de progressie van chronische veneuze aandoeningen. In **Hoofdstuk 5** is de taille omtrek en kuitspierpomp functie gerelateerde fysieke activiteit onderzocht in relatie tot de progressie van chronische veneuze aandoeningen. Data is verzameld van patiënten uit de eerstelijnszorg, tweedelijnszorg en met een gelegenheidssteekproef uit de algemene populatie in Nederland. In totaal zijn 74 participanten (leeftijd >40 jaar) met een chronisch veneuze aandoening (varices,

oedeem, huidverkleuringen en veneuze ulcera) gerekruteerd en gediagnosticeerd met een duplex scan. De volgende fysieke metingen werden uitgevoerd: De taille omtrek, beweeglijkheid van de enkel en het aantal stappen per dag (accelerometer). Patiëntkarakteristieken en fysieke activiteit werden in kaart gebracht door middel van een vragenlijst. We hebben 29 patiënten met varices en 43 patiënten met een gevorderd stadium van chronische veneuze aandoeningen geïncludeerd. De gemiddelde leeftijd van de studiepopulatie was 68.5 jaar met een meerderheid aan vrouwen. Met een multivariabele logistische regressie werd aangetoond dat abdominale obesitas (OR 3.9, 95% CI: 1.3-12.3) en gereduceerde dorsaalflexie van de enkel (OR 5.9, 95% CI: 1.8-19.4) onafhankelijk gerelateerd zijn aan een gevorderd stadium van chronische veneuze aandoeningen. Zowel abdominale obesitas als de reductie in dorsaalflexie van de enkel waren in de meeste gevallen minstens vijf jaar aanwezig. De lange duur van de abdominale obesitas en reductie in dorsaalflexie van de enkel maakt het aannemelijk dat het risicofactoren zijn voor de progressie van chronische veneuze aandoeningen. Het meten en behandelen van de risicofactoren zou onderdeel moeten worden van de huidige zorg om zo de veneuze functie bij deze patiënten te verbeteren.

De cross-sectionele studie in Hoofdstuk 5 toont aan dat het aantal stappen per dag niet gerelateerd was aan een gevorderd stadium van chronische veneuze aandoeningen. Om deze reden hebben wij fysieke activiteit bij de patiënten in de cross-sectionele studie verder onderzocht. Het doel van de studie in **Hoofdstuk 6** was het onderzoeken van de mate van fysieke activiteit en het vergelijken hiervan met de aanbevelingen voor fysieke activiteit van de Wereld Gezondheidsorganisatie. Fysieke activiteit werd onderzocht met een gestandaardiseerde vragenlijst en accelerometers. De accelerometers werden gebruikt om sedentair gedrag, lichte fysieke activiteit en matige tot zware activiteit te meten. Zestig procent van de studiepopulatie had multimorbiditeit die mogelijk de mate van fysieke activiteit beïnvloed. Slechts 34% van de patiënten voldeden aan de beweegrichtlijn van de Wereld Gezondheidsorganisatie en 39% van de patiënten gaven aan minstens 30 minuten te wandelen op minimaal 5 dagen per week. Data van de accelerometers liet zien dat 73% van de patiënten geen 30 minuten aaneengesloten matige tot intensieve inspanning bereikte. Metingen van matig tot intensieve activiteit (gemeten in bouts van 10 minuten aaneengesloten activiteit) toonde een mediaan van 85 (21-158) minuten per week. Daarnaast vertoonden patiënten sedentair gedrag met een mediaan van 6 (4.3-7.5) uur per dag. Het aantal stappen per dag verschilde significant tussen patiënten met varices en patiënten met een gevorderd stadium van chronische veneuze aandoeningen met een mediaan verschil van 29% (7747

[5858-9604] vs. 5536 [4510-8438]). Het onderzoek laat zien dat de fysieke activiteit bij patiënten met chronische veneuze aandoeningen insufficiënt is. Om de veneuze terugstroom en kuitspierpomp te optimaliseren zou fysieke inactiviteit behandeld moeten worden in de zorg voor chronische veneuze aandoeningen. Verder onderzoek is nodig om te onderzoeken of het gericht verhogen van fysieke activiteit de progressie van chronische veneuze aandoeningen kan vertragen.

In **Hoofdstuk 7** hebben we de huidige zorg voor patiënten met een chronische veneuze aandoening in Nederland onderzocht. In de cross-sectionele studie is hiervoor data verzameld over de kwaliteit van leven, behandeling en follow-up met behulp van (gevalideerde) vragenlijsten. De meerderheid van de patiënten had één of meerdere fysieke klachten die leiden tot een vermindering in de kwaliteit van leven. Daarnaast had meer dan 30% van de patiënten met veneuze problematiek geen invasieve behandeling ondergaan ten tijde van het onderzoek. De helft van de patiënten met een huidige veneuze insufficiëntie was behandeld voor een insufficiëntie van één de stamvenen in het verleden. Niet-invasieve behandelingen zoals oefeningen voor de kuitspier en het advies om te wandelen werd genoemd door 4%-23% van de patiënten. Daarnaast was 90% van de patiënten niet therapietrouw met betrekking tot het dragen van therapeutisch elastische kousen. Deze resultaten geven aan dat de huidige zorg voor chronische veneuze aandoeningen in Nederland ontoereikend is. Een samenwerking tussen eerstelijns en tweedelijns zorg is cruciaal in het managen van deze aandoening die onschuldig lijkt, maar in werkelijkheid zeer complex is.

In **Hoofdstuk 8** worden de bevindingen en de klinische relevantie hiervan besproken. Het doel van dit proefschrift was het identificeren van patiënten met chronische veneuze aandoeningen die risico lopen op progressie van de aandoening, om meer inzicht te geven in deze risicofactoren en het verkrijgen van een overzicht van de huidige zorg voor patiënten met chronische veneuze aandoeningen in Nederland.

Verminderde beweeglijkheid van de enkel en abdominale obesitas zijn gerelateerd aan gevorderde stadia van chronische veneuze aandoeningen. Andere literatuur ondersteunt de hypothese dat obesitas en verminderde mobiliteit een individueel en gezamenlijk effect hebben op de progressie van chronische veneuze aandoeningen (en vice versa). Obesitas en verminderde mobiliteit hebben ook een negatief effect op de behandeling voor chronische veneuze aandoeningen zoals invasieve behandeling van varices en ambulante compressie therapie. Het indirecte bewijs van de onderzoeken in dit proefschrift en andere literatuur laat de suggestie dat screening, monitoring en behandeling van obesitas en verminderde mobiliteit

de behandeling van chronische veneuze aandoeningen ten goede komt en wellicht progressie kan voorkomen. Verder onderzoek is nodig om te testen of screening, monitoring en behandeling van leefstijl gerelateerde risicofactoren de progressie van chronische veneuze aandoeningen significant kan verlagen. Verder onderzoek moet ook uitwijzen of de juiste zorg voor deze risicofactoren de klachten, symptomen en behandeluitkomsten van patiënten met chronische veneuze aandoeningen kan verbeteren.

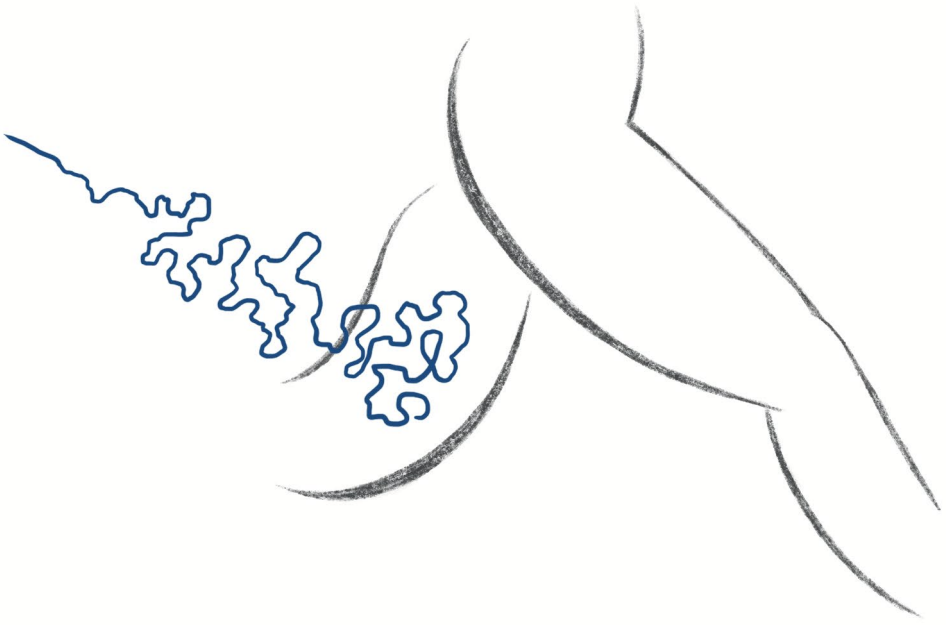
Bij de patiënten met chronische veneuze aandoeningen in dit onderzoek was de fysieke activiteit laag en was een reductie in mobiliteit een veelvoorkomend probleem. In veruit de meeste gevallen was de reductie in mobiliteit, vaak veroorzaakt door een andere aandoening, al aanwezig voordat een veneus ulcus cruris ontstond. Het meten, monitoren en behandelen van obesitas en verminderde mobiliteit zou onderdeel moeten zijn van de huidige zorg. De algemene vergrijzing, afname van fysieke activiteit en toename van overgewicht en obesitas van de algehele Nederlandse populatie roept op tot actie.

De behandelbare risicofactoren (arteriële hypertensie, obesitas en insufficiënte fysieke activiteit) voor chronische veneuze aandoeningen zijn tevens risicofactoren voor cardiovasculaire aandoeningen in het algemeen. Chronische veneuze aandoeningen zouden daarom een meer prominente plaats verdienen in de zorg voor cardiovasculaire aandoeningen. Het is tijd om de cosmetische reputatie van varices achter ons te laten en te erkennen dat dit kan leiden tot chronische veneuze aandoeningen en dus een cardiovasculaire aandoening die kan resulteren in ernstige en beperkende stadia met een verhoogde mortaliteit.

Naast de tekortkomingen in de huidige zorg ervaren niet alle patiënten met chronische veneuze aandoeningen klachten, of relateren ze de klachten en symptomen niet aan chronische veneuze aandoeningen waardoor zij geen zorg vragen. Niet alle patiënten in de studies waren daarom met een duplex onderzoek gediagnosticeerd of waren onder behandeling. Daarnaast was de follow-up van patiënten die wel zorg hadden ontvangen nihil. De eerste stap in het verhogen van de vroege (h) erkenning van chronische veneuze aandoeningen in de gezondheidszorg is het implementeren van een body-of-knowledge van chronische veneuze aandoeningen in het gezondheidszorgonderwijs.

Tot slot, dit proefschrift laat het belang zien van het onderzoeken van een patiënt als individu en niet slechts te focussen op de chronische veneuze aandoening. In de praktijk zou de patiënt als individu onderzocht moeten worden voor het identificeren van (het stadium van) de chronische veneuze aandoening en alle mogelijke risicofactoren die gerelateerd zijn aan de progressie van chronische veneuze

aandoeningen. Het is nu aan de beroepsverenigingen in de gezondheidszorg om hun richtlijnen te vernieuwen gericht op de herkenning van chronische veneuze aandoeningen en de bijbehorende risicofactoren. Richtlijnen zouden een adequate screening, diagnostisering, behandeling en monitoring moeten beschrijven voor chronische veneuze aandoeningen en de bijbehorende risicofactoren. Voor het ontwikkelen van een dergelijke klinische richtlijn is een samenwerking met medische specialisten, huisartsen, praktijkondersteuners, huidtherapeuten, diëtisten en fysiotherapeuten essentieel.



Dankwoord

Het dankwoord. De reis is ten einde. Het was een bijzonder leerzame en mooie reis die geresulteerd heeft in een waar boek. Zonder de hulp van velen was dit proefschrift nooit tot stand gekomen. Daarom wil ik graag een aantal mensen in het bijzonder bedanken.

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Laten we dansen!

Audrey

Curriculum Vitae

Audrey Maria Meulendijks was born April 30th 1989 in Maastricht. She studied dermal therapy at the University of Applied Sciences Utrecht. After briefly working as a dermal therapist she proceeded to study for a Master's degree in Epidemiology at Maastricht University. After completing the Master she started as a PhD student at the University Medical Centre Utrecht in collaboration with the University of Applied Sciences Utrecht focussing on the risk factors and progression of chronic venous disease. Currently she works as a Post-doc at Maastricht University where she studies risk factors for the development of congenital anomalies.

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